Trimethylsilylacetic Acid Dianion: Application to Organic Synthesis

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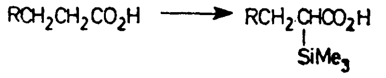
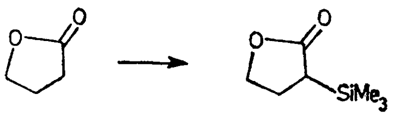
Summary Trimethylsilylacetic acid readily forms the dianion (**2**) providing highly efficient routes to α-trimethylsilylcarboxylic acids, α,β-unsaturated acids, and α-trimethylsilyl-γ-butyrolactones; the latter can then be converted into α-ylidene-γ-butyrolactones, α-bromo-γ-butyrolactones and γ-butyrolactones.

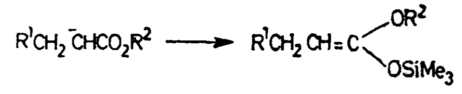
Recently we required a method exclusively to introduce the α-trimethylsilyl group adjacent to carbonyl functions (equations 1 and 2) but the reaction of ester enolates and lactone enolates with trimethylsilylchloride gives predominantly *O*-silyl keten acetals (equations 3 and 4). For example it has been demonstrated that substitution on the α-carbon atom of esters (excluding acetates) favours predominantly *O*-silylated products,[1] and that treatment of the lactone enolate of γ-butyrolactone with Me_3SiCl results in a >90% yield of *O*-silylated material.[2] Our attempts to C-silylate the enolate of γ-butyrolactone at −78° in tetrahydrofuran (THF) have resulted in <9% isolated yield of α-trimethylsilyl-γ-butyrolactone. Similarly, the reaction of ketone enolates with silylating agents results in the formation of silyl enol ethers with no evidence of *C*-silylation.[3]



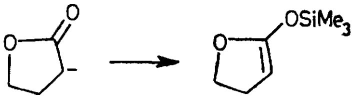
$$RCH_2CH_2CO_2H \longrightarrow RCH_2\underset{\displaystyle SiMe_3}{\underset{|}{C}}HCO_2H \qquad (1)$$



(2)

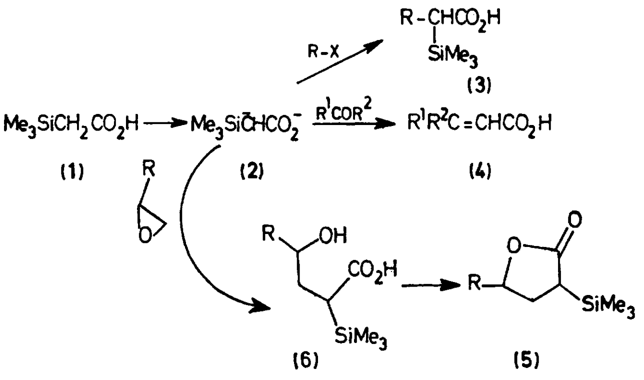


$$R^1CH_2\overset{-}{C}HCO_2R^2 \longrightarrow R^1CH_2CH{=}C\begin{matrix}OR^2\\ OSiMe_3\end{matrix} \qquad (3)$$



(4)

One method to circumvent the problems associated with *C*- versus *O*-silylation of ester and lactone enolates is to alkylate the dianion (**2**) of trimethylsilylacetic acid (**1**) (Scheme 1). We now report that trimethylsilylacetic acid readily forms the dianion (**2**) on treatment with lithium diisopropylamide (LDA), and that (**2**) provides efficient routes to α-trimethylsilylcarboxylic acids (**3**), α,β-unsaturated carboxylic acids (**4**), and α-trimethylsilyl-γ-butyrolactones (**5**); the latter undergo a variety of useful transformations (Scheme 2).

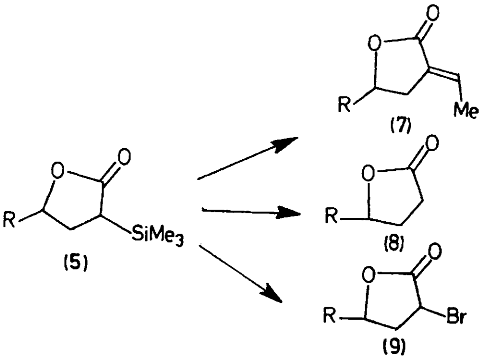


Scheme 1

Treatment of trimethylsilylacetic acid (**1**)[4] with 2·2 equiv. LDA in THF at 0° gave the soluble dianion (**2**). When (**2**) was quenched with D_2O–DCl, the recovered trimethylsilylacetic acid contained *ca.* 1·0 deuterium atom at the α-carbon, showing that an excellent yield of the dianion (**2**) is produced.

The dianion (**2**) can be used for the conversion of carbonyl compounds to α,β-unsaturated carboxylic acids in high yield.[5] For example a solution of trimethylsilylacetic acid dianion in THF at −78° was treated with cyclohexanone. Extractive workup gave cyclohexylideneacetic acid in 83% yield. The following conversions were also accomplished using the dianion (**2**): benzaldehyde → cinnamic acid (88%, $E/Z = 1:1$); hexanal → oct-2-enoic acid (90%, $E/Z = 3:2$); cyclopentanone → cyclopentylideneacetic acid (84%). In the case of cyclohexanone and cyclopentanone there was no indication that any β,γ-unsaturated carboxylic acid was present.

We also wanted to prepare α-trimethylsilyl-γ-butyrolactones (**5**) hoping to use them as intermediates in the preparation of α-ylidene-γ-butyrolactones. The dianion (**2**) reacts at room temperature in very high yield with epoxides providing a general entry into the α-trimethylsilyl-γ-butyrolactone system, *e.g.* reaction of (**2**) with ethylene oxide gave a 94% yield of the hydroxy acid (**6**; R = H). Azeotropic removal of water (benzene, TsOH, reflux) yielded α-trimethylsilyl-γ-butyrolactone (**5**; R = H) in quantitative yield. In a similar fashion propylene oxide provided the γ-lactone (**5**; R = Me) (70% overall) and the epoxide of oct-1-ene provided the γ-lactone (**5**; R = C_6H_{13}) in 80% overall yield. Attempts to open ethylene oxide with the lithium enolate derived from ethyl trimethylsilylacetate in THF resulted in complete recovery of the starting material.



Scheme 2

α-Ylidenation[6] of α-trimethylsilyl-γ-butyrolactone (**5**; R = H) was demonstrated with acetaldehyde. Enolate formation was carried out at −78° using lithium triphenylmethide in THF. Use of LDA resulted in yields of α-ylidene lactones which were generally 20% lower. This apparently is due to Michael addition of diisopropylamine to the α-ylidene lactone unit. In the case of (**5**; R = H) a 76% yield of *E*-α-ylidene-γ-butyrolactone (**7**; R = H) was isolated. Likewise, (**5**; R = Me and R = C_6H_{13}) afforded similar products with acetaldehyde in 80% and 60% yields respectively. Reaction of (**5**; R = H) with bromine in methylene chloride provides a 97% yield of γ-bromobutyrolactone (**9**; R = H), while treatment of (**5**; R = C_6H_{13}) with concentrated HCl in THF affords γ-butyrolactone (**8**; R = C_6H_{13}) in 98% yield.

We have also demonstrated that the dianion (**2**) undergoes high yield alkylation at room temperature thus providing access to a variety of α-trimethylsilylcarboxylic acids which have been difficult to prepare. Some typical results are given in the Table.

Table Alkylation of the dianion (**2**)

R–X	Yield of (**3**)/%[a]
Benzyl bromide	90
Methyl iodide	95
n-Butyl iodide	87
Ethyl iodide	98
Iodomethyl phenyl sulphide	60
Geranyl bromide	84

[a] Yields are for pure compounds.

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[5] The affinity of a suitably substituted silyl group to an alkoxide has been demonstrated: D. J. Peterson, *J. Org. Chem.*, 1968, **33**, 780; T. H. Chan, E. Chang, and E. Vinokur, *Tetrahedron Letters*, 1970, 1137; F. A. Carey and A. S. Court, *J. Org. Chem.*, 1972, **37**, 939, 1926; D. Seebach, B.-Th. Grobel, A. K. Beck, M. Braun, and K.-H. Geiss, *Angew. Chem. Internat. Edn.*, 1972, **11**, 443. See also K. Shimoji, H. Taguchi, K. Oshima, H. Yamamoto, and H. Nozaki, *J. Amer. Chem. Soc.*, 1974, **96**, 1620; S. L. Hartzell, D. F. Sullivan, and M. W. Rathke, *Tetrahedron Letters*, 1974, 1403.

[6] For routes to α-ylidene-γ-butyrolactones see H. Zimmer and T. Pampalone, *J. Heterocyclic Chem.*, 1965, **2**, 95; G. A. Howie, P. E. Manni, and J. M. Cassady, *J. Medicin. Chem.*, 1974, **17**, 840; T. Minami, I. Niki, and T. Agawa, *J. Org. Chem.*, 1974, **39**, 3236; for a review of α-methylene lactone synthesis see P. A. Grieco, *Synthesis*, 1975, 67.