hexene (2 mL, 19 mmol) in benzene solution was used, led to a complex mixture of products, mostly polymeric, but compounds **2**, **3** and **4** were absent. A more detailed, quantitative investigation of the oxidation process was beyond our original research interest.

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Isolation and Reactions of α-Lithio *N,N*-Dimethylacetamide

Richard P. Woodbury and Michael W. Rathke*[1]

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

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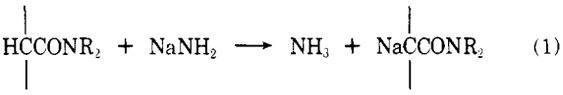
α-Lithio *N,N*-dimethylacetamide (**1**) was obtained as a white solid by reaction of *N,N*-dimethylacetamide with lithium diisopropylamide in pentane. From ^1H NMR evidence, a lithium–oxygen bonded structure is proposed. THF solutions of **1** could be generated at 0 °C and were stable for several days at room temperature. Reactions of **1** with organic halides, aldehydes, ketones, and epoxides are described.

Although metalated derivatives of amides possessing α-aryl or other carbanion-stabilizing groups were known much earlier,[2] the first syntheses of α-metalated derivatives of simple *N,N*-dialkylamides were reported in 1966 by Gassman[3] and by Needles[4] using sodamide as the base in liquid ammonia[3] or benzene[4] (eq 1). Since that time, lithiated amides have



$$\text{HCCONR}_2 + \text{NaNH}_2 \longrightarrow \text{NH}_3 + \text{NaCCONR}_2 \qquad (1)$$

been made using lithiated 1,3,5-trithiane as base,[5] or, more efficiently, lithium diethylamide in hexamethylphosphoramide[6] or lithium diisopropylamide in tetrahydrofuran (THF).[7-9]

We describe here our own observations on the preparation of lithiated *N,N*-dimethylacetamide and its reactions with a variety of electrophiles.

Results and Discussion

Stability and Isolation of Lithio *N,N*-Dimethylacetamide. Solutions of α-lithio *N,N*-dimethylacetamide (**1**) were prepared by dropwise addition of *N,N*-dimethylacetamide (**2**) to THF solutions of lithium diisopropylamide at dry ice temperature. Quenching the solutions with glacial acetic acid gave 95–100% recovery of the amide (eq 2). Solutions of **1** allowed to reach room temperature remained homogeneous and colorless. Quenching returned 90–95% of **2** after 19 h at room temperature, and 75–80% after 3 days. Small amounts (5–10%) of the condensation product, *N,N*-dimethylacetoacetamide, were detected in the quenched mixtures after 1 day. Identical results were obtained by preparing **1** at 0 °C in THF rather than at −78 °C.

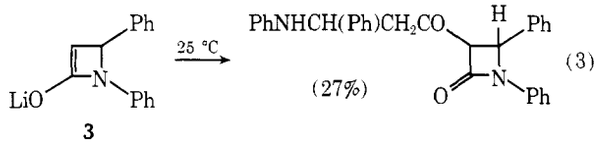
$$\underset{\mathbf{2}}{\text{CH}_3\text{CON(CH}_3)_2} + \text{LiN[CH(CH}_3)_2]_2 \xrightarrow[-78\ ^\circ\text{C}]{\text{THF}} \underset{\mathbf{1}}{\text{LiCH}_2\text{CON(CH}_3)_2} + \text{HN[CH(CH}_3)_2]_2$$

$$\xrightarrow[-78\ ^\circ\text{C}]{\text{HOAc}} \text{LiOAc} + \text{CH}_3\text{CON(CH}_3)_2 \qquad (2)$$

(95–100%, GLC)

Addition of **2** to solutions of lithium diisopropylamide in pentane at 0 °C resulted in the immediate formation of a white precipitate. Removal of solvent and amine under reduced pressure gave **1** as a white solid in quantitative yield. Quenching weighed samples of the solid with glacial acetic acid returned **2** in 90% yield. Exposure to air for several minutes turned the solid black; however, samples of the solid were stored in sealed bottles for several weeks with no evidence of change (as judged by appearance and by recovery of **2** on quenching). The ^1H NMR spectrum of the solid (pyridine solution) shows two partially resolved doublets (δ 3.15, 1 H, 2.93, 1 H) and a sharp singlet (δ 2.63, 6 H).

Solutions of α-lithio *N,N*-dimethylacetamide have been obtained previously,[5-7] but there are no prior reports of its stability or of attempts to isolate the pure material. The lithium enolate of a β-lactam, **3**, was reported to be reasonably



$$\xrightarrow[25\ ^\circ\text{C}]{} \text{PhNHCH(Ph)CH}_2\text{CO} \quad (27\%) \qquad (3)$$

3

stable at −78 °C, but condensation occurred (27%) on warming a THF solution to room temperature for 20 min.[8] From the method of preparation and reaction with organic halides[4] (several hours in refluxing benzene, 5–60% yields of alkylation products) it may be deduced that sodio *N,N*-dimethylacetamide (**4**, eq 4) is much more stable than this.

$$\text{CH}_3\text{CON(CH}_3)_2 \xrightarrow[\text{C}_6\text{H}_6,\ 65\ ^\circ\text{C}]{\text{NaNH}_2} \underset{\mathbf{4}}{\text{NaCH}_2\text{CON(CH}_3)_2} \xrightarrow[65\ ^\circ\text{C}]{\text{RX}} \text{RCH}_2\text{CON(CH}_3)_2 \qquad (4)$$

Our results indicate that **1** is sufficiently stable that its solutions may be generated at 0 °C rather than the usual −78 °C. Its stability is especially high when compared to analogous lithium ester enolates. For example, solutions of lithio *tert*-butyl acetate (**5**)[10] have a half-life of less than 2 h at room temperature (eq 5).[11]

$$\underset{\mathbf{5}}{\text{LiCH}_2\text{CO}_2\text{C(CH}_3)_3} \xrightarrow[25\ ^\circ\text{C}]{\text{THF}} \text{LiOC(CH}_3)_3 + [\text{CH}_3\text{COCHCO}_2\text{C(CH}_3)_3]\text{Li} \qquad (5)$$

Table I. Reaction of α-Lithio *N,N*-Dimethylacetamide (1) with Organic Halides

RX	Registry no.	Product	Registry no.	Yield, %[a]
CH_3I	74-88-4	$CH_3CH_2CON(CH_3)_2$[b]	758-96-3	62
$CH_3CH_2CH_2Br$	106-94-5	$CH_3CH_2CH_2CH_2CON(CH_3)_2$[c]	6225-06-5	90
$(CH_3)_2CHBr$	75-26-3	$(CH_3)_2CHCH_2CON(CH_3)_2$[d]	5370-28-5	26
$C_6H_5CH_2Br$	100-39-0	$C_6H_5CH_2CH_2CON(CH_3)_2$[e]	5380-31-9	99

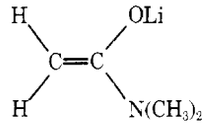
[a] Yields by GLC; isolated yields were 5–10% lower. [b] ^1H NMR (CCl_4, Me_4Si) δ 2.93 (s, 3 H), 2.84 (s, 3 H), 2.17 (q, 2 H), 1.03 (t, 3 H). [c] ^1H NMR (CCl_4, Me_4Si) δ 2.97 (s, 3 H), 2.87 (s, 3 H), 2.33 (t, 2 H), 1.47 (m, 4 H), 1.00 (t, 3 H). [d] ^1H NMR (CCl_4, Me_4Si) δ 2.91 (s, 3 H), 2.81 (d, 3 H), 2.0 (d, 2 H), 2.0 (m, 1 H), 0.90 (d, 6 H). [e] ^1H NMR (CCl_4, Me_4Si) δ 7.3 (s, 5 H), 2.8 (s, 6 H), 2.8 (t, 2 H), 2.4 (t, 2 H).

Table II. Reaction of α-Lithio *N,N*-Dimethylacetamide (1) with Carbonyl Compounds

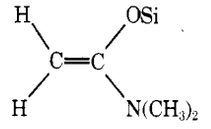
Carbonyl	Registry no.	Product	Registry no.	Yield, %[a]
CH_3COCH_3	67-64-1	$(CH_3)_2COHCH_2CON(CH_3)_2$[b]	61665-47-2	99
c-$C_6H_{10}O$	108-94-1	c-$C_6H_{10}(OH)CH_2CON(CH_3)_2$[c]	20428-64-2	97
CH_3CHO	75-07-0	$CH_3CHOHCH_2CON(CH_3)_2$[d]	57270-73-2	98[e]
CH_3CH_2CHO	123-38-6	$CH_3CH_2CHOHCH_2CON(CH_3)_2$[f]	20428-63-1	91[e]

[a] Yields by GLC; isolated yields were 10–15% lower. Satisfactory analytical data for all compounds were submitted for review. [b] ^1H NMR (CCl_4, Me_4Si) δ 4.54 (s, 1 H), 2.94 (s, 3 H), 2.86 (s, 3 H), 2.24 (s, 2 H), 1.17 (s, 6 H); IR (CCl_4) 3450 (OH), 1635 cm^{-1} (C=O). [c] ^1H NMR (CCl_4, Me_4Si) δ 4.43 (s, 1 H), 2.93 (s, 3 H), 2.84 (s, 2 H), 2.17 (s, 2 H), 1.50 (m, 10 H); IR (CCl_4) 3420 (OH), 1635 cm^{-1} (C=O). [d] ^1H NMR (CCl_4, Me_4Si) δ 4.0 (m, 1 H), 3.74 (d, 1 H), 2.93 (s, 3 H), 2.86 (s, 3 H), 2.27 (t, 2 H), 1.07 (d, 3 H); IR (CCl_4) 3480 (OH), 1650 cm^{-1} (C=O). [e] Reaction at −78 °C; yields at 0 °C were negligible. [f] ^1H NMR (CCl_4, Me_4Si) δ 3.87 (s, 1 H), 3.52 (m, 1 H), 2.93 (s, 3 H), 2.84 (s, 3 H) 2.24 (d, 2 H), 1.37 (m, 2 H), 0.90 (t, 3 H); IR (CCl_4) 3475 (OH), 1640 cm^{-1} (C=O).

The ^1H NMR spectrum of **1** closely resembles that of its silyl analogue, **6**,[12] and is evidence for a lithium–oxygen



1 (δ 3.16, d, 1 H; 2.93, d, 1 H; 2.63, s, 6 H)



6 (δ 2.89, d, 1 H; 2.86, d, 1 H; 2.43, s, 6 H)

$LiCH_2CON(CH_3)_2$

7

bonded structure.[13] The two methylene hydrogens in the lithium–carbon bonded structure **7** would be expected to have identical chemical shifts. Similar lithium–oxygen bonded structures have been reported for the lithium enolates of ketones[14] and esters.[10] It is interesting to note that, unlike **2**, both **1** and **6** exhibit only a single *N*-methyl resonance. Presumably, this is due to decreased conjugation of the nitrogen electron pair in **1** and **5**, resulting in a faster rotation around the C_1–N bond.

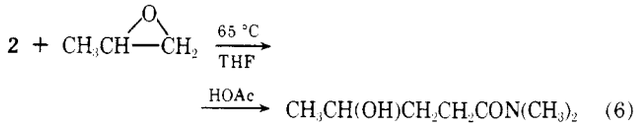
The ability to obtain amine-free samples of **1** should prove useful for certain synthetic applications; however, the direct use of THF solutions of **1** containing 1 equiv of diisopropylamine is more convenient and we used such solutions for our survey of the reactions of **1** with electrophiles.

Reaction of α-Lithio *N,N*-Dimethylacetamide with Organic Halides. Solutions of **1** (0.5 M) in THF were prepared by addition of *N,N*-dimethylacetamide to lithium diisopropylamide at 0 °C. Slightly more than 1 equiv of organic halide was added and the reaction mixtures were allowed to reach room temperature. After 30 min, the reaction mixtures were quenched and the yield of alkylation product determined. Results obtained with a number of halides are shown in Table I.

No dialkylation products were detected in the reaction mixture from **1** with either methyl iodide or isopropyl bromide. The relatively low yields obtained with isopropyl bromide are presumably due to a competing elimination with this secondary halide.

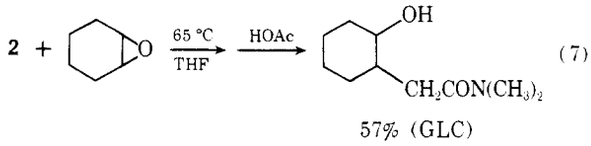
Reaction with Carbonyl Compounds. Solutions of **2** (0.5 M) in THF were reacted with a number of aldehydes and ketones with results shown in Table II. The reaction proceeds satisfactorily with ketones at 0 °C; however, very low yields of β-hydroxy amides were obtained with aldehydes at this temperature, presumably owing to competing aldol condensation. Nearly quantitative yields were obtained by reaction at dry ice temperature and quenching at this same low temperature after brief reaction periods. In the only previous study of the reaction of **1** with carbonyl compounds, nearly complete enolization was reported with cyclohexanone and only a 4% yield of the corresponding β-hydroxy amide was obtained.[5]

Reaction with Epoxides. Reaction of 0.5 M solutions of **1** with either propylene oxide or cyclohexene oxide at 25 °C gave only negligible yields of γ-hydroxy amides. However, satisfactory yields were obtained after 2 h at reflux temperature (eq 6, 7). Yields obtained for the reaction of **1** with cyclohexene oxide compare favorably with those reported for closely related enolates. For example, the lithium enolate of *tert*-butyl acetate gave only an 8% yield of γ-hydroxy ester with cyclohexene oxide.[15] The lithium enolate of lithium acetate reacted satisfactorily with a number of steroidal epox-



2 + $CH_3CH(O)CH_2$ 65 °C, THF → HOAc → $CH_3CH(OH)CH_2CH_2CON(CH_3)_2$ (6)

85% (GLC)



2 + epoxide 65 °C, THF → HOAc → OH, $CH_2CON(CH_3)_2$ (7)

57% (GLC)

ides,[16] but only an 18% yield of γ-hydroxy acid was obtained with cyclohexene oxide.[17]

Experimental Section

NMR spectra were recorded on a Varian T-60 with Me_4Si internal standard. Infrared spectra were recorded in CCl_4 solution using a Perkin-Elmer 237B grating spectrometer. GLC analyses were performed with a Varian 920 using 6 ft × 0.25 in. stainless steel columns packed with 3% Carbowax 20M on non-acid-washed Chromosorb G support. *n*-Butyllithium (Aldrich) was titrated before use by the procedure of Watson and Eastham.[18] Diisopropylamine was distilled from CaH_2 and stored under nitrogen. THF was distilled from the sodium ketyl of benzophenone and stored under nitrogen. *N,N*-Dimethylacetamide was distilled and stored under nitrogen. All other reagents were obtained commercially (Aldrich) and used directly.

Preparation of α-Lithio *N,N*-Dimethylacetamide (1). Procedure A. A 50-mL round-bottom flask equipped with magnetic stirring, septum inlet, and mercury bubbler was flushed with nitrogen and charged with 10 mL of pentane and 6.30 mL (10 mmol) of a solution of *n*-butyllithium in hexane. The flask was immersed in an ice–water bath and 1.4 mL (10 mmol) of diisopropylamine was injected. The cooling bath was removed and the reaction mixture was stirred for 5 min at room temperature. Volatile material was removed under vacuum. The residue of lithium diisopropylamide was dissolved by injection of 20 mL of THF. The flask was then immersed in an ice–water bath and 0.95 mL (10 mmol) of *N,N*-dimethylacetamide was added dropwise. After 15 min of stirring, the resultant solution of **1** was ready for use.

Stability Studies. THF solutions of **1** prepared by procedure A (above), containing 5 mmol of an internal standard, were maintained at 25 ± 1 °C with a water bath. Aliquots (0.5 mL) were removed periodically with a syringe and injected into a 1 M solution of glacial acetic acid (0.25 mmol) in ether. The resultant suspensions were centrifuged to remove lithium acetate and analyzed directly by GLC for recovered *N,N*-dimethylacetamide. *N,N*-Dimethylacetoacetamide was detected (<10% after 60 h, based on starting **1**) in the quenched samples and was identified by comparison to authentic material.[19]

Isolation of α-Lithio *N,N*-Dimethylacetamide (1). A solvent-free sample of lithium diisopropylamide (10 mmol) was obtained as described in procedure A and dissolved in 20 mL of pentane. The solution was cooled in an ice–water bath and 0.95 g (10 mmol) of *N,N*-dimethylacetamide was added dropwise. After 15 min of stirring at 0 °C, the volatile material was removed under vacuum to leave a white solid residue of **1**, 0.93 g (100%). Anal. Calcd for C_4H_8LiNO: C, 51.65; H, 8.61; N, 15.06. Found: C, 51.44; H, 8.70; N, 14.86. The NMR spectrum of **1** was obtained by injection of sufficient pyridine to form a 1.0 M solution, which was transferred to an NMR tube with Teflon tubing and nitrogen pressure. Purity of the solid was determined by quenching 0.5 M THF solutions with 1 equiv of glacial acetic acid and analyzing (GLC) for recovered *N,N*-dimethylacetamide.

Alkylation of 1. The procedure described for the reaction of **1** with benzyl bromide is representative. A 0.5 M solution of **1** (10 mmol) in THF at 0 °C was prepared as described in procedure A. Benzyl bromide (1.30 mL, 11 mmol) was injected all at once and the solution allowed to reach room temperature. After 30 min, 20 mL of pentane was added to precipitate lithium bromide. GLC analysis indicated a 99% yield of alkylation product. Evaporation followed by flask vacuum distillation gave 1.59 g (90%) of *N,N*-dimethyl-3-phenylpropanoamide.

Identification of alkylation products was established by comparison (GLC retention times, NMR spectra) with samples obtained commercially or by reaction of the appropriate acid chlorides with dimethylamine.

Reaction of 1 with Aldehydes and Ketones. The procedure described for the reaction with cyclohexanone is representative. A 0.5 M solution of **1** (10 mmol) in THF at 0 °C was prepared as described in procedure A. Cyclohexanone (1.1 mL, 11 mmol) was injected all at once and the reaction mixture was allowed to reach room temperature. After 30 min, 10 mL of a 1 M solution of acetic acid in ether was injected. Lithium acetate was removed by filtration. GLC analysis established a 97% yield of product. Evaporation followed by flash vacuum distillation gave 1.63 g (88%) of *N,N*-dimethyl-2-(1-hydroxycyclohexyl)acetamide.

Reaction of **1** with aldehydes was accomplished in a similar manner except that the aldehyde was added to solutions of **1** maintained at −78 °C. Reactions were quenched at −78 °C after stirring for 30 min.

NMR spectra of products are shown in Table II; all products gave elemental analyses (C, H, N) within established limits.

Reaction of 1 with Propylene Oxide. A 0.5 M solution of **1** (10 mmol) in THF was prepared as described in procedure A. Propylene oxide (0.75 mL, 11 mmol) was injected and the reaction mixture was refluxed for 2 h. After cooling to room temperature, 10 mL of a 1 M solution of acetic acid in ether was injected and the resultant precipitate of lithium acetate removed by filtration. GLC analysis established an 85% yield of product. Samples of pure *N,N*-dimethyl-4-hydroxypentamide were obtained by preparative GLC: NMR (CCl_4) δ 3.57 (m, 1 H), 3.10 (s, 1 H), 2.97 (s, 3 H), 2.83 (s, 3 H), 2.33 (t, 2 H), 1.67 (m, 2 H), 1.10 (d, 3 H); IR (CCl_4) 3425 (–OH), 1640 cm^- (C=O). Anal. Calcd for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 57.89; H, 10.38; N, 9.59.

Reaction of 1 with Cyclohexene Oxide. A procedure identical with the above using cyclohexene oxide gave *N,N*-dimethyl-2(2-hydroxycyclohexyl)acetamide by preparative GLC: NMR (CCl_4) δ 2.97 (s, 3 H), 2.83 (s, 3 H), 2.40 (d, 2 H), 3.63 (s, 1 H), 2.77 (m, 1 H), 1.0–2.1 (m, 9 H); IR (CCl_4) 3420 (OH), 1640 cm^{-1} (C=O). Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.88; H, 10.38; N, 7.45.

Acknowledgment is made to the National Science Foundation for partial support of this work.

Registry No.—**1**, 56579-98-7; lithium diisopropylamide, 4111-54-0; *N,N*-dimethylacetamide, 127-19-5; propylene oxide, 75-56-9; *N,N*-dimethyl-4-hydroxypentamide, 61665-46-1; cyclohexene oxide, 286-20-4; *N,N*-dimethyl-2(2-hydroxycyclohexyl)acetamide, 36764-07-5.

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