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Boronated thiophenols: a preparation of 4-mercaptophenylboronic acid and derivatives

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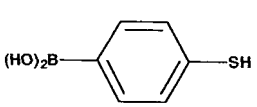
Abstract

4-Mercaptophenylboronic acid derivatives were prepared by a metallation/boration sequence from S-protected 4-bromothiophenols; the *t*-butyldimethylsilylthioether was found suitable to allow subsequent regeneration of the mercapto group after boration. The parent compound, 4-mercaptophenylboronic acid, could thus be obtained and was subsequently S-alkylated; 4-boronophenylthioacetic acid was prepared without the need to protect the boronic acid group. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: BNCT; Boronates; Boronic acid; Mercapto; Thioethers

1. Introduction

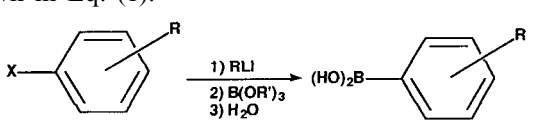
There is current interest in the preparation of boronated analogues of biomolecules [1], particularly in light of their possible use for boron neutron capture therapy (BNCT) [2,3]. A thiol-bearing boron cluster $B_{12}H_{11}SH$ [4]—known as borocaptate, mercaptoborate or BSH—was the first clinically useful compound for BNCT assays [5]. Here we present the preparation of 4-mercaptophenylboronic acid (**1**), which we believe may interact in vivo similarly to borocaptate; furthermore this compound, by alkylation of the thiol group, could provide access to boronated analogues of thioethers known to interfere with melanogenesis [6,7] and therefore possibly to give melanoma-seeking agents suitable for BNCT.



1

That boronic acid **1** had yet to be prepared was quite surprising to us, as other *para*-functionalized phenylboronic derivatives such as the hydroxy [8] or amino [9] derivatives have been known for a long time. This could underline some difficulties for an efficient preparation of **1** as we experienced during the present work and as described below.

A boronic acid group is usually introduced on aromatic rings by a metallation/boration sequence as shown in Eq. (1).



(1)

Reaction of 4-bromo-thiophenol (X = Br, R = *p*-SH) with two equivalents [10,11] of *n*-, *sec*- or *t*-butyl lithium at −78°C followed by quenching with trimethyl borate resulted in complicated reaction mixtures which gave no evidence of the formation of **1** (R = *p*-SH). The *ortho*-directing effect of the thiolate in such metallations, which has been experienced previously [12,13], might here have played a detrimental role and protection of the thiol group was thus considered.

First, the readily available *p*-methylthiophenyl boronic acid (**2**) [14,15] was prepared but cleavage of the S-methyl group of **2**, using acidic conditions (such as hydrochloric acid, boron tribromide) or iodotrimethylsilane failed to give **1**, boronic acid (**2**)

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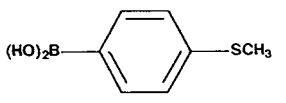
being recovered. Similar disappointing results were observed with the protected boronate **3**, obtained by esterification of **2** with *d,l*-1,3-diphenylpropane-1,3-diol (a method recently disclosed for protection of boronic acids [16]). As the use of basic conditions [17,18] to regenerate the thiol group from thiomethyl ethers are incompatible with the base-sensitive boronic acid of **2** or **3**, other S-protecting groups were then evaluated, starting with the known [19] tetrahydropyranyl derivative **4**.



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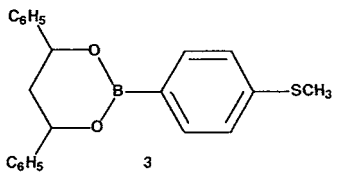
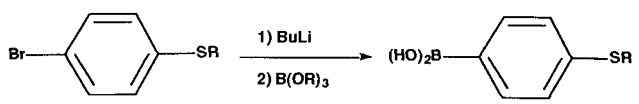


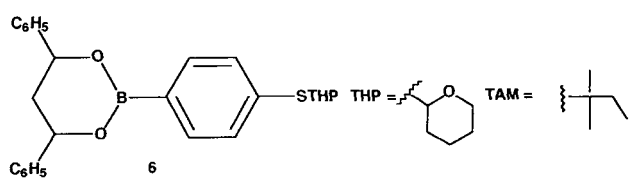
3

After metallation of **4** with *n*-butyl lithium and treatment with triisopropylborate at low temperature, the S-protected boronic acid **5** was isolated (90%), which could be esterified to **6** (90%) by reaction [16] with *d,l*-1,3-diphenylpropane-1,3-diol. From both **5** or **6**, however, acidic treatment (H^+, BBr_3, or $(CH_3)_3SiI$) as well as reactions with Ag^+ or Hg^{2+} salts known for their affinity to sulphur, failed to cleanly deprotect the S-THP ether.



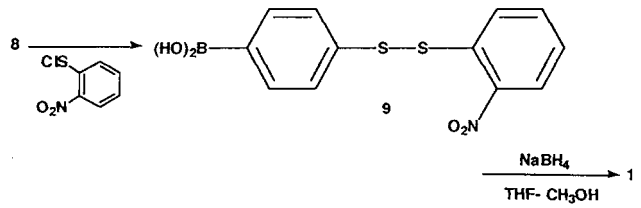
4: R = THP
7: R = TAM

5: R = THP
8: R = TAM

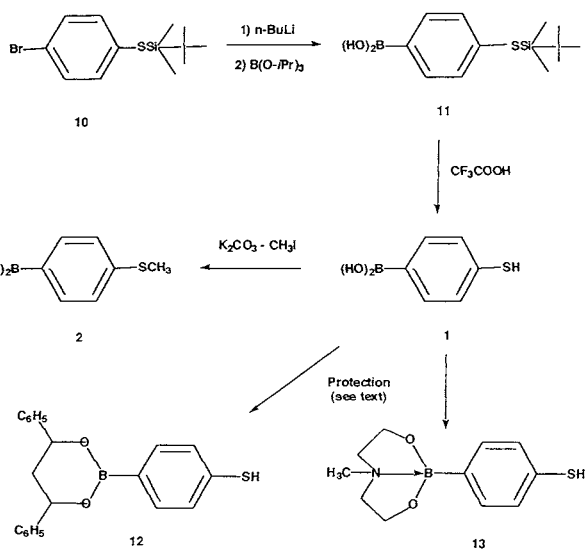


6

The use of a more acid-sensitive protecting group was then considered and upon reaction of 4-bromothiophenol with 2-methyl-but-1-ene, the *t*- amyl (TAM) [20] thioether (**7**) was prepared (95%); this, to our knowledge, is the first example of the use of TAM for protection of a thiol group. Thioether **7** was then converted to boronic acid **8** (85%) by the general metallation/boration sequence (Eq. (1)). Upon treatment of **8** with *ortho*-nitrosulphenyl chloride [21], cleavage of the S-TAM protecting group was observed and yielded the expected unsymmetrical disulfide **9** (70%). Subsequent reduction [22] of this dithioether with sodium borohydride then afforded the desired 4-mercaptophenylboronic acid **1**, but in low yield (< 20%).

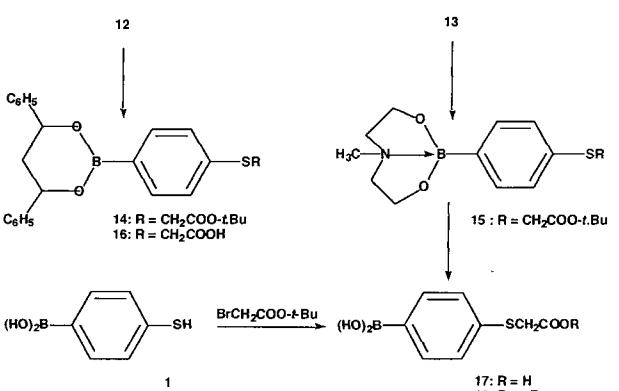


To get a more efficient preparation of **1**, other thiol protecting groups (trityl, silyl) were examined and the *t*-butyldimethylsilyl (TBDMS) thioether [23] proved to be the right choice. Lithiation of **10** at − 78°C was followed by reaction with an excess of triisopropyl borate to afford the S-silylated boronic acid **11** (77%). The thiol-protecting group of **11** could then be removed by reaction with trifluoroacetic acid to afford **1** (88%), without damage to the boronic acid; this straightforward procedure thus yielded 4-mercaptophenylboronic acid in preparative yield (> 60% overall from 4-bromothiophenol).



10 11 2 1 12 13

Protection of the boronic acid group of **1** could be effected by reaction with a diol, such as *d,l*-1,3-diphenylpropan-1,3-diol [16] or *N*-methyldiethanolamine, to give esters **12** (86%) or **13** (85%), respectively. To confirm its structure, **1** was also converted by reaction with methyl iodide to the known S-methyl thio ether **2** [13,14].



Reaction of boronates **12** and **13** with *t*-butyl bromoacetate in the presence of a base afforded the corresponding S-alkyl derivatives **14** (71%) and **15** (65%), respectively; this was followed by treatment with trifluoroacetic acid, which removed only the carboxylic ester protecting group from **14** (to give **16**) but both acid protecting groups of **15** (to give **17**). A shorter route to **17**, a boronated analogue of *p*-hydroxyphenylthioacetic acid, is given by direct alkylation of **1** with *t*-butyl bromoacetate (to give **18**) followed by acidic deprotection, i.e. without need to protect the boronic acid group.

4-Mercaptophenylboronic acid **1** being now made readily available, the preparation of boronated analogues of aromatic thio derivatives which might interfere with melanogenesis can now be initiated; the preparation of such boronated melanoma-seeking agents for potential use in BNCT is presently undertaken in our laboratory.

2. Experimental

2.1. General

Dry tetrahydrofuran was obtained by distillation over sodium/benzophenone under Ar and acetonitrile was stored on 4 Å molecular sieves before use. *d,l*-1,3-Diphenylpropane-1,3-diol was prepared according to the literature [24]. Standard abbreviations are used for NMR description of spectra and the residual absorption of the NMR solvent was taken as the internal reference.

2.2. (4-Bromophenylthio)-dimethyl-tertbutyl-silane (*10*)

To a solution of 4-bromothiophenol (9.45 g, 50 mmol) in dry tetrahydrofuran (30 ml) stirred under Ar at 4°C, was added sodium hydride (2.2 g of a 60% dispersion in mineral oil, 55 mmol, 1.1 equiv). After evolution of gas had ceased (30 min), *t*-butyldimethylsilyl chloride (11.3 g, 75 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature (r.t.) for 14 h. After filtration on Celite and evaporation of the volatiles, bulb-to-bulb distillation (50°C at 5 mmHg) afforded **10** (13.6 g, 92%) as a colorless liquid which crystallized on standing. Mp 253–255°C; (literature: Eb 93–94°C (1 mmHg) [23]).^{1}H-NMR (250 MHz, $CDCl_3$): δ 0.2 (s, 6H), 1.0 (s, 9H), 7.55 (m, 2H), 8.05 (m, 2H). ^{13}C-NMR ($CDCl_3$, 66.5 MHz): δ −3.7, 17.8, 25.5, 123.6, 128.8, 130.4, 131.6.

2.3. 4-[(Dimethyl-tertbutyl-silyl)thio]-phenylboronic acid (*11*)

Under Ar, a solution of **10** (11.36 g, 38 mmol) in dry tetrahydrofuran (20 ml) was stirred at −78°C and *n*-butyl lithium (37.5 ml, 1.6 M in *n*-hexane, 60.8 mmol, 1.6 equiv) was added dropwise. After stirring for 15 min, tri-isopropyl borate (46.2 ml, 198 mmol, 5.2 equiv) was added. The mixture was stirred at −78°C for 2 h, then at −20°C for 2 h and finally overnight at room temperature. Water (20 ml) was added and the mixture was concentrated to one third under reduced pressure. Extraction was performed with diethyl ether and the organic layer was washed with water, dried (sodium sulfate) and concentrated under reduced pressure. The residue was taken up in diethyl ether/*n*-pentane to afford **11** (7.96 g, 77%) as white cristals; the yield was 86% on a 1 mmol scale. Mp 253–255°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.2 (s, 6H), 1.0 (s, 9H), 7.55 (m, 2H), 8.05 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ −3.2, 19.1, 26.4, 133.6, 134.9, 135.7, 137.9.

2.4. 4-Mercaptophenylboronic acid (*1*)

To a solution of **11** (2.49 g, 10 mmol) in dichloromethane (10 ml) was added trifluoroacetic acid (7.7 ml, 100 mmol, 10 equiv) and the now purple solution was stirred overnight. After evaporation of the volatiles under reduced pressure, the residue was taken up in water to afford **1** (1.35 g, 88%) as white crystals. Mp 218–220°C. IR: ν 3273, 2338, 2374, 1587, 1395 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3 + CD_3OD$) δ 7.1 (m, 2H), 7.6 (m, 2H).^{13}C-NMR (62.5 MHz, $CDCl_3 + CD_3OD$) δ 125.5, 127.4, 134.0.

2.5. 4-Methylthiophenylboronic acid (*2*)

To a solution of **1** (154 mg, 1 mmol) in acetonitrile (5 ml) were added potassium carbonate (456 mg, 3.3 mmol, 3.3 equiv), and methyl iodide (0.62 ml, 10 mmol, 10 equiv). After stirring overnight, water was added and the mixture was extracted with dichloromethane. The organic layer was washed with water, dried (sodium sulfate) and the volatiles were removed under reduced pressure. The white powder thus obtained was recrystallised (diethyl ether) to afford **2** (103 mg, 61%) as white crystals; this material was compared to an authentic sample prepared according to reference [15]. M.p.: 206–207°C (literature: 208.5–209.5 [14], 205–208°C [15]).

2.6. d,l-(4,6-Diphenyl-2-(4-mercaptophenyl)-1,3,2-dioxaborinane (*12*)

To a solution of **1** (770 mg, 5 mmol) in tetrahydrofuran (10 ml) was added *d,l*-1,3-diphenylpropane-1-3 diol (1.1 g, 5 mmol, 1 equiv). The solution was stirred for 30 min and dried with sodium sulfate. After filtration and evaporation of the volatiles, the residue was purified by chromatography on silica gel (dichloromethane) to afford **12** (1.490 g, 86%) as white crystals.

M.p. 271–272 °C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 2.4 (m, 2 H), 5.2 (m, 2 H), 7.1 and 7.9 (AA'XX' system, 2×2H each), 7.3–7.6 (m, 10H). ^{13}C-NMR ($(CD_3)_2CO$), 75 MHz) δ 42.0, 71.1, 125.9, 126.3, 127.3, 127.4, 128.2, 128.3, 128.8, 129.2, 135.3, 143.1.

2.7. 2-(4-Mercaptophenyl)-6-methyl-1,3,6,2-dioxaazaborocane (13)

To a solution of **1** (770 mg, 5 mmol) in tetrahydrofuran (10 ml) was added *N*-methyl-diethanolamine (0.63 ml, 5.5 mmol, 1.1 equiv). After stirring for 30 min, diethyl ether was added (20 ml) and this solution was washed with water (4×20 ml). Drying (sodium sulfate) of the organic layer and evaporation of the volatiles afforded **13** (1.007 g, 85%) as white crystals. M.p. 226–228°C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 2.25 (s, 3 H), 2.8–3.2 (m, 4 H), 4.0–4.3 (m, 4 H), 7.5 and 8.1 (AA'XX' system, 2×2H each). ^{13}C-NMR ($CDCl_3$, 62.5 MHz): δ 47.5, 60.1, 62.0, 125.4, 127.2, 134.1, 140.4.

2.8. d,l-2-(4-(t-Butyloxycarbonylmethylthiophenyl)-4,6-diphenyl-1,3,2-dioxaborinane (14)

To a solution of **12** (338 mg, 0.98 mmol) in dry acetonitrile (3 ml) were added potassium carbonate (207 mg, 1.5 mmol, 1.5 equiv), *t*-butyl bromoacetate (0.20 ml, 1.5 mmol, 1.5 equiv) and sodium iodide (22 mg, 0.15 mmol, 0.15 equiv). After stirring for 20 h, the solution was concentrated under reduced pressure and water was added to the residue. The mixture was extracted with dichloromethane and after washing and drying, the yellow oil was purified by chromatography on silica gel (dichloromethane) to afford **14** (321 mg, 70%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.4 (s, 9H), 3.6 (s, 2H), 7.2 and 7.9 (AA'XX' system, 2×2H each), 7.3–7.6 (m, 10H).

2.9. 2-(4-(t-Butyloxycarbonylmethylthiophenyl)-6-methyl- 1,3,6,2-dioxaazaborocane (15)

Starting with **13** (249 mg, 1 mmol), the procedure used for the preparation of **14** was chromatography on silica gel, 99:1 CH_2Cl_2/CH_3OH, then gave **15** (213 mg, 65%). ^{1}H-NMR ($CDCl_3$, 200 MHz) 1.4 (s, 9H), 2.3 (s, 3H), 2.9 (m, 2H), 3.1 (m, 2H), 3.6 (s, 3H), 4.1 (m, 4H), 7.4 (m, 2H), 8.0 (m, 2H).

2.10. 2-(4-Carboxymethylthiophenyl)-4,6-diphenyl-1,3,2-dioxaborinane (16)

To a solution of **14** (226 mg, 0.49 mmol) in dichloromethane (5 ml) was added trifluoroacetic acid (0.38 ml, 4.93 mmol, 10 equiv). The solution was stirred for 2 h before evaporation of the volatiles under reduced pressure. The crystals thus obtained were washed with water and dried to yield **16** (122 mg, 54%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.4 (m, 2H), 3.6 (s, 2H), 5.2 (m, 2H), 7.1 and 7.9 (AA'XX' system, 2×2H each), 7.3–7.6 (m, 10H).

2.11. 4-Carboxymethylthiophenyl boronic acid (17)

From **15**, or **18**, the above procedure, used for the deprotection of **14**, was used; the white powder thus obtained was thoroughly washed with diethyl ether to yield **17** (80%). IR: ν 3480, 3257, 1775, 1383 cm^{-1}. ^{1}H-NMR ($CDCl_3 + CD_3OD$, 200 MHz) δ 3.5 (s, 2H), 7.1 (m, 2H) 7.5 (m, 2H). ^{13}C-NMR ($CDCl_3 + CD_3OD$, 75 MHz) δ 37.9, 127.6, 134.0, 137.6, 171.7.

2.12. 4-(t-Butyloxycarbonylmethylthio)-phenyl boronic acid (18)

To a solution of **1** (462 mg, 3 mmol) in acetonitrile (10 ml) were added potassium carbonate (1.368 g, 9.9 mmol, 3.3 equiv), *t*-butyl bromoacetate (1.29 ml, 9.9 mmol, 3.3 equiv) and sodium iodide (50 mg, 0.33 mmol, 0.33 equiv). After 20 h stirring, the volatiles were removed under reduced pressure. The residue was partitioned between water and dichloromethane. The organic layer was washed with water, dried (sodium sulfate) and evaporated under reduced pressure. The yellow oil was purified by chromatography on silica gel to afford **18**, eluting with 49:1 CH_2Cl_2/CH_3OH, (0.57 g, 71%) as a colorless oil. IR: ν 3249, 2963, 1722, 1591 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.4 (s, 9H), 3.55 (s, 2H), 7.3 (m, 2H), 7.6 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 27.8, 36.6, 82.1, 127.8, 133.9, 134.8, 168.8.

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References

[1] C. Morin, Tetrahedron 50 (1994) 12521–12569.
[2] M.F. Hawthorne, Angew. Chem. 105 (1993) 997–1033; Angew. Chem. Int. Ed. Engl. 32 (1993) 950–984.
[3] A.H. Soloway, W. Tjarks, B.A. Barnum, F.-G. Rong, R.F. Barth, I.M. Codogni, J.G. Wilson, Chem. Rev. 98 (1998) 1515–1562.
[4] A.H. Soloway, H. Hatanaka, M.A. Davis, J. Med. Chem. 10 (1967) 714–717.
[5] H. Hatanaka, W.H. Sweet, K. Sano, F. Ellis, Pure Appl. Chem. 63 (1991) 373–374.
[6] K. Jimbow, T. Iwashina, F. Alena, K. Yamada, J. Pankovich, T. Umemura, J. Invest. Dermatol. 100 (1993) 231S–238S.
[7] G. Prota, Progr. Chem. Org. Nat. Prod. 64 (1995) 94–148.

[8] H. Gilman, L. Santucci, D.R. Swayampati, R.O. Ranck, J. Am. Chem. Soc. 79 (1957) 3077–3081.
[9] K. Torssell, Arkiv Kemi 10 (1957) 473–481.
[10] A.M. Tickner, G.K. Huang, K. Gombatz, R.J. Mills, V. Novack, K.S. Webb, Synth. Commun. 23 (1993) 2497–2505.
[11] H. Selnick, M.L. Bourgeois, J.W. Butcher, E.M. Radzilowski, Tetrahedron Lett. 34 (1993) 2042–2046.
[12] S. Masson, J.-F. Saint-Clair, M. Saquet, Synthesis (1993) 485–486.
[13] F.D. Toste, I.W.J. Still, J. Am. Chem. Soc. 117 (1995) 7261–7262.
[14] L. Santucci, H. Gilman, J. Am. Chem. Soc. 80 (1958) 193–196.
[15] M.H. Norman, H.D. Smith, C.W. Andrews, F.L.M. Tang, C.L. Cowan, R.P. Steffer, J. Med. Chem. 38 (1995) 4670–4678.
[16] C. Malan, C. Morin, G. Praekher, Tetrahedron Lett. 37 (1996) 6705–6708.
[17] R.N. Young, J.Y. Gauthier, W. Coombs, Tetrahedron Lett. 25 (1984) 1753–1756.
[18] G.A. Pinchard, C. Dallaire, M. Gingras, Tetrahedron Lett. 39 (1998) 543–546.
[19] A. Claussner, F. Nique, J.-G. Teutsch, P. Van de Velde, European Patent 471612.
[20] B. Figadère, X. Franck, A. Cavé, Tetrahedron Lett. 34 (1993) 5893–5894.
[21] A. Fontana, J. Chem. Soc. Chem. Commun. (1975) 976–977.
[22] A. Ookawa, S. Yokohama, K. Soai, Synth. Commun. 16 (1986) 819–825.
[23] A. Hirao, H. Sione, S. Wakabayashi, S. Nakahama, K. Yamaguchi, Macromolecules 27 (1994) 1835–1841.
[24] J.-P. Deprès, C. Morat, J. Chem. Educ. 69 (1992) A232–A239.