Transfer Reactions Involving Boron. XXII. The Position-Specific Preparation of Dialkylated Ketones from Diazo Ketones and Methyl Vinyl Ketone *via* Vinyloxyboranes[1]

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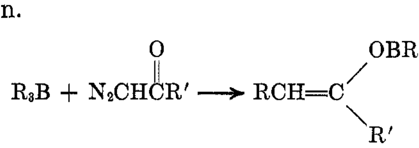
Received January 12, 1971

Vinyloxyboranes, formed in the reaction of trialkylboranes with diazo ketones or by the radical addition of trialkylboranes to methyl vinyl ketone, react with methyl- or *n*-butyllithium to form the corresponding lithium enolates and lithium tetraalkylboron. The enolates thus generated undergo facile alkylation in highly position-specific reactions. The overall procedure leads to the formation of α,α- and α,β-dialkylated ketones from diazo ketones and methyl vinyl ketone, respectively, in good yield.

The base-catalyzed alkylation of ketones has received considerable attention. In general, ketones having α hydrogens on both α-carbon atoms undergo base-catalyzed enolate formation at each α position leading to competitive alkylation at both α positions. House and coworkers[3] have shown that enolates do not equilibrate unless there is a hydrogen ion donor available in the reacting system. The product-alkylated ketones are capable of acting as the hydrogen ion donor, thus leading to the equilibration of enolates, as well as the polyalkylation of the initial ketone. Numerous procedures have been developed to circumvent alkylation at both α positions and the polyalkylation of ketones. These procedures have involved the use of blocking and activating functional groups,[4] the position-specific formation of enolates by reduction of α,β-unsaturated ketones[5] or α-substituted ketones,[5,6] and the formation, trapping, separation, and regeneration of enolates.[7-9]

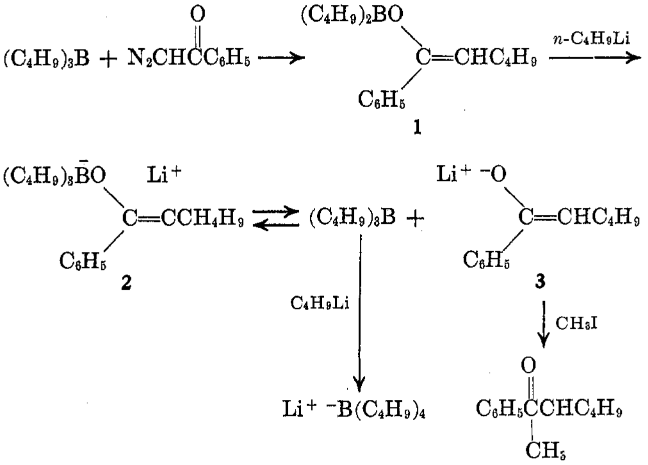
House and Trost[7] have described the cleavage of enol acetates with methyllithium to give enolates which could then be alkylated in a high degree of position specificity. The pure enol acetates were prepared by the reaction of the sodium enolates, formed by the reaction of the ketones with sodium hydride, with acetic anhydride followed by separation by preparative glpc. Stork and Hudrlik[8] have described similar procedures for the generation of enolates from methyllithium and trimethylsilyl enol ethers (again requiring the separation of the isomeric enol ethers by preparative glpc or fractional distillation). Pereyre and coworkers have described the preparation of tin enol ethers by the radical addition of trialkyltin hydride to α,β-unsaturated ketones.[9a,b] Subsequent cleavage of the tin enol ethers with methyllithium leads to the formation of lithium enolates which can be alkylated.[9c,d,e]

Our recent observation that vinyloxyboranes are formed in the reactions of trialkylboranes with diazo ketones[10] has led us to investigate the utilization of such intermediates for the generation of enolates followed by alkylation.


$$R_3B + N_2CH\overset{\overset{O}{\|}}{C}R' \longrightarrow RCH{=}C\begin{matrix}\diagup OBR_2\\ \diagdown R'\end{matrix}$$

Results and Discussion

The reaction of diazoacetophenone with tri-*n*-butylboron in dry tetrahydrofuran produces the vinyloxyborane **1**.[10] Direct treatment of crude **1** with 2 molar equiv of *n*-butyllithium in hexane followed by the addition of 1 molar equiv of methyl iodide produces an overall 72% yield of 2-hexyl phenyl ketone. The use of less than 2 molar equiv of *n*-butyllithium results in lower yields of the dialkylated product. We picture the reaction as involving attack by *n*-butyllithium on **1** to



form the tetracoordinate boron species **2** which reversibly dissociates to tri-*n*-butylboron and the lithium enolate. The second equivalent of *n*-butyllithium presumably assists in the formation of the free enolate by irreversibly removing the tri-*n*-butylboron as lithium tetra-*n*-butylboron.[11] The lithium tetrabutylboron formed in the reaction does not react with the product ketones at room temperature over the course of several

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[1] Submitted by P. W. W. in partial fulfillment of the requirements for the Ph.D. thesis, University of Notre Dame, 1971.

[2] (a) Alfred P. Sloan Research Fellow, 1967–1969; (b) NDEA Fellow, 1967–1970.

[3] H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965).

[4] H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965.

[5] M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

[6] D. Caine, *J. Org. Chem.*, **29**, 1868 (1964).

[7] H. O. House and B. M. Trost, *ibid.*, **30**, 2502 (1965).

[8] G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4464 (1968).

[9] (a) M. Pereyre and J. Valade, *Bull. Soc. Chim. Fr.*, 1928 (1967); (b) M. Pereyre, B. Bellegarde, J. Mendelsohn, and J. Valade, *J. Organometal. Chem.*, **11**, 97 (1968); (c) M. Pereyre and Y. Odic, *Tetrahedron Lett.*, 505 (1969); (d) Y. Odic and M. Pereyre, *C. R. Acad. Sci., Ser. C*, **269**, 469 (1969); (e) Y. Odic and M. Pereyre, *ibid.*, **270**, 100 (1970).

[10] D. J. Pasto and P. W. Wojtkowski, *Tetrahedron Lett.*, 215 (1970).

[11] Lithium and sodium tetraalkylboron compounds have been prepared previously.[12] These compounds are reported to undergo rather slow hydrolysis and air oxidation (0.5–16% hydrolysis in water at room temperature for 16 hr and 50% oxidation in tetrahydrofuran at 35° for 16 hr[12]). These compounds are considerably less reactive than lithium tetramethylaluminum toward hydrolysis, oxidation, and reaction with aldehydes and ketones.[13]

[12] R. Damico, *J. Org. Chem.*, **29**, 1971 (1964).

[13] D. J. Pasto and R. Snyder, *ibid.*, **30**, 1634 (1965).

hours as demonstrated in a control reaction of a ketone with lithium tetrabutylboron (prepared by the reaction of *n*-butyllithium with tri-*n*-butylboron[12]).

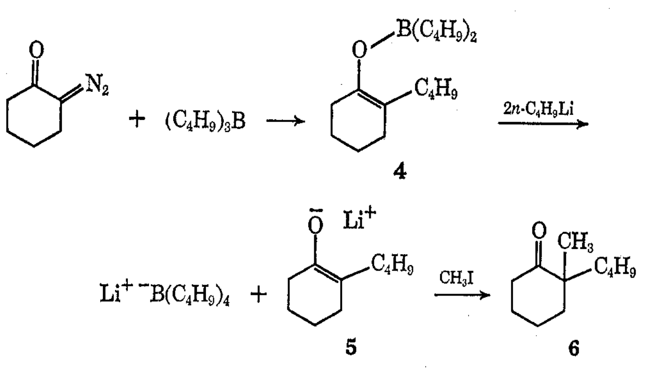
The enolate **3** can also be generated from **1** using methyllithium or potassium *tert*-butoxide, although in the latter case considerably lower yields of dialkylated product are obtained. Enolate **3** was also reacted with 1 molar equiv of benzyl chloride giving 1-phenyl-2-hexyl phenyl ketone in 47% yield. In the alkylation reactions involving **3**, no polyalkylation products were detected. The results of the reactions of vinyloxyborane **1** with different bases and alkylating agents are summarized in Table I.

TABLE I

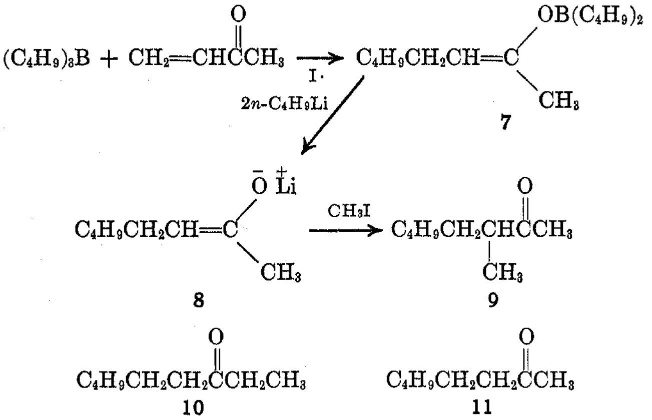
ALKYLATION OF ENOLATE ANION DERIVED FROM 1

Base (molar equiv)	Alkylating agent	Yield, %
n-C_4H_9Li (2)	CH_3I	72
n-C_4H_9Li (1)	CH_3I	56
CH_3Li (2)	CH_3I	69
n-C_4H_9Li (2)	$C_6H_5CH_2Cl$	47
K^+ $^-$O-*tert*-Bu (1)	$C_6H_5CH_2Cl$	31

In the foregoing system only a single enolate anion can be formed. A more challenging problem which has received considerable attention is the selective generation of a single enolate anion from an unsymmetrical acyclic or cyclic ketone, which can potentially form two different, isomeric enolate anions, followed by the position-specific alkylation of that enolate anion. We have investigated the utility of the present procedure with both an unsymmetrical acyclic and cyclic system.[14] Reaction of diazocyclohexanone[15] with tri-*n*-butylboron in dry tetrahydrofuran led to the formation of vinyloxyborane **4**. Treatment of crude **4** with *n*-butyllithium in hexane followed by the addition of methyl iodide produced only low and variable yields of the desired product **6**. Removal of the tetrahydrofuran from crude **4** followed by distillation of **4** under a nitrogen atmosphere and subsequent treatment with *n*-butyllithium and methyl iodide produced **6** in 61% yield. Analysis of the reaction product by glpc and mass spectrometry indicated the presence of a few per cent of 2-*n*-butylcyclohexanone and no more than trace quantities of polymethylation products. The presence of the isomeric alkylation product, 2-methyl-6-*n*-butylcyclohexanone, could not be detected by glpc.



The reaction of crude vinyloxyborane **7**,[10] formed by the conjugate radical addition of tri-*n*-butylboron to methylvinyl ketone,[16] with *n*-butyllithium followed by the addition of methyl iodide produced only low yields of the expected alkylation product **9**. As with **4**, distillation of **7** followed by the treatment with *n*-butyllithium and methyl iodide produced the expected product **9** in reasonable yield (59%), in addition to **10** (11%), **11** (10%), and approximately 3% of unidentified polyalkylated products (by mass spectral analysis). The formation of **10** and the polyalkylation products from **8** is not atypical. It is well documented that acyclic enolate anions such as **8** lose both their position specificity and undergo polyalkylation to a greater extent than cyclic enolate anions such as **5**.[14]



The formation of position-specific alkylated ketones from diazo ketones and methyl vinyl ketone *via* vinyloxyboranes appears to be advantageous over the other methods of enolate anion formation in that only one positional isomer of the vinyloxyborane is formed, thus precluding the necessity of separation of the enol derivatives prior to enolate anion generation. The ready availability of acyclic diazo ketones (from acid chlorides with diazoalkanes), methyl vinyl ketone, and trialkylboranes (by hydroboration of olefins) provides for a rather flexible synthetic approach to the preparation of ketones of various structures. These facts, coupled with the fact that vinyloxyboranes can be prepared in large quantities, allow for a *smooth position-specific introduction of two alkyl groups* in a single sequence of reactions starting from simple and readily available precursors.

Experimental Section

Dialkylation of Diazoacetophenone. A. Preparation of 2-Hexyl Phenyl Ketone.—To a cooled (0°) solution of 6.35 mmol of di-*n*-butyl-(1-phenyl-1-hexenyloxy)borane (**1**) in 10 ml of tetrahydrofuran, prepared by the reaction of 6.35 mmol of diazoacetophenone with 6.35 mmol of tri-*n*-butylboron in tetrahydrofuran, was added dropwise 6.6 ml of 1.92 *M* (12.7 mmol) methyllithium in diethyl ether (or the other bases as indicated in Table I). The ice bath was removed and the reaction mixture was allowed to stir for 1 hr at room temperature. Methyl iodide (6.35 mmol) was added and the reaction mixture was allowed to stir for 90 min. The reaction mixture was diluted with ether and was repeatedly washed with water. The organic phase was dried over magnesium sulfate and the solvent was removed under reduced pressure. Analysis of the residue by glpc indicated the presence of only 2-hexyl phenyl ketone (69%). The residue was subjected to distillation giving pure product: bp 115° (3.3 mm)

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[14] L. E. Hightower, L. R. Glasgow, K. M. Stone, D. A. Albertson, and H. A. Smith, *J. Org. Chem.*, **35**, 1881 (1970), and references contained therein. See also ref 8.

[15] M. Rosenberger, P. Yates, J. B. Hendrickson, and W. Wolf, *Tetrahedron Lett.*, 2285 (1964).

[16] A. Suzuki, A. Arase, H. Matsumoto, M. Itoh, H. C. Brown, M. M. Rogic, and M. W. Rathke, *J. Amer. Chem. Soc.*, **89**, 5708 (1967).

[lit.[17] bp 109–111° (3 mm)]; ν_{max} 1682 cm^{-1}; nmr δ 0.6–2.0 (m, 9 H), 1.7 (d, J = 7.0 Hz, 3 H), 3.33 (m, 1 H), and 7.35 and 7.96 (m, 5 H each).

B. Phenyl 1-Phenyl-2-hexyl Ketone.—Treatment of the enolate **3** with benzyl chloride followed by work-up as described above produced phenyl 1-phenyl-2-hexyl ketone (for yields see Table I): bp 145° (0.55 mm); ν_{max} 1675 cm^{-1}; nmr δ 0.6–2.0 (m, 9 H), 2.91 (m, 2 H), 3.70 (m, 1 H), and 7.1–7.8 (m, 10 H). The product was identical in all respects with an authentic sample prepared by the benzylation of the enolate anion of caprophenone generated by treatment of caprophenone with sodium hydride in monoglyme.

Dialkylation of Diazocyclohexanone. Preparation of 2-Methyl-2-*n*-butylcyclohexanone.—To a solution of 1.82 g (14.7 mmol) of diazocyclohexanone[15] in 2 ml of tetrahydrofuran maintained under a nitrogen atmosphere was added 2.68 g (14.7 mmol) of tri-*n*-butylboron in 2 ml of tetrahydrofuran. The reaction mixture was stirred at room temperature for 2 hr. The reaction mixture was distilled under a nitrogen atmosphere giving 2.83 g (70%) of **4** as a pale yellow liquid: bp 97° (0.32 mm); ν_{max} 1687 cm^{-1} ($\nu_{C=C}$) with no absorption in the carbonyl region. The distillate was dissolved in 5 ml of tetrahydrofuran and the solution was cooled in an ice bath. A solution of *n*-butyllithium in hexane (20.8 mmol) was added dropwise and the resulting reaction mixture was allowed to stir at room temperature for 1 hr. Methyl iodide (2.9 g, 20.8 mmol) was then added and the reaction mixture was stirred for 30 min and was then worked up as described above. Analysis of the product by glpc indicated the presence of 2-methyl-2-*n*-butylcyclohexanone (61%) and 2-*n*-butylcyclohexanone[18] (6%). The 2-methyl-2-*n*-butylcyclohexanone was isolated by preparative glpc, ν_{max} 1705 cm^{-1}. The 2,4-dinitrophenylhydrazone had mp 140–141° (lit.[19] mp 139–140°).

Dialkylation of Methyl Vinyl Ketone. Preparation of 3-Methyl-2-octanone.—To a solution of 3.59 g (15.1 mmol) of **7** in 9 ml of tetrahydrofuran maintained at 0° was added dropwise 11.3 ml of 2.67 M (30.2 mmol) *n*-butyllithium in hexane. The reaction mixture was allowed to stir at room temperature for 1 hr. A solution of 4.29 g (30.2 mmol) of methyl iodide in 1 ml of tetrahydrofuran was added and the resulting mixture was stirred at room temperature for 30 min, whereupon the reaction mixture was worked up as described above. Analysis of the product mixture by glpc showed the presence of 3-methyl-2-octanone (59%), 3-nonanone (16%), 2-octanone (10%), and 3% of unidentified products. The 3-methyl-2-octanone was isolated by preparative glpc: ν_{max} 1710 cm^{-1}; nmr δ 0.7–1.8 (m, 14 H), 2.12 (s, 3 H), and 2.47 (m, 1 H); mass spectrum m/e 142, 127, 99, 72.

Registry No.—**1**, 29128-31-2; **4**, 29199-34-6; **7**, 29199-35-7; diazoacetophenone, 3282-32-4; tri-*n*-butylboron, 122-56-5; diazocyclohexanone, 3242-56-6; methyl vinyl ketone, 78-94-4.

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[17] T. I. Temnikova, A. K. Petryaeva, and S. S. Skorokhodov, *Zh. Obshch. Khim.*, **25**, 1575 (1955).

[18] Identified by comparison with an authentic sample obtained by the hydrolysis of vinyloxyborane **4**.

[19] S. Boatman, T. M. Harris, and C. R. Hauser, *J. Amer. Chem. Soc.*, **87**, 82 (1965).

Enthalpies of Transfer of Transition States in the Menshutkin Reaction from a Polar Protic to a Dipolar Aprotic Solvent[1]

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Received December 8, 1970

The rates of the reaction of pyridine with six benzyl halides in methanol and dimethylformamide (DMF) were determined at 25.0 and 50.0°. The heats of solution of the reactants in these two solvents were determined at 25.0°. From these data the enthalpies of transfer of the transition states of these reactions from methanol to dimethylformamide were calculated. In all cases the lower activation enthalpy in the dipolar aprotic solvent was found to be caused *entirely* by greater solvation of the transition state in the dipolar aprotic solvent rather than by solvation effects on the reactants. Some effects upon this transition state of changes in the leaving group and in the substrate are discussed.

The Menshutkin reaction has long been regarded as one of the best examples of solvent effects upon reaction rate. Since ions are formed from neutral reactants in this reaction, large increases in rate have been observed with increases in the polarity of the solvent.[3] In addition to correlation of rates with dielectric constant,[4] Z values,[5] and polarizability,[6] it appears that there is an interesting effect on change from a polar protic to a dipolar aprotic solvent of similar dielectric constant.

The effect of this solvent change on the free energies of activation of SN2 reactions has been the subject of thorough studies by Parker and coworkers,[7] and, in the case of the Menshutkin reaction, by Abraham.[3b] These authors discuss this solvent effect in terms of the free energy of transfer of the transition state in these reactions from a polar protic to a dipolar aprotic solvent. Another variable, namely the solvent effect on the volume of activation of the Menshutkin reaction, has been studied by Brower.[8]

Although the effect on rate of a change from a polar protic to a dipolar aprotic solvent is not great and both rate increases[9] and rate decreases[9,10] have been reported, there does seem to be a consistent decrease in the enthalpy of activation in the dipolar aprotic solvent.[9,10] This decrease in the $\Delta H^{\ddagger}$ can be attributed to two possible causes.

The first, and most common, explanation is that desolvation of the nucleophile or base in the aprotic solvent relative to the protic solvent raises the energy of the reactants, thus diminishing the energy gap between the reactants and the transition state. The second explanation is that the lowering of the activation energy

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[1] (a) A preliminary report of a part of this work appeared in *Chem. Commun.*, 194 (1968). (b) This work was supported in part by the National Science Foundation under its Undergraduate Science Education Program, 1963–1965.

[2] Taken in part from the M. A. thesis of A. Nudelman, Brooklyn College, Feb 1964.

[3] (a) N. Menschutkin, *Z. Phys. Chem.*, **5**, 589 (1890); (b) for a more recent discussion, see M. H. Abraham, *Chem. Commun.*, 1307 (1969).

[4] S. Eagle and J. Warner, *J. Amer. Chem. Soc.*, **61**, 488 (1939).

[5] E. M. Kosower, *ibid.*, **80**, 3267 (1958).

[6] J. D. Reinheimer, J. D. Harley, and W. W. Meyers, *J. Org. Chem.*, **28**, 1575 (1963).

[7] E. C. F. Ko and A. J. Parker, *J. Amer. Chem. Soc.*, **90**, 6447 (1968), and earlier papers.

[8] K. R. Brower, *ibid.*, **85**, 1401 (1963); see also H. Heydtman, *Z. Phys. Chem.*, **54**, 237 (1967).

[9] (a) J. W. Baker and W. S. Nathan, *J. Chem. Soc.*, 519 (1935); (b) B. O. Coniglio, D. E. Giles, W. R. McDonald, and A. J. Parker, *J. Chem. Soc., B*, 152 (1966).

[10] H. Essex and O. Gelomini, *J. Amer. Chem. Soc.*, **48**, 883 (1926).