REVIEWS

1,3-Oxazines and 1,3-Thiazines, Intermediates of Interest in Organic Syntheses

Richard R. SCHMIDT

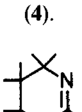
Institut für Organische Chemie, Biochemie und Isotopenforschung der Universität Stuttgart,
D-7 Stuttgart, Azenbergstraße 14/16

Recent methods using derivatives of 1,3-oxazine and 1,3-thiazine as intermediates in organic syntheses are reviewed, attention chiefly being paid to publications which have appeared since earlier compilations[1,2] and up to and including 1970. This review includes syntheses and reactions of

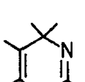
1. 5,6-Dihydro-4*H*-1,3-oxazines (**1**)
2. 4*H*-1,3-Oxazines (**2**)
3. $1^{\oplus}$-1,3-Oxazinium Salts (**3**) and $1^{\oplus}$-1,3-Thiazinium Salts (**4**).

Neuere Methoden der Verwendung von Derivaten des 1,3-Oxazins und des 1,3-Thiazins als Zwischenprodukte für weiterführende organische Synthesen werden in einer Übersicht zusammengestellt. Dabei sollen vor allem die Arbeiten Berücksichtigung finden, die seit früheren Zusammenfassungen über diese Verbindungsklassen[1,2] bis einschließlich 1970 erschienen sind. Das Thema umfaßt Synthesen und Reaktionen von

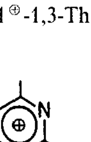
1. 5,6-Dihydro-4*H*-1,3-Oxazinen (**1**)
2. 4*H*-1,3-Oxazinen (**2**)
3. $1^{\oplus}$-1,3-Oxazinium-Salzen (**3**) und $1^{\oplus}$-1,3-Thiazinium-Salzen (**4**).



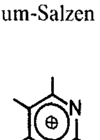
1



2



3



4

1. 5,6-Dihydro-4*H*-1,3-oxazines; Synthesis and Reactions

1.1. Synthesis

5,6-Dihydro-4*H*-1,3-oxazines (**1**) were first prepared by Gabriel[3,4,5] from 3-halopropylamines and carboxylic acid chlorides or from 3-aminopropanols with activated carboxylic acids[6]. The methods designated as a and b in Fig. 1 serve as linkage schemes for the synthesis of these cyclic ester imides.

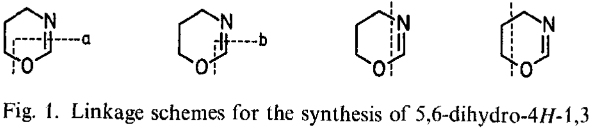
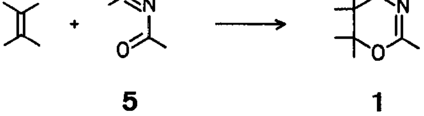


Fig. 1. Linkage schemes for the synthesis of 5,6-dihydro-4*H*-1,3-oxazines (**1**)

In recent years, cycloaddition reactions have chiefly been utilized for the synthesis of **1**. Thus, Ritter et al.[7], Lynn[8], and Meyers[9] were able by reaction of propane-1,3-diols with nitriles in strong mineral acid to obtain alkyl- and aryl-substituted compounds. This synthesis follows linkage scheme c (Fig. 1). The course of the reaction corresponds to that of a polar cycloaddition reaction[10,11,41]. From the propane-1,3-diol with the acid there results as an intermediate the most stable carbonium ion. In a two-stage reaction, this strongly electrophilic polar 1,4-system then reacts with the nitrile to give the acid adduct of **1**, from which **1** can be liberated with base.

From linkage scheme d (Fig. 1) it is obvious that **1** should also be accessible by reactions analogous to Diels-Alder additions, that is by reaction of N-acylimines (**5**) with olefins.



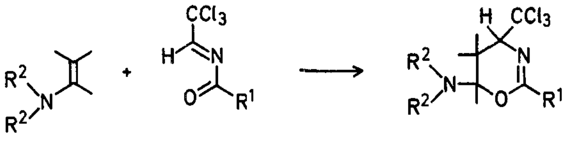
5 **1**

---

[1] Z. Eckstein, T. Urbanski, Advan. Heterocyclic Chem. **4**, 311 (1963).

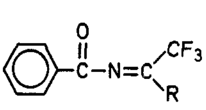
[2] R. C. Elderfield, E. E. Harris, *Thiazines and Benzothiazines*, in R. C. Elderfield, *Heterocyclic Compounds*, Vol. 6, John Wiley & Sons, New York, 1957, p. 601.

In fact, it has been possible to verify this hypothesis. The instability of the N-acylimines (5)[12] is caused by a strong polarization of the electrons; therefore so far only those representatives of the class of compounds have been isolated which are substituted on the methylene carbon atom by correspondingly electronegative atoms or atom-groups to act as a counterbalance[13,43]. The electrophilic nature of these N-acylimines (5) then makes possible a reaction with the most reactive olefins. Thus, cycloaddition of **5a** is possible with enamines carrying the most varied of substituents to give **1a**[14].



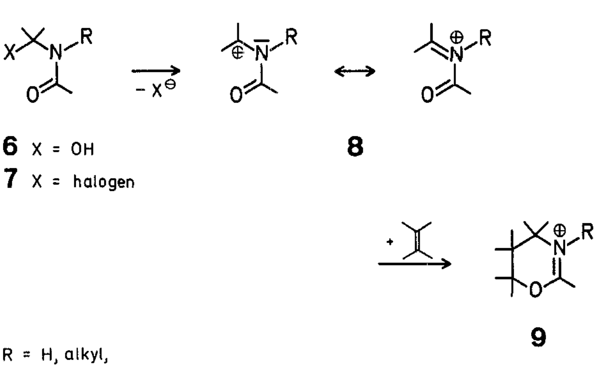
5a **1a**

Examples have been published of cycloadditions of even more electron-poor N-acylimines **5b**, **c** to the less reactive enol ethers and the olefin isobutylene[15].



5b R = $-CF_3$
c R = $-CF_2-NO_2$

It may be recognized from these findings that cycloaddition to the usual olefins could succeed if the *electrophilic nature of the N-acylimine (5) were further enhanced*. The chief candidates are N-protonated or also N-alkylated derivatives (**8**, R = H or alkyl) of the N-acylimines, which can be formed *in situ* from N-(1-hydroxyalkyl)-carboxamides (**6**) or N-(1-haloalkyl)-carboxamides (**7**)[14,16,17]. The polar 1,4-systems **8** thus formed should then yield the 5,6-dihydro-4*H*-1,3-oxazine salts **9** with olefins.



6 X = OH
7 X = halogen
8
9

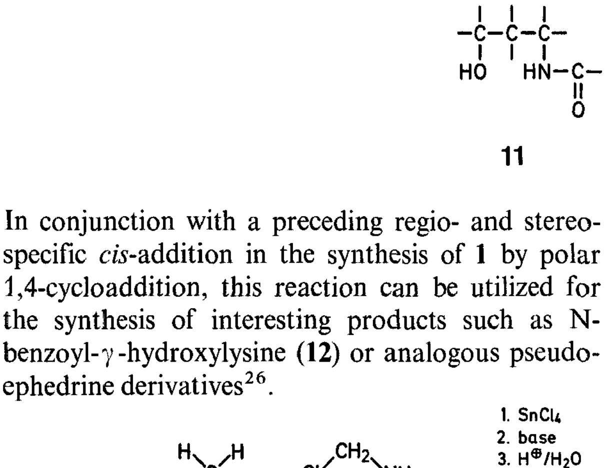
The investigations of Schmidt[17–20], Seeliger et al.[21,22], and others[14,23,24] confirmed this concept. Despite the highly electrophilic nature of the polar 1,4-system **8**, it was possible to show that the course of the reaction is probably that of a synchronous $[\pi^2s+\pi^4s]$-cycloaddition[19,20]. The wide scope for varying the reaction yields a convenient route to variously substituted 5,6-dihydro-4*H*-1,3-oxazines **1**. General methods for preparing **1** by this route have been published only recently[14,20].

A further simplification of the method is possible when the reaction is carried out as a three-component reaction starting from the carboxylic acid amide, formaldehyde (or a formaldehyde derivative), and an olefin[20,25].

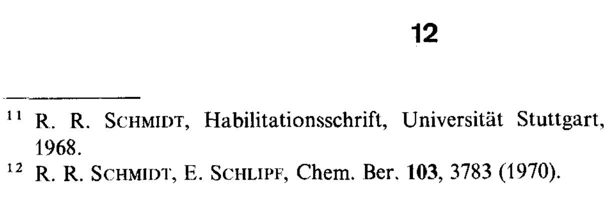
1.2 Reactions

1.2.1. Hydrolysis

The long-known acidic hydrolysis[5] of the 5,6-dihydro-4*H*-1,3-oxazines **1** leads firstly to the salts of the 3-aminopropyl ester **10**. After liberation of the corresponding bases, rearrangement to the thermodynamically more stable 3-hydroxypropylamides **11** takes place.



In conjunction with a preceding regio- and stereospecific *cis*-addition in the synthesis of **1** by polar 1,4-cycloaddition, this reaction can be utilized for the synthesis of interesting products such as N-benzoyl-γ-hydroxylysine (**12**) or analogous pseudoephedrine derivatives[26].

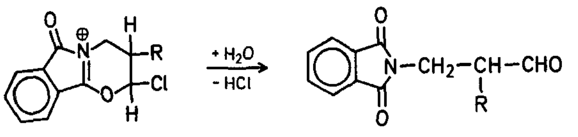


12

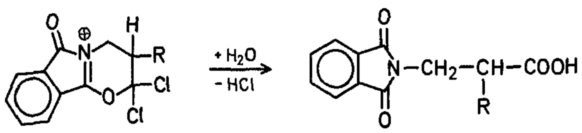
---

[3] S. Gabriel, P. Elfeldt, Chem. Ber. **24**, 3213 (1891).
[4] S. Gabriel, H. Ohle, Chem. Ber. **50**, 819 (1917).
[5] S. Gabriel, Liebigs Ann. Chem. **409**, 305 (1915).
[6] For variations of this method, see Z. Eckstein, T. Urbanski, Advan. Heterocyclic Chem. **4**, 311 (1963).
[7] E. J. Tillmanns, J. J. Ritter, J. Org. Chem. **22**, 839 (1957).
[8] J. W. Lynn, J. Org. Chem. **24**, 711 (1959).
[9] A. I. Meyers, J. Org. Chem. **25**, 145, 1147 (1960).
[10] R. R. Schmidt, Tetrahedron Lett. **1968**, 3443.
[11] R. R. Schmidt, Habilitationsschrift, Universität Stuttgart, 1968.
[12] R. R. Schmidt, E. Schlipf, Chem. Ber. **103**, 3783 (1970).

Similarly, the addition of N-chloromethylphthalimide or N-hydroxymethylphthalimide to vinyl chloride and *cis*- and *trans*-1,2-dichloroethylene to give **13** and the corresponding addition to 1,1-dichloroethylene, trichloroethylene, and 1-bromo-2,2-dichloroethylene and derivatives to give **15** and their hydrolysis were employed by Bott[23,24,27] for the synthesis of N-phthaloyl-β-aminoaldehydes **14** and N-phthaloyl-β-aminocarboxylic acids **16** (examples, see Table 1).



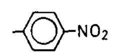
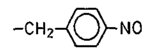
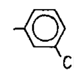
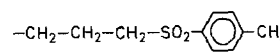
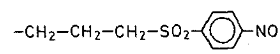
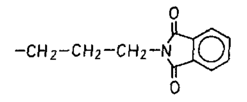
13 **14**



15 **16**

2-(4-Nitrobenzyl)-3-phthalimidopropanoic Acid[24] (16b):
A solution, cooled to +5°, of N-hydroxymethylphthalimide (3.00 g) in 95% sulfuric acid (35 ml) is treated with 1,1-dichloro-3-(4-nitrophenyl)-propene (2.00 g) and stirred for 2 hr at 5-10°. The crude product obtained after hydrolysis with ice is stirred for 1-2 hr in water (300 ml) at 60°, isolated by filtration, and dried in vacuo at 80°; yield: 2.88 g (94%); m.p. 213-214° (from propanoic acid/water 1:1).

Table 1. Derivatives of 3-Phthalimidopropanal and Phthalimidopropanoic Acid[23,24,a]

Compound	R	Yield %	m.p.
14a	H	83	[b]
14b	Cl	51	101-103°
16a		90	216-217°
16b		94	213-214°
16c		92	111-112°
16d		94	135-136°
16e		95	196-196.5°
16f		93	114-115°[c]
16g	Br	91	172-173°

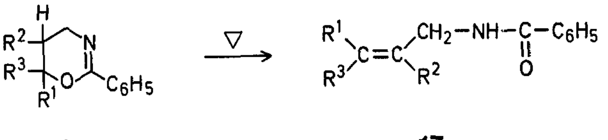
[a] N-Hydroxymethyl-maleimide, N-hydroxymethyl-tetrachlorophthalimide, and N-hydroxymethyl-trichloroacetamide were reacted analogously[24].

[b] Isolated as the semicarbazone.

[c] The crystals contain 0.5 mol propanoic acid per mol **16f**.

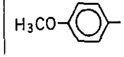
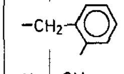
1.2.2. Thermolysis

Thermolysis of the 5,6-dihydro-4*H*-1,3-oxazines (**1**) gives, with fragmentation of the (C-6)—O and a (C-5—H) bond, quantitative yields of the amidomethylation products **17** of the olefins employed in the synthesis of **1** in accordance with linkage scheme d[20,21] (Fig. 1). In the few examples investigated, exclusively *trans*-olefins were isolated as reaction products[20].



1 **17**

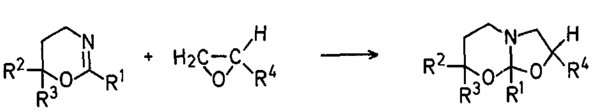
Table 2. Thermolysis of 2-Phenyl-5,6-dihydro-4*H*-1,3-oxazines (**1**) to N-(Δ^2-Alkenyl)-benzamides (**17**)

R^1	R^2	R^3	Thermolysis temperature	References
H	H		200°	20
H			230°	20
CH_3	H	CH_3	210°[a]	21

[a] Thermolysis in the presence of acid.

1.2.3. Addition Reactions

The C=N double bond of **1** is not markedly susceptible to addition. However, the acid-catalyzed hydrolysis to salts of the 3-aminopropyl ester **10** proceeds relatively readily. Similarly, epoxides can be added to give, with ring scission, the corresponding orthocarboxylic acid derivative **18**[22].



1 **18**

---

[13] K. Grohe, E. Degener, H. Holtschmidt, H. Heitzer, Liebigs Ann. Chem. **730**, 133 (1969); and references cited therein.

[14] H. E. Zaugg, Synthesis **1970**, 49.

[15] Y. V. Zeifman, N. P. Gambaryan, L. A. Simonyan, R. B. Minasyan, J. L. Knunyants, Z. Obshch. Khim. **37**, 2476 (1967); Engl. Edit., p. 2355,

[16] H. Hellmann, Angew. Chem. **69**, 463 (1957).
H. Hellmann, G. Opitz, α-Aminoalkylierung, Verlag Chemie, Weinheim, 1960, p. 64-79.

[17] R. R. Schmidt, Chem. Ber. **98**, 334 (1965).

[18] R. R. Schmidt, Angew. Chem. **81**, 576 (1969); Angew. Chem. Internat. Edit. **8**, 602 (1969).

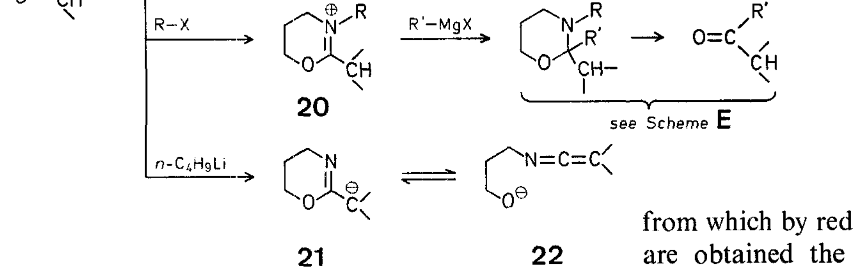
[19] R. R. Schmidt, R. Machat, Angew. Chem. **82**, 322 (1970); Angew. Chem. Internat. Edit. **9**, 311 (1970).

Table 3. 5,7-Dioxa-1-azabicyclo[4.3.0]nonanes (**18**) from 5,6-Dihydro-4*H*-1,3-oxazines (**1**) and Oxiranes[22]

R^1	R^2	R^3	R^4	Yield %	b.p./torr
C_6H_5	H	C_2H_5	$-CH_2-O-C_6H_5$	68	162–164°/0.05
C_6H_5	CH_3	CH_3	$-CH_2-O-C_6H_5$	61	175°/0.05 (m.p. 106.5°)
CH_3	H	H	C_6H_5	27	107°/0.05
n-$C_{11}H_{23}$	H	C_6H_5	$-CH_2-O-CH_2-CH=CH_2$	61	190–196°/0.05

1.2.4. Multistage Syntheses with 1,3-Oxazine Derivatives

According to investigations by Meyers et al.[28–39,47], 2-alkyl-5,6-dihydro-4*H*-1,3-oxazines (see Scheme **A**) can be reduced with sodium borohydride or sodium borodeuteride to the tetrahydro-1,3-oxazine derivatives **19**, which are readily hydrolyzable to aldehydes and propanolamine. On the other hand, Grignard reagents are not capable of adding to these dihydro-1,3-oxazines. The 5,6-dihydro-4*H*-1,3-oxazine thus performs, as a cyclic ester imide, the function of a carboxyl-protecting group. Organometallic compounds smoothly undergo the expected addition reaction with N-quaternized oxazinium salts **20**. The relatively slight CH-acidity of C—H bonds α to C—2 can be utilized for the production of nucleophilic carbanions **21**. In an equilibrium reaction, these carbanions can undergo transformation to the ketene imines **22**, which are capable of entering into electrophilic reactions. These facts found by Meyers et al.[28–39,47] were employed by these workers for numerous interesting syntheses (see Schemes **B**, **C**, **D**, and **E**).



Scheme A

1.2.4.1. Alkylation of the Carbanions Obtained from 2-Alkyl-5,6-dihydro-4*H*-1,3-oxazines and Organometallic Compounds

Starting materials for these syntheses were the 5,6-dihydro-4*H*-1,3-oxazines **23** accessible from aliphatic nitriles and 2,4-dihydroxy-2-methylpentane by polar 1,4-cycloaddition according to linkage scheme c (Fig. 1). The reaction of **23a–c** with butyllithium in absolute tetrahydrofuran at −78° gave, after ~2 hr, the strongly nucleophilic carbanions **24**. These carbanions are key substances for numerous further reactions (Scheme **B** and Table 4). They react with various alkylating agents to give the 5,6-dihydro-4*H*-1,3-oxazines **25** substituted at the carbon α to C-2. Aldehydes or deuterated aldehydes (**27**) are easily obtainable from compounds **25** in very high yields by sodium borohydride or borodeuteride reduction to the tetrahydro-1,3-oxazine derivatives **26** and subsequent acidic hydrolysis[28,37,38]. Analogously, with bifunctional alkylating agents, especially dihaloalkanes, by treating twice with base there is brought about an intramolecularly cyclizing alkylation to give the dihydro-4*H*-1,3-oxazines **29** from which by reduction and acidic hydrolysis there are obtained the cycloalkanealdehydes **30**[30]. The functional C-halogen bond in the intermediate **28**, can, however, also be utilized for a cyanide substitution to give the nitrile **33** (Z=—CN) or, because of the inactivity of **28** towards Grignard reagents, for a Grignardization to **33** (Z=MgBr)[33]. Both

---

[20] R. R. Schmidt, Chem. Ber. **103**, 3242 (1970).

[21] W. Seeliger, W. Diepers, Liebigs Ann. Chem. **697**, 171 (1966).

compounds in turn represent intermediates for further reactions, utilizing the protective-group function of the 5,6-dihydro-4*H*-1,3-oxazines. Thus hydrolysis to carboxylic acid derivatives **34**[33] and reduction and hydrolysis to the corresponding aldehydes has particularly been made use of[37].

Epoxides (oxiranes) can also be employed as alkylating agents for the carbanions **24**. From the 2-(3-hydroxyalkyl)-5,6-dihydro-4*H*-1,3-oxazines **32**, after reduction and hydrolysis there can be obtained the γ-hydroxyaldehydes **37** which exist in equilibrium with their isomers **38**. Via reactions of the hydroxy function in **32** there can be prepared correspondingly modified aldehydes **36**.

Aldehydes and ketones may also be used[29] as electrophilic reactants for the carbanions **24**. Via lithium complexes, by protonation there are formed dihydro-1,3-oxazine derivatives **31**. Sodium borohydride reduction and subsequent acidic hydrolysis of **31** gives the α,β-unsaturated carbonyl compounds **35** in high yields.

Table 4 gives a representative cross-section of the hitherto reported examples of the preparation of carbonyl compounds according to Scheme **B**.

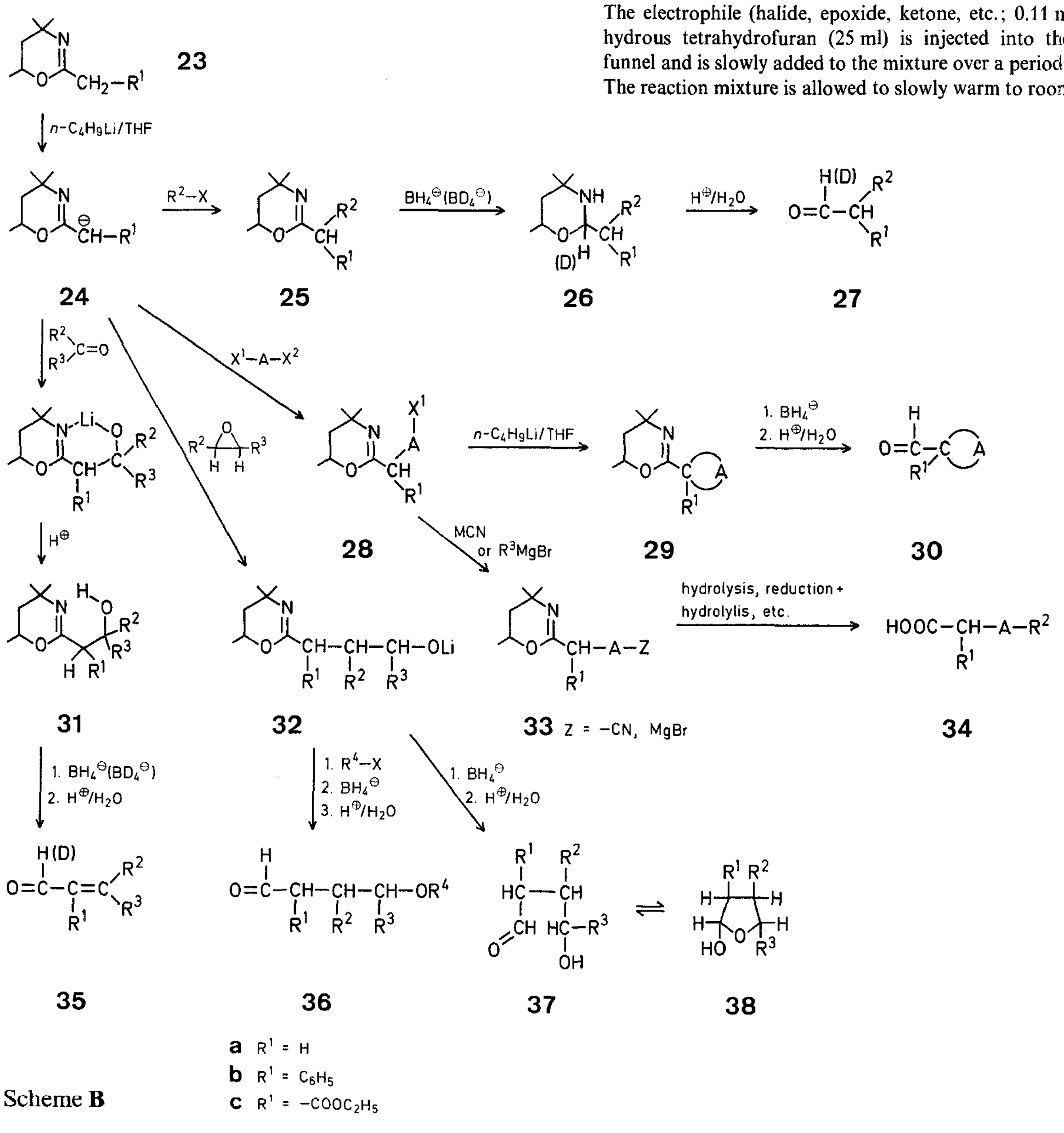
Preparation of Carbanions 24 of 2-Methyl- or 2-Benzyl-5,6-dihydro-4*H*-1,3-oxazines (23a, b); General Procedure[40]:

A 500-ml three-necked flask equipped with a magnetic stirring bar, a 75-ml addition funnel topped with a rubber septum, and a nitrogen inlet tube is successively evacuated and flushed with nitrogen. Anhydrous tetrahydrofuran (100 ml) and 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine (**23a**; 14.1 g, 0.10 mol) are added from a syringe through the rubber septum. The stirred solution is cooled to −78° (Dry Ice/acetone bath) and a 1.6 *M* solution of butyllithium in hexane (69.0 ml, 0.11 mol) is injected into the addition funnel. The butyllithium is added dropwise over a period of 1 hr. Approximately 1 hr after the addition is complete, a yellow precipitate forms. This is indicative of complete anion formation. The anion may not precipitate if more than the indicated quantity of solvent is employed.

The use of *t*-butyllithium in place of *n*-butyllithium will generate the carbanion **24** within a few minutes, thus shortening the procedure by several hours.

Alkylation of Carbanion 24 to 27, 30, 34, 35, 36, and 37; General Procedure[40]:

The electrophile (halide, epoxide, ketone, etc.; 0.11 mol) in anhydrous tetrahydrofuran (25 ml) is injected into the addition funnel and is slowly added to the mixture over a period of 30 min. The reaction mixture is allowed to slowly warm to room tempera-



Scheme **B**

ture, by which time the yellow precipitate disappears. The mixture is then poured into ice water (100 ml) and acidified to pH 2–3 with 9 *N* hydrochloric acid. The acidic solution is extracted with pentane (3 x 75 ml) and basified by careful addition of 40% sodium hydroxide solution, ice being added to keep the mixture cool during the neutralization. The resultant oil is extracted with ether (3 x 75 ml). The ether extracts are dried with anhydrous potassium carbonate, then the ether is removed by rotatory evaporation to give the crude alkylated dihydro-1,3-oxazine; yield: 90–98%.

Reduction of 5,6-Dihydro-4*H*-1,3-oxazines[40]:

Tetrahydrofuran (100 ml), 95% ethanol (100 ml), and the crude 5,6-dihydro-4*H*-1,3-oxazine obtained according to the preceding recipe are successively introduced into a 600-ml beaker. The mixture is cooled to −35° to −40° and stirred magnetically. The pH is adjusted to ~7 by the addition of 9 *N* hydrochloric acid. To the mixture is then added, alternately so that pH 6–8 is maintained, a solution of sodium borohydride (3.78 g, 0.10 mol) in water (4–5 ml) containing 1 drop of 40% aqueous sodium hydroxide, and 9 *N* hydrochloric acid. The addition is best carried out using two addition funnels or 50-ml burets. After the addition is complete, stirring is continued for 1 hr at −35° to −45°, a pH of 7 being maintained by the occasional addition of hydrochloric acid. The solution is then poured into water (~100 ml) and made alkaline with 40% aqueous sodium hydroxide. The layers are separated, the aqueous phase is extracted with ether (3 x 75 ml), the combined organic solutions are washed with saturated sodium chloride solution, and are dried with potassium carbonate. The solvent is removed using a rotatory evaporator to give the crude tetrahydro-1,3-oxazine; yield: 90–99%.

Cleavage of the Tetrahydro-1,3-oxazine to the Aldehyde[40]:

By Steam Distillation: Oxalic acid hydrate (50.4 g, 0.40 mol) and water (~150 ml) are introduced into a 250-ml flask fitted with a distillation head, an addition funnel, and a steam-inlet tube. Steam is introduced into the solution and the tetrahydro-1,3-oxazine (~0.1 mol) is added dropwise over a 20 min period. The addition funnel is then washed down with 1 *M* oxalic acid (5 ml). The steam distillation is continued until the distillate is free from organic material, then the distillate is extracted with pentane or ether (3 x 50 ml). The extracts are dried with sodium sulfate. Removal of the solvent gives the pure aldehyde. In some cases, distillation of the product may be necessary.

By Hydrolysis: This procedure is used in the case of water-soluble aldehydes and of aldehydes that are insufficiently volatile to make steam distillation practical. The crude tetrahydro-1,3-oxazine (0.1 mol) is added to a solution of oxalic acid hydrate (50.4 g, 0.40 mol) in water (150 ml). The mixture is refluxed for 2 hr and the resultant cloudy solution is extracted with ether, pentane, or dichloromethane (depending on the nature of the aldehyde). The organic extracts are washed with 5% sodium hydrogen carbonate solution and dried with sodium sulfate. The solvent is evaporated and the residue distilled or recrystallized.

Preparation of Cycloalkanealdehydes (30)[40]:

Tetrahydrofuran (250 ml) and 2-benzyl-4,4,6-trimethyl-5,6-dihydro-4*H*-1,3-oxazine (10.9 g, 0.05 mol) are introduced into a 500-ml three-neck flask equipped with a nitrogen inlet tube, a rubber septum, and a magnetic stirrer. The solution is cooled to −78° and a 1.6 *M* solution (32.0 ml, 0.06 mol) of butyllithium in hexane is added dropwise. After the addition is complete, stirring is continued for 1 hr, 1,4-dibromobutane (11.5 g, 0.05 mol) is

Table 4. Preparation of Carbonyl Compounds According to Scheme **B**

Compound	R^1	R^2	R^3	A	Yield[a] %	m.p. of 2,4-DNP	References
27a	H	CH_3	—	—	60	149–150°	28
27b	H	$-CH_2-CH=CH_2$	—	—	53	116–118°	28
27c	H	$-CH_2-CH_2-OC_2H_5$	—	—	54	88–89°	28
27d	H	$-CH_2-C_6H_5$	—	—	54	153–154°	28
27e	C_6H_5	CH_3	—	—	70	137–138°	28
27f	H	$-(CH_2)_5-CN$	—	—	47	76–77°	37
30a	H	—	—	$-(CH_2)_2-$	69	184–185°	30
30b	H	—	—	$-(CH_2)_3-$	20	155–157°	30
30c	H	—	—	$-(CH_2)_4-$	36	153–154°	30
30d	C_6H_5	—	—	$-(CH_2)_2-$	62	193–195°	30
30e	C_6H_5	—	—	$-(CH_2)_3-$	49	156–158°	30
30f	C_6H_5	—	—	$-(CH_2)_4-$	60	166–168°	30
30g	$-COOC_2H_5$	—	—	$-(CH_2)_4-$	72	134–135°	30
34a	H	$-CO-C_6H_5$	—	$-(CH_2)_5-$	90[b]	85°	33
34b	H	D	—	$-(CH_2)_5-$	80[b]	—	33
35a	H	H	n-C_4H_9	—	61	144–145°	29
35b	H	H	C_6H_5	—	64	200–201°	29
35c	H	CH_3	CH_3	—	50	221–222°	29
35d	H	$-(CH_2)_5-$		—	53	193–195°	29
35e	H	$-(CH_2)_4-$		—	63	180–181°	29
35f	H	cholest-3-ylidene		—	69	110–112°	29
35g	H	CH_3	C_6H_5	—	50	200–202°	29
35h	C_6H_5	$-(CH_2)_4-$		—	54	165–166°	29
36a	H	H	H	$R^4=C_2H_5$	59	88–89°	31
36b	H	H	H	$R^4=-CO-C_6H_5$	67	103–105°	31
37a	H	H	H	—	63	116–118°	31
37b	H	H	C_6H_5	—	68	106–107°	31
37c	H	$-(CH_2)_4-$		—	57	78–79°	31
37d	C_6H_5	H	H	—	69	99–101°	31
37e	C_6H_5	H	C_6H_5	—	61	146–147°	31
37f	C_6H_5	$-(CH_2)_4-$		—	59	174–175°	31

[a] All yields refer to the overall reaction, based on **23** employed.

[b] Yield is based on the final reaction step.

then added, and the mixture is allowed to react at −78° for 30 min. Then, a 1.6 *M* solution (32.0 ml, 0.06 mol) of butyllithium in hexane is added with stirring and the mixture is allowed to slowly warm to −50° and kept at that temperature for 2 hr. The mixture is finally poured into ice water (150 ml), acidified to pH 2–3, and extracted with ether. The ether extract is discarded. The aqueous solution is made alkaline by the addition of 40% aqueous sodium hydroxide and extracted with ether. The ether extract is dried with potassium carbonate and the solvent removed using a rotatory evaporator; yield of derivative **29**: 90–97%.

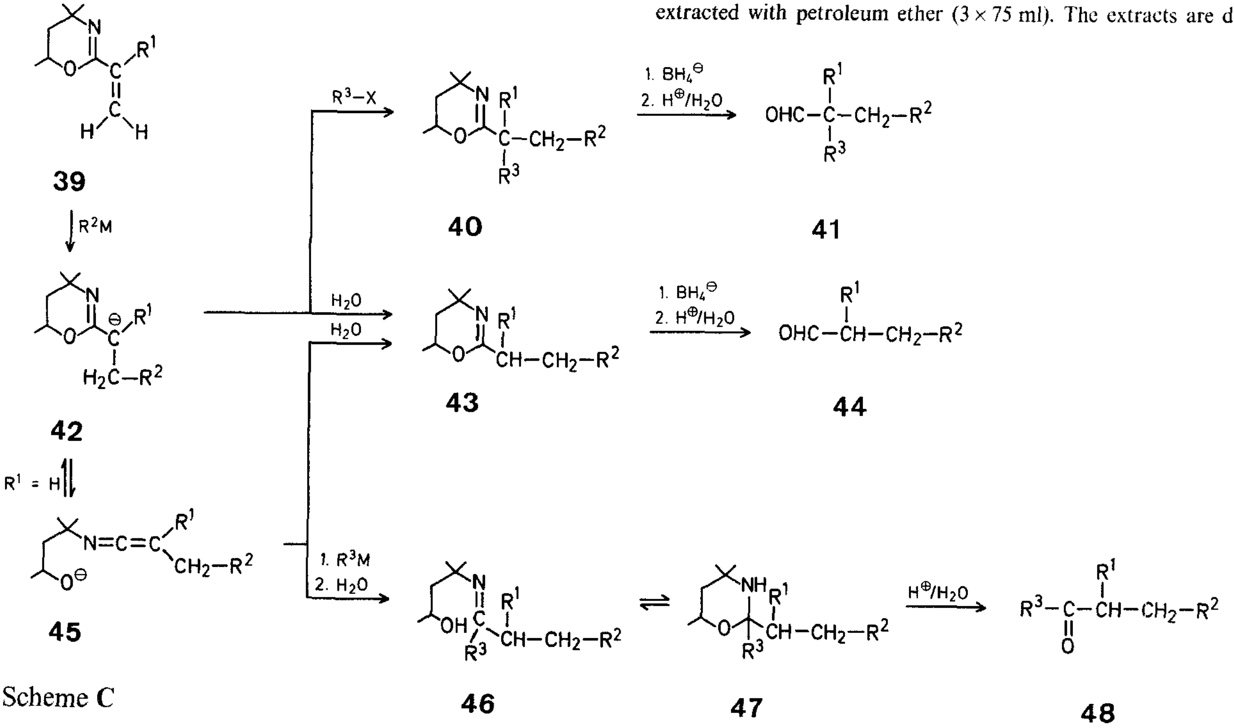
In the case of the 2-methyl-5,6-dihydro-4*H*-1,3-oxazine **23a**, the cyclization step is carried out using 2 equivalents of butyllithium. The reduction and cleavage of derivative **29** to the cycloalkanealdehyde **30** is carried out using the procedures given above.

1.2.4.2. Syntheses Starting with 2-Vinyl-5,6-dihydro-4*H*-1,3-oxazines

Interesting intermediates for the synthesis of variously substituted carbonyl compounds by the reactions shown in Scheme **B** for 2-alkyl-5,6-dihydro-4*H*-1,3-oxazines (**23**) are the 2-vinyl-5,6-dihydro-4*H*-1,3-oxazines (**39**), which are accessible by the same route as **23**[8] (see Scheme C and Table 5). Organometallic compounds add smoothly to the β carbon atom to give the carbanions **42** comparable with **24**. If molar proportions are used and R^1 is H, by neutralization of **42** there are obtained the 2-ethyl-5,6-dihydro-4*H*-1,3-oxazines **43**. Upon reduction and hydrolysis, compounds **43** give very good yields[34,35,47] of the propanal derivatives **44**. Like the carbanions **24**, the carbanions **42** can be submitted to reaction with alkylating agents to give 2-ethyl derivatives of the type **40**, so that after reduction and hydrolysis the substituted propanals **41** are obtained.

The carbanions of the 2-alkyl-5,6-dihydro-4*H*-1,3-oxazines **42** can, depending on the substituents (aryl substituents stabilize the carbanion **42** by an electronic effect) and on the degree of substitution (polysubstitution favors the ketene imine **45** by a steric effect) undergo conversion into the open-chain ketene imines **45**, the equilibrium lying predominantly or exclusively on the side of **45** in the case where R^1 is other than H or phenyl[34,35,38]. In addition, the equilibrium can also be shifted to the side of the ketene imines **45** by elevation of temperature. The electrophilic character of these intermediates hinders alkylation. In contrast to this, renewed reaction takes place on addition of further Grignard reagent. The organometallic compound is added to the C=N double bond of the ketene and then with water there follows a recyclization of the open-chain compound **46** to the tetrahydro-1,3-oxazine derivative **47**. By the acidic hydrolysis of **47**, ketones of the structure **48** are obtained in good yields by this reaction pathway.

2-Methyl-3-phenylpropanal[42] (**41**, $R^1=H$, $R^2=C_6H_5$, $R^3=CH_3$): *2-(1-Phenyl-prop-2-yl)-4,4,6-trimethyl-5,6-dihydro-4H-1,3-oxazine* (**40**, $R^1=H$, $R^2=C_6H_5$, $R^3=CH_3$): A solution of 4,4,6-trimethyl-2-vinyl-5,6-dihydro-4*H*-1,3-oxazine (**39**, $R^1=H$; 10.0 g, 0.06 mol) and methyl iodide (6.1 ml, 0.09 mol) in tetrahydrofuran (100 ml) is cooled to −60° (Dry Ice/acetone) under nitrogen. The stirred solution is treated dropwise over a period of 30 min with ethereal 3.0 *M* phenylmagnesium bromide (51 ml, 0.16 mol). After complete addition, the mixture is stirred for 1 hr at −60 to −65° and then slowly allowed to warm to room temperature. The excess Grignard reagent is decomposed by the careful addition of water (10 ml) and the contents of the flask are poured into ice water (200 ml), acidified to pH 2–3 with dilute hydrochloric acid and extracted with petroleum ether (3 × 75 ml). The extracts are dis-



Scheme C

---

[22] W. Seeliger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W. Thier, H. Hellmann, Angew. Chem. **78**, 913 (1966); Angew. Chem. Internat. Edit. **5**, 875 (1966).

[23] K. Bott, Tetrahedron Lett. **1970**, 4185.

[24] K. Bott, Tetrahedron Lett. **1970**, 4301.

[25] C. Giordano, G. Ribaldone, G. Borsotti, Synthesis **1971**, 92.

carded and the aqueous solution is basified with 40% aqueous sodium hydroxide solution. The oil that appears is extracted with ether (3 x 100 ml) and the extracts are dried with potassium carbonate and concentrated to give the crude product; yield: 14.8 g (93%). The product is sufficiently pure for use in the next step.

2-(1-Phenyl-prop-2-yl)-4,4,6-trimethyltetrahydro-1,3-oxazine: The method for reducing the C=N double bond in **40** is identical with that already described[40] (Section 1.2.4.1.). Reagent: sodium borohydride (2.5 g, 0.06 mol); yield of crude product: 13.7 g (93%).

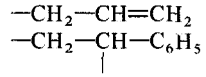
2-Methyl-3-phenylpropanal: The crude tetrahydro-1,3-oxazine (13.1 g) is added dropwise to a boiling solution of oxalic acid (33.4 g) in water (150 ml) and the aldehyde collected in the steam distillate. The distillate is extracted with ether (3 x 50 ml), the extract dried with sodium sulfate, and the solvent removed to give the aldehyde; yield: 6.0 g (77 %). The oberall yield is 66 % based on **39**.

The same result is obtained starting from the carbanions **24** of 2-alkyl-4,4,6-tetramethyl-5,6-dihydro-4*H*-1,3-oxazines having two suitable substituents on the (2-)C-α atom. Due to steric hindrance, this carbanion undergoes ring opening, particularly at elevated temperatures, to give a ketene imine (**45**) which can then add organometallic compounds.

In the presence of water, ketene imines **45** are converted into the 5,6-dihydro-4*H*-1,3-oxazines **43**, which are also formed by hydrolysis of **42**.

Table 5 gives a representative cross section of the examples reported of the preparation of aldehydes and ketones according to Scheme **C**.

Table 5. Aldehydes and Ketones Prepared According to Scheme **C**

Compound	R^1	R^2	R^3	Yield[a] %	m.p. of 2,4-DNP	References
41a	H	C_6H_5	CH_3	71	122–123°	32
41b	H	C_6H_5	$-CH_2-C_6H_5$	60	165–166°	32
41c	H	C_6H_5	$-CH_2-CH{=}CH_2$	43	125–126°	32
41d	H	C_6H_5	 $-CH_2-\underset{OH}{CH}-C_6H_5$	44	168–172°	32
41e	H	C_2H_5	$-CH_2-C_6H_5$	72	86–87°	32
41f	H	$-CH{=}CH_2$	$-CH_2-C_6H_5$	31	76–77°	32
44a	CH_3	c-C_6H_{11}	H	80	146–148°	34
44b	C_6H_5	t-C_4H_9	H	71	172–173°	35
44c	C_6H_5	c-C_6H_{11}	H	94	155–157°	35
48a	CH_3	n-C_4H_9	n-C_4H_9	79	—	34
48b	CH_3	t-C_4H_9	CH_3	73	65°	34
48c	CH_3	C_6H_5	C_6H_5	47	134°	34
48d	C_6H_5	t-C_4H_9	CH_3	84	120–122°	35
48e	C_6H_5	c-C_6H_{11}	CH_3	79	126–127°	35
48f	C_6H_5	n-C_4H_9	n-C_4H_9	68[35], 78[38]	—	35, 38
48g	C_6H_5	t-C_4H_9	C_6H_5	13	—	35
48h	C_6H_5	sec-C_4H_9	CH_3	83	84–86°	35

[a] Overall yields, based on **39**.

1.2.4.3. Aldehydes and Isocyanates by Ring-Cleavage Reactions

A rapid ring cleavage of the 5,6-dihydro-4*H*-1,3-oxazine ring system takes place when the 2-unsubstituted 4,4,6-trimethyl-5,6-dihydro-4*H*-1,3-oxazine **49** and the 2-bromo derivative **50** are treated with butyllithium in tetrahydrofuran at −78° in order to obtain the carbanion **54**[39] (see Scheme **D** and Table 6). Comparable heterocyclic carbanions have been particularly investigated by Breslow[44] in the thiamine field. In a rapid secondary reaction, however, **54** rearranges to the isocyanide **55** which, after neutralization, can be converted thermally into the starting material **49**. If the base treatment of **49** is carried out with organometallic compounds in absolute ether, there surprisingly takes place an addition to the C=N double bond to give the tetrahydro-1,3-oxazine **51**. By acidic hydrolysis of **51**

---

[26] R. R. SCHMIDT, unpublished results.

[27] K. BOTT, Chem. Commun. **1969**, 1304.

[28] A. I. MEYERS, A. NABEYA, H. W. ADICKES, J. R. POLITZER, J. Amer. Chem. Soc. **91**, 763 (1969).

[29] A. I. MEYERS, A. NABEYA, H. W. ADICKES, J. M. FITZPATRICK, G. R. MALONE, J. R. POLITZER, J. Amer. Chem. Soc. **91**, 764 (1969).

[30] A. I. MEYERS, H. W. ADICKES, J. R. POLITZER, W. N. BEVERUNG, J. Amer. Chem. Soc. **91**, 765 (1969).

[31] H. W. ADICKES, J. R. POLITZER, A. I. MEYERS, J. Amer. Chem. Soc. **91**, 2155 (1969).

[32] A. I. MEYERS, A. C. KOVELESKY, Tetrahedron Lett. **1969**, 1783.

[33] A. I. MEYERS, J. R. POLITZER, B. K. BANDLISH, G. R. MALONE, J. Amer. Chem. Soc. **91**, 5886 (1969).

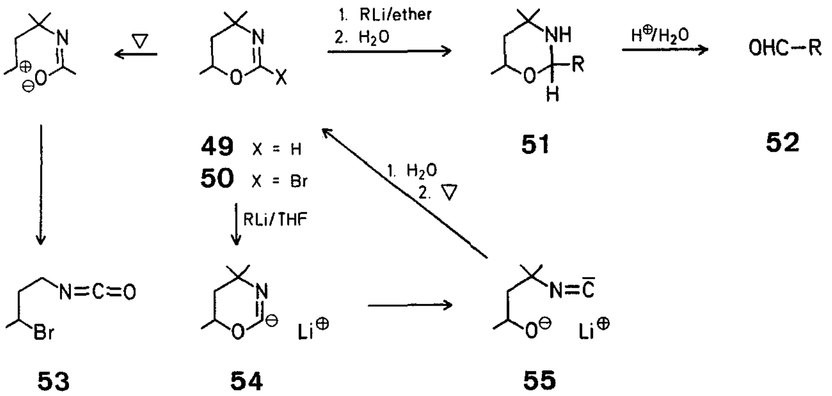
[34] A. I. MEYERS, A. C. KOVELESKY, J. Amer. Chem. Soc. **91**, 5887 (1969).

[35] A. I. MEYERS, A. C. KOVELESKY, Tetrahedron Lett. **1969**, 4809.

[36] A. I. MEYERS, E. M. SMITH, J. Amer. Chem. Soc. **92**, 1084 (1970).

[37] A. I. MEYERS, G. R. MALONE, H. W. ADICKES, Tetrahedron Lett. **1970**, 3715.

there can be isolated the aldehydes **52**. Compound **50** does not react at all under these conditions. However, it can be converted by thermolysis into the 3-bromopropyl isocyanate **53**, probably via a dipolar intermediate.



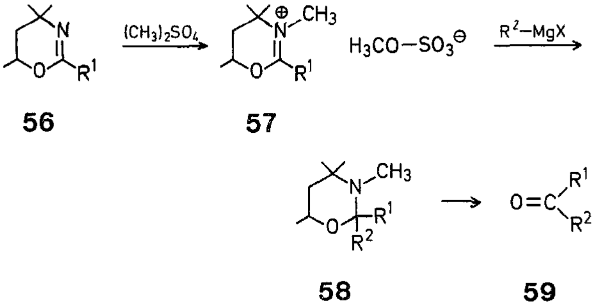
Scheme D

Table 6. *Compounds* **52** *Prepared in Accordance with Scheme* **D**[39]

Compound	R	Yield %	m.p. of 2,4-DNP
52a	n-C_4H_9	66	107–108°
52b	t-C_4H_9	55	208–209°

1.2.4.4. Syntheses via Quaternization of 5,6-Dihydro-4*H*-1,3-oxazines

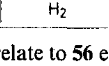
By quaternization of 2-alkyl-5,6-dihydro-4*H*-1,3-oxazines **56** with dimethyl sulfate to the N-methyl-1,3-oxazolinium compounds **57**, the electrophilic reactivity is enhanced to such an extent that Grignard compounds are able to add to the C=N double bond[36] (Scheme E and Table 7). The N-methylated tetrahydro-1,3-oxazines **58** obtained give, upon hydrolysis, high yields of the ketones **59**.



Scheme E

The scope for variation of these reactions discovered by Meyers et al. (Scheme **B**–**E**), which can be and have been particularly utilized for the synthesis of variously substituted carbonyl compounds, is underlined by the examples summarized in Tables 4–7.

Table 7. Ketones **59** Prepared in Accordance with Scheme **E**[36]

Compound	R^1	R^2	Yield[a] %	m.p. of 2,4-DNP
59a	$-CH_2-CH_2-C_6H_5$	C_2H_5	78	108–115°
59b	$-CH_2-CH_2-C_6H_5$	n-C_4H_9	71[b]	118–120°
59c	$-CH_2-CH_2-C_6H_5$	t-C_4H_9	29	175–176°
59d	C_6H_5	C_2H_5	70	190°
59e	$-\underset{C_6H_5}{CH}-CH_2-CH=CH_2$	CH_3	56	121–123°
59f		n-C_4H_9	35	108–110°

[a] All yields relate to **56** employed.
[b] With butyllithium, a yield of only 51% of **59b** is obtained.

2. 4*H*-1,3-Oxazines; Syntheses and Reactions

2.1. Synthesis

4*H*-1,3-Oxazines were early synthesized by Wohl[45], Gabriel[3,4,5], and Karrer[46] from β-aminoketones by acylation to β-acylaminoketones and subsequent cyclization with phosphorus(V)-chloride, polyphosphoric acid, or oxalic acid (linkage scheme a, Fig. 2).

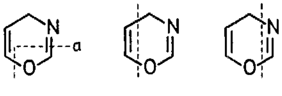


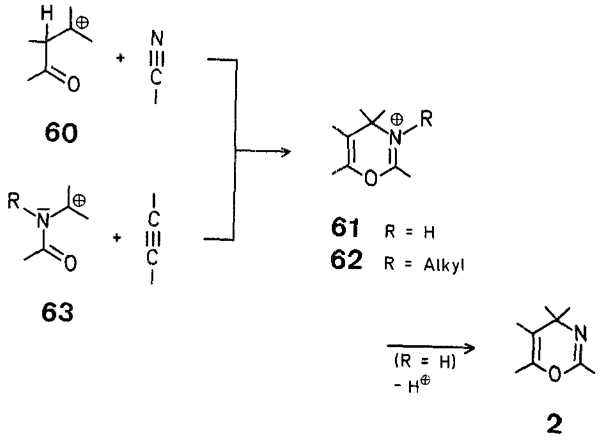
Fig. 2. Linkage schemes for the synthesis of 4*H*-1,3-oxazines (**2**).

If the molecule is broken down in accordance with b and c (Fig. 2), the cycloaddition of an N-acylimine to an acetylenic group (b), or the cycloaddition of an α,β-unsaturated carbonyl compound to a nitrile (c) can be recognized as possible principles for the synthesis of 4*H*-1,3-oxazines. No work has yet been published on either route, although both ought to

---

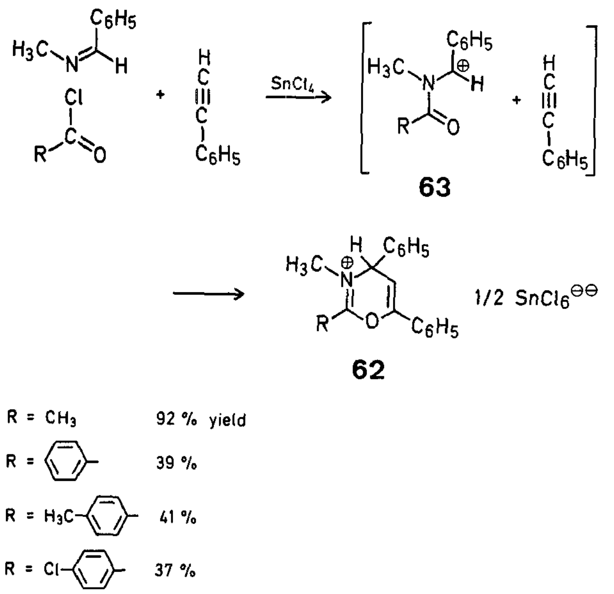
[38] A. I. Meyers, E. M. Smith, Tetrahedron Lett. 1970, 4355.
[39] A. I. Meyers, A. W. Adickes, Tetrahedron Lett. 1969, 5151.

succeed in the presence of appropriate polarizing substitution of the starting materials. Apart from increasing the reactivity of the diene analogues by appropriate substitution, this can also be achieved by protonization or alkylation to the corresponding carbonium ions. In fact, by cycloaddition of the polar 1,4-systems **60** and **63** to nitriles and acetylenes, Schmidt et al.[17,48,49] and Lora-Tamayo et al.[50] were able to obtain independently the substituted 4*H*-1,3-oxazinium salts **61** and **62** in high yields, the carbonium ions **60** and **63** being formed in situ from the corresponding *β*-chlorocarbonyl compounds[17,48,49,50] and the N-chloroalkylamides[17] by the action of tin(IV)-chloride.



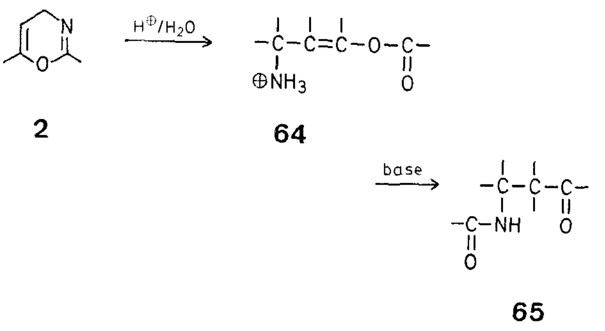
In the case of R = H, the salts **61** can be converted quantitatively into the corresponding bases **2**.

The reaction with the acetylene derivatives can also be carried out as a three-component reaction[51]. Thus, starting from an aldimine, by addition of carboxylic acid chloride, alkyne, and tin(IV)-chloride the 1,3-oxazinium salts **62** can be synthesized via the isolable 1,4-polar system **63**.

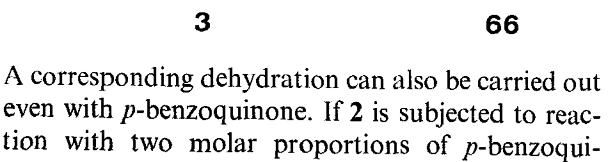


2.2. Reactions

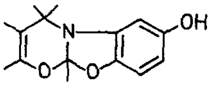
The long-known acid hydrolysis[3,4,5,46] of the 4*H*-1,3-oxazines **2** leads initially to the salts of the 3-aminoenol esters **64**. Upon liberation of the corresponding bases there follows a rearrangement to the *β*-acylaminocarbonyl compound **65**. Beyond this, until very recently hardly any reaction of **2** had been published.



HMO calculations on 2,4,6-triphenyl-4*H*-1,3-oxazine (**2**) and the corresponding *$1^{\oplus}$-1,3*-oxazinium ion (**3**) indicated that **3** is very much poorer in energy than **2**. The energy difference is essentially attributable to the transition from **2** to the heteroaromatic 6π system **3**. Accordingly, the conversion of **2** into **3** with elimination of hydride should be a thermodynamically favoured process and, because of the high tendency to conversion, it should be easy to find a suitable hydride acceptor. Actually, when equimolar amounts of trityl perchlorate and **2** were subjected to reaction in absolute acetonitrile it has been possible to obtain perchlorates of **3** in almost quantitative yields[45]. Hydrolysis of these salts leads quantitatively[49] to the *β*-acylaminocarbonyl compounds **66**.



A corresponding dehydration can also be carried out even with *p*-benzoquinone. If **2** is subjected to reaction with two molar proportions of *p*-benzoquinone in chlorinated hydrocarbons in the presence of a molar amount of water, **66** and quinhydrone are obtained quantitatively. The reaction proceeds via an isolable 1:1 adduct of structure **67** formed from **2** and *p*-benzoquinone[49].



67

---

[40] J. M. Fitzpatrick, G. R. Malone, J. R. Politzer, H. W. Adickes, A. I. Meyers, Org. Prep. Proceed. 1, 193 (1969).

Aryl-substituted compounds **66**, in particular, are readily obtainable by these reactions. Aliphatic and functionally substituted compounds **66** may be prepared by acylation of corresponding enaminoketones. With anhydrous perchloric acid, with cyclizing condensation, all these compounds can likewise be converted into $1^{\oplus}$-1,3-oxazinium salts[11,49] (**3**). 4*H*-1,3-Oxazines (**2**) are therefore readily accessible intermediates for convenient syntheses of $1^{\oplus}$-1,3-oxazinium salts (**3**).

Table 8 gives a representative cross section of the 1,3-oxazinium salts prepared according to the above-described procedures.

2,4,6-Triphenyl-4*H*-1,3-oxazine[17]:
A solution of 3-chloro-1,3-diphenyl-1-oxopropane (4.9 g, 0.02 mol) and benzonitrile (2.05 g) in absolute chloroform (20 ml) is treated with tin(IV)-chloride (5.12 g, 0.02 mol). The mixture is stirred for 1 hr at room temperature. The product is isolated by filtration and washed well with chloroform; yield: 78 g (64%); m.p. 204°. Treatment with aqueous ammonia and recrystallization from ethanol gives 2,4,6-triphenyl-4*H*-1,3-oxazine; yield: 82%; m.p. 106°.

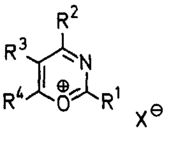
2,4,6-Triphenyl-$1^{\oplus}$-1,3-oxazinium Perchlorate (3a); Procedure A[48]:
A solution of 2,4,6-triphenyl-4*H*-1,3-oxazine (3.11 g, 10.0 mmol) in absolute acetonitrile (40 ml) is treated at room temperature with trityl perchlorate (3.42 g, 10.0 mmol). After 30 min, the mixture is cooled to 0° and the product is isolated by filtration and washed with small amounts of absolute acetonitrile and absolute ether. Further product is obtained by addition of absolute ether to the mother liquor; total yield: 3.5 g (86%) of analytically pure **3a**.

6-Ethoxy-4-methyl-2-phenyl-$1^{\oplus}$-1,3-oxazinium Perchlorate (3c); Procedure B[49]:
An ice-cooled, stirred solution of ethyl *β*-benzoylaminocrotonate (mixture of *E*- and *Z*-form; 20 g, 86 mmol) in absolute chloroform (100 ml) and acetic acid anhydride (35 ml) is slowly treated dropwise with 70% perchloric acid (7.5 ml, 86 mmol). The product is collected by filtration and washed free of acetic anhydride with absolute ether; yield: 17.0 g (63%) of **3c**.

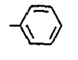
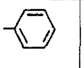
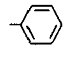
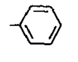
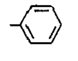
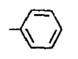
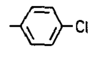
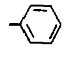
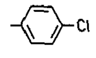
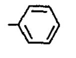
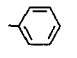
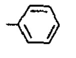
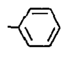
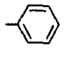
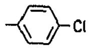
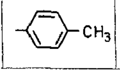
Bis-[2,6-diphenyl-$1^{\oplus}$-1,3-oxazinium] Hexachlorostannate (3i); Procedure C[11]:
A solution of *β*-chlorovinyl phenyl ketone (**68**; 0.02 mol) and benzonitrile (0.02 mol) in absolute chloroform (20 ml) is treated with tin(IV)-chloride (0.01 mol), then heated to reflux temperature for 2 hr. After cooling, precipitated product is isolated by filtration and washed well with absolute chloroform. The product is analytically pure; yield: 39%; m.p. 190–200° (dec.).

2,4,6-Triphenyl-$1^{\oplus}$-1,3-oxazinium Pentachlorostannate (3j); Procedure D[17]:
A stirred solution of N-benzoylbenzimidoyl chloride (2.43 g, 0.02 mol) and phenylacetylene (1.11 g, 0.011 mol) in absolute chloroform (10 ml) is treated with tin(IV)-chloride (2.6 g, 0.01 mol) at 0°. The mixture is allowed to react for 30 min at 0°. The precipitated product is isolated by filtration and washed well with absolute chloroform; yield: 3.9 g (64%); m.p. 218–227° (dec.).

Table 8. $1^{\oplus}$-1,3-Oxazinium Salts (**3**) prepared according to Procedures A–E



3

3	R^1	R^2	R^3	R^4	$X^{\ominus}$	Procedure	Yield %	m.p.	References
a			H		$ClO_4^{\ominus}$	A, B	86, 98	295–300°	48, 49
b		H	H		$ClO_4^{\ominus}$	A	94	—	48
c		$-CH_3$	H	$-OC_2H_5$	$ClO_4^{\ominus}$	B	64	110°	49
d		$-CH_3$	H	$-OC_2H_5$	$ClO_4^{\ominus}$	B	65	124°	49
e	*t*-C_4H_9	$-CH_3$	H	$-OC_2H_5$	$ClO_4^{\ominus}$	B	30	98°	49
f		$-CH_3$	H	$-CH_3$	$ClO_4^{\ominus}$	B	91	124°	49
g		$-CH_3$	H	$-N(CH_3)_2$	$ClO_4^{\ominus}$	B	80	242°	49
h		$-OC_2H_5$	H	$-OC_2H_5$	$ClO_4^{\ominus}$	B	86	110°	49
i		H	H		$\frac{1}{2}SnCl_6^{\ominus\ominus}$	C	39	190–200° (dec.)	11
j			H		$SnCl_5^{\ominus}$	D	64	218–227° (dec.)	17
k		$-SCH_3$	$-(CH_2)_4-$		$J^{\ominus}$	E	94	150° (dec.)	52
l		$-SCH_3$	$-(CH_2)_4-$		$J^{\ominus}$	E	75	171°	48
m		$-SCH_3$	$-(CH_2)_4-$		$J^{\ominus}$	E	78	160–164°	48

4-Methylthio-2-phenyl-5,6-tetramethylene-1$^{\oplus}$-1,3-oxazinium Iodide (3k); Procedure E^{52}:

2-Phenyl-5,6-tetramethylene-4-thiono-4*H*-1,3-oxazine (70, R = C_6H_5; 2.43 g, 0.01 mol) in boiling acetone (30 ml) is treated dropwise with a solution of methyl iodide (2.1 g, 0.015 mol) in acetone (5 ml). Compound **70** only partially goes into solution, but is transformed into the deep-red needles of **3k**. In order to complete the reaction, the mixture is refluxed for a further 30 min, and is then allowed to cool. The product is isolated by suction, washed with acetone, and dried in vacuo; yield: 3.62 g (94 %). The salt, which is already analytically pure, can be recrystallized from glacial acetic acid, acetonitrile, or nitromethane.

3. 1$^{\oplus}$-1,3-Oxazinium and 1$^{\oplus}$-1,3-Thiazinium Salts

3.1. Synthesis of 1$^{\oplus}$-1,3-Oxazinium Salts

In addition to already mentioned syntheses of the 1$^{\oplus}$-1,3-oxazinium salts **3** from **2** by hydride elimination and from **66** by cyclizing condensation with strong acids, the heterocyclic system **3** can also be built up by 1,4-cycloaddition. If the linkage schemes a and b (Fig. 3) are taken as a basis, salts **3** should be accessible by addition of polar 1,4-systems to nitriles and acetylene derivatives. Both routes have been successfully pursued. Thus, it was possible to prepare **3** directly starting from α,β-unsaturated β-chlorocarbonyl compounds (**68**) and nitriles in the presence of eletrophilic metal halides (route a)[11].

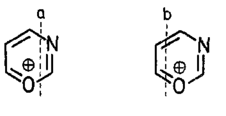
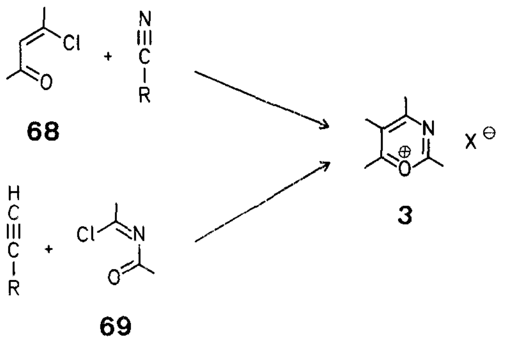
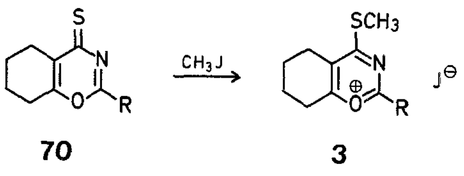


Fig. 3. Linkage schemes for the synthesis of 1$^{\oplus}$-1,3-oxazinium salts

Passage through vinylcarbonium ions has not been confirmed experimentally in this reaction. Similarly, starting from N-acylimidoyl chlorides **69** and acetylene derivatives in the presence of tin(IV) chloride it was possible to obtain **3** via a resonance-stabilized, isolable vinylcarbonium ion (route b)[17]. However, the two first-mentioned methods are to be preferred over routes a and b (see Table 8).

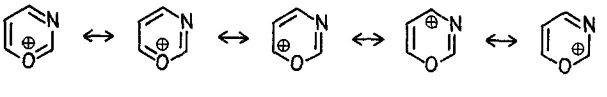


The first 1$^{\oplus}$-1,3-oxazinium salt (**3**, R = C_6H_5) was prepared by Hünig and Hübner [52] from the 4-thiono-1,3-oxazine **70** by alkylation at sulfur with methyl iodide, a procedure which is certainly capable of extension[48].

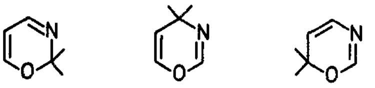


3.2. Reactions of 1$^{\oplus}$-1,3-Oxazinium Salts

As expected, 1$^{\oplus}$-1,3-oxazinium salts (**3**; or 3-aza-pyrylium salts) are, like pyrylium salts[53], electrophilic compounds. This fact is made clear by a simple consideration of the most important mesomeric forms.



In the ground state, therefore, the oxygen atom and the carbon atoms in positions 2, 4, and 6 carry a positive charge. Electrophilic attack of the oxygen atom does not lead to a stable molecule, but electrophilic attack of the carbon atoms in the 2-, 4-, and 6-positions does. With a nucleophilic reactant, there can result the corresponding 2*H*-, 4*H*-, and 6*H*-1,3-oxazines.

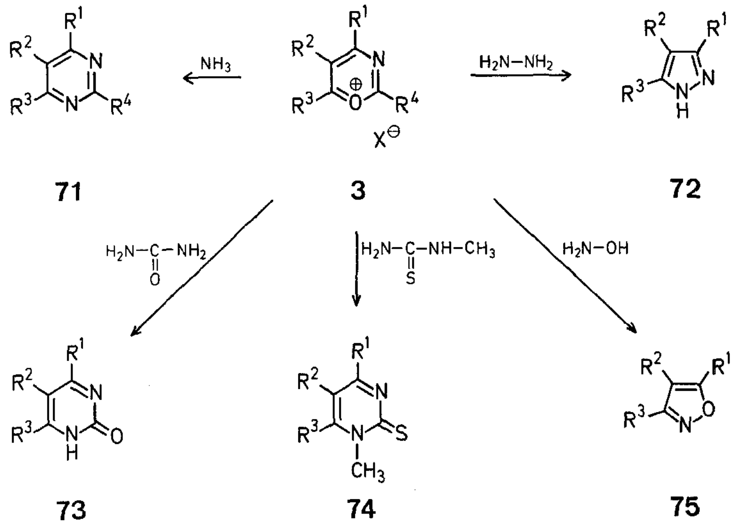


Electronegativity considerations, HMO calculations on starting materials and end products, and calculations of the energy profile over the reaction coordinates lead to the expectation, both for the thermodynamically and the kinetically controlled reaction, of an order of reactivity C-2 > C-4 > C-6, so that in each case the corresponding 2*H*-1,3-oxazine should be the predominant or exclusive end product. The investigations of Schmidt et al.[11,17,48,49,54,55,56] with various nucleophilic oxygen, nitrogen, carbon, and sulfur compounds have shown, however, that this postulate is not fulfilled. The product-determining attack of nucleophilic reagents takes place preferentially at the 6-position to form 6*H*-1,3-oxazines as intermediates, further reactions such as ring scission and recyclization generally taking place. It is true that in the first, obviously reversible reaction step it has been possible with alkylmalodinitrile carbanion as the nucleophile to show that all three isomeric oxazines can be formed and isolated in comparable amounts[57]. Where, however, a hydrogen bond is present on the α-position of the nucleophile, as with the malodinitrile carbanion, this is not possible; the product corresponding to attack in the 6-position is isolated in good yield as the end product in an irreversible subsequent reaction although the corresponding end product of attack in the 2-position is of comparable thermodynamic stability. This fact is in contradiction to a general thermodynamic control of products.

$1^{\oplus}$-1,3-Oxazinium salts are consequently suitable for transferring variously substituted unsaturated C_3 residues onto nucleophilic reagents. This fact makes them particularly interesting from the preparative point of view.

3.2.1. Reactions of $1^{\oplus}$-1,3-Oxazinium Salts with Nucleophilic Oxygen or Nitrogen Compounds

Water, ammonia, hydrazine, and urea and their derivatives have so far been employed as nucleophilic oxygen and nitrogen compounds in reactions with $1^{\oplus}$-1,3-oxazinium salts (**3**)[11,17], the products set out in Scheme **F** being obtained upon ring cleavage and, possibly, renewed ring closure.



Scheme F

The investigation of the substituent-dependent rate of hydrolysis of **3** to **66** supports a nucleophilic attack by the water molecule on the 6-position of **3**[11]. Ammonolysis leads smoothly to pyrimidines **71**[17,52]. Towards bifunctional nucleophilic reagents, **3** behaves as an activated β-dicarbonyl compound and the pyrimidine, pyrazole, and 1,2-oxazole derivatives **72**–**75** are formed[11,17].

3.2.2. Reactions of $1^{\oplus}$-1,3-Oxazinium Salts with Nucleophilic Carbon Compounds

Carbanions of CH-acidic compounds, phenoxides, enamines, and Grignard compounds have been employed[11,48,49,54] as nucleophilic or potentially nucleophilic carbon compounds in reactions with **3**.

3.2.2.1. Reactions with CH-Acidic Compounds[11,48,49]

On reaction of 2,4,6-triphenyl-1,3-oxazinium perchlorates (**3**) with an equimolar amount of malodinitrile in absolute acetonitrile, with cautious addition of a slight excess of base to liberate the carbanion, the pyridine derivative **80** and the butadiene derivative **78** can be obtained in high overall yield. The course of the reaction is shown in Scheme **G**. There firstly result (via the non-isolable 1,3-oxazine derivative **76**) the two geometrically isomeric butadiene derivatives **77** and **78**; these can be isolated together when a slightly less than the molar quantity of base is slowly added to the reaction mixture. The configuration of **77** favors cyclization. In solution, compounds **77** are already converted at room temperature (or even more rapidly by base catalysis) into **79**; by spontaneous acyl migration in an allyloid system they rearrange into the pyridine derivatives **80**. Compounds **78** can likewise be readily converted into **80** thermally. Upon reaction of compounds **3** with alkylmalodinitriles under extremely anhydrous conditions it is possible to isolate **76** with the isomeric 1,3-oxazines[57]. Compounds of the type **76** are apparently only stable when the substituents in the 6-position do not carry an acidic α-hydrogen atom.

Upon reaction of compounds **3** with malodinitrile, only the tetrahydroisoquinoline derivatives **81** are obtained.

The reaction of compounds **3** with other carbanions of CH-acidic compounds follows an analogous course. The manifold possibilities of ring-chain

---

[41] Review on this topic: R. R. Schmidt, Angew. Chem., in press.

[42] A. C. Kovalesky, A. I. Meyers, Org. Prep. Proceed. **1**, 213 (1969).

[43] I. Weygand, W. Steglich, F. Fraunberger, Angew. Chem. **79** 822 (1967); Angew. Chem. Internat. Edit. **6**, 808 (1967) and references cited therein.

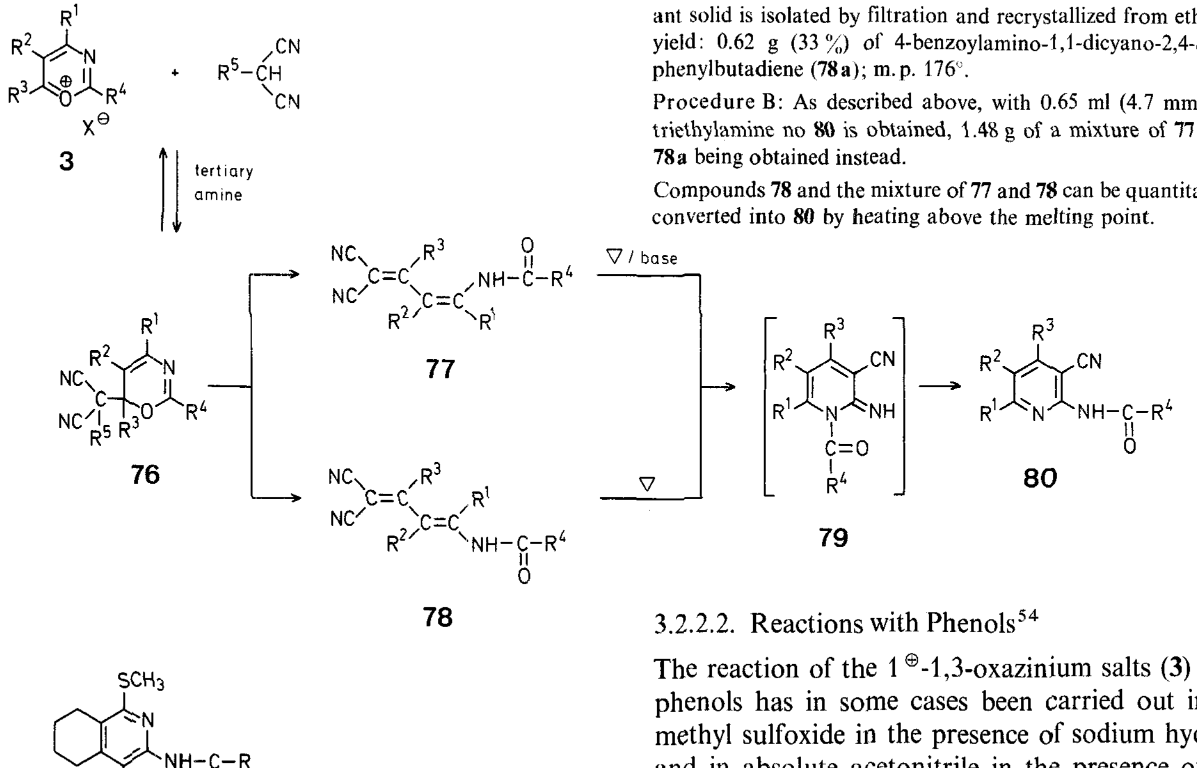
[44] R. Breslow, E. McNelis, J. Amer. Chem. Soc. **80**, 3719 (1958); **81**, 3080 (1959); **82**, 2394 (1960).

[45] K. Wohl, Chem. Ber. **34**, 1914 (1901).

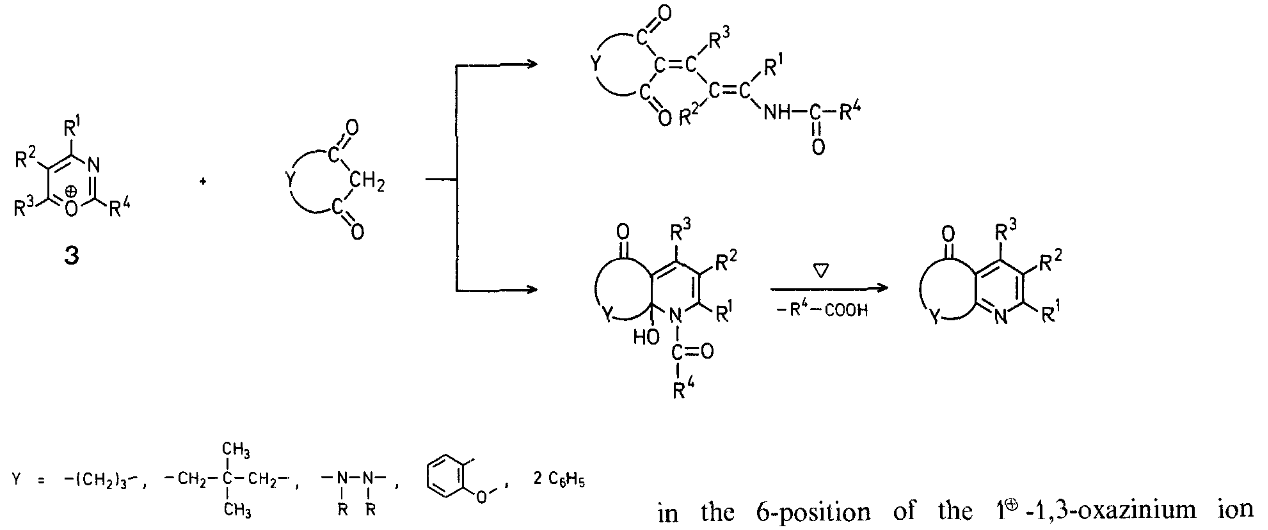
[46] P. Karrer, A. Miyamichi, Helv. Chim. Acta **9**, 336 (1926).

[47] A. I. Meyers, E. M. Smith, A. F. Jurjevich, J. Amer. Chem. Soc. **93**, 2314 (1971).

tautomerism and of interesting subsequent reactions have still hardly been investigated. Examples of such possibilities are summarized in Scheme **H**.



Scheme G



Scheme H

Table 9 gives a representative cross section of the examples investigated.

Reaction of 2,4,6-Triphenyl-1,3-oxazinium Perchlorate (3a) with Malodinitrile[48]:

Procedure A: A mixture of 2,4,6-triphenyl-1,3-oxazinium perchlorate (2.05 g, 5.0 mmol), malodinitrile (0.40 g, 6.0 mmol) and absolute acetonitrile (25 ml) is treated dropwise with triethylamine (0.75 ml, 5.3 mmol). A colorless precipitate is soon deposited from the resultant yellow solution and after 20 min is isolated by filtration and recrystallized from acetonitrile; yield: 1.12 g (60 %) of 2-benzoylamino-3-cyano-4,6-diphenylpyridine. The mother liquor is concentrated and treated with water. The resultant solid is isolated by filtration and recrystallized from ethanol; yield: 0.62 g (33 %) of 4-benzoylamino-1,1-dicyano-2,4-*cis*-diphenylbutadiene (**78a**); m.p. 176°.

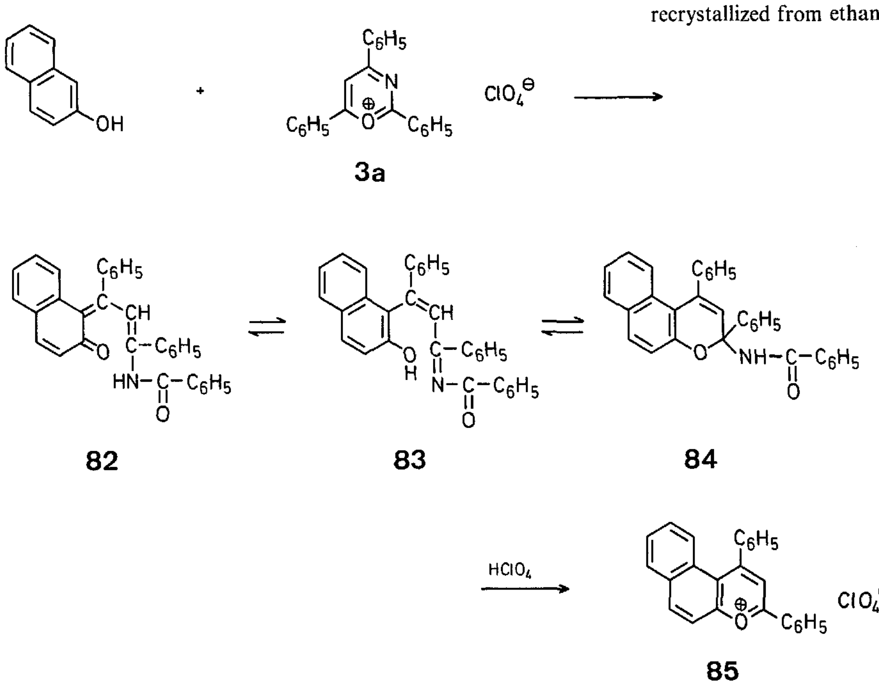
Procedure B: As described above, with 0.65 ml (4.7 mmol) of triethylamine no **80** is obtained, 1.48 g of a mixture of **77a** and **78a** being obtained instead.

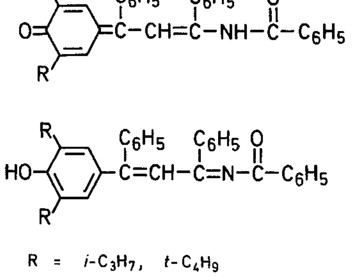
Compounds **78** and the mixture of **77** and **78** can be quantitatively converted into **80** by heating above the melting point.

3.2.2.2. Reactions with Phenols[54]

The reaction of the $1^{\oplus}$-1,3-oxazinium salts (**3**) with phenols has in some cases been carried out in dimethyl sulfoxide in the presence of sodium hydride and in absolute acetonitrile in the presence of triethylamine at room temperature[11,56]. The product-determining nucleophilic attack of the generally very selectively reacting phenoxide ions takes place in the 6-position of the $1^{\oplus}$-1,3-oxazinium ion (Scheme **I**). Here also various aspects support the reversibility of the first reaction step[11]. In the reaction of 2-naphthoxide ion with **3**, the benzo[*f*]chromene **84** is obtained as reaction product via **82** and **83**. Compound **84** can be converted into benzo[*f*]chromylium salt **85** with perchloric acid. The reactions of **3** with 4-*t*-butylphenol, resorcinol, and α-naphthol proceed analogously. α-Naphthol is attacked by the $1^{\oplus}$-1,3-oxazinium ion not in the 4-position but, presumably for thermodynamic reasons, in the 2-position. If the position *ortho* to the hydroxy group is blocked, as in 2,6-di-*t*-butylphenol and 2,6-diisopropylphenol, electrophilic attack by **3** in the *p*-position is observed. In the case of 2,6-di-*t*-butylphenol it is possible, depending on the reaction conditions, to obtain the tautomers **86** and **87** in pure form.

3-Benzoylamino-1,3-diphenyl-3*H*-naphtho[2,1-*b*]pyran (84)[11]:
Sodium hydride (0.55 g; ~ 50 % suspension in oil) is suspended in absolute dimethyl sulfoxide (20 ml). To this suspension, *β*-napthol (1.44 g, 0.01 mol) is added with stirring at 15°. After completion of the evolution of hydrogen, 2,4,6-triphenyl-1,3-oxazinium perchlorate (4.10 g, 0.01 mol) is added with stirring. After 1 hr, the mixture is poured with stirring into ice water. The solid product is isolated by filtration, well washed with water, and recrystallized from ethanol; yield: 3.54 g (78 %); m.p. 180–184°.



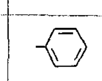
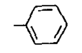
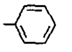
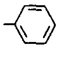
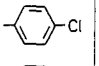
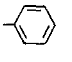
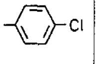
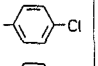
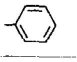

86

87

Scheme I

4-(3-Benzoylamino-1,3-diphenylpropenylidene)-2,6-di-*t*-butylcyclohexadienone (86, R = *t*-C_4H_9)[11]:
A mixture of 2,6-di-*t*-butylphenol (1.03 g, 5 mmol), 2,4,6-triphenyl-1,3-oxazinium perchlorate (2.05 g, 5 mmol), and absolute acetonitrile (20 ml) is treated with triethylamine (0.51 g, 5 mmol) at room temperature. The clear orange-red solution obtained after 5 min soon deposits an orange-red precipitate which is isolated by filtration after 1 hr and recrystallized from absolute acetonitrile; yield: 2.3 g (89 %); m.p. 184°.

Table 9. Butadiene and Pyridine Derivatives **78** and **80** Prepared by Procedure A

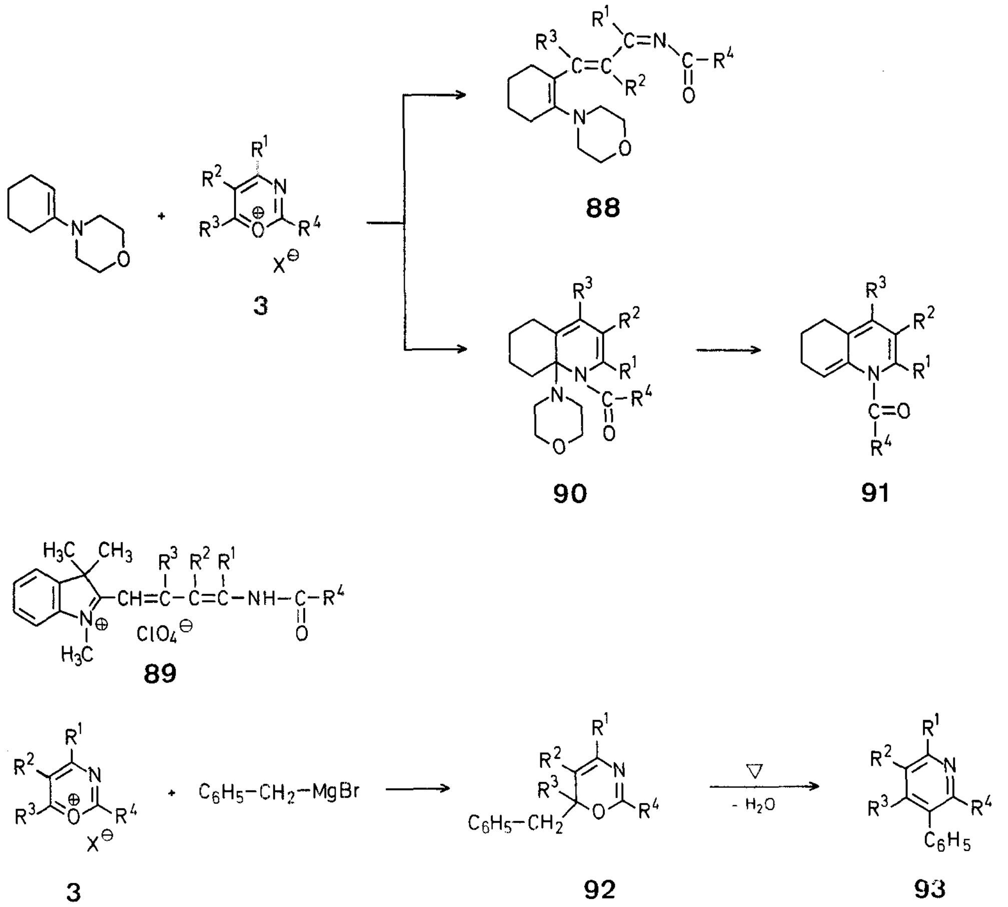
	R¹	R²	R³	R⁴	Yield %		m.p.		References
					78	80	78	80	
a		H			33	60	176°	242°	48
b	CH_3	H	$-OC_2H_5$		36	24	126°	165°	49
c	CH_3	H	$-OC_2H_5$		32	27	142°	181°	49
d	CH_3	H	CH_3		32	—	150°	—	49
e	CH_3	H	CH_3		22	24	139°	182°	49
f	CH_3	H	$-N(CH_3)_2$		73	—	210°	—	49
g	$-SCH_3$	$-(CH_2)_4-$			—	50	—	226–227°	48

3.2.2.3. Reactions with Enamines[11]

Enamines are generally attacked by electrophilic reagents at the nucleophilic β-carbon atom. This applies also for $1^{\oplus}$-1,3-oxazinium ions[11,48]. From morpholinocyclohexene and **3** there are obtained two isomeric products to which spectroscopic findings assign the structures **88** and **90**. As expected, **90** can readily be converted with hydrochloric acid into the tetrahydroquinoline **91**. On reaction of Fischer base with **3**, compound **89** is obtained in high yield as a red dye salt.

3.2.2.4. Reactions with Grignard Compounds[11]

The reaction of the ambivalent $1^{\oplus}$-1,3-oxazinium salts **3** with the rather reactive nucleophilic Grignard reagents is not expected to proceed with high selectivity. Nevertheless, from the reaction of 2,4,6-triphenyl-1,3-oxazinium perchlorate with benzylmagnesium bromide it was possible to obtain 6-benzyl-2,4,6-triphenyl-6*H*-1,3-oxazine (**92**, $R^1=R^3=R^4=C_6H_5$, $R^2=H$) in good yield. Compound **92** can be converted into 2,3,4,6-tetraphenylpyridine (**93**, $R^1=R^3=R^4=C_6H_5$, $R^2=H$) in high yield (Scheme J).



Scheme J

1-Benzoyl-2,4-diphenyl-1,5,6,7-tetrahydroquinoline[11] (**91**, $R^1=R^3=R^4=C_6H_5$, $R^2=H$):

1-Benzoyl-2,4-diphenyl-8a-morpholino-1,5,6,7,8,8a-hexahydroquinoline (**90**, $R^1=R^3=R^4=C_6H_5$, $R^2=H$): 2,4,6-Triphenyl-1,3-oxazinium perchlorate (2.05 g, 5 mmol) is added with stirring to a solution of 1-morpholinocyclohexene (3.34 g, 0.02 mol) in absolute acetonitrile (20 ml). The slightly lemon-yellow precipitate deposited from the reaction mixture after 90 min is isolated by filtration and recrystallized from acetonitrile; yield: 1.0 g (42 %) of **88**; m.p. 151°. Upon storage of the mother liquor in the refrigerator, colorless **90** crystallizes out; yield: 0.70 g (30 %). The product may be recrystallized from petroleum ether; m.p. 162°.

1-Benzoyl-2,4-diphenyl-1,5,6,7-tetrahydroquinoline: Compound **90** (5 mmol) is refluxed in ethanol (10 ml)/conc. hydrochloric acid (5 ml) for 1 hr. After cooling, the reaction mixture is treated with water (80 ml). The resultant precipitate is isolated by filtration and recrystallized from ethanol; yield: 72 %; m.p. 165°.

2,3,4,6-Tetraphenylpyridine (**93**, $R^1=R^3=R^4=C_6H_5$, $R^2=H$)[11]:

6-Benzyl-2,4,6-triphenyl-6 H-1,3-oxazine (**92**, $R^1=R^3=R^4=C_6H_5$, $R^2=H$): A solution of benzylmagnesium bromide (0.02 mol) in a small amount of ether is added dropwise with stirring to a suspension of 2,4,6-triphenyl-1,3-oxazinium perchlorate (4.10 g, 10 mmol) in absolute dichloromethane (50 ml). After 5 hr, the reaction mixture is treated with ice water and the ethereal phase is separated off, dried, and concentrated. The residual oil is crystallized from low-boiling petroleum ether. Recrystallization of the product from ligroin is also possible. Yield: 3.0 g (70 %); m.p. 124°.

2,3,4,6-Tetraphenylpyridine: 6-Benzyl-2,4,6-triphenyl-6*H*-1,3-oxazine (1.0 g, 25 mmol) is heated until gas bubbles form. After completion of the reaction, the mixture is cooled, the glassy product crystallized from a small amount of ethanol, and isolated by filtration; yield: 0.81 g (85 %); m. p. 180° (Ref.[58], m.p. 179°).

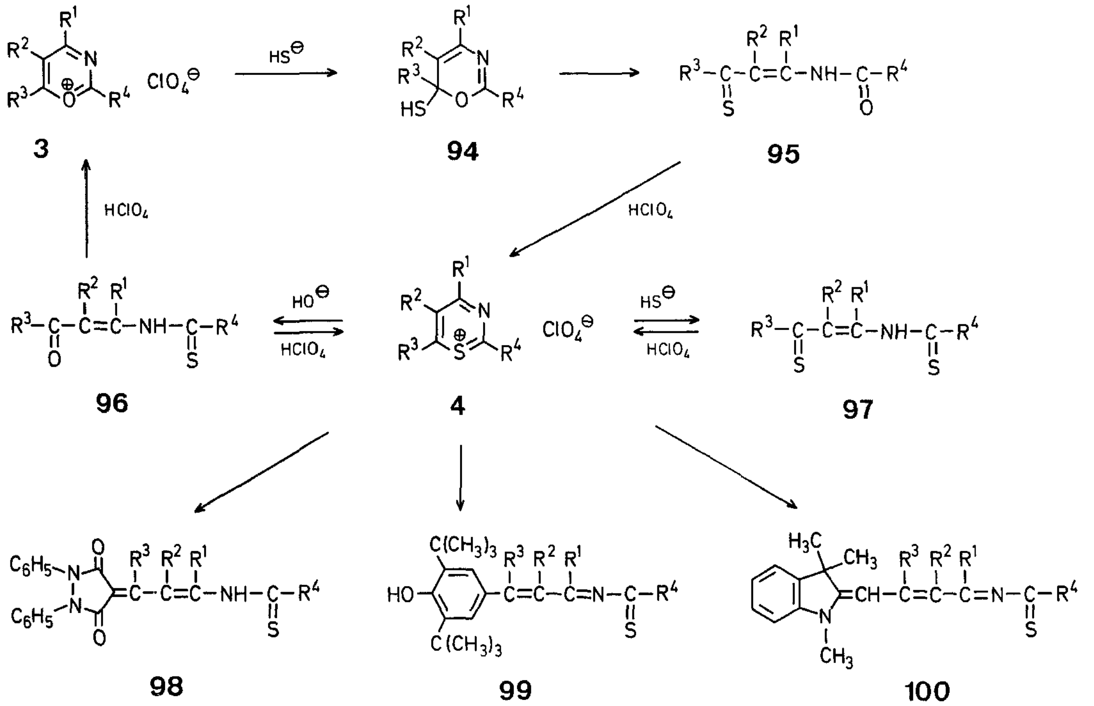
3.2.3. Reactions of $1^{\oplus}$-1,3-Oxazinium Salts with Nucleophilic Sulfur Compounds

The reaction of $1^{\oplus}$-1,3-oxazinium perchlorates (**3**) with hydrogen sulfide in absolute acetonitrile gives high yields of orange-red to dark-red compounds to which structure **95** is assigned. Compounds **95** result via **94** from attack of the 6-position by hydrogen sulfide anion, HS$^{\ominus}$ (Scheme **K**). Analogously to the cyclization of the corresponding β-acylaminovinylcarbonyl compounds to **3**, compounds **95** could be converted with anhydrous perchloric acid into the $1^{\oplus}$-1,3-thiazinium salts **4**. With compounds **4**, a new ambivalent electrophilic system becomes available for corresponding reactions.

2,4,6-Triphenyl-1,3-thiazinium Perchlorate (4a)[55]**:**
Absolute acetonitrile (40 ml) is saturated with hydrogen sulfide at 0°. 2,4,6-Triphenyl-1,3-oxazinium perchlorate (4.10 g, 10 mmol) is then added and the stirred mixture is treated dropwise with triethylamine (1.01 g, 10 mmol). After 15 min, conc. perchloric acid (1.20 ml) is added at 0°. The yellow crystalline product deposited from the orange-yellow solution is isolated by filtration, washed with absolute acetonitrile, and recrystallized from absolute acetonitrile; yield: 2.70 g (63 %); m.p. 280–282°.

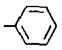
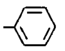
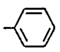
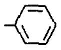
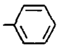
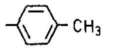
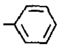
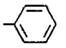
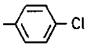
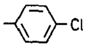
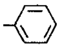
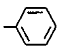
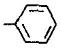
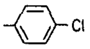
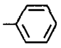
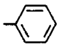
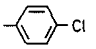
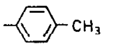
3.3. Reactions of $1^{\oplus}$-1,3-Thiazinium Salts (4)[55]

The reactions of the $1^{\oplus}$-1,3-thiazinium salts **4** with nucleophilic oxygen, carbon, and sulfur compounds parallel those of the $1^{\oplus}$-1,3-oxazinium salts **3**. With sodium hydroxide, nucleophilic attack by hydroxide ion in the 6-position and subsequent ring scission leads to the formation of the thioamides **96** isomeric to **95** (Scheme **K**). As nucleophilic carbon compounds there have so far been subjected to reaction with **4** the carbanion of 3,5-dioxo-1,2-diphenylpyrrolidine, 2,6-



Scheme K

Table 10. $1^{\oplus}$-1,3-Thiazinium Perchlorates (4) Prepared from $1^{\oplus}$-1,3-Oxazinium Perchlorates and Hydrogen Sulfide

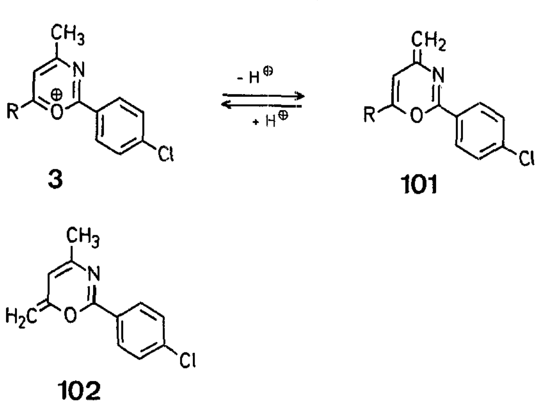
	R¹	R²	R³	R⁴	Yield %	m.p.	References
a		H			63	280–282°	55
b		H			91	238–241°	55
c		H			65	206–208°	55
d		H			55	257–260°	55
e		H			61	253–255°	55
f	CH₃	H	$-OC_2H_5$		63	112°	55
g	CH₃	H	$-OC_2H_5$		78	125°	55
h	CH₃	H	$-OC_2H_5$		71	123°	55

di-*t*-butylphenol, and 2-methylene-1,1,3-trimethyl-dihydroindole. Analogously to the reactions with $1^{\oplus}$-1,3-oxazinium salts (**3**) there are obtained the corresponding thioamides **98**, **99** and **100**. The reaction with hydrogen sulfide leads, as expected, to the dithiono compound **97**. Recyclization of **97** leads back, with elimination of hydrogen sulfide, to the starting material. The situation is different with the $HO^{\ominus}$ reaction product **96**; depending on the substituents, either **4** or a mixture of **3** and **4** is obtained. According to these findings, in addition to the $1^{\oplus}$-1,3-oxazinium salts **3** the $1^{\oplus}$-1,3-thiazinium salts **4** are also suitable for transferring variously substituted unsaturated C_3 residues to nucleophilic reactants.

3.4. Action of Base on $1^{\oplus}$-1,3-Oxazinium Salts[56]

The electron requirement of the $1^{\oplus}$-1,3-oxazinium salts can, especially with the 2-, 4-, and 6-alkyl-substituted members of this class of compounds, also be compensated by elimination of a proton from a (α-)C—H bond. This competitive reaction to nucleophilic addition is in particular to be expected with strong bases of low nucleophilic character; it leads to interesting hetero analogs of fulvenes.

The choice of the base for the elimination of a proton from **3** is decisive. The sensitivity to hydrolysis and the great tendency to self-condensation of **3** and fulvene-related compound **101** require an absolute anhydrous medium and substantial separation of **3** and **101** by two different phases. The best results have been obtained with triethylamine as solvent and base. By brief reaction of **3** with triethylamine at room temperature it was possible to bring about conversion into the fulvene analogs **101**, which are very unstable in air.



Scheme L

Table 11. 6-Substituted 2-(4-Chlorophenyl)-4-methylene-1,3-oxazines (**101**) Prepared from 6-Substituted 2-(4-Chlorophenyl)-4-methyl-$1^{\oplus}$-1,3-Oxazinium Salts[56]

101	R	Yield %	m.p.
a	OC_2H_5	42	80°
b	C_6H_5	70	108°
c	CH_3	48	74°

2-(4-Chlorophenyl)-6-ethoxy-4-methylene-1,3-oxazine (101a)[56]: 2-(4-Chlorophenyl)-6-ethoxy-4-methyl-1,3-oxazinium perchlorate (7.0 g, 0.02 mol) is gradually added at 0° with vigorous stirring to absolute triethylamine (100 ml) in a nitrogen atmosphere. After 10 min, the mixture is filtered and the filtrate is concentrated. The yellow residue is carefully recrystallized from ethanol; yield: 2.1 g (42 %); m.p. 80°.

The preferential reactivity of the C-6 atom of the 6-methyl-$1^{\oplus}$-1,3-oxazinium salts under nucleophilic attack would lead to the expectation of predominant or exclusive formation of the 6-methylene derivative **102** on reaction with base. Surprisingly, however, the heterofulvene analog **101c** is isolated as the sole product. This discrepancy between the position of highest α-CH acidity and the position of the preferred product-determining attack is subject of further investigations.

$1^{\oplus}$-1,3-Oxazinium and $1^{\oplus}$-1,3-thiazinium salts (**3** and **4**) are accordingly interesting intermediates for the synthesis of derivatives of pyrazole, 1,2-oxazole, pyridine, pyrimidine, quinoline, isoquinoline, 1,3-oxazines, chromenes, chromylium salts, unsaturated aldehydes, vinylogous quinone methides, *β*-acylaminovinylcarbonyl compounds, and butadiene, to name only the most important reaction possibilities (see Schemes **F**–**L** and Tables 8–11). Central to these reactions is attack of the C-6 atom of salts **3** and **4** by nucleophilic reagents.

The author would like to express his sincere thanks to Prof. B. Bredereck, to the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie for their valuable Support of own work in this review.

Received: June 7, 1971

---

[48] R. R. Schmidt, Chem. Ber. **98**, 3892 (1965).

[49] R. R. Schmidt, D. Schwille, S. Sommer, Liebigs Ann. Chem. **723**, 111 (1969).

[50] M. Lora-Tamayo, R. Madroñero, G. G. Muñoz, H. Leipprand, Chem. Ber. **97**, 2234 (1964).

[51] R. R. Schmidt, Angew. Chem. **77**, 218 (1965); Angew. Chem. Internat. Edit. **4**, 241 (1965).

[52] S. Hünig, K. Hübner, Chem. Ber. **95**, 937 (1962).

[53] K. Dimroth, Angew. Chem. **72**, 331 (1960).
W. Schroth, Z. Chem. **4**, 281 (1964).

[54] R. R. Schmidt, Tetrahedron Lett. **1965**, 4357.

[55] R. R. Schmidt, D. Schwille, Chem. Ber. **102**, 269 (1969).

[56] R. R. Schmidt, D. Schwille, H. Wolf, Chem. Ber. **103**, 2760 (1970).

[57] R. R. Schmidt, D. Schwille, unpublished results.

[58] E. Knoevenagel, H. Schmidt, Liebigs Ann. Chem. **281**, 50 (1894).