of the sample for 8 h at 50–60 °C, characteristic peaks of *N,N*-dimethylacetamide (**4b**) were observed at δ 3.01 (s, NCH_3), 2.93 (s, NCH_3), and 1.97 (s, CH_3CO) along with the multiplet at 4.05 (H-5) consistent with the formation of **3b** (reaction 27% complete). After additional heating at 90 °C for 6 h, the reaction was about 75% complete.

Acknowledgment. We thank the National Institute of Health for support of this research and Modesto Junior College for a sabbatical leave (M.H.G.).

Registry No. 1, 85939-88-4; **2a**, 98-09-9; **2b**, 108-24-7; **3a**, 86669-27-4; **3b**, 86669-28-5; **3c**, 86669-29-6; **4a**, 14417-01-7; **4b**, 127-19-5.

Unusual Reduction of an α-Oxo Ester by Lithium Diisopropylamide

John Harold Hoare and Peter Yates*

Lash Miller Chemical Laboratories, University of Toronto, Toronto, Ontario, Canada M5S 1A1

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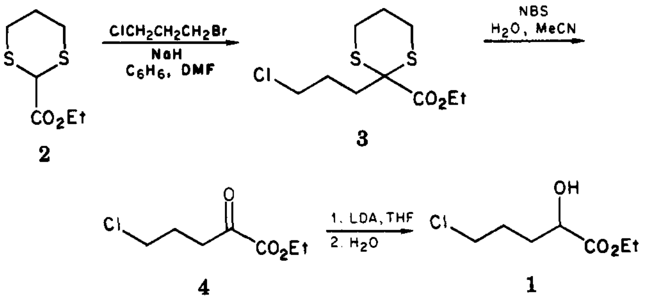
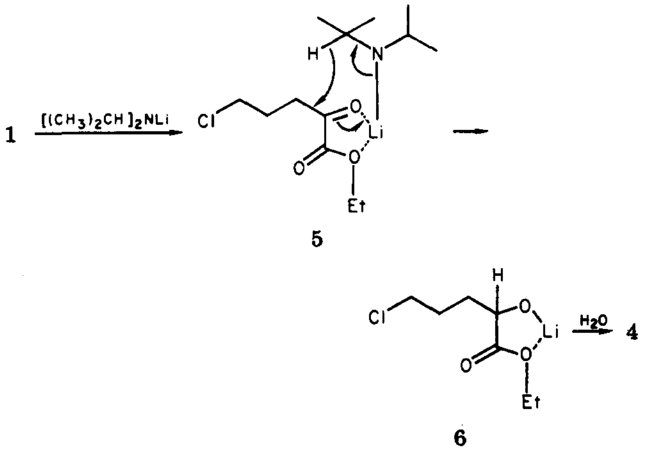
In the course of another investigation, we had occasion to attempt to generate the enolate ion of ethyl 5-chloro-2-oxopentanoate (**1**) by treatment of lithium diisopropylamide (LDA). We report here as a caveat to others our unexpected observation that such treatment brings about reduction of **1**. The α-oxo ester **1** was prepared by the route shown in Scheme I: alkylation of ethyl 1,3-dithiane-2-carboxylate (**2**) with 1-bromo-3-chloropropane by the general procedure of Eliel and Hartmann[1] gave **3**, which on treatment with *N*-bromosuccinimide in aqueous acetonitrile[2] gave **1**. Reaction of **1** with LDA in tetrahydrofuran at −78 °C resulted in its reduction to ethyl 5-chloro-2-hydroxypentanoate (**4**). The structural assignment is based on the elemental composition and IR, ^1H NMR, and ^{13}C NMR spectra of the product (see Experimental Section). Although the yield of **4** after purification was low, the ^1H NMR spectrum of the crude reaction product showed it to consist of **4** and ~5% of starting material **1** with no significant amount of other products.

Lithium diisopropylamide has previously been reported to reduce α-methoxy and α-halo ketones[3] and nonenolizable ketones,[3-5] but this is the first case to our knowledge where reduction occurs of a ketone that belongs to none of these categories.[6] We suggest that the presence of the carboxylic ester group leads to strong complexation with lithium as in **5**; the LDA then delivers a hydride ion to give **6** via a six-membered transition state (Scheme II), as postulated previously.[3,7] Similar complexation could account for the efficient reduction of α-oxo esters to α-hydroxy esters by halomagnesium alkoxides.[8] It is also possible that analogous complexation involving the α substituent facilitates the reduction of α-methoxy and α-halo ketones by LDA.

Scheme I



Scheme II



Experimental Section

Ethyl 5-Chloro-2-oxopentanoate (1). Ethyl 1,3-dithiane-2-carboxylate (**2**) (10.0 g, 52 mmol) was alkylated with 1-bromo-3-chloropropane (24.6 g, 157 mmol) and sodium hydride (50% oil dispersion; 2.68 g, 55.8 mmol) in 3:1 benzene–dimethylformamide (88 mL). After workup, the crude product was distilled at 116–117 °C (0.025 torr) to give 2-carbethoxy-2-(2-chloropropyl)-1,3-dithiane (**3**) (12.1 g, 86%): IR λ_{max} ($CHCl_3$) 5.82 μm; ^1H NMR ($CDCl_3$) δ 4.25 (q, J = 7 Hz, 2 H), 1.7–3.8 (m, 12 H), 1.33 (t, J = 7 Hz, 3 H).

A solution of **2** (8.06 g, 30.0 mmol) in acetonitrile (10 mL) was added quickly, dropwise, to a solution of *N*-bromosuccinimide (32.1 g, 180 mmol), silver perchlorate (24.9 g, 120 mmol), and 2,6-lutidine (6.42 g, 60 mmol) in aqueous 80% acetonitrile (150 mL) that was cooled in an ice bath. The ice bath was removed, and the mixture was stirred for 15 min at room temperature. The solution was poured into 1:1 methylene chloride–hexanes (150 mL), washed with saturated aqueous NH_4Cl, saturated aqueous Na_2SO_3, and saturated aqueous NaCl, dried, filtered, and concentrated. The crude product was distilled at 76–77 °C (1.25 torr) to give ethyl 5-chloro-2-oxopentanoate (**1**) (2.41 g, 45%); IR λ_{max} ($CHCl_3$) 5.78 μm; ^1H NMR ($CDCl_3$) δ 4.30 (q, J = 7 Hz, 2 H), 3.68 (t, J = 6 Hz, 2 H), 3.12 (t, J = 6 Hz, 2 H), 1.9–2.4 (m, 2 H), 1.37 (t, J = 7 Hz, 3 H); MS, *m/e* (relative intensity) 142 (14), 107 (3), 105 (9), 69 (100); exact mass calcd for $C_7H_{10}O_3$ (M − HCl) 142.0630, found 142.0641; calcd for $C_4H_6{}^{35}ClO$ (M − $CO_2C_2H_5$) 105.0088, found 105.0102.

Reaction of Ethyl 5-Chloro-2-oxopentanoate (1) with Lithium Diisopropylamide: Formation of Ethyl 5-Chloro-2-hydroxypentanoate (4). Ethyl 5-chloro-2-oxopentanoate (**1**) (2.00 g, 11.2 mmol) in dry tetrahydrofuran (4 mL) was syringed dropwise with stirring into a solution of lithium diisopropylamide (4.86 mL of 2.30 M *n*-BuLi in hexane, 1.75 mL of diisopropylamine; 11.1 mmol) in dry tetrahydrofuran (50 mL) under nitrogen

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[1] Eliel, E. L.; Hartmann, A. A. *J. Org. Chem.* **1972**, *37*, 505.

[2] Seebach, D. *Synthesis* **1969**, 17.

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

[4] Scott, L. T.; Carlin, K. J.; Schultz, T. H. *Tetrahedron Lett.* **1978**, 4367. Ashby, E. C.; Goel, A. B.; DePriest, R. N. *Ibid.* **1981**, *22*, 4355.

[5] Cf.: Monkiewicz, J.; Pietrusciewicz, K. M.; Bodalski, R. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1980**, *25*, 351.

[6] See, however, footnote 24 in ref 3. Since the submission of this note, we have observed that methyl pyruvate and ethyl 2-oxopentanoate are reduced by LDA under similar conditions to methyl lactate (22%) and ethyl 2-hydroxypentanoate (69%), respectively, indicating that reduction of **1** by LDA is not dependent on the presence of the γ-chloro substituent.

[7] However, we cannot exclude a single electron transfer mechanism as proposed for the reduction of aromatic ketones by LDA.[4]

[8] Lapkin, I. I.; Karavanov, N. A. *J. Gen. Chem. USSR (Engl. Transl.)* **1960**, *30*, 2659.

at −78 °C. The solution turned light yellow after addition was complete. Stirring was continued for 40 min at −78 °C, and then the reaction mixture was treated with saturated aqueous $(NH_4)_2SO_4$. The organic phase was removed, and the aqueous phase was washed with methylene chloride. The combined organic phases were dried, filtered, concentrated, and molecularly distilled [40 °C (0.005 torr)]. The distillate was chromatographed on silica with methylene chloride as eluent. The eluted product (R_f 0.39) was molecularly distilled at 40 °C (0.005 torr) to give ethyl 5-chloro-2-hydroxypentanoate (4) as a liquid (660 mg): IR ($CHCl_3$) λ_{max} 2.90, 5.79 μm; ^1H NMR ($CDCl_3$) δ 4.20 (q, J = 7 Hz, 2 H), 4.07 (m, 1 H), 3.4–3.7 (m, 2 H), 3.00 (s, 1 H), 1.7–2.1 (m, 4 H), 1.30 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 174.9 (s), 69.9 (d), 61.8 (t), 44.7 (t), 31.6 (t), 28.2 (t), 14.2 (q); MS, m/e (relative intensity) 165 (1), 163 (3), 127 (4), 109 (15), 107 (44), 71 (100). Anal. Calcd for $C_7H_{13}ClO_3$: C, 46.54; H, 7.25; Cl, 19.63. Found: C, 45.99; H, 7.21; Cl, 19.51.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for support of this work.

Registry No. 1, 86633-06-9; 2, 20462-00-4; 3, 86633-07-0; 4, 86633-08-1; 1-bromo-3-chloropropane, 109-70-6; lithium diisopropylamide, 4111-54-0.

Coupling Reactions of Higher Order Cuprates with Primary Halides: Extremely Mild and Efficient Substitution Reactions of Bromides and Chlorides

Bruce H. Lipshutz,*[1] David Parker,[2] and
Joseph A. Kozlowski

*Department of Chemistry, University of California,
Santa Barbara, California 93106*

Robert D. Miller

IBM Research Laboratory, San Jose, California 95193

Received January 18, 1983

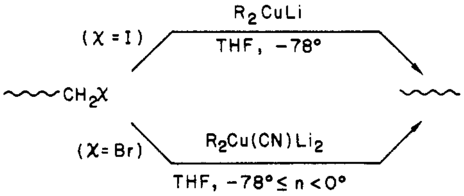
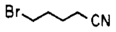
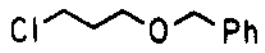
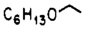
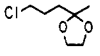
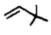
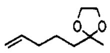
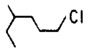
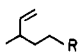
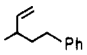
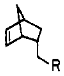
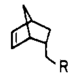
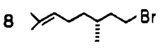
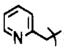
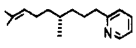
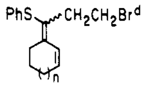
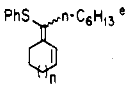


Table I. Reactions of $R_2Cu(CN)Li_2$ with Primary Halides

entry	substrate	cuprate/ conditions	equiv	product(s)	yield, %
1		n-$Bu_2Cu(CN)Li_2$ THF, −50°, 2.5h	1.3	$C_8H_{17}CN$	92[b]
2		n-$Pr_2Cu(CN)Li_2$ THF, 0°, 6h	2.0		81[b]
3		n-$Bu_2Cu(CN)Li_2$ THF, −50°, 2.5h	2.0	$C_{11}H_{24}$	95[a]
4		 $_2Cu(CN)Li_2$ THF, rt, 24h	4.0		58[a]
5		s-$Bu_2Cu(CN)Li_2$ THF, −78°, 0.75h	1.1		89[a]
6		$Ph_2Cu(CN)Li_2$			
	a, R = Br	THF, rt, 6h	2.0		91[a]
	b, R = OTs	THF, rt, 24h	2.0		95[a]
7		n-$Bu_2Cu(CN)Li_2$			
	a, R = Br	THF, 0°, 3.5h	1.7	R′ = n-Bu	91[a]
	b, R = OTs	THF, 0°, 21 h	2.0	R′ = n-Bu	30[a]
	c, R = OMs	THF, rt, 7h	2.0	R′ = OH	[c]
8		 $_2Cu(CN)Li_2$ THF, −50°, 3h	1.4		93[b]
9	[d]	n-$Bu_2Cu(CN)Li_2$ THF, −35°, 20h	2.0	[e]	
	a, n = 1				74[b]
	b, n = 2				72[b]

[a] By quantitative VPC. [b] Isolated yield of chromatographically pure product. [c] Only the alcohol was isolated. [d] See ref 7a. [e] See ref 7b.

Among the many uses of organocuprate reagents in synthesis, the coupling between primary halides and ligands bound to copper constitutes one of the most common procedures for carbon–carbon bond construction.[3] Typically, primary iodides are the substrates of choice in terms of reactivity and efficiency, with tempertures as low as −78 °C routinely used with Gilman reagents.[3] The corresponding bromides couple well, although considerably higher temperatures (ca. 0 °C) and larger quantities of reagent may be needed.[3,4] In some of our recent work elucidating the stereochemical consequences of substitution chemistry at secondary unactivated centers,[5] it was found that treatment of a primary iodide with n-$Bu_2Cu(CN)Li_2$ led to a mixture of products rapidly at −100 °C. This result suggested that primary *bromides* might react with higher order, mixed cuprates $R_2Cu(CN)Li_2$ (1) under conditions normally characteristic of iodides with lower order species. In view of the difficulties oftentimes surrounding the preparation and handling of iodides in general (e.g., light sensitivity), we have investigated the possibility of utilizing a more stable bromide as a functional equivalent (reactivity-wise) of an iodide toward displacement by simply switching from copper halide to CuCN-based technology. We now report that, indeed, both chlorides and, in particular, bromides readily react in high yields with reagents 1 at remarkably reduced tempertures relative to those called for under the influence of R_2CuLi (2).[3,4]

A fairly broad sampling of functionalized substrates was examined as illustrated in Table I. Insofar as primary bromides are concerned, most reactions took place at −50 °C or below where alkyllithium-derived cuprates were involved (entires 1, 3, and 8). Thus, in addition to a straight-chain example (entry 3), clean displacement of bromide in 5-bromovaleronitrile (entry 1) afforded pelargononitrile in 92% isolated yield. Substituted pyridines could also be prepared by using the reagent formed from lithiated picoline[6] and CuCN (entry 8). Less reactive reagents (e.g., 1, R = Ph, entry 6a) required higher temperatures, in this case room temperature for 6 h, without, however, compromising reaction efficiency. Likewise,

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[1] Recipient of an American Cancer Society Junior Faculty Research Award, 1981–1983.

[2] Recipient of University of California Reagents Fellowship, 1981–1982.

[3] Posner, G. H. *Org. React. (N.Y.)* **1975**, *22*, 253.

[4] Whitesides, G. M.; Fischer, W. F.; San Fillippo, J.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871.

[5] Lipshultz, B. H.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 4696.

[6] Lithiated 2-picoline was prepared following the basic recipe of Danishefsky et al. for the metalation of 2,6-lutidine, substituting n-BuLi as base in place of PhLi; Danishefsky, S.; Cain, P. *J. Org. Chem.* **1974**, *39*, 2925.

0022-3263/83/1948-3334$01.50/0