



2-Methyl-2-propanol as solvent for *o*-iodoxybenzoic acid (IBX) oxidation of 1° alcohols to aldehydes

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ABSTRACT

2-Methyl-2-propanol has been demonstrated to be an effective solvent for IBX oxidation of 1° alcohols to the corresponding aldehydes. IBX has a measurable, but low, solubility in 2-methyl-2-propanol and thus partially avoids the drawbacks inherent in the solubility problems associated with IBX without resorting to less desirable solvents. This may be particularly useful where solubility of the alcohol is also at issue.

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Aldehydes are extremely important targets and intermediates in organic synthesis but their preparation by selective oxidation from primary alcohols can be difficult relative to the full oxidation to carboxylic acids. As such the development of methods for this simple transformation has a long and varied history. However, some of the more historically prominent methods have significant drawbacks. Cr(VI) reagents¹ (Jones,² Collins/Sarrett,³ PCC⁴) are toxic and often their use involves a difficult workup. Swern⁵ requires low temperature, a solvent that can be difficult to remove, and generates stench. TEMPO⁶/oxidant lacks tolerance for many functional groups. As such, there is growing interest in the use of hypervalent iodine compounds such as the Dess–Martin periodinane⁷ and *o*-iodoxybenzoic acid (IBX)⁸ as mild, selective reagents for this transformation that also have relatively low toxicity.⁹ Indeed, IBX is the synthetic precursor to the Dess–Martin reagent and where possible and applicable its use may be preferred.

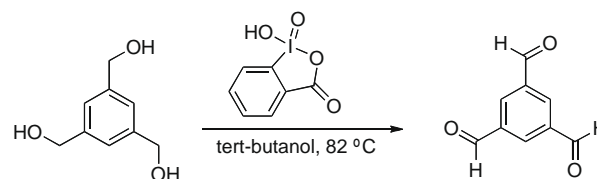
One remaining drawback¹⁰ to the use of IBX for this purpose had been the need to use the high boiling solvent DMSO for the procedure because it was the only solvent in which IBX was soluble. This barrier has recently been removed as a result of More and Finney's observation that a variety of solvents may be suitable for the reaction despite the lack of (or low) IBX solubility.¹¹ They argue that the IBX in these alternative solvents serves as a (de facto) solid phase reagent that, along with its similarly insoluble byproducts, can be removed from the reaction mixture by simple filtration. Additional efforts to ameliorate the solubility problem include application in DMF¹² (in which IBX has been found to be soluble), ionic liquids,¹³ mixed solvent/phase transport,¹⁴ structural modification,¹⁵ polymer support,¹⁶ and use of IBX as a catalyst.¹⁷ All these efforts speak to the utility of IBX but also point out that its solubility in common solvents remains a problem for which new solu-

tions are still sought. Solubility continues to be cited explicitly as an ongoing barrier to the simple utility of IBX.

In our work toward the synthesis of fluorescent chemosensors we had the occasion to need 1,3,5-triformylbenzene. Two recently reported syntheses were effected with IBX in DMSO (modest yields).¹⁸ In order to avoid that solvent we deferred to More and Finney's methodology but were met with mild disappointment because the precursor, 1,3,5-tris-(hydroxymethyl)benzene, is insoluble in any of the solvents reported. The low solubility (or insolubility) of IBX **and** the substrate led to unsatisfactory yield over a few hours. 1,3,5-Tris-(hydroxymethyl)benzene is, however, highly soluble in hydroxylic or protic solvents. As such we attempted the oxidation (Scheme 1) in *tert*-butanol (often overlooked as a possible solvent for such transformations).

The quantitative isolated yield of the desired trialdehyde prompted us to briefly explore the general applicability of 2-methyl-2-propanol as solvent for IBX oxidations of primary alcohols. Perhaps as important as the solubility of the alcohol in the solvent, we found that IBX has a measurable solubility in *tert*-butanol of 0.8 mg/mL at 20 °C and 4.9 mg/mL in refluxing *tert*-butanol.

In general for the oxidation reaction¹⁹ approximately 200 mg of alcohol was dissolved in 25 mL of *tert*-butanol and IBX (2 equiv) was added. The mixture was stirred and heated to reflux for about 1 h. Although the IBX did not completely dissolve in the solvent, as



Scheme 1. A representative transformation.

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Table 1
Representative reactants and products

Entry	Alcohol	Product	Reaction time (h)	Yield (%)
1			1	>95
2			1	>95
3			1	95
4			2	80
5			2	90
6			1.5	95
7			1.5	50 ^a

^a Product likely lost in rotary evaporation.

the reaction proceeded the visible appearance of the mixture changed from a clear solution with granular IBX to a suspension of very fine solid. Because this occurs without stirring, it provides some evidence for dissolution equilibria for IBX and its reaction byproduct(s). The reaction was found (by tlc) to occur at room temperature, although reaction times were much greater than 10 h. After the reaction was complete the *t*-butanol was removed by rotary evaporation. Taking advantage of the insolubility of IBX and its byproducts in most other solvents, the residue could be dissolved in dichloromethane/hexane and filtered giving a clean solution of the aldehyde. When traces of IBX byproducts persisted they could be removed by filtration through a plug of silica. The applicability of the method for aliphatic, allylic, and benzylic alcohols is demonstrated in Table 1 including for 2-phenylethanol which is sometimes overlooked in such series perhaps because homobenzylic alcohols sometimes undergo C–C bond cleavage or other further reaction.²⁰

IBX and other hypervalent iodine reagents remain an active area of exploration for organic oxidation reactions. Insolubility of IBX in most common organic solvents has resulted in many efforts to broaden the scope of IBX application. We have found *tert*-butanol to be a suitable solvent for the oxidation of primary alcohols to aldehydes particularly where a hydroxylic solvent is necessary for dissolution of the substrate. The relative low toxicity and low cost of *tert*-butanol may make this a desirable alternative for many such applications.

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Supplementary data

Copies of ¹H and ¹³C NMR spectra are available for verification of purity. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.045.

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19. *Representative procedure/2-naphthaldehyde.* 2-naphthalenemethanol (0.150 g, 0.95 mmol) was dissolved with stirring in 25 mL 2-methyl-2-propanol. To this was added IBX (0.535 g, 1.96 mmol). The mixture was stirred and heated to reflux for 1 h. The mixture was quickly filtered by vacuum and the filtrant was washed with a 20 mL portion of CH₂Cl₂. The filtrate was rotary evaporated to an off-white solid. This residue was taken up in 25 mL CH₂Cl₂/hexane (1:1) and vacuum filtered. Solvent was removed from filtrate by rotary evaporation to give an off-white solid (0.15 g, 0.96 mmol, 100%). ¹H NMR (CDCl₃, 500 MHz) δ 10.08 (s, 1H), 8.21 (s, 1H), 7.90 (m, 2H), 7.82 (m, 2H), 7.57 (t, 1H), 7.52 (t, 1H). ¹³C NMR (CDCl₃, 500 MHz) δ 192.17, 136.35, 134.49, 134.02, 132.54, 129.47, 129.06, 129.01, 128.01, 127.03, 122.64.
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