Formation of the Lithium Enolate of *N,N*-Dimethyl-2-trimethylsilylacetamide. Reaction with Carbonyl Compounds and Epoxides

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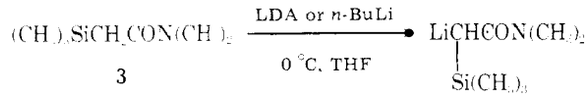
Addition of *N,N*-dimethyl-2-trimethylsilylacetamide to either lithium diisopropylamide or *n*-butyllithium generates the lithium enolate **4**, which was isolated as a white solid. The enolate is stable for several days in THF solution at 25 °C. Reaction of the enolate with aldehydes or ketones gives α,β-unsaturated amides. Reaction of the enolate with epoxides gives products corresponding to addition followed by 1,4 migration of the trimethylsilyl grouping from carbon to oxygen.

The lithium enolates of α-trimethylsilyl esters, **1**, react with aldehydes or ketones to give excellent yields of α,β-unsaturated esters.[1] We recently reported that enolates of *N,N*-dialkylamides have appreciably greater stability than the corresponding ester enolates.[2] Consequently, it seemed likely that enolates of α-trimethylsilylamides, **2**, would have synthetic advantages over **1**. We report here the results of a study on the formation and stability of **2**, together with information on its reactions with aldehydes, ketones, and epoxides.

1 2

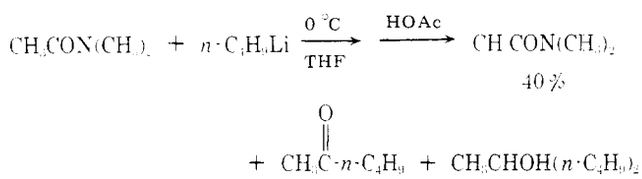
Results and Discussion

Formation and Isolation of Lithio-*N,N*-dimethyl-2-trimethylsilylacetamide. Addition of *N,N*-dimethyl-2-trimethylsilylacetamide, **3**, to THF solutions of lithium diisopropylamide, LDA, at 0 °C formed the lithium enolate, **4**.

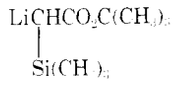


3 4

Quenching the reaction mixture with acetic acid gave a quantitative recovery of **3**. Surprisingly, the same results were obtained using *n*-butyllithium as the base. Presumably, the bulky trimethylsilyl grouping of **3** prevents addition of *n*-butyllithium to the carbonyl group. Thus, addition of the less hindered *N,N*-dimethylacetamide to solutions of *n*-butyllithium in THF gave predominantly addition products. The ability to generate **4** by means of *n*-butyllithium may be of synthetic advantage when amine-free solutions are required.



Solutions of **4** prepared by either method are stable for several days at room temperature. For example, quenching the reaction mixtures after 6 days returns 90–95% of **3**. In contrast, the corresponding ester enolate, **5**, must be generated at dry ice temperature and undergoes rapid self-condensation on warming to room temperature.[1a]



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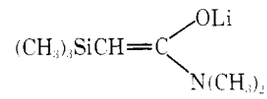
Addition of **3** to solutions of LDA in pentane gave a white precipitate assumed to be an amine complex of **4**. Removal of solvent and diisopropylamine under reduced pressure gave **4** as a white solid in 95% yield. Quenching weighed samples of **4** with glacial acetic acid gave 99–100% recovery of **3** (GLC). The solid turns brown on exposure to air; however, samples stored in sealed bottles have remained colorless for several months. The solid is soluble in dry pyridine and ^{1}H-NMR and ^{13}C-NMR spectra were obtained with the solution. For comparison, the ^{1}H-NMR[2] and ^{13}C-NMR data for the lithium enolate of *N,N*-dimethylacetamide, **6**, in pyridine solution



4

^{1}H NMR δ 2.90 (s, 1 H), 2.76 (s, 6 H), 0.33 (s, 9 H)

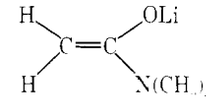
^{13}C NMR δ 174.69 (C_1), 56.00 (C_2), 39.34 (NCH_3), 2.35 ($SiCH_3$)

$(CH_3)_3SiCH_2CON(CH_3)_2$

3

^{1}H NMR δ 2.80 (s, 3 H), 2.73 (s, 3 H), 1.96 (s, 2 H), 0.13 (s, 9 H)

^{13}C NMR δ 171.10 (C_1), 37.72 (NCH_3), 34.46 (NCH_3), 24.67 (C_2), 0.56 ($SiCH_3$)



6

^{1}H NMR: δ 3.16 (d, 1 H), 2.93 (d, 1 H), 2.63 (s, 6 H)

^{13}C NMR δ 169.39 (C_1), 55.99 (C_2), 39.53 (NCH_3)

were also obtained. We note that the two *N*-methyl groupings, which are nonequivalent in **3**, are equivalent by both ^{1}H and ^{13}C NMR in the enolates **4** and **6**. Presumably, this is indicative of a lessened resonance interaction of the nitrogen electron pair in the enolates. Considering the similarity of the spectra of **4** to those of **6** (for which an oxygen–lithium structure was proposed[2]) an oxygen–lithium bonded structure for **4** seems likely.

Reaction of 4 with Aldehydes and Ketones. THF solutions of **4** were prepared by reaction of **3** with LDA at 0 °C and treated with an equivalent amount of an aldehyde or ketone. Quenching after 15 min, followed by GLC analysis, gave the results shown in Table I. Good yields of α,β-unsaturated amides were obtained with ketones and with nonenolizable aldehydes. However, the enolizable aldehydes, acetaldehyde,

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Table I. Reaction of Lithio-*N,N*-dimethyltrimethylsilylacetamide (4) with Carbonyl Compounds

Carbonyl	Registry no.	Product	Yield, %[a]
CH_3COCH_3	67-64-1	$(CH_3)_2C{=}CHCON(CH_3)_2$	86
CH_3COCH_3		$(CH_3)_2C{=}CHCON(CH_3)_2$	94 (82)[b]
c-$C_6H_{10}O$	108-94-1	c-$(C_6H_{10}){=}CHCON(CH_3)_2$	94 (85)
c-$C_6H_{10}O$		c-$(C_6H_{10}){=}CHCON(CH_3)_2$	92[c]
C_6H_5CHO	100-52-7	$C_6H_5CH{=}CHCON(CH_3)_2$	85
$C_6H_5CH{=}CHCHO$	14371-10-9	$C_6H_5CH{=}CHCH{=}CHCON(CH_3)_2$	90 (89)
CH_3CHO	79-07-0	$CH_3CH{=}CHCON(CH_3)_2$	10
CH_3CHO		$CH_3CH{=}CHCON(CH_3)_2$	9[b]
CH_3CH_2CHO	123-38-6	$CH_3CH_2CH{=}CHCON(CH_3)_2$	15

[a] GLC yield, isolated yields in parentheses. [b] Reaction at dry ice temperature. [c] 4 prepared by reaction of *n*-butyllithium with 3.

and propionaldehyde gave only negligible yields. In these cases, major amounts (70–80%) of the starting amide 3 were found in the quenched reaction mixture together with a variety of higher boiling products. Presumably, 4 reacts with these aldehydes mainly by enolization.

$$4 + RCH_2CHO \rightarrow RHC{=}CHOLi + 3$$

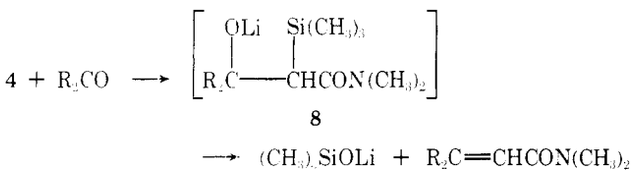
Attempts to overcome this problem by reaction of the aldehyde with 4 at dry ice temperature were unsuccessful. However, slightly higher yields of the corresponding α,β-unsaturated amide from the reaction with acetone were obtained at dry ice temperature (see Table I).

The reagent adds in a 1,2 fashion with the α,β-unsaturated aldehyde, *trans*-cinnamaldehyde.

$$4 + C_6H_5CH{=}CHCHO \rightarrow C_6H_5CH{=}CHCH{=}CHCON(CH_3)_2$$
7

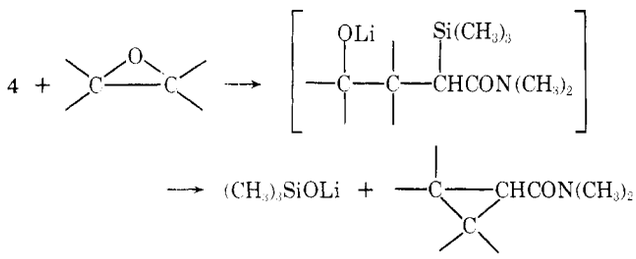
The product (7) is a 60:40 mixture of *trans*-2,*trans*-4 and *cis*-2,*trans*-4 isomers. Consequently, although the stereochemistry of the original double bond is retained, there appears to be little stereoselectivity in the formation of the new double bond. Similar observations have been made for the corresponding reactions of aldehydes with the ester enolate 1.[1b] Finally, the reaction appears to work equally well with amine-free 4 prepared by reaction of 3 with *n*-butyllithium, as judged by the results obtained with cyclohexanone (Table I).

Reaction of 4 with Epoxides. Reaction of 4 with carbonyl compounds presumably occurs by an initial addition to the carbonyl grouping followed by a fast 1,2 elimination of lithium trimethylsilyloxide.[3] A similar sequence with epoxides would give cyclopropanes by a 1,3 elimination.[4] We note that such a reaction with the ester enolate 5 is unlikely to succeed be-

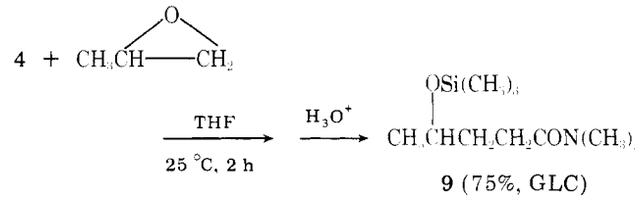


cause of the low reactivity of epoxides and the instability of 5.[1a]

A THF solution of 4 was treated with an equivalent amount



of propylene oxide. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by GLC analysis of quenched aliquots. After 2 h, starting material was consumed, and a single product, 9, was present

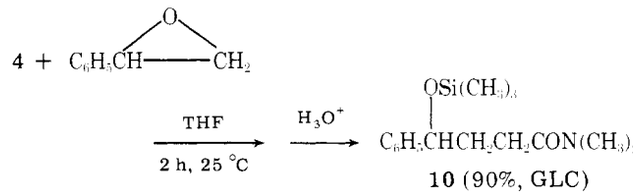


in 75% yield. The structure of 9 was deduced from its ^{1}H-NMR spectrum and by synthesis from the corresponding alcohol.

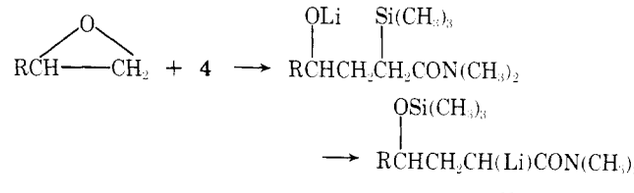
$$CH_3CHOHCH_2CH_2CON(CH_3)_2 + (CH_3)_3SiCl \xrightarrow{Et_3N} 9$$

Refluxing reaction mixtures of 4 and propylene oxide for periods of several days led to a gradual loss of 9, but only much higher boiling products were formed with no evidence for cyclopropane compounds.

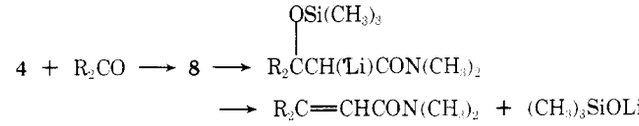
Reaction of 4 with styrene oxide proceeded similarly and a 90% yield (GLC) of the corresponding product, 10, was obtained.



These results are rationalized by assuming an initial addition of 4 at the less substituted side of the epoxide, followed by a 1,4 migration of silicon from carbon to oxygen to form the amide enolate, 11. That 11 is inert to cyclopropane formation



was confirmed by refluxing a reaction mixture containing 9 and LDA. Complete recovery of 9 was obtained by quenching after 12 h. Although the lack of cyclopropane formation is discouraging, we note that the results possibly represent the first observation of a 1,4 migration of silicon from carbon to oxygen[5] and also are suggestive that the reaction of 4 with



carbonyl compounds proceeds by initial 1,3 migration of silicon followed by elimination.

Experimental Section

^{1}H-NMR spectra were recorded on a Varian T-60 with Me_4Si internal standard. ^{13}C-NMR spectra were recorded with a Varian CFT-20 spectrometer using external D_2O for locking signal. 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.[6] Diisopropylamine was distilled from CaH_2 and stored under nitrogen. THF was distilled from the sodium ketyl of benzophenone just prior to use. All other reagents were obtained commercially and used directly.

Preparation of Lithio-*N,N*-dimethyl-2-trimethylsilylacetamide (4). A 50-mL round-bottom flask equipped with magnetic stirrer, septum inlet, and mercury bubbler was flushed with argon and charged with 10 mL of pentane and 6.3 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 after 5 min of stirring at 25 °C, volatile material was removed under vacuum. The white residue of LDA was dissolved in 20 mL of THF and the flask was immersed in an ice–water bath. *N,N*-Dimethyl-2-trimethylsilylacetamide,[7] 1.6 mL (10 mmol), was injected dropwise. After 10 min of stirring in the ice bath, the colorless solution of 4 was used directly for reaction with carbonyl compounds or epoxides.

Stability Studies of 4. A solution of 4 was prepared as described above and warmed to room temperature. Aliquots (0.5 mL) were removed periodically and quenched by addition of 0.02 mL of glacial acetic acid. The mixture was centrifuged and analyzed by GLC for recovered **3.** The recovery of **3** was 100% after 1 h, 95% after 3 days, and 92% after 6 days. The initially colorless reaction mixture was light yellow after 6 days.

Preparation of 4 for NMR Analyses. A 0.5 M solution of LDA in pentane was prepared as described above and maintained at 0 °C. *N,N*-Dimethyl-2-trimethylsilylacetamide (1.6 mL, 10 mmol) was added dropwise and a white precipitate formed immediately. After 15 min of stirring at 0 °C, the solvent and amine were removed under vacuum to obtain a white residue of **4** weighing 1.57 g (95% yield). The solid was dissolved in 10 mL of dry pyridine and NMR spectra were obtained.

Reaction of 4 with Aldehydes and Ketones. A solution of 4 (10 mmol) in THF prepared as described above and maintained at ice–water temperature was treated with 10 mmol of the aldehyde or ketone. The solution was then warmed to 25 °C and allowed to stir for 15 min. At the end of this period, the reaction mixture was quenched by addition of 5 mL of 2 M HOAC. The separated organic layer was analyzed by GLC for α,β-unsaturated amide. The solvent was stripped off and the product was isolated. The following α,β-unsaturated amides were prepared. *N,N*-Dimethyl-3-methyl-2-butenoamide (from 4 with acetone): ^{1}H NMR (CCl_4, internal Me_4Si) δ 5.63 (s, 1 H), 2.87 (s, 6 H), 1.83 (d, 3 H), 1.77 (d, 3 H). *N,N*-Dimethyl-2-cyclohexylideneacetamide (from 4 with cyclohexanone): ^{1}H NMR (CCl_4 internal Me_4Si) δ 5.35 (s, 1 H), 2.88 (s, 6 H), 2.54 (m, 2 H), 2.10 (m, 2 H), 1.57 (m, 5 H); IR (CCl_4) 1640 (C=O), 1625 cm^{-1} (C=C). *N,N*-Dimethyl-5-phenyl-*cis*-2,*trans*-4-pentadienoamide (from 4 with *trans*-cinnamaldehyde): mp 39–41 °C (lit.[8] mp 38–40 °C); ^{1}H NMR (CCl_4 internal Me_4Si) δ 7.8 (d, d, 1 H, J = 15, 11 Hz), 7.3 (m, 5 H), 6.0 (d, d, 1 H, J = 11, 1 Hz), 3.1 (bs, 6 H). *N,N*-Dimethyl-5-phenyl-*trans*-2,*trans*-4-pentadienoamide (from 4 with *trans*-cinnamaldehyde): mp 98–100 °C (lit.[8] mp 100–102 °C); ^{1}H NMR (CCl_4, internal Me_4Si) δ 7.4 (m, 6 H), 6.9 (m, 2 H), 6.45 (d, 1 H, J = 15 Hz), 3.1 (bs, 6 H). The products from reaction of 4 with benzaldehyde, acetaldehyde, and propanal were identified by comparison with authentic samples (GLC retention times).

Reaction of 4 with Propylene Oxide. A solution of 4 (10 mmol) in THF was prepared as described above and maintained at 25 °C. Propylene oxide (0.76 mL, 11 mmol) was injected and the solution was stirred for 2 h. The reaction mixture was then quenched with 0.6 mL (11 mmol) of glacial acetic acid. GLC analysis revealed the only traces of **3** and the presence of *N,N*-dimethyl-4-trimethylsiloxypentanoamide (9) in 75% yield. Pure samples of **9** were obtained by preparative GLC: ^{1}H NMR (CCl_4, internal Me_4Si) δ 3.81 (m, 1 H), 2.94 (s, 3 H), 2.84 (s, 3 H), 2.21 (t, 2 H), 1.60 (m, 2 H), 1.10 (d, 3 H), 0.10 (s, 9 H).

Reaction of 4 with Styrene Oxide. Using the procedure described above for propylene oxide, GLC analysis indicated the formation of *N,N*-dimethyl-4-phenyl-4-trimethylsiloxybutanoamide (**10**) in 90% yield. Pure samples of **10** were obtained by preparative GLC: ^{1}H NMR (CCl_4, internal Me_4Si) δ 7.16 (s, 5 H), 4.75 (t, 1 H), 2.94 (s, 6 H), 2.27 (t, 2 H), 1.94 (m, 2 H), 0.10 (s, 9 H); IR (CCl_4) 1645 cm^{-1} (C=O).

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Registry No.—**3,** 23184-28-3; **4,** 65378-64-5; **6,** 56579-98-7; **9,** 65378-65-6; **10,** 65378-66-7; *N,N*-dimethyl-3-methyl-2-butenoamide, 42902-94-3; *N,N*-dimethyl-2-cyclohexylideneacetamide, 65378-67-8; *N,N*-dimethyl-5-phenyl-*cis*-2,*trans*-4-pentadienoamido, 65378-68-9; *N,N*-dimethyl-5-phenyl-*trans*-2,*trans*-4-pentadienoamido, 21497-23-4; propylene oxide, 75-56-9; styrene oxide, 96-09-3.

References and Notes

(1) (a) S. L. Hartzell, D. F. Sullivan, and M. W. Rathke, *Tetrahedron Lett.*, 1403 (1974); (b) K. Shimoji, H. Taguchi, K. Oshima, H. Yamamoto, and H. No *J. Am. Chem. Soc.*, **96,** 1620 (1974).
(2) R. P. Woodbury and M. W. Rathke, *J. Org. Chem.*, **42,** 1688 (1977)
(3) Alcohol products analogous to **8** have been isolated after short reaction times (at −78 °C) of the ester enolate **5** with cyclohexanone.[1a]
(4) Reaction of epoxides with phosphorus ylides analogous to **4** at 200 °C is reported to give cyclopropanes: D. B. Denny, J. J. Vill, and M. J. Boskin, *J. Am. Chem. Soc.*, **84,** 3944 (1962).
(5) It is, of course, possible that the rearrangement is an intermolecular process. We have no evidence bearing on this point.
(6) S. C. Watson, and J. F. Eastham, *J. Organomet. Chem.*, **9,** 165 (1967).
(7) *N,N*-Dimethyl-2-trimethylsilylacetamide was prepared as described by: M. W. Rathke and R. P. Woodbury, *J. Org. Chem.*, **42,** 3961 (1977).
(8) D. H. R. Barton, G. Hewitt, and P. G. Sammes, *J. Chem. Soc. C,* **1,** 16 (1969).