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Friedel–Crafts Acylation Reactions Using Esters

Subhash P. Chavan,*[a] Sumanta Garai,[a] Achintya Kumar Dutta,[b] and Sourav Pal[b]

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Intermolecular and intramolecular Friedel–Crafts acylation reactions of various aliphatic and aromatic esters at room temperature with the use of very simple reagents and activating groups in are described. The products were obtained in good yield (60–85 %). The detailed mechanistic pathway was studied by DFT calculations and supported by experimental evidence.

Introduction

Inter- and intramolecular Friedel–Crafts acylation of aromatic rings is one of the most fundamental, important, and useful C–C bond-forming reactions in organic and industrial chemistry for the synthesis of aromatic ketones and important synthetic intermediates.[1] Conventionally unstable and sensitive acylating reagents such as acid chlorides[2] and anhydrides[3] have been employed as acylating agents with suitable Lewis acids by following appropriate protocols. Acids[4] have also been shown to undergo Friedel–Crafts acylation reactions under harsh conditions. Hence, the development of stable, ready-to-use, and easy-to-handle reagents is very important for Friedel–Crafts acylation reactions.

Esters are more stable, less expensive, easily purified, and easier to handle than conventional acylating agents. Hence, esters would be ideal choice if they could be used as substitutes of conventional acylating agents, but because of their low reactivity, their utilization in Friedel–Crafts reactions remains a challenging problem.

Recently, Baba et al.[5] reported indium tribromide catalyzed Friedel–Crafts acylation reactions with esters, but there are some drawbacks to their protocol. Their methodology is restricted to a narrow range of substrates (only *tert*-butyl esters participated in the reaction), and it requires the use of costly reagents. Derivatives of Meldrum's acid[6] and enol esters[7] have also been used in Friedel–Crafts acylation reactions. There are some isolated reports of Friedel–Crafts inter- and intramolecular acylation reactions of esters that involve the use of harsh reagents such as poly(phosphoric acid) and triflic acid, but they are not of general use.[8,9]

Our quest for a suitable ester that could be used as an acylating agent encouraged us to search for an activating group that could activate the ester for Friedel–Crafts acylation reactions. Generally, anhydrides are known to react faster and act as better electrophiles than esters. There are some isolated reports on the Friedel–Crafts acylation reaction of α-acetoxybutendioic anhydride (**2a**). Pevarello et al.[10] and Mi et al.[11] reported the Friedel–Crafts acylation of **2a** with 1,2-dichlorobenzene and benzene, respectively, under reflux conditions. In both of these reactions, the anhydride carbonyl group participated in the acylation reaction in the presence of an ester carbonyl group to form the corresponding α-hydroxy keto acid. Interestingly, when we treated **2a** with different aromatic compounds, we were surprised to note that the anhydride group acted as an activating group; the acylation reaction took place at the less electrophilic ester carbonyl group in very short time at

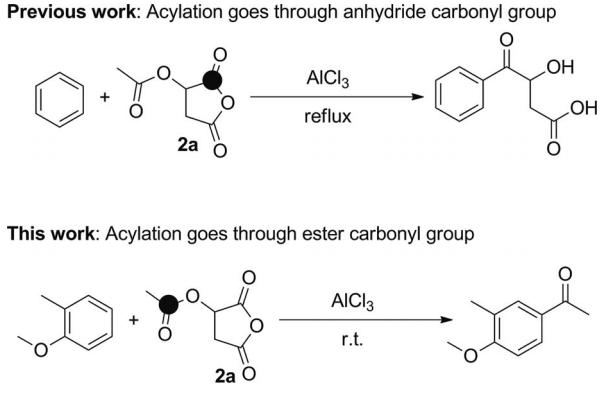

Figure 1. Friedel–Crafts acylation reaction of α-acetoxybutendioic anhydride.

[a] CSIR-NCL (National Chemical Laboratory), Division of Organic Chemistry,
Dr. Homi Bhabha Road, Pune, Maharashtra, India 411008
Fax: +91-20-5892629
E-mail: sp.chavan@ncl.res.in
Homepage: http://www.ncl.org.in/ocd/files/staff/SPC_Group/homePage.html
[b] Physical Chemistry Division
CSIR-NCL (National Chemical Laboratory)

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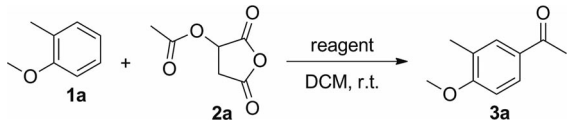
room temperature (Figure 1). We also observed that tartaric anhydride, the methyl and ethyl esters of malic acid, and tartaric acid also acted as activation groups.

Results and Discussion

To the best of our knowledge, there is no report on the direct Friedel–Crafts acylation reaction with the use of activated esters in the presence of $AlCl_3$. Herein, we wish to report our findings on the facile Friedel–Crafts acylation reactions of esters that occur at room temperature in very short times to produce products in good yields with high regioselectivity.

Thus, as a test case, the intermolecular acylation of electron-rich 2-methylanisole (**1a**) with 2,5-dioxotetrahydrofuran-3-yl acetate (**2a**) was studied in search of effective reagents and reaction conditions. Accordingly, Friedel–Crafts acylation of **1a** with **2a** in the presence of $AlCl_3$ at room temperature furnished aromatic ketone **3a** in 74% yield. When $BF_3{\cdot}OEt_2$[12] and triflic acid[13] were used as reagents, the yield was 60 and 50%, respectively (Table 1, entries 2 and 3).

Table 1. Effect of reagents on the acylation of 2-methylanisole.



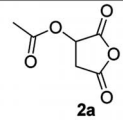
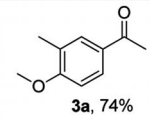
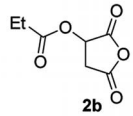
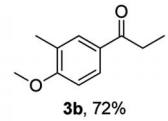
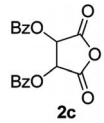
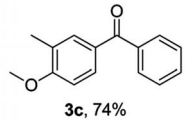
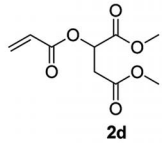
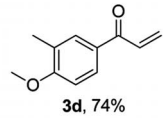
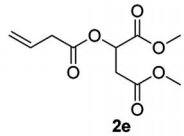
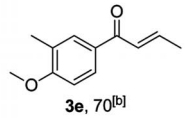
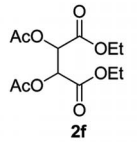
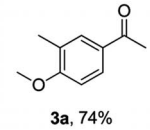
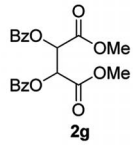
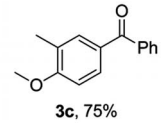
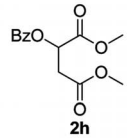
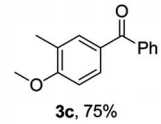
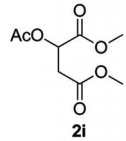
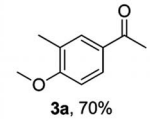
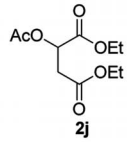
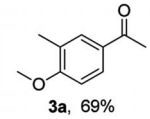
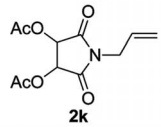
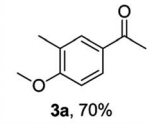
Entry	Reagent	Time [min]	Yield [%]
1	$AlCl_3$	10	72
2	$BF_3{\cdot}OEt_2$	720	60
3	CF_3SO_3H	1200	50
4	$ZnCl_2$	overnight	SM[a] was recovered
5	ZnO	overnight	SM[a] was recovered
6	$FeCl_3$	120	SM[a] decomposed

[a] Starting material.

We next examined other catalysts that have been reported to catalyze Friedel–Crafts acylation reactions of activated aromatic compounds with acid chlorides, anhydrides and acids. However, with the use of an activated ester, the starting material was surprisingly recovered when $ZnCl_2$ and ZnO[14] were used as reagents, whereas the starting material decomposed when $FeCl_3$[15] was used (Table 1, entries 4–6).

After establishing the optimum reaction conditions, we studied various types of esters to examine the scope of the reaction (Table 2).The influence of the activating group and the side chain of the ester on the acylation efficiency were examined by using $AlCl_3$ with **1a** at room temperature as the standard reaction conditions (Table 2). An increase in the number of carbon atoms in the acid part of the ester, that is, acetate ester **2a**, propionate ester **2b**, benzoate ester **2c**, acryloyl ester **2d**, and allyl ester **2e**, had no adverse effect on the efficiency of the reactions, as the corresponding ketones were furnished in similar yields (72–74%; Table 2, entries 1–5). We also varied the activating group to study its effect on the efficiency of the reaction. Accordingly,

Table 2. Acylation of 2-methylanisole with different acylating agents.

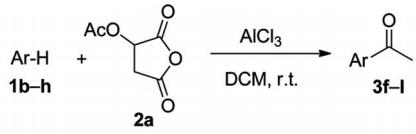
Entry	2[a]	Time [min]	Product, yield [%]
1	 2a	10	 3a, 74%
2	 2b	10	 3b, 72%
3	 2c	10	 3c, 74%
4	 2d	overnight	 3d, 74%
5	 2e	720	 3e, 70[b]
6	 2f	15	 3a, 74%
7	 2g	10	 3c, 75%
8	 2h	10	 3c, 75%
9	 2i	20	 3a, 70%
10	 2j	20	 3a, 69%
11	 2k	120	 3a, 70%

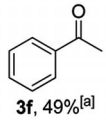
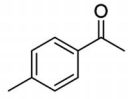
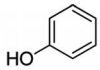
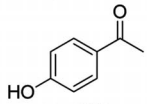
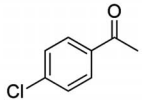
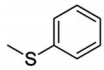
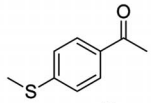
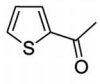
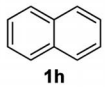
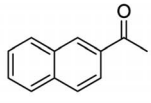
[a] Some esters were prepared by a literature procedure, whereas others are commercially available. [b] Only isomerized product was isolated.

when the activating group was changed from malic anhydride to the ethyl or methyl ester of malic acid or tartaric acid, hardly any effect on the yield and reaction time was observed (69–75%, 10–20 min; Table 2, entries 6–10), and acylation proceeded smoothly with the ester when an imide (i.e., **2k**) was the activating group (Table 2, entry 11).

This protocol can also be applied to different aromatic rings, which give the corresponding ketones in very short times and in good yields at room temperature. Heterocyclic compounds and polycyclic compounds also participated in this Friedel–Crafts acylation reaction and gave moderate yields (Table 3).

Table 3. Acylation of different aromatic compounds with the same acylating agents.

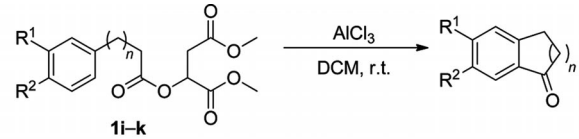


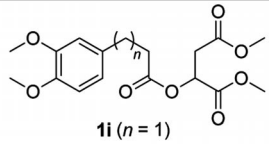
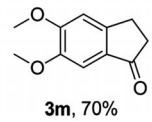
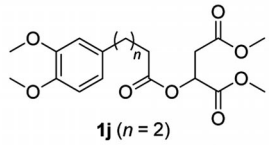
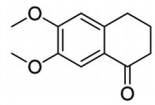
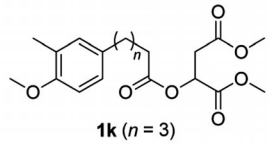
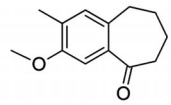
Entry	1	Time [min]	Product, yield [%]
1	 **1b**	overnight	 **3f**, 49%[a]
2	 **1c**	360	 **3g**, 70%
3	 **1d**	15	 **3h**, 70%
4	 **1e**	360	 **3i**,60%
5	 **1f**	overnight	 **3j**, 69%[b]
6	 **1g**	360	 **3k**, 40%
7	 **1h**	overnight	 **3l**, 55%

[a] Other 50% is acid.[11] [b] Based on recovery of the starting material.

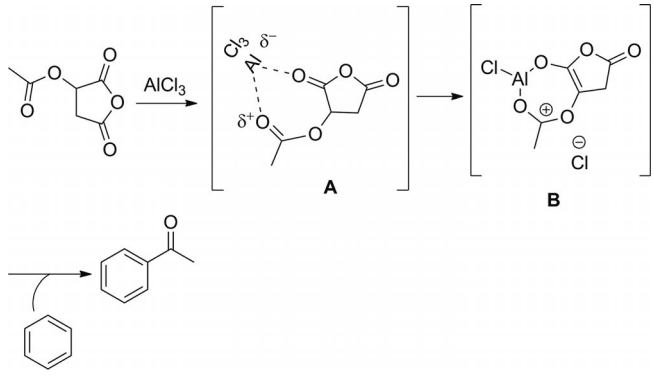
The efficient and simple reaction conditions led us to investigate intramolecular Friedel–Crafts acylation reactions. Our methodology was equally efficient in the preparation of 1-tetralone, 1-indanone, and a seven-membered ring (Table 4).

Table 4. Intramolecular Friedel–Crafts acylation reaction.



Entry	1	Time [min]	Product, yield [%]
1	 **1i** (*n* = 1)	120	 **3m**, 70%
2	 **1j** (*n* = 2)	120	 **3n**, 70%
3	 **1k** (*n* = 3)	30	 **3o**, 65%

A plausible reaction pathway for the inter- and intramolecular Friedel–Crafts acylation reactions of esters is illustrated in Scheme 1. Activation of the carbonyl group of the ester occurs by chelation of the Lewis acid to the adjacent carbonyl group of the anhydride (intermediate **A**) to form a seven-membered ring. As a result of the chelation, ionic intermediate **B** is formed. The carbonyl carbon atom bears a positive charge in this intermediate, and it is thus activated to participate in the acylation reaction (Scheme 1).



Scheme 1. Proposed mechanism for the $AlCl_3$ catalyzed Friedel–Crafts acylation of ester.

Comprehensive theoretical calculations were performed to rationalize these unusual and unexpected experimental observations and presumptions regarding the formation of activated adduct **B**, which results in chemoselective acylation. We first optimized our proposed adduct (Figure 2, intermediate **B**) with the DFT-B3LYP method and the 6-31G*$^{++}$ basis set with the PCM model to incorporate solvent effects, preceded by calculation of the Fukui functions.[16]

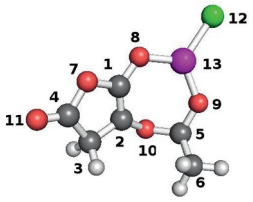


Figure 2. Activated adduct for the acylation reaction.

From the atom-condensed Fukui function of the activated adduct we observed that the electrophilic Fukui function (f_a^+) at position C-5 has the highest index, which suggests that the ester carbonyl carbon center is more prone to act as an electrophilic center than the anhydride carbonyl carbon center (Table 5).

Table 5. Condensed electrophilic Fukui functional (f_a^+) for the adduct.

Carbon no.	C1	C2	C3	C4	C5	C6
f_a^+	0.0247	0.019	0.009	0.009	0.242	0.053

Our presumptions were further confirmed by transition-state calculations. Transition state TS1 for the unexpected ester carbonyl centered product is 36.67 kcal/mol more stable than transition state TS2, which is for the expected anhydride carbonyl centered product. This results in the preferential formation of the former and confirms our inference from Fukui function analysis (Figure 3).

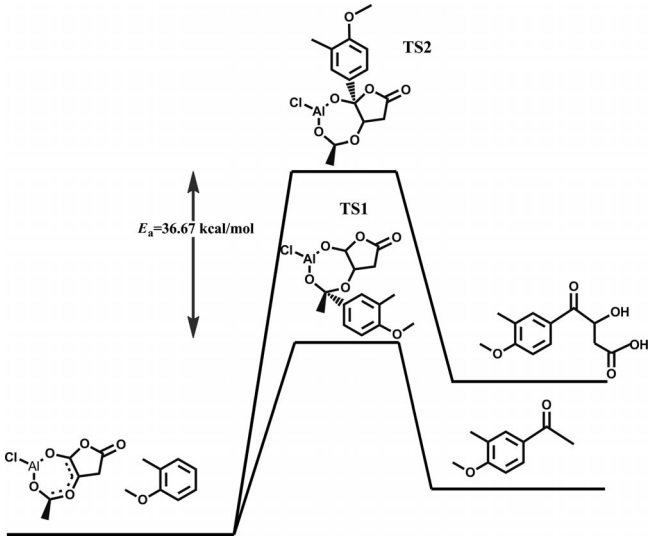
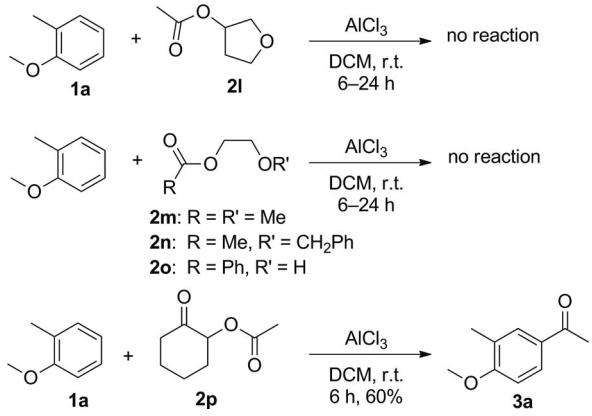


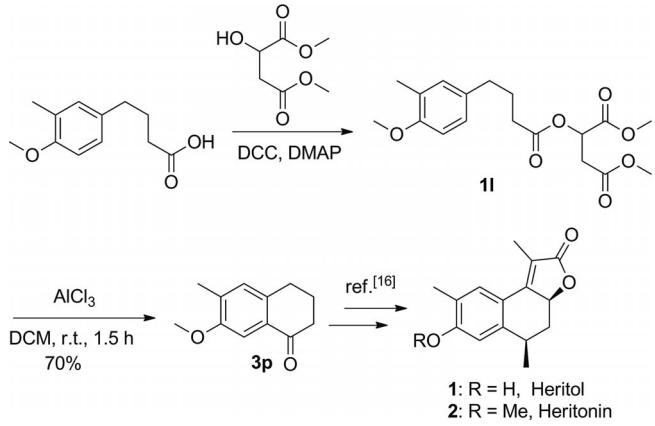
Figure 3. Energy profile diagram for unexpected and expected products.

To gain mechanistic insight, further experiments were carried out. We synthesized tetrahydrofuran acetate ester **2l** lacking a carbonyl group. Accordingly, when substrate **2l** was subjected to the reaction with **1a** under the optimized reaction conditions, the starting materials were recovered, even after stirring for 24 h at room temperature as well as under reflux conditions. To ascertain whether the presence of the oxygen atom of the lactone or ester activates the ester, we synthesized compounds **2m**–**o**. However, starting materials were recovered when the reaction was performed with substrates **2m**–**o**. We also synthesized activated ester **2p** bearing a ketone, which underwent facile acylation with **1a** (Scheme 2). This result supports our observations that the presence of an α-carbonyl functionality may activate the ester by complexation with $AlCl_3$.



Scheme 2. Studies on the Friedel–Crafts acylation reaction pathway.

Advantages of our acylation methodology were demonstrated by the synthesis of 1-tetralone **3p**,[17] which is a precursor to heritol and heritonin, from highly stable ester **1l** (Scheme 3). The transformation from the acid was earlier reported by our group by using trifluoroacetic anhydride and CF_3CO_2H. The additional advantage of our protocol over the existing method is that there is no need to generate/handle unstable, hazardous, and moisture-sensitive acid chlorides. The esters can be prepared and stored over extended periods of time and can be used straight from the shelf for the reactions; thus, our protocol is very user friendly.



Scheme 3. Direct synthesis of 1-tetralone intermediate **3p** (precursor to heritol and heritonin).

Conclusions

We have developed simple and efficient Friedel–Crafts acylation reactions by using various aliphatic and aromatic esters. This methodology was also extended to intramolecu-

lar Friedel–Crafts acylation reactions to synthesize 1-indanone, 1-tetralone, and seven-membered ring derivatives in good yields. Our methodology has several advantages: (1) Simple reaction conditions and simple reagents are used. (2) Stable esters that can be stored at room temperature for long periods of time are used. (3) The activating groups are simple, commercially available, and cheap, and they can also be prepared easily in the laboratory. (4) The reaction proceeds with equal efficiency for inter- and intramolecular Friedel–Crafts acylation reactions. (5) High yields and high selectivities are obtained. (6) It can be used for both aliphatic and aromatic esters. (7) It can be scaled up easily (see the Supporting Information). We believe this protocol, owing to its robustness, simplicity, and efficiency, should find widespread usage amongst practicing synthetic organic chemists.

Experimental Section

General Procedure for the Friedel–Crafts Acylation Reaction: To a cold (0 °C), magnetically stirred solution of aromatic compound (1 equiv.) and the corresponding anhydride or ester (1.2 equiv.) in anhydrous DCM was added anhydrous crystalline aluminum chloride (4 equiv.[18]) in one portion under an atmosphere of nitrogen. The resulting mixture was warmed to room temperature, and the red-orange reaction mixture was stirred at room temperature until completion of the reaction. The reaction mixture was then poured into ice-cooled 10% aqueous HCl, and the aqueous layer was extracted with DCM. The combined organic extract was dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude reaction mixture was purified by flash silica gel column chromatography (SiO_2; petroleum ether/ethyl acetate).

Supporting Information (see footnote on the first page of this article): Instrumentation and chemicals, experimental procedures, characterization data, theoretical studies, and copies of the NMR spectra.

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[18] We also tried the reaction with 1 equiv. $AlCl_3$, but the reaction did not go to completion.

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