Synthesis of 2-amino-4-(methoxycarbonyl)phenylboronic acid hydrochloride, a key intermediate for the synthesis of quinolines derivatives

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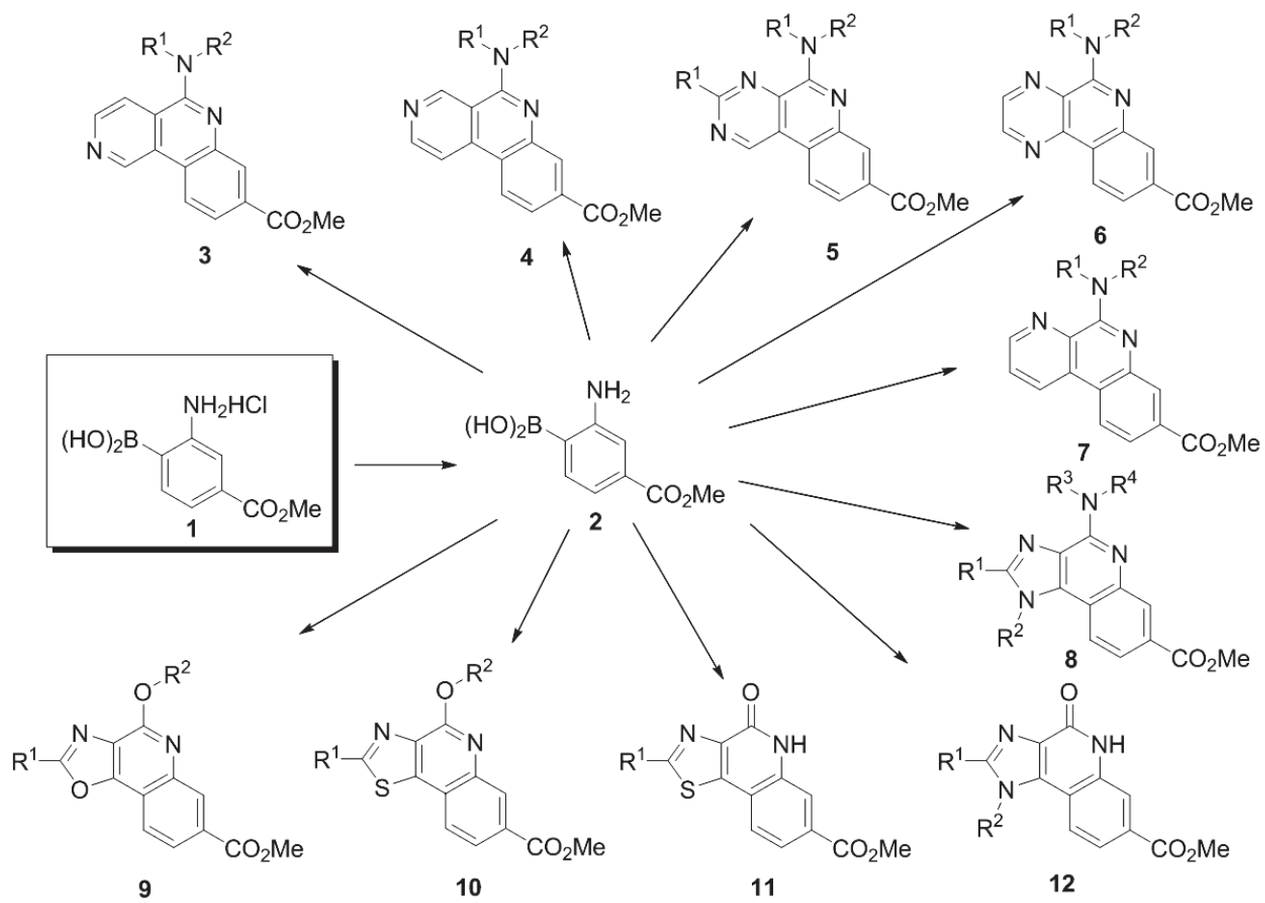
A practical and efficient process for the synthesis in good yield of 2-amino-4-(methoxycarbonyl)phenylboronic acid hydrochloride from *p*-bromo toluene has been developed *via* borylation, oxidation, nitration, esterification and hydrogenation.

Keywords: 2-amino-4-(methoxycarbonyl)phenylboronic acid hydrochloride, borylation, oxidation, nitration, esterification, hydrogenation

In the search for biologically active compounds as potential drug candidates, the efficient synthesis of both libraries and individual heterocyclic small molecules is of major importance to the pharmaceutical industry.[1] Approaches involving a sequence of regiocontrolled halogenation followed by palladium-catalysed coupling reaction based upon a heterocyclic scaffold have been successfully developed.[2] In particular, functionalised arylboronic acids and arylboronates are highly valuable because consecutive cross-coupling is possible from these compounds, which can rapidly lead to the complex structure of target molecules.[3] Among these compounds, 2-amino-4-(methoxycarbonyl)phenylboronic acid hydrochloride **1** is a versatile synthetic intermediate used in cross-coupling reaction for the preparation of a wide variety of natural products and biologically active compounds,[4,5] such as pyrimidoquinolines,[6] imidazoquinolines,[7] thiazoquinolines and oxazoquinolines[8] derivatives. These possess various types of significant biological properties as vaccine adjuvants, such as antiHIV, antituberculosis, anticancer, antimycobacterial (Scheme 1). For example, imiquimod (a simple imidazoquinoline) is an FDA-approved immune response modifier administered as a cream on the skin for the treatment of cutaneous tumours. Imiquimod exerts its immunostimulatory effects through TLK 7 expression on plasmacytoid dendritic cells and B cells in humans.[9]

Despite the recognised importance of 2-amino-4-(methoxycarbonyl)phenylboronic acid hydrochloride in



Scheme 1 Representative compounds based on 2-amino-4-(methoxycarbonyl)phenylboronic acid hydrochloride **1**.

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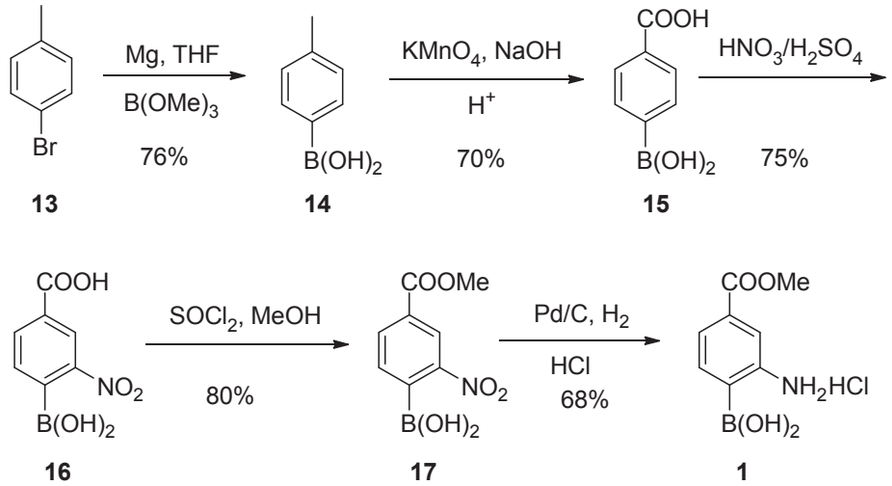


Scheme 2 Preparation of 2-amino-4-(methoxycarbonyl)phenylboronic acid hydrochloride **1**.

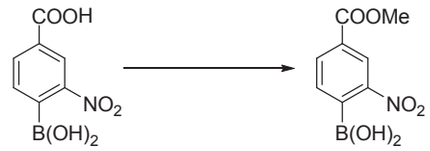
synthesis, to the best of our knowledge, there are no readily available published methods to prepare this compound in the accessible chemical literature. Thus, we now describe a practical and efficient process for the preparation of 2-amino-4-(methoxycarbonyl)phenylboronic acid hydrochloride. Using smooth and simple reaction procedures from readily available starting materials, this method of synthesis provides easy access to the target compound (Scheme 2).

Results and discussion

During the first-step involving the preparation of *p*-tolylboronic acid **14** from bromotoluene **13**, the methyl borate should be completely free from methyl alcohol, since the latter caused a marked diminution in the yield, apparently greater than could be accounted for on the basis of the Grignard reagent being destroyed by the alcohol. Since methyl borate forms an azeotropic mixture with methyl alcohol from which it is relatively difficult to remove the last traces of methyl alcohol, washing with cold concd sulfuric acid was used to obtain the purified methyl borate. Preliminary tests showed that the reaction conditions were improved by adding the *p*-tolylmagnesium bromide to an ether solution of methyl borate under noncryogenic conditions (−12 °C), instead of the procedure used by Chan,[10] thus avoiding cryogenic conditions (−78 °C). Subsequently, the resulting boronic acid **14** was readily converted to **16** by oxidation with potassium permanganate in an alkaline solution. After a preliminary study of the nitration of boronic acid, a satisfactory procedure was developed, whereby *p*-carboxyphenylboronic acid **15** was easily nitrated at room temperature by a mixture of fuming nitric acid and sulfuric acids to yield a single product 2-nitro-carboxyphenylboronic acid **16**. Note that if the boronic acid **15** was first esterified, and the esterified product was then nitrated, some byproducts were produced that were difficult to separate. During the next esterification process (Table 1), 1.2 equiv. of $SOCl_2$ was used in the refluxing methanol. A simple aqueous workup afforded relatively pure product **17** in 80% yield (Table 1, entry 4), which was suitable for use in the next hydrogenation step. In comparison with traditional conc. sulfuric acid-activated esterification reaction, the present procedure both avoided the previously-reported harsh reaction conditions and improved the yield of product.

Finally, after careful exploration of other reducing reagents such as hydrazine hydrate, Fe/HOAc and Zn/HOAc (Table 2), the 2-amino-4-(methoxycarbonyl)phenylboronic acid hydrochloride **1** was smoothly obtained through Pd/C hydrogenation under 1 atm H_2 pressure in 68% yield (Table 2, entry 4).

Table 1 Screening of activating reagents in the esterification reaction of **16**[a]

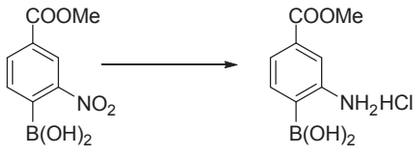


16 **17**

Entry	Activating reagent	Product	Yield/%
1[b]	Conc. H_2SO_4	**17**	65
2[c]	DMAP	**17**	70
3[c]	DCC	**17**	72
4[d]	$SOCl_2$	**17**	80
5[d]	$(COCl)_2$	**17**	77

[a]The reaction was carried out in refluxed methanol for 3 h.
[b]Conc. H_2SO_4 (0.08 equiv.) was used. [c] DMAP (0.1 equiv.) or DCC (0.1 equiv.) was used.
[d]$SOCl_2$ (1.2 equiv.) or $(COCl)_2$ (1.2 equiv.) was used.
[e]Isolated yield based on compound **16**.

Table 2 Screening of reducing reagents in the hydrogenation reaction of **17**[a]



17 **1**

Entry	Reducing reagents	Reaction temperature/°C	Product	Yield/%[f]
1[b]	Pd/C + $N_2H_4H_2O$	65 °C	**1**	40
2[c]	Fe/HOAc	65 °C	**1**	50
3[d]	Zn/HOAc	65 °C	**1**	43
4[e]	Pd/C + H_2	40 °C	**1**	68

[a]The reaction was carried out in methanol for 8 h.
[b]Pd/C (10 g mol^{-1}), $N_2H_4H_2O$ (1.6 equiv.) was used.
[c]Fe (40 g mol^{-1}) was used.
[d]Zn (40 g mol^{-1}) was used.
[e]Pd/C (10 g mol^{-1}), H_2 (1 atm) was used.
[f]Isolated yield based on compound **17**.

A practical and efficient process for the preparation of 2-amino-4-(methoxycarbonyl)phenylboronic acid hydrochloride, a key compound in the formation of many quinolines derivatives is described. To develop a process for this important compound with overall efficiency, each procedure was carefully surveyed to ensure the optimal results. Eventually, a facile as well as cost-effective process has been developed through borylation, oxidation, nitration, esterification, hydrogenation reaction to afford the target compound in good yield and high quality.

Experimental

Solvents and reagents were purchased from Sigma-Aldrich and used without further purification. Melting points were determined on a Mettler FP5 apparatus and are uncorrected. NMR spectra were recorded on Bruker DRX 400 MHz spectrometer using $CDCl_3$ as solvent, and TMS as internal standard. High resolution mass spectra were recorded on Applied Biosystems Mariner System 5303.

p-Tolylboronic acid (**14**)*:* Magnesium turnings (0.72 g, 30 mmol) were placed in a round-bottomed flask and then flame-dried under N_2. bromotoluene (5.1 g, 30 mmol) dissolved in pure ether (20 mL) was added slowly with an addition funnel to the flask. The reaction mixture was gently refluxed for 3 to 4 h. After cooling, the Grignard reagent was transferred to a solution of (3.1 g, 30 mmol) of $(CH_3O)_3B$ in pure ether (10 mL) at –12 °C and stirred overnight slowly warming up to room temperature. After acidification with 10% HCI (10 mL), the product was extracted into ether (3 × 100 mL) and dried (sodium sulfate). The solvent was then removed under reduced pressure, and the product was precipitated by hexane with further recrystallisation from water. *p*-Tolylboronic acid **14** (3.1 g) was obtained in 76% yield as white needles. m.p. 244–245 °C (lit.[10] 243–244 °C).

p-Carboxyphenylboronic acid (**15**): *p*-Tolylboronic acid **14** (7.5 g, 55 mmol) was dissolved in water (350 mL) containing sodium hydroxide (4.5 g). The stirred mixture was treated with a solution of potassium permanganate (16.6 g, 105 mmol) in water (500 mL) as follows. The permanganate solution was divided into eight portions, each of which was added in turn every hour. After all portions of the permanganate solution had been added, the mixture was stirred overnight. Excess permanganate was destroyed by the addition of Na_2SO_3, and the manganese dioxide was filtered off. The filtrate was concentrated to about 200 mL below 40 °C, and then acidified carefully with hydrochloric acid. The crystals that were separated were collected, washed with water, and recrystallised from water to afford compound **15** (6.39 g, 70% yield), m.p. 230–233 °C (lit.[11] 232–234 °C).

2-Nitro-4-carboxyphenylboronic acid (**16**): A stirred slurry of *p*-carboxyphenylboronic acid (3.0 g) in concentrated sulfuric acid (20 g) was treated with fuming nitric acid (1.5 g). A complete solution occurred and the mixture was allowed to stir for 3 h at room temperature, before being poured onto ice. The solution was filtered, washed with a small amount of water and dried. The solid was further recrystallised from water to give 2-nitro-4-carboxyphenylboronic acid **16** (2.9 g, 75% yield) as pale yellow needles, m.p. 262–263 °C (lit.[12] 260–261 °C).

4-(Methoxycarbonyl)-2-nitrophenylboronic acid (**17**)*:* $SOCl_2$ (23 g, 0.19 mol) was slowly added to a solution of 2-nitro-4-carboxyphenylboronic acid 2 (35 g, 0.16 mol) in methanol (350 mL) dropwise, After the reaction mixture had been refluxed for 3 h, it was poured into cold ice water and then stirred for another 0.5 h. The reaction mixture was filtered and then rinsed with EtOAc. The resulting filtercake was dried to give the corresponding 4-(methoxycarbonyl)-2-nitrophenylboronic acid **17** (28.9 g, 80% yield). m.p. 158–161 °C. ^{1}HNMR (d_6-DMSO) δ 8.55–8.58 (d, 1H, J=5.3 Hz), 8.39 (b, 2H), 8.26–8.28 (m, 1H), 7.73 (d, 1H, J=7.6 Hz), 3.92 (s, 3H). HRMS calcd for $C_8H_8BNO_6$ $[M]^+$ 225.0445; found: 225.0439.

2-Amino-4-(methoxycarbonyl)phenylboronic acid hydrochloride (**1**): Concentrated hydrochloric acid (18 g) was added to a solution of 4-(methoxycarbonyl)-2-nitrophenylboronic acid **3** (30 g, 0.13 mol) in methanol (300 mL). After the reaction mixture had been hydrogenated over 10% Pd/C (1.3 g, 10 g mol^{-1}) under 1 atm pressure at 40 °C for 8 h, the catalyst was removed by filtration through Celite®, washed with MeOH and concentrated under reduced pressure. The residue was rinsed with acetone, then filtered. The resulting filtercake was dried under vacuum to afford 2-amino-4-(methoxycarbonyl)phenylboronic acid hydrochloride **1** (21.0 g, 68% yield). m.p. 178–180 °C, which matched that observed for the corresponding product purchased from Combi-Blocks Company. ^{1}H NMR (d_6-DMSO) δ 7.83–7.85 (d, 1H, J=8.0 Hz), 7.59–7.63 (m, 2H), 3.86 (s, 3H). ^{13}C NMR (d_6-DMSO) δ 165.9, 138.5, 136.9, 132.6, 127.2, 123.3, 53.0. HRMS calcd for $C_8H_{11}BClNO_4$ $[M]^+$ 231.0470; found: 231.0473.

This work was supported by the National Natural Science Foundation of China (21072046).

Received 19 September 2014; accepted 7 November 2014
Paper 1402922 doi: 10.3184/174751914X14175346572646
Published online: 19 December 2014

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