An Efficient Synthesis of β-Aroylacrylic Acid Ethyl Ester by the Friedel–Crafts Reaction in the Presence of Diethyl Sulfate

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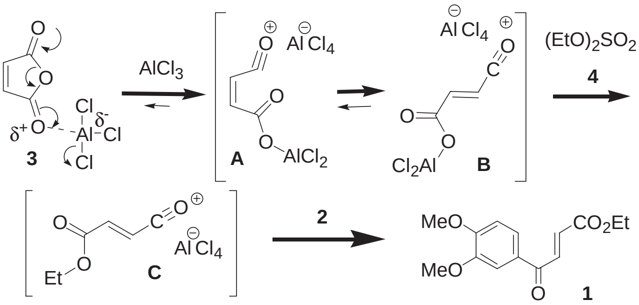
An β-Aroylacrylic acid ethyl ester such as ethyl (*E*)-4-(3,4-dimethoxyphenyl)-4-oxo-2-butenoate (**1**) can be obtained in good yield and with excellent purity by way of the Friedel–Crafts reaction in which 1,2-dimethoxybenzene (**2**) is treated with maleic anhydride (**3**) and aluminum chloride in the presence of diethyl sulfate (**4**) under mild conditions.

The Friedel–Crafts reactions are very well established in organic synthesis.[1] Typically, the reaction is performed using alkyl halide, acid anhydride, acid chloride, or sulfonyl chloride in the presence of a Lewis acid such as aluminum chloride or boron trifluoride.[1] β-Aroylacrylic acid esters have attracted much interest because of their antibacterial activity and are important synthetic intermediates in the field of medical science, agriculture, biology, and perfume.[2]

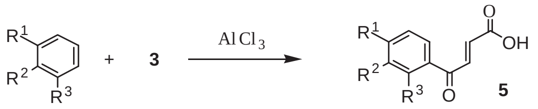
Generally, β-aroylacrylic acids such as (*E*)-4-(4-methoxyphenyl)-4-oxo-2-butenoic acid (**5a**) and (*E*)-4-(3,4-dimethylphenyl)-4-oxo-2-butenoic acid (**5b**) were prepared in high yield by way of general Friedel–Crafts reaction on treating methoxybenzene or xylene and **3** with an excess amount of aluminum chloride (Table 1, Entries 1 and 2). However, in the case of **2** and **3** at 10–15 °C, the desired product, (*E*)-4-(3,4-dimethoxyphenyl)-4-oxo-2-butenoic acid (**5c**), was obtained in only 7% yield (Table 1, Entry 3). On the other hand, when the reaction was carried out at 50–55 °C, demethylation took place to form (*E*)-4-(4-hydroxy-3-methoxyl)-4-oxo-2-butenoic acid (**5d**) as a by-product in 24% yield (Table 1, Entry 4). We presumed that the nucleophilicity of **2** would be remarkably decreased in the reaction of **2** with **3** owing to the coordination of aluminum chloride with two oxygen atoms on benzene ring. In order to confirm our presumption, we subjected 1,2,3-trimethoxybenzene, 1,4-benzodioxan and 1,2-methylenedioxybenzene[3] to the Friedel–Crafts reaction under similar conditions. The results are summarized in Table 1 (Entries 5, 6, and 7). As we feared, the reactions did not take place smoothly at 15–20 °C and gave us complex mixtures at 50–55 °C for these three substrates. Consequently, **1** and **5c** have been prepared as follows:

The target ester **1** has been prepared by the reaction of **2** and ethyl (*E*)-3-chlorocarbonyl-2-propenoate (**6**) with a Lewis acid.[4] However, it is difficult to prepare **6** selectively from **3** and ethanol in the presence of thionyl chloride.[5] Bianchi et al. reported the preparation of **1** by aldol condensation of 3,4-dimethoxyacetophenone (**7**) and ethyl glyoxylate[6] in two steps from **2** after the starting **7** was prepared from **2**.[7] Even after the above publications, the efficient preparation of **1** is still a difficult problem because of the several reaction steps needed, a long reaction time, and the total low yields. Herein, we would like to report a novel preparation of **1** with excellent purity by the Friedel–Crafts reaction treating **2** with **3** and $AlCl_3$ in the presence of **4**, which is very efficient and applicable to the synthesis in an industrial scale.[8] Our working hypothesis is shown in Scheme 1, that is, the Friedel–Crafts reaction could be accelerated by trapping **B** with diethyl sulfate to form **C** which could not return to **B** and acts as a strong electrophile.



Scheme 1. Working hypothesis of the Friedel–Crafts reaction in the presence of diethyl sulfate.

Table 1. General Friedel–Crafts reactions



Entry	Substrate	**3** /mol	$AlCl_3$ /mol	Temp /°C	Time /h	Yield /%
1[a]	$R^1 = MeO, R^2 = R^3 = H$	1.75	1.3	10–15	1.0	76
2[b]	$R^1 = R^2 = Me, R^3 = H$	1.00	1.0	rt	0.5	76
3[a]	$R^1 = R^2 = MeO, R^3 = H$	1.75	1.3	10–15	14	7
4[a,c]	$R^1 = R^2 = MeO, R^3 = H$	1.75	1.3	50–55	14	29
5[a]	$R^1 = R^2 = R^3 = MeO$	1.75	1.3	10–15	1.0	N.D.
6[a]	$R^1 = R^2 = –OCH_2CH_2O–, R^3 = H$	1.75	1.3	10–15	1.0	4
7[a]	$R^1 = R^2 = –OCH_2O–, R^3 = H$	1.75	1.3	10–15	1.0	N.D.

[a] The reaction was carried out in C_6H_5Cl. [b] The reaction was carried out in CH_2Cl_2. [c] 4-(4-Hydroxy-3-methoxyphenyl)-4-oxo-2-butenoic acid was obtained in 24% yield.

In the first place, the Friedel–Crafts reaction of **2** with **3** (1.2 mol) and $AlCl_3$ (1.2 mol) was examined in the presence of **4** (1.2 mol) in chlorobenzene at 50 °C to form the desired ester **1** in 71% relative yield (HPLC) in 1 h along with a by-product, ethyl(*E*)-4-(4-ethoxy-3-methoxyphenyl)-4-oxo-2-butenoate (**8**) (Table 2, Entry 1). In order to increase the relative yield of **1**, the molar ratios of **3**, $AlCl_3$ and **4** were investigated, analyzing by HPLC. The ester **1** was obtained in 76% relative yield when **3** (1.75 mol), $AlCl_3$ (1.3 mol), and **4** (1.4 mol) were used (Table 2, Entry 6). Next, screening of the effect of various other Lewis acids such as $TiCl_4$, $ZnCl_2$, $SnCl_4$, $FeCl_3$, $Sc(OTf)_3$, TfOH, *p*-toluenesulfonic acid, Zeolite (β), etc. was done in the above model reaction; however, the desired product was not detected

Table 2. The Friedel–Crafts reaction in the presence of diethyl sulfate

$$\underset{\text{(1 mol)}}{\mathbf{2}} \xrightarrow[\text{C}_6\text{H}_5\text{Cl, 50 °C, 1 h}]{\mathbf{3},\,\mathbf{4},\,\text{AlCl}_3} \mathbf{1} + \text{Ethyl}(E)\text{-4-(4-ethoxy-3-methoxyphenyl)-4-oxo-2-butenoate } \mathbf{(8)}$$

Entry	**3**/mol	**4**/mol	$AlCl_3$/mol	**2**/%[a]	**1**/%[a]	**8**/%[a]
1	1.2	1.2	1.2	10	71	11
2	1.5	1.2	1.2	20	62	9.8
3	2.0	1.2	1.2	13	70	8.9
4	1.75	1.4	1.2	6.1	74	12
5	2.0	1.6	1.2	16	67	8.7
6	**1.75**	**1.4**	**1.3**	**5.6**	**76**	**11**
7	1.75	1.4	1.1	9.8	71	11

[a]The ratio of **2**/**1**/**8** was determined by HPLC.

Table 3. Effect of temperature on the Friedel–Crafts reaction in the presence of diethyl sulfate

$$\underset{\text{(1 mol)}}{\mathbf{2}} \xrightarrow[\text{C}_6\text{H}_5\text{Cl, Temp, 1 h}]{\mathbf{3}\text{ (1.75 mol)}, \mathbf{4}\text{ (1.4 mol)}, \text{AlCl}_3\text{ (1.3 mol)}} \mathbf{1} + \mathbf{8}$$

Entry	Temp/°C	**2**/%[a]	**1**/%[a]	**8**/%[a]
1	5–10	31	68	0.1
2	**10–15**	**21**	**78**	**0.6**
3	15–20	19	77	1.5
4	20–30	15	77	3.0
5	50	5.6	76	11

[a]The ratio of **2**/**1**/**8** was determined by HPLC.

except in the case of $AlCl_3$.

Thus, $AlCl_3$ was chosen as the preferable Lewis acid for this Friedel–Crafts reaction.

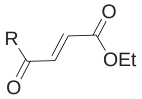
The suitable temperature conditions were then examined for the reaction under the above-mentioned molar ratios (Table 3). When the reaction was carried out at 10–15 °C, the desired ester **1** was obtained in 78% relative yield along with **8** (0.6% relative yield; Table 3, Entry 2). In higher temperatures, the yield of **8** was increased relatively by way of demethylation followed by ethylation with **4** (Table 3, Entries 3, 4, and 5).

The Friedel–Crafts reaction in the presence of diethyl sulfate for several compounds having oxygen atoms on benzene ring was tried; the results are summarized in Table 4. The ethyl ester of **5a** could be obtained directly from methoxybenzene in fairly good yield (Table 4, Entry 1); also, the desired esters could be prepared respectively from 1,2,3-trimethoxybenzene, 1,4-benzodioxan, and 1,2-methylenedioxybenzene within 1 h (Table 4, Entries 2, 3, and 4). Although it was assumed that 1,2-dimethoxybenzene (**2**) would form an intermediate **5c** at first, followed by the effective esterification with **4** in this reaction system, the esterification did not take place in the case of **5c** with **4** and $AlCl_3$ in chlorobenzene at 10–15 °C within 2 h.

Based on these results, the Friedel–Crafts reaction by use of **2**, **3**, and $AlCl_3$ in the presence of **4** is assumed to proceed as our working hypothesis shown in Scheme 1. It was considered that, in the absence of **4**, an excess amount of $AlCl_3$ would generally be assumed to be coordinated with the carbonyl oxygen atoms of **3** to form initially a ring-opened acylium (*Z*)-intermediate (**A**) as a counter ion. While **A** would be preferential to the ring-closed system (**3**), only a small amount of **A** would be isomerized to E-isomer (**B**), which could be a good accepter of the Friedel–Crafts reaction. In addition, the nucleophilicity of **2** would be decreased owing to coordination of $AlCl_3$ to the oxygen atoms on benzene ring, so **2** would react with **3** very slowly. On the other hand, in the presence of **4**, the acylium ion (**A**) and/or (**B**) could react with **4** smoothly to produce the esterified acylium ion (**C**) as an irreversible reaction. Consequently, the equilibrium among **3**, **A**, and **B** would be moved one-sidedly to ethoxycarbonyl acylium ion (**C**) leading to the desired (*E*)-compound (**1**) as a major product in good yield. Thus, it was clarified that $(EtO)_2SO_2$ (**4**) plays an indispensable role in the present new reaction.

Table 4. The new Friedel–Crafts reaction for some substrates

$$\underset{\text{(1 mol)}}{\text{Substrate}} \xrightarrow[\text{C}_6\text{H}_5\text{Cl, 10–15 °C, 1 h}]{\mathbf{4}\text{ (1.4 mol)}\;\; \mathbf{3}\text{ (1.75 mol)}, \text{AlCl}_3\text{ (1.3 mol)}}$$



Entry	Substrate	Yield/%[a]
1	Methoxybenzene	63
2	1,2,3-Trimethoxybenzene	41
3	1,4-Benzodioxan	58
4	1,2-Methylenedioxybenzene	28

[a]Isolated yield.

Thus, a new and efficient method has been presented for the preparation of β-aroylacrylic acid ethyl ester such as ethyl (*E*)-4-(3,4-dimethoxyphenyl)-4-oxo-2-butenoate (**1**) in good yield and excellent purity at 10–15 °C in 1 h.[9] In this Friedel–Crafts reaction, it is important that the key reagent, $(EtO)_2SO_2$, works as an agent trapping acylium ion produced from maleic anhydride and $AlCl_3$ by an ethyl source and not allowed to revert to the starting material and serves as a trigger so that the following Friedel–Crafts reaction proceeded smoothly. Further study on this type of Friedel–Crafts reaction is now in progress in our laboratory.

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9 **Procedure of the Friedel–Crafts reaction in the presence of diethyl sulfate:** Into a stirred solution of **3** (34.3 g, 0.35 mol) and **4** (43.2 g, 0.28 mol) in chlorobenzene (78 mL) was added $AlCl_3$ (34.7 g, 0.26 mol) and **2** (28.0 g, 0.20 mol) at 10–15 °C under N_2 atmosphere. The reaction mixture was stirred at 10–15 °C for 1 h and poured into 150 mL of 0.03 M HCl (aq) at 10–30 °C. The organic layer was separated, washed with 0.03 M HCl (aq) followed with 5% Na_2CO_3 aq, and then concentrated in vacuo. The desired compound was purified by recrystallization from ethanol (8 mL).

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