Pergamon

Tetrahedron Letters, Vol. 38, No. 15, pp. 2617-2620, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00443-7

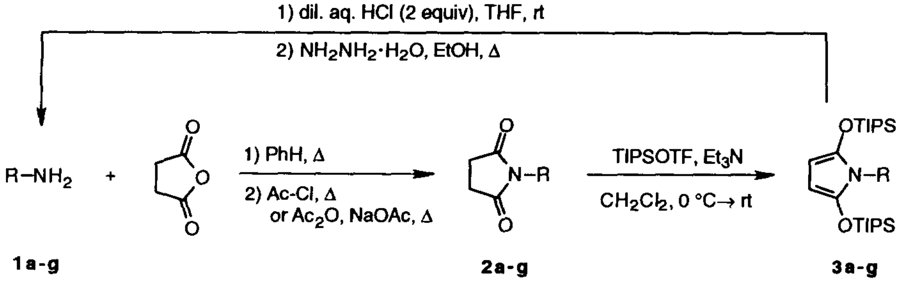
DIPROTECTION OF PRIMARY AMINES AS *N*-SUBSTITUTED-2,5-BIS[(TRIISOPROPYLSILYL)OXY]PYRROLES (BIPSOP)

Stephen F. Martin* and Chris Limberakis
Department of Chemistry and Biochemistry, University of Texas at Austin
Austin, Texas 78712 USA

Abstract. Primary amines are diprotected as their 2,5-bis[(triisopropylsilyl)oxy]pyrrole derivatives (BIPSOP). This protecting group is stable to strong bases such as organolithiums and alkoxides at 0 °C and to temperatures up to about 150 °C. Removal may be accomplished by a mild two step sequence. © 1997 Elsevier Science Ltd.

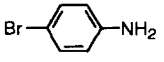
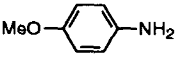
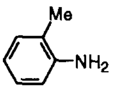
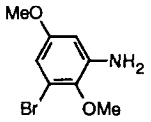
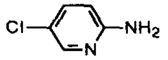
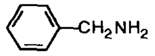
Problems associated with the orthogonal protection of multiple functional groups are commonly encountered during the synthesis of complex natural products.[1] In this context the repertoire of available groups for the diprotection of primary amines is particularly limited, although this function has been protected using 2,5-dimethylpyrrole,[2] stabase,[3] benzostabase,[4] triazones,[5] *N*,*N*-bistrimethylsilyl,[6] *N*,*N*-diallyl,[7] and *N*,*N*-dibenzyl[8] arrays. During the course of a program directed toward the asymmetric synthesis of the ansamycin antibiotic herbimycin A, we needed a diprotecting group for a primary aryl amine that would be stable to organolithium reagents but that could also be removed under mild conditions in the presence of acid labile functionality. Examination of known protecting groups revealed that none was well-suited to the task as they either required conditions for their removal that were incompatible with other functionality or could not be installed in satisfactory yield. It was thus necessary to design a novel means of masking a primary amine. We have recently discovered that primary amines may be readily diprotected as their 2,5-bis[(triisopropylsilyl)oxy]pyrrole (BIPSOP) derivatives and that deprotection may be achieved under mild conditions. The general protocol is outlined in Scheme 1.

Scheme 1



To illustrate the efficacy of the 2,5-bis[(triisopropylsilyl)oxy]pyrrole (BIPSOP) moiety as a protecting group for primary amines, the series of amines **1a**-**1g** was converted into the *N*-substituted pyrroles **3a**-**3g** in about 68-87% overall yield (Table 1).[9] The first step involved transformation of the amines **1a-g** into the succinimides **2a**-**2g** by reaction with succinic anhydride followed by cyclodehydration of the intermediate amide acids with acetyl chloride[10] or acetic anhydride/ sodium acetate.[11] Subsequent reaction of **2a**-**2g** with triisopropylsilyl triflate in the presence of Et_3N gave the desired pyrroles **3a-g**. Although 2,5-bis[(trimethylsilyl)oxy]pyrroles are known,[12] they are rather labile, so the triisopropylsilyl group was selected to enhance the stability of the protecting group toward the action of alkyllithium reagents and acid. The BIPSOP protecting group was removed in two facile steps commencing with the hydrolysis of the triisopropylsilyl groups and cleavage of the resulting imide with hydrazine in refluxing ethanol.[13] The imide may also be removed by reduction with $NaBH_4$ in *i*-PrOH/H_2O to give an amido alcohol that is heated in refluxing *i*-PrOH/H_2O containing AcOH (pH 4-5).[14]

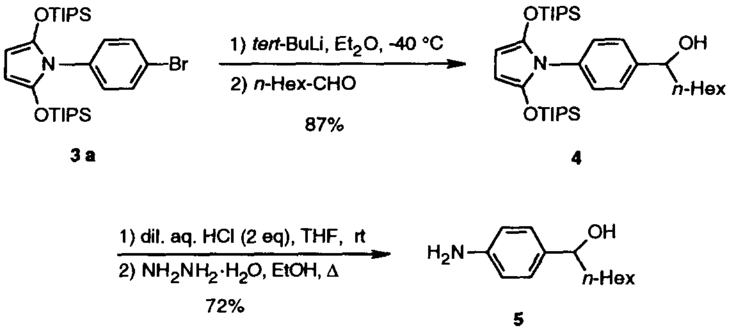
Table 1. Protection of Primary Amines.

Amine **1a-g**	% Yield of Imides **2a-g**	% Yield of Pyrroles **3a-g**	% Overall Yield
 **1a**	92[a]	90	83
 **1b**	95[a]	90	86
 **1c**	94[a]	83	78
 **1d**	94[a]	93	87
 **1e**	93[a]	88	82
 **1f**	84[a]	88	74
TBDPSO-$(CH_2)_5NH_2$ **1g**	75[b]	90	68

[a] Acetyl chloride used for imide formation. [b] Acetic anhydride/sodium acetate used for imide formation.

To illustrate the synthetic utility of this protecting group, **3a** was treated with 2 eq of *tert*-BuLi at -40 °C to effect the metal-halogen exchange, and the intermediate aryllithium reagent was trapped with *n*-heptanal to give **4** in 87% yield. The BIPSOP protected **4** could be purified on a neutral alumina column eluting with a hexanes/EtOAc/Et_3N (80:1:1) mixture. The protecting group was removed in 72% yield by sequential reaction of **4** with dilute acid followed by refluxing the succinimide thus obtained in ethanol containing hydrazine to deliver the aniline **5**.

Scheme 2



We have shown that a series of primary amines may be diprotected as *N*-substituted-2,5-bis[(triisopropylsilyl)oxy]pyrrole (BIPSOP) derivatives. We have found that the bis[(triisopropylsilyl)oxy]pyrrole ring is stable to strong bases such as organolithium reagents (-78 °C to rt), heating at temperatures up to 150 °C, and chromatography on neutral alumina. BIPSOP derivatives may also be stored in a freezer under Ar for several weeks. Removal of the BIPSOP protecting group may then be effected under mild conditions that are compatible with acid-sensitive functionality or protecting groups. As such, the BIPSOP moiety exhibits some definite advantages over other groups that have been used for the diprotection of primary amines.

Acknowledgments. We thank the National Institutes of Health and the Robert A. Welch Foundation for their generous financial support.

REFERENCES AND NOTES

1. For reviews, see: (a) Greene, T. W. Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley-Interscience: New York, 1991, p. 309-405. (b) Kocienski, P. *Protecting Groups*; Georg Thieme Verlag: Stuttgart, 1994, p 185-243.
2. Bruekelman, S. P.; Leach, S. E.; Meakins, G. D.; Tirel, M. D. *J. Chem. Soc., Perkin Trans 1* **1984**, 2801.
3. (a) Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787. (b) Guggenheim, T. L. *Tetrahedron Lett.* **1984**, *25*, 1253.
4. (a) Bonar-Law, R. P.; Davis, A. P.; Dorgan, B. J. *Tetrahedron Lett.* **1990**, *31*, 6721. (b) Bonar-Law, R. P.; Davis, A. P.; Dorgan, B. J. *Tetrahedron Lett.* **1990**, *31*, 6725.
5. (a) Knapp, S.; Hale, J. J.; Bastos, M.; Gibson, F. S. *Tetrahedron Lett.* **1990**, *31*, 2109. (b) Knapp, S.; Hale, J. J.; Bastos, M.; Molina, A.; Chen, K. Y. *J. Org. Chem.* **1992**, *57*, 6239.
6. (a) Walton, D. R. M. *J. Chem Soc. (C)* **1966**, 1706. (b) Broser, W.; Harrer, W. *Angew Chem., Int. Ed. Engl.* **1965**, *4*, 1081. (c) Bonar-Law, R. P.; Davis, A. P. *J. Chem. Soc., Chem. Comm.* **1989**, 1050.

7. Laguzza, B. C.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 1483.
8. Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew Chem., Int. Ed. Engl.* **1987**, *26*, 1141.
9. **General Procedure for Protection/Deprotection of Primary Amines.**

   Protection: A solution of the amine **1a** (671 mg, 3.90 mmol) and succinic anhydride (411 mg, 4.10 mmol) in anhydrous benzene (8 mL) was heated under reflux for 1–2 h. (In general the progress of this reaction was followed by TLC.) After cooling to rt, the solvent was removed under reduced pressure, and freshly distilled acetyl chloride (11 mL) was added. The mixture was heated at reflux for 1 h during which time the solution became homogeneous, and the reaction was judged complete by TLC. The excess acetyl chloride was removed at atmospheric pressure, and the resulting pale yellow solid was washed with Et_2O (3 x 2 mL) to give 909 mg (92%) of imide **2a** as a white solid. A mixture of the imide **2a** (493 mg, 1.94 mmol), TIPSOTF (1.15 mL, 4.27 mmol), and Et_3N (864 μL, 6.21 mmol) in anhydrous CH_2Cl_2 (8 mL) was stirred at rt for 2 h. The solution was concentrated under reduced pressure and hexane (20 mL) was added. The mixture was cooled to 0 °C, and cold saturated aqueous $NaHCO_3$ was added slowly. The layers were separated, and the organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow liquid. The TBDPSOH was removed by heating in a Kügelrohr apparatus (130 °C bath temp, 0.1 Torr) to give 991 mg (90%) of **3a**.

   Deprotection A solution of the triisopropylsilyloxypyrrole **3a** (309 mg, 0.546 mmol) in THF (7 mL) containing 0.5 *N* aqueous HCl (2.18 mL, 1.09 mmol) was stirred for 10 min at rt. Saturated aqueous NaCl (4 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure, and the crude succinimide was washed with hexanes (2 x 10 mL). A solution of this succinimide in EtOH (3 mL) containing hydrazine monohydrate (133 μL, 2.74 mmol) was heated at reflux for 20 h. The solvent was removed under reduced pressure. The residue was triturated with Et_2O (3 x 10 mL), and the combined ethereal supernatants were concentrated under reduced pressure to give 77 mg (82%) of *p*-bromoaniline.
10. Cotter, R. J.; Sauers, C. K.; Whelan, J. M. *J. Org. Chem.* **1961**, *26*, 10.
11. (a) Cava, M. P.; Deana, A. A.; Muth, K.; Mitchell, M. J. *Org. Synth. Coll. Vol. V* **1973**, 944. (b) Pavia, M. R.; Moos, W. H.; Hershenson, F. M. *J. Org. Chem.* **1990**, *55*, 560. (c) Smith, A. L.; Hwang, C.-K.; Pitsinos, E.; Scarlato, G. R.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1992**, *114*, 3134.
12. (a) Frick, U.; Simchen, G. *Liebigs Ann. Chem.* **1987**, 839. (b) Kates, M. J.; Schauble, J. H. *J. Org. Chem.* **1995**, *60*, 6676.
13. (a) Wasserman, H. H.; Robinson, R. P.; Carter, C. G. *J. Am. Chem. Soc.* **1983**, *105*, 1697. (b) Makurina, V. I.; Chuvurin, A. V.; Karnozhitskaya, T. M.; Chernykh, V. P. *J. Org. Chem. USSR* **1990**, *26*, 1978.
14. (a) Osby, J. O.; Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 2093. (b) Dasgupta, F.; Garegg, P. J. *J. Carbohydr. Chem.* **1988**, *7*, 701.

(*Received in USA* 5 *February* 1997; *revised* 25 *February* 1997; *accepted* 26 *February* 1997)