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Tf_2O as a rapid and efficient promoter for the dehydrative Friedel–Crafts acylation of aromatic compounds with carboxylic acids

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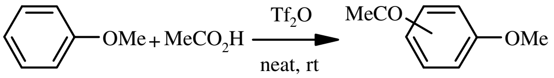
Abstract—The Friedel–Crafts acylation of aromatic compounds with carboxylic acids was investigated in the presence of Tf_2O. The reaction was carried out efficiently and very rapidly under mild reaction conditions without the need of any catalyst.

The Friedel–Crafts acylation (FC-acylation) of aromatic compounds is an important transformation in organic synthesis leading to aromatic ketones which are used in the manufacture of fine chemicals and pharmaceuticals.[1] Typically, acid chlorides are used as the acylating agent and stoichiometric or greater than stoichiometric amounts of Lewis acids such as $AlCl_3$ and $SnCl_4$ are required.[2] This procedure has serious drawbacks since the metallic oxophilic promoters and acid chlorides cause environmental problems due to strongly acidic waste streams. In addition, corrosion, spent acid disposal, difficulty in purifying the desired products and the necessity for more than stoichiometric amounts of acid catalysts are other disadvantages of the classical method.

To minimize these problems, several new methods involving carboxylic acids as acylating agents have been used.[3] Carboxylic acids are probably the best acylating reagents since they are common precursors of acid chlorides and anhydrides and their reactions produce water as the only by-product. The FC-acylation via mixed anhydrides prepared in situ from carboxylic acids has been achieved by the combined use of an activating agent and a catalyst such as *p*-trifluoromethylbenzoic anhydride and $SiCl_4$–$AgClO_4$,[4] trifluoroacetic anhydride and H_3PO_4,[5] trifluoroacetic anhydride and $AlPW_{12}O_{40}$,[6] or perfluoroalkanoic anhydride and $Bi(OTf)_3$.[7] The mixed anhydride methods have several advantages including the easy availability of carboxylic acids and use of mild reaction conditions. The development of more efficient activating agents, especially those not requiring a catalyst are highly desirable.

Herein, we report a new protocol employing trifluoromethylsulfonic anhydride (Tf_2O) for the acylation of aromatic compounds with carboxylic acids under mild reaction conditions without any catalyst (Scheme 1).

The activity of Tf_2O as a promoter for the FC-acylation of different aromatic compounds with acetic acid was examined and the results are summarized in Table 1. Anisole was allowed to react with acetic acid in the presence of Tf_2O under solvent-free conditions at room temperature. The corresponding aryl ketone was obtained very rapidly in 98% yield. However, the desired *p*-isomer was obtained in 91% along with 7% of the *o*-isomer. The reaction did not proceed without Tf_2O, implying that Tf_2O is the active promoter. An increase in the amount of Tf_2O had no significant effect on the reaction. The FC-acylation of 1-methylnaphthalene under the present reaction conditions occurred with high regioselectivity and only the *p*-isomer (4-acetyl-1-methylnaphthalene)



Scheme 1.

Keywords: Friedel–Crafts acylation; Aromatic ketones; Carboxylic acids; Tf_2O; Solvent-free.

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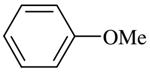
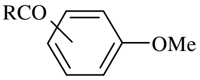
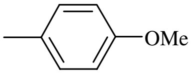
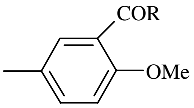
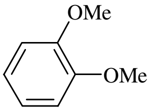
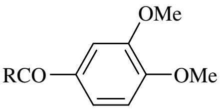
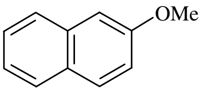
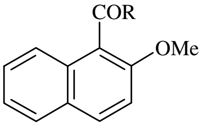
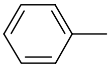
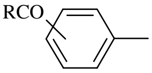
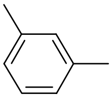
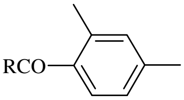
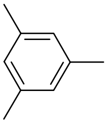
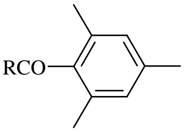
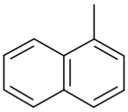
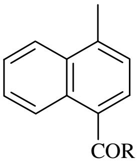
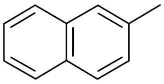
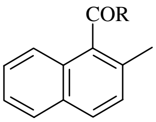
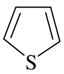
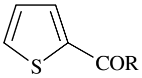
Table 1. Acylation of aromatic compounds with carboxylic acids using Tf_2O

Entry	Substrate	Product[a]	$R = CH_3$		$R = Ph$[d]	
			Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)
1			<1	98 *o*:*p* = 7:93	1	96
2			3	97	4	95
3			3	95	3	95
4			2[c]	87	4[e]	80
5			7	91 *o*:*p* = 30:70	7[e]	85 *o*:*p* = 20:80
6			5	97	5	90
7			4	93	4	86
8			5	72	4[e]	68
9			8	65	3[e]	68
10			2	98	3	93

[a] The products were characterized by comparison of their spectroscopic data with those reported in the literature.

[b] Isolated yields.

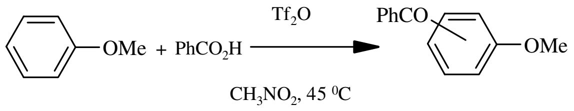
[c] The reaction was carried out in nitromethane (1 ml).

[d] The reactions were carried out in nitromethane (2 ml).

[e] The reactions were carried out at 45 °C.

was obtained. The acylation reactions with 2-methylnaphthalene and 2-methoxynaphthalene afforded 1-acetyl-2-methylnaphthalene and 1-acetyl-2-methoxynaphthalene, respectively, as the sole products indicating the high selectivity in these reactions. However, when toluene was reacted with acetic acid in the presence of Tf_2O, the corresponding aromatic ketones were produced in 91% yield with an *ortho*:*para* ratio of 30:70. Thiophene, as a heterocyclic compound, also reacted well under the same reaction conditions. In the case of phenol or aniline, the O- or N-acylation product was obtained and no C-acylation product was produced. With solid 2-methoxynaphthalene, nitromethane was needed as solvent.

The benzoylation of various aromatic compounds in the presence of Tf_2O was studied to examine the scope and limitations of the reaction. When benzoic acid was used instead of acetic acid for the reaction with anisole, no ketone was obtained under our reaction conditions. A possible reason for this is that the reaction mixture is heterogenous as benzoic acid is solid and is insoluble in the reaction mixture. However, when nitromethane (2 ml) was added to the reaction mixture, anisole was

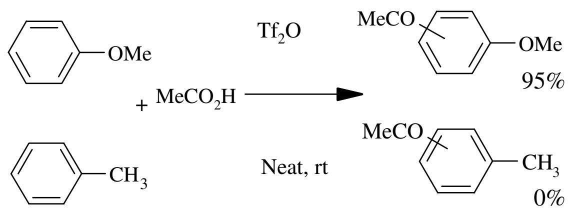


Scheme 2.

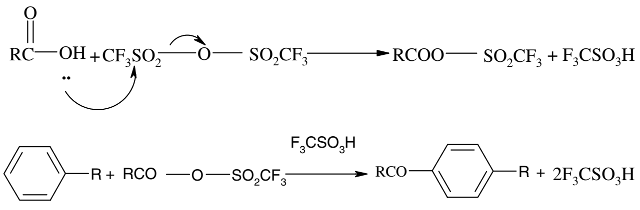
rapidly converted into the corresponding ketone in 96% yield (Scheme 2).

Table 1 includes results for the Tf$_2$O-mediated benzoylation of aromatics. Interestingly, anisole was converted to *p*-acetyl anisole with high regioselectivity while, toluene was benzoylated to the corresponding aryl ketones with an *ortho*:*para* ratio of 20:80. Deactivated benzenes such as chlorobenzene and iodobenzene were inactive towards both acetic and benzoic acids under these reaction conditions.

A competitive experiment was carried out to follow the selectivity of the reaction. Thus, a mixture of anisole and toluene (1:1) was reacted with acetic acid in the presence of Tf$_2$O under solvent-free conditions at room temperature. Methoxyacetophenone was obtained as the sole product in 95% yield indicating a high selectivity between alkoxy and methyl groups on the benzene ring (Scheme 3).



Scheme 3.



Scheme 4.

A possible reaction mechanism is presented in Scheme 4 in which the mixed anhydride was produced initially which then reacted with the aromatic compound in the presence of TfOH (Scheme 4).

The literature results of the FC-acylation reactions of aromatic compounds with carboxylic acids in the presence of a catalyst and using trifluoroacetic anhydride as the acylating agent are listed in Table 2. The reaction in the presence of Tf$_2$O without using any catalyst is also included. The FC-acylation reaction reported here is comparable with the other methods.

In conclusion, we have developed an FC-acylation of aromatic compounds with carboxylic acids as acylating agents in the presence of Tf$_2$O without using any catalyst under mild conditions.[11,12] Short reaction times, high efficiency and high selectivity of the products are advantages of this method.

Acknowledgement

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Table 2. Comparison of the literature results for the FC-acylation of aromatic compounds with carboxylic acids using anhydrides with the result using this method

Entry	Acid	Aromatic compound	Conditions	Catalyst	Yield (%)	Time
1	Benzoic acid	Anisole	TFAA (1.5 equiv), 30 °C	Bi(OTf)$_3$	98	12 h[7]
2	Benzoic acid	Anisole	TFAA (1.5 equiv), rt	AlPW$_{12}$O$_{40}$	96	2.5 h[6]
3	Benzoic acid	Anisole	TFAA (1.5 equiv), rt	Al$_2$O$_3$	80	10 min[8]
4	Phenyl acetic acid	Anisole	TFAA (4 equiv), rt	H$_3$PO$_4$	80	1 min[9]
5	*p*-MeO$_2$S-phenyl acetic acid	Toluene	TFAA (2 equiv), 80 °C, toluene	TfOH	83	1 h[10]
6	Benzoic acid	Anisole	Tf$_2$O (1.1 equiv), 45 °C, nitromethane	No catalyst	96	1 min

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11. *General procedure for the acetylation*: acetic acid (1 mmol, 0.057 ml) and triflic anhydride (1.1 mmol, 0.18 ml) were mixed together and stirred at room temperature for 1 min, then the aromatic compound (1 mmol) was added to the mixture. After completion of the reaction (monitored by TLC), saturated $NaHSO_4$ solution (20 ml) was added to destroy unreacted triflic anhydride or acetic acid. The organic layer was extracted with Et_2O (3 × 10 ml) and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded the crude product which was purified by column chromatography.
12. *General procedure for benzoylation*: benzoic acid (1 mmol, 0.122 g) and triflic anhydride (1.2 mmol, 0.2 ml) were mixed in nitromethane (2 ml), and heated at 45 °C until the benzoic acid dissolved. The aromatic compound (1 mmol) was added to the mixture and the progress of the reaction was monitored by TLC. On completion of the reaction, the solvent was evaporated on a rotary evaporator and a saturated solution of $NaHSO_4$ (20 ml) was added to destroy unreacted triflic anhydride or benzoic acid. The organic layer was extracted with Et_2O (3 × 10 ml) and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded the crude product which was purified by column chromatography.