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Tetrahedron Letters 45 (2004) 309–312
Tetrahedron Letters

Facile conversion of lactols to lactones using IBX

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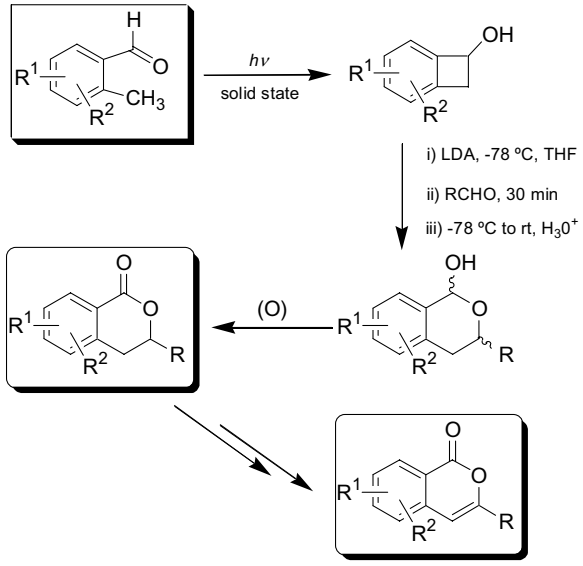
Received 8 August 2003; revised 21 October 2003; accepted 29 October 2003

Abstract—Lactols, which are insoluble or only sparingly soluble in most of the organic solvents that are generally employed for oxidation, are converted to lactones using *o*-iodoxybenzoic acid (IBX) in a facile manner under modified experimental conditions [EtOAc–DMSO (9:1) mixture at reflux] in good to excellent isolated yields (66–91%).

In continuation of our recent studies on photocyclization of *o*-alkylaromatic aldehydes to benzocyclobutenols in the solid-state,[1] we wished to elaborate the latter intermediates into biologically important and structurally diverse dihydroisocoumarins and isocoumarins following the reaction sequence in Scheme 1. While the lactols were readily prepared from the precursor cyclobutenols by deprotonation using LDA followed by ring opening and subsequent condensation with electrophilic aldehydes,[2] their further oxidation to dihydroisocoumarins proved unfruitful with a variety of oxidation reagents, viz., PCC, PDC, Jones, Swern, Dess–Martin periodinane (DMP), etc. It was realized that the failure to oxidize lactols to lactones was due to poor solubility of lactols in the solvents (dichloromethane and acetone) employed for conducting the oxidation reactions. This led us to explore the use of the hypervalent *o*-iodoxybenzoic acid (IBX) in DMSO.[3] We were particularly encouraged by a recent report involving the use of IBX as a suspended solid for oxidation of alcohols in a variety of solvents.[4] Herein we report our results on the facile conversion of a variety of sparingly/difficultly soluble lactols into lactones using IBX under modified conditions. The results described herein are of particular significance in view of the fact that the oxidation of lactols to lactones using IBX in DMSO has previously been reported *not to proceed to* an *appreciable degree*.[5] Further, it is noteworthy that the oxidation of lactols has been accomplished in three instances[6] with modified-IBX, viz., 1-hydroxy-1,3-dihydro-3,3-bis(trifluoromethyl)-1,2-benziodoxole-1-oxide (GDMP, Grieco Dess–Martin periodinane), and *not* with IBX.



Scheme 1.

As mentioned earlier, the diastereomeric mixtures of lactols **1**–**8** were prepared starting from benzocyclobutenols,[2] which in turn were available from solid-state photolysis of the precursor aldehydes.[1] In agreement with the previous report,[5] oxidation of lactols **1**–**8** with IBX in DMSO at room temperature was found to occur only sluggishly, despite the clear solubility of the lactols. However, the conversion was found to be complete with 1.2 equiv of IBX at elevated temperatures, i.e., at 80 °C in

Keywords: Lactols; Lactones; IBX; Oxidation.
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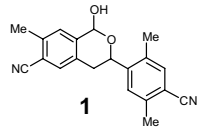
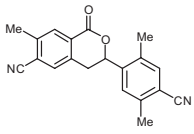
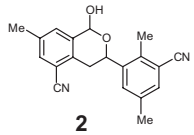
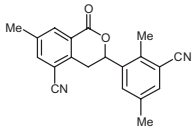
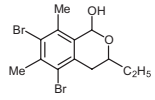
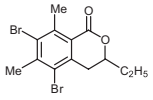
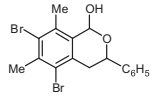
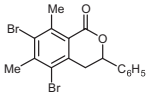
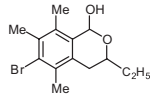
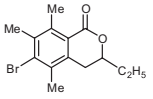
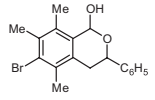
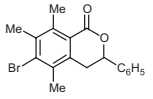
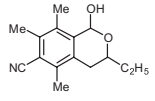
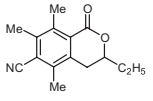
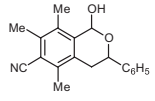
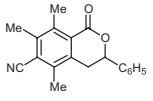
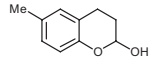
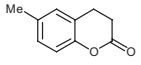
doi:10.1016/j.tetlet.2003.10.174

Table 1. The results of conversion of lactols **1**–**9** to the corresponding lactones using IBX

Lactol	Lactone	Solvent	Yield (%)[a]
 **1**		[b]	74
 **2**		[b]	90
 **3**		[b]	80
 **4**		[b]	76
 **5**		[b]	77
 **6**		[b]	82
 **7**		[b]	66
 **8**		[b]	91
 **9**		[b]	20[c]
		DMSO[d]	—
		C_6H_6[e]	80
		$CHCl_3$[e]	80
		EtOAc[e]	60

[a] Isolated yield.
[b] EtOAc–DMSO (9:1) mixture, reflux, 2.5–3.0 h.
[c] The remainder was an intractable material.
[d] At room temperature (ca. 30 °C) for 0.5 h. Several intractable products were revealed by TLC analysis.
[e] Reflux, ca. 10 h.

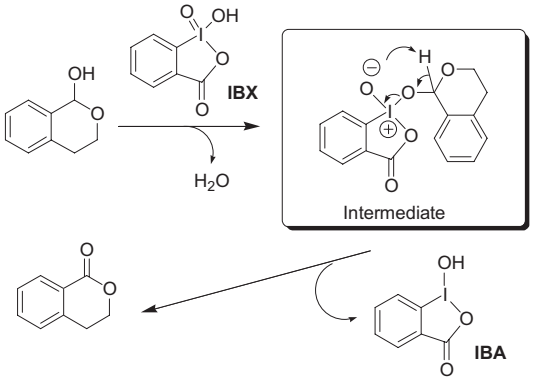
a mixed solvent system consisting of ethyl acetate–DMSO in a 9:1 ratio; the latter was employed to avoid obvious complications with the use of DMSO. In this solvent system, all the lactols **1**–**8** were clearly soluble at the ethyl acetate reflux temperature, although IBX remained as a suspended material.[7] In all cases, the reaction was complete (as monitored by TLC analysis) in 2.5–3 h, and the lactones were isolated in 66–91% yields (Table 1).[8] Thus, the reason for the failure to observe oxidation of lactols to lactones at room temperature in the present instance and in the previous attempts[5] must be attributable to the experimental conditions that precluded the activation barriers for bimolecular reactions from being overcome. Notably, the lactols **3**–**8** undergo

oxidation in the same amount of time as that required for lactols **1** and **2**, in spite of the fact that the latter are more congested.

To test the generality, the oxidation of lactol **9**, which does not contain the hydroxy group at the benzylic position, was examined. While the oxidation with 1.2 equiv of IBX in DMSO at room temperature led to an intractable mixture as revealed by TLC analysis, the oxidation in a heterogeneous phase in chloroform, ethyl acetate or benzene at reflux yielded the lactone in respectable isolated yields, albeit in longer reaction times. The best results were observed with benzene and chloroform as the solvents (Table 1). While the advantage of heterogeneous reaction conditions is clearly evident, the intriguing solvent dependence cannot be readily explained.

The mechanism of formation of the lactones may be described in a manner analogous to that described for the conversion of alcohols to aldehydes or ketones.[9] Accordingly, the attack of the lactol should furnish the intermediate in Scheme 2, which may decompose to the lactone and IBA (iodosobenzoic acid), the reduction product of IBX. Given the same mechanistic scenario for the oxidation of alcohols and lactols, what then is the cause of the higher activation barrier in the latter that necessitates comparatively higher temperatures for oxidation? We believe that the presumed steric factors[5] cannot be entirely responsible, as lactol **9** also requires higher temperature in a variety of solvents. Furthermore, lactols **1**, **2**, and **3**–**8** undergo oxidation without any perceptible difference in the rates as reflected from the reaction times for complete conversion. Rather, the stereoelectronic effects[10] emanating from the presence of an additional oxygen in the intermediate (Scheme 2), when compared to that resulting from the attack of simple alcohols on IBX, may be decisive in the decomposition of the intermediate into IBA and the lactone.

Although discovered more than a decade ago,[11] there has been renaissance of interest in recent years in employing IBX for oxidations;[9,12] a variety of IBX-mediated oxidations have been uncovered. Although several reagents may be employed for the oxidation of lactols, the advantage offered by IBX for substrates with poor solubility except in a solvent such as DMSO is singularly remarkable. We believe that the facile lactol to lactone conversion described herein will constitute an invaluable addition to the repertoire of transformations mediated by the inexpensive IBX, which is fast becoming indispensable in organic oxidations.



Scheme 2.

Acknowledgements

We thank the Department of Science and Technology for financial support. N.S. and P.M. are grateful to C.S.I.R. for junior and senior research fellowships, respectively.

References and Notes

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8. In a typical experiment, 0.1 g of the lactol (0.35–0.5 mmol) and 1.2 equiv of IBX in 10 mL of the ethyl acetate–DMSO (9:1) mixture were heated at reflux. The progress of the reaction was monitored by TLC analysis. After 2.5–3.0 h, the reaction mixture was cooled, the insoluble matter was filtered, and the resultant product mixture was subjected to short pad silica-gel column chromatography to isolate pure lactones.
   The characterization data for representative lactols and lactones are given below. It should be noted that the lactols in some cases were diastereomeric mixtures, with one of the isomers being present only as a minor constituent (ca. <20%). The data given below are for the major diastereomers.
   1: Colorless crystalline powder, mp 216 °C (dec); IR (KBr) cm^{-1} 3405, 2923, 2223; ^1H NMR (DMSO-d_6, 400 MHz) 2.32 (s, 3H), 2.44 (s, 3H), 2.46 (s, 3H), 2.76 (dd, 1H, $J_1 = 16.3$ Hz, $J_2 = 11.7$ Hz), 2.98 (dd, 1H, $J_1 = 16.6$ Hz, $J_2 = 2.4$ Hz), 5.27 (dd, 1H, $J_1 = 11.6$ Hz, $J_2 = 2.7$ Hz), 6.00 (d, 1H, $J = 6.1$ Hz), 7.15 (d, 1H, $J = 6.1$ Hz), 7.35 (s, 1H), 7.54 (s, 1H), 7.588 (s, 1H), 7.591 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) 18.0, 19.7, 19.8, 32.8, 64.6, 90.9, 110.8, 111.3, 118.1, 118.2, 127.9, 129.4, 132.67, 132.68, 133.89, 133.93, 139.2, 139.3, 140.8, 145.0; FAB-MS 319 (M+H), 301, 273, 232. Anal. Calcd for $C_{20}H_{18}N_2O_2$ (MW 318.38): C, 75.45; H, 5.70; N, 8.80. Found: C, 75.05; H, 6.21; N, 8.52.
   1-Lactone: Colorless crystalline powder, mp 218–220 °C; IR (KBr) cm^{-1} 1724, 2224, 2926; ^1H NMR ($CDCl_3$,

400 MHz) 2.34 (s, 3H), 2.53 (s, 3H), 2.62 (s, 3H), 3.07 (dd, 1H, $J_1 = 16.6$ Hz, $J_2 = 2.9$ Hz), 3.21 (dd, 1H, $J_1 = 16.3$ Hz, $J_2 = 12.4$ Hz), 5.70 (dd, 1H, $J_1 = 12.2$ Hz, $J_2 = 2.9$ Hz), 7.44 (s, 1H), 7.56 (s, 2H), 8.11 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 18.3, 20.1, 20.2, 33.5, 76.5, 112.9, 116.6, 117.6, 117.9, 127.7, 128.0, 131.3, 131.9, 132.6, 134.4, 136.1, 140.2, 140.6, 141.8, 163.5; FAB-MS 317 (M+H), 299, 273. Anal. Calcd for $C_{20}H_{16}N_2O_2$ (MW 316.36): C, 75.93; H, 5.10; N, 8.90. Found: C, 76.25; H, 4.93; N, 9.38.

3: Colorless crystalline powder, mp 178–179 °C; IR (KBr) cm^{-1} 3320, 2915; ^{1}H NMR (DMSO-d_6+$CDCl_3$, 400 MHz) 1.00 (t, 3H, $J = 7.6$ Hz), 1.60–1.66 (m, 2H), 2.27 (dd, 1H, $J_1 = 16.4$ Hz, $J_2 = 11.6$ Hz), 2.36 (s, 3H), 2.58 (s, 3H), 2.72 (dd, 1H, $J_1 = 16.4$ Hz, $J_2 = 3.4$ Hz), 4.07–4.09 (m, 1H), 5.83 (d, 1H, $J = 5.6$ Hz); ^{13}C NMR (DMSO-d_6+$CDCl_3$, 100 MHz) 9.6, 19.2, 25.1, 28.1, 35.4, 66.1, 89.2, 124.7, 126.3, 132.3, 133.1, 134.8, 136.3; FAB-MS 365 (M+H), 347, 267, 219, 149. Anal. Calcd for $C_{13}H_{16}Br_2O_2$ (MW 364.08): C, 42.90; H, 4.43. Found: C, 43.05; H, 4.07.

3-Lactone: Colorless crystalline powder, mp 98–99 °C; IR (KBr) cm^{-1} 2970, 1715; ^{1}H NMR ($CDCl_3$, 400 MHz) 1.09 (t, 3H, $J = 7.3$ Hz), 1.77–1.82 (m, 1H), 1.86–1.91 (m, 1H), 2.73 (s, 3H), 2.75 (s, 3H), 2.70–2.80 (m, 1H), 3.22 (dd, 1H, $J_1 = 16.8$ Hz, $J_2 = 2.4$ Hz), 4.25–4.31 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 9.4, 22.4, 26.5, 27.6, 35.5, 78.5, 123.0, 125.3, 129.5, 138.9, 141.4, 143.1, 164.0; FAB-MS 363 (M+H), 319, 283, 227. Anal. Calcd for $C_{13}H_{14}Br_2O_2$ (MW 362.06): C, 43.13; H, 3.90. Found: C, 43.55; H, 3.47.

4: Colorless crystalline powder, mp 225 °C (dec); IR (KBr) cm^{-1} 3441, 2908; ^{1}H NMR (DMSO-d_6+$CDCl_3$, 400 MHz) 2.38 (s, 3H), 2.54–2.60 (m, 1H), 2.57 (s, 3H), 2.97 (dd, 1H, $J_1 = 17.2$ Hz, $J_2 = 3.4$ Hz), 5.22 (d, 1H, $J = 11.7$ Hz), 5.99 (d, 1H, $J = 5.1$ Hz), 7.30–7.40 (m, 5H); ^{13}C NMR (DMSO-d_6 + $CDCl_3$, 100 MHz) 19.2, 25.2, 37.9, 67.1, 89.8, 124.5, 125.9 (×2), 126.6, 127.3, 128.1, 132.8, 134.9, 136.5, 141.7; FAB-MS 413 (M+H), 395, 273, 219. Anal. Calcd for $C_{17}H_{16}Br_2O_2$ (MW 412.12): C, 49.54; H, 3.91. Found: C, 49.98; H, 4.38.

4-Lactone: Colorless crystalline powder, mp 175–177 °C; IR (KBr) cm^{-1} 2922, 1716; ^{1}H NMR ($CDCl_3$, 400 MHz) 2.76 (s, 3H), 2.79 (s, 3H), 3.15 (dd, 1H, $J_1 = 17.0$ Hz, $J_2 = 12.0$ Hz), 3.47 (dd, 1H, $J_1 = 17.0$ Hz, $J_2 = 2.7$ Hz), 5.39 (d, 1H, $J = 11.7$ Hz), 7.39–7.49 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) 22.5, 26.6, 38.1, 78.5, 123.0, 125.2, 126.2, 128.7, 128.8, 129.8, 137.9, 138.6, 141.7, 143.5, 163.5; FAB-MS 411 (M+H), 393, 273, 219. Anal. Calcd for $C_{17}H_{14}Br_2O_2$ (MW 410.11): C, 49.80; H, 3.41. Found: C, 50.22; H, 3.96.

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