themally equilibrated reaction solution contained in the curvette in the thermostatted cell holder of a Shimadzu UV250 spectrophotometer as described before.[29]

Rate constants in the range of 0.1-1.0 $s^{-1}$ were measured on a LKB 2238 UVICORD SII UV monitor which was coupled with a HI-TECH Scientific SFA-II Rapid Kinetics Accessory. Stock solution of ortho ester (ca. $1.5 \times 10^{-4}$ M) in a $5 \times 10^{-5}$ M sodium hydroxide solution and aqueous acidic buffer solution were introduced into two different reservoirs. After thermal equilibration, an equal volume of these solution was injected into the UV cell to initiate the hydrolysis experiment. The data were fed as voltage signals, via the interface and the analogue-digital converter, to an Apple II microcomputer.

Rate constants in the range from 1.0 to 100 $s^{-1}$ were measured on HI-TECH SCIENTIFIC stopped-flow SF-51 spectrometer. The aqueous acidic buffer and the stock solution of ortho ester (ca. $1.5 \times 10^{-4}$ M) in $5 \times 10^{-5}$ M NaOH were loaded in two reservoirs, after thermal equilibration, an equal volume was injected into the curvette. The data collection was controlled by an Apple IIe microcomputer via an ADS-1 interface unit. The programs for controlling the data collection were purchased from HI-TECH. A DASAR system (data acquisition, storage and retrieval system) from HI-TECH was used to collect the data.

Reactions were normally followed to greater than 90% completion, and first-order rate constants were calculated using a generalized least-square method.[30] The standard deviations for most of the first-order rate constants were less than 4%. Second-order rate constant for the reactions were obtained as the slopes of plots of the first-order rate constants against $[H^+]/101^{-pH}$ using linear least-square method. Reaction solutions, whose ionic strengths were maintained constant with potassium chloride ($I$ = 1.0 M), had their pHs adjusted with HCl and sodium acetate ($1 \times 10^{-4}$ M). The pHs of the solutions were checked constantly.

**Supplementary Material Available:** Tables of spectral data and $^1H$ NMR spectra (23 pages). Ordering information is given on any current masthead page.

(29) Capon, B.; Kwok, F. C. *J. Am. Chem. Soc.* **1989**, *111*, 5346.

(30) Wentworth, W. E. *J. Chem. Educ.* **1965**, *42*, 96.

# On the Structure and Reactivity of Lithium Diisopropylamide (LDA) in Hydrocarbon Solutions. Formation of Unsolvated Ketone, Ester, and Carboxamide Enolates

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*Received January 9, 1991*

Enolizations of ketones, *tert*-butyl esters, and carboxamides by solvent-free lithium diisopropylamide (LDA) in hexane or toluene are described. Enolates are isolated as spectroscopically pure, white (often crystalline) solids. Solubilities of the enolates in hexane range from highly soluble to completely insoluble. Enolizations of aldehydes, methyl esters, and acetone afford complex mixtures. Analysis of [$^6$Li]LDA and [$^6$Li,$^{15}$N]LDA in hexane by $^6$Li and $^{15}$N NMR spectroscopy show evidence of an equilibrium mixture of at least three cyclic oligomers.

## Introduction

During the course of our investigations of the structure and reactivity of lithium diisopropylamide (LDA) and its propensity to form mixed aggregates with ketone enolates, we had occasion to make several observations. We rediscovered[1] that LDA has an appreciable solubility in hexane at ambient temperatures, which, in turn, affords a fairly efficient method of purification by recrystallization. Solutions of LDA in hexane readily supersaturate, affording transiently stable solutions exceeding 0.1 M even below -78 °C. As initially noted by Rathke[2a] and Lochmann[2b] during the course of metalations of hindered esters,[3,4] hydrocarbon solutions of unsolvated LDA afford solid (often crystalline) enolates of high purity when treated with carbonyl-containing substrates at ambient or elevated temperatures.[5] Noting that donor solvent-free lithiations could prove useful in a process research setting where ethereal solutions at cryogenic temperatures can be prohibitively costly, we describe a number of representative enolizations by donor solvent-free LDA.[2,5,6] We also include preliminary structural studies indicating that LDA in hexane resides as a distribution of at least three and possibly as many as five cyclic oligomers.[7]

## Results and Discussion

**Enolizations.** The results of enolizations of standard carbonyl compounds are summarized in Table I. Spectroscopic data are summarized in Table II. Enolizations could be carried out using recrystallized (prepurified) LDA or LDA generated in situ from *n*-BuLi and diisopropylamine with little difference in the end result. The in situ

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(1) Kamienski, C. W.; Lewis, D. H. *J. Org. Chem.* **1965**, *30*, 3498.

(2) (a) Rathke, M. W.; Sullivan, D. F. *J. Am. Chem. Soc.* **1973**, *95*, 3050. (b) Lochmann, L.; Lim, D. *J. Organomet. Chem.* **1973**, *50*, 9.

(3) For other examples of enolizations by hydrocarbon-soluble lithium bases, see: Heathcock, C. H.; Lampe, J. *J. Org. Chem.* **1983**, *48*, 4330. Arnett, E. M. Unpublished results. Beck, A. K.; Hoekstra, M. S.; Seebach, D. *Tetrahedron Lett.* **1977**, 1187. Seebach, D.; Weller, T.; Protschuk, G.; Beck, A. K.; Hoekstra, M. S. *Helv. Chem. Acta* **1981**, *64*, 716. Yoshifuji, M.; Nakamura, T.; Inamoto, N. *Tetrahedron Lett.* **1987**, *28*, 6325. See also ref 4.

(4) Preparation and use of donor solvent-free LDA: Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462. Kopka, I. E.; Fataftah, Z. A.; Rathke, M. W. *J. Org. Chem.* **1987**, *52*, 448. Reetz, M.; Maier, W. F. *Leibigs Ann. Chem.* **1980**, 1471. Moss, R. J.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 1992. Tobia, D.; Rickborn, B. *J. Org. Chem.* **1989**, *54*, 777. See also ref 6.

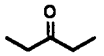
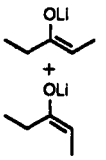
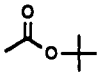
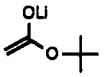
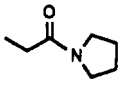
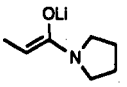
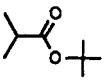
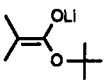
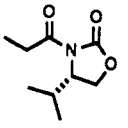
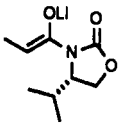
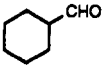
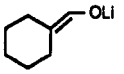
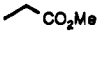
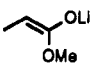
(5) For a recent review on the physicochemical studies of ketone enolates and phenolates, see: Jackman, L. M. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: New York, in press. See also: Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737.

(6) Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* **1989**, *111*, 6772.

(7) For an extensive review of structure studies on N-Li species, see: Gregory, K.; Schleyer, P. v. R.; Snaith, R. *Adv. Organomet. Chem.*, in press.

0022-3263/91/1956-4435$02.50/0 

**Table I. Lithium Enolates from Hydrocarbon Solvent**

| entry | substrate | enolate | solvent | % isolated yield |
|---|---|---|---|---|
| 1 |  |  | hexane | 82 (85)[a] |
| 2 |  |  | toluene | 75 |
| 3 |  |  | hexane | 51 (59)[a] |
| 4 |  |  | hexane | 14 |
| 5 |  |  | hexane | 67 |
| 6 |  |  | hexane | 70 |
| 7 |  |  | hexane | 76 |
| 8 |  |  | hexane | 79 |
| 9 |  |  | hexane | 50 |
| 10 |  |  | hexane | complex mixtures |
| 11 |  |  | hexane | complex mixtures |
| 12 |  |  | hexane | complex mixtures |

[a] Isolated yield using LiTMP.

procedure has obvious advantages over the procedure based on prepurified LDA. The prominence of the latter in Table I stems from our added concern over purity during the course of mixed aggregate structural studies to be described elsewhere.[8,9] Although we sporadically observed upfield doublets in the $^1H$ NMR spectra indicative of 2–5% amine solvation or lithium amide mixed aggregation,[2,9] the enolates generally were isolated in very high (>97%) purity as shown by both $^1H$ and $^{13}C$ NMR spectroscopy.[10,11] The poor yield of 3-pentanone enolate in entry 4 (as well as some of the moderate yields) stems from very high enolate solubilities in hexane.

In cases where regio- or stereoselectivity was at issue, the results were mixed. Enolization of 3-pentanone (entry 4) affords a 1:1.5 mixture of *E* and *Z* isomers in the crude solution (as shown by TMSCl trapping[12]) and a 4–8:1 ratio in the crystalline enolate isolated from cold hexane at −20 °C. These contrast with the 2–3:1 ratios observed for LDA/THF-derived lithiations. Enolizations in entries 6 and 9 afford single geometric isomers (presumed as drawn[13]). The enolization of 2-methylcyclohexanone affords the less substituted enolate in very high (45–55:1) selectivity as shown by TMSCl trapping and comparison with authentic samples of enol silyl ethers.[14] This compares favorably with literature reports[14] on LDA in ethereal solvents at −78 °C. The $^1H$ and $^{13}C$ NMR spectra of the 2-methylcyclohexenolate product show an approximate 1:1 mixture of two structure forms with each displaying vinyl hydrogen resonances. These spectroscopic properties may be a consequence of homo- and heterochiral mixed aggregation.[15]

The complex reaction products isolated from the lithiations of aldehydes, methyl esters, and acetone (entries 10–12) constitute the most notable failures.[16] We suspect that condensations with unreacted starting material are at the root of the problem.[17] We hasten to add that the rate of enolate precipitation (immediately, entries 1, 2, 5, 6, 8, 9, 11, 12; only upon concentration and cooling to −20 °C, entries 3, 4, 7, 10) does not appear to be a determinant of reaction efficacy.

**Solution Structure of LDA in Hexane.** The solution structure of LDA was studied using both [$^6$Li]LDA and [$^6$Li,$^{15}$N]LDA.[18,19] The presence of a number of cyclic

(8) Galiano-Roth, A. S.; Kim, Y.-J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.*, in press.

(9) For an excellent review on the effects of aggregation and mixed aggregation on the structure and reactivity of organolithium compounds, see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

(10) Slightly higher yields could be obtained using lithium 2,2,6,6-tetramethylpiperidide,[11] but at a substantial increase in cost.

(11) Lappert, M. F.; Slade, M. J.; Singh, A.; Atwood, J. L.; Rogers, R. D.; Shakir, R. *J. Am. Chem. Soc.* **1983**, *105*, 302. Dougherty, C. M.; Olofson, R. A. *Org. Synth.* **1978**, *58*, 3743. For a detailed description of the preparation of crystalline LiTMP, see: Hall, P.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.*, in press.

(12) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495. Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959. Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Tetrahedron Lett.* **1978**, 2079.

(13) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 3, Chapter 1.

(14) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979.

(15) Stereochemistry of aggregation: Fraenkel, G.; Beckenbaugh, W. E.; Yang, P. P. *J. Am. Chem. Soc.* **1976**, *98*, 6878. Klumpp, G. W.; Vos, M.; de Kanter, F. J. J. *J. Am. Chem. Soc.* **1985**, *107*, 8292. See also ref 18a.

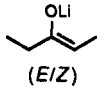
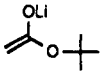
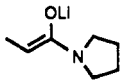
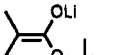
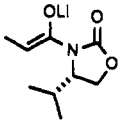
(16) The potassium enolate of acetone can be prepared by direct metalation of acetone with potassium hexamethyldisilazide: Hartwig, J. F.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 5670.

(17) The instability of unhindered ester enolates even in the solid state has been clearly documented: Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403. Häner, R.; Laube, T.; Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 5396. Siekaly, H. R.; Tidwell, T. T. *Tetrahedron* **1986**, *42*, 2587. Fehr, C.; Galindo, J. *J. Org. Chem.* **1988**, *53*, 1828.

(18) (a) Kallman, N.; Collum, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 7466. (b) Jackman, L. M.; Scarmoutzos, L. M.; Porter, W. *J. Am. Chem. Soc.* (1987), *109*, 6524. (c) Jackman, L. M.; Scarmoutzos, L. M. *J. Am. Chem. Soc.* **1988**, *110*, 5348. (d) Jackman, L. M.; Scarmoutzos, L. M.; Smith, B. D.; Williard, P. G. *J. Am. Chem. Soc.* **1988**, *110*, 6058. (e) Galiano-Roth, A. S.; Michaelides, E. M.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 2658. (f) Depue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *109*, 5518. (g) Gilchrist, J.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1990**, *112*, 4069. (h) For $^{15}$N chemical shift studies at ambient temperatures, see: Ide, S.; Iwasawa, K.; Yoshino, A.; Yoshida, T.; Takahashi, K. *Magn. Reson. Chem.* **1987**, *25*, 675. Konishi, K.; Yoshino, A.; Katoh, M.; Matsumoto, K.; Takahashi, K.; Iwamura, H. *Chem. Lett.* **1982**, 169. Barchiesi, E.; Bradamante, S. *J. Phys. Org. Chem.* **1990**, *3*, 139. Mansour, T. S.; Wong, T. C.; Kaiser, E. M. *J. Chem. Soc., Perkin Trans. 2* **1985**, 2045.

(19) The mixture of the three major cyclic oligomers of [$^6$Li,$^{15}$N]LDA in hexane exhibited the following spectroscopic properties: $^6$Li NMR (hexane, −95 °C) $\delta$ 2.99 (t, $J_{Li-N}$ = 6.4 Hz), 2.85 (t, $J_{Li-N}$ = 6.4 Hz), 2.81 (t, $J_{Li-N}$ = 6.4 Hz); $^{15}$N NMR (hexane, −100 °C) $\delta$ 32.01 (quint, $J_{Li-N}$ = 6.4 Hz), 30.72 (quint, $J_{Li-N}$ = 6.4 Hz), 29.51 (quint, $J_{Li-N}$ = 6.4 hz). Broad band decoupled $^6$Li and $^{15}$N spectra each show three clearly resolved singlets. The corresponding $^6$Li NMR spectra of [$^6$Li]LDA (no $^{15}$N label) at −65 °C show the three major resonances at 3.13, 3.00, and 2.95 ppm along with additional fully reproducible minor (<5%) resonances at 3.08 and 3.04 ppm that may correspond to other cyclic oligomers. It is likely that some of the apparent temperature dependence of the $^6$Li chemical shifts stem from a temperature dependence of the 0.3 M $^6$LiCl/MeOH capillary.

Table II. $^1H$ NMR and $^{13}C$ NMR Data Recorded at 25 °C

| LiOC$^a$=C$^b$ | $^1H$ NMR C$^a$ | $^1H$ NMR others | $^{13}C$ NMR C$^a$ | $^{13}C$ NMR C$^b$ | $^{13}C$ NMR others | solvent |
|---|---|---|---|---|---|---|
|  | 4.59 (b t)<br>$J$ = 3.2 Hz | 1.83 (m)<br>2.31 (m) | 159.8 | 90.5 | 33.9, 25.2<br>24.6 | $C_6D_6$/2 equiv THF |
|  | 4.80 (b t)<br>4.75 (b t) | 1.25–2.28 (m) | 162.9<br>162.6 | 94.2<br>93.7 | 36.2, 32.7, 25.2<br>21.1, 20.9, 19.8 | $C_6D_6$ |
|  (E/Z) | 4.51 (q)<br>4.29 (q)<br>$J$ = 7.0 Hz | 2.16 (m)<br>1.66 (m)<br>1.13 (m) | 162.8<br>161.2 | 90.3<br>88.6 | 32.5, 12.6, 12.0<br>26.9, 12.3, 10.5 | $C_6D_6$ |
|  | 3.24<br>3.09 | 1.55 | 164.9 | 76.1 | 58.5, 28.8 | $C_6D_6$/1 equiv THF |
|  | 3.44 (q)<br>$J$ = 6.2 Hz | 3.23 (b t)<br>2.05 (d)<br>1.63 (b q) | 163.5 | 63.4 | 48.9, 26.2, 12.6 | $C_5D_5N$ |
|  | 4.02<br>3.93 | 1.19 | 177.0 | 76.8 | 37.3, 29.3 | $C_6D_6$ |
|  | | 2.08<br>1.87<br>1.48 | 158.5 | 74.1 | 73.3, 30.4<br>20.2, 19.7 | $C_5D_5N$ |
|  | 3.65–3.33 (m)<br>2.39–2.90 (m) | 2.10 (d)<br>0.81 (d)<br>0.38 (d) | 158.7 | 76.6 | 149.5, 62.3, 61.1<br>27.1, 17.7, 14.6<br>10.7 | $C_6D_6$ |

oligomers was evidenced by the appearance of five discrete resonances in the $^6Li$ spectra of [$^6Li$]LDA in slow exchange even at 25 °C (Figure 1A). (The minor resonances are highly reproducible and batch-independent.) The corresponding $^6Li$ and $^{15}N$ NMR spectra of [$^6Li$,$^{15}N$]LDA show overlapping triplets and quintets (respectively) with coupling constants in the range of 6.3–6.5 Hz (Figure 1B and C).[19] The severe overlap renders the effort required for a detailed study unjustifiable. Nevertheless, it appears that these resonances correspond to cyclic dimers, trimers, and higher oligomers suggested to be present for other donor solvent-free lithium amide derivatives.[7,20] Upon addition of ≥1.0 equiv of THF, all $^6Li$ resonances are replaced by a single resonance at 1.94 ppm (−100 °C) corresponding to the previously characterized disolvated dimer with no residual impurities detectable.[6]

## Summary and Conclusion

We have described enolizations using donor solvent-free LDA in hexane solutions at ambient temperatures and further suggest that the procedure might obviate the need for ethereal solvents at reduced temperatures that can be costly on industrial scales. While it is not clear at this time whether the chemistry of the resulting enolates can be extended to accommodate these conditions, the wealth of additives that have been used to modify enolate reactivity and selectivity lends cause for optimism. In any case, the procedure affords a practical source of enolate substrates for detailed physicochemical studies.

## Experimental Section

**Reagents and Solvents.** Toluene, tetrahydrofuran (THF), *n*-hexane, and all deuterated solvents were distilled from blue or purple solutions containing sodium benzophenone ketyl under vacuum. The hydrocarbon stills contained 1% tetraglyme to dissolve the ketyl. $^6Li$ metal (95.5% enriched) was obtained from Oak Ridge National Laboratory. Ethyllithium and [$^6Li$]ethyllithium were prepared by the standard literature procedure[21] as described in detail below. $^{15}NH_4Cl$ (99%) was obtained from Cambridge Isotope Laboratory and used without further purification. Unlabeled diisopropylamine was obtained from Aldrich and purified by fractional distillation from $CaH_2$. The diphenylacetic acid used to determine the solution titers[22] required recrystallization from methanol and sublimation at 120 °C under full vacuum to obtain reproducible results. *tert*-Butyl isobutyrate[23] and pyrrolidinopropionamide[24] were prepared by standard methods. The remainder of the carbonyl-containing substrates were obtained from Aldrich, purified by careful fractional distillation, and shown to be >98% pure by gas chromatography. Air- and moisture-sensitive materials were manipulated under argon or nitrogen using standard glovebox, vacuum line, and syringe techniques.

**Enolizations.** The following are representative procedures for the preparation and isolation of donor solvent-free enolates listed in Table I.

**Method A: Purified LDA.** A suspension of prepurified LDA (1.30 g, 12.1 mmol) and *n*-hexane (30 mL) in a 100-mL flask was heated to reflux to dissolve the LDA and then cooled back to room temperature. A solution of 2-methylcyclohexanone (1.47 mL, 12.1 mmol) in hexane (5 mL) was added dropwise via gas tight syringe. After addition was complete, the homogenous, colorless solution

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(23) *tert*-Butyl isobutyrate was made from *t*-BuOH/isobutyryl chloride/$NEt_2$ at rt. A standard extractive workup and fractional distillation afforded >98% pure material.

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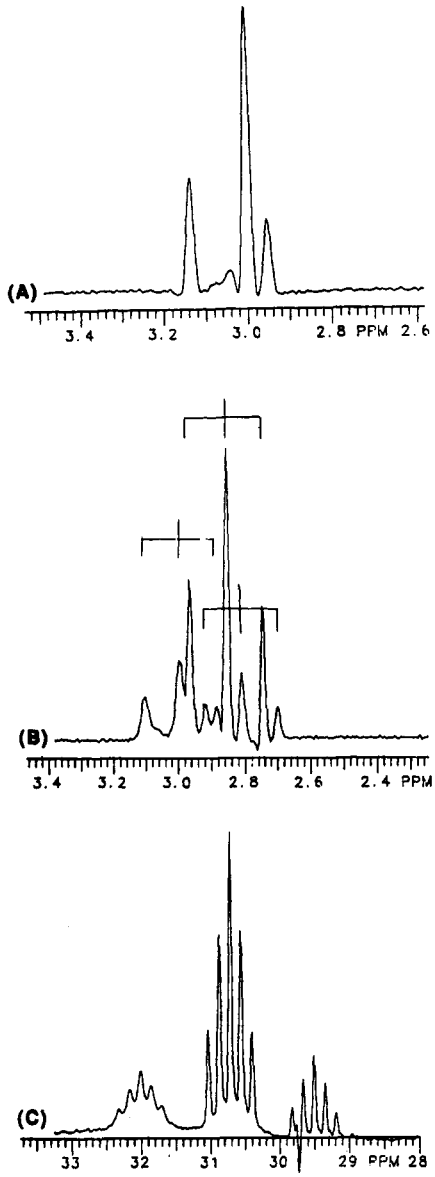


**Figure 1.** (A) $^{6}$Li NMR spectrum of 0.1 M [$^{6}$Li]LDA in hexane at −65 °C. (B) $^{6}$Li NMR spectrum of 0.1 M [$^{6}$Li,$^{15}$N]LDA in hexane at −95 °C. (C) $^{15}$N NMR spectrum of 0.1 M [$^{6}$Li,$^{15}$N]LDA at hexane at −100 °C. See ref 19 for details of the spectroscopic data.

was stirred at rt for 30 min and then evacuated to dryness to remove the diisopropylamine. (Crystallization was not observed if the crude reaction was cooled directly, presumably due to the formation of amine solvates.[6]) Addition of hexane (5 mL) and cooling the flask in the freezer at −20 °C afforded 0.73 g (51% yield) of 6-methylcyclohexenolate. Following quenching of a sample of product with chlorotrimethylsilane in THF at −78 °C, gas chromatographic analysis with comparison to authentic samples showed an approximate 50:1 selectivity for the formation of the less substituted (kinetic) enolate. The less soluble enolates (Table I; entries 1, 2, 5, 6, 8, 9, 11, 12) were filtered directly from the reaction mixture without intermediate evacuation of solvent.

**Method B: In Situ Generated LDA.** To a 100-mL round-bottom flask charged with *n*-hexane (50 mL) and diisopropylamine (4.0 mL, 28.5 mmol) at rt was added 1.6 M *n*-BuLi (28.5 mmol). The resulting homogeneous solution was stirred for 1.0 h, at which time 2-methylcyclohexanone (3.46 mL, 28.5 mmol) in hexane (5 mL) was added dropwise via syringe. After being stirred for an additional 30 min, the reaction was worked up as described in method A to afford 1.89 g (48% yield) of 6-methylcyclohexenolate.

**[$^{15}$N]Diisopropylamine.** The following represents a substantial improvement over the previously described[6] preparation of $^{15}$N labeled diisopropylamine. A nitrogen-flushed 250-mL round-bottom flask fitted with a septum was charged sequentially with $^{15}NH_4Cl$ (3.0 g, 55 mmol), $NaCNBH_3$ (6.9 g, 110 mmol), NaOAc (6.6 g, 80.5 mmol), and powdered 4-Å molecular sieves (0.5 g). After the vessel was cooled to 0 °C, MeOH (150 mL) was added followed by HOAc (0.44 mL, 7.7 mmol), acetone (12.2 mL, 165 mmol), and dodecane (1.25 mL; internal GC standard) with rapid stirring. After 3 h at rt the reaction was judged to be complete by GC analysis of aliquots quenched with 3 N NaOH and extracted with ether. (Note: elevated temperatures caused up to 20% incorporation of the $^{14}$N from $NaCNBH_3$ into the final product.) The pH was adjusted to 4 with glacial acetic acid and the flask pumped to dryness in vacuo in order to remove unreacted ketone. The solids were then partially dissolved in 30 mL of MeOH and the solution adjusted to pH 14 with solid NaOH pellets to hydrolyze the borate salts. After being stirred for 1 additional h, the solution was adjusted back to pH 4 with HOAc and the solvent was removed in vacuo. Upon partial dissolution of the solids with 30 mL of 2-propanol followed by filtration, bubbling gaseous HCl through the filtrate resulted in precipitation of crude $(i\text{-Pr})_2{}^{15}$NH·HCl, which was filtered and dried. Recrystallization from 1:1 THF/*i*-PrOH afforded 6.89 g (91% yield based on $^{15}NH_4Cl$) of pure material: $^{1}$H NMR ($D_2O$) $\delta$ 3.37 (≥7 line m, 1 H, $J$ = 6.4 Hz), 1.18 (dd, 6 H, $J_{H\text{-}H}$ = 6.5 Hz, $J_{N\text{-}H}$ = 4.4 Hz); $^{13}C\{^{1}H\}$ NMR ($D_2O$) $\delta$ 40.0 (CH, $^{1}J_{N\text{-}C}$ < 1 Hz), 10.0 ($CH_3$, $^{2}J_{N\text{-}C}$ < 1 Hz). The free amine was isolated by dissolving the $(i\text{-Pr})_2{}^{15}$NH·HCl in 3 N NaOH (50 mL) at 0 °C, extracting once with 25 mL of $Et_2O$, drying the organic extracts with $CaH_2$ until effervescence subsided (45 min), and fractionally distilling the ether followed by the amine. The $(i\text{-Pr})_2{}^{15}$NH was isolated in 41% overall yield (2.26 g), exhibited spectroscopic properties as described previously,[6] and was shown to be >98% pure by GC.

**[$^{6}$Li,$^{15}$N]LDA.** Our most effective procedure devised to date for the synthesis and purification of donor solvent-free LDA is as follows. A 100-mL round-bottom flask is charged sequentially with doubly recrystallized, doubly sublimed [$^{6}$Li]ethyllithium (772 mg, 22 mmol) and degassed dry hexane (80 mL). Following heating to dissolve the ethyllithium and cooling to 0 °C, [$^{15}$N]-diisopropylamine (2.25 g, 22 mmol) is added in one portion by gas-tight syringe. The solution is stirred for 10 h at rt at which time it is filtered to remove trace solid residue. After the faint yellow filtrate is cooled in an ice bath, the resulting white solid is isolated by filtration, redissolved, and recrystallized from fresh hexane. The mother liquor is evaporated, and the resulting pale yellow solid is doubly recrystallized. The combined yield is 2.10 g (89% yield) of spectroscopically pure [$^{6}$Li,$^{15}$N]LDA. In older samples that have acquired small quantities of impurities, sublimation under full vacuum at 90 °C affords pure material in >70% weight recovery.

**[$^{6}$Li]Ethyllithium.** Into a two-neck 250-mL round bottom flask fitted with a argon/vacuum hose adapter and mechanical stirrer (with a nichrome wire rather than Teflon paddle) is added 40 mL of light mineral oil, 3.6 g (0.6 mol) of gram-sized pieces of $^{6}$Li metal, and 35–40 mg of sodium metal. The flask is evacuated with slow stirring until the oil is degassed. Following back-filling the flask with Ar, the mixture is then heated using a Bunsen burner (**caution: fire hazard**) while being stirred rapidly enough to ensure full mixing of the sodium and lithium of differing densities. The heating is continued until the metals melt, at which point the mixture is cooled rapidly with a 20 °C bath while maintaining rapid stirring. The mechanical stir rod is replaced by a magnetic spin bar. The flask is immediately equipped with a vacuum line filter and immediately evacuated to remove the oxygen. After back-filling with argon, the resulting lithium sand is filtered and washed with hexane. The flask containing the oily filtrate is then replaced with a 250-mL round-bottom flask containing a magnetic spin bar. Approximately 125 mL of benzene is vacuum transferred onto the Li sand. To the stirring suspension of lithium in benzene at 0 °C is slowly added 22 mL (0.3 mol) of bromoethane freshly distilled from $P_2O_5$. After the solution is stirred for 14 h, the purple residue is filtered away from the ethyllithium solution and the benzene is removed under reduced pressure. The crude ethyllithium is recrystallized from 125 mL of hexane and collected by filtration at −78 °C. After removal of the filtrate, the ethyllithium is transferred using a glovebox into a new flask fitted with a fresh filtering assembly. A second recrystallization from hexane followed by two sublimations from a 90 °C bath under full vacuum with a 35 °C cold

finger (refluxing $Et_2O$) affords pure [$^6$Li]ethyllithium in 20–80% (typically 50–60%) isolated yields. For optimal results, the [$^6$Li]ethyllithium should be freshly sublimed before each use: $^{13}C[^1H]$NMR (17.6 °C, $C_6D_6$) $\delta$ 11.67 and 0.51; $^1$H NMR (17.6 °C, $C_6D_6$) $\delta$ 1.24 (t, 3 H, $J_{H-H}$ = 7.9 Hz), –0.99 (q, 2 H, $J_{H-H}$ = 7.9 Hz).

**Acknowledgment.** We thank Dr. Lendon Pridgen of SmithKline Beecham Pharmaceuticals for generous samples of the oxazolidinone chiral auxiliary. We acknowledge the National Science Foundation Instrumentation Program (CHE 7904825 and PCM 8018643), the National Institutes of Health (RR02002), and IBM for support of the Cornell Nuclear Magnetic Resonance Facility. We also thank the National Institutes of Health for direct support of this work.

# *N*-(1-Benzotriazol-1-ylalkyl)amides, Versatile α-Amidoalkylation Reagents. 1. α-Amidoalkylation of CH Acids

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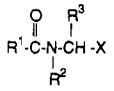
*Received January 22, 1991*

*N*-(1-Benzotriazol-1-ylalkyl)amides **2**, easily prepared from an amide and an aldehyde with benzotriazole, react smoothly with CH acids under mild conditions to give the α-amidoalkylation products in good yields. Benzotriazole aminals also react with CH acids in the presence of methyl iodide.

## Introduction

Amidoalkylations have found versatile applications in organic synthesis as a valuable alternative to the Mannich reaction.[1] In addition to providing ready access to primary and secondary amines, amidoalkylation (for reviews, see refs 2–4) is applicable to a considerably broader spectrum of reactivity than the Mannich reaction and has been used in syntheses of α- and β-amino acids,[5,6] β-amino ketones,[7] β-lactams,[8] and porphyrins.[9] Intramolecular amidoalkylations have received much attention in new approaches to alkaloid synthesis.[10]



1

X = OH, OR, OCOR, Halogen, NHCOR, $NR_2$

Numerous amidoalkylation reactions have been reported in the last two decades.[2-4] In most cases, the electrophilic amidoalkylation reagents can be represented by the structure **1**,[4] where X is one of the leaving groups indicated and $R^2$ may be a hydrogen, alkyl, or second acyl group. Compounds sufficiently nucleophilic to undergo reaction with these amidoalkylating agents include carbanions derived from active methylene compounds, activated aromatic and heteroaromatic compounds, olefins, and acetylenes. However, previous methods for amidoalkylation using the presently available reagents **1** with the leaving groups X listed all possess limitations and/or disadvantages:

(a) X = OH. The most frequently used amidoalkylation reagents in recent reports have been *N*-(α-hydroxyalkyl)amides. However, the strongly acidic reaction conditions usually employed, e.g., concentrated sulfuric acid, can produce byproducts or completely divert the course of the reaction.[2] Thus, several attempts to amidomethylate malonic ester with *N*-(hydroxymethyl)benzamide or *N*-(hydroxymethyl)phthalimide in sulfuric acid failed,[11,12] and the amidoalkylation of aliphatic nitro compounds gave low yields (20–33%).[13] In addition, the application of reagents with X = OH appears to be limited to cases where $R^3$ = $CO_2Et$, $CO_2H$, $CCl_3$, or H.

(b) X = OR or OCOR. These amidoalkylating agents, which are ethers and esters of *N*-(α-hydroxyalkyl)amides, have generally required preparation by electrochemical methods: anodic oxidation of N-alkylated amides in organic acids[14] and alcohols[15] or by other inconvenient routes.[16] Furthermore, the ethers and esters of *N*-(α-hydroxyalkyl)amides employed for the α-amidoalkylation of active CH compounds have mostly been limited to those of cyclic amides.[4]

(c) X = halogen. These reagents are so reactive that it is often difficult to prepare, isolate, purify, and store them.[4,17] They are frequently prepared in situ from *N*-α-hydroxyalkyl precursors and immediately treated with substrate and catalyst, but this often results in low-yield amidoalkylations[17-19] and to side product formation.[4]

(d) X = NHCOR. Although the reagents are easily accessible, the amidoalkylating conditions are usually severe, e.g., concentrated sulfuric acid[20] or hot polyphosphoric acid,[21] under which side reactions are to be expected, especially for active methylene compounds. Only half a molar equivalent of the amide is utilized, and the leaving group is also an amide, which could be inconvenient during purification of amidoalkylated products.

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