



Ionic liquid [bmim]Br assisted chemoselective benzylic C—H oxidations using *tert*-butyl hydroperoxide



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ABSTRACT

A mild and efficient, ionic-liquid-assisted green protocol for the chemoselective oxygenation of benzylic C—H bonds to corresponding ketones using ionic liquid [bmim]Br with *tert*-butyl hydroperoxide has been developed. The method reported in this paper has the advantages of [bmim]Br acting as recyclable solvent and reagent. The usage of additives such as acids or bases and metal salts is not required. The developed strategy is further extended to oxidation of secondary alcohols to respective ketones under similar optimized reaction conditions.

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1. Introduction

Chemoselective oxygenation of C—H bonds of hydrocarbons under mild reaction conditions is one of the most useful and significant transformation in organic chemistry and it has made a tremendous breakthrough in the production of fine chemicals, feedstock for pharmaceutical, perfume, dyes, and agrochemical industries. [1–3] In an attempt to achieve this goal, multiple stoichiometric inorganic oxidants such as NaBrO₃ [4,5] Cr and Mn reagents along with various additional oxidants such as TBHP and H₅IO₆ [6] have been used. Furthermore, the reported methods on oxidation of arylalkanes were performed using several metal catalysts such as Cr, Co, Mn, Rh, Ru, Zn, Fe, Bi etc. with various oxidants, namely O₂, *tert*-butyl hydroperoxide (TBHP), and H₂O₂ [7–9]. However, most of the metal catalyzed systems suffer from limitations such as use of high reaction temperature, toxic metals, less selectivity, formation of by-products and use of additives (acids and bases); which makes the isolation of the product difficult [10]. Organocatalysts such as IBX (*o*-iodoxy benzoic acid) [11], molecular oxygen [1] alkyl peroxides [12,13], NHPi, [14] and AIBN [15] have been used to overcome the above mentioned limitations. Despite numerous efforts, reported methods still suffer from usage of large volumes of volatile organic solvents, stoichiometric reagents, irradiation of light or high temperatures [16–18].

On the other hand, ionic liquids (ILs) are well known as “green solvents” for replacing traditional organic solvents owing to their non-volatile and non-flammable nature. ILs have found several applications in

organic synthesis as solvents, catalysts, and reagents attributed to their characteristic properties such as low vapor pressure, chemical and thermal stability and electrochemical window [19–21]. In a continuation to our ongoing research efforts towards the development of chemoselective oxidation methods for various critical organic transformations [22–27], herein we report a cost effective, practical, safe, and eco-friendly method for the oxidization of a variety of alkylarenes to afford the corresponding carbonyl compounds with TBHP in ionic liquid ([bmim]Br) under mild reaction conditions (Scheme 1).

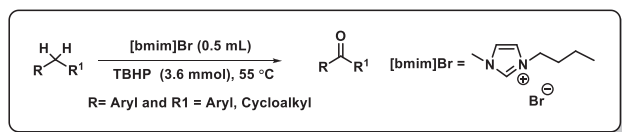
2. Materials and methods

2.1. General experimental procedures

All the reactions were carried out in 25 mL round bottom flask. Commercially available starting materials and other chemicals are purchased from Sigma-Aldrich chemicals, SD-fine chemicals (India). 70% aq. TBHP purchased from Sigma-Aldrich chemicals and used in reactions without further purification. Ionic liquid ([bmim]Br) was prepared and purified as per reported literature methods. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence lamp. Silica gel (particle size 100–200 mesh) purchased from Merck, was used for chromatography. ¹H NMR spectra were recorded on a Bruker 400 MHz instrument. Spectra were reported relative to Me₄Si (δ 0.0 ppm) or CHCl₃ residual peak (δ 7.26 ppm). ¹³C 100 MHz NMR were reported relative to CDCl₃ (δ 77.16 ppm). All the products were characterized by NMR, GC–MS and ESI mass spectra. The first-order peak patterns are indicated as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quadruplet). Complex non-first-order signals are indicated as m

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Scheme 1. Oxygenation of benzylic C–H bonds.

(multiplet). FTIR spectra were recorded on a Nicolet 6700 spectrometer and are reported in frequency of absorption (cm^{-1}). GC–MS are recorded on instrument Perkin Elmer mass spectrometer

3. Experimental

3.1. General procedure for oxygenation of benzylic C–H bonds

Charged 0.5 mmol of 3-(9H-fluoren-2-yl)prop-2-yn-1-ol **13a** (110 mg, 0.5 mmol), 0.5 mL of [bmim]Br and TBHP (0.5 mL, 3.6 mmol) were taken in a round bottom flask and heated to 55 °C until completion of the reaction. The reaction course was monitored by TLC. After completion of the reaction, the reaction mixture was extracted using ethyl acetate (3×4 mL). The organic layer was concentrated under vacuum and purified by column chromatography on silica gel to afford the desired product as 2-(3-hydroxyprop-1-yn-1-yl)-9H-fluoren-9-one **13b** Yellow Solid; yield: 75%, mp 148–150 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.69 (m, 2H), 7.56 (dd, 1H), 7.50 (m, 2H); 7.48 (d, 1H), 7.32 (m, 1H), 4.51 (s, 2H), 1.83 (br, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 193.0, 144.0, 143.9, 137.9, 134.9, 134.3, 134.2, 129.5, 127.4, 124.5, 123.4, 120.7, 120.3, 88.9, 84.9, 51.6. ESI-MS Calculated for $\text{C}_{16}\text{H}_{10}\text{O}_2$: Theoretical mass: 234.2, Observed mass: 234.1.

3.2. General procedure for oxidation of secondary alcohol

Charged 0.5 mmol of 1,3-diphenylprop-2-yn-1-ol **15a** (104 mg, 0.5 mmol), 0.5 mL of [bmim]Br and TBHP (0.5 mL, 3.6 mmol) were taken in a round bottom flask and heated to 55 °C until completion of the reaction. The reaction course was monitored by TLC. After completion of the reaction, the crude mixture was extracted with ethyl acetate (3×4 mL). The organic layer was concentrated under reduced pressure and purified by column chromatography on silica gel to afford the desired product, 1,3-diphenylprop-2-yn-1-one **15b** as yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 8.25 (d, 2H), 7.71–7.63 (m, 3H), 7.55–7.42 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): 178.0, 136.9, 134.2, 133.1, 130.9, 129.7, 128.8, 128.7, 120.2, 93.1, 86.9. GC–MS Calculated for $\text{C}_{15}\text{H}_{10}\text{O}$: Theoretical mass: 206.24, Observed mass: 206.20.

3.3. General procedure for recyclability of the ionic liquid

Upon completion of the reaction, water and ethyl acetate were added to the reaction mixture due to their miscibility with IL [bmim]Br and product respectively. The aqueous layer was extracted, concentrated under high vacuum and the resulting IL was reused for the subsequent experiments. The organic extracts upon evaporation afforded the respective ketone in quantitative yields (Table 5).

4. Results and discussion

First set of experiments were carried out using fluorene (0.5 mmol) as a model substrate, oxidant, TBHP (3.6 mmol) at 55 °C up to 20 h using [bmim]Br and various organic solvents such as toluene, tetrahydrofuran (THF), chloroform, ethyl acetate and acetonitrile (Table 1). Among the employed solvents, chloroform, acetonitrile and ethyl acetate afforded the corresponding ketone (Table 1, Entries 6, 1 and 2). Nevertheless, the reaction was incomplete even after 20 h and was not selective and

Table 1
Optimization of solvent for oxygenation of benzylic C–H bonds.

| Entry ^a | Solvent | Oxidant | Yield ^b |
|--------------------|---------------------------------------|---------|--------------------|
| 1 | Ethyl acetate | TBHP | 20 |
| 2 | Acetonitrile | TBHP | 30 |
| 3 | Acetonitrile(2 mL)/[bmim]Br (50 mol%) | TBHP | 90 |
| 4 | Toluene | TBHP | Trace |
| 5 | Tetrahydrofuran | TBHP | Trace |
| 6 | chloroform | TBHP | 21 |
| 7 | – | TBHP | Trace |
| 8 | [bmim]Br | TBHP | 95 |
| 9 | [bmim]BF ₄ | TBHP | 95 |
| 10 | [bmim]PF ₆ | TBHP | 62 |
| 11 | [bmim]Cl | TBHP | 55 |
| 12 | H ₂ O | TBHP | 42 |

^a All experiments were carried out using 0.5 mmol substrate and TBHP 3.6 mmol (70% *t*-BuOOH in H₂O).

^b Isolated yields.

gave several undesired by-products. The reaction did not proceed at all when THF and toluene were used as solvents. Next, the reaction was carried out with similar ionic liquid by varying the counter anions such as [bmim]BF₄, [bmim]Br, [bmim]PF₆ and [bmim]Cl. Interestingly, [bmim]BF₄ and [bmim]Br were found to be the best solvents which gave the corresponding fluorenone with a maximum yield of 95% in 20 h (Table 1, Entries 8 and 9), whereas [bmim]PF₆ and [bmim]Cl gave moderate yield (Table 1, Entries 10 and 11). The reaction when carried out using water as solvent gave the desired product with less yield (42%) (Table 1, Entry 12). However, due to the easy availability and synthesis of [bmim]Br, further experiments were carried out using the latter. Furthermore, the catalytic efficiency of the [bmim]Br was studied in the presence of acetonitrile as solvent. Surprisingly, reaction was found to be selective and gave quantitative yield of the corresponding ketone (Table 1, Entry 3). Though [bmim]Br can be used in a catalytic amount, further experiments were carried out using 0.5 mL of [bmim]Br attributed to its recyclable property.

Second set of experiments were carried out using various oxidants such as hydrogen peroxide, urea hydrogen peroxide (UHP), and TBHP. TBHP was found to be the best oxidant among the rest as it gave 95% yield within 20 h of reaction time (Table 2, Entry 4). In addition, TBHP was known to be the superior oxygen source for variety of organic oxygenation reactions and also possess good thermal stability [28,29]. Subsequently, we have carried out the reactions at 55 °C using 0.5 mmol of fluorene and varying concentrations of TBHP from 1.4 mmol to

Table 2
Optimization studies on the oxygenation of benzylic C–H bonds.

| Entry ^a | Oxidant | mmol | Temp. | Time | Yield ^b |
|--------------------|-----------------------------------|------------|--------------|-------------|--------------------|
| 1 | 30% H ₂ O ₂ | 4.5 | 55 °C | 70 h | 22 |
| 2 | 50% H ₂ O ₂ | 4.5 | 55 °C | 70 h | 32 |
| 3 | UHP | 3.6 | 55 °C | 70 h | 30 |
| 4 | TBHP | 3.6 | 55 °C | 20 h | 95 |
| 6 | TBHP | 2.1 | 55 °C | 65 h | 95 |
| 7 | TBHP | 1.4 | 55 °C | 70 h | 95 |
| 8 | – | – | 55 °C | 70 h | – |
| 9 | TBHP | 3.6 | 45 °C | 80 h | 60 |
| 10 | TBHP | 3.6 | RT | 7 days | 47 |

^a All experiments were carried out using 0.5 mmol (83 mg) fluorene, [bmim]Br (0.5 mL), Oxidant.

^b Isolated yields.

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