Green Protocol for the O–H Insertion of α-Diazoketones with Alcohols and Water Using Ionic Liquid [Bmim]BF₄

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(Received August 4, 2003; CL-030720)

 α -Diazoketones undergo readily O–H insertion reactions with alcohols and water in hydrophilic [bmim]BF₄ ionic liquid in the absence of any acid catalyst to furnish α -alkoxy and α -hydroxy ketones in excellent yields under neutral conditions. The recovered ionic liquid can be easily reused in four to five cycles with consistent in activity. The use of ionic liquid helps to avoid the use of acid catalysts as well as environmentally unfavorable volatile organic solvents.

 α -Hydroxy ketones are useful intermediates in organic synthesis especially in asymetric aldol reactions.¹ α -Diazoketones are versatile building blocks for the synthesis of many biologically active natural products.² The ready availability, relative stability, and facile decomposition of α -diazocarbonyl compounds under acid or thermal or photochemical conditions make them useful intermediates in organic synthesis.³ Furthermore, α -diazoketones undergo a variety of transformations such as cyclopropanation, aziridine formation, ylide formation, C-H, X-H insertion reactions and cyclization reactions.⁴ The carbene reactions are chemoselective, which allow new carbon-carbon and carbon-hetero atom bond formation under mild conditions. Recently, asymmetric version of diazo insertions have also been reported to afford enantiomerically enriched compounds.⁵ Typically, transition metal catalysts such as Rhodium and Copper salts are employed to promote the insertion reactions of α -diazocarbonyl compounds.⁶ Although, diazoinsertion reactions are typically catalyzed by transition metal salts, new catalytic systems are being continuously explored in search of improved efficiencies and cost effectiveness. Both protic acids and Lewis acids including metal triflates have been reported for the O-H insertion of α -diazocarbonyl compounds.⁷ However, most of these methods often involve the use of acid catalysts which always demand aqueous work-up for the catalyst separation, recycling and disposal. Furthermore, some of them involve the use of harsh conditions, expensive reagents and suffer from the lack of simplicity and also the yields and selectivities reported are far from satisfactory owing to the occurance of several side reactions. In view of the increasing synthetic importance of α -hydroxyketones as synthons in asymmetric aldol reactions, the development of simple, convenient, and environmentally friendly approaches are desirable. In recent times, ionic liquids have emerged as a substitute and alternative solvents for the immobilization of transition metal catalysts, Lewis acids, and enzymes.⁸ They are being used as green solvents with interesting properties such as tunable polarity, high thermal stability, immiscibility with a number of organic solvents, negligible vapor pressure, and ease of recyclability.⁹ They are referred to as 'designer solvents' as their properties such as hydrophilicity, hydrophobicity, Lewis acidity, viscosity, and density can be altered by the fine-tuning of parameters such as the choice of organic cation, inorganic anion, and the length of alkyl chain attached to an organic cation (Figure 1).

These structural variations offer flexibility to the chemist to devise the most idealized solvent, catering to the needs of any par-



Figure 1.

ticular process. Since ionic liquids are entirely composed of ions, they can provide an ideal reaction medium for reactions that involve reactive ionic intermediates. Owing to the stabilization of charged intermediates by ionic liquids, they can promote enhanced selectivities and reaction rates. As a result of their green credentials and potential to enhance reaction rates and selectivities, ionic liquids are finding increasing applications in organic synthesis.¹⁰ However, there are no examples of the use of ionic liquids for the O–H insertion of diazoketones with alcohols and water.

With an ever-increasing quest for exploration of newer reactions in ionic liquids, we report herein for the first time the use of ionic liquids as green solvents for the O–H insertion reactions of α -diazocarbonyl compounds with water and alcohols to afford α -hydroxy- and α -alkoxy ketones in excellent yields. For example, treatment of diazoacetophenone with water at 80 °C in the absence of any acid catalyst in [bmim]BF₄ afforded 2-hydroxy acetophenone in 85% yield (Scheme 1).

The reaction proceeds smoothly in [bmim]BF₄ ionic liquid without the need of any acid catalyst. The remarkable catalytic activity of [bmim]BF₄ prompted us to study it further in reactions with other α -diazocarbonyl compounds. Interestingly, a variety of α -diazoketones reacted efficiently with water and alcohols under the reaction conditions to give the corresponding α -hydroxyand α -alkoxy ketones as products of O–H insertion. Diazoketone derived from cyhalothric acid also gave similar results. Both aromatic and aliphatic diazoketones afforded the respective α -alkoxyand α -hydroxy ketones in excellent yields with high selectivity. A variety of substrates including tert-butyl, isopropyl, allylic, benzylic, propargylic alcohols, and cyclopropyl carbinols underwent smoothly O-H insertion reactions with α -diazoketones to give the corresponding α -alkoxy ketones (Table 1). The products could be easily separated by simple extraction with diethyl ether. No side product arising from Wolff rearrangement was observed under these reaction conditions. Other side products such as α -halo ketones (as products of halide insertion) arising especially from Lewis acids such as indium or aluminium halides, were not detected under these conditions. To compare the efficacy of ionic liquids, we have carried out the reactions both in hydrophobic [bmim]PF₆ and hydrophilic [bmim]BF4 ionic liquids. Among them, [bmim]BF4 was found to be the most effective and giving the best

Scheme 1.

Table 1. [Bmim]BF₄-catalyzed OH-insertion reactions of α -diazo ketones

Entr	y <i>α</i> ⊢Diazoketone 1	Alcohol 2	Producta 3	Reaction Tme /h	Yield⊧ /%
a (H ₂ O	CI , , , , , , , , OH CF ₃ X	4.5	86
b	н	≫он		3.5	90
c		→он		5.0	85
d		√∩н		4.5	87
e		CI~_OH		6.0	82
f	"	∽∽он		~ 5.0	84
g		H ₂ O	ОН	5.0	85
h	н	//^ОН		4.0	91
i	н	Ph OH		Ph 4.5	87
j		√ОН		5.0	92
k	н	∽∽он		4.5	83
ı	n	Ph [^] OH	C Ph	5.0	85
m		≻он	СІСОН	5.5	82
n	н	≫^он	CI CI CI CI	4.5	90
0		Ph ^{OH}	CI C	5.0	83
р		√ОН		4.0	89

^aAll products were charactarized by ¹H NMR, IR and MS. ^bIsolated and unoptimized yields.

results. Similar results were also obtained with ionic liquids having longer alkyl chains such as 1-hexyl-3-methylimidazolium tetrafluoroborate [hmim]BF4 or 1-octyl-3-methylimidazolium tetrafluoroborate [octmim]BF4. These air and moisture stable ionic liquids can be easily recovered and reused after activation at 80 °C for 3-4 h. Thus, activated [bmim]BF₄ ionic liquid was recycled for several times with consistent in activity, even after fourth cycle the product **3b** was obtained with the similar yield and purity of those obtained in the first cycle. No trace of impurites derived from ionic liquids were detected by GLC analysis of the products. Ionic liquids used in this study were obtained from Fluka and also prepared from the readily available and inexpensive N-methyl imidazole, 1-chlorobutane, and sodium hexafluorophosphate or sodium tetrafluroborate and their purity was determined by comparing of their ¹H NMR spectra with commercial samples. The purity of [bmim]PF₆ ionic liquid is \geq 97.0% (NMR). The use of ionic liquids as reaction medium for this reaction avoids the use of moisture sensitive reagents or heavy metal Lewis acids or solid acids as promoters thereby minimizing the production of toxic or corrosive acid waste during workup. In order to compare the efficiency of ionic liquids, the reactions were also conducted in organic solvents such as acetonitrile and chloroform. In these organic solvents in the absence of Lewis acids, the diazoketones were unreacted and completely recovered even under refluxing conditions. In ionic liquid even in the absence of acid catalyst, the reactions proceeded smoothly with high efficiency. It is noteworthy to mention that O–H insertion of α -diazoketones with alcohols proceeds smoothly at room temperature when using 5 mol % of bismuth triflate in [bmim]BF₄. In the absence of catalyst, high temperature (80 °C) and longer reaction times (3.5–6 h) are typical to achieve comparable yields to those obtained with 5 mol % of Bi(OTf)₃ in [bmim]BF₄. The scope of this method is illustrated with various diazoketones and a wide range of alcohols and the results are presented in the Table.

In summary, [bmim]BF₄ ionic liquid has been employed for the first time as an efficient and recyclable reaction media for the O–H insertion of α -diazoketones with alcohols and water to afford α -alkoxy- and α -hydroxy-ketones respectively. Ionic liquid plays a dual role of catalyst and the promoter. The diazoketones (electrophilic carbenes) show increased reactivity in ionic liquids thereby reducing the reaction times and improving the yields. The simple experimental and product isolation procedures combined with ease of recovery and reuse of ionic liquids is expected to contribute to the development of green strategy for the preparation of α -alkoxyand α -hydroxy ketones.

BVS thanks CSIR, New Delhi, for the award of fellowship.

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- General procedure: A mixture of α -diazoketone (1 mmol) and alcohol (2 mmol) or water (3 mmol) in 1-butyl-3-methylimidazolium tetrafluoroborate (3 mL) were stirred at 80 °C for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with diethyl ether $(3 \times 10 \text{ mL})$. The combined ether extracts were concentrated in vacuo and the resulting product was directly charged onto a small silica gel column and eluted with a mixture of ethyl acetate:n-hexane (2:8) to afford pure alkoxy or hydroxy ketone. The remaining ionic liquid was further washed with ether and recycled in subsequent runs. Spectroscopic data for selected products:3b: ¹H NMR (200 MHz, CDCl₃) δ: 1.25 (s, 3H), 1.38 (s, 3H), 2.30 (dd, 1H, J = 8.1, 8.5 Hz), 2.58 (d, 1H, J = 8.1 Hz), 3.99–4.05 (m, 4H), 5.20–5.30 (m, 2H), 5.80–5.97 (m, 1H), 6.98 (d, 1H, J = 8.5 Hz). IR (KBr) ν 3080, 2929, 1711, 1651, 1412, 1291, 1139, 953, 732 cm⁻¹. EIMS: *m/z*: 296 M⁺, 225, 197, 161, 141, 71, 41. **3p**: ¹H NMR (200 MHz, CDCl₃) δ : 0.15–0.25 (m, 2H), 0.48–0.57 (m, 2H), 1.0–1.15 (m, 1H), 3.35 (d, 2H, $J=6.5\,{\rm Hz}), 4.60$ (s, 2H), 7.45 (d, 2H, J = 8.0 Hz), 7.90 (d, 2H, J = 8.0 Hz). IR (KBr) ν 3084, 2924, 1695, 1590, 1488, 1401, 1283, 1226, 1132, 1092, 980, 826 cm⁻¹. EIMS: *m*/*z*: 224 M,⁺ 154, 139, 125, 111, 75, 55, 39.