

Clean Synthesis in Water: Darzens Condensation Reaction of Aromatic Aldehydes with Phenacyl Chloride

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The Darzens condensation reaction of aromatic aldehydes with phenacyl chloride proceeded very efficiently in a water suspension medium in the presence of triethylbenzylammonium chloride and only *trans*-2,3-epoxy-1,3-diaryl-1-propanones were formed which can be isolated simply by filtration. The structures of these compounds were confirmed by elemental analysis, IR and ¹H NMR spectra. Their configurations are in agreement with that of the same compounds reported in the literature. Compared to the classical Darzens condensation, this new method has the advantages of good yields, high stereoselectivity, low running cost inexpensive and environmentally benign procedure.

Keywords clean synthesis, water, Darzens condensation, aromatic aldehydes, phenacyl chloride

Introduction

Carbon-carbon bond formation is the fundamental reaction in organic synthesis and the Darzens condensation reaction represents one of the classical C—C bond-forming processes,¹ and its variants have been used extensively in many important synthesis. The classical Darzens condensation can be performed as routine procedure in the presence of a strong base (RONa, ROK or NaNH₂) in organic solvents under anhydrous condition.^{1,2} However, these methods are highly laborious and/or in low yields, and are not suitable for large scale preparation.

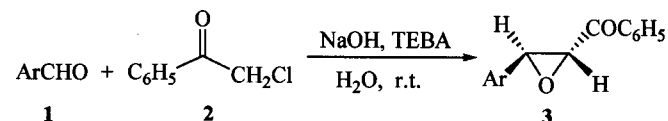
The need to reduce the amount of toxic waste and byproducts arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods.³ One of the most promising approaches uses water as reaction medium.⁴ Breslow,⁵ who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic chemistry in 1980s. In recent years, there has been increasing recognition that water is an attractive medium for many organic reactions.⁶ The aqueous medium with respect to organic solvent is less expensive, less dan-

gerous and environment-friendly, while it allows the control of the pH and the use of microaggregates such as surfactants. Generally, the low solubility⁷ of most reagents in water is not an obstacle to the reactivity, which, on the contrary, is reduced with the use of cosolvents. We are interested in performing organic reactions in water and have investigated Knoevenagel condensation and addition reactions.⁸ As a part of our research to develop a green chemistry by one-pot synthesis of target molecules in water alone as the reaction medium, the Darzens condensation reaction of aromatic aldehydes with phenacyl chloride for the preparation of *trans*-2,3-epoxy-1,3-diaryl-1-propanones performed in water is reported.

Results and discussion

An equimolar mixture of aromatic aldehyde (1), phenacyl chloride (2) and NaOH in the presence of triethylbenzylammonium chloride (TEBA) as a cationic surfactant in a small amount of water was stirred at room temperature for 2—14 h. The crude product was collected by filtration, washed with water and purified by recrystallization to give *trans*-2,3-epoxy-1,3-diaryl-1-propanones (3) in good yields (Scheme 1). The results are summarized in Table 1.

Scheme 1



Oxiranes have *cis* and *trans* isomers such as *cis*-3a (m. p. 96—97 °C) and *trans*-3a (m. p. 89—90 °C⁹). But only the *trans* isomer was obtained by this method. The products 3a, 3c, 3f, 3h and 3i are known, their configurations are in agreement with the same compounds prepared by House¹⁰ using alkaline epoxidation of the corresponding unsaturated ketone. The remaining products might

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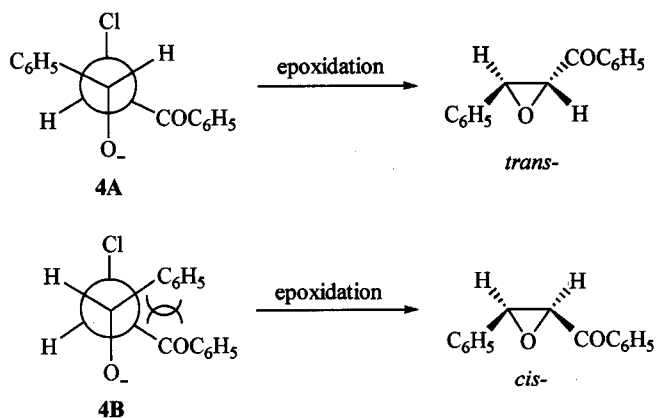
Table 1 Darzens condensation of aromatic aldehydes (**1**) with phenacyl chloride (**2**) in water

Entry	Compound	Ar	Time (h)	Yield (%)
1	3a	C ₆ H ₅	3	91
2	3b	4-FC ₆ H ₄	4.5	91
3	3c	4-ClC ₆ H ₄	4	95
4	3d	4-BrC ₆ H ₄	3.5	99
5	3e	2,4-Cl ₂ C ₆ H ₃	4.5	95
6	3f	4-CH ₃ C ₆ H ₄	14	84
7	3g	2-NO ₂ -5-ClC ₆ H ₃	2.5	92
8	3h	4-NO ₂ C ₆ H ₄	2.5	95
9	3i	2-NO ₂ C ₆ H ₄	2	91
10	3j	3-NO ₂ C ₆ H ₄	3	97

safely be assigned to be the same configuration.

The mechanism of the base-catalyzed condensation of benzaldehyde with phenacyl chloride was reported.¹¹ The reaction is of third order, the rate-determining step involving benzaldehyde, phenacyl chloride and hydroxyl ion. This fact is that enolizations of phenacyl chloride and epoxide formation from the chlorohydrin are both much more rapid than the attack of phenacyl chloride anion on benzaldehyde chlorohydrin.

The observed stereoselectivity for the formation of epoxide based on the different conformation for the anions can be explained by the two important conformations **4A** and **4B**. Conformation **4A**, which is non-eclipsed conformation, may be favored because the steric hindrance effects are minimized (the phenyl group and benzoyl group being in *anti*-positions), and if the cyclization occurs, the *trans* conformation products are obtained. However, the eclipsed conformation **4B** is less favored due to the steric interactions between the phenyl group and benzoyl group in *syn*-positions so, it is difficult to form the *cis* products (Scheme 2).

Scheme 2

In conclusion, we have reported a good yield one-pot procedure at room temperature in water for the synthesis of *trans*-2,3-epoxy-1,3-diaryl-1-propanones (**3**), by the reaction of aromatic aldehydes with phenacyl chloride. Compared to the classical Darzens condensation, this new

method has the advantage of good yields, high stereoselectivity, inexpensive reagents and environmentally friendly reaction conditions.

Experimental

Melting points are uncorrected. Infrared spectra were recorded on an IR-8101 spectrometer in KBr with absorption in cm⁻¹. ¹H NMR spectra were recorded on a Inova-400 spectrometer as CDCl₃ solutions. *J* values are in Hz. Chemical shifts are expressed in δ downfield from internal tetramethylsilane. Microanalysis was carried out on a Perkin Elmer 2400 II instrument.

General procedure for the synthesis of *trans*-2,3-epoxy-1,3-diaryl-1-propanone (**3**)

A suspension of a mixture of **1** (5 mmol), **2** (0.77 g, 5 mmol), NaOH (0.24 g, 6 mmol) and TEBA (0.1 g) was stirred in water (10 mL) at room temperature for 2–14 h. The crystalline power formed was collected by filtration, washed with water and recrystallized from EtOH to give pure **3**.

Trans-2,3-epoxy-1,3-diphenyl-1-propanone (**3a**)

M.p. 89–90 °C (lit.¹¹ 88.8–90.0 °C); ¹H NMR (CDCl₃) δ: 4.09 (s, 1H, C₃-H), 4.31 (s, 1H, C₈-H), 7.39–7.41 (m, 5H, ArH), 7.48–7.52 (m, 2H, ArH), 7.63 (t, *J* = 7.2 Hz, 1H, ArH), 8.02 (d, *J* = 8.4 Hz, 2H, ArH); IR (KBr) ν: 1687, 1584, 1490, 1434, 1385, 1238, 892, 831, 776, 752, 696 cm⁻¹. Anal. calcd for C₁₅H₁₂O₂: C 80.34, H 5.39; found C 80.53, H 5.04.

Trans-2,3-epoxy-1-phenyl-3-(4'-fluorophenyl)-1-propanone (**3b**) M.p. 88–89 °C; ¹H NMR (CDCl₃) δ: 4.07 (s, 1H, C₃-H), 4.27 (s, 1H, C₂-H), 7.08–7.13 (m, 2H, ArH), 7.34–7.38 (m, 2H, ArH), 7.51 (t, *J* = 7.2 Hz, 2H, ArH), 7.63 (t, *J* = 7.2 Hz, 1H, ArH), 8.01 (d, *J* = 8.4 Hz, 2H, ArH); IR (KBr) ν: 1687, 1601, 1513, 1451, 1398, 1217, 1157, 1010, 894, 847, 757, 689 cm⁻¹. Anal. calcd for C₁₅H₁₁FO₂: C 74.37, H 4.58; found C 74.63, H 4.39.

Trans-2,3-epoxy-1-phenyl-3-(4'-chlorophenyl)-1-propanone (**3c**) M.p. 79–80 °C (lit.¹⁰ 78.9–79.5 °C); ¹H NMR (CDCl₃) δ: 4.07 (s, 1H, C₃-H), 4.26 (s, 1H, C₂-H), 7.32 (d, *J* = 8.4 Hz, 2H, ArH), 7.39 (d, *J* = 8.4 Hz, 2H, ArH), 7.51 (t, *J* = 7.2 Hz, 2H, ArH), 7.64 (t, *J* = 7.2 Hz, 1H, ArH), 8.01 (d, *J* = 7.2 Hz, 2H, ArH); IR (KBr) ν: 1686, 1595, 1494, 1450, 1431, 1394, 1237, 1089, 1014, 893, 839, 821, 798, 778, 704, 685 cm⁻¹. Anal. calcd for C₁₅H₁₁ClO₂: C 69.64, H 4.29; found C 69.87, H 4.35.

Trans-2,3-epoxy-1-phenyl-3-(4'-bromophenyl)-1-propanone (**3d**) M.p. 88–90 °C; ¹H NMR (CDCl₃) δ: 4.06 (s, 1H, C₃-H), 4.25 (s, 1H, C₂-H), 7.24–7.26 (m, 2H, ArH), 7.49–7.56 (m, 4H, ArH), 7.64 (t, *J* = 7.2 Hz, 1H, ArH), 8.01 (d, *J* = 7.2 Hz, 2H, ArH); IR (KBr) ν: 1658, 1579, 1484, 1446, 1293,

1010, 888, 808, 698 cm^{-1} . Anal. calcd for $\text{C}_{15}\text{H}_{11}\text{BrO}_2$: C 59.43, H 3.66; found C 59.68, H 3.47.

Trans-2,3-epoxy-1-phenyl-3-(2', 4'-dichlorophenyl)-1-propanone (**3e**) M.p. 104–106 °C; ^1H NMR (CDCl_3) δ : 4.15 (s, 1H, $\text{C}_3\text{-H}$), 4.37 (s, 1H, $\text{C}_2\text{-H}$), 7.33–7.36 (m, 2H, ArH), 7.43 (s, 1H, ArH), 7.52 (t, $J = 7.2$ Hz, 2H, ArH), 7.65 (t, $J = 7.2$ Hz, 1H, ArH), 8.04 (d, $J = 7.6$ Hz, 2H, ArH); IR (KBr) ν : 1698, 1594, 1475, 1448, 1415, 1380, 1334, 1231, 1102, 1050, 1013, 900, 845, 825, 778, 696 cm^{-1} . Anal. calcd for $\text{C}_{15}\text{H}_{10}\text{Cl}_2\text{O}_2$: C 61.46, H 3.44; found C 61.53, H 3.27.

Trans-2,3-epoxy-1-phenyl-3-(4'-methylphenyl)-1-propanone (**3f**) M.p. 76–77 °C (lit.¹⁰ 77.2–78.2 °C); ^1H NMR (CDCl_3) δ : 2.39 (s, 3H, CH_3), 4.05 (s, 1H, $\text{C}_3\text{-H}$), 4.30 (s, 1H, $\text{C}_2\text{-H}$), 7.21–7.28 (m, 4H, ArH), 7.49 (t, $J = 7.2$ Hz, 2H, ArH), 7.63 (t, $J = 7.2$ Hz, 1H, ArH), 8.01 (d, $J = 7.2$ Hz, 2H, ArH); IR (KBr) ν : 1680, 1596, 1450, 1394, 1235, 1175, 1006, 885, 805, 786, 751, 690 cm^{-1} . Anal. calcd for $\text{C}_{16}\text{H}_{14}\text{O}_2$: C 80.65, H 5.92; found C 80.91, H 5.74.

Trans-2,3-epoxy-1-phenyl-3-(2'-nitro-5'-chlorophenyl)-1-propanone (**3g**) M.p. 155–156 °C; ^1H NMR (CDCl_3) δ : 4.24 (s, 1H, $\text{C}_3\text{-H}$), 4.65 (s, 1H, $\text{C}_2\text{-H}$), 7.49–7.55 (m, 3H, ArH), 7.63–7.67 (m, 1H, ArH), 7.73 (s, 1H, ArH), 8.02 (d, $J = 7.2$ Hz, 2H, ArH), 8.19 (d, $J = 8.4$ Hz, 1H, ArH); IR (KBr) ν : 1688, 1597, 1522, 1451, 1408, 1341, 1231, 1183, 1010, 938, 914, 888, 839, 720 cm^{-1} . Anal. calcd for $\text{C}_{15}\text{H}_{10}\text{ClNO}_4$: C 59.32, H 3.32, N 4.61; found C 59.58, H 3.42, N 4.78.

Trans-2,3-epoxy-1-phenyl-3-(4'-nitrophenyl)-1-propanone (**3h**) M.p. 150–151 °C (lit.⁹ 151–152 °C); ^1H NMR (CDCl_3) δ : 4.21 (s, 1H, $\text{C}_3\text{-H}$), 4.28 (s, 1H, $\text{C}_2\text{-H}$), 7.50–7.58 (m, 4H, ArH), 7.66 (t, $J = 7.2$ Hz, 1H, ArH), 8.02 (d, $J = 8.4$ Hz, 2H, ArH), 8.28 (d, $J = 8.8$ Hz, 2H, ArH); IR (KBr) ν : 1677, 1597, 1517, 1447, 1396, 1339, 1232, 1107, 1068, 1007, 881, 845, 772, 744, 703, 665 cm^{-1} . Anal. calcd for $\text{C}_{15}\text{H}_{11}\text{NO}_4$: C 66.91, H 4.12, N 5.20; found C 67.03, H 4.07, N 5.26.

Trans-2,3-epoxy-1-phenyl-3-(2'-nitrophenyl)-1-propanone (**3i**) M.p. 111–112 °C (lit.⁹ 113–114 °C); ^1H NMR (CDCl_3) δ : 4.23 (s, 1H, $\text{C}_3\text{-H}$), 4.65 (s, 1H, $\text{C}_2\text{-H}$), 7.50 (t, $J = 7.2$ Hz, 2H, ArH), 7.58–7.66 (m, 2H, ArH), 7.76 (d, $J = 4.8$ Hz, 2H, ArH), 8.03 (d, $J = 8.8$ Hz, 2H, ArH), 8.23 (d, $J = 8.8$ Hz, 2H, ArH); IR (KBr) ν : 1687, 1597, 1518, 1449, 1400, 1341, 1228, 1010, 911, 837, 775, 737, 687 cm^{-1} . Anal. calcd for $\text{C}_{15}\text{H}_{11}\text{NO}_4$: C 66.91, H 4.12, N 5.20; found C 67.18, H 3.93, N 5.07.

Trans-2,3-epoxy-1-phenyl-3-(3'-nitrophenyl)-1-propanone (**3j**) M.p. 115–117 °C; ^1H NMR (CDCl_3) δ : 4.22 (s, 1H, $\text{C}_3\text{-H}$), 4.32 (s, 1H, $\text{C}_2\text{-H}$), 7.50–

7.54 (m, 2H, ArH), 7.61–7.66 (m, 2H, ArH), 7.73 (d, $J = 7.6$ Hz, 1H, ArH), 8.03 (d, $J = 7.2$ Hz, 2H, ArH), 8.25 (s, 1H, ArH); IR (KBr) ν : 1696, 1596, 1531, 1450, 1351, 1231, 1101, 1010, 929, 874, 805, 777, 736, 705, 679 cm^{-1} . Anal. calcd for $\text{C}_{15}\text{H}_{11}\text{NO}_4$: C 66.91, H 4.12, N 5.20; found C 66.99, H 3.97, N 5.16.

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