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# USES OF Si-N BONDS IN ORGANIC SYNTHESIS. A DIRECT SYNTHESIS OF FUNCTIONAL PROTECTED PROPARGYLIC PRIMARY AMINES.

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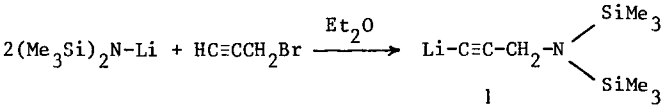
Summary : An easy route to lithium N,N-bis(trimethylsilyl)aminomethylacetylide **1** is described. Reactions of **1** with electrophiles give rise to various protected primary amines.

Our current interest in the synthetic applications of compounds with silicon-nitrogen bonds [1], led us to study the use of hexamethyldisilazane (HMDS) for the synthesis of functional protected primary amines. Alkali bis(trimethylsilyl)amides, readily obtained from commercial HMDS, are widely used as strong bases in organic syntheses [2], but they have rarely been used for the preparation of primary amines [3-5]. Herein we report a straightforward route to a variety of protected amines bound to functional groups.

By analogy to the reaction of metal amides with propargyl halides [6], lithium bis-(trimethylsilyl)amide in ether was found to react with propargyl bromide to give a solution of lithium N,N-bis(trimethylsilyl)aminomethylacetylide **1** (eq-1).

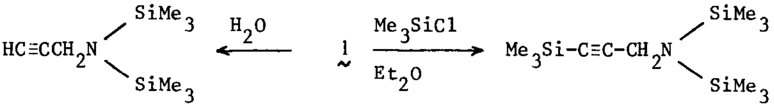


$$2(Me_3Si)_2N\text{-}Li + HC{\equiv}CCH_2Br \xrightarrow{Et_2O} Li\text{-}C{\equiv}C\text{-}CH_2\text{-}N(SiMe_3)_2$$

**1**

(1)

The formation of **1** in high yield was established by quenching the reaction mixture with water and chlorotrimethylsilane allowing isolation of propargylic amines **2** and **3** respectively in 78 % yield (eq-2).

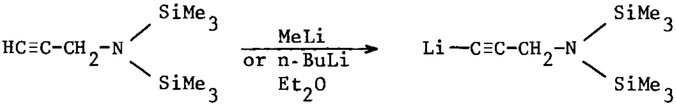


$$HC{\equiv}CCH_2N(SiMe_3)_2 \xleftarrow{H_2O} \mathbf{1} \xrightarrow[Et_2O]{Me_3SiCl} Me_3Si\text{-}C{\equiv}C\text{-}CH_2N(SiMe_3)_2$$

**2**, 78 %   **3**, 78 %

(2)

The ethereal solution of **1** obtained according to eq-1, however contains one equivalent of HMDS. An HMDS free ethereal solution of **1** can be prepared quantitatively by the metallation of propargyl amine **2** with n-butyl or methyllithium (eq-3).

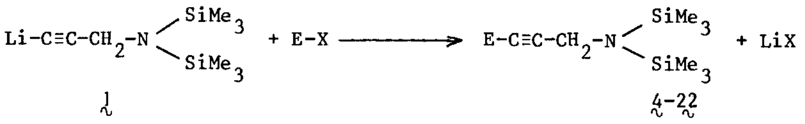


$$HC{\equiv}C\text{-}CH_2\text{-}N(SiMe_3)_2 \xrightarrow[Et_2O]{MeLi \text{ or } n\text{-}BuLi} Li\text{—}C{\equiv}C\text{-}CH_2\text{-}N(SiMe_3)_2$$

**2**   **1**

(3)

The intermediate 1 represents a propargyl amine synthon [7] : its reactions with various electrophiles can offer a straightforward route to functional primary amines from propargyl bromide and HMDS. Therefore we studied the reactivity of lithium α-aminoacetylide 1 towards various organic electrophiles (eq-4).



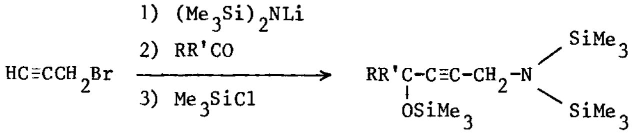
$$\underset{1}{\text{Li-C}\equiv\text{C-CH}_2\text{-N}(\text{SiMe}_3)_2} + \text{E-X} \longrightarrow \underset{4-22}{\text{E-C}\equiv\text{C-CH}_2\text{-N}(\text{SiMe}_3)_2} + \text{LiX} \tag{4}$$

[E-X = R-X, aldehyde, ketone, α-enone....]

The results are summarised in table 1.

The reactions of primary alkyl iodides or bromides in refluxing THF gave good yields of the substituted propargylic amines (entries 1-5). Under the same reaction conditions, no reaction occured with alkyl chloride allowing a selective substitution of 4-chloro 1-bromo-butane (entry 6). Reaction of 2 moles of 1 with 1,5 dibromopentane led the diacetylenicdiamine 9 (entry 7) in 58 % yield.

The reactions of 1 with ketones or aldehydes gave rise to acetylenic aminoalcohols which were isolated as their trimethylsilyl derivatives. These compounds can be obtained in a one-pot reaction starting from propargyl bromide (eq-5).



$$\text{HC}\equiv\text{CCH}_2\text{Br} \xrightarrow[\text{3) Me}_3\text{SiCl}]{\text{1) (Me}_3\text{Si)}_2\text{NLi} \quad \text{2) RR'CO}} \text{RR'}\underset{\text{OSiMe}_3}{\text{C}}\text{-C}\equiv\text{C-CH}_2\text{-N}(\text{SiMe}_3)_2 \tag{5}$$

Yields in the range of 40 to 53 % were obtained (entries 8-11). However, higher yields were obtained when using lithium reagent 1 prepared by metallation of propargylamine 2 (entries 12-13). In the case of α β-unsaturated carbonyl compounds, 1,2-addition to the carbonyl group was observed (entries 14-16).

The lithium acetylide 1 was also used to prepare functional acetylenic amines. The reaction of chloromethylmethyl ether gave good yield of the expected aminoether (entry 17). Ynones were also obtained via the manganate reagents [8], however moderate yields were obtained owing to a competing acylation at the nitrogen atom (entries 18-19). The reaction of ethylchloroformiate with the lithium reagent 1 gave the acetylenic ester in 70 % yield (entry 20). It is noteworthy that the carboethoxylation of propargylphthalimide was unsuccessful [9], intermediate 1 thus provide an interesting synthesis of the acetylenic ester 22.

Lithium acetylide 1 represents an attractive propargylamine synthon. It provides a short route to various substituted and functional acetylenic amines to which synthetic efforts have been recently directed [10] since they for example represent precursors of allenic compounds [11-13].

Table 1 : Reactions of $Li\text{-}C\equiv C\text{-}CH_2\text{-}N(SiMe_3)_2^{a}$ (1) with electrophiles

| Entry | Electrophile | React. cond.[b] | Acetylenic amine | Yields[c] (%) |
|---|---|---|---|---|
| 1 | $CH_3I$ | (A) | 4 $CH_3C\equiv CCH_2N(SiMe_3)_2$ | 88 |
| 2 | $C_2H_5I$ | (A) | 5 $C_2H_5C\equiv CCH_2N(SiMe_3)_2$ | 88 |
| 3 | $CH_2{=}CH\text{-}(CH_2)_4I$ | (A) | 6 $CH_2{=}CH(CH_2)_4C\equiv CCH_2N(SiMe_3)_2$ | 72 |
| 4 | $C_2H_5Br$ | (B) | 5 $C_2H_5C\equiv CCH_2N(SiMe_3)_2$ | 75 |
| 5 | $n\text{-}C_4H_9Br$ | (B) | 7 $n\text{-}C_4H_9C\equiv CCH_2N(SiMe_3)_2$ | 65 |
| 6 | $Cl\text{-}(CH_2)_4Br$ | (B) | 8 $Cl(CH_2)_4C\equiv CCH_2N(SiMe_3)_2$ | 73 |
| 7 | $Br(CH_2)_5Br$ | (B) | 9 $CH_2[(CH_2)_2C\equiv CCH_2N(SiMe_3)_2]_2$ | 58 |
| 8 | $C_2H_5CHO$ | (C) | 10 $C_2H_5CH(OSiMe_3)C\equiv CCH_2N(SiMe_3)_2$ | 41[d] |
| 9 | $n\text{-}C_3H_7CHO$ | (C) | 11 $nC_3H_7CH(OSiMe_3)C\equiv CCH_2N(SiMe_3)_2$ | 40[d] |
| 10 | $(CH_3)_2CHCHO$ | (C) | 12 $(CH_3)_2CHCH(OSiMe_3)C\equiv CCH_2N(SiMe_3)_2$ | 53[d] |
| 11 | $PhCH_3CO$ | (C) | 13 $PhCH_3C(OSiMe_3)C\equiv CCH_2N(SiMe_3)_2$ | 40[d] |
| 12 | PhCHO | (D) | 14 $PhCH(OSiMe_3)C\equiv CCH_2N(SiMe_3)_2$ | 68 |
| 13 | $\overline{(CH_2)_4C}O$ | (D) | 15 $\overline{(CH_2)_4C}(OSiMe_3)C\equiv CCH_2N(SiMe_3)_2$ | 70 |
| 14 | $CH_3CH_2CH{=}C(CH_3)CHO$ | (C) | 16 $C_2H_5CH{=}C(CH_3)CH(OSiMe_3)C\equiv CCH_2N(SiMe_3)_2$ | 35[d] |
| 15 | $PhCH{=}CHCHO$ | (C) | 17 $PhCH{=}CHCH(OSiMe_3)C\equiv CCH_2N(SiMe_3)_2$ | 37[d] |
| 16 | $\overline{(CH_2)_3CH{=}CHC}O$ | (D) | 18 $\overline{(CH_2)_3CH{=}CHC}(OSiMe_3)C\equiv CCH_2N(SiMe_3)_2$ | 92 |
| 17 | $MeOCH_2Cl$ | (B) | 19 $MeOCH_2C\equiv CCH_2N(SiMe_3)_2$ | 78 |
| 18 | PhCOCl | (E) | 20 $PhCOC\equiv CCH_2N(SiMe_3)_2$ | 35 |
| 19 | $(CH_3CO)_2O$ | (E) | 21 $CH_3COC\equiv CCH_2N(SiMe_3)_2$ | 45 |
| 20 | EtOOCCl | (F) | 22 $EtOOCC\equiv CCH_2N(SiMe_3)_2$ | 70 |

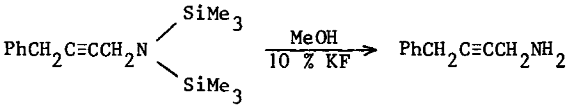
a - Prepared from $HC\equiv CCH_2N(SiMe_3)_2$ 2 unless otherwise stated

b - Reactions conditions : (A) = refluxing THF for 3 to 12 hours ; (B) = refluxing THF for 48 to 72 hours ; (C) = -78°C to 20°C in $Et_2O$ for 2 hours followed by quenching with $Me_3SiCl$ (20°C, 24 h) ; (D) = - 78°C to 20°C in THF followed by quenching with $Me_3SiCl$ (20°C, 24 h) ; (E) = i) $MnCl_2$ (- 30°C, 4 h) , ii) PhCOCl or $(CH_3CO)_2O$ (- 30°C to 20°C, 10 h) ; (F) = - 78°C to 20°C in $Et_2O$ for 3 hours.

c - Calculated with respect to $HC\equiv CCH_2N(SiMe_3)_2$

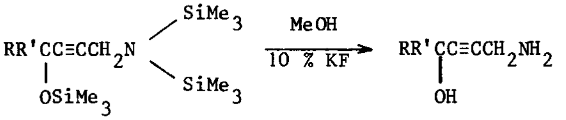
d - Calculated with respect to propargyl bromide (one-pot reaction).

The primary amine can be regenerated using dilute acid solutions [3] or by simply stirring in methanol in the presence of potassium fluoride (eq-6,7).



$$PhCH_2C\equiv CCH_2N\begin{smallmatrix}\diagup SiMe_3\\ \diagdown SiMe_3\end{smallmatrix} \xrightarrow[10\ \%\ KF]{MeOH} PhCH_2C\equiv CCH_2NH_2$$

(6)



$$RR'\underset{OSiMe_3}{\underset{|}{C}}C\equiv CCH_2N\begin{smallmatrix}\diagup SiMe_3\\ \diagdown SiMe_3\end{smallmatrix} \xrightarrow[10\ \%\ KF]{MeOH} RR'\underset{OH}{\underset{|}{C}}C\equiv CCH_2NH_2$$

(7)

R = H, R' = Ph 78 %
R = H, R' = EtCH=C(Me) 90 %

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