Darzens condensation reaction in water

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Received 14th March 2001
First published as an Advance Article on the web 25th May 2001

Darzens condensation of benzaldehyde with phenacyl chloride proceeded very efficiently in a water suspension medium and the products were isolated simply by filtration.

Introduction

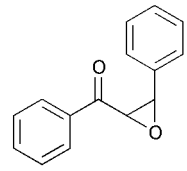
The Darzens condensation reaction is an important C–C bond forming reaction[1] and is usually carried out in organic solvents under dry conditions.[2] We have now found that Darzens condensation reactions of benzaldehydes **1** with phenacyl chloride **2** proceeds very efficiently in a water suspension medium and that 2,3-epoxy-1,3-diphenyl-1-propanone derivatives **3** are obtained simply by filtration. Enantioselective Darzens condensation reaction in the presence of a chiral chinchonidinium salt is also reported.

Results and discussion

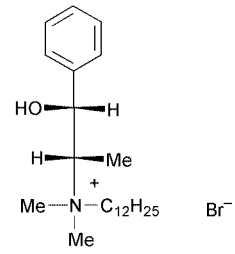
An equimolar mixture of benzaldehyde **1a** , phenacyl chloride **2** and NaOH in a small amount of water was stirred at room temperature for 2 h. The crude product was collected by filtration, washed with water and dried in a desiccator to give 2,3-epoxy-1,3-diphenyl-1-propanone **3a** in 94% yield. When the reaction was carried out using KOH, LiOH or $Ca(OH)_2$ as base, **3a** was obtained in 93, 92 and 93% yield, respectively. However, reaction with relatively weaker bases, $Ba(OH)_2$ and K_2CO_3 gave **3a** in lower yields (Table 1).

Similarly, Darzens condensation reactions of **1b–i** with **2** in the presence of NaOH proceeded very efficiently and the products **3b–i** were obtained in good yields as shown in Table 2. In comparison, conventional method for preparation of **3a** in aqueous dioxan requires a longer reaction time (12 h) at lower temperature (0 °C).[3] This completely organic solvent-free procedure is valuable since waste minimization, simple operation and easier product work-up can be achieved.

It has been reported that enantioselective Darzens reaction of **1** with **2a** in the presence of chiral phase-transfer catalyst **5** affords a 90:10 mixture of *trans*-**3a** (3.9% ee) and *cis*-**4a** in 81% yield under phase-transfer conditions.[4] We have found that Darzens reaction in the presence of *N*-benzylcinchonidinium chloride **6** proceeded more selectively in a water suspension medium and only *trans*-**3a** (12% ee) was obtained in 90% yield.



4a



5

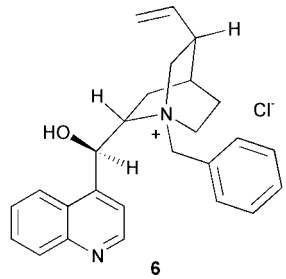


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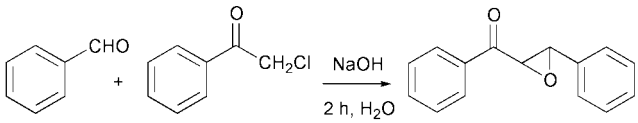
Table 1 Darzens condensation of benzaldehyde **1a** with phenacyl chloride **2** in water



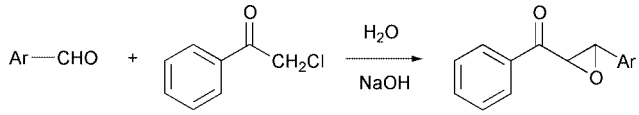
1a **2** **3a**

Entry	Base	Yield (%)
1	NaOH	94
2	KOH	93
3	LiOH	92
4	$Ca(OH)_2$	93
5	$Ba(OH)_2$	77
6	K_2CO_3	46

Green Context

The avoidance of volatile organic solvents in chemical processing is an important goal for green chemistry. The use of water as a solvent is somewhat controversial: while it is safe to handle and use, separation of the organics at the end of the reaction and subsequent clean-up of the dirty water can be major difficulties. Here these problems are at least partly overcome since the reaction is close to 100% atom efficient and the product can be easily separated by filtration. The reaction described is an important C–C bond forming reaction and the survival of the epoxy function and the effectiveness of the method in an enantioselective synthesis are added attractions of this aqueous solvent-based procedure. ***JHC***

Table 2 Darzens condensation of aldehydes **1a**–**i** with phenacyl chloride **2** in water



1 **2** **3**

Compound **1**	Ar	Time/h	Yield (%)	Mp/°C
a	Ph	2	94	82–85[3]
b	C_6H_4Me-4	2	91	60–70[5]
c	C_6H_4Cl-4	2	98	47–50[5]
d	C_6H_4Br-4	3	95	55–58[6]
e	C_6H_4OMe-4	2	89	69–73[6]
f	C_6H_4Ph-4	4	93	57–59
g	C_6H_4Cl-3	3	98	56–59
h	$C_6H_3Cl_2$-3,4	3	91	103–106
i	C_6H_3Br-3-OMe-4	3	86	59–62

Experimental

Typical procedure for Darzens condensation reaction in a water suspension medium

A suspension of a mixture of benzaldehyde **1a** (0.21 g, 1.94 mmol), phenacyl chloride **2** (0.30 g, 1.94 mmol) and NaOH (0.08 g, 2 mmol) was stirred in water (3 ml) at room temperature for 2 h. The crystalline powder formed was collected by filtration, washed with water and dried in a desiccator to give 2,3-epoxy-1,3-diphenyl-1-propanone **3a** (0.41 g, 94% yield). The crude crystals thus obtained were recrystallized from EtOH to give pure **3a** (mp 82–85 °C) as colorless prisms.

Typical procedure for enantioselective Darzens condensation reaction in a water suspension medium

A suspension of a mixture of benzaldehyde **1a** (0.21 g, 1.94 mmol), phenacyl chloride **2** (0.30 g, 1.94 mmol), *N*-benzylcinchonidinium chrolide **6** (0.82 g, 1.94 mmol) and NaOH (0.08 g, 2 mmol) was stirred in water (3 ml) at room temperature for 2 h. The crystalline powder formed was collected by filtration, washed with water and dried in a desiccator to give 2,3-epoxy-1,3-diphenyl-1-propanone **3a** (0.39 g, $[\alpha]_D$ −26° (*c* 0.13, CH_2Cl_2), 12% ee) in 90% yield. The optical purity of (−)-**3a** was determined by HPLC analysis using a DAICEL CHIRALCEL OJ column (hexane–2-Pr^{i}OH 9:1, 0.3 ml min^{-1}, 254 nm).

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