Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 6775–6778
Tetrahedron Letters

Facile catalyzed acylation of heteroatoms using $BiCl_3$ generated in situ from the procatalyst BiOCl and acetyl chloride

Rina Ghosh,* Swarupananda Maiti and Arijit Chakraborty

Department of Chemistry, Jadavpur University, Kolkata 700 032, India

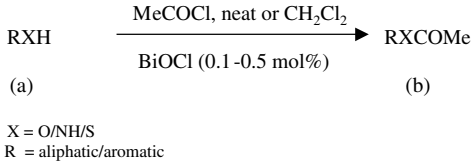
Received 7 May 2004; revised 28 June 2004; accepted 9 July 2004
Available online 28 July 2004

Abstract—Acylation of a variety of alcohols, phenols, aliphatic and aromatic amines, a thiol and a thiophenol proceeds efficiently using $BiCl_3$ generated in situ from the procatalyst BiOCl and acetyl chloride in a solvent or under solventless conditions, furnishing the corresponding acylated derivatives in very good to excellent yields.
© 2004 Elsevier Ltd. All rights reserved.

Protection of heteroatoms by acylation is a very frequently employed organic transformation because of the mild deprotection methods available.[1] Acylation of hydroxy groups can be effected by carboxylic acids or derivatives like anhydrides,[1] acid chlorides,[1] acyl imidazoles[2a] or acyl ureas[2b] in the presence of bases such as Et_3N, pyridine, DMAP,[3a] Bu_3P[3b] or Lewis acids such as $MgBr_2$,[4a] $ZnCl_2$,[4b] $CoCl_2$,[4c] $TaCl_5$,[4d] $InCl_3$,[4e] $ZrCl_4$[4f] and $RuCl_3$.[4g] Some recent reports include metal triflates,[5] perchlorates[6] or supported reagents like HBF_4–SiO_2,[7a] $HClO_4$–SiO_2,[7b] KF–Al_2O_3,[7c] Nafion-H[7d] or yttria–zirconia,[7e] clay[7f] and zeolite HSZ-360.[7g] Iodine,[8] ionic liquids,[9] twisted amides[10] and *Pseudomonas capacia* PS lipase absorbed on Celite[11] have also been employed for acetylation of alcohols and phenols. However, the reported methods are not always devoid of disadvantages in terms of yields, chemoselectivity, moisture sensitivity, load and cost of the catalysts. Sometimes, the reagents are highly toxic, flammable or explosive. Thus, the search for newer mild and efficient methodologies for acylation continues.

Very recently, Bi(III) salts such as $Bi(OTf)_3$[5c] and $BiOClO_4$[6c] have been reported to effect acylation of heteroatoms with acid anhydrides. Bi(III) salts have served as Lewis acid catalysts for various other organic reactions[12] and are particularly important because of their low toxicity[13] and low cost; amongst these, $BiCl_3$ has been widely studied. BiOCl is an oxy salt of Bi(III) whose Lewis acidity is very low[6c] but it can generate $BiCl_3$ on reaction with an acyl chloride and thus can act as a procatalyst and has been utilized in Friedel–Crafts acylation reactions.[14] The toxicity level of BiOCl is very low[13] and it is highly stable and readily available. We report herein the efficacy of BiOCl, in catalytic amounts, for the in situ generation of $BiCl_3$ vis-à-vis acylation of different heteroatoms in reactions with acyl chlorides (Scheme 1 and Table 1).

At the outset, β-naphthol was chosen as a model substrate and the minimum load of procatalyst and the acylating reagent (acetyl chloride) was ascertained using varying amounts of these in different solvents. The best results were obtained on treatment of β-naphthol in the



Scheme 1.

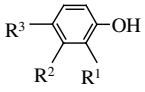
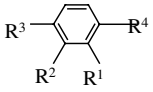
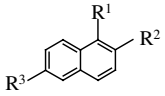
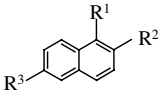
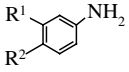
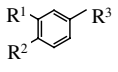
Table 1. Acetylation of β-naphthol based on BiOCl (0.5 mol%) and AcCl (2 equiv) in different solvents at room temperature

Entry	Solvent	Time	Yield (%)
1	CH_2Cl_2	45 min	94
2	CH_3CN	1 h	91
3	THF	12 h	53
4	$PhCH_3$	12 h	85

Keywords: Catalyzed; Acylation; Procatalyst; BiOCl; $BiCl_3$.
* Corresponding author. E-mail: ghoshrina@yahoo.com

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.07.044

Table 2. Acylation of heteroatoms based on BiOCl–acyl chloride

Entry	Substrate (RXH)	Method A[a] (CH_2Cl_2)		Method B[b] (neat)		Product[c] (RXAc)
	(a)	Time	Yield (%)	Time	Yield (%)	(b)
1	R = $CH_3(CH_2)_3$–	10 min	92	2 min	95	R = $CH_3(CH_2)_3$–
2	R = $CH_3(CH_2)_5$–	10 min	93	0.5 min	97	R = $CH_3(CH_2)_5$–
3	R = $CH_3(CH_2)_7$–	30 min	95	1 min	96	R = $CH_3(CH_2)_7$–
4	R = $(CH_3)_3C$–	15 min	93	4 min	96	R = $(CH_3)_3C$–
5	R = $PhCH_2$–	5 min	98	0.5 min	97	R = $PhCH_2$–
6	R = $Ph(CH_2)_2$–	5 min	96	0.5 min	97	R = $Ph(CH_2)_2$–
7	Mannitol	1.5 d	94	4 h min	98	Mannitol hexaacetate
8	Cyclohexanol	5 min	94	2 min	92	Cyclohexyl acetate
9	Benzoin	1.5 h	96	5 min	96	Benzoin acetate
10	Cholesterol	30 min	96	10 min	94	Cholesteryl acetate
11	Methyl α-D-Glcp	5 h	94	1.5 h	98	Methyl α-D-Glcp $(OAc)_4$
12	(+)-Menthol	5 min	93	—	—	Menthyl acetate
13	Allyl alcohol	3 min	86	—	—	Allyl acetate
14	Propargyl alcohol	6 min	92	—	—	Propargyl acetate
						
15	$R^1 = CO_2Me$, $R^2 = R^3 = H$	8 h	96	1.5 h	96	$R^1 = CO_2Me$, $R^2 = R^3 = H$, $R^4 = OAc$
16	$R^1 = R^2 = H$, $R^3 = Br$	30 min	98	1 min	98	$R^1 = R^2 = H$, $R^3 = Br$, $R^4 = OAc$
17	$R^1 = R^3 = H$, $R^2 = Me$	2.5 h	90	5 min	98	$R^1 = R^3 = H$, $R^2 = Me$, $R^4 = OAc$
18	$R^1 = OH$, $R^2 = R^3 = H$	1 h	84	15 min	98	$R^1 = OAc$, $R^2 = R^3 = H$, $R^4 = OAc$
19	$R^1 = R^3 = H$, $R^2 = OH$	2.5 h	91	5 min	98	$R^1 = R^3 = H$, $R^2 = OAc$, $R^4 = OAc$
20	$R^1 = R^2 = H$, $R^3 = OH$	30 min	96	5 min	98	$R^1 = R^2 = H$, $R^3 = OAc$, $R^4 = OAc$
21	$R^1 = NO_2$, $R^2 = R^3 = H$	6 h	49[d]	2.5 h	96[h]	$R^1 = NO_2$, $R^2 = R^3 = H$, $R^4 = OAc$
22	$R^1 = R^3 = H$, $R^2 = NO_2$	3 h	93	30 min	95	$R^1 = R^3 = H$, $R^2 = NO_2$, $R^4 = OAc$
23	$R^1 = R^2 = H$, $R^3 = NO_2$	5 h	95	30 min	98	$R^1 = R^2 = H$, $R^3 = NO_2$, $R^4 = OAc$
24	$R^1 = Ac$, $R^2 = R^3 = H$	24 h	92	12 h	91	$R^1 = Ac$, $R^2 = R^3 = H$, $R^4 = OAc$
						
25	$R^1 = R^3 = H$, $R^2 = OH$	45 min	94	3 min	93	$R^1 = R^3 = H$, $R^2 = OAc$
26	$R^1 = R^3 = H$, $R^2 = OH$	30 min	95[f]	3 min	94[f]	$R^1 = R^3 = H$, $R^2 = OAc$
27	$R^1 = R^3 = H$, $R^2 = OH$	30 min	93[f,g]	3 min	95[f,g]	$R^1 = R^3 = H$, $R^2 = OAc$
28	$R^1 = OH$, $R^2 = R^3 = H$	12 h	95	5 min	94	$R^2 = R^3 = H$, $R^1 = OAc$
29	$R^1 = H$, $R^2 = R^3 = OH$	1 h	98	2 h	92	$R^2 = R^3 = OAc$, $R^1 = H$
30	$R^1 = R^3 = H$, $R^2 = OH$	19 h	70	5 h	93	$R^1 = R^3 = H$, $R^2 = OBz$
31	$R^1 = OH$, $R^2 = R^3 = H$	1.5 d	88	12 h	97	$R^1 = OBz$, $R^2 = R^3 = H$
32	$R^1 = R^3 = H$, $R^2 = OH$	12 h	95	—	—	$R^1 = R^3 = H$, $R^2 = OOCCH_2Ph$
33	$CH_3(CH_2)_7OH$	1.5 d	94	6 h	91	$CH_3(CH_2)_7OBz$
						
34	$R^1 = H$, $R^2 = Cl$	10 min	96[e]	10 min	95	$R^1 = H$, $R^2 = Cl$, $R^3 = NHAc$
35	$R^1 = NO_2$, $R^2 = H$	5 min	94[e]	—	—	$R^1 = NO_2$, $R^2 = H$, $R^3 = NHAc$
36	$R^1 = H$, $R^2 = NO_2$	5 min	94[e]	3 min	93	$R^1 = H$, $R^2 = NO_2$, $R^3 = NHAc$
37	$R^1 = OH$, $R^2 = H$	5.5 h	94[e]	3 h	93	$R^1 = OAc$, $R^2 = H$, $R^3 = NHAc$
38	$PhCH_2NH_2$	30 min	98[e]	—	—	$PhCH_2NHAc$
39	CH_3CH_2SH	30 min	96	4 min	95	CH_3CH_2SAc
40		40 min	92	5 min	98	

[a] Using 0.5 mol% BiOCl.
[b] Using 0.1 mol% BiOCl.
[c] All products were characterized by IR, NMR and also by comparing the physical data with those of known compounds.
[d] In refluxing $(CH_2Cl)_2$.
[e] In CH_3CN.
[f] Scale-up (~30-fold) experiment.
[g] With recovered BiOCl.
[h] Under sonication.

presence of 0.5 mol% BiOCl and acetyl chloride (2 equiv) in dichloromethane, which generated the β-naphthyl acetate in 45 min and in 94% yield (Table 1, entry 1; Table 2, entry 25). Yields in acetonitrile, tetrahydrofuran and toluene were 91%, 53% and 85%, respectively (Table 1; entries 2–4). Similar acetylation of α-naphthol (entry 28), 2,6-dihydroxynaphthalene (entry 29) and other phenolic compounds containing electron withdrawing (entries 15, 21–24) and electron donating substituents (entries 16–20) on the aromatic ring proceeded satisfactorily in almost quantitative yields (Table 2). While acetylation of *o*-nitrophenol in refluxing dichloroethane was sluggish, complete conversion was accomplished in neat conditions after sonication for 2.5 h (Table 2, entry 21). Compounds containing primary (entries 1–3, 5,6), secondary (entries 7–12) and tertiary (entry 4) hydroxyl groups were easily acetylated in excellent yields (Table 2) under the present conditions without any competitive side reactions of the secondary and tertiary alcohols. Quantitative acetylation of D-mannitol and α-D-glucopyranoside (entries 7 and 11, Table 2) was achieved with no competitive acetylation of the anomeric methoxy group[15] in case of the second substrate. The method is also applicable to the acetylation of chiral alcohols such as cholesterol and (+)-menthol (entries 10 and 12, Table 2) in very high yields and optical purity. Acetylation of allyl alcohol (entry 13) and propargyl alcohol (entry 14) also proceeded smoothly to their respective acetates in 86% and 92% yields (Table 2).

The scope of this simple acylation was further extended to the benzoylation of β-naphthol, α-naphthol and octanol (entries 30, 31 and 33, Table 2) with benzoyl chloride–BiOCl. However, a large excess of benzoyl chloride (~5 equiv) was necessary to effect complete benzoylation. Similar acylation of β-naphthol with phenylacetyl chloride was also possible to give the corresponding ester with almost quantitative conversion (95%, Table 2, entry 32).

The generality of the present methodology was further established by the acetylation of amine and aniline derivatives. However, with these substrates, the best results were obtained in acetonitrile. Thus, each of *p*-chloroaniline (entry 34), *m*- and *p*-nitroanilines (entries 35 and 36), *m*-hydroxyaniline (entry 37) and benzylamine (entry 38) were readily acetylated in acetonitrile (Table 2). The general procedure of acetylation was equally applicable to ethanethiol and thiophenol (Table 2, entries 39 and 40), which yielded their respective acetylated products in 96% and 92% yields.

All the substrates could be acetylated under solvent-free conditions in excellent yields using even lower amounts of BiOCl (0.1 mol%) and in shorter reaction times (method B, Table 2), thus, making the present acylation procedure environmentally friendly.

The preparative efficacy of this procedure was verified by a scaling up (~30-fold) experiment with β-naphthol (Table 2, entry 26). Complete acetylation was possible with even 1.5 equiv of acetyl chloride. After aqueous work-up, BiOCl can be regenerated from the aqueous layer and can be reused with equal efficacy (Table 2, entry 27). A scale-up experiment (~30-fold) under neat conditions with BiOCl (0.1 mol%) and 1.5 equiv of acetyl chloride was also equally fruitful (yield 94%, method B, Table 2, entry 26).

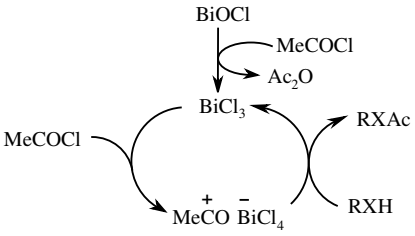


Figure 1. In situ generation of $BiCl_3$ from BiOCl and its catalytic regeneration after acylation.

As has already been noted, BiOCl in reaction with acyl chloride generates $BiCl_3$[14] in situ that in turn acts as a Lewis acid catalyst and activates the acylating reagent. After the acylation reaction, $BiCl_3$ is regenerated and thus the catalytic cycle (Fig. 1) is carried on.

The present method tolerates the presence of C=C, C≡C, CO_2R, COR and NO_2 groups in the substrates and is thus a chemoselective procedure in the presence of the above functionalities. No Fries rearrangement products could be detected in the acylation of any of the phenolic substrates.

In conclusion, we have demonstrated that BiOCl, in reaction with an acyl chloride, is an efficient procatalyst for the in situ generation of $BiCl_3$ vis-à-vis acylation of alcohols, phenols, aliphatic and aromatic amines, a thiol and a thiophenol. The advantages of the present method are: BiOCl is an inexpensive, readily available and moisture stable procatalyst, the load of this reagent is quite low, and it has a very low toxicity level (LD_{50} in rats, oral: 22 g/kg),[13] the reaction conditions are mild and simple, yields of the products are excellent in solution as well as in solventless conditions; moreover, BiOCl can be regenerated[14] and reused without any loss of its procatalytic activity. The conversion under solventless conditions along with the reusability, very low price and low toxicity level of the procatalyst make this method a more eco-friendly alternative to other existing methodologies and a suitable procedure for industrial application.

General procedure for acetylation: (a) Method A (in solvent)—To a mixture of substrate (1 equiv) and BiOCl (0.5 mol%) in CH_2Cl_2 (or in CH_3CN for amines, 4 ml) was added acetyl chloride (2 equiv) and the mixture was stirred at room temperature. After completion of the reaction (TLC) the mixture was diluted with CH_2Cl_2, then washed subsequently with brine (20 ml), saturated aq $NaHCO_3$ (2×15 ml) and H_2O (20 ml). The organic layer was dried over Na_2SO_4 and concentrated to dryness. The crude product was filtered through SiO_2 or crystallized before taking spectral data.

(b) Method B (under neat conditions)—To a mixture of substrate (1 equiv) and BiOCl (0.1 mol%) was added acetyl chloride (1.5 equiv) with stirring at room temperature. After completion of the reaction the mixture was processed as described in Method A.

Acknowledgements

We gratefully acknowledge the financial assistance from CSIR, New Delhi to R.G. (Scheme No. 01/1672/00/EMR-II) and to S.M. (JRF) and from UGC, New Delhi to A.C. (SRF).

References and notes

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.
2. (a) Kamijo, T.; Harada, H.; Iizuka, K. *Chem. Pharm. Bull.* **1984**, *32*, 2560–2564; (b) Dhanon, M. K.; Olsen, R. K.; Ramaswamy, K. *J. Org. Chem.* **1982**, *47*, 1962–1965.
3. (a) Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981; (b) (i) Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358–3359; (ii) Vedejs, E.; Bennet, N. S.; Conn, L. M.; Diver, S. T.; Gingras, M.; Lin, S.; Oliver, P. A.; Peterson, M. J. *J. Org. Chem.* **1993**, *58*, 7286–7288.
4. (a) (i) Vedejs, E.; Daugulis, O. *J. Org. Chem.* **1996**, *61*, 5702–5703; (ii) Pansare, S. V.; Malusare, M. G.; Rai, A. N. *Synth. Commun.* **2000**, *30*, 2587–2592; (b) Baker, R. H.; Bordwell, F. G. In *Org. Synth. Coll. Vol. 3*; Wiley: New York, **1955**; p 141; (c) Ahmad, S.; Iqbal, J. *Tetrahedron Lett.* **1986**, *27*, 3791–3794; (d) Chandrasekhar, S.; Ramachander, T.; Takhi, M. *Tetrahedron Lett.* **1998**, *39*, 3263–3266; (e) Chakraborti, A. K.; Gulhane, R. *Tetrahedron Lett.* **2003**, *44*, 6749–6753; (f) Chakraborti, A. K.; Gulane, R. *Synlett* **2004**, 627–630; (g) De, S. K. *Tetrahedron Lett.* **2004**, *45*, 2919–2922.
5. (a) (i) Barrett, A. G. M.; Braddock, D. C. *Chem. Commun.* **1997**, 351–352; (ii) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 4413–4414; (iii) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560–4567; (b) Chauhan, K. K.; Frost, C. G.; Love, I.; Waite, D. *Synlett* **1999**, 1743–1744; (c) (i) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2877–2879; (ii) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *J. Org. Chem.* **2001**, *66*, 8926–8934; (d) (i) Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *Chem. Commun.*, **1996**, 2625–2626; (ii) Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, *63*, 2342–2347; (e) Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Nardi, M.; Bartoli, G.; Romeo, R. *Tetrahedron Lett.* **2003**, *44*, 5621–5624; (f) (i) Chandra, K. L.; Saravanan, P.; Singh, R. K.; Singh, V. K. *Tetrahedron* **2002**, *58*, 1369–1374; (ii) Saravanan, P.; Singh, V. K. *Tetrahedron Lett.* **1999**, *40*, 2611–2614.
6. (a) Nakae, Y.; Kusaki, I.; Sato, T. *Synlett* **2001**, 1584–1586; (b) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Synlett* **2003**, 39–42; (c) Chakraborti, A. K.; Gulhane, R.; Shivani *Synlett* **2003**, 1805–1808; (d) Miyashita, M.; Shiina, I.; Miyoshi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1516.
7. (a) Chakraborti, A. K.; Gulhane, R. *Tetrahedron Lett.* **2003**, *44*, 3521–3525; (b) Chakraborti, A. K.; Gulhane, R. *Chem. Commun.* **2003**, 1896–1897; (c) Yadav, V. K.; Babu, K. G.; Mittal, M. *Tetrahedron* **2001**, *57*, 7047–7051; (d) Kumareswaran, R.; Pachamuthu, K.; Vankar, Y. D. *Synlett* **2000**, 1652–1654; (e) Kumar, P.; Pandey, R. K.; Bodas, M. S.; Dongare, M. K. *Synlett* **2001**, 206–209; (f) Li, A. X.; Li, T. S.; Ding, T. H. *Chem. Commun.* **1997**, 1389–1390; (g) Ballini, R.; Bosica, G.; Carloni, S.; Ciaralli, L.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1998**, *39*, 6049–6052.
8. (a) Borah, R.; Deka, N.; Sarma, J. C. *J. Chem. Res. (S)*, **1997**, 110–111; (b) Kartha, K. P. R.; Field, R. A. *Tetrahedron* **1997**, *53*, 11753–11766.
9. Forsyth, S. A.; MacFarlane, D. R.; Thomson, R. J.; von Itzstein, M. *Chem. Commun.* **2002**, 714–715.
10. Yamada, S.; Sugaki, T.; Matsuzaki, K. *J. Org. Chem.* **1996**, *61*, 5932–5938.
11. Allevi, P.; Ciuffreda, P.; Longo, A.; Anastasia, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2915–2924.
12. (a) Huang, Y.-Z.; Zhou, Z.-L. In *Comprehensive Organometallic Chemistry*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: NY, 1995; Vol. 11, pp 502–513; (b) Suzuki, H.; Ikegami, T.; Matano, Y. *Synthesis* **1997**, 249–267; (c) Marshall, J. A. *Chemtracts* **1997**, *10*, 1064–1075; Vidal, S. *Synlett* **2001**, 1194–1195; (d) Komatsu, N. In *Organobismuth Chemistry*; Suzuki, H., Matano, Y., Eds.; Elsevier: Amsterdam, 2001; Chapter 5, pp 371–440; (e) Le Roux, C.; Dubac, J. **2002**; pp 181–200; (f) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373–8397.
13. Suzuki H. In *Organobismuth Chemistry*; Suzuki, H., Matano, Y., Eds.; Elsevier: Amsterdam, 2001; Chapter 1, pp 18–20.
14. Répichet, S.; Le Roux, C.; Roques, N.; Dubac, J. **2003**, *44*, 2037, pp 2037–2040.
15. (a) Christensen, G. M. *J. Org. Chem.* **1962**, *27*, 1442–1443; (b) Dasgupta, F.; Singh, P. P.; Srivastava, H. C. *Carbohydr. Res.* **1980**, *80*, 346–349; (c) Bhaskar, P. M.; Loganathan, D. *Tetrahedron Lett.* **1998**, *39*, 2215–2218; (d) McPhail, D. R.; Lee, J. R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1992**, *114*, 1905–1906.