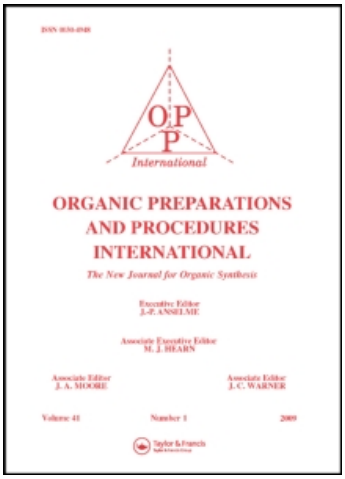

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF SOME ISOTHIOCYANATOPHENYLBORONIC ACIDS

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To cite this Article Ramalingam, Kondareddiar and Nowotnik, David P.(1991) 'SYNTHESIS OF SOME ISOTHIOCYANATOPHENYLBORONIC ACIDS', Organic Preparations and Procedures International, 23: 6, 729 — 734
To link to this Article: DOI: 10.1080/00304949109458247
URL: http://dx.doi.org/10.1080/00304949109458247

ORGANIC PREPARATIONS AND PROCEDURES INT., 23 (6), 729-734 (1991)

SYNTHESES OF SOME ISOTHIOCYANATOPHENYLBORONIC ACIDS

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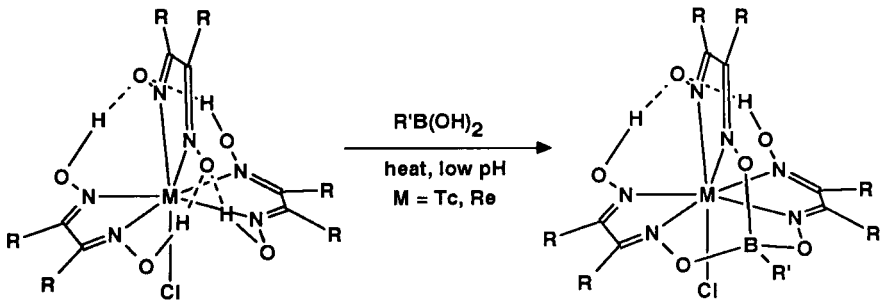
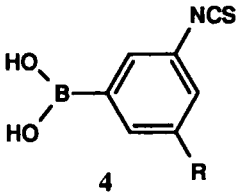
Monoclonal antibodies have been labeled with a variety of radioisotopes,[1,2] such as ^{99m}Tc, ^{111}In, ^{186}Re, and ^{67}Ga, primarily for the detection and therapy of tumors. ^{99m}Tc is the preferred radionuclide for imaging in nuclear medicine because of its ideal physical properties, and a wide variety of ^{99m}Tc complexes have been developed for clinical imaging applications.[3] Because of the similarity between technetium and rhenium, one strategy in the development of radionuclide agents for tumor therapy has been the application of technetium chemistry to the β-emitting rhenium isotopes ^{186}Re and ^{188}Re. Studies in our laboratories led to the development of series of similar technetium and rhenium complexes termed, respectively, as BATOs (boronic acid adducts of technetium dioximes)[4] and BAReOs (boronic acid adducts of rhenium dioximes).[5] The final step in the formation of BATOs[6] and BAReOs[5] is summarized below.



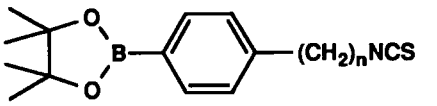
Technetium complexes in which the boronic acid R-group is alkyl (for example, CH_3, $(CH_3)_2CHCH_2$) have shown clinical utility as imaging agents of myocardial[7] and cerebral[8] blood flow. By incorporation of the protein-reactive isothiocyanate[9-11] in the R-group of the boronic acid, BATO complexes were made which could be used to label monoclonal antibodies.[12, 13] This report describes the synthesis of boronic acid bifunctional reagents which are used for labeling monoclonal antibodies with the radioisotopes of technetium and rhenium.

The amine precursor (**3b**) to 3-carboxy-5-isothiocyanatophenylboronic acid (**4b**) was prepared by the nitration of 3-carboxyphenylboronic acid (**1**)[14] with a mixture of fuming nitric acid



4

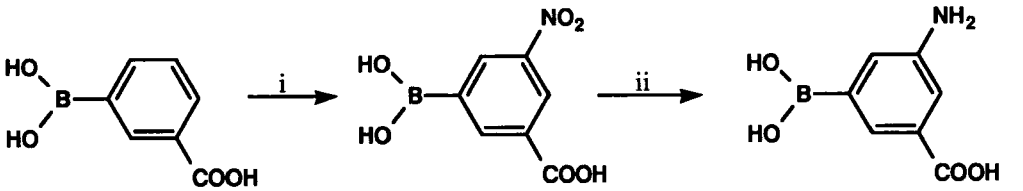
a) R = H b) R = CO_2H



10

a) n = 1 b) n = 2

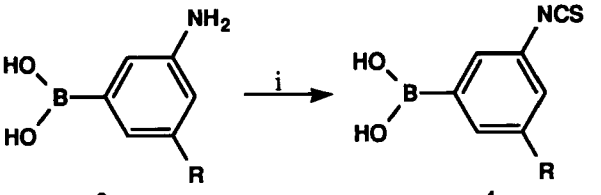
and sulfuric acid at room temperature. Hydrogenation of the resulting 3-nitro-5-carboxyphenylboronic acid (**2**) over Raney nickel gave 3-carboxy-5-aminophenylboronic acid (**3b**). The aminoboronic acid (**3b**) was then reacted with thiophosgene in 3N HCl at room temperature to afford 3-carboxy-5-isothiocyanatophenylboronic acid (**4b**) in 55% yield.



1 2 3b

i) HNO_3, H_2SO_4; ii) H_2, Raney Ni, 50 psi

Treatment of commercially available 3-aminophenylboronic acid (**3a**) with thiophosgene in acetone in the presence of triethylamine gave 3-isothiocyanatophenylboronic acid (**4a**) in 43% yield.[10]

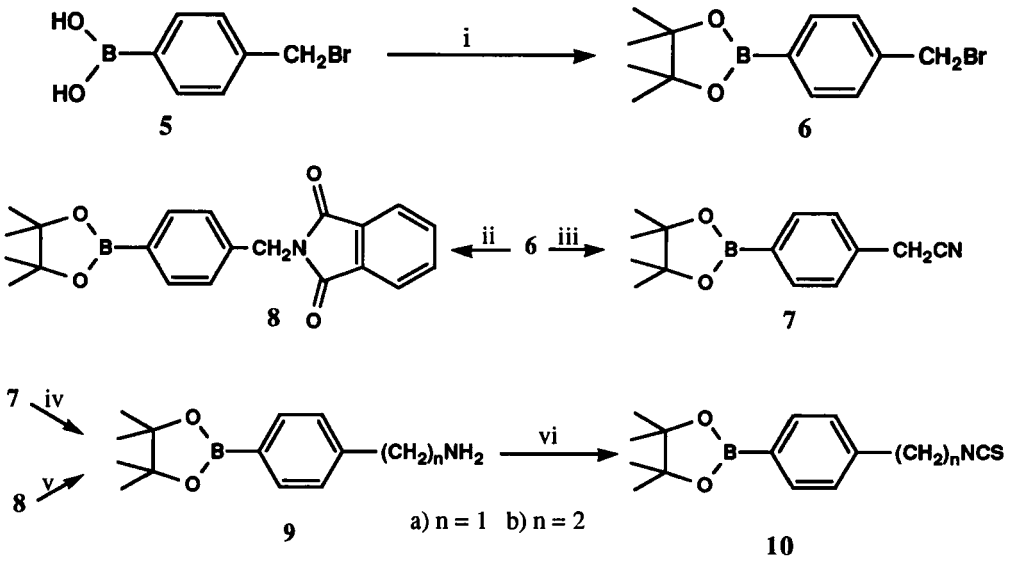


3 4

a) R = H b) R = CO_2H

i) Cl_2C=S, Et_3N, acetone, 0° or Cl_2C=S, 3N HCl, RT

The synthetic route for the preparation of the isothiocyanates (**10a**) and (**10b**) is given below. 4-Bromomethyboronic acid (**5**)[15] was protected as its pinacol derivative (**6**) which was then reacted with potassium phthalimide in acetone to afford the phthalimido derivative (**8**). Hydrazinolysis of the phthalimido derivative gave the amine (**9a**). This was smoothly converted to the isothiocyanate (**10a**) with thiophosgene in acetone in the presence of triethylamine. Nitrile (**7**) was prepared by reaction of (**6**) with sodium cyanide in DMF. Catalytic reduction of the nitrile using Rhodium on alumina powder (5%) in ethanolic ammonia gave the amine (**9b**). Isothiocyanate (**10b**) was obtained in 62% yield by reaction of **9b** with thiophosgene in methylene chloride.



i) Pinacol, hexane, RT; ii) Potassium phthalimide, acetone; iii) NaCN, DMF
iv) Rhodium on alumina (5%); v) NH_2NH_2, CH_3OH; vi) $Cl_2C{=}S$, Et_3N, CH_2Cl_2, 0°

EXPERIMENTAL SECTION

^1H NMR spectra were recorded on a 270 MHz JEOL-FX spectrophotometer in $CDCl_3$ and DMSO-d_6. Chemical shifts are reported in ppm downfield from TMS. CI mass spectra were recorded on a Finnigan-TSQ spectrometer. FAB mass spectra were recorded on VG-ZAB-2F spectrometer from a matrix of glycerol and dimethyl sulfoxide. Elemental analyses were determined in-house by Bristol-Myers Squibb Microanalytical department. All chemicals were purchased from Aldrich Chemical Company.

3-Isothiocyanatophenylboronic Acid. (4a).- To a cooled (0°) solution of 3-aminophenylboronic acid (**3a**, 2.24 g, 0.013 mol) in acetone (50 mL) was added dropwise a solution of thiophosgene (1 mL, 0.013 mol) in chloroform (5 mL) over a period of 0.5 hr. The reaction mixture was stirred at 0° for 1 hr and at room temperature for 12 hr. The solvent was evaporated on a rotary evaporator and the residue was triturated with ether and filtered to remove the triethylamine hydrochloride. The ethereal solution was evaporated to give a brown oil. This was chromatographed on silica gel (30 g) using acetone-chloroform (7:3) as eluent. Fractions containing the product were collected and evaporated to give a light brown solid. It was crystallized from ethyl acetate-hexane to yield 0.92 g (43%) of a pale yellow solid. mp. 166-167°. ^1H NMR (DMSO-d_6): δ 7.62 (m, 3H, BOH and ArH), 7.80 (m, 3H, ArH).

Anal. Calcd. for $C_7H_6BNO_2S{\cdot}0.25H_2O$: C, 46.00; H, 3.59; N, 7.67; S, 17.54
Found: C, 46.17; H, 3.48; N, 7.59; S, 17.71

3-Nitro-5-carboxyphenylboronic Acid (2).- To a stirred slurry of 3-carboxyphenylboronic acid (**1**, 5 g, 0.03 mol) in concentrated sulfuric acid (15 mL) was added fuming nitric acid (15 mL, d = 1.54). The reaction mixture was stirred at RT for 45 min and poured into ice (150 g). The precipitate of

nitro acid was collected, washed with water and dried. The yield was 3.35 g (53%), mp. 235-237°, lit.[14] mp. of 235-240°. ^{1}H NMR (DMSO-d_6): δ 8.63 (m, 3H, ArH and BOH), 8.76 (d, 1H, ArH), 8.81 (d, 1H, ArH). MS: FAB $(M+H+Gly-2H_2O)^+ = 268^+$, $(M-H+Gly-2H_2O)^- = 266^-$.

3-Amino-5-carboxyphenylboronic Acid (3b).- A solution of 3-nitro-5-carboxyphenyl-boronic acid (**2**, 3.3 g, 0.016 mol) in absolute ethanol (25 mL) was hydrogenated in the presence of Raney nickel (1 g) at 50 psi for 4 hrs in a Parr shaker. The catalyst was removed by filtration and the solvent was removed on a rotary evaporator. The solid obtained was recrystallized from water to yield 2.6 g (92%), mp. 210-212°, lit.[14] mp. 212-215°. ^{1}H NMR (DMSO-d_6): δ 2.08 (s, 2H, NH_2), 7.86-7.97 (m, 3H, ArH), 8.34(s, 2H, OH). MS: FAB $(M+H+Gly-2H_2O)^+ = 238^+$, $(M-H+Gly-2H_2O)^- = 236^-$.

3-Isothiocyanato-5-carboxyphenylboronic Acid (4b).- To a solution of 3-amino-5-carboxyphenylboronic acid (**3b**, 150 mg, 0.08 mmol) in 3N HCl (3 mL) was added thiophosgene (92 mg, 0.08 mmol) and the reaction mixture was stirred at room temperature. The white solid which was formed after 20 min, was collected, washed with water, dried, and crystallized from hexane/ethyl acetate to yield 98.5 mg (55%), mp. > 350°. ^{1}H NMR (DMSO-d_6): δ 7.19 (m, 2H, ArH), 7.58 (s, 1H, ArH) 7.90 (s, 2H, OH); MS: FAB $(M+Gly-2H_2O+H)^+ = 280^+$, $(M+Gly-2H_2O-H)^- = 278^-$.

Anal. Calcd. for $C_8H_6BNO_4S \cdot 0.3H_2O$: C, 42.06; H, 2.91; N, 6.13

Found: C, 42.51; H, 2.87; N, 5.68

Pinacol 4-Bromomethylphenylboronate (6).- Pinacol (5.0 g, 0.4 mol) was added to a slurry of 4-bromomethylphenylboronic acid (**5**, 8.6 g, 0.04 mol)[15] in hexane (100 mL). The reaction mixture was stirred at room temperature for 24 hrs. Hexane was evaporated on a rotary evaporator and the resulting white solid was crystallized from pentane to yield 6.1 g (52%), mp. 79-81°. ^{1}H NMR ($CDCl_3$): δ 1.3 (s, 12H, CH_3), 4.45 (s, 2H, CH_2), 7.3 and 7.8 (d, 4H, ArH). MS: (m/e) 296 and 298.

Anal. Calcd. for $C_{13}H_{18}BBrO_2$: C, 52.57; H, 6.11; Br, 26.90

Found: C, 52.36; H, 5.93; Br, 27.21

Pinacol 4-(Phthalimidomethyl)phenylboronate (8).- To a solution of pinacol 4-bromomethylphenylboronate (**6**, 14.8 g, 0.05 mol) in acetone (200 mL) was added potassium phthalimide (10.2 g, 0.06 mol). The reaction mixture was refluxed for 12 hrs. Acetone was removed on a rotary evaporator and the residue was treated with water. The precipitated solid was collected and air dried to yield 16.5 g (90%). It was crystallized from hexane, mp. 165-166°. ^{1}H NMR ($CDCl_3$): δ 1.3 (s, 12H, CH_3), 4.85 (s, 2H, CH_2), 7.4-7.8 (m, 8H, ArH). MS: $(M+H)^+ = 364^+$.

Anal. Calcd. for $C_{21}H_{22}BNO_4$: C, 69.40; H, 6.10; N, 3.85

Found: C, 69.42; H, 5.89; N, 3.90

Pinacol 4-(Aminomethyl)phenylboronate (9a).- Phthalimido derivative **8** (13.1 g, 0.04 mol) was added to a solution of hydrazine hydrate (2.5 mL) in methanol (150 mL) and the mixture was boiled for 12 hrs. A white solid was formed, which was removed by filtration. The filtrate was concentrated to a small volume. Water was added to the residue and the resultant solution was basified with sodium hydroxide solution. The oil which formed was extracted with ethyl acetate. The ethyl acetate

solution was washed with water and dried with sodium sulfate. Evaporation of ethyl acetate afforded 6.5 g (73%) of yellow viscous oil. This product was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 1.3 (s, 12H, CH_3), 3.85 (s, 2H, CH_2), 7.3 (d, 2H, ArH), 7.8 (d, 2H, ArH). MS: $(M+H)^+ = 234$.

Pinacol 4-(isothiocyanatomethyl)phenylboronate (10a).- To a solution of the amine **9a** (0.23 g, 1 mmol) in methylene chloride (5mL) was added triethylamine (0.15 g, 1.5 mmol). The solution was cooled to 0°, and thiophosgene (0.12 g, 1.05 mmol) was added. The mixture was stirred at 0° for 0.5 hr and at RT for 6 hrs. The solvent was removed and the residue was chromatographed over silica gel (hexane/ethyl acetate, 7:3). Fractions containing the product were collected and evaporated to afford **3** as a yellow solid. It was crystallized from petroleum ether (35-65°) to yield 162 mg (59%), mp. 86-87°. ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 12H, CH_3), 4.73 (s, 2H, CH_2), 7.3 (d, 2H, ArH), 7.8 (d, 2H, ArH). MS: $(M+NH_4^+) = 293^+$.

Anal. Calcd. for $C_{14}H_{18}BNO_2S$: C, 61.11; H, 6.59; N, 5.09; S, 11.65
Found: C, 61.55; H, 6.70; N, 4.76; S, 11.24

Pinacol 4-(cyanomethyl)phenylboronate (7).- Sodium cyanide (0.98 g, 0.02 mol) was added to a solution of **6** (2.96 g, 0.01 mol) in DMF (100 mL) and stirred at RT for 24 hrs. The reaction mixture was poured into water (250 mL) and extracted with ether (3x75 mL). The combined ethereal extracts were washed with water and dried (Na_2SO_4). Evaporation of ether afforded an orange viscous oil which solidified on standing to yield (1.28 g, 53%). A sample was crystallized from hexane/ethyl acetate, mp. 62-63°. ^{1}H NMR ($CDCl_3$): δ 1.3 (s, 12H, CH_3), 3.85 (s, 2H, CH_2), 7.24 (d, 2H, ArH), 7.8 (d, 2H, ArH). MS: $(M+NH_4)^+ = 261$.

Anal. Calcd. for $C_{14}H_{18}BNO_2$: C, 69.17; H, 7.46; N, 5.76
Found: C, 69.30; H, 7.37; N, 5.62

Pinacol 4-(2-Aminoethyl)phenylboronate (9b).- To a solution of 4-(cyanomethyl)phenylboronate **7** (0.64 g, 2.6 mmol) in ethanolic ammonia (25 mL) was added rhodium on alumina powder (5%, 250 mg) and the mixture was hydrogenated at 50 lbs/sq. inch for 24 hrs. The catalyst was removed by filtration and the solvent was evaporated on a rotary evaporator to afford the desired product as a thick yellow oil (0.56 g, 87%), which was used as such for the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 12H, CH_3), 2.75 (t, 2H, $C\underline{H}_2NH_2$), 2.95 (t, 2H, $C\underline{H}_2CH_2NH_2$), 7.26 (d, 2H, ArH), 7.8 (d, 2H, ArH). MS: $(M+H)^+ = 248^+$.

Pinacol 4-(2-isothiocyanatoethyl)phenylboronate (10b).- The title compound was prepared in 62% yield from **9b** (0.46g, 2.0 mmol), triethylamine (0.25 g, 2.5 mmol), and thiophosgene (0.24 g, 2 mmol) in dry methylene chloride, as described for the synthesis of **10a** It was crystallized from petroleum ether (35-60°) at -20°, mp. 49-50°. ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 12H, CH_3), 2.75 (t, $C\underline{H}_2NH_2$), 3.0 (t, 2H, $C\underline{H}_2CH_2NH_2$), 3.72 (t, 2H, $C\underline{H}_2NCS$), 7.26 (d, 2H, ArH), 7.80 (d, 2H, ArH). MS: $(M+H)^+ = 290^+$.

Anal. Calcd. for $C_{15}H_{20}BNO_2S$: C, 62.27; H, 6.97; N, 4.84; S, 11.06
Found: C, 62.16; H, 6.82; N, 5.06; S, 10.98

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(Received July 1, 1991; in revised form Spetmber 23, 1991)