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Bromine–magnesium exchange of 5-bromo-2-picoline via an organomagnesium complex $^{n}\mathrm{Bu}_2{}^{i}\mathrm{PrMgLi}$: a new preparation methodology of functionalized picolines under noncryogenic conditions

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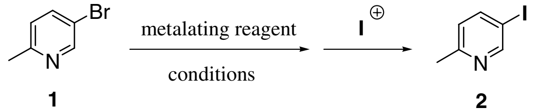
Abstract—The organomagnesium complex $^{n}\mathrm{Bu}_2{}^{i}\mathrm{PrMgLi}$, readily prepared from ^{n}BuLi and ^{i}PrMgCl (2:1), is quite efficient for the bromine–magnesium exchange of 5-bromo-2-picoline under noncryogenic conditions (at −10 °C). The resulting picolylmagnesium complex reacts with various electrophiles to afford functionalized picolines.

Functionalized picolines are important components for the synthesis of biologically active natural products and pharmaceutically active ingredients. Recently, as part of our drug development research, the preparation of 5-substituted-2-picolines from 5-bromo-2-picoline (**1**) was required. One of the most common methods for the synthesis of functionalized pyridines is a halogen–metal exchange of the halopyridine, followed by trapping with an electrophile.[1] Among transmetalations, lithiation is the most useful method. Unfortunately, these methodologies often require low-temperature conditions which are economically disfavored due to higher operational and capital costs. Moreover, the lithiated pyridine species are typically unstable because the electronically deficient pyridine ring is readily attacked intermolecularly by anionic species. Additionally, it is difficult to prepare the metalated 2-picoline species because of the acidic protons on the C-2 methyl group.[2] It has been reported that the lithiation of 5-bromo-2-picoline with ^{n}BuLi in THF generated the lithiopicoline at −100 °C.[3] We wish to report our new mild metalation conditions to prepare a thermodynamically stable and highly nucleophilic magnesium complex.

First, we examined the halogen–metal exchanges of 5-bromo-2-picoline (**1**) using several metalating reagents in THF (Table 1). The exchange reactions were evaluated by the iodination of the resulting metalated species to give 5-iodo-2-picoline (**2**). The bromine–lithium exchange reaction using ^{n}BuLi at −78 °C did not go to completion because of the occurrence of side reactions,

Table 1. Iodination of metalating reagent prepared from 5-bromo-2-picoline (**1**)



1 **2**

Entry	Metalating reagent	Reaction conditions	Yield[a] of **2** (%)
1	^{n}BuLi	THF, −78 °C, 0.25 h	52
2	^{n}BuLi + LiOMe (1.0 equiv)	THF, −78 °C, 0.25 h	32
3	^{i}PrMgCl (1.0 equiv)	THF, rt, 20 h	Trace
4	$^{n}\mathrm{Bu}_2{}^{i}\mathrm{PrMgLi}$ (0.33 equiv)	THF, −10 °C, 0.5 h	90
5	$^{n}\mathrm{Bu}_2{}^{i}\mathrm{PrMgLi}$ (0.50 equiv)	THF, −10 °C, 0.5 h	>99

[a] Yields were determined by HPLC analysis.

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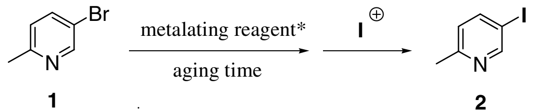
for example, deprotonation, addition of ^{n}BuLi to the substrate, and β-elimination of an anion to form benzyne (52%, entry 1). The use of aggregate base of ^{n}BuLi and LiOMe, which possesses moderate basicity, was also produced less than the optimal results (32%).[4] It has been reported that pyridylmagnesium halides could be prepared by a halogen–magnesium exchange of halopyridines with ^{i}PrMgCl or ^{i}Pr$_2$Mg.[1f–11] We applied this protocol to the preparation of metalated 2-picoline, but the exchange yield was low (entry 3).

We recently demonstrated that magnesium complexes are efficient reagents for the regioselective mono-halogen–metal exchange of dibromoarenes (benzene, pyridine, and thiophene).[5a] Because these magnesium complexes (R_3MgLi) exhibited both basic and nucleophilic properties,[5] they could potentially generate metalated 2-picolines without proton transfer from the C-2 methyl group.[6] Additionally, this protocol could offer a significant advantage for large-scale syntheses because it can be carried out under noncryogenic conditions. Thus, we applied the bromine–magnesium exchange method to 5-bromo-2-picoline (**1**) with our magnesium complex (^{n}Bu$_2$^{i}PrMgLi, 0.33 equiv).[7] The desired 5-iodo-2-picoline (**2**) was obtained in 90% yield (entry 4). Furthermore, the transmetalation went to completion when 0.50 equiv of ^{n}Bu$_2$^{i}PrMgLi was employed (entry 5).[8]

We next examined the stability of the metalated species. We found that the picolylmagnesium intermediate was stable in THF at −10 °C, giving **2** in 96% yield, even after aging for 2 h before treatment with iodine (Table 2). In contrast, the lithiated intermediate was unstable even under cryogenic conditions (−78 °C).

We then examined the reaction with various electrophiles of the magnesium complex. These were generated with 0.50 equiv of ^{n}Bu$_2$^{i}PrMgLi via a halogen–magnesium exchange reaction of 5-bromo-2-picoline (**1**) (Table 3). The magnesium complex showed excellent nucleophilicity. Reaction with benzaldehyde, DMF, and allyl bromide afforded alcohol **3a**, aldehyde **3d**, and propene **3e** in 85–93% yields (entries 1, 4, and 5). The reaction of the picolylmagnesium complex with acid chlorides provided ketones **3b** and **3c**, but the yields were moderate (52%, entry 2; 57%, entry 3) due to side reactions, for example, over-arylation. The reaction with thiuram disulfide furnished the corresponding thiuram aryl sulfide **3f** in 89% yield (entry 6).

Table 2. Stabilities of metalating reagents prepared from 5-bromo-2-picoline (**1**)

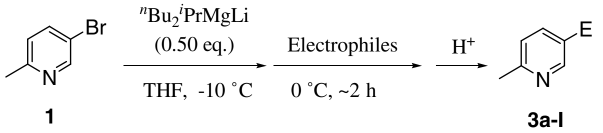


* ^{n}Bu$_2$^{i}PrMgLi (0.50 equiv) ; -10 °C
^{n}BuLi (1.0 equiv) ; -78 °C

Aging time (h)	Yield[a] of **2** (%)	
	^{n}Bu$_2$^{i}PrMgLi (0.50 equiv)	^{n}BuLi (1.0 equiv)
0.25	—	52
0.5	>99	16
2	96	13

[a] Yields were determined by HPLC analysis of reaction aliquots.

Table 3. Picolylmagnesium complex: trapping with various electrophiles



Entry	Electrophile	E	3	Yield[a] (%)
1	PhCHO	CH(OH)Ph	**3a**	93
2[b]	PhCOCl	C(O)Ph	**3b**	52
3	$(CH_3)_3COCl$	$C(O)C(CH_3)_3$	**3c**	57
4	$(CH_3)_2NCHO$	CHO[c]	**3d**	85
5	$CH_2{=}CHCH_2Br$	$CH_2CH{=}CH_2$	**3e**	92
6[c]	^{i}Pr$_2$NC(S)SSC(S)N^{i}Pr$_2$	SC(S)N^{i}Pr$_2$	**3f**	89

[a] Yields were determined by HPLC or GC analysis.
[b] Inverse addition: picolylmagnesium complex was added to the solution of the electrophile.
[c] After quenching with aq acid.

In conclusion, we have demonstrated that the magnesium complex, ^{n}Bu$_2$^{i}PrMgLi, is an efficient reagent for the preparation of metalated picolines under noncryogenic conditions. The prepared picolylmagnesium complex reacts efficiently with various electrophiles in good yields. This is a quite general method for the preparation of functionalized picolines.

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7. The use of $^{n}\mathrm{Bu_3MgLi}$ was also attempted, but it formed a thick sticky slurry and afforded low reproducibility (the yield was 2–3% lower). Therefore, we selected $^{n}\mathrm{Bu_2}{}^{i}\mathrm{PrMgLi}$, which did not form such the thick sticky slurry.
8. Typical experimental procedure (Table 1, entry 5): Butyllithium (1.58 M solution in hexane, 0.63 mL, 1.0 mmol) was added to a solution of isopropylmagnesium chloride (2.08 M solution in THF, 0.24 mL, 0.5 mmol) in THF (2 mL) at 0 °C. After stirring for 15 min, the resulting mixture was cooled to −10 °C and a solution of 5-bromo-2-picoline (**1**) (0.17 g, 1 mmol) in THF (1 mL) was added. The mixture was stirred for 30 min at −10 °C, and then a solution of iodine (457 mg, 1.8 mmol) in THF (1 mL) was added. The reaction mixture was stirred for an additional 2 h at 0 °C, and then the reaction was quenched with AcOH (0.15 mL, 2.7 mmol) and diluted with EtOH. The combined mixture was assayed by means of HPLC to afford 218 mg of iodide **2** (99.5% assay yield).
   Compound **2**: ^{1}H NMR (500 MHz, $\mathrm{CDCl_3}$): δ 8.70 (d, $J = 2.1$ Hz, 1H, Ar–H), 7.86 (dd, $J = 2.1$, 8.2 Hz, 1H, Ar–H), 6.95 (d, $J = 8.2$ Hz, 1H, Ar–H), 2.50 (s, 3H, $\mathrm{CH_3}$); ^{13}C NMR (125 MHz, $\mathrm{CDCl_3}$): δ 157.65, 155.45, 144.74, 125.56, 89.94, 24.27.