

Oxidation of Benzyl Ethers to Benzoate Esters Using a Novel Hypervalent Iodine Reagent

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January 24, 2003

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Hypervalent iodine reagents have found extensive use in synthetic organic chemistry as mild and selective oxidizing agents. We recently reported the synthesis of a water-soluble derivative of *o*-iodoxybenzoic acid (IBX) capable of effecting chemoselective oxidation of allylic and benzylic alcohols in user and eco-friendly solvents. This modified IBX reagent (*m*IBX) has also been shown to effect oxidative transformations of benzyl ethers to benzoate esters as well as to the corresponding benzaldehyde derivatives. Oxidations of a series of benzyl ethers have been carried out to investigate the compatibility of the reagent with various functional groups. A reaction pathway that involves two successive single electron transfer (SET) steps is proposed for the direct oxidation of benzyl ethers to benzoate esters. The proposed mechanism also explains the formation of benzaldehyde derivatives as products via oxidative cleavage of benzyl ethers. Synthesis of a radical probe substrate to establish the involvement of radical intermediates during the oxidation is also reported.

ACKNOWLEDGEMENTS

First and foremost I would like to thank the Department of Chemistry at Western Illinois University for letting me conduct my research at their premise and for letting me use their facilities. I would also like to thank the Illinois Junior Academy of Science for awarding me the President s Research Grant for partial financial support of this research. My thanks are also due to Mr. Ryan Wright, Ms. Cho Cho Khine, Mr. Ron Ruebush, and Mrs. Debbie Carithers of the Department of Chemistry at WIU, Mr. Thomas Johnson, my Science Club advisor, and Dr. Fran Karanovich and the Macomb School District for their help and encouragement during my research. Last but not least I would like to thank my father, Dr. T. K. Vinod, for supervising and mentoring me while I conducted my research.

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INTRODUCTION

Oxidative transformation of functional groups is of paramount importance in synthetic organic chemistry (Hudlick_, 1990; Sheldon and Kochi, 1986). Syntheses of mild, selective, and user-friendly oxidizing agents and the demonstration of simple, cost-effective, and easy-to-perform experimental protocols using such reagents have provided synthetic bench chemists with a variety of reagents to carry out oxidations on molecules bearing sensitive functional groups (Corey and Suggs, 1975; Larock, 1989; Mancuso and Swern, 1981). The emerging interest in Green Chemistry (Anastas and Williamson, 1998; Anastas *et. al.*, 2000) and the growing awareness of the effect of chemical waste on our environment have forced chemists to look for environmentally benign reagents and reaction media to conduct their reactions in (Hudlick_, 1998; Li, 2000). Hypervalent iodine reagents, both λ^3 -iodanes [I(III) compounds] and λ^5 -iodanes [I(V) compounds], have found extensive use in synthetic organic chemistry as mild and selective oxidizing agents (Varvoglis, 1992; Zhdankin and Stang, 1999). One of the main advantages of these polyvalent organoiodine reagents over the more commonly used metal-based oxidizing agents is their benign environmental character. The explosive growth of this area is evident from the several reviews authored by leading researchers in the field within the last three to four years (Varvoglis, 1997; Wirth and Hirt, 1999; Zhdankin and Stang, 2002).

Though a voluminous amount of research has been done lately in advancing the chemistry of λ^3 -iodanes, the extent of effort in the area of λ^5 -iodanes, venerable members of which include *o*-iodoxybenzoic acid (IBX, **1**) (Frigerio and Santagostino, 1994; Frigerio *et. al.*, 1995) and Dess-Martin periodinane (DMP, **2**) (Dess and Martin, 1983), has been relatively sparse. IBX and DMP, the structures of which are shown in Fig. 1, are both non-toxic

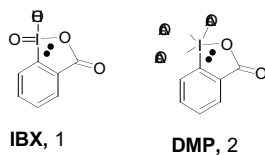


Fig. 1 Structures of two common λ^5 iodanes

and acclaimed oxidizing agents, finding use in the selective oxidation of alcohols to the corresponding carbonyl compounds without the danger of the over oxidation of primary alcohols to carboxylic acids (Dess and Martin, 1983; Dess and Martin, 1991; Frigerio and Santagostino, 1994; Frigerio *et. al.*, 1995). A recent series of elegant papers from Nicolaou laboratories have identified several hitherto unknown oxidative transformations, including a selective oxidation of benzylic carbons to the corresponding aldehydes/ketones, with IBX in wet DMSO and/or wet DMSO-fluorobenzene mixtures (Nicolaou *et. al.*, 2000; Nicolaou *et. al.*, 2001; Nicolaou *et. al.*, 2002). The moisture present in the solvent (DMSO) was considered as a possible source of oxygen in the final product. The trapping of the benzylic carbocation intermediate by water and a subsequent oxidation of the benzyl alcohol by IBX were suggested as one of the possible paths for the overall conversion. This particular report caught our attention since we have been interested in synthesizing hypervalent iodine based "green oxidants. The tolerance of water in the reaction medium by IBX in the selective oxidation of benzylic carbons, as reported by Nicolaou, prompted us to synthesize a water-soluble derivative of IBX. We hoped that the

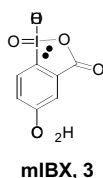


Fig. 2 Structure of *mIBX*

attachment of a hydrophilic carboxylic acid group onto the benzene ring of IBX would yield the required water-soluble reagent. The synthesis of **3**, which we named *m*IBX, for modified IBX, is accomplished in five steps from commercially available 3-nitrophthalic acid and has been recently published in *Tetrahedron Letters* (Thottumkara and Vinod, 2002). The reagent is readily soluble in water and is found to be a chemoselective oxidant (*vide infra*) for allylic and benzylic alcohols (Thottumkara and Vinod, 2002).

The noted chemoselectivity and the fact that oxidation takes place in water readily precludes the widely accepted mechanism of oxidation of benzylic alcohols using Iodine (V) reagents, first proposed by Dess and Martin (1991) and later adopted by Friergerio *et. al* (1994). According to this mechanism, the initial step is a ligand exchange, with the hydroxy group on the hypervalent iodine being replaced by the alcohol as an alkoxy unit. This is an equilibrium step with water as the other product. The presence of water in the reaction medium should disfavor this step, thus preventing the oxidation of benzylic alcohols in wet solvent systems. However, the fact that the oxidation did occur indicates that an alternate mechanism is involved, one that can tolerate the presence of water. The ready oxidation of benzylic/allylic alcohols to the

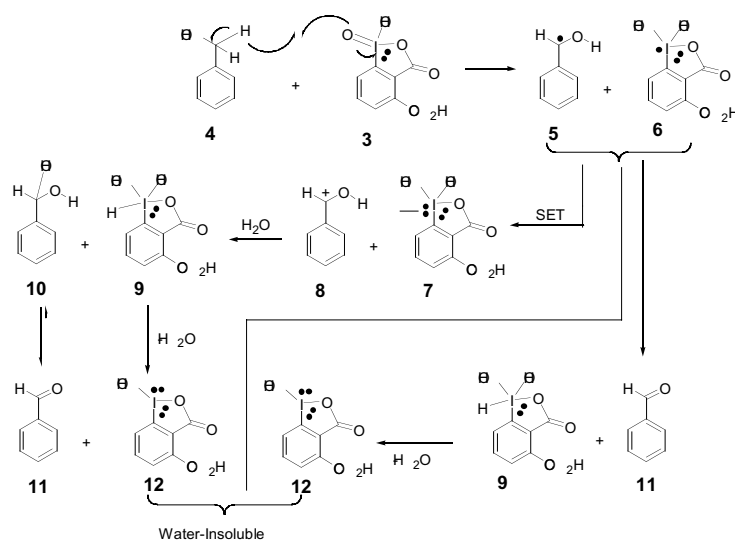


Fig. 3 Plausible mechanisms for chemoselective oxidation using *m*IBX

corresponding carbonyl compounds using *mIBX* in water and other aqueous solvent mixtures, and the lack of oxidation of non-benzylic/allylic alcohols prompted us to propose two plausible mechanisms for the chemoselective oxidation in water, and are shown in Fig. 3. An enthalpically favored H-atom abstraction (Feray *et. al.*, 2001) from the benzylic site produces the stable α -alkoxy radical, **5**, which can be oxidized to benzaldehyde in one of two ways. A single electron transfer (SET) from **5** to the odd-electron species, **6**, produces the benzylic carbocation **8** which can then be attacked by water to give the unstable *gem*-diol, **10**, after a proton abstraction by **7**. The unstable *gem*-diol decomposes to give **11**. Alternatively, conversion of the α -alkoxy radical intermediate **5** to benzaldehyde (**11**) could occur through a second H-abstraction, this time by the odd electron moiety in **6**. Both paths provide the desired carbonyl compound along with an iodosobenzoic acid derivative, **12**, which is insoluble in water and thus precipitates out during reaction. Though conclusive evidence favoring one mechanism over the other has not been obtained, we believe that the latter mechanism is probably not in operation because it involves the homolytic dissociation of the strong O-H bond involved (Jonsson *et. al.*, 1994; Lowry and Richardson, 1987)

Many benzylic/allylic alcohols were oxidized in high yields using *mIBX* in water and other aqueous solvent mixtures (Thottumkara and Vinod, 2002). Several pertinent observations were made from our initial oxidation studies. It was observed that *mIBX* tolerates a variety of functional groups during oxidation, and over-oxidation of alcohols is never observed, even when electron rich substituents are present on the benzene ring. It was also noted that the chemoselective oxidation of 1-phenyl-1,2-ethanediol is not accompanied by cleavage of the vicinal diol, a common problem encountered during the oxidation of vicinal diols using other oxidizing agents.

A careful analysis of the two oxidation pathways shown in Fig. 3 indicated that if the SET mechanism was the predominant or exclusive reaction pathway, then it should be possible

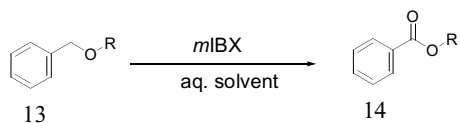


Fig. 4 Direct oxidation of benzyl ethers to benzoate esters

to directly oxidize benzyl ethers to the corresponding benzoate esters, as illustrated in Fig. 4. According to the proposed mechanism, oxidation is initiated by a hydrogen atom abstraction from the benzylic site followed by a single electron transfer from the resulting radical and both steps could occur irrespective of whether the initial substrate is an alcohol or an ether. The impetus for achieving the ether oxidation, carried out in an eco-friendly manner, lies in the fact that alcohol groups are commonly protected as benzyl ethers during multi-step syntheses and that the availability of a convenient and high-yielding protocol for the direct oxidation of benzyl ethers to the corresponding benzoate esters will allow synthetic chemists to treat the benzyl group (of benzyl ethers) as a latent benzoate functionality that can be removed through hydrolysis without effecting the other reducible functional groups in the molecule. Though easy hydrogenolysis of the benzyl group is a convenient way of deprotecting an alcohol, the hydrogenolytic method cannot be used if the molecule has additional reducible groups present in it (Greene and Wuts, 1999).

The focus of the ongoing research is to identify eco-friendly protocols for the oxidation of benzyl ethers to the corresponding benzoate esters using *mIBX*. Our preliminary results have indicated that the oxidation of benzyl ethers to esters is accompanied by the oxidative cleavage of the substrate to the corresponding benzaldehyde derivatives. An SET-based mechanism that explains the formation of both ester and aldehyde from the oxidation of benzyl ethers is

proposed. Successfully identifying the presence of radical intermediates in the reaction pathway is also an objective of the current project.

MATERIALS AND METHODS

General Procedures

All melting points are uncorrected and were recorded using a Mel-Temp apparatus. ^1H nuclear magnetic resonance (NMR) spectra were recorded at 300 MHz using deuterated solvents (CDCl_3 , acetone- d_6 , DMSO- d_6 , D_2O). Infrared spectra were recorded using a Shimadzu IR 8400 Spectrometer. Mass spectra were recorded using a Shimadzu-QP5050 GC-MS instrument. The gas chromatograph (GC) column in this instrument is a DB-5 coated capillary column 30 m long and with 0.25 mm internal diameter (i.d.). The following GC program was used for all the experiments: Oven temperature-80 $^{\circ}\text{C}$ (2 min), 80 to 250 $^{\circ}\text{C}$ at 20 $^{\circ}\text{C}/\text{min}$, injector temperature-250 $^{\circ}\text{C}$, GC-MS interface temperature 250 $^{\circ}\text{C}$. The mass spectrometer was set to operate in the positive ion mode with electron impact as the ionization method. The mass range was scanned from 80-600 daltons (Da) with a 3.00-min solvent delay. Thin layer chromatography (TLC) was employed to monitor the progress of the reactions. Column chromatography was carried out with SiO_2 (Fisher Scientific, 60-200 mesh). All reactions and chromatographic separations were all carried out in well-ventilated fumehoods. Solvent evaporation were carried out under reduced pressure using a Rotavap. Proper care (lab coat, rubber gloves, and safety goggles) was exerted whenever in the laboratory and whenever handling chemicals.

Solvents and reagent chemicals were purchased from commercial vendors (Aldrich Chemical Company, Lancaster Chemicals, and Fluka). Deuterated solvents were obtained from Cambridge isotope laboratories.

The following abbreviations have been used throughout this section when describing NMR spectroscopic and mass spectrometric data for the compounds: ^1H NMR: s-singlet, d-doublet, t-triplet, br s-broad singlet; mass spectrometric data (MS): m/z -mass to charge ratio, M^+ -molecular ion.

4-bromomethylbenzoic acid, 16

N-bromosuccinimide (NBS) (7.69 g, 44.06 mmol) was added in two portions, 8 h apart, to a refluxing solution of commercially available *p*-toluic acid (5.0g, 44.06 mmol) in 100 mL of benzene (Caution: Benzene is a potential carcinogen and due care should be taken in handling this solvent). Each addition was followed by the addition of a few milligrams of benzoyl peroxide, and the reaction was left at reflux overnight. After this period, the solution was cooled, the solvent evaporated in a fumehood to obtain the crude product along with succinimide. Trituration of the crude product using 100 mL CHCl_3 was performed overnight and filtered to give **16** (6.93 g, 90%) as a white solid, mp 225-228 ...C; IR (KBr) 3200, 2980, 2800, 1678, 1425, 1288, 943, 601 cm^{-1} ; mass spectrum m/z 216/214 (M^+), 137, 107, 89; ^1H NMR (CDCl_3), δ 4.50 (s, 2H), 7.50 (AA BB, 2H), 8.08 (AA BB, 2H).

4-methoxybenzyl bromide, 31

Sodium borohydride (NaBH_4) (0.140 g, 3.68 mmol) was slowly added to a stirring solution of 4-anisaldehyde (1.0g, 7.35 mmol) in a methanol/THF mixture (1:1 v/v, 40 mL) at RT. The reaction mixture was left stirring overnight and the progress of the reaction was monitored using TLC. After the completion of the reaction, it was carefully acidified (dil. HCl) and extracted with dichloromethane (CH_2Cl_2) and water. The organic layer was collected, dried (MgSO_4), and evaporated to yield the 4-methoxybenzyl alcohol as a yellow oil and was subjected to bromination as follows. Phosphorous tribromide (0.971 g, 3.6 mmol) in 10 mL

toluene was slowly added to a stirring solution of 4-methoxybenzyl alcohol (1 g, 7.25 mmol) in 50 mL toluene. The mixture was left stirring at room temperature (RT) overnight and the reaction was monitored using TLC. After completion of the reaction, the reaction mixture was poured into water and layers separated out. The organic layer was collected, dried (MgSO₄), and evaporated to yield **31** as a white solid, mp 43-44 ...C; IR (KBr) 3050, 2990, 1425, 1310, 1288, 625 cm⁻¹; ¹H NMR (CDCl₃), δ 3.80 (s, 3H), 4.55 (s, 2H), 6.78 (AA BB, 2H), 8.08 (AA BB, 2H).

2-methoxybenzyl bromide was also similarly prepared from 2-anisaldehyde.

Representative Synthesis of Benzyl Ethers

The benzyl ethers used in this study were synthesized through solvolysis of the corresponding benzyl bromides. The representative procedure below describes the synthesis of methyl 4-bromophenylmethyl ether (**22**) from 4-bromobenzyl bromide.

4-bromobenzyl bromide (3 g, 12 mmol) was dissolved in 100 mL methanol and refluxed overnight. After this period, the solvent was evaporated off to obtain the crude product which was redissolved in CH₂Cl₂ (100 mL) and washed with water in a separatory funnel. The bottom layer was separated, dried (MgSO₄), filtered, and evaporated to give **22** (2.41 g, 100%) as a clear liquid. Mass spectrum, *m/z* 202/200 (M⁺), 171, 121; ¹H NMR (CDCl₃), δ 3.4 (s, 3H), 4.4 (s, 2H), 7.2 (AA BB, 2H), 7.46 (AA BB, 2H).

Representative Example for Oxidation of Benzyl Ethers

The procedure described below is a representative example for the oxidation of benzyl ethers using *m*IBX in nitromethane/water mixtures at 75-80 ...C.

Modified *o*-iodoxybenzoic acid (0.087 g, 0.27 mmol) was added to a solution of methyl 4-nitrophenylmethyl ether (0.03g, 0.18 mmol) in a CH₃NO₂/water mixture (1:1 v/v, 8 mL). The

solution was then left stirring at 75-80 ...C for 12. During the reflux the solution turned yellow. After the reflux period, the solution was filtered, extracted with CH₂Cl₂, dried (MgSO₄), filtered, and evaporated to give the crude product which was separated using preparative TLC (SiO₂ plates, eluent 2:1 CH₂Cl₂ : Pet. ether) to give 4-nitrobenzaldehyde (0.0041 g, 15%) and methyl 4-nitrobenzoate (0.016 g, 50%). These products were identical in all respects to commercially available samples as determined by GC-MS.

RESULTS

The benzyl ethers used in this study were procured commercially or were synthesized in-house from the corresponding benzyl bromides. The benzyl bromides needed for the synthesis were prepared either from the corresponding toluene derivatives using N-bromosuccinimide (NBS) or from the corresponding aldehydes through reduction followed by bromination using PBr₃. Our initial efforts were directed towards the synthesis of a benzyl ether, soluble or

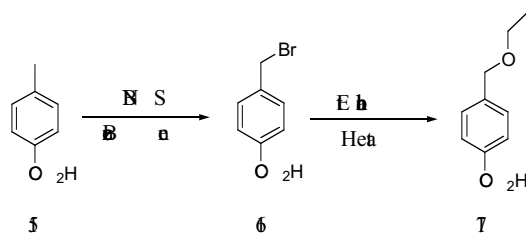


Fig. 5 Synthesis of 17

sparingly soluble in water, to enable us to establish the use of *m*IBX as an ether oxidizing agent in water. 4-Carboxyphenylmethyl ethyl ether, **17**, was chosen as the initial target molecule and synthesis of **17** was accomplished in two steps from commercially available 4-toluic acid (**15**) as shown in Fig. 5. Treatment of **15** with NBS in refluxing benzene gave 90% yield of the benzyl bromide **16** as a white solid, mp 225-228 ...C. Solvolysis of **16** using ethanol provided the ether as a white solid, mp 201-202 ...C.

The availability of **17**, which is sparingly soluble in water, allowed us to investigate the use of *m*IBX as a potential oxidant for benzyl ethers. The initial oxidation of **17** was carried out in D₂O at RT using 3.0 eq. of *m*IBX and the progress of the reaction was monitored by ¹H NMR. The oxidation of **17** is illustrated in Fig.6. Analysis of the reaction mixture after 12 h at 55 ...C, indicated the formation of 4-carboxybenzaldehyde (**18**), the identity of which was further confirmed by GC-MS analysis of the reaction mixture. The presence of aldehyde, **18** (~30-40%), in the reaction mixture was unexpected; however, a careful evaluation of the proposed reaction mechanism indicated that formation of an aldehyde product is feasible (*vide infra*).

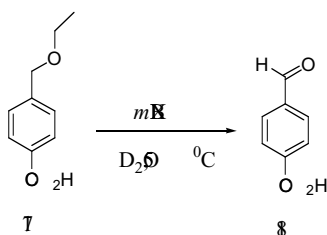


Fig.6 Oxidation of **17** in D₂O

At this juncture, we wanted to include substrates bearing varying functional groups on the benzene ring, other than the carboxyl group, in our ether oxidation studies. We were aware of the solubility problems that could potentially arise when dealing with benzyl ethers that are not soluble in water. To further our oxidation studies, several additional benzyl ethers were synthesized and attempts were made to find a suitable eco-friendly solvent mixtures for the ether oxidations.

Benzyl isopropyl ether (**19**) and benzyl *tert*-butyl ether (**20**) were prepared by solvolysis of benzyl bromide using the appropriate alcohols. Similarly, ethanolysis of 4-nitrobenzyl bromide and 4-bromobenzyl bromide yielded ethers **21** and **22**, respectively, in quantitative yields. The syntheses of 4-methoxyphenylmethyl methyl ether (**23**) and 2-methoxyphenylmethyl methyl ether (**24**) were synthesized from the corresponding

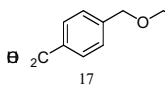
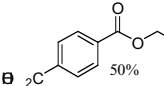
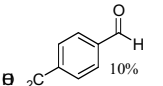
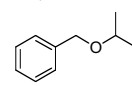
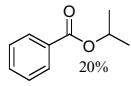
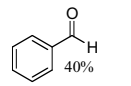
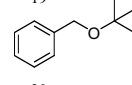
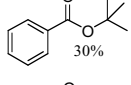
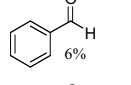
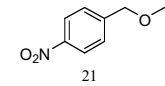
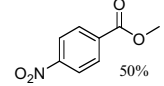
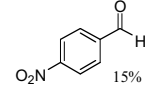
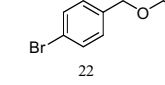
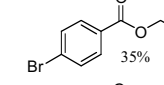
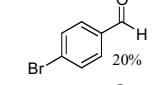
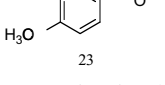
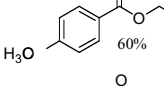
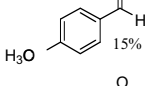
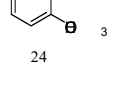
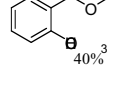
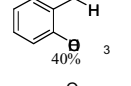
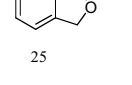
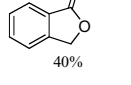
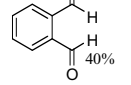
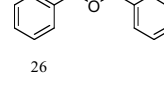
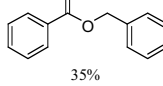
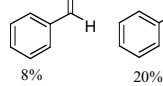

benzaldehydes as follows. Reduction of 4-anisaldehyde (**27**) and 2-anisaldehyde (**28**) using sodium borohydride (NaBH_4) gave the corresponding benzyl alcohols, **29** and **30** respectively. The bromination of **29** and **30** using PBr_3 gave 4-methoxybenzyl bromide (**31**) and 2-methoxybenzyl bromide (**32**) which were solvolized to yield the desired ethers. Representative experimental procedures for the syntheses of ethers are given in the Materials and Methods section above. Commercially available phthalan (**25**) and dibenzyl ether (**26**) were also employed as substrates in this study.

Having synthesized the desired substrates, we began to look for suitable aqueous solvent mixtures containing organic co-solvents that would provide optimized yields. Several solvent systems were tested, including ethanol (EtOH)/water, acetone (CH_3COCH_3)/water, tetrahydrofuran (THF)/water, and nitromethane (CH_3NO_2)/water mixtures. Oxidation reactions carried out in the latter two provided both esters and the appropriate aldehydes as products (see Table 1). However, reactions carried out in THF /water mixtures were complicated by the fact that THF also was oxidized to yield γ -butyrolactone during the reaction. The results of the oxidation reactions carried out in nitromethane/water mixtures are listed in Table 1.

The reactions listed in Table 1 were carried out in a 1:1 v/v mixture of CH_3NO_2 and H_2O at 75-80 ...C over a period of 3-4 h. In most instances, the yields reported are isolated yields after preparative thin layer chromatographic (TLC) separation of the products. The yields reported for entries 7 and 9 (Table 1) are GC yields. In all cases, except for entry 2 (Table 1), the aldehyde was isolated as the minor product. The oxidative cleavage of dibenzyl ether (entry 9) is expected to be accompanied by the formation of an equivalent amount of benzyl alcohol (Fig. 9 *vide infra*). However, the detection of more benzyl alcohol than benzaldehyde in the final reaction mixture is puzzling and we are currently standardizing this reaction to find the optimum

yields of the products. In addition, as evidenced by entries 1, 4, 5, 6, and 7 (Table 1) *m*IBX tolerates a variety of functional groups on the benzene ring of the substrate.

TABLE 1
Oxidation of benzyl ethers using *m*IBX

Entry	Substrate	Ester	Aldehyde
1		 50%	 10%
2		 20%	 40%
3		 30%	 6%
4		 50%	 15%
5		 35%	 20%
6		 60%	 15%
7		 40%	 40%
8		 40%	 40%
9		 35%	 8% and  20%

Though the possibility of formation of benzaldehydes through oxidative cleavage of benzyl ethers was overlooked initially, the mechanism proposed below readily explains the formation of both esters and aldehydes from this reaction. The proposed mechanism also alludes to the possibility of tuning the reaction to give either the ester or aldehyde depending on the pH of the reaction medium.

DISCUSSION AND CONCLUSIONS

In our search for a suitable solvent system for ether oxidations, THF/water mixtures were tested among others. Reactions done in this solvent mixture were complicated by the fact that THF was concomitantly oxidized to γ -butyrolactone during the oxidation of benzyl ethers as noted in the Results section. This observation prompted us to investigate the use of *mIBX* as a potential oxidizing agent for non-benzylic ethers. An attempted oxidation of THF to γ -butyrolactone using *mIBX* (in the absence of a benzyl ether) was unsuccessful, as shown in

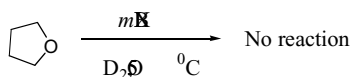


Fig.7 Attempted oxidation of THF using *mIBX*

Fig. 7. The noted lack of oxidation of THF (in the absence of benzyl ethers) led us to compare the bond dissociation energies of the C-H bond α to the oxygen in both benzyl ethers and THF to find an explanation for the observed chemoselectivity. The bond dissociation energies of 367.8 kJ/mol for the $\text{C}_6\text{H}_5\text{CH}_2\text{-H}$ bond and 384.9 kJ/mol for the tetrahydrofuran-2-yl-H bond (Feraý *et. al.*, 2001) gave us an indication that the abstraction of the benzylic C-H bond by *mIBX* is certain to be favored over the abstraction of the $\text{C}\alpha\text{-H}$ bond of THF. Moreover, the difference in the rate of abstraction is likely to be more than what is indicated by the difference in bond dissociation energies as noted above. This is due to the fact that the presence of the oxygen atom in benzyl ether is expected to lower the bond dissociation energy of the relevant C-H bond from the 367.8 kJ/mol value noted for C-H bond in toluene. Thus, when both THF and a benzyl ether are present in the reaction mixture, *mIBX* is expected to selectively abstract the hydrogen from the benzylic carbon of benzyl ether, rather than the C-H bond α to oxygen in THF. The

formation of γ -butyrolactone under such circumstances is believed to occur as follows. The reactive radical intermediate **28** formed from the benzyl ether can initiate the oxidation of THF

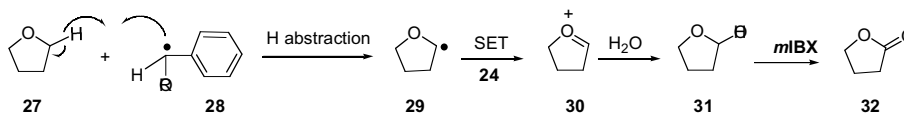


Fig. 8 Oxidation of THF in the Presence of Benzylic Radicals

as shown in Fig. 8. An abstraction of the C α -H in THF by **28** will initiate a cascade of reactions shown above, resulting in the formation of γ -butyrolactone.

Based on the fact that *mIBX* oxidizes benzyl ethers but not THF or any other nonbenzylic ethers, we concluded that the first step in our ether oxidations is the favored C-H abstraction

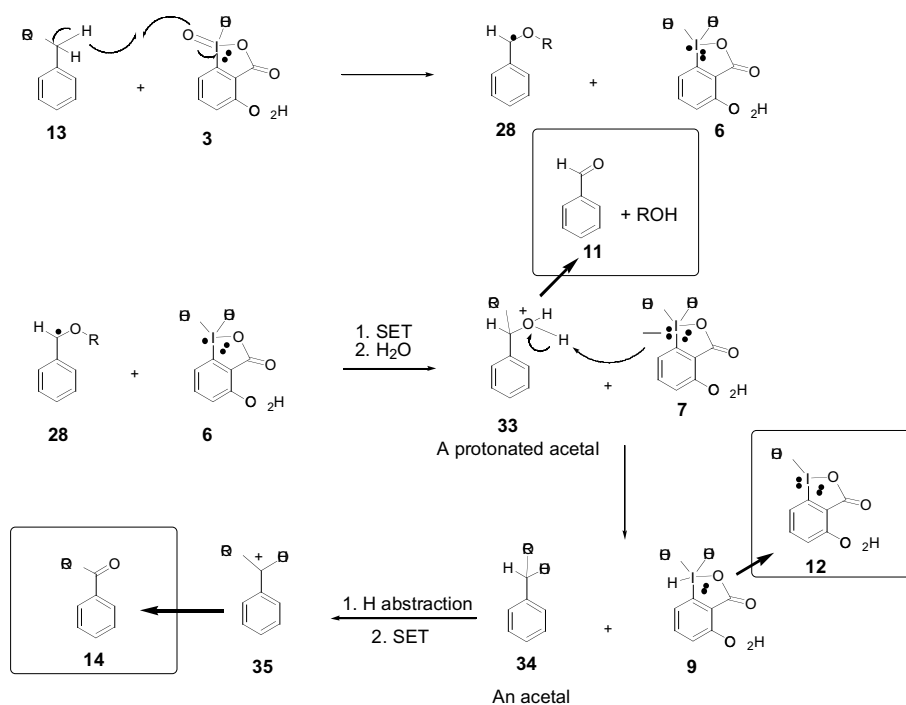


Fig. 9 Mechanism of oxidation of benzyl ethers using *mIBX*

from the benzylic carbon by *mIBX* to give the benzyloxy radical **28** and the odd electron hypervalent iodine derivative **6**. An SET from **28** to **6** produces a benzyl carbocation (not shown) which can readily get attacked by water present in the reaction medium to give the protonated hemiacetal **33** and the anionic hypervalent derivative **7**. A ready decomposition of the protonated hemiacetal, **33** (Lowry and Richardson, 1987) produces benzaldehyde (**11**); net conversion being an oxidative cleavage of the benzyl ether to the corresponding benzaldehyde. A rapid proton transfer from the protonated hemiacetal, **33**, to the anionic hypervalent derivative, **7**, as indicated in the mechanism above, will generate a hemiacetal **34** along with hypervalent iodine derivative **9**. Loss of H₂O from **9** produces the insoluble iodosobenzoic acid derivative, **12**, isolated as the reduced form of *mIBX* from the reaction. The benzylic C-H bond of acetal **34** should be even more easily abstracted by *mIBX* due to the enhanced stability of the resulting radical, which can subsequently transfer an electron (SET) to **6** to give a carbocation that in turn will lose a proton to give the ester, **14**.

We believe that the product distribution (aldehyde vs ester) from the oxidation of benzyl ether using *mIBX* in nitromethane-water mixtures can be controlled by manipulating the pH of the reaction medium. As per the mechanism above, the fate of the protonated hemiacetal intermediate **33** is what determines the ultimate product composition. By carrying out the oxidation reaction in presence of alkali metal carbonates (i.e. at a higher pH) one can ensure that the protonated hemiacetal intermediate **33** will be rapidly deprotonated to give hemiacetal **34** which in turn will yield the ester product. On the other hand reactions carried out at lower pH should favor the formation of aldehydes. We are currently investigating the product distributions from reactions carried out in presence of added alkali metal carbonates as well as 4-toluenesulfonic acid.

To unequivocally establish the involvement of radical intermediates during the oxidation we have recently synthesized **37**, a suitable radical probe. The benzyl radical generated from **37**, when oxidized by *m*IBX could participate in a 5-*exo* cyclization to yield **38**, an indane derivative, the isolation and characterization of which should confirm the intermediacy of the radical. The synthesis of **37** is accomplished in two steps from commercially available 2-bromobenzylbromide (**35**) as shown in Fig. 10. The oxidation reaction carried out aq. nitromethane and the absence of olefinic resonances in the ¹H NMR spectrum of the crude

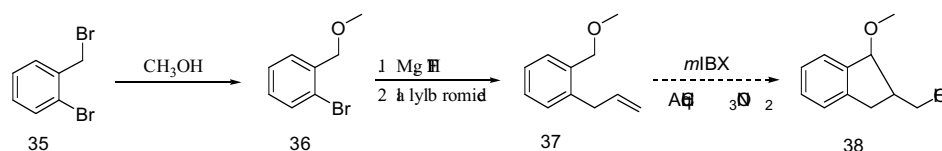


Fig 10 Synthesis of **37**, a radical probe

product is indicative of olefin participation in is expected to shed light on the reaction mechanism proposed above.

In summary, the direct oxidation of benzyl ethers to esters and aldehydes have been achieved using the recently synthesized user and eco-friendly hypervalent iodine reagent, **3**. The mechanism proposed for the oxidative transformation provides an explanation for the formation of esters and aldehydes from the reaction. On going efforts are directed towards the investigation of the role of pH on product distribution and to unequivocally establish the presence of radical intermediates along the reaction path.

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