Pergamon

Tetrahedron Letters 40 (1999) 5333–5336

TETRAHEDRON LETTERS

Diphenylsilyldiethylene- (DPSide-) Group: A New Primary Amine Protection

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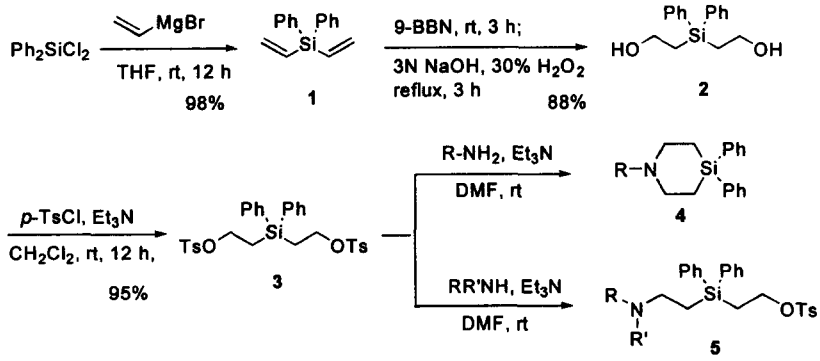
Received 9 April 1999; revised 7 May 1999; accepted 14 May 1999

Abstract: Diphenylsilydiethylene- (DPSide-) group has been developed as a new primary amine protecting group. The new protecting group exhibits novel orthogonality against other commonly used amine-protecting groups and excellent chemoselectivity for unbranched α-amino acid esters. Removal of this protecting group was effected under mild fluoride-based cleavage conditions.

Amino groups abound in molecules possessing biological activities such as alkaloids, peptides and nucleotides. Proper choice of protecting groups for the amino functionality plays a critical role in the manipulation and synthesis of such compounds. Several widely employed amine-protecting groups include benzyl, *tert*-butyloxycarbonyl- (*t*-Boc-), benzyloxycarbonyl- (Cbz-), 9-fluorenylmethyloxycarbonyl- (Fmoc-), trimethylsilylethyloxycarbonyl- (Teoc-), and phthalimide (-NPhth) groups.[1] It is of a paramount importance for these protecting groups to exhibit orthogonality[2] against each other. From our continuing efforts in the synthesis of unnatural amino acid analogues, we have been looking for primary amine protecting groups which do not leave an acidic proton on nitrogen and resist acidic, basic and hydrogenolytic conditions and found that protecting groups that meet these requirements are rare.[1,3] In this note, we wish to report a new silicon-based protecting group derived from bis[2-(*p*-toluenesulfonyloxy)ethyl]diphenylsilane (**3**), which not only satisfies the above criteria but exhibits novel chemoselectivity towards unbranched α-amino esters.



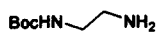
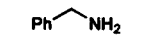
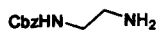
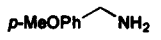
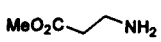
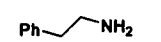
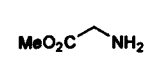
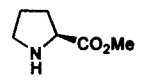
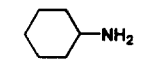
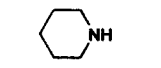
Scheme 1. Preparation and reactions of the silyl protecting agent 3

Preparation of the reagent **3** and subsequent protection reactions of amines are shown in Scheme 1. Reaction of dichlorodiphenylsilane with vinylmagnesium bromide provided diphenyldivinylsilane (**1**).[4] Hydroboration[5] of compound **1** using 9-borabicyclo[2.2.1]nonane (9-BBN) and *p*-toluenesulfonylation of

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00970-3

subsequent diol **2**[6] furnished the ditosylate **3**[7] in overall 82% yield from dichlorodiphenylsilane. In order to investigate the utility of **3** as a novel amine-protecting agent, we have carried out reactions of various primary- and secondary amines with **3**. As summarized in Table 1, all the primary amines examined, when treated with **3** and triethylamine in DMF (1.0~0.5 M) at room temperature for 12 to 24 h, furnished the desired diphenylsilyldiethylene-protected amines (**4**) in good to excellent yields (entries 1-8).[8] In the case of secondary amines (entries 9 and 10), however, the major products were tertiary amine derivatives (**5**) having only one of the two *p*-toluenesulfonyl groups displaced by the amine. In addition, a small quantity (less than 5%) of a quaternary ammonium salt was formed as a by-product. Though tertiary amines such as triethylamine and diisopropylethylamine did not appear to participate in the reaction with the silyl reagent, reactions at higher temperature (>50 °C) resulted in the decomposition of the silyl reagent.

Table 1. Results of DPSide-protection of amines with 3.[9]

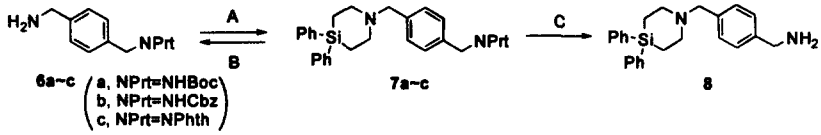
Entry	Amine	Time (h)	Yield (%)[a]	Entry	Amine	Time (h)	Yield (%)[a]
1		12	91	6		12	96
2		12	94	7		24	92
3		24	90	8		18	85
4		24	92	9		24	73[b]
5		12	90	10		24	50[b]

[a]Isolated yields of compound **4** after silica gel column chromatography. [b]Yield of compound **5**.

With the successful protection of primary amines using **3** in hand, we decided to investigate in detail the orthogonality of the DPSide- group with other commonly used amine protecting groups (Table 2). For this purpose, we have prepared singly-protected *p*-xylenediamines having Boc-, Cbz-, and Phthalimide groups (**6a**, **6b**, and **6c**, respectively).[10] These derivatives were converted to orthogonally protected diamine derivatives (**7a-c**) with **3** in high yields following the reaction conditions described above (entries 1-3, Table 2). Generally cleavage of silyl- and silylethyl-[11] protecting groups is accomplished by treatment with tetrabutylammonium flouride (TBAF), hydrogen fluoride or cesium fluoride in THF, DMF or CH_3CN.[12] In the case of the 4-silapiperidines **4**, employment of either TBAF or CsF alone has given only a partial success in the deprotection reactions. However, *a combination of TBAF and CsF (1:1) in DMF or THF* has smoothly effected desilylation furnishing the desired free amines in high yields. Using these reaction conditions, deprotection of silyl groups was completed in the presence of Boc-, Cbz-, or phthalimde groups (entries 4-6, Table 2) at rt for 2 h to furnish the desired monoamine derivatives (**6a-6c**, respectively). Finally, the Boc-, Cbz-, and phthalimide protecting groups were removed in the presence of the DPSide- protecting group to compound **8** in excellent yields according to the conventional methods[1] (entries 7-9, Table 2).

Having identified the compatibility of the DPSide- group with other common amine-protecting roups, we turned our attention to the relative reactivity of the silyl protecting reagent **3** towards amino groups under

Table 2. Orthogonal protection and deprotection reactions involving the silyl protecting reagent 3 in the presence of Boc, Cbz, or phthalic groups.[9]



Entry	Starting material	Reaction Path	Reaction conditions	Product	% Yields[a]
1	6a			7a	85
2	6b	A	3, Et_3N, DMF, rt, 24 h	7b	89
3	6c			7c	80
4	7a			6a	87[b]
5	7b	B	TBAF-CsF (1:1) DMF, rt, 2 h	6b	92[b]
6	7c			6c	80
7	7a		TFA, CH_2Cl_2, rt, 2 h	8	95
8	7b	C	Pd/C, H_2, EtOAc, rt 12 h	8	98
9	7c		NH_2NH_2, MeOH, rt, 2 h	8	89

[a]Isolated yields after silica gel chromatography. [b]Two sets of column chromatorgraphies on silica gel (mesh 70-230) were required eluting first with ethyl acetate then with acetone to obtain products free from TBAF.

different steric environments. Since α-amino acid derivatives are frequently encountered in the synthesis of peptides and peptidomimetics, we were curious to see whether the reactivity of the sily reagent **3** could be differentiated with representative α-amino acid derivatives having different steric requirements. As outlined in Table 3, reactions of **3** with amino esters having no branching at α-position such as glycine benzyl ester and β-alanine methyl ester proceeded smoothly (92 and 89%, respectively, entries 1 and 2). However, in the case of α-branched α-amino esters such as alanine methyl ester and benzyl esters of phenylalanine and valine, the reactions were very slow and mostly unchanged starting materials were recovered after 24 h (entries 3-5, Table 3, respectively). In a competition experiment, where a mixture of phenylalanine benzyl ester and glycine methyl ester was subjected to reactions with 1.0 equiv of **3**, most of the glycine ester was converted to the protected product (82%), whereas only a small amount (<5%) of the protected form was obtained in the case of phenylalanine benzyl ester (entry 6, Table 3).

In summary, we have devised diphenylsilyldiethylene- (DPSide-) group as a new protection for primary amine derivatives. The new protecting group exhibited resistance to acidic, basic or hydrogenolytic conditions required for the deprotection of *t*-Boc-, Phth-, and Cbz- groups, respectively, thus showing excellent orthogonality against these common amine-protecting groups. The new reagent also exhibited good chemoselectivity for the protection of unbranched α-amino esters against branched ones. Further study on the scope and synthetic application of the new protecting group is in progress.

Acknowledgment: The authors wish to thank the Ministry of Health and Welfare of the Republic of Korea for financial support (HMP-96-D-1-1015) and Dr. Bongyong Lee at Yuhan Corp. for helpful discussion.

Table 3. Chemoselectivity in the reactions of reagent 3 with various amino esters.[9]

Amino ester $\xrightarrow[\text{DMF, rt, 24h}]{\text{3, } Et_3N}$ *N*-Protected amino ester

Entry	Amino ester	*N*-Protected amino ester	Recovered amino ester
1	Gly-OMe	92%	–[a]
2	β-Ala-OMe	89%	–[a]
3	Ala-OBn	3.8%	>90%
4	Phe-OBn	5%	>90%
5	Val-OBn	<1%	>90%
6	Phe-OBn + Gly-OMe	P-Gly-OMe (82%) P-Phe-OBn (<5%)	

[a]Starting amino esters were not detected upon HPLC analysis.

References and notes

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2. For the definition of "orthognoality" in protecting groups, see reference 1b, pp. 2-3.
3. For cyclic disilazane, see: Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787.
4. For a preparation through a slightly different route, see: Buell, G. R.; Corriu, R.; Guerin, C.; Spialter, L. *J. Am. Chem. Soc.* **1970**, *92*, 7424.
5. a) Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765; b) Soderquist, J. A.; Brown, H. C. *J. Org. Chem.* **1980**, *45*, 3571.
6. Compound **2**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55 (m, 4H), 7.35 (m, 6H), 4.80 (t, 4H, J_{ab}= 7.7 Hz), 2.90 (s, 2H), 1.55 (t, 4H, J_{ab}=7.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 134.99, 134.68, 129.23, 127.99, 59.32, 18.05.
7. Compound **3**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, 4H, J_{ab}=8.3 Hz), 7.38 (m, 10H), 7.31 (d, 4H, J_{ab}=8.31 Hz), 4.10 (t, 4H, J_{ab}=8.4 Hz), 2.42 (s, 6H), 1.57 (t, 4H, J_{ab}=8.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.56, 134.38, 132.20, 132.07, 130.08, 129.73, 128.22, 127.63, 68.05, 21.48, 14.72.
8. A representative procedure: To a stirred solution of **6b** (100 mg, 0.37 mmol) and **3** (540 mg, 0.93 mmol) in 0.50 mL DMF was added 0.13 mL Et_3N at room temperature. After 24 h, water (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (20 mL). The organic layer was washed with water (2x15 mL) and dried over anhyd $MgSO_4$. The filtrate was concentrated and chromatographed (silica gel; Hex:EtOAc=1:1) to give **7b** as a white solid (170 mg, 0.330 mmol, 89%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55-7.20 (m, 19H), 5.15 (s, 2H), 5.05 (br s, 1H), 4.35 (d, 2H, J_{ab}= 5.9 Hz), 3.55 (s, 2H), 2.80 (t, 4H, J_{ab}= 6.2 Hz) 1.37 (t, 4H, J_{ab}= 6.2 Hz); ^{13}C NMR (75 MHz) δ 156.85, 137.47, 136.91, 136.05, 135.13, 129.86, 129.65, 128.97, 128.59, 128.41, 127.89, 127.41, 67.28, 62.70, 52.70, 45.34, 11.64; HRMS (FAB, M^++H) calcd for $C_{32}H_{35}N_2O_2Si$ 507.2468, found 507.2458.
9. All new compounds exhibited satisfactory ^{1}H and ^{13}C NMR, IR, and low and high resolution mass spectroscopic data for the indicated structures.
10. (a) For selective monoprotection of diamines with Boc_2O, see: Krapcho, A. P.; Kuell, C. S. *Synth. Commun.* **1990**, *20*, 2559; (b) For selective Cbz protection of diamines, see: Atwell, G. J.; Denny, W. A. *Synthesis* **1984**, 1032; (c) For phthalimide protection, see: Soine, T. O.; Buchdahl, M. R. *Org. Syn. Coll. Vol. IV*, 106.
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12. a) Boehm, T. L.; Showalter, H. D. H. *J. Org. Chem.* **1996**, *61*, 6498; b) Kessar, S. V.; Singh, P.; Kaur, N. P.; Chawla, U.; Shukla, K.; Aggarwal, P.; Venugopal, D. *J. Org. Chem.* **1991**, *56*, 3908; c) Johnson, C.R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281.