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Communications to the Editor

Mild and Selective Synthesis of an Aryl Boronic Ester by Equilibration of Mixtures of Boronic and Borinic Acid Derivatives

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Abstract:

Quenching of aryl Grignard reagents with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (isopropyl pinacol borate) under noncryogenic conditions can lead to mixtures of the corresponding boronic ester along with, generally undesired, borinic acid derivatives. We have found that in certain cases gentle heating of the crude reaction mixtures leads to complete equilibration to give the borinic esters as the sole product which can then be isolated in high yield. This novel equilibration can reduce the need for use of cryogenic conditions or large excesses of reagents to obtain selectivity during boronic ester syntheses.

Introduction

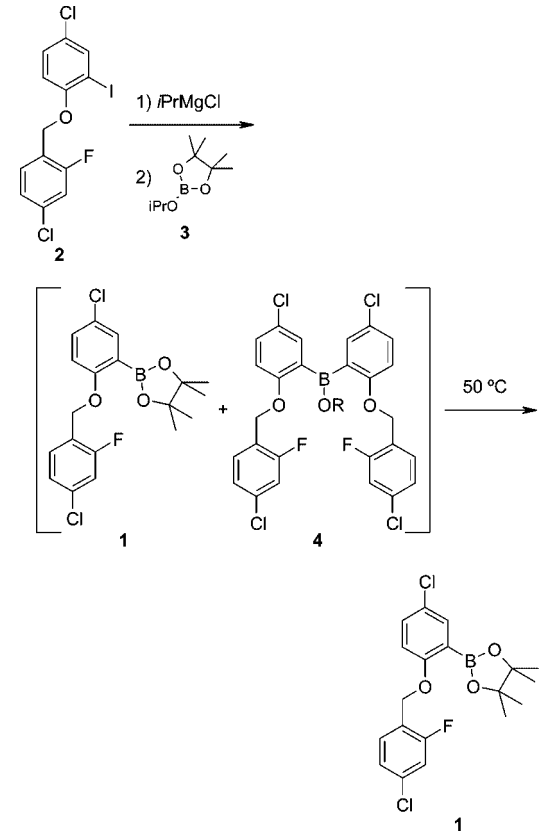
As part of a synthetic programme a convenient procedure was required for the synthesis of pinacol boronic ester **1** on multikilogram (multi-kg) scale.

Aryl boronic acids and esters[1] have become ubiquitous in synthetic chemistry in both industrial and academic settings, predominantly due to their straightforward use in a wide range of transition metal-catalysed coupling reactions.[2] The most common way to access these compounds is by the electrophilic trapping of aryl metal species (generally the aryllithium or Grignard reagent) with a borate ester. Unfortunately this reaction often leads to borinic acid and borane byproducts which arise from second and third additions of the aryl metal reagent into the borate ester. Several options are available to minimise formation of these generally undesired byproducts, most notably use of cryogenic conditions,[3] in situ quenching protocols,[4] and/or large excesses of hindered alkyl borate esters[3] such as triisopropyl borate or isopropyl pinacol borate. Whilst the necessity for use of such conditions does not prevent the reactions from being carried out on large scale, use of more ambient temperatures and only stoichiometric amounts of the borate esters is highly desirable from a process efficiency and operability point of view.[5] Also, in a number of cases, particularly those involving electron-rich aryl groups, the borinic acid is often still formed in significant quantities irrespective of the reaction conditions used.[6] We have found that in certain cases mixtures of boronic and borinic acid derivatives formed under relatively mild reaction conditions can be readily equilibrated to give solely the boronic ester with high selectivity.

Results and Discussion

On a small scale, selective formation of the desired boronic ester **1** was readily accomplished in high yield by iodine magnesium exchange of iodide **2** using *i*-PrMgCl in THF at −10 °C followed by addition of isopropyl pinacol borate (**3**) (Scheme 1). After warming to room temperature overnight and aq workup the desired product could be obtained by crystallisation from heptane. Levels of the undesired borinic acid

Scheme 1. **Equilibration of mixtures of boronic and borinic acid derivatives**



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(1) For leading references see: (a) Hall, D. G. *Boronic Acids*; Wiley: New York, 2005.
(2) For leading references see: (a) De-Meijere, A.; Diederich, F. *Metal Catalyzed Cross Coupling Reactions*; Wiley; New York, 2004.
(3) Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316–1319.
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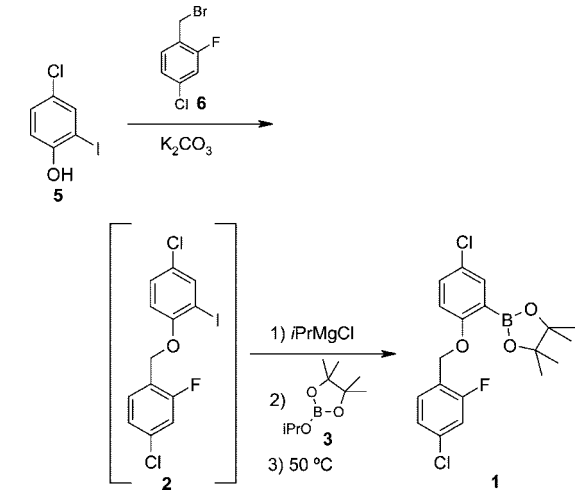
derivatives **4** were shown to be kept to trace amounts either by very slow addition of **3**, maintaining the internal temperature at −10 °C until complete addition had occurred or, alternatively, by very rapid addition of the borolane in one portion. Conversely if only 0.6 equiv of **3** was added and the reaction allowed to warm to room temperature, up to 60% of the borinic acid **4** (R = H) was formed. This did not look ideal for scale up as very fast addition was likely to be impossible and very slow addition is inefficient from a processing perspective. Interestingly, during our development work we had noticed that the borinic acid derivatives in the crude reaction mixture slowly converted to the desired boronate **1** if the reaction mixture was allowed to stir at room temperature for extended periods of time. Gentle heating of these reaction mixtures accelerated this equilibration, and thus, even a reaction mixture containing artificially high levels of the borinic acid of up to 60% could be completely equilibrated through to the desired boronic ester simply by warming the reaction mixture to 50 °C for 1 h. This observation meant that upon scale up we would be able to carry out the addition in a relatively uncontrolled fashion and still obtain high selectivity for the desired product. As far as we are aware this type of equilibration has not been reported previously; however, it is not entirely unexpected, as it is known that the boronic acid derivatives are the thermodynamically more stable species.[1]

On scale up to the pilot plant we opted to telescope the boronate formation onto formation of iodide **2** the isolation of which was complicated by a voluminous crystal form. Thus 4-chloro-2-iodophenol (**5**) was alkylated with 4-chloro-2-fluorobenzyl bromide (**6**) using K_2CO_3 in acetone. After concentration, dilution with toluene, and an aqueous workup the toluene solution of **2** was dried by azeotropic distillation before being cooled to −10 °C and treated with *i*-PrMgCl in THF to effect iodine−magnesium exchange. The Grignard reagent obtained was treated with **3** and allowed to warm to room temperature, giving the desired boronic ester containing up to 30% of the undesired borinic acid derivatives (Scheme 2). Warming this crude reaction mixture to 50 °C for 1 h promoted complete equilibration to the desired product **1** which was isolated by crystallisation from 2-propanol in 78% yield and >99.9% purity.

Several experiments were run to further probe this interesting observation. The parent system, using phenyl magnesium chloride (**7a**), along with simply substituted derivatives using both *p*- and *o*-methoxy phenylmagnesium bromide (**7b** and **7c**) were investigated. Solutions of the desired boronates (**8a**−**c**) containing artificially elevated levels of the borinic acid derivatives **9a**−**c** were prepared by addition of 1 equiv of Grignard reagent to a solution of 0.6 equiv of the borolane at 0 °C. After stirring for 30 min a further 0.6 equiv of borolane was added, and the mixtures were then warmed to promote equilibration to the boronate. The relative amounts of borinic acid and boronic acid derivatives were monitored by LC/UV analysis using dimethoxybenzene as an internal standard (Table 1).

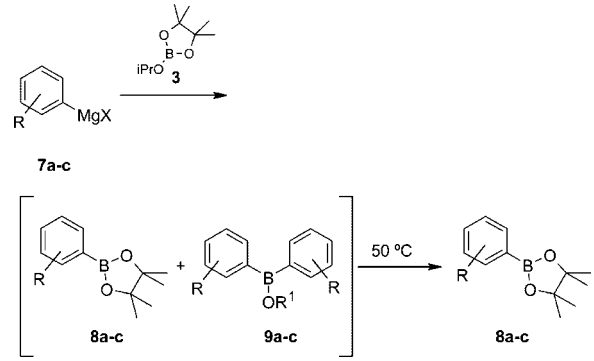
The parent case using phenyl magnesium chloride initially gave a 1.2:1 mixture of borinic and boronic acid derivatives;

Scheme 2. **Pilot-plant scale synthesis of boronate 1**



upon warming no change in this mixture was observed even after extended periods at reflux (Table 1, entry 1). Using *p*-methoxyphenylmagnesium bromide, a 1:1.2 mixture of borinic and boronic acid derivatives was formed, and again no conversion was observed upon heating the reaction mixture (entry 2). In contrast upon gentle warming of the reaction mixture derived from *o*-methoxyphenylmagnesium bromide rapid equilibration to almost entirely the boronate **8c** was observed (entry 3). In this series of experiments it therefore appears that the presence of an *o*-alkoxy group is vital for this equilibration to proceed.

Table 1. **Use of simplified Grignard reagents**



				product ratio **8:9**	
entry	Grignard	R	X	initial	final
1	**7a**	H	Cl	45:55	no conversion[a]
2	**7b**	*p*-OMe	Br	55:45	no conversion[a]
3	**7c**	*o*-OMe	Br	42:58	94:6[b]

[a] No conversion even after 16 h at reflux. [b] Ratio of products after 1.5 h at 50 °C.

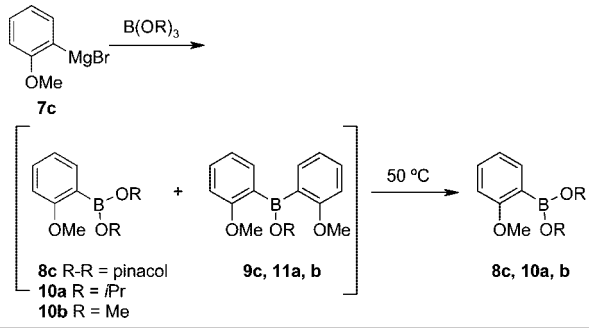
We next briefly investigated use of alternative borate esters (Table 2) in the hope we would be able use a more readily available derivative in place of the relatively expensive isopropyl pinacol borate (**3**).

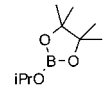
The mixture of borinic and boronic acid derivatives derived from isopropyl pinacol borate, as has been seen, readily equilibrated with gentle warming to give almost exclusively boronate **9c** (Table 2, entry 1). When triisopropyl borate is used

(6) Winkle, D. D.; Schaab, K. M. *Org. Process Res. Dev.* **2001**, *5*, 450–451.

instead, equilibration did occur; however, it was very slow, and competitive proto-deboronation occurred (entry 2). When the simplest borate ester trimethyl borate was used, no equilibration of the initially formed mixture was observed (entry 3); it thus appears that the use of isopropyl pinacol borate is a necessity for efficient equilibration.

Table 2. **Use of alternative borate esters**



Entry	$B(OR)_3$	cmpds	Product Ratio initial	Product Ratio final
1		**8c:9c**	45:55	94:6[a]
2	$B(OiPr)_3$	**10a:11a**	40:60	80:20[b]
3	$B(OMe)_3$	**10b:11b**	31:69	no conversion[c]

[a] Ratio of products after 1.5 h at 50 °C. [b] Ratio of products after 30 h at reflux, under these conditions approximately 20% of the proto-deboronated product was also observed. [c] No conversion observed even after 16 h at reflux.

In summary we have shown that in certain cases reaction mixtures containing both borinic and boronic acid derivatives, obtained by the quenching of aryl Grignard reagents with isopropyl pinacol borate, undergo equilibration upon gentle warming to give only the boronic ester with high selectivity. This observation enables the selective synthesis of certain boronic esters under milder conditions than previously realisable, thus facilitating reaction scale up. We have demonstrated this process on multi-kg scale by the successful synthesis of pinacol boronic ester **1** and expect it to be applicable to the synthesis of a range of other building blocks in the pharmaceutical and fine chemicals industries.

Experimental Section

Reagents and solvents were purchased from commercial sources and were used as received. ^{1}H NMR spectra were recorded at 400 MHz. Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t= triplet, q = quartet, quin = quintet, sep = septet, m = multiplet, b = broad), coupling constant, J (Hz) and integration. ^{13}C NMR spectra were recorded at 100 MHz. Data for ^{13}C NMR are reported in terms of chemical shifts (ppm), and multiplicity (as above) followed by coupling constant (Hz) for fluorine-containing compounds. High-resolution mass spectra (HRMS) were recorded by the Chemical Development Analytical Sciences department at GSK, Stevenage. Elemental analysis was carried out at Butterworth Laboratories Ltd., Teddington.

Preparation of Pinacol Boronic Ester 1. To a solution of 4-chloro-2-iodophenol (**5**) (21.5 kg, 84.5 mol) and 4-chloro-2-fluorobenzyl bromide (**6**) (18.9 kg, 84.5 mol, 1 equiv) in acetone (215 L) at 21 °C was added anhydrous 325 grade potassium carbonate (23.4 kg, 169 mol, 2 equiv). The stirred suspension was heated at reflux for 1 h. The solution was concentrated to 75 L by atmospheric pressure distillation, and toluene (150 L) was added before the organic solution was washed with water (2 × 172 L). Additional toluene (194 L) was added and the solution concentrated to 172 L by atmospheric pressure distillation.

The obtained solution was cooled to −10 °C (causing partial precipitation of iodide **2**) and then treated with isopropylmagnesium chloride in THF (47.3 kg, 48.6 L of a 20% w/w solution in THF, 92.0 mol, 1.09 equiv) at a rate that maintained the temperature between −5 and −12 °C. During this addition the SM initially completely redissolved, and towards the end of the addition the aryl Grignard reagent partially precipitated. 2-Isopropoxy-4,4,5,5-tetramethyldioxaborolane (19.6 kg, 21.5 L, 105 mol, 1.24 equiv) was added, causing the temperature to rise to ∼10 °C. The reaction mixture was allowed to warm to 21 °C and then was further warmed to 50 °C for 1 h before being cooled to 21 °C and quenched with 50% saturated NH_4Cl solution (183 L). The aqueous phase was separated, and the organics were filtered before being washed with water (2 × 172 L) and then concentrated by distillation at atmospheric pressure to ∼65 L. IPA (366 L) was added and the solution concentrated to 129 L by atmospheric pressure distillation and then cooled to 70 °C before being seeded. The mixture was held at 70 °C for 1 h, before being further cooled to 0 °C, and held at that temperature for 1 h. The product was collected by filtration and the cake washed with cold IPA (130 L at 0 °C). The damp product was dried overnight in a vacuum oven at 30 °C to furnish **1** as a white solid, 26.3 kg, 78.4%, >99.9% a/a purity by LC/UV. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 12 H), 5.08 (s, 2 H), 6.86 (d, J = 8.8 Hz, 1 H), 7.08 (dd, J = 9.8, 2.0 Hz, 1 H), 7.17 (dd, J = 8.3, 1.7 Hz, 1 H), 7.35 (dd, J = 8.8, 2.7 Hz, 1 H), 7.67 (d, J = 2.7 Hz, 1 H), 7.94 (t, J = 8.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 63.8, 83.8, 113.3, 115.6 (d, J = 24 Hz), 123.3 (d, J = 13 Hz), 124.3 (d, J = 3 Hz), 126.2, 130.0 (d, J = 5 Hz), 132.2, 133.9 (d, J = 10 Hz), 136.4, 159.4 (d, J = 247 Hz), 161.3. HRMS (EI^+) calculated for $C_{13}H_9O^{35}Cl_2F$ ($MH^+ - BC_6H_{12}O_2$) 270.0014; found 270.0003. Anal. Calcd for $C_{19}H_{20}BCl_2FO_3$: C, 57.36; H, 5.07; B, 2.97; Cl, 17.26; F, 3.36. Found: C, 57.42; H, 4.98; B, 3.01; Cl, 17.49; F, 3.11.

Preparation of Borinic Acid 4 (R = H). An authentic sample of **4** (R = H) was isolated by preparative chromatography from a mixture of the boronate and borinic acid: A solution of iodide **2** (5 g, 12.6 mmol, 1 equiv) in toluene 40 mL was cooled to −10 °C before being treated with a 2 M solution of isopropylmagnesium chloride in THF (6.9 mL, 13.8 mmol, 1.1 equiv) at a rate that maintained the temperature below −3 °C. The reaction was allowed to warm to 0 °C before being treated with 2-isopropoxy-4,4,5,5-tetramethyldioxaborolane (1.55 mL, 7.6 mmol, 0.6 equiv) and then being allowed to warm further to room temp. After 10 min at room temp the reaction was quenched by addition of saturated NH_4Cl solution (40 mL).

The aqueous phase was separated and the organic phase further washed with water (2 × 40 mL) before being concentrated to dryness under reduced pressure. The crude product obtained was dissolved in hot IPA (30 mL) and the solution then cooled to 0 °C, promoting precipitation of the product. The suspension was held at 0 °C for 1 h before the solids were collected by filtration, washing with cold IPA (2 × 15 mL). The damp product was dried under vacuum at 30 °C overnight to furnish 2.0 g of a white solid shown by LC/UV analysis to be a 2:3 mixture of the borinic acid **4** (R = H) and the boronate **1**. A small sample of the pure borinic acid **4** (R = H) (10 mg, 99.1% a/a purity by LC/UV) for analysis was obtained by preparative mass directed HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (s, 4 H), 6.90 (d, J = 9.5 Hz, 2 H), 7.05 (dd, J = 8.2, 1.6 Hz, 2 H), 7.09 (dd, J = 9.8, 2.0 Hz, 2 H), 7.20 (t, J = 8.0 Hz, 2 H), 7.33 − 7.36 (m, 4 H), 8.42 (bs, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 62.9, 113.1, 115.7 (d, J = 25 Hz), 122.9 (d, J = 14 Hz), 124.3 (d, J = 4 Hz), 124.6, 129.5, 130.7 (d, J = 5 Hz), 132.6, 133.1 (d, J = 11 Hz), 159.5 (d, J = 249 Hz), 159.7. HRMS (ESI$^+$) calculated for $C_{36}H_{17}O_3B^{35}Cl_3{}^{37}ClF_2Na$ $(MNa)^+$ 590.9861; found 590.9841.

Acknowledgment

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Supporting Information Available

Experimental details and analytical data for the synthesis of *o*- and *p*-methoxyphenylborinic acids; experimental details for equilibration experiments; details of HPLC methods and retention times for all described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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