

InCl₃/IBX: a novel reagent system for the conversion of glycols into α,β -unsaturated δ -lactones

J. S. Yadav,* B. V. Subba Reddy and Ch. Suresh Reddy

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India

Received 7 January 2004; revised 1 March 2004; accepted 12 March 2004

Abstract—The combination of indium trichloride with iodoxybenzoic acid (IBX) has been utilized for the first time as a novel reagent system for the one-pot synthesis of 2,3-dideoxy-D-hex-2-enono-1,5-lactones from glycols. The reaction proceeds smoothly in aqueous media and the products are obtained in good yields. This method is suitable for the oxidation of glycols bearing olefin functionality.

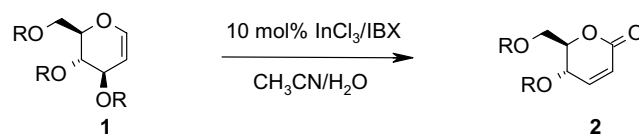
© 2004 Elsevier Ltd. All rights reserved.

Naturally occurring carbohydrates have been extensively used as chiral pool starting materials in the synthesis of biologically active natural products.¹ The ready availability of a wide range of carbohydrates in Nature, each having several chiral centres, coupled with their well-defined stereochemistry, make them useful intermediates in organic synthesis.² Glycols are versatile chiral building blocks for the synthesis of glycoconjugates and polyether antibiotics.³ Glycols are known to undergo acid-catalyzed allylic rearrangement with various nucleophiles to afford pseudoglycols or 2,3-unsaturated glycosides.^{4,5} In particular, 2,3-dideoxyhex-2-enono-1,5-lactones derived from glycols and peracids⁶ are useful precursors for the synthesis of various optically active heterocycles such as pyrazolidin-3-ones and isoxazolidin-5-ones.⁷ Alternatively, PCC has been used for the conversion of glycols into α,β -unsaturated δ -lactones.⁸ Hypervalent iodine reagents have attracted increasing interest as oxidants in organic synthesis due to their mild, selective and environmentally benign oxidizing properties.⁹ Among various hypervalent iodine reagents, iodoxybenzoic acid (IBX) is a versatile oxidizing agent because of its high efficiency, easy availability, mild reaction conditions and its stability to moisture and air.¹⁰ A wide functional group tolerance and high-yielding reactions, without over oxidation have made IBX very familiar for the oxidation of alcohols even in the presence of olefins, thioethers and amino

groups.¹¹ In recent reports, the use of IBX as a mild oxidant has been extended to many other elegant oxidative transformations.¹² Recently, indium halides have emerged as versatile Lewis acid catalysts imparting high regio-, chemo- and diastereoselectivity for a variety of organic transformations. Compared to conventional Lewis acids, indium trichloride in particular has advantages of low catalyst loading, moisture stability and catalyst recycling.¹³

In this article, we report a mild and efficient protocol for the synthesis of α,β -unsaturated δ -lactones from glycols using catalytic InCl₃ in combination with a stoichiometric amount of IBX as a novel reagent system (Scheme 1).

Treatment of 3,4,6-tri-*O*-acetyl-D-glucal in water with 10 mol% InCl₃ and 2.5 equiv of IBX in refluxing acetonitrile resulted in the formation of 4,6-di-*O*-acetyl-2,3-dideoxy-D-erythro-hex-2-enono-1,5-lactone in 82% yield. Similarly, various other D-glucals such as 3,4,6-tri-*O*-benzoyl, 3,4,6-tri-*O*-allyl and 3,4,6-tri-*O*-benzyl-D-glucal derivatives were converted into their corresponding 2,3-dideoxy-D-hex-2-enono-1,5-lactones using this procedure (Table 1, entries b–d). Other glycols such

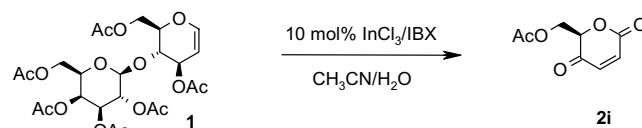


Scheme 1.

Keywords: Glycols; Indium reagents; Hypervalent iodine reagents; Enelactones.

* Corresponding author. Tel.: +91-4027193434; fax: +91-4027160512; e-mail: yadav@iict.ap.nic.in

as 3,4,6-tri-*O*-acetyl-*D*-galactal, 3,4-di-*O*-acetyl-*L*-rhamnal, 3,4-di-*O*-acetyl-*D*-xylal and 3,4-di-*O*-acetyl-*D*-arabinal also afforded the respective enelactones in fairly good yields under similar conditions (Table 1, entries e–h). However, the hexa-*O*-acetyl-*D*-lactal derived from the disaccharide, α -*D*-lactose, gave 3,6-dioxo-(2*R*)-3,6-dihydro-2*H*-2-pyranylmethyl acetate (Scheme 2).



Scheme 2.

In the oxidation of disaccharides, cleavage of the glycosidic bond was observed under the reaction conditions. All products were characterized by ^1H , ^{13}C NMR and IR spectroscopy and also by comparison with authentic compounds.⁶ Mechanistically, the reaction is

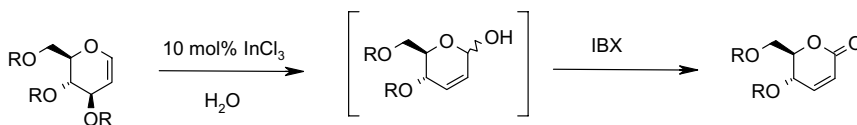
initiated by InCl_3 induced allylic rearrangement of glycal with water to form an intermediate 2,3-dideoxy-hex-2-enopyranoside, which on subsequent oxidation by IBX results in the formation of the corresponding enelactone (Scheme 3).

Table 1. Oxidation of *D*-glycals to α,β -unsaturated δ -lactones using InCl_3/IBX in water/ CH_3CN

Entry	Glycals 1	Lactones 2^a	Reaction time (h)	Yield ^b (%)
a			6.0	82
b			7.5	85
c			6.0	79
d			5.5	83
e			8.0	76
f			6.0	85
g			6.5	80
h			6.0	75
i			7.0	65

^a All products were characterized by IR, ^1H , ^{13}C NMR and mass spectroscopy.

^b Isolated and unoptimized yields.



Scheme 3.

In all cases, the reactions were carried out in a water/acetonitrile (1:9) solvent system. Since indium trichloride is stable in water, no precautions needed to be taken to exclude moisture from the reaction medium. Furthermore, this method does not require stringent reaction conditions. The experimental procedure is quite simple and convenient affording the desired products in good yields. Among various catalysts such as scandium triflate, ytterbium triflate, cerium triflate and indium triflate employed for this transformation, indium trichloride was found to be the most effective catalyst in terms of conversion and reaction rates. Low conversions (40–55%) were obtained when the reactions were carried out using 5 mol% $\text{Sc}(\text{OTf})_3$ and 2.5 equiv of IBX in refluxing acetonitrile–water (9:1). Furthermore, the combination of IBX with conventional Lewis acids such as $\text{BF}_3 \cdot \text{OEt}_2$, TiCl_4 and TMSOTf failed to give the desired enolactones. The scope and generality of this process is illustrated with respect to various glycols and the results are presented in Table 1.¹⁴

In summary, we describe a novel procedure for the preparation of 2,3-dideoxy-D-hex-2-enono-1,5-lactones from glycols using InCl_3/IBX . This method is not only applicable to simple acetyl glycols but also to highly functionalized benzyl, benzoyl and allyl glycols. This new reagent system provides a simple and convenient method for the preparation of optically active α,β -unsaturated δ -lactones.

Acknowledgements

B.V.S. and Ch.S.R. thank CSIR, New Delhi for the award of fellowships.

References and notes

- (a) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: Oxford, 1984; (b) Hanessian, S.; Lou, B. *Chem. Rev.* **2000**, *100*, 4443–4463.
- (a) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545–8599; (b) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed.* **1996**, *35*, 1380–1419.
- (a) Danishefsky, S. J.; Allen, J. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 836–863; (b) Nicolaou, K. C.; Mitchel, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576–1624.
- (a) Ferrier, R. J.; Prasad, N. J. *J. Chem. Soc. C* **1969**, 570–572; (b) Ferrier, R. J. *Adv. Carbohydr. Chem Biochem.* **1969**, *24*, 199–266; (c) Fraser-Reid, B. *Acc. Chem. Res.* **1985**, *18*, 347–354; (d) Wieczorek, E. *Acros Organics Acta* **2003**, *10*, 13–14.
- (a) Takhi, M.; Adel-Rahman, A. A. H.; Schimdt, R. R. *Synlett* **2001**, 427–429; (b) Takhi, M.; Adel-Rahman, A. A. H.; Schimdt, R. R. *Tetrahedron Lett.* **2001**, *42*, 4053–4056; (c) Yadav, J. S.; Reddy, B. V. S.; Raju, A. K.; Rao, C. V. *Tetrahedron Lett.* **2002**, *43*, 5437–5440.
- (a) Mieczkowski, J.; Jurczak, J.; Chmielewski, M.; Zamojski, A. *Carbohydr. Res.* **1977**, *56*, 180–182; (b) Jarglis, P.; Lichtenhaler, F. W. *Tetrahedron Lett.* **1982**, *23*, 3781–3784.
- Panfil, I.; Mostowicz, D.; Chmielewski, M. *Polish J. Chem.* **1999**, *73*, 1099–1110.
- Rollin, P.; Sinay, P. *Carbohydr. Res.* **1981**, *98*, 139–142.
- (a) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic: San Diego, 1997; (b) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271–1287.
- (a) Hartman, C.; Meyer, V. *Chem. Ber.* **1893**, *26*, 1727; (b) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178; (c) Kitamura, T.; Fujiwara, Y. *Org. Prep. Proc. Int.* **1997**, *29*, 409–458.
- Wirth, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 2812–2814.
- (a) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 993–996; (b) Nicolaou, K. C.; Barn, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233–2244.
- (a) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149–11176; (b) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16–22; (c) Ghosh, R. *Indian J. Chem.* **2001**, *40B*, 550–557.
- General procedure: A mixture of 3,4,6-tri-O-acetyl-D-glucal (1 mmol) and InCl_3 (10 mol%) and IBX (2.5 mmol) in acetonitrile–water (10 mL, 9:1) was stirred at 80 °C for the appropriate time. After complete conversion, as indicated by TLC, the reaction mixture was filtered and washed with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford pure enolactone. 4,6-Di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enono-1,5-lactone **2a**: liquid, $[\alpha]_D^{27} + 127.5$ (c 1.0, CHCl_3); ^1H NMR (CDCl_3 , 200 MHz): δ 2.08 (s, 3H, $-\text{COCH}_3$), 2.10 (s, 3H, $-\text{COCH}_3$), 4.25 and 4.30 (each dd, 1H, $J = 4.0$, 11.5 Hz, H-6,6'), 4.65 (dt, 1H, $J = 7.5$, 4.0 Hz, H-5), 5.50 (dt, 1H, $J = 2.9$, 7.5 Hz, H-4), 6.10 (dd, 1H, $J = 1.7$, 10.0 Hz, H-2), 6.75 (dd, 1H, $J = 2.9$, 10.0 Hz, H-3). ^{13}C NMR (CDCl_3 , 50 MHz): δ 20.4, 20.5, 61.8, 63.3, 77.2, 122.2, 142.9, 160.1, 169.5, 170.1. IR (KBr): ν 3077, 2957, 1745, 1640, 1372, 1220, 1113, 1049, 976, 819, 771 cm^{-1} . FAB Mass: m/z : 228 (M^+), 155, 126, 97, 84, 68. 4,6-di-O-benzyl-2,3-dideoxy- α -D-erythro-hex-2-enono-1,5-lactone **2d**: liquid, $[\alpha]_D^{27} + 54.8$ (c 1.4, CHCl_3); ^1H NMR (CDCl_3 , 200 MHz): δ 3.70 and 3.73 (each dd, 1H, $J = 3.9$, 11.6 Hz, H-6,6'), 4.35–4.65 (m, 6H, H-4, H-5, $-\text{H}_2\text{C}-\text{Ph}$), 5.95 (dd, 1H, $J = 1.8$, 10.0 Hz, H-2), 6.80 (dd, 1H, $J = 3.0$, 10.0 Hz, H-3), 7.20–7.35 (m, 10H). ^{13}C NMR (CDCl_3 , 50 MHz): δ : 67.8, 68.6, 72.2, 73.5, 79.9, 96.0, 120.5, 127.7, 128.4, 128.8, 136.9, 137.5, 146.2, 162.4. IR (KBr): ν 3028, 2917, 2867, 1719, 1634, 1455, 1372, 1229, 1099, 1039, 972, 819, 744 cm^{-1} . FAB Mass: m/z : 324 (M^+), 155, 126, 97, 84, 68.