Synthesis of Carbocyclic Spiro Compounds via Intramolecular Alkylation Routes

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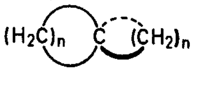
Intramolecular alkylation processes which lead to the formation of compounds with a free carbocyclic spiro linkage are reviewed.

Es werden intramolekulare Alkylierungen beschrieben, bei denen Verbindungen mit einer freien carbocyclischen Spiro-Verknüpfung entstehen.

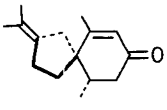
In 1900 Baeyer[1] introduced the name "spirocyclane" for those bicyclic hydrocarbons "welche ein beiden Ringen gemeinschaftliches quaternares Kohlenstoffatom enthalten: Spirocyclane, von 'spira' die Brezel". Thus the origin of spiro is from the Latin meaning spiral, which Baeyer construed to be like a pretzel. Of course, it should be noted that, due to the tetrahedral nature of the spiro carbon such that the two cycles lie in perpendicular planes, it forms a type of "pretzel" not commonly available.



The scope of the present review is a survey of intramolecular alkylations as synthetic routes to carbocyclic spiro compounds. Only processes leading to free carbocyclic systems (a free spiro union is one constituting the only union, direct or indirect, between two rings) will be considered[2]. Many other common reactions such as carbene or carbenoid additions to exocyclic olefins, cycloadditions, acyloin condensations, acylations, Dieckmann cyclizations, etc., which have found application for the preparation of spiro compounds, are beyond the goal of the present review.

The nomenclature of spiro compounds has been extensively discussed[2] and two fragmentary reviews dealing with spiro systems have been published[3]. Spirocyclic compounds have attracted considerable attention recently from the standpoints of synthesis and reactivity[4]. Many natural products have been characterized as possessing spiro linkages (e.g.

β-vetivone (1)[5], hinesol (2)[6], β-vetispirene (3)[7], α-alaskene (4)[8], α-chamigrene (5)[9], illudin S (6)[10], spirolaurenone (7)[11], and pronuciferine (8)[12], along with others).



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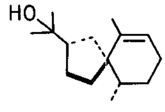

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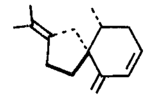

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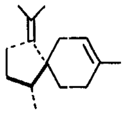

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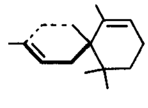

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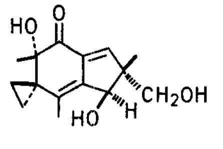

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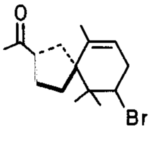

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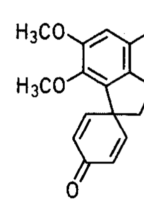

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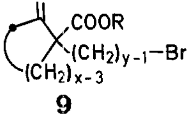
The synthetic routes have been categorized into the type of process by which the spiro linkage is formed. This classification should allow one to readily find a desired system or a potential approach for preparation of a new spiro compound.

1. Intramolecular Dehydrohalogenations, Dehydrotosylations, and Related Processes

If two groups or atoms to be eliminated are separated by three or more carbons, the product will be cyclic. Intramolecular alkylations of this type have found application for the synthesis of spiro compounds of various ring size. In the preparation of a three-membered ring, for example, this process can also be classified as a 1,3- or γ-elimination.

1.1. 2-(ω-Bromoalkyl)cycloalkanones

The alkylation of the metal enolate salts of 2-ethoxycarbonylcycloalkanones with an α,ω-dibromoalkane readily yields the monoalkylated keto esters **9**. Hydrolysis and decarboxylation of **9** yields **10**, which readily undergoes basic cyclization of the enolate salt in high yields to produce spiranones **11**.



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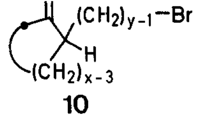

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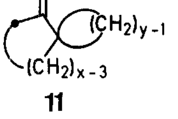

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This overall process has been successfully adapted to the synthesis of **11** where x and y show considerable variation. In the preparation of the enolate anion **10** (y=4), a considerable amount of by-product is formed via competitive alkylation on oxygen. The spiranones of type **11** prepared by this cyclization are tabulated in Table 1.

Table 1. Cyclization Reactions of 2-(ω-Bromoalkyl)cycloalkanones (**10**)

x	y	Base	Yield (%) of **11**	References
5	3	30% aq. KOH	34–97	13–18
5	4	$NaOCH_3/C_6H_6$ (65°)	32	19[a]
5	4	KOC_4H_9-*t*/C_6H_6	30	22, 23[b]
5	5	KOC_4H_9-*t*/C_6H_6	75	22
5	5	35% aq. KOH	73–85	20, 24, 25
5	6	35% aq. KOH	68–85	18, 20, 24–26
6	3	30% aq. KOH	9[c]	17
6	4	KOC_4H_9-*t*/C_6H_6	8	23[d]
6	5	KOC_4H_9-*t*/C_6H_6	70–76	22
7	4	KOC_4H_9-*t*/C_6H_6		22[e]
7	5	KOC_4H_9-*t*/C_6H_6	75	22
8	5	$NaH/H_3COCH_2CH_2OCH_3$	82	27
8	6	$NaH/H_3COCH_2CH_2OCH_3$	87	27

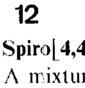
[a] In a previous paper[20] yields of 40–60% of **11** (x=5, y=4) had been reported. Reference 19 reports a 23% yield of **11** (x=5, y=4) following Mayer's procedure. Careful G.L.C. analysis of the reaction product obtained from Mayer's procedure[20] indicates that treatment of **10** (x=5, y=4) with potassium hydroxide/benzene yields 37% of **11** (x=5, y=4), 61% of the enol ether **12**, and 2% of **13**. Various other bases were utilized and variable yields of **11** and **12** were obtained. Spiroketone **11** (x=5, y=4) was isolated as a 1:1 mixture with **12**. Cope and co-workers[21] also report the isolation of 4% of **13** from the cyclization of **10** (x=5, y=4).

[b] Reference 23 reports that repetition of the work of Mayer and co-workers[20] on treatment of **10** (x=5, y=4) with boiling aqueous potassium hydroxide yields 13% of **11** (x=5, y=4), 15% of **12**, and 6% of **13**. Careful analysis of the product from the KOC_4H_9-*t*/benzene cyclization reported by Christol and coworkers[22] indicates the presence of 22% of **11**, 30% of **12**, and 19% of **13** (V.P.C.).

[c] Overall yield from 2-ethoxycarbonylcyclohexanone.

[d] Christol and co-workers[22] report a 70% yield of **11** (x=6, y=4) in this reaction. However, the major product of this reaction is enol ether **14**[23].

[e] Because of the reinvestigations carried out in references 19 and 23 on related systems, this structural assignment must be questioned. The product formed no 2,4-dinitrophenylhydrazone or semicarbazone, and it appears likely that the product is the enol ether **15**.



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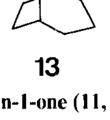

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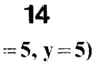

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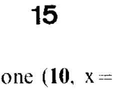

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Spiro[4,4]nonan-1-one (11, x=5, y=5)[20]:

A mixture of 2-(ω-bromobutyl)cyclopentanone (**10**, x=5, y=5) (219 g) and a 35% potassium hydroxide solution (800 g) is refluxed for 24 hours. The mixture is cooled, the top layer separated and purified by distillation. A nearly quantitative yield of **11** (x=5, y=5) is obtained: b.p. 82.5–83°/13 torr; $d_{20}^{24}=0.9995$; $n_D^{20}=1.4777$.

1.2. Detosylations of Steroidal α,β-Unsaturated Ketones and β,γ-Unsaturated Cyclohexenones

Spirocyclopropyl analogs of several steroids have been prepared by internal detosylations of appropriately positioned 2-tosyloxyethyl groups. Treatment of **16** (R=Tos) with potassium *t*-butoxide in *t*-butyl alcohol for 1.5 hours at 40° leads to **17** (52% yield from **16** (R=H))[28].

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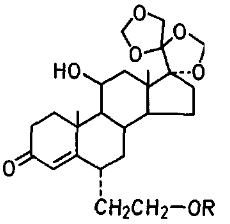
[1] A. Baeyer, *Ber. dtsch. chem. Ges.* 33, **3771** (1900).



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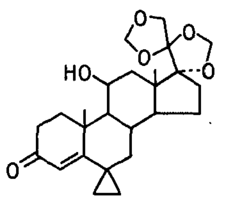

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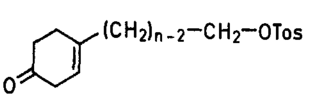
Additional examples of detosylations performed under similar experimental conditions can be found in other patents[29,30,31].

Intramolecular alkylation of β,γ-unsaturated ketones such as **18** leads to spirenones **19** in several cases. Treatment of one equivalent of **18** (n = 3) with 10 drops of *t*-butyl alcohol in dioxane and one equivalent of sodium hydride followed by refluxing for 11 to 17 hours yields **19** (n = 3) (29–35%)[32]. In a similar manner, reaction of **18** (n = 5) leads to **19** (n = 5) (28%)[33].



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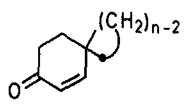

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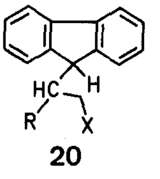
1.3. 9-(ω-Haloalkyl)fluorenes

The dehydrohalogenations of 9-(ω-haloalkyl)fluorenes (**20**) lead to the spirocyclopropane derivatives **21**. Treatment of **20** (R = H, X = Cl) with solid potassium hydroxide at 200° for a few minutes leads to **21** (R = H) in an 80% yield[34]. Similarly, reactions of **20** (R = H, X = Br) and **20** (R = CH_3, X = Cl) lead to **21** (R = H) and **21** (R = CH_3) in 90 and 84% yields, respectively[35].



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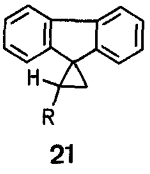

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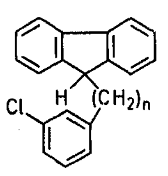
1.3.1. 9-[ω-(*m*-Chlorophenylalkyl)]fluorenes

Treatment of **22** (n = 2 or 3) with sodium amide in toluene leads to **23** (n = 2 or 3) in 45 and 20% yields, respectively[36]. A benzyne intermediate is undoubtedly involved in these cyclizations.



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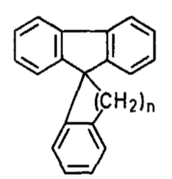

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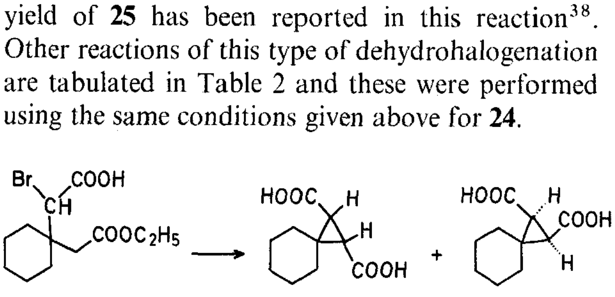
1.4. α-Halo-β,β-cycloalkyl Glutaric Acids and Esters

The formation of spiro compounds has been reported by Beesley, Thorpe, and Ingold[37] in the treatment of compounds such as **24** with a concentrated potassium hydroxide solution at 150°! It is of interest to note the experimental conditions. The addition of **24** is done as rapidly as possible to the concentrated potassium hydroxide solution at 150°. The reaction mixture is cooled, acidified, and the crude product collected. In the case of **24**, product **25** was isolated in about a 60% yield while the *cis*-diacid **26** was isolated in small amounts. The stereochemical assignments were based on thermal anhydride formation from **26** but not from **25**. More recently, a 17% yield of **25** has been reported in this reaction[38]. Other reactions of this type of dehydrohalogenation are tabulated in Table 2 and these were performed using the same conditions given above for **24**.



24 **25** **26**

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[2] International Union of Pure and Applied Chemistry, *J. Amer. Chem. Soc.* **82** 5560 (1960).
Union Internationale de Chimie Pure et Applique, *Bull. Soc. Chim. France* **1958**, 1205.
"*Nomenclature of Organic Chemistry*" (IUPAC), Butterworths, London, p. 40 (1958).
N. Lozac'h, "*La Nomenclature en Chimie Organique*," Masson et Cie, Editeurs, 120, Boulevard Saint-Germain, Paris, VI^e, pps. 90–94 (1967).
J. E. Rush, L. J. White, *J. Chem. Doc.* **10**, 195 (1970).

[3] E. H. Rodd, Ed., "*Chemistry of Carbon Compounds*," Part IIA, Elsevier Publ. Co., pps. 298–308 (1953).
S. Coffey, Ed., "*Rodd's Chemistry of Carbon Compounds*," 2nd Ed., IIC, Elsevier Publ. Co., pps. 20–31 (1969).

[4] B. S. Thyagarajan, Ed., "*Mechanism of Molecular Migrations*," Vol. 3, pps. 1–66, W. R. Dolbier, Jr., Wiley-Interscience (1971).

[5] J. A. Marshall, P C. Johnson, *J. Org. Chem.* **35**, 192 (1970).

[6] J. A. Marshall, S. F. Brady, *J. Org. Chem.* **35**, 4068 (1970).

[7] N. H. Andersen, M. S. Falcone, D. D. Syrdal, *Tetrahedron Lett.* **1970**, 1759.

[8] N. H. Andersen, D. D. Syrdal, *Tetrahedron Lett.* **1970**, 2277.
N. H. Andersen, D. D. Syrdal, *Tetrahedron Lett.* **1972**, 899.

[9] Y. Ohta, Y. Hirose, *Tetrahedron Lett.* **1968**, 2483.
A. Tanaka, H. Uda, A. Yoshikoshi, *Chem. Commun.* **1968**, 56.

[10] T. C. McMorris, M. Anchel, *J. Amer. Chem. Soc.* **87**, 1594 (1965).

[11] M. Suzuki, E. Kurosawa, T. Irie, *Tetrahedron Lett.* **1970**, 4995.

[12] K. L. Stuart, M. P. Cava, *Chem. Revs.* **68**, 321 (1968); a typical example of a small but important group of proaporphine alkaloids.

[13] R. Mayer, H. J. Schubert, *Chem. Ber.* **91**, 768 (1958).

[14] E. M. Kosower, M. Ito, *Proc. Chem. Soc.* **1962**, 25.

[15] D. E. Applequist, J. A. Landgrebe, *J. Amer. Chem. Soc.* **86**, 1543 (1964).

[16] J. J. Gajewski, *J. Amer. Chem. Soc.* **92**, 3688 (1970).

[17] J. K. Crandall, R. J. Seidewand, *J. Org. Chem.* **35**, 697 (1970).

[18] G. D. Christiansen, D. A. Lightner, *J. Org. Chem.* **36**, 948 (1971).

[19] C. F. Wilcox, Jr., G. C. Whitney, *J. Org. Chem.* **32**, 2933 (1967).

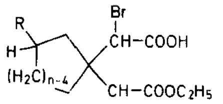
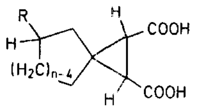
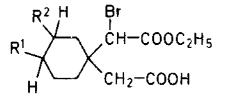
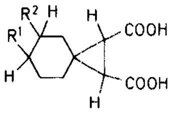
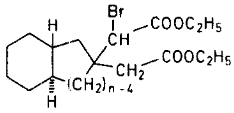
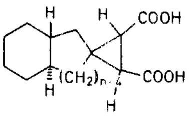
[20] R. Mayer, G. Wenschuh, W. Töpelmann, *Chem. Ber.* **91**, 1616 (1958).

[21] A. C. Cope, J. M. Grisar, P. E. Peterson, *J. Amer. Chem. Soc.* **82**, 4299 (1960).

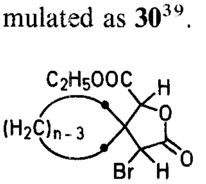
[22] H. Christol, M. Mousseron, F. Plenat, *Bull. Soc. Chim. France* **1959**, 543.

[23] S. J. Etheredge, *J. Org. Chem.* **31**, 1990 (1966).

Table 2. Spirocyclopropyl Systems from α-Bromo-diesters or-monoesters

Starting Material	Products		Yield (%)	References
		R = H, n = 5	—	39
		R = CH_3, n = 5	—	40
		R = H, n = 7	38	42
		$R^1 = CH_3$, $R^2 = H$	—	41
		$R^1 = H$, $R^2 = CH_3$	—	41
		n = 5	40	43
		n = 6	38	44

Treatment of the bromolactone **27** (n = 6) with boiling 64% aq. potassium hydroxide was initially reported as yielding the spirocyclopropanol **28** (n = 6)[37]. However, a recent study of this reaction reveals that the structure of the product of this reaction is probably **29**[38]. Treatment of **27** (n = 7) with 64% potassium hydroxide yielded a compound formulated as **28** (n = 7) (3%)[42]. This structural assignment must also be erroneous based on the work of Larsen and co-workers[38] and recent studies of cyclopropanol stabilities. It might also be noted that treatment of bromolactone **27** (n = 5) with 25% potassium hydroxide yields a lactone formulated as **30**[39].



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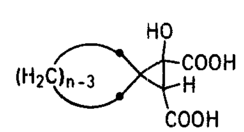

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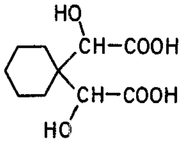

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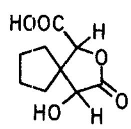

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1.5. Phenylspiro[2.2]pentane from the Deamination of a Quaternary Aminium Compound

Reaction of the quaternary aminium salt **31** with sodium amide in liquid ammonia leads to the γ-elimination product 1-phenylspiro[2.2]pentane (**32**) in a 46% yield[45].

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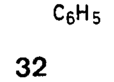

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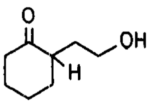
1.6. Intramolecular Dehydration of 2-(2-Hydroxyethyl)cyclohexanone

Treatment of **33** with dicyclohexylcarbodiimide at 150° leads to a 60% yield of a mixture containing 25% of **34** and 75% of **35**. Intermediate **36** is the probable precursor of **34** (and **35** by intramolecular nucleophilic displacement from the enol form)[46].



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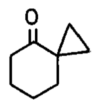

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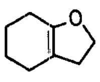

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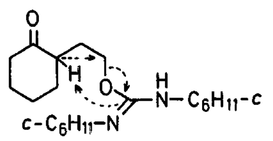

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[24] A. P. Krapcho, M. Benson, *J. Amer. Chem. Soc.* **84**, 1036 (1962).

[25] A. P. Krapcho, R. Donn, *J. Org. Chem.* **30**, 641 (1965).

[26] R. Mayer, W. Topelmann, *Chem. Ber.* **91**, 1764 (1958).

[27] A. P. Krapcho, J. E. McCullough, *J. Org. Chem.* **32**, 2453 (1967).

[28] *Netherlands Patent Appl.* 6603853 (Upjohn Co.); *C. A.* **66**, 65747 (1967).

[29] *Netherlands Patent Appl.* 6603804 (Upjohn Co.); *C.A.* **66**, 65746 (1967).

[30] *Netherlands Patent Appl.* 6603861 (Upjohn Co.); *C.A.* **66**, 65720 (1967).

[31] *Brit. Patent* 1065189, Smith, Kline, and French Laboratories; *C.A.* **67**, 91029 (1967).

[32] J. H. Fassnacht, N. A. Nelson, *J. Org. Chem.* **27**, 1885 (1967).

[33] M. T. Wuesthoff, B. Rickborn, *J. Org. Chem.* **33**, 1311 (1968).

[34] E. J. Greenhow, D. McNeil, E. N. White, *J. Chem. Soc.* **1952**, 986.
S. Wawzonek, E. Dufek, *J. Amer. Chem. Soc.* **78**, 3530 (1956).

[35] E. J. Greenhow, D. McNeil, *J. Chem. Soc.* **1965**, 3204.

[36] R. W. Hoffmann, "*Dehydrobenzene and Cycloalkynes*" Academic Press (1967), pps. 153 and 155.

[37] R. M. Beesley, C. K. Ingold, J. F. Thorpe, *J. Chem. Soc.* **107**, 1080 (1915).

[38] H. O. Larson, G. S. K. Sung, *Aust. J. Chem.* **15**, 261 (1962).

[39] O. Becker, J. F. Thorpe, *J. Chem. Soc.* **117**, 1579 (1920); interesting comments are presented in this paper concerning the difficulty in performing these reactions.

[40] R. D. Desai, *J. Chem. Soc.* **1932**, 1065.

[41] R. D. Desai, *J. Chem. Soc.* **1932**, 1047.

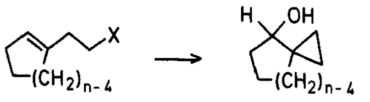
[42] J. W. Baker, C. K. Ingold, *J. Chem. Soc.* **123**, 122 (1923).

[43] A. Kandiah, *J. Chem. Soc.* **1931**, 952.

1.7. Neighboring Group Participation Routes

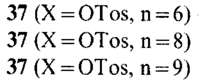
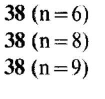
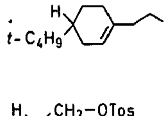
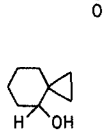
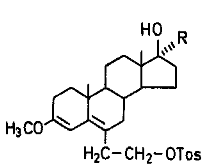
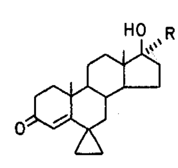
1.7.1. Double Bond Participation in Solvolysis Reactions

The solvolyses in buffered aqueous acetone of unsaturated esters (**37**, X = OTos) with a double bond properly positioned lead to spiranols as exemplified by the following generalized scheme (**37**→**38**). In certain cases, good yields of the spiranols have been obtained. The major competitive route is formation of the bicyclo[n.2.0]alkyl systems. Cyclizations of this type are tabulated in Table 3.



37 **38**

Table 3. Double Bond Participation Leading to Spirocyclopropyl Systems

Ester	Spiranol	Yield (%)	References
37 (X = OTos, n = 4)	**38** (n = 4)	trace[a]	47
37 (X = OBrs, n = 5)	**38** (n = 5)	10[b]	48
37 (X = OTos, n = 6)	**38** (n = 6)	65[a]	49
37 (X = OTos, n = 8)	**38** (n = 8)	80[a]	51
37 (X = OTos, n = 9)	**38** (n = 9)	30[a]	51
		42[a]	50
		36[a]	52
		—	53

R = H[c], HC≡C–, Cl–C≡C–, HC≡C–CH$_2$–

[a] Performed in 20% aqueous acetone using a calcium carbonate buffer for 10–14 days at 85°.

[b] Performed in acetic acid using a sodium acetate buffer followed by treatment of products with lithium aluminum hydride.

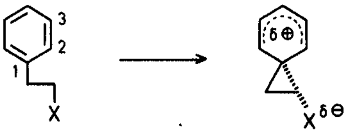
[c] Treated with tosyl chloride at 0°, heated to 27°, then 3 drops of water added and allowed to stand for 16 hours. No yields listed.

1.7.2. Deaminations

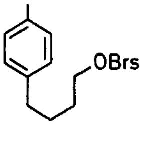
The conversion of cycloalken-1-ylethylamines (**37**, X = NH$_2$) to cyclopropane spiro systems can be accomplished in certain cases by deamination with nitrous acid[49, 51]. As in the previous cases of double bond participation reactions, the formation of bicyclo[x.2.0]alkyl systems is competitive. The cyclopropane spiro alcohol to cyclobutanol ratio is dependent on the pH of the medium. The spiranols undergo acid catalyzed rearrangement into the bicyclo[x.2.0] systems and low pH conditions must be avoided. Reaction of **37** (n = 6, 7, 8, or 9; X = NH$_2$) in aqueous perchloric acid with sodium nitrite at 60° (pH = 4–6) leads to **38** (n = 6, 7, 8, or 9) in 70, 40, 50, and 15% yields, respectively.

1.7.3. Aryl Participation Reactions

According to the generalizations formulated by Winstein and co-workers[54], the participation by a phenyl group in a solvolysis reaction to form a spiro linkage is symbolized by Ar_1-X, Ar denoting the aryl group. The subscript, 1, refers to the position in the participating aryl group involved in the creation of the cycle at the transition state for an anchimerically assisted ionization, the size of the ring being indicated by the number following, in this case, X. An example of an Ar_1-3 type is shown below.



The anionic nature of a participating group is indicated by a – superscript. The formation of spirodienones was first demonstrated by Winstein and Baird by Ar_1^--5 participation of a neighboring phenoxy group in the transformation of **39** to **40**[55, 56, 57]. The reaction of **39** with a slight excess of potassium *t*-butoxide in anhydrous *t*-butyl alcohol leads to **40** in about a 50% yield. The reaction of **41** with sodium methoxide in absolute methanol as solvent led to the spectroscopic detection of **42** (Ar_1^--3 route)[55, 56]. The successful isolation of **42** was subsequently reported[58, 59].



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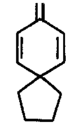

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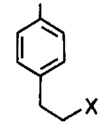

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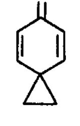

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[44] K. A. N. Rao, *J. Chem. Soc.* **1930**, 1162.

[45] C. L. Bumgardner, *J. Org. Chem.* **29**, 767 (1964).

[46] C. Alexandre, F. Rouessac, *Bull. Soc. Chim. France* **1971**, 1837.
C. Alexandre, F. Rouessac, *Tetrahedron Lett.* **1970**, 1011.

[47] K. B. Wiberg, J. E. Hiatt, *J. Amer. Chem. Soc.* **90**, 6495 (1968).

[48] W. D. Closson, G. T. Kwiatkowski, *Tetrahedron Lett.* **1964**, 3831.
W. D. Closson, G. T. Kwiatkowski, *Tetrahedron*, **21**, 2779 (1965).

[49] M. Hanack, H. J. Schneider, *Liebigs Ann. Chem.* **686**, 8 (1965).
M. Hanack, H. J. Schneider, *Angew. Chem.* **76**, 783 (1964); *Angew. Chem. Internat. Edit.* **3**, 698 (1964).
M. Hanack, H. J. Schneider, *Angew. Chem.* **79**, 709 (1967); *Angew. Chem. Internat. Edit.* **6**, 666 (1967).
M. Hanack, *Angew. Chem.* **77**, 624 (1965); *Angew. Chem. Internat. Edit.* **4**, 603 (1965).

[50] L. Joris, P. von R. Schleyer, R. Gleiter, *J. Amer. Chem. Soc.* **90**, 327 (1968).

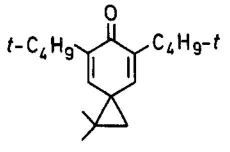
[51] M. Hanack, H. Schneider-Bernlöhr, H. J. Schneider, R. Hüttinger, G. Wentrup, *Liebigs Ann. Chem.* **717**, 41 (1968);

[52] H. Schneider-Bernlöhr, H. J. Schneider, M. Hanack, *Tetrahedron Lett.* **1967**, 1425.

[53] V. Georgian, K. G. Holden, *U.S. Patent* 3373157, *C.A.* **69**, 52422 (1968).

Passage of an ethereal solution of **41** (X = Br) through a column of basic alumina pretreated with a strong aqueous potassium hydroxide solution yielded a 10^{-3} *M* solution of **42** in ether. By careful evaporation, crystalline **42** was obtained. The dienone reacts with a variety of reagents to open the 3-membered ring and restore the aromatic ring. The report of the synthesis of **43** is also mentioned[59]. In subsequent papers dealing with synthesis of **42**, Shuster and Polowczyk[60] slightly modified the Baird and Winstein synthesis, and this led to more reproducible results. The maximum yield of **42** from **41** (X = Br) is about 4%.

The synthesis of **45** has also been reported in a 2% yield commencing with **44** via the Ar_1^--3 participation route[61].



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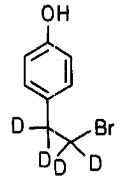

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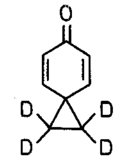
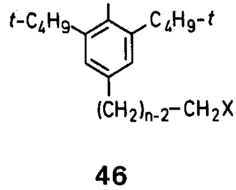


45

The di-*t*-butylspirodienones **47** (n = 3 and 5) have been prepared by intramolecular alkylation (Ar_1^--3 and Ar_1^--5) of the corresponding phenols **46** (n = 3 and 5)[62].



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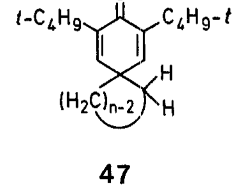
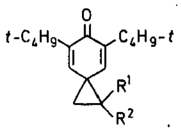


47

Although the unsubstituted spirodienone **42** is quite unstable, the *t*-butyl groups in **47** (n = 3), due perhaps to their steric hindrance to reactions at the carbonyl group, enhance its stability so that it sublimes without decomposition. The spirocycles **47** have also been obtained from **46** (n = 3 and 5, X = Br) by passing hexane solutions through a column containing aluminum oxide which has previously been treated with a 20% sodium hydroxide solution.

The synthesis of 1-substituted-5,7-di-*t*-butylspiro-[2.5]octa-4,7-dien-6-ones is described in the intramolecular cyclization of substituted tosylates using potassium *t*-butoxide/*t*-butyl alcohol via the Ar_1^--3 route[63]. These results are tabulated below (Table 4).

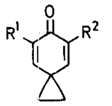
Table 4. Synthesis of 1-Substituted-5,7-di-*t*-butylspiro[2.5]octa-4,7-dien-6-ones



R^1	R^2	Yield (%)
H	H_3C	63
H	C_2H_5	85
H	n-C_3H_7	75
H	i-C_3H_7	55
H	C_6H_5	75
H_3C	H_3C	76

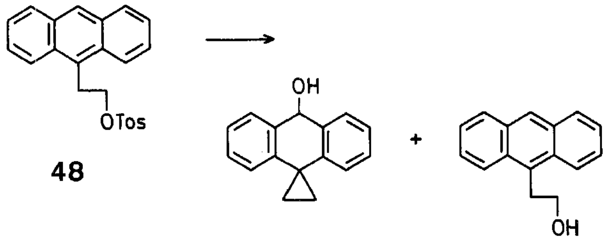
The synthesis of 5,7-dialkylspiro[2.5]octa-4,7-dien-6-ones from the open chain tosylates (Ar_1^--3 participation) has also been reported by treatment with potassium *t*-butoxide/*t*-butyl alcohol[64]. These results are tabulated in Table 5.

Table 5. 5,7-Dialkylspiro[2.5]octa-4,7-dien-6-ones

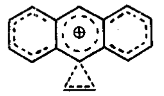


R^1	R^2	Yield (%)
t-C_4H_9	t-C_4H_9	82
c-C_6H_{11}	c-C_6H_{11}	50
H_3C	t-C_4H_9	76
i-C_3H_7	i-C_3H_7	59
H_3C	H_3C	22

The reaction of **48** in 60% aqueous dioxane (sodium hydrogen carbonate added as a buffer) leads to **49** and **50**[65]. The intervention of Ar_1-3 participation is suggested as leading to the ion **51** which undergoes subsequent attack by water. The alcohol **50** is the thermodynamically more stable product.



49 **50**



51

In addition to the Ar_1^--5 routes leading to **40** and **47** (n = 5), which were previously mentioned, other examples of this reaction have been reported. These examples of Ar_1^--5 routes to spirodienones are summarized in Table 6.

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[54] S. Winstein, R. Heck, S. Lapponte, R. Baird, *Experientia* **12**, 138 (1956).

[55] S. Winstein, R. Baird, *J. Amer. Chem. Soc.* **79**, 756 (1957).

[56] R. Baird, S. Winstein, *J. Amer. Chem. Soc.* **84**, 788 (1962).

[57] B. Rickborn, M. T. Wuesthoff, *J. Amer. Chem. Soc.* **92**, 6894 (1970).
M. Julia, B. Malassine, *Tetrahedron Lett.* **1971**, 987.

[58] S. Winstein, R. Baird, *J. Amer. Chem. Soc.* **79**, 4238 (1957).

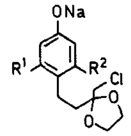
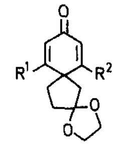
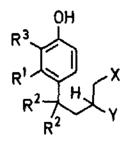
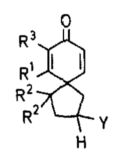
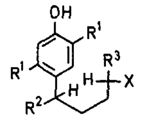
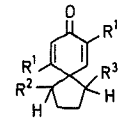
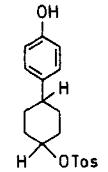
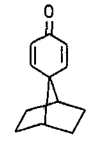
[59] R. Baird, S. Winstein, *J. Amer. Chem. Soc.* **85**, 567 (1963).

[60] D. I. Schuster, C. J. Polowczyk, *J. Amer. Chem. Soc.* **88**, 1722 (1966).

[61] D. I. Schuster, I. S. Krull, *J. Amer. Chem. Soc.* **88**, 3456 (1966).
D. I. Schuster, I. S. Krull, *Mol. Photochem.* **1**, 107 (1969).

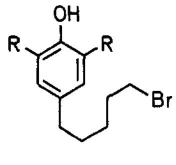
[62] V. V. Ershov, I. S. Belostotskaya, *Bull. Acad. Sci. USSR* **1965**, 1274.

Table 6. Ar_1^--5 Routes to Spirodienones

Phenol	Product		Yield (%)	Reference
		$R^1=R^2=H$	—[a]	66
		$R^1=R^2=CH_3$	80[a]	67
		$R^1=CH_3, R^2=R^3=H, X=Br, Y=OThp$	—	68
		$R^1=R^3=Y=H, R^2=CH_3, X=OTos$	25	69
		$R^1=OCH_3, R^2=R^3=Y=H, X=OBrs$	80	70
		$R^1=R^2=Y=H, R^3=OCH_3, X=OBrs$	7	70
		$R^1=CH_3, R^2=R^3=Y=H, X=OBrs$	45	71
		$R^1=R^2=Y=H, R^3=CH_3, X=OBrs$	42	71
		$R^1=CH_3, R^2=R^3=H, X=OTos$	60	72
		$R^1=H, R^2=COOC_2H_5, R^3=CH_3, X=Br$	—	73
		$R^1=H, R^2=CH_3, R^3=COOCH_3, X=Br$	—	74
			8	75

[a] By pyrolysis of the dry salt, all other reactions carried out using potassium *t*-butoxide/*t*-butyl alcohol.

The Ar_1^--6 participation route has found some success in approaches to six-membered rings. By heating the potassium salt of **52** (R = H) in *t*-butyl alcohol at 170°, spirodienone **53** (R = H) is obtained in an 88% yield[76]. Treatment of **52** ($R=t\text{-}C_4H_9$) with potassium *t*-butoxide in *t*-butyl alcohol for 16 hours at reflux leads to **53** ($R=t\text{-}C_4H_9$) in a 98% yield[77].



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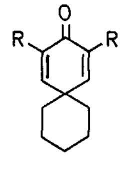
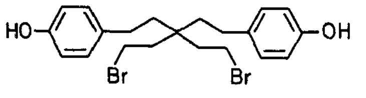


53

Treatment of **54** with a little potassium *t*-butoxide/*t*-butyl alcohol leads to a 37% yield of **55**, and with a 2–3 fold excess of potassium *t*-butoxide, **56** is produced directly from **54** (72%) or from **55**[78]



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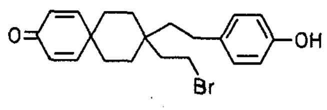

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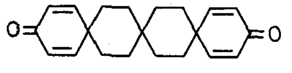


56

2. Intramolecular Processes Followed by Intramolecular Dehydrohalogenations and Similar Cyclizations

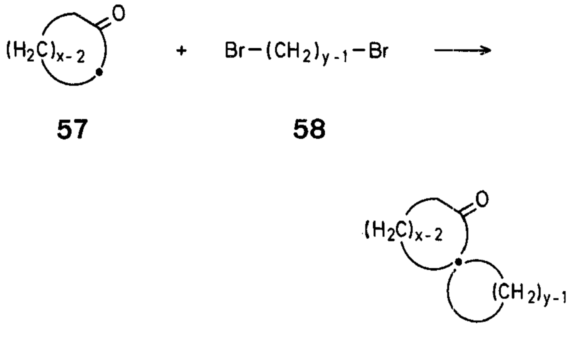
2.1. Di- and Tetraalkylations of Ketonic Substrates with α,ω-Dihaloalkanes

2.1.1. Cycloalkanones

This method, developed in 1957[79], consists of a single operational procedure using the cyclic ketone, the α,ω-dibromoalkane, and two equivalents of a base such as potassium *t*-butoxide or sodium *t*-pentoxide in a solvent such as benzene. In this process the intermediate intermolecular alkylation product **10** is not isolated but immediately cyclized to **11**. These dialkylation processes appear to be limited to the formation of five- and six-membered rings. Seven-membered cycles are formed in low yield and the smaller rings cannot be formed directly in this manner. Alkylation of cyclohexanone with 1,3-dibromopropane leads to 2-allylcyclohexanone, and with 1,2-dibromoethane no reaction occurs. Cyclopentanone cannot be dialkylated in this procedure because of its rapid self-condensation[79]. Table 7 lists some dialkylations performed on various cyclic ketones with several α,ω-dihaloalkanes utilizing potassium *t*-butoxide as the base and benzene as the solvent according to the following equation.

---

[63] A. A. Volod'kin, I. S. Belostotskaya, V. V. Ershov, *Bull. Acad. Sci. USSR* **1967**, 1328.
I. S. Belostotskaya, A. A. Volod'kin, V. V. Ershov, *Bull. Acad. Sci. USSR* **1968**, 1033.



57 58

59

Table 7. Dialkylation of Unsubstituted Cyclic Ketones

Starting Materials x in **57**	y in **58**	Product x, y in **59**	Yield (%)	References
6	5	6, 5	70	79, 80
7	5	7, 5	30–50	79, 81[a], 82
6	6	6, 6	30–60	18, 25, 79, 82, 83
6	7	6, 7	8	22
7	6	7, 6	41–50	81, 82, 84, 85, 86
12	5	12, 5	19[b]	87

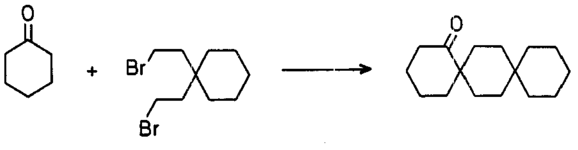
[a] Potassium triethylcarbinolate in xylene was used.

[b] Sodium hydride in xylene at 80–90° was used; the bicyclo product was also isolated in 19% yield.

Spiro[5.5]undecan-1-one (59, x = 6, y = 6)[79]**:**

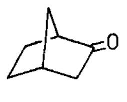
To excess *t*-butyl alcohol is added potassium (9.75 g, 0.2 g-atom). After complete reaction, the alcohol is removed by distillation and to the potassium *t*-butoxide is added anhydrous benzene (150 ml). In one portion, a mixture of cyclohexanone (9.8 g, 0.1 mol) and 1,5-dibromopentane (25.6 g, 0.1 mol) is added. The mixture is heated 3 hours at reflux with stirring. On cooling, water (50 ml) is added, then 15% hydrochloric acid (150 ml). The benzene layer is separated and the water layer extracted with ether. The combined organic layers are dried over sodium sulfate and the solvent removed by distillation. On fractionation, the spiranone is obtained; yield: 60%; b.p. 130–132°/0.25 torr; m.p. 47°.

Treatment of cyclohexanone with the dibromide **60** in toluene using potassium *t*-butoxide leads directly to the dispiranone **61** (20%)[88].

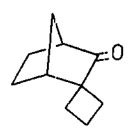


60 61

The dialkylation of norcamphor **62** with 1,3-dibromopropane (sodium amide as the base in ether as the solvent) leads to **63** (3%)[89].

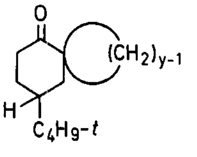


62

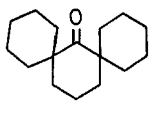


63

The dialkylation of 4-*t*-butylcyclohexanone with 1,4-dibromobutane or 1,5-dibromopentane proceeds in good yields to give **64**. In benzene using potassium *t*-butoxide, **64** (y = 5 or 6) is obtained in 53 and 39% yields, respectively, while treatment of 4-*t*-butylcyclohexanone with potassium triethylcarbinolate as base in toluene leads to 60 and 70% yields of **64**, respectively[90].

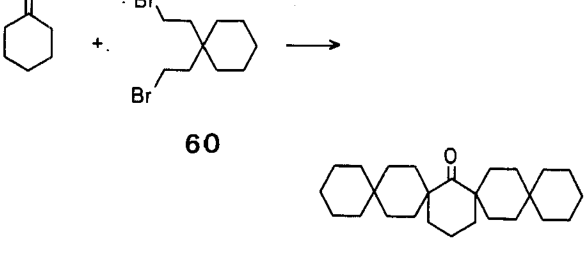


64



65

The preparation of dispiranone **65** can be accomplished in yields of 14–17% by reaction of cyclohexanone with 4.4 equivalents of potassium *t*-butoxide and 1,5-dibromopentane in refluxing benzene for 3 days[88]. The yield of **65** can be increased to 60% when potassium triethylcarbinolate is the base using xylene as the solvent[81]. In the latter procedure two one-mol portions of the dihalide are added during the course of the reaction. Wynberg[88] reports the formation of **66** (1%) as a by-product in the following reaction.



66

2.1.2. Spiranones

The procedure described above is directly applicable to the synthesis of dispiro and polyspiro ketones. Equivalent quantities of the spiranone and the α,ω-dibromoalkane in toluene are treated with 2.2 equivalents of potassium *t*-butoxide[88]. Brugidou and Christol[81] have reported that the use of potassium triethylcarbinolate in xylene leads to higher yields of dispiro ketones in this reaction. The results of these investigations are tabulated below (Table 8).

---

[64] V. V. Ershov, I. S. Belostotskaya, V. I. Volod'kina, *J. Org. Chem. USSR* 3, 490 (1967).

[65] L. Eberson, J. P. Petrovich, R. Baird, D. Dyckes, S. Winstein, *J. Amer. Chem. Soc.* **87**, 3504 (1965).

[66] S. D. Dorling, J. Harley-Mason, *Chem. & Ind.* **1959**, 1551.

[67] A. Ogiso, M. Kurabayashi, H. Nagahori, H. Mishima, *Chem. Pharm. Bull. Japan*, **18**, 1283 (1970).

[68] P. C. Mukharji, P. K. Sen Gupta, *Chem. & Ind.* **1970**, 533.

[69] D. I. Schuster, W. V. Curran, *J. Org. Chem.* **35**, 4192 (1970).

[70] A. Wacek, H. Hemetsberger, *Monatsh. Chem.* **97**, 744 (1966).

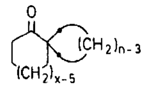
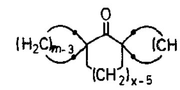
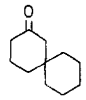
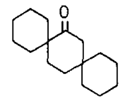
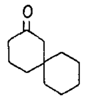
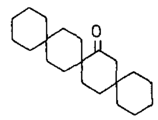
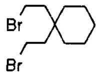
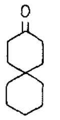
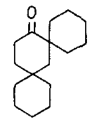
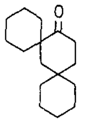
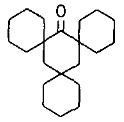
[71] H. Hemetsberger, *Monatsh. Chem.* **99**, 1225 (1968).

[72] P. J. Kropp, *Tetrahedron* **21**, 2183 (1965)

[73] T. G. Crandall, R. G. Lawton, *J. Amer. Chem. Soc.* **91**, 2127 (1969).

[74] E. J. Corey, N. N. Girotra, C. T. Mathew, *J. Amer. Chem. Soc.* **91**, 1557 (1969).

Table 8. Alkylations of Spiranones with α,ω-Dihaloalkanes (Br—A—Br) Leading to Di- and Polyspiranones

Spiranone	Product	Br—A—Br	Yield (%)	References
		$Br-(CH_2)_5-Br$	$x=5, m=6, n=5$: 80	81
		$Br-(CH_2)_5-Br$	$x=5, m=n=6$: 80	81
		$Br-(CH_2)_4-Br$	$x=5, m=n=5$: 75	81
		$Br-(CH_2)_4-Br$	$x=6, m=n=5$: 40	81
		$Br-(CH_2)_5-Br$	$x=6, m=6, n=5$: 60	81
		$Br-(CH_2)_4-Br$	$x=6, m=5, n=6$: 60	81
		$Br-(CH_2)_5-Br$	$x=6, m=n=6$: 37	88
		$Br-(CH_2)_5-Br$	29	88
			20	88
		$Br-(CH_2)_5-Br$	42	88
		$Br-(CH_2)_5-Br$	26	88

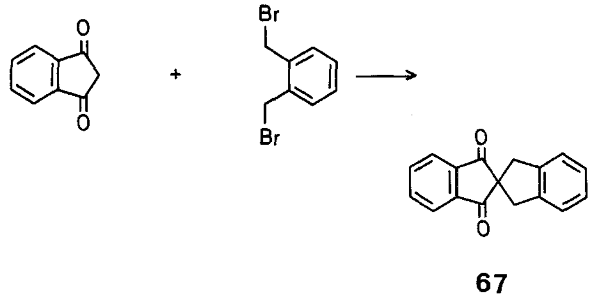
Dispiro[4.1.5.2]tetradecan-6-one[81]:

Potassium metal (9.75 g, 0.2 g-atom) is added to excess triethylcarbinol. When the metal has completely reacted, the excess alcohol is removed and anhydrous xylene (150 ml) is added to the white residue. With stirring, a mixture of spiro[4.4]nonan-1-one (13.8 g, 0.1 mol) and 1,5-dibromopentane (23 g, 0.1 mol) is added rapidly. The reaction mixture is refluxed for 24 hours. On cooling water (70 ml) and then 15% hydrochloric acid (150 ml) are added. The xylene layer is separated, the aqueous layer extracted with ether, and the combined extracts dried over sodium sulfate. The solvent is evaporated and the dispiranone distilled; yield: 16.5 g (80%); b.p. 118–120°/1 torr; m.p. 35°.

2.1.3. Aromatic Ketones

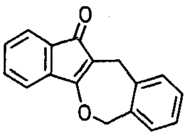
The one-operational step dialkylation procedure has also been found to be an excellent synthetic route to spiranones with aromatic rings. The examples of the utility of this method are listed in Table 9.

In an early article dealing with synthesis of spirocyclic systems, Fecht[97] reported the following reaction.



67

Radulescu[98] reinvestigated this reaction and claimed that Fecht's compound **67** was impure. In a later paper, Radulescu[99] proposed that the structure **67** was incorrect and reformulated **67** as enol ether **68** which arises by intramolecular alkylation on oxygen.



68

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[75] R. Barner, A. S. Dreiding, H. Schmid, *Chem. & Ind.* **1958**, 1437.

[76] A. S. Dreiding, *Helv. Chim. Acta* **40**, 1812 (1957).

[77] J. D. McClure, *J. Org. Chem.* **27**, 2365 (1962).

[78] R. S. Atkinson, A. S. Dreiding, *Helv. Chim. Acta* **50**, 23 (1967).

[79] M. Mousseron, R. Jacquier, H. Christol, *Bull. Soc. Chim. France* **1957**, 346.

[80] K. Schank, W. Pack, *Chem. Ber.* **102**, 1892 (1969).

[81] J. Brugidou, H. Christol, *Bull. Soc. Chim. France* **1968**, 1141.

[82] A. P. Krapcho, J. E. McCullough, K. V. Nahabedian, *J. Org. Chem.* **30**, 139 (1965).

[83] R. K. Hill, R. T. Conley, *J. Amer. Chem. Soc.* **82**, 645 (1960).

[84] R. T. Conley, M. C. Annis, *J. Org. Chem.* **27**, 1961 (1962).

[85] J. A. Dixon, P. A. Naro, *J. Org. Chem.* **25**, 2094 (1960).

[86] P. A. Naro, J. A. Dixon, *J. Org. Chem.* **26**, 1021 (1961).

[87] H. Nozaki, H. Yamamoto, T. Mori, *Canad. J. Chem.* **47**, 1107 (1969).

[88] H. A. P. De Jongh, H. Wynberg, *Tetrahedron* **20**, 2553 (1964).

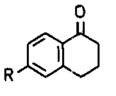
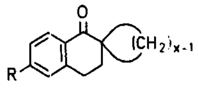
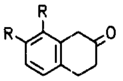
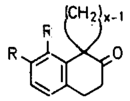
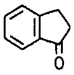
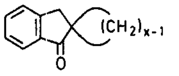
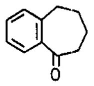
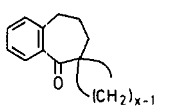
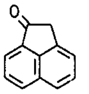
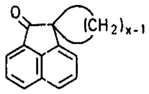
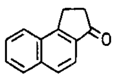
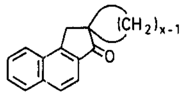
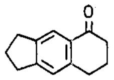
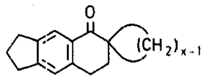
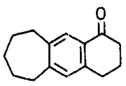
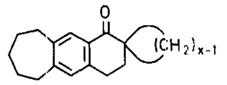
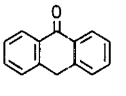
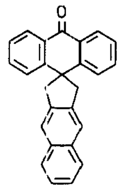
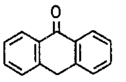
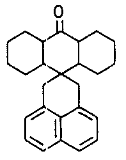
[89] R. Sauers, A. Shurpik, *J. Org. Chem.* **32**, 3120 (1967).

[90] H. Christol, A. P. Krapcho, C. Arnal, R. C. H. Peters, *Tetrahedron Lett.* **1969**, 2799.
J. P. Charles, H. Christol, G. Solladie, *Bull. Soc. Chim. France* **1972**, 1124.

[91] T. W. Doyle, T. T. Conway, *Tetrahedron Lett.* **1969**, 1889.

[92] L. H. Lerner, *Ger. Patent* 1919082; *C. A.* **72**, 66702 (1970).

Table 9. Dialkylations of Aromatic Ketones[a]

Ketone	Product	Ring size x	Yield (%)	Reference
		5 6 6 7	80 (R = H) 80 (R = H) — (R = OCH_3) 33 (R = H)	79, 91 79, 92 92 22
		3 3 5 6	50[b] (R = H) 30[b] (R = OCH_3) 70 (R = H) 70 (R = H)	93 93 79 79
		5 6	50 50	79 79
		5 6	65 70	94 94
		5 6	70 70	95 95
		5 6	58 54	95 95
		5 6	83 73	95 95
		5 6	80 77	95 95
		—	2[c]	96
		—	2[c]	96

[a] All dialkylations were performed using the appropriate α,ω-dibromoalkane and potassium *t*-butoxide in benzene except where noted.

[b] Potassium *t*-butoxide in dimethyl sulfoxide.

[c] Lithium methoxide in refluxing dioxan or toluene.

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[93] S. L. Keely, Jr., A. J. Martinez, F. C. Tahk, *Tetrahedron Lett.* **1969**, 2763.
S. L. Keely, Jr., A. J. Martinez, F. C. Tahk, *Tetrahedron* **26**, 4729 (1970).

[94] H. Christol, Y. Delhoste, M. Mousseron, *Bull. Soc. Chim. France* **1959**, 1238.

[95] H. Christol, D. D. Koulodo, M. Mousseron, F. Plenat, *Bull. Soc. Chim. France* **1960**, 1573.

[96] R. A. Keller, *J. Amer. Chem. Soc.* **90**, 1940 (1968).

[97] H. Fecht, *Ber. dtsch. chem. Ges.* **40**, 3883 (1907).

[98] D. Radulescu, *Bull. Soc. Sti. Bucarest* **21**, 32 (1912); *Chem. Zentralblatt* **83**, II, 1363 (1912).

[99] D. Radulescu, *Bull. Soc. Chim. France* **37**, 916 (1925).

[100] A. P. Krapcho, G. A. Richard, Unpublished Results.

[101] D. Radulescu, *Bull. Soc. Sti. Cluj* **1**, 335 (1922); *C. A.* **18**, 1661 (1924).

[102] H. Christol, M. Mousseron, R. Salle, *Bull. Soc. Chim. France*, **1958**, 556.

[103] M. S. Newman, V. de Vries, R. Darlak, *J. Org. Chem.* **31**, 2171 (1966).

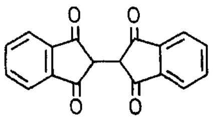
[104] H. Krieger, H. Routsalainen, J. Montin, *Chem. Ber.* **99**, 3715 (1966).

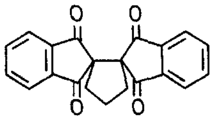
[105] G. Opitz, H. Mildenberger, *Liebigs Ann. Chem.* **650**, 115 (1961).

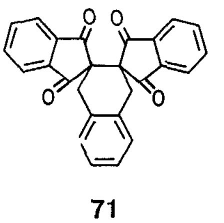
[106] D. J. Dunham, R. G. Lawton, *J. Amer. Chem. Soc.* **93**, 2074 (1971).

A recent reinvestigation of this reaction[100] yielded 15% of crude product which contained **67** and **68** in a 1:10 ratio. Pure **67** and **68** could be isolated by recrystallization and the structures are in accord with their N.M.R. spectra.

The preparation of the first dispiro systems has been reported by Radulescu[101]. The reaction of the dry dipotassium salt of **69** in anisole (140°, 4 hours) with 1,3-dibromopropane and *o*-xylylenedibromide yielded products formulated as **70** and **71**, respectively.


69

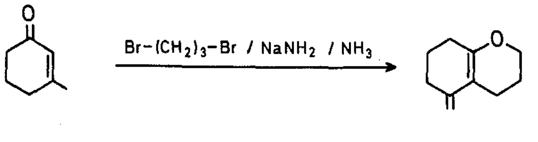

70


71

2.1.4. α,β- and β,γ-Unsaturated Ketones

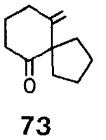
The use of α,β- or β,γ-unsaturated ketones in the one step dialkylation procedure has found synthetic utility for preparation of spirenones. These reactions are tabulated in Table 10.

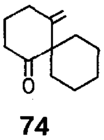
Newman and co-workers[103] reported that the reaction of 3-methylcyclohex-2-enone with 1,3-dibromobutane takes the following course to yield the enol ether **72** in 53% yield.

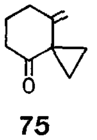


72

One notes again the difficulty in forming the four-membered carbocyclic spiro ring in a reaction of this type. Newman also showed that the spiro compounds **73** and **74** were stable to isomerization under acidic conditions, and suggested that the thermodynamically stable isomer is formed in these dialkylation processes. Heating **73** or **74** with *p*-toluenesulfonic acid in ethanol, benzene, or by heating the neat samples for 2 hours effected no change. However, compound **75** underwent a total isomerization into **76** on refluxing with *p*-toluenesulfonic acid in ethanol as solvent for 5 hours.


73


74


75

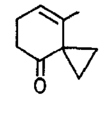
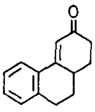
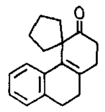
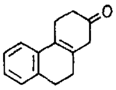
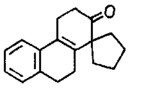
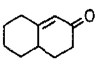
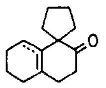
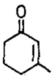
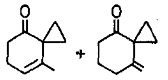
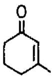
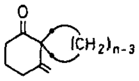
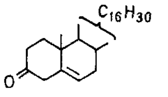
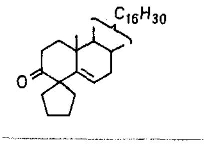

76

Table 10. Dialkylations of Unsaturated Ketones

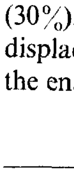
Ketone	Product	Yield (%)	Reference
		80[a]	102
		80[a]	102
		30[a]	102
		26[b]+15	103
		(n=5) 58[b] (n=6) 22[b]	103 103
		75[a]	103

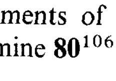
[a] Use of potassium *t*-butoxide in benzene.
[b] Use of sodium amide in liquid ammonia.

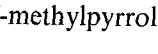
A mechanistic scheme has been proposed to rationalize the products of these reactions[103].

2.1.5. Enamine Dialkylations

The reaction of 1-pyrrolidinocyclopentene (**77**) with 1,4-diiodobutane in acetonitrile and with ethyldicyclohexylamine has been reinvestigated[104] and the product previously formulated as bicyclic[105] is shown to be spiroketone **78** (23% yield). The dispiranone **79** was also isolated in a 13% yield.


77

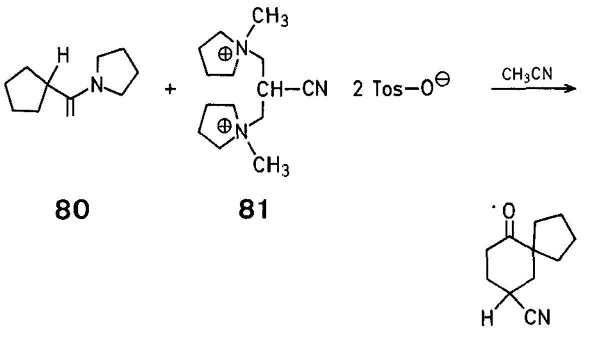

78


79

One example of an α,α′-annelation of an enamine has been reported. Reaction of **80** with **81** yields **82** (30%). The formation of **82** occurs via successive displacements of *N*-methylpyrrolidine from **81** by the enamine **80**[106].

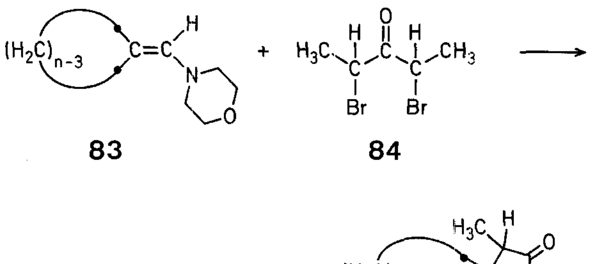
---

[107] R. Noyori, K. Yokoyama, S. Makino, Y. Hayakawa, *J. Amer. Chem. Soc.* **94**, 1772 (1972).
[108] K. Ichikawa, O. Itoh, T. Kawamura, *Bull. Chem. Soc. Japan* **41**, 1240 (1968).
[109] P. K. Paul, *J. Ind. Chem. Soc.* **8**, 717 (1931).
[110] G. S. Saharia, B. R. Sharma, *Acta Phys. Chem. Szeged* **14**, 109 (1968); *C. A.* **71**, 60817 (1969).
[111] L. Schmerling, J. P. West, *J. Amer. Chem. Soc.* **74**, 2885 (1952).
[112] R. Y. Levina, T. I. Tantsyreva, *Dokl. Akad. Nauk. SSSR* **89**, 697 (1953); *C.A.* **48**, 6972 (1954).



80 **81** **82**

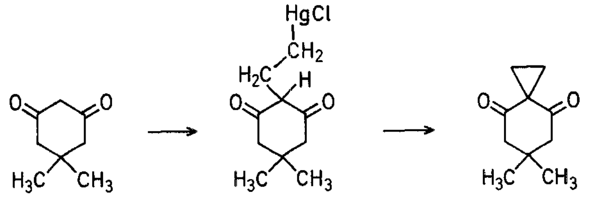
An interesting spironannelation reaction has recently been developed. Reaction of enamines **83** (n = 6 or 12) with **84** in the presence of diiron nonacarbonyl in dry benzene leads to **85** (n = 6 or 12) in yields of 70 and 65%, respectively[107].



83 **84** **85**

2.2. Treatment of Dimedone with β-Acetoxyethylmercury(II) Acetate

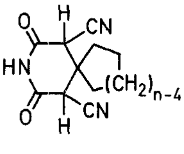
A solution of β-acetoxyethylmercury(II) acetate (prepared by introducing ethylene into acetic acid containing mercury(II) acetate and perchloric acid) was treated with dimedone. Reaction at 10–20° for 7 days followed by addition of sodium chloride produces **86** (35% yield). Treatment of **86** with an equimolar amount of aqueous potassium hydroxide (40%) at 40° for 3 hours leads to a 90% yield of **87**[108].



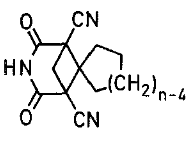
86 **87**

2.3. Guareschi Imide Dialkylations

The Guareschi imides **88** obtained from cyclic ketones, ethyl cyanoacetate, and ammonia are useful intermediates for the preparation of four-membered spiro ring systems. The imides **88** are refluxed with sodium methoxide (3 equivalents) to form the disodium salts which, on addition of diiodomethane and heating, yield the spiro analogs **89**. Spiro systems prepared by this method where n = 5, 6, and 7 have been reported[109,110].



88

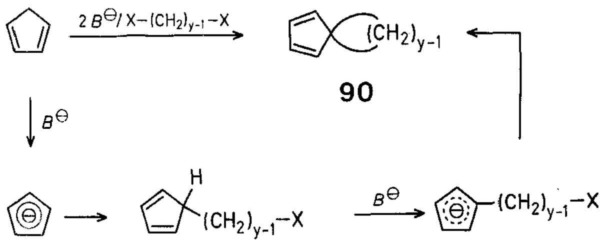


89

2.4. Dialkylations of Compounds with Non-ketonic Active Methylene Groups

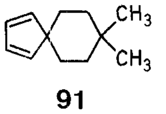
2.4.1. Cyclopentadiene

The basis of this procedure is the successive displacement via cyclopentadienyl anions of the terminal halogen atoms from an α,ω-dihaloalkane. The first example of this cyclization procedure appears to have been reported by Schmerling and West[111].



90

These authors report the formation of 8,8-dimethylspiro[4.5]deca-1,3-diene (**91**) in a 20% yield from the reaction of 1,5-dibromo-3,3-dimethylpentane with cyclopentadiene using sodium in liquid ammonia. The reaction was also performed using sodium ethoxide as the base in ethanol as solvent and **91** was obtained in a 20% yield.



91

Shortly thereafter, Levina and Tantsyreva[112] reported that the reaction of cyclopentadiene with sodium in liquid ammonia followed by addition of 1,4-dibromobutane yielded 20% of spiro[4.4]nona-1,3-diene (**90**, y = 5). Additional examples of the synthetic utility of this reaction are tabulated in Table 11.

---

[113] R. Y. Levina, N. N. Mezentsova, O. V. Lebedev, *Zhur. Obshch. Khim.* **25**, 1097 (1955); *C.A.* **50**, 3257 (1956).

[114] B. F. Hallam, P. L. Pauson, *J. Chem. Soc.* **1958**, 646.

[115] G. Chiurdoglu, B. Tursch, *Bull. Soc. Chim. Belges* **66**, 600 (1957).

[116] B. A. Kazanski, E. V. Sobolev, V. T. Aleksanyan, L. A. Nakhapetyan, M. Yu. Lukina, *Proc. Acad. Sci. USSR* **159**, 1265 (1964); *C.A.* **62**, 8976 (1965).

[117] K. Alder, H. J. Ache, F. H. Flock, *Chem. Ber.* **93**, 1888 (1960).

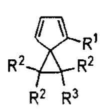
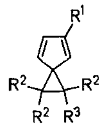
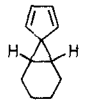
[118] K. Alder, H. J. Ache, *Chem. Ber.* **95**, 503 (1962).

[119] N. A. Belikova, L. I. Kovalenko, M. A. Moskaleva, M. Ordubadu, A. F. Plate, Kh. E. Sterin, R. S. Yagminas, *J. Org. Chem. USSR* **4**, 1314 (1968).

[120] W. R. Roth, K. Enderer, *Liebigs Ann. Chem.* **730**, 82 (1969).

[121] R. A. Clark, R. A. Fiato, *J. Amer. Chem. Soc.* **92**, 4736 (1970).

Table 11. Cyclopentadiene/Base/α,ω-Dihaloalkane Cyclizations

Spiro Products	Reaction Conditions	Yield (%)	References
90, y = 3	Na/liq. $NH_3/BrCH_2CH_2Br/NaNH_2$	18–75	113–124
	$NaNH_2$/THF/$BrCH_2CH_2Br$	54–70	15, 125–128
 **92**  **93**	1. $NaNH_2/NH_3$ 2. $H_3C—J$ 3. $NaNH_2$ 4. $BrCH_2CH_2Br$	30–55 [$R^1 = CH_3$, $R^2 = R^3 = H$: **92**:**93** = 2.8]	114[a], 129
	As above using CD_3Br	—[b] [$R^1 = CD_3$, $R^2 = R^3 = H$]	130
	$NaNH_2/NH_3/BrCD_2CD_2Br$	—[b] [$R^1 = CH_3$, $R^2 = R^3 = D$]	130
	Na/liq. $NH_3/H_3CCHBrCH_2Br$	—[b] [$R^1 = R^2 = H$, $R^3 = CH_3$]	130, 131
90, y = 4	Na/liq. $NH_3/Br(CH_2)_3Br$	9	115[c]
90, y = 5	Na/liq. NH_3 (or $NaNH_2$/THF or $NaNH_2$/liq. NH_3)/$Br(CH_2)_4Br$	12–53	114, 116, 125, 126, 134–138
90, y = 6	—	—	137
	Na/liq. NH_3/1,2-dibromocyclohexane	10	115

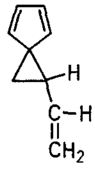
[a] Reports only product **92** present (55%).

[b] Yield not given.

[c] Comments are made in ref. 132 on this report of the preparation of this compound. Numerous attempts to prepare this spirodiene led only to polymeric products. It is also reported in ref. 133 that this diene could not be isolated by distillation (use of sodium/liquid ammonia and 1-bromo-3-chloropropane). The crude reaction product, however, leads to a 4–5% yield of spiro[3.4]octane on catalytic hydrogenation.

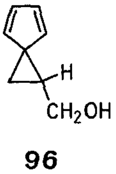
The reaction of cyclopentadiene with 1,4-dichloro-2-butene (two successive equivalent portions of potassium *t*-butoxide in *t*-butyl alcohol) leads to **94** (1–2%) and **95** (32%)[139].

94



95

The reaction of cyclopentadienylsodium (sodium/tetrahydrofuran) with epichlorohydrin leads to **96** in about a 65% yield[140].



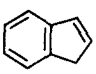
96

Spiro[2.4]hepta-1,3-diene (90, y = 3)[117]:

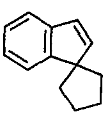
To a solution of sodium (11.5 g, 0.5 mol) in liquid ammonia (400 ml) at −70° there is added cyclopentadiene (44 g, 0.66 mol). With stirring, 1,2-dibromoethane (94 g, 0.5 mol) is added dropwise at −70°. After evaporation of most of the ammonia, the residue is treated with ether (200 ml) and water (50 ml). The ether layer is separated and dried over magnesium sulfate. The ether is distilled and the residue fractionated to give the product; yield: 75%; b.p. 57°/100 torr.

2.4.2. Indenes

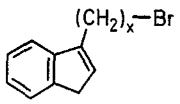
The reaction of indene (**97**) with an aqueous sodium hydroxide solution, triethylbenzylaminium chloride, and 1,4-dibromobutane leads to a 67% yield of 1,1-tetramethyleneindene (**98**)[141]. A similar reaction using 1,3-dibromopropane or 1,5-dibromopentane leads to **99** (x = 3) and **99** (x = 5), respectively, in yields of 45 and 52%.



97



98



99

The reaction of **100** with the system dichlorofluoromethane and oxirane in the presence of tetraethylaminium bromide at 150° in a sealed tube leads to a 10% yield of the spiro compound **101**[142]. This product no doubt arises from reaction of **100** with oxirane as the expected carbene reaction did not occur (steric hindrance is proposed).

---

[122] D. Helmlinger, P. DeMayo, M. Nye, L. Westfelt, R. B. Yeats, *Tetrahedron Lett.* **1970**, 349.

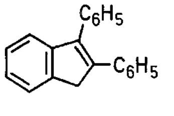
[123] B. M. Trost, *J. Org. Chem.* **34**, 3644 (1969).

[124] J. Ipaktschi, *Tetrahedron Lett.* **1969**, 2153.

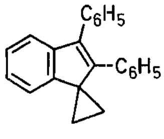
[125] C. F. Wilcox, Jr., R. R. Craig, *J. Amer. Chem. Soc.* **83**, 3866 (1961).

[126] H. Tanida, T. Yano, M. Ueyama, *Bull. Chem. Soc. Japan* **45**, 946 (1972).

[127] H. Prinzbach, W. Eberbach, M. Klaus, G. von Veh, *Chem. Ber.* **101**, 4066 (1968).



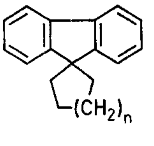
100



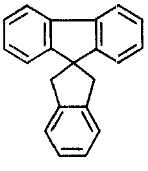
101

2.4.3. Fluorenes

The reaction of fluorene in an aqueous sodium hydroxide solution in the presence of triethylbenzylaminium chloride with 1,4-dibromobutane leads to a 64% yield of **102** (n = 1)[143]. The preparation of **102** (n = 2) has been reported by the dialkylation of the potassium salt of fluorene with 1,5-dibromopentane[144]. The reaction of fluorene with potassium hydroxide and *o*-xylidenedibromide leads to **103**[97].

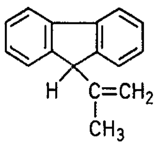


102

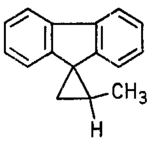


103

The reaction of the potassium salt of 9-cyanofluorene with 2-methyloxirane gives excellent yields of a compound formulated as 9-isopropenylfluorene (**104**)[145]. It was suggested that this compound is the spirofluorene **105** and its mechanism of formation was discussed[35].



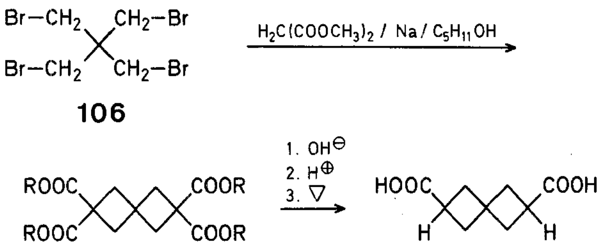
104



105

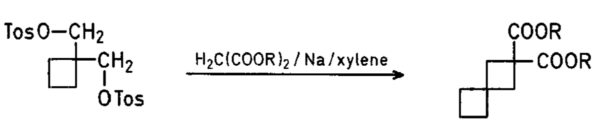
2.4.4. Malonate Esters. Reactions with α,ω-Dihaloalkanes and Ditosylates

The one step synthesis of a spiro compound was first reported by Fecht[97] in the reaction of pentaerythritol tetrabromide (**106**) with the sodium salt of dimethyl malonate. The reaction leads directly to **107**, which on hydrolysis and decarboxylation yields 15–20% of spiro[3.3]heptane-2,6-dicarboxylic acid (**108**).



106 **107** **108**

This type of reaction has been exhaustively investigated (see references in Table 12) using 1,3-ditosylates as in the following example to give **109**. Excellent yields are obtained in most cases.



109

The examples utilizing this reaction for forming spiro or polyspiro linkages with four-membered rings are tabulated below (Table 12).

Table 12. 1,3-Dihaloalkanes[a] or 1,3-Ditosylates[b]—Diethyl Malonate Reactions

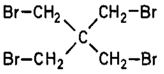
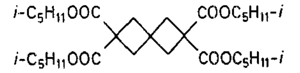
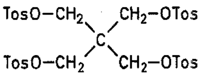
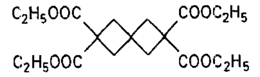
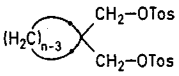
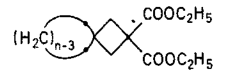
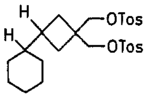
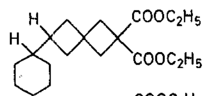
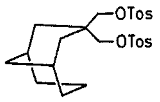
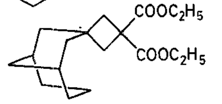
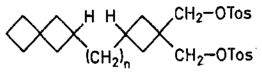
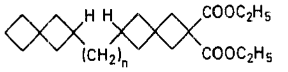
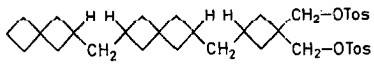
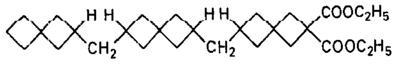
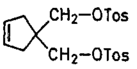
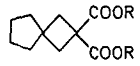
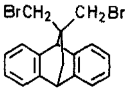
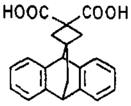
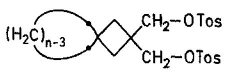
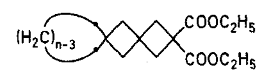
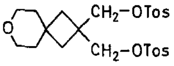
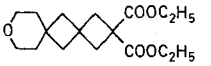
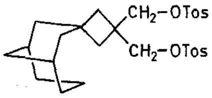
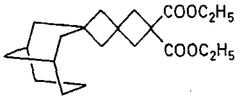
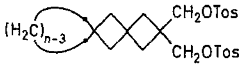
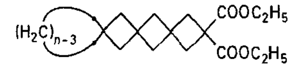
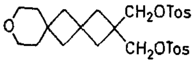
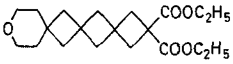
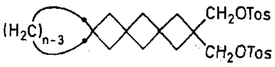
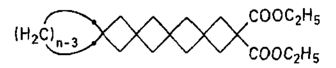
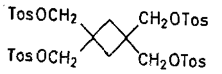
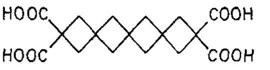
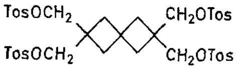
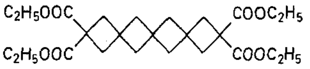
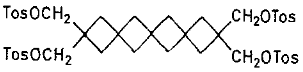
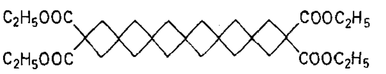
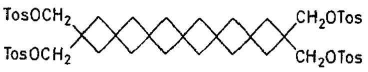
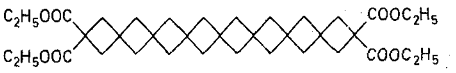
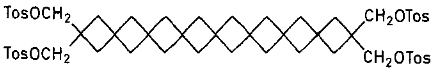
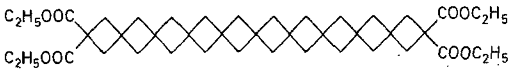
Starting Material	Product		Yield (%)	Reference
			75–80	97, 146–149
			65	150
		n = 4 n = 5 n = 6 n = 6 n = 7	57 50 60 28 80	151, 152[c] 151 151 153[a,d] 154
			84	155
			57	156
		n = 1 n = 2	40 50	157 157
			40	157

Table 12, continued

Starting Material	Product		Yield (%)	Reference
		$R=C_2H_5$ $R=CH_3$	42 13	158
			2	159[c]
		$n=4$ $n=5$ $n=6$ $n=7$	76 80 78 75	151 151 151 154
			92	160
			67	156
		$n=6$ $n=7$	80 68	161 154
			87	160
		$n=5$ $n=6$ $n=7$	81 85 52	161 161 154
			67	162[f]
			62	150
			90	150
			~100 (crude)	150
			90 (crude)	150

[a] Use of sodium/isopentyl alcohol and diethyl malonate. Ester interchange occurs, and the isopentyl ester is obtained.

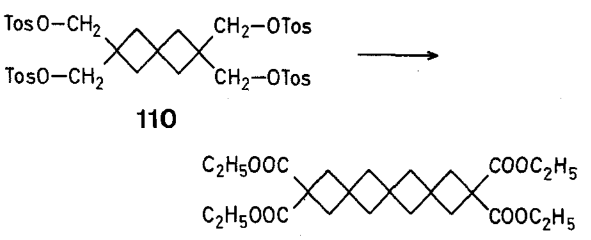
[b] All the ditosylate reactions were performed by placing the sodium metal in xylene and the diethyl malonate was then added dropwise. The mixture was heated to 150–160° and the ditosylate added. Heating was continued at this temperature for various periods.

[c] Use of the dimesylate.

[d] Use of the dibromide.

[e] Use of potassium *t*-pentoxide—diethyl malonate followed by saponification.

[f] After saponification.



110

111

Tetraethyl Trispiro[3.1.1.3.1.1]tridecan-2,2,10,10-tetracarboxylate (111)[150]:

Sodium (30 g) is granulated in absolute xylene (250 ml). After cooling, this is transferred to a 2-l-three-necked flask and more xylene (950 ml) is added. The flask is equipped with a condenser, dropping funnel, and stirrer. With stirring, diethyl malonate (307 g) is added dropwise. The mixture is heated to boiling, the tetratosylate (**110**, 198 g) is added in portions, and refluxing is continued for 18 hours. On cooling, a little water is added, and some unreacted tetratosylate is obtained by filtration. The aqueous phase is washed with xylene. The xylene extracts are washed with water and dried over sodium sulfate. The xylene and diethyl malonate are removed under vacuo, and the product distilled; yield: 68 g (62%). Redistillation gives the pure tetraester **111**; b.p. 176–179°/0.01 torr.

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[128] J. M. E. Krekels, J. W. de Haan, H. Kloosterziel, *Tetrahedron Lett.* **1970**, 2751.

[129] S. McLean, P. Haynes, *Tetrahedron* **21**, 2313 (1965).

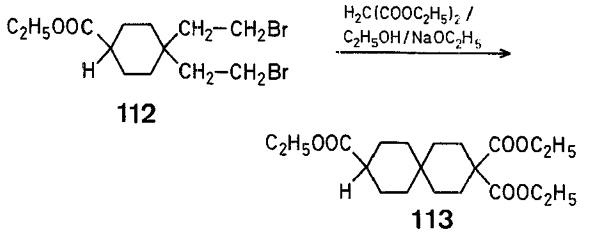
[130] F. Meyer, P. Haynes, S. McLean, A. G. Harrison, *Can. J. Chem.* **43**, 211 (1965).

[131] S. W. Staley, J. J. Rocchio, *J. Amer. Chem. Soc.* **91**, 1565 (1969).

[132] C. F. Wilcox, Jr., C. C. Whitney, *J. Org. Chem.* **32**, 2933 (1967).

[133] Ya. M. Slobodin, T. V. Tsukshverdt, *J. Org. Chem. USSR* **3**, 1928 (1967).

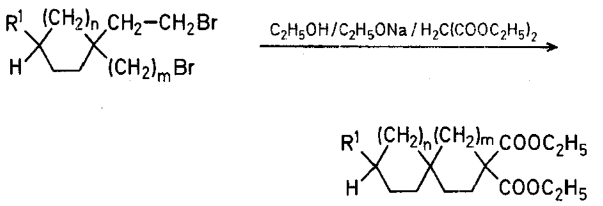
The preparation of **113** from **112** is reported to proceed in a 67% yield[163].



112

113

In a patent, this procedure[164] was employed on systems **114**–**117** and leads to the products **118**–**121**.



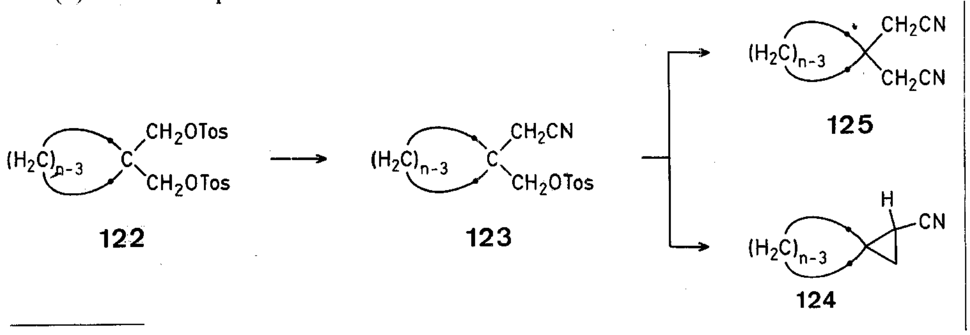
114: m=n=2, R^1=H
115: m=2, n=1, R^1=H
116: m=n=2, R^1=CH_3
117: m=1, n=2, R^1=H

118: m=n=2, R^1=H, 68% yield
118: m=2, n=1, R^1=H, 77%
120: m=n=2, R^1=CH_3, 77%
121: m=1, n=2, R^1=CH_3, 54%

2.5. Intermolecular Displacements Followed by Cyclizations

2.5.1. Spirocyanocyclopropane Systems

Treatment of 2,2-cycloalkyl-1,3-propanediol ditosylates of general formula **122** with sodium cyanide leads initially to **123**. These latter compounds undergo internal cyclization to yield spirocyanocyclopropanes **124** and/or react with another equivalent of cyanide ion to produce the 2,2-cycloalkylglutaronitriles **125**. The ratio of **124**:**125** is highly dependent on the ring size of **123**. Hexamethylphosphoric triamide containing a small amount of water is utilized as the solvent, a small amount of potassium iodide is added, and the reaction is heated at 95° for varying periods[165]. The results of this study are illustrated in Table 13 insofar as ring size (n) affects the product distribution.



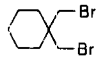
122

123

125

124

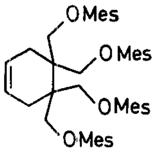
Table 13. Reation of 2,2-Cycloalkyl-1,3-propanediol Dibromide (**126**) or Ditosylates (**122**) with Sodium Cyanide.

Starting Material	Reaction Time (h)	Yield (%) of **124**[a]
 **126**	3	76
122, n=3	15	0
122, n=4	15	10
122, n=5	15	62
122, n=6	15	76

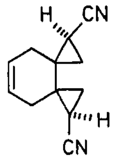
[a] Established by N.M.R. analysis of the crude reaction mixture containing only **124** and **125**.

The intramolecular displacement reaction leading from the intermediate **123** is a function of the distance of the carbon bearing the tosylate group relative to the anion formed adjacent to the cyanide group. This distance would be reflected in the internal angles of the rings, the smaller the ring angle (as in the 3- and 4-rings) the greater the distance between the carbon bearing the cyanide group and the one holding the tosylate group. Intramolecular cyclization in these two cases would be unfavorable, and mainly **125** (n=3 or 4) would be expected. This is perhaps a good example of the so-called Thorpe-Ingold effect[166].

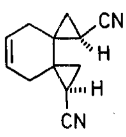
Treatment of tetramesylate **127** with sodium cyanide in dimethyl sulfoxide at 130° for 24 hours leads to a 95% yield of four products separated by chromatography and formulated as **128**, **129**, **130**, and **131** by a combination of N.M.R., chemical equilibration, and dipole moment measurements[167].



127



128



129

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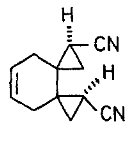
[134] N. I. Shuikin, I. I. Voznesenskaya, *Bull. Acad. Sci. USSR* **1966**, 1944; *C.A.* **66**, 64855 (1967).

[135] G. F. Grant, P. L. Pauson, *J. Organometallic Chem.* **9**, 553, (1967).

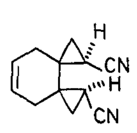
[136] V. A. Mironov, A. P. Ivanov, Ya. M. Kimelfeld, L. I. Petrovskaya, A. A. Akhrem, *Tetrahedron Lett.* **1969**, 3347.

[137] L. M. Dane, J. W. de Haan, H. Kloosterziel, *Tetrahedron Lett.* **1970**, 2755.

[138] V. A. Mironov, A. P. Ivanov, A. A. Akhrem, *USSR Patent* 263591; *C.A.* **73**, 3700 (1970).



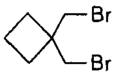
130



131

2.5.2. Phosphorous Ylid Displacements

Treatment of the dihalide **132** with two mol of a salt free solution of methylenetriphenylphosphorane leads to a 43% yield of **133**[168]. The salt-free solution of the ylid of **133** in tetrahydrofuran is treated with benzaldehyde to yield **134** (75%). This reaction appears to be quite adaptable to the future synthesis of spiro linkages of various ring sizes. The oxidation of the ylid of **133** with oxygen would lead to the ketone corresponding to **134**[169].



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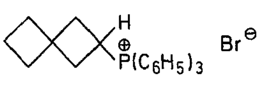
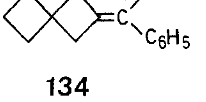


133

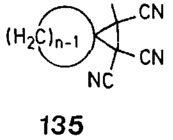


134

2.6. Michael Additions followed by Intramolecular Eliminations

2.6.1. Tetracyanocyclopropyl Systems (Wideqvist Reaction)

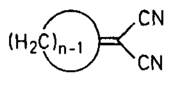
The reaction of monobromomalonitrile with cyclic ketones in the presence of potassium iodide leads to spiro derivatives with a tetracyanocyclopropane ring. This reaction was first studied by Wideqvist[170] and was subsequently investigated by Hart and coworkers[171,172]. The reaction appears to be fairly general for the preparation of spiro compounds of type **135**[171]. No products were obtained with larger rings (n = 10, 12, or 15).



135

n	yield (%)
4	60
5	76
6	92
7	25
8	4
9	7

It has been demonstrated[172] that the cycloalkylidene malononitriles **136** react readily at room temperature in aqueous ethanol to produce spiro tetracyclopropanes in excellent yields. The yields of **135** from this latter process are as follows (n, %): 5, 53; 6, 97; 10, 34; 12, 94; 15, 36. Compound **137** was also prepared by this procedure in a 39% yield. The preparation of **138** was unsuccessful. A mechanism has been proposed for these cyclizations[171,172].



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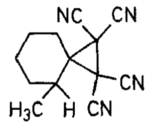

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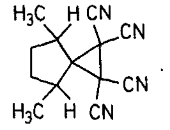
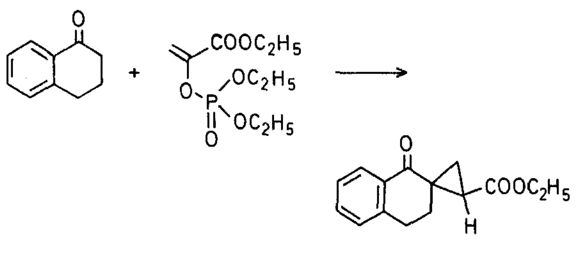


138

2.6.2. Conjugate Enolate Additions followed by Cyclizations to Spiroketones

The reaction of 1-tetralone with triethylphosphorenol pyruvate in the presence of a strong base (anion of dimethyl sulfoxide/dimethyl sulfoxide) yields the spirocyclopropyl ketone **139** (80%)[173]. Compound **139** is also formed from 1-tetralone and ethyl α-chloroacrylate in a 30% yield.



139

The reaction probably proceeds via initial Michael addition of the tetralone anion to first yield **140**, which then undergoes formation of anion **141**, followed by nucleophilic displacement of X to yield **139**.

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[139] D. Schönleber, *Chem. Ber.* **102**, 1789 (1969).

[140] K. Bangert, V. Boekelheide, *Tetrahedron Lett.* **1963**, 1119.
M. Neuenschwander, D. Meuche, H. Schaltegger, *Helv. Chim. Acta* **46**, 1760 (1960). This paper revises to **96** a different structure originally proposed by H. Schaltegger, *Helv. Chem. Acta* **45**, 1368 (1962).

[141] M. Mąkosza, *Tetrahedron Lett.* **1966**, 4621.
M. Mąkosza, *Pol. Patent* 55535; *C.A.* **70**, 106254 (1969).

[142] F. Nerdel, G. Blume, P. Weyerstahl, *Tetrahedron Lett.* **1969**, 3867.

[143] M. Mąkosza, *Bull. Acad. Pol. Sci. Chim.* **15**, 165 (1967); *C.A.* **67**, 64085 (1967).

[144] G. R. Pettit, E. G. Thomas, *Chem. & Ind.* **1963**, 1758.

[145] G. M. Badger, J. W. Cook, F. Schwarz, *J. Chem. Soc.* **1952**, 117.

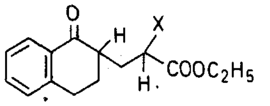
[146] H. J. Backer, H. B. J. Schurink, *Rec. Trav. Chim.* **50**, 921 (1931).
H. Wynberg, J. P. M. Houbiers, *J. Org. Chem.* **36**, 834 (1971).

[147] J. Gore, J. M. Denis, P. Leriverend, J. M. Conia, *Bull. Soc. Chim. France*, **1968**, 2432.

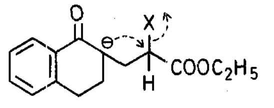
[148] S. E. Janson, W. J. Pope, *Proc. Roy. Soc.* **A 154**, 53 (1936).

[149] L. M. Rice, C. H. Grogan, *J. Org. Chem.* **26**, 54 (1961).

[150] E. Buchta, W. Merk, *Liebigs Ann. Chem.* **694**, 1 (1966).
E. Buchta, W. Merk, *Naturwissenschaften* **50**, 441 (1963).

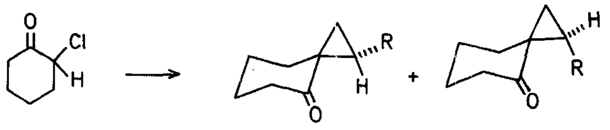


140 (X = $-\mathrm{OP(O)(OC_2H_5)(OC_2H_5)}$, Cl)



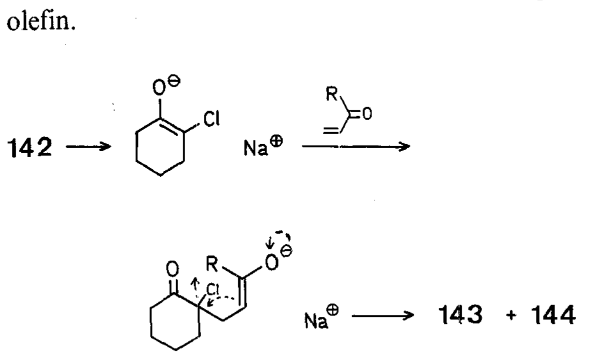
141

The reaction of 2-chlorocyclohexanone (**142**) with methyl vinyl ketone in the presence of sodium hydride in a 50/50 mixture of benzene/hexamethylphosphoric triamide leads to a mixture **143** ($R=COCH_3$, 90%) and **144** ($R=COCH_3$, 10%) in a 50% yield.



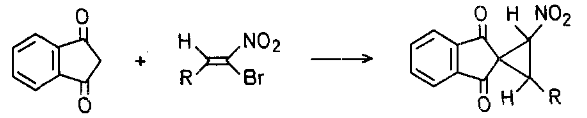
142 **143** **144**

Similarly, reaction of **142** with methyl acrylate leads to a 60% yield of **143** ($R=COOCH_3$, 80%) and **144** ($R=COOCH_3$, 20%)[174]. In these reactions the use of hexamethylphosphoric triamide is suggested as exerting a selective solvation on the cation of the enolate and maximizing the reactivity of the carbanion on the carbon bearing the chlorine atom for intermolecular reaction with the electrophilic olefin.



R = CH_3, OCH_3

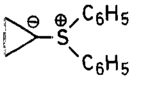
The synthesis of nitrospirocyclopropanes can be accomplished by the following reaction pathway. Treatment of **145** with **146** leads to **147** ($R=C_2H_5$, 60%) and **147** ($R=3\text{-}O_2N\text{—}C_6H_4$, 70%)[175].



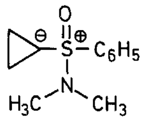
145 **146** **147**

2.6.3. Nucleophilic Cycloalkylidene and Alkylidene Transfer Reactions

The reaction of ylids **148**[176] and **149**[177] with α,β-unsaturated carbonyl compounds results in the selective transfer of cyclopropylidene to the α,β-carbon-carbon double bond to form substituted spiropentanes. Isolated carbon-carbon double bonds are not susceptible to cyclopropylidene transfer. Examples of the applications of cyclopropylidene transfer reactions from **148** and **149** to various α,β-unsaturated ketones and Mannich bases are listed in Table 14.



148



149

Reaction of ylid **149** with cyclohexanone produces initially an unstable dispiro epoxide **150** which rearranges to **151** during attempted isolation by preparative G.L.C.[177]. In a similar manner, **148** on treatment with cyclohexanone leads to 61% (sodium salt of dimethyl sulfoxide/dimethoxyethane, −45°) and 81% (potassium hydroxide in dimethyl sulfoxide, 25°) of **151**[176,178]. It might be noted that reaction of the phosphorus ylid **152** with cyclohexanone produces the olefin **153**. Treatment of norcamphor with **148** leads to **154** (86%) and **155** (14%) in yields of 65% (sodium salt of dimethyl sulfoxide/dimethoxyethane, −40°) and 92% (potassium hydroxide/dimethyl sulfoxide, 25°)[176]. The anion **156** reacts with **157** to yield **158** (39%) (dimethyl sulfoxide, 20 hours, 25°)[177]. These reactions proceed via Michael additions followed by intramolecular displacements.

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[151] E. Buchta, K. Geibel, *Liebigs Ann. Chem.* **648**, 36 (1961).

[152] B. Rickborn, M. T. Wuesthoff, *J. Amer. Chem. Soc.* **92**, 6894 (1970).

[153] E. R. Buchman, E. H. Deutsch, G. I. Fujimoto, *J. Amer. Chem. Soc.* **75**, 6228 (1953).

[154] E. Buchta, M. Fischer, *Chem. Ber.* **99**, 1509 (1966).

[155] E. Buchta, H. Ahne, *Chem. Ber.* **98**, 2651 (1965).

[156] E. Buchta, S. Billenstein, *Liebigs Ann. Chem.* **692**, 53 (1966).

[157] E. Buchta, S. Billenstein, *Liebigs Ann. Chem.* **685**, 74 (1965).

[158] E. J. Grubbs, D. J. Lee, A. G. Bellettini, *J. Org. Chem.* **31**, 4069 (1966).

[159] D. E. Applequist, J. D. Roberts, *J. Amer. Chem. Soc.* **78**, 4012 (1956).

[160] E. Buchta, W. Theuer, *Liebigs Ann. Chem.* **666**, 81 (1963).

[161] E. Buchta, K. Geibel, *Liebigs Ann. Chem.* **648**, 36 (1961).

[162] C. M. Sharts, A. H. McLeod, *J. Org. Chem.* **30**, 3308 (1965).

[163] L. M. Rice, K. R. Scott, *J. Org. Chem.* **32**, 1966 (1967).

[164] L. M. Rice, C. H. Grogan *U.S. Patent* 3350442 (tri-Kem Corp); *C.A.* **68**, 86893 (1968).

[165] J. Seyden-Penne, M. C. Roux-Schmitt, *Bull. Soc. Chim. France* **1968**, 3810.

[166] P. von R. Schleyer, *J. Amer. Chem. Soc.* **83**, 1368 (1961).

[167] T. Winkler, W. von Philipsborn, J. Altman, D. Ginsburg, *Helv. Chim. Acta* **52**, 1603 (1969).

[168] H. J. Bestmann, E. Kranz, *Angew. Chem.* **79**, 95 (1967); *Angew. Chem. Internat. Edit.* **6**, 81 (1967).
H. J. Bestmann, E. Kranz, *Chem. Ber.* **102**, 1802 (1969).

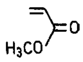
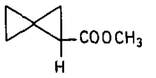
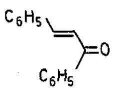
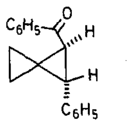
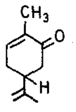
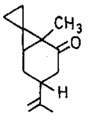
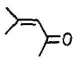
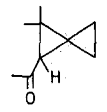
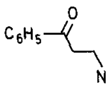
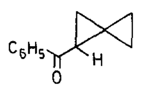
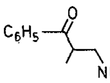
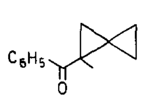
[169] H. J. Bestmann, O. Kratzer, *Chem. Ber.* **96**, 1899 (1963). Report oxidations of ylids to ketones.

[170] S. Wideqvist, *Arkiv. Kemi. Mineral Geol., B.* **20**, No. 4 (1945); *C.A.* **41**, 1621 (1947).

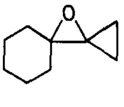
[171] H. Hart, F. Freeman, *J. Org. Chem.* **28**, 1220 (1963).

[172] H. Hart, Y. C. Kim, *J. Org. Chem.* **31**, 2784 (1966).

Table 14. Cyclopropylidene Transfer Reactions

α,β-Unsaturated Compound	Ylid	Product	Yield (%)	Reference
	**148**		41[a], 83[b]	176
	**148** **149**		55[a], 79[b], 95[c]	176, 177
	**148**		67[a], 75[b]	176
	**149**		61[d]	177
	**149**		85[d,e]	177
	**149**		57[c,f]	177

[a] Sodium salt of dimethyl sulfoxide/dimethoxyethane, −45°.
[b] Potassium hydroxide/dimethyl sulfoxide, 25°.
[c] Dimethyl sulfoxide, 25°, 15 min.
[d] Dimethyl sulfoxide, 25°, 10 h.
[e] Proceeds via β-elimination to first form the α,β-unsaturated ketone.
[f] Dimethyl sulfoxide, 25°, 40 h.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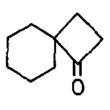
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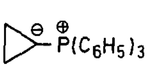

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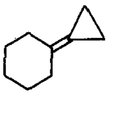
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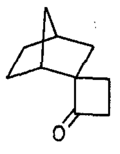
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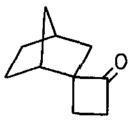
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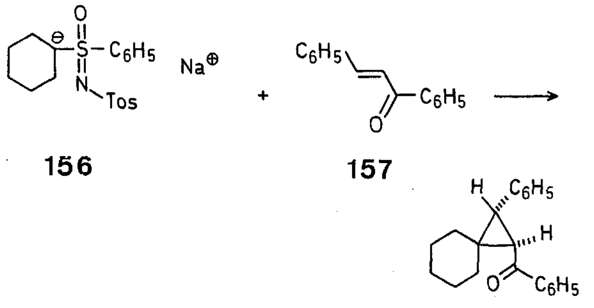

156 + **157** ⟶ **158**

Dimethylsulfoxonium methylide (generally prepared from sodium hydride in dimethyl sulfoxide and trimethylsulfoxonium iodide) undergoes reaction with exocyclic α,β-unsaturated ketones to yield spiro cyclopropane derivatives. Examples of this type of reaction are listed in Table 15

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[173] U. Schmidt, *Angew. Chem.* 77, 216 (1965); *Angew. Chem. Internat. Edit.* **4**, 238 (1965).

[174] M. Causse-Zoller, R. Fraisse-Jullien, *Bull. Soc. Chim. France* **1966**, 430.

[175] V. M. Berestovitskaya, A. S. Sopova, V. V. Perekalin, *J. Org. Chem. USSR* **3**, 1659 (1967).

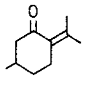
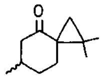
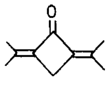
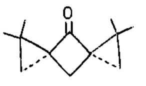
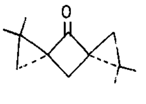
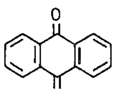
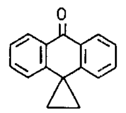
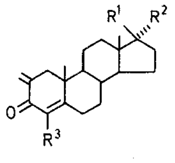
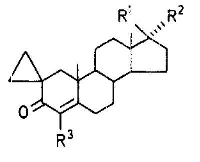
[176] B. M. Trost, M. J. Bogdanowicz, *J. Amer. Chem. Soc.* **93**, 3773 (1971).

[177] C. R. Johnson, G. F. Katekar, R. F. Huxol, E. R. Janiga, *J. Amer. Chem. Soc.* **93**, 3771 (1971).

[178] B. M. Trost, R. La Rochelle, M. J. Bogdanowicz, *Tetrahedron Lett.* **1970**, 3449.

[179] C. Agami, J. L. Pierre, *Bull. Soc. Chim. France* **1969**, 1963.

Table 15. Dimethylsulfoxonium Methylide[a] Additions to α-Alkylidene Ketones and α-Methylene Ketones

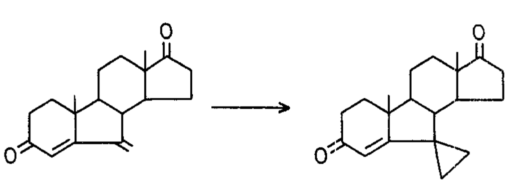
Ketone	Product	Yield (%)	Reference
		60	179
		10	180
		90	—
		—	181[b]
		$R^1 = OH, R^2 = R^3 = H$; 100 $R^1 = OAc, R^2 = R^3 = H$; 100 $R^1 = OH, R^2 = CH_3, R^3 = H$; — $R^1 = OH, R^2 = R^3 = CH_3$; —	182, 183 182, 183 182[c] 182

[a] Generally prepared by treatment of trimethylsulfoxonium iodide with sodium hydroxide in dry dimethyl sulfoxide followed by addition of the substrate and then allowing the reaction to proceed at room temperature for varying periods.

[b] Trimethylsulfoxonium iodide and sodium hydroxide in dimethylformamide.

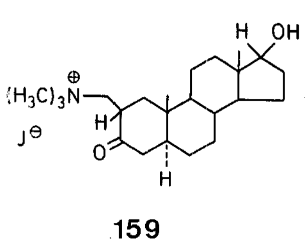
[c] Three other steroidal derivatives of this type are reported in this paper.

The reaction of dimethylsulfoxonium methylide with many heteroannular dienone steroidal systems leads to 6,6-ethylene systems. One example of this type of reaction is illustrated below[184,185]. Other related reactions are in the patent literature[31,185–188].

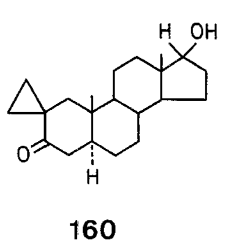


Fluorene-9-one azine on treatment with excess dimethylsulfoxonium methylide yields 70% of fluorene-9-spirocyclopropane[189].

The reaction of Mannich base methiodides with dimethylsulfoxonium methylide in the presence of an equivalent amount of sodium hydride leads to the corresponding spiro cyclopropyl systems. These reactions indoubtedly proceed via the intermediacy of the α-methylene ketones[183]. Compound **159** yields **160** (79%) while **161** yields **162** (63%).



159



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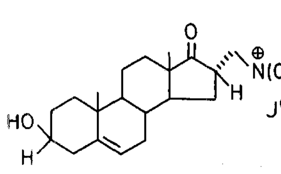

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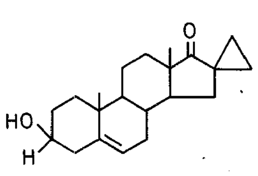


162

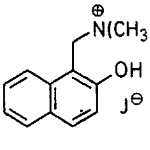
The Mannich base methiodide of β-naphthol (**163**) on treatment with excess dimethylsulfoxonium methylide in dimethyl sulfoxide leads to **164** (50%)[190]. Similarly, treatment of o-hydroxybenzyltrimethylaminium iodide (**165**) with dimethylsulfoxonium methylide gives **166** (47%). Both reactions probably proceed through the transient formation of the corresponding quinone methides **167**. Michael addition to **167** followed by intramolecular displacement of dimethyl sulfoxide by the phenoxide oxygen would lead to **164** and **166**, respectively. A mechanism involving initial formation of a spiro ketone

---

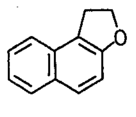
[180] J. P. Davreux, A. Bruylants, *Bull. Cl. Sci. Acad. Roy. Belg.* **54**, 823 (1968); *C.A.* **71**, 112857 (1969).

[181] C. Kaiser, C. L. Zirkle, *U.S. Patent* 3546228; *C.A.* **74**, 99724 (1971).

168 and its subsequent isomerization to the dihydrofurans might also be possible.



163



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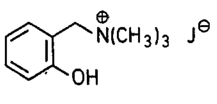

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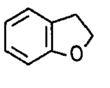

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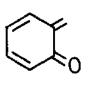

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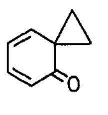


168

The reaction of dimethylsulfoxonium methylide with α-halocarbonyl compounds has been applied to the synthesis of cyclopropane containing spiro systems[191]. Addition of the haloketone to a cold solution of the ylid followed by a few hours reaction at room temperature yields the spiro derivatives tabulated in Table 16.

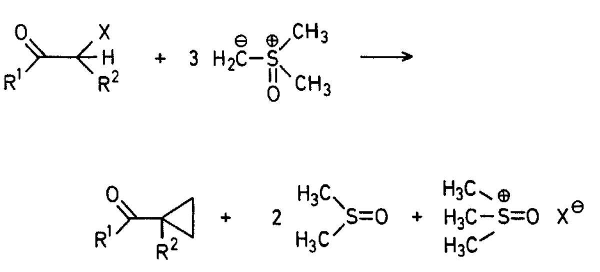
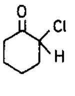
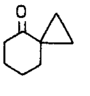
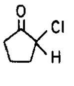
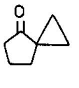
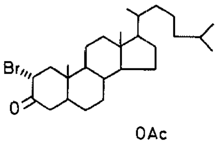
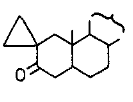
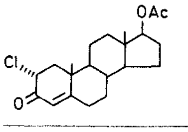
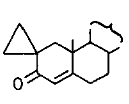
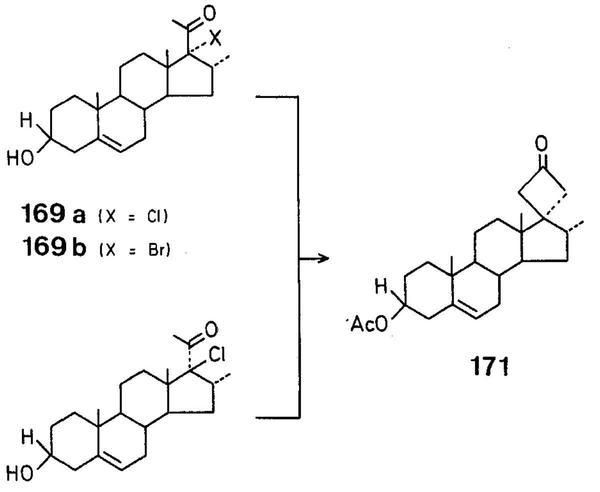


Table 16. α-Haloketones Treated with Dimethylsulfoxonium Methylide

Haloketone	Product	Yield (%)
		28
		30
		15
		13

The yields of the products are poor but the accessibility of the haloketones obviates this drawback. Two mechanisms have been suggested[191].

The reaction of 17-halogeno-16-α-methyl-20-oxasteroids **169a**, **169b**, and **170** with a mixture of trimethylsulfoxonium iodide in dimethyl sulfoxide and sodium hydroxide leads to formation of a product which on acetylation affords the spirocyclobutanone **171** in yields of 35–55%[192–194].

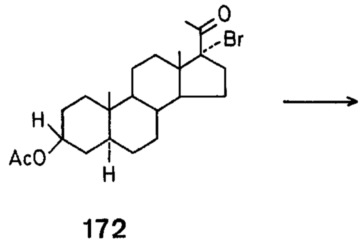


169 a (X = Cl)
169 b (X = Br)

170

171

Analogous reaction of ketone **172** leads to **173** (8%) and **174** (17%)[193,194]. The reaction is proposed as proceeding through a spirocyclopropane intermediate (as has been proposed in the Favorski rearrangement).



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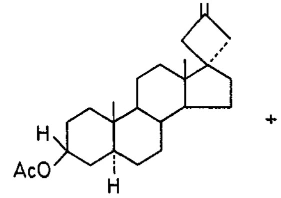

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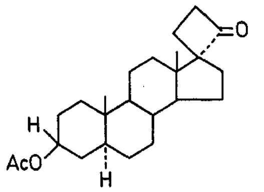


173 **174**

The reaction of 1-bromocyclohexyl methyl ketone, **175**, with trimethylsulfoxonium iodide and sodium hydroxide in dimethyl sulfoxide yields **176**[192]. The preparation of **177**, and its 5,6-dehydro derivative, from **178** (X = Cl or Br) is also reported[192].

---

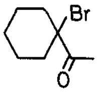
[182] D. E. Evans, G. S. Lewis, P. J. Palmer, D. J. Weyell, *J. Chem. Soc.* (C) **1968**, 1197.

[183] H. G. Lehmann, H. Müller, R. Wiechert, *Chem. Ber.* **98**, 1470 (1965).

[184] K. G. Holden, J. F. Kerwin, *German Patent (DBP)* 1294962, (Smith Kline and French Laboratories); *C.A.* **71**, 61672 (1969).

[185] *Brit. Patent* 1076218 (Smith Kline and French Laboratories); *C.A.* **68**, 59805 (1968).

[186] M. G. Lester, O. Stephenson, V. Petrow, *Brit. Patent* 1089945; *C.A.* **68**, 114874 (1968).



175

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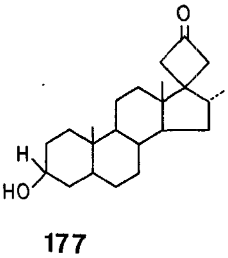

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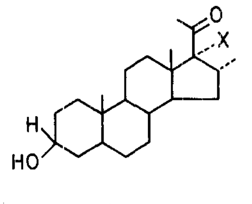
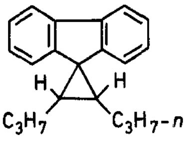


178

The reaction of fluorenone with methylenetriphenylphosphorane (in dimethyl sulfoxide using sodium hydride) leads to a 24% yield of **21** ($R=H$)[195,196]. The Witting reaction between fluorenone and excess *n*-butylidenetriphenylphosphorane yields **179** (50%)[196]. The reaction of 9-butylidenefluorene (**180**) with *n*-butylidenetriphenylphosphorane yields **179** (52%)[196].



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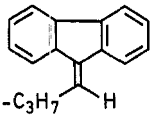
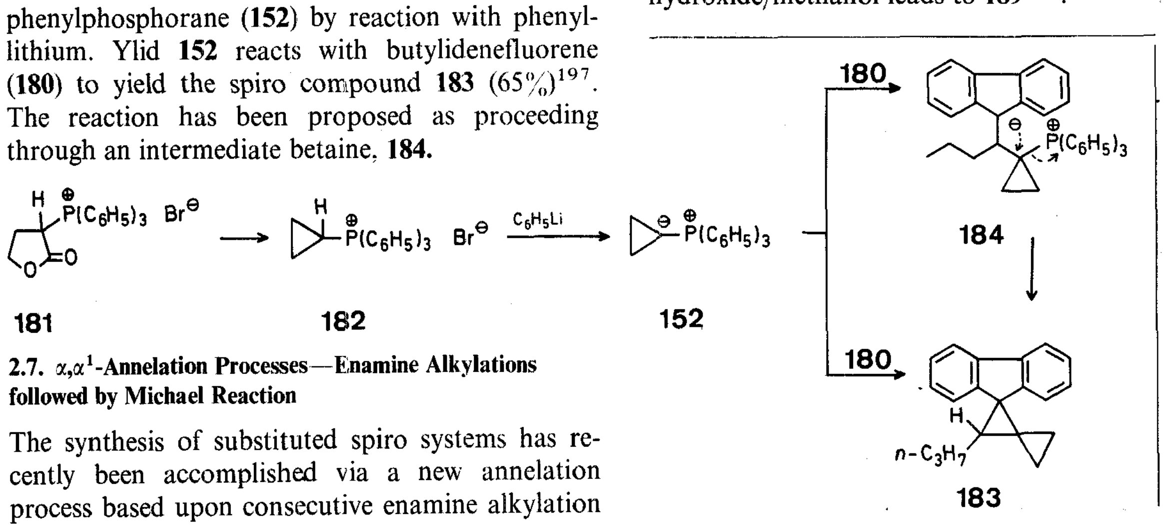


180

When the phosphonium salt **181** is heated above its melting point, carbon dioxide is lost and cyclopropyltriphenylphosphonium bromide (**182**) is formed. This can be converted into cyclopropylidenetriphenylphosphorane (**152**) by reaction with phenyllithium. Ylid **152** reacts with butylidenefluorene (**180**) to yield the spiro compound **183** (65%)[197]. The reaction has been proposed as proceeding through an intermediate betaine, **184**.

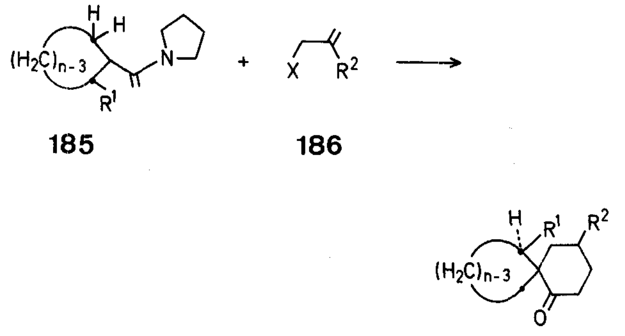


181 **182** **152** **184** **183**

2.7. α,α^1-Annelation Processes—Enamine Alkylations followed by Michael Reaction

The synthesis of substituted spiro systems has recently been accomplished via a new annelation process based upon consecutive enamine alkylation and a Michael reaction.

Treatment of **185** ($n=5$, $R^1=H$), **185** ($n=6$, $R^1=H$), or **185** ($n=5$, $R^1=CH_3$) with **186** ($X=Br$, $R^2=COOCH_3$) in benzene followed by addition of triethylamine in acetonitrile and refluxing and then treatment with aqueous acetic acid leads to **187** ($n=5$, $R^1=H$, $R^2=COOCH_3$), **187** ($n=6$, $R^1=H$, $R^2=COOCH_3$) or **187** ($n=5$, $R^1=CH_3$, $R^2=COOCH_3$) in 78, unspecified, and 78% yields, respectively. Treatment of **185** ($n=5$, $R^1=H$) with **186** ($X=Cl$, $R^2=CN$) leads to **187** ($n=5$, $R^2=CN$) in an unspecified yield[106].



185 **186** **187**

2.8. Michael additions

2.8.1. Single Michael additions

A precursor of the naturally occurring sesquiterpene acorone has been prepared by an intramolecular Michael addition. Treatment of **188** with potassium hydroxide/methanol leads to **189**[198].

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[187] D. E. Evans, *Brit. Patent* 1066729 (Parke, Davis and Co.); *C. A.* **67**, 44026 (1967).

[188] *Brit. Patent* 1127106 (Smith Kline and French Laboratories); *C. A.* **70**, 4404 (1969).

[189] B. C. Elmes, *Tetrahedrom Lett.* **1971**, 4139.

[190] E. Breuer, D. Melumad, *Tetrahedron Lett.* **1969**, 1875.

[191] P. Bravo, G. Gaudiano, C. Ticozzi, A. Umani-Ronchi, *Tetrahedron Lett.* **1968**, 4481; *Gazz. Chim. Ital.* **100**, 566 (1970).

[192] R. Wiechert, *Ger. Offen. (DOS)* 1912236; *C. A.* **73**, 109992 (1970).

[193] R. Wiechert, *Angew. Chem.* **82**, 219 (1970); *Angew. Chem. Internat. Edit.* **9**, 237 (1970).

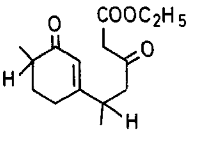
[194] R. Wiechert, *Ger. Offen. (DOS)* 1937613; *C. A.* **74**, 100303 (1971).

[195] R. Greenwald, M. Chaykovsky, E. J. Corey, *J. Org. Chem.* **28**, 1128 (1963).

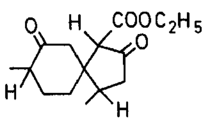
[196] R. Mechoulam, F. Sondheimer, *J. Amer. Chem. Soc.* **80**, 4386 (1958).

[197] H. J. Bestmann, Th. Denzel, R. Kunstmann, J. Lengyel, *Tetrahedron Lett.* **1968**, 2895.
H. J. Bestmann, *Angew. Chem.* **80**, 628 (1968); *Angew. Chem Internat. Edit.* **7**, 640 (1968).

[198] A. R. Pinder, S. J. Price, R. M. Rice, *J. Org. Chem.* **37** 2202 (1972) and references cited therein.



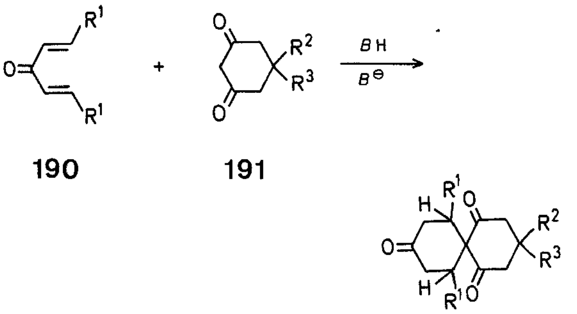
188



189

2.8.2. Double Michael Additions

The double Michael reaction, as exemplified by the following generalized reaction scheme, has found some applicability for the synthesis of spiro ketones. This reaction can be performed in a single operational step in which the overall process is an intermolecular Michael addition followed by an intramolecular Michael addition.



190 **191** **192**

Examples of this double cyclization are tabulated below (Table 17).

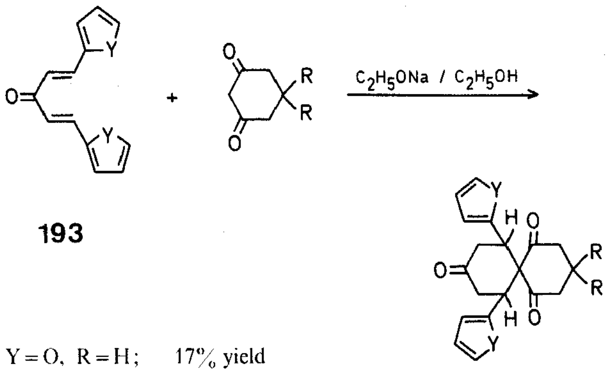
Table 17. Preparation of Spiranones from **190** and **191**

Dienone **190**	1,3-Dione **191**	Yield (%) of **192**	References
$R^1 = C_6H_5$	$R^2 = R^3 = H$	45	199[a]
$R^1 = C_6H_5$	$R^2 = R^3 = CH_3$	40	199[a], 200
$R^1 = H$	$R^2 = R^3 = H$	33	199[a]
$R^1 = H$	$R^2 = R^3 = CH_3$	22	199[a]
$R^1 = 4\text{-}H_3CO{-}C_6H_4$	$R^2 = R^3 = CH_3$	—	200[b]
$R^1 = C_6H_5$	$R^2 = C_6H_5$, $R^3 = H$	—	200[b]
$R^1 = 4\text{-}H_3CO{-}C_6H_4$	$R^2 = H$, $R^3 = C_6H_5$	—	200[b]

[a] Performed using sodium ethoxide in ethanol or ethanol/ether.

[b] No yields listed. Performed as in a (above) and also in acetic acid.

A similar double cyclization has been successfully exploited in the following sequence[201].

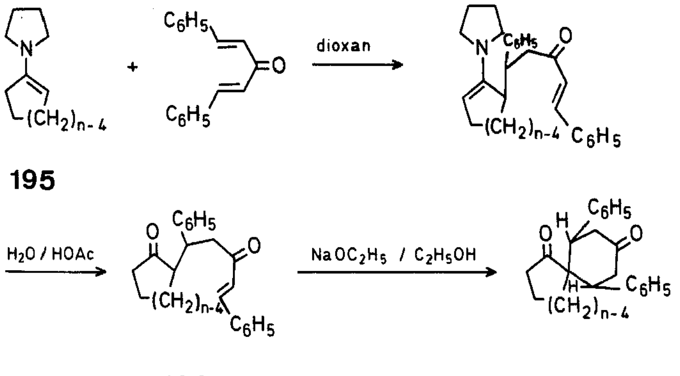


193

194

Y = O, R = H; 17% yield
Y = S, R = CH_3; 25%
Y = S, R = H; 20%
Y = O, R = CH_3; 27%

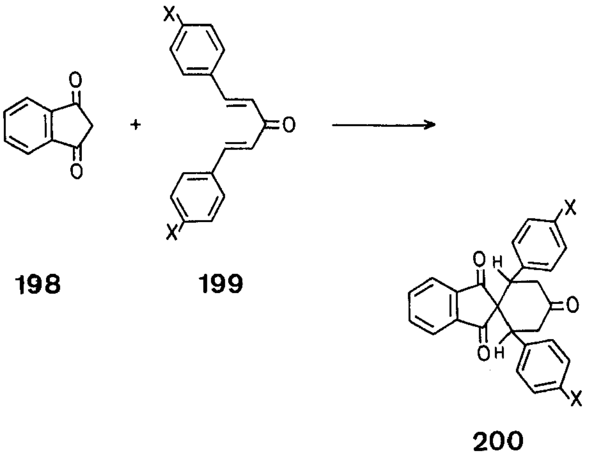
Treatment of cyclohexanone with dibenzalacetone using sodium ethoxide in ethanol yields the spiroketone **197** (n = 6, 5.3%)[202]. Only intractable tars were obtained when this reaction was attempted with cyclopentanone. The yields of these condensations can be dramatically increased by utilizing the enamines of cyclopentanone and cyclohexanone **195** (n = 5 or 6) as starting materials. The intermediates **196** [n = 5 (55%) and n = 6 (80%)] can be isolated and the intramolecular cyclization performed using sodium ethoxide/ethanol leads to **197** (60% for n = 5, 64% for n = 6)[202].



195

196 **197**

The reaction of indan-1,3-dione (**198**) with various *para*-substituted dibenzalacetones (**199**) has been recently reported as yielding **200** (X = H, OCH_3, Cl)[203].



198 **199**

200

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[199] H. A. P. De Jongh, H. Wynberg, *Rec. Trav. Chim.* **82**, 202 (1963).

[200] I. Y. Shternberg, Y. F. Freimanis, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.* **5**, 590 (1969); *C. A.* **72**, 54870 (1970).

[201] H. A. P. De Jongh, H. Wynberg, *Tetrahedron* **21**, 515 (1965).

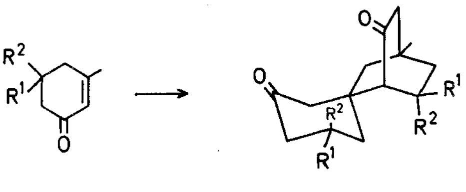
[202] H. A. P. De Jongh, F. J. Gerhartl, H. Wynberg, *J. Org. Chem.* **30**, 1409 (1965).

[203] I. Y. Shternberg, Y. F. Freimanis, *J. Org. Chem. USSR* **4**, 1044 (1968).

[204] G. Büchi, J. H. Hansen, D. Knutson, E. Koller, *J. Amer. Chem. Soc.* **80**, 5517 (1958).

[205] J. P. Morizur, B. Furth, J. Kossanyi, *Bull. Soc. Chim. France* **1967**, 1422.

The dimerizations of substituted 2-cyclohexen-1-ones (**201**) with strong bases lead to spiro systems **202**. The dimerization of **201** ($R^1=R^2=H$) with sodium amide in ether leads to **202** ($R^1=R^2=H$, 53%)[204]. This product is also obtained by refluxing **201** ($R^1=R^2=H$) with potassium hydroxide in benzene or ether (39%)[205,206]. Treatment of **201** ($R^1=H$, $R^2=CH_3$) with sodium amide yields **202** ($R^1=H$, $R^2=CH_3$) as an isomeric mixture in yields of 25 and 27%[204,205]. Similarly, reaction of **201** ($R^1=H$, $R^2=CH_3$) leads to an isomeric mixture of **202** (($R^1=H$, $R^2=CH_3$) on treatment with potassium hydroxide in benzene or ether (88%)[205,206]. Isophorone (**201**, $R^1=R^2=CH_3$) on treatment with sodium amide or potassium hydroxide in ether or benzene leads to **202** ($R^1=R^2=CH_3$) (40–80%)[204–206]. Self-condensation of isophorone in aqueous sodium hydroxide yields non-spiro products[207].



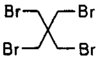
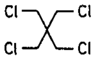
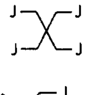
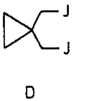
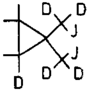
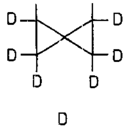
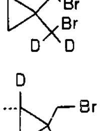
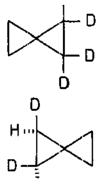
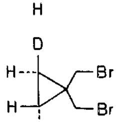
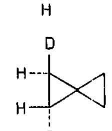
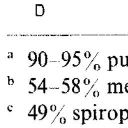
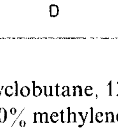
201 **202**

3. Intramolecular Dehalogenations and Related Reactions

3.1. Reductions Leading to Spiropentanes

The reaction of zinc with 1,3-dihalides to form cyclopropanes appears to have been first exploited by Gustavson and bears his name[208,209]. The product from the treatment of pentaerythritol tetrabromide with zinc in aqueous alcohol was originally formulated as vinyl cyclopropane[210]. Subsequently,

Table 18. 1,3-Dehalogenations Leading to Spiropentanes

Compound	Product	Conditions	Yield (%)	Reference
		$Na_4EDTA/NaJ/C_2H_5OH/Zn$ dust Zn/molten $H_3CCONH_2/NaJ/Na_2CO_3$ $Zn/C_2H_5OH/NaJ/Na_2CO_3$ Na/dioxan	80[a] 40 24–28[b] 51[c]	213 214 215 216
		$Zn/H_3CCONH_2/Na_2CO_3$	10	217
		Na/dioxan $Zn/H_3CCONH_2/Na_2CO_3$	61[d] 50	216 217
		Na/dioxan	54[e]	216
		Na/dioxan	21	216
		$Zn/NaOH/EDTA/NaJ/C_2H_5OH/H_2O$	94	218
		$Zn/NaOH/EDTA/NaJ/C_2H_5OH/H_2O$	—	219
		$Zn/NaOH/EDTA/NaJ/C_2H_5OH/H_2O$	—	219

[a] 90–95% purity.
[b] 54–58% methylenecyclobutane, 13–18% 2-methyl-1-butene, and 1–3% 1,1-dimethylcyclopropane also found.
[c] 49% spiropentane, 30% methylenecyclobutane, and 21% 2-methyl-1-butene.
[d] 44% spiropentane, 43% methylenecyclobutane, and 13% 2-methyl-1-butene.
[e] 50% spiropentane, 35% methylenecyclobutane, and 15% 2-methyl-1-butene.

---

[206] G. Kabas, *Brit. Patent* 1095797, W. R. Grace, and Co.; *C. A.* **68**, 49182 (1968).
G. Kabas, *Chimia* **21**, 260 (1967).

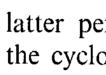
[207] G. Kabas, H. C. Rutz, *Tetrahedron* **22**, 1219 (1966).

[208] G. Gustavson, *J. Prakt. Chem.* **36**, 300 (1887).

a number of investigators studied this debromination and many conflicting statements appear as to the actual product(s) from this reaction[211]. All of the data for many investigations of this reaction leads one to conclude that the major product is methylenecyclobutane along with lesser amounts of 2-methyl-1-butene and spiropentane[211,212]. It is to be noted that in the presence of added zinc dibromide the product is methylenecyclobutane (86%) with no detectable spiropentane[212].

An improved synthesis of spiropentane was then developed by Applequist and co-workers[213] by addition of tetrasodium ethylenediaminetetraacetate to the reaction mixture to remove free zinc ion, the latter perhaps catalyzing rearrangement of **203** to the cyclobutane skeleton. An 81% yield of hydrocarbon, consisting of 94% spiropentane, 4.2% 2-methyl-1-butene, 0.7% 1,1-dimethylcyclopropane, and 0.6% methylenecyclobutane results.

The applicability of this reductive dehalogenation for the synthesis of spiropentane and its deuterated analogs is illustrated by the examples tabulated in Table 18.



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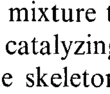
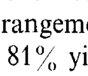


204



205

Treatment of the methylenecyclopropane ditosylate (**204**, R = OTos) with zinc/tetrasodium ethylenediaminetetraacetate/sodium iodide in aqueous ethanol leads to **205** in an unspecified yield[220]. The use of the dibromide **204** (R = Br) leads to a definite improvement in the yield of **205** (separated from 2,3-dimethylbutadiene by G.L.C.)[221].

The electrochemical reduction of pentaerylthritol tetrabromide leads to spiropentane in a good yield[222]. Similarly, electrochemical reduction of **203** leads to spiropentane (38% yield)[223].

Spiropentane[213]:

In a 5-l three-necked creased flask fitted with a high-speed stirrer, a solids-addition apparatus, and a water-cooled condenser in series with a spiral condenser (arranged for distillation) and two dry-ice traps, was placed disodium dihydrogen ethylenediaminetetraacetate (852 g, 2.57 mol), sodium hydroxide (297 g, 7.43 mol) dissolved in water (510 ml), 95% ethanol (1470 ml), and sodium iodide (20.7 g, 0.138 mol). The mixture was heated to reflux, and zinc dust (214.5 g, 3.28 g-atom) was then added. A slow stream of nitrogen was passed through the system to carry volatile products to the cold traps, and pentaerythritol tetrabromide (321 g, 0.828 mol) was added slowly to the stirred, refluxing mixture. After the addition was complete, the mixture was stirred at reflux temperature for 1 hour. The condensate in the cold traps was washed with two 150 ml portions of a cold, saturated solution of sodium chloride in water and then dried over Drierite to give the crude spiropentane; yield: 45.5 g (81%). G.L.C. analysis showed this material to be of 94% purity. Spiropentane free of unsaturated impurities was obtained by rough titration of a 20% (by volume) solution of the hydrocarbon in ethylene dibromide with bromine, followed by distillation through a 4.5-foot spiral wire column; b.p. 36.5–37.5°.

3.2. Reactions Leading to Spirocyclopropyl Systems

Other spirocyclopropyl systems have been prepared by dehalogenation of various dihalo substrates. Examples of these routes are tabulated in Table 19.

The debromination of 1,1-bis[bromomethyl]cyclooctane (**210**, n = 8) with zinc dust in aqueous alcohol

Table 19. Formation of Three-membered Spiro Compounds

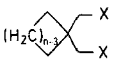
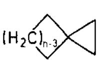
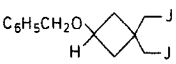
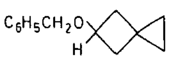
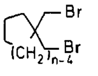
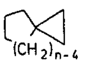
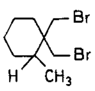
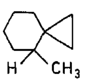
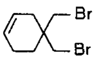
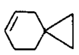
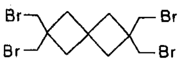
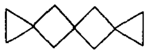
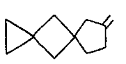
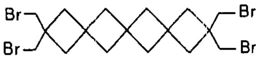
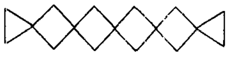
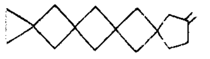
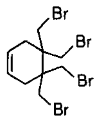
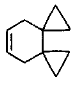
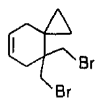
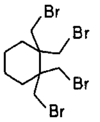
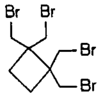
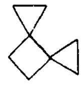
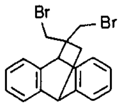
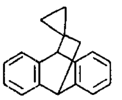
Starting Compound	Product	Conditions	Yield (%)	Reference
		$Zn/Na_4EDTA/NaJ/C_2H_5OH/H_2O$ $Zn/C_2H_5OH/H_2O$	n = 4, x = J; 60 n = 4, x = Br; —[a]	224 225
		$Zn/C_2H_5OH/H_2O$	86	147
		Zn/C_2H_5OH or $Zn/C_2H_5OH/NaJ/Na_2CO_3$ $Zn/C_2H_5OH/H_2O$	n = 5 35[b] n = 6 71–73[c]	226 209, 227
		$Zn/C_2H_5OH/H_2O$	58[d]	209
		Zn/C_2H_5OH	—	228
	 **206**  **207**	$Zn/CH_3OH/H_2O$	80[e]	229

Table 19, continued

Starting Compound	Product	Conditions	Yield (%)	Reference
	 **208**  **209**	$Zn/C_2H_5OH/H_2O$	69[f]	229
		$Zn/CH_3OH/H_2O/$ reflux/8 hrs	—	230, 231, 232
		$Zn/CH_3OH/H_2O/$ reflux 2.5 hr	—	230, 231
		$Zn/CH_3OH/H_2O$	68	230, 231
		$Zn/C_2H_5OH/H_2O$	—[g]	233
		$Zn/C_2H_5OH/H_2O$	95	159

[a] Purified by G. L. C.

[b] 90% crude yield which contains 65% methylenecyclohexane.

[c] Contaminated by 1,1-dimethylcyclohexane (27% by G. L. C. analysis, ref. 227).

[d] Crude yield 89%, perhaps impure.

[e] Crude product yield. G.L.C. showed the presence of 90% **206** and 10% **207** in the mixture. Pure **206** could be isolated by bromine addition to the mixture followed by fractional distillation or by preparative G.L.C. Pure **207** was isolated by G.L.C. Addition of disodium dihydrogen ethylenediaminetetraacetate/sodium hydroxide and a small amount of sodium iodide to the zinc reaction of the tetrabromide produced only **206** (33%).

[f] A mixture of **208** and **209** was isolated in a 69% yield. Pure **208** was isolated by bromine treatment of the mixture followed by distillation. Pure **209** was not isolated but was estimated to constitute about 10% of the crude reaction mixture.

[g] Also isolated from this reaction was 2,5-dimethylhexa-1,5-diene. The ratio of spiro compound to diene was 5.5 to 1.

is reported to yield a 9:1 mixture of **211** (n = 7) and the expected product **212** (n = 8) (52%). If the reaction is carried out in the presence of sodium ethylenediaminetetraacetate/sodium iodide/sodium hydroxide/aqueous ethanol only **211** (n = 7) is obtained[234]. The debromination of **210** (n = 7) with zinc in aqueous ethanol is reported to yield a mixture of equal amounts of **211** (n = 6) and **212** (n = 7) (41% overall yield)[235]. In the presence of sodium ethylenediaminetetraacetate/sodium hydroxide/ aqueous ethanol, and sodium iodide a 42% yield of **212** (n = 7) is formed (98% purity)[235]. The formulations **211** (n = 6 or 7) must surely be questioned as products from these dehalogenations[236].

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[209] R. W. Shortridge, R. A. Craig, K. W. Greenlee, J. M. Derfer, C. E. Boord, *J. Amer. Chem. Soc.* **70**, 946 (1948). See this reference for a historical commentary on the use of zinc and a protonic solvent for the preparation of cyclopropanes.

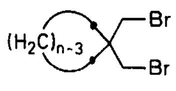
[210] G. Gustavson, *J. Prakt. Chem.* **54**, 97 (1896).
G. Gustavson, *C. R. Acad. Sci.* **123**, 242 (1896).

[211] S. F. Marrian, *Chem. Rev.* **43**, 149 (1948); for earlier references.

[212] J. D. Roberts, C. W. Sauer, *J. Amer. Chem. Soc.* **71**, 3925 (1949) and references cited therein.
Y. M. Slobodin, I. N. Shokhov, *Zhur. Obshchei Khim.* **21**, 2005 (1951); *C. A.* **46**, 6598 (1952); and references cited therein.

[213] D. E. Applequist, G. F. Fanta, B. W. Henrikson, *J. Org. Chem.* **23**, 1715 (1958).
M. C. Flowers, H. M. Frey, *J. Chem. Soc.* **1961**, 5550
G. R. De Mare, L. G. Walker, O. P. Strausz, H. E. Gunning, *Can. J. Chem.* **44**, 457 (1966).
G. Dallinga, R. K. Van der Draai, L. H. Toneman, *Rec. Trav. Chim.* **87**, 897 (1968).
A. D. Buckingham, E. E. Burnell, C. A. de Lange, *Mol. Phys.* **17**, 205 (1969).

[214] M. J. Murray, E. H. Stevenson, *J. Amer. Chem. Soc.* **66**, 314, 812 (1944).



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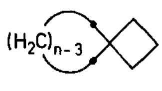

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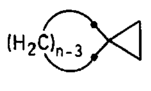
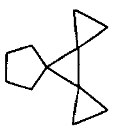
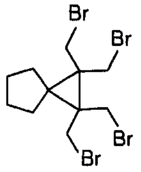


212

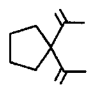
Several unsuccessful attempts to prepare spiro linkages via 1,3-dehalogenations are of interest. In an attempt to prepare **213**, it was found that treatment of **214** with zinc dust (disodium dihydrogen ethylenediaminetetraacetate/sodium hydroxide/water/ethanol) leads to a 73% yield of **215**[237].



213

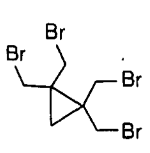


214



215

Similarly, treatment of **216** under conditions utilized for reaction of **214** leads to diene **217** and no dispiro compound **218** could be isolated[233]. Treatment of **216** with Na in dioxane leads to a complex mixture containing some **217** and no **218**[233].



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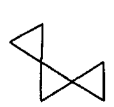
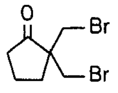
217



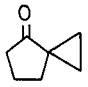
218

3.3. Reductions Leading to Spirocyclopropyl Ketones

The reaction of 2,2-bis[bromomethyl]cycloalkanones with zinc leads to excellent yields of spiranones (e.g., **219** is converted to **220** in a 90% yield)[238]. The applicability of this debromination to the synthesis of spiranones is illustrated by the examples tabulated in Table 20.



219



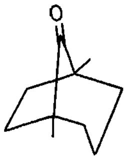
220

Spiro[2.4]heptan-4-one (220)[238]:

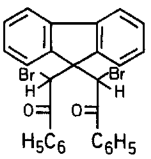
To 2,2-bis(bromomethyl)cyclopentanone (2.7 g, 0.01 mol) is added zinc powder (3 g), water (15 ml), and ethanol (15 ml). The suspension is heated to boiling for 2 hours with stirring. Upon cooling, the mixture is extracted twice with 10 ml portions of dichloromethane. The extracts are washed with water and dried over sodium carbonate. The solvent is evaporated and the residue (quantitative yield) is separated by preparative chromatography (SE 30, 3 m, 150°). The mixture is 90% of the spiranone **220** and 10% of 3-methylcyclohex-2-ene-1-one.

3.4. Reductions of α,α'-Dihaloketones

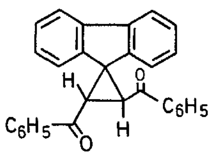
Treatment of **226** with zinc and sodium iodide in acetone leads to the spirofluorene **227**[242].



225

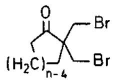
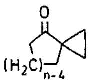
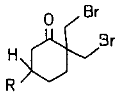
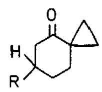
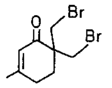
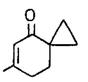
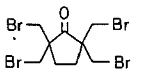
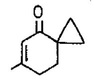
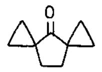
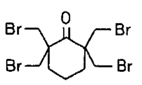
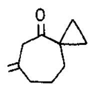
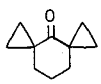


226



227

Table 20. Debrominations of 2,2-Bis[bromomethyl]cycloalkanones

Reactant[a]	Product	Yield (%)	Reference
		n=5; 90[b] n=7; 100 n=8; 100[c]	238 239 239
		R=H; 100 R=CH$_3$; —	239 238
		—	238
	 **221**  **222**	221; 50 222; 50	238, 240, 241
	 **223**  **224**	223; 40 224; 60	239, 241[d]

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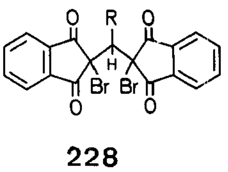
[a] Use of zinc in 50% aqueous methanol.

[b] 10% of the product is 3-methylcyclohexenone.

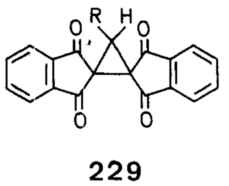
[c] Use of zinc/methanol/ethylenediaminetetraacetic acid/sodium iodide.

[d] The addition of the di- or mono-sodium salt of ethylenediaminetetraacetic acid leads to 5–10% of **225** in the mixture[241].

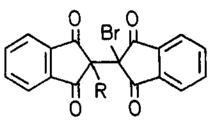
The preparation of cyclopropane derivatives is described from 2,2′-dibromo-2,2′-alkylenebis[1,3-indandiones] **228**[243]. Treatment of the dibromides **228** with zinc dust and ethanol yields the dispiro compounds **229**. The following yields for the conversion of **228** to **229** are reported: **229**, $R = C_2H_5$ (83%); **229**, $R = i\text{-}C_4H_9$ (84%), **229**, $R = i\text{-}C_5H_{11}$ (72%)[243]. Treatment of **228** with diethylamine in dioxane also leads to **229** in yields of 98% (**229**, $R = CH_3$), 98% (**229**, $R = C_2H_5$), and 97% (**229**, $R = i\text{-}C_3H_7$)[243]. Compounds **229** ($R = CH_3$ or $i\text{-}C_4H_9$) on treatment with bromine yield **230** ($R = CH_3—CHBr—$) and **230** ($R = i\text{-}C_4H_9—CHBr—$), respectively. Compound **230** ($R = CH_3—CHBr—$) is reconverted into **229** ($R = CH_3$) with diethylamine. Compound **230** ($R = i\text{-}C_4H_9—CHBr—$) is reconverted into **229** ($R = i\text{-}C_4H_9$) with zinc dust.



228



229

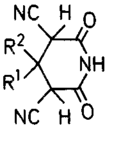


230

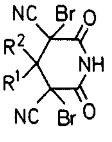
The conversions of **228** into **229** have also been reported for the following compounds by use of diethylamine: **229** ($R = C_6H_5$); **229** ($R = 4\text{-}O_2N—C_6H_4$); **229** ($R = 3\text{-}O_2N—C_6H_4$)[244]; **229** $R = 4\text{-}Cl—C_6H_4$), **229** ($R = 4\text{-}Br—C_6H_4$), **229** ($R = 4\text{-}J—C_6H_4$), and **229** ($R = 2{,}4\text{-}di\text{-}Cl—C_6H_3$)[244].

3.5. Reductive Cyclizations of Guareschi Imide Dibromides

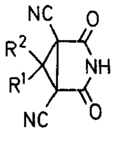
It has been reported by Guareschi that the imides of the general type **231**, obtained from the condensation of ketones with ethyl cyanoacetate and ammonia, lead to the dibromo derivatives **232** on bromination. On heating these dibromo derivatives, or on treatment with formic acid or alcohol and heating, compounds of type **233** result[245]. This reaction has found some utility for the synthesis of spiro compounds from the imides **231** ($R^1 = R^2 = —(CH_2)_x—$) prepared from cyclic ketones[246-250].



231



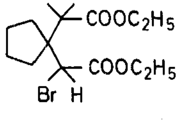
232



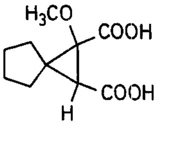
233

3.6. α,α'-Dibromo-β,β-cycloalkylglutaric Esters

Treatment of the cyclopentane dibromo ester **234** with methanol/potassium hydroxide has been reported to yield a mixture of the hydroxy acid **28** (n = 5) and the methoxy analog **235**[251]. One must assume that structure **28** (n = 5) is erroneous[38] although structure **235** seems likely[252]. The methoxy acids **235** (34%) were obtained by ether extraction of the crude reaction products (*cis* and *trans* isomers). By treatment with acetyl chloride, a *cis* anhydride could be isolated and a *trans* diacid. The *cis* anhydride was converted to the *cis* diacid. Other structures comparable to **235** have appeared without any real evidence supporting these formulations[40,41,43,44].

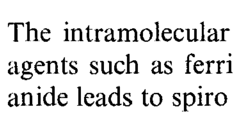


234

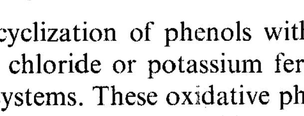


235

The reaction of **236** with diethyl malonate (sodium ethoxide/ethanol) leads to a product formulated as **237** (n = 6, 38%)[253]. Similarly, **234** has been transformed into a product formulated as **237** (n = 5)[254]. No structural evidence is presented for these formulations.



236



237

4. Free Radical Cyclizations

4.1. Oxidative Phenol Couplings

The intramolecular cyclization of phenols with reagents such as ferric chloride or potassium ferricyanide leads to spiro systems. These oxidative phenol coupling processes play a key role in the biosynthesis of phenolic alkaloids and other natural products[255]. Examples of intramolecular oxidative phenol coupling reactions for the syntheses of diversified structures are tabulated in Table 21. Three-, five-, six-, and seven-membered rings have been formed by this type of cyclization.

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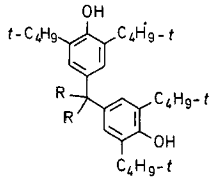
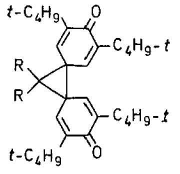
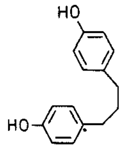
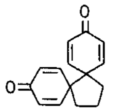
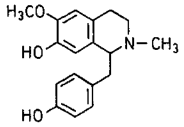
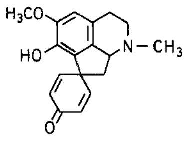
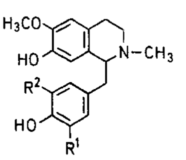
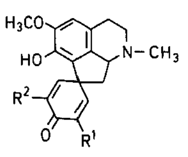
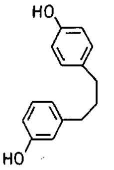
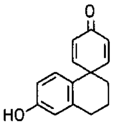
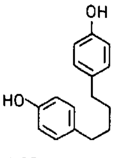
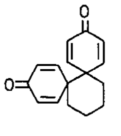
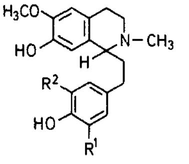
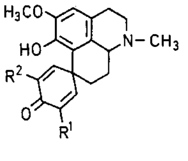
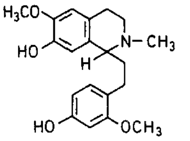
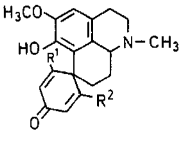
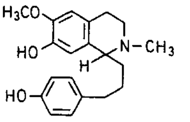
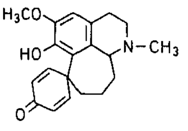
[215] V. A. Slabey, *J. Amer. Chem. Soc.* **68**, 1335 (1946).
D. W. Scott, H. L. Finke, W. N. Hubbard, J. P. McCullough, M. E. Gross, K. D. Williamson, G. Waddington, H. M. Huffman, *J. Amer. Chem. Soc.* **72**, 4664 (1950).

[216] H. O. House, R. C. Lord, H. S. Rao, *J. Org. Chem.* **21**, 1487 (1956).

[217] Y. M. Slobodin, I. N. Shokhor, *Zhur. Obshchei Khim.* **23**, 42 (1953); *C. A.* **48**, 543 (1954).

Table 21. Intramolecular Oxidative Phenol Coupling Reactions

Phenol	Product	Conditions	Yield (%)	Reference
		aqueous alkaline $K_3Fe(CN)_6$ MnO_2/C_6H_6	R = CH_3 — R = C_6H_5 100	256 257
		$K_3Fe(CN)_6/NaOH/C_6H_6$	20	258
		$K_3Fe(CN)_6$ (8% $NH_4OAc/CHCl_3$)	2	259
		alkaline $K_3Fe(CN)_6$	4[a]	260
		$VOCl_3$/ether, −78° for 2.5 h, reflux 10 h $K_3Fe(CN)_6/H_2O$ $FeCl_3/H_2O$ $Mn(acac)_3/CH_3CN$	76 4 7 10	264 264 264 264
		$K_3Fe(CN)_6/NaOH/C_6H_6$	15	258
		hydrochloride $FeCl_3/H_2O$	46[b]	265
$R^1 = OCH_3$, $R^2 = H$	$R^1 = H$, $R^2 = OCH_3$ or $R^1 = OCH_3$, $R^2 = H$	$K_3Fe(CN)_6$/8% $NH_4OAc/CHCl_3$ $K_3Fe(CN)_6$	16[b] 31	265 266
$R^1 = R^2 = OCH_3$	$R^1 = R^2 = OCH_3$	hydrochloride/$FeCl_3/H_2O$ alkaline $K_3Fe(CN)_6$	18 49	265 267
$R^1 = R^2 = H$	$R^1 = R^2 = H$	hydrochloride/$FeCl_3/H_2O$	19	265
	 $R^1 = H$, $R^2 = OCH_3$ or $R^1 = OCH_3$, $R^2 = H$	$FeCl_3/H_2O$	26[c]	268
		$K_3Fe(CN)_6/CHCl_3/NH_4OAc/H_2O$	1	269

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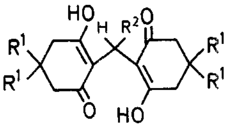
[a] A mixture of dienones with $R^1 = OCH_3$, $R^2 = H$ and $R^1 = H$, $R^2 = OCH_3$ was obtained. Other related cyclizations can be found in references 261 through 263.

[b] A mixture of isomers was obtained which could be separated when $R^1 = OCH_3$, $R^2 = H$ or $R^1 = H$, $R^2 = OCH_3$.

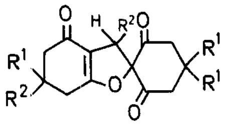
[c] Isolated only one dienone of uncertain configuration.

4.2. Oxidative Couplings of Methylene-bis[dimedones]

Treatment of methylene-bis[dimedone] **238** ($R^1 = CH_3$, $R^2 = H$) with a solution of iron(III) hexacyanoferrate (III) leads to intramolecular oxidative carbon-oxygen coupling to yield spiro enol ether **239** ($R^1 = CH_3$, $R^2 = H$; 28%)[270,271,272].

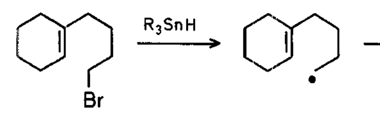


238

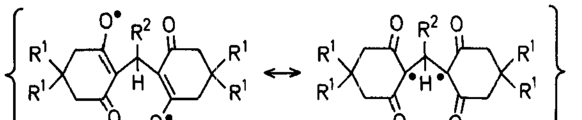


239

The latter probably arises via the short-lived stabilized diradical **240** which undergoes exclusive carbon-oxygen intramolecular coupling.



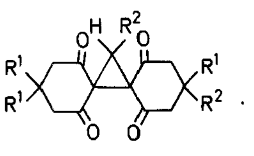
244 **244a**



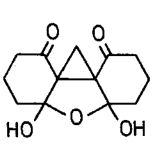
240

Enol ether **239** ($R^1 = CH_3$, $R^2 = H$) is reported to be identical to the compound previously prepared by Radulescu and Georgescu[273] from the reaction of the disodium salt of **238** ($R^1 = CH_3$, $R^2 = H$) with iodine in ether and formulated as **241** ($R^1 = CH_3$, $R^2 = H$). Kondrat'eva and co-workers[274] have also obtained **239** ($R^1 = CH_3$, $R^2 = H$) in the reaction of **238** ($R^1 = CH_3$, $R^2 = H$) with bromine in chloroform. These workers also repeated the reaction reported by Radulescu[273] and obtained the same product as that obtained with bromine in chloroform.

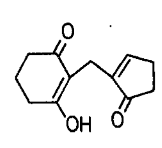
Mattsson[270-272] reports a different result in the reaction of **238** ($R^1 = R^2 = H$) with iron(III) hexacyanoferrate (III). One compound, isolated in a 28% yield, on melting or sublimation loses the elements of methanol and leads to the spiro enol ether **239** ($R^1 = R^2 = H$). The other compound, isolated in a yield of 22%, is formulated as **242**. A short path distillation of **242** leads to two new ketonic products formulated as **241** ($R^1 = R^2 = H$) and **243**. The formation of **243** from **241** ($R^1 = R^2 = H$) is discussed. Various ring opening reactions of **241** ($R^1 = R^2 = H$) have been studied[271]. In further studies, Mattsson reports two coupling products **241** ($R^1 = CH_3$, $R^2 = CH_3CH_2$) and **241** ($R^1 = CH_3$, $R^2 = COCH_3$) from intramolecular oxidation of the corresponding substituted methylene-bis-1,3-cyclohexandiones[275,276].



241



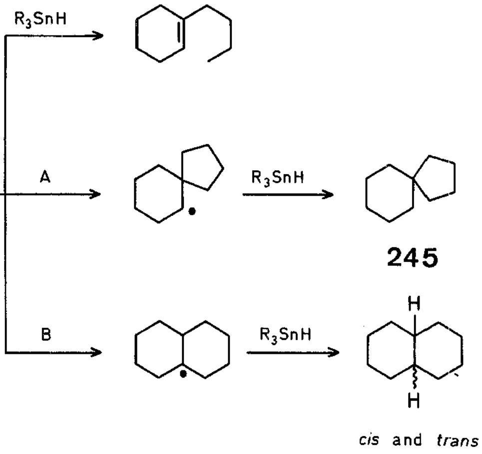
242



243

4.3. Radical Cyclizations at Double Bonds

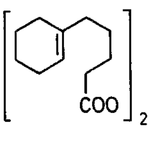
The reaction of **244** with tri-*n*-butyltin hydride in benzene leads to the formation of spiro[4.5]decane (**245**). The intermediary of radical **244a** is proposed, which undergoes cyclization via paths A and B.



Using **244** at a concentration of 0.04 *M* (benzene solution) and a trialkyltin hydride (0.02 *M*), a 36% yield of **245** can be obtained[277].

The thermal decomposition of **246** has been studied in various solvents and yields of **245** are 36, 24, and 22% of the reaction mixture in the solvents cyclohexane, benzene and benzene-cumene, respectively. The overall yields are 25, 20, and 37%, respectively[277].

When **246** and copper(II) octanoate are heated in benzene, 6–21% of spirene **247** is obtained (dependent on copper(II) octanoate concentration; no **245** is formed)[278]. When **246** and copper(II) octanoate are heated in acetic acid, 2.2% of **247** and 5.1% of **245** are obtained. The formation of **247** is suggested as arising via oxidation of the spiro radical by copper(II).



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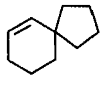

247

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[218] W. von E. Doering, J. C. Gilbert, *Tetrahedron Suppl.* 7, 397 (1966).

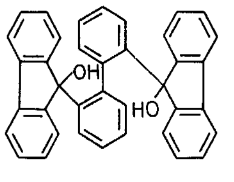
[219] J. C. Gilbert, *Tetrahedron* **25**, 1459 (1969).

[220] W. R. Dolbier, Jr., *Tetrahedron Lett.* **1968**, 393.

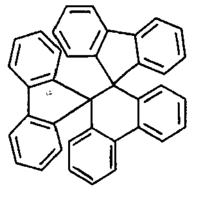
[221] W. R. Dolbier, Jr., K. Akiba, J. M. Riemann, C. A. Harmon, M. Bertrand, A. Bezaguet, M. Santelli, *J. Amer. Chem. Soc.* **93**, 3933 (1971).

4.4. Substituted Difluorenol Coupling

Treatment of **248** with glacial acetic acid, tin(II) chloride monohydrate, concentrated hydrochloric acid, 24 hours at 80–85° leads to the C—C radical coupling product **249** (15%)[279].



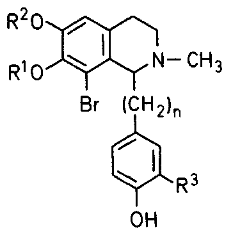
248



249

4.5. Photochemical Dehydrobrominations

The synthesis of proaporphine alkaloids by photolysis of 8-bromo-1-(4-hydroxylbenzyl)-isoquinolines (**250**, n = 1) has been reported. Irradiation of **250** ($R^1 = R^2 = CH_3$, $R^3 = H$, n = 1) for 7 hours in the presence of sodium hydroxide in an aqueous methanol solution with a Hanovia 450 W mercury lamp yields (±)-pronuciferine (**251**, $R^1 = R^2 = CH_3$, $R^3 = R^4 = H$, n = 1) in a 10% yield[280]. When the photolysis is performed in an ethanolic sodium hydroxide solution in the presence of copper powder, the yield is increased to 17%. Under the same conditions, **250** $R^1 = R^2 = CH_3$, $R^3 = OCH_3$, n = 1) yields an isomeric mixture of **251** ($R^1 = R^2 = CH_3$, $R_3 = OCH_3$, $R^4 = H$, n = 1) and **252** ($R^1 = R^2 = CH_3$, $R^3 = H$, $R^4 = OCH_3$, n = 1) in an overall yield of 10.5%[280]. Irradiation of **250** ($R^1 = R^2 = CH_3$, $R^3 = H$, n = 1) in aqueous sodium hydroxide in the presence of sodium borohydride yields the spirodienol **252**. The sodium borohydride is used to prevent further photolysis of the light sensitive dienone[281]. The irradiation of **250** ($R^1 = R^2 = CH_3$, $R^3 = OCH_3$, n = 2) yields an isomeric mixture of **251** ($R^1 = R^2 = CH_3$, $R^3 = OCH_3$, $R^4 = H$, n = 2) and **251** ($R^1 = R^2 = CH_3$, $R^3 = H$, $R^4 = OCH_3$, n = 2)[280].



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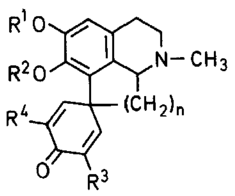
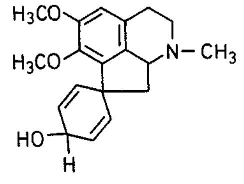


251



252

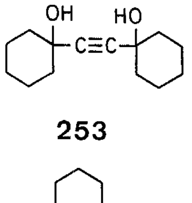
The irradiation of **250** ($R^1 = CH_3$, $R^2 = R^3 = H$, n = 1) in an aqueous sodium hydroxide solution yields **251** ($R^1 = CH_3$, $R^2 = R^3 = R^4 = H$, n = 1) (7%)[282]. If the photolysis is performed in aqueous sodium hydroxide in the presence of sodium iodide, the yield is increased to 10%.

5. Acid-Catalyzed Cyclizations

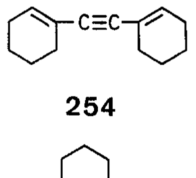
5.1. Cyclodehydrations of Alcohols

The acid-catalyzed cyclizations of alcohols possessing an appropriately positioned double bond or an aromatic ring for cyclization of a cationic center formed at the original site of the —OH group (or a rearranged cationic center) lead to formation of spiro linkages. In certain cases the ene system resulting from dehydration of the original alcohol may be formed prior to reprotonation and cyclization. Examples of acidic cyclizations starting with relatively simple alcohols are tabulated in Table 22. Cyclizations of structurally more complex alcohols to spiro systems can be found in references 279 and 292 through 307.

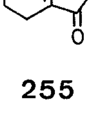
The dehydration and cyclization of **253** (treatment of **253** with 40% sulfuric acid at reflux for 2½ hours to first produce **254**) followed by refluxing with 90% formic acid leads to spiro ketones **255** (small amount) and **256** (64% overall yield)[312,313,314].



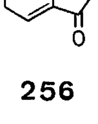
253



254



255



256

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[222] M. R. Rifi, *J. Amer. Chem. Soc.* **89**, 4442 (1967).

[223] M. R. Rifi, *J. Org. Chem.* **36**, 2017 (1971).

[224] D. E. McGreer, *Canad. J. Chem.* **38**, 1638 (1960).

[225] E. Buchta, W. Merk, *Chimia* **22**, 193 (1968).

[226] Ya. M. Slobodin, M. V. Blinova, *Zhur. Obshchei Khim.* **24**, 621 (1954); *C. A.* **49**, 5317 (1955).

[227] Ya. M. Slobodin, T. V. Tsukshverdt, *J. Org. Chem. USSR* **3**, 1928 (1967).

[228] S. W. Staley, *J. Amer. Chem. Soc.* **89**, 1532 (1967).

[229] E. Buchta, W. Merk, *Liebigs Ann. Chem.* **716**, 106 (1968).

[230] D. S. Magrill, J. Altman, D. Ginsburg, *Israel J. Chem.* **7**, 479 (1969); *C. A.* **71**, 101393 (1969).

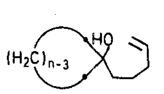
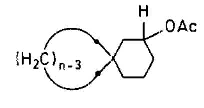
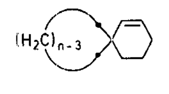
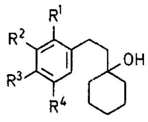
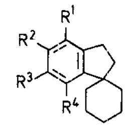
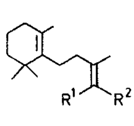
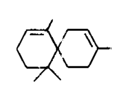
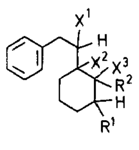
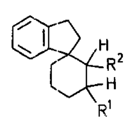
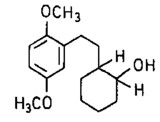
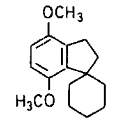
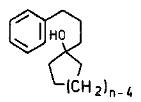
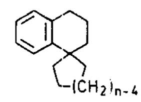
[231] J. Altman, E. Babad, J. Pucknat, N. Reshef, D. Ginsburg, *Tetrahedron* **24**, 975 (1968).

[232] A. de Meijere, *Angew. Chem.* **82**, 934 (1970); *Angew. Chem. Internat. Edit.* **9**, 899 (1970).

[233] E. Buchta, A. Kröniger, *Chimia* **23**, 225 (1969).

[234] Y. M. Slobodin, T. V. Tsukshverdt, *J. Org. Chem. USSR* **7**, 1202 (1971).

Table 22. Acid-Catalyzed Intramolecular Cyclizations of Alcohols

Starting Alcohol	Product(s)	Conditions	Yield (%)		Reference
	 **257**	HOAc/Ac$_2$O/TosOH, 24h	**257** (n = 5)	58	283
			258 (n = 5)	12	
		HOAc/Ac$_2$O/HClO$_4$, 24h	**257** (n = 5)	87	283
			258 (n = 5)	13	
	 **258**	H$_3$PO$_4$, 135°	**258** (n = 6)	74	284
		HOAc/Ac$_2$O/TosOH, 75°, 24h	**257** (n = 6)	50	283
			258 (n = 6)	10	
		HOAc/Ac$_2$O/HClO$_4$, 75°, 0.5h	**257** (n = 6)	95	283
			258 (n = 6)	5	
		90% H$_2$SO$_4$	$R^1 = R^2 = R^3 = R^4 = H$	4	285
		P$_2$O$_5$	$R^1 = R^2 = R^3 = R^4 = H$	20	286, 287
		conc. H$_2$SO$_4$, 5°	$R^1 = R^2 = R^3 = R^4 = H$	20	288
		conc. H$_2$SO$_4$, 5°	$R^1 = OCH_3$, $R^2 = R^3 = R^4 = H$	5	288
		conc. H$_2$SO$_4$, 5°	$R^2 = OCH_3$, $R^1 = R^3 = R^4 = H$	95	288
		conc. H$_2$SO$_4$, 5°	$R^3 = OCH_3$, $R^1 = R^2 = R^4 = H$	5	288
		85% H$_3$PO$_4$, 1 h; P$_2$O$_5$ added, 85–95°, 1 h	$R^1 = R^4 = OCH_3$, $R^2 = R^3 = H$	56	289
		J$_2$/C$_6$H$_6$	$R^1 = CH_2OH$, $R^2 = H$ $R^1 = H$, $R^2 = CH_2OH$	25	308
		90% H$_2$SO$_4$	$X^1 = OH$, $R^1 = R^2 = X^2 = X^3 = H$	15	285
		85% H$_2$SO$_4$	$X^2 = OH$, $R^1 = CH_3$ $R^2 = X^1 = X^3 = H$	trace	290
		SOCl$_2$/AlCl$_3$	$X^3 = OH$, $R^2 = C_2H_5$, $R^1 = X^1 = X^2 = H$	—	291
		85% H$_3$PO$_4$		—	289
		85% H$_2$SO$_4$	n = 5	30–91	309, 310, 311
		85% H$_2$SO$_4$	n = 6	93	310

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[235] Y. M. Slobodin, T. V. Tsukshverdt, *J. Org. Chem. USSR* **7**, 1205 (1971).

[236] A. P. Krapcho, E. Jahngen, Unpublished Results.

[237] E. Buchta, W. Merk, *Liebigs Ann. Chem.* **695**, 34 (1966).

[238] P. Leriverend, J. M. Conia, *Bull. Soc. Chim. France* **1966**, 116.

[239] P. Leriverend, J. M. Conia, *Bull. Soc. Chim. France* **1966**, 121.

[240] A. P. Krapcho, R. C. H. Peters, J. M. Conia, *Tetrahedron Lett.* **1968**, 4827.

[241] A. P. Krapcho, R. C. H. Peters, *Chem. Commun.* **1968**, 1615.

[242] L. Horner, E. Lingnau, *Liebigs Ann. Chem.* **591**, 21 (1955).

[243] L. Geita, G. Vanags, *Bull. Inst. Politeh. Iasi* **9**, 171 (1963); *C.A.* **61**, 14596 (1964).

[244] L. Geita, V. A. Pestunovich, G. Vanags, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.* (**1**), 106 (1968); *C.A.* **69**, 35789 (1968).

[245] I. Guareschi, *Gazz. Chim. Ital.* **48**, 83 (1918); and references cited therein.

[246] S. F. Birch, J. F. Thorpe, *J. Chem. Soc.* **121**, 1821 (1922).

[247] S. S. G. Sircar, *J. Chem. Soc.* **1927**, 1257.

[248] S. F. Birch, W. H. Gough, G. A. R. Kon, *J. Chem. Soc.* **119**, 1315 (1921).

[249] V. Squintani, *Atti. Accad. Sci. Torino* **48**, 675 (1912); *C.A.* **7**, 3496 (1913).

[250] G. S. Saharia, B. R. Sharma, *Acta Phys. Chem.* **14**, 109 (1969); *C.A.* **71**, 60817 (1969).

[251] E. W. Lanfear, J. F. Thorpe, *J. Chem. Soc.* **123**, 1683 (1923).

[252] R. N. McDonald, R. R. Reitz, *Chem. Commun.* **1971**, 90.

[253] C. K. Ingold, J. F. Thorpe, *J. Chem. Soc.* **115**, 320 (1919).

[254] C. K. Ingold, E. W. Lanfear, J. F. Thorpe, *J. Chem. Soc.* **123**, 3140 (1923).

[255] A. I. Scott, *Quart. Rev.* **19**, 1 (1965); for a review.

[256] E. A. Chandross, R. Kreilick, *J. Amer. Chem. Soc.* **85**, 2530 (1963).

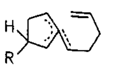
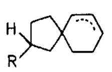
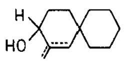
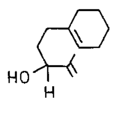
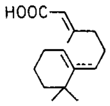
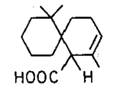
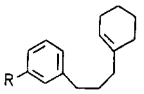
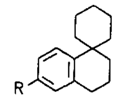
[257] H. D. Becker, *J. Org. Chem.* **32**, 2115 (1967).

[258] M. N. Afzal, A. D. Allbutt, A. Jordaan, G. W. Kirby, *Chem. Commun.* **1969**, 996.

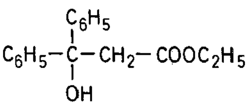
[259] T. Kametani, H. Yagi, *Chem. Commun.* **1967**, 366.
T. Kametani, H. Yagi, *J. Chem. Soc.* (C) **1967**, 2182.

[260] A. R. Battersby, T. H. Brown, *Proc. Chem. Soc.* **1964**, 85.
A. R. Battersby, T. H. Brown, J. H. Clements, *J. Chem. Soc.* **1965**, 4550.

Table 23. Acid-Catalyzed Cyclizations of Unsaturated Substrates

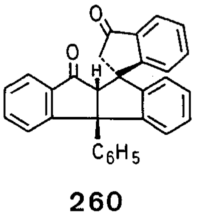
Starting material	Product	Conditions	Yield (%)	Reference
		84% H_2SO_4, 5–10° then 120°	R = H: 50 R = CH_3: 50	316 316
		$BF_3 \cdot (C_2H_5)_2O/C_6H_6$	30–40	317
		$HCOOH/H_2SO_4$, 50–60°, 6 h	30	318
		$AlCl_3/CS_2$, 0°, 7 h	R = H: 75 R = OCH_3: —	319 287

Dienyne **254** can be cyclized by reaction with 85% formic acid (65%) or with concentrated sulfuric acid/acetic acid (50–60%). Treatment of **259** with concentrated sulfuric acid (24 hours, room temperature) leads to the isomeric ketones **260** and **261** (total yield, 77%) which can be separated by crystallization and column chromatography[315]. The mechanism of formation of these products is discussed.



$$C_6H_5-\overset{C_6H_5}{\underset{OH}{C}}-CH_2-COOC_2H_5$$

259



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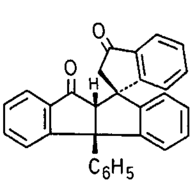


261

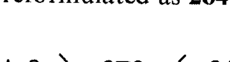
5.2. Unsaturated Substrate Cyclizations

The acid catalyzed cyclization of ene-ene or ene-aromatic systems is applicable to the syntheses of spiro linkages. Some of the simpler examples of this type of cyclization are tabulated in Table 23. Additional examples can be found in references 293, 307, 319 through 323.

5.3. Intramolecular Acid-Catalyzed Cyclizations Followed by Intramolecular Cyclizations

5.3.1. Acetylenic Diol or Diacetate Condensations with Aromatic Compounds

In the original study of the condensations of acetylenic diols or diacetates with aromatic substrates such as benzene or toluene, Lagidze and co-workers[324] reported that the reaction of diacetate **262** with benzene in the presence of aluminium trichloride yielded **263**. This product was subsequently reformulated as **264**[325,326].



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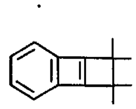

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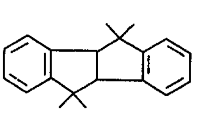

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[261] A. H. Jackson, J. A. Martin, *Chem. Commun.* **1965**, 142.
A. H. Jackson, J. A. Martin, *J. Chem. Soc.* (C) **1966**, 2222.

[262] M. Shamma, W. A. Slusarchyk, *Chem. Commun.* **1965**, 528.

[263] T. Kametani, I. Noguchi, *Chem. Pharm. Bull. Japan* **16**, 2451 (1968).

[264] M. A. Schwartz, R. A. Holton, S. W. Scott, *J. Amer. Chem. Soc.* **91**, 2800 (1969).

[265] T. Kametani, F. Satoh, H. Yagi, K. Fukumoto, *J. Org. Chem.* **33**, 690 (1968).
T. Kametani, H. Yagi, F. Satoh, K. Fukumoto, *J. Chem. Soc.* (C) **1968**, 271.
T. Kametani, K. Fukumoto, H. Yagi, F. Satoh, *Chem. Commun.* **1967**, 878.

[266] A. R. Battersby, E. McDonald, M. H. G. Munro, R. Ramage, *Chem. Commun.* **1967**, 934.

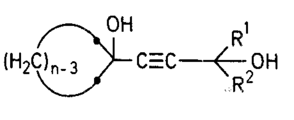
[267] A. R. Battersby, R. B. Bradbury, R. B. Herbert, M. H. G. Munro, R. Ramage, *Chem. Commun.* **1967**, 450.

[268] T. Kametani, F. Satoh, *Chem. Pharm. Bull. Japan* **17**, 814 (1969).

[269] T. Kametani, T. Satoh, H. Yagi, H. Iida, S. Tanaka, *Chem. Commun.* **1968**, 224.

[270] O. H. Mattsson, C. A. Wachtmeister, *Tetrahedron Lett.* **1967**, 1855.
O. H. Mattsson, C. A. Wachtmeister, *Acta Chem. Scand.* **22**, 79 (1968).

By commencing with cyclic acetylenic diols, spiro aromatics of type **264** can be obtained. The condensation of **265** (n = 5, $R^1 = R^2 = CH_3$) with toluene in the presence of aluminium trichloride leads to **266** ($R^1 = R^2 = CH_3$)[327]. Similarly, treatment of **265** (n = 5, $R^1 = H$, $R^2 = n\text{-}C_3H_7$) with toluene leads to **266** ($R^1 = H$, $R^2 = n\text{-}C_3H_7$)[328,329].



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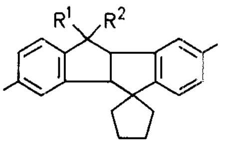

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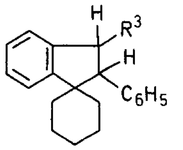
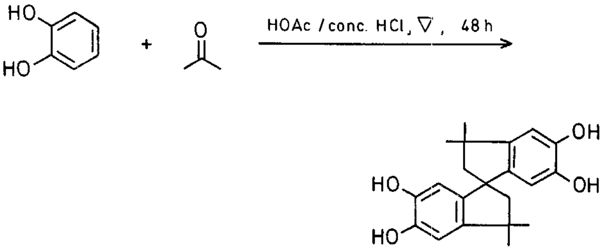


267

A different course of reaction occurs when one alcohol is secondary. Treatment of benzene with **265** (n = 6, $R^1 = H$, $R^2 = CH_3$) or **265** (n = 6, $R^1 = H$, $R^2 = n\text{-}C_3H_7$) with aluminium trichloride (the corresponding diacetates may also be used) leads to **267** ($R^3 = C_2H_5$) and **267** $R^3 = n\text{-}C_4H_9$)[327].

5.3.2. 1,1'-Spiroindane Systems

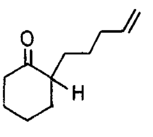
Certain phenols susceptible to electrophilic substitution at a position *para* to a hydroxyl group undergo interesting transformations on acid catalyzed condensation with acetone (and several other ketones) to yield 1,1'-spiroindane systems. After original structural formulations were shown to be erroneous, the spiro structures seem reasonably sound. The following reaction is illustrative[330]. For additional examples of other related reactions and cyclizations pertinent to the mechanism of formation of these spiroindanes the reader is referred to references 322, and 331 through 351.



6. Thermal Cyclizations

6.1. Conia Cyclizations

The thermal cyclization of cyclic ketones carrying a 1-butenyl residue is a useful preparative method to spiranone systems[352]. The thermolysis of **268** at 350° (1 hour) leads quantitatively to **269**[352,253].



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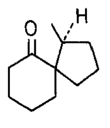
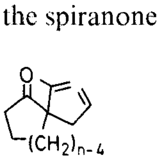


269

Compounds of type **270** also undergo thermal cyclizations. On thermolysis of **270** the Cope rearrangement products **271** are transitorily formed, and these latter products (300°) readily cyclize to the spiranones **272**[354].



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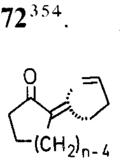

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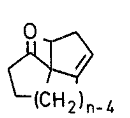

272

In all cases the cyclization leads to the formation of a five-membered ring. Examples of the applicability of these thermal cyclizations are tabulated in Table 24.

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[271] O. H. Mattsson, G. Sundstrom, C. A. Wachtmeister, *Acta Chem. Scand.* **24**, 2219 (1970).
O. H. Mattsson, G. Sundstrom, *Acta Chem. Scand.* **24**, 1454 (1970).

[272] O. H. Mattsson, G. Sundstrom, C. A. Wachtmeister, *Acta Chem. Scand.* **25**, 206 (1971).

[273] D. Radulescu, V. Georgescu, *Bull. Soc. Chim. France* **37**, 187 (1925).

[274] G. V. Kondrat'eva, G. A. Kogan, S. I. Zav'yalov, *Bull. Acad. Sci. USSR* **1962**, 1353.

[275] O. H. Mattsson, *Acta Chem. Scand.* **22**, 2479 (1968).

[276] O. H. Mattson, B. Sjoquist, C. A. Wachtmeister, *Acta Chem. Scand.* **24**, 3326 (1970).

[277] D. L. Struble, A. L. J. Beckwith, G. E. Gream, *Tetrahedron Lett.* **1968**, 3701.

[278] D. L. Struble, A. L. J. Beckwith, G. E. Gream, *Tetrahedron Lett.* **1970**, 4795.

[279] G. Wittig, W. Schoch, *Liebigs Ann. Chem.* **749**, 38 (1971).

[280] T. Kametani, T. Sugahara, H. Sugi, S. Shibuya, K. Fukumoto, *Tetrahedron* **27**, 5993 (1971).
T. Kametani, T. Sugahara, H. Sugi, S. Shibuya, K. Fukumoto, *Chem. Commun.* **1971**, 724.
T. Kametani, K. Fukumoto, *Accts. Chem. Res.* **5**, 212 (1972).

[281] Z. Horii, Y. Nakashita, C. Iwata, *Tetrahedron Lett.* **1971**, 1167.

[282] T. Kametani, H. Sugi, S. Shibuya, K. Fukumoto, *Chem. & Ind.* **1971**, 818.

[283] M. Nojima, T. Nagai, N. Tokura, *J. Org. Chem.* **33**, 1970 (1968).

[284] N. D. Zelinskii, N. V. Elagina, *Doklady Akad. Nauk. SSSR* **87**, 755 (1952); *C.A.* **48**, 542 (1954).

[285] D. Perlman, D. Davidson, M. T. Bogert, *J. Org. Chem.* **1**, 288 (1936).

[286] J. Van de Kamp, E. Mosettig, *J. Amer. Chem. Soc.* **58**, 1062 (1936).

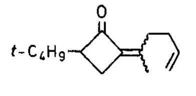
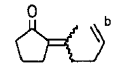
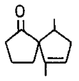
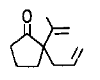
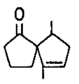
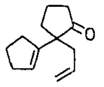
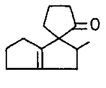
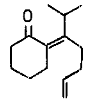
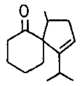
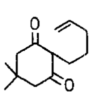
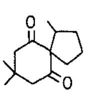
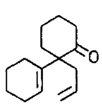
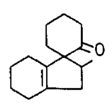
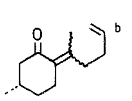
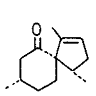
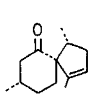
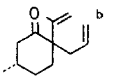
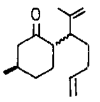
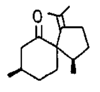
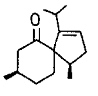
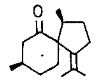
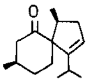
[287] J. W. Cook, C. L. Hewett, A. M. Robinson, *J. Chem. Soc.* **1939**, 168.

[288] H. Christol, A. Gaven, Y. Pietrasanta, J. L. Vernet, *Bull. Soc. Chim. France* **1971**, 4510.

[289] R. A. Barnes, *J. Amer. Chem. Soc.* **75**, 3004 (1953).

[290] D. Perlman, M. T. Bogert, *J. Amer. Chem. Soc.* **59**, 2534 (1937).

Table 24. Thermal Cyclizations to Spiro Ketones

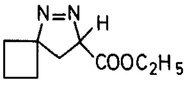
Reactant[a]	Product	Yield (%)	Reference
		—	354[c]
 [b]		40	354
		40	354
		40	354
		—	355
		100	356
		100	354
 [b]	 	100	354
 [b]	as above	100	354
	   	—[d]	355

[a] Heated in a sealed tube at 250–300° for periods of 20–120 min.
[b] Isomeric mixture.
[c] Degradation.
[d] Separation via thin-layer chromatography followed by G. L. C.

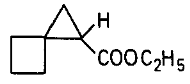
6.2. Thermal and Photochemical Decompositions of Spiro Pyrazoline Adducts

In certain cases in the addition of diazo compounds to unsaturated substrates the pyrazoline adducts can be isolated. Thermal or photochemical decomposition of these adducts leads to loss of nitrogen and formation of a carbon-carbon bond to produce a spiro linkage.

The reaction of lithium ethoxide in ethereal solutions with *N*-cyclobutyl-*N*-nitrosourea at −40° leads to solution of diazocyclobutane. Addition of ethyl acrylate yields the pyrazoline **273**, which on thermolysis yields about 30% (V.P.C.) of **274**[357].

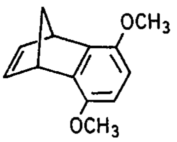


273



274

The thermal decomposition of diazofluorene in the presence of **275** in benzene leads to an 85% yield of the 1-pyrazoline **276**. The decomposition of **276** at 190° in *trans*-decalin leads to a 50% yield of **277**[358]. Other related reactions have been reported[359–367].



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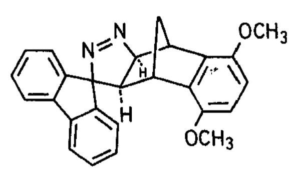

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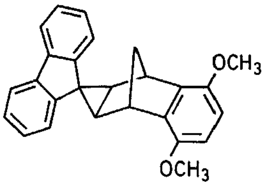

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[291] J. D. Fulton, R. Robinson, *J. Chem. Soc.* **1933**, 1463.

[292] R. A. Barnes, L. Gordon, *J. Amer. Chem. Soc.* **71**, 2644 (1949).

[293] J. C. Cook, C. L. Jewett, W. V. Mayneord, E. Roe, *J. Chem. Soc.* **1934**, 1727.

[294] R. G. Clarkson, M. Gomberg, *J. Amer. Chem. Soc.* **52**, 2881 (1930).

[295] J. H. Weisburger, E. K. Weisburger, F. E. Ray, *J. Amer. Chem. Soc.* **72**, 4253 (1950).

[296] G. Haas, V. Prelog, *Helv. Chim. Acta* **52**, 1202 (1969).

[297] E. V. Svedres, G. L. Jenkins, *J. Amer. Pharm. Assoc.* **41**, 68 (1950).

[298] J. H. Weisburger, E. K. Weisburger, F. E. Ray, *J. Amer. Chem. Soc.* **72**, 4250 (1950).

[299] P. M. G. Bavin, *Canad. J. Chem.* **38**, 1148 (1960).
P. M. G. Bavin, M. J. S. Dewar, *J. Chem. Soc.* **1955**, 4479.

[300] F. Bergmann, H. E. Eschinazi, *J. Amer. Chem. Soc.* **66**, 183 (1944).
F. Bergmann, S. Israelashwili, *J. Amer. Chem. Soc.* **68**, 1 (1946).

[301] R. N. Jones, *J. Amer. Chem. Soc.* **66**, 185 (1944).

[302] D. H. Hey, J. A. Leonard, C. W. Rees, *J. Chem. Soc.* **1963**, 3125.

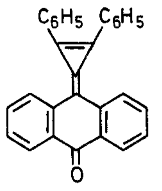
[303] G. W. Kenner, M. J. T. Robinson, C. M. B. Tylor, B. R. Webster, *J. Chem. Soc.* **1962**, 1756.

[304] H. Wynberg, G. J. Heeres, P. Jordens, H. J. M. Sinnige, *Rec. Trav. Chim. Pays-Bas* **89**, 545 (1970).

[305] E. Bergmann, H. Hoffmann, H. Meyer, *J. Prakt. Chem.* (2) **135**, 253 (1932).

[306] C. F. Koelsch, *J. Amer. Chem. Soc.* **55**, 3394 (1933); reformulation of the product in reference 298.

The methylenecyclopropene **278** with diazoethane/tetrahydrofuran at −15° yields 59% of **279** (R = H) and 16% of **280** (R = H)[368].



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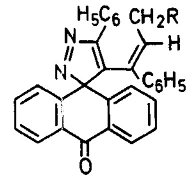

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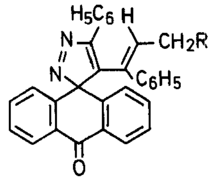
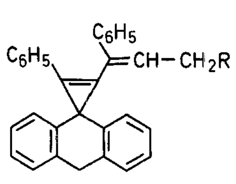


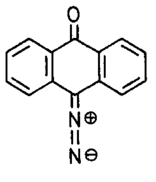
280

A similar reaction of **278** with diazopropane leads to **279** (R = CH_3) in 68% and **280** (R = CH_3) in 13% yields. The thermal decomposition (200°) of **279** (R = H) or **280** (R = H) yields **281** (R = H), 68% yield in the case of **279** (R = H). The thermal decomposition (205°) of **279** (R = CH_3) or **280** (R = CH_3) leads to **281** (R = CH_3), 64% in the case of **279** (R = CH_3). The mechanistic rationalizations for these interesting additions are discussed.

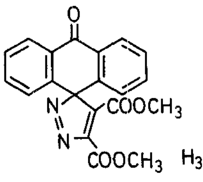


281

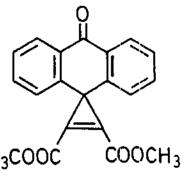
The reaction of **282** with dimethyl acetylenedicarboxylate in benzene at 20–30° yields **283**. Photolysis of **283** leads to the unstable cyclopropene **284** (47%)[369].



282

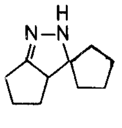


283



284

The reaction of α,β-unsaturated carbonyl compounds with hydrazine leads to pyrazoline derivatives. These pyrazolines on heating with hot alkali can be converted into spirocyclopropane derivatives. Reaction of 2-cyclopentylidenecyclopentanone with hydrazine followed by distillation of the pyrazoline **285** in the presence of potassium hydroxide and platinum leads to **286** (29%)[370]. Distillation of **285** over calcium oxide/sodium hydroxide yields **286** (76%)[371]. Treatment of 2,5-dicyclopentylidenecyclopentanone with hydrazine followed by distillation over calcium oxide/sodium hydroxide yields **287** (51%)[371].



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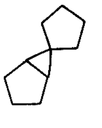

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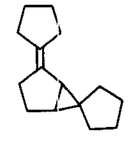
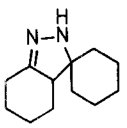
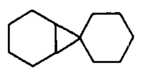


287

The reaction of 2-cyclohexylidenecyclohexanone with hydrazine has been reported to yield the pyrazoline **288** in a quantitative yield[372]. Thermal decomposition of **288** with potassium hydroxide and platinized clay plates at 250° leads to **289** (50%)[372].



288



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[307] C. F. Koelsch, R. V. White, *J. Org. Chem.* **6**, 602 (1941).

[308] T. Kato, S. Kanno, Y. Kitahara, *Tetrahedron* **26**, 4287 (1970). S. Kanno, T. Kato, Y. Kitahara, *Chem. Commun.* **1967**, 1257.

[309] H. Adkins, J. W. Davis, *J. Amer. Chem. Soc.* **71**, 2955 (1949).

[310] D. Perlman, D. Davidson, M. T. Bogert, *J. Org. Chem.* **1**, 300 (1936).

[311] M. Levitz, M. T. Bogert, *J. Amer. Chem. Soc.* **64**, 1719 (1942).

[312] L. H. Schwartzman, *J. Org. Chem.* **15**, 517 (1950); revision of structures proposed in references 313 and 314. R. B. Woodward, *J. Amer. Chem. Soc.* **64**, 76 (1942).

[313] P. S. Pinkney, G. A. Nesty, R. H. Wiley, C. S. Marvel, *J. Amer. Chem. Soc.* **58**, 972 (1936).

[314] R. P. Linstead, A. L. Walpole, *J. Chem. Soc.* **1939**, 842, 850.

[315] S. Wawzonek, N. A. Randen, *J. Org. Chem.* **36**, 1116 (1971).

[316] C. S. Marvell, L. A. Brooks, *J. Amer. Chem. Soc.* **63**, 2630 (1941).

[317] A. Mondon, *Liebigs Ann. Chim.* **585**, 43 (1954).

[318] Cl. Daesslé, H. Schinz, *Helv. Chim. Acta* **39**, 2118 (1956).

[319] J. W. Cook, C. L. Hewett, *J. Chem. Soc.* **1933**, 1098. J. W. Cook, C. L. Hewett, *J. Chem. Soc.* **1934**, 365. F. A. Askew, *J. Chem. Soc.* **1935**, 512.

[320] W. E. Bachmann, M. C. Kloetzel, *J. Amer. Chem. Soc.* **59**, 2207 (1937).

[321] R. H. Martin, S. Vassart, *Bull. Soc. Chim. Belges* **61**, 234 (1952); *C.A.* **47**, 11176 (1953).

[322] W. Baker, H. L. Williams, *J. Chem. Soc.* **1959**, 1295.

[323] W. V. Curran, *J. Chem. Soc.* (D) **1971**, 478.

[324] R. M. Lagidze, N. R. Loladze, *Soobshch. Akad. Nauk. Gruz., SSR* **16**, 607 (1955); *C.A.* **50**, 11960 (1956).

[325] J. E. H. Hancock, D. R. Scheuchenpflug, *J. Amer. Chem. Soc.* **80**, 3621 (1958); and references cited therein.

[326] R. M. Lagidze, L. P. Chigogidze, N. K. Iremadze, D. G. Chavchanidze, *Soobshch. Akad. Nauk. Gruz., SSR*, **57**, 69 (1970); *C.A.* **73**, 55862 (1970).

[327] R. M. Lagidze, G. G. Samsonia, *Tr. Inst. Khim. Akad. Nauk. Gruz., SSR* **17**, 181 (1964); *C.A.* **63**, 11384 (1965).

[328] R. M. Lagidze, N. K. Iremadze, L. P. Chigogidze, Sh. D. Kuprava, *Khim. Atsetilena* **1968**, 232; *C.A.* **70**, 106238 (1969).

[329] R. M. Lagidze, N. K. Iremadze, L. P. Chigogidze, Sh. D. Kuprava, G. G. Samsoniya, *J. Org. Chem. USSR* **1**, 2003 (1965).

[330] W. Baker, *J. Chem. Soc.* **1934**, 1678; references to earlier structural formulations can be found here.

[331] W. Baker, D. M. Besly, *J. Chem. Soc.* **1939**, 1421; isolated as diacetate then saponified to the phenol.
S. Hagishita, K. Kuriyama, M. Hayashi, Y. Nakano, K. Shingu, M. Nakagawa, *Bull. Soc. Chem. Japan* **44**, 496 (1971).

[332] I. M. Bilik, A. M. Serebryanyi, R. L. Globus, V. G. Brudz, *J. Gen. Chem. USSR* **33**, 478 (1963).

[333] F. Mattu, P. Pirisi, L. Sancio, B. Follesa, M. R. Manca-mura, R. Perra, *Rend. Seminario Fac. Sci. Univ. Cagliari* **35**, 155 (1965); *C.A.* **65**, 15321 (1966).

[334] R. H. Burgess, J. C. McGowan, V. Griffiths, *Brit. Patent* 951932; *C.A.* **61**, 9639 (1964).

[335] C. H. Fisher, R. W. Furlong, M. Grant, *J. Amer. Chem. Soc.* **58**, 820 (1936).

[336] L. Schuler, *U.S. Patent* 3126380 (Knoll A.-G. Chemische Fabriken); *C.A.* **61**, 3045 (1964).

[337] R. F. Curtis, *J. Chem. Soc.* **1962**, 415.

[338] W. Baker, J. C. McGowan, *J. Chem. Soc.* **1938**, 347.

[339] A. Müller, A. Strassen, H. Haeussler, W. D. Arndt, *Ger. Patent (DBP)* 1092648; *C.A.* **55**, 24114 (1961); no yield listed.

[340] L. Taimr, H. Pivcova, J. Pospisil, *Tetrahedron Lett.* **1968**, 3707.

[341] W. Baker, D. M. Besly, *J. Chem. Soc.* **1939**, 195.

[342] H. Haeussler, W. D. Arndt, *Ger. Patent (DBP)* 1084260; *C.A.* **55**, 18687 (1961).

[343] L. Taimr, J. Pospisil, *Chem. & Ind.* **1969**, 456.

[344] S. V. Zavgorodnii, A. V. Strashnenko, *J. Org. Chem. USSR* **1**, 103 (1965).

[345] L. R. C. Barclay, R. A. Chapman. *Canad. J. Chem.* **42**, 25 (1964).

[346] I. Kawasaki, K. Matsuda, T. Kaneko, *Bull. Chem. Soc. Japan* **44**, 1986 (1971).

[347] R. F. Curtis, *Chem. & Ind.* **1960**, 928.

[348] R. F. Curtis, K. O. Lewis, *J. Chem. Soc.* **1962**, 418.

[349] A. Hoffmann, *J. Amer. Chem. Soc.* **51**, 2542 (1929).

[350] R. A. Barnes, B. D. Beitchman, *J. Amer. Chem. Soc.* **76**, 5430 (1954).

[351] L. M. Adams, R. J. Lee, F. T. Wadsworth, *J. Org. Chem.* **24**, 1186 (1959).

[352] F. Rouessac, P. Beslin, J. M. Conia, *Tetrahedron Lett.* **1965**, 3319.

[353] J. M. Conia, F. Leyendecker, *Bull. Soc. Chim. France* **1967**, 830; and references cited therein.

[354] J. M. Conia, P. Le Perchec, *Tetrahedron Lett.* **1965**, 3305.
J. M. Conia, P. Le Perchec, *Bull. Soc. Chim. France* **1966**, 278, 281, 287.

[355] J. M. Conia, J. P. Drouet, J. Gore, *Tetrahedron* **27**, 2481 (1971).

[356] F. Leyendecker, G. Mandville, J. M. Conia, *Bull. Soc. Chim. France* **1970**, 549.

[357] D. E. Applequist, D. E. McGreer, *J. Amer. Chem. Soc.* **82**, 1965 (1960).

[358] J. R. De Member, N. Filipescu, *J. Amer. Chem. Soc.* **90**, 6425 (1968).

[359] N. Filipescu, J. R. De Member, *Tetrahedron* **24**, 5181 (1968).

[360] N. Filipescu, J. R. De Member, F. L. Minn, *J. Amer. Chem. Soc.* **91**, 4169 (1969).

[361] N. Filipescu, J. R. Bunting, *J. Chem. Soc.* (B) **1970**, 1498.

[362] H. Dürr, R. Sergio, W. Gombler, *Angew. Chem.* **84**, 215 (1972); *Angew. Chem. Internat. Edit.* **11**, 224 (1972).

[363] J. van Alphen, *Rec. Trav. Chim.* **62**, 491 (1943).

[364] G. Ege, *Tetrahedron Lett.* **1963**, 1667.

[365] H. Reimlinger, *Chem. Ber.* **100**, 3097 (1967).

[366] D. S. C. Chang, N. Filipescu, *J. Amer. Chem. Soc.* **94**, 4170 (1972).

[367] G. Baum, R. Bernard, H. Shechter, *J. Amer. Chem. Soc.* **89**, 5307 (1967).

[368] T. Eicher, E. von Angerer, *Chem. Ber.* **103**, 339 (1970).

[369] J. C. Fleming, H. Shechter, *J. Org. Chem.* **34**, 3962 (1969).

[370] N. D. Zelinski, N. I. Shuikin, *J. Russ. Phys. Chem. Soc.* **62**, 1343 (1930); *C. A.* **25**, 2420 (1931).
S. D. Koch, *U.S. Patent* 3113419; *C.A.* **60**, 9084 (1964).

[371] I. E. Dolgii, A. P. Meshcheryakov, I. B. Shvedova, *Izv. Akad. Nauk. SSSR, Ser. Khim.* **9**, 2135 (1968); *C.A.* **70**, 77429 (1969).

[372] G. Laber, *Liebigs Ann. Chem.* **588**, 79 (1954).