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Heteroaryl manganese reagents: direct preparation and reactivity studies

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Abstract—Direct preparation of various heteroaryl manganese reagents was performed by using highly active manganese (Mn$*$) and heteroaryl halides. The resulting organomanganese reagents were coupled with electrophiles such as aryl halides, vinyl halides, and benzoyl chlorides under mild reaction conditions. The corresponding coupling products were obtained in good yields.

Current interest in the synthesis of natural products containing heteroaromatic moieties as building blocks for pharmaceutical industries, material science, and supramolecular chemistry has resulted in considerable effort in developing new synthetic methods.[1]

Among the extensive studies for the preparation of heteroaryl compounds, organometallic reagents are frequently used and mainly prepared from metal–halogen exchange reactions or the methathesis of the corresponding organolithium and organomagnesium derivatives.[2] However, this approach limits the number of functional groups that can be tolerated. The same disadvantage was observed when organozinc reagents were prepared by transmetalation of organolithium and organomagnesium reagents.[3] To alleviate the difficulty, direct preparation of heteroaryl zinc reagents by using Rieke zinc has been reported.[4]

In our continuing studies on the utility of active manganese, we examined the range of oxidative addition and cross-coupling reactions with a broad range of heterocyclic halides. Until now, active manganese prepared by the Rieke method has been shown to exhibit superior activity to organic halides under mild reaction conditions. The resulting organomanganese reagents have also shown a great reactivity toward several electrophiles in excellent yields.[5] In spite of the importance of π-deficient heteroaryl manganese halides, few results have been reported about the preparation and application of heteroaromatic manganese reagents.[6]

Here, we wish to report the direct formation of heteroaryl manganese halides and the results of several cross-coupling reactions. In addition, palladium-catalyzed cross-coupling reaction of heteroaryl manganese reagents is also described.

In general, heteroaryl manganese halides are easily prepared by the reaction of highly active manganese with various heteroaryl halides under mild reaction conditions. And, it is of interest that cross-coupling reaction of these reagents with acid chlorides was accomplished without using any transition metal catalyst which is required for the reaction of organozinc reagents. The corresponding ketones were obtained in good isolated yield (Scheme 1). The results of the cross-coupling reactions are summarized in Tables 1 and 2.

The oxidative addition of Mn$*$ was completed using 3 equiv of Mn$*$ and 1 equiv of the corresponding halides in a few hours at room temperature except with 3-bromofuran (Table 1, entries 6 and 11). The following coupling reactions were performed in an hour at room temperature as well. It is noteworthy that the acylation reaction of N-containing π-deficient heteroaryl compound such as pyridine becomes readily feasible through direct preparation and reaction of pyridinylmanganese reagents (Table 1, entries 1, 4, 8, and 9). This is particularly

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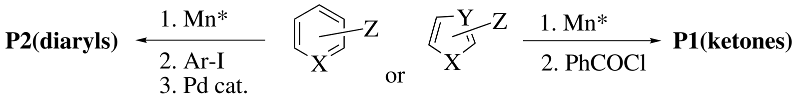
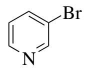
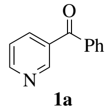
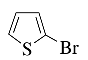
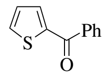
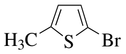
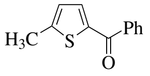
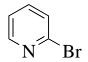
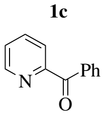
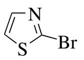
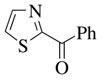
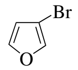
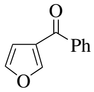
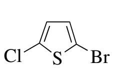
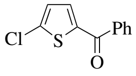
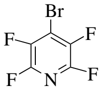
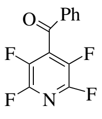
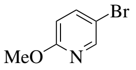
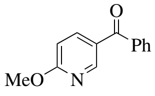
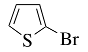
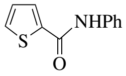
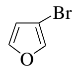
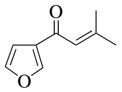
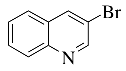


X, Y = Hetero atoms (N, O, S)
Z = Br

Scheme 1.

Table 1. Reactions of heteroaryl manganese bromides with benzoyl chloride

Entry	Substrate	Product[a]	Yield[b] (%)
1		 **1a**	61
2		 **1b**	92
3		 **1c**	90
4		 **1d**	33
5		 **1e**	55
6[c]		 **1f**	60
7		 **1g**	88
8		 **1h**	71
9		 **1i**	65
10[d]		 **1j**	80
11[c]		 **1k**	67
12		—	0

[a] All products were fully characterized by ^{1}H, ^{13}C NMR, and HR-MS.

[b] Isolated yield (based on organomanganese reagent).

[c] 4 equiv of Mn∗ was used for oxidative addition.

[d] Phenyl isocyanate was used as electrophile.

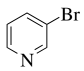
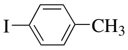
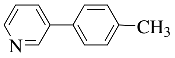
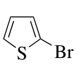
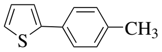
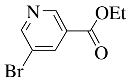
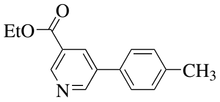
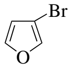
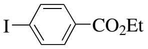
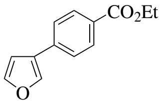
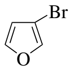
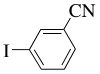
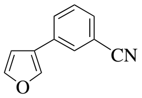
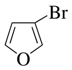
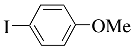
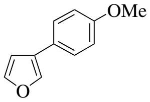
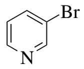
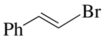
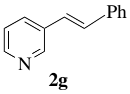
significant considering the fact that Fridel–Crafts acylation or alkylation cannot be done in the pyridine ring. Substituted thiophene derivatives were also examined demonstrating that these thienyl reagents could be prepared readily by the direct oxidative addition of active manganese to thiophene halides with regioselectivity and no decomposition of the thiophene ring at room temperature. These thiophene derivatives have attracted much attention in both material and pharmaceutical sciences[7] (Table 1, entries 2, 3, 7, and 10). In the case of entry 7, selective oxidative addition and coupling reaction with benzoyl chloride was observed. When phenyl isocyanate was used as the electrophile (Table 1, entry 10), the reaction gave a secondary amine product. As to heteroaryl five-membered rings, it was interestingly shown that furanic ketones or 3-acyl-furans were easily obtained through the acylation of a 3-furyl manganese derivative. (Table 1, entries 6 and 11). It is well known that such acylations are very difficult because of the low stability of these organometallic reagents, which must be prepared and used at low temperature.[8] However, the organomanganese reagents were readily prepared with highly active manganese and 3-bromofuran at room temperature. They have been used to prepare the derivative of natural furanic ketones (perilla ketone).[9]

Other possible substrates were also tested for the reactivity studies. However, in the case of 3-bromoquinoline as an example (Table 1, entry 12), the reaction gave a high yield of the reduced product, and no coupling product was observed.

Cross-coupling reactions with functionalized aryl halides were also investigated in the presence of a catalytic amount of Pd catalyst. The corresponding C–C bond forming products were obtained in good yield as shown in Table 2. The reactions were also performed readily in a few hours at room temperature. Interestingly, 3-stilbazole (Table 2, entry 7), which is used in a photo responsive chemical system in plants,[10] was readily prepared by the reaction of pyridinylmanganese bromide with β-bromostyrene under the applied conditions. Additionally, furanic manganese bromides and thienyl manganese bromides underwent cross-coupling reactions with electrophiles containing different functional groups in good yields.

In conclusion, organomanganese reagents were easily prepared via direct oxidative addition of highly active manganese to a variety of heteroaryl compounds and the resulting organomanganese reagents gave the expected cross-coupling products in good yields under mild reaction condition.[11] It is noteworthy that

Table 2. Cross-coupling reactions of heteroaryl manganese reagents[a]

Entry	Substrate	Electrophile	Product[b]	Yield[c] (%)
1		 **A**	 **2a**	72
2		**A**	 **2b**	91
3		**A**	 **2c**	54
4			 **2d**	60
5			 **2e**	66
6			 **2f**	56
7			 **2g**	58

[a] Performed in the presence of 2 mol% $Pd[P(Ph_3)]_4$.

[b] All products were fully characterized by ^1H, ^{13}C NMR, and HR-MS.

[c] Isolated yield (based on electrophile).

functional groups such as ester and cyano are tolerated by the highly active manganese. Further investigations of using organomanganese reagents in synthetic organic chemistry are in progress due to the increasing demand of the functionalized heteroaryl organometallics.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.06.092.

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11. The following is a typical procedure for palladium-catalyzed cross-coupling reactions of heteroaryl manganese reagents with electrophiles: to a slurry of Rieke manganese (9.0 mmol) in THF (15 ml) under argon was added 2-bromothiophene (3.0 mmol) at room temperature. The mixture was stirred at room temperature for 3 h. 1,2-Dibromoethane (7.0 mmol) was added neat to the reaction mixture at 0 °C and the mixture was allowed to warm to room temperature over 20 min. The resulting thienylmanganese bromide was cannulated via a cannula into a flask containing iodotoluene (2.0 mmol) and $Pd[P(Ph)_3]_4$ (0.06 mmol) at 0 °C over 20 min. After cannulation was completed, the reaction mixture was stirred at rt for 1–2 h. The reaction was quenched with 2 M HCl (5 ml), then extracted with ether (2 × 10 ml). The combined organic layers were sequentially washed with saturated $NaHCO_3$, $Na_2S_2O_3$, and brine solutions, then dried over Na_2SO_4, and concentrated under vacuum. Flash chromatography (ethyl acetate/hexanes) afforded 4-thienyltoluene in 90% isolated yield.