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Tributylmagnesium ate complex-mediated novel bromine–magnesium exchange reaction for selective monosubstitution of dibromoarenes

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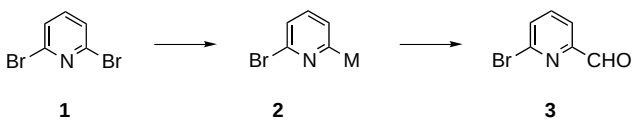
Abstract—Lithium tributylmagnesate complex (n-Bu_3MgLi), readily prepared from n-BuLi and n-BuMgCl (2:1), is a novel metallation agent. It is quite efficient for the selective mono-bromine–magnesium exchange of 2,6-dibromopyridine (**1**) under non-cryogenic conditions (at −10°C) to give a stable magnesate intermediate. Subsequent treatment with DMF gave 6-bromo-2-formylpyridine (**3**) in excellent yield. This method is also applicable for selective monosubstitution of several other kinds of dibromoarenes.

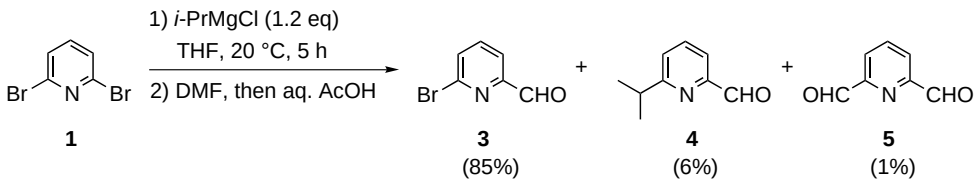
In the course of the process development for a novel muscarinic M_3 antagonist,[1] we required selective mono-formylation of 2,6-dibromopyridine (**1**) via a bromine–metal exchange reaction (Scheme 1). Selective mono-metallation of **1** appears to be a key transformation for the synthesis of biologically important compounds[2] and several procedures for the lithium–bromine exchange of **1** giving **2** (M = Li) using n-BuLi have been reported.[3] However, these methods require cryogenic conditions (−40 to −78°C) and are not practical for industrial-scale operation. The development of a practical and scalable process, which does not need cryogenic conditions, has been quite desirable. In this article, we describe a novel scalable bromine–magnesium exchange reaction of **1** utilizing the magnesium ate complex n-Bu_3MgLi. The application to several aryl and heteroaryl dibromides is also described.



1 **2** **3**

Scheme 1.

The magnesium–bromine exchange reaction of **1** with i-PrMgCl at ambient temperature has been reported recently by Quéguiner et al.[4] We applied their protocol to the preparation of **3**. However, even using our optimized conditions (Scheme 2), the desired exchange reaction was relatively sluggish (>5 h at 20°C) and a slight excess of i-PrMgCl was necessary to complete the reaction. In addition, the formation of an alkylated side product **4** (>5%) was not prevented.[5] On the other hand, it should be noted that the organomagnesium



1 **3** (85%) **4** (6%) **5** (1%)

Scheme 2.

Keywords: aryl halides; exchange reactions; formylation; magnesium and compounds; metallation.

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intermediate (**2**: M = MgCl) was very stable at 20°C and no significant decomposition was observed, even after aging for 24 h. Knochel et al. have recently reported that the analogous *i*-Pr_2Mg-induced exchange reaction shows a similar reactivity to *i*-PrMgCl.[6] These results prompted us to investigate a magnesium ate complex (R_3MgLi), which should exhibit the reactivity between *n*-BuLi and *i*-PrMgCl/*i*-Pr_2Mg, giving a stable metallated species under non-cryogenic conditions. The use of magnesium ate complexes for the halogen–metal exchange has not been known until a recent report by Oshima et al.[7]

The ate complex *n*-Bu_3MgLi can be prepared by mixing equimolar amounts of *n*-Bu_2Mg and *n*-BuLi according to the literature.[8] Since *n*-Bu_2Mg can be prepared from *n*-BuMgCl and *n*-BuLi,[9] we thus chose *n*-BuMgCl as a more convenient and safer alternative to *n*-Bu_2Mg. We therefore prepared *n*-Bu_3MgLi by mixing *n*-BuMgCl (in THF) and *n*-BuLi (in hexane) in the ratio of 1:2;[10] the ^1H and ^{13}C NMR observations showed the existence of a single species distinctly different from either *n*-BuMgCl or *n*-BuLi.[11] The bromine–magnesium exchange reaction of **1** with the *n*-Bu_3MgLi (0.35 mol equiv.; 1.05 equiv. of Bu) proceeded efficiently at −10°C in toluene,[12] giving an almost pure mono-metallated intermediate (97% in peak area of HPLC).[13] Subsequent treatment with DMF gave the desired aldehyde **3** in 95% yield (Scheme 3). Interestingly, several protocols for the halogen–metal exchange using metal ate complexes have been published previously.[7b,14] In all reports, however, only one or two alkyl groups are functional at the expense of other alkyl groups. Thus, these methods appear unsatisfactory with regard to economy and product quality. Conversely, in our protocol, *all three alkyl groups* in the ate complex participate in the magnesium–bromine exchange.

It should be noted that the metallated intermediate was very stable in toluene at −10°C, giving **3** in 90% yield, even after aging for 10 h before the treatment with DMF. The intermediate appears to be a magnesate complex such as **6**, different from a mixture of dipyridyl magnesium and 2-bromo-6-lithiopyridine (**2**, M = Li) since the lithiated intermediate was unstable under similar conditions, as shown in Table 1.

Solvent effects on the selective metallation are shown in Table 2. The selection of the reaction solvent was important to control the reactivity. The exchange reaction of *n*-Bu_3MgLi was quite selective for **1** in toluene and a maximum of 0.5% of diformyl product **5**, via dimetallation, was obtained. A slight excess of the reagent (1.2 mol equiv.) did not affect the selectivity (entry 2). Even with the use of 1.5 mol equiv. of *n*-Bu_3MgLi, only 2% of **5** was obtained (entry 3). In THF, an accurate charge of the reagent was necessary to obtain an acceptable yield of **3** (entry 4). An excess of the reagent (1.5 mol equiv.) in THF caused a significant formation of **5** (43%) (entry 5).

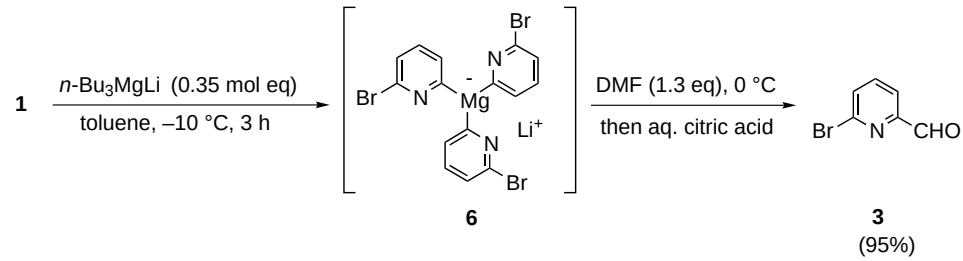
Effects of the ratio of *n*-BuMgCl to *n*-BuLi on the reagent activity are also shown in Table 2. An undercharge of *n*-BuLi to *n*-BuMgCl decreased the reactivity due to formation of a mixture of *n*-Bu_3MgLi and *n*-Bu_2Mg (entry 6). It is known that *n*-Bu_2Mg is almost inert to **1** under the reaction conditions. The overcharge of *n*-BuLi did not reduce the yield of **3** (entry 7). In this case, a higher-ordered magnesate (*n*-Bu_4MgLi_2) might be partly generated. The reagent prepared from the ratio of *n*-BuLi to *n*-BuMgCl (3:1) was probably *n*-Bu_4MgLi_2[8] and showed a similar reactivity to *n*-Bu_3MgLi (entry 8).

We next examined the application of this protocol to other dibromoarenes and dibromoheteroarenes. The results are summarized in Table 3. To avoid the precipitation of the magnesate intermediate, THF was added to toluene for some substrates. In all cases, <2% of dimetallation was obtained. 1,4- and 1,3-Dibromobenzene gave the corresponding mono-formylated benzene in good yields (entries 1 and 2). The exchange of 1,4-dibromo-2-fluorobenzene was selective at the 1-position to afford 4-bromo-2-fluorobenzaldehyde in 92% assay yield (entry 3). 3,5-Dibromopyridine gave

Table 1. Stability of the ate complex **6** versus 2-bromo-6-lithiopyridine (**2**: M = Li) at −10°C

Aging time (h)[a]	Yield of **3** (%)	
	Via **6**	Via **2** (M = Li)
0.5	97	90
1	95	70
3	93	53
10	90	–[b]

[a] Aging time after the treatment of **1** and *n*-Bu_3MgLi (0.35 equiv.) or *n*-BuLi (1.0 equiv.).
[b] No data.



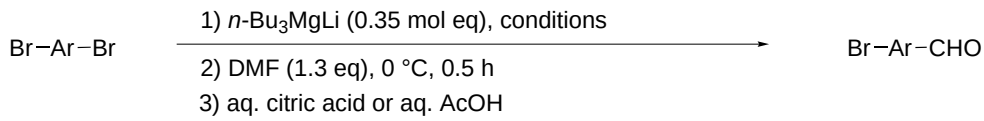
Scheme 3.

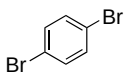
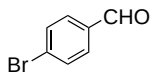
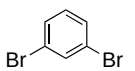
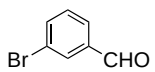
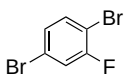
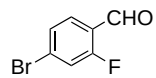
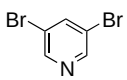
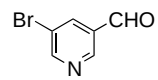
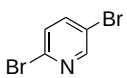
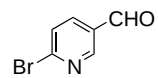
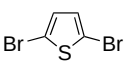
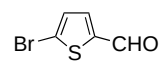
Table 2. Solvent effects on the selective exchange (entries 1–5) and the effects of the ratio of *n*-BuMgCl and *n*-BuLi on the reagent activity (entries 6–8)[a]

Entry	Reagent	Ratio	Solvent	Yield (%)		
	n-BuMgCl/*n*-BuLi (mol equiv. to **1**)			**3**	**5**	**1**
1	0.35/0.7 (1.05)	1:2	Toluene	95	<0.5	0.2
2	0.4/0.8 (1.2)	1:2	Toluene	95	<0.5	0
3	0.5/1.0 (1.5)	1:2	Toluene	90	2	0
4	0.35/0.7 (1.05)	1:2	THF	90	5	0
5	0.5/1.0 (1.5)	1:2	THF	49	43	0
6	0.4/0.7 (1.1)	1:1.75	Toluene	63		27
7	0.4/0.9 (1.3)	1:2.25	Toluene	96		0
8	0.3/0.9 (1.2)	1:3	Toluene	95		0.2

[a] Reactions were carried out in toluene at −10°C. DMF was added after 2 h of aging.

Table 3. *n*-Bu_3MgLi-mediated mono-formylation of dibromoarenes and dibromoheteroarenes



entry	substrate	solvent [a]	conditions: temp., time	metallation [b]: mono- / di-	product	yield (%) [c]
1		A	0 °C, 5 h [d]	88.5 / < 0.1		84
2		A	0 °C, 1.5 h [d]	92.0 / n.d.		99
3		B	0 °C, 1 h	91.9 / < 2		92
4		C	–10 °C, 1.5 h	97.7 / < 0.1		78
5		C	0 °C, 1.25 h then 20 °C, 1 h [d]	77.1 / 1.7		71
6		A	–10 °C, 3 h	90.7 / 1.6		73 [e]

[a] A: toluene; B: toluene-THF (5:1); C: toluene-THF (1:1). [b] Determined by HPLC (area%) after quenching with methanol.
[c] Assay yield by means of HPLC. [d] 0.40 eq of *n*-BuMgLi was used. [e] Isolated yield.

the corresponding aldehyde in 78% isolated yield (entry 4) and 2,5-dibromopyridine afforded selectively 6-bromo-3-pyridinecarboxaldehyde in 71% assay yield (entry 5). 2,5-Dibromothiophene was also cleanly metallated to give the corresponding aldehyde in 73% isolated yield (entry 6).

In summary, lithium tributylmagnesate complex (*n*-Bu_3MgLi) is an efficient reagent for selective mono-formylation of dibromoarenes and dibromo-heteroarenes via bromine–magnesium exchange reaction. This novel reaction can be carried out under non-cryogenic conditions (at −10°C) and therefore offers a significant advantage for large-scale production. This method was used for the preparation of 25 kg of **3** (91% assay yield) in our laboratory.[15] Further studies on the reaction mechanism and the other applications are currently underway.

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9. Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: New York, 1995; pp. 61–71.
10. The reagent, prepared from *n*-Bu_2Mg and *n*-BuLi (1:1), showed similar reactivity to the reagent from *n*-BuMgCl.
11. ^1H NMR (toluene–THF (2:1), 25°C) for the mixture of *n*-BuLi and *n*-BuMgCl (2:1) showed one triplet peak (metal-CH_2-) at δ −0.54, while both *n*-BuLi and *n*-BuMgCl showed a doublet-of-triplets at −0.87 and −0.42, respectively. ^{13}C NMR also showed different resonance (δ 8.9) from *n*-BuLi (δ 9.1) and *n*-BuMgCl (δ 6.8). Purchased *n*-Bu_2Mg (Fluka) showed resonance at δ −0.49 (^1H NMR) and δ 7.2 (^{13}C NMR). D_2O in a sealed capillary was used for NMR locking. THF was used to obtain a homogeneous solution.
12. 11% of hexane and 6% of THF in toluene. The reaction in absolute toluene, by the evaporation of THF (from *n*-BuMgCl) and hexane (from *n*-BuLi), gave similar results.
13. The mono-metallated intermediate was identified as 2-bromopyridine (HPLC) after quenching a reaction mixture aliquot with methanol.
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15. Procedure for the formylation of **1** using *n*-Bu_3MgLi: To a solution of *n*-BuLi (1.63 M in hexane, 45.8 kg, 109 mol) in toluene (52 L) was added *n*-BuMgCl (1.95 M in THF, 26.9 kg, 54.5 mol) at −10 to 0°C over 0.5 h, and the mixture was stirred at −10°C for 0.5 h. A solution of **1** (34.9 kg, 145 mol) in toluene (262 L) was added dropwise over 1 h while maintaining the temperature of the mixture below −5°C. The resulting suspension was stirred at −10°C for 2.5 h and then transferred into a cooled (−10°C) solution of DMF (14.0 kg, 189 mol) in toluene (50 L) over ca. 0.5 h. The mixture was aged at −10 to −5°C for 0.5 h and then quenched with aq. citric acid (56.6 kg in 105 L of H_2O). After stirring the mixture below 20°C for 10 min, the organic layer was separated, washed with H_2O (105 L), and then assayed by mean of HPLC: 25.0 assay kg of **3** (91% assay yield).