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Active esters as acylating reagents in the Friedel–Crafts reaction: trifluoromethanesulfonic acid catalyzed acylation of ferrocene and pyrene

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ABSTRACT

The Friedel–Crafts acylation of electron-rich arenes (ferrocene and pyrene) with *N*-hydroxysuccinimidyl, 2,3,5,6-tetrafluorophenyl and phenyl esters of benzoic and *p*-methoxybenzoic acid, activated by superacidic trifluoromethanesulfonic acid is reported. The reactive acylating intermediate in this system is presumably an acyl triflate or its protonated form.

Friedel–Crafts acylation of arenes is a fundamental C–C bond-forming reaction[1] and constitutes an important method for the preparation of aromatic ketones, which are used as intermediates in syntheses of pharmaceuticals, dyes, fragrances and agrochemicals. Unfortunately, this method suffers from several severe drawbacks, one of them being the use of toxic, corrosive and moisture-sensitive acylating reagents such as acyl halides and anhydrides. Carboxylic acid esters, which are cheap, stable and easily manipulated compounds are, as a rule, too weak as electrophiles to achieve arene acylation. However, it has been reported by Olah et al.[2] that methyl benzoate, protolytically activated by excess superacidic trifluoromethanesulfonic (triflic) acid, is a reactive acylating reagent toward various aromatic compounds. The reaction was carried out at 85 °C in the presence of excess arenes. Activation of esters for Friedel–Crafts acylation was also accomplished using dimethylchlorosilane and indium(III) bromide.[3] The reactive intermediate in this system is presumably $RCOOSi(Cl)Me_2$.

The so-called active esters, including *N*-hydroxysuccinimidyl (NHS) or 2,3,5,6-tetrafluorophenyl esters, are readily accessible and stable compounds exhibiting high electrophilic reactivity toward amino groups. They are widely used for synthesis, labeling, cross-coupling and immobilization of biomolecules mostly via C–N bond formation.[4] In continuation of our studies aimed at the application of functionalized or biologically important acids (or derivatives thereof) in Friedel–Crafts reaction,[5] we became interested in the use of active esters as arene acylating reagents. We felt that these esters may be more reactive than classical alkyl esters and that Friedel–Crafts acylation with these reagents could be performed under milder conditions than those applied for methyl benzoate.[2] They might be used when acyl halides or anhydrides are not available or are difficult to synthesize.

To test this hypothesis we chose the electron-rich aromatic compounds, ferrocene and pyrene. These arenes are very reactive in Friedel–Crafts reactions (ferrocene $\sim 3 \times 10^6$ and pyrene $\sim 10^2$ times more reactive than benzene[6,7]), and their synthetic chemistry has attracted considerable attention in recent years because of their various applications. Ferrocene derivatives are used as redox-active biomolecule labels, ligands for homogenous catalysis, nonlinear optical materials, promising candidates for drugs, etc.[8] Pyrene derivatives bearing carbonyl functions display strong and environment-sensitive fluorescence and are used as molecular sensors, switches, and bioprobes.[9]

Herein we report that ferrocene and pyrene are efficiently acylated with active *N*-hydroxysuccinimidyl or 2,3,5,6-tetrafluorophenyl esters of benzoic and *p*-methoxybenzoic acid in the presence of triflic acid (TfOH). To our knowledge, this constitutes the first example of the use of active esters for the formation of a C–C bond.

We used active *N*-hydroxysuccinimidyl esters **2a**,**b** and tetrafluorophenyl esters **2c**,**d** as well as phenyl esters **2e**,**f** (Scheme 1) for this study.[10,11]

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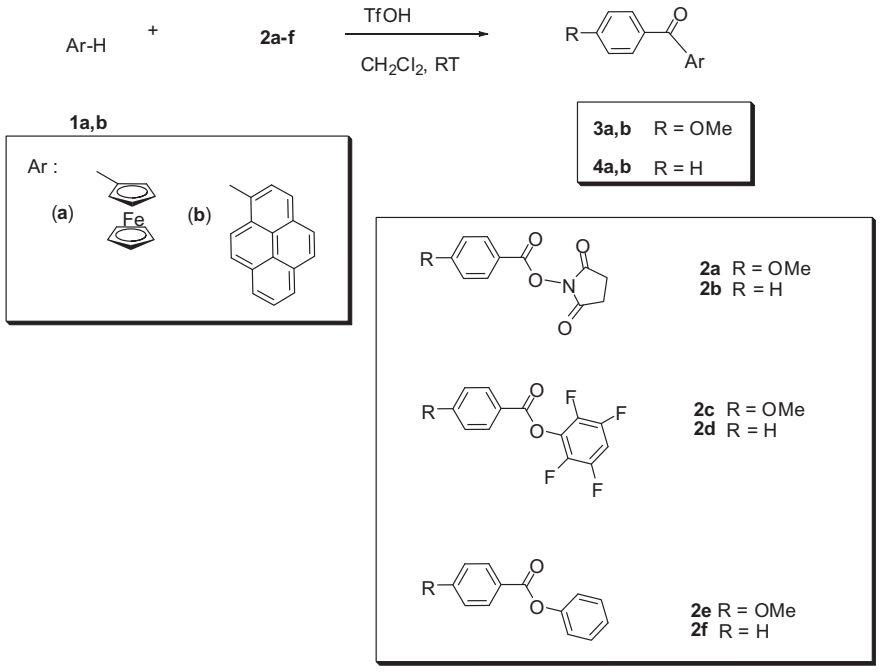


Scheme 1. Acylation of ferrocene (**1a**) and pyrene (**1b**) with esters **2a–f** in the presence of TfOH.

Table 1
Acylation of ferrocene (**1a**) and pyrene (**1b**) with *N*-succinimidyl *p*-methoxybenzoate (**2a**) in the presence of TfOH[a]

Entry	Arene	Arene/**2a**/TfOH [b]	Arene conversion (%)	Product	Yield[c] (%)
1	**1a**	1:1:1	19	**3a**	15 (79)
2	**1a**	1:1:2	44	**3a**	37 (84)
3	**1a**	1:1:3	61	**3a**	42 (69)
4	**1a**	1:1:5	88	**3a**	38 (43)
5	**1a**	1:2:1	27	**3a**	18 (67)
6	**1a**	1:2:2	49	**3a**	39 (80)
7	**1a**	1:2:3	97	**3a**	89 (92)
8	**1a**	1:2:5	99	**3a**	89 (90)
9	**1a**	1:2:10	99	**3a**	78 (79)
10	**1a**	1:3:3	96	**3a**	87 (91)
11	**1b**	1:2:3	80	**3b**	60 (75)
12	**1b**	1:2:5	82	**3b**	57 (70)

[a] Reaction conditions: CH_2Cl_2, rt, 1 h.
[b] Molar ratio.
[c] Isolated yields; yields in parentheses based on the consumed arene.

Table 2
Acylation of ferrocene and pyrene with esters **2a–f**[a]

Entry	Arene	Ester	Arene conversion (%)	Product[13]	Yield[b] (%)
1	**1a**	**2a**	97	**3a**	89 (92)
2	**1a**	**2b**	83	**4a**	45 (54)
3	**1a**	**2c**	84	**3a**	58 (69)
4	**1a**	**2d**	65	**4a**	10 (15)
5	**1a**	**2e**	80	**3a**	42 (52)
6	**1a**	**2f**	56	**4a**	11 (20)
7	**1b**	**2a**	80	**3b**	60 (75)
8	**1b**	**2b**	71	**4b**	30 (42)
9	**1b**	**2c**	79	**3b**	47 (59)
10	**1b**	**2d**	73	**4b**	27 (37)
11	**1b**	**2e**	62	**3b**	27 (44)
12	**1b**	**2f**	20	**4b**	7 (35)

[a] Reaction conditions: CH_2Cl_2, rt, 1 h; ratio of arene/ester/TfOH = 1:2:3.
[b] Isolated yields; yields in parentheses based on the consumed arene.

Initially we found that ester **2a** reacted with arenes **1a**,**b** in the presence of TfOH in dichloromethane at room temperature to afford *p*-methoxybenzoyl compounds **3a**,**b**.[12,13]

Optimization of the reaction conditions (Table 1) showed that the highest yields of **3a**,**b** were obtained using an arene/ester/TfOH molar ratio of 1:2:3. Despite the use of an excess of the ester we did not observe the formation of diacylated products. In the case of pyrene the reaction was regioselective and afforded exclusively 1-acylpyrenes.

We next applied the optimized conditions for the reactions of ferrocene and pyrene with esters **2b**–**f** (Table 2).

It can be seen from Tables 1 and 2 that more electron-rich esters of *p*-methoxybenzoic acids were more reactive than the corresponding esters of benzoic acid. Accordingly, we found that the electron-poor esters of *p*-nitrobenzoic acid were not reactive. In all cases, tetrafluorophenyl esters were less reactive than their *N*-hydroxysuccinimidyl counterparts. Interestingly, phenyl esters were also slightly reactive. On the other hand, a control experiment showed that methyl benzoate was completely inert under the same reaction conditions.

In order to gain insight into the structure of the acylating intermediate we studied the ^1H and ^{13}C NMR spectra of ester **2a** in the presence of various amounts of TfOH. The ^1H NMR spectra are shown in Figure 1.

The addition of TfOH results in the appearance of a set of signals shifted downfield relative to the signals of **2a**, and one signal shifted upfield relative to the signal of the NHS moiety of this ester. This signal was assigned to *N*-hydroxysuccinimide (as verified by addition of this compound to the NMR tube). A similar effect was observed in the ^{13}C NMR spectrum. The spectra can be interpreted in terms of the equilibrium shown in Scheme 2. Obviously, all species can be (at least partly) protonated by excess acid, which explains the observed downfield shifts of all the signals with an increasing amount of acid.

It is known that the acyl triflates are strong acylating agents toward arenes.[15] Therefore, we suggest that **5** or its protonated form is involved in the Friedel–Crafts reaction under study. The

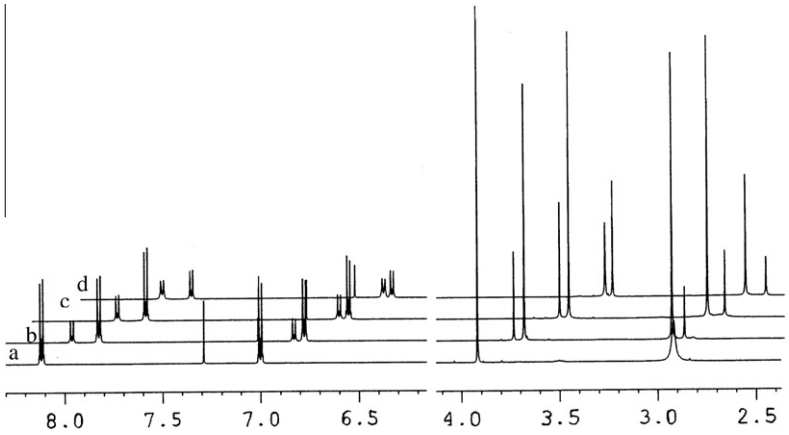
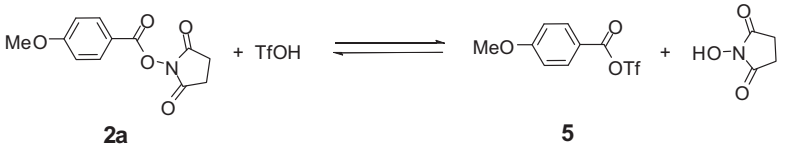


Figure 1. ^{1}H NMR spectra of **2a** (600 MHz) in $CDCl_3$ containing: (a) 0 equiv; (b) 1 equiv; (c) 3 equiv and (d) 5 equiv of TfOH.



Scheme 2. Equilibrium observed in the **2a**–TfOH system.

intermediacy of *p*-methoxybenzoic acid or its protonated form was excluded since we did not observe the acylation of ferrocene by this acid in the presence of TfOH under the same reaction conditions.

In conclusion, we have demonstrated that *N*-hydroxysuccinimidyl, tetrafluorophenyl and phenyl esters of benzoic and *p*-methoxybenzoic acid are activated by triflic acid under milder conditions than an alkyl ester (methyl benzoate), and can be used for efficient Friedel–Crafts acylation of electron-rich arenes such as ferrocene and pyrene. To the best of our knowledge, the reactions described in this work constitute the first example of the use of active esters for the formation of C–C bonds. Its scope and limitations are currently under study and the results will be published in due course.

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