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Ionic Liquid-Mediated Darzens Condensation: An Environmentally-Friendly Procedure for the Room-Temperature Synthesis of α,β-Epoxy Ketones

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This room-temperature Darzens condensation of α-chloroacetophenone with various aromatic aldehydes mediated by [bmim][BF_4] ionic liquid in the presence of sodium *tert*-butoxide resulted in the sole formation of good to excellent yields of *trans*-α,β-epoxy ketones in short time periods. In contrast, *tert*-butyl 2-chloroacetate underwent Darzens reactions with aldehydes giving mixtures of both *cis* and *trans* products with low selectivity. In all reactions, the ionic liquid was recovered and reused in the subsequent reactions without significant loss of activity.

Keywords: Ionic liquids, Room temperature, Darzens reaction, α,β-Epoxy ketones

INTRODUCTION

The overwhelming demand to design green and safe chemical procedures in the past three decades has dictated the use of safer and less toxic media with more environmental compatibility [1]. In this context, ionic liquids have emerged as very powerful substitutes for regular molecular solvents from both economical and environmental points of view [2]. Relatively low volatility, no chance of explosion, thermal stability, and ease of handling are among the reasons to consider ionic liquids as environmentally-benign alternatives for conventional solvents. Easy separation of the products from ionic liquids is an additional advantage in many instances. Of the various ionic liquids, those with the 1-butyl-3-methyl-1*H*-imidazolium moiety show great promise as eco-friendly catalytic systems for organic transformations at room temperature [3].

One of the most versatile tools in synthetic organic chemistry for the preparation of α,β-epoxy carbonyl compounds is the condensation of α-halo carbonyl moieties with aldehydes and ketones, known as the Darzens reaction [4]. In addition, this reaction is a very powerful method for one-carbon homologation of aldehydes and ketones [5]. The Darzens reaction is traditionally carried out in the presence of strong bases and mechanistically includes an aldol reaction of an α-halo carbonyl compound with an aldehyde to form a C-C bond followed by an intramolecular annulation of the intermediate halohydrin compound to form an epoxy product.

Many alterations to the traditional procedure of the reaction were made in recent years to enhance the synthetic applications of the Darzens reaction by the use of phase-transfer catalysts [6], enantioselective reagents [7], aqueous alkaline media [8], ammonium ylides [9], and Lewis acid catalysis [10]. However, the majority of available methods involve Darzens reactions of haloacetate esters, and little investigation of α-haloketones, in this respect, has been carried out. We recently reported a general procedure for Darzens reactions of α-haloketones with aromatic aldehydes

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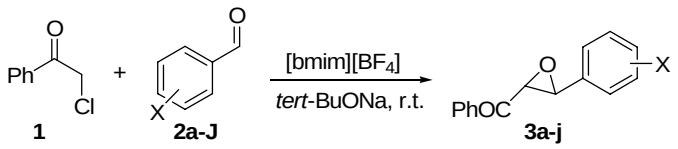


Scheme 1

using KF/Al_2O_3 [11]. Based on this experience and in continuation of our previous investigations on the development of environmentally compatible reactions [12], we herein introduce a novel procedure for the condensation of aromatic aldehydes with active methylene compounds mediated by recyclable [bmim][BF_4] ionic liquid leading to the synthesis of α,β-epoxy ketones (Scheme 1).

EXPERIMENTAL

General

Reactions were monitored by TLC and GC. NMR spectra were obtained on a FT-NMR Bruker Ultra Shield™ (500 MHz) or Bruker AC 80 MHz as $CDCl_3$ solutions and the chemical shifts were expressed as δ units with Me_4Si as the internal standard. Gas chromatograms were obtained using a Fisons 8000 apparatus. All chemicals and reagents were purchased from commercial sources. Aldehydes were purified prior to use.

Typical Experimental Procedure for the Preparation of 3 (or 4)

To a mixture of the aldehyde (1.0 mmol), $PhCOCH_2Cl$ (or *tert*-BuO_2CCH_2Cl) (1.1 mmol), and [bmim][BF_4] (1.0 g) was added *tert*-BuONa (1.1 mmol) and the mixture was stirred at room temperature until TLC and GC experiments showed complete disappearance of the starting aldehyde. The mixture was extracted with diethyl ether (3 × 5 ml), the extracts were combined, the ethereal phase was dried over Na_2SO_4, and the volatile portion was removed under reduced pressure. The product was purified using short column chromatography with silica-gel and *n*-hexane/EtOAc (7:1), if necessary.

Recovery of the Ionic Liquid

After ethereal extraction of the products, the ionic liquid was washed with diethyl ether (8 ml), dissolved in CH_2Cl_2 (5 ml), and dried over Na_2SO_4. The CH_2Cl_2 portion was then evaporated under reduced pressure at 60 °C and 95% of the ionic liquid was recovered and successfully reused in next reaction.

Selected Spectral Data

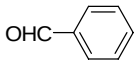
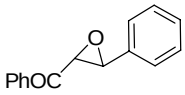
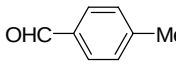
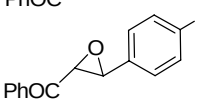
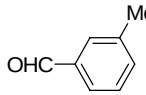
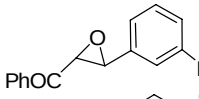
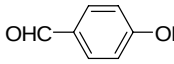
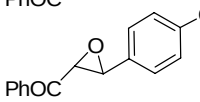
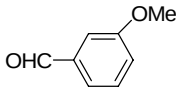
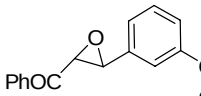
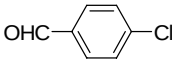
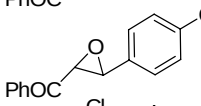
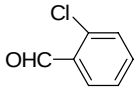
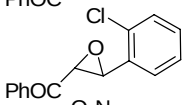
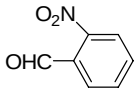
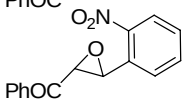
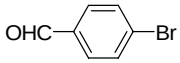
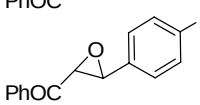
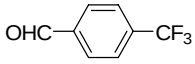
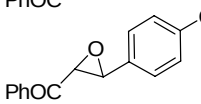
***trans*-2,3-Epoxy-1-(3-methoxyphenyl)-3-phenylpropan-1-one (3e).** White crystals were obtained in 95% yield, m.p.: 79-80 °C; IR (KBr, cm^{-1}) 1682, 1591, 1257; ^{1}H NMR ($CDCl_3$) δ (ppm) = 3.87 (s, 3H), 4.10 (d, 1H, *J* = 2 Hz), 4.32 (d, 1H, *J* = 2 Hz), 6.94-6.97 (m, 2H), 7.02 (d, 1H, *J* = 7.5 Hz), 7.35 (dd, 1H, *J* = 7.5, 7.5 Hz), 7.53 (dd, 2H, *J* = 7.5, 7.5 Hz), 7.66 (dd, 1H, *J* = 7.5, 7.5 Hz), 8.05 (dd, 2H, *J* = 1.5, 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) = 55.8, 59.7, 61.4, 111.3, 115.2, 118.7, 128.8, 129.3, 130.3, 134.5, 135.9, 137.6, 160.5, 193.5; MS (70 eV) m/z (%): 254 (M^+), 225, 149, 105. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.34; H, 5.47.

***trans*-2,3-Epoxy-1-(2-chlorophenyl)-3-phenylpropan-1-one (3g).** White crystals were obtained in 90% yield, m.p.: 72-73 °C; IR (KBr, cm^{-1}) 1687, 1228, 1022; ^{1}H NMR ($CDCl_3$) δ (ppm) = 4.21 (d, 1H, *J* = 2 Hz), 4.44 (d, 1H, *J* = 2 Hz), 7.35 (dd, 2H, *J* = 3.5, 7 Hz), 7.40-7.45 (m, 2H), 7.54 (dd, 2H, *J* = 7.5, 7.5 Hz), 57.66 (dd, 1H, *J* = 7.5, 9.5 Hz), 8.09 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) = 7.6, 60.5, 126.6, 127.7, 128.8, 129.3, 129.8, 130.2, 133.7, 134.2, 134.5, 135.8, 193.2; MS (70 eV) m/z (%): 258 (M^+), 223, 165, 105. Calcd. for $C_{15}H_{11}ClO_2$: C, 69.64; H, 4.29. Found: C, 69.47; H, 4.24.

***trans*-2,3-Epoxy-1-(2-nitrophenyl)-3-phenylpropan-1-one (3h).** Light pink crystals were obtained in 91% yield, m.p.: 109-110 °C; IR (KBr, cm^{-1}) 1686, 1332, 1227; ^{1}H NMR ($CDCl_3$) δ (ppm) = 4.26 (d, 1H, *J* = 2 Hz), 4.67 (d, 1H, *J* = 2 Hz), 7.52 (dd, 2H, *J* = 7.5, 8 Hz), 7.59 (ddd, 1H, *J* = 4, 5.5, 9 Hz), 7.65 (dd, 1H, *J* = 7.5, 7.5 Hz), 7.77 (d, 2H, *J* = 4 Hz), 8.05 (dd, 2H, *J* = 1, 8.5 Hz), 8.24 (d, 1H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) = 58.1, 60.0, 125.4, 127.8, 128.9, 129.3, 129.9, 133.0, 134.5, 135.1, 135.8, 147.9, 192.9; MS (70 eV) m/z (%): 269 (M^+), 183, 135, 105. Calcd. for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12. Found: C, 66.70; H, 4.06.

***trans*-2,3-Epoxy-1-(4-bromophenyl)-3-phenylpropan-1-one (3i).** White crystals were obtained in 92% yield, m.p.: 88-89 °C; IR (KBr, cm^{-1}) 1663, 1438, 1297; ^{1}H NMR ($CDCl_3$) δ (ppm) = 4.08 (d, 1H, *J* = 2 Hz), 4.29 (d, 1H, *J* = 2 Hz), 7.29 (d,

Table 1. Room Temperature [bmim][BF_4]-Mediated Reactions of $PhCOCH_2Cl$

Entry	Aldehyde		Product		Time (h)	Yield (%)[a]
1		**2a**		**3a**	3 h	90
2		**2b**		**3b**	3 h	88
3		**2c**		**3c**	3 h	89
4		**2d**		**3d**	3 h	80
5		**2e**		**3e**	3 h	95
6		**2f**		**3f**	2 h	96
7		**2g**		**3g**	2 h	90
8		**2h**		**3h**	1 h	91
9		**2i**		**3i**	2 h	92
10		**2j**		**3j**	1 h	95

[a]Isolated yields.

2H, *J* = 8.5 Hz), 7.52-7.58 (m, 4H), 7.66 (dd, 1H, *J* = 7, 7.5 Hz), 8.04 (dd, 2H, *J* = 1, 8 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) = 59.2, 61.3, 123.5, 127.9, 128.8, 129.4, 132.4, 134.6, 135.0, 135.8, 193.1; MS (70 eV) m/z (%): 302 (M^+), 275, 194, 105. Calcd. for $C_{15}H_{11}BrO_2$: C, 59.43; H, 3.66. Found: C, 59.19; H, 3.58.

***tert*-Butyl-3-phenyloxirane-2-carboxylate (4a).** Isolated in 60% yield. ^{1}H NMR for the *cis* isomer ($CDCl_3$) δ (ppm) = 1.09 (s, 9H), 3.60 (d, 1H, *J* = 4.7 Hz), 4.10 (d, 1H, *J* = 4.7 Hz), 7.19-7.26 (m, 5H).

***tert*-Butyl-3-(4-methylphenyl)oxirane-2-carboxylate (4b).** Isolated in 84% yield. ^{1}H NMR for the *cis* isomer ($CDCl_3$) δ (ppm) =1.13 (s, 9H), 2.24 (s, 3H), 3.60 (d, 1H, *J* = 4.5 Hz), 4.09 (d, 1H, *J* = 4.5 Hz), 6.98-7.26 (m, 4H).

***tert*-Butyl-3-(4-bromophenyl)oxirane-2-carboxylate (4i).** Isolated in 85% yield. ^{1}H NMR for the *cis* isomer ($CDCl_3$) δ (ppm) = 1.15 (s, 9H), 3.63 (d, 1H, *J* = 4.6 Hz), 4.09 (d, 1H, *J* = 4.6 Hz), 7.15-7.43 (m, 4H).

RESULTS AND DISCUSSION

The results obtained for the condensation of α-chloroacetophenone **1** with various aldehydes **2a-j** are summarized in the Table 1. The complete conversion of the equimolar mixture of **1**, benzaldehyde, and *tert*-BuONa in [bmim][BF_4] to a single product was observed after 3 h.

Following extraction, the *trans* product **3a** was obtained in 90% yield (entry 1).

The same reaction was conducted in the presence of other reagents to evaluate the effect of various bases (Table 2). The formation of smaller quantities of **3a** was detected after several hours and the rest of the starting materials were recovered. To illustrate the generality of the reaction, other aldehydes bearing electron-releasing groups or electron-withdrawing groups (Table 1, entries 2-10) were subjected to the same conditions. Again, reactions completed within 1-3 h to form exclusively *trans* products **3b-j** in 80-96% yields. Products were characterized by spectroscopic methods, and the results were matched with those available in the literature [9]. In all experiments, the medium was recovered after extraction of the products and was effectively reused in the following reactions.

To examine the substrate dependency of this procedure, α-chloroacetophenone was replaced with *tert*-butyl 2-chloroacetate. Under these conditions, for all of the aldehydes, reactions were slower, reaching completion within 12 h, giving mixtures of both *cis* and *trans* products with low stereoselectivity. The condensation of benzaldehyde and electron-rich 4-methoxybenzaldehyde with *tert*-butyl 2-chloroacetate gave lower quantities of their respective products with similar stereoselectivity (Table 3).

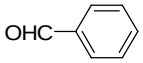
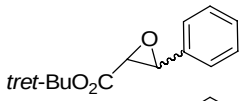
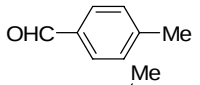
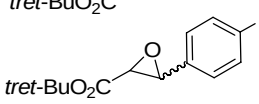
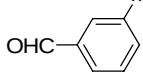
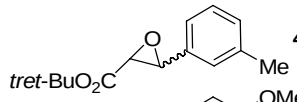
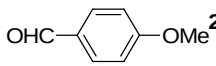
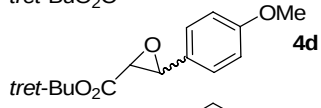
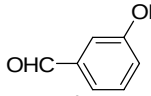
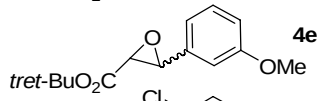
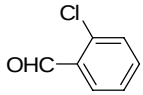
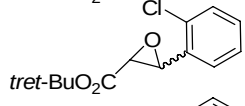
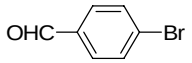
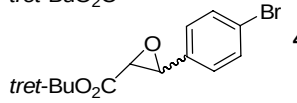
In conclusion, we disclose a novel and efficient room-temperature procedure for Darzens condensation of active methylene compounds with different aldehydes using an ionic

Table 2. Effect of Various Bases on the Condensation of Benzaldehyde with $PhCOCH_2Cl$

Entry	Base	Yield (%)[a]
1	*tert*-BuONa	90
2	EtONa	-
3	KOH	70
4	Et_3N	41
5	morpholine	-

[a]GC yields after 3 h.

Table 3. Room Temperature [bmim][BF_4]-Mediated Reactions of *tert*-BuO_2CCH_2Cl

Entry	Aldehyde		Product		*cis*:*trans*[a]	Time (h)	Yield (%)[b]
1		**2a**		**4a**	2.3:1	9	60
2		**2b**		**4b**	3.2:1	11	84
3		**2c**		**4c**	3.6:1	11	90
4		**2d**		**4d**	2.3:1	12	45
5		**2e**		**4e**	2.7:1	10	74
6		**2g**		**4g**	1.4:1	7	76
7		**2i**		**4i**	2:1	7	85

[a]Ratios determined by ^1H NMR. [b]Isolated yields.

liquid media. The use of inexpensive reagents, generality of the reaction, sole formation of *trans* compounds in the case of α-chloroacetophenone, and rapid completion of the process are the advantages of this method. In particular, employment of a recoverable ionic liquid media highlights the environmental safety of the procedure in addition to avoiding the use of hazardous solvents required in other reported methods [6a,6b,9a,10a]. Moreover, due to the limited number of procedures for Darzens condensation of α-haloketones, this work is a useful addition to the present literature archive.

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