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Technical Notes

A Large, Laboratory-Scale Synthesis of [4-(2-(2*H*)-Tetrahydropyranyloxy)phenyl]boronic Acid

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Abstract:

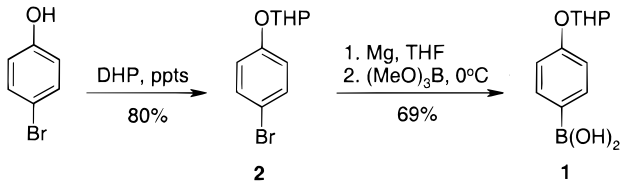
A large, laboratory-scale synthesis of a useful intermediate for coupling reactions, [4-(2-(2*H*)-tetrahydropyranyloxy)phenyl]-boronic acid, is described.

Introduction

Arylboronic acids are extensively used in cross-coupling reactions utilising methodology first described by Suzuki and co-workers.[1] However, boronic acids can sometimes be difficult to prepare on large scale in high yield and purity.

We ultimately required kilo quantities of protected 4-hydroxyphenylboronic acid from which the phenol group could be released under mild conditions. We had previously used commercially available 4-methoxyphenylboronic acid but found that the harsh deprotection conditions, required to remove the methyl group after the cross-coupling reaction of the boronic acid, were incompatible with other functionalities in our molecules. The THP-protecting group for phenols can be removed under mild conditions, for example, tosic acid in methanol (pH ≅ 2), and we therefore decided to develop a route to boronic acid **1** (see Scheme 1). This material has been prepared previously[2] using a *tert*-butyllithium-mediated transmetalation of 2-(4-bromophenoxy)-(2*H*)-tetrahydropyran **2** followed by reaction with trimethyl borate at −90 °C. On a large scale *tert*-butyllithium presents a handling problem, and we therefore decided a Grignard reagent[3] route to this boronic acid, as mentioned but not experimentally described in a footnote in the literature,[4] was a safer way to proceed.

Scheme 1



2 **1**

Results and Discussion

To optimise the preparation of the boronic acid **1** we initially required a kilo batch of bromide **2**. This was achieved by protecting 4-bromophenol as its THP ether using dichloromethane as solvent and PPTS as catalyst. Washing the reaction with 2 M sodium hydroxide solution ensures that the reaction mixture is alkaline prior to the solvent exchange for ethanol and subsequent crystallisation. Efficient cooling is essential during the crystallisation due to the exothermic nature of the process, and, if allowed to crystallise without cooling, the product can melt.

With a kilo of bromide **2** in hand a series of reactions were carried out, investigating the synthesis of the boronic acid. At first we decided to prepare the Grignard reagent of bromide **2** and react that at low temperature (−70 °C) with triisopropyl borate which is reportedly superior to other trialkyl borates for use in forming boronic acids.[5] Contrary to the literature precedent[3] we found that Grignard reagent formation was easily initiated with a crystal of iodine, the reaction starting in approximately 5 min. However, subsequent reaction of the Grignard reagent with triisopropyl borate gave a low yield of product (∼20−47%) after work-up: 10% aqueous ammonium chloride, concentration in vacuo, slurry of the product in ether:isohexane, and then filtration. The reaction mixture always contained a highly UV active, nonpolar impurity, and we wondered if this impurity was being formed at the expense of the desired product. The impurity was shown not to be a simple Wurtz type product from the Grignard formation although it was a dimer. The exact structure remains undetermined.

It was noticed that, after the ammonium chloride work-up, an oily product was obtained if the reaction was not stirred out overnight before phase separation. This is likely to be due to the slow hydrolysis of the isopropyl esters under the slightly basic conditions; pH was ≅8 after quench. Acid could not be used to increase the rate of the ester hydrolysis because the THP group would have been removed. We also noticed that the product decomposed if it was heated too strongly on the rotary evaporator or in a drying oven (see stability table, Table 1). An attempt at solvent removal at atmospheric pressure resulted in decomposition of the

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(2) James, R.; Phillips, P. J.; Ballard, P. G.; Bradbury, R. H. (Zeneca Pharmaceuticals). EP 0 749 964 A1, WO 9640681 A1, 1996.

(3) Ruenitz, P. C.; Bourne, C. S.; Sullivan, K. J.; Moore, S. A. *J. Med. Chem.* **1996**, *39*, 4853.

(4) Malan, C.; Morin, C.; Preckher, G. *Tetrahedron Lett.* **1996**, *37*, 6705.

(5) *Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, 1995; p 5180.

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Table 1. **THP benzene boronic acid stability**[a]

THP benzene boronic acid (THP BBA)	1 week stability (area %)		2 week stability (area %)	
	THP BBA (Rt∼12.3 min)	decomposition product (Rt∼3.9 min)	THP BBA (Rt∼12.3 min)	decomposition product (Rt∼3.9 min)
room temperature	98.8	0.6	98.5	0.7
40 °C	98.2	1.1	97.5	2.0
60 °C	3.2	76.2	57.8	40.4

[a] The results show the level of decomposition product in the 60 °C stability samples is lower at 2 weeks than at 1 week. This indicates decomposition is not constant and may be localised depending on the homogeneity, and local storage conditions of the sample.

product. It is possible for the boronic acid to eliminate water on heating, forming anhydrides. The water thus generated in the presence of the boronic acid functionality can provide a pH low enough to remove the THP-protecting group. It was found necessary to dry the organic extract over magnesium sulfate before concentration for this reason. The stability of the solid isolated product was measured as a function of time and temperature as shown in Table 1.

At this point we decided to replace the triisopropyl borate with the trimethyl borate as used in the literature[2] whilst keeping the temperature cold (−70 °C). An improved yield of 83% was achieved on 40 g scale. In addition it was noticed that the hydrolysis of the boronic acid methyl ester groups was much quicker than that for the isopropyl esters. Careful concentration in vacuo without over-heating followed by the ether:isohexane slurry, to remove the UV active impurity, also helped to increase this yield.

The use of low temperature was ultimately found to be unnecessary, and the reaction could be carried out at 0 °C.

Finally, the slurry solvent was changed from the highly volatile ether:isohexane mixture to ethyl acetate:isooctane which could be used more safely in a pilot plant.

Experimental Section

General. Melting points were recorded on a capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument. Chemical shifts for ^{1}H NMR are reported in ppm downfield relative to TMS as an internal standard in $CDCl_3$ or DMSO-d_6.

Reactions were monitored by HPLC analysis.[6]

2-(4-Bromophenoxy)-(2*H*)-tetrahydropyran (2).[7] 4-Bromophenol (1.025 kg, 5.92 mol) and dichloromethane (2.5 L) were added to a 10 L flask fitted with a condenser, and the mixture stirred under a nitrogen atmosphere; the temperature fell to 6 °C as the 4-bromophenol dissolved. 3,4-Dihydro-2*H*-pyran (580 mL, 6.85 mol) was added in one portion, and the temperature rose to 14 °C. Pyridinium *p*-toluenesulfonate (10.0 g, 40 mmol) was added in one portion, and the temperature rose to reflux within 10 min. After a further 10 min the temperature began to slowly fall, and the mixture was left to stir for 19 h. A solution of aqueous sodium hydroxide (2 M, 1 L) was added, and the mixture stirred vigorously for 2 h. The mixture was separated and the organic phase transferred to a 5 L flask fitted for distillation. The flask was heated under a nitrogen atmosphere, and 2 L of solvent was distilled at 40 °C. Absolute ethanol (3 L) was added, and distillation was continued. After a further 1 L of solvent had been removed, more absolute ethanol was added (500 mL). Distillation and solvent addition was continued until the head temperature reached 78 °C; this required another 500 mL of absolute ethanol. The mixture was cooled to room temperature, with stirring, overnight. The cold solution was seeded (370 mg) whilst stirring, and an exothermic crystallisation began that was moderated by ice-cooling. When the temperature of the mixture reached 4 °C, the product was vacuum-filtered and washed with absolute ethanol (1 L). The crystalline product was dried in a vacuum oven to give the title compound (1.225 kg, 80%): mp 53.5−56.5 °C (lit.[2] mp 51−53 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (dt, 2H), 6.94 (dt, 2H), 5.37 (t, 1H), 3.87 (td, 1H), 3.65−3.55 (m, 1H), 2.1−1.9 (m, 1H), 1.9−1.8 (m, 2H), 1.8−1.5 (m, 3H).

[4-(2-(2*H*)-Tetrahydropyranyloxy)phenyl]boronic acid (1). Dry tetrahydrofuran (700 mL) was added to bromide **2** (400 g, 1.56mol). As the solid dissolved, the temperature fell from 20 °C to 7 °C and generated approximately 1 L of solution.

Magnesium metal turnings (38 g, 1.58mol) and dry tetrahydrofuran (100 mL) followed by three crystals of iodine were added, under a nitrogen atmosphere, to a 2 L flask fitted with a condenser. After the solution stirred at room temperature for 1 min, a portion (∼100 mL) of the bromide **2** solution was added. After 5 min the reaction initiated, and within a further 5 min it reached reflux. At this point the reaction frothed vigorously for 5 min. When the frothing had ceased, the remainder of the bromide **2** solution was added in 20−40 mL portions over 35 min. After complete addition the solution was kept at reflux for 1 h and then cooled to 35 °C.[8]

Tetrahydrofuran (1 L) and trimethyl borate (500 mL, 4.46mol) were added, under a nitrogen atmosphere, to a 10 L flask. The solution was initially cooled to −14 °C and the Grignard reagent then added over 30 min at 0 °C (± 5 °C); a gray-white precipitate formed. After the resulting suspension stirred for 40 min at 0 °C (± 5 °C), a solution of aqueous ammonium chloride (10%, 2.5 L) was added, and the

(6) Details are available in the Supporting Information.

(7) Synthesis of this compound is unoptimised. The order of addition of the reactants would have to be addressed on a larger scale to avoid uncontrolled exotherms. This could be done by slow addition of 3,4-dihydro-2H-pyran to a solution of phenol and catalyst.

(8) The Grignard reagent does not deteriorate after 24 h standing at room temperature although it does partly precipitate from solution at the concentration used.

temperature rose from − 5 °C to 20 °C; the solution pH was ≅8. After the solution stirred for 18 h,[9] ethyl acetate (1.25 L) was added. The mixture was stirred vigorously for 1 h before the organic phase was separated, dried over anhydrous magnesium sulfate (100 g), and vacuum-filtered. The filtrate was added in portions to a 3 L flask and concentrated under vacuum (30 mbar), keeping the internal temperature at <25 °C. When the bulk of the solvent had been removed, a pink solid formed, and the concentration was stopped. Ethyl acetate:2,2,4-trimethylpentane (1:9) (2 L) was added, and the resulting slurry stirred for 10 min before being vacuum-filtered. The solid was washed with ethyl acetate:2,2,4-trimethylpentane (1:9) (1 L) and air-dried. The product was then dried in a vacuum oven to give the title compound as a white solid (239 g, 69%).

Purity > 93% (peak area) by reverse phase HPLC.[10]

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.86 (bs, 2H), 7.71 (d, 2H), 6.96 (d, 2H), 5.69 (t, 1H), 3.8−3.7 (m, 1H), 3.6−3.5 (m, 1H), 2.0−1.4 (m, 6H).

(9) This stirring time can be reduced to 20 min if time is available to complete the full work-up procedure.

(10) The material obtained was pure enough for use in our cross-coupling reactions. The product can be recrystallised if necessary.[2]

Acknowledgment

Thanks to Dr. Adrian M. Clarke for carrying out the time/temperature stability measurements on the boronic acid.

Supporting Information Available

Details of HPLC method. This material is available free of charge via the Internet at http://pubs.acs.org.

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