ORGANIC LETTERS

2002
Vol. 4, No. 17
3001−3003

A Simple and Advantageous Protocol for the Oxidation of Alcohols with *o*-Iodoxybenzoic Acid (IBX)

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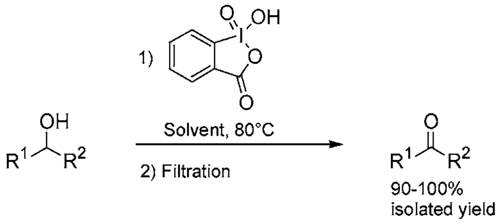
Received June 26, 2002

ABSTRACT



An efficient, user-friendly procedure for the oxidation of alcohols using IBX is described. Simply heating a solution of the alcohol in the presence of suspended IBX followed by filtration and removal of the solvent gives excellent yields of the corresponding carbonyl compounds. We illustrate this procedure with a panel of primary and secondary alcohol substrates and note that it allows recycling and reuse of the oxidant.

IBX (*o*-iodoxybenzoic acid) has gained great popularity as a mild oxidant for the conversion of alcohols to aldehydes or ketones.[1,2] IBX is virtually insoluble in most organic solvents, and the perception that solubility is a prerequisite for reactivity accounts for the great length of time between the discovery of IBX and the first practical applications of it in DMSO (the only solvent in which it does dissolve).[3,4] While not entirely inconvenient, the limitations of DMSO as a solvent are apparent and are sufficient to have motivated two independent syntheses of solid-phase analogues of IBX (polystyrene- and silica-bound).[5] In each case, the authors correctly note that these solid-phase reagents expand the range of viable solvents, simplify separation of oxidation byproducts, and facilitate recovery and reuse of the oxidant. We wish to point out that, in contrast to the dominant notion, IBX is an effective heterogeneous oxidant in most organic solvents. Indeed, the limited solubility of IBX makes it a de facto solid-phase reagent, with all of the commensurate benefits.

We have found that, at elevated temperatures, IBX is sufficiently soluble in most organic solvents to permit clean oxidation of alcohols to the corresponding aldehydes and ketones (Tables 1 and 2).[6,7,8,9] The primary differences

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[1] (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019−8022. (b) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272−7276. (c) De Munari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996**, *61*, 9272−9279. See also ref 2a.

[2] IBX has also found use in several other oxidative transformations. For an overview, see: (a) Wirth, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2812−2814. For more recent developments, see: (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, W. K.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233−2244. (c) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245−2258.

[3] IBX was first prepared over 100 years ago: Hartman, C.; Mayer, V. *Chem. Ber*. **1893**, *26*, 1727.

[4] Prior to its use as a terminal oxidant in its own right, IBX was identified as a valuable precursor to the Dess−Martin periodinane: Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287, and references therein.

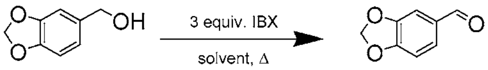
[5] (a) Mülbaier, M.; Giannis, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4393−4394. (b) Sorg, G.; Mengel, A.; Jung, G.; Rademan, J. *Angew. Chem., Int. Ed.* **2001**, *39*, 4395−4397.

[6] Caution! IBX, like other hypervalent iodine oxidants, can explode on impact or heating. See: Plumb, J. B.; Harper, D. J. *Chem. Eng. News* **1990**, *68* (29), 3.

[7] The use of THF leads to solvent oxidation as the primary reaction, affording only small amounts of the desired aldehyde. The use of toluene leads to intractable dark-colored reactions; we suspect that both IBX decomposition and toluene oxidation are involved, although IBX does not oxidize toluene in EtOAc.

10.1021/ol026427n CCC: $22.00

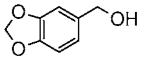
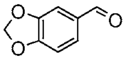
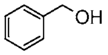
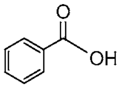
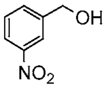
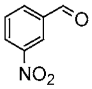
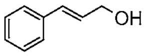
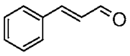
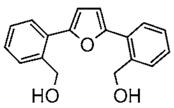
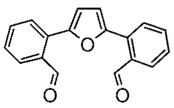
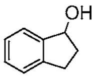
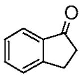
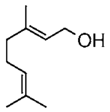
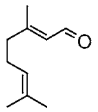
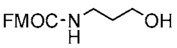
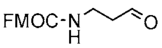
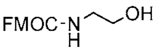
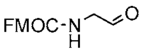
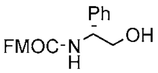
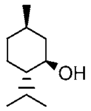
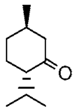
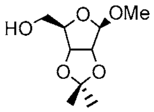
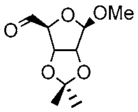
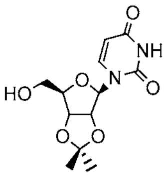
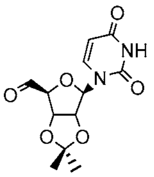
Table 1. Solvent Optimization[a]



solvent	yield(%)[b]	time	temp (°C)
EtOAc	90	3.25 hr	80
$CHCl_3$	80	6.5 hr	55
DCE	90	3 hr	80
acetone	100	45 min	55
PhH	91	6.5 hr	80
CH_3CN	94	25 min	80
THF	0[c]	—	80
$PhCH_3$	0[c]	—	80

[a] All reactions carried out on 1 mmol scale. [b] Isolated yield. [c] Solvent oxidation observed.

Table 2. Substrate Scope

entry	alcohol	product	Yield(%)
1			90
2			100[b,c]
3			90
4			90
5			100[d]
6			100[e]
7			95[f]
8			100
9			100
10		decomp.	0[b]
11			95
12			93[g]
13			90[g]

[a] All oxidations were carried out with 3 equiv of IBX in EtOAc at 80 °C, unless otherwise noted. [b] See text. [c] NMR yield. [d] Reaction performed in 2:1 EtOAc/acetone. [e] 85% conversion. [f] Reaction performed in 1,2-DCE. [g] Reaction performed in CH_3CN.

between solvents are their stability to IBX and the slight solubility (or lack thereof) of the IBX-derived byproducts. We regard EtOAc and DCE as the solvents of choice because they are inert and all byproducts are insoluble at room temperature, such that no purification is required beyond simple filtration. Reactions in several other solvents provided higher yields and shorter reaction times, but required chromatographic purification. The oxidation proceeds well with as few as 1.1 equiv of IBX, but an increased reaction rate is observed with excess oxidant. As a matter of convenience, we settled on 3 equiv to examine the solvent and substrate scope of the oxidation.

This protocol for the use of IBX is broadly applicable and insensitive to the presence of air or moisture. Virtually every alcohol investigated was converted to the corresponding carbonyl compound in >90% yield and substantially free of impurities by ^{1}H NMR and TLC analysis (Table 2) with two exceptions.[10] The first exception was benzyl alcohol (Table 2, entry 2) which, for reasons still under investigation, was quantitatively oxidized to benzoic acid under our reaction conditions.[11] Oxidation of Fmoc-phenylglycinol (Table 2, entry 10), the second exception, leads to consumption of starting material without formation of isolable product, presumably due to instability of the α-aminoaldehyde. Note, however, that Fmoc-glycinal and unstable ribose- and uridine-derived aldehydes are isolated in excellent yield and purity. Also worthy of mention is the clean oxidation of menthol to menthone (Table 2, entry 11), which was not accomplished efficiently with either of the solid-phase IBX variants.[5] Significantly, this protocol is also amenable to

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(8) We cannot exclude the possibility that these oxidations occur at the interface of solvent and undissolved IBX. However, three points argue against this: the oxidation is independent of apparent IBX morphology, a solvent dependence is observed, and yields are reproducibly high.

(9) An early report (ref 1b) describes a single instance in which IBX in THF oxidizes benzil to benzoin.

(10) The alcohols in Table 2 are commercially available and were used as received, with the following exceptions. Entry 5: Prepared by Stille coupling of 2,5-bis(trimethylstannyl)furan with *o*-iodobenzyl alcohol (Fang, A. G., Finney, N. S., unpublished results). Entries 9, 10: Prepared by reaction of amino alcohol with 1 equiv of FmocOSu. Entry 12: Prepared according to Leonard, N. J.; Carraway, K. L. *J. Heterocycl. Chem.* **1966**, *3*, 485.

(11) Benzaldehyde is also oxidized to benzoic acid under these conditions. We believe this is the first report of IBX allowing conversion of an alcohol or aldehyde to the corresponding carboxylic acid.

preparative work, as the oxidation in Table 2, entry 12 has been performed on a 30 mmol scale with identical yield and purity.

As a final point, we have found that the IBX byproducts isolated by filtration can be reoxidized to active IBX using standard procedures.[12,13] The regenerated IBX is indistinguishable from IBX freshly prepared from *o*-iodobenzoic acid. Thus, the insolubility of IBX, previously regarded as problematic, can be exploited to provide all of the advantages of resin-bound IBX equivalents without requiring sophisticated reagent preparation. We anticipate that this protocol will be of broad interest and use to the chemical community.[14]

Acknowledgment. The authors gratefully acknowledge the National Institutes of Health for support of this research (NIGMS-GM60875; NIGMS-GM07240 training grant support for J.D.M.) and the National Science Foundation for support of the Departmental NMR facilities (CHE-9709183). The authors thank Prof. Jay Siegel for helpful discussion.

Supporting Information Available: ^{1}H NMR spectra for all crude oxidation products and complete spectroscopic data for the oxidation product of Table 2, entry 5. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Frigerio, M.; Santogostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537−4538.

(13) In a representative (and unoptimized) case, the IBX and IBX byproducts were recovered essentially quantitatively by filtration from the oxidation of 0.87 mmol of piperonyl alcohol with 1.2 equiv of IBX in EtOAc. ^{1}H NMR analysis of the crude mixture indicates the primary component to be iodosylbenzoic acid (IBA). (For NMR characterization of IBX and IBA, see: Bunton, C.A., Foroudian, H. J., Gillitt, N. D. *J. Phys. Org. Chem.* **1999**, *12*, 758.). No residual IBX is present, although we observe signals that we tentatively assign to a single compound of the same oxidation state (I(V)). The recovered solids were oxidized with aqueous Oxone, precipitated by cooling, and isolated by filtration, as described in ref 11, providing 50% yield of recovered material, which is identical to authentic IBX by ^{1}H NMR (DMSO-d_6).

(14) Representative experimental procedure: Piperonyl alcohol (0.15 g, 1.00 mmol) was dissolved in ethyl acetate (7 mL, 0.14 M final concentration), and IBX (0.84 g, 3.00 mmol) was added. The resulting suspension was immersed in an oil bath set to 80 °C and stirred vigorously open to the atmosphere. After 3.25 h (TLC monitoring), the reaction was cooled to room temperature and filtered through a medium glass frit. The filter cake was washed with 3 × 2 mL of ethyl acetate, and the combined filtrates were concentrated to yield 0.14 g (90% yield, >95% pure by ^{1}H NMR) of piperonal as a waxy solid.