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Synthesis and crystal structure of 4-amino-3-fluorophenylboronic acid

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Abstract—4-Amino-3-fluorophenyl boronic acid has been synthesized from 4-bromo-2-fluoroaniline by protecting the amine group and then carrying out a lithium–bromine exchange, followed by addition of trimethyl borate and then acidic hydrolysis. We obtained a 47% yield. We also measured the X-ray crystal structure. This derivative has a relatively low boronic acid pK_a value of 7.8 when acetylated or attached to acrylamide hydrogels. It also contains a pendant amine which facilitates attachment to polymers, for example. We are using this compound to construct glucose sensing materials that operates at the physiological pH of bodily fluids.

There is a continuing interest in the synthesis of new boronic acid derivatives. This interest stems from the importance of boronic acids in the synthesis of biologically active compounds, and the use of boronic acids themselves as pharmaceutical agents. In the area of synthetic chemistry, boronic acids have been widely used in Suzuki cross-coupling reactions,[1] Petasis reaction,[2] asymmetric synthesis of amino acids,[3] Diels–Alder reactions,[4] protection of diols,[5] selective reduction of aldehydes,[6] carboxylic acid activation,[7,8] and as reagents and starting materials in organic synthesis.[9]

In the field of medicinal chemistry, amino-boronic acids have been used as boron neutron capture (BNCT) therapy agents,[10] as transduction components in feedback controlled drug delivery polymers,[11] for the development of enzyme inhibitors like protease inhibitors,[12] and as antibody mimics for polysaccharides.[13,14] Boronic acid derivatives have also been used for carbohydrate affinity chromatography.[15,16]

The ability of boronic acids to reversibly bind to sugars has long been recognized.[17] For example, boronic acid derivatives have been polymerized in the presence of sugars to create imprinted sugar binding sites,[18,19] which have been utilized, for example, in the racemic resolution of sugars.[18] In addition, boronic acid derivatives have been widely utilized for carbohydrate sensing.[20–38] The use of boronic acids for carbohydrate sensing was recently reviewed by James and Shinkai.[39]

We have been using boronic acid derivatives to fabricate novel carbohydrate and glucose sensing photonic crystal materials.[27,28] We have attached boronic acid derivatives to an acrylamide hydrogel which contains an embedded array of ~100 nm polystyrene particles where the spacing is ~200 nm. This array Bragg diffracts light to report on the hydrogel volume. These carbohydrate and glucose sensing materials are called intelligent polymerized crystalline colloidal arrays (IPCCA) and are designed to determine glucose in body fluids such as in blood and in tear fluid. We have developed a photonic glucose sensor, which utilizes phenylboronic acid groups as the glucose recognition element.[28] Glucose binds to two boronate sites to form crosslinks. These crosslinks cause the hydrogel volume to shrink, which results in a blue shift of the diffracted light in proportion to the glucose concentration.

Our first IPCCA sensors utilized aminophenylboronic acid which had a pK_a bound to the hydrogel of ~8.5. Since our target is to sense glucose in bodily fluids it was essential to synthesize a boronic acid derivative whose pK_a was closer to the physiological pH 7.4. The boronic acid pK_a value strongly influences its affinity for carbohydrate derivatives containing cis diols at any solution pH. The boronate derivatives show much higher affinities to carbohydrates than do the boronic

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acid forms.[22,39–41] Thus, for physiological glucose sensing, we require boronic acid derivatives with pK_a close to or below the physiological pH 7.4.

Many attempts have been made to synthesize low pK_a boronic acid ligands. A commonly used expedient to lower the pK_a value of boronic acid derivatives is to introduce electron-withdrawing groups such as nitro-, fluoro- or carboxy groups into the aromatic ring.[42,43] For instance, *p*-nitrophenylboronic acid[42] has a pK_a value 7.0 according to Singhal et al., but the application of this derivative for in vivo glucose monitoring is problematic due to its potential carcinogenicity. 4-Carboxyphenylboronic acid has a pK_a value of 7.86 in the form of methylamide derivative.[44] Unfortunately, this derivative is insufficiently soluble in water (5 mM of 4-carboxybenzeneboronic acid forms cloudy suspension in water).[44] Fluoro-containing boronic acid derivatives have lower pK_a values, such as 7.2 for [3,5-bis(trifluoromethyl)phenyl]boronic acid.[45] Unfortunately, this derivative does not have a functional group to couple to a polymer matrix.

This motivated us to synthesize 4-amino-3-fluorophenyl boronic acid as a low pK_a boronic acid derivative, which contains an amino group for easy coupling to the carboxyls of hydrolyzed acrylamide hydrogels. Thus, we, for the first time, synthesized a fluoro derivative of amino phenyl boronic acid. This species shows a pK_a of 7.8 when attached to the hydrogel. In addition, this fluoro derivative of phenyl boronic acid may also be a useful starting material for the preparation of drug candidate molecules and enzyme inhibitors.[46]

1. Experimental

Anhydrous solvents were used as provided (in sure/seal bottles) and reactions were performed under a nitrogen atmosphere. All glassware was flame dried under nitrogen atmosphere prior to use. ^{1}H and ^{13}C NMR were collected at 300 and 75 MHz, respectively, in either $CDCl_3$ or D_2O.

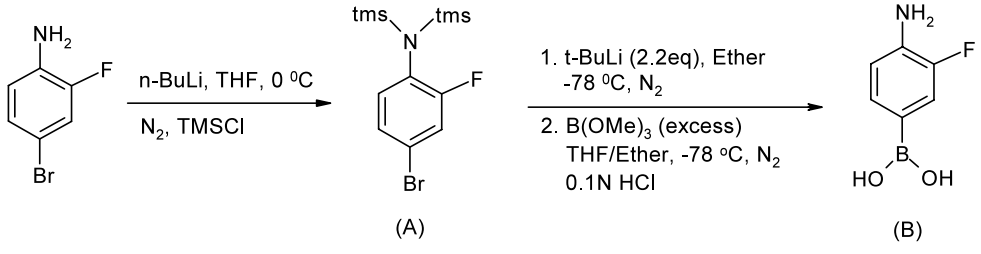
1.1. (A) Preparation of trimethylsilyl-protected 4-bromo-2-fluoroaniline

In a 250 ml three-necked round-bottomed flask equipped with stirring bar, 5 g (26.3 mmol) of 4-bromo-2-fluoro aniline (Acros) was dissolved in approximately 50 ml of dry tetrahydrofuran (THF, Aldrich) under nitrogen atmosphere. 36.2 ml (57.9 mmol) of *n*-BuLi in 1.6 M of hexane (Aldrich) was added by using a syringe and syringe pump over 2.5 h while keeping the reaction mixture at 0°C. The reaction mixture turned dark purple and finally dark brown. Then 7.5 ml (57.9 mmol) of trimethylsilyl chloride (TMSCl, Aldrich) was added to the flask by using a syringe and syringe pump over 1.5 hours. The reaction flask was warmed to room temperature and stirred overnight under nitrogen. The solvent was removed via vacuum evaporation, and the thick black residue was vacuum distilled. Four fractions were collected over a boiling range of 30–70°C, 70–80°C, 80–90°C, and above 90°C. The last two colorless fractions contained 4.5 g of the pure compound A (Scheme 1), yield 47%. ^{1}H NMR ($CDCl_3$): δ 7.28 (d, 2H), 6.84 (t, 1H), 0.3 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 133, 127, 124, 123, 119, 115, 1.8. MS (EI) m/z calcd for $C_{12}H_{21}BrFNSi_2$: 334. Found: 335 (M+H).

1.2. (B) Preparation of 4-amino-3-fluorophenylboronic acid

A 100 ml round-bottomed flask equipped with a stirring bar was flame dried. 4.5 g (13.5 mmol) of compound A was introduced into the flask and was degassed with six vacuum–nitrogen backfill cycles. 7.5 ml of dry ether (Aldrich) was added to the flask and the container was cooled to −78°C in a dry ice/acetone bath. 17.5 ml (29.6 mmol) of *tert*-butyl lithium (*t*-BuLi, 1.7 M in pentane, Aldrich) was added to the flask using a syringe and syringe pump over 0.5 h. The reaction mixture turned pale yellow. In a separate flame dried flask, a solution of trimethylborate ($B(OMe)_3$, 5.5 ml, Aldrich) in 5.8 ml of THF was cooled to −78°C. The contents of the first flask containing compound A and *t*-BuLi (as well as, dry ether washings) were rapidly transferred into the second flask with a syringe.

The reaction mixture was stirred for 15–20 min, at which point it turned orange and a white precipitate appeared. The flask was slowly warmed to room temperature, at which point 63 ml of 0.1 N HCl was added. The reaction mixture was stirred overnight, and then extracted with ether (2×10 ml) and the water layer was removed. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to yield a yellowish oil which was precipitated in pentane at 0°C to give a light yellow solid in 1.3 g (45%) yield. The substance is moisture sensitive and should be stored under a nitrogen atmosphere in a refrigerator. ^{1}H NMR (D_2O): δ 7.28 (d, 2H), 6.84 (t, 1H). ^{13}C NMR (D_2O): δ 153, 150,



Scheme 1. Synthesis of 4-amino-3-fluorophenylboronic acid.

137, 130, 120, 117. MS m/z cacld for $C_9H_{11}BFNO_3$: 211.00. Found: 211.05 (M+Gly–$2H_2O$). m/z cacld for $C_{16}H_{21}BFNO_2$: 289.160. Found: 289.165 (pinanediol derivative).

1.3. Crystal structure of 4-amino-3-fluorophenylboronic acid

Crystals of 4-amino-3-fluorophenylboronic acid were grown from aqueous solution at a temperature of –8°C. A clear needle-like crystal of 0.29×0.12×0.12 mm^3 was used for data collection. X-Ray diffraction was measured using radiation with a wavelength of 0.71073 Å at 150.0 K. The crystal showed a monoclinic crystal system, space group $P2(1)/c$. The same monoclinic space group has been observed for other boronic acid derivatives such as, for instance, *m*-aminophenylboronic acid hydrochloride.[47] Crystal data are: $Z=4$, $a=15.370(6)$, $b=5.247(2)$, $c=9.370(3)$ Å, $\beta=105.834(7)°$, $V=727.0(5)$ $Å^3$, density (calculated) $=1.416$ mg/m^3, absorption coefficient 0.119 mm^{-1}. Of the 7597 reflections measured in the $3<2\theta<60$ range, 2490 unique reflections were used in the structure solution by direct methods. Refinement on F^2 converged at $R_F=0.0494$ ($I>2\sigma(I)$), $wR_F{}^2=0.1314$ (all data). Further details of the crystallographic data can be found in the Supporting Information (CCDC deposition number 216907).

Figure 1 shows an ORTEP plot of the molecule. Boron bond lengths and angles are comparable with those found in other boronic acid derivative.[48,49] All three substituents on the benzene ring are involved in one or more hydrogen bonds between molecules of the unit cell.

The crystal structure data fully confirm the structure of our novel boronic acid derivative. We also synthesized the acetamido derivative of this 4-amino-3-fluorophenylboronic acid and find that it shows a pK_a value of 7.8. Our work with this derivative attached to our IPCCA demonstrates that it functions well as the recognition agent for a photonic crystal sensing material which can determine glucose in bodily fluids such as blood and tear fluid[28] at physiologically relevant glucose concentrations.

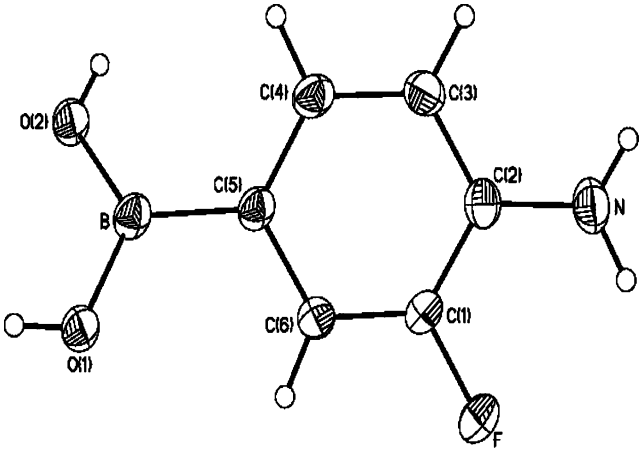


Figure 1. ORTEP plot of the 4-amino-3-fluorophenylboronic acid.

Acknowledgements

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