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Pyridinium *o*-iodoxybenzoate as a safe form of a famous oxidant

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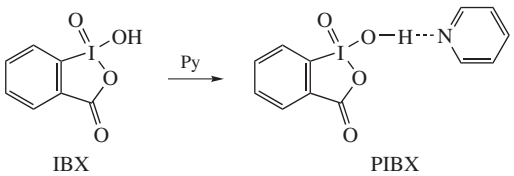
The stable pyridinium salt of *o*-iodoxybenzoic acid (PIBX) that is easy to obtain can serve as a convenient substitute of IBX as an oxidant. PIBX is safer, has neutral properties behaves as an equivalent to IBX in the oxidation of alcohols to ketones or aldehydes in polar solvents (DMF, DMSO), and provides higher oxidation rate in THF due to better solubility.

o-Iodoxybenzoic acid (existing as tautomer, *viz*. 1-hydroxy-1-oxo-1*H*-1λ^5-benzo[*d*][1,2]iodoxol-3-one, IBX) finds an extensive and ever-expanding application in synthetic organic chemistry as a multi-purpose oxidant. IBX was first introduced in 1994 as a convenient oxidant of alcohols to carbonyl compounds[1] and has since become a reagent of choice for dozens of oxidation processes, which are often unique (see recent reviews[2]).

Though IBX is now often used in chemistry, two practical problems have not been yet solved adequately. The first one is practical insolubility of IBX in organic solvents except for dimethylsulfoxide (DMSO). However, DMSO has low dissolving capacity for lipophilic substrates and low volatility, which complicates product isolation. In search for DMSO substitute, nearly all common laboratory solvents were tested; of these, tetrahydrofuran[3,4] (THF), *tert*-butanol,[5] ethyl acetate[6] and dimethylformamide[7,8] (DMF) may be noted in particular. However, only in DMF oxidation of alcohols was found to occur at room temperature at nearly the same rate as in DMSO, owing to a considerable solubility of IBX in DMF (up to 0.1 mol dm^{-3}). In other solvents, this reaction requires heating for several hours, which is often undesirable.

The potential explosiveness of IBX[9] presents yet another problem: it decomposes violently on heating above 200 °C, which is accompanied by a flame and a loud bang.[2(c),10] For this reason, IBX is commercially available only in a stabilised form (SIBX)[11] as a mixture with benzoic and isophthalic acids containing 45% IBX.[12] Herein, we suggest a different solution of this problem.

While searching for a new solvent for IBX we tested pyridine. An IBX suspension (280 mg) in dry pyridine (1 ml) at ambient temperature (24–28 °C) and with occasional superficial stirring first undergoes slow (1–2 h) dissolution of a part of IBX to a concentration of ~100 mg cm^{-3}, followed by faster precipitation of a new compound as small colourless crystals, which ceased with complete IBX dissolution in 12–24 h. Filtration with subsequent washing of the crystals with pyridine (0.5 ml) and drying *in vacuo* (1 Torr) gives 354 mg (99%) of IBX pyridinium salt (PIBX).[†,‡] This salt remains unchanged on storage for three years in the absence of bright light; slow heating results in its gradual decomposition in the range of 200–255 °C, leaving a dark non-melting material. Upon fast heating, PIBX decomposes at 240 °C with a small clap and violet vapours but no flame. This behaviour on heating characterises PIBX as a much more stable compound than IBX. Attempts to explode PIBX by impact (using a steel hammer on a metal anvil) failed.



IBX PIBX

It has been known for a long time that IBX possesses a considerable acidity and forms salts with metal cations.[10] Recently, p$K_a^{H_2O}$ 2.40 was measured[13] and the IBX tetra-*n*-butylammonium salt was reported,[14] which showed no oxidative properties. Therefore, the formation of the pyridinium salt, *i.e.* PIBX, could not be unexpected. The facility of PIBX preparative synthesis is due to the high IBX solubility in pyridine (>100 mg cm^{-3}) and the very low solubility of the resulting PIBX (<2 mg cm^{-3}). On the other hand, we failed to obtain the IBX 2,6-dimethylpyridinium salt: no changes occurred for three days in a suspension of IBX in 2,6-dimethylpyridine, despite the higher basicity of this amine (p$K_a^{H_2O}$ 6.72[15]) in comparison with pyridine. This fact can be attributed to the total insolubility of IBX in 2,6-dimethylpyridine.

PIBX is nearly insoluble in THF, MeCN, acetone, *tert*-butanol and dichloromethane, highly soluble in DMSO and moderately soluble in DMF (up to 0.19 mol dm^{-3})[§] to give a neutral solution (unlike that of IBX) which remains stable for a few days. NMR spectra of a PIBX solution in DMSO-d_6[‡] are nearly a superposition of the spectra of IBX and pyridine. Dissociation of PIBX to components is also observed upon keeping a PIBX suspension in acetonitrile, when 35% of the precipitate is converted to IBX in 24 h, while pyridine appears in the supernatant fluid. Such a behaviour in solvents explains why the oxidative properties of IBX are retained in PIBX, as we demonstrate here for several hydroxyl-containing substrates (Table 1).[¶]

In all the examples presented in Table 1, in terms of all parameters (oxidant excess, rate, yield), oxidation of substrates by treatment with PIBX in DMF occurs almost identically to that with IBX under the same conditions (see ref. 3 for substrates **1**, **3**, **5** and ref. 9 for substrate **7**). The same picture is observed for sub-

[†] The same results were obtained in numerous runs with scaling up, higher amounts of pyridine, and vigorous stirring.

[‡] PIBX: IR (KBr, ν/cm^{-1}): 696, 748, 784, 840, 1376, 1436, 1560, 1600, 3048, 3072, 3420. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.40 (dist. t, 2H, 2H$_{\beta\text{-Py}}$), 7.78–7.86 (m, 2H, H-4, H-5), 7.97–8.05 (m, 2H, H-3, H-5), 8.15 (d, 1H, H-2, J 7.8 Hz), 8.58 (d, 2H, 2H$_{\alpha\text{-Py}}$, J 4.3 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 124.92, 130.07, 131.53, 132.90, 133.27, 146.63, 167.51 (all for IBX), 124.04, 136.62, 149.27 (all for Py). Found (%): C, 40.23, 40.39; H, 3.08, 3.02; I, 35.56, 35.66; N, 4.05, 3.95. Calc. for $C_{12}H_{10}INO_4$ (%): C, 40.13; H, 2.81; I, 35.64; N, 3.90.

[§] In this context, solubility is understood as the maximal amount of PIBX that dissolves *completely* in a given amount of the solvent. The solution saturated with the excess of PIBX can possess a higher concentration (with a pyridine : IBX ratio > 1) due to partial extraction of pyridine from the undissolved PIBX fraction (see further). Low concentrations of pyridine enhance the solubility of PIBX (or IBX) in organic solvents.

strates **9** and **12**, whose oxidation with IBX occurs in anomalous ways[16] and the same anomalies are observed with PIBX.

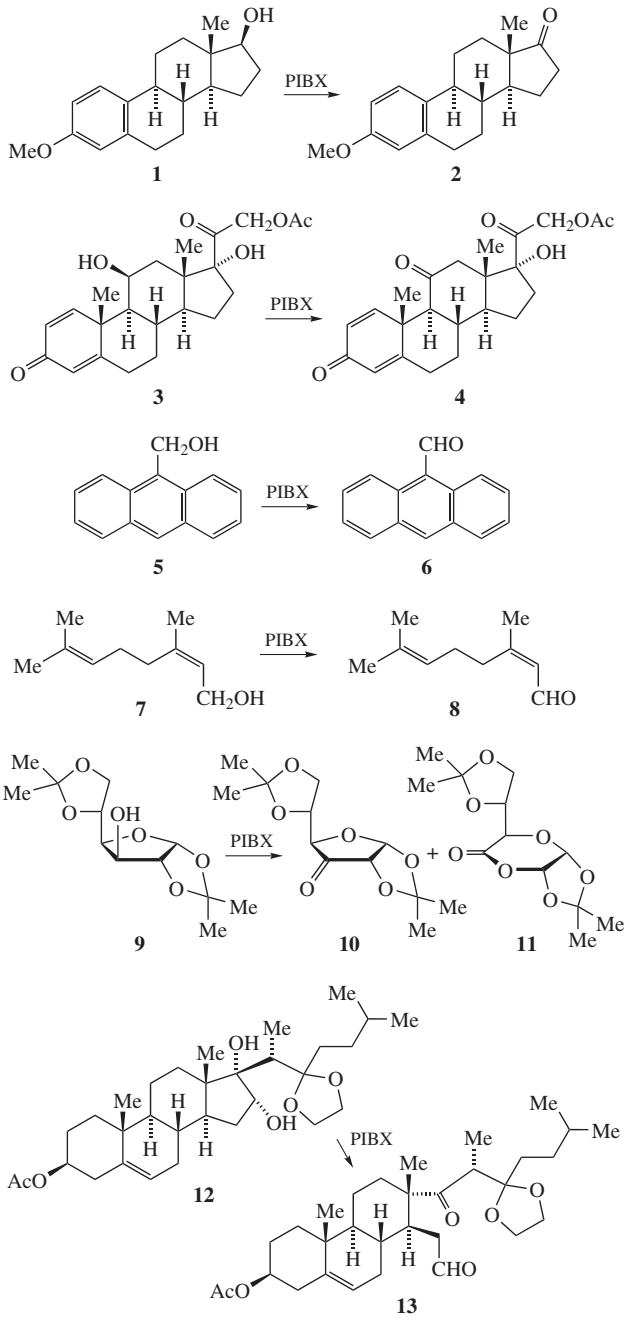


Table 1 Oxidation of alcohols with PIBX in DMF at ambient temperature.

Entry	Alcohol[a]	PIBX (equiv.)	Time/h	Product[b]	Yield (%)[c]
1	**1**	1.2	4	**2**	92
2	**1**	1.5	24[d]	**2**	95[e]
3	**3**	1.2	4	**4**	97
4	**5**	1.2	4	**6**	97
5	**7**	1.2	2.5	**8**	87[f]
6	**9**	3[g]	24	**10** + **11** (2:1)	77[h]
7	**12**	1.6	4	**13**	97[i]

[a] See general procedure,¶ 0.1–1 mmol scale. [b] All the products were individual compounds as judged by TLC and NMR spectra (except for the binary mixture in entry 6) and were identified by comparison with authentic samples or (compounds **10**,[18] **11**[16] and **13**) spectral data.‡‡ [c] Isolated yields. [d] Reaction in THF.†† [e] Under the same conditions, the reaction with IBX provides a 60% conversion. [f] Partial loss of the volatile product during evaporation of solvents. [g] With addition of 3 Å molecular sieves (700 mg per mmol PIBX).[19,§§] [h] The products had the same composition when IBX was used. [i] The same product was formed with IBX.

A considerable difference between PIBX and IBX is observed if THF is used as the solvent. With PIBX oxidation of alcohol **1** in THF is completed in 24 h, whereas IBX provides only a 60% conversion within the same period of time.†† The nearly twice faster reaction with PIBX is very likely to result from the higher solubility of PIBX in organic solvents that in DMF is nearly twice as high as that of IBX (see above).

Dissociation of PIBX on dissolution in DMSO allows us to consider that an IBX solution in DMSO containing some pyridine is equivalent to a PIBX solution. Such *in situ* generated PIBX was already successfully used to perform various oxidative reactions of IBX with acid-labile substrates or products where IBX acidity caused or might cause side processes.[17] In such cases, the use of the neutral PIBX is beneficial.

To conclude, we suggest the readily available PIBX as a convenient substitute for IBX, a widely-used oxidative reagent, at least in the oxidation of alcohols to the corresponding carbonyl compounds. In comparison with IBX, its pyridinium salt (PIBX) is safer, has neutral properties and the same oxidizing ability in polar solvents (DMF, DMSO) and, owing to its higher solubility, has a superior oxidizing ability in THF and potentially in other non-polar solvents.

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¶ *General procedure (similar to the procedure of oxidation with IBX*[1]*).* Crystalline PIBX (1.2–3 molar equiv.) was added to a solution of an alcohol in dry DMF (3–4 ml per mmol PIBX) and the suspension was vigorously stirred at ambient temperature (24–28 °C) using a Teflon-coated magnet for a period of time specified in Table 1 until the alcohol was completely converted (TLC control). During the reactions course, a gradual dissolution of the heavy PIBX precipitate was observed, sometimes to give a transparent solution, followed by the appearance of a light white precipitate of iodosobenzoic acid. The mixture was diluted 5–6-fold with CH_2Cl_2 (or Et_2O, or EtOAc, or another solvent, depending on the polarity of the target product), stirred for 5 min, and the suspension was filtered through a column with Al_2O_3 or silica gel (2 g per mmol of the alcohol). The filtrate was concentrated in a rotary evaporator at < 50 °C, in the end in a vacuum of <5 Torr. The residue left upon evaporation was a carbonyl compound that was pure according to TLC and NMR (or a mixture of products in the case of substrate **9**).

†† These reactions were carried out by the general procedure in which DMF was replaced by THF.

‡‡ *1,2:5,6-Di*-O-*isopropylidene-α-D*-ribo-*hexofuranos-3-ulose* **10**: ^{1}H NMR (500 MHz, $CDCl_3$) (in a mixture with compound **11**) δ: 1.34 (s, 6H, 2Me), 1.436 and 1.45 (2s, 2×3H, 2Me), 4.02–4.04 and 4.10 (m and dd, 1H, C^6H_2, *J* 6.5 and 8.4 Hz), 4.39 (d, 1H, H-2, *J* 4.4 Hz), 4.55 (d, 1H, H-4, *J* 3.5 Hz), 4.66 (td, 1H, H-5, *J* 6.5 and 3.5 Hz), 6.14 (d, 1H, H-1, *J* 4.5 Hz) (*cf.* ref. 18).

1,2:6,7-Di-O-*isopropylidene-3-oxa-α-D*-ribo-*4-heptopyranos-4-ulose* **11**: ^{1}H NMR (500 MHz, $CDCl_3$) (in a mixture with compound **10**) δ: 1.39, 1.442, 1.450 and 1.58 (4s, 4×3H, 4Me), 4.33–4.55 (m, 4H, H-5, H-6, H-7), 5.71 (d, 1H, H-2, *J* 3.8 Hz), 5.88 (d, 1H, H-1, *J* 3.8 Hz) (*cf.* ref. 16).

3β-Acetoxy-17-oxo-22,22-ethylenedioxy-16,17-secocholest-5-en-16-al **13**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.882 and 0.886 (2s, 3H, $C^{26}H_3$, $C^{27}H_3$), 1.01 (s, 3H, $C^{18}H_3$), 1.12 (d, 3H, $C^{21}H_3$, *J* 7.0 Hz), 1.23 (s, 3H, $C^{19}H_3$), 2.03 (s, 3H, OAc), 2.06 (ddd, 1H, H-15a, *J* 3.6, 6.8 and 17.3 Hz), 2.18 (br. dd, 1H, H-15b, *J* 1.9 and 17.3 Hz), 3.37 (q, 1H, H-20, *J* 7.0 Hz), 3.80–3.98 (m, 4H, OCH_2CH_2O), 4.60 (tt, 1H, H-3, *J* 4.8 and 11.4 Hz), 5.34 (br. d, 1H, H-6, *J* 5.2 Hz), 9.77 (br. d, 1H, $C^{16}HO$, *J* 3.1 Hz).

§§ Acceleration of alcohol **9** oxidation by molecular sieves is known.[19]

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