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Oxidative magnesiation of halogenopyridines: introduction of electrophilic substituents to the pyridine moiety under the Barbier condition

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Abstract—Oxidative magnesiation of halogenopyridines was carried out using active magnesium prepared by the reduction of magnesium chloride, to give pyridinylmagnesium halides, which were treated with electrophiles to afford the corresponding pyridine derivatives.

Metalation of organic compounds is a useful method to introduce an electrophilic substituent. Because nitrogen-containing six-membered heteroaromatics (abbreviated as heteroaromatics), such as pyridine, are usually inert to electrophiles, metalation of heteroaromatics is an important synthetic technique.

Lithiation of halogenopyridines is accomplished by using alkyllithium[1,2] or lithium naphthalenide[3,4] as a lithiating reagent, but these reactions require low temperature (e.g. −78°C). On the contrary, magnesiopyridines are stable enough compared to lithiopyridines to be prepared at room temperature. However, magnesiopyridines are usually prepared by the reaction of halogenopyridines with alkylmagnesium halide (the halogen–magnesium exchange reaction),[5–10] and only one report[11] about the oxidative magnesiation of 3-bromopyridines using a magnesium metal is known.

In recent years, the chemistry of active magnesium (indicated as Mg*), which is prepared by the reduction of magnesium halide using alkali metal, has been investigated.[12] So, we examined the synthesis of a pyridine Grignard reagent from the corresponding halogenopyridine and Mg*.

Preparation of Mg*: Under an argon atmosphere, a mixture of lithium (83.3 mg, 12.0 mmol), naphthalene (1538 mg, 12.0 mmol), magnesium dichloride (571 mg, 6.00 mmol) and dry THF (30 ml) was stirred at room temperature until lithium was completely consumed (4–5 h) to give a pale green suspension of Mg* (about 0.2 M). The amount of these reagents may be used in proportion to that of the substrate.

At first the reaction of 2-chloro-, 2-bromo-, or 2-iodopyridine with Mg* was carried out as shown in Table 1. The oxidative magnesiation of 2-iodopyridine with Mg* in the presence of pivalaldehyde as an electrophile proceeded at 0–35°C to give 2,2-dimethyl-1-(2-pyridinyl)-1-propanol in 55–67% yield (entries 4–6). The oxidative magnesiation was inhibited when excess aldehyde compared to Mg* was used (entry 7). When 2-chloro- or 2-bromopyridine was used as a substrate, the magnesiation at 20–30°C hardly proceeded, and the reaction under reflux gave the product in low yield (entries 1–3). Both 3- and 4-iodopyridine were magnesiated to afford the product (entries 8, 9).

The experiment proceeded as follows: To a suspension of Mg* (6.00 mmol) in dry THF (30 ml) at an appropriate temperature inside, pivalaldehyde (4.50 mmol) was added in one portion. A solution of halogenopyridine (1.50 mmol) in THF (10 ml) was added dropwise (for 5–10 min) so as to keep the appropriate temperature. The mixture was stirred for 30 min, quenched with aqueous HCl and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and treated with silica gel chromatography (eluted with hexane–ethyl acetate (2:1)) to give 2,2-dimethyl-1-(2-pyridinyl)-1-propanol.

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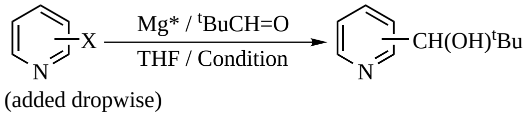
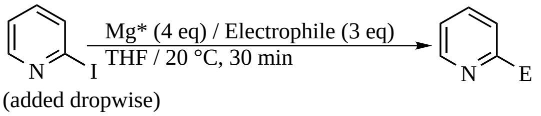
Table 1. Magnesiation of 2-halogenopyridines under the Barbier condition



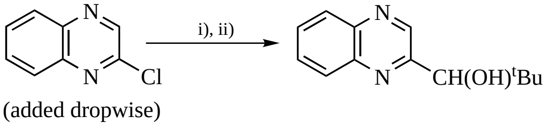
Entry	X	Reagents		Conditions	Yield (%)
		Mg* (equiv.)	^{t}BuCH=O (equiv.)		
1	2-Cl	3	2	25–30°C, 24 h	0
2	2-Cl	3	2	Reflux, 2 h	21
3	2-Br	4	3	20°C, 30 min	Trace
4	2-I	4	3	0°C, 30 min	67
5	2-I	4	3	20°C, 30 min	65
6	2-I	4	3	35°C, 30 min	55
7	2-I	4	5	20°C, 30 min	42
8	3-I	4	3	20°C, 30 min	73
9	4-I	4	3	20°C, 30 min	64

Table 2. Reaction of 2-pyridinylmagnesium iodide with some electrophiles



Entry	Electrophile	-E	Yield (%)
1	^{t}BuCH=O	-CH(OH)^{t}Bu	65
2	E_2C=O	-C(OH)Et_2	50
3	PhMeCHCH=O	-CH(OH)CHPhMe	35
4	PhCH=O	-CH(OH)Ph	17

Table 3. Magnesiation of 2-chloroquinoxaline under the Barbier condition



Reagents and conditions: (i) Mg* (4 equiv.)/^{t}BuCH=O (3 equiv.) THF/condition; (ii) H_3O^+.

Entry	Conditions	Yield (%)
1	0°C, then raised to 20°C	40
2	−20°C, 10 min	51
3	−40°C, then raised to 20°C	51

Next, the oxidative magnesiation of 2-iodopyridine in the presence of a variety of carbonyl compounds was undertaken (Table 2). The use of each carbonyl compound (pivalaldehyde, 3-pentanone, 2-phenylpropionaldehyde and benzaldehyde) as an electrophile for the magnesiation afforded the corresponding alcohols in various yields.

Lithiation of quinoxaline derivatives using a tellurium–lithium exchange reaction followed by addition of pivalaldehyde was already reported,[13] but the Wurtz-type coupling reaction proceeded to give the 2,2′-quinoxaline dimmer even at −78°C because the quinoxaline ring is highly reactive with nucleophiles. So, the Barbier reaction was applied to the magnesiation of 2-chloroquinoxaline and the desired product was obtained as shown in Table 3. It should be noted that the chloro compound, which is regarded as an inert substrate for the metalation, can be magnesiated without requiring low temperature.

In conclusion, we have accomplished the oxidative magnesiation of halogenopyridines using Mg*. As the Barbier reaction enables the magnesio derivatives to be trapped with electrophiles quickly, it may make it possible to magnesiate many nitrogen-containing halogenoheteroaromatics under mild conditions.

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