

A Stabilized Formulation of IBX (SIBX) for Safe Oxidation Reactions Including a New Oxidative Demethylation of Phenolic Methyl Aryl Ethers

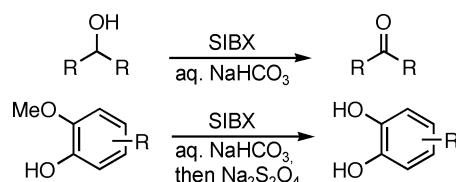
Aurélié Ozanne,[†] Laurent Pouységu,^{†,‡} Dominique Depernet,[§]
Bruno François,[§] and Stéphane Quideau^{*,†,‡}

Institut Européen de Chimie et Biologie, 16 avenue Pey-Berland,
F-33607 Pessac, France, Laboratoire de Chimie des Substances Végétales,
Centre de Recherche en Chimie Moléculaire, Université Bordeaux I,
351 cours de la Libération, F-33405 Talence Cedex, France, and
SIMAFEX, 16 avenue des Fours-à-Chaux, F-17230 Marans, France

s.quideau@iecb-polytechnique.u-bordeaux.fr

Received June 4, 2003

ABSTRACT



R = alkyl, allyl or benzyl group

SIBX is a nonexplosive formulation of IBX that can be used as a suspension in a variety of standard organic solvents such as refluxing EtOAc and THF to oxidize safely alcohols into aldehydes and ketones. The use of hot THF is limited to the oxidation of allylic and benzylic alcohols. Most yields are comparable to those obtained with IBX or DMP. SIBX can also be used to perform oxygenative demethylation of 2-methoxyarens into orthoquinones and catechols.

The utility of hypervalent iodine(V) compounds such as the Dess–Martin periodinane reagent (DMP)¹ and its benziodoxole oxide precursor 2-iodoxybenzoic acid (IBX)^{1b,2} has been amply evidenced by many successful demonstrations of their selectivity in oxidation reactions.^{2b,3} These λ^5 -iodanes have also found uses in many other synthetic transformations^{3c,4} and often constitute environmentally benign alternatives to heavy metal-based systems. However, industrial applications

of DMP and IBX are limited because both reagents suffer from major safety concerns related to their violent decomposition under impact and/or heating.^{2d,5} Modified IBX-like reagents have been introduced as nonexplosive oxidants,^{6,9}

[†] Institut Européen de Chimie et Biologie.
[‡] Laboratoire de Chimie des Substances Végétales.
[§] SIMAFEX.

(1) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
(b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
(2) (a) Hartmann, C.; Meyer, V. *Chem. Ber.* **1893**, *26*, 1727–1732. (b) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.
(c) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272–7276. (d) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.

(3) (a) Vavogliss, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, CA, 1997. (b) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271–1287. (c) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 2812–2814. (d) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001–3003. (e) Surendra, K.; Krishnaveni, N. S.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2003**, *68*, 2058–2059. (f) Wirth, T. *Top. Curr. Chem.* **2003**, *224*, 185–208.

(4) (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523–2584. (b) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258 and previous papers in the same series. (c) Wu, Y.; Huang, J.-H.; Shen, X.; Hu, Q.; Tang, C.-J.; Li, L. *Org. Lett.* **2002**, *4*, 2141–2144. (d) Bose, D. S.; Srivinas, P. *Synlett* **1998**, 977–978. (e) Bose, D. S.; Narsaiah, A. V. *Synth. Commun.* **1999**, *29*, 937–941.
(5) (a) Plumb, J. B.; Harper, D. J. *Chem. Eng. News* **1990**, July 16, 3. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

but their preparation necessitates additional steps.^{6a,b,9} It thus became desirable to find a means of stabilizing IBX to enable its safe utilization in chemical synthesis.

Research conducted at SIMAFEX led to a nonexplosive white-powder formulation of IBX composed of a mixture of benzoic acid (22%), isophthalic acid (29%), and *o*-iodoxybenzoic acid itself (49%).⁷ In this letter, we wish to highlight the performances of this new oxidizing system, which we referred to as SIBX for “Stabilized IBX”, in alcohol and phenol oxidation reactions for comparison with those of IBX and DMP.

We started our investigation by searching for the most appropriate solvent system to accommodate the use of SIBX. Like IBX, SIBX is not soluble in most standard organic solvents, so we initially evaluated its capacity of oxidizing an alcohol in DMSO, in which it readily dissolves^{2b,c} (Table 1, entry 1). In search of another solvent system that would

Table 1. Oxidation of Selected Alcohols with SIBX in NMP or DMSO

entry	alcohol ^a	product	yield (%)
1			73 ^b IBX \Rightarrow 99 ^{2b}
2			86 ^c DMP \Rightarrow 94 ^{1a}
3			70 ^c DMP \Rightarrow 84 ^{1a}
4			87 ^c IBX \Rightarrow 86 ^{3e} –95 ^{3d}

^a All reactions were carried out on a 10-mmol scale at room temperature for 2 h with 1.2 equiv of SIBX. ^b DMSO. ^c NMP.

allow reactions to be performed rapidly at room temperature, *N*-methylpyrrolidone (NMP) was used.⁸ Although SIBX is only sparingly soluble in NMP, oxidation of a selection of primary and secondary alcohols worked well at room temperature on multigram scales (Table 1).

The common perception that IBX must be completely dissolved for expressing its full oxidizing reactivity has recently been proven wrong by More and Finney,^{3d} who observed that suspensions of IBX in heated solutions of piperonyl alcohol (**9**) in common organic solvents furnished the corresponding aldehyde **10** in satisfactory yields.^{3d} We repeated the same solvent optimization with SIBX (Table

2). Our results are for the most part in agreement with More and Finney’s observations.^{3d} Among noteworthy differences is the fact that the oxidation worked very well in THF and toluene. THF actually emerged as the best solvent in this study, affording the highest yield of **10** in the shortest period of time.

Table 2. Solvent Optimization^a

solvent	time (h)	temp (°C)	yield (%)
EtOAc	1.3	77	90
CH ₃ CN	0.5	82	96
acetone	2.0	56	90
THF	0.5	60	99
PhCH ₃	1.5	80	100
CH ₂ Cl ₂	17.0	rt	92
NMP	1.0	rt	68
DMSO ^b	0.5	rt	66

^a All reactions were carried out on a 1.0-mmol scale. ^b SIBX in solution; SIBX in suspension in all of the other reaction solvents used.

Another series of benzylic and allylic alcohols was then submitted to SIBX in suspension in THF at 60 °C to furnish the corresponding aldehydes or ketones (Table 3). Initial

Table 3. SIBX-Mediated Oxidation of Benzylic and Allylic Alcohols

entry	alcohol ^a	product	yield (%)
1			87 IBX \Rightarrow 90 ^{3e}
2			85 IBX \Rightarrow 97 ^{2b} DMP \Rightarrow 91 ^{1a}
3			92 mIBX \Rightarrow 81 ⁹
4			100 IBX \Rightarrow 90 ^{3d}
5			82 ^b IBX \Rightarrow 95 ^{3d}

^a Reactions were carried out in THF on a 0.5- to 1.0-mmol scale at 60 °C for 0.5–1 h with 1.2 equiv of SIBX per alcohol function. ^b In THF/DMSO (9:1) at room temperature.

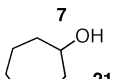
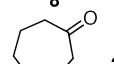
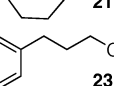
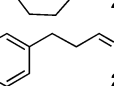
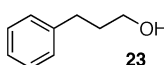
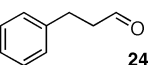
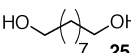
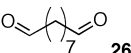
attempts to oxidize geraniol (**19**) under these conditions, however, led to the formation of an insoluble white gel from which no product could be extracted. Geranial (**20**) was nevertheless obtained in a high yield by performing the oxidation in a 9:1 THF/DMSO solvent mixture at room

(6) (a) Stickley, S. H.; Martin, J. C. *Tetrahedron Lett.* **1995**, 36, 9117–9120. (b) Zhdankin, V. V.; Smart, J. T.; Zhao, P.; Kiprof, P. *Tetrahedron Lett.* **2000**, 41, 5299–5302. (c) Zhdankin, V. V.; Koposov, A. Y.; Netzel, B. C.; Yashin, N. V.; Rempel, B. P.; Ferguson, M. J.; Tykwinski, R. R. *Angew. Chem.* **2003**, 115, 2244–2246.

temperature (Table 3, entry 5). In all cases, yields were comparable with those obtained with DMP or IBX (Table 3). Although these SIBX-mediated oxidations are usually not sensitive to air or moisture, all reactions were carried out under nitrogen. This precaution was especially useful for the conversion of benzyl alcohol (**13**) into benzaldehyde (**14**) (Table 3, entry 2), which is otherwise readily oxidized into benzoic acid.^{3d} This over-oxidation was particularly problematic, since one of the IBX stabilizers is benzoic acid. Oxidation of the vicinal diol **15** occurred without oxidative cleavage to furnish the desired diketone **16** in 92% yield (Table 3, entry 3).⁹

We then turned our attention to the oxidation of a selection of aliphatic alcohols in THF (Table 4). Cycloheptanol (**21**)

Table 4. SIBX-Mediated Oxidation of Aliphatic Alcohols

entry	alcohol ^a	product	yield (%)
1			93 ^b
2			77 ^c IBX \Rightarrow 98 ^{4b}
3			93
4			77 DMP \Rightarrow 92 ¹²

^a Reactions were carried out in EtOAc on a 0.5- to 1.0-mmol scale at reflux temperature for 2–6 h with 1.2 equiv of SIBX per alcohol function.

^b See Table 1 for comparison; a large-scale reaction was also performed overnight on 10 g (i.e., 64 mmol) of **7** to furnish **8** in 90%. ^c In THF at 60 °C for 0.5 h.

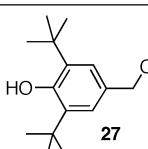
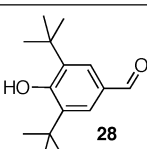
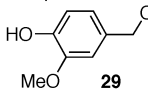
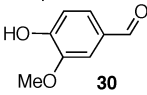
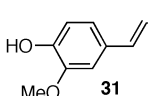
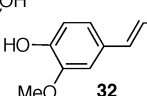
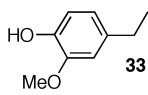
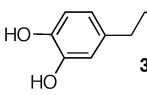
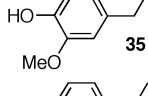
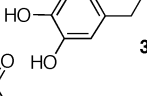
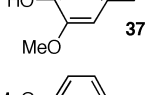
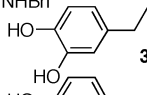
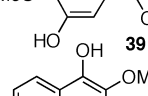
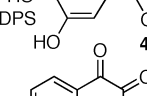
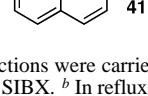
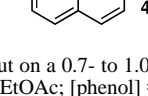
was oxidized into cycloheptanone (**22**) in a good yield of 77% in only 30 min in THF at 60 °C (Table 4, entry 2). Of particular note is the fact that no dehydrogenation product was observed. This is in contrast to observations made by Nicolaou et al.^{4b,10} on the formation of α,β -unsaturated carbonyl compounds from saturated alcohols with use of IBX in DMSO. Here, even when performing the reaction in DMSO at 60 or 90 °C with 2 to 3 equiv of SIBX,^{10b} only cycloheptanone (**22**) was observed. Other secondary and primary alcohols such as menthol (**7**), 3-phenylpropanol (**23**), and 1,9-nonanediol (**25**) were not converted in good yields into carbonyl compounds under the aforementioned conditions, because SIBX reacted with THF. We indeed verified that SIBX (100 mg in 1.0 mL of the indicated solvent under nitrogen) is not stable over a prolonged period of time either in THF at 60 °C or in toluene at 80 °C. Ring-opened aldehydic products were observed in hot THF after 1 h and SIBX was consumed over 2 h in hot toluene to cleanly furnish benzaldehyde. The SIBX formulation is thus no different than straight IBX in the sense that solvent oxidation may occur,^{3d,9} but this problem appears limited to the less reactive substrates such as aliphatic primary alcohols.^{3f,11} Aliphatic alcohols were thus oxidized by using 1.2 equiv of SIBX in refluxing ethyl acetate (Tables 2 and 4), a solvent also selected for IBX-mediated oxidations by More and Finney.^{3d} Under these conditions, **7** was cleanly oxidized into

8 in 6 h (Table 4, entry 1), and **23** and **25** into **24** and **26**¹² over 2 h in 93% and 77% yield, respectively (Table 4, entries 3 and 4).

The use of suspensions of SIBX in inert solvents such as EtOAc (Table 4), or even in THF in the case of allylic and benzylic alcohol oxidations (Table 3), shares the technical advantages already noted for IBX under similar reaction conditions.^{3d} First, no silica gel chromatography was required to purify products, for the carboxylic acid stabilizers are efficiently removed by slightly basic aqueous washes. Second, the main IBX byproduct, that is iodosylbenzoic acid (IBA), can be recovered by filtration and recycled via oxidation into IBX with oxone.^{3d}

Our continuing interest in the oxidation chemistry of arenols¹³ then led us to examine the behavior of phenolic alcohols in the presence of SIBX (Table 5). The 4-hy-

Table 5. SIBX-Mediated Oxidation of Phenolic Alcohols

entry	alcohol ^a	product	time (h)	yield (%)
1 ^b			1.5	94
2 ^c			6	32
3 ^c			7	18
4 ^c			16	77 ^d
5 ^c			12	89 ^d
6 ^c			16	41 ^d
7 ^c			16	97 ^d
8 ^c			60	83

^a Reactions were carried out on a 0.7- to 1.0-mmol scale with 1.2 to 2.1 equiv of SIBX. ^b In refluxing EtOAc; [phenol] = 0.14 M. ^c In THF at room temperature; [phenol] = 0.05 M. ^d Workup with aq. Na₂S₂O₄.

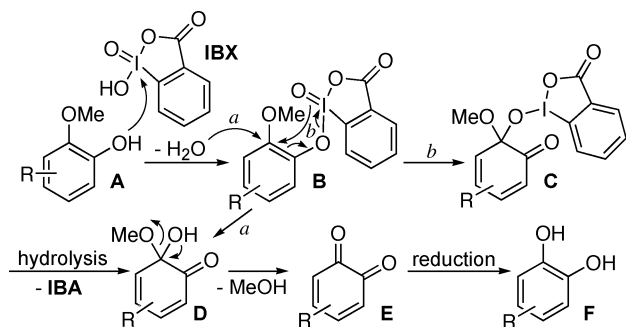
droxymethylphenol **27** was cleanly oxidized into the aldehyde **28** in refluxing EtOAc (entry 1). The steric demand of the two *tert*-butyl groups adjacent to the phenolic hydroxyl group certainly prevented any reaction at this locus. Furthermore, the aldehyde function likely deactivated the arenol ring toward any secondary phenol oxidation. Phenols bearing electron-withdrawing groups such as carbonyl-based and

nitro functions, are known to resist IBX oxidations.¹⁴ More electron-rich 4-hydroxymethyl-2-methoxyphenols such as **29** and its vinylogous derivative **31** led to vanillin (**30**) and coniferaldehyde (**32**) in moderate yields (entries 2 and 3). These aldehydes also failed to undergo any oxidation with SIBX, so the inefficiency of their preparation from **29** and **31** is probably due to a competing phenolic oxidation prior to the transformation into aldehydes.

The outcome of such a phenolic oxidation could not be delineated from the reactions with **29** and **31**, but we surmised that a formal demethylation of these 2-methoxyphenols into orthoquinones could be operational in a manner similar to that can be achieved with periodates.¹⁵ This hypothesis was verified by treating eugenol (**33**) with SIBX in THF at room temperature for 16 h. A mildly basic hydrolysis of the reaction mixture, which was immediately followed by a reductive workup with Na₂S₂O₄ to prevent any degradation of the reactive orthoquinone product, furnished catechol **34** in a remarkable 77% yield (entry 4).

A mechanistic description of this IBX-mediated demethylation is depicted in Scheme 1. We view this reaction as an

Scheme 1



ionic process during which phenol **A** first adds to the iodine(V) center of IBX to give the λ^5 -iodanyl intermediate **B**. The molecule of water hence eliminated could serve as an oxygen source, but this route (a) would produce directly a reactive orthoquinone **E**. The intramolecular delivery of an oxygen from the λ^5 -iodanyl moiety of **B** is the route (b) we favor because it involves the formation of a more stable λ^3 -iodanyl

orthoquinol monoketal **C** and it better supports the excellent regioselectivity observed in this oxygenative demethylation. The same chemistry rationalizes the IBX-mediated ortho-oxygenation of phenols recently described by Pettus et al.^{14a} and by us.^{14b} Four other examples of this new demethylation reaction are shown in Table 5 (entries 5–8). Dehydroeugenol (**35**) was converted into catechol **36** in 89% yield (entry 5). An excellent yield was obtained in the case of the demethylation of the silyloxy derivative **39** without loss of the silyl group (entry 7). Finally, the demethylation of 2-methoxynaphthol (**41**) gave rise to the stable naphthoquinone **42**, which could be isolated as such in high yield (entry 8). Another aspect of the versatility of IBX has thus been unveiled by performing these SIBX-mediated oxygenative demethylations of 2-methoxyphenols into orthoquinones and catechols.

Acknowledgment. We wish to thank SIMAFEX and the Association Nationale de la Recherche Technique (CIFRE No. 301/2002) for their financial support and Aurélie Ozanne's graduate research assistantship.

Supporting Information Available: Experimental details and characterization data for all compounds. This material is available free of charge via Internet at <http://pubs.acs.org>.

OL0349965

(7) Depernet, D.; François, B. WO 02/057210 A1, PCT/FR02/00189, US 2002/0107416; *Chem. Abstr.* **2002**, 137, 109123. Explosive tests were negative in compliance with the 92/69-A14 EEC directive. SIBX is available at SIMAFEX, contact dominique.depernet@simafex.com or benoitj@simafex.com for further inquiries.

(8) Frigerio, M.; Santagostino, M.; Sputore, S. EP 0/658/533 A1; *Chem. Abstr.* **1995**, 123, 285513.

(9) mIBX = modified IBX, see: Thottumkara, A. P.; Vinod, T. K. *Tetrahedron Lett.* **2002**, 43, 569–572.

(10) (a) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, 41, 993–996. (b) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, 122, 7596–7597.

(11) Lei, Z.; Denecker, C.; Jegasothy, S.; Sherrington, D. C.; Slater, N. K. H.; Sutherland, A. J. *Tetrahedron Lett.* **2003**, 44, 1635–1637.

(12) Roels, J.; Metz, P. *Synlett* **2001**, 6, 789–790.

(13) (a) Quideau, S. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 539–573. (b) Quideau, S.; Pouységu, L. *Org. Prep. Proc. Int.* **1999**, 31, 617–680. (c) Quideau, S.; Feldman, K. S. *Tetrahedron: Symposium-in-Print* **2001**, 57, ix–x.

(14) (a) Magdziak, D.; Rodríguez, A. A.; Van De Water, R. W.; Pettus, T. R. *Org. Lett.* **2002**, 4, 285–288. (b) Quideau, S.; Pouységu, L.; Deffieux, D.; Ozanne, A.; Gagnepain, J.; Fabre, I.; Oxoby, M. *ARKIVOC* **2003**, 6, 106–119.

(15) (a) Adler, E.; Hernestam, S. *Acta Chem. Scand.* **1955**, 9, 319–334.

(b) Adler, E.; Magnusson, R. *Acta Chem. Scand.* **1959**, 3, 505–519.