SHORT PAPER

J. Chem. Research (S), 2003, 694–695

Ytterbium(III) trifluoromethanesulfonate catalysed Friedel–Crafts acylation of substituted thiophenes

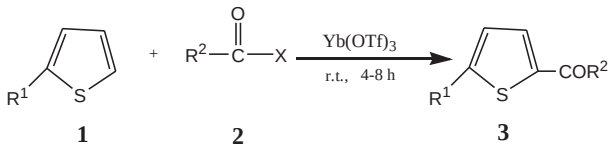
Weike Su* and Can Jin

College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P.R. China

Ytterbium(III) trifluoromethanesulfonate [$Yb(OTf)_3$] has been used to catalyse Friedel–Crafts acylation of substituted thiophenes in different solvents to produce several intermediates of pharmaceuticals and pesticides with good yields. The amount of catalysis was discussed and $Yb(OTf)_3$ could be reused without loss of activity.

Keywords: ytterbium(III) trifluoromethanesulfonate, Friedel–Crafts acylation, thiophenes

Aluminium trichloride ($AlCl_3$)[1] had been used in Friedel–Crafts reactions for the synthesis of aromatic ketones. However, this method required more than stoichiometric amounts of $AlCl_3$ and the discards were harmful to the environment, because $AlCl_3$ could not be reused owing to its instability in aqueous solution.[2,3] Acidic promoters and metal oxides had been used to catalyse these reactions,[4-7] but the substrates were limited to activated benzenes. Unlike conventional Lewis acids, ytterbium trifluoromethanesulfonate [$Yb(OTf)_3$] in catalytic quantity could promote these reactions smoothly and could be reused easily. Kobayashi *et al.* have reported that [$Yb(OTf)_3$] catalysed Friedel–Crafts acylation of benzene and naphthalene with good yields.[8-13] Even some deactivated benzenes could be acylated with catalysis by rare earth metal triflates.[14-18] Most recently, Kobayashi also reported Friedel–Crafts acylation of heteroaromatics catalysed by [$Yb(OTf)_3$].[19] Herein we wish to report Friedel–Crafts acylation of thiophenes with electron-withdrawing substituents catalysed by [$Yb(OTf)_3$] (Scheme 1).



1 **2** **3**

Scheme 1

Results and discussion

[$Yb(OTf)_3$], as a reusable Lewis acid, can catalyse the reactions of substituted thiophenes in nitromethane, chloroform or nitrobenzene at room temperature (Scheme 1). The results are listed in Table 1.

We found that the reactions proceeded smoothly with catalytic amount of [$Yb(OTf)_3$] at room temperature. The reactions did not take place in the absence of lanthanide triflate or when [$Yb(H_2O)_9$]$(OTf)_3$ was used as catalyst. The yields was not obviously affected with different amount of [$Yb(OTf)_3$], 0.1 equiv. of catalyst was enough (Entries 2–4) and an excessive amount of [$Yb(OTf)_3$] did not increase the yields. From Table 1, we also found that the reaction of acyl chloride with substituted thiophenes was quicker than that of anhydride, and the yield was higher (Entries 2 and 5). Furthermore, alkyl acyl chloride reacted with thiophenes more easily than aromatic acyl chloride (Entries 2, 10 and 17). In addition, the solvents also affected the yields, the yield was the highest (Entry 7) when nitromethane was used as solvent and the lowest when carbon tetrachloride was used (Entry 9). Unfortunately, when 2,5-dichlorothiophene was used as substrate in the same condition, no desired product was detected.

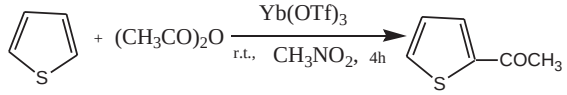
Table 1 $Yb(OTf)_3$ catalysed Friedel–Crafts acylation of substituted thiophenes[a]

Entry	$Yb(OTf)_3$/eq.	Time /h	Solvent	R^1	R^2	X	Product	Yield[b]/%
1	None	4	CH_3NO_2	H	CH_3	Cl	**3a**	ND[c)]
2	0.1	4	CH_3NO_2	H	CH_3	Cl	**3a**	91
3	0.05	4	CH_3NO_2	H	CH_3	Cl	**3a**	85
4	0.2	4	CH_3NO_2	H	CH_3	Cl	**3a**	91
5	0.1	4	CH_3NO_2	H	CH_3	OAc	**3a**	79
6	0.1	4	$CHCl_3$	H	CH_2CH_3	Cl	**3b**	83
7	0.1	4	CH_3NO_2	Br	CH_3	Cl	**3c**	89
8	0.1	4	$CHCl_3$	Br	CH_3	Cl	**3c**	78
9	0.1	4	CCl_4	Br	CH_3	Cl	**3c**	61
10	0.1	8	CH_3NO_2	H	*p*-$CH_3C_6H_4$	Cl	**3d**	78
11	0.1	8	CH_3NO_2	Br	*p*-$CH_3C_6H_4$	Cl	**3e**	76
12	0.05	8	$PhNO_2$	Br	*p*-$CH_3C_6H_4$	Cl	**3e**	62
13	0.1	4	CH_3NO_2	Cl	*p*-$CH_3C_6H_4$	Cl	**3f**	74
14	0.1	4	CH_3NO_2	Cl	CH_2CH_3	Cl	**3g**	90
15	0.1	4	CH_3NO_2	Cl	CH_3	Cl	**3h**	90
16	0.1	4	$CHCl_3$	Br	CH_2CH_3	Cl	**3i**	77
17	0.1	8	CH_3NO_2	H	C_6H_5	Cl	**3j**	79

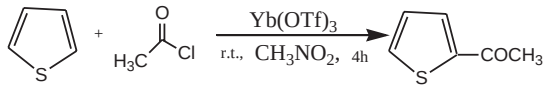
[a]The reaction were carried out using 1 equiv. of substituted thiophenes and 1.5 equiv. of acyl chloride or anhydride (1 mole = 1 equiv.).
[b]Based on thiophenes or substituted thiophenes.
[c]Not detected.

* To receive any correspondence. E-mail: suweike@zjut.edu.cn
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

We have also investigated the effect of different acylating agents on the reaction. The results were summarised in Table 2. From Table 2 we found that 0.1 equiv. of [$Yb(OTf)_3$] and 2 equiv. acetic anhydride was the optimised condition when acetic anhydride was used as acylating agent (Entry 5) and 0.1 equiv. of [$Yb(OTf)_3$] and 1.5 equiv. of acetyl chloride was the optimised condition when acetyl chloride was used as acylating agent (Entry 12).



Scheme 2



Scheme 3

Table 2 $Yb(OTf)_3$ catalysed Friedel-Crafts acylation of thiophene

Entry	$Yb(OTf)_3$ /equiv.	Acylating agent	/equiv.[b]	Yield[a]/%
1	0.05	$(CH_3CO)_2O$	1	70
2	0.05	$(CH_3CO)_2O$	2	76
3	0.05	$(CH_3CO)_2O$	3	76
4	0.1	$(CH_3CO)_2O$	1	75
5	0.1	$(CH_3CO)_2O$	2	83
6	0.1	$(CH_3CO)_2O$	3	84.5
7	0.2	$(CH_3CO)_2O$	2	86
8	0.05	CH_3COCl	1	83
9	0.05	CH_3COCl	1.5	87
10	0.05	CH_3COCl	2	90
11	0.1	CH_3COCl	1	88
12	0.1	CH_3COCl	1.5	91
13	0.2	CH_3COCl	1.5	92

[a]Based on thiophenes or substituted thiophenes.
[b]1 mole = 1 equiv.

To sum up, the reaction proceeded smoothly in the presence of catalytic amounts of [$Yb(OTf)_3$] at room temperature with good yields. The effect of different solvents was obvious, and the yield was the highest when nitromethane was used.

Experimental

^1H NMR spectra were recorded on a Bruker AC-80 instrument with $CDCl_3$ as the solvent with TMS as an internal standard. IR spectra were recorded using KBr pellets on a VECTOR22 Infrared Spectrophotometer. MS spectra were determined on a HP5989B instrument. Melting points were uncorrected. $Yb(OTf)_3$ was prepared from ytterbium oxide and trifluoromethanesulfonic acid in water according to the literature.[20] All reagents used are commercially available.

General procedure: 2-Bromothiophene (2 mmol, 326 mg), [$Yb(OTf)_3$] (0.2 mmol, 124 mg), acetic chloride (3 mmol, 235.5 mg), nitromethane (5 ml) were sequentially added into a dry three-neck flask. After the mixture was stirred at room temperature for 4 h, it turned into red, then the mixture was washed with water (10 ml), saturated sodium bicarbonate aqueous (10 ml), water (10 ml×3) subsequently, then the mixture was extracted by chloroform and the combined organic layer was dried by anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. It was purified by TLC to yield **3c** (89%, 365 mg). The aqueous layer was concentrated *in vacuo* to give white, crystal line $[Yb(H_2O)_9](OTf)_3$ which was then heated at 190°C for 4 h *in vacuo* to give 112 mg [$Yb(OTf)_3$] (90.3%).

3a: M.p. 8–9°C (Lit.[21], 8–10°C) ^1H NMR ($CDCl_3$) ppm δ: 2.56 (3H, s, CH_3), 7.06–7.17 (1H, m, ArH), 7.60–7.72 (2H, m, ArH); IR (cm^{-1}) 3100, 2955, 2924, 1659 (C=O), 1517, 1414, 719.

3b: B.p. 114–115°C (Lit.[22], 114–115°C) ^1H NMR ($CDCl_3$) ppm δ: 1.21 (2H, t, CH_3), 2.87 (2H, q, CH_2), 7.05–7.15 (1H, m, ArH), 7.55–7.72 (2H, m, ArH); IR (cm^{-1}) 3103, 2979, 2938, 1665 (C=O), 1518, 1416, 723.

3c: M.p. 93–94°C (Lit.[23], 94.5–95°C); ^1H NMR ($CDCl_3$) ppm δ: 2.48 (3H, s, CH_3), 7.09 (1H, d, ArH), 7.38 (1H, d, ArH); IR (cm^{-1}) 3098, 2974, 2933, 1650 (C=O), 1522, 1410, 685.

3d: M.p. 71–72°C (Lit.[24], 72°C); ^1H NMR ($CDCl_3$) ppm δ: 2.43 (3H, s, CH_3), 7.09–7.33 (3H, m, ArH), 7.62–7.83 (4H, m, Ar-H); IR (cm^{-1}) 3074, 3038, 2958, 2917, 1624 (C=O), 1603, 1512, 1414, 843, 727; MS *m/z* 202 (M^+ 76.35), 187 (28.95), 174 (6.12), 119 (100.00), 111 (93.39), 91 (61.72), 84 (21.64), 65 (56.71).

3e: M.p. 75–76°C (Lit.[25], 76–78°C) ^1H NMR ($CDCl_3$) ppm δ: 2.43 (3H, s, CH_3), 7.10–7.42 (3H, m, ArH), 7.69–7.98 (3H, m, ArH); IR (cm^{-1}) 3076, 3039, 2954, 2918, 1624 (C=O), 1604, 1516, 1412, 845, 729.

3f: M.p. 86–87°C (Lit.[26], 87°C); ^1H NMR ($CDCl_3$) ppm δ: 2.46 (3H, s, CH_3), 7.20–7.37 (3H, m, ArH), 7.90–8.09 (3H, m, ArH); IR (cm^{-1}) 3094, 3055, 2924, 2855, 1628 (C=O), 1609, 1513, 1417, 834, 750.

3g: M.p. 45–46°C (Lit.[23], 46.5–47.5°C), ^1H NMR ($CDCl_3$) ppm δ: 1.21 (3H, t, CH_3), 2.81 (2H, q, CH_2), 6.96 (1H, d, ArH), 7.46 (1H, d, ArH); IR (cm^{-1}) 3098, 2979, 2938, 1666 (C=O), 1604, 1528, 1421, 724.

3h: M.p. 45–46°C (Lit.[23], 45.5–46°C); ^1H NMR ($CDCl_3$) ppm δ: 2.46 (3H, s, CH_3), 7.01 (1H, d, ArH), 7.41 (1H, d, ArH); IR (cm^{-1}) 3100, 2885, 1655 (C=O), 1530, 1425, 692.

3i: M.p. 52°C (Lit.[23], 52–53°C); ^1H NMR ($CDCl_3$) ppm δ: 1.20 (3H, t, CH_3), 2.81 (2H, q, CH_2), 7.09 (1H, d, ArH), 7.41 (1H, d, ArH); IR (cm^{-1}) 3087, 2975, 2934, 1659 (C=O), 1524, 1415, 723.

3j: M.p. 55°C (Lit.[27], 56–58°C); ^1H NMR ($CDCl_3$) ppm δ: 7.11–7.89 (8H, m, ArH); IR (cm^{-1}) 3099, 2981, 1632, 1414, 1294, 841, 722, 717.

We are grateful to the National Natural Science Foundation of China (No. 20276072).

Received 21 June 2003; accepted 5 September 2003
Paper 03/1986

References

1 L.I. Belen'kii, A.P. Yakubov and Y.L. Gol'dfarb, *Zh. Org. Khim.* 1975, **11**, 424-431.
2 G.A. Olah, *Friedel–Crafts and Related Reactions.* Interscience, New York, 1964, Vol. III, Part 1.
3 G.A. Olah, *Friedel–Crafts Chemistry*. Wiley-Interscience, New York, 1973.
4 T. Mukaiyama, H. Nagaoka, M. Ohshima and M. Urakami, *Chem. Lett.*, 1986, 165.
5 M. Hino and K. Arata, *Chem. Lett.*, 1978, 325.
6 T. Yamaguchi, A. Mitoh and K. Tanabe, *Chem. Lett.*, 1982, 1229.
7 R. Sreekumar and R. Padmakumar, *Synth. Commum.*, 1997, **27**, 777
8 S. Kobayashi, M. Sugiura, H. Kitagawa and W.W.-L. Lam *Chem. Rev.* 2002**, 102**, 2227.
9 A. Kawada, S. Mitamura and S. Kobayashi, *J. Chem. Soc. Chem. Commum.*, 1993, 1157.
10 A. Kawada, S. Mitamura, J. Matsuo, T. Tsuchiya and S. Kobayashi, *Bull. Chem. Soc. Jpn.*, 2000, **73**, 2325.
11 A. Kawada, S. Mitamura and S. Kobayashi, *Synlett.*, 1994, 545.
12 A. Kawada, S. Mitamura and S. Kobayashi, *Chem. Commum.*, 1996, 183.
13 S. Kobayashi and I. Komoto, *Tetrahedron* 2000, **56**, 6463.
14 I. Hachiya, M. Moriwaki and S. Kobayashi, *Tetrahedron Lett.*, 1995, **36**, 409.
15 I. Hachiya, M. Moriwaki and S. Kobayashi, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 2053.
16 S. Kobayashi and S. Iwamoto, *Tetrahedron Lett.*, 1998, **39**, 4697.
17 J. Matsuo, K. Odashima and S. Kobayashi, *Synlett.*, 2000, 403.
18 S. Kobayashi and I. Komoto and J.Matsuo, *Adv. Synth. Cata.*, 2001, **71**, 343.
19 I. Komoto, J.Matsuo and S. Kobayashi, *Topics in Catalysis*, 2002, **19**, 43.
20 J.H. Fosberg, V.T. Spaziano, T.M. Balasubramanian, G.K. Liu, S.A. Kinsley, C.A. DuckWorth, J.J. Poteruca, P.S. Brown and J.L. Miller, *J. Org. Chem.*, 1987, **52**, 1017.
21 Sadtler research laboratories, INC. *Sadtler Standard N. M. R. Spectra*, 1980, **1-3**, 123M.
22 Sadtler research laboratories, INC. *Sadtler Standard N. M. R. Spectra*, 1980, **31-34**, 21211M.
23 M.W. Farrar and R. Levine, *J. Am. Chem. Soc.*, 1950, **72**, 3695.
24 J.J. Spurlock *J. Am. Chem. Soc.*, 1953, **75**, 1115.
25 F. Fumio, Y. Nobuo, I. Kensaku, Y. Osamu, *Ger. Offer.* 2,503,216.
26 Ng. Ph. Buu-Hof, Ng. Hoán, Ng. D. Xuong, *Rec. Trav. Chim.*, 1950, 1083.
27 C. Lane and J. Nagarkatti, *Aldrich*, 1998–1999, 163.