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A convenient method for the synthesis of α-silylacetic acids

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Abstract

A method is described for the preparation of α-silylacetic acids of the type $R_3SiCH_2CO_2H$ by treating trimethylsilyl acetate with LDA followed by quenching with chlorosilanes.

α-Trialkylsilylacetic acids are important intermediates in organic synthesis. They undergo thermal and base-catalyzed rearrangements to isomeric acyloxysilanes[1] and their dianions provide highly efficient routes to α,β-unsaturated acids and butyrolactones.[2] Also, they are used widely for various biological purposes, such as preparing labelled diethyl malonate[3] and synthesizing α,β-unsaturated thiol esters[4] and α-silyl thioesters.[5,6] Nevertheless, a more extensive use of such versatile compounds has been hampered by the low yields, lack of selectivity and relatively high cost.

Sommer et al.[7] were the first to report the synthesis of α-silylacetic acids by the carbonation of Grignard reagents derived from the appropriate chlorides. However, this method was too costly and resulted in low yields. Following that work, a more detailed and improved procedure was published much later by Weguny and Schafer[8] Emde and Simchen[9] prepared trimethylsilylacetic acid by using trimethylsilyl trifluoromethanesulfonate as the silylating reagent, but the yield of the product was also poor. Ainsworth and Kuo[10] reported that $ClSiMe_3$ reacts with the dianion of acetic acid to give equal amounts of *O*- and *C*-silyl derivatives. It is also claimed[11] that if the enolate is formed in a mixture of ether and THF and refluxed for 24 h prior to quenching with trimethylchlorosilane, the α-silyl ester is obtained in 70% yield. Apparently, it turned out that the latter quoted yield is not always reproducible, and is highly sensitive to the experimental conditions.[12]

Moreover, when Hudrlik et al.[13] applied the same experimental conditions but used different silylating agents, O → C migration of the trimethylsilyl group was detected.

The observation that C-silylation of esters of acetic acid is quite sensitive to the bulkiness of the silyl group or 'softness' of the electrophilic silicon moiety is known.[14] For example, Larson and coworkers reported[15,16] the α-silylation of esters and lactones and found that the yields of the C-silylation products depended on the nature of the silyl group.

Based on the above data, it seems that to date and to the best of our knowledge, there is no general method for the preparation of α-silylacetic acids in a reproducible way that delivers good yields. Herein we report a useful and general method for the synthesis of α-silylacetic acids using common and commercially available starting materials.

Following the procedure described in Ref.15, initially we attempted to prepare α-diphenylmethylsilyl acetic acid from the corresponding ethyl and *tert*-butyl esters. However, in our hands, hydrolyzing ethyl and *tert*-butyl-α-diphenylmethylsilyl esters under both mild basic[17] and acidic[18] conditions always resulted in the desilylation of the desired products. Attempts to hydrolyze *tert*-butyl-α-diphenylmethylsilyl esters under neutral conditions[19] led to the same result. Finally, we adopted the experimental conditions described by Ainsworth and Kuo[10] showing that trimethylsilyl esters of carboxylic acids can readily hydrolyze in the presence of ammonium chloride.

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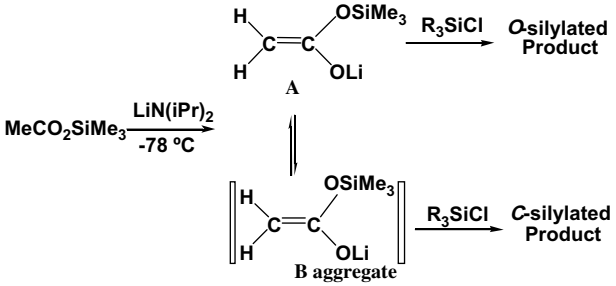
In the present work we used silyl esters (instead of alkyl esters) as precursors and examined the C-silylation of trimethylsilyl acetate ($CH_3CO_2SiMe_3$) with a variety of silylating agents to afford good yields of the corresponding C-silylated products (Table 1, entries 1–6).[20]

We found that the yield of the C-silylated product increases when the lithium enolate salt is allowed to stand at −78 °C for 2 h prior to quenching with the alkylchlorosilane. However, if the enolate salt is immediately quenched at −78 °C, the yield of the C-silylated product is reduced significantly. We also found that after adding a chlorosilane, continuous cooling of the reaction mixture at −78 °C for an additional 2 h was necessary to produce a higher yield of the C-silylated product. We assume that the rate of silylation at carbon is slow at this low temperature, and therefore, a rapid heating to room temperature shifts the equilibrium towards O-silylation, resulting in a decrease in the yield of the C-silylated product.

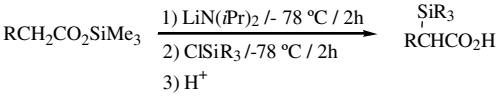
There is no general method to assign the structures of lithium enolates in solutions, except for isolated cases. However, mechanistic studies of enolate alkylations have afforded diverse hypotheses. The reaction could proceed via dimer-[21] or tetramer-based[22] intermediates. Recently, it has been shown that the C-alkylation of β-amino esters proceeds via hexameric enolates, which exist as such both in the solid state and in THF solution.[23]

Based on the above observations, the existence of a C-lithiated ester enolate has been ruled out. Therefore, it is likely that O- versus C-silylation depends on the equilibrium between the two OLi structures, monomeric 'A' and aggregated 'B', as depicted in Scheme 1. Recent work[24] has proven that hexameric enolate (OLi structure B) undergoes C-alkylation directly without deaggregation. Consequently, it is conceivable that the 2 h reaction time before quenching (described above) is required to obtain an aggregation state allowing efficient C-silylation at low temperature.

After the successful preparation of α-silyl acetic acids from trimethylsilylacetate we attempted the reaction with



Scheme 1. Equilibrium between the two O-lithiated structures.



Scheme 2. α-Silylation of trimethylsilyl esters.

Table 1
Yields of α-silylcarboxylic acids of the type $(R_3Si)CH(R)CO_2H$

Entry	R	R_3	Yield of product (%)
1 (**1**)	H	Me_3	72[a]
2 (**2**)	H	*n*-Pr_3	77[b]
3 (**3**)	H	*i*-Pr_3	72[b,c]
4 (**4**)	H	Ph_3	70[a]
5 (**5**)	H	$Me_2(Ph)$	75[a]
6 (**6**)	H	$Ph_2(Me)$	78[a]
7 (**7**)	Cl	$Ph_2(Me)$	50[b]
8	Ph	$Ph_2(Me)$	Trace

[a] Yield of pure compound.

[b] Yield is based on ^1H NMR integration due to difficulties in purification by column chromatography and separation from siloxanes ($R_3SiOSiR_3$) impurities.

[c] This particular acid was obtained as its trimethylsilyl ester. So far, attempts to hydrolyze it have failed. It undergoes decomposition (C–Si desilylation) in 1 N HCl, stirring for 1 h, at 50 °C, or for 24 h at rt or in 2 N NaOH for 1 h at rt.

trimethylsilyl esters of other carboxylic derivatives of the type $RCH_2CO_2SiMe_3$ (R = Cl, Ph), which can stabilize a carbanion at the α position (entries 7–8, Table 1, and Scheme 2), aiming towards higher yields of the desired C-silylated products. The α-silylation of these esters was examined with diphenylmethylchlorosilane which was preferred over trimethylchlorosilane due to it being a 'softer' electrophile and therefore, more reactive towards the carbon terminus of the ambient nucleophile. Consequently, C-silylation is favoured with diphenylmethylchlorosilane, whereas O-silylation is favored with trimethylsilylchlorosilane.[15] Surprisingly, the yield of the product with $ClCH_2CO_2SiMe_3$ decreased (entry 7) compared to those obtained with $CH_3CO_2SiMe_3$ (entries 1–6), while that with $PhCH_2CO_2SiMe_3$ was almost nil. These results indicate that the inductive effect plays a minor role compared with steric effects. Therefore, the yield of the C-silylated product is dictated mostly by the bulkiness of the group attached to the carbon at the α position, that is, it increases in the order H > Cl > Ph.

In conclusion, the present study describes the experimental conditions under which C-silylation is preferred over O-silylation of lithiated trimethylsilyl esters. Apparently, the outcome is very sensitive to the experimental reaction conditions, substitution pattern at the α position of the silylated esters and the nature of the silylated chlorosilane reagent.

Acknowledgement

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Supplementary data

Experimental procedures, characterization data and copies of ^1H, ^{13}C and ^{29}Si NMR spectra of all the α-silylacetic (and other) acids are presented. Supplementary data

associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.050.

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20. In a one-pot reaction, trimethylsilyl acetate (21.0 mmol) in 5 ml of THF was added dropwise to a solution of LDA (24.0 mmol) in 50 ml of dry THF at −78 °C. The reaction mixture was stirred for 2 h at −78 °C before quenching with trialkylchlorosilane (24.0 mmol). After stirring for 2 additional hours at −78 °C the reaction was warmed to room temperature. A solution of saturated sodium chloride (30 ml) was added and the reaction mixture was hydrolyzed with 1 N HCl to pH 3. The aqueous layer was extracted with diethyl ether (30 ml × 3) and the combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, filtered and concentrated. The residual crude product was dissolved in 30 ml of THF, and 20 ml of saturated ammonium chloride solution was added. The reaction mixture was then stirred at room temperature for 1 h. Afterwards the aqueous layer was extracted with diethyl ether (30 ml × 3) and the combined organic extracts were washed with water and dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residual product was crystallized from hexane to give α-(trialkylsilyl) acetic acids in good yields. Based on this method, two new α-silyl products have been prepared: α-tri-*n*-propylsilylacetic acid (**2**) and α-triisopropylsilyl trimethylsilylacetate (**3**). *Spectral data of tri-n-propylsilylacetic acid* (**2**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.64–0.68 (m, 6H), 0.96 (t, $J = 17.5$ Hz, 9H), 1.27–1.43 (m, 6H), 1.90 (s, 2H), 11.85 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.1, 17.0, 18.3, 23.2, 180.7; ^{29}Si NMR (100 MHz, $CDCl_3$) δ 4.3; IR 1687 cm^{-1}; MS (MALDI-TOF) *m*/*z* calcd for $C_{11}H_{24}O_2Si$: 216.40. Found 238.93 (MNa^+), 260.90 ($M2Na^+$). *Spectral data of α-triisopropylsilyl trimethylsilylacetate* (**3**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 9H), 1.06 (d, $J = 7.5$ Hz, 18H), 1.26–1.28 (m, 3H), 1.94 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.3, 12.0, 17.9, 29.0, 173.2; ^{29}Si NMR (100 MHz, $CDCl_3$) δ 1.2, 18.7; LCMS (ESI) *m*/*z* calcd for $C_{14}H_{32}O_2Si_2$: 288.6. Found 289.1 (MH^+), 311.0 (MNa^+).
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