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tert-Buyldiphenylsilylethyl ("TBDPSE"): A Practical Protecting Group for Phenols

Brian S. Gerstenberger and Joseph P. Konopelski*

Department of Chemistry and Biochemistry, University of California, Santa Cruz, California 95064

joek@chemistry.ucsc.edu

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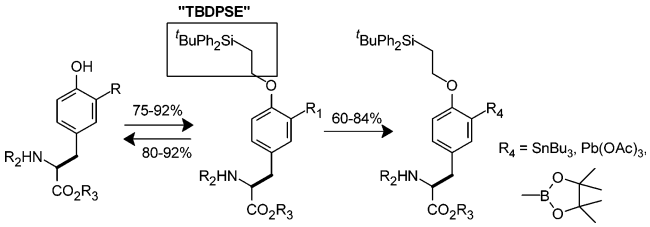
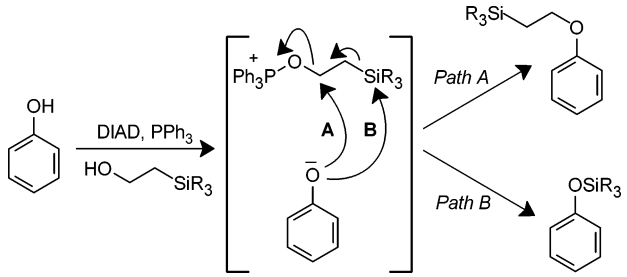


A new protection group for phenols, the 2-(*tert*-butyldiphenylsilyl)ethyl (TBDPSE) group, has been prepared and investigated. Protection of a variety of substituted phenols proceeds in good to excellent yield. The group is stable to mild acid, base, hydrogenolysis conditions, and lithium/halogen exchange on the protected phenol. Removal is achieved with strong acid or standard fluoride treatment.

Successful syntheses of organic molecules often hinge on protection plans that mask and unmask particular functional groups without affecting others. Although there is a vast array of well-documented protection groups,[1,2] modern complex syntheses require the continual invention of new, selective strategies.[3] In support of one of our current total synthesis ventures there was need for a protection group for the phenol functionality that could (1) be deprotected without the use of acid, (2) survive significant base and organometallic manipulations, (3) have minimum steric impact on the ortho position of the protected phenol, and (4) display a level of orthogonality with standard protection schemes used in amino acid chemistry. A survey of the literature suggested that the β-trialkylsilylethyl group would satisfy the need for both orthogonality with other functionalities and minimization of steric bulk around the ortho position.[4] However, the known trialkylsilylethyl groups had the strong disadvantage of low yield in the protection step, verified in this laboratory, which decreased our enthusiasm. In this paper we would like to report the synthesis and use of a new practical protection group, the 2-(*tert*-butyldiphenylsilyl)ethyl (TBDPSE) group, which can be introduced and removed in high yield and exhibits the desired range of orthogonality that attracted us initially to this class of compounds.

SCHEME 1



The two previously described trialkylsilylethyl groups, 2-(trimethylsilyl)ethyl (TMSE) and 2-(dimethylphenylsilyl)ethyl (DMPSE), have found utility in the protection of carboxylic acids,[5] secondary alcohols,[6] and phosphates.[7,8] Their use in protection of phenols has been very limited beyond the two initial papers by Kemp[4,9] due to low yields in the protection reaction. Both groups are introduced via an intermolecular Mitsunobu coupling of the free phenol with the corresponding 2-trialkylsilylethanol. The poor yields in these reactions are believed to be due to competing nucleophilic attacks of the phenol anion, as shown in Scheme 1. Path A leads to desired trialkylsilylethyl material via standard attack of phenoxide on the activated carbon of the alkoxyphosphonium ion. Alternatively, phenoxide attack on the silicon of the activated Mitsunobu intermediate via path B leads to the corresponding trialkylsilyl ether. Although the mixture of trialkylsilyl ether and trialkylsilylethyl ether can be separated by flash chromatography, or trialkylsilyl ether can be converted back to free phenol, this reaction is not practical. From the initial publications and Scheme 1, it would appear that increasing the bulk of the trialkylsilyl moiety would lead to higher yields of desired product. Our initial efforts, therefore, focused on finding a trialkylsilyl group that would allow maximization of 2-trialkylsilylethyl ether formation with phenols.

Initial attempts at repeating the literature work with iodotyrosine derivative **1** and commercially available 2-(trimethylsilyl)ethanol led to the expected unsatisfactory isolated yield (34%) accompanied by a significant amount of trimethylsilyl protected phenol. Similarly lackluster results were obtained with 2-(diphenylmethylsilyl)ethanol (42% desired material, 40% direct trialkylsilyl transfer, Table 1). Having exhausted the commercial starting materials, the more bulky 2-*tert*-butyldiphenylsilylethanol was synthesized according to the literature procedure (Scheme 2).[10] Standard generation of vinyllithium and capture with the requisite chlorosilane

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.
(2) Kocieński, P. J. *Protecting Groups*; Thieme: Stuttgart, Germany, 2000.
(3) For some recent examples, see: (a) Lipsutz, B. H.; Papa, P.; Keith, J. M. *J. Org. Chem.* **1999**, *64*, 3792−3793. (b) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *Org. Lett.* **2003**, *5*, 1999−2001.
(4) Fotouhi, N.; Kemp, D. S. *Int. J. Peptide Protein Res.* **1993**, *41*, 153−161.
(5) See ref 1, p 399.
(6) Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D. *Tetrahedron Lett.* **1986**, *27*, 3345−3348.
(7) Krotz, A. H.; Wheeler, P.; Ravikumar, V. T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2406−2409.
(8) Honda, S.; Hata, T. *Tetrahedron Lett.* **1981**, *22*, 2093−2096.
(9) Fotouhi, N.; Bowen, B. R.; Kemp, D. S. *Int. J. Peptide Protein Res.* **1992**, *40*, 141−147.
(10) Soderquist, J. A.; Rivera, I.; Negron, A. *J. Org. Chem.* **1989**, *54*, 4051−4055.

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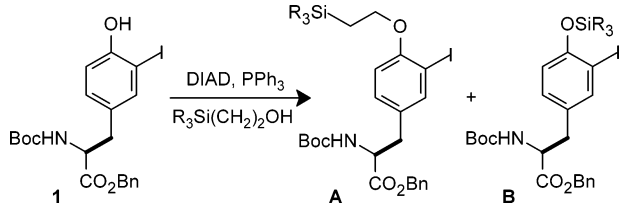
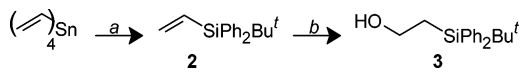
TABLE 1. Protection of 1 with 2-Trialkylsilylethanols



entry	R_3Si	A (%)	B (%)
1	Me_3Si	34	60
2	Ph_2MeSi	42	40
3	*t-BuPh₂Si*	***4*: *92%***	*0*

SCHEME 2[a]



[a] Reagents and conditions: (a) 2.2 *n*-BuLi, −78 °C, 4 h, then Bu^tPh_2SiCl −78 to 0 °C, 4 h, 84%; (b) 9-BBN dimer, then H_2O_2, 96%.

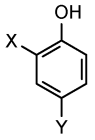
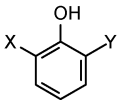
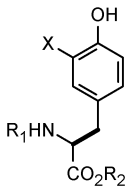
afforded *tert*-butyldiphenylvinylsilane (**2**). Regioselective hydroboration and hydrolysis of **2** (9-BBN/H_2O_2) led to the desired 2-(*tert*-butyldiphenylsilyl)ethanol (**3**) in 80% overall yield from *tert*-butyldiphenylchlorosilane. The Reformatsky conditions employed by Kemp[4] for the synthesis of β-trimethylsilylethanol failed for the production of **3**, presumably due to the bulk of the *tert*-butyldiphenylsilyl halide.[11]

With the desired alcohol in hand, Mitsunobu coupling of tyrosine derivative **1** (1.0 equiv) with **3**, PPh_3, and DIAD (1.2 equiv each) in CH_2Cl_2 afforded **4** in excellent (92%) yield with no appreciable trialkylsilyl ether byproduct (Table 1, entry 3). It would appear that the high steric presence of the *tert*-butyldiphenylsilyl group both prevents the attack of phenoxide on the silicon atom and transports TBDPSE into the realm of useful phenol protection groups.

To document the range of utility, various phenols were subjected to the standard reaction conditions (Table 2). Simple ortho-substituted phenols (compounds **1**, **5** through **7**, **11**, **12**) undergo protection in excellent yield regardless of the electronic character of the substituents. Two of the three examples of 2,6-disubstituted phenols (**8** and **9**) proceed to *tert*-butyldiphenylsilylethyl ethers in acceptable yields and reaction times when performed under conditions of high reaction concentrations and sonication.[12] The extremely hindered 2,6-di-*tert*-butylphenol (**10**) was unreactive.[13] Standard treatment with TBAF affords the free phenol. In certain instances, TFA can also be employed (vide infra).

The stability and orthogonality of TBDPSE with other standard protection groups was investigated with tyrosine derivatives **4**, **19**, and **20**, as these represent the most demanding substrates in Table 2. As was reported for other trialkylsilylethyl ethers,[4] TBDPSE phenols are stable in mild acid (5% TFA), but labile in 50% or neat

TABLE 2. TBDPSE Protection and Deprotection of Phenols

Phenol	Protection, Yield (%)	Deprotection, Yield(%)
		
5 X = Br, Y = H	**13**, 98	89
6 X = CH_2CO_2Me, Y = H	**14**, 91	90
7 X = OMe, Y = CHO	**15**, 90	81
		
8 X = CH_2CO_2Me, Y = Br	**16**, 60[a]	85
9 X = Y = Me	**17**, 57[a]	83
10 X = Y = Bu	**18**, 00	--
		
11 X = H, R_1 = Fmoc,R_2 = Me	**19**, 75	92[b]
12 X = H, R_1 = Boc, R_2 = Bn	**20**, 90	80
1 X = I, R_1 = Boc, R_2 = Bn	**4**, 92	75

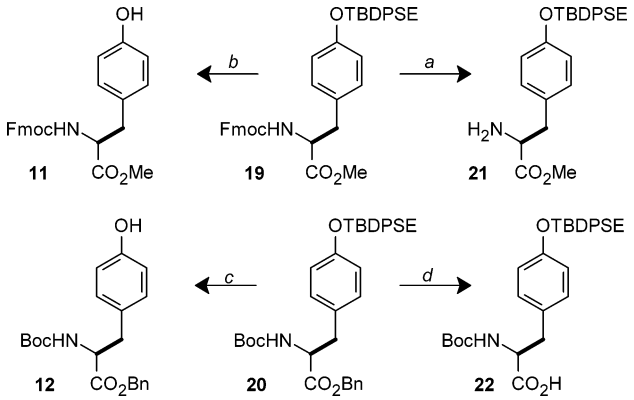
[a] For experimental conditions, see Supporting Information. [b] TFA deprotection, see Supporting Information.

TFA. This property can be exploited when TBDPSE is used in an Fmoc amine protection scheme. Fmoc-Tyr-(OTBDPSE)-OMe (**19**) was selectively deprotected to corresponding free amine **21** by treatment with 20% piperidine. Alternatively, reaction with 50% TFA in CH_2Cl_2 afforded Fmoc protected free phenol **11** in 92% yield with no racemization (Scheme 3). With a TBDPSE (phenol)/Boc (amine) strategy (**20**), deprotection of TBDPSE by standard TBAF treatment affords desired free phenol **12** in good yields in enantiomerically pure form (80%). Unfortunately, the sensitivity of TBDPSE to 50% TFA does not allow for clean selective deprotection of the Boc amine without deprotection of the phenol with this reagent. Finally, TBDPSE is robust enough to survive the cleavage of the benzyl ester of **20** to free acid **22** by either hydrogenolysis with hydrogen gas and 10% palladium on carbon as catalyst (90%) or hydrolysis with lithium hydroxide (84%).

Minimum steric bulk near the ortho positions of the tyrosine phenol was necessitated by the desire to perform

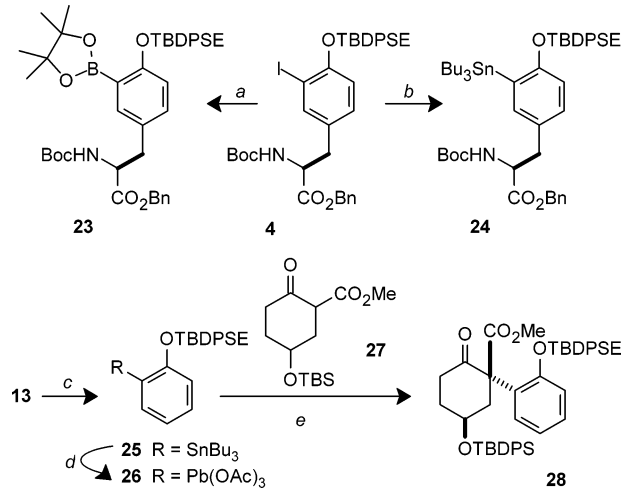
(11) Fessenden, R. J.; Fessenden, J. S. *J. Org. Chem.* **1967**, *32*, 3535−3537.
(12) Lepore, S. D.; He, Y. *J. Org. Chem.* **2003**, *68*, 8261−8263.
(13) For recent work on protection of very hindered phenols, see: Hansen, M. M.; Riggs, J. R. *Tetrahedron Lett.* **1998**, *39*, 2705−6.

SCHEME 3[a]



[a] Reagents and conditions: (a) 20% piperidine, CH_2Cl_2, 1 h, 86%; (b) 50% TFA, CH_2Cl_2, 1 h, 92%; (c) TBAF, 80%; (d) H_2, 10% Pd/C, 90%, or LiOH, aq MeOH, 84%.

SCHEME 4[a]



[a] Reagents and conditions: (a) bis(pinacolato)diboron, cat. Pd(dppf)$_2$, 61%; (b) bis(tributyltin), $PdCl_2(PPh_3)_2$, 55%; (c) *n*-BuLi, Bu_3SnCl, 88%; (d) $Pb(OAc)_4$, cat. $Hg(OAc_F)_2$, 86%; (e) **27**, $ClCH_2CH_2Cl$, 84%.

exchange reactions at these sites. Although the trialkylsilyl group of TBDPSE is very bulky, thus allowing facile and high-yield preparation, the ethyl spacer minimizes the steric bulk of the protection group at adjacent ring positions. As shown in Scheme 4, TBDPSE protection allows for the formation of either bulky boronate **23** or tributylstannyl compound **24** from iodotyrosine **4**. Compound **13** undergoes lithium/halogen exchange on route to stannane **25**, which smoothly undergoes transformation to corresponding aryllead(IV) derivative **26**.[14] Coupling of **26** with ketoester **27** affords **28** in excellent yield.[15]

In conclusion, 2-(*tert*-butyldiphenylsilyl)ethyl (TBDPSE) protection can be installed in good to excellent yields from the easily obtained silyl ethanol. This group has demonstrated utility in standard protection schemes, allowing for selective deprotection of a number of the most common groups while maintaining phenol integrity. Both ortho-substituted and 2,6-disubstituted phenols can be transformed into TBDPSE elaborate-protected systems, which can participate in a variety of organometallic reactions.

(14) For a recent review of aryllead(IV) reagents, see: Elliott, G. I.; Konopelski, J. P. *Tetrahedron* **2001**, *57*, 5683−5705.

(15) Stereochemistry of **28** is assigned based on our previous research. See: Konopelski, J. P.; Lin, J.; Wenzel, P. J.; Deng, H.; Elliott, G. I.; Gerstenberger, B. S. *Org. Lett.* **2002**, *4*, 4121−4124.

Experimental Section

***tert*-Butyldiphenylvinylsilane (2).** Tetravinyltin (5.00 mL, 28.56 mmol, 1.0 equiv) was dissolved in THF (28 mL) and cooled to 0 °C. *n*-Butyllithium (25.13 mL, 62.8 mmol, 2.5 M in hexanes, 2.2 equiv) was slowly added dropwise and the resulting mixture was stirred for 30 min at −40 °C and then at 0 °C an additional 30 min. The resulting vinyllithium solution was cooled to −78 °C and neat *tert*-butyldiphenylchorosilane (15.23 mL, 58.6 mmol, 2.0 equiv) was slowly added dropwise. The cooling bath was removed and the resulting mixture was allowed to come to room temperature and stirred for 1 h. The reaction was then quenched with H_2O (50 mL) and the organic layer was separated. The aqueous layer was washed with pentanes (30 mL × 3) and the organic layers were combined, dried with $MgSO_4$, and concentrated in vacuo. The resulting oil was run through a plug of silica with hexanes resulting in a colorless oil (13.23 g, 84%) that was carried on without further purification. ^{1}H NMR δ 7.62−7.59 (m, 4 H), 7.40−7.33 (m, 6 H), 6.56 (dd, J = 17, 20 Hz, 1 H), 6.27 (dd, J = 3.5, 17 Hz, 1 H), 5.67 (dd, J = 3.5, 20 Hz, 1 H), 1.08 (s, 9 H); ^{13}C NMR δ 136.7, 136.4, 134.4, 133.6, 129.2, 127.7, 27.8, 18.1; IR (thin film) 3050.3, 2989.7, 2928.7, 1106.9, 700.5 cm^{-1}; HRMS [M + H] calcd for $C_{18}H_{22}Si$ 267.15636, found 267.15636.

2-(*tert*-Butyldiphenylsilyl)ethanol (3). Compound **2** (15.69 g, 58.88 mmol, 1 equiv) was dissolved in THF (60 mL) and 9-BBN dimer (14.37 g, 58.88 mmol, 1.0 equiv) dissolved in THF (60 mL) was added slowly. The resulting mixture was stirred for 2 h at room temperature. H_2O (60 mL) and sat. NaOH (60 mL) were added then the reaction mixture, followed by slow addition of 33% H_2O_2 (60 mL). Once evolution of gas had stopped (approximately 1 h), the organic layer was then separated. The aqueous layer was washed with ethyl acetate (30 mL × 3), and the organic layers were combined, dried with $MgSO_4$, and concentrated in vacuo. The resulting oil was chromatographed on silica gel with 2:8 ethyl acetate/hexanes as the eluent, affording the desired compound as a white solid (16.68 g, 96%). Mp 66−68 °C; ^{1}H NMR δ 7.63−7.60 (m, 4 H), 7.43−7.35 (m, 6 H), 3.71−3.67 (m, 2 H), 1.64−1.60 (m, 2 H), 1.36 (br s, 1 H), 1.06 (s, 9 H); ^{13}C NMR δ 136.0, 134.4, 129.5, 128.0, 60.4, 27.9, 18.1, 16.3; IR (thin film) 3337.7, 3070.4, 2929.1, 1426.8, 1105.8 cm^{-1}; HRMS [M + Na] calcd for $C_{18}H_{24}OSiNa$ 307.14887, found 307.17483.

Representative Experimental Procedure: *N*-*t*-Boc-O-*tert*-butyldiphenylsilylethyl-3-iodo-L-tyrosine Benzyl Ester (4). Triphenylphosphine (0.922 g, 3.52 mmol, 1.2 equiv) was dissolved in THF (7.5 mL) and the mixture was cooled to 0 °C. To this solution were added DIAD (0.69 mL, 3.52 mmol, 1.2 equiv), tyrosine derivative **1** (1.45 g, 2.93 mmol, 1.0 equiv), and 2-(*tert*-butyldiphenylsilyl)ethanol **3** (1.00 g, 3.52 mmol, 1.2 equiv). The ice bath was removed and the mixture was stirred for 15 min at room temperature. The solvent was removed in vacuo and the resulting oil was purified via column chromatography with 2:8 ethyl acetate/hexanes as the eluent and affording the desired material as a white solid (2.06 g, 92%). Mp 44−46 °C; ^{1}H NMR δ 7.60−7.80 (m, 4 H), 7.48 (br s, 1 H), 7.26−7.45 (m, 11 H), 6.80 (d, J = 8 Hz, 1 H), 6.33 (d, J = 8 Hz, 1 H), 5.11 (q, J = 12.2 Hz, 2 H) 4.96 (d, J = 8.1 Hz, 1 H), 4.54−4.52 (m, 1 H), 3.96−3.93 (m, 2 H), 2.99−2.90 (m, 2 H), 1.88−1.84 (m, 2 H), 1.42 (s, 9 H), 1.08 (s, 9 H); ^{13}C NMR δ 171.6, 156.6, 155.1, 140.3, 136.0, 135.2, 134.5, 134.4, 130.2, 130.0, 129.6, 128.7, 128.6, 128.6, 128.1, 112.1, 86.8, 80.0, 67.2, 66.6, 54.6, 36.9, 28.4, 27.8, 18.2, 12.1; IR (thin film) 3435.6, 2930.4, 1715.8, 1167.2, 700.9 cm^{-1}; HRMS [M + Na] calcd for $C_{39}H_{46}INO_5SiNa$ 786.20823, found 786.17534; $[\alpha]^{25}_D$ −11.2 (*c* 5, $CHCl_3$).

Representative Deprotection Procedure: Free Phenol 12. Compound **20** (0.100 g, 0.157 mmol, 1.0 equiv) was dissolved

in THF (1 mL). To this solution was added 1.0 M TBAF (0.313 mL, 0.313 mmol in THF, 2.0 equiv) and the mixture was stirred at 40 °C overnight. The resulting solution was concentrated in vacuo and the resulting oil was taken up in EtOAc (5 mL). The solution was washed with water (5 mL × 3), dried with $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by column chromatography, using 3:7 ethyl acetate/hexanes as the eluent, to afford the desired product **12** as a white solid in 80% yield. Mp 121−123 °C; ^{1}H NMR δ 7.37−7.29 (m, 5 H), 6.86 (d, J = 8.4 Hz, 2 H), 6.66 (d, J = 8.4 Hz, 2 H), 5.82 (br s, 1 H), 5.13 (dd, J = 12.2, 42.4 Hz, 2 H), 5.02 (d, J = 8.2 Hz, 1 H), 4.57 (dd, J = 6.0, 14.0 Hz, 1 H), 3.03−2.96 (m, 2 H), 1.42 (s, 9 H); ^{13}C NMR δ 172.2, 155.5, 155.2, 135.3, 130.6, 128.8, 127.6, 115.7, 80.4, 67.4, 54.8, 37.6, 28.5; IR (thin film) 3368.4, 2978.1, 1689.5, 1516.4 cm^{-1}; HRMS [M + H] calcd for $C_{21}H_{26}NO_5$ 372.18055, found 372.19299; $[\alpha]^{25}_D$ −40.7 (*c* 12.5, MeOH).

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Supporting Information Available: General procedures, complete spectroscopic data, and ^{1}H 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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