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Darzens Reaction Promoted by KF/ Alumina: A Novel Stereoselective Method for Rapid and Efficient Synthesis of *trans*α,β-Epoxy Ketones

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Abstract: The Darzens condensation of α -chloroacetophenone with various aromatic aldehydes mediated by potassium fluoride on alumina at room temperature resulted in formation of good to excellent yields of *trans*- α , β -epoxy ketones in short time periods.

Keywords: darzens reaction, solid-phase synthesis, KF/alumina, α , β -epoxy ketones

The push toward development of green and environmentally benign chemistry in the past three decades has dictated the use of safer and less hazardous reagents and media capable of inducing versatile organic transformations with fewer side products and solvent requirements.^[1] In this context, potassium fluoride on alumina (KF/Al₂O₃)^[2] has emerged as a very powerful solid-phase reagent for various organic functional manipulations such as ring-closure reactions,^[3] epoxidation of alkenes,^[4] ether synthesis,^[5] amide^[6] and amine^[7] chemistry, Michael addition,^[8] aldol condensation,^[9] rearrangement processes,^[10] and cycloaddition reactions.^[11] A number of advantages are associated with the use of this reagent, such as avoiding the cleavage step usually required in solid-phase syntheses,^[12]

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decrease of solvent use, no special handling requirements, easy monitoring of reactions, and convenient workup procedure by removal of the solid from the reaction mixture via a simple filtration.

Condensation of α -halo carbonyl moieties with aldehydes and ketones, known as the Darzens reaction, is one of the most versatile tools in synthetic organic chemistry for the preparation of α,β -epoxy carbonyl compounds.^[13] In addition, this reaction is a very powerful method for onecarbon homologation of aldehydes and ketones.^[14] 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,^[15] enantioselective reagents,^[16] aqueous alkaline medium,^[17] ammonium ylides,^[18] and Lewis acid catalysis.^[19] Despite these modifications, use of strong basic media is still required^[17] in many of these procedures, or stoichiometric amounts of an expensive reagent are used.^[15] Moreover, the majority of available methods involve Darzens reactions of haloacetate esters, and not much investigation on α -haloketones side has been carried out. A search in the literature reveals a report by Yamawaki et al. containing a single example of a Darzens reaction performed in the presence of KF/Al₂O₃ in benzene.^[20] Based on this example and in continuation of our previous experiences with solid-phase chemistry,^[21] we decided to evaluate the generality of Darzens reactions of α -haloketones with aromatic aldehydes in the presence of KF/Al₂O₃ under more environmentally benign conditions (Scheme 1).

Table 1 presents the results obtained from the condensation of α -chloroacetophenone **1** with various aldehydes bearing electronwithdrawing or electron-releasing groups **2a**–**j**. We first examined the reaction using a suspension of KF/Al₂O₃ in a 1:1 mixture of α -chloroacetophenone and benzaldehyde at room temperature. The course of the reaction was monitored by thin-layer chromatography (TLC) and gas chromatography (GC) until complete disappearance of the starting aldehyde was observed, in less than 2 h. Simple extraction of the mixture by ethyl acetate and removal of the volatile portion showed formation of a single *trans* product **3a** in 92% yield (entry 1).



Scheme 1.

Table 1. Darzens reaction of aldehydes 2a-j with 1 in the presence of KF/Al₂O₃

Entry	Aldehyde	Product	Yield ^a (%)
1	C ₆ H ₅ CHO	PhOC Jan 3a	92
2	4-MeC ₆ H ₄ CHO	PhOC 0 3b	90
3	4-MeOC ₆ H ₄ CHO	PhOC O OMe	83
4	3-MeOC ₆ H ₄ CHO	PhOC 3d	95
5	4-CIC ₆ H ₄ CHO		96
6	2-ClC ₆ H ₄ CHO	PhOC 0 3f	92
7	4-NO ₂ C ₆ H ₄ CHO	PhOC O NO ₂	94
8	2-NO ₂ C ₆ H ₄ CHO	PhOC O 3h	99
9	4-BrC ₆ H ₄ CHO	PhOC 0 Br	93
10	4-CF ₃ C ₆ H ₄ CHO	PhOC O CF ₃	97

^aIsolated yields.

The promoting effect of the solid support was examined by stirring a mixture of the two reactants in the absence of KF or alumina. In these cases, formation of only small quantities of **1a** was detected after several hours, and the majority of the starting materials were recovered. In addition, when the reaction was repeated in a solution of benzene using Ando's procedure,^[20] only 65% of *trans* **3a** was obtained after 24 h, illuminating the devastating effect of the solvent.

To illustrate the generality of the reaction, other aldehydes bearing electron-releasing groups (entries 2–4) or electron-withdrawing groups (entries 5–10) were subjected to the same conditions. Similarly, reactions completed within 1-2h to form exclusively *trans* products 3b-j in

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83–99% yield. Products were characterized by spectroscopic methods, and the results were matched with those available in the literature.^[18a,20a]

Additional test reactions were conducted to examine the substrate dependency of this procedure by subjecting a mixture of *tert*-butyl 2-chloroacetate and benzaldehyde to the same reaction conditions. As a result, 97% of two geometric isomers of **4** were obtained with a low *cis/trans* stereoselectivity of 1/2. A similar mixture in benzene gave only 68% of **4** with the same stereoselectivity after 10 h (Scheme 2).

In conclusion, we disclose a novel and efficient procedure for Darzens reactions of α -chloroacetophenone with aldehydes promoted by KF/Al₂O₃ under very mild conditions. Use of inexpensive reagents, the generality of the reaction, sole formation of *trans* compounds in short time periods, and use of no other additives or solvent are the advantages of the present work. Further studies to apply this methodology to other α -halo carbonyl compounds are also under investigation.

Experimental

Melting points were determined with a Buchi melting-point apparatus and are uncorrected. IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer. NMR spectra were obtained on a FT-NMR Bruker Ultra ShieldTM (500 MHz) as CDCl₃ solutions using TMS as internal standard reference. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. GC-MS spectra were obtained on a Fisons 8000 Trio instrument at ionization potential of 70 eV. TLC experiments were carried out on precoated silica-gel plates using hexane/EtOAc (5:1) as the eluent. GC experiments were performed using a Varian CP-3800 instrument equipped with capillary column CP-SIL 5 CB with length of 30 m and 0.32 i.d. Compounds 3a-3c,^[22] 3e,^[22] 3g,^[22] and 3j^[23] have been previously reported. Reagents were purchased from commercial sources. Aldehydes were purified before use.

Preparation of KF/Alumina^[24]

To a stirred solution of potassium fluoride (20 g) in water (150 ml), neutral alumina (60–80 mesh, 30 g) in water (150 ml) was added. After 30 min, the water was evaporated in a rotary evaporator at $\sim 60^{\circ}$ C. When most of the

water has been removed, the remaining mixture was heated to $140-150^{\circ}$ C and maintained at that temperature under vacuum (5 mmHg) for 6 h to give 50 g of KF-alumina reagent.

Typical Darzens Procedure

A mixture of the aldehyde (10 mmol), ketone **1** (11 mmol), and KF/Al₂O₃ (5 g) was stirred at room temperature until TLC and GC experiments showed complete disappearance of the starting aldehyde. The mixture was extracted with EtOAc (3×50 mL), the extracts were combined, and the volatile portion was removed under reduced pressure. The product was purified with short column chromatography over silica-gel using hexane/ EtOAc (7:1), if necessary.

Data

trans-2,3-Epoxy-1-(3-methoxyphenyl)-3-phenylpropan-1-one (3d)

White crystals were obtained in 95% yield, mp 79–80°C; IR (KBr, cm⁻¹) 1682, 1591, 1257; ¹H NMR (CDCl₃) δ 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), 7.51 (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); ¹³C NMR (CDCl₃) δ 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 C₁₆H₁₄O₃: C, 75.57; H, 5.55. Found: C, 75.34; H, 5.47.

trans-2,3-Epoxy-1-(2-chlorophenyl)-3-phenylpropan-1-one (3f)

White crystals were obtained in 92% yield, mp 72–73°C; IR (KBr, cm⁻¹) 1687, 1228, 1022; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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 C₁₅H₁₁ClO₂: 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 99% yield, mp $109-110^{\circ}$ C; IR (KBr, cm⁻¹) 1686, 1332, 1227; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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 C₁₅H₁₁NO₄: 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 93% yield, mp 88–89°C; IR (KBr, cm⁻¹) 1663, 1438, 1297; ¹H NMR (CDCl₃) δ 4.08 (d, 1H, J = 2 Hz), 4.29 (d, 1H, J = 2 Hz), 7.29 (d, 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); ¹³C NMR (CDCl₃) δ 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 C₁₅H₁₁BrO₂: C, 59.43; H, 3.66. Found: C, 59.19; H, 3.58.

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