Pergamon

Tetrahedron Letters, Vol. 38, No. 2, pp. 191-194, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02271-X

Protection of a Protecting Group:Preparation of Stable *N*-Silylated t-Butyl Carbamates

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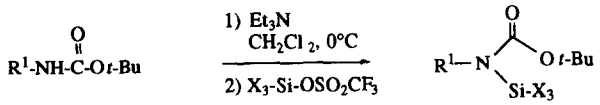
Abstract: The practical preparation of *N*-silylated carbamates (typified by 1) is reported. These compounds are synthesized in high yields by treating *N*-*t*-Boc-protected primary amines with silyl triflate reagents in dichloromethane in the presence of triethylamine.

Recently, we reported a novel approach to the asymmetric synthesis of *N*-*t*-Boc-Phenylsarcosine.[2] That synthesis involved an enantioselective deprotonation at the benzylic position of *N*-*t*-Boc-*N*-Methylbenzylamine using the chiral complex *s*-BuLi/(-)sparteine, followed by a stereoselective carboxylation. However, attempts to prepare *N*-*t*-Boc-Phenylglycines by the same strategy failed to give enantioenriched products due to the removal of the more acidic carbamate proton. To overcome this problem, we sought to protect temporarily the carbamate group. For this purpose, we report the facile synthesis of *N*-silylated t-butyl carbamates[3] with the general structure of **1**. These molecules could be valuable in organic synthesis in addition to their use in enantioselective deprotonation. They could also be used in peptide synthesis to block *N*-*t*-Boc groups.

Compounds like **1** have been synthesized from aliphatic amines, α-benzylic amines, and amino acid substrates by using different silylating agents. In a typical procedure[4] (Scheme 1), a *N*-*t*-Boc-protected primary amine **2** was treated with triethylamine and a silyl triflate reagent in dichloromethane at 0°C under anhydrous conditions for 10 min to give carbamate derivatives **1** in 89-98% yields. The results obtained with a variety of substrates and reagents are collected in Table 1.



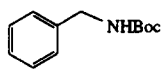
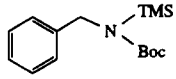
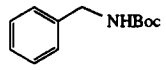
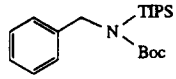
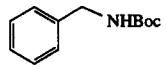
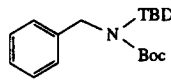
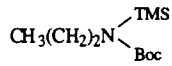
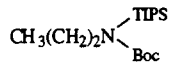
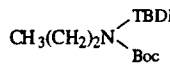
2 **1**

Scheme 1

The compounds are synthesized easily with excellent yields. For the benzylic compounds, we obtained 89 to 98% yield and for the aliphatic compounds, 90 to 95% yield. They are stable at room temperature and can

be chromatographed on silica gel using hexanes/ethyl acetate with 1% triethylamine as eluent. They support strongly basic conditions,[6] but are hydrolyzed rapidly to the corresponding *N*-*t*-Boc derivative with HCl 1N or

Table 1. Reactions of *N*-*t*-Boc-protected amines with silylating reagents

Substrates	Silylating reagents	Products[5]	Isolated Yields(%)
	TMS-Tf		92
	TIPS-Tf		98
	TBDMS-Tf		89
$CH_3(CH_2)_2NHBoc$	TMS-Tf		95
$CH_3(CH_2)_2NHBoc$	TIPS-Tf		92
$CH_3(CH_2)_2NHBoc$	TBDMS-Tf		90

with fluoride reagents.[7] The characterization of these compounds was done by ^1H and ^{13}C NMR, FTIR and mass spectrometry.[5]

Spectral data obtained support the structure of compounds like **1**. However, careful spectral analysis could not ruled out the formation of the O-silylated analog **3**.[8] But, X-ray crystallography showed that the product obtained using *N*-*t*-Boc-*p*-methoxy benzylamine is the *N*-silylated derivative illustrated in Figure 1.

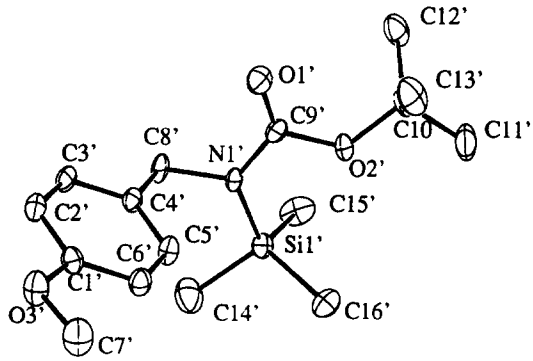
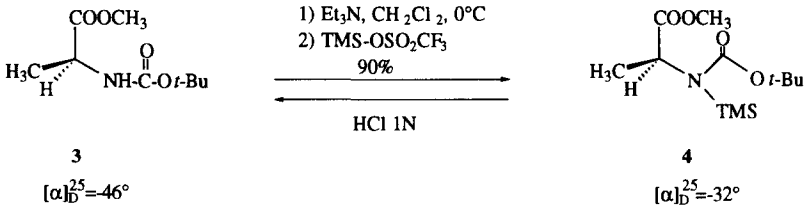


Figure 1. ORTEP view of *N*-TMS-*N*-*t*-Boc-*p*-methoxy benzylamine obtained by X-ray crystallography.[9]

To determine the applicability of *N*-silylated carbamates to amino acids and peptides, we treated *N*-*t*-Boc-L-alanine methyl ester **3** under the conditions mentioned above (Scheme 2). The doubly protected alanine **4** was obtained in 90% yield.[4] This compound is stable at room temperature and was easily hydrolyzed back to the *N*-*t*-Boc derivative with HCl 1N. After hydrolysis, the amino acid had the same optical rotation demonstrating that the reaction conditions do not lead to racemization of the adjacent chiral center.



3
$[\alpha]_D^{25}$=-46°

4
$[\alpha]_D^{25}$=-32°

Scheme 2

In summary, we report the synthesis of *N*-silylated carbamates. These compounds are prepared rapidly and easily in good yields. They are stable under basic conditions and easily hydrolyzed back to the corresponding *N*-*t*-Boc derivatives under mild acidic conditions or with fluoride reagents. Also, we have shown that we can protect and recover amino acids without racemization. We are currently working to enantioselectively deprotonate at the benzylic position these *N*-silylated carbamates.

Acknowledgements. We thank Marc Drouin for the X-ray analysis and Merck Frosst Canada, NSERC of Canada, FCAR of Québec, and the Université de Sherbrooke for the financial support of this work.

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4. A representative procedure for the preparation of the *N*-silylated carbamates is as follow: To a solution of **2** in dichloromethane at 0°C was added 1.1 eq of Et_3N, then dropwise 1.1 eq of TMSTf. The mixture was stirred for 5 min at 0°C then warmed to room temperature. After quenching with saturated sodium bicarbonate, the organic phase was washed with satured $NaHCO_3$ (3 times), then dried with anhydrous $MgSO_4$. The crude compound (oil) was purified by flash chromatography (Hexanes/ethyl acetate 9.5/0.5 + 1% of Et_3N) to give pure compound.
5. Data for: ***N*-trimethylsilyl-*N*-*t*-butyloxycarbonyl benzylamine**: ^1H NMR (300 MHz, C_6D_6), δ= 0.17 (s, 9H, TMS), 1.41 (s, 9H, ^{t}butyl), 4.40 (s, 2H, CH_2), 7.11-7.22 (m, 5H, H aromat.); ^{13}C NMR (75.5 MHz, C_6D_6), δ 158.0, 141.0, 126.0-128.0, 79.4, 47.6, 28.1, 0.5; IR (neat): 3100-3000, 1702 cm^{-1} (-C=N); HRMS (EI) calc. for $C_{15}H_{26}O_2NSi$ (M^+) 280.1733 found 280.1729. ***N*-triisopropylsily-**

***N*-*t*-butyloxycarbonyl benzylamine**: ^{1}H NMR (300 MHz, C_6D_6), δ= 1.15 (d, 18H, CH_3 of TIPS, *J*=7.5 Hz), 1.40 (s, 9H, ^{t}butyl), 1.45 (m, 3H, CH of TIPS), 4.40 (s, 2H, CH_2), 7.10 (t, 1H, H_4 aromat., *J*=7.5 Hz), 7.23 (t, 2H, $H_{3\text{-}5}$ aromat., *J*=7.3 Hz), 7.34 (d, 2H, $H_{2\text{-}6}$, *J*=7.6 Hz); ^{13}C NMR (75.5 MHz, C_6D_6), δ 159.0, 141.5, 126.0-128.0, 79.5, 49.0, 28.0, 18.5, 13.5; IR (neat): 3100-3000, 1685 cm^{-1} (-C=N); HRMS (EI) calc. for $C_{21}H_{38}O_2NSi$ (M^+) 364.2672 found 364.2679. ***N*-*t*-butyldimethylsily-*N*-*t*-butyloxycarbonyl benzylamine**: ^{1}H NMR (300 MHz, C_6D_6), δ= 0.19 (s, 6H, CH_3 of TBDMS), 0.96 (s, 9H, ^{t}butyl of TBDMS), 1.38 (s, 9H, ^{t}butyl), 4.40 (s,2H, CH_2), 7.00-7.28 (m, 5H, Haromat.); ^{13}C NMR (75.5 MHz, C_6D_6), δ 159.0, 142.0, 126.0-128.0, 79.5, 49.1, 28.3, 27.4, 19.8; IR (neat): 3100-3000, 1697 cm^{-1} (-C=N); HRMS (EI) calc. for $C_{18}H_{32}O_2NSi$ (M^+) 322.2202 found 322.2207. ***N*-trimethylsilyl-*N*-*t*-butyloxycarbonyl propylamine**: ^{1}H NMR (300 MHz, C_6D_6), δ= 0.19 (s, 9H, TMS), 0.78 (t, 3H, CH_3, *J*=7.7 Hz), 1.41 (s, 9H, ^{t}butyl), 1.40-1.54 (m, 2H, CH_2), 3.10 (m, 2H, CH_2-N);^{13}C NMR (75.5 MHz, C_6D_6), δ 158.0, 79.1, 46.1, 28.4, 24.7, 11.4, 0.9; IR (neat): 3000-2800, 1706 cm^{-1} (-C=N); HRMS (EI) calc. for $C_{11}H_{26}O_2NSi$ (M^+) 232.1733 found 232.1738. ***N*-triisopropylsilyl-*N*-*t*-butyloxycarbonyl propylamine**: ^{1}H NMR (300 MHz, C_6D_6), δ= 0.87 (t, 3H, CH_3, *J*=7.6 Hz), 1.17 (d, 18H, CH_3 of TIPS, *J*=7.5 Hz), 1.36 (m, 3H, CH of TIPS), 1.46 (s, 9H, ^{t}butyl), 1.62-1.80 (m, 2H, CH_2), 3.08 (m, 2H, CH_2-N); ^{13}C NMR (75.5 MHz, C_6D_6), δ 158.5, 79.0, 47.5, 28.5, 25.0, 19.0, 13.5, 12.0; IR (neat): 3000-2800, 1680 cm^{-1} (-C=N); HRMS (EI) calc. for $C_{17}H_{38}O_2NSi$ (M^+) 316.2672 found 316.2669. ***N*-*t*-butyldimethylsilyl-*N*-*t*-butyloxycarbonyl propylamine**: ^{1}H NMR (300 MHz, C_6D_6), δ= 0.20 (s, 6H, CH_3 of TBDMS), 0.79 (t, 3H, CH_3, *J*=7.7 Hz), 0.97 (s, 9H, ^{t}butyl of TBDMS), 1.41 (s, 9H, ^{t}butyl), 1.57-1.62 (m, 2H, CH_2), 3.06 (m, 2H, CH_2-N); ^{13}C NMR (75.5 MHz, C_6D_6), δ 158.3, 79.3, 47.7, 28.4, 27.6, 24.7, 19.8, 11.6; IR (neat): 3000-2800, 1698 cm^{-1} (-C=N); HRMS (EI) calc. for $C_{14}H_{32}O_2NSi$ (M^+) 274.2202 found 274.2209. ***N*-trimethylsilyl-*N*-*t*-butyloxycarbonyl-L-alanine, methyl ester 4**: ^{1}H NMR (300 MHz, C_6D_6), δ= 0.22 (s, 9H, TMS), 1.36 (s, 9H, ^{t}butyl), 1.52 (d, 3H, CH_3, *J*=7.0 Hz), 3.38 (s, 3H, -OCH_3), 3.87 (m, 1H, CH); ^{13}C NMR (75.5 MHz, C_6D_6), δ 172.6, 157.5, 79.8, 52.7, 51.1, 27.9, 17.3, 0.5; IR (neat): 3000-2800, 1750 (C=O), 1696 cm^{-1} (-C=N); GC-MS: m/z = 276, 204, 160, 116, 57; $[\alpha]_D^{25}$ =-32° (c=1.2 in MeOH).

6. To verify stability, *N*-trimethylsilyl-*N*-*t*-butyloxycarbonyl benzylamine was treated with 1.1 eq of *s*-BuLi•TMEDA in Et_2O at -78°C for 3h. After quenching with water and usual work up, the starting material was recovered in more than 92%.
7. Treatment of *N*-silylated carbamates **1** with TBAF (1 M in THF) leads to *N*-*t*-Boc-protected primary amine **2** in quantitative yields in less than 10 min.
8. a) Chang, Y.H.; Chiu, F.T.; Zon, G. *J. Org. Chem.*, **1981**, *46*, 342. b) Jancke, H.; Engelhardt, G. *J. Organometal. Chem.*, **1977**, *134*, 21. c) Daly, W.H.; Holle, H.J. *J. Org. Chem.*, **1974**, *39*, 1597.
9. Crystallographic data for **1** have been deposited at the Cambridge Crystallographic Data Center: $C_{16}H_{27}NO_3Si$: MW= 310.1833, space group $P2_1/c$, a=11.655(3), b=13.045(4), c=14.046(6)Å, b=78.25(3)°, V=1811.8(13)Å^{-3}, Z=4, D_{meas}: 1.129 g.cm^{-3}, λ(Cu Ka)= 1.54184, T=200 °K, μ=12.0 cm^{-1}, F(000)=666, Scan mode: θ-2θ, θ=2.0 to 143.6°, final R=0.054 for 3159 reflections.

(*Received in USA* 2 *May* 1996; *revised* 8 *November* 1996; *accepted* 12 *November* 1996)