Tetrahedron Vol 37, No. 23, pp. 3997 to 4006, 1981
Printed in Great Britain

0040-4020/81/233997-10$02.00/0
Pergamon Press Ltd

CYCLIC VINYL ETHER CARBANIONS—II

PREPARATION AND APPLICATIONS TO THE SYNTHESIS OF CARBONYL COMPOUNDS

ROBERT K. BOECKMAN, JR.[1]* and KENNETH J. BRUZA
Department of Chemistry, Wayne State University, Detroit, MI 48202, U.S.A.

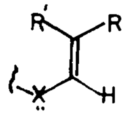
(*Received in U.S.A.* 11 *April*, 1981)

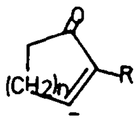
Abstract—Conditions for metalation of a variety of cyclic vinyl ethers and reaction of the resulting carbanions with electrophiles are described. Effects of the vinyl ether structure on the relative rates of metalation are discussed. Applications of this methodology to the construction of various types of carbonyl compounds are presented.

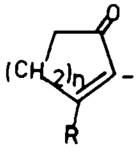
The use of heteroatom facilitated metalation for the preparation of synthetically useful and otherwise inaccessible carbanions has seen tremendous growth in the past several years. Among the useful developments are the carbanions derived from allylic ethers,[2] allylic halides,[3] and allylic thioethers.[4] Preparation of dipole stabilized carbanions,[5] and heteroatom directed metalation of certain acyclic systems[6] has further increased the synthetic scope of the metalation process.

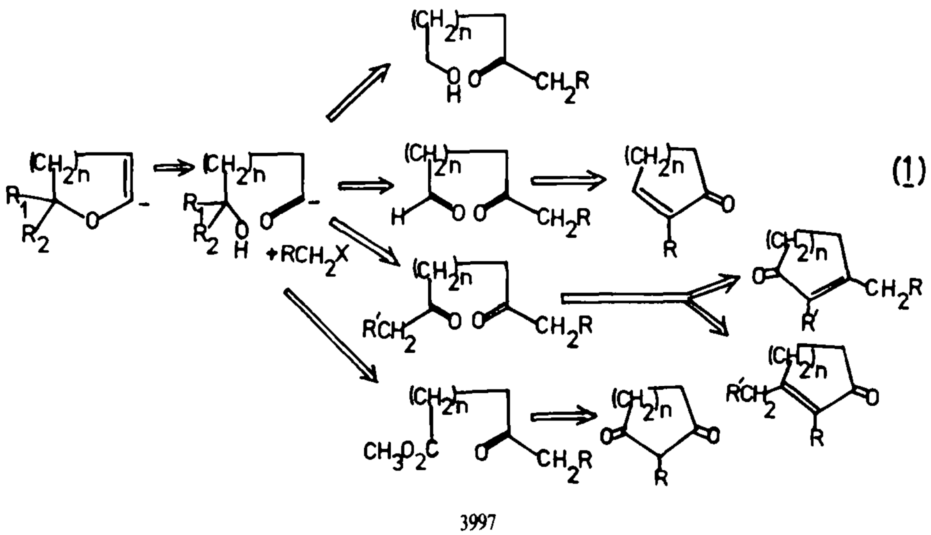
This paper will deal with aspects of the preparation and utility of the carbanions derived from cyclic vinyl ethers. This class of compound represents a subgroup of the general sturcture **1**, in which the presence of a heteroatom on the double bond facilitates proton abstraction by a suitable base. Examples exist in which a variety of heteroatoms function to facilitate proton removal including O,[7] S[8] and N.[9] Our interest in the problem was prompted by recognition that cyclic analogs of the simple vinyl ethers examined by Baldwin[7] and Schöllkopf[7] could function as masked bifunctional CO anions, which upon further transformation could afford a variety of cyclic carbonyl compounds. The overall transformations are shown in eqn (1), and suggest that by use of an appropriate primary carbon electrophile, these species become formally equivalent to the cyclic α and β acyl vinyl carbanions **2–3** reacted with RX when considering the overall transformation.

When we began our work only three instances of the preparation of this sort of carbanion had been reported. Initially, Paul and Tchelitcheff had investigated the reaction of dihydropyran with pentyl sodium.[10] Subsequently, Rautenstrauch and Schlosser reported evidence that such carbanions could be prepared by metalation with nBuLi in certain instances.[11–13] No preparatively useful and general procedure for metalation of substances of this type was available, and little or no


(1)


(2)
n=1,2


(3)
n=1,2


(1)

investigation of the reactivity of the resulting carbanions had been undertaken. However, Riobe *et al.* have also been investigating this chemistry and their initial studies were reported along with our own in 1977.[14–15]

Preparation of the vinyl ethers

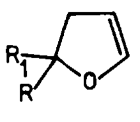
We elected to study the series of dihydrofurans **4–6** and the dihydropyrans **7–13**, ortho ester **14** was not examined. However, it would appear likely that its behavior would mirror that of **6**. The majority of the dihydropyrans which were not commercially available were prepared by the Diels–Alder reaction of acrolein or crotonaldehyde and the appropriate vinyl ether or keteneacetal.[16] In the case of ether **8**, this substance was propared by chlorination-dehydrochlorination of **7**.[17] Methyl dihydropyran **9** was obtained by reduction of lactone **15**[18] with Dibal-H and elimination (MsCl/Py/Δ).

2,3 Dihydrofuran (**4**) was prepared by photoisomerization of the commercially available 2,5 isomer in the presence of $Fe(CO)_5$.[19] The remaining dihydrofurans (**5–6**) were propared by the general sequence shown in eqn (2).[20] The overall yields of **5** and **6** were in the range of 30–40%.

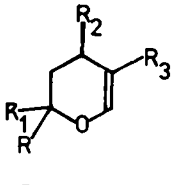
Metalation studies

Our initial studies sought to determine the optimal base for selective metalation of **7**. We investigated the use of nBuLi,sBuLi and tBuLi. Although minor amounts ($\leqslant$5% by NMR) of metalation were detected for the first two lithium reagents, nowhere near the ideal of quantitative conversion to the carbanion occurred with stoichiometric amounts of lithium reagent. We did not examine extensively the use of chelating agents such as TMEDA to facilitate metalation, due to the desire to minimize the presence of extraneous substances during subsequent reactions of the carbanions and to permit simplified workup procedures. Riobe *et al.* report the successful use of nBuLi for the preparation of the carbanion of **7** (as well as **8**), which apparently stems from use of high temperatures.[15] We turned to the use of tBuLi as the metalating agent.[21] We observed complete conversion of **7** to its carbanion with ~1 eq. of this Li reagent in THF at about 0° as judged by both NMR and deuterium oxide quenching experiments. The anion proved stable for at least several hrs at room temperature in THF. Little or no reaction was observed at −78° or until the temperature reached about 0° whereupon the characteristic yellow color of the THF solvated Li species (2tBuLi·THF) was rapidly discharged.[22] We examined the use of other ethereal and hydrocarbon solvents such as ethyl ether, dimethoxyethane (DME) and n-pentane but these were uniformly unsatisfactory providing <5% metalation as judged by deuterium incorporation. This strongly implicates the solvated dimer 2tBuLi-THF as the species which is actually involved in the metalation. THF is known to be particularly effective in disrupting the aggregated structure of the *t*-BuLi as it is present in hydrocarbon media.[23]

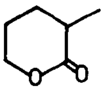
Extension of the above studies to the other dihydrofurans and pyrans (**4–6**, **8–12**) uncovered a significant variation of reactivity with structure. For example, treatment of **10** with tBuLi in THF as above resulted in low (<5%) conversion to the carbanion. It was ascertained by following the reaction by NMR that a significant amount of tBuLi was consumed by attack on the solvent as described by Bates.[24] Accordingly, we were able to overcome this difficulty by use of only minimal amounts of THF in pentane (~2 eq/eq of tBuLi) and by use of ~2 eq of tBuLi/eq of vinyl ether. Employing these conditions resulted in essentially quantitative conversion of **10** to its anion. For preparative purposes, solutions of the anion were diluted with THF which served to destroy any excess tBuLi remaining. The origin of the requirement for excess metalating agent is not completely clear. However, complexation of the metalating agent by the additional oxygen present in **10** is conceivable. In the same manner, it was ascertained that use of ~3 eq of tBuLi was required to efficiently



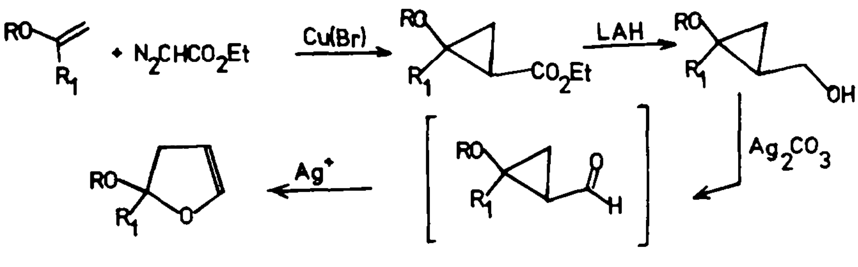
4 $R = R_1 = H$
5 $R = H;\ R_1 = oiBu$
6 $R = CH_3;\ R_1 = OCH_3$
14 $R = R_1 = OCH_3$



7 $R=R_1=R_2=R_3=H$
8 $R=R_1=R_2=H; R_3=Cl$
9 $R=R_1=R_2=H; R_3=CH_3$
10 $R=H; R_1=OCH_3; R_2=R_3=H$
11 $R=CH_3; R_1=OCH_3; R_2=R_3=H$
12 $R=H; R_1=OEt; R_2=CH_3; R_3=H$
13 $R=R_1=OEt; R_2=R_3=H$



(15)



(2)

Table 1.

Vinyl Ether	Eq. tBuLi	Rel Rate[c]
4	1	0.84
5	2	0.65
6	3[a]	—[d]
7	1	1.0
8	1	1.56
9	large excess[b]	—[b]
10	2	0.77
11	3	0.63
12	1.5-1.8	0.93
13	1.5-1.8	0.82

(a) a mixture of the desired anion and 2-methylfuran obtained

(b) no reaction occurred

(c) an equimolar mixture of 7 and a second furan or pyran (1 mmol of each) were treated with 1 mmol of tBuLi at 0°C for 10 min, quenched with D_2O and the pyrans (furans) isolated and analyzed by NMR (triplicate runs)

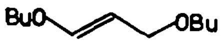
(d) Not accurately accessible due to competing side reactions

generate the anion derived from **11**. The remaining dihydropyrans and furans underwent metalation under conditions comparable to **7**, **10** or **11** as shown in Table 1. Some limitations were encountered. The presence of alkyl groups at the β position appears to preclude metalation under these conditions. Also, a competitive elimination to the furan was observed in the case of **6**. This may result from coordination of the oxygen of the OMe group by Li which, coupled with the increased stabilization of the intermediate, leads to more rapid elimination. Use of bulky alkyl groups to retard this process by inhibiting Lewis acid assistance has not yet been investigated.

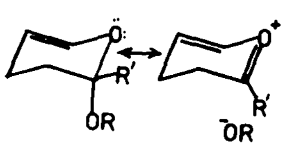
Upon noting the apparent differences in reactivity suggested by the data in Table 1, we were led to determine the relative rates of metalation of a representative series of dihydropyrans and furans. These data, also shown in Table 1, were obtained from competition experiments for limited quantities of metalating agent (tBuLi) by analysis of the ratios of residual undeuterated vinyl ethers after quenching with D_2O. The appropriate control experiments established that $>95\%$ of the tBuLi is consumed in deprotonation and that no exchange occurs between the anions once formed which would result in deuterium scrambling.

It is interesting to note that, qualitatively, the requirements for several-fold excess of tBuLi to achieve complete metalation in some cases, are not reflected in the relative rates of metalation (e.g. **7** vs **11**). This, again, suggests complexation or aggregation phenomena as suggested earlier, although the minimum mole ratio of metalating agent for complete conversion was not firmly established in the preparative experiments. However, the relative changes in metalation rates are consistent within the pyran and furan series (e.g. **4** vs **5** and **7** vs **10**) upon substitution of OMe for H. Overall the dihydrofurans have slightly lower kinetic acidities than the corresponding pyrans.

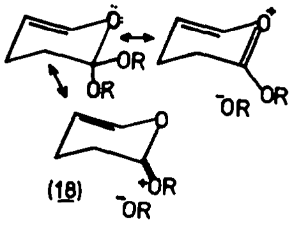
The question of regiospecificity in metalation (allylic vs vinyl) is significant. At no time did we observe any evidence of allylic metalation, with the possible exception of **6**, although the mechanism of the elimination has not been established and need not proceed by prior allylic metalation. The question of regiospecificity was also addressed by Gould and Remillard who examined the metalation of the bis ether **16**, finding exclusive vinyl metalation.[25] The results were interpreted on the basis of molecular orbital calculations which suggested that the selectivity for kinetic proton removal from the vinyl position in **16** derives from population of the antibonding σ^* orbital of the adjacent vinyl H-bond by n electrons formally associated with oxygen, resulting in a weakening of this bond.[26] In spite of the relatively small changes in kinetic acidity in the series we have examined, the trends observed appear to fit this qualitative model. The additional substituents would exert an influence which would either increase or decrease this hyperconjugative weakening of the α H-bond. In the case of alkoxy substituents in **10** and **11** the effects oppose one another and in the case of chlorine in **8** they are complementary (Fig. 1). In fact, the trends observed for increasing alkoxy substituents also correlate with



(16)



(17)



(18)

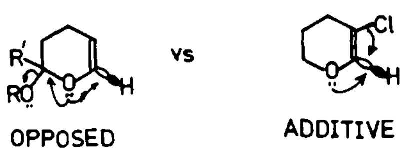


Fig. 1

expected conformational effects on the resonance contribution (shown in Fig. 1) due to the anomeric effect. To exert the maximal reduction in kinetic acidity the alkoxy group must be positioned axial with respect to the ring, the conformation in which the maximum contribution of resonance of the type shown (**17**) occurs. The changes observed when comparing **10** and **11** mirror the change in the relative proportion of molecules with the alkoxy substituent axial (74 vs 100% respectively).[27] In the case of **13**, two O atoms participate in the delocalization (**18**) so the electron demand on the ring O is decreased in spite of all molecules having one alkoxy group axial, resulting in approximately the same rate of metalation as **10**.

We have also examined whether these effects are associated solely with the cyclic nature of systems like **10**, **11** and **13**. We prepared ether **19**, an acyclic analog of **10**, by protection of bromoethanol with ethyl vinyl ether catalyzed by dichloroacetic acid affording **20** (81%) which was dehydrohalogenated by distillation from KOH (71%) to provide **19**.

Metalation of acyclic ether **19** showed qualitatively the same behavior as **10**, requiring two equivalents of tBuLi for efficient metalation. The position of metalation was demonstrated by D_2O quenching and addition of the carbanion derived from **19** to octanal affording **21** in 43% yield.

Reactions with electrophiles

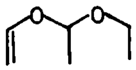
The carbanions derived from vinyl ethers **4–7** and **10–13** react readily with a variety of electrophilic reagents providing the expected addition products in good to excellent yield. A selection of examples of the addition of these carbanions to aldehydes and ketones is shown in Table 2. Addition to α, β unsaturated aldehydes and ketones proceeds in 1,2 fashion exclusively, and selectivity for ketones over esters is exhibited. Little or no enolization is apparent in these reactions, although the extremely hindered system, fenchone, failed to afford any addition product with the anion derived from **7**.

The anions are capable of acylation provided the correct acylating agents are utilized. Poor yields result from attempts at acylation with reactive acylating agents such as acid chlorides or anhydrides. Use of unreactive acylating agents results in multiple addition to the extent reaction occurs. To this degree, these carbanions mirror the usual reactivity patterns of hard unstabilized organometallics. However, use of N,N-dialkyl amides permits acylation in reasonable yield as indicated by the formation of **22** and **23** upon reaction of the anion derived from **7** with N,N-dimethylacetamide and N,N-dimethylformamide in 41% (~70% by NMR) and 30% (~75% by NMR) yields respectively (unoptimized). The anions derived from **7** and **10** also provide ketene hemithioacetals **24** and **25** in 79% and 86% yields respectively upon reaction with diphenyldisulfide. In the absence of a strongly Lewis acidic counterion, these anions open epoxides sluggishly if at all. For example, the anion derived from **7** affords adduct **26** upon reaction with isobutylene oxide in only 20% yield. Nevertheless, these systems offer the potential for rapid assembly of certain difficultly accessible classes of compounds such as **24**. In general, the yields of purified materials are high. In some instances the lower yields reported result from difficulties encountered in isolation and purification of the substances due to water solubility, volatility or sensitivity. It is generally the case that the crude material is pure enough for further transformation without need of extensive purification. Often this results in substantially increased overall yields (70–80% vs 30–50%).

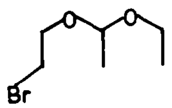
These adducts of addition to carbonyl compounds can be unmasked hydrolytically under extremely mild conditions, one of the major advantages of this class of masked CO anions. Hydrolysis of a representative group of adducts was effected by ~2N H_2SO_4 in THF at room temperature as shown in Table 3.

However, the most interesting and potentially useful aspect of this methodology arises from reaction of these carbanions with alkyl halides and further transformation of the masked polycarbonyl systems thus obtained.

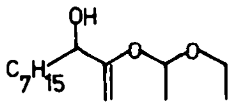
In general, the carbanions derived from the cyclic vinyl ethers **4–7** and **9–13** are only moderately nucleophilic toward alkyl halides, requiring use of only more reactive alkylating agents. Primary and secondary allylic bromides and iodides, saturated primary iodides, and some primary bromides undergo alkylation readily, the latter groups, however, only in the presence of HMPA to increase the nucleophilicity of the carbanions. Alkyl chlorides and tosylates were unreactive. Generally, tem-



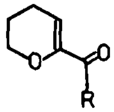
(19)



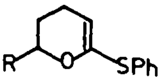
(20)



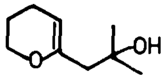
(21)



(22) $R=CH_3$
(23) R=H

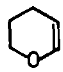
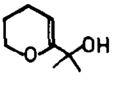
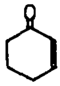
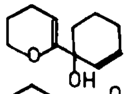
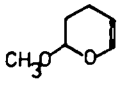
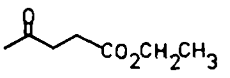
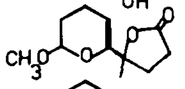
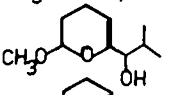
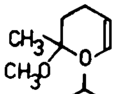
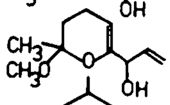
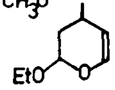
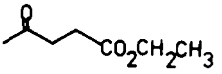
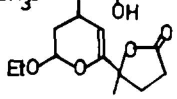
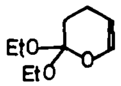
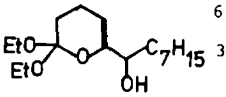
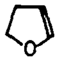
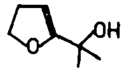
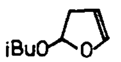
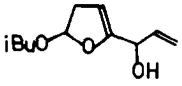
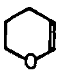
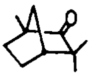


(24) R=H
(25) $R=OCH_3$



(26)

Table 2.

Case	Reactant[a]	Carbonyl Component	Product	Yield[b]
1				86%
2	"			68%
3				86%
4	"	$(CH_3)_2CHCHO$		66%
5		$CH_2{=}CHCHO$		50%
6				47%
7		$C_7H_{15}CHO$		65%[c] 30%
8				78%
9		$CH_2{=}CHCHO$		68%[d]
10			—	N.R.

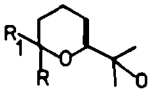
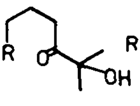
a) Typical procedure involves reaction of the derived anion (1 eq.) with the carbonyl compound (1 eq.) at -78°C in THF.

b) Isolated yields of purified products. Crude yields of reasonably pure products much higher in some cases.

c) Yield determined by NMR

d) Yield based upon recovered starting material

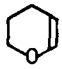
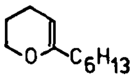
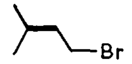
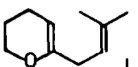
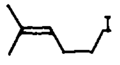
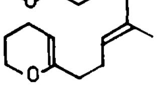
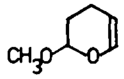
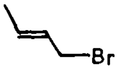
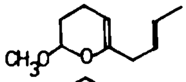
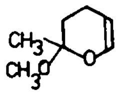
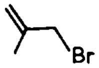
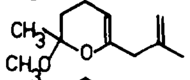
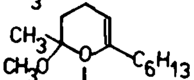
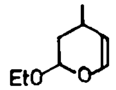
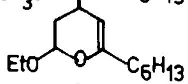
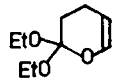
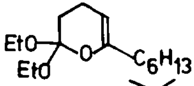
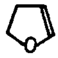
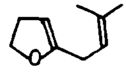
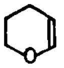
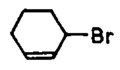
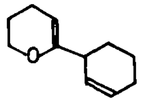
Table 3.

Adduct		Product		Yield[a]
	$R{=}R_1{=}H$		$R{=}CH_2OH$	47%
"	$R{=}H;R_1{=}OCH_3$	"	$R{=}CHO$	96%
"	$R{=}R_1{=}OEt$	"	$R{=}CO_2Et$	58%

a) Isolated yield of chromatographically purified material.

peratures of 0°C to room temperature were required. Although the stability of these anions was not examined above room temperature, use of more forcing conditions may permit successful alkylation in unreactive cases. However, under the standard conditions (room temp/THF/HMPA (~1 eq/eq anion)) secondary octyl iodide failed to react. In simple cases, the halide was treated as the limiting reagent, due to the difficulties associated with removing unreacted halide from the alkylated products, and reactions were routinely run with 1.6–1.7 equivs of anion per equiv, of halide. A representative series of cases is shown in Table 4 which reflects the scope and limitations of the alkylation process. Again yields are cited for purified materials, which in many instances are substantially lower than the yields of crude but acceptably pure materials obtained prior to purification, due to the

Table 4.

Case	Vinyl Ether	Alkyl Halide	Product	Yield[a]
1		$C_5H_{11}CH_2I$		55%
2	"			53%
3	"			52%
4				61%
5				33% (70%)[b]
6	"	$C_5H_{11}CH_2I$		63%[b]
7		"		74%[b]
8		"		80%[b]
9				67%
10				60%

a) Isolated yields of chromatographically purified or distilled product.

b) Yield determined by NMR based upon recovered starting material.

hydrolytic sensitivity of these substances and their propensity for polymerization during distillation even in base-washed apparatus.

One notable side reaction was encountered which reflects the delicate balance between nucleophilicity and basicity in these systems. While crotyl, methallyl and β, β-dimethylallyl halides all underwent alkylation, use of allyl bromide or iodide routinely resulted primarily in recovery of starting vinyl ether with only minor amounts (10–20%) of the desired alkylation products being produced under a variety of conditions. In this case, deuterium quenching experiments revealed not the apparent lack of reactivity but rather proton transfer resulting in metalation of the allylic halide. The ease with which this occurs has been documented recently by McDonald[3] and has been observed previously by Reich in the alkylation of some selenium stabilized anions.[28] Yet it is noteworthy that alkylation of a homoallyl halide proceeds without elimination (case 3, Table 4). It is clear, however, that these anions are much more like true organometallics rather than more stabilized anions, usually employed for C–C bond formation, and are therefore likely to behave as bases rather than nucleophiles in reaction with hindered systems.

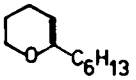
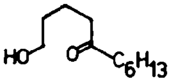
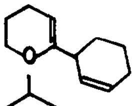
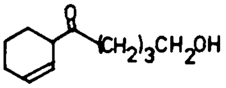
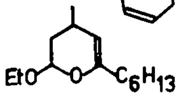
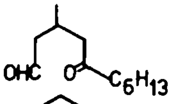
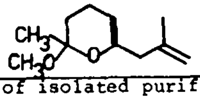
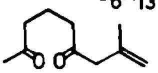
Nevertheless, the limitations in the structure of the halide are relatively few and the ready transformation of the alkylated dihydropyrans and furans made accessible by this methodology to polycarbonyl compounds and related cyclization products reveals the considerable utility of this methodology in the construction of polyfunctional systems.

Hydrolysis of the alkylated dihydropyrans and furans proceeds under the same mild conditions (~2N HCl or 2N H_2SO_4 in THF) as described previously affording the intermediate hydroxy ketones or dicarbonyl systems in generally high yield as shown in Table 5. Conditions are sufficiently mild so as to preclude aldol or other condensation, and permit the isolation of β,γ-unsaturated ketones without double bond isomerization. Other hydrolytic methods which can be employed include aq. oxalic acid/THF and wet silica gel in ether if even milder hydrolytic conditions are required.

A more efficient method for producing cyclized products involves direct conversion of the vinyl ether to the cyclized material without isolation of any intermediate hydrolysis products. The aldol chemistry employed has been investigated extensively with a view to understanding the factors which control the regiochemistry of the cyclization. It has been established that the reaction can be run under both kinetic and thermodynamic control and that the ring size (5 or 6) being formed influences the rate controlling step.[29,30] Some representative examples of these conversions are listed in Table 6.

It is interesting to note that case 1 afforded the intermediate aldol **27** in good yield (65%) if the starting vinyl ether was treated with acid at room temperature for short periods (1 h). Cases 1 and 2 illustrate one feature of

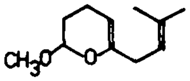
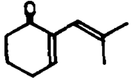
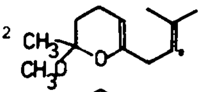
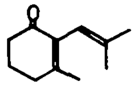
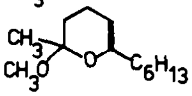
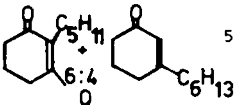
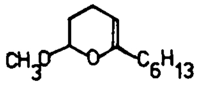
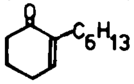
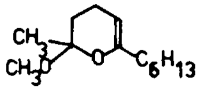
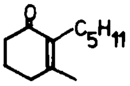
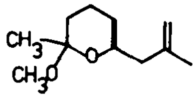
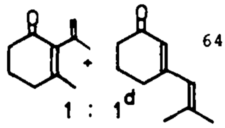
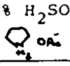
Table 5.

Case	Vinyl Ether	Product	Yield[a]
1			97%
2			77%
3			53%
4			32% (72%)[b]

a) Yield of isolated purified product

b) Crude yield of reasonably pure (>90% by NMR) material

Table 6.

Case	Vinyl Ether[a]	Reaction Conditions[b]	Product(s)	Yield[e]
1		HCl/45°C/4h		82%
2		HCl/R.T./48h		50%
3		1)HCl/THF 2)NaOH/EtOH/RT/2.5h	 6:4	58%
4		HCl/45°C/14h		52%
5		1)HCl/THF 2)NaOH/CH$_3$OH/65°C/0.3h		72%
6		1)HCl/THF 2)DBU/CH$_3$OH/65°C/48h	 1 : 1[d]	64%
7	"	1)HCl/THF 2)KOH/MeOH/65°C	" " 80 : 20	72%
8	"	1)5% H$_2$SO$_4$//Δ^c 2)KOH/MeOH	" " 20 : 80	65%
9	"	1)5% H$_2$SO$_4$/  /Δ^c 2)  /PhH/80°C/1h	" " 0 : 100	17%

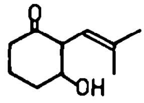
a) Yields of products are based upon starting vinyl ether

b) When both acid and base treatment are required, no purification of the intermediate was performed

c) Hydrolysis under the more vigorous conditions afforded the conjugated diketone CH$_3$CO(CH$_2$)$_3$COCH=C(CH$_3$)$_2$ which was isolated in 77% yield.

d) Ratio determined by NMR

e) Yields cited are total yields of chromatographically purified materials



(27)

this methodology. Use of allylic halides permits preparation of the general class of α vinyl cyclohexenones very efficiently. The method is, of course, governed and limited by the regiochemistry inherent in the final aldol dehydration sequence which is highly substrate structure dependent and sensitive to the exact nature of the catalyst and reaction conditions employed.[29,30] It is usually the case that at elevated temperatures, thermodynamic product control is observed (see cases 3 and 5).[29] However, considerable control over the product distribution is sometimes possible by adjusting the conditions for hydrolysis and subsequent cyclization (see cases 6–9). In general, reactions generating keto aldehydes can be induced to provide dehydration products (case 4) under acidic conditions. However, those systems generating diketones do not readily undergo cyclization-dehydration under the acidic hydrolysis conditions, and basic conditions must be employed. The intermediate hydrolysis products, although isolable in generally good yield (see Table 5), were directly treated with base as indicated to afford cyclized products. In the case of certain systems (cases 6–9), the integrity of the intermediate β,γ-unsaturated diketone can be maintained (cases 6–7) or under more vigorous acidic conditions, the α,β-unsaturated diketone may be obtained. This of course profoundly affects the product distribution arising from the subsequent aldo dehydration reactions permitting selection of either tri or tetra substituted enone as the major product.

Obviously, the possibilities for extension of this methodology to the production of diketones, to use in annulation reactions and other similar processes are manifold. Results from ongoing studies in these areas will be the subject of future reports from these laboratories.

EXPERIMENTAL

M.p.s were determined with a Thomas–Hoover capillary m.p. apparatus and are uncorrected. B.p.s are uncorrected. Bulb to bulb distillations were performed using a Büchi Kugelrohr distillation oven and temps reported are oven temps. IR spectra were obtained on a Perkin-Elmer 137 spectrophotometer and are reported in reciprocal centimeters (cm^{-1}) using polystyrene as standard. NMR spectra were recorded on a Varian T-60 (60 MHz) spectrometer and are reported in PPM(δ) relative to TMS. Carbon 13 NMR spectra were obtained using a JEOL JNM-FX60 F.T.NMR spectrometer (60 MHz proton). Mass spectra were recorded on an AEI MS-902 mass spectrometer. Exact mass data were obtained by peak matching and were recorded at the NIH Regional Mass Spectrometry Facility at Michigan State University. Microanalyses were performed by Midwest Microlab, Indianapolis, Indiana.

All solvents and reagents reported as anhydrous were dried by distillation from an appropriate drying agent (ethers–LAH). HMPA was Aldrich grade and was distilled from CaH before use. All reactions involving organometallic reagents were performed under an argon atmosphere.

General procedure for the preparation of dihydropyrans

2-*Methoxy*-2-*methyl*-3,4-*dihydro*-2(H)-*pyran* (**11**). A mixture of 2-methoxypropene[31] (3.1g; 43 mmol), acrolein (2.4g; 43 mmol) and a catalytic amount of 2,6-di-t-butylphenol was heated at 180°C in a sealed tube for 2hr. The contents of the tube were distilled at reduced pressure affording 2.47 g (45%) of the title compound as a colorless liquid b.p. 32–34°C (13 mm) (lit[16] 37°C/16 mm). IR (film): 2400, 1650, 1450, 1370 cm^{-1}; NMR (CDCl$_3$): δ 6.26 (d, 1, J = 7 Hz), 4.93–4.67 (m, l), 3.33 (s, 3), 2.13–1.73 (m, 4), 1.43 (s, 3). Found: C, 65.44; H, 9.46. Calc. for $C_9H_{16}O_3$: C, 65.63; H, 9.38). 9.38).

2,2 *Diethoxy*-3, 4-*dihydro*-2(H)-*pyran* (13). The general procedure above was followed affording **13** in 60% yield, bp 60–62°C (13 mm). IR (film): 2920, 2880, 1660, 1440, 1340; NMR (CDCl$_3$): δ: 6.23 (d, 1, J = 7 Hz); 4.93–4.63 (m, 1), 3.67 (q, 4, J = 7 Hz), 2.30–1.87 (m, 4), 1.23 (t, 6, J = 7 Hz): 4.93–1.87 (m, 4), 1.23 (t, 6, J = 7 Hz). Found: C, 62.52; H, 9.58. Calc. for $C_9H_{16}O_3$: C, 62.79; H, 9.30).

General procedure for the preparation of dihydrofurans

2-(2-*Methylpropoxy*)-2, 3-*dihydrofuran* (5). A solution of ethyl diazoacetate (11.4g; 0.1 mol) in 10 mL isobutyl vinyl ether (GAF) was added dropwise to a gently refluxing suspension of copper-bronze (6.35 g; 0.1 g-atom) in 40 mL isobutyl vinyl ether over 3 hr. After a reflux period of 16 hr, the cooled mixture was filtered and the cake washed with anhyd ether until the filtrates were colorless. The combined filtrates were concentrated by distillation of the solvent at atmospheric pressure, followed by distillation of the residue under reduced pressure to afford 13.54 g of the expected cyclopropyl ester as a mixture of *cis* and *trans* isomers, bp 64–66°C (1 mm) (73%); IR (film): 2890, 1725, 1440, 1370 cm^{-1}; NMR (CDCl$_3$): δ 4.27 (q, 2, J = 7 Hz), 3.68 (t, 1), 3.33 (m, 2), 2.08–1.1 (m, 4), 1.23 (t, 3, J = 7 Hz), 1.0 (d, 6, J = 7 Hz). Material of this purity was used directly in the following procedure.

A soln of the cyclopropyl ester (16.8g, 0.09 mol) in 50 mL anhyd ether was added dropwise over 0.5 hr to a gently refluxing suspension of LAH (7.6 g; 0.2 mol) in 200 mL anhyd ether. After an additional 3 hr at reflux and stirring at room temp. overnight, the mixture was successively treated (caution) dropwise with water (7.6 mL), 15% NaOH (7.6 mL) and water (22.8 mL). The precipitated salts were removed by filtration and the salts washed copiously with ether. Concentration of the combined ethereal filtrates in vacuo and distillation of the residue under reduced pressure (short path) provided the expected cyclopropyl carbinol 11.8 g (92%), b.p. 64–65°C (1.8 mm); IR (film): 3320, 2920, 2820, 1450 cm^{-1}; NMR (CDCl$_3$); δ 4.07–3.07 (m, 5), 3.0–2.53 (m, 1), 2.17–1.07 (m, 2), 0.95 (d, 6), 0.78–0.2. (m, 2). Material of this purity was used directly in the following procedure.

A suspension of Fetizon's reagent[32] (silver carbonate on Celite) (90 g; 0.2 mol) in 400 mL anhyd benzene was dried by azeotropic distillation under argon for 1 hr. The cyclopropyl carbinol (6.0 g; 0.0417 mol) in 20 mL benzene was added in one portion and the resulting mixture heated at reflux for 3 hr. The hot mixture was filtered by gravity and the filter cake washed repeatedly with hot benzene (total volume ~ 1L). The benzene was removed by distillation at atmospheric pressure, and the residual liquid was fractionally distilled to afford 3.1 g (64%) of **5**, b.p. 61–63° (20 mm) and 1.1 g of recovered cyclopropyl carbinol b.p. 125–130°C (20 mm); IR (film): 2900, 1635, 1460, 1360 cm^{-1} NMR (CDCl$_3$): δ 6.45 (q, 1), 5.6 (dd, 1), 5.05 (q, 1), 3.82–3.12 (m, 2), 2.85–2.53 (m, 2), 0.97 (d, 6). (Found: 142.0994. Calc. for $C_{13}H_{14}O_2$: 142.0996).

2-*Methoxy*-2-*Methyl*-2,3-*dihydrofuran* (**6**)

Using the general procedures described above, reaction of 2-methoxypropene and ethyl diazoacetate afforded the corresponding cyclopropyl ester in 60% yield; reduction of this ester by LAH afforded the related cyclopropyl carbinol in 92% yield, and oxidation of this carbinol with Fetizon's reagent afforded ~ 60% yield of **6**. The volatility of **6** prevented easy isolation and removal of all traces of benzene. The use of a higher homolog of the starting propenyl ether should make related substances readily available.

General procedures for metalation and reaction with electrophiles

2-(3, 4-*Dihydro*-2(H)-*pyran*-6-*yl*)-2-*propanol*. A soln of dihydropyran (2.0 g; 23.8 mmol) in 5 mL anhyd THF at −78°C was treated with a soln of tBuLi in pentane (14 mL of a 1.7 M soln, 23.8 mmol). The flask was then transferred to a bath at 0°C (ice), held at this temp for 0.5 hr at −78°C, and then allowed to warm slowly to room temp. The mixture was diluted with sat aqNH_4Cl (1 ml) and ether (50 mL), stirred rapidly, the layers separated, and the organic phase washed with sat aqNaCl (2 × 10 mL) and dried ($MgSO_4$). Removal of the solvent *in vacuo* and distillation at 65–70°C (20 mm) (Kugelrohr) afforded 2.86 g of the title compound (86%); IR (film): 3330, 2890, 1670, 1450 cm^{-1}; NMR ($CDCl_3$): δ 4.88 (t, 1), 4.08 (t(br), 2), 2.37–1.53 (m, 5), 1.38 (s, 6). Exact mass (Found: 142.0994. Calc. for $C_8H_{14}O_2$: 142.0996).

3,4-Dihydro-2H-pyran-6-carboxaldehyde. A soln of the anion of **7** in THF (20 mL) was prepared from 3.0 g (35.7 mmol) of **7** and tBuLi in pentane (16.5 mL, 35.7 mmol) as described above and cooled to −78°C. A soln of DMF (3.65 g; 50 mmol) in 3.0 mL THF was added dropwise over 5 min, and the mixture allowed to warm slowly to room temp. After quenching with 10% aqNH_4Cl, the products were isolated by ether extraction as described above. Removal of the solvents afforded 3.5 g of crude but acceptably pure material (87%). The substance underwent significant decomposition during distillation at reduced pressure affording 1.2 g of the title aldehyde (30%) b.p. 82–84°C (5 mm); IR (film): 2820, 2700, 1690, 1640, 1400 cm^{-1}; NMR ($CDCl_3$): δ 9.18 (s, 1), 5.87 (t, 1), 4.12 (t(br), 2), 2.53–2.13 (m, 2), 2.13–1.67 (m, 2). Exact mass (Found: 112.0520. Calcd. for $C_6H_8O_2$; 112.0524).

6-n-Hexyl-3,4-dihydro-2H-pyran. A soln of the anion of **8** in THF (9.0 mL) was prepared as described above from **7** (924 mg, 11 mmol) and tBuLi in pentane (4.35 mL, 10.0 mmol) and held at 0°C (ice bath) during dropwise addition of n-hexyl iodide (1.4 g; 6.6 mmol) in 4 mL THF. Stirring was continued at 0°C for 0.75 hr and then the soln was warmed to room temp for 0.5 hr. After quenching with sat aqNH_4Cl, ether extraction as described above afforded after concentration *in vacuo* 1.59 g of crude products. Purification by column chromatography (basic Al_2O_3 act I) with elution by hexane afforded 604 mg (55%) of the title compound as a colorless liquid; IR (film): 2880, 2850, 1680, 1470 cm^{-1}; NMR ($CDCl_3$): δ 4.50 (t(br), 1), 4.00 (t, 2), 2.20–1.73 (m, 6), 1.73–1.10 (m, 8), 0.90 (t, 3). Exact mass Found: 168.1514. Calc. for $C_{11}H_{20}O$: 168.1518.

6-Phenylthio-3,4-dihydro-2H-pyran (**24**). A soln of the anion of **7** in THF (5 mL) was prepared as previously described from **7** 420 mg, 5 mmol) and tBuLi in pentane (2.7 mL, 5.0 mmol) and cooled to −78·C. Diphenyldisulfide (1.07 g; 5.0 mmol) in 3.0 mL THF was added dropwise. After 0.25 hr at −78°C, the mixture was allowed to warm slowly to room temp. The products, after quenching with sat aqNH_4Cl, were isolated by ether extraction as usual. The residue after concentration was distilled at 88–92°C (0.8 mm) (Kugelrohr) to afford 855 mg (79%) of **24**; IR (film): 3030, 2890, 2850, 1640, 1475, 1440 cm^{-1}; NMR ($CDCl_3$): δ 7.37 (s(br), 5), 5.40 (t, 1), 4.10 (t, 2), 2.40–1.47 (m, 4). (Exact mass Found: 192.0615. Calc. for $C_{11}H_{12}OS$: 192.0608).

1-(3,4-Dihydro-2H-pyran-6-yl)-2-methyl-2-propanol (**26**). A soln of the anion of **7** in THF (5 mL) was prepared from **7** (840 mg; 10 mmol) and tBuLi in pentane (5.25 mL. 10 mmol) as described above, and the soln held at 10°C (ice–water bath). A soln of 1,2 epoxy-2-methylpropane (720 mg; 10 mmol) and anhyd HMPA (1.79 g, 10 mmol) in 3 mL THF was added by syringe. After stirring at room temp for 1 hr, the mixture was worked up as usual with ether/sat NH_4Cl to afford upon concentration *in vacuo* and distillation (Kugelrohr) at 72–75°C (0.8 mm) **26** (312 mg; 20%). IR (film): 3330, 2920, 1670, 1460 cm^{-1}; NMR ($CDCl_3$): δ 4.65 (t, 1), 4.10 (t, 2), 3.00 (s(br), 1), 2.27 (s, 2), 2.1–1.33 (m, 4), 1.28 (s, 6).

4-(2-Methoxy-3, 4-dihydro-2H-pyran-6-yl)-4-hydroxypentanoic lactone. A stirred soln of **10** (570 mg, 5 mmol) in 2 mL anhyd THF at −78°C was treated dropwise with tBuLi in pentane (5.9 mL; 10 mmol). After 0.25 hr at −78°C, the bath was exchanged for an ice bath (0°C) and the mixture held at this temp for 0.5 hr. After dilution with an additional 5 mL THF, the mixture was recooled to −78°C, a soln of ethyl levulinate (720 mg; 5 mmol) in 2 mL THF was added dropwise and the mixture allowed to warm slowly to room temperature. The mixture was worked up as usual with sat aqNH_4Cl ether and the residue after concentration *in vacuo* was distilled (Kugelrohr) at 80°C (0.8 mm) to afford the title lactone (827 mg, 78%); IR(film): 2880, 1760, 1670, 1440 cm^{-1}; NMR ($CDCl_3$): δ 5.10–4.90 (m, 2), 3.48 (s, 3), 2.82–1.67 (m, 8), 1.55 (s, 3). (Exact mass Found: 212.1049. Calc. for $C_{11}H_{16}O_4$: 212.1042).

2-Methoxy-6-(3-methyl-2-buten-1-yl)-3,4-dihydro-2H-pyran. A soln of the anion derived from **10** in 1 mL THF was prepared from **10** (388 mg, 3.4 mmol) and tBuLi in pentane (4.0 mL, 6.8 mmol) and the soln recooled to −78°C after addition of anhyd HMPA (716 mg, 4.0 mmol) in 8 mL anhyd THF. To the resulting mixture was added, dropwise at −78°C, soln of 1-bromo-3-methyl-2-butene (298 mg; 2.0 mmol) in 2 mL anhyd THF. The mixture was allowed to warm slowly to room temp and stir 16 hr. After the usual sat aqNH_4Cl ether workup, the crude residue obtained by concentration of the organic extracts *in vacuo* was passed through a small column of basic alumina (act. I) to afford the title pyran (258 mg, 71%). Distillation of this material (Kugelrohr) at 70–75°C (20 mm) afforded slightly purer material (222 mg, 61%); IR (film): 2870, 1670, 1440 cm^{-1}; NMR (CCl_4): δ 5.25 (*t*, 1), 4.90 (*t*, 1), 4.52 (*m*, 1), 3.47 (*s*, 3), 2.67 (d, 2), 2.10–1.43 (m, 4), 1.77 (s, 3); 1.68 (s, 3). (Exact mass Found: 182.1307. Calc. for $C_{11}H_{18}O_2$: 182.1298).

Preparation of acyclic alkoxy vinyl ether

2-Bromoethyl-1-ethoxyethyl ether (**20**). A soln of 2-bromoethanol (12.5 g; 0.1 mol) and dichloroacetic acid (1.56 g; 12 mmol) was treated dropwise with ethyl vinyl ether (10.8 g; 0.15 mol) with ice cooling to keep the temp. below 45°C. After completion of the addition, a second portion of dichloroacetic acid was added, and the mixture stirred for 16 hr at room temp. Solid Na_2CO_3 (2.0 g 20 mmol) was added and the mixture stirred 3 hr and filtered through Celite and the filter cake washed with 100 mL ether. Concentration of the combined filtrates *in vacuo* and distillation (short path) of the residue afforded the title compound 15.9 g (81%) b.p. 70–73°C (20 mm); IR (film): 3020, 2870, 1440 cm^{-1}; NMR (CCl_4): δ 4.77 (q, 1), 4.00–3.27 (m, 6), 1.30 (d, 3), 1.22 (t, 3).

1-Ethoxyethyl vinyl ether (**19**). A mixture of 2-bromoethyl-1-ethoxyethyl ether (14.8 g; 75.2 mmol) and KOH (16.8 g; 300 mmol) was heated to reflux under argon. After 1 hr, the mixture was cooled and then distilled (short path) at atmospheric pressure to afford the title compound 4.6 g (71%) b.p. 101–102°C; IR (film): 2950, 2880, 1645, 1440 cm^{-1}; NMR ($CDCl_3$): δ 6.55 (dd, 1), 5.03 (q, 1), 4.72–3.33 (m, 4), 1.43 (d, 3), 1.23 (t, 3). (Found: C, 61.83; H, 10.24. Calc for $C_6H_{12}O_2$: C, 62.07; H, 10.34).

Metalation of 1-ethoxyethyl vinyl ether. A soln of 1-ethoxyethyl vinyl ether (354 mg; 3.05 mmol) in anh THF was treated at −78°C with tBuLi in pentane (3.8 mL; 6.1 mmol) according to the usual procedure. After the normal warming period to 0°C, the soln was recooled to −78°C and treated dropwise with a soln of octanal (515 mg; 4.0 mmol) in 2.0 ml anhyd THF. The resulting mixture was allowed to warm slowly to room temp and worked up as usual with sat aqNH_4Cl ether to afford upon concentration *in vacuo* 702 mg of crude material (95%). Purification of this material by medium pressure chromatography on Florisil (EtOAc/hexane 2 : 3) provided 320 mg (43%) of adduct **21**; IR(film): 3350, 2900, 1650, 1450 cm^{-1}; NMR ($CDCl_3$): δ 5.23 (q, 1), 4.50–3.30 (m, 4), 2.63–0.67 (m, 22).

Hydrolysis and hydrolytic cyclization of alkyl dihydropyrans

2-Methyl-1-nonen-4, 8-dione. A soln of 2-methoxy-2-methyl-6(2-methyl-2-propen-1-yl)-3, 4 dihydro-2H-pyran (728 mg: 4.0 mmol) was dissolved 25 mL THF, mL of ~2N HCl was added and the mixture was stirred at room temp for 4 hr. The mixture was diluted with ether (50 mL) and washed with 5% aq$NaHCO_3$ (2 × 15 mL) and dried over $MgSO_4$. Removal of the solvent *in vacuo* afforded 440 mg of crude but acceptably pure dione (65%). Further purification by chromatography on silicagel (EtOAc/hexane 1 : 4) afforded pure dione 215 mg (32%): IR (film): 2890, 1710, 1450, 1430 cm^{-1}; NMR ($CDCl_3$): δ 5.03–4.80 (m, 2), 3.08 (s, 2), 2.62–2.25 (m, 6), 2.13 (s, 3), 1.78 (s(br), 3); MS: *m/e* = 168 (P^+).

2-(2-Methyl-1-propen-1-yl)-2-cyclohexen-1-one. A soln of 2-methoxy-6-(2-methyl-2-propen-1-yl)-3,4-dihydro-2H-pyran (25 mg; 0.147 mmol) in 3.0 THF was treated with 0.25 ml of ~2N HCl and the mixture was heated to 45°C with stirring for 4 hr. The mixture was diluted with ether (14 mL) and washed with 5% aq$NaHCO_3$ (1 × 2 mL), dried over $MgSO_4$ and evaporated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane 1:4) afforded 18 mg (82%) of the title enone; IR(film); 2890, 1680, 1450, 1435 cm^{-1}; NMR ($CDCl_3$): δ 7.00–6.70 (m, 1), 6.18–6.10 (m, 1), 2.77–2.33 (m, 4), 2.30 1.98 (m, 2), 1.85 (s, 3), 1.75 (s, 3); MS: *m/e* 150 (P^+).

3-Methyl-2-(2-propenyl)-2-cyclohexen-1-one and 3-(2-methyl-1-propenyl)-2-cyclohexen-1-one. A soln of 2-methyl-1-nonen-4,8-dione (56 mg; 0.333 mmol) in 3.5 ml MeOH was treated with 1% aqKOH (0.5 mL) and the mixture heated for 24 hr at reflux under argon. The mixture was neutralized with 10% HCl and diluted with ether (20 mL). The organic phase was washed with sat aqNaCl (1 × 5 ml), dried over $MgSO_4$ and evaporated affording 50 mg (96%) of crude material. Purification by chromatography (silica gel in EtOAc/benzene 1:4) afforded 23 mg (46%) of 3-methyl-2-(-propenyl)-2-cyclohexen-1-one; IR (film) : 2890, 1670, 1630, 1450, 1435 cm^{-1}; NMR ($CDCl_3$): δ 5.27 (m, 1), 4.77 (m, 1), 2.67–2.27 (m, 4), 2.20–1.45 (m, 2), 1.93 (s, 3), 1.80 (s, 3); MS: *m/e* = 150 (P^+); and 6 mg (12%) of 3-(2-methyl-1-propenyl)-2-cyclohexen-1-one; IR (film): 2900, 1660, 1600, 1600, 1450 cm^{-1}: NMR ($CDCl_3$): δ 6.08–5.42 (m, 2), 2.58–2.27 (m, 4), 1.93 (s, 6), 2.27–1.57 (m, 2); MS: *m/e* = 150(P^+).

Acknowledgement—The authors wish to thank the National Institutes of Health, National Institutes of General Medical Sciences for their generous support of this research by the award of research grant GM-29290.

REFERENCES

[1] Fellow of the A. P. Sloan Foundation (1976–1980); Research Career Development Awardee (CA-00702) 1976–1981.

[2] D. A. Evans, G. C. Andrews and B. Buckwalter, *J. Am. Chem. Soc.* **96**, 5560 (1974); W. C. Still, T. L. MacDonald, *Ibid.* **96**, 5561 (1974).

[3] T. L. Macdonald, B. A. Narayanan and D. E. O'Dell, *J. Am. Chem.* **46**, 1504 (1981).

[4] J. F. Biellmann, J. D. Ducep, *Tetrahedron Letters* 5629 (1968); for an extensive compilation of other substituted allyl anions see E. Ehlinger and P. Magnus, *J. Am. Chem. Soc.* **102**, 5004 (1980).

[5] P. Beak, M. Baillargeon and L. G. Carter, *J. Org. Chem.* **43**, 4255 (1978).

[6] H. W. Gschwend and H. R. Rodriguez, *Org. React.* **26**, 1 (1979).

[7] U. Schöllkopf and P. Hänssle, *Justus Liebigs Ann.* **763**, 208 (1972); J. E. Baldwin, G. A. Höfle and O. W. Lever Jr., *J. Am. Chem. Soc.* **96**, 7125 (1974).

[8] K. Oshima, K. Shimoji, H. Takahashi, H. Yamamoto and H. Nozaki, *J. Am. Chem. Soc. Ibid.* **95**, 2694 (1973).

[9] D. M. Stout, T. Takaya and A. I. Meyers, *J. Org. Chem.* **60**, 563 (1975).

[10] R. Paul, S. Tchelitcheff, *Bull. Soc. Chim. Fr.* 808 (1952).

[11] V. Rautenstrauch, *Helv. Chim. Acta* **55**, 594 (1972).

[12] M. Schlosser, B. Schaub, B. Spahic and G. Sleiter, *Ibid.* **56**, 2166 (1973).

[13] B. Schaub and M. Schlosser, *Ibid.* **58**, 556 (1975).

[14] R. K. Boeckman Jr. and K. J. Bruza, *Tetrahedron Letters*, 4187 (1977).

[15] O. Riobe, A. Lebouc and J. Delaunay, *Acad. Sci. Paris* **284**, 281 (1977).

[16] R. I. Longley Jr. and W. S. Emerson, *J. Am. Chem. Soc.* **72**, 3079 (1950).

[17] B. Schaub and M. Schlosser, *Helv. Chim. Acta* **58**, 556 (1975).

[18] K. Kurata, S. Tanaka and K. Takahashi, *Chem. Pharm. Bull.* **24**, 538 (1976).

[19] A. J. Hubert, A. Georis, R. Warin and P. Teyssie, *J. Chem. Soc.* Perkin II 366 (1972).

[20] B. L. Buckwalter, Ph. D. Dissertation, Indiana University, Bloomington, Indiana, 1973; Alonso, M., Ph.D. Dissertation, Indiana University, Bloomington, Indiana 1975.

[21] Rautenstrauch's early experiments also indicated that use of nBuLi as metallating agent for preparative purposes was unlikely to be useful.

[22] F. A. Settle, M. Haggerty and J. F. Eastham, *J. Am. Chem. Soc.* **86**, 2076 (1964).

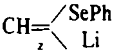
[23] Similar observations were made by Baldwin during his studies of metallation of methyl vinyl ether, cf Ref. 7.

[24] R. B. Bates, L. M. Kroposki and D. E. Potter, *J. Org. Chem.* **37**, 560 (1972).

[25] S. J. Gould and B. D. Remillard, *Tetrahedron Letters*, 4353 (1978).

[26] A. R. Rossi, B. D. Remillard and S. J. Gould *Ibid.* 4357 (1978).

[27] This correlation cannot be interpreted in mechanistic terms since the Curtin-Hammett principle precludes such a variation assuming conformational interconversion is more rapid than metalation, which appears likely.

[28] Reich and Willis have observed the dimer $PhCHCH_2Ph$ in attempts to alkylate  $CH_2{=}\langle\substack{SePh\\ Li}$ with benzyl bromide; H. J. Reich and W. W. Willis Jr. Unpublished results.

[29] S. Danishefsky and A. Zimmer, *J. Org. Chem.* **41**, 4059 (1976).

[30] P. M. McCurry Jr. and R. K. Singh, *Ibid.* **38**, 2910 (1973).

[31] M. S. Newman and M. C. Vander Zwan, *Ibid.* **38**, 2910 (1973).

[32] M. Fetizon and M. Golfier, *C. R. Acad. Sci. Paris* **267**, 900 (1968).