Dipole-Stabilized Carbanions: Secondary (α-Lithioalkyl)alkylamine Synthetic Equivalents from *N,N*-Dialkyl-2,2-diethylbutyramides

Summary: Lithiation of *N,N*-dialkyl-2,2-diethylbutyramides adjacent to nitrogen followed by addition to an aldehyde or ketone, an acid-driven nitrogen to oxygen rearrangement, and basic hydrolysis provides secondary (α-lithioalkyl)alkylamine synthetic equivalents.

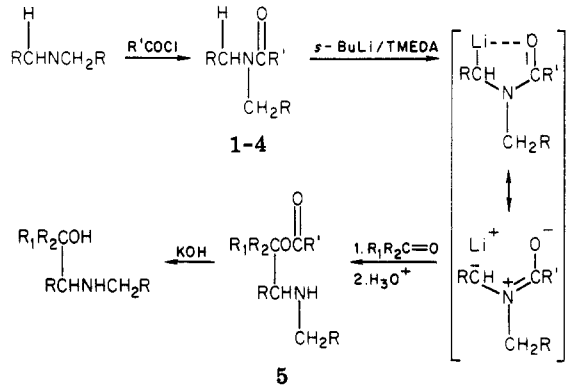
Sir: The development of procedures for efficiently achieving electrophilic substitution α to the nitrogen of amines has been stimulated by observations which establish that direct lithiation can be achieved by removal of a proton from a carbon adjacent to nitrogen if the nitrogen bears a strongly electron-withdrawing group.[1,2] The formally dipole-stabilized organolithium reagent thus produced can be a useful intermediate in a sequence which provides the α-lithio amine synthetic equivalent. Such methodology, which offers a new strategy for the elaboration of amines, is of considerable current interest.

Although the requisite acidity of amides and the direct preparation of stable sterically hindered α-azalithio amide derivatives have been reported, the synthetic use of these species generally has been restricted to methyl, allyl, and benzyl amides.[3-5] However, in a recent paper Meyers and Ten Hoeve reported that lithiation can be achieved not only at the methyl of a number of *N*-methyl-*N*-alkylformamidines but also α to the nitrogen of a pyrrolidine formamidine. These authors also noted that analogous secondary positions of other formamidines can be metalated.[6]

We report that the *N,N*-dialkyl-2,2-diethylbutyramides provide secondary (α-lithioalkyl)alkylamine synthetic equivalents which add readily to aldehydes and ketones to give alcohol amides. These products undergo an acid-driven rearrangement to amino esters and subsequent basic hydrolysis to amino alcohols to provide a sequence for electrophilic α-hydroxyalkylation of amines as outlined in Scheme I.

The lithiations and electrophilic substitutions of *N,N*-dimethyl-2,2-diethylbutyramide (**1**), *N,N*-diethyl-2,2-diethylbutyramide (**2**), pyrrolidinyl-2,2-diethylbutyramide (**3**), and piperidyl-2,2-diethylbutyramide (**4**) are summarized in Table I. Lithiation and trapping with carbonyl electrophiles can be conveniently achieved at 0 °C in ether. An important feature of this sequence is the acid-driven

Scheme I[a]



[a] R' = $(C_2H_5)_3C$.

Scheme II

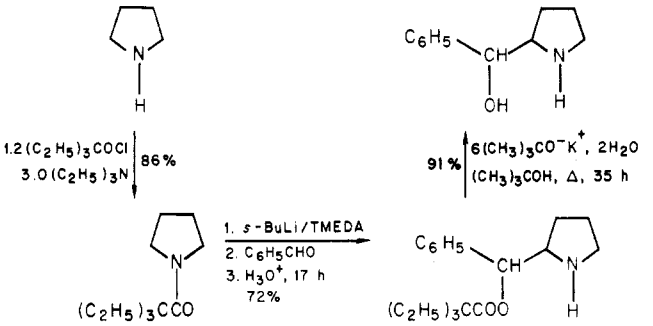


Table I. Lithiation and Electrophilic Substitution of *N,N*-Dialkyl-2,2-diethylbutyramides 1-4 Adjacent to Nitrogen

amide	electrophile	product[a] (% yield)
1, R = H	CH_3OD	R'CONCH$_3$CH$_2$D (90, >95% d_1)[b]
1	$(C_6H_5)_2CO$	R'CONCH$_3$CH$_2$COH$(C_6H_5)_2$ (91)
2, R = CH_3	C_6H_5CHO	**5**; R = CH_3, R_1, R_2 = C_6H_5, H (48)[c]
3, R,R = $(CH_2)_2$	CH_3OD	R'CONCHD$(CH_2)_3$ (94, 92% d_1)[d]
3	C_6H_5CHO	**5**; R,R = $(CH_2)_2$, R_1, R_2 = C_6H_5, H (72)
3	n-$C_6H_{13}CHO$	**5**; R,R = $(CH_2)_2$, R_1, R_2 = n-C_6H_{13}, H (85)
3	$(CD_3)_2CO$	**5**; R,R = $(CH_2)_2$, R_1, R_2 = $(CD_3)_2$ (69)[e]
3	$(CH_3)_2CO$	**5**; R,R = $(CH_2)_2$, R_1, R_2 = $(CH_3)_2$ (37)[e]
3	$(C_6H_5)_2CO$	R'CONCHCH$((C_6H_5)_2OH)(CH_2)_3$ (35)
4, R,R = $(CH_2)_3$	CH_3OD	R'CONCHD$(CH_2)_4$ (89, 86% d_1)[d]
4	C_6H_5CHO	**5**; R,R = $(CH_2)_3$, R_1, R_2 = C_6H_5, H (72)
4	n-$C_6H_{13}CHO$	**5**; R,R = $(CH_2)_3$, R_1, R_2 = n-C_6H_{13}, H (67)
4	$(CD_3)_2CO$	**5**; R,R = $(CH_2)_3$, R_1, R_2 = $(CD_3)_2$ (64)[e]

[a] Yields are for analytically pure material; all new compounds were characterized by analytical and spectral data. [b] Percent deuteration based on ^{1}H NMR analysis. [c] Lithiation at −78 °C with 4 equiv of *s*-BuLi. [d] Percent deuteration based on mass spectral analysis. [e] Acid-promoted rearrangement for 11 h.

N to O migration of the acyl group in hot methanol–hydrochloric acid which aids in isolation and purification of the substituted amino ester and allows basic hydrolysis to the substituted amine.[7] The lower yields for the reactions

(1) For a review of dipole-stabilized carbanions see P. Beak and D. B. Reitz, *Chem. Rev.*, **78**, 275 (1978).

(2) Routes to α-lithio amine synthetic equivalents not based on carboxamides include: (a) primary and activated secondary derivatives from isonitriles, D. Stafforst and U. Schöllkopf, *Justus Liebigs Ann. Chem.*, 28 (1980), and references cited therein; (b) primary derivatives from imines, T. Kauffmann, H. Berg, E. Köppelmann, and D. Kuhlmann, *Ber.*, **110**, 2659 (1977), and references cited therein; (c) primary, secondary and tertiary derivatives from nitroso amines, D. Seebach and W. Wykypiel, *Synthesis*, 423 (1979), and references cited therein.

(3) P. Beak and R. Farney, *J. Am. Chem. Soc.*, **95**, 4771 (1973); D. Seebach and W. Lubosch, *Angew. Chem., Int. Ed. Engl.*, **15**, 313 (1976); P. Beak, B. G. McKinnie, and D. B. Reitz, *Tetrahedron Lett.*, 1839 (1977); R. Schlecker and D. Seebach, *Helv. Chim. Acta*, **60**, 1459 (1977).

(4) R. Schlecker, D. Seebach, and W. Lubosch, *Helv. Chim. Acta*, **61**, 512 (1978); T. Hassel and D. Seebach, *ibid.*, **61**, 2237 (1978).

(5) (a) J. C. L. Armande and U. K. Pandit, *Tetrahedron Lett.*, 897 (1977); (b) D. Seebach and T. Hassel, *Angew. Chem., Int. Ed. Engl.*, **17**, 274 (1978); (c) T. L. Macdonald, *J. Org. Chem.*, **45**, 193 (1980); (d) J. C. L. Armande and U. K. Pandit, *Recl. Trav. Chim. Pays-Bas.*, **99**, 87 (1980); (e) J.-J. Lohmann, D. Seebach, M. A. Syfrig, and M. Yoshifuji, *Angew. Chem., Int. Ed. Engl.*, **20**, 128 (1981). See A. N. Tischler and M. H. Tischler, *Tetrahedron Lett.*, 3407 (1978), for cases of (α-lithiobenzyl)lithioamide and (α-lithioallyl)lithioamide derivatives.

(6) A. I. Meyers and W. Ten Hoeve, *J. Am. Chem. Soc.*, **102**, 7125 (1980).

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of lithiated amides from 3 and 4 with acetone as compared to deuterioacetone probably reflect the operation of a deuterium isotope effect on enolization which is competitive with the addition. An example of the use of this approach to provide α-hydroxyalkylation of an amine is outlined for pyrrolidine in Scheme II. A similar sequence with piperidine proceeds in yields of 77%, 72%, and 53% for the steps shown. The 2,2-diethylbutyric acid is also recovered in high yield from the hydrolysis and is thereby available to be recycled in the sequence. A typical experimental procedure is given at the end of this communication.

The use of *n*-butyllithium instead of *sec*-butyllithium results in yield which are ca. 20% less than those listed in Table I. Attempted alkylations of α-lithioalkyl amides were not successful and were not pursued because cleavage of the products was anticipated to be difficult; hydrolysis of **3** required heating in 50% sulfuric acid at 130 °C for 30 h.

Steric hindrance of the carbonyl group in the 2,2-diethylbutanamides provides protection of the carbonyl during lithiation but sufficient access for rearrangement and subsequent hydrolytic cleavage. Exceptional steric hindrance by the triethylcarbinyl group is precedented in Brown's studies of F strain and Newman's "rule of six" and has been recently discussed quantitatively.[8,9] Development of the synthetic potential and understanding of the underlying structure stability relationships of these novel and useful α-heteroatom dipole-stabilized carbanions is a matter of continuing interest.[10]

The procedure was as follows. To a diethyl ether solution (30 mL) containing 0.45 mL (3 mmol) of tetramethylethylenediamine (TMEDA) and 2.3 mL (2.8 mmol) of *s*-BuLi (1.20 M in cyclohexane) was added 494 mg (2.51 mmol) of **3** in 5 mL Et_2O at −78 °C. The reaction mixture was stirred at 0 °C for 45 min, followed by the addition of 0.3 mL (3 mmol) of benzaldehyde at −78 °C. After the solution was allowed to warm to room temperature, 40 mL of Et_2O was added; the ethereal solution was washed with 10% HCl solution and saturated NaCl solution and dried ($MgSO_4$). Removal of solvent gave an oily product which was treated with 30 mL of 2:1 methanol–hydrochloric acid (concentrated) at reflux for 17 h. The cooled solution was extracted three times with CH_2Cl_2; the combined organic layer washed once with saturated NaCl solution and once with 10% NaOH solution and dried ($MgSO_4$). Removal of solvent gave the crude ester from which 547 mg of pure ester (72% yield) was isolated by flash chromatography.

Acknowledgment. We are grateful to the National Institutes of Health, Institute of General Medicine, for support of this work and to Professor A. I. Meyers for disclosing his work prior to publication.

Registry No. 1 (R = H; R′ = $(C_2H_5)_3C$), 78986-71-7; 2 (R = CH_3; R′ = $(C_2H_5)_3C$), 78986-72-8; 3 (R_1R = $(CH_2)_2$; R′ $(C_2H_5)_3C$), 78986-73-9; 4 (R_1R = $(CH_2)_3$; R′ = $(C_2H_5)_3C$), 78986-74-0; 5 (R = CH_3; $R_2C_6H_5$, H; R′ = $(C_2H_5)_3C$), 78986-75-1; 5 (R_1R = $(CH_2)_2$, R_2 = C_6H_5, H, R^1 = $(C_2H_5)_3C$), 78986-76-2; 5 (R, R = $(CH_2)_2$; R_2 = C_6H_{13}, H; R^1 = $(C_2H_5)_3C$), 78986-77-3; 5 (R, R = $(CH_2)_2$; R_2 = $(CD_3)_2$; R^1 = $(C_2H_5)_3C$), 78986-78-4; 5 (R,R = $(CH_2)_2$; R_2 = $(CH_3)_2$; R^1 = $(C_2H_5)_3C$), 78986-79-5; 5 (R,R = $(CH_2)_3$; R_2 = C_6H_5, H; R^1 = $(C_2H_5)_3C$), 78986-80-8; 5 (R, R = $(CH_2)_3$; R_2 = $C_6H_{13}H$; R^1 = $(C_2H_5)_3C$), 78986-81-9; 5 (R, R = $(CH_2)_3$; R_2 = $(CD_3)_2$; R^1 = $(C_2H_5)_3C$), 79005-33-7; CH_3OD, 1455-13-6; $(C_6H_5)_2CO$, 119-61-9; C_6H_5CHO, 100-52-7; $C_6H_{13}CHO$, 111-71-7; $(CD_3)_2CO$, 666-52-4; $(CH_3)_2CO$, 67-64-1; $(C_2H_5)_3CCONCH_3CH_2D$, 78986-82-0; $(C_2H_5)_3CCONCH_3CH_2COH(C_6H_5)_2$, 78986-83-1; $(C_2H_5)_3CCONCHD(CH_2)_3$, 78986-84-2; $(C_2H_5)_3CCONCHC((C_6H_5)_2OH)(CH_2)_3$, 78986-85-3; $(C_2H_5)_3CCONCHD(CH_2)_4$, 78986-86-4.

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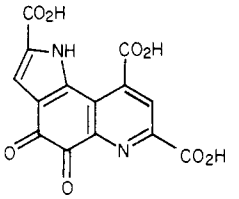
Total Synthesis of Methoxatin, the Coenzyme of Methanol Dehydrogenase and Glucose Dehydrogenase

Summary: The first total synthesis of the bacterial coenzyme methoxatin has been successfully completed starting from readily available 2,3-dimethoxytoluene.

Sir: Methylotrophic bacteria are organisms capable of utilizing C_1 compounds such as methane and methanol as their sole source of cellular carbon.[1] A promising commerical process has been developed for synthesis of single-cell protein from methanol by such a microorganism.[2] These bacteria each contain a methanol dehydrogenase that is capable of oxidizing both primary alcohols and formaldehyde.[3] Recently these bacterial methanol dehydrogenases have all been found to contain an unusual, low molecular weight coenzyme[4,5] for which the name methoxatin has been suggested.[5] Methoxatin has been assigned the unique pyrroloquinoline quinone structure 1 on the basis of limited spectral data[4a] and by an X-ray



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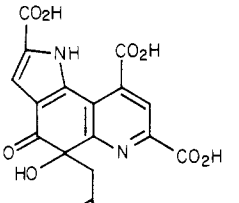

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(7) The formation of an ammonium salt which drives the N to O migration has been used by Seebach et al. in a similar case,[5e] and has precedent in the literature. See: D. A. Evans and L. R. McGee, *J. Am. Chem. Soc.*, **103**, 2876 (1981); A. Rüegger, M. Kuhn, H. Lichti, H.-R. Loosli, R. Huguenin, C. Quiquerez, and A. von Wartburg, *Helv. Chim. Acta*, **59**, 1075 (1976); L. V. Pavlova and F. Y. Rachinskii, *Usp. Khim. (Engl. Transl.)* **37**, 587 (1968).

(8) J. Hine, "Structural Effects on Equilibria in Organic Chemistry", Wiley, New York, 1975, pp 229–234; M. S. Newman, "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, 1956, pp 201–248; A. Panaye, J. A. MacPhee, and J.-E. Dubois, *Tetrahedron Lett.*, 3485 (1980).

(9) C. Lion, J.-E. Dubois, J. A. MacPhee, and Y. Bonzougou [*Tetrahedron*, **35**, 2077 (1979)] have recently reported that sterically hindered esters with substitution comparable to 1-4 undergo dealkylation on treatment with *n*-propyllithium at 0 °C.

(10) For examples of analogous thioesters and esters see: D. B. Reitz, P. Beak, R. F. Farney, and L. S. Helmick, *J. Am. Chem. Soc.*, **100**, 5428 (1978); P. Beak and L. G. Carter, *J. Org. Chem.*, **46**, 2363 (1981).

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(3) Anthony, C.; Zatman, L. J. *Biochem. J.* **1967**, *104*, 960 and references cited.

(4) (a) Duine, J. A.; Frank, J.; Verwiel, P. E. *Eur. J. Biochem.* **1980**, *108*, 187. (b) Duine, J.; Frank, J. *Biochem. J.* **1980**, *187*, 213. (c) Duine, J. A.; Frank, J. *Ibid.* **1980**, *187*, 221.

(5) Salisbury, S. A.; Forrest, H. S.; Cruse, W. B. T.; Kennard, O. *Nature (London)* **1979**, *280*, 843.

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