The Catalytic Friedel-Crafts Acylation Reaction of Aromatic Compounds with Carboxylic Anhydrides Using Combined Catalyst System of Titanium(IV) Chloride Tris(trifluoromethanesulfonate) and Trifluoromethanesulfonic Acid

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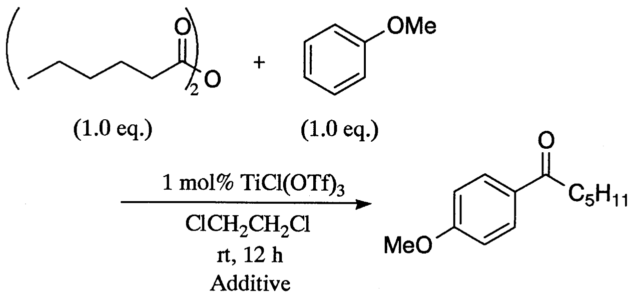
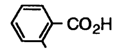
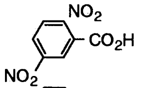
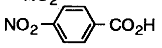
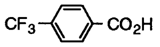
Various aromatic ketones are prepared in good to high yields with carboxylic anhydrides using combined catalyst system of $TiCl(OTf)_3$ and TfOH.

The Friedel-Crafts acylation reaction is one of the most important reactions for preparing of various ketones by carbon-carbon bond forming reaction, and is one of the major methods for the synthesis of aromatic ketones. The reaction is generally carried out by using acylating reagents such as acyl chlorides, carboxylic anhydrides or carboxylic acids in the presence of an excess amount of an acidic promoter due to consumption of the promoter by coordination to the produced aromatic ketones. On the other hand, other Lewis acids such as iron sulfates,[1] iron oxides,[2] diphenylboryl hexachloroantimonate,[3] iron(III) chloride,[4] $Hf(OTf)_4$[5] etc., have been used for accelerating of the *catalytic* Friedel-Crafts acylation reaction of aromatic compounds with acyl chlorides or carboxylic anhydrides. The use of trifluoromethanesulfonic carboxylic anhydrides, generated from acyl chlorides and trifluoromethanesulfonic acid,[6] was also reported. Further, by employing H_3PO_4[7] or active cationic species generated from silicon(IV) chloride and silver perchlorate[8] as a catalyst, mixed anhydride methods for the synthesis of aromatic ketones by the Friedel-Crafts acylation reactions between aromatic compounds and free carboxylic acids or trimethylsilyl carboxylates were reported. Recently, utilization of unique characteristic property of titanium(IV) compounds such as $TiCl(OTf)_3$ or $TiCl_2(OTf)_2$ was studied and the effective catalytic esterification reaction between equimolar amounts of free carboxylic acids and alcohols was performed effectively by using the catalyst in the presence of 200 mol% of octamethyl cyclotetrasiloxane.[9] In this communication, we would like to describe a useful catalytic Friedel-Crafts acylation reaction using active cationic catalyst, $TiCl(OTf)_3$. When the reaction of anisole and hexanoic anhydride was carried out by using 1 mol% of $TiCl(OTf)_3$ in 1,2-dichlroethane at room temperature, the desired reaction proceeded smoothly to produce 1-(4-methoxyphenyl) hexane-1-one in 59% yield. The addition of octamethyl cyclotetrasiloxane resulted in the formation of a trace amount of the desired product as shown in Table 1 although the use of the siloxane made a drastic effect on the catalytic esterification reaction as reported in the previous communication. It was supposed that octamethylcyclotetrasiloxane preferentially caught water in the preceding catalytic esterification reaction. In the present Friedel-Crafts acylation reaction, however, the siloxane was not effective because water was not found. While the addition of strong protonic acids as co-catalysts did increase the yields (Table 1, Entry 8,9), the addition of chlorotrimethylsilane or the combine use with other Lewis acid such as AlF_3 or SbF_3 gave poor results. The use of protic acid as 10-camphorsulfonic acid was not effective (Table 1, Entry 10) either. Finally, a good result was obtained in the reaction of anisole and hexanoic anhydride by using combined catalyst system of 1 mol% of $TiCl(OTf)_3$ and 10 mol% of TfOH was used. On the other hand, the reaction did not proceed when the only addition of 4-nitrobenzoic acid or 4-trifluoromethylbenzoic acid was employed, and the product was obtained in 19% yield when 10 mol% of TfOH was used alone.

Table 1. Effect of additives

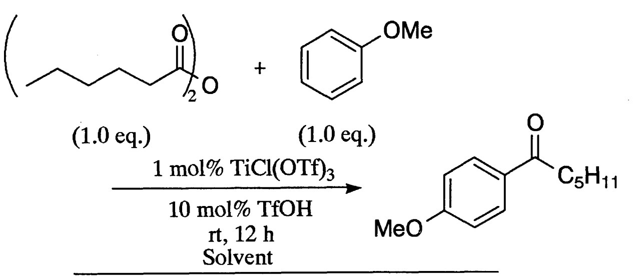


Entry	Aditive (mol%)	yield /%
1	none	59
2	$(Me_2SiO)_4$ (200)	trace
3	TMS-Cl (100)	trace
4	AlF_3 (20)	45
5	SbF_3 (20)	51
6	 (50)	34
7	 (50)	52
8	 (50)	75
9	 (50)	85
10	CSA[a](10)	26
11	TfOH (10)	98

[a] 10-camphorsulfonic acid.

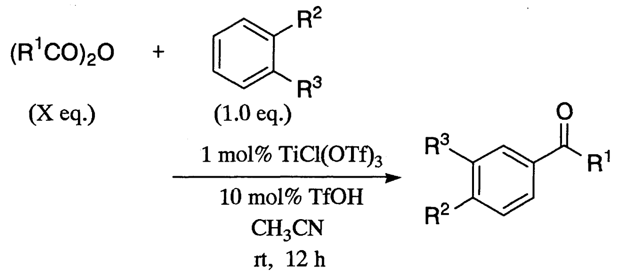
Concerning the catalyst cycle of this Friedel-Crafts acylation reaction, it is assumed that the active cationic catalyst of $TiCl(OTf)_3$ activates the carboxylic anhydride and generates a catalytic amount of trifluoromethanesulfonic carboxylic anhydride along with titanium carboxylate. The active mixed anhydride immediately reacts with the aromatic compound to give the

Table 2. Effect of solvents



Entry	Solvent	yield /%
1	$ClCH_2CH_2Cl$	98
2	$MeNO_2$	56
3	$CHCl_3$	74
4	CH_2Cl_2	71
5	CH_3CN	98

Table 3. Synthesis of aromatic ketones



Entry	R^1	X /eq.	R^2	R^3	yield /%
1	$CH_3(CH_2)_4$-	1.0	OMe	H	98
2	$(CH_3)_2CH$-	1.0	OMe	H	90
3	$(CH_3)_3C$-	1.0	OMe	H	68
4	Ph-	1.0	OMe	H	90
5	$CH_3(CH_2)_4$-	1.0	OMe	OMe	94
6	$(CH_3)_2CH$-	1.0	OMe	OMe	89
7	$(CH_3)_3C$-	1.0	OMe	OMe	66
8	Ph-	1.0	OMe	OMe	94
9	$CH_3(CH_2)_4$-	1.0	OMe	Me	97
10	$(CH_3)_2CH$-	1.0	OMe	Me	96
11	$(CH_3)_3C$-	1.0	OMe	Me	64
12	Ph-	1.0	OMe	Me	88
13[a]	$CH_3(CH_2)_4$-	—	Me	H	66
14[b]	$CH_3(CH_2)_4$-	1.5	Me	Me	61

[a] The reaction was carried out in toluene.

[b] The reaction was carried out at 50 °C.

desired aromatic ketone and titanium carboxylate regenerates the catalyst by TfOH.

The effect of solvents was examined and the respective results are shown in Table 2. Chloroalkanes such as 1,2-dichlroethane and acetonitrile were suitable solvents for this reaction, while the yield was low when nitromethane was used (Table 2, Entry 2).

Several examples of the Friedel-Crafts acylation reaction are shown in Table 3. In Entries 1 through 12, the reaction proceeded smoothly at room temperature in acetonitrile to give the corresponding aromatic ketones in good to high yields from equimolar amounts of aromatic compounds and carboxylic anhydrides. When toluene was used as a solvent, the reaction with hexanoic anhydride gave 1-(4-methylphenyl)hexane-1-one in 66% yield (Entry 13). In the case of using o-xylene, the reaction had to be carried out with an excess amount of hexanoic anhydride at 50 °C (Entry 14).

A typical experimental procedure is described for the reaction of anisole and hexanoic anhydride in the presence of a catalytic system of $TiCl(OTf)_3$ and TfOH; to a solution of $TiCl(OTf)_3$ (0.002 mmol) in acetonitrile (2 ml) a solution of TfOH (0.02 mmol) in acetonitrile (1 ml), a solution of hexanoic anhydride (0.20 mmol) in acetonitrile (1 ml) and a solution of anisole (0.20 mmol) in acetonitrile (1 ml) were successively added. The reaction mixture was stirred for 12 h at room temperature and then quenched with aqueous sodium hydrocarbonate. After the usual work up, the crude product was purified by column chromatography on silica gel to afford 1-(4-methoxyphenyl) hexane-1-one in 98% yield.

Thus, the catalytic Friedel-Crafts acylation reaction of aromatic ketones was established by the reaction of equimolar amounts of anisole, veratrole or 2-methylanisole with several carboxylic anhydrides in the presence of catalytic amounts of $TiCl(OTf)_3$ and TfOH in acetonitrile. It is noted that these Friedel-Crafts acylation reactions also proceed smoothly when toluene and o-xylene were used.

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