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LITHIUM DIISOPROPYLAMIDE AS A HYDRIDE DONOR. REDUCTION OF ALDEHYDES.

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Summary: Lithium diisopropylamide reduces aldehydes to the corresponding alcohols and also forms adducts with aldehydes. Both processes can compete with enolization.

Lithium diisopropylamide (LDA) is a very widely used reagent in modern organic synthesis; its high basicity and low nucleophilicity make it a very useful proton abstractor.[1] However, the ability of LDA to reduce organic compounds has attracted far less attention, although several interesting cases of such reductions have been observed during the last two decades.[2] In connection with a study of the complexation of lithium dialkylamides with carbonyl compounds, we have observed a fast and facile reduction of aldehydes by LDA.

Table: $RCHO + LiN^{i}Pr_2 \longrightarrow RCH_2OH$

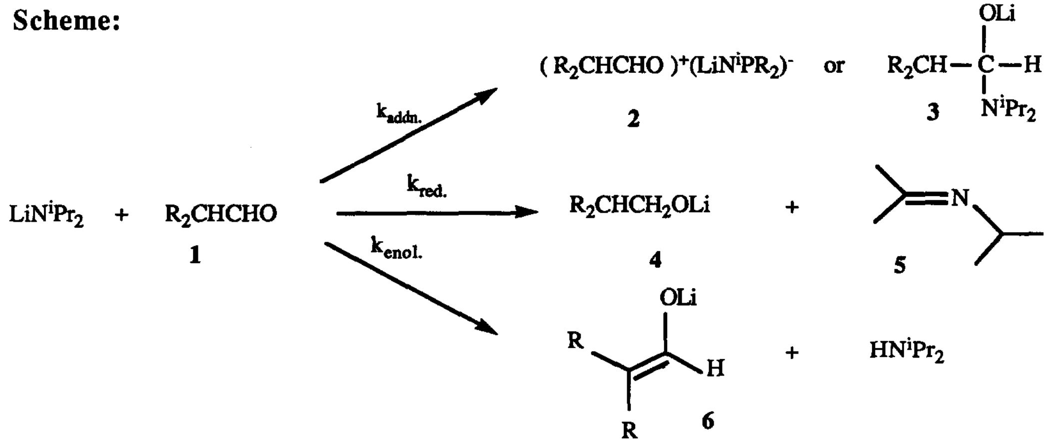
entry	*R*	*isolated alcohol (% yield)*	*[alcohol]/[aldehyde]*
1	C_6H_5	31	36 : 64[a]
2	p - $CF_3C_6H_4$	48	69 : 31[a]
3	m - $CF_3C_6H_4$	25	60 : 40[a]
4	p - ClC_6H_4	45	46 : 54[a]
5	p - MeC_6H_4	24	24 : 76[a]
6	p - $OMeC_6H_4$	15	18 : 82[a]
7	t - Bu	25	58 : 42[b]
8	cyclohexyl	40	42 : 58[b]
9	s - Bu	9	22 : 78[b]
10	n - pentyl	4	7 : 93[b]

a. Determined by GC after quenching; reactions at -85°C in THF for 3 min.
b. In Et_2O; -60°C; 3 min.

Thus when benzaldehyde was added to a solution of LDA in diethyl ether, tetrahydrofuran (THF) or hexane, benzyl alcohol (up to 35%) and benzaldehyde (up to 60%) were isolated from the post-reaction mixture. Subsequent experiments established that the reaction was general; aromatic, aliphatic and also enolizable aldehydes underwent the reduction with LDA. Data for substituted benzaldehydes are summarized in the Table (entries 1-6). A strong influence of the nature of the substituent on the efficiency of the reduction is clearly visible.The electron withdrawing substituents (entries 2, 3, 4) promote the reduction and the electron donating ones (entries 5, 6) suppress it. When an additional equivalent of n-butyllithium (n-BuLi), designed as aldehyde scavenger, was added to the mixture containing 1 mmol of an aldehyde and 1 mmol of LDA, only traces (1 - 3%) of the addition product (1-aryl-1-pentanol) were observed by GC. Also, when 1 equivalent of p-trifluoromethylbenzaldehyde was added to a mixture of benzaldehyde and LDA no p-trifluoromethylbenzyl alcohol was detected in the products.

We propose the following scheme to rationalize the above observations: an aldehyde can interact with LDA to form an addition product which could be a charge transfer complex 2, analogous to the complex observed by Wittig in the reaction of lithium diphenylamide with benzophenone,[2c,d] or a product of a nucleophilic addition of LDA to the carbonyl group as proposed previously by Kowalski and co-workers in their study on α-substituted ketones.[2g] Since we did not observe any compounds resulting from additions of n-BuLi to aldehydes even when mixtures of aldehydes and LDA were stirred with n-BuLi for several hours, the addition product seems to be rather stable under the reaction conditions.

Scheme:

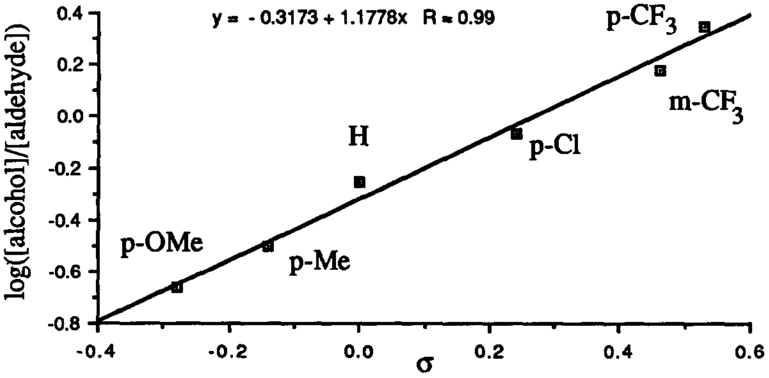


LDA can also transfer a hydride ion to yield the appropriate alkoxide 4 and the imine 5.[2g,i] Compound 4 could also originate via a single electron transfer (SET) mechanism or via the hydride transfer from 3 in a Cannizzarro reaction. The first possibility seems unlikely in view of the recent findings by Newcomb, who concluded that the SET mechanism does not play a role in the reaction of LDA with benzophenone.[2i,j] The Cannizzarro reaction is excluded by the absence of N,N-diisopropylbenzamides in the products.

Finally if an aldehyde contains an α-CH it can undergo enolization. Our data for reactions of the enolizable aldehydes with LDA are summarized in the Table (entries 8 - 10).[3] Substantial amounts of the alcohols were isolated from the reactions (volatility of the aldehydes and the alcohols makes isolation difficult). The bulk of the starting aldehyde was also recovered in each case, and the amounts of polymeric by-products, presumably originating via the aldol reaction-dehydration were small. When a mixture of 1 mmol of LDA and 1 mmol of cyclohexanecarboxaldehyde in Et_2O was treated with 1mmol of n-BuLi, no addition of n-BuLi to the aldehyde was observed, and 44% of the starting aldehyde was detected in the products along with the alcohol (45%). Further, when cyclohexanecarboxaldehyde - LDA was quenched with trimethylsilyl chloride (using Corey's internal quench procedure[4]) only 10% of the silyl enol ether was formed and 40% of the starting aldehyde was recovered along with the silylated alcohol. This shows that the addition of LDA plays a significant role in reactions of enolizable aldehydes; addition and reduction can successfully compete with enolization.

We were able to correlate the conversion rate of aromatic aldehydes to the alcohols with Hammett σ Constants (Figure). The correlation is linear, and the slope value (which corresponds to the difference between ρ for the reduction and ρ for the addition) indicates that the reduction is more sensitive to electronic effects than the addition.

Figure: $R\text{-}C_6H_4CHO + LiN^iPr_2 \longrightarrow R\text{-}C_6H_4CH_2OH$



Clearly more experimental work has to be done before the mechanism of the reduction of aldehydes by LDA is firmly established. The nature of the addition products needs to be determined as well.[5] There are, of course, reagents for effecting the reduction of aldehydes. However, an understanding of the precise role of LDA, its reductive properties and its addition to aldehydes is important, in view of its widespread use in alkylations and aldol reactions.

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3. General procedure: A solution of LDA (1 mmol) was prepared by adding n-BuLi (1 mmol) in hexane (ca. 0.4 mL) to diisopropylamine (1 mmol) in THF or Et_2O (3 mL) at 0^oC and stirred for 10 min. The solution was then cooled to the reaction temperature (-60^oC or -85^oC), and an aldehyde (1 mmol) in THF or ether (1 mL), precooled to the reaction temp., was added rapidly. The reaction was quenched after 1-3 min. by adding 1 mL of NH_4Cl aq. The organic phase was separated, and its contents were analyzed by GC. Standards (parent aldehydes and pure alcohols) were used to calibrate the GC response and to evaluate the absolute amounts of the aldehydes and the alcohols present. The solution was then dried ($MgSO_4$), the solvent was removed and the products were isolated and their structures were verified by NMR.
4. Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* **1984**, *25*, 495-8.
5. Newcomb (ref. 2i) proposed an aldol-type adduct $Ph_2C(OH)CH_2C(Me)=N^iPr$ to account for "benzophenone trapping". Since analogous adducts in our case would originate from deprotonation of imine **5**, the amount of which is sometimes small (c.f. Table, entries 5 and 6), this explanation is not likely to apply.

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