Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 49 (2008) 80–84

Modified *o*-methyl-substituted IBX: room temperature oxidation of alcohols and sulfides in common organic solvents

Jarugu Narasimha Moorthy,* Nidhi Singhal and Kalyan Senapati

Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India

Received 23 August 2007; revised 22 October 2007; accepted 2 November 2007
Available online 6 November 2007

Abstract— *o*-Methyl-substituted **Me-IBX** is the first modified analog of IBX that oxidizes alcohols in common organic solvents at room temperature, due to a composite of two factors, that is, low solubility and hypervalent twisting-promoted rate enhancement. Furthermore, the reagent is efficient for selective oxidation of sulfides to sulfoxides, a transformation that otherwise occurs only sluggishly with standard IBX. The facile synthetic accessibility and its mild as well as non-hazardous nature render **Me-IBX** a stable equivalent of Dess–Martin periodinane reagent in organic oxidations.

IBX, the precursor of the well-known Dess–Martin periodinane (DMP) reagent, has gained importance as a convenient, mild and non-toxic oxidation reagent in contemporary organic oxidation chemistry.[1] Its virtual insolubility in common organic solvents prevented its application in oxidation reactions for almost a century. Frigerio and Santagostino[1c] showed for the first time in 1994 that IBX can be employed in DMSO for the conversion of alcohols to carbonyl compounds. In recent years, Nicolaou and co-workers[1d–n] have uncovered a range of transformations mediated by IBX in DMSO at elevated temperatures. This has led to a sudden surge of interest in IBX oxidations.[1o–s] While advantages such as the ease of handling, its environmentally benign attributes and ready accessibility render IBX a reagent of choice, its insolubility in common organic solvents and explosive nature[2] constitute undesirable and debilitating impediments. The insolubility has been traced to the occurrence of strong halogen (C–I···O=C) and hydrogen (O–H···O) bonds in its crystal lattice.[3] As the solvation energy must overcome the strong lattice forces involving halogen and hydrogen bonds, IBX is soluble only in a highly polar and aprotic solvent such as DMSO, which is not a preferred solvent. To overcome the limitations as to its insolubility and explosive nature, a variety of IBX analogs (Chart 1)[4] have been reported in the literature by Dess and Martin,[5] Thottumkara and Vinod,[6] Zhdankin et al.[7] and others.[8] In fact, IBX itself has been shown to oxidize alcohols in common organic solvents when heated at reflux.[9] However, this protocol suffers from the disadvantage that 3 equiv of the reagent is employed for oxidation of each hydroxy group and the reaction is conducted at the reflux temperature of the solvent.

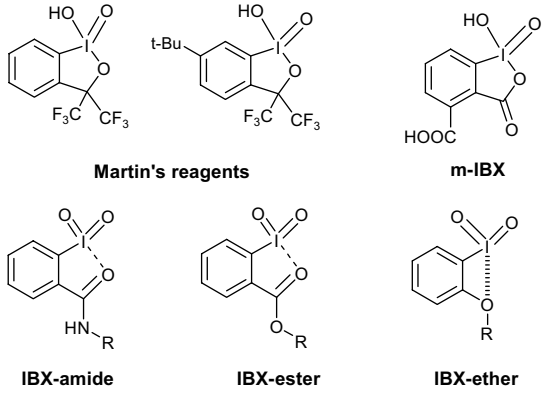


Chart 1. Various modified analogs of IBX.

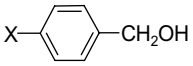
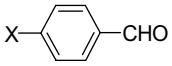
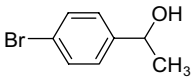
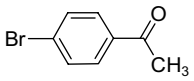
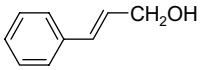
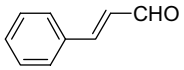
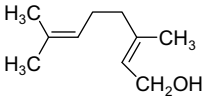
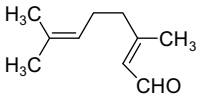
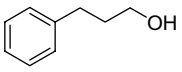
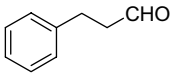
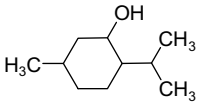
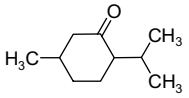
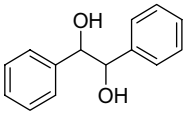
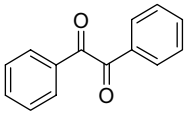
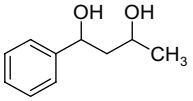
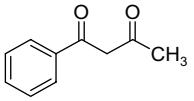
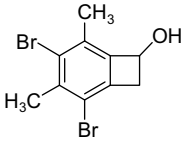
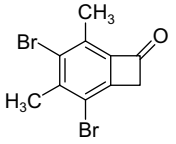
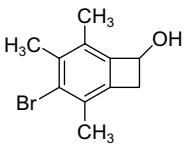
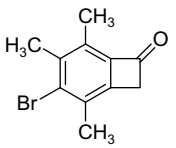
In continuation of our recent studies on IBX oxidations,[10] we wished to explore a different approach that avoids or suppresses the strong intermolecular forces operative in the crystal lattice of IBX such that it becomes soluble in common organic solvents. We surmised that the substitution of a bulky group at the

* Corresponding author. Tel.: +91 512 2597438; fax: +91 512 2597436; e-mail: moorthy@iitk.ac.in

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.013

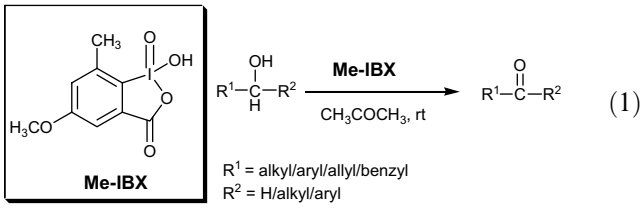
position *ortho* to the iodine atom in IBX might render intermolecular interactions in the crystal lattice weaker, if not completely suppressed. This proposition appeared compelling in the light of the 100-fold rate enhancement predicted *theoretically* for an *o*-methyl substituent due to the so-called '*hypervalent twisting*'.[11] We thus targeted the synthesis of *o*-methyl-substituted **Me-IBX**, and the exploration of its reactivity at rt in common organic solvents; the rationale for the choice of **Me-IBX** was—(i) it could be readily prepared starting from 3,5-dimethylphenol and (ii) the *p*-methoxy group may contribute to increasing the solubility in organic solvents. Herein, we report that the *modified* **Me-IBX** oxidizes a variety of alcohols in common organic solvents at rt with short reaction times (Eq. 1). Further, we show that **Me-IBX** also oxidizes sulfides to sulfoxides, a conversion that

Table 1. Results of oxidation of alcohols with **Me-IBX**[a]

Entry	Substrate	Time (h)	Product	Yield[b] (%)
				
1	X = Br	0.2		98
2	X = NO_2	0.2		98
3	X = OCH_3	0.2		95
4		0.2		98
5		0.2		91
6		0.2		80
7		0.6		81
8		1.5		90
9	Pregnenolol acetate	1.0	Pregnenolone acetate	98
10	Cholestanol	2.0	Cholestanone	97
11		0.5[c]		90
12		12.0[c]		98
13		0.5		93
14		0.5		90

[a] All oxidations were performed in acetone as a solvent at rt by employing 1.5 equiv of the reagent, unless mentioned otherwise.
[b] Isolated yields.
[c] 3.0 equiv of the reagent.

does not otherwise occur with standard IBX in the absence of added acid.[12]

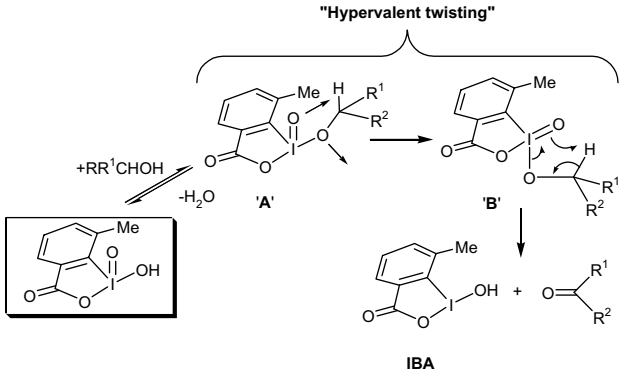


(1)

The reagent **Me-IBX** was conveniently prepared as follows. Iodination followed by methylation of 3,5-dimethylphenol yielded 4-iodo-3,5-dimethylanisole in a 66% yield. $KMnO_4$ oxidation in pyridine–water led to a 2:3 mixture of 2-iodo-3-methyl-5-methoxybenzoic acid and 2-iodo-5-methoxyisophthalic acid in 80% yield. Oxidation of the former with oxone yielded **Me-IBX** in 80% yield.[13]

The oxidation of *p*-bromobenzyl alcohol to the corresponding aldehyde was initially examined as a representative case in a variety of solvents such as CH_3COCH_3, $CHCl_3$, EtOAc, CH_3CN and THF. In all of these solvents, the oxidation occurred efficiently upon stirring the alcohol with **Me-IBX** at rt (25–30 °C); while the reaction went to completion within 10 min in CH_3COCH_3, CH_3CN, EtOAc and THF (^1H NMR spectroscopy), it took 90 min when $CHCl_3$ was employed as the solvent. Thus, with acetone as the solvent, a variety of alcohols were found to be oxidized to the corresponding carbonyl compound with 1.5 equiv of the reagent for each of the hydroxy functionalities.[14] A perusal of the results in Table 1 shows that a broad range of alcohols were smoothly oxidized in quantitative yields and with short reaction times; the only exception was a 1,3-diol (entry 12).

How do the oxidations occur at room temperature? Notably, the reagent is not entirely soluble in common organic solvents and was, indeed, employed as a suspension. Whereas the solubility of the standard IBX in dry acetone, under saturated conditions, was found to be ca. 0.02 g/100 mL, the reagent **Me-IBX** was found to exhibit a ca. 5–6-fold higher solubility. Presumably, this low, yet respectable solubility in conjunction with the *hypervalent twisting*-promoted rate enhancement, which was predicted by Su and Goddard[11] from theoretical calculations, augment the conversion of alcohols progressively to the corresponding carbonyl compounds. The fact that the reactions were complete for some cases in a few minutes points to the very high reactivity of **Me-IBX**; it should be emphasized that standard IBX does not work except in DMSO at room temperature even after prolonged reaction times. The hypervalent twisting, as described by Su and Goodard[11] is a coordinated motion of the ligands attached to iodine driven by the necessity of generating a stable and planar form of IBA from its precursor alkoxyperiodinane intermediate. Accordingly, the alkoxyperiodinane intermediate 'A' (Scheme 1), formed subsequent to exchange of the hydroxyl group with an alcohol, must undergo a rate-determining twisting motion to its isomeric structure

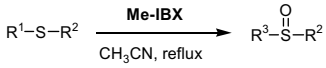


Scheme 1. Rate-determining 'hypervalent twisting' of Goddard et al. involved in the oxidation of alcohols with **Me-IBX**.

'B' to eliminate the carbonyl compound to form IBA. Substitution of a methyl group at the *ortho* position has been predicted to accelerate the twisting motion due to the repulsive steric interactions, which would be relieved once the motion is complete.

The higher reactivity of *o*-methyl-substituted IBX is revealed in the oxidations of sulfides to sulfoxides. The latter conversion has been reported to occur only sluggishly with standard IBX in the absence of any acid/additive.[12] Remarkably, **Me-IBX** was found to oxidize sulfides to sulfoxides in CH_3CN under reflux conditions (Eq. 2);[15] overoxidation to sulfones was not observed. The results of oxidation of a range of sulfides are collected in Table 2. A plausible mechanism for the sulfide to sulfoxide oxidation is shown in Scheme 2. The isolation of diphenyl disulfide (entries 1 and 3) and aldehyde (entry 4) during the oxidation of some cases suggest an electron transfer-mediated mechanistic pathway (Scheme 2). Studies on the reactivity of a variety of *o*-substituted IBX derivatives are currently underway in our laboratories.

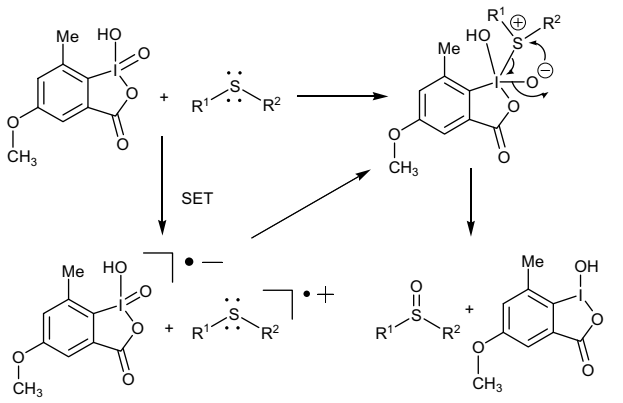
Table 2. Results of oxidation of sulfides to sulfoxides with **Me-IBX**[a]



(2)

Entry	Substrate		Time (h)	Yield[b] (%)
	R^1	R^2		
1	Ph	Me	0.5	70[c]
2	Ph	Et	0.4	90
3	Ph	$PhCH_2$	0.5	40[c]
4	Ph	*p*-BrC6H4CH2	0.2	85[d]
5	Ph	Ph	17.0	>90[e]
6	Ph	*p*-OMePh	1.0	85
7	Ph	*p*-NO_2Ph	1.0	>90[f]
8	*n*-C_8H_{17}	C_2H_5	0.3	>90[g]

[a] All oxidations were performed by employing 1.1 equiv of the reagent.
[b] Isolated yields.
[c] PhS–SPh was isolated as a minor product.
[d] ArCHO also formed as a minor product.
[e] Conv. 60–80%.
[f] Conv. 28%.
[g] At rt (25–30 °C).



Scheme 2. A plausible mechanism for oxidation of sulfides to sulfoxides.

In summary, we have shown that a variety of alcohols are oxidized in a facile manner to the corresponding carbonyl compounds at rt with a *modified o*-methyl-substituted IBX; we believe that limited solubility of **Me-IBX** at room temperature in common organic solvents in conjunction with theoretically predicted *hypervalent twisting*-promoted rate enhancement[11] augment the conversion of alcohols to the corresponding carbonyl compounds. To the best of our knowledge, **Me-IBX** constitutes the first *modified* analog of IBX that oxidizes alcohols in common organic solvents at rt. Also, the reagent is efficient for the selective oxidation of sulfides to sulfoxides. Given its facile synthetic accessibility from a cheap starting material, **Me-IBX** may constitute a stable equivalent of the DMP reagent for oxidations.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.013.

Acknowledgements

We thank the Department of Science and Technology, India for the financial support. N.S. is grateful to CSIR, India for a senior research fellowship.

References and notes

1. (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **2002**, *102*, 2523; (b) Ladziata, U.; Zhdankin, V. V. *ARKIVOC* **2006**, *9*, 26; (c) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019; (d) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596; (e) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L. *Angew. Chem., Int. Ed.* **2000**, *39*, 625; (f) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2001**, *123*, 3183; (g) Nicolaou, P. S.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2678; (h) Nicolaou, K. C.; Baran, P. S.; Remo, K.; Zhong, Y.-Li.; Sugita, K.; Zou, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 202; (i) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233; (j) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245; (k) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993; (l) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Scott, T. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 996; (m) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4077; (n) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192; (o) Ngouansavanh, T.; Zhu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3495; (p) Kirsch, S. F. *J. Org. Chem.* **2005**, *70*, 10210; (q) Crone, B.; Kirsch, S. F. *Chem. Commun.* **2006**, 764; (r) Ngouansavanh, T.; Zhu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3495; (s) Arote, N. D.; Bhalerao, D. S.; Akamanchi, K. G. *Tetrahedron Lett.* **2007**, *47*, 3651.
2. Plumb, B.; Harper, D. J. *Chem. Eng. News* **1990**, 3.
3. (a) Gougoutas, J. Z. *Cryst. Struct. Commun.* **1981**, *10*, 489; (b) Stevenson, P. J.; Treacy, A. B.; Nieuwenhuyzen, M. *J. Chem. Soc., Perkin Trans. 2* **1997**, 589.
4. Most of these modified analogs of IBX work efficiently for reactive benzylic alcohols. In contrast, the oxidation of aliphatic alcohols occurs over long durations.
5. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
6. Thottumkara, A. P.; Vinod, T. K. *Tetrahedron Lett.* **2002**, *41*, 569.
7. (a) Zhdankin, V. V. *Curr. Org. Synth.* **2005**, *2*, 121; (b) Zhdankin, V. V.; Smart, J. T.; Zhao, P.; Kiprof, P. *Tetrahedron Lett.* **2000**, *41*, 5299; (c) Zhdankin, V. V.; Koposov, A. Y.; Netzel, B. C.; Yashin, N. V.; Rempel, B. P.; Ferguson, M. J.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 2194; (d) Zhdankin, V. V.; Litvinov, D. N.; Koposov, A. Y.; Ferguson, M. J.; McDonald, R.; Tykwinski, R. R. . *Chem. Commun.* **2004**, 106; (e) Zhdankin, V. V.; Koposov, A. Y.; Litvinov, D. N.; Ferguson, M. J.; McDonald, R.; Luu, T.; Tykwinski, R. R. *J. Org. Chem.* **2005**, *70*, 6484; (f) Koposov, A. Y.; Zhdankin, V. V. *Synthesis* **2005**, 22; (g) Koposov, A. Y.; Karimov, R. R.; Geraskin, I. M.; Nemykin, V. N.; Zhdankin, V. V. *Org. Lett.* **2006**, *71*, 8452.
8. (a) Ozanne, A.; Pouysegu, L.; Depernet, D.; Francois, B.; Quideau, S. *Org. Lett.* **2003**, *5*, 2903; (b) Ozanne, A.; Quideau, S. *Tetrahedron Lett.* **2006**, *47*, 5869.
9. More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001.
10. Moorthy, J. N.; Singhal, N.; Senapati, K. *Org. Biomol. Chem.* **2007**, *5*, 767, and references therein.
11. Su, J. T.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2005**, *127*, 14146.
12. Shukla, V. G.; Salgaonkar, P. D.; Akamanchi, K. G. *J. Org. Chem.* **2003**, *68*, 5422.
13. *Preparation of* **Me-IBX**. To a solution of 2-iodo-3-methyl-5-methoxybenzoic acid (4.2 g, 14.4 mmol) in 50.0 mL of H_2O was added 13.3 g (21.6 mmol) of oxone. The resultant mixture was stirred at 70 °C for 6.0 h. The solid precipitate was filtered and dried under vacuum to afford 3.73 g (80%) of a hypervalent iodine compound which was confirmed by spectroscopic techniques as a modified **Me-IBX**; IR (KBr) cm^{-1} 3462, 1665, 733; ^1H NMR (DMSO-d_6, 400 MHz) δ 2.72 (s, 3H), 3.86 (s, 3H), 7.14 (s, 1H), 7.35 (s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 100 MHz) δ 20.0, 55.9, 112.8, 123.3, 135.8, 138.2, 141.4, 161.8, 167.4; ESI-MS (M−H) Calcd for $C_9H_8IO_5$ 322.9417; found 322.9416.
14. *General procedure for oxidation of alcohols with* **Me-IBX** *in acetone.*[16] **Me-IBX** (1.5 equiv) in 10.0 mL of acetone was stirred for 5–10 min, and to this mixture 1–2 mmol of the alcohol was introduced. The reaction mixture was stirred for appropriate duration (see Table 1). The progress of the reaction was monitored by TLC analysis. After comple-

tion of the reaction, the solid material from the reaction mixture was filtered. Concentration of the filtrate followed by silica gel column chromatography led to isolation of the pure oxidation product.

15. *General procedure for oxidation of sulfides with* **Me-IBX** *in acetonitrile.*[16] In a typical experiment, 1–2 mmol of the sulfide in 10.0 mL of acetonitrile was stirred for a few min, and to this mixture 1.1 equiv of the modified **Me-IBX** was introduced. The reaction mixture was heated at reflux for the appropriate time (see Table 2). The progress of the reaction was monitored by TLC analysis. After completion of the reaction, the reaction mixture was treated with $NaHCO_3$ and brine. The organic layer was dried over anhyd Na_2SO_4 and solvent removed in vacuo. Silica gel column chromatography of the crude mixture yielded the pure product, which was characterized by spectroscopic data.
16. Standard IBX is reported to explode, cf. Ref. 2. We have not observed such attributes for **Me-IBX** even at acetonitrile reflux.