SHORT PAPER

J. Chem. Research (S),
2003, 638–641

Efficient and chemoselective conversion of aryl aldehydes to their azalactones catalysed by Bi(III) salts under solvent free conditions

Mohammad Mehdi Khodaei*, Ahmad Reza Khosropour* and Saied Jabar Hoseini Jomor

Department of Chemistry, Razi University, Kermanshah 67149, Iran

$Bi(NO_3)_3.5H_2O$, $Bi(TFA)_3$ and $Bi(OTf)_3$ were found to be highly powerful and practical catalysts for the synthesis of azalactones under solvent free conditions with excellent yields. In addition, high chemoselectivity for this synthesis has been achieved. Selective condensation of aryl aldehydes in the presence of aliphatic aldehydes, is another advantage of this procedure.

Keywords: azalactones, Bi (III) salts, chemoselectivity

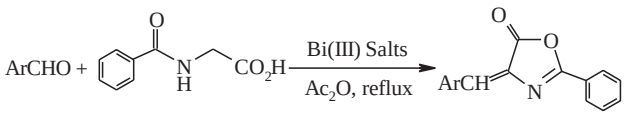
Azalactones are important classes of heterocycles that have attracted much synthetic interest. These compounds are particularly useful precursor for the synthesis of aminoacids,[1] peptides,[2] heterocycles,[3] biosensors[4] and antitumor or antimicrobial compounds.[5] Development of facile and environmental friendly synthetic methods to azalactones constitutes an active area of investigation.

The most well-known route to azalactones is the Erlenmeyer method that involves the direct condensation of aldehydes with hippuric acid using anhydrous sodium acetate as a basic catalyst in acetic anhydride.[6] Various reagents like $Pb(OAc)_2$,[7] SO_3 in DMF[8] and polyphosphoric acid[9] are known to effect this condensation. Recently several inorganic heterogeneous reagents used for this synthesis are Al_2O_3-H_3BO_3,[10] supported KF,[11] $Bi(CH_3CO_2)_3$,[12] $ZnCl_2$[13] and $ZnCl_2$ by using microwave irradiation.[14] These methods are suitable but because some of these reagents are highly corrosive and difficult to handle these methods have been limited to small-scale synthesis. Due to the importance of these compounds as synthons in organic synthesis, a simple and high yielding one-pot approach for this transformation is highly desirable.

Many recent papers describing the use of bismuth compounds in organic transformation pointed out its use as being ecologically friendly,[15] in addition, bismuth derivatives have been widely used in medicine.[16] Most bismuth salts are commercially available, inexpensive and easy to handle.

Due to our continued interest in the use of Bi(III) salts[17] as environmentally friendly reagents for organic synthesis, we now wish to report that $Bi(NO_3)_3.5H_2O$, $Bi(TFA)_3$ and $Bi(OTf)_3$ are highly efficient catalysts for synthesis of azalactones under solvent free conditions. The highly catalytic nature of these reagents and their wide applicability should make this procedure an attractive alternative to existing methods for azalactone formation (Scheme 1).

The experimental procedure for synthesis of these compounds is straightforward and involves stirring the aldehyde, hippuric acid and acetic anhydride in the presence of the Lewis acids under reflux conditions. A wide variety of aromatic aldehydes underwent smooth reactions to give the corresponding azalactones in good to excellent yields under catalysis of $Bi(NO_3)_3.5H_2O$, $Bi(TFA)_3$ and $Bi(OTf)_3$ (Table 1, Entries 1–14).



Scheme1

Interestingly, we observed that salicylaldehyde (Entry 14) with $Bi(NO_3)_3.5H_2O$ gave two products, while $Bi(TFA)_3$ and $Bi(OTf)_3$ afforded only the phenolic azalactone and no acetate derivative was obtained. Under the same reaction conditions, aliphatic aldehydes reacted sluggishly and the products yields was much lower than those obtained with aromatic aldehydes.

Recently, $Bi(CH_3CO_2)_3$ has been proposed as an efficient activator for this kind of transformation because it allows the reaction to be carried out under mild conditions.[12] Therefore, the comparison between $Bi(CF_3CO_2)_3$ and $Bi(CH_3CO_2)_3$ is very useful when evaluating the extraordinary activity of the former. Results reported in Table 1 show that $Bi(CF_3CO_2)_3$ is at least 10 times more reactive than $Bi(CH_3CO_2)_3$.

In order to explore further the synthetic utility of this procedure, we have also investigated competitive reactions (Table 2). This selectivity has not been reported previously and can be considered as a useful practical achievement in this synthesis.

As shown in Table 2, we found that aromatic aldehydes were converted to the products with high selectively in the presence of aliphatic aldehydes.

In conclusion, we have developed an efficient, high yield and ecological friendly method for azalactone synthesis. In addition, high chemoselectivity, mild reaction conditions, easy work-up, highly catalytic nature of the reagents, low toxicity and low cost of the Lewis acids, fast reaction rates and insensitivity of these salts to air and moisture are worthy advantages of this method.

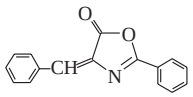
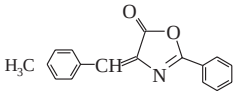
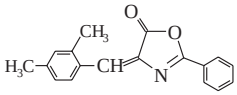
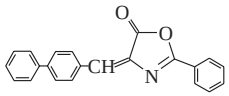
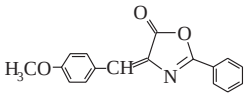
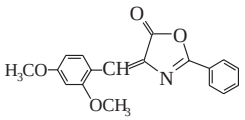
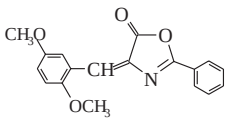
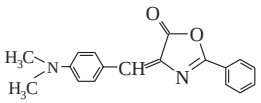
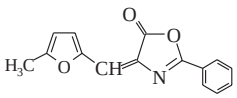
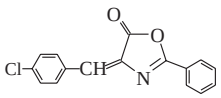
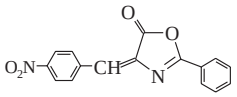
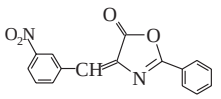
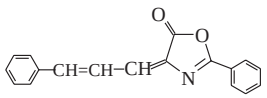
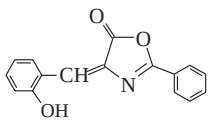
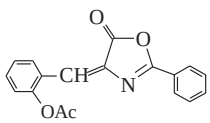
Experimental

All yields refer to isolated products. The products were characterised by comparison with authentic samples. All ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 200 MHz spectrophotometer in $CDCl_3$ or CD_3SOCD_3 as a solvent. Melting points were determined using a Gallen-Kamp melting point apparatus. $Bi(TFA)_3$ and $Bi(OTf)_3$ were prepared according to the described procedures.[18]

General experimental procedure: To a solution of aldehydes (1 mmol) and hippuric acid (1.1 mmol) in acetic anhydride (3.3 mmol) was added the catalyst (0.1 mmol of $Bi(NO_3)_3.5H_2O$ or 0.01 mmol of $Bi(TFA)_3$ or 0.02 mmol of $Bi(OTf)_3$). The reaction mixture was stirred under reflux conditions for the appropriate time according to Table 1. The progress of the reaction was followed by TLC or GLC. After the reaction was finished, the reaction mixture was cooled to room temperature and ethanol (10 ml) was added to it. It was then stirred for 10 min until a yellow solid precipitated. The

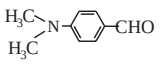
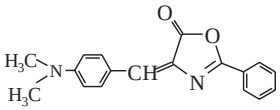
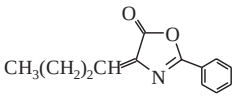
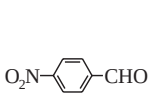
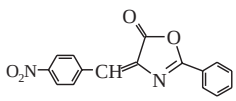
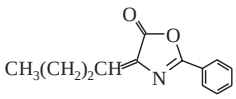
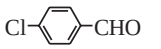
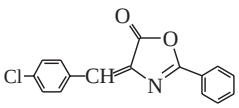
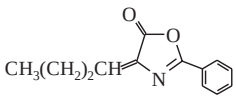
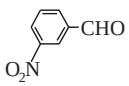
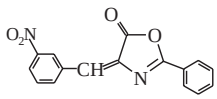
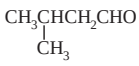
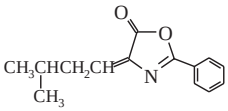
*To receive any correspondence. E-mail: arkhosrpour@razi.ac.ir
†This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Conversion of aldehydes to their corresponding azalactones in the presence of Bi(III) salts[a]

Entry	Product	Yield/%[b] (*t*/min)			M.p./°C	
		$Bi(NO_3)_3.5H_2O$	$Bi(TFA)_3$	$Bi(OTf)_3$	Found	Reported
1		72(60)	86(60)	85(30)	165	168[10]
2		77(60)	83(60)	86(60)	141	143[19]
3		85(60)	87(60)	91(60)	149	152[6]
4		77(60)	84(20)	95(20)	160[20]	162[21]
5		75(60)	85(60)	88(10)	155	156[10]
6		68(20)	74(25)	80(20)	174	172[19]
7		79(20)	78(30)	83(20)	170	167[19]
8		75(5)	77(5)	85(10)	210	213[10]
9		86(40)	90(60)	93(15)	139	141[10]
10		74(60)	73(10)	89(15)	186	185[10]
11		71(5)	77(5)	81(10)	238	241[10]
12		76(20)	78(15)	85(15)	164	165[19]
13		72(60)	89(60)	92(60)	128	132[6]
14		67(5)	78(10)	87(60)	173	171[6]
		15	0	8		

[a]All products were identified by comparison of their physical and spectroscopic data with those of authentic samples; [b]isolated yields

Table 2 Competitive conversion of aldehydes to azalactone derivatives catalyzed by Bi(III) salts

Entry	Aldehyde	Product	Yield/%[a] (*t*/min)		
			$Bi(NO_3)_3.5H_2O$	$Bi(TFA)_3$	$Bi(OTf)_3$
1			72(15)	75(15)	80(20)
	$CH_3CH_2CH_2CHO$		0	0	0
2			68(15)	72(15)	73(20)
	$CH_3CH_2CH_2CHO$		0	0	0
3			70(60)	72(15)	85(20)
	$CH_3CH_2CH_2CHO$		0	0	0
4			69(30)	72(20)	85(15)
			0	0	0

[a]Isolated yields.

mixture was allowed to stand overnight, and then it was cooled in an ice bath. The crude azalactones were obtained after filtration and washing with hot water. Recrystallisation from acetone/water afforded the pure azalactone.

We thank Razi University Research Council for partial support of this work.

Received 3 June 2003; accepted 7 July 2003
Paper 03/1946

References

1 (a) J.T. Konkel, J. Fan, B. Jayachandran and K.L. Kirk, *J. Fluorine Chem.*, 2002, **115**, 27; (b) K. Gootwald and D. Seebach, *Tetrahedron*, 1999, **55**, 723; (c) J. Meiwes, M. Schudock and G. Kretzschmar, *Tetrahedron Asymmetry*, 1997, **8**, 527; (d) D. Seebach, G. Jaeschke, K. Gottwald, K. Matsuda, M. Breuning and G. Bringmann, *Tetrahedron*, 1997, **22**, 7359; (e) C. Cativela, M.D. Diaz-de-Villegas, J.I. Garcia, A.I. Jimenez, *Tetrahedron*, 1997, **53**, 4479; (f) F.M. Bautista, J.M. Campelo, D.L. Garcia and J. M. Marinas, *Amino Acids*, 1992, **2**, 87.

2 (a) S.N. Mitra, S. Dey, S. Karthikeyan and T.P. Singh, *Biopolymers*, 1997, **41**, 1997; (b) F. Cavalier and J. Verducci, *Tetrahedron Lett.*, 1995, **36**, 4425.

3 (a) A. Avenoza, J.H. Busto, C. Cativiela and J.M. Peregrina, *Tetrahedron Lett.*, 2002, **43**, 4167; (b) R. Cannella, F. Clerici, M.L. Gelmi, M. Penso and D. Pocar, *J. Org. Chem.*, 1996, **61**, 1854; (c) P.D. Croce, R. Ferraccioli and C. La-Rosa, *J. Chem. Soc. Perkin Trans. 1*, 1994, 2499; (d) R. Bossio, S. Marcaccini, R. Pepino and P. Paoli, *J. Heterocycl. Chem.*, 1994, **31**, 729.

4 (a) A.C. Chikere, B. Galunsky, V. Schünemann and V. Kasche, *Enzyme. Microb. Technol.*, 2001, **28**, 168; (b) J. Penalba, R. Puchades, A. Maquieira, S. Gee and B.D. Hammock, *Biosens. Bioelectron.*, 2000, **15**, 99; (c) M.A. Gonzalez-Martinez, R. Puchades, A. Maquieira, I. Ferrer, M.P. Marco and D. Barceló, *Anal. Chim. Acta.*, 1999, **386**, 201; (d) S. Kojima, H. Ohkawa, T. Hirano, S. Maki, H. Niwa, M. Ohashi, S. Inouye and F.I. Tsuji, *Tetrahedron Lett.*, 1998, **39**, 5242.

5 (a) M.L. Gelmi, F. Clerici, A. Melis, *Tetrahedron*, 1997, **53,** 1843; (b) A.H. Abd-el-Rahm, E.M. Kandeel, E.A. Abdel-Razik, I.A. El-Ghamry, *An. Quim.*, 1993, **89**, 237.

6 (a) M. Kitazawa, R. Higuchi, M. Takahashi, T. Wada and H. Sasabe, *J. Phys. Chem.*, 1995, **99**, 14784; (b) S. Icli, H. Icil, S. Alp, H. Koc, A. McKillop, *Spectrosc. Lett.*, 1994, **27**, 1115; (c) A. Patra, G. Ghosh, P.K. Mukhopadhyay, *J. Ind. Chem. Soc.*, 1987, **64**, 414; (d) S.P. Dhoubhadel, *J. Ind. Chem. Soc.*, 1986, **63**,

757; (e) R. Filler, *Advances in Heterocyclic Chemistry*, Academic Press, New York, 1954, 75.
7 (a) C. Cativiela, M.D. Diaz-de-villegas and J.A. Galvez, *Tetrahedron Lett*., 1999, **40**, 1027; (b) C. Cativiela and E. Melendez, *Synthesis.* 1978, 832.
8 E. Baltazzi and E.A. Davis, *Chemy Ind. (Lond.)* 1962, 929.
9 Y.S. Rao, *J. Org. Chem*., 1976, **41**, 722.
10 (a) J. Kashyap, A.B. Chetry, P.J. Das, *Synth. Commun*., 1998, **28**, 4187; (b) H.J. Ringold, B. Loeken, G. Rosenkranz and F. Sondheimer, *J. Am. Chem. Soc*., 1956, **78**, 816.
11 F.M. Bautista, J.M. Campelo, A. Garcia, D. Luna, J.M. Marinas and A.A. Romero, *J Chem. Soc. Perkin Trans. 2*, 2002, 227.
12 K.A. Monk, D. Sarapa and R.S. Mohan, *Synth. Commun.* 2000, **30**, 3167.
13 P.S. Rao and R.V. Venkatratnam, *Ind. J. Chem.* 1994, **33B**, 984.
14 M. Kidwai, R. Kumar and P. Kumar, *Ind. J. Chem.* 1996, **35B**, 1004.
15 (a) S. Cunha, B.R. Lima and A.R. Souza, *Tetrahedron Lett*., 2002, **43**, 49; (b) E.M. Keramane, B. Boyer and J.P. Roque, *Tetrahedron*, 2001, **57**, 1909; (c) E.M. Keramane, B. Boyer and J.P. Roque, *Tetrahedron Lett.*, 2001, **42**, 855; (d) H. Laurent-Robert and J. Dubac, *Synlett*, 1998, 1138.
16 (a) H. Suzuki and Y. Matano, *Organobismuth Chemistry*, Elsevier, Amsterdam, 2001; (b) J. Reglinski, *In Chemistry of Arsenic Antimony and Bismuth*, Blacki Academic and Professional, New York, 1998; (c) H. Suzuki, T. Ikagami, Y. Matano, *Synthesis*, 1997, 249; (d) J.A. Marshall, *Chemtracts*., 1997, 1064.
17 (a) I. Mohammadpoor-Baltork and A.R. Khosropour, *Monatshefte für Chemie*, 2002, **133**, 189; (b) I. Mohammadpoor-Baltork, M.M. Khodaei and K. Nikoofar, *Tetrahedron Lett*., 2002, **44**, 591; (c) I. Mohammadpoor-Baltork, H. Aliyan and A.R. Khosropour, *Tetrahedron*, 2001, **57,** 5851; (d) I. Mohammadpoor-Baltork and A.R. Khosropour, *Molecules*, 2001, **6**, 996; (e) I. Mohammadpoor-Baltork, A.R. Khosropour and H. Aliyan, *J. Chem. Res.(S)*, 2001, **7**, 780; (f) I. Mohammadpoor-Baltork, A.R. Khosropour and H. Aliyan, *Synth. Commun.*, 2001, **22**, 3411.
18 (a) S. Répichet, A. Zwick, L. Vendier, C. Le Roux and J. Dubac, *Tetrahedron Lett*., 2002, **43**, 993; (b) C.D. Garner and B. Hughes, *Advances in Inorganic Chemistry and Radiochemistry*, Vol 17. Academic Press, New York, 1975; (c) S. Singh and A.R.D. Verma, *Indian J. Chem.*, 1983, **22A**, 814.
19 (a) H.D. Dakin, *J. Biol. Chem.*, 1911, **9**, 151; (b) H.D. Dakin, *J. Biol. Chem*., 1911, **9**, 11; (c) Pschorr, V.R. *Justus Liebig's Annalen der Chimie* 1912, **391**, 40; (d) R.L. Douglas and J.M. Gulland, *J. Chem. Soc*., 1931, 2893; (e) M. Crawford and W.T. Little, *J. Chem. Soc*., 1959, 729; (f) F.W. Shueler and S.C. Wang, *J. Am. Chem. Soc*., 1950, **72**, 2220.
20 *for entry* **4:** IR (KBr) 3026, 1776, 1744 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$) δ 7.37 (1H, s); 7.4-7.78 (10H, m); 8.24 (2H, d, *J*=10.5 Hz); 8.31(2H, d, *J*= 9.5 Hz), ^{13}C NMR ($CDCl_3$) δ 125.3(C), 126(CH); 126.8(C); 127.5(CH); 127.7(CH); 127.9(CH); 128.2(CH); 128.5(CH); 128.8(CH); 128.2(CH); 129.4(CH); 130.2(C); 131,7(CH); 132.9(C); 133.4(CH); 133.6(CH); 133.7(CH); 140.5(CH); 144.2(C); 163.9(CH); 168.1(C); 169.2(C); MS (EI): 325 (M+). Anal. Calcd for $C_{22}H_{15}NO_2$: C, 81.23%; H, 4.61%; N, 4.31% . found: C, 81.47%; H, 4.83%; N, 4.71%.
21 This product was prepared by established method using Erlenmeyer procedure in the presence of Ac_2O and NaOAc and melting point of the product compared with that obtained by this new method.