Triisopropylsilyloxycarbonyl ("Tsoc"): A New Protecting Group for 1° and 2° Amines

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The plethora of protecting groups for basic nitrogen which can be found in the literature attest to the importance of this aspect of amine chemistry.[1] While interesting and clever new choices continue to appear on a quite frequent basis,[2] the field is nonetheless essentially dominated by use of the Boc,[3] Cbz,[4] and Fmoc[5] moieties, presumably owing to their proven service. Unlike protecting group chemistry of alcohols, which is heavily weighted toward silicon, relatively few amine derivatives are available which take advantage of a chemospecific fluoride-mediated unmasking. The hydrolytic lability of silylated amines (e.g., sta-base)[6] has encouraged use of heartier carbamate (e.g., Teoc; $C(O)OCH_2CH_2SiMe_3$)[7] and sulfonamide (e.g., SES; $SO_2CH_2CH_2TMS$)[8] residues. However, these are rather expensive and require steps for precursor preparation. Moreover, while deprotection of Teoc is oftentimes effected by mild fluoride ion, a SES derivative requires CsF in refluxing CH_3CN. Noticeably absent from this repertoire is the *direct* preparation[9] of a stable protecting group analogous to Boc, Cbz, and Fmoc (i.e., a carbamate) which contains a readily available trisubstituted silicon atom attached directly to oxygen (Figure 1). In this report we describe the triisopropylsilyloxycarbonyl moiety (i.e., the Tsoc group) as a novel, easily formed, and isolable carbamate protecting group for primary and secondary amines.

Protection. *N*-Tsoc derivatives are easily fashioned by initially treating the amine dissolved in DMF or CH_2Cl_2 containing Et_3N (1−3 equiv) at −78 °C with dry CO_2 gas or with crushed dry ice. After ca. 30−60 min, the mixture containing the carbamic acid salt **1** is treated with TIPS-OTf (1 equiv).[10] Warming to room temperature followed by a standard aqueous extractive workup and chromatography on SiO_2 affords the protected material (Scheme 1).

Several illustrative examples can be found in Table 1. Yields tend to be good in most cases. Notably, hydroxyl group protection is not necessary (entries 2, 8, and 9). While less basic anilines lead to the anticipated carbamates, anilines which are further deactivated by attachment of an electron-withdrawing group (entry 7) did not go to completion. Other silyl carbamates, such as that formed using *t*-$BuPh_2SiCl$ (to give **2**, Scheme 2), can also be isolated, an alternative should a more hearty derivative bearing a UV tag be desireable. Moreover, success using this silylating agent implies that less reactive, and less expensive, chlorides may be employed.

Amino acid esters were given special attention, in particular concerning the issues of racemization and compatibility with the Boc, Cbz, and Fmoc groups. Both L-Phe-OMe and L-Leu-OMe were readily converted to their *N*-Tsoc

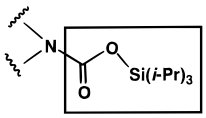
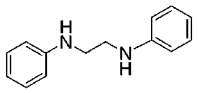
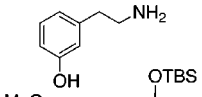
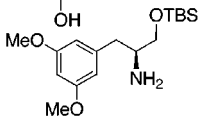
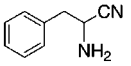
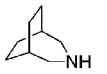
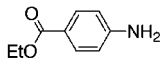
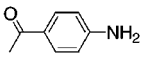
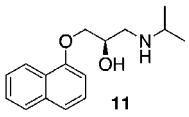
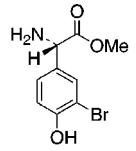
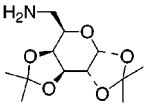


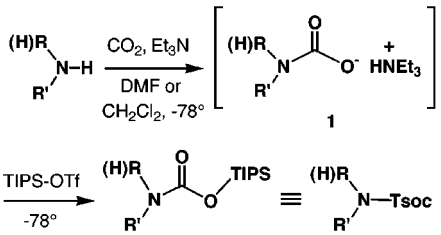
Figure 1.

Table 1. Tsoc Protection/Deprotection of Amines

Entry	Substrate	Protection[a] Yield (%)[b]	Deprotection Yield (%)[b]
1		82-87[c]	88
2		84[c]	91
3		94	81
4		94	89
5		80	94[d]
6		78	94
7		56	96
8	 **11**	87	93
9		84	91
10		92	89

[a] Using carbon dioxide gas. [b] Isolated, chromatographically purified materials. [c] Using dry ice. [d] GC yield using decane as an internal standard.

Scheme 1



(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991; 2nd ed. Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994.

(2) For recent representative reports, see: Sinha, S.; Ilankumaran, P.; Chandrasekaran, S. *Tetrahedron Lett.* **1999**, *40*, 771; Fukase, Y.; Fukase, K.; Kusumoto, S. *ibid.* **1999**, *40*, 1169.

(3) Tarbell, D. S.; Yamamoto, Y.; Pope, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **1972**, *69*, 730.

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(5) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404.

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(9) The corresponding TBS analogues have been made from *N*-Boc derivatives using TBS-OTf; cf. Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150; *J. Org. Chem.* **1990**, *55*, 870.

(10) Knausz, D.; Meszticzky, A.; Szakacs, L.; Csakvari, B. *J. Organomet. Chem.* **1983,** *256*, 11. Inesi, A.; Mucciante, V.; Rossi, L. *J. Org. Chem.* **1998**, *63*, 1337. See also: Cragg, R. H.; Lappert, M. F. *J. Chem. Soc. A* **1966**, 82. Yoder, C. H.; Komoriya, A.; Kochanowski, J. E.; Suydam, F. H. *J. Am. Chem. Soc.* **1971**, *93*, 6515.

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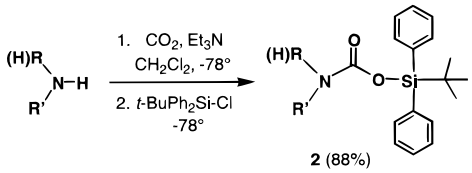
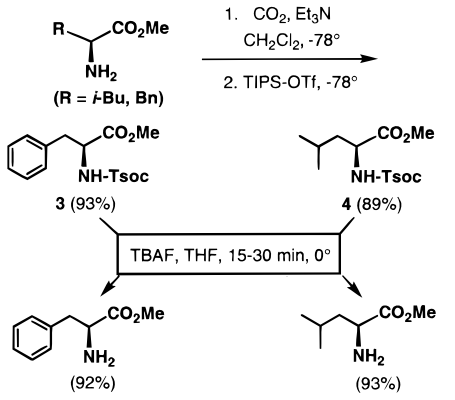
Scheme 2



Scheme 3



derivatives **3** and **4**, respectively (Scheme 3). To test the prospects for selective deprotection, derivative **3** was admixed with its corresponding Boc (**5**), Cbz (**6**), and Fmoc (**7**) analogues (1:1 in each case; Figure 2). Exposure of these mixtures to TFA, catalytic H_2 over Pd/C in EtOAc, and morpholine, respectively, under standard deprotection conditions[1] afforded the free amino acid esters in close to quantitative yields, while the *N*-Tsoc materials were recovered virtually unchanged.

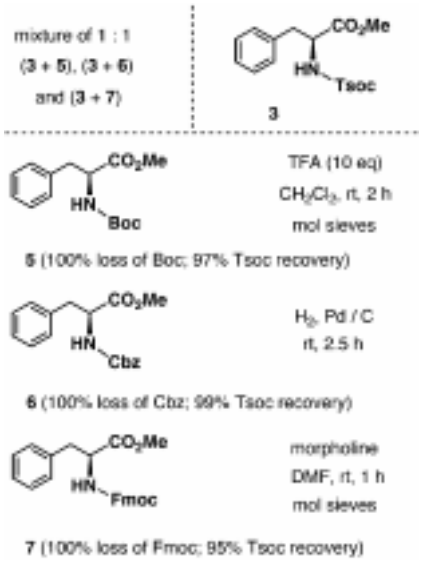
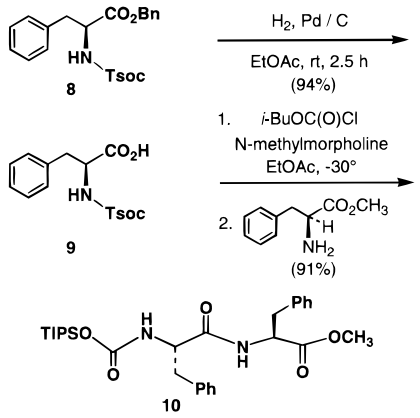


Figure 2. Compatibility studies: Tsoc vs Boc, Cbz, and Fmoc.

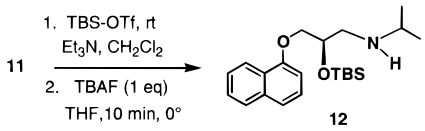
Use of the Tsoc moiety in peptide construction was also briefly examined. Thus, hydrogenation of the *N*-Tsoc benzyl ester of L-phenylalanine (**8**) to **9**, followed by coupling with L-phenylalanine methyl ester, afforded dipeptide **10** in 86% overall isolated yield (Scheme 4).

Deprotection. As anticipated, *N*-Tsoc derivatives are readily converted to the corresponding free amines under the influence of fluoride ion. Commercially available TBAF in THF at 0 °C to rt (15−30 min) is sufficient to effect desilylation. Several examples of this unmasking, likewise, are illustrated in Table 1. Application of this fluoride treatment to amino acid esters **3** and **4** (Scheme 3) afforded the

Scheme 4



Scheme 5



expected free amines. Analyses of isolated L-Phe-OMe·HCl by comparison of its optical rotation ($[\alpha]^{24}_D = 34°$ ($c = 1.5$, EtOH)) with that of an authentic sample ($[\alpha]^{24}_D = 34°$ ($c = 1.5$, EtOH)), as well as by inspection of the NMR spectrum of its derived Mosher amide, indicated that no erosion in optical purity in either the "on" or "off" step had occurred.

The facility with which Tsoc carbamates can be unraveled suggests that even silyl ethers may withstand their fluoride-induced cleavage. Such a finding would then allow for concurrent silicon-based *hydroxyl* group protection. Using the *N*-Tsoc derivative of propanolol TBS ether (**11**, in Table 1) as a test case, indeed, treatment with TBAF (1 equiv) in THF at 0 °C for 10 min cleanly gave the deprotected TBS silyl ether **12** (97%; Scheme 5).

In summary, a readily installed, fluoride-labile protecting group for basic nitrogen has been developed,[11] the deprotection of which is orthogonal to conditions normally used for Boc, Cbz, and Fmoc carbamates. Applications of the Tsoc moiety to other synthetic situations, including its potential in solid-phase syntheses, are under study and will be reported in due course.

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Supporting Information Available: General procedures, complete spectroscopic data, and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) **General procedure** (compound 4; dry ice method): An oven-dried 25 mL round-bottomed flask containing a stir bar was cooled under an argon atmosphere to room temperature and then charged with L-leucine methyl ester (80 mg, 0.61 mmol), Et_3N (0.17 mL, 0.61 mmol), and CH_2Cl_2 (6 mL). With a stream of argon over the solution, dry ice (ca. 20−50 equiv) was added. After 30 min of stirring, TIPSOTf (0.16 mL; 0.61 mmol; 1.0 equiv) was added via syringe. The solution was allowed to warm to rt and then poured into a separatory funnel containing H_2O. The organics were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ and brine and then dried over anhydrous $MgSO_4$. After filtration and solvent removal in vacuo, purification by column chromatography (95: 5 petroleum ether:EtOAc) afforded 188 mg (89%) of a white solid. Two rotomers of the carbamate are observed in a ratio of 4:1. TLC [80:20 petroleum ether:EtOAc] $R_f = 0.74$; mp 82−83 °C; IR (neat) 2943, 2867, 1747, 1660, 1530, 1020, cm^{-1}; bracketed spectral data shows the minor rotomer ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, $J = 6.6$ Hz, 6H) [0.95 (d, $J = 6.2$ Hz, 6H)], 1.08 (d, $J = 7.5$ Hz, 18H), 1.29 (m, $J = 7.9$ Hz, 3H), 1.50−1.74 (m, 2H), 3.73 (s, 3H) [3.71 (s, 3H)], 4.35 (m, $J = 5.1$, 9.2, 14.1 Hz, 1H) [4.22 (m, $J = 5.0$, 9.0, 9.4 Hz, 1H)], 5.08 (d, $J = 9.0$ Hz, 1H) [4.81 (d $J = 8.4$ Hz, 1H)]; LRCIMS *m/e* 346 (23), 302 (100), 258 (17), 230 (19), 200 (19), 157 (14), 144 (9); HRCIMS calcd for $C_{17}H_{36}NO_4Si$ $(M + H)^+$ 346.2415, found 346.2413.