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Effective lithiation of 3-bromopyridine: synthesis of 3-pyridine boronic acid and variously 3-substituted pyridines

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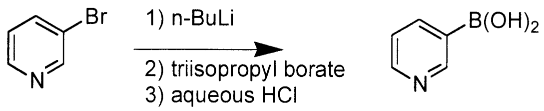
Abstract—By using toluene as a solvent, 3-lithiopyridine can be generated cleanly at −50°C. The addition of various electrophiles affords useful building blocks, such as the 3-pyridine boronic acid in 87% isolated yield. © 2002 Elsevier Science Ltd. All rights reserved.

Substituted pyridines are important components of drug candidates. Recently, we required 3-pyridine boronic acid (**1**) as an intermediate in a Suzuki cross-coupling. Although the compound is commercially available, it is expensive (>$100/g) and often only small quantities can be obtained. Herein, we describe an improved process for the lithiation of 3-bromopyridine and the preparation of 3-pyridine boronic acid, which is capable of producing kilogram quantities of the building block. In addition the method is amenable to the synthesis of a variety of 3-substituted pyridines in excellent yields.



Both magnesium– and lithium–halogen exchange of 3-bromopyridine have been reported in the literature.[1,2] Although magnesium–halogen exchange offers many advantages,[1] in this specific case, isopropyl magnesium chloride exchange did not give satisfactory results due to poor solubility and poor conversions.[3] The resulting 3-pyridylmagnesium chloride formed a very dense precipitate, which was quite unreactive with electrophiles. Reaction with triisopropyl borate only gave a 36% yield of pyridine boronic acid.[4] The assay yield was slightly better at 55% with a modified procedure using a 1:2 mixture of BuMgCl:BuLi,[4,5] but again the solubility was a major problem. Because of the poor solubility of 3-pyridylmagnesium chloride, the alternative lithium–halogen exchange was investigated. Although 3-bromopyridine can be cleanly converted to 3-pyridyl lithium in diethyl ether affording a 99% assay yield of 3-pyridine boronic acid, ether is impractical for large-scale operations. A common problem with the lithium–halogen exchange of bromopyridines in THF is the relative acidity of bromopyridines resulting in de-protonation.[6] Extremely low temperatures (−100°C) are needed to minimize this side reaction. In THF at −60°C with a normal addition mode, a dark-green solution was produced. Only a 44% yield of the boronic acid was achieved after the quench with triisopropyl borate. To overcome the deprotonation an inverse-addition mode was tested. The assay yield was much better at 81%. The stability of 3-pyridyl lithium itself in THF was very good at ≤−50°C. With this result the reaction of the anion was studied with a variety of electrophiles.

In addition to changing the lithiation conditions for 3-bromopyridine, the use of a non-coordinating solvent was considered (Table 1). Normally, lithium halogen exchange does not work well without a coordinating solvent like THF to disassociate the BuLi aggregate. In this case, however, the pyridine nitrogen may suitably activate this exchange. When toluene was used as a solvent, a nice free-flowing yellow solid of 3-pyridyl lithium was generated. The assay yield of 3-pyridine boronic acid was improved to 98% and the product was isolated as a crystalline solid in 87% yield.[7] Since the boronic acid is very polar and water soluble, isolation was difficult. Even with saturating the aqueous layer with sodium chloride only a 70% recovery of the product was achieved with each THF extraction. After

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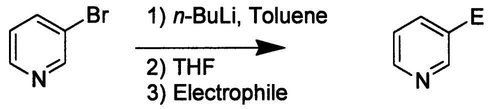
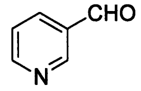
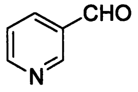
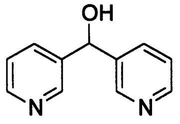
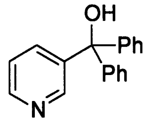
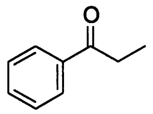
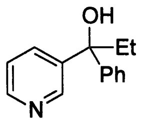
Table 1. Preparation of 3-pyridine boronic acid

Entry	Reagent	Solvent/temp. (°C)	Assayed yield (%)
a	$Me_2CHMgCl$	THF/25	36
b	*n*-BuMgCl/*n*-BuLi (1:2)	THF/−5	55
c	*n*-BuLi	THF/−60	44
d	*n*-BuLi (reversed addition)	THF/−60	81
e	*n*-BuLi	Toluene/−50	98
f	*n*-BuLi (reversed addition)	Toluene/−50	98
e	*n*-BuLi	Ether/−50	99

Table 2. 3-Lithiopyridine reaction with various electrophiles



Entry	Eletrophile	Product	Isolalted Yiled
1	DMF		90%
2			88%
3	Benzophenone		94%
4			94%

three extractions the recovery was increased to 97%. The combined extracts were concentrated and the product was re-dissolved in methanol/THF (1:1). The insoluble salts were removed by filtration and the final product was crystallized by switching the solvent from methanol/THF to acetonitrile.

Interestingly, when toluene was used as the solvent, both normal and reversed additions gave the same result. The pyridyl lithium, which precipitated as a yellow solid from toluene, could be dissolved by adding one volume of THF. This solution of 3-lithiopyridine could conveniently be reacted with a variety of electrophiles with satisfactory results (Table 2).[8,9]

In conclusion, we have shown that 3-lithiopyridine can be easily generated in toluene and have demonstrated a practical way to prepare 3-pyridine boronic acid in 87% isolated yield. In addition this protocol can be easily applied to the preparation of a variety of 3-substituted pyridines.

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3. Conversion between isopropyl magnesium chloride (1.05 equiv.) with 3-bromopyridine is around 85%. This is determined by quenching the anion with water and assaying for the resultant pyridine and starting 3-bromopyridine.
4. (a) A major by-product was bis-pyridine boronic acid. The double addition occurred with triisopropyl borate at room temperature; (b) Fisher, F. C.; Havinga, E. *Rec. Trav. Chim.* **1965**, *84*, 439.
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R.; Song, J. Z.; Tschaen, D.; Wada, T.; Zewge, D.; Volante, R. P.; Reider, P. J.; Tomimoto, K. *J. Org. Chem.* **2001**, *66*, 6775.

6. Cai, D.; Hughes, D. L.; Verhoeven, T. R. *Tetrahedron Lett.* **1996**, *37*, 2537.
7. **Typical procedure**: Toluene (600 mL) in a 2 L 3-necked flask, equipped with an overhead stirrer, was cooled down to −60°C. *n*-BuLi (2.5 M in hexane, 220 mL, 0.55 mol) was mixed with the toluene. After the internal temperature reached −60°C, a solution of 3-bromopyridine (79.0 g, 48.2 mL, 0.50 mol) in toluene (200 mL) was added. The internal temperature was maintained at <−50°C by controlling the rate of addition. A yellow solid precipitated. The resulting slurry was aged for 15–30 min, then THF (200 mL) was added slowly, keeping the internal temperature at <−50°C. The mixture was aged for 15 min, then triisopropyl borate (138 mL, 0.60 mol) was added over 2 min. The solids dissolved and a brown homogeneous solution was obtained. The reaction solution was warmed to −15°C and quenched with 2.7N HCl (484 mL, 1.3 mol). The phases were separated and organic layer was washed with water (30 mL). The aqueous layers were combined, neutralized with 10N NaOH to pH 7, and extracted with THF (3×500 mL). The organic layers were combined and concentrated to dryness. The resulting solid was dissolved with THF (250 mL) and methanol (250 mL). This mixture was filtered to remove inorganic salts and the solids were washed with THF/MeOH (1:1; 100 mL). The combined filtrate and wash was concentrated. The solvent composition was switched to acetonitrile (500 mL) by distillation whereupon the product crystallized. The solids was filtered and dried to give 54.3 g of product as 98 wt% material in 87% yield. HPLC assay of this product was achieved with a YMC ODS-AQ column (4.6×250) giving a 5.3 min retention time at 1 mL/min flow rate eluting with 2% acetonitrile/water/0.1% $HClO_4$. ^1H NMR (CD_3OD, 400 MHz), δ 8.76, s, 1H; 8.51, dd, $J=2$, 5 Hz, 1H; 8.23, d, $J=7.5$ Hz, 1H, and 7.48, m, 1H; ^{13}C NMR (D_2O, CF_3COOD, 100 MHz) δ, 126.1, 133.5 (broad), 140.9, 144.1, 151.0. Elemental analysis for calcd for $C_5H_6BNO_2$: C, 48.86; H, 4.92; N, 11.40; B, 8.8. Found: C, 49.58; H, 4.06; N, 11.42%. It is not unusual for a boronic acid to fail elemental analysis since the functionality is frequently a mixture of free boronic acid and anhydride forms. LC–MS found 124.1 (M+H), 106.3 (M−OH). The boronic acid was used directly in Suzuki couplings without further purification.
8. Since the resulting *n*-BuBr can slowly react with 3-lithiopyridine to form 3-butylpyridine in THF/toluene, extended aging is not recommended.
9. Satisfactory analyses of the pyridine adducts were obtained (^1H and ^{13}C NMR, elemental analysis, and LC–MS).