## THE "BENZOSTABASE" PROTECTING GROUP FOR PRIMARY AMINES; APPLICATION TO AROMATIC AMINES

R.P. Bonar-Law, A.P. Davis,\* and B.J. Dorgan Department of Chemistry, Trinity College, Dublin 2, Ireland

Summary: Anilines can be protected as "benzostabase" (BSB) derivatives by dehydrogenative silylation with 1,2-bis(dimethylsilyl)benzene. The derivatives have useful acid stability and are stable to chromatography on silica gel. It is demonstrated that the BSB group can be carried through a number of C-C bond-forming reactions.

During recent work on the synthesis of host molecules for biomimetic chemistry,<sup>1</sup> we developed a need for amino-substituted organometallic synthons of the general form 1. Surveying the options for protecting groups P, we realised that, for our purpose at least, few were satisfactory and none was ideal. Although a great many protecting groups are available for primary amines,<sup>2</sup> there are only a handful which will not quench or otherwise react with strongly basic reagents. Of these, some are so stable that removal will often cause problems (e.g. *N*,*N*-dibenzyl,<sup>2,3</sup>, *N*,*N*-diallyl,<sup>4</sup> and the heterocyclic system in 2<sup>5</sup>) while others are rather labile and will only serve for temporary protection (e.g. *N*,*N*-bis-trimethylsilyl<sup>6,1</sup> and the "stabase" group, as in 3<sup>7</sup>). Although the last of these has been widely used, it is actually quite labile to acidic hydrolysis and has limited stablity to silica gel (see below, and accompanying communication).<sup>8</sup> It seemed that a bis-silyl protecting group for -NH<sub>2</sub> which was less vulnerable to acid than stabase, and in particular was stable to flash chromatography,<sup>9</sup> would be a valuable addition to synthetic methodology. Reasoning that replacing alkyl by aryl substituents on Si should increase acid stability,<sup>10</sup> and that increasing the rigidity of the 5-membered ring in stabase might increase stability in general, we investigated "benzostabase" (BSB, as in 4) as a protecting group for primary amines and now report that, for the protection of anilines, it does indeed come close to fulfilling our aim. Results involving aliphatic amines are presented in the following communication.



Our reagent for the introduction of BSB is 1,2-bis(dimethylsilyl)benzene 5, readily synthesized from 1,2-dibromobenzene, dimethylchlorosilane and magnesium.<sup>11</sup> As shown in Scheme 1 and Table 1, treatment of various anilines 6 with 5 and either  $(Ph_3P)_3RhCl$  (neat or in toluene) or CsF (in HMPA), at elevated temperatures, gave the corresponding BSB derivatives 7.<sup>12</sup> In general the protected anilines were stable, crystalline solids, although some decolourised over a period of days unless stored under argon. A useful feature of this procedure is that reagent 5 is air and moisture-stable, and thus far easier to handle than the dichloride 8 generally used to introduce stabase (see below). There is precedent for the use of transition

metal catalysts,<sup>13</sup> including  $(Ph_3P)_3RhCl$ ,<sup>13a</sup> in the dehydrogenative silvlation of amines, but as far as we know the use of fluoride ion has not previously been reported.<sup>14</sup>



Table 1: Protected anilines 7 synthesized according to Scheme 1

Compound No.	Ar	Catalyst (mol%)	Solvent	Reaction Time, h	Reaction Temp, °C	Yield, <sup>a</sup> %
<b>7</b> a	Ph	(PPh <sub>3</sub> ) <sub>3</sub> RhCl (0.4)	-	14	80	72 (95)
7b	p-Br-C <sub>6</sub> H <sub>4</sub> -	(PPh3)3RhCl (0.2)	toluene	25	120	77
7b	p-Br-C <sub>6</sub> H <sub>4</sub> -	CsF (90)	HMPA	3.5	120	92 (100)
7c	m-Br-C <sub>6</sub> H <sub>4</sub> -	CsF (30)	HMPA	4	120	71
7d	o-Br-C <sub>6</sub> H <sub>4</sub> -	CsF (130)	HMPA	20	120	75
7e	o-Br-C <sub>6</sub> H <sub>4</sub> -	CsF (110)	HMPA	20	120	85

\* Isolated by recrystallisation. Figures in brackets are crude yields estimated by n.m.r.

For comparative purposes, we also wished to synthesize the stabase derivative 10. The original procedure for this compound required that aniline 6 (Ar = p-Br-C<sub>6</sub>H<sub>4</sub>) be treated with 2 equivalents of butyllithium before reaction with dichloride 8, while a newer method involved the preparation of a silazane as a reagent.<sup>15</sup> Both these silylating agents are moisture-sensitive, and as neither procedure seemed convenient we attempted a dehydrogenative variant. As shown in Scheme 2, reduction of 8 with LiAlH<sub>4</sub> gave 9,<sup>16</sup> which reacted cleanly with the aniline under F<sup>-</sup> catalysis to give 10. Although this method has been neither generalised nor optimised, it should prove a useful alternative to the earlier procedures.



6722

Scheme 2





BSB derivative 7b and stabase derivative 10 were used to test the stability of the two protecting groups to acid hydrolysis and to silica gel. In general, the stability of Si-O and Si-N derivatives to silica gel chromatography is strongly dependant on the polarity of the eluant. Thus, in this case, both the stabase and BSB derivatives ran cleanly on t.l.c. with hexane/ether (1:1) as eluant. However, on decreasing the polarity to hexane/ether (5:1), the stabase derivative showed significant decomposition (detectable as streaking) while 7b was still stable. Not until the hexane/ether ratio was increased to 40:1 did we observe (very slight)

decomposition of the BSB derivative. Aiming for a more quantitative assessment of the relative acid stabilities, we dissolved 10 and 7b in hexane/ether (2:1) and stirred rapidly with aqueous HCl (1.124M), following the decomposition of each by g.c.. Both derivatives decayed with roughly lst-order kinetics, t<sub>1/2</sub> for 10 and 7b being ca. 20 sec and 12 min. respectively. 7b in hexane/ether (1:1) was completely stable to washing with ice cold  $H_3PO_4$  aq. (1M) but was partially decomposed by ice cold HCl aq. (2M).

Finally, in order to demonstrate the synthetic utility of BSB protection for primary anilines, we carried out various simple synthetic sequences as outlined in Scheme 3. It should be noted that three of the BSB derivatives (12, 13, and 14) were isolated by flash chromatography and that, as well as acid hydrolysis,  $(CF_3CO)_2O$  or TBAF may be used for deprotection.<sup>17</sup>

Acknowledgement: We are grateful to EOLAS (the Irish science and technology agency) and the SCIENCE programme of the European Community for support of this work.

## **References and Footnotes**

- R.P. Bonar-Law and A.P. Davis, J. Chem. Soc., Chem. Commun., 1989, 1050. 1.
- T.W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York, 1981. 2.
- L. Velluz, G. Amiard, and R. Heymes, Bull. Soc. Chim. Fr., 1954, 1012; M.T. Reetz, M.W. Drewes, 3. and A. Schmitz, Angew. Chem., 1987, 99, 1186; Angew. Chem. Int. Ed. Engl., 1987, 26, 1141. B.C. Laguzza and B. Ganem, Tetrahedron Lett., 1981, 22, 1483.
- 4.
- 5. S.P. Bruckelman, S.E. Leach, G.D. Meakins, and M.D. Tirel, J. Chem. Soc., Perkin Trans. 1, 1984, 2801.
- 6. D.R.M. Walton, J. Chem. Soc. (C), 1966, 1766; W. Broser and W. Harrer, Angew. Chem., 1965, 77, 1139; Angew. Chem. Int. Ed. Engl., 1965, 4, 1081.
- S. Djuric, J. Venit, and P. Magnus, Tetrahedron Lett., 1981, 22, 1787. 7.
- Chromatography is reported to be possible on silica gel saturated with ammonia; T. Högberg, Acta. 8. Pharm. Suecica, 1986, 23, 414.
- 9. Overman et al. have reported that R-NH-SiBu<sup>1</sup>Ph<sub>2</sub> is stable to chromatography on silica gel. However, these derivatives still contain one N-H, which will presumably quench a strongly basic reagent. See L.E. Overman, M.E. Okazaki, and P. Mishra, Tetrahedron Lett., 1986, 27, 4391.
- 10. cf. Ref 9 and the mechanistic work of Eaborn and co-workers on N-trialkylsilylaniline hydrolysis; A.R. Bassindale, C. Eaborn, and D.R.M. Walton, J. Organometal. Chem., 1970, 25, 57; ibid, 1972, 43, 265. W.Fink, Helv. Chim. Acta, 1974, 57, 1020.
- 11.
- 12. General procedures; (a) The aniline (3 mmol) and silane 5 (3.8 mmol) in dry HMPA (1 ml) are added to anhydrous CsF and the suspension stirred at 120<sup>O</sup>C under Ar (see Table 1). After cooling, the mixture is dissolved in hexane/ether (1:1, 20 ml), washed with pH 7 phosphate buffer (0.4M, 2 x 4 ml), and dried ( $K_2CO_3$ ). Evaporation of solvent followed by recrystallisation gives 7. (b) As for (a) except that toluene (2.5 ml) is used as solvent and (Ph<sub>3</sub>P)<sub>3</sub>RhCl (5 mg, 5.5 µmol) as catalyst. For example (a) J.D. Citron and L.H. Sommer, J. Org. Chem., 1967, 32, 2470; (b) H. Kono. I. Ojima,
- 13. M. Matsumoto, and Y. Nagai, Org. Prep. Proced. Int., 1973, 5, 135.
- Fluoride-catalysed dehydrogenative silylation of alcohols, however, is well-established; see, for 14. example, R.J.P. Corriu, R. Pertz, and C. Reye, Tetrahedron, 1983, 39, 999.
- 15. T.L. Guggenheim, Tetrahedron Lett., 1984, 25, 1253.
- V.F. Mironov, V.P. Kozyukov, and V.D. Sheludyakov, Dokl. Akad. Nauk. SSSR, 1968, 179, 600; Chem. 16. Abstr., 1968, 69, 87092w.
- 17. Partial deprotection also occurred during the hydrogenation of 14, possibly due to adventitious water.

(Received in UK 29 August 1990)