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# Mg-promoted carbon-acylation of aromatic aldehydes and ketones

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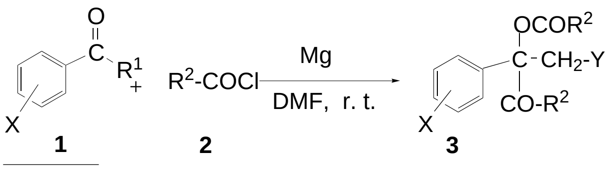
**Abstract**—Reductive cross-coupling of aromatic aldehydes and ketones with aliphatic acid chlorides promoted by Mg turnings in DMF at room temperature brought about efficient *C*-acylation to afford the corresponding α-acyloxy-α-aryl ketones in good yields. Treatment of α-methoxy or α-acetoxyacetophenones under similar conditions gave the corresponding α-acyloxystyrenes exclusively. The reaction may be initiated by electron transfer from Mg to the carbonyl groups of the substrates. © 2002 Elsevier Science Ltd. All rights reserved.

The generation and the utilization of an acyl anion or its chemical equivalents[1] have attracted much attention because of their high potentiality in organic synthesis. A variety of metal acyl complexes containing lithium,[2–4] divalent samarium[5–8] and zirconocene[9,10] have been developed as an 'unmasked acyl anion' in recent years. The reaction[5–10] of this reactive intermediate with aldehydes and ketones efficiently gives the corresponding α-hydroxy ketones (acyloins).[11] However, their synthetic utility has been limited to some extent owing to use of expensive reagents or poisonous carbon monoxide, and troublesome procedures. Electroreductive[12–15] and Mg-promoted *C*-acylation[16] of α,β-unsaturated carbonyl compounds were also reported by us[12,13,16] and other groups.[14,15]

In this study, we wish to report facile Mg-promoted *C*-acylation of aromatic aldehydes and ketones **1** in the presence of aliphatic acid chlorides **2** to give the corresponding α-acyloxy-α-aryl ketones **3** in good yield (Eq. (1)). The hydrolysis products, the corresponding α-hydroxy ketones, would be obtained from the reaction of **1** with an 'unmasked acyl anion', although the present reaction does not involve an acyl anion itself as the reactive species.



(1)

The present reductive coupling may be characterized by novelty of a reaction mode, easy availability and environmental safety of the reagents, a simple procedure, mild conditions, usefulness of the products[‡] and good yields.

A typical procedure is as follows: A solution of *m*-chlorobenzaldehyde (**1d**) (10 mmol) dissolved in anhydrous *N*,*N*-dimethylformamide (DMF: 10 mL) was added dropwise at 5–10°C under a nitrogen atmosphere with magnetical stirring into a suspension of propionyl chloride (**2a**) (100 mmol) and Mg turnings (50 mmol) for Grignard reaction without any pre-treatment in anhydrous DMF (40 mL). Exothermic reaction took place and the mixture was cooled with an ice–water bath, and was allowed to stir at 10–15°C overnight after the addition. After usual work-up of the reaction mixture, 1-propioxy-1-(*m*-chlorophenyl)buta-2-one (**3e**) was isolated in 91% yield by preparative column chromatography.

The results for the present reductive acylation of a variety of ring-substituted aromatic aldehydes and ketones **1a**–**m** with aliphatic acid chlorides **2a**–**e** are summarized in Table 1.[§,¶] It may be a general tendency that the presence of electron-withdrawing groups on the phenyl ring of **1**

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*Keywords*: carbonyl compounds; acylation; magnesium and compounds; coupling reaction.

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[‡] The products, α-acyloxy-α-aryl ketones **3**, may be useful synthetic intermediates for pharmaceutical drugs for the central nervous system such as dopamine, epinephrine and ephedrine.

[§] All of the products **3a**–**m** and **7a**–**d** showed satisfactory behaviors in spectroscopic analyses ($^1$H and $^{13}$C NMR, IR and MASS).

[¶] Simply reduced benzylic alcohol esters **4** and dimeric 1,2-diarylpinacol derivatives **5** were obtained as the by-products in small amounts depending on the properties of the starting substrates **1** and/or the acid chlorides **2**.

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**Table 1.** Mg-promoted *C*-acylation of aromatic carbonyl compounds (**1**) with acid chlorides (**2**)

| Entry | Aromatic carbonyl compound (**1**) | | Acid chloride (**2**) | Product (**3**) |
|---|---|---|---|---|
| | X | $R^1$ | $R^2$ | Yield (%) |
| 1 | H | H (**1a**) | $C_2H_5$ (**2a**) | 61 (**3a**) |
| 2 | *m*-$OCH_3$ | H (**1b**) | $C_2H_5$ (**2a**) | 71 (**3b**) |
| 3 | *m*-$OCH_3$ | H (**1b**) | $C_3H_7$ (**2b**) | 77 (**3c**) |
| 4 | *m*-F | H (**1c**) | $C_3H_7$ (**2b**) | 79 (**3d**) |
| 5 | *m*-Cl | H (**1d**) | $C_2H_5$ (**2a**) | 98 (**3e**) |
| 6 | *m*-Cl | H (**1d**) | $C_3H_7$ (**2b**) | 84 (**3f**) |
| 7 | *p*-Cl | H (**1e**) | $C_2H_5$ (**2a**) | 65 (**3g**) |
| 8 | *p*-Cl | H (**1e**) | $C_3H_7$ (**2b**) | 76 (**3h**) |
| 9 | *p*-$CH_3$ | H (**1f**) | $C_2H_5$ (**2a**) | 51 (**3i**) |
| 10 | H | $CH_3$ (**1g**) | $CH_3$ (**2c**) | 56 (**3j**) |
| 11 | H | $CH_3$ (**1g**) | $C_2H_5$ (**2a**) | 58 (**3k**) |
| 12 | H | $CH_3$ (**1g**) | $C_3H_7$ (**2b**) | 61 (**3l**) |
| 13 | H | $CH_3$ (**1g**) | *i*-$C_3H_7$ (**2d**) | 93 (**3m**) |
| 14 | H | $CH_3$ (**1g**) | *t*-$C_4H_9$ (**2e**) | 99 (**3n**) |
| 15 | H | $C_2H_5$ (**1h**) | $C_2H_5$ (**2a**) | 49 (**3o**) |
| 16 | H | *i*-$C_3H_7$ (**1i**) | $C_2H_5$ (**2a**) | 30 (**3p**) |
| 17 | H | $C_6H_5$ (**1j**) | $C_2H_5$ (**2a**) | 89 (**3q**) |
| 18 | *m*-Cl | $CH_3$ (**1k**) | $C_2H_5$ (**2a**) | 91 (**3r**) |
| 19 | *p*-Cl | $CH_3$ (**1l**) | $C_2H_5$ (**2a**) | 73 (**3s**) |
| 20 | *m*-$OCH_3$ | $CH_3$ (**1m**) | $C_2H_5$ (**2a**) | 70 (**3t**) |

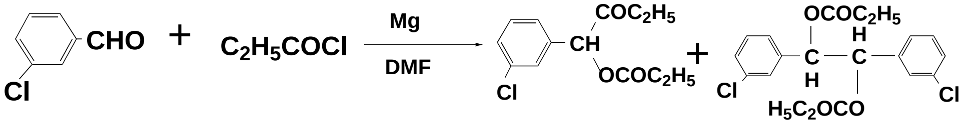
Reaction conditions: Substrate **1** (10 mmol), acid chloride **2** (100 mmol), Mg (50 mmol), DMF (50 mL), temp. 5–15°C, one night, under a $N_2$ atmosphere.

brought about a considerable increase in yield of the desired products **3**, whereas electron-donating groups on the aromatic ring of **1** gave a decrease in that of **3**, providing a good correlation in Hammett's plot (yield of **3** versus σ) possessing a positive *ρ*-value (a series of entries 1, 2, 4, 5, 7, 9, and that of entries 10, 18, 19, 20). Furthermore, steric hindrance around the carbonyl carbon atoms of **1** gave a significant influence on the yield of **3**. Thus, as the substituent $R^1$ of **1** is more bulky, the yield of **3** distinctly decreased (entries 11, 15, 16). On the other hand, it may be quite noteworthy that an increase in bulkiness of the substituent $R^2$ of aliphatic acid chlorides **2** brought about a remarkable increase in yield of the products **3** (entries 10–14). This unexpected phenomenon may suggest some instability of acid chlorides **2** depending on a decrease in bulkiness of the substituent $R^2$ under the reaction conditions.

In order to obtain useful information for the reaction mechanism of the present reductive cross-coupling, some control experiments were accomplished. First, it was found that a difference in the addition mode led to a large effect on product yield. Thus, the dropwise addition of a DMF solution of propionyl chloride (**2a**) into a suspension of *m*-chlorobenzaldehyde (**1d**) and Mg metal in DMF afforded 1-propioxy-1-(*m*-chlorophenyl)butan-2-one (**3e**) and dimeric 1,2-(*m*-chlorophenyl)pinacol derivative (**5e**) in 55 and 32% yields, respectively, while the dropwise addition of a DMF solution of **1d** into a solution of **2a** and Mg metal in DMF brought about exclusive formation of **3e** (Y = 98%) accompanying none of **5e**, as shown in Scheme 1.

Secondly, use of propionic anhydride instead of propionyl chloride as an acylating agent in the reaction of **1d** resulted in the formation of three types of products, *C*-acylation product **3e**, simply hydrogenated benzylic alcohol ester **4e**, and dimeric product **5e** in 42, 15 and 33% yields, respectively. Furthermore, treatment of phenacyl derivatives **6** possessing an acetoxy or a methoxy group with Mg metal in the presence of aliphatic acid chlorides (**2a**,**e**) under similar conditions led to selective formation of the corresponding enol esters **7** as the main products in satisfactory yields (Scheme 2).

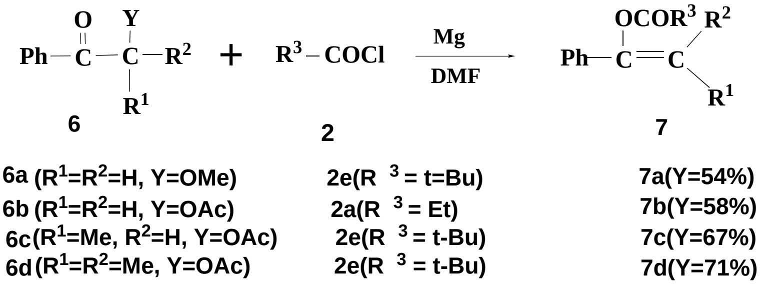
Although detailed reaction mechanisms of the present Mg-promoted *C*-acylation of carbonyl compounds **1** are not clear as yet, these experimental facts indicate that the reductive coupling proceeds through radical anion intermediates **8A** and **8B**, generated by electron transfer from Mg metal to aromatic carbonyl compounds **1a**–**m** and **6a**–**d**. In the case that the substituent Y is an alkyl group, the intermediates **8A** are subjected to subsequent electrophilic attack of acid chlorides **2** followed by the second electron transfer from Mg-metal to generate the O-anions **9**, and dimerization of **8B** affords the O,O′-dianions **10**. On the other hand, elimination of Y from **8A** followed by the second electron transfer takes place predominantly to give the enolate anions **11** when Y is a methoxy or an acetoxy group (Scheme 3).



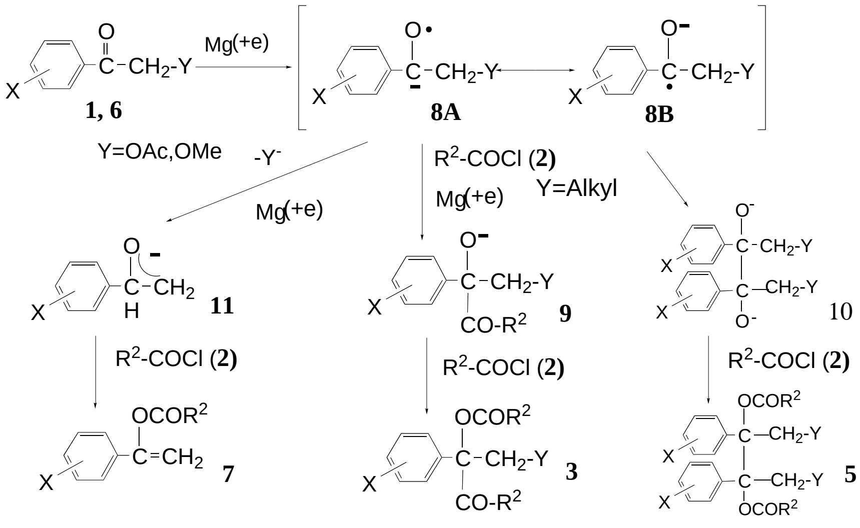
**1d** **2a** **3e** **5e**

| | 3e | 5e |
|---|---|---|
| **Dropwise Addition of 1d into a DMF solution of 2a and Mg** | 98% | 0% |
| **Dropwise Addition of 2a into a DMF solution of 1d and Mg** | 55% | 32% |

**Scheme 1.** Effect of the addition mode.



**Scheme 2.** Mg-promoted elimination–addition of phenacyl derivatives.



**Scheme 3.** Proposed mechanism.

## Acknowledgements

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