Acylation of aromatic compounds with isocyanates catalyzed by ytterbium(III) triflate : environmentally friendly

W. K. Su*, J. J. Li and D. W. Yang

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

E-mail : suweike@zjut.edu.cn Fax : 86-571-88320420

Manuscript received 16 December 2003, accepted 11 May 2004

Aromatic compounds can be acylated by isocyanates in the presence of catalytic amount of ytterbium(III) triflate [Yb(OTf)₃] to obtain the corresponding *N*-substituted benzamides in good yields under neutral conditions. The catalyst can easily be recovered and reused without any loss of activity.

Since the first utilization of Yb(OTf)₃ by Forsberg *et al.*¹, Yb(OTf)₃ as an all-purpose Lewis acid, it has been found widely used in organic syntheses². For instance, Yb(OTf)₃ was found to catalyze the Aldol reaction³, Mannich-type reaction⁴, Diels-Alder reaction⁵, Friedel-Crafts acylation and alkylation⁶. However, to the best of our knowledge Yb(OTf)₃ catalyzed acylation of aromatic compounds by isocyanates has not been reported up to date. Herein, we wish to report the reaction using Yb(OTf)₃ as the catalyst (Scheme 1).

Scheme 1

The acylation reaction of aromatic compounds with isocyanates in the presence of aluminum chloride was first reported by Leuckart⁷. Billeter found that benzenesulfonyl isocyanate was mixed with benzene in the presence of AlCl₃, similarly *N*-(benzenesulfonyl)benzamide was obtained⁸. This reaction has been evaluated elaborately more recently by Effenberger and Gleiter⁹ using Friedel-Crafts-type catalysts. Recently, Mcfarland reported the optimal ratio (substrate : catalyst) and the mechanism of the reaction catalyzed by aluminum chloride¹⁰. However, a common problem, particularly in industrial process, is that these reactions require excess amount of the conventional Lewis acid which cannot be reused because of its instability in the usual aqueous media. Unlike conventional Lewis acids Yb(OTf)₃ can be easily recovered and be reused after the reaction is completed¹¹. These properties of Yb(OTf)₃ made them attractive alternative to Lewis acids such as aluminum

chloride. Actually, this reaction catalyzed by Yb(OTf)₃ was possible and run well in RT.

Results and discussion

From Table 1, it can be found that *p*-(toluenesulfonyl) isocyanate or phenyl isocyanate can react with aromatic compounds to afford the desired benzamides in satisfactory yields. Unfortunately, no desired products were detected when the substrate was nitrobenzene even for a long time under reflux conditions (i, j).

The experimental evidence showed that catalytic amount of Yb(OTf)₃ (0.1 equiv.) could promote this reaction smoothly at RT. Smaller amount of catalyst resulted in the

Table 1. Friedel-Crafts reaction of isocyanates with aromatic compounds in the presence of ytterbium triflate*

Compd.	R ¹	R ²	Reaction time/h	Yield/% ^a
3a	<i>p</i> -H ₃ CC ₆ H ₄ SO ₂	H	2	90
b	<i>p</i> -H ₃ CC ₆ H ₄ SO ₂	CH ₃	2	91
c	<i>p</i> -H ₃ CC ₆ H ₄ SO ₂	CH ₃ O	2	84
d	<i>p</i> -H ₃ CC ₆ H ₄ SO ₂	Cl	2	72
e	<i>p</i> -H ₃ CC ₆ H ₄ SO ₂	Naphthalene	2	86 ^b
f	C ₆ H ₅	H	2	82
g	C ₆ H ₅	CH ₃	2	74
h	C ₆ H ₅	CH ₃ O	2	79
i	<i>p</i> -H ₃ CC ₆ H ₄ SO ₂	NO ₂	10	0
j	C ₆ H ₅	NO ₂	10	0

*Isocyanates 1 mmol, aromatic compounds 1.2 mmol, Yb(OTf)₃ 0.1 mmol were used.

^aIsolated yields were based on isocyanates. All compounds were characterized using ¹H NMR and IR.

^bThe product was *N*-(*p*-toluenesulfonyl)-1-naphthamide.

partial unreacted substrate even for a long time. Under higher temperature, the products consisted of both *N*-(*p*-toluenesulfonyl)benzamide and (phenyl)-*p*-tolyl sulfone (**3a**). In addition, it was found in our experiment that the reaction did not take place in the absence of Yb(OTf)₃ or in the presence of Yb(OTf)₃·(H₂O)_x. Various reports on the use of lanthanide catalysts have focused on their recyclability^{2a,b}. We decided to demonstrate that this was possible in our system and the catalyst remaining in the aqueous phase was recovered by removing the water through heating and then drying under vacuum at 100° for 2 h in nearly quantitative yield. According to the typical procedure (**3a**), we repeated three times by recycle catalyst with the following yields : 87, 86 and 86% (Table 2).

Table 2. Catalyst recovery and its activity*

Use	Mol% cat.	Reaction time/h	Yield%	Cat recovered
1st	10	2	90	98
2nd	10	2	87	98
3rd	10	2	86	98
4th	10	2	86	97

*The preparation of *N*-(*p*-toluenesulfonyl)benzamide.

In conclusion, we have demonstrated that the Yb(OTf)₃ can catalytically promote the reaction smoothly under suitable conditions with simple operation. As the catalyst, Yb(OTf)₃ was superior to previous Brønsted and Lewis acids, and overcame the problems encountered with classical Lewis acids. The mechanism of the reaction is not known, but the advantages were obvious for synthesis of this type of benzamides.

Experimental

Isocyanates were prepared from their corresponding amines¹². Benzene and toluene were dried over sodium prior to use. Anisole, chlorobenzene and CH₂Cl₂ were dried over anhydrous calcium chloride. M.ps. were obtained with a capillary melting point apparatus and were uncorrected. IR spectra were recorded using KBr pellets on Vector-22 IR spectrophotometer. ¹H NMR was determined on Bruker AC-400 spectrometer with TMS as an internal standard. Organic solvents were obtained from commercial sources. Preparative TLC separations were carried out with silica gel GF-254 coated glass plates.

Typical procedure for synthesis of *N*-substituted benzamides : A mixture of Yb(OTf)₃ (62 mg, 0.1 mmol), *p*-toluenesulfonyl isocyanate (0.20 g, 1 mmol), benzene (0.94 g, 1.2 mmol) in anhydrous CH₂Cl₂ (15 ml) was stirred at RT for 2 h. Subsequently, the solution was washed with

water (5 × 2 ml). The aqueous layer was extracted with diethyl ether (15 × 3 ml). Yb(OTf)₃ can be recovered from aqueous mixture by removing the water. The combined organic layer was evaporated under reduced pressure. The crude product was purified by preparative TLC (cyclohexane : ethyl acetate = 2 : 1) to afford **3a** (0.249 g, 90% yield) as a white solid. The characterization and spectral data of the products are as follows : **3a** m.p. 145–146° (lit.¹³ 147°); $\nu_{\max}$ 3315 (N–H), 1710 cm^{−1} (C=O); ¹H NMR δ (CDCl₃) 10.11 (1H, s), 7.95–7.39 (9H, m), 2.35 (3H, s); **3b** m.p. 135–136° (lit.¹⁰ 137–138°); $\nu_{\max}$ 3300 (N–H), 1700 cm^{−1} (C=O); ¹H NMR δ (CDCl₃) 10.10 (1H, s), 8.18–6.87 (8H, m), 2.36 (3H, s), 2.28 (3H, s); **3c** m.p. 175–176° (lit.¹⁴ 176–177°); $\nu_{\max}$ 3220 (N–H), 1700 cm^{−1} (C=O); ¹H NMR δ (CDCl₃) 10.07 (1H, s), 8.12–6.83 (8H, m), 3.65 (3H, s), 2.35 (3H, s); **3d** m.p. 192–194° (lit.¹⁰ 192–194°); $\nu_{\max}$ 3225 (N–H), 1701 cm^{−1} (C=O); ¹H NMR δ (CDCl₃) 10.18 (1H, s), 7.98–7.39 (8H, m), 2.36 (3H, s); **3e** m.p. 146–147° (lit.¹⁰ 146–148°); $\nu_{\max}$ 3255 (N–H), 1697 cm^{−1} (C=O); ¹H NMR δ (CDCl₃) 10.53 (1H, s), 8.50–7.39 (11H, m), 2.37 (3H, s); **3f** m.p. 161–162° (lit.¹⁴ 163°); $\nu_{\max}$ 3346 (N–H), 1625 cm^{−1} (C=O); ¹H NMR δ (DMSO-*d*₆) 10.30 (1H, s), 7.98–7.12 (10H, m); **3g** m.p. 133–134° (lit.¹⁵ 134°); $\nu_{\max}$ 3353 (N–H), 1649 cm^{−1} (C=O); ¹H NMR δ (DMSO-*d*₆) 10.26 (1H, s), 7.87–7.09 (9H, m), 2.39 (3H, s); **3h** m.p. 153–155° (lit.¹⁴ 154–156°); $\nu_{\max}$ 3342 (N–H), 1658 cm^{−1} (C=O); ¹H NMR δ (DMSO-*d*₆) 10.09 (1H, s), 7.96–7.07 (9H, m), 3.96 (3H, s).

Acknowledgement

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

References

1. J. 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.
2. (a) R. W. Marshman, *Aldrichim. Acta*, 1995, **28**, 77; (b) S. Kobayashi, *Synlett*, 1994, 689; (c) S. Kobayashi, M. Sugiura, H. Kitagawa and W.-L. Lam, *Chem. Rev.*, 2002, **102**, 2227.
3. S. Kobayashi, *Chem. Lett.*, 1991, 2187.
4. R. Annunziata, M. Cinquini, F. Cozzi, V. Molteni and O. Schupp, *Tetrahedron*, 1996, **52**, 2573.
5. A. C. Kinsman and M. A. Kerr, *Org. Lett.*, 2000, **2**, 823.
6. C. E. Song, W. H. Shim, E. J. Roh and J. H. Choi, *Chem. Commun.*, 2000, 1695; A. G. M. Barrett, D. C. Braddock, J. P. Henschke and E. R. Walker, *J. Chem. Soc., Perkin Trans. 1*, 1999, 873; P. Harrington and M. A. Kerr, *Tetrahedron Lett.*, 1997, **38**, 5949.
7. R. Leuckart, *Ber.*, 1885, **18**, 873.
8. O. C. Billeter, *Ber.*, 1904, **37**, 690.

Note

9. F. Effenberger and R. Gleiter, *Ber.*, 1964, **97**, 472.
10. J. W. Mcfarland and C. Y. Lucila, *J. Org. Chem.*, 1970, **35**, 123.
11. S. Kobayashi and I. Hachiya, *J. Org. Chem.*, 1994, **59**, 3590.
12. Z. Y. Xu, X. H. Du and W. K. Su, *J. Indian Chem. Soc.*, 2002, **79**, 962.
13. A. Kepemp and H. Stephen, *J. Chem. Soc.*, 1948, 110.
14. J. I. G. Cadogan, "Dictionary of Organic compounds", 6th. ed., Chapman & Hall, London, U.K., 1996, **1**, p. 559.
15. M. Mayouf and Y.-T. Park, *J. Photochem. Photobiol. A : Chem.*, 2002, **150**, 115.