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o-Iodoxybenzoic acid in dimethylformamide as a convenient reagent for the oxidation of alcohols to aldehydes and ketones

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DMF dissolves *o*-iodoxybenzoic acid (up to 0.1 mol dm^{-3}) and, therefore, is a solvent of choice for the reactions with *o*-iodoxybenzoic acid simplifying significantly a product isolation procedure due to a higher volatility. The reaction rate and selectivity of the oxidation of alcohols to corresponding carbonyl compounds with *o*-iodoxybenzoic acid in DMF are close to those in DMSO.

o-Iodoxybenzoic acid [1-hydroxy-1,2-benzoiodoxol-3(1*H*)-one, IBX], previously known during 100 years[1] as a compound almost insoluble in organic solvents, was found in 1994[2] to be easily soluble in dimethyl sulfoxide (DMSO).† Since then this easily available iodine(V) compound finds quickly expanding applications in organic chemistry as a versatile and selective oxidant. First, IBX served in a central reaction of organic synthesis, namely, for the oxidation of hydroxyl groups to carbonyls.[2] IBX in DMSO is a preferable reagent for the oxidation of primary and secondary alcohols and α-glycols to corresponding aldehydes, ketones and α-diketones.[4] Other valuable reactions with IBX as an oxidant were developed, *e.g.*, α,β-dehydrogenation of aldehydes and ketones,[5,6] the syntheses of γ- and δ-lactols,[7] *o*-quinones,[8] imines,[9] amino sugars[10] and nitriles,[11] the oxidations of benzylic methylene and methyl groups into carbonyl groups,[6] unsaturated anilides into lactams,[6,12] regeneration of carbonyl groups from oximes,[13,14] tosylhydrazones,[13] dithioketals[9,15] *etc.*[16–18]

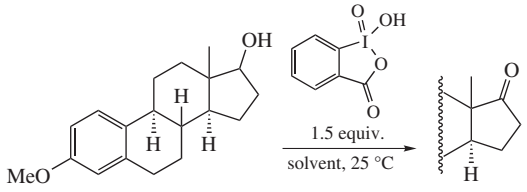
In the majority of these reactions, DMSO was used as a solvent for IBX and substrates, often with various co-solvents (THF, Me_2CO, PhMe, PhF, Py) in the cases of lipophilic substrates. Obvious limitations of DMSO as a solvent (low volatility making necessary aqueous extraction and frequently chromatographic isolation procedure, low solubility of lipophilic substrates) motivated the search of its replacement. For the oxidation of alcohols, there are proposals to use IBX as the suspensions in EtOAc, MeCN or $(CH_2Cl)_2$ at 80 °C,[19] in THF, Me_2CO or other common solvents at 56–82 °C,[20] and as solutions in ionic liquids[21] or $Bu_4NBr/CH_2Cl_2/H_2O$.[22] For other type oxidations with IBX, the reaction media were THF,[10,16(c)] DMF,[8] $CHCl_3$,[8] MeCN[16(c),(e)] or a solution of Et_4NBr in it,[11] and a solution of β-cyclodextrin in aqueous Me_2CO.[13,15,16a] The problem of a limited solubility of IBX was solved by other means, such as the synthesis of an IBX structural analogue (mIBX) with an enhanced solubility,[23] IBX immobilisation on polystyrene or silica gel,[24] and *in situ* regeneration of IBX catalytical quantities.[25] The general drawbacks of the majority of these variants are slow reaction rates needing prolonged heating, which is not always acceptable for sensitive substrates, and low solubility of complicated substrates in aqueous media.

Strangely enough, published data on the solubility of IBX in organic solvents are scanty and somewhat contradictory. In 1994, Frigerio and Santagostino[2] reported the easy, during 5–20 min, dissolution of IBX in DMSO with a solution concentration up to 1.5 mol dm^{-3}, as well as the virtual IBX insolubility in $(CH_2)_4SO_2$, DMF, MeCN, THF, Me_2CO, $CHCl_3$ and CH_2Cl_2. A year later, Corey[7(b)] reported the formation of an IBX solution (0.3 mol dm^{-3}) in DMSO–Me_2CO (1:3.7) mixture after dissolution for 1 h. However earlier, in 1989–90, Katritzky mentioned the solubility of IBX in DMSO, as well as in DMF,[3] and published its ^{13}C NMR spectrum in $CDCl_3$–[$^2H_7$]DMF.[26] Although Katritzky's statement has not been unnoticed,[2] it was not explained.

The possible explanation lies, in our opinion, in the known[27] polymeric nature of IBX in a crystalline state. Therefore, IBX dissolution has to be preceded by its depolymerization (facilitated by solvation). This factor results in the slow dissolution process in DMSO cited above. The dissolution of IBX in less solvating solvents could proceed even more slowly and be left undetected.

Indeed, we have found that IBX dissolves slowly in DMF. The suspension of crystalline IBX‡ in DMF (30 mg ml^{-1}) dissolves partially (10 mg ml^{-1} in supernatant) on stirring for 3 h at 23 °C and forms a clean solution after 12 h with an IBX concentration of 0.1 mol dm^{-3}. An aliquot (1.00 ml) of this solution left a glassy residue, which retained strongly some DMF. The residue after 1 h drying at 70 °C/0.2 Torr (34 mg) contained the components in the molar ratio IBX:*o*-OIC_6H_4COOH (IBA): *o*-IC_6H_4COOH (IBB):DMF = 1.05:0.50:0.10:1.00 (according to ^1H NMR analysis). These facts are deemed to be evidence for

Table 1 Solvent selection.



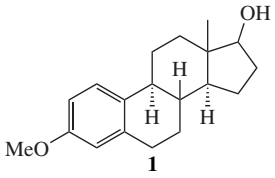
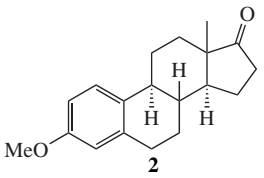
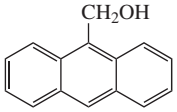
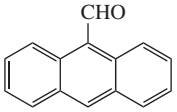
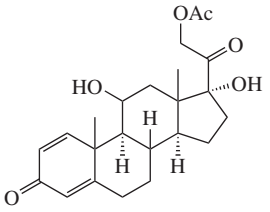
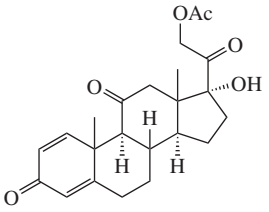
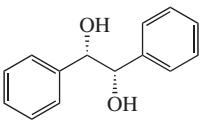
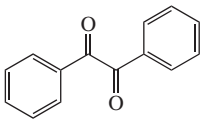
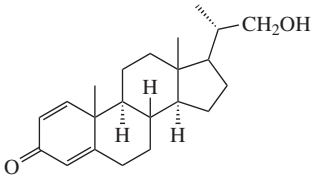
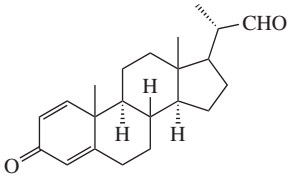
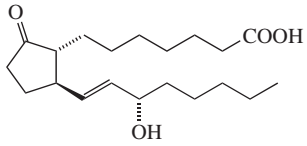
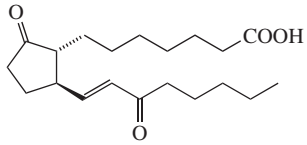
1 **2**

Entry	Solvent[a]	Yield[b] (%)	
		after 2 h	after 20 h
1	DMF[c]	50	100
2	Me_2CO[c]	20	60
3	THF	10	60
4	CH_2Cl_2	5	30
5	MeCN	<5	30
6	$(MeOCH_2)_2$	<5	10
7	C_6H_6	<5	<10
8	EtOAc	<5	<10
9	Bu^tOH	0	<5

[a]Reactions were carried out in given solvents (400 μl) on a 50-μmol scale at 25 °C with 1.5 equiv. of IBX. [b]Chromatographic yield, balance is the starting **1**. [c]1.2 equiv. of IBX.

† Formally speaking, the solubility of IBX in [$^2H_6$]DMSO and [$^2H_7$]DMF has been first mentioned by other authors in 1989.[3]

Table 2 Oxidation of alcohols with IBX in DMF.

Entry	Alcohol[a]	IBX equiv.	Solvent (ml per mmol of IBX)	*t*/h	Product[b]	Yield[c] (%)
1	 **1**	1.2	DMF (4.0)	4	 **2**	98
2		1.5	DMF (5.0)	2		96
3		1.2	DMF (2.0) + THF (2.0)	4		98
4		1.2	DMF (2.0) + Me_2CO (2.0)	4		98
5		1.5	THF (5.0) + Bu^tOH (0.3)	48		95
6		1.2	DMF (4.0)	7.5		100
7		1.2	DMF (4.0)	5		99
8		2.2	DMF (3.5)	4		98
9		1.2	DMF (3.5)	3.5		90
10		1.2	DMF (3.5)	2.5		98[d,e]

[a]Reactions were carried out on a 1 mmol scale at room temperature (23–25 °C). [b]All products were TLC and ^{1}H NMR homogeneous and were identified by direct comparison with the authentic samples. [c]Isolated yield. For the isolation method, see general procedure. [d]Silica gel filtration on isolation. [e]The oily product isolated in 101% yield retained strongly 3.3 wt% DMF.

the existence of the stable amorphous 1:1 complex of IBX with DMF.§

The obtained 0.1 M solution continues to dissolve, even more slowly, additionally added IBX. However, the maximal IBX solubility could not be measured because IBA starts to crystallize off from the solution after 5–7 days of stirring due to IBX reduction by DMF. An attempt to determine analogously IBX solubility in THF resulted only in the estimation of the possible solubility as being not higher than 1 mg cm^{-3} due to the known[12,19,20] oxidation of THF in a contact with IBX.¶

The finding of the appreciable solubility of IBX in DMF made interesting to investigate DMF as a solvent for the reactions with IBX. DMF has not been tested in this respect in several reported searches of the best organic solvents alternative to DMSO in these reactions.[11,16(*c*),(*g*),19,20] We know only one work where DMF was used as a solvent in a reaction with IBX, the oxidation of phenols to *o*-quinones.[8]

The effectiveness of solvents in the oxidation of secondary alcohol **1** to corresponding ketone **2** with suspended IBX at room temperature is shown in Table 1. DMF (entry 1) is the most effective, it secures significantly higher reaction rate than THF and MeCN (entries 3 and 5), which were found by Ozanne *et al.*[20] to be the optimal solvents in alcohol oxidation at 60–82 °C. EtOAc (entry 7) is totally useless at room temperature although this solvent was found by More and Finney[19] as one of the best at 80 °C.

The preparative oxidation of alcohols with IBX suspended in DMF at room temperature†† (see Table 2) demonstrated that the reactions in this solvent proceed practically identical to those in DMSO. The rates of oxidations in DMF and DMSO[4] are very similar, higher excess of IBX appreciably accelerates oxidation (entry 2), the addition of co-solvents decelerates the process

‡ IBX of ≥ 99% purity obtained by the Frigerio method[28] was used in this work. A sample as 0.2–0.3 mm crystals was employed in a solubility study, and a sample as white powder served in oxidation reactions.

Caution! IBX should be handled with a due care because an explosion incident has been reported,[29] moreover, on heating above 200 °C IBX decomposes vigorously with a flame and a bang. For applications as a suspended reagent a potentially unsafe grinding of IBX in a mortar was not used, IBX in the form of fine powder was obtained by the fast crystallization in the course of its synthesis. The authors did not experienced any unpleasant incidents during the work with IBX.

§ The presence of IBA (and IBB) in the residue after evaporation of IBX solution in DMF is considered to be mainly due to the reduction of IBX on heating in the process of intensive evaporation of DMF, because IBA is less soluble in DMF than IBX. DMF in the residue is retained due to IBX only since IBA and IBB both crystallize from DMF without solvent (our observation).

¶ The suspension of IBX in THF (10 mg cm^{-3}) was stirred periodically during 15 days without dissolution. An aliquot (1.00 ml) of the supernatant left after evaporation 8 mg of non-volatile residue as a viscous oil with some white powder. This residue contained (according to ^{1}H NMR analysis) 2–3 mg of IBA and IBB (55:45) as main aryl components, the balance was a complicated mixture of THF oxidation products analogous to that described in ref. 12.

insignificantly (entries 3 and 4). Primary alcohols are cleanly oxidized to corresponding aldehydes without overoxidation (entries 6 and 9), α-glycol is equally well oxidized to corresponding α-diketone (entry 8). The oxidation is entirely chemoselective for the primary and secondary hydroxyl groups, *i.e.,* the sensitive functional groupings (*tert*-α-ketol, dienone, anisole) remain intact. 1.1–1.2 equiv. of IBX for each hydroxyl group of a substrate are enough for a quantitative oxidation as oxidation of DMF practically does not proceed during the reaction period. The course of oxidation could be observed visually: the heavy sediment of IBX, which occupies at first a small part of the reaction volume, gradually diminished and disappeared, but instead a fine white precipitate of IBA appears in the whole reaction volume at 20–40% conversion of an alcohol. This precipitate of IBA thickens significantly the reaction mixture in the end of reaction but does not hamper stirring.

Being similar to DMSO in the characteristics mentioned above on the application as a solvent in reactions with IBX, DMF possesses significant advantage due to much greater volatility (bp 153 °C/760 Torr, 50 °C/18 Torr, 25 °C/3.7 Torr). Therefore, the isolation of high-boiling products of the oxidations in DMF can be performed without aqueous treatment, extraction and chromatography, merely by the filtration (to remove IBA) and filtrate evaporation at < 50 °C in a laboratory vacuum. This simple isolation procedure provides nearly quantitative yields of analytically pure products. At the same time, without additional manipulations, one isolates > 90% of formed IBA, which could be used in economic synthesis of IBX,[28] and regenerates DMF.

All products in Table 2 were isolated with this procedure and did not contained (with a single exception) traces of DMF, IBX, IBA or IBB. The exception is prostaglandin derivative (entry 10) which due to the presence of a free carboxyl group retained very strongly the traces of DMF removable by aqueous washing only. In similar cases or for low-molecular-weight alcohols, an oxidation method in a low-boiling solvent and at room temperature is desirable. Our endeavour in this direction met only limited success. Alcohol **1**, a substrate with a medium rate of oxidation to ketone **2**, was quantitatively oxidized at room temperature in THF, but only after 48 h, using 1.5 equiv. of IBX and catalysis by Bu^{t}OH[‡‡] (entry 5).

In conclusion, DMF is a convenient alternative to DMSO as a solvent in the frequently used reaction of alcohol oxidation to the corresponding carbonyl compounds with IBX because of the possibility to simplify the isolation procedure. Moreover, the great similarity of the reaction results obtained in DMF and DMSO allows us to suppose that DMF could also serve as a convenient solvent in other reactions with IBX as the reagent.

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[††] *General procedure.* Solid IBX (1.1–1.5 equiv. for each oxidized hydroxyl group of a substrate) was added as a single portion to the solution of alcohol in absolute DMF (3.5–5.0 ml per mmol of IBX) and the suspension was vigorously stirred with teflon magnet at room temperature (23–25 °C), until total conversion of the alcohol (and intermediate products in the case of α-glycols) according to TLC analysis. In the course of the reactions the starting white suspension pales gradually, sometimes until transparency, then again becomes milk-white and thickens. The mixture was diluted with 5–6 volumes of CH_2Cl_2 (or Et_2O, or EtOAc, or other solvent, depending on the polarity of a formed ketone), stirred 5 min and filtered through a small Al_2O_3 column (or silica gel in the case of acidic compounds) (2 g mmol^{-1} of alcohol). The filtrate was rotoevaporated to dryness at < 50 °C, finally in vacuum < 5 Torr. If evaporation residue is not completely soluble in CH_2Cl_2 (due to traces of IBX-derived products), the residue was filtered once more through the already used column and evaporated. The obtained residue is an oxidation product pure by TLC and NMR analyses. The top of the column contains IBA, pure by NMR, which can be collected with a > 90% yield.

[‡‡] We found in some separate experiments that the addition of a small quantity of Bu^{t}OH (2 equiv. to IBX) accelerates by a factor of 2–3 the oxidation of alcohols with IBX in THF, and an increase in Bu^{t}OH quantity (up to 8 equiv.) does not enhance further the catalytical effect. The interaction between Bu^{t}OH and IBX with the equilibrium formation of the covalent adduct Bu^t–IBX is known.[30] Bu^{t}OH itself is not suitable as a solvent for oxidations with IBX (entry 9 in Table 1).