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Facile Synthesis of Phthalides from Methyl *ortho*-Iodobenzoates and Ketones via an Iodine–Magnesium Exchange Reaction Using a Silylmethyl Grignard Reagent

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Facile Synthesis of Phthalides from Methyl *ortho*-Iodobenzoates and Ketones via an Iodine–Magnesium Exchange Reaction Using a Silylmethyl Grignard Reagent

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Phthalides have been easily prepared by the treatment of methyl *o*-iodobenzoates with a silylmethyl Grignard reagent in the presence of ketones. The electron-withdrawing ester moiety of methyl *o*-iodobenzoates and the low nucleophilicity of the silylmethyl Grignard reagent prompted a smooth iodine–magnesium exchange reaction, at room temperature, without affecting the ester moiety or resulting an undesired reaction with electrophilic ketones. This simple method, wherein special control of the reaction temperature was unnecessary, has allowed the synthesis of various phthalides, including a phenolphthalein derivative.

Keywords: Iodine–magnesium exchange | Grignard reagent| Phthalide

Aryl anions are useful intermediates for the syntheses of various aromatic compounds.[1] Halogen–metal exchange reactions are widely used methods to generate aryl anions from aryl halides.[1–4] In particular, halogen–metal exchange using magnesium ate complexes, including isopropylmagnesium chloride lithium chloride complex (turbo Grignard reagent)[3] and lithium tributylmagnesate,[4] which facilitate the rapid halogen–magnesium exchange of aryl iodides or bromides, have been commonly used. However, the high nucleophilicity of these reagents requires the reaction to be performed in a controlled manner at low temperature, limiting the substrate scope and making the experimental handling cumbersome and complicated. Herein, we report that the use of a low-nucleophilic silylmethyl Grignard reagent allowed for the efficient iodine–magnesium exchange of methyl *o*-iodobenzoates at room temperature without affecting the ester moiety even in the presence of ketones to afford phthalides.

During the course of our recent studies on aryne chemistry,[5–7] we have demonstrated that aryne species are generated efficiently from *o*-iodoaryl triflates via an iodine–magnesium exchange reaction using a silylmethyl Grignard reagent (Figure 1A).[7] Based on this method, various arynes bearing a transformable functional group,[6e,6i,7,8] such as a terminal alkyne moiety,[7a] azido group,[7d] ester moiety,[7c] triflyloxy group,[7b,7f,7g] or halogeno group,[7j] were generated efficiently, via which a variety of aromatic compounds were synthesized. These studies disclosed the potential usefulness of the moderately nucleophilic silylmethyl Grignard reagent in synthetic organic chemistry.[7,9]

We were interested in the unique reactivity that the silylmethyl Grignard reagent showed; and thus, explored its general applicability for the iodine–magnesium exchange reaction. When iodobenzene (**1**) was treated with (trimethylsilyl)methylmagnesium chloride in tetrahydrofuran (THF) at room temperature in the presence of benzophenone (**2a**), **1** was mostly recovered (Figure 1B). Trityl alcohol (**3**), which could be produced via the iodine–magnesium exchange of **1** followed by reaction of the resulting phenylmagnesium chloride with ketone **2a**, was not obtained. Instead, 1,1-diphenyl-2-(trimethylsilyl)ethanol (**4**) was obtained in low yield. This result clearly showed that the iodine–magnesium exchange of simple iodobenzene (**1**) did not occur and the addition of the silylmethyl Grignard reagent to ketone **2a** proceeded. Given that the *ortho*-triflyloxy group facilitated the iodine–magnesium exchange in the generation of arynes from *o*-iodoaryl triflates, we conceived of introducing an electron-withdrawing and chelating directing group to iodobenzene to promote the iodine–magnesium exchange reaction. Based on this idea, we treated a mixture of methyl *o*-iodobenzoate (**5a**) and ketone **2a** with (trimethylsilyl)methylmagnesium chloride, which afforded 3,3-diphenylphthalide (**6a**) in 40% yield (Figure 1C and Table 1, entry 1). This result indicated that an aryl anion species was generated via the iodine–magnesium exchange of **5a** and nucleophilic addition of the resulting aryl anion to ketone **2a** followed by cyclization afforded phthalide **6a**.

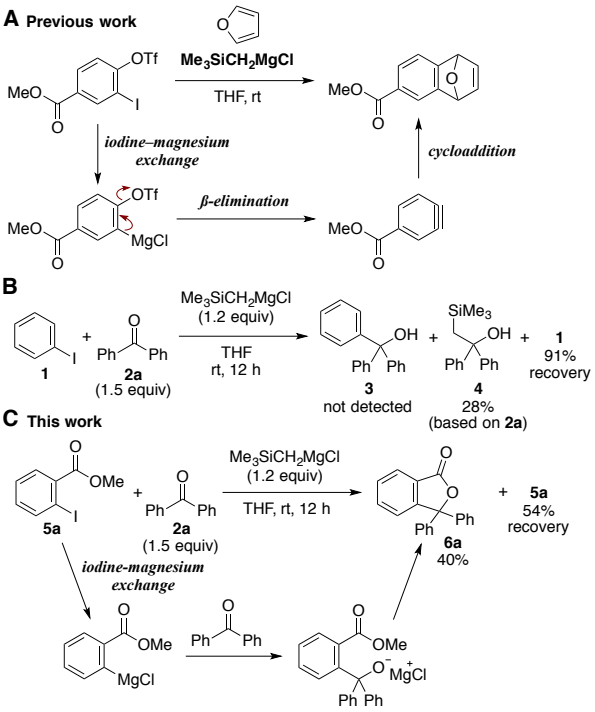
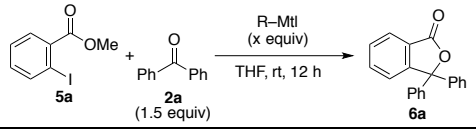


Figure 1. Transformations via the iodine–magnesium exchange reaction triggered by a silylmethyl Grignard reagent. (A) Our previous study involving the generation of arynes from *o*-iodoaryl triflate-type precursors. (B) Attempted iodine–magnesium exchange of iodobenzene (**1**). (C) Phthalide synthesis from ester **5a** and ketone **2a**.

Table 1. Optimization of the reaction conditions

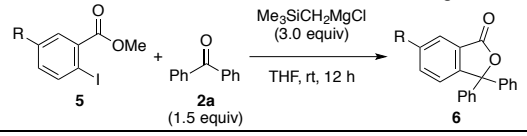


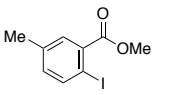
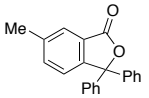
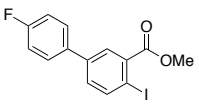
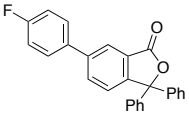
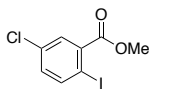
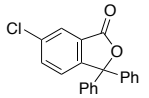
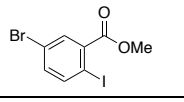
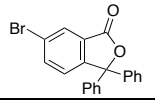
Entry	R–MtI	x	Conversion/%[a]	Yield/%[a]
1	Me_3SiCH_2MgCl	1.2	46	40
2	*n*-BuLi	1.2	63	10
3	*i*-PrMgCl·LiCl	1.2	17	5
4	*n*-Bu_3MgLi	1.2	100	0
5[b]	Me_3SiCH_2MgCl	1.2	61	58
6	Me_3SiCH_2MgCl	3.0	100	87[c]

[a]Yields determined by ^{1}H NMR analysis, unless otherwise noted. [b]The reaction was performed at 60 °C for 12 h. [c] Isolated yields.

Because phthalides are an important class of molecules[10] often found in natural products, drug candidates, and functional molecules, we embarked on optimization studies for this transformation (Table 1). In contrast to the silylmethyl Grignard reagent (entry 1), the use of *n*-butyllithium (entry 2), turbo Grignard reagent (entry 3), or lithium tributylmagnesate (entry 4) as an activator for iodine–metal exchange were entirely unsatisfactory. Based on the good material balance observed when 1.2 equiv of silylmethyl Grignard reagent was used (entry 1), we examined the reaction using this reagent. Although simply performing the reaction at higher temperature (60 °C) improved the yield of phthalide **6a**, significant amount of **5a** still remained (entry 5). Increasing the amount of Grignard reagent to 3.0 equiv in order to consume **5a** completely resulted in a significant improvement in the yield of **6a** (entry 6).[11]

Table 2. Reactions between various esters **5** and benzophenone (**2a**)

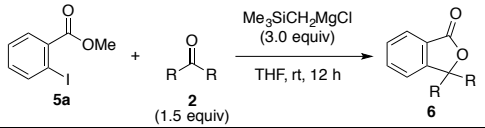


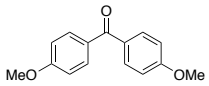
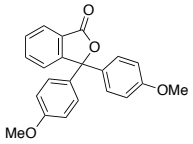
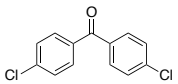
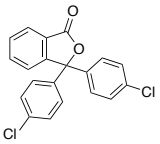
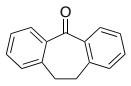
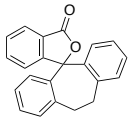
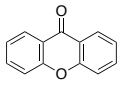
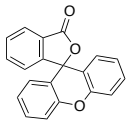
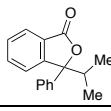
Entry	Ester	5	Phthalide	6	Yield/%[a]
1		**5b**		**6b**	69
2		**5c**		**6c**	51
3		**5d**		**6d**	53
4		**5e**		**6e**	51

[a]Isolated yields.

The optimized conditions were successfully applied to the synthesis of functionalized phthalides in only one step from functionalized methyl *o*-iodobenzoates (Table 2). For example, the iodine–magnesium exchange of methyl-substituted ester **5b** in the presence of ketone **2a** under the optimized conditions afforded phthalide **6b** in good yield (entry 1). Halogeno group-containing substrates, such as 4-fluorophenyl-, chloro-, or bromo-substituted methyl *o*-iodobenzoates **5c**–**5e**, also reacted smoothly with ketone **2a** to afford phthalides **6c**–**6e**, leaving non-iodine halogeno groups untouched (entries 2–4).

Table 3. Reactions between ester **5a** and various ketones **2**



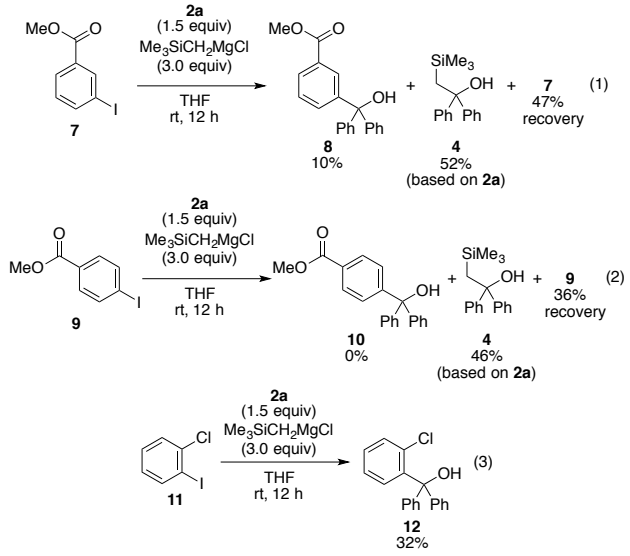
Entry	Ketone	2	Phthalide	6	Yield/%[a]
1		**2b**		**6f**	66
2		**2c**		**6g**	38
3		**2d**		**6h**	79
4		**2e**		**6i**	0[b]
5		**2f**		**6j**	0
6		**2g**		**6k**	78

[a]Isolated yields. [b]A complex mixture of products was obtained.

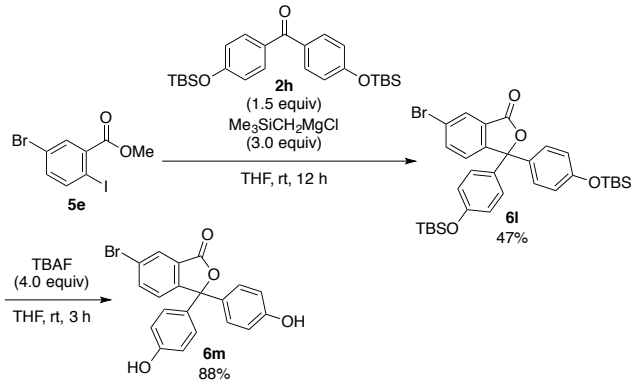
Various ketones were also applicable to the phthalide synthesis (Table 3). Reactions of ester **5a** with 4,4'-dimethoxybenzophenone (**2b**) or 4,4'-dichlorobenzophenone (**2c**) afforded the corresponding phthalides **6f** or **6g**, respectively (entries 1 and 2).[12] The reaction with dibenzo-fused cycloheptadienone **2d** proceeded efficiently to afford spiro-phthalide **6h** in high yield (entry 3). Unfortunately, the reaction of **5a** with xanthone (**2e**) was unsuccessful and phthalide **6i** was inaccessible by this method (entry 4). Acetophenone (**2f**) was also an unfavorable substrate for this transformation, possibly due to the preceding deprotonation of the acidic α-proton of **2f**, leading to an aldol reaction (entry 5). In contrast, isobutyrophenone (**2g**) with a bulkier alkyl group reacted smoothly with the *o*-(methoxycarbonyl)phenylmagnesium intermediate, generated in situ via the iodine–magnesium exchange of **5a**, to afford the corresponding phthalide **6k** in high yield (entry 6).

To gain insight into the effect of the ester moiety in the iodine–magnesium exchange reaction, we examined the reactions of methyl *m*-iodobenzoate (**7**) or methyl *p*-iodobenzoate (**9**) with benzophenone (**2a**) under the optimized conditions for phthalide synthesis (eqs 1 and 2). From these

reactions, only a small amount of alcohol **8** or none of **10** was obtained. Also the deiodinated methyl benzoate was not obtained, suggesting that these substrates were unsuitable for the iodine–magnesium exchange reaction. Alternatively, alcohol **4**, which was formed by addition of the Grignard reagent to ketone **2a**, was obtained along with significant recovery of the iodobenzoates. These results indicate that the electron-withdrawing and directing effect by the *ortho*-ester moiety play a critical role for facilitating the iodine–magnesium exchange reaction using the silylmethyl Grignard reagent. We also found that iodobenzene derivative **11**, with an electron-withdrawing and directing chloro group at the *ortho*-position, also lead to magnesiation to afford alcohol **12** in moderate yield (eq 3).



The facile method for phthalide synthesis rendered functionalized phenolphthalein derivatives[13] easily accessible. For example, treatment of methyl 5-bromo-2-iodobenzoate (**5e**) with the silylmethyl Grignard reagent in the presence of 4,4'-bis(silyloxy)benzophenone **2h** afforded phthalide **6l** in moderate yield. Subsequent desilylation of **6l** successfully provided bromo-substituted phenolphthalein derivative **6m**[13b] in high yield. This simple two-step procedure would allow for the synthesis of a wide range of phenolphthalein derivatives by changing the ester and ketone to other substrates.



Scheme 1. Synthesis of bromo-substituted phenolphthalein **6m**.

In summary, we have shown that an *ortho*-ester moiety on iodoarenes prompts a smooth iodine–magnesium exchange reaction with a silylmethyl Grignard reagent at room temperature, even in the presence of ketones. This method enabled the preparation of various phthalides from *o*-iodobenzoic acid esters and ketones without special attention to the reaction temperature. Further studies, involving the synthetic applications of these arylmagnesium intermediates generated using a silylmethyl Grignard reagent, are now in progress.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.xxxxxx.

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