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Preparation of Nitrogen-Containing π-Deficient Heteroaromatic Grignard Reagents: Oxidative Magnesiation of Nitrogen-Containing π-Deficient Halogenoheteroaromatics Using Active Magnesium

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Abstract: The oxidative magnesiation of nitrogen-containing π-deficient halogenoheteroaromatics using active magnesium was accomplished. Both magnesiation followed by addition of a carbonyl compound (Grignard reaction) and magnesiation in the presence of a carbonyl compound (Barbier reaction) were carried out to afford the corresponding product. Especially, the latter method enabled fused halogenodiazines such as 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine or 2-chloroquinoxaline to magnesiate at a mild temperature (−20 to 30 °C).

Since many natural products or medicinal drugs are made up of nitrogen-containing π-deficient heteroaromatics, studies of these compounds are of much interest to many chemists. It is well-known that π-deficient heteroaromatics react with nucleophiles to give the corresponding substituted product. On the other hand, it is usually difficult to introduce an electrophilic substituent into π-deficient heteroaromatics mainly for two reasons. One is that π-deficient heteroaromatics hardly undergo electrophilic substitution (e.g., Friedel−Crafts acylation), and the other is that metalation of π-deficient heteroaromatics has been reported insufficiently. For example, preparation of lithiopyridine is accomplished by the reaction of halogenopyridine with alkyllithium[1,2] or lithium naphthalenide[3,4] or by the reaction of telluropyridine with alkyllithium,[5] but these reactions require a low temperature such as −78 °C. On the contrary, magnesiopyridine is stable enough compared to lithiopyridine to be prepared at room temperature.[6] However, magnesiopyridine is usually prepared by the reaction of bromo- or iodopyridine, which is less available and expensive compared to chloropyridine, with alkylmagnesium halide (the halogen−magnesium exchange reaction),[6−11] and only one report[12] about the oxidative magnesiation of 3-bromopyridine derivative using a magnesium metal is known. Recently, study of the oxidative magnesiation of halogenopyridines using active magnesium has been reported by us.[13] We applied this method to the oxidative magnesiation of some π-deficient halogenoheteroaromatics and report the results in this paper.

Table 1 shows the results of oxidative magnesiation of halogenopyridines followed by addition of some carbonyl compounds (Grignard reaction). Oxidative magnesiation of 2-chloro-, 2-bromo-, and 2-iodopyridine took place at −20 to 30 °C followed by addition of propionaldehyde to give 1-(2-pyridinyl)-1-propanol (entries 1−6). Analogous results were obtained when benzaldehyde (entry 7) or benzophenone (entry 8) was used as an electrophile. It should be noted that even chloropyridine was magnesiated, whereas magnesiation of a chloropyridine derivative hardly proceeded using isopropylmagnesium halide (chlorine−magnesium exchange).[6−11] Oxidative magnesiation of 2-halogenopyridine followed by addition of 2-phenylpropionaldehyde (entries 9 and 10), pivalaldehyde (entries 11 and 12), and 3-pentanone (entry 13) gave pyridine (observed by TLC) and a small amount of the product. These results can be explained as follows: 2-Pyridinylmagnesium halide is prepared smoothly by the reaction of 2-halogenopyridine and Mg*. When a bulky aldehyde (2-phenylpropionaldehyde and pivalaldehyde) or a ketone (3-pentanone) is used as an electrophile, however, 2-pyridinylmagnesium halide cannot react with the electrophile and reacts with water at posttreatment to afford pyridine.

Table 2 describes the results of oxidative magnesiation of halogenopyridines in the presence of carbonyl compounds (Barbier reaction). To our surprise, the relationship of carbonyl compounds to yields of the products in Table 2 were apparently different from that of Table 1. The magnesiation of 2-iodopyridine in the presence of propionaldehyde afforded no product with the recovery of the substrate (entries 1 and 2). The corresponding product was obtained only in 17% yield when benzaldehyde was used in this reaction (entry 3). On the contrary, the oxidative magnesiation of 2-iodopyridine in the presence of pivalaldehyde or 3-pentanone at 0−35 °C gave the product in 50−67% yields (entries 6−8 and 13), whereas the same reaction under the condition of Table 1 did not proceed. The oxidative magnesiation was inhibited when excess aldehyde compared to Mg* was used (entry 9). When 2-chloro- or 2-bromopyridine was

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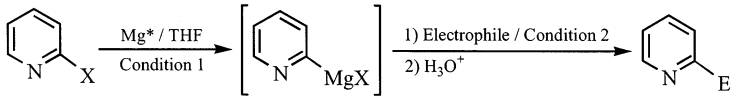
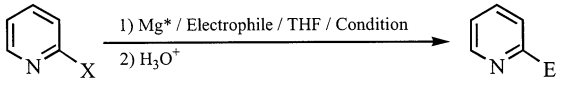
TABLE 1. Oxidative Magnesiation of 2-Halogenopyridine Followed by Addition of Some Carbonyl Compounds



		amount (equiv)						
entry	X	Mg*	electrophile	electrophile	E	condition 1	condition 2	yield (%)
1	Cl	4	4	EtCH=O	2−CH(OH)Et	30 °C, 15 min	25−30 °C, 17 h	56
2	Cl	4	4	EtCH=O	2−CH(OH)Et	30 °C, 3 h	25−30 °C, 17 h	54
3	Br	4	4	EtCH=O	2−CH(OH)Et	30 °C, 15 min	25−30 °C, 19 h	52
4	Br	4	4	EtCH=O	2−CH(OH)Et	30 °C, 2 h	25−30 °C, 14 h	60
5	I	4	4	EtCH=O	2−CH(OH)Et	−20 °C, 30 min	warmed to 25 °C	46
6	I	3	5	EtCH=O	2−CH(OH)Et	20 °C, 5 min	25 °C, 1 h	40
7	Cl	3	5	PhCH=O	2-CH(OH)Ph	20 °C, 5 min	25 °C, 1 h	65
8	Cl	3	5	Ph_2C=O	2-C(OH)Ph_2	0 °C, 5 min	25 °C, 1 h	56
9	Cl	4	4	PhMeCHCH=O	2−CH(OH)CHMePh	30 °C, 1 h	25∼30 °C, 17 h	20[a]
10	I	2	2	PhMeCHCH=O	2−CH(OH)CHMePh	20 °C, 30 min	25 °C, 20 min	24[a]
11	Br	3	5	^{t}BuCH=O	2−CH(OH)^{t}Bu	20 °C, 4 h	25 °C, 30 min	6[a]
12	I	4	3	^{t}BuCH=O	2−CH(OH)^{t}Bu	20 °C, 4 h	25 °C, 18 h	14[a]
13	Br	4	4	Et_2C=O	2-C(OH)Et_2	30 °C, 1 h	25−30 °C, 19 h	0[a]

[a] Generation of pyridine was observed by TLC.

TABLE 2. Oxidative Magnesiation of 2-Halogenopyridines under Barbier Conditions



		amount (equiv)					
entry	X	Mg*	electrophile	electrophile	E	condition	yield (%)
1	I	4	3	EtCH=O	2-CH(OH)Et	−78 °C, 10 min to rt	0[a]
2	I	4	3	EtCH=O	2-CH(OH)Et	20 °C, 30 min	0[a]
3	I	4	3	PhCH=O	2-CH(OH)Ph	20 °C, 30 min	17
4	I	4	3	Ph_2C=O	2-C(OH)Ph_2	20 °C, 30 min	71
5	I	4	3	PhMeCHCH=O	2-CH(OH)CHMePh	20 °C, 30 min	35
6	I	4	3	^{t}BuCH=O	2-CH(OH)^{t}Bu	0 °C, 30 min	67
7	I	4	3	^{t}BuCH=O	2-CH(OH)^{t}Bu	20 °C, 30 min	65
8	I	4	3	^{t}BuCH=O	2-CH(OH)^{t}Bu	35 °C, 30 min	55
9	I	4	5	^{t}BuCH=O	2-CH(OH)^{t}Bu	20 °C, 30 min	42
10	Br	4	3	^{t}BuCH=O	2-CH(OH)^{t}Bu	20 °C, 30 min	tr[a]
11	Cl	3	2	^{t}BuCH=O	2-CH(OH)^{t}Bu	25−30 °C, 24 h	0[a]
12	Cl	3	2	^{t}BuCH=O	2-CH(OH)^{t}Bu	reflux, 2 h	21[a]
13	I	4	3	Et_2C=O	2-C(OH)Et_2	20 °C, 30 min	50

[a] The substrate was observed by TLC.

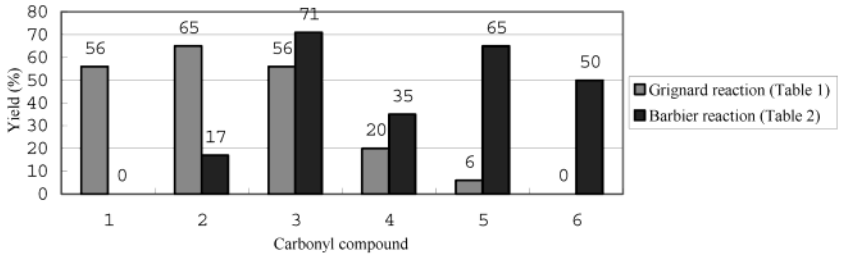
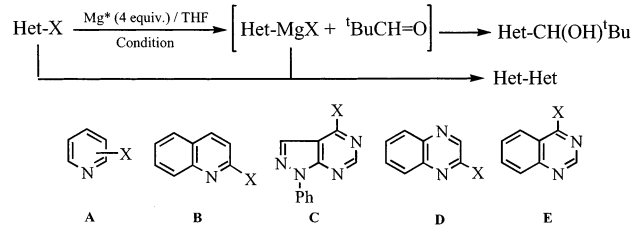


FIGURE 1. Magnesiation of 2-halogenopyridines shown in Tables 1 and 2. Comparison of the yield of products. (1) EtCH=O; (2) PhCH=O; (3) Ph_2C=O; (4) PhMeCHCH=O; (5) ^{t}BuCH=O; (6) Et_2C=O.

used as a substrate, the magnesiation at 20−30 °C hardly proceeded, and the reaction under reflux gave the corresponding product in a low yield (entries 10−12). These results would indicate that Mg* and the oxygen atom of a carbonyl compound make a coordinate state and Mg* becomes inert.

Figure 1 displays the relationship of carbonyl compounds to yields of the products in Tables 1 and 2. The results would be based upon two factors: affinity of a carbonyl compound for Mg* and reactivity of 2-pyridinylmagnesium halide. Grignard reaction using a bulky aldehyde (e.g., pivalaldehyde) or a ketone (e.g., 3-pentanone) hardly proceeded because these carbonyl compounds had insufficient reactivities with the Grignard reagent (RMgX), which comes to equilibrium with R_2Mg and MgX_2 to be a stable form in THF. On the other hand, Barbier reaction using these carbonyl compounds proceeded to afford the corresponding products, because as

TABLE 3. Oxidative Magnesiation of Halogenoheteroaromatics under Barbier Conditions



entry	substrate	X	condition	yield (%) Het-CH-(OH)^{t}Bu	yield (%) by-product
1	**A**	3-I	20 °C, 30 min	73	
2	**A**	4-I	20 °C, 30 min	64	
3	**B**	2-Cl	−20 °C, 30 min	14[a]	
4	**B**	2-Cl	20 °C, 30 min	28	
5	**B**	2-Br	−20 °C, 30 min	59	
6	**B**	2-Br	20 °C, 30 min	42	
7	**C**	Cl	−20 °C, 30 min	41	
8	**C**	Cl	0 °C, 15 min	43	
9	**C**	Br	−20 °C, 30 min to 25 °C	47	
10	**D**	Cl	−40 °C, 5 min	51	
11	**D**	Cl	−20 °C, 10 min	51	
12	**D**	Cl	0 °C, 5 min	40	
13	**E**	Cl	−70 °C, 10 min	0[a]	21[b]
14	**E**	Cl	−20 °C, 10 min	0	45[b]

[a] The substrate was recovered or observed by TLC. [b] 4,4′-Biquinazolinyl.

soon as Grignard reagent generated, the carbonyl compound reacted immediately with the "active" Grignard reagent. It was found that propionaldehyde and benzaldehyde were not suitable for Barbier reaction. These results may indicate that nonbulky aldehydes have easy access to Mg* so that 2-iodopyridine is unable to be magnesiated.

Since many nitrogen-containing π-deficient heteroaromatics, especially fused diazines as shown in Table 3, are highly reactive with nucleophiles, metalation of these compounds requires a low temperature. For example, 7-iodo-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine is lithiated at the 7-position,[14] but this reaction requires −100 °C and gives the corresponding products in low yield. Moreover, lithiation of quinoxaline or quinazoline using tellurium-lithium exchange reaction gave the dimer (2,2′-biquinoxalinyl or 4,4′-biquinazolinyl) even at −78 °C.[15] Thus, we applied the Barbier-type magnesiation to some nitrogen-containing π-deficient halogenoheteroaromatics.

Table 3 shows the oxidative magnesiation of some halogenoheteroaromatics in the presence of pivalaldehyde. 3-Iodopyridine and 4-iodopyridine were smoothly magnesiated to afford the product in 73% and 64% yields, respectively (entries 1 and 2). 2-Chloro- or 2-bromoquinoline reacted with Mg* in the presence of pivalaldehyde at −20 °C to afford the corresponding product in 14−59% yields (entries 3−6), whereas 2-chloro- or 2-bromopyridine was hardly magnesiated at 20 °C. The 4-chloro or 4-bromo derivative of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine, 2-chloroquinoxaline was magnesiated to give the corresponding products in moderate yields without extra cooling such as −78 °C (entries 7−12). Especially, since a method to introduce an electrophilic substituent to the quinoxaline moiety has not been established, this Barbier-type magnesiation would be a useful method. The reaction of 4-chloroquinazoline afforded no desired product and gave 4,4′-biquinazolinyl in 21−45% yields even though under the Barbier conditions (entries 13 and 14). This result may indicate that 4-quinazolinylmagnesium chloride, which was inert to pivalaldehyde, reacted with the substrate, 4-chloroquinazoline. It was found that many fused heteroaromatics were more reactive toward oxidative magnesiation than monocyclic heteroaromatics such as pyridine.

In conclusion, two magnesiating reactions (Grignard reaction and Barbier reaction) of nitrogen-containing π-deficient halogenoheteroaromatics have been accomplished. Even a chloro compound, which was regarded as an inert substrate for the metalating reaction, was magnesiated without requiring low temperature.

Experimental Section

All manipulations were carried out under an argon atmosphere. Tetrahydrofuran was distilled from lithium aluminum hydride and triphenylmethane before use. Halogenopyridines and 3-bromoquinoline are commercially available. 4-Halogeno-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidines, 2-halogenoquinoxalines, and 4-chloroquinazoline were prepared by the reaction of the corresponding hydroxy compound with triphenylphosphine and *N*-halogenosuccinimide.[16,17] Melting points were not corrected.

Preparation of Mg*.[18,19] Under 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 tetrahydrofuran (30 mL) was stirred at room temperature until the lithium was completely consumed (2−3 h) to give a gray suspension of Mg* (about 0.2 M). The amount of these reagents may be used in proportion to that of the substrate.

Oxidative Magnesiation of 2-Halogenopyridines Followed by Addition of Carbonyl Compounds (Grignard Reaction). General Procedure of Table 1. To a suspension of Mg* in tetrahydrofuran, a solution of 2-halogenopyridine in tetrahydrofuran was added dropwise so as to maintain the given temperature inside the flask (Condition 1). After the mixture was stirred for an appropriate time (Condition 1), an electrophile was added and the mixture was stirred (Condition 2). The reaction mixture was quenched with aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and treated with silica gel chromatography to give the corresponding product.

Oxidative Magnesiation of Halogenoheteroaromatics in the Presence of Carbonyl Compounds (Barbier Reaction). General Procedure of Tables 2 and 3. To a suspension of Mg* in tetrahydrofuran was added a carbonyl compound at the temperature shown in Tables 2 and 3. A solution of halogenoheteroaromatics in tetrahydrofuran was added dropwise so as to maintain the given temperature. The mixture was stirred for the time shown in Tables 2 and 3 and raised to room temperature. The reaction mixture was quenched with aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and treated with silica gel chromatography to give the corresponding product.

1-(2-Pyridinyl)-1-propanol[20] was purified with silica gel chromatography (eluted with hexanes−ethyl acetate (2:5)) as pale yellow oil. ^{1}H NMR ($CDCl_3$) ppm: δ 0.94 (3H, t, J = 7.3 Hz), 1.31−2.12 (2H, m), 3.00−4.40 (1H, br), 4.68 (1H, t, J = 5.8

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Hz), 7.05−7.35 (2H, m), 7.68 (1H, td, J = 7.6 Hz, 1.6 Hz), 8.53 (1H, d, J = 4.8 Hz).

Phenyl(2-pyridinyl)methanol[21] was purified with silica gel chromatography (eluted with hexanes−ethyl acetate (1:1)) as pale yellow solids. Mp 59 °C (lit. 76−78 °C). ^{1}H NMR ($CDCl_3$) ppm: δ 4.30−6.00 (1H, br), 5.74 (1H, s), 7.03−7.49 (7H, m), 7.61 (1H, td, J = 7.7 Hz, 1.8 Hz), 8.56 (1H, d, J = 5.1 Hz).

Diphenyl(2-pyridinyl)methanol[22] was purified with silica gel chromatography (eluted with hexanes−ethyl acetate (10:1)) as white solids. Mp 101 °C (lit. 105 °C). ^{1}H NMR ($CDCl_3$) ppm: δ 6.23 (1H, brs), 6.92−7.47 (12H, m), 7.62 (1H, td, J = 7.7 Hz, 1.4 Hz), 8.56 (1H, dd, J = 4.8 Hz, 1.4 Hz).

2-Phenyl-1-(2-pyridinyl)-1-propanol[6] was purified with silica gel chromatography (eluted with hexanes−ethyl acetate (2:1)) as white solids. Mp 80−82 °C. ^{1}H NMR ($CDCl_3$) ppm: δ 1.27 (3H, d, J = 7.0 Hz), 2.60−3.96 (1H, br), 2.86−3.26 (1H, m), 4.80 (1H, d, J = 5.5 Hz), 6.91 (1H, d, J = 7.8 Hz), 6.98−7.41 (6H, m), 7.52 (1H, td, J = 7.8 Hz, 1.3 Hz), 8.51 (1H, dd, J = 4.8 Hz, 1.3 Hz).

2,2-Dimethyl-1-(2-pyridinyl)-1-propanol[23] was purified with silica gel chromatography (eluted with hexanes−ethyl acetate (2:1)) as pale yellow oil. ^{1}H NMR ($CDCl_3$) ppm: δ 0.92 (9H, *s*), 4.35 (2H, brs), 7.06−7.34 (2H, m), 7.48−7.77 (1H, m), 8.46−8.66 (1H, m).

3-(2-Pyridinyl)-3-pentanol[4] was purified with silica gel chromatography (eluted with hexanes−ethyl acetate (12:1)) as colorless oil. Bp 122 °C/13 mmHg. ^{1}H NMR ($CDCl_3$) ppm: δ 0.68 (6H, t, J = 7.4 Hz), 1.82 (2H, q, J = 7.3 Hz), 1.85 (2H, q, J = 7.3 Hz), 5.21 (1H, brs), 7.07−7.39 (2H, m), 7.56−7.83 (1H, m), 8.44−8.61 (1H, m).

2,2-Dimethyl-1-(3-pyridinyl)-1-propanol[24] was purified with silica gel chromatography (eluted with ethyl acetate) as white powder. Mp 89−90 °C (lit. 81−83 °C). ^{1}H NMR ($CDCl_3$) ppm: δ 0.90 (9H, *s*), 3.63 (1H, brs), 4.37 (1H, s), 7.19 (1H, dd, J = 7.9 Hz, 4.8 Hz), 7.67 (1H, dt, J = 7.9 Hz, 1.8 Hz), 8.25−8.45 (2H, m).

2,2-Dimethyl-1-(4-pyridinyl)-1-propanol[25] was purified with silica gel chromatography (eluted with ethyl acetate) as a white powder. Mp 112 °C (lit. 115.5−116.5 °C). ^{1}H NMR ($CDCl_3$) ppm: δ 0.92 (9H, s), 2.90−3.50 (1H, br), 4.35 (1H, s), 7.22 (2H, d, J = 4.6 Hz), 8.42 (2H, d, J = 4.6 Hz).

2,2-Dimethyl-1-(2-quinolinyl)-1-propanol[4,26] was purified with silica gel chromatography (eluted with hexanes−ethyl acetate (4:1)) as yellow oil. ^{1}H NMR ($CDCl_3$) ppm: δ 0.98 (9H, s), 4.20−5.10 (1H, br), 4.53 (1H, brs), 7.14−7.95 (4H, m), 8.09 (2H, d, J = 8.4 Hz).

2,2-Dimethyl-1-(1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-1-propanol[15,27] was purified with silica gel chromatography (eluted with hexanes−ethyl acetate (3:1)) as pale yellow solids. Mp 115 °C (lit. 125−126 °C). ^{1}H NMR ($CDCl_3$) ppm: δ 1.03 (9H, s), 3.74 (1H, brs), 4.77 (1H, brs), 7.29−7.68 (3H, m), 8.10−8.35 (2H, m), 8.36 (1H, s), 9.04 (1H, s).

2,2-Dimethyl-1-(2-quinoxalinyl)-1-propanol was purified with silica gel chromatography (eluted with hexanes−ethyl acetate (3:1)) as yellow oil. Bp 165 °C /0.9 mmHg. ^{1}H NMR ($CDCl_3$) ppm: δ 1.00 (9H, s), 4.06 (1H, d, J = 6.7 Hz), 4.65 (1H, d, J = 6.7 Hz), 7.62−7.88 (2H, m), 7.94−8.22 (2H, m), 8.83 (1H, s). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.21; H, 7.64; N, 12.87.

4,4′-Biquinazolinyl[28] was purified with silica gel chromatography (eluted with hexanes−ethyl acetate (1:2)) as pale yellow solids. ^{1}H NMR ($CDCl_3$) ppm: δ 7.48−7.74 (2H, m), 7.82−8.10 (4H, m), 8.10−8.32 (2H, m), 9.54 (2H, s).

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