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A Mild Oxidizing Reagent for Alcohols and 1,2-Diols: o-Iodoxybenzoic Acid (IBX) in DMSO

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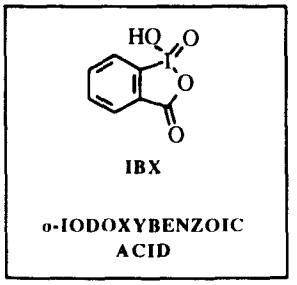
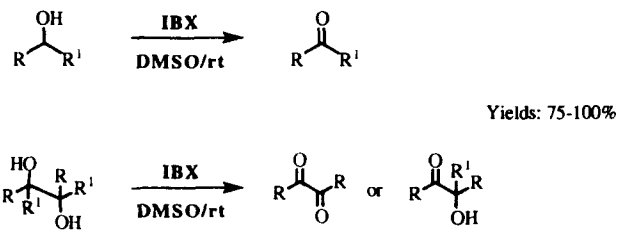
Abstract: o-Iodoxybenzoic acid (IBX) smoothly oxidizes primary and secondary alcohols to aldehydes and ketones, respectively. 1,2-Diols are converted to α-ketols or α-diketones without any oxidative cleavage of the glycol C-C bond. **IBX** oxidations are easily conducted in DMSO solution at room temperature, with yields ranging from good to quantitative.

The oxidation of an alcoholic group to a carbonyl is a central reaction in organic chemistry and several methods are available, covering a variety of experimental conditions. However, this reaction, due to its pivotal role in synthetic chemistry, still continues to receive great attention in order to discover new oxidants with peculiar features (*e. g.*: TPAP, TEMPO, dimethyldioxirane).[1]

In particular, the oxidation of 1,2-diols to α-ketols or α-diketones represents a transformation that always has to overcome the problem of the oxidative cleavage of the glycol C-C bond and only few methods are available for such a reaction.[2] Indeed mild reagents (*e. g.*: TPAP,[1b] MnO_2,[2d] PCC[3]) produce mainly, if not exclusively, the C-C cleavage products.

We now wish to report that **o-iodoxybenzoic acid**[4] (**IBX**: 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide), a compound first prepared in 1893,[4a] **smoothly oxidizes** primary and secondary **alcohols** to aldehydes and ketones, respectively, and **1,2-diols** to α–ketols or α–diketones **without any oxidative cleavage of the glycol bond. IBX** oxidations are easily conducted in DMSO solution at room temperature; yields range from good to quantitative.





R, R^1 = H, Alkyl, Aryl, Heteroaryl

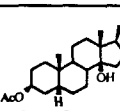
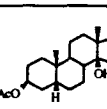
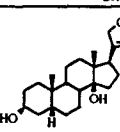
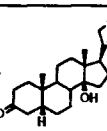
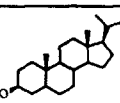
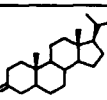
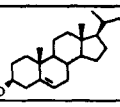
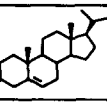
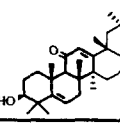
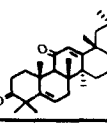
In recent years, **IBX** has been widely utilized for the preparation of Dess-Martin periodinane,[4b,c] a well known oxidant, while **IBX** itself has never been used as a reagent in organic synthesis, probably because "its virtual insolubility in common organic solvents has discouraged the study of its chemical properties", as Dess and Martin stated[4c] in 1991.

We prepared[5] **IBX** according to the Dess-Martin procedure,[4c] and found that, contrary to literature data,[4c,6] it dissolves readily in DMSO[7] (clear solutions up to 1,5 M are easily obtained), while it is virtually insoluble in sulfolane, DMF, CH_3CN, $CHCl_3$, CH_2Cl_2, acetone and THF. **IBX**, in contrast to Dess-Martin periodinane,[4b,c] is stable to moisture and the oxidation can be performed in an open flask without any particular precaution (such as inert atmosphere and dry solvent). Moreover, it is also possible to use a co-solvent such as THF for compounds (Ex.11, 12) that do not dissolve readily in DMSO or when a reaction temperature below 15 °C is required (Ex 18).

The oxidant properties of **o-iodoxybenzoic acid (IBX)** are markedly different from those of its close analogues iodoxybenzene and m-iodoxybenzoic acid[8].

Thus, whilst the latter oxidize benzyl alcohols to benzaldehydes only at high temperature (benzene / 80 °C/ 5-10 hr) or in AcOH (rt / 24 hr), **IBX** in DMSO oxidizes benzyl alcohol to

Table 1: IBX Oxidation of Alcohols

Ex. n°	1,2-Diol	Molar ratio[a]	Time (hrs)	Product	Yield[b] %
1		1.1	0.25		97[c]
2		1.1	0.75		88
3		1.1	0.25		99
4		1.1	1		82
5		1.1	4.5		91
6		2.2	2		98
7		1.9	2		98
8		1.1	2.5		100
9		1.1	0.25		95
10		2	3		92
11		1.5[d]	5		89
12		6[d]	2		75
13		10	1		78
14		1.5	4		90

a: mmol of IBX/mmol of alcohol. b: yields of isolated compounds (flash chromatography or crystallisation). c: compound isolated by distillation.
d: Reaction in DMSO/THF (1/1).

benzaldehyde in 15 min at rt (Table 1, Ex. 1). Moreover **IBX**, in contrast to both Dess-Martin periodinane[4c,2d] and iodoxybenzene derivatives,[8] smoothly oxidizes 1,2-glycols to α-ketols or α-diketones (Table 2) without cleaving the glycol C-C bond.

Table 1 (Alcohols) and Table 2 (1,2-Diols) show a summary of **IBX** oxidations.

Oxidation with IBX in DMSO - General Procedure

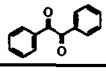
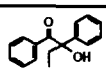
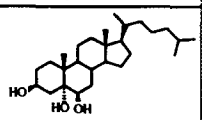
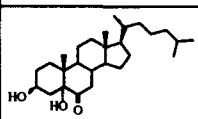
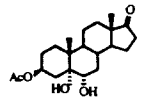
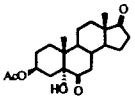
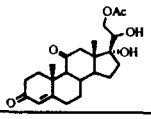
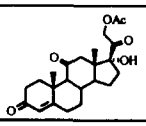
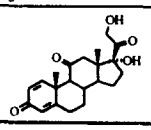
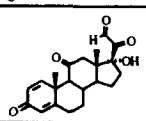
IBX (1 -10 mmol) is dissolved in DMSO. 0.4-1.0 M solutions are routinely used for preparative oxidation reactions. The dissolution of **IBX** in DMSO requires 5-20 min. The compound to oxidize (1 mmol) is then added either as a solid, or liquid or dissolved in DMSO (and/or, if necessary, in THF). The reaction is monitored by TLC. Work-up is easily performed by dilution of the reaction mixture with water, filtration of the white precipitate and extraction of the reaction mixture with an organic solvent. The compound is then isolated and purified by standard techniques.

IBX in DMSO oxidizes primary alcohols to aldehydes at room temperature, without over-oxidation to acids (Ex. 1-7), and secondary alcohols to ketones (Ex. 8-14). Also, sterically hindered alcohols are easily oxidized at room temperature in a few hours (Ex. 8, 9, 14).

IBX oxidizes γδ-unsaturated alcohols to the corresponding carbonyls in good yields (Ex. 5, 12-13) while Dess-Martin periodinane[4c] as well as TPAP[1b] oxidize them only in low to moderate yields. The oxidation of a chiral primary alcohol (Ex. 7) proceeds without epimerization.

It is worth noting that the furan and pyridine rings (Ex. 2, 3) are not oxidized by **IBX** in DMSO. Double bonds, both conjugated and isolated (Ex.5, 6, 10, 12-14, 23, 24) are not affected. Tertiary alcohols (Ex. 7, 10, 18, 20-24) do not interfere during **IBX** oxidation.

Table 2: IBX Oxidation of 1,2-Diols

Ex. n°	1,2-Diol	Molar ratio[a]	Time (hrs)	Product	Yield[b] %
15		2.5	3		100[c]
16		2.5	3.5		81
17		2.5	5		78
18		1.5[d]	3		86
19		2.5	2		93
20		1.5	1.5		98
21		1.5	0.75		85[e]
22		6	1		85
23		2[f]	3		93
24		2	24		86

a: mmol of IBX/mmol of 1,2-diol. b: yields of isolated compounds (flash chromatography or crystallisation). c: yield determined by NMR spectroscopy. d: Reaction in DMSO/THF (1/1). Reaction temperature = 0 °C. e: Also isolated 12% of 3,6-diketo derivative. f: Reaction temperature = 50 °C.

1,2-Diols are cleanly oxidized, with the stoichiometric amount of **IBX** in DMSO (1.0-1.5 mol/secondary alcohol) to α-diketones (*sec,sec*-1,2-diols: Ex. 15-17, 19) or α-ketol (*sec,tert*-1,2-diols: Ex. 18, 20-23). With a deficiency of oxidant (0.5-0.8 mol/secondary alcohol), *sec,sec*-1,2-diols are oxidised to a mixture of products (ketol and diketone), thus suggesting that the kinetics of oxidation of the diol and the ketol are similar. Indeed also α-ketols are easily oxidised to α-dicarbonyls (Ex. 24). Its is worth underlining that **IBX** in DMSO seems to oxidize preferentially 1,2-diols *versus* secondary alcohols (Ex. 21).

The amount of **IBX** used in preparative reactions may vary from one mol to several mol (*e.g.* 6-10 mol: Ex. 12, 13, 22) per mol of oxidizable alcoholic group. The use of several mol of **IBX** merely accelerates the kinetics of the oxidation process without modifying the nature of the final products. For instance, the oxidation of 3β-acetoxy-5α,6α-dihydroxyandrostan-17-one to the corresponding 6-keto derivative (Ex. 22) proceeds in 1 h using 6 mol of **IBX** (yield: 85%), while using 1.1 mol the reaction is still uncomplete after 16 hrs (yield: 10%).

In conclusion **IBX** in DMSO represents a mild and cheap reagent for the oxidation of alcohols and 1,2-diols.

REFERENCES AND NOTES

CAUTION: IBX has been reported to be explosive upon heavy impact and heating over 200 °C: Plumb, J. B. and Harper, D. J., *Chem. Eng. News* **1990**, (July 16) 3. See also ref 4c: note 3e and IBX preparation on page 7278.

1. a) TPAP: Griffith W. P. and Ley S. V., *Aldrichim. Acta* **1990**, *23*, 13. b)TPAP: Acosta C. K., Rao P. N., Kim H. K. *Steroids* **1993**, *58*, 205. c) TEMPO: Inokuchi T., Matsumoto S., Nishiyama T., Torii S., *J. Org. Chem.* **1990**, *55*, 462. d) Dimethyldioxirane: Murray, R. W. *Chem. Rev.*, **1989**, *89*, 1187.
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4. a) Hartman C. and Meyer V., *Chem. Ber.* **1893**, *26*, 1727. b) Dess D. B. and Martin J. C., *J. Org. Chem.*, **1983**, *48*, 4155. c) Dess B. D. and Martin J. C., *J. Am. Chem. Soc.*, **1991**, *113*, 7277.
5. IBX was prepared according to the Dess-Martin procedure (ref 4b and 4c: oxidation of o-iodobenzoic acid with $KBrO_3$), but after the water washing, it was rinsed with anhydrous acetone and diethyl ether instead of ethanol, m. p. 226-234 °C. (ref. 4a: 233 °C; ref. 4c: 232 - 233 °C; ref. 7a: 224-225 °C). IR(film) 1640 cm^{-1}(Bell R. and Morgan K., *J. Chem. Soc.* **1960**, 1209, IR: 1640 cm^{-1}; ref. 6b, IR: 1638 cm^{-1}:). ^{1}H-NMR (DMSO-d_6): 8.15 (1H, d), 8.01 (1H, d), 7.98 (1H, t), 7.84 (1H, t). ^{13}C-NMR (DMSO-d_6): 167.49, 146.59, 133.39, 132.97, 131.36, 130.10, 124.99. Anal Calcd. for $C_7H_5IO_4$: C, 30.30; H, 1.80; I, 45.32. Found: C, 30.13, H, 1.75, I, 45.05.
6. a) Katritzky A. R., Duell B. L., Gallos J. K., *Org. Magn. Reson.*, **1989**, *27*, 1007. b) Katritzky A. R., Savage G. P., Gallos J. K., Dupont Durst H., *J. Chem. Soc.,Perkin Trans 2*, **1990**, 1515.
7. Katritzky[6a] prepared IBX by oxidation of o-iodobenzoic with chlorine. This compound (mp 224-225 °C) is reported to be insoluble in DMSO, while it dissolves in $CDCl_3$/DMF-d_7 (NMR data reported in Ref. 6b). We prepared four batches of IBX (20 g each) according to ref. 4b and note 5. Every batch has the same mp, NMR, IR and solubility in DMSO and DMSO-d_6.
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