

A Practical Synthesis of Pyridylboranes via Magnesium-Halogen Exchange

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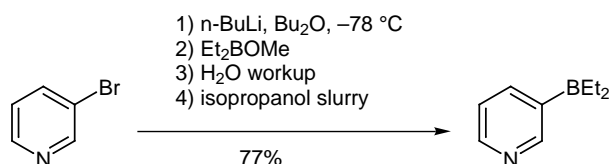
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Abstract: Dialkylpyridylboranes can be prepared by the reaction of the corresponding pyridylmagnesium chloride with diethylmethoxyborane at 0–25 °C. The pyridylmagnesium chlorides are generated from the corresponding bromopyridines via magnesium-halogen exchange reaction.

Key words: magnesium halogen exchange, pyridylborane, Grignard reagent, metalation

Dialkylpyridylboranes are very useful reagents in cross-coupling reactions to prepare substituted pyridine derivatives.¹ The current process for the synthesis of these materials involves the lithium-bromine exchange on the bromopyridine followed by trapping of the lithiopyridine with diethylmethoxyborane or triethylborane.²

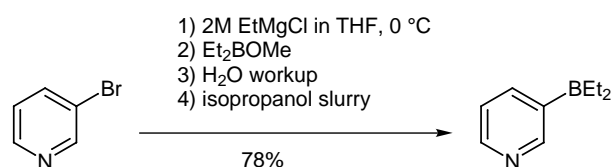


Scheme 1

This reaction must be run at low temperature (< –40 °C in ether, < –100 °C in THF) in order to prevent the anion from migrating, elimination of the bromide to form pyridynes, deprotonation, migration of the halide, and addition of the alkyl lithium to the pyridine during the metal-halogen exchange (Scheme 1).³ The low temperature required for this reaction adds to the cost and difficulty of producing large quantities of these materials commercially.

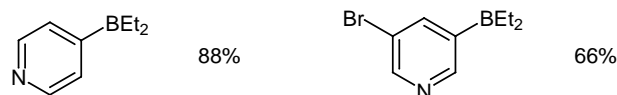
While pyridyllithium reagents are known to decompose at low temperatures, the corresponding Grignard reagents are kinetically stable up to much higher temperatures (>25 °C). However, the magnesiopyridines are notoriously difficult to generate directly from the corresponding halide and magnesium(0).⁴ The use of magnesium-halogen exchange reactions to generate heteroaryl Grignard reagents from the heteroaryl halide and an alkyl or aryl magnesium halide are well known.^{5,6} This reaction was utilized in the direct generation of pyridyl Grignard reagents from the pyridyl halide, magnesium(0), and a reactive alkylhalide such as ethylbromide (the entrainment method).⁵ The for-

mation of pyridyl Grignard reagents via direct reaction with stoichiometric quantities of alkyl or aryl Grignard reagents has also been previously reported.⁷ This process can be run within a wide temperature range as high as 40 °C and generates the halomagnesiopyridine under mild conditions. We have found that 3-pyridyl magnesium chloride generated in this manner reacts readily with diethylmethoxyborane at 0 °C to produce the desired diethylpyridylborane in comparable yield (Scheme 2) and quality to that made by the reaction of the corresponding lithiated pyridine at low temperature (Scheme 1).



Scheme 2

This procedure can also be followed to produce diethyl-4-pyridylborane and diethyl-3-(5-bromopyridyl)borane from 4-bromopyridine and 3,5-dibromopyridine in 88% and 66% yields respectively (Figure).⁸



Figure

Diethyl-3-pyridylborane:

To a 2 M solution of isopropyl magnesium chloride in tetrahydrofuran (200 mL, 0.4 mol) at 0 °C under nitrogen was added 3-bromopyridine (34.5 mL, 0.36 mol) over 45 min., keeping the temperature of the reaction mixture during the addition between 10–25 °C. The mixture was stirred for an additional 1 hour at 0 °C after the addition. Diethylmethoxyborane (52.6 mL, 0.4 mol) was added drop-wise between 10 °C–25 °C (cooled with ice bath) over 30 min. The reaction mixture was then stirred at 0 °C for 1 h and then the reaction was allowed to warm to room temperature overnight. The reaction was quenched by 2 N HCl (200 mL) at 0 °C. The pH of the aqueous layer was adjusted to 7 using sodium carbonate, and the mixture was extracted with ethyl acetate (3 × 150 mL), washed with brine (150 mL), dried over sodium sulfate, and concentrated in vacuo. The crude material was slurried in isopropanol and filtered, providing the product as a white solid (41.5 g, 0.282 mol) in 78% yield. This material was identical to an authentic sample purchased from Aldrich (NMR, mp).

^1H NMR (CDCl_3) δ 8.0 (d, $J = 5$ Hz, 1 H), 7.7 (d, $J = 6$ Hz, 1 H), 7.5 (s, 1 H), 7.2 (dd, $J = 1.9, 8$ Hz, 1 H), 0.6 (m, 2 H), 0.4 (m, 6 H). ^{13}C NMR (CDCl_3) δ 149.3, 144.0, 141.1, 123.6, 14.6, 9.3. mp 172.0–175.5 °C.

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