414 **RESEARCH PAPER** JUNE, 414–415 JOURNAL OF CHEMICAL RESEARCH 2004

Acetylation reactions of amines with ethyl acetate catalysed by ytterbium trifluoromethethanesulfonate

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Catalytic amounts of ytterbium trifluoromethethanesulfonate [Yb(OTf)$_3$] have been used to catalyse the acetylation reactions of amines with ethyl acetate under mild and neutral conditions.

Keywords: ytterbium trifluoromethethanesulfonate, ethyl acetate, amide

The chemistry of ytterbium trifluoromethethanesulfonate [Yb(OTf)$_3$] is of current interest in organic synthesis. Ytterbium triflate, as a new versatile Lewis acid, has been used in many organic reactions as a catalyst, which can be reused easily without any loss of activity.[1-5] For example, the first utilisation of Ln(OTf)$_3$ in organic synthesis was reported by Forsberg and co-workers in amidine synthesis. In the presence of a catalytic amount of Ln(OTf)$_3$, amines reacted with nitriles to give a variety of products including *N,N'*-disubstituted amidines and triazines depending on the molar ratios of the amines to the nitriles. Excess of the amines favored formation of *N,N'*-disubstitutedamidines, while an excess of the nitriles gave predominantly triazines.[6]

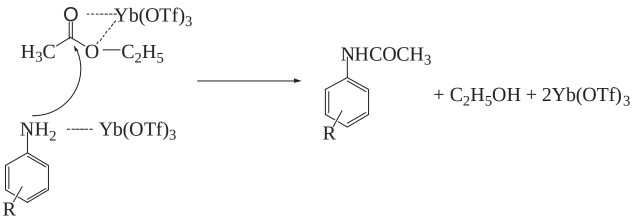
Ethyl acetate, as a conventional solvent, is an inert towards amines. But in the presence of a Lewis acid, it can be activated. Herein we wish to report the acetylation reactions of amines with ethyl acetate under mild and neutral conditions (Scheme 1). The results are shown in Table 1.

From Table 1, it can be seen that ethyl acetate reacts with aromatic amines to afford the desired amides in moderate yields. Unfortunately, when the substrate is *p*-nitroaniline, the corresponding product **3** was not detected even after a long time under reflux conditions. Further examination of the reaction conditions revealed effects of reaction temperature and the amount of Yb(OTf)$_3$. We found that the results were satisfactory when two substrates were treated with Yb(OTf)$_3$ under reflux. It was also found that 5% equiv. of Yb(OTf)$_3$ was enough to accomplish the reaction. If the reaction was carried out using 10% equiv. of Yb(OTf)$_3$ no significant improvements in term of yields or reaction time were observed, while smaller amounts decreased yield and prolonged reaction times. It is important to note that the catalyst could be recovered and reused without loss of activity. The reaction to give compound **3c** has been in fact repeated with the catalyst extracted with water, concentrated *in vacuo* and dried at 190°C for 4 h (Entry j).

In summary, we have demonstrated that the inexpensive, commercially available complex Yb(OTf)$_3$ is a powerful catalyst for the acetylation reactions of amines with ethyl acetate. 5% equiv. of Yb(OTf)$_3$ is enough to complete the reaction, and the catalyst can recovered and reused easily without any loss of activity. Although the detailed mechanism of the above reaction has not clarified, the formation of products **3** may possibly be described by the mechanism presented in Scheme 2.

$$\underset{\mathbf{1}}{RNH_2} + \underset{\mathbf{2}}{CH_3COOC_2H_5} \xrightarrow[\text{reflux, 5 h}]{Yb(OTf)_3} \underset{\mathbf{3}}{RNHCOCH_3} + \underset{\mathbf{4}}{C_2H_5OH}$$

Scheme 1



Scheme 2

Table 1 Acetylation reactions of amines with ethyl acetate catalysed by Yb(OTf)$_3$ [a]

Entry	R	Time/h	Yield%[b]
a	Ph	5	78
b	*p*-MeOC$_6$H$_4$	5	68
c	*p*-MeC$_6$H$_4$	5	67
d	*m*-MeC$_6$H$_4$	5	65
e	*o*-MeC$_6$H$_4$	5	58
f	*p*-ClC$_6$H$_4$	5	73
g	3,5-dichloroC$_6$H$_4$	5	75
h	*p*-CH$_3$OCH$_2$CH$_2$C$_6$H$_4$	5	69
i	*p*-NO$_2$C$_6$H$_4$	20	0
j	*p*-ClC$_6$H$_4$	5	74[c]

[a] Ethyl acetate 5 ml, amine 1 mmol, 5% equiv. of Yb(OTf)$_3$ as used.
[b] Isolated yields based on amine.
[c] The recovered Yb(OTf)$_3$ was reused.

Experimental

All reagents used are commercially available. ^{1}H NMR spectra were recorded on a Varian-400 MHz instrument using CDCl$_3$ or DMSO-*d$_6$* as the solvent with TMS as an internal standard. IR spectra were recorded on a AVATAR-370 Infrared Spectrophotometer. Melting points were determined on a Digital Melting Point Apparatus WRS-1B and are uncorrected. Mass spectra were recorded on a Thermo Finnigan LCQ advantage (ESI). Microanalysis was carried out on a Carlo-Erba 1106 instrument. Yb(OTf)$_3$ was prepared from Ytterbium oxide and trifluoromethanesulfonic acid in water according to the literature.[7]

General procedure

The amine (1 mmol), Yb(OTf)$_3$ (0.05 mmol) and ethyl acetate (5 ml) were taken in a dry there-neck flask at room temperature, and the mixture was refluxed for a given time (see Table 1). It was then treated with 5 ml water and extracted with ethyl acetate (10 ml). After drying with anhydrous MgSO$_4$, ethyl acetate was removed under reduced pressure and the residue purified by TLC (cyclohexane / ethyl acetate = 1 / 1) to obtain the corresponding products.

3a: m.p. 113–114°C (Lit.[8] 114°C); ^{1}H NMR (CDCl$_3$) δ: 7.62 (1H, br s, NH), 7.51–7.07 (5H, m, ArH), 2.16 (3H, s, CH$_3$); IR (KBr) ν: 1665 cm^{-1}.

3b: m.p. 130–130.6°C (Lit.[9] 130–132°C); ^{1}H NMR (CDCl$_3$) δ: 7.70 (1H, br s, NH), 7.39 (2H, d, *J*=8.8Hz), 6.82 (2H, d, *J*=8.8Hz), 3.78(3H, s, OCH$_3$), 2.13 (3H, s); IR (KBr) ν: 1669 cm^{-1}.

3c: m.p. 147–147.5°C (Lit.[8]. 146–147.5°C); ^{1}H NMR (CDCl$_3$) δ: 7.50 (1H, br s, NH), 7.37 (2H, d, *J*=8.4Hz), 7.10 (2H, d, *J*=8.4Hz), 2.29 (3H, s), 2.13 (3H, s); IR (KBr) ν: 1664 cm^{-1}.

3d: m.p. 64.1–64.6°C (Lit.[10] 63–64°C); ^{1}H NMR (CDCl$_3$) δ: 7.75 (1H, br s, NH), 6.90–7.34 (4H, m, ArH), 2.31 (3H, s), 2.15 (3H, s); IR (KBr) ν: 1664 cm^{-1}.

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3e: m.p. 106–107°C (Lit.[8] 107–108°C); ^{1}H NMR ($CDCl_3$) δ: 7.68 (1H, br s, NH), 7.03–7.56 (4H, m, ArH), 2.30 (3H, s); 2.09 (3H, s); IR (KBr) ν: 1655 cm^{-1}.

3f: m.p. 178–178.5°C (Lit.[8] 177–179°C); ^{1}H NMR (DMSO-d_6) δ: 10.10 (1H, br s, NH), 7.62 (2H, d, *J*=8.4Hz), 7.34 (2H, d, *J*=8.4Hz), 2.05(3H, s); IR (KBr) ν: 1666 cm^{-1}.

3g: m.p. 189.1–189.4°C; ^{1}H NMR ($CDCl_3$) δ: 7.79 (1H, br s, NH), 7.50 (2H, s), 7.08 (1H, s), 2.17 (3H, s); IR (KBr) ν: 1667 cm^{-1}; (ESI) MS *m/z* 203.9, 207.9 $(M+H)^+$; Anal. calcd for $C_8H_7Cl_2NO$: C 47.29, H 3.45, N, 6.90; found C 47.30, H 3.46, N 6.92.

3h: m.p. 84.5–85.1°C; ^{1}H NMR ($CDCl_3$) δ: 7.54 (1H, br s, NH), 7.41 (2H, d, *J*=8.4Hz), 7.16 (2H, d, *J*=8.4Hz), 3.57 (2H, t, *J*=6.8Hz), 3.35 (3H, s, OCH_3), 2.84 (2H, t, *J*=6.8Hz), 2.15 (3H, s); IR (KBr) ν: 1662 cm^{-1}; (ESI) MS *m/z* 193.9 $(M+H)^+$; Anal. calcd for $C_{11}H_{15}NO_2$: C 68.39, H 7.77, N, 7.25; found C 68.40, H 7.79, N 7.26.

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

Received 24 December 2003; accepted 20 May 2004
Paper03/2270

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