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Mg-Promoted Regio- and Stereoselective C-Acylation of Aromatic α,β-Unsaturated Carbonyl Compounds

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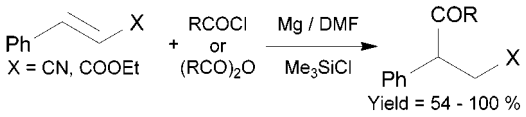
ABSTRACT



Treatment of aromatic α,β-unsaturated carbonyl compounds with Mg turnings in the presence of acid anhydrides/TMSCl or acyl chlorides in DMF brought about a facile and efficient cross-coupling to give C-acylation products, which are useful 1,4-dicarbonyl compounds, in good to excellent yields in a regio- and stereoselective manner. The reaction may be initiated by electron transfer from magnesium to the substrates.

Conjugate addition of an acyl anion and its equivalents to α,β-unsaturated carbonyl compounds may be one of the most attractive and challenging subjects for preparing 1,4-dicarbonyl compounds, which are important synthetic intermediates of useful cyclopentenones, cyclopenta-1,3-diones, butenolides, and furans.[1] However, the synthetic utility of the acyl anion has been considerably limited because of its instability, difficulties in generation, and treatment.[2] Furthermore, application of its chemical equivalents in organic synthesis generally requires troublesome and complicated procedures for their protection and deprotection.[3]

We previously reported the electroreductive C-acylation of α,β-unsaturated esters and nitriles in the presence of acid anhydrides to form γ-ketoesters and nitriles.[4] We report here Mg-promoted regio- and stereoselective C-acylation of aromatic α,β-unsaturated carbonyl compounds **1** with acid anhydrides/TMSCl or acyl chlorides **2** to give the corresponding γ-keto carbonyl compounds **3** in good to excellent yields. As a result of the high regio- and stereoselectivity, facile procedure, simple equipment, high potential for large-scale preparation, and mild reaction conditions, this reaction seems to be one of the most promising methods for the synthesis of compounds that may be expected to be formed from the conjugate addition of an acyl anion to **1**.

A typical procedure is as follows. To a solution of ethyl cinnamate (**1a**, 5 mmol), propionic anhydride(**2b**, 75 mmol), and magnesium turnings for a Grignard reaction (15 mmol)[5] in freshly distilled *N*,*N*-dimethylformamide (DMF, 50 mL)

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(1) (a) Hassner, A. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, pp 541−577. (b) Ellison, R. A. *Synthesis* **1973**, 397. (c) Ho, T.-L. *Synth. Commun.* **1974**, *4*, 265. (d) Herrmann, J. L.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 3275−3278. (e) Cregge, R. J.; Hermann, J. L.; Richman, J. E.; Romanet R. F.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2595−2598. (f) Hermann, J. L.; Richman, J. E.; Romanet R. F.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2599−2602. (g) Jonsson, E. U.; Johnson, C. R. *J. Am. Chem. Soc.* **1971**, *93*, 5309−5311. (h) Schneider, P. W.; Bravard, D. C.; McDonaid, J. W.; Newton, W. E. *J. Am. Chem. Soc.* **1972**, *94*, 8641−8642. (i) Chavdarian, C. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1975**, *97*, 3822−3823. (j) Miyashita, M.; Yanami, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1976**, *98*, 4679−4681.

(2) For recent reports on the generation and reaction of an acyl anion, see: (a) Seyferth, D.; Weinstein, R. M.; Hui, R. C.; Wang, W.-L.; Archer, C. M. *J. Org. Chem.* **1991**, *56*, 5768−5773. (b) Ryu, I.; Hayama, Y.; Hirai, A.; Sonoda, N.; Orita, A.; Ohe, K.; Murai, S. *J. Am. Chem. Soc.* **1990**, *112*, 7061−7063. (c) Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 493−494 and references therein.

(3) Larock, R. C., *Comprehensive Organic Transformation*, 2nd ed.; Wiley-VCH: New York, 1999; pp 1435−1450 and references therein.

(4) (a) Shono, T.; Nishiguchi, I.; Ohmizu, H. *J. Am. Chem. Soc.* **1977**, *99*, 7396−7397. (b) Ohno, T.; Aramaki, H.; Nakahiro, H.; Nishiguchi, I. *Tetrahedron* **1996**, *52*, 1943−1952. (c) Kise, N.; Hirata, Y.; Hamaguchi, T.; Ueda, N. *Tetrahedron Lett.* **1999**, *40*, 8125−8128.

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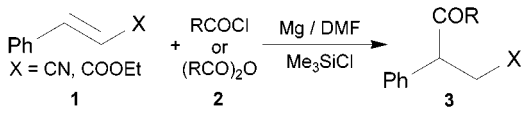
was added trimethylsilyl chloride (TMSCl, 15 mmol) in several portions at 5−10 °C with magnetic stirring under a nitrogen atmosphere. The resulting solution was stirred for 15 h at room temperature. After a routine workup of the reaction mixture, ethyl 3-phenyl-4-oxohexanoate (**3b**) was isolated in a 84% yield by column chromatography.

Scheme 1



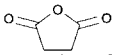
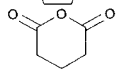
This Mg-promoted cross-coupling was remarkably accelerated by the addition of TMSCl[6,7] when acid anhydrides were used as the acylating agents.

Thus, the reaction of **1a** without any TMSCl after 2 h resulted in the exclusive recovery (90%) of **1a** and minor formation (5%) of the product **3b**, whereas that in the presence of 3 molar equiv of TMSCl after 2 h led to the major formation (62%) of **3b** and minor recovery (30%) of **1a**. Under the optimized conditions where the relative proportions of **1**:Mg:TMSCl:**2** was 1:3:3:15, a variety of acylated products **3a**−**l** were obtained in good to excellent yields from the present Mg-promoted C-acylation of aromatic α,β-unsaturated carbonyl compounds **1a**−**d** with the corresponding acylating agents **2**, as shown in Table 1.[8] The reaction proceeded smoothly with acylating agents **2** bearing various functional substituents such as a chloro or a carbomethoxy group.

Because of the ready availability of various acid chlorides, it is interesting that the use of acyl chlorides[9] instead of a combination of acid anhydrides and TMSCl as the acylating agents did not appear to affect the reaction, and the corresponding acylated products were obtained in good yields. Furthermore, the reaction of ethyl cinnamate (**1a**) with cyclic acid anhydrides led to the facile formation of useful keto α,ω-dicarboxylic acid monoesters. On the other hand, the similar reactions by electroreductive methods using acyl chlorides or cyclic acid anhydrides resulted in a low yield of the acylated products and the formation of complex product mixtures.[4]

Moreover, high stereoselectivity is another noteworthy feature of the present Mg-promoted coupling. Thus, similar

Table 1. Mg-Promoted Regioselective Carbon-Acylation of Aromatic Alkenoic Acid Derivatives **1**[a]

entry	X in **1**	acylating agent **2**	R in **3**	Isolated yield (%)
1	COOEt (**1a**)	$(CH_3CO)_2O$	(**3a**) CH_3	64
2	COOEt (**1a**)	CH_3COCl	(**3a**) CH_3	71
3	COOEt (**1a**)	$(CH_3CH_2CO)_2O$	(**3b**) CH_2CH_3	84
4	COOEt (**1a**)	CH_3CH_2COCl	(**3b**) CH_2CH_3	73
5	COOEt (**1a**)		(**3c**) $(CH_2)_2COOH$	84
6	COOEt (**1a**)		(**3d**) $(CH_2)_3COOH$	61
7	COOEt (**1a**)	$PhCH_2COCl$	(**3e**) CH_2Ph	76
8	COOEt (**1a**)	$CH_3(CH_2)_4COCl$	(**3f**) $(CH_2)_4CH_3$	54
9	COOEt (**1a**)	$EtOCO(CH_2)_2COCl$	(**3g**) $EtOCO(CH_2)_2$	100
10	COOEt (**1a**)	$Cl(CH_2)_3COCl$	(**3h**) $Cl(CH_2)_3$	93
11	$COCH_3$ (**1b**)	$(CH_3CO)_2O$	(**3i**) CH_3	67
12	$COCH_3$ (**1b**)	CH_3COCl	(**3i**) CH_3	43
13	CN (**1c**)	$(CH_3CO)_2O$	(**3j**) CH_3	76
14	CN (**1c**)	CH_3COCl	(**3j**) CH_3	44
15	COOEt (**1d**)[b]	$(CH_3CO)_2O$	(**3k**) CH_3	49
16	COOEt (**1e**)[c]	$(CH_3CO)_2O$	(**3l**) CH_3	50

[a] The reaction was carried out at 5−10 °C for 15 h in a DMF solution of a substrate **1**, an acylating agent **2** (15 molar equiv), Mg turnings (3 molar equiv) and TMSCl (3 molar equiv, when **2** is acid anhydride). [b] The phenyl group was substituted by a 1-naphthyl group. [c] The phenyl group was substituted by a 2-naphthyl group.

treatment of 3-alkylated coumarins **5a**−**d** with acid anhydrides **2**/TMSCl gave exclusively one stereoisomer **6a**−**d**-**[A]** (isomer ratios of **6a**−**d[A]**/**6a**−**d[B]**, 92−98/8−2)[10,11] of the acylated products (**6a**−**d**) with a *cis*-configuration between the 3-alkyl group and the 4-acyl group, as shown in Table 2.

On the other hand, the electroreduction of coumarin **5a** in a DMF solution containing propionic anhydride, TMSCl, and tetraethylammonium tosylate using a divided cell equipped with carbon rods as an anode and a cathode, followed by the same workup procedure as that in the Mg-promoted reaction, resulted in the formation of stereoisomeric mixtures (yield 18%) of **6a[A]** and **6a[B]** (61/39) along with the

(5) Magnesium turnings for a Grignard reaction can be used without any pretreatment.

(6) Although the detailed role of TMSCl is still unclear as described in our recent paper on Mg-promoted reductive cross-coupling of ethyl β-arylacylates with aldehydes, three main roles may be postulated, i.e., activation of the surface of magnesium metal, stabilization of anionic intermediates generated by electron transfer from magnesium, and activation of electrophiles by coordination to the oxygen atom of carbonyl compounds.

(7) Ohno, T.; Ishino, Y.; Tsumagari, Y.; Nishiguchi, I. *J. Org. Chem.* **1995**, *60*, 458−460.

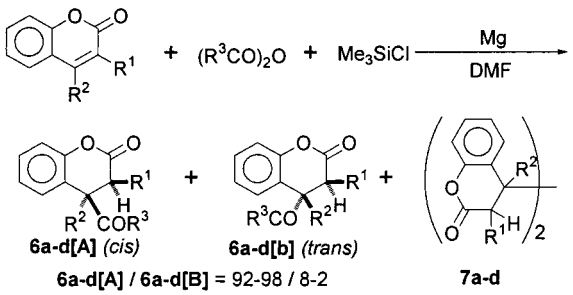
(8) All of the products obtained in this study were characterized by a variety of spectroscopic methods (^{1}H NMR, ^{13}C NMR, MS, IR) and elemental analysis, as shown in Supporting Information.

(9) Since acyl chlorides may also be able to activate the surface of magnesium metal, the reaction using acyl chlorides as acylating agents took place smoothly in the absence of TMSCl.

(10) The stereochemistry of **6[A]** and **6[B]** was determined by detailed analysis of the coupling constants J_{3H-4H} between protons at the 3- and 4-positions in their ^{1}H NMR spectra as reported in the literature.[11] For example, the values of J_{3H-4H} for **6a[A]** and **6a[B]** are 4.88 and 3.91 Hz.

(11) Alberola, A.; Calvo, B.; Ortega, A. G.; Vicente, M.; Granda, S. G.; Maelen, J. F. *J. Chem. Soc., Perkin Trans. 1* **1991**, 203−209.

Table 2. Mg-Promoted Stereoselective Carbon-Acylation of Coumarin Derivatives

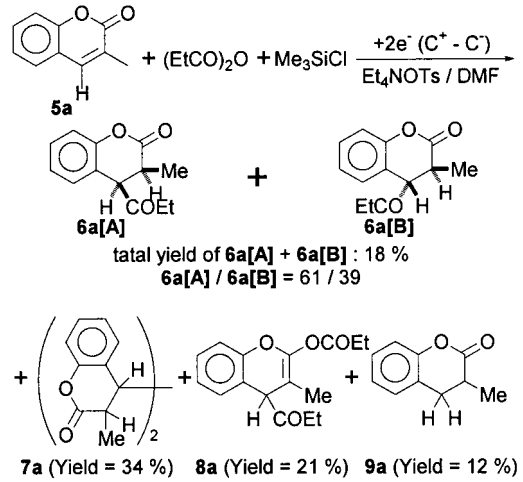


				isolated yield (%)		
entry	R^1	R^2	R^3	**6**[a]	**7**	**6[A]:6[B]**
a	Me	H	Et	33	43	97:3
b	Et	H	Et	40	19	98:2
c	Me	Me	Et	41		98:2
d	Ph	Me	Me	63		92:8

[a] Total yield of **6[A]** and **6[B]**.

formation of a dimerization product (**7a**, yield 34%), an enol propionate (**8a**, yield 21%), and a dihydrocoumarin (**9a**, yield 12%), indicating nonstereoselective acylation in this electrochemical method. A similar nonstereoselectivity was also observed in the electroreductive acylation of 1-carbethoxycyclohexene.[4a]

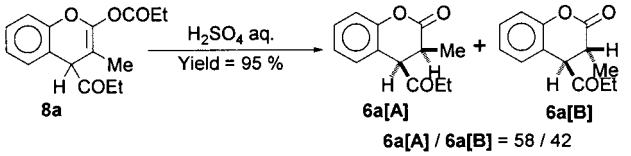
Scheme 2



Furthermore, treatment of the 2-propioxy-3-methyl-4-propionylbenzopyrane(**8a**) with 10% aqueous H_2SO_4 also gave a stereoisomeric mixture of **6a[A]** and **6a[B]** (58/42), indicating that the stereoselectivity of the Mg-promoted C-acylation did not arise in the stereoselective hydrolysis of **8a** during the workup but rather in the course of the reaction (Scheme 3).

On the basis of these experimental results, the following reaction scheme may be proposed as one of the most

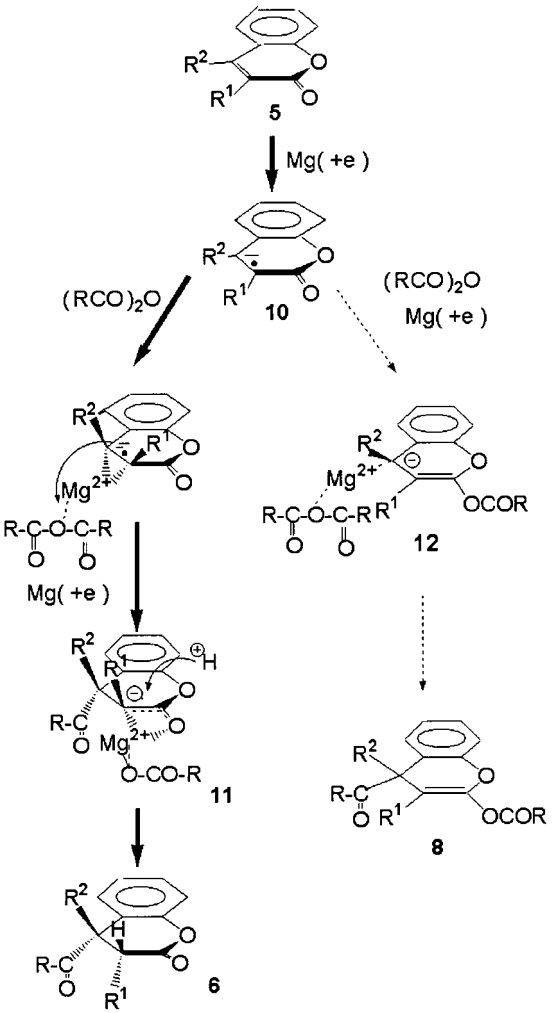
Scheme 3



plausible mechanisms (Scheme 4). The first electron transfer from magnesium to a coumarin **5** gives the corresponding anion radical **10**. Electrophilic attack of the 4-position of the anion radical **10** by acid anhydrides may take place from the same side of the Mg^{2+} cation that interacts somewhat with the acid anhydrides, followed by the almost concerted second electron transfer from magnesium to give a carbanion center at the 3-position of the generated carbanion **11**. Subsequent protonation to **11** then occurs from the opposite side of the Mg^{2+} cation and the 4-acyl group, leading to exclusive formation of the single stereoisomers **6a−d[A]**.

The limited formation of the enol ester **8a** in the Mg-promoted coupling and the formation of a stereoisomeric

Scheme 4. Proposed Reaction Mechanism of Mg−Promoted Carbon-Acylation of Coumarins



mixture of **6a[A]** and **6a[B]** upon acid-catalyzed hydrolysis of **8a** may support regioselective C-acylation at the 4-positions of anion radicals of **5a**−**d** followed by almost concerted second electron transfer from magnesium to give the more stable C3-carbanion **11** rather than the less stable C4-carbanion through the enol esterification of radical anions of **5a**−**d** with acid anhydride followed by almost concerted second electron transfer.

In conclusion, Mg-promoted cross-coupling of aromatic α,β-unsaturated carbonyl compounds **1** with acyl chlorides or acid anhydrides/TMSCl brought about facile, efficient, regio- and stereoselective C-acylation to give useful 1,4-dicarbonyl compounds **2** in good to excellent yields and had some desirable features in comparison with the electrochemical methods.[4] These acylated products are identical to those formed by the conjugated addition of a difficult-to-generate acyl anion to the starting activated olefins, although the present Mg-promoted reaction does not involve an acyl anion itself as a reactive species.

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Supporting Information Available: Experimental procedure for the reaction of **1** and **5** with acid anhydride/trimethylsilyl chloride or acyl chloride and spectroscopic data for the products **3a**−**l**, **6a**−**d**, **7a,b**, **8a**, and **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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