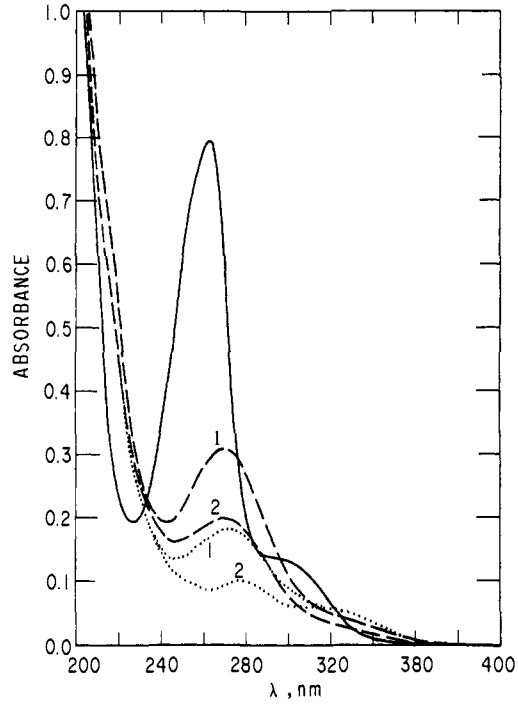


Figure 2. Uv absorption spectrum of **1a** in anaerobic acetonitrile: ——, as prepared; - - -, 1-min (1) and 12-hr (2) after addition of excess $NaBH_4$; . . ., 30 sec (1) and 4 min (2) after exposure to air.

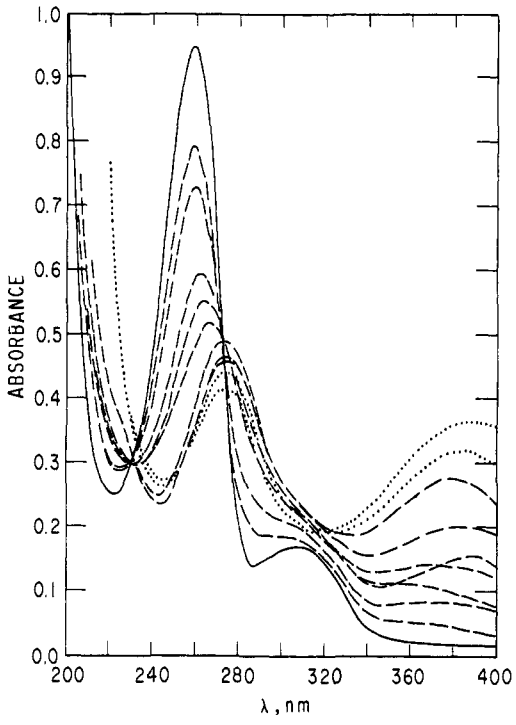


Figure 3. Uv absorption spectrum of **1b** in aerobic acetonitrile: ——, freshly prepared; - - -, 1-min intervals after addition of $NaBH_4$; . . ., 1-min intervals after further addition of excess $NaBH_4$.

spectrum of **2b** (E_{274} = 12,300),[11] representing a yield of 61%. Over a period of several minutes the absorption at 274 nm diminished with appearance of a new peak at 368 nm which gradually shifted to 376 nm; an isosbestic point occurred at 322 nm (Figure 3). The peak at 368 nm probably corresponds to the formation of 1,2-bis(4-nitrophenyl)diazane;[11] the gradual bathochromic shift of this peak is due to formation of an as yet unidentified species. When a solution of the species absorbing at 274 nm is made alkaline, the spectrum is drastically altered, indicating the destruction of the initial reduction product; this is in accord with the known sensitivity of aryldiazenes to base.[2d]

We conclude that diazene intermediates are indeed formed in the reduction of benzenediazonium salts by borohydride. Furthermore, the accessibility of the starting materials makes this reduction an attractive route to the synthesis of new aryldiazenes, and may facilitate design of an aryldiazene which is stable to oxygen, or which can be isolated as a pure compound. We are currently exploring these possibilities in our laboratory.

Acknowledgment. We thank Professor Edward M. Kosower for helpful discussions. Support of this work by the National Institutes of Health through Grant No. HE 13581 is gratefully acknowledged.

Charles E. McKenna, T. G. Traylor*
Chemistry Department, Revelle College
University of California, San Diego
La Jolla, California 92037

Received February 1, 1971

Dihydro-1,3-oxazines. XIII. Synthesis of Specifically Alkylated Unsymmetrical Ketones. A Method for Assembling Ketones with α-(Quaternary Carbons)

Sir:

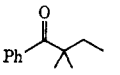
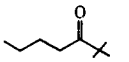
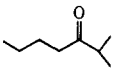
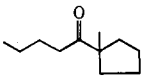
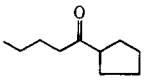
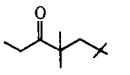
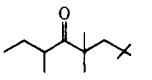
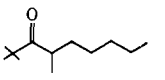
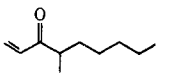
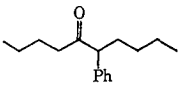
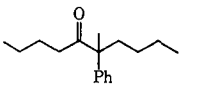
There have been a number of recent reports on novel synthesis of ketones possessing diverse structural features which involve organoboranes,[1] organocopper,[2] organoiron,[3] and organolithium[4] reagents. In none of these cases has there been demonstrated that bulky (*e.g.*, tertiary alkyl, isopropyl) substituents can be introduced into the ketone unless the substrate initially contained this preconstructured substituent. This is not surprising since all of the above would require the tertiary alkyl group to be introduced as a halide or its organometallic derivative which are usually unreliable as a source of these moieties.

We now report a method for preparing unsymmetrical ketones **5** and **8** by stepwise introduction of three or four groups, respectively. Furthermore, and perhaps more significantly, the method allows for the preparation of α-(quaternary carbon) ketones of varied structure and specifically alkylated in one of two available sites.

The sequence incorporates an α,α-disubstituted dihydro-1,3-oxazine (**1**) containing two of the substituents (Table I) for the intended ketonic product. These substituents are introduced *via* a variety of facile reactions previously reported from this laboratory.[5]

(1) H. C. Brown and M. M. Rogic, *J. Amer. Chem. Soc.*, **91**, 4304 (1969); H. C. Brown, H. Nambu, and M. M. Rogic, *ibid.*, **91**, 6852 (1969); H. C. Brown and G. W. Kabalka, *ibid.*, **92**, 714 (1970).
(2) G. H. Posner and C. E. Whitten, *Tetrahedron Lett.*, 4647 (1970).
(3) Y. Sawa, M. Ryang, and S. Tsutsumi, *ibid.*, 5189 (1969).
(4) (a) E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 4, 1075, 1077 (1965); (b) H. M. Walborsky, W. H. Morrison, and G. E. Niznik, *J. Amer. Chem. Soc.*, **92**, 6675 (1970); (c) A. I. Meyers and A. C. Kovelesky, *ibid.*, **91**, 5887 (1969); (d) A. I. Meyers and E. M. Smith, *ibid.*, **92**, 1084 (1970); (e) A. I. Meyers and A. C. Kovelesky, *Tetrahedron Lett.*, 4809 (1969).

Table I. Unsymmetrical Ketones from Organolithiums, Alkyl Iodides, and **1**

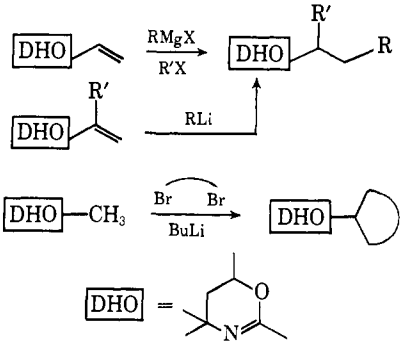
Entry	Oxazine R	Oxazine R′	R″Li[b]	R‴I[c]	Ketone (%)[d]
1	Me	Me[a]	PhLi	EtI	 (50)
2	Me	Me	*n*-BuLi	MeI	 (60)
3	Me	Me	*n*-BuLi	None	 (73)
4		$-(CH_2)_4-$	*n*-BuLi	MeI	 (63)
		$-(CH_2)_4-$	*n*-BuLi	None	 (58)
6	Me	Neopentyl	EtLi	MeI	 (65)
7	Me	Neopentyl	*sec*-BuLi	None	 (63)
8	Me	*n*-Amyl	*tert*-BuLi	None	 (53)
9	Me	*n*-Amyl	CH_2=CHLi	None	 (45)
10	Ph	*n*-Bu	*n*-BuLi	None	 (77)
11	Ph	*n*-Bu	*n*-BuLi	MeI	 (63)

[a] Prepared in 60% yield from isobutyronitrile and 2-methyl-2,4-pentanediol according to Ritter and Tillmanns.[5] [b] Commercial organolithiums (Lithium Corp., Bessemer City, N. C.) were utilized as received. Concentrations described on the labels were found to be within ±2%. The organolithiums were added over a 20-min period to ~1 *M* solutions of the oxazines in THF cooled to −78°. [c] Added neat (1.3–1.4 equiv) to the reaction mixture at 0° after allowing the latter to reach room temperature, stirred for 6–12 hr. [d] Obtained by refluxing **4** or **7** in 12% oxalic acid for 1.5 hr; direct extraction with ether or pentane gave the ketone. Products were distilled and examined by their vpc and ir, nmr, and mass spectra. All gave satisfactory elemental analyses.

When a solution of **1** in THF is treated with 2.0 equiv of an organolithium reagent at −78° the first equivalent removes the α-proton, which produces the lithio ketenimine **2** as a result of rearrangement of the α-carbanion. The second equivalent adds in rapid succession to the ketenimine, giving rise to the alkylated dilithio enamine **3**.[6] If the reaction mixture, after reaching room temperature, is hydrolyzed, good yields of the tetrahydro-1,3-oxazine **4** are obtained; after oxalic acid cleavage the trialkylated ketone **5** (Table I, entries 3, 5, 7, 8, 9, and 10) is produced.

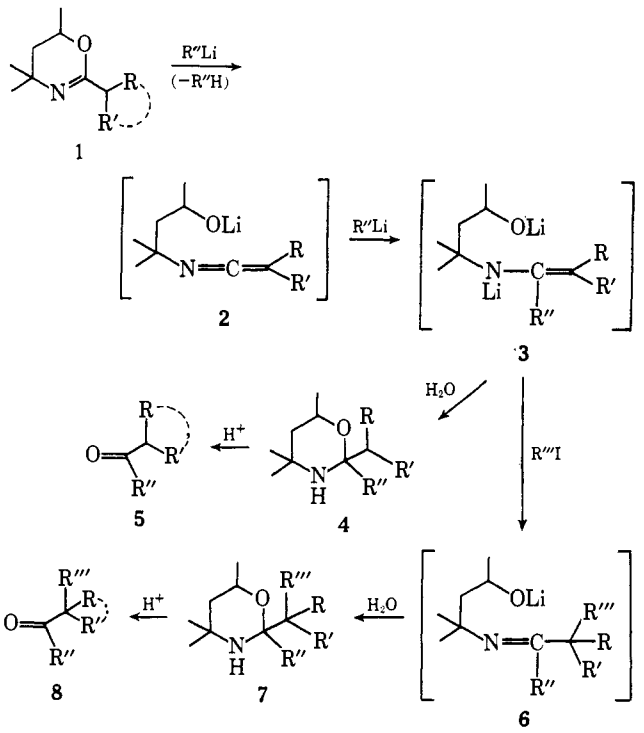
On the other hand, if instead of terminating the sequence by hydrolysis of **3**, the latter is treated with an alkyl iodide at room temperature, a mild exothermic reaction ensues and the lithio imine **6** is formed which, upon hydrolysis, leads to a good yield of the tetrahydro-1,3-oxazine (**7**). Oxalic acid treatment of **7** produces the tetraalkylated ketone **8** (Table I, entries, 1, 2, 4, 6, and 11).

(5) Elaboration of commerically available (Columbia Organic Chemicals) dihydro-1,3-oxazines provides the α,α-disubstituted derivatives according to the following (A. I. Meyers and A. C. Kovelesky, *Tetrahedron Lett.*, 1783 (1969); ref 4c,e; A. I. Meyers ,*et al.*, *J. Amer. Chem. Soc.*, **91**, 765 (1969))

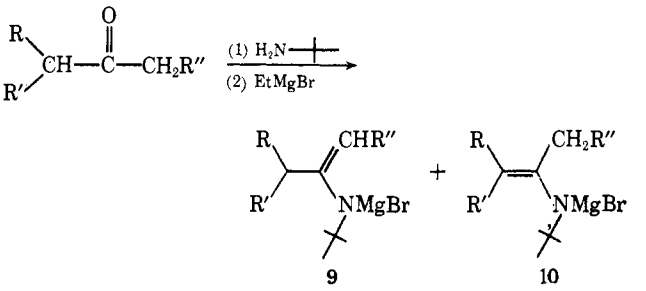


Experimental procedures have been published: J. M. Fitzpatrick, G. R. Malone, I. R. Politzer, H. W. Adickes, and A. I. Meyers, *Org. Prep. Proced.*, 1, 193 (1969); A. C. Kovelesky and A. I. Meyers, *ibid.*, 1, 213 (1969). Alternatively, 1 may be prepared directly from the dialkylacetonitrile and 2-methyl-2,4-pentanediol according to E. J. Tillmanns and J. J. Ritter, *J. Org. Chem.*, 22, 839 (1957).

(6) In a temperature study of this reaction, it has been found that proton abstraction from 1 and addition to 2 proceed in rapid succession only between −15 and 0°, except when R or R′ is phenyl. Below these temperatures little or no proton abstraction occurs. If the reaction mixture is hydrolyzed at −78°, complete recovery of 1 is observed. The synthesis is nevertheless initiated at −78° since cleaner products are obtained over those formed by addition of RLi at −10 to 0°.



The obvious advantages of this method lie in the fact that not only can a series of unsymmetrical ketones be obtained containing bulky groups but quaternary carbons may be assembled in a stepwise introduction of substituents. The linear geometry of the ketenimine **2** is undoubtedly responsible for allowing sterically endowed organometallics to add smoothly (entries 7 and 8), while the α-(tertiary alkyl) groups are formed *via* an enamine alkylation (**3** → **6**). The latter process is akin to Stork's alkylation of magnesium salts of enamines to form α-alkyl aldehydes.[7] This sequence, although most elegant for aldehydes and their α-(tertiary alkyl) derivatives, gives, for ketones, the enamine derived from the least substituted α-carbon, **9**, and not the enamine related to this study, **10**. Thus, the addition of organometallics to the ketenimine **2** provides us with a highly versatile intermediate and nicely complements the method of Stork.[8] Vpc analyses of the



α-(tertiary alkyl) ketones **8** indicated no trace of isomeric ketones, which eliminated any concern over the structural integrity of the lithio enamine **3** (and any mobility between lithio-metalated enamines such as **9** and **10**).

(7) G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963).

(8) We have also observed that RMgX adds readily to the ketenimine **2** but cannot be used as the base to remove the proton in **1** in the manner in which RLi is employed. We are therefore investigating methods to prepare **2** as a stable isolable intermediate so that the method may be expanded to include RMgX. In a recent experiment we have successfully converted **1** to the ketenimine *O*-silyl ether [**2**, Li = $(Me)_3Si$] utilizing lithium diisopropylamide followed by trimethylchlorosilane.

In effect, this approach also allows for the specific introduction of alkyl groups into ketones having enolizable protons in the α and α' positions (*e.g.*, entries 4 and 5) by *constructing* the ketone from simple fragments. It also provides a useful alternative to ketone syntheses originating from carboxylic acid derivatives and organometallics.[9] Another dividend derived from this method is the ready availability of nonenolizable ketones, which is a major limitation to the Haller–Bauer[10] synthesis of α-(tertiary alkyl) acids and amides.

We are investigating further extensions of this process to allow for formation of α,α-dialkyl cyclic ketones as well as addition of other nucleophiles to the ketenimine **2**.

Acknowledgment. Financial assistance from the National Science Foundation (Grant No. GP-22541), Petroleum Research Fund, administered by the American Chemical Society, and National Institutes of Health (Grant No. GM 06248-10) is gratefully acknowledged. We are also indebted to the Lithium Corporation of America for generous supplies of organolithium reagents used in this study.

(9) D. A. Shirley, *Org. React.*, **8**, 28 (1954).

(10) K. E. Hamlin and A. W. Weston, *ibid.*, **9**, 1 (1957).

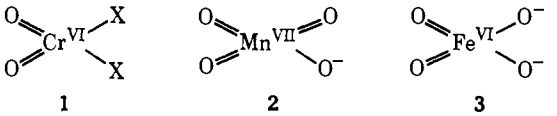
(11) Postdoctoral of the Medical Research Council of Canada, 1968–1970.

A. I. Meyers,* E. M. Smith,[11] A. F. Jurjevich
Department of Chemistry, Wayne State University
Detroit, Michigan 48202
Received January 30, 1971

Oxotransition Metal Oxidants as Mimics for the Action of Mixed-Function Oxygenases. "NIH Shift" with Chromyl Reagents

Sir:

In recent years there has been considerable interest and speculation concerning the nature of the biological oxidant in iron-based, mixed-function oxygenases. Surprisingly, no one appears to have noted the striking similarity between reactions catalyzed by oxygenases and those effected by oxotransition metal compounds of chromium (**1**) and manganese (**2**). The most characteristic roles of mixed-function oxygenases are stereo-



specific hydroxylation of aliphatic hydrocarbons and epoxidation of olefinic and aromatic substances, the last[1] resulting in the celebrated "NIH shift." Permanganate (**2**) and chromyl species (**1**, X = OH, Cl, OAc) have long been known to hydroxylate hydrocarbons with at least partial retention,[2] and chromyl acetate (**1**, X = OAc) epoxidizes olefins with retention of the olefinic geometry.[3] Thus, of the three reactions most typical of mixed-function oxygenases, only the hydroxylation of aromatic substrates with concomitant NIH shift was unknown for these oxotransition metal

(1) D. M. Jerina, J. W. Daly, B. Witkop, P. Zaltzman-Nirenberg, and S. Udenfriend, *J. Amer. Chem. Soc.*, 90, 6525 (1968).

(2) K. B. Wiberg, "Oxidation in Organic Chemistry," Academic Press, New York, N. Y., 1965.

(3) W. Kruse, *Chem. Commun.*, 1610 (1968).