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Ytterbium (III) trifluoromethanesulfonate catalysed Friedel–Crafts acylation of 1-methylpyrrole in ionic liquid

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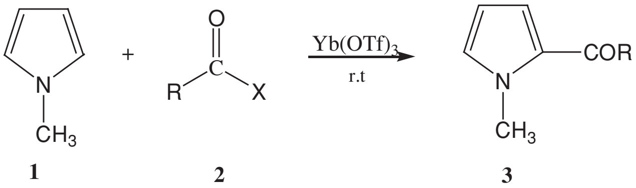
In the presence of a catalytic amount of ytterbium (III) trifluoromethanesulfonate [$Yb(OTf)_3$], 1-methylpyrrole can easily react with acyl chlorides in an ionic liquid [bpy][BF_4](bpy=1-butylpyridine) to form corresponding ketones in satisfactory yield. The recyclability of the ionic liquid/catalyst system is demonstrated

Keywords: Friedel–Crafts acylation, $Yb(OTf)_3$, ionic liquid, 1-methylpyrrole

Aromatic Friedel–Crafts reactions are an important means of adding functionality to simple carbon compounds and as such, are of great importance to many sectors of chemistry.[1] In a typical Friedel–Crafts acylation reaction catalysed by a conventional Lewis acid such as $AlCl_3$, an aromatic compound undergoes electrophilic substitution with an acylation agent and a stable adduct compound is formed between the catalyst and the carbonyl oxygen of the ketone product. Thus, more than the stoichiometric amount of $AlCl_3$ is required to achieve complete reaction.[2] Furthermore, these conventional catalysts are sensitive to moisture, so they cannot be recovered and reused and a large amount of inorganic waste materials are produced after the reaction, which is not in accordance with the rule of an environmentally green process. Metal trifluromethanesulfonates (triflates), as great active and effective water-tolerant Lewis acids, have received much attention and they have been one of the best substitutes of $AlCl_3$.[3-9] In recent years, room temperature ionic liquids, which are entirely composed of ions, have also emerged as an ideal medium for reactions that involve reactive ionic intermediates.[10-14] James and his coworkers have reported Friedel–Crafts reactions of aromatics and acyl chlorides catalysed by metal triflates immobilised in an ionic liquid.[15,16] The reaction rates were enhanced and the yields were improved obviously compared with those in conventional molecular solvents. Furthermore the reactions are easier to handle and the solvent/catalyst system can be recycled conveniently.

On the other hand, heteroaromatic ketones are potentially useful intermediates for the synthesis of pharmaceuticals.[17-18] Here we report Friedel–Crafts acylation of 1-methylpyrrole with acid anhydrides or acyl chlorides catalysed by $Yb(OTf)_3$ in [bpy][BF_4].



Scheme 1

Results and discussion

The acylation reactions of 1-methylpyrrole with acid anhydrides or acyl chlorides proceeded smoothly in the presence of $Yb(OTf)_3$ immobilised in [bpy][BF_4] at room temperature (Scheme 1). The results are listed in Table 1.

As shown in Table 1, the acylation catalysed by $Yb(OTf)_3$ took place in good to excellent yields in an ionic liquid at room temperature. However, another two known methods: the Vilsmeier–Haack acylations[19] of the pyrroles and the $Mg(ClO_4)_2/Ac_2O$ reagent[20] for the synthesis of the corresponding ketones did not give us the same satisfactory result and there were two isomers in low yields if $AlCl_3$[21] was used as the catalyst. Moreover, $Yb(OTf)_3$ was used only in a catalytic amount (10% mol with respect to acyl chlorides) and an excessive amount of the catalyst was not available to increase the yields (entries 2–4). The reactions did not take place in the absence of $Yb(OTf)_3$ or when $Yb(OTf)_3.9H_2O$ was used as the catalyst.

From Table 1, we found that the reactions proceeded in a conventional molecular solvent giving lower yields than those in [bpy][BF_4] even after an extended time(entries 3, 5 and 6). We think that such increase of reaction rates and yields could at least partly be attributed to the increased stabilisation of reactive, charged intermediates in [bpy][BF_4].[15] $Yb(OTf)_3$

Table 1 $Yb(OTf)_3$ catalysed Friedel–Crafts acylation of 1-methylpyrrole[a]

Entry	$Yb(OTf)_3$/equiv.	T/h	Solvent	R	X	Product	Yield/%[b]
1	None	4	[bpy][BF_4]	CH_3	Cl	–[c]	–
2	0.05	1.5	[bpy][BF_4]	CH_3	Cl	**3a**	85
3	0.1	1.5	[bpy][BF_4]	CH_3	Cl	**3a**	93
4	0.2	1.5	[bpy][BF_4]	CH_3	Cl	**3a**	93
5	0.1	4.0	CH_2Cl_2	CH_3	Cl	**3a**	80
6	0.1	4.0	CH_3NO_2	CH_3	Cl	**3a**	85
7	0.1	1.5	[bpy][BF_4]	CH_3	OAc	**3a**	72
8	0.1	1.5	[bpy][BF_4]	CH_2CH_3	Cl	**3b**	92
9	0.1	1.5	[bpy][BF_4]	$(CH_2)_2CH_3$	Cl	**3c**	90
10	0.1	2	[bpy][BF_4]	C_6H_5	Cl	**3d**	83
11	0.1	2	[bpy][BF_4]	C_6H_5	$O_2CC_6H_5$	**3d**	70
12	0.1	2	[bpy][BF_4]	$CH_2C_6H_5$	Cl	**3e**	85
13	0.1	2	[bpy][BF_4]	$CH{:}CHC_6H_5$	Cl	**3f**	78
14	0.1	1.5	[bpy][BF_4]	CH_2Cl	Cl	**3g**	80

[a]The reactions were carried out using 1.5 equiv. of acyl chloride and 1 equiv. of N-methylpyrrole(1mol=1 equiv.), other general conditions see experimental. [b]The yields were based on 1-methylpyrrole. [c]No reaction.

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Table 2 The recyclability of solvent/catalyst system[a]

Recycle	Yield/%[b]	Yield/%[c]	Yield/%[d]
1	93	92	83
2	92	90	80
3	90	89	79

[a]Reaction conditions see experimental. Different acyl chlorides were used: [b]acetyl chloride, [c]propionyl chloride and [c]benzoyl chloride.

also afforded ketones in good yields for the Friedel–Crafts acylation using acid anhydrides as acylating agents (entries 7 and 11). Furthermore, alkyl acyl chlorides reacted with 1-methylpyrrole more easily than aromatic acyl chlorides.

It is also noteworthy that the solvent/catalyst ([bpy][BF$_4$]/Yb(OTf)$_3$) system could be reused without any special handling and the recovered Yb(OTf)$_3$ catalysed the same reaction without decrease in catalytic activity. The results are summarised in Table 2.

In summary, the Friedel–Crafts acylation reaction of 1-methylpyrrole and acyl chlorides or acid anhydrides has been demonstrated using Yb(OTf)$_3$ as the catalyst in [bpy][BF$_4$]. The reaction rates were enhanced and the yields were also improved. Recycling of the solvent/catalyst system was demonstrated.

Experimental

^{1}H NMR spectra were obtained with a Varian 400-MHz spectrometer with TMS as an internal standard. IR spectra were recorded on a Nicolet Avatar 370 infrared spectrophotometer. Melting points were uncorrected. Yb(OTf)$_3$ was prepared from ytterbium oxide and trifluoromethanesulfonic acid in water according to the literature.[22] [bpy][BF$_4$] was prepared according to a published procedure, vacuum-dried and stored under an atmosphere of dry dinitrogen.[23] All other chemicals used are commercially available.

A typical reaction procedure is given for the acylation by acyl chlorides. A round-bottomed flask was charged with Yb(OTf)$_3$ (0.124 g, 2 mmol) and dried under vacuum for 1h with stirring and flushing several times with dry dinitrogen. [bpy][BF$_4$] (2 ml) was added and the mixture was stirred for 10 min until homogenous. Then, acetyl chloride (0.225 g, 3 mmol) and 1-methylpyrrole (0.162 g, 2 mmol) were added. The reaction proceeded at room temperature under an atmosphere of dry dinitrogen. Upon completion of the reaction, the organics were extracted with Et$_2$O. When recycling the solvent/catalyst system, fresh acylating agent and 1-methylpyrrole were added after drying of the solvent/catalyst for 30min at 80 °C under vacuum. The combined extracts were washed with water, saturated sodium bicarbonate aqueous and brine. After removing the solvent, the product was purified by TLC.

3a: Oil[24]; ^{1}H NMR(CDCl$_3$) ppm δ: 2.43 (3H, s, CH$_3$), 3.93 (3H, s, NCH$_3$), 6.11 (1H, d, d, *J*=2.4Hz, *J*=4.0Hz, ArH), 6.79 (1H, t, *J*=2.0Hz, ArH), 6.94 (1H, d, d, *J*=1.6Hz, *J*=4.0Hz, ArH);. IR(film)/cm^{-1}: ν_{max}: 1645(C=O).

3b: Oil [25]; ^{1}H NMR(CDCl$_3$) ppm δ: 1.16 (3H, t, *J*=7.2Hz, CH$_3$), 2.78 (2H, q, *J*=7.6Hz, CH$_2$), 3.93 (3H, s, NCH$_3$), 6.10 (1H, d, d, *J*=2.4Hz, *J*=4.0Hz, ArH), 6.78 (1H, t, *J*=2.0Hz, ArH), 6.94 (1H, d, d, *J*=1.6Hz, *J*=4.0Hz, ArH); IR(film)/cm^{-1}: ν_{max}: 1652(C=O).

3c: Oil[26], ^{1}H NMR(CDCl$_3$) ppm δ: 0.96 (3H, t, *J*=7.6Hz, CH$_3$), 1.70–1.75 (2H, m, CH$_2$), 2.73 (2H, t, *J*=7.6, CH$_2$), 3.94 (3H, s, NCH$_3$), 6.11 (1H, d, d, *J*=2.4Hz, *J*=4.0Hz, ArH), 6.79 (1H, t, *J*=2.0Hz, ArH), 6.95 (1H, d, d, *J*=2.0Hz, *J*=4.0Hz, ArH); IR(film)/cm^{-1}: ν_{max}: 1626 (C=O).

3d: Oil[27], ^{1}H NMR(CDCl$_3$) ppm δ: 4.02 (3H, s, NCH$_3$), 6.14 (1H, d, d, *J*=2.0Hz, *J*=3.6Hz, ArH), 6.74 (1H, t, *J*=2.0Hz, ArH), 6.92 (1H, d, d, *J*=2.0Hz, *J*=4.0Hz, ArH), 7.43–7.81 (5H, m, ArH); IR(film)/cm^{-1}: ν_{max}: 1650 (C=O).

3e: Oil[21], ^{1}H NMR(CDCl$_3$) ppm δ: 3.91 (3H, s, NCH$_3$), 4.07 (2H, s, CH$_2$), 6.14 (1H, d, d, *J*=2.0Hz, *J*=4.0Hz, ArH), 7.08 (1H, t, *J*=2. Hz, ArH), 6.81 (1H, d, d, *J*=2.0Hz, *J*=4.0Hz, ArH), 7.22–7.34(5H, m, ArH); IR(film)/cm^{-1}: ν_{max}: 1646 (C=O).

3f: M.p. 112–113 °C (Lit.[28], 111–112 °C); ^{1}H NMR(CDCl$_3$) ppm δ: 4.03 (3H, s, NCH$_3$), 6.18 (1H, d, d, *J*=2.4Hz, *J*=4.0Hz, ArH), 6.86 (1H, t, *J*=2.0Hz, ArH), 7.06 (1H, d, d, *J*=2.0Hz, *J*=4.4Hz, ArH), 7.35–7.65 (7H, m, –CH=CH–, ArH); IR(KBr)/cm^{-1}: ν_{max}: 1645(C=O).

3g: M.p. 47 °C (Lit.[29], 47–48 °C); H NMR(CDCl$_3$) ppm δ: 3.95 (3H, s, NCH$_3$), 4.51 (2H, s, CH$_2$), 6.16 (1H, d, d, *J*=2.4Hz, *J*=4.4Hz, ArH), 6.89 (1H, t, *J*=2.0Hz, ArH), 6.98 (1H, d, d, *J*=2.0Hz, *J*=4.4Hz, ArH); IR(KBr)/cm^{-1}: ν_{max}: 1651(C=O).

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