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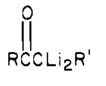
α-Keto Dianions. New Reactive Intermediates

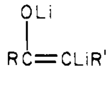
Sir:

Herein we report the preparation of a previously unrealized class of reactive intermediates for organic synthesis, α-keto dianions **1** (R′ = H or alkyl).[1] This name, suggestive of structure **1a**, was



1a

$\mathrm{R\overset{O}{\overset{\|}{C}}CLi_2R'}$



1b

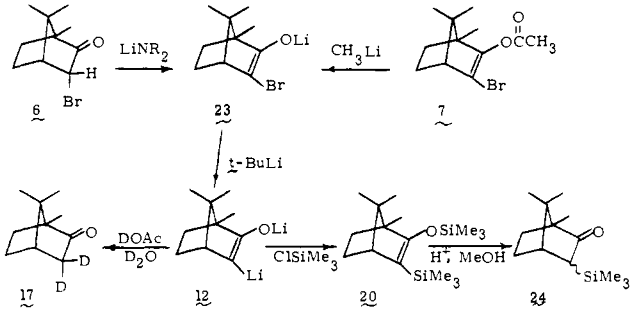
$\mathrm{R\overset{OLi}{\overset{|}{C}}{=}CLiR'}$

chosen since it best reflects the mode of preparation and synthetic utility of these intermediates. Structure **1b**, however, is probably a more reasonable depiction of this species, having the enolate charge localized mostly on oxygen, with the second charge held orthogonal to the enolate π system in an sp^2 orbital of carbon. Consistent with such a picture, these dianions resemble vinyllithium in their initial reactivity, are fairly stable in ether or tetrahydrofuran (THF) solution at room temperature, and lead directly to ketone products (or ketone enolate derivatives) in their reactions.

Dianions **1** can be prepared from the lithium enolates of both primary and secondary α-bromo ketones by metal–halogen exchange in ether by using *tert*-butyllithium. The exact procedure used depends upon the method of enolate preparation, and thus far two general procedures have been employed. Method A involves enolate formation directly from the halo ketone with lithium hexamethyldisilazide (1.05 equiv) in ether at 0 or −78 °C.[5] The resulting solution is then treated at −78 °C with sufficient *tert*-butyllithium (usually 3.5 equiv in practice) to deprotonate the disilazane, exchange the bromine, and destroy the *tert*-butyl bromide formed.[6] The −78 °C bath is removed for 5–15 min, during which time dianion formation is completed. Method B involves generating the bromo enolate anion from the bromo enol acetate in ether at 0 °C by using 2.2 equiv of methyllithium. The resulting amine-free solution, upon treatment with *tert*-butyllithium (2.2 equiv) at −78 °C followed by warming to room temperature, affords dianion as before. Method A has also been used successfully with primary iodo ketones.

Using these procedures, we have been able to prepare α-keto dianions **10**–**14** from the halides **2**–**9** (Table I). The existence of these dianions was determined by either deuteration or silylation or both. For example, either *endo*-3-bromocamphor (**6**) (Scheme I) or the corresponding bromo enol acetate (**7**)[7] could be used to generate dianion **12** via bromo enolate **23**.[8] Quenching a cold solution of the dianion with deuterioacetic acid in deuterium oxide afforded in 90% yield camphor-*3*-d_2 (**17**) (contaminated by only 5% of the d_1 compound). Quenching the dianion with excess chlorotrimethylsilane at −78 °C, followed by warming to room temperature, produced the disilylated enol ether **20**[9] in near quantitative yield. Crucial to obtaining the enol ether and not the silyl ketone **24** from this sequence was addition of several equivalents of triethylamine to the reaction mixture, just prior to dilution with hexane and washing with cold sodium bicarbonate solution. In this manner, dideuterio ketones **15**–**17** and disilylated enol ethers **18**–**22** were obtained as indicated in Table I.

Scheme I



Several results included in the table are worthy of special comment. Surprisingly, the iodo enolate anion derived from **2** undergoes metal–halogen exchange with methyllithium; this suggests that despite the presence of two proximal negative charges dianion **10** is of comparable or lesser basicity than methyllithium. Methyllithium is not reactive enough, however, to exchange the corresponding bromo enolate derived from **3** at any appreciable rate; even *n*-butyllithium is slow enough in bromo enolate anion exchange reactions that competing processes make dianion formation (e.g., **10** or **12**) impractical with this reagent.

Formation of dianions **13** and **14**, from bromides **8**[5] and **9**,[11] is especially significant in light of recent work by Harris[4,1] indicating that cyclohexanone enolate deprotonates to give the α,α'-dianion. It is clear from the NMR spectra of **21** and **22** that little or none of the isomeric enol ethers expected from the α,α'-dianions in these cases are present. Formation and silylation of dianions **13** and **14** occur regiospecifically, without any scrambling to the α,α'-dianions.

Facile hydrolysis of the disilyl enol ethers to α-silyl ketones has been observed for several of the compounds studied. In the silylation of dianion **10**, quenching of the reaction mixture with 3 equiv of dilute HCl, followed by 30 min of stirring at room temperature, affords not enol ether **18** but rather α-trimethylsilylacetophenone.[12,13] Similarly, crude enol ether **19** is converted by silica gel chromatography into pure 3,3-dimethyl-1-(trimethylsilyl)-2-undecanone (62% based on iodide **4**). Finally, the

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[1] While several species related to α-keto dianions have been studied,[2] only one example of such an intermediate has been reported.[2a] Kaiser mentions that 2,4,6-trimethylacetophenone can be doubly deprotonated by *n*-butyllithium on the α-carbon. We have not repeated this experiment but have been unable to achieve dianion formation from the lithium enolates of acetophenone or camphor under these conditions. Recently, Harris reported[4] that the enolates of acetone and cyclohexanone afford α,α'-dianions with *n*-butyllithium while that of 2,2-dimethyl-3-pentanone affords none of the α,α-dianion. Thus, α-keto dianion formation by direct deprotonation of enolates does not appear generally feasible, and Kaiser's result may be unique to that compound.

[2] (a) An α-keto dianion: Kaiser, E. M.; Solter, L. E.; Schwarz, R. A.; Beard, R. D.; Hauser, C. R. *J. Am. Chem. Soc.* **1971**, *93*, 4237. (b) The dianion from *o*-bromophenol: Gilman, H.; Jones, R. G. *Org. Ract. (N.Y.)* **1951**, *6*, 352. (c) The formal dianion of ketene: Hoppe, I.; Schöllkopf, U. *Liebigs Ann. Chem.* **1979**, 219. (d) The saturated β-alkoxide lithium dianion: Barlvenga, J.; Fānanaâs, F. J.; Yus, M. *J. Org. Chem.* **1979**, *44*, 4798. (e) β-Lithioenamines: Duhamel, L; Valnot, J. -Y. *Tetrahedron Lett.* **1979**, 3319. (f) 2-Ethoxyvinyllithium: Wollenberg, R. H.; Albizati, K. F.; Peries, R. *J. Am. Chem. Soc.* **1977**, *99*, 7365. For other dianions of synthetic interest, see ref 3.

[3] Carbonyl-containing α,α'-dianions bearing two charge-stabilizing groups are well-known; for a number of references, see: (a) Stowell. J. C. "Carbanions in Organic Synthesis", Wiley: New York, 1979; p 100. (b) Vinick, F.; Pan, Y.; Gschwed, H. W. *Tetrahedron Lett.* **1978**, 4221. (c) McMurry, J. E.; Musser, J. H. *J. Org. Chem.* **1975**, *40*, 2556. Primary nitro dianions have recently been investigated: (d) Lehr, F.; Gounermann, J.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 2258.

[4] Hubbard, J. S.; Harris, T. M. *J. Am. Chem. Soc.* **1980**, *102*, 2110.

[5] Kowalski, C.; Creary, X.; Rollin, A. J.; Burke, M. C. *J. Org. Chem.* **1978**, *43*, 2601.

[6] Corey, E. J.; Beams, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

[7] Joshi, G. C.; Chambers, W. D.; Warnhoff, E. W. *Tetrahderon Lett.* **1967**, 3613.

[8] Attempts to enolize *endo*-3-bromocamphor (**6**) by using lithium 2,2,6,6-tetramethylpiperidide, a reagent which gives clean enolization of many α-substituted ketones,[5] afford ~30% *reduction* to the simple nonhalogenated camphor enolate anion, when the reaction is done in ether at −78 °C. This is reminiscent of the reaction of **6** with *n*-butyllithium, in which appreciable reduction was observed.[7]

[9] All new compounds afforded proper combustion or exact mass spectral analysis, as well as suitable IR and NMR spectra.

[10] 1-Iodo-3,3-dimethyl-2-undecanone was prepared via alkylation (70%) of isobutyric acid dianion[16] with octyl bromide; methyllithium addition (93%) to the carboxylic acid product;[17] monobromination (68%) of the methyl ketone;[18] and displacement of bromide by iodide[19] (92%).[9]

[11] Bromo enol acetate **9** is obtained by taking 6-methyl-2-bromocyclohexanone, as formed at −78 °C by the procedure of Stotter and Hill,[20] and without workup adding this solution to lithium hexamethyldisilazide at −78 °C; quenching with acetic anhydride then affords **9** in 50% yield.

[12] Kuivila, H. G.; Maxfield, P. L. *J. Organomet. Chem.* **1967**, *10*, 41.

[13] A small amount of C–Si bond hydrolysis affording acetophenone (~7%) is difficult to prevent; see: Hauser, C. R.; Hance, C. R. *J. Am. Chem. Soc.* **1952**, *74*, 5091.

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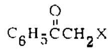
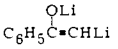
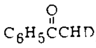
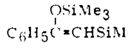
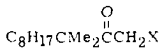
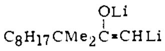
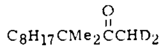
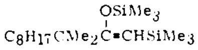
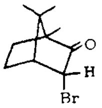
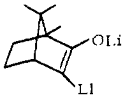
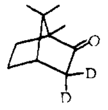
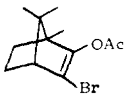
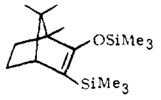
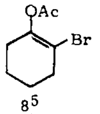
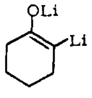
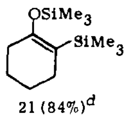
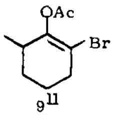
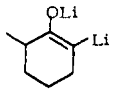
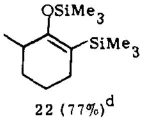
Table I

Starting Halide	Method	Dianion	DOAc/D_2O Product (yield)	ClSiMe$_3$ Product (yield)
 $C_6H_5\overset{O}{C}CH_2X$ 2 (X=I)	A^{a,b}	 $C_6H_5\overset{OLi}{C}{=}CHLi$ 10	 $C_6H_5\overset{O}{C}CHD_2$ 15 (94%)^f	 $C_6H_5\overset{OSiMe_3}{C}{=}CHSiMe_3$ 18 (70%)^d
3 (X=Br)	A	10	15 (77%)^e	
 $C_8H_{17}CMe_2\overset{O}{C}CH_2X$ 4 (X=I)[10]	A^{a,c}	 $C_8H_{17}CMe_2\overset{OLi}{C}{=}CHLi$ 11	 $C_8H_{17}CMe_2\overset{O}{C}CHD_2$ 16 (68%)^d	 $C_8H_{17}CMe_2\overset{OSiMe_3}{C}{=}CHSiMe_3$ 19 (g)
5 (X=Br)	A^a	11	16 (85%)^f	
 6	A	 12	 17 (90%)^e	
 7[7]	B	12	17 (92%)^e	 20 (98%)^{f,h}
 8[5]	B	 13		 21 (84%)^d
 9[11]	B	 14		 22 (77%)^d

[a] THF solvent. [b] MeLi used for exchange. [c] Exchange reaction never warmed above -78°. [d] Distilled or chromatographed product. [e] Determined by VPC. [f] Isolated crude product. [g] Analytical sample obtained via prep. VPC; preparative sample hydrolyzed on chromatography affording pure α-silyl ketone in 62% yield. [h] Spectrally identical with pure product.

crude silylation product **20** on stirring with 10^{-3} M trifluoroacetic acid in methanol[14] affords a mixture of *endo*- and *exo*-3-trimethylsilylcamphor (**24**) in 64% yield (based on bromide 7). Thus, silylation of α-keto dianions provides a convenient new route to these α-silyl ketones.

Silylation of simple ketone enolates generally produces only O-silylated products.[15] Unique to α-keto dianions is the silylation *on carbon* of an anion adjacent to a "ketone". Other methods used to modify the reactivity or reaction regiospecificity of enolates generally rely on the introduction of extraneous functional groups which must be removed from the ketone products in subsequent steps.[3] By contrast, the differing and unique reactivity of α-keto dianions is achieved *without need of any functional groups in the dianion other than the oxygen desired in the final ketone product.* Given the simplicity inherent in these dianions, coupled with their ease of formation, stability, and novel reactivity, we expect this species will add a new dimension to ketone enolate chemistry. Further studies of α-keto dianions are in progress.

Note Added in Proof: While cyclic α-keto dianions are fairly stable at room temperature in ether, we have recently found that dianion **10** begins decomposing to acetylenic products within 10 min of warming in this solvent; in THF, however, little decomposition is observed even after 20 min at room temperature. Also, we have found that 2,4,6-trimethylacetophenone does not afford an α-keto dianion under the reported conditions as claimed,[1] but instead affords the simple ketone enolate. In a different study, small amounts of α-keto dianion-containing trianion species were observed by Klein, J.; Medlik-Balan, A. *J. Org. Chem.* **1976**, *41*, 3307.

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Conrad J. Kowalski,* M. Lynn O'Dowd, M. Carmel Burke
Kevin W. Fields
Department of Chemistry, University of Notre Dame
Notre Dame, Indiana 46556

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(14) Creary, X.; Rollin, A. J. *J. Org. Chem.* **1979**, *44*, 1017.

(15) For a recent review discussing the O-silylation of ketone enolates, see: Rasmussen, J. K. *Synthesis* **1977**, 91.

(16) Creger, P. L. *J. Am. Chem. Soc.* **1967**, *89*, 2500.

(17) Gunar, V. I.; Zavyalov, S. I. *Dokl. Akad. Nauk. SSSR* **1960**, *132*, 829.

(18) Weihe, G. R.; McMorris, T. C. *J. Org. Chem.* **1978**, *43*, 3942.

(19) Albano, E. L.; Horton, D. *J. Org. Chem.* **1969**, *34*, 3519.

(20) Stotter, P. L.; Hill, K. A. *J. Org. Chem.* **1973**, *38*, 2576.