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An improved synthesis of 1-methyl-1*H*-pyrazole-4-boronic acid pinacol ester and its corresponding lithium hydroxy ate complex: application in Suzuki couplings

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ABSTRACT

An improved synthesis of 1-methyl-1*H*-pyrazole-4-boronic acid pinacol ester via isolation of the corresponding lithium hydroxy ate complex is described. The hydroxy ate complex is available in one pot from 4-bromo-1-methyl-1*H*-pyrazole and triisopropyl borate, and is isolated by filtration in high yield. Furthermore, the resulting lithium hydroxy ate complex has long-term bench stability and can be employed directly in Suzuki couplings without the need for added base.

A key step of an ongoing drug development programme at Merck involved Suzuki coupling of 1-methyl-1*H*-pyrazole-4-boronic acid pinacol ester **1** with a 3-chloropyridine derivative. Although gram quantities of **1** were available, the cost on multiple kilogram scale prompted efforts to develop a scaleable synthesis of ester **1**.

The ester **1** is a useful reagent for the addition of a 1-methylpyrazole group to aryl or heteroaryl groups by Suzuki coupling.[1] This aryl-pyrazole functionality is found in a range of drug candidates and pharmaceutically active compounds for a variety of therapeutic targets.[2a–f]

The synthesis of ester **1** has been reported to afford a 30% yield of the product starting from 4-bromo-1-methyl-1*H*-pyrazole **2** in a two-step process.[3] Low temperature lithium–halogen exchange followed by a trimethylborate quench and an aqueous ammonium chloride treatment gave the corresponding boronic acid **3** which was subsequently treated with pinacol and 4 Å molecular sieves to give ester **1** (Scheme 1). It was felt that this chemistry would provide a good starting point to develop a scaleable synthesis of ester **1**. However, yield and operational improvements would be required. In this Letter, we report an improved synthesis of the ester **1** and show that the corresponding 'ate' complex can be easily isolated and used directly in Suzuki couplings without the need for additional base.

Previous work on the preparation of aryl boronic acids and esters had indicated that an in situ quench procedure involving the addition of BuLi to a mixture of aryl bromide and triisopropyl borate could give superior yields compared with the traditional stepwise anion formation and alkylborate quench.[4] This procedure was investigated for bromide **2**.

This in situ quench methodology gave a significantly cleaner profile and 90% conversion of bromide **2** into boronic acid **3** compared with <50% under the stepwise conditions. Optimising the quantities of BuLi (from 1.2 to 1.5 equiv) and triisopropyl borate (from 1.2 to 1.3 equiv) improved the conversion to 100%. Adjusting the solvent composition from 1:4 THF/toluene (20 volumes) to 1:1 THF toluene (12 volumes) improved volume efficiency and reduced viscosity at low temperatures. However, isolation of boronic acid **3** remained problematic due to its poor stability, thus a through process to the more stable 1-methyl-1*H*-pyrazole-4-boronic acid pinacol ester **1** without isolation of acid **3** was investigated.

It was noted that quenching the reaction with pinacol gave ester **1** after warming to room temperature. However, isolation of pure **1** was still a considerable challenge due to its high aqueous solubility, partial hydrolysis of the ester and proto-deborylation.

In an attempt to obviate the difficulties encountered during work-up, 5 equiv of water was added to the reaction mixture and the solution aged at room temperature affording a white solid, which was filtered and identified as the lithium hydroxy ate complex **5**. ^{1}H NMR analysis of the product showed that the 12H singlet for pinacol had been split into two 6H singlets, which supports the tetrahedral nature of boron as shown in (Fig. 1). The lithium hydroxy ate complex **5** was found to be a bench-stable solid which showed no signs of decomposition after >1 year. Similar trihydroxyborate species have recently been synthesised by Cammidge et al. from crude arylboronic acids by treatment with sodium hydroxide to provide a discrete species instead of the mixture of anhydrides typically observed with boronic acids.[5a] In addition, Zhichkin et al. recently demonstrated the in situ isopropoxy protection of halogenated arylboronate pinacol esters which has allowed their use in metal–halogen exchange reactions.[5b]

Trihydroxyborate **4** could be formed from the corresponding boronic acid **3** in a similar manner by adding 5 equiv of water

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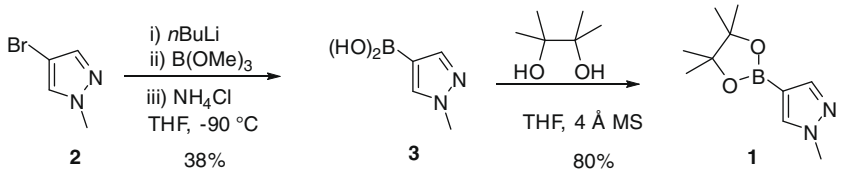


Scheme 1. The literature synthesis of ester **1**.[3]

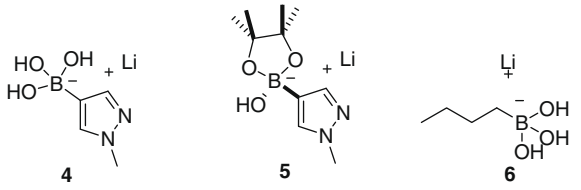


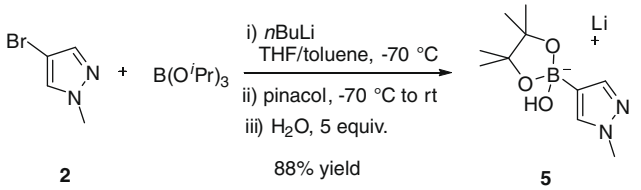
Figure 1. Lithium hydroxy ate complexes.

and by ageing at room temperature; however, **4** was always contaminated with small amounts of lithium hydroxybutyl boronic acid **6** which led us to pursue scale-up of the lithium hydroxy ate complex **5**. The synthesis was found to be scaleable and high yielding, affording complex **5** in a single pot from 4-bromopyrazole **2** in 88% yield on a multi-gram scale (Scheme 2).[6] This process was later demonstrated on multi-kilo scale in 77% yield and on multiple occasions by a third party vendor.

Neutralisation of the lithium hydroxy ate complex **5** to ester **1** (methyl *tert*-butyl ether, acetic acid, followed by drying over sodium sulfate) was achieved in 80% yield. This constitutes an improved procedure for the synthesis of ester **1** from pyrazole bromide **2** in 70% yield over two steps, compared with the previously reported synthesis which achieved a 30% yield. However, we were pleased to find that the neutralisation step was found to be unnecessary as the lithium hydroxy ate complex **5** was shown to be active in the desired Suzuki coupling; moreover, this reaction proceeded without the need for added base providing a straightforward and convenient method to carry out the Suzuki reaction.

The reaction of **5** with a range of aryl chlorides was examined to determine if this was a generally useful reagent for Suzuki couplings with aryl chlorides. The conditions developed by Fu were employed and the reactions of lithium hydroxy ate complex **5** were compared with those of ester **1** using KF as the base (Table 1).[7a,7b]

Instead of being merely comparable with ester **1** and KF, the lithium hydroxy ate complex **5** was shown to give superior performance in all the examples studied. The series of electron-rich, electron-poor, aryl, and hindered aryl chlorides showed a greater than 10 time increase in the reaction rate using the lithium hydroxy ate complex **5** compared with the ester **1** using KF as the base. In most cases, complete conversion was achieved using complex **5** in less than 2 h, the exception to this being the highly electron-rich 2,4-dimethoxychlorobenzene (**11a**, entry 5), the reaction of which slowed significantly and then stalled after around 5 h at 75% conversion due to decomposition of the lithium hydroxy ate complex **5**.[8]



Scheme 2. One-pot synthesis of **5** from **2**.

As expected, the more electron-poor aryl chlorides (**7a**, **8a**, **9a** and **13a**, entries 1, 2, 3 and 7) had the fastest reaction rates, achieving complete conversion in an hour or less. In general, the electron-rich aryl chlorides (**10a**, **12a** and **14a**, entries 4, 6 and 8) required 2 h to reach complete conversion which is still favourable when compared with the typical 80–90% conversion in 24 h observed when the ester **1** and KF are used.

When KF was replaced with LiOH in a Suzuki reaction using ester **1**, the rate of reaction observed was comparable to when lithium hydroxy ate complex **5** was used directly suggesting that LiOH is an excellent choice of base for these examples.

An improved synthesis of the desired pinacol ester **1** has been demonstrated utilising a scaleable one-pot reverse addition protocol to generate the boronic acid **3** and subsequent lithium hydroxy ate complex **5** which was easily isolated in high yield by filtration. Simple neutralisation then afforded ester **1** in an improved overall 70% yield from pyrazole bromide **2** compared with the 30% yield obtained earlier. However, the excellent reactivity with both electron-rich and electron-poor aryl chlorides, and long-term bench stability of lithium hydroxy ate complex **5** show that it is a more easily accessible and useful reagent than ester **1** with the added advantage that no additional base is required to carry out the Suzuki couplings.

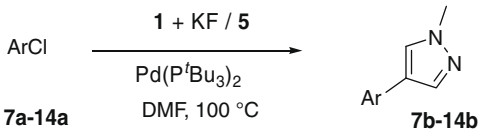
4-Bromo-1-methyl-1*H*-pyrazole (2)

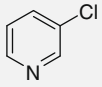
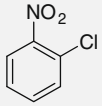
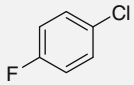
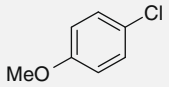
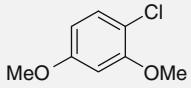
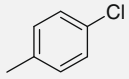
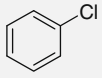
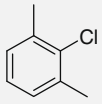
Potassium hydroxide (306 g, 3.67 mol) was carefully added to a mixture of pyrazole (200 g, 2.94 mol) in water (300 mL) whilst maintaining the internal temperature below 30 °C. Iodomethane (230 mL, 3.67 mol) was added over 70 min whilst maintaining the internal temperature below 37 °C. The mixture was allowed to slowly cool to rt and aged for 2 h. CH_2Cl_2 (250 mL) was added and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2 (2 × 250 mL). The combined organics were then washed with brine (50 mL) and concentrated to a volume of approximately 900 mL (85% yield for 1-methylpyrazole). To the CH_2Cl_2 solution of 1-methylpyrazole was added a solution of bromine (151 mL, 2.94 mol) in CH_2Cl_2 (350 mL) over 45 min; the internal temperature was kept below 29 °C with cooling. After 1 h ageing at 25 °C, the reaction was quenched with 10% sodium sulfite (700 mL) and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2 (2 × 250 mL) and the combined organics were washed with saturated brine (150 mL) and then dried over anhydrous sodium sulfate, filtered and concentrated to a colourless oil (368 g, 96 wt %, 75%).[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.34 (s, 1H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 130.0, 92.9, 39.4.

(1-Methyl-1*H*-pyrazol-4-yl)boronic acid pinacol ester lithium ate complex (5)

4-Bromo-1-methylpyrazole (**2**, 101 g, 96 wt %, 600 mmol) was placed in a 3 L three-neck flask equipped with an overhead stirrer, a temperature probe and a nitrogen bubbler. Tetrahydrofuran (600 mL) and toluene (600 mL) were added and the stirred solution

Table 1
Suzuki coupling of aryl chlorides **7a**–**14a** with pinacol ester **1** and lithium hydroxy ate complex **5**



Entry	ArCl		Time for >98% conversion using **5**[a,d]	Yield[c] (%)	Conversion after 24 h using **1**[b,d]
1		**7a**	1 h	94	99
2		**8a**	<10 min	79	100% in 90 min
3		**9a**	<30 min	90	91
4		**10a**	2 h	85	87
5		**11a**	75% conversion in 5 h	58	78
6		**12a**	2 h	89	92
7		**13a**	30 min	90	86
8		**14a**	2 h	92	89

[a] 5 mmol ArCl, 5 mol % Pd(P^{t}Bu$_3$)$_2$, 2.0 equiv **5**, DMF (15 mL), 100 °C.
[b] 5 mmol ArCl, 5 mol % Pd(P^{t}Bu$_3$)$_2$, 2.0 equiv **1**, 2.2 equiv KF, DMF (15 mL), 100 °C.
[c] Isolated yields of **7b**–**14b** after work-up, column chromatography and crystallisation.
[d] Conversion measured by HPLC analysis at 210 nm.

was degassed three times by vacuum/nitrogen cycles and left under an atmosphere of nitrogen. Triisopropyl borate (147 g, 181 mL, 780 mmol) was added and the mixture was cooled to −74 °C. *n*-Hexyllithium (2.3 M in hexanes, 391 mL, 900 mmol) was added over 90 min whilst maintaining the internal temperature below −67 °C. The viscous solution was aged for 15 min before adding pinacol (106 g, 900 mmol). The mixture was then warmed to 25 °C over 40 min. The mixture was aged for 80 min and then cooled to 20 °C. Dropwise addition of water (54 mL, 3 mol) over 10 min formed a white slurry. The slurry was aged for 2.5 h at rt and the solids were isolated by filtration and washed with MTBE (2 × 250 mL). The solids were dried on the filter paper for 10 min and then dried in a vacuum oven at 35 °C for 16 h (150.1 g, 88%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.07 (s, 1H), 7.02 (s, 1H), 3.68 (s, 3H), 3.38 (s, 4H, H_2O), 1.64 (s, 1H, OH), 1.05 (s, 6H), 0.91 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.6, 132.1, 76.9, 75.8, 37.4, 26.3, 26.2.

Typical Suzuki coupling using lithium ate complex 5

Aryl chloride (5 mmol), Pd(P^{t}Bu$_3$)$_2$ (0.25 mmol, 128 mg) and lithium ate complex **5** (10 mmol, 2.85 g, 81.5 wt %) were placed under an atmosphere of nitrogen. Anhydrous DMF (15 mL) was added and the mixture was degassed three times by vacuum/nitrogen cycles. The mixture was heated to 100 °C under nitrogen and aged at this temperature until almost complete conversion (by HPLC) was achieved or the reaction stalled [2,4-dimethyoxy-1-chlorobenzene]. The mixture was then cooled to rt and diluted with MTBE (20 mL) and 2 M HCl (15 mL). The layers were separated and the MTBE layer was extracted with 2 M HCl (15 mL), then 6 M HCl (2 × 15 mL). The acidic aqueous layers were combined and CH_2Cl_2 (25 mL) was added. The mixture was carefully [*Caution*: exothermic] basified with 50% aqueous NaOH (12–13 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL then 10 mL) and the combined CH_2Cl_2 layers were concentrated. Pure

product was isolated by column chromatography (0–100% gradient EtOAc in hexane) followed by crystallisation from MTBE-heptane.

Typical Suzuki coupling using ester 1

Aryl chloride (5 mmol), $Pd(P^tBu_3)_2$ (0.25 mmol, 128 mg), ester **1** (10 mmol, 2.08 g) and KF (11 mmol, 639 mg) were placed under an atmosphere of nitrogen. Anhydrous DMF (15 mL) was added and the mixture was degassed three times by vacuum/nitrogen cycles. The mixture was heated to 100 °C under an atmosphere of nitrogen and aged at this temperature for 24 h [the reaction of 2-chloronitrobenzene was complete within 2 h, Table 1, entry 2]. The mixture was then cooled to rt and diluted with MTBE (20 mL) and 2 M HCl (15 mL). The layers were separated and the MTBE layer was extracted with 2 M HCl (15 mL), then 6 M HCl (2 × 15 mL). The acidic aqueous layers were combined and CH_2Cl_2 (25 mL) was added. The mixture was carefully [*Caution*: exothermic] basified with 50% aqueous NaOH (12–13 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL then 10 mL) and the combined CH_2Cl_2 layers were concentrated. Pure product was isolated by column chromatography (0–100% gradient EtOAc in hexane) followed by crystallisation from MTBE-heptane.

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Supplementary data

Supplementary data (product data and ^1H and ^{13}C NMR spectra for compounds **7b** to **14b**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.105.

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6. The purity of lithium hydroxy ate complex **5** was determined by NMR, HPLC, GC and careful titration and determined to be 81.5 wt % after filtration and methyl *tert*-butyl ether wash. The balance of the wt % was made up with water (10.4 wt %, GC-TCD), LiOH (4.6 wt %, titration) and residual solvents (3.9 wt %, GC).
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8. A larger initial charge of lithium hydroxy ate complex **5** gave some additional conversion.
9. The remaining 4 wt % is made up of residual CH_2Cl_2 and <1% amounts of 1-methylpyrazole and 4-bromopyrazole.