One-Pot Multicomponent Synthesis of β-Acetamido Ketones Based on $BiCl_3$ Generated in situ from the Procatalyst BiOCl and Acetyl Chloride

Rina Ghosh,* Swarupananda Maiti, Arijit Chakraborty

Department of Chemistry, Jadavpur University, Kolkata 700032, India
E-mail: ghoshrina@yahoo.com

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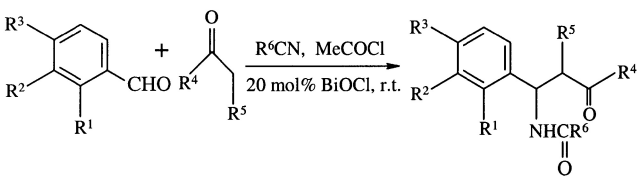
Abstract: Aromatic aldehydes react in one pot at room temperature with enolizable ketones and acetonitrile in the presence of acetyl chloride and catalytic amount of BiOCl producing the corresponding β-acetamido ketones in very high to excellent yields. $BiCl_3$ generated in situ from BiOCl and acetyl chloride catalyzes the multicomponent reaction.

Key words: multicomponent reaction, BiOCl, procatalyst, $BiCl_3$, β-acetamido ketone

Because of significant advantages over conventional linear type synthesis, one-pot multicomponent reactions have emerged as an improved synthetic strategy for tailor-made structural scaffolds and combinatorial libraries in drug discovery process.[1] β-Acetamido- or amino ketones[2] are potential intermediates for the synthesis of other important molecules like 1,3-amino alcohols,[3a,b] units common in natural nucleoside peptide antibiotics, e.g., nikkomycins or neopolyoxins.[3d,e] Multicomponent routes leading to β-acetamido ketones reported by Iqbal et al. are based on Lewis acid catalysts such as $CoCl_2$[4a,b] or Montmorillonite K10 clay.[4c]

Recently, Bi(III) salts have gained much interest in organic synthesis[5] for their Lewis acidity and low toxicity level.[5b] BiOCl is a readily available, moisture stable precursor of the desired Bi(III) salt. Its Lewis acidity is low,[6] but it can generate $BiCl_3$ in reaction with acetyl chloride, which has also been established and utilized by Dubac et al. in Friedel–Crafts acylation reaction.[7] Moreover, it has also got a very low toxicity level, LD_{50} rat (oral): 22g/kg.[5b]



Scheme 1

In continuation to our systematic scanning on the efficacy of BiOCl-based organic reaction,[8] we report herein our interesting observations on the multicomponent synthesis of the title compounds based on $BiCl_3$ generated in situ from the procatalyst BiOCl and acetyl chloride. A variety of aromatic aldehydes (**1**–**9**) reacted with enolizable ketones (**10**–**13**) and acetonitrile (reactant as well as solvent) at room temperature in the presence of 20 mol% of BiOCl and ca. 2 equivalents of acetyl chloride (Scheme 1, Table 1 and Table 2).[9,10] Comparative experiments on the one-pot synthesis of β-acetamido ketone (**14**) from benzaldehyde (**1**), acetophenone (**10**), acetyl chloride and acetonitrile in the presence of different Bi(III) salts like BiOCl, $BiCl_3$, $Bi_2(SO_4)_3$, $BiO(NO_3)$ and other metal salts such as $FeCl_3$, $AlCl_3$ and $ZnCl_2$ reveal that among all these BiOCl is the reagent of choice in terms of yield, moisture stability and ease of handling (Table 1). The minimum load of BiOCl was optimized to be 20 mol% (entries 1 and 2, Table 1). Thus, in a model experiment, when benzaldehyde (**1**, ca. 1 equivalent) was reacted with acetophenone (**10**, ca. 1 equivalent) and acetyl chloride (ca. 2 equivalents) in the presence of BiOCl (20 mol%) in acetonitrile (3 mL) at room temperature, the corresponding β-acetamido ketone (**14**) was formed in 7 hours in 92% yield (entry 2, Table 1; entry 1, Table 2). Each of *o*-, *m*-, or *p*-nitrobenzaldehyde (**2**–**4**) reacted separately with acetophenone and other components furnishing the corresponding β-acetamido ketones in very good to excellent yields (entries 5–7, Table 2). Similarly, aromatic aldehydes (**5**–**7**) containing electron-donating groups also reacted efficiently. Thus, reaction of *p*-chloro-, *p*-methoxy- or *m*-hydroxy benzaldehyde (entries 8–10, Table 2) fur-

Table 1 One-Pot Synthesis of β-Acetamido Ketone from Benzaldehyde, Acetophenone, Acetyl Chloride and Acetonitrile in the Presence of Different Metal Salts

Entry	Metal salt	Metal salt (mol%)	Time (h)	Yield (%) of product
1	BiOCl	15	12	79
2	BiOCl	20	7	92
3	$BiCl_3$	20	3.5	92
4	$Bi_2(SO_4)_3$	20	9	90
5	$BiONO_3$	20	10	80
6	$FeCl_3$	20	24	77
7	$AlCl_3$	20	19	78
8	$ZnCl_2$	20	6	86

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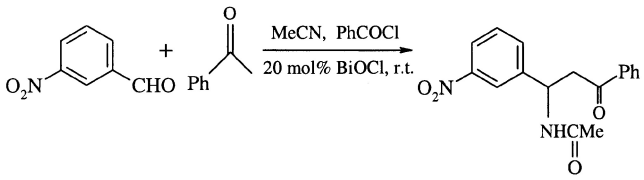
nished the respective desired products in excellent yields, although *N*,*N*-dimethylamino benzaldehyde was reluctant to react under the standard reaction condition. Acetonitrile as well as benzonitrile took part in this multicomponent reaction. Reaction of benzaldehyde and acetophenone with benzonitrile in the presence of BiOCl and acetyl chloride also proceeds in dichloromethane (entry 12) or in neat condition (entry 13) affording the corresponding β-benzamido ketone (**22**) in good yields. As reported earlier,[8] like acetyl chloride, benzoyl chloride was also capable of generating $BiCl_3$ from BiOCl (Scheme 2). Thus, reaction of *m*-nitrobenzaldehyde (**3**) and acetophenone (**10**) with acetonitrile in the presence of BiOCl (20 mol%) and benzoyl chloride (ca. 5 equivalents) furnished the corresponding β-acetamido ketone (**16**) in high yield (Scheme 2, Table 2, entry 14). The present procedure was equally fruitful with an α-unsubstituted ketone such as *p*-methoxyacetophenone (**11**) leading to the corresponding desired product (**21**) in excellent yield (entry 11, Table 2).

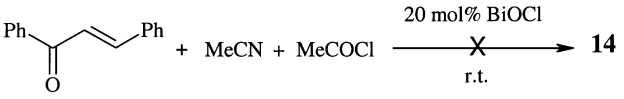


Scheme 2

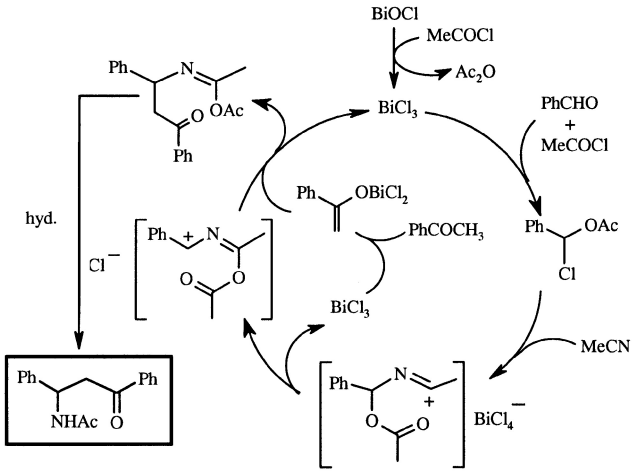
To explore further the scope and limitation of this methodology we also examined the reaction of aromatic aldehydes with α-substituted enolizable ketones (**12**, **13**). Thus, when benzaldehyde (**1**) was reacted with ethyl methyl ketone (**12**) and acetonitrile in the presence of BiOCl and acetyl chloride, the β-acetamido ketone (**23**) generated from the more substituted enolate was obtained in 75% yield with moderately good diastereoselectivity (*syn*/*anti* 1:5, entry 15, Table 2). Similarly, propiophenone (**13**) reacted separately with benzaldehyde (**1**, entry 16), *p*-chloro- or *o*-nitro or *o*-hydroxy benzaldehyde (**5**, **2** and **9**, entries 17, 18 and 20, Table 2) and also with vaniline (**8**, entry 19, Table 2) resulting in their respective β-acetamido ketones (**25**–**28**) with concomitant acetylation of the phenolic -OH group in relevant substrates (entries 19 and 20) in good to excellent yields, although in poor diastereoselectivities (dr ca. 1.3 to ca. 2). Interestingly, selectivity was in favor of the *anti* isomer from *o*-funtionalized benzaldehydes (**2** and **9**, entries 18 and 20, Table 2) unlike the *m*- or *p*-substituted benzaldehyde (**5** and **3**).

The preparative efficacy of the present procedure was established by a scaling-up experiment (ca. 10 fold) with benzaldehyde (**1**), acetophenone (**10**) and acetonitrile using BiOCl and acetyl chloride in solvent (entry 2, Table 2) and in solvent-less condition (entry 3, Table 2), which furnished the desired β-acetamido ketone (**14**) in excellent yields in both of these cases. After the reaction BiOCl was regenerated from the aqueous extract by precipitation with alkali and repeating experiments (5 recycles) with the regenerated and re-isolated BiOCl also proceeded with equal efficacy without any loss in the activity of the regenerated procatalyst (entry 4, Table 2).

To evaluate, whether the reaction proceeds via chalcone-type intermediate, chalcone was treated separately with acetonitrile in the presence of BiOCl and acetyl chloride but the mixture failed to give any β-acetamido ketone even after 3 days (Scheme 3). Acetonitrile is probably incorporated in the aldehyde-derived intermediate with subsequent acetate migration and coupling with the ketone enolate, following a pathway similar to that proposed by Iqbal et al. in a $CoCl_2$-catalyzed reaction.[4b] The probable catalytic cycle and the mechanistic pathway may be depicted as shown in Scheme 4.



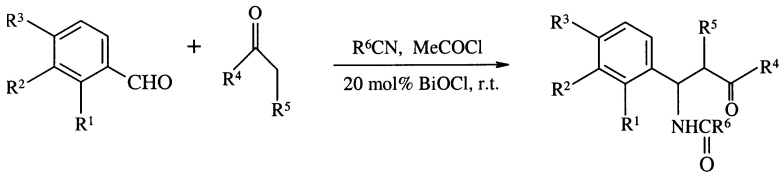
Scheme 3



Scheme 4

In summary, we have demonstrated the efficacy of $BiCl_3$ in situ generated from the procatalyst BiOCl towards the catalyzed one-pot multicomponent synthesis of β-acetamido ketones from a variety of aromatic aldehydes, enolizable ketones, acetyl chloride and aceto- or benzonitrile. The notable feature of the present procedure lies in the stability of BiOCl, its easy availability, low cost, very low toxicity and recyclability without any loss of its activity. Although the diastereoselectivity of the reaction from α-substituted enolizable ketones were poor, but the general high to excellent yields of the α-unsubstituted ketone-derived title compounds in solvent and also in neat condition, along with the reusability and low toxicity of the procatalyst, make it a suitable alternative to the reported methods particularly for the synthesis of the β-acetamido ketones based on α-unsubstituted ketones and for their industrial application.

Table 2 One-Pot Synthesis of β-Acetamido Ketones



1–9 **10**, R^4 = Ph, R^5 = H; **11**, R^4 = *p*-OMe-C_6H_4-, R^5 = H; **12**, R^4 = Me, R^5 = Me; **13**, R^4 = Ph, R^5 = Me — **14–28**

Entry	Aromatic aldehyde	β-Acetamido ketone	Time (h)	Yield, %[a] (mp, °C)	*syn*/*anti*
1	$R^1 = R^2 = R^3 = H$ (**1**)	$R^1 = R^2 = R^3 = R^5 = H$, R^4 = Ph, R^6 = Me (**14**)	7	92 (104–105)	–
2	$R^1 = R^2 = R^3 = H$ (**1**)	$R^1 = R^2 = R^3 = R^5 = H$, R^4 = Ph, R^6 = Me (**14**)	7	91[b]	–
3	$R^1 = R^2 = R^3 = H$ (**1**)	$R^1 = R^2 = R^3 = R^5 = H$, R^4 = Ph, R^6 = Me (**14**)	7	92[c]	–
4	$R^1 = R^2 = R^3 = H$ (**1**)	$R^1 = R^2 = R^3 = R^5 = H$, R^4 = Ph, R^6 = Me (**14**)	7	90,[d] 92[e]	–
5	$R^1 = NO_2$, $R^2 = R^3 = H$ (**2**)	$R^1 = NO_2$, $R^2 = R^3 = R^5 = H$, R^4 = Ph, R^6 = Me (**15**)	12	84 (191–192)	–
6	$R^2 = NO_2$, $R^1 = R^3 = H$ (**3**)	$R^2 = NO_2$, $R^1 = R^3 = R^5 = H$, R^4 = Ph, R^6 = Me (**16**)	8	91 (139–140)	–
7	$R^3 = NO_2$, $R^1 = R^2 = H$ (**4**)	$R^3 = NO_2$, $R^1 = R^2 = R^5 = H$, R^4 = Ph, R^6 = Me (**17**)	8	64 (154)	–
8	$R^1 = R^2 = H$, R^3 = Cl (**5**)	$R^1 = R^2 = R^5 = H$, R^3 = Cl, R^4 = Ph, R^6 = Me (**18**)	10	80 (150)	–
9	$R^1 = R^2 = H$, R^3 = OMe (**6**)	$R^1 = R^2 = R^5 = H$, R^3 = OMe, R^4 = Ph, R^6 = Me (**19**)	9	90 (110–112)	–
10	$R^1 = R^3 = H$, R^2 = OH (**7**)	$R^1 = R^3 = R^5 = H$, R^2 = OAc, R^4 = Ph, R^6 = Me (**20**)	4.5	93 (114–115)	–
11	$R^1 = R^2 = R^3 = H$ (**1**)	$R^1 = R^2 = R^3 = R^5 = H$, R^4 = p-MeO-C_6H_4, R^6 = Me (**21**)	4	91 (130)	–
12	$R^1 = R^2 = R^3 = H$ (**1**)	$R^1 = R^2 = R^3 = R^5 = H$, $R^4 = R^6$ = Ph (**22**)	12	55[f] (194–195)	–
13	$R^1 = R^2 = R^3 = H$ (**1**)	$R^1 = R^2 = R^3 = R^5 = H$, $R^4 = R^6$ = Ph (**22**)	12	55[g]	–
14	$R^2 = NO_2$, $R^1 = R^3 = H$ (**3**)	$R^2 = NO_2$, $R^1 = R^3 = R^5 = H$, R^4 = Ph, R^6 = Me (**16**)	1d	68[h]	–
15	$R^1 = R^2 = R^3 = H$ (**1**)	$R^1 = R^2 = R^3 = H$, $R^4 = R^5 = R^6$ = Me (**23**)	2	75	1:5[i]
16	$R^1 = R^2 = R^3 = H$ (**1**)	$R^1 = R^2 = R^3 = H$, R^4 = Ph, $R^5 = R^6$ = Me (**24**)	8	94	2:1[j]
17	$R^1 = R^2 = H$, R^3 = Cl (**5**)	$R^1 = R^2 = H$, R^3 = Cl, R^4 = Ph, $R^5 = R^6$ = Me (**25**)	2	81	1.8:1[j]
18	$R^1 = NO_2$, $R^2 = R^3 = H$ (**2**)	$R^1 = NO_2$, $R^2 = R^3 = H$, R^4 = Ph, $R^5 = R^6$ = Me (**26**)	10	72	1:2.2[j]
19	R^1 = H, R^2 = OMe, R^3 = OH (**8**)	R^1 = H, R^2 = OMe, R^3 = OAc, R^4 = Ph, $R^5 = R^6$ = Me (**27**)	11	83	1.6:1[j]
20	R^1 = OH, $R^2 = R^3 = H$ (**9**)	R^1 = OAc, $R^2 = R^3 = H$, R^4 = Ph, $R^5 = R^6$ = Me (**28**)	12	60	1:1.4[j]

[a] Chromatographed yield.
[b] Scale-up experiment (ca. 10 fold).
[c] Under neat condition (ca. 10 fold).
[d] With recovered BiOCl.
[e] Yield after 5 recycles using recovered BiOCl.
[f] Using PhCN (ca. 2 equiv) in CH_2Cl_2.
[g] Using PhCN (ca. 3 equiv) in neat condition.
[h] Using PhCOCl (ca. 5 equiv) instead of MeCOCl.
[i] Ratio of methine protons of *syn* and *anti* isomers (by ^{1}H NMR).
[j] Ratio of isolated yields (by preparative TLC) of *syn* and *anti* isomers.

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References

(1) (a) Terret, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123. (c) Thomson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (d) Tietze, L. F.; Lieb, M. E. *Curr. Opin. Chem. Biol.* **1998**, *2*, 363. (e) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.

(2) (a) Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron* **1996**, *37*, 9221. (b) Loh, T.-P.; Wei, L.-L. *Tetrahedron Lett.* **1998**, *39*, 323. (c) Lima, P. G.; Sequeira, L. C.; Costa, P. R. R. *Tetrahedron Lett.* **2001**, *42*, 3525. (d) Wabnitz, T. C.; Spencer, J. B. *Tetrahedron Lett.* **2002**, *43*, 3891.

(3) (a) Barluenga, J.; Viado, A. L.; Aguilar, E.; Fustero, S.; Olano, B. *J. Org. Chem.* **1993**, *58*, 5972. (b) Enders, D.; Moser, M.; Geibel, G.; Laufer, M. C. *Synthesis* **2004**, 2040. (c) Barluenga, J.; Olano, B.; Fustero, S. *J. Org. Chem.* **1985**, *50*, 4052. (d) Dähn, U.; Hagenmaier, H.; Höhne, H.; König, W. A.; Wolf, G.; Zähner, H. *Arch. Microbiol.* **1976**, *107*, 249. (e) Kobinata, K.; Uramoto, M.; Nishii, M.; Kusakabe, H.; Nakamura, G.; Isono, K. *Agric. Biol. Chem.* **1980**, *44*, 1709.

(4) (a) Mukhopadhyay, M.; Bhatia, B.; Iqbal, J. *Tetrahedron Lett.* **1997**, *38*, 1083. (b) Bhatia, B.; Reddy, M. M.; Iqbal, J. *J. Chem. Soc., Chem. Commun.* **1994**, 713. (c) Bahulayan, D.; Das, S. K.; Iqbal, J. *J. Org. Chem.* **2003**, *68*, 5735.

(5) (a) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373. (b) Suzuki, H. In *Organobismuth Chemistry*; Suzuki, H.; Matano, Y., Eds.; Elsevier: Amsterdam, **2001**, Chap. 1, 18–20. (c) Huang, Y.-Z.; Zhou, Z.-L. In *Comprehensive Organometallic Chemistry*, Vol. 11; Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon: New York, **1995**, 502–513. (d) Suzuki, H.; Ikegami, T.; Matano, Y. *Synthesis* **1997**, 249. (e) Marshall, J. A. *Chemtracts* **1997**, *10*, 1064. (f) Vidal, S. *Synlett* **2001**, 1194. (g) Komatsu, N. In *Organobismuth Chemistry*; Suzuki, H.; Matano, Y., Eds.; Elsevier: Armsterdam, **2001**, Chap. 5, 371–440. (h) Le Roux, C.; Dubac, J. *Synlett* **2002**, 181. (i) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *Angew. Chem. Int. Ed.* **2000**, *39*, 2877. (j) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *J. Org. Chem.* **2001**, *66*, 8926.

(6) Chakraborti, A. K.; Gulhane, R.; Shivani *Synlett* **2003**, 1805.

(7) Répichet, S.; Le Roux, C.; Roques, N.; Dubac, J. *Tetrahedron Lett.* **2003**, *44*, 2037; and references cited therein.

(8) Ghosh, R.; Maiti, S.; Chakraborty, A. *Tetrahedron Lett.* **2004**, *45*, 6775.

(9) **General Experimental Procedure**: To a solution of aldehyde (1 mmol), enolizable ketone (1 mmol) and BiOCl (20 mol%) in dry MeCN (4 mL) MeCOCl (2 mmol) was added and the reaction mixture was stirred at r.t. After completion of the reaction (checked by TLC, Table 1) the mixture was diluted with CH_2Cl_2 and washed with brine solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the pooled organic layer was then washed subsequently with H_2O (1 × 6 mL), $NaHCO_3$ (1 × 6 mL) and finally with H_2O (1 × 6 mL). The organic layer was dried over Na_2SO_4, concentrated and the residue was purified by column filtration on silica gel.

(10) All products were characterized by NMR, IR spectroscopy and/or elemental analysis and by comparing the physical data with those in the literature.[4] The following spectral data are representative:
Compound **21**: White crystals [EtOAc–petroleum ether (60–80 °C)]; mp 130 °C. IR (KBr): 3270, 1675, 1640, 1598, 1570, 1525, 1420, 1365, 1250, 1205, 1170, 1020, 990, 830, 800, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.00 (s, 3 H), 3.31–3.39 (dd, 1 H, *J* = 5.95, 16.59 Hz), 3.64–3.71 (dd, 1 H, *J* = 5.28, 16.57 Hz), 3.84 (s, 3 H), 5.53 (m, 1 H), 6.86 (br s, 1 H), 6.89 (br d, 2 H, *J* = 8.82 Hz), 7.18–7.34 (m, 5 H), 7.88 (br d, 2 H, *J* = 8.81 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.37, 42.76, 50.02, 55.46, 113.80, 126.41, 127.30, 128.55, 129.66, 130.45, 141.07, 163.77, 169.49, 197.08. Anal. Calcd for $C_{18}H_{19}O_3N$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.65; H, 6.82; N, 4.67.
Compound **22**: White crystals [EtOAc–petroleum ether (60–80 °C)]; mp 194–195 °C. IR (KBr): 3285, 1685, 1635, 1545, 1525, 1400, 1350, 1310, 1290, 1225, 1200, 755, 735, 700, 690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.57–3.64 (dd, 1 H, *J* = 5.38 Hz, 17.45 Hz), 3.87–3.95 (dd, 1 H, *J* = 4.94, 17.45 Hz), 5.85 (m, 1 H), 7.44–7.62 (m, 7 H), 7.78 (br d, 1 H, *J* = 7.8 Hz), 7.84–7.93 (m, 5 H), 8.10 (br d, 1 H, *J* = 8.11 Hz), 8.28 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.55, 49.63, 121.39, 122.48, 127.11, 128.16, 128.74, 128.89, 129.64, 131.98, 132.89, 133.67, 134.09, 136.21, 143.47, 166.89, 198.63. Anal. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.57; H, 4.84; N, 7.48. Found: C, 70.16; H, 4.96; N, 7.23.