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Magnesiation of functionalized iodobenzenes at room temperature: clarification of the stability of ethoxycarbonylphenylmagnesium iodides

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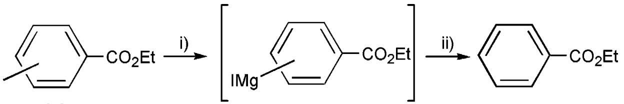
Abstract—Magnesiation of functionalized aromatic halide, ethyl 3- or 4-iodobenzoate, was accomplished using active magnesium. The resulting phenylmagnesium iodides decomposed little by little in proportion to extension of the reaction time at room temperature. The magnesiation followed by addition of carbonyl compounds gave the corresponding adducts in good to moderate yields.

Metalation of an aromatic compound is a useful technique to introduce an electrophilic substituent into an aromatic moiety. Especially, since arylmagnesium halide is stable and has mild reactivity compared to aryllithium, preparation of functionalized arylmagnesium compounds has been developed by many chemists.[1–7] The halogen–magnesium exchange, reaction of the corresponding aryl halide with other Grignard reagent (RMgX)[1–5] or trialkylmagnesates (R_3MgLi),[6,7] is a popular method to generate functionalized arylmagnesium compounds. However, the halogen–magnesium exchange reaction requires low temperature (between −20 and −78 °C) because the Grignard reagent is reactive with functional groups such as an ester group. Another magnesiating method, oxidative addition of magnesium into functionalized bromobenzene derivatives was reported by Lee et al.[8] In the paper the magnesiation of *tert*-butyl bromobenzoates using active magnesium (Mg^*) was accomplished at −78 °C, but the magnesiation of ethyl or methyl bromobenzoates failed at the temperature. They speculated that a possible explanation might be the coordination of the ester group to the magnesium surface, blocking the active sites of the metal and thus preventing the oxidative addition step. So we performed the magnesiation of ethyl 4-iodobenzoate (**1**), ethyl 3-iodobenzoate (**2**), and ethyl 2-iodobenzoate (**3**), which are more reactive than the bromo compounds toward metalation. As shown in Scheme 1, magnesiation[9] of **1**, **2**, and **3** using Mg^*[10] between −70 and −60 °C was accomplished followed by quenching with water to afford ethyl benzoate in 71%, 76%, 72%, respectively.

Lee et al.[8] also described that raising the temperature to −50 °C permitted the magnesiation of bromobenzoic acid esters, but at the higher temperatures, more byproducts were formed, which limited the scope of the reaction. In order to clarify the reaction temperature–yield relationship, magnesiation of **1**, **2**, and **3** was carried out under various temperatures. To our surprise, the magnesiation of **1** and **2** proceeded at several temperatures (−70, −40, −10, and 25 °C) and it was found that the resulting Grignard reagents are stable for 10–30 min even at room temperature. On the contrary,



1,2

71% (**1**: Ethyl 4-iodobenzoate; -70 °C, 10 min)
76% (**2**: Ethyl 3-iodobenzoate; -70 °C, 30 min)
72% (**3**: Ethyl 2-iodobenzoate; -60 °C, 10 min)

Reagents : i) Mg^* (2.5 equiv.) / THF; ii) H_3O^+.

Scheme 1. Magnesiation of ethyl iodobenzoates using Mg^*.

Keywords: Magnesiation; Grignard reagent; Active magnesium.

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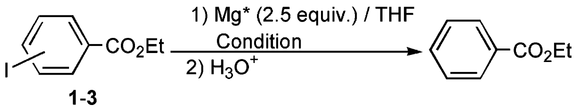
Table 1. Reaction temperature–yield relationship in the magnesiation of ethyl iodobenzoates followed by addition of water



Entry	Substrate	Condition	Yield (%)
1	**1**	−40 °C, 10 min	68
2	**1**	−10 °C, 10 min	67
3	**1**	25 °C, 30 min	61
4	**2**	−40 °C, 10 min	70
5	**2**	−10 °C, 10 min	68
6	**2**	25 °C, 10 min	53
7	**3**	−40 °C, 10 min	66
8	**3**	−10 °C, 10 min	21[a]
9	**3**	25 °C, 10 min	0

[a] As a mixture with inseparable byproducts.

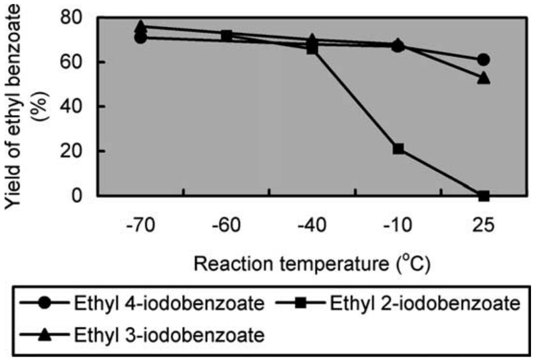
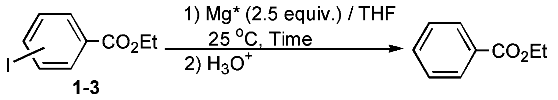
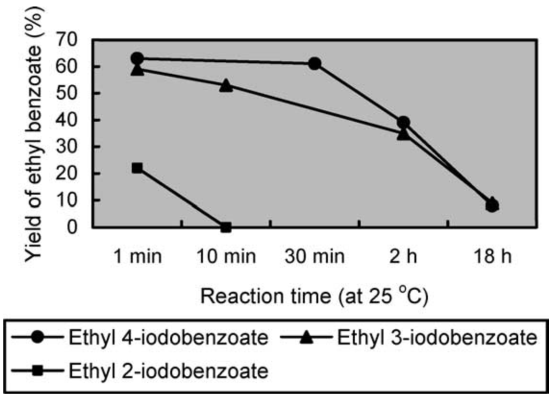


Table 2. Reaction time–yield relationship in the magnesiation of ethyl iodobenzoates at 25 °C followed by addition of water



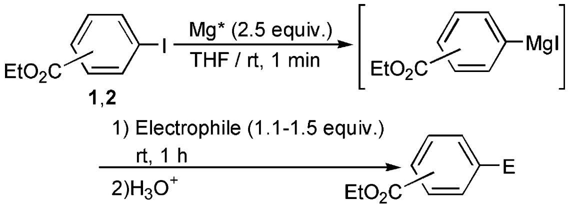
Entry	Substrate	Time	Yield (%)
1	**1**	1 min	63
2	**1**	2 h	39
3	**1**	18 h	8
4	**2**	1 min	59
5	**2**	2 h	35
6	**2**	18 h	9
7	**3**	1 min	22



magnesiation of **3** showed interesting results: Yield of the product declined when the magnesiation was performed at −10 or 25 °C, whereas at −40 °C or lower temperature the product was obtained in good yields (Table 1).

Next, the magnesiation of **1**, **2**, and **3** at 25 °C for various reaction times was carried out. As shown in Table 2,

Table 3. Magnesiation of ethyl iodobenzoates followed by addition of carbonyl compounds



Entry	Substrate	Electrophile	E	Yield (%)
1	**1**	EtCH=O[a]	CH(OH)Et	62
2	**1**	^{i}PrCH=O	CH(OH)^{i}Pr	71
3	**1**	^{t}BuCH=O	CH(OH)^{t}Bu	39
4	**1**	$Ph_2C{=}O$[a]	$C(OH)Ph_2$	65
5	**1**	$Et_2C{=}O$	$C(OH)Et_2$	54
6	**1**	$^{i}Pr_2C{=}O$[a]	$C(OH)^{i}Pr_2$	29
7	**2**	EtCH=O	CH(OH)Et	64
8	**2**	$Et_2C{=}O$	$C(OH)Et_2$	42
9	**3**	EtCH=O	CH(OH)Et	0
10[b]	**3**	EtCH=O	CH(OH)Et	0
11	**3**	$Et_2C{=}O$	$C(OH)Et_2$	0
12[b]	**3**	$Et_2C{=}O$	$C(OH)Et_2$	0

[a] Five equivalents of an electrophile was used.

[b] Condition: −60 °C, 1 min/−60 °C to rt.

the yield of the product declined in proportion to extension of the reaction time. It was found the magnesiation of the substrate **1**, **2** was completed in 1 min.

Table 3 shows the results of the magnesiation of **1**, **2**, and **3** at room temperature (25–30 °C) for 1 min followed by addition of some carbonyl compounds to give the products.[11] Reaction of **1** and **2** afforded the corresponding adducts in good to moderate yields (entries 1–8). When a hindered carbonyl compound was used as an electrophile, yield of the product declined. The rule was similar to our previous report.[12] Magnesiation of **3** followed by addition of carbonyl compounds at room temperature (entries 9 and 11) or −60 °C, and raised to room temperature (entries 10 and 12) gave no product. Decomposition of the Grignard reagent would proceed faster than addition of carbonyl compounds into the aromatic moiety.

In conclusion, we have accomplished a useful and advantageous method to prepare ethyl ester substituted phenylmagnesium iodides using active magnesium, at room temperature and clarified the relationship between stability of the resulting Grignard reagent and reaction temperature/reaction time.

References and notes

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9. General procedure: To a suspension of Mg^* (6.00 mmol) in tetrahydrofuran (30 mL), the substrate (2.4 mmol) was added at −70 °C and the mixture was stirred for an appropriate time. The reaction mixture was quenched with 1 N hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, and treated with silica gel chromatography to give ethyl benzoate.
10. Preparation of Mg^*: Under argon atmosphere, a mixture of lithium wire (ALDRICH, Catalog No. 27,832-7; 83.3 mg, 12.0 mmol), naphthalene (1538 mg, 12.0 mmol), magnesium chloride powder (ALDRICH, Catalog No. 24,413-9; 571 mg, 6.00 mmol), and tetrahydrofuran (30 mL) was stirred at room temperature until 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.
11. Chemical properties of new products: *Ethyl 4-(1-hydroxypropyl)benzoate*: Colorless oil. Bp. 185 °C/11 mmHg. Anal. calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.90; H, 7.84. *Ethyl 4-(1-hydroxy-2-methylpropyl)benzoate*: Colorless oil. Bp. 168 °C/12 mmHg. Anal. calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.00; H, 8.36. *Ethyl 4-(1-hydro-xy-2,2-dimethylpropyl)benzoate*: White solids. Mp. 112–113 °C. Anal. calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.10; H, 8.55. *Ethyl 4-(hydroxydiphenylmethyl)-benzoate*: Pale yellow oil. Bp. 255 °C/13 mmHg. Anal. calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.45; H, 6.11. *Ethyl 4-(1-ethyl-1-hydroxypropyl)benzoate*: Pale yellow oil. Bp. 180 °C/11 mmHg. Anal. calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.12; H, 8.56. *Ethyl 4-(1-hydroxy-2-methy-l-1-[1-methylethyl]propyl)-benzoate*: White solids. Mp. 185 °C/12 mmHg. Anal. calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.67; H, 9.15. *Ethyl 3-(1-hydroxypropyl)benzoate*: Slight yellow oil. Bp. 177 °C/15 mmHg. Anal. calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.38; H, 7.73. *Ethyl 3-(1-ethyl-1-hydroxypropyl)benzoate*: Slight yellow oil. Bp. 178 °C/14 mmHg. Anal. calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.18; H, 8.48.
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