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THE "BENZOSTABASE" PROTECTING GROUP FOR PRIMARY AMINES; APPLICATION TO ALIPHATIC AMINES

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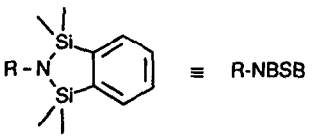
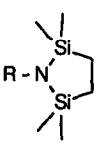
Summary: *The "benzostabase" (BSB) protecting group has been applied to primary aliphatic amines. It can be introduced* via *a dehydrogenative silylation employing an air- and moisture-stable reagent, and is appreciably more acid-stable than the related "stabase" group. BSB protection has been used in a stereoselective synthesis of amino-alcohols involving the addition of organometallic reagents to protected amino-aldehydes under "non-chelation control".*

The preceding communication reports the development of the "benzostabase" (BSB) group, as in **1**, as a new bis-silyl protecting group for primary anilines.[1] Compared to the related "stabase" group,[2] as in **2**, it showed significantly greater stability to acidic hydrolysis and to chromatography on silica gel. In this Letter, we describe the application of BSB protection to primary aliphatic amines.



≡ R-NBSB

1



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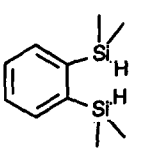
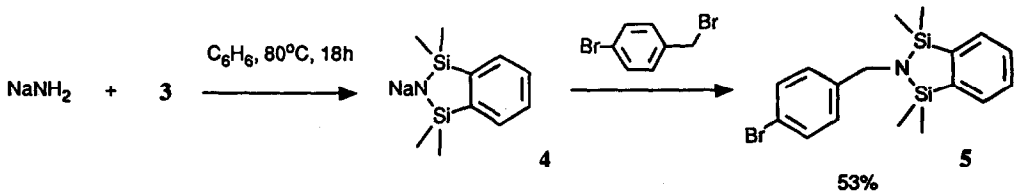


3

Treatment of primary amines RNH_2 with 1,2-bis(dimethylsilyl)benzene **3** in the presence of various catalysts gave BSB derivatives **1** *via* dehydrogenative silylation.[3] Some of the results are summarised in Table 1. Although several sets of conditions proved effective, we found $PdCl_2$ (2 mol%) in toluene under reflux to be the most convenient and versatile. When applied to esters of α-amino-acids, there was no sign of racemisation (*vide infra*) nor of carbonyl reduction. As noted previously,[1] this type of methodology has practical advantages over the displacement of chloride from chlorosilanes, as usually used to introduce stabase.[2] Unlike chlorosilanes, compounds containing Si-H are air- and moisture-stable (at least in the medium term) and can be handled without special precautions.[4]

An alternative potential synthesis of aliphatic *N*BSB derivatives is demonstrated in Scheme 1. Loss of hydrogen to give the intermediate **4** occurred without an added catalyst, presumably because of the strongly basic nature of the reaction mixture.[5] The method was only applied for the synthesis of **5**, as shown, but could presumably be generalised.[6]



Scheme 1

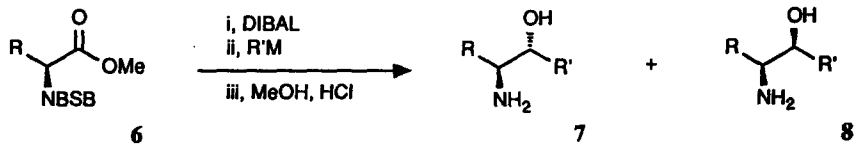
Table 1: Protection of primary aliphatic amines as BSB derivatives **1** *via* dehydrogenative silylation with **3**.

Amine	Catalyst	Conditions	Yield of **1**[a]
Ph(CH)NH$_2$	10% Pd/C	benzene, 50°C, 48h	87% (95%)
	CsF (0.75 eq.)	HMPA, 120°C, 16h	(95%)
	CsF (0.75 eq.)	DMF, 100°C, 30h	(95%)
	TBAF (0.5 eq.)	80°C, 96h (no solvent)	(90%)
Ph(CH)NH$_2$	$PdCl_2$ (0.02 eq.)	toluene, reflux, 17h	69%
R(CH)(NH$_2$)C(=O)OR'	$PdCl_2$ (0.02 eq.)	toluene, RT /reflux, 36h	82% (R = $PhCH_2$, R' = Et) 80% (R = $PhCH_2$, R' = Me) 81% (R, R' = Me)

[a] Isolated by distillation. Figures in brackets are crude yields estimated by n.m.r.

As expected, we had no difficulty in forming an organolithium reagent from **5**. Treatment with lithium in THF, followed by quenching with water, resulted in clean formation of **1** (R = CH_2Ph).[7]

To illustrate its potential, the BSB protecting group was applied to the stereoselective synthesis of amino-alcohols as shown in Scheme 2. In a one-pot procedure, esters **6** (see Table 1) were reduced with DIBAL followed by Grignard-type addition and deprotection to give mixtures of **7** and **8** as indicated. Control experiments showed that the products were enantiomerically pure, confirming also the optical purity of **6**. The major diastereomers **7** correspond to non-chelation control, in line with the results obtained using the *N,N*-dibenzyl protecting group.[8] Relative to the latter, the simple hydrolytic removal of BSB constitutes a significant advantage; *N,N*-dibenzyl requires H_2/Pd for deprotection, conditions which also lead to undesired hydrogenation of double bonds which may be present in the target molecule.



6 7 8

R	R'	M	7 : 8	Crude yield (pure product)
CH_2Ph	Ph	MgBr	85 : 15	75% (55%)
CH_2Ph	Ph	Li	>95 : <5	68% (53%)
CH_2Ph	CH_2=CH-	MgBr	>95 : <5	55% (40%)
CH_3	Ph	MgBr	>95 : <5	73% (60%)

Scheme 2

Having found that aromatic *N*BSB derivatives were sufficiently stable for routine flash chromatography,[1] we had hoped that this would also be true of the aliphatic analogues. Unfortunately this did not prove to be the case; although **1** (R= $PhCH_2$) was unchanged by rapid passage through silica gel when dissolved in ether, the use of less polar eluants resulted in decomposition. A measure of the acid-stability of BSB and stabase derivatives was given by an experiment in which **1** (R = $PhCH_2$) and its stabase analogue **2** (R = $PhCH_2$) were dissolved in hexane/ether (2:1) and stirred rapidly with pH 3 aqueous phthalate buffer. Analysis by g.c. showed that both compounds decomposed with roughly first-order kinetics, the half-lives being *ca.* 30 and 6 min respectively. It appears therefore that, as expected, aliphatic *N*BSB derivatives should be less vulnerable to acid hydrolysis than their stabase analogues. However, it is not clear why this difference (a factor of 6) should be so much smaller than that for the corresponding derivatives of aromatic amines (a factor of 36[1]).

In conclusion, we feel that the protection of aliphatic primary amines as BSB derivatives should prove a useful addition to synthetic methodology. This new protecting group is complementary to stabase in that it can be introduced *via* a dehydrogenative silylation and has additional acid-stability which may be valuable in some circumstances.

General procedures:

BSB derivatives of esters of α-amino acids. The α-amino acid ester (see Table 1) and 1,2-bis(dimethylsilyl)benzene **3** (1.24 eq.) are dissolved in dry toluene and added to $PdCl_2$ (2 mol%). Effervescence occurs immediately, and the mixture turns black. The mixture is stirred at room temperature for 24 h then heated under reflux until conversion is complete (the progress of the reaction can be followed by g.c.). If necessary, further portions of **3** and $PdCl_2$ are added. After cooling to room temperature hexane is added and the mixture is washed with pH 7 phosphate buffer. The organic phase is dried (Na_2SO_4), solvent is removed under reduced pressure and the product isolated by vacuum distillation.

Amino-alcohols 7 and 8. The solution of an ester **6** (1 mmol) in dry toluene (25 ml) is treated with DIBAL (1 mmol, 20% solution in hexane) at -78°C. After stirring at -78°C for 2 h, 4 mmol of RMgX or RLi in ether are added, and the mixture is allowed to reach room temperature within 10 h. Water (2 ml) is added, the precipitated hydroxides are removed by decantation and most of the solvents are removed. The residue is taken up in methanol (5 ml) and treated with HCl aq. (1M, 20 ml). The solution is extracted with ether (3 x 10 ml), treated with K_2CO_3 (until pH 9) and extracted again with ethyl acetate. The combined extracts are dried over $MgSO_4$ and the crude product chromatographed with EtOAc/CH_3OH (15:1) containing NH_3 (6%) as eluant.

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References and Footnotes

1. R.P. Bonar-Law, A.P. Davis, and B.J. Dorgan, accompanying communication.
2. S. Djuric, J.Venit, and P. Magnus, *Tetrahedron Lett.*, 1981, **22**, 1787.
3. An alternative, but low-yielding, synthesis of **1** involves the bis-hydrosilylation of nitriles; R.J.P. Corriu, J.J.E. Moreau, and M. Pataud-Sat, *J. Organometal Chem.*, 1982, **228**, 301.
4. In one sample of **3** which was stored for more than 6 months in a loosely stoppered container, minimal decomposition was observed (g.c. analysis).
5. cf. the preparation of potassium hexaethyldisilazide from potassium amide and triethylsilane; C.A. Kraus and W.K. Nelson, *J. Am. Chem. Soc.*, 1934, **56**, 195.
6. $(Me_3Si)_2NNa$ has been used similarly for the synthesis of a variety of bis(trimethylsilyl)-protected primary amines; H.J. Bestmann and G. Wölfel, *Chem. Ber.*, 1984, **117**, 1250.
7. cf. the earlier use of the organolithium reagent derived from $(Me_3Si)_2NCH_2$-*p*-C_6H_4Br; R.P. Bonar-Law and A.P. Davis, *J. Chem. Soc., Chem. Commun.*, 1989, 1050.
8. M.T. Reetz, M.W. Drewes, and A. Schmitz, *Angew. Chem.*, 1987, **99**, 1186; *Angew. Chem. Int. Ed. Engl.*, 1987, **26**, 1141.

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