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Efficient Darzens condensation reactions of aromatic aldehydes catalyzed by polystyrene-supported phase-transfer catalyst

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Abstract

The development of the highly diastereoselective and the clean catalytic synthesis of glycidic acid derivatives via Darzens condensation reaction is summarized. The Darzens reaction of α-chloroester and nitrile with aromatic aldehydes under mild conditions proceeds in the presence of polystyrene-supported quaternary ammonium salt (polystyrene-supported triethylammonium chloride, Ps-TEAC) as a phase-transfer catalyst (PTC) to give the corresponding cis- and trans-desired products in satisfactory yields. The polymer-supported catalyst can be separated from filtration and reused efficiently.

Keywords: Polystyrene-supported; Phase-transfer catalyst; Darzens condensation; Aromatic aldehydes

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1. Introduction

Development of catalytic carbon–carbon and carbon–oxygen bond-forming reaction is one of the most challenging aspects of organic synthesis [1] and the Darzens condensation reaction represents one of the classical C–C and C–O bond-forming processes [2]. The Darzens condensation is one of the most potential methodologies for the preparation of α, β-epoxy carbonyl compounds that have been extensively used in many important syntheses [3]. However, few successful examples of the catalytic diastereoselective synthesis of α, β-epoxyesters via carbon–carbon and carbon–oxygen bond-forming reactions are reported [4,5].

The Darzens reactions of chloroketones and sulfones, which are catalyzed by phase-transfer catalysts [6–8], have been reported recently. Although recent advances have made this route more attractive, development of cheaper, simpler, and more efficient and recyclable, phase-transfer catalysts is highly desirable. One of the most important technical problems in the industrial phase-transfer catalyst (PTC) applications using soluble phase-transfer catalysts, such as quaternary ammonium salts, is the need to separate the catalysts from the reaction mixture and its subsequent reuse or disposal. This problem usually increases the process expense, and may also affect the purity of the reaction products and byproducts disposal, giving rise to negative environmental impacts.

Immobilization of the catalyst on a polymeric matrix can provide a simple solution to this problem [9]. The polymer-supported PTCs (Ps-PTCs) are a great progress of PTC because they combine the advantages of homogenous and heterogeneous catalysts, such as separation simplicity; by only filtration can the catalyst be separated from the mixture of reactants and repeatedly used, especially for expensive chiral catalysts [10].

As a part of our research to develop a green chemistry methodology by one-pot synthesis of target molecules catalyzed by polystyrene-supported triethylammonium chloride (Ps-TEAC; Scheme 1), the Darzens condensation reaction of α-chloroethyl acetate and α-chloroacetonitrile with aromatic aldehydes for the synthesis of glycidic acid derivatives is reported.

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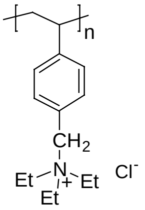
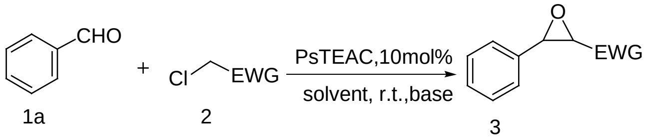


Scheme 1. The structure of polymer-supported triethylammonium chloride (Ps-TEAC).



Scheme 2. The Darzens reaction of benzaldehyde with α-chloroester and nitrile.

2. Result and discussion

The procedure of Ps-PTC-catalyzed Darzens reaction, synthesis of **3** (Scheme 2): to a mixture of benzaldehyde (1a), 1.2 equimolar of **2** (Scheme 2), and Ps-TEAC (10 mol% for quaternary ammonium salt) suspended in solvent (10 ml), after 20 min stirring at room temperature, base (1.2 eq.) was added. After stirring for a period of time at room temperature until the reaction was completed, the reaction was quenched with water and the catalyst was filtered out. The filtrate was extracted with ethyl acetate (15 ml × 3), and the combined organic layer was washed with brine and solvent, dried with anhydrous sodium sulfate and concentrated under reduced pressure. Following purification by flash column chromatography, the isolated yield was obtained.

Our initial studies of this process focused on developing an optimum set of reaction conditions for this reaction. We have investigated the effect of solvents, reaction time, bases, and found the reaction was strongly influenced by solvents and base. The results are summarized in Table 1.

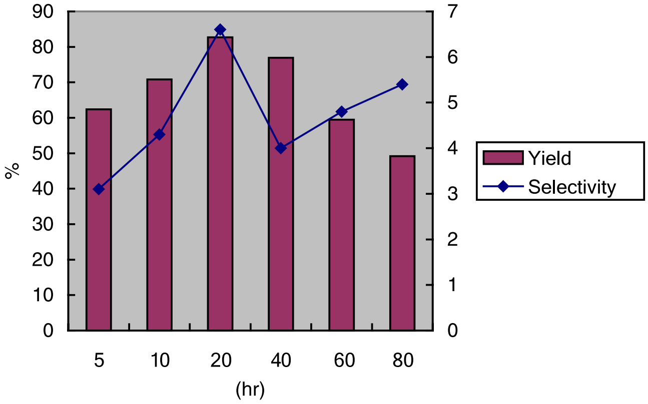


Fig. 1. Effect of reaction time on diastereoseletivity of Darzens reaction of benzaldehyde with α-chloro ester.

As shown in Table 1, THF is a suitable solvent for this Darzen reaction. Toluene made the reaction suspension too ropy to stir to be well-dispersed. We found weaker bases such as LiOH were not suitable to use in this reaction (entries 5 and 8). The product was obtained in low yield without Ps-TEAC catalyst (entry 9). In addition, the reaction should not be lasted for a long time, because opening of the epoxy ring of 3a can be promoted by strong base.

Fig. 1. shows the effect of reaction reaction time on diastereoseletivity of Darzens reaction of benzaldehyde with α-chloroester catalyzed by Ps-TEAC. At first, the conversion increased smoothly and the diastereoselectivity is highest at 20 h; afterwards, the selectivity and yields began to decrease gradually with the reaction time because the disired cis isomer can be epimerized to the corresponding trans isomer under strongly basic conditions.

Encouraged by these results, we examined other substrates under similar reaction conditions. As shown in Table 2, the combination of a catalytic amount of polymer supported PTC and KOH in THF at room temperature was used for the Darzen reaction of other aromatic aldehydes. Several electron-rich and electron-poor benzaldehydes, such as CH_3-, Br-, CH_3O- and NO_2-substituted benzaldehydes were applied to this reaction. As expected, these conditions were quite sufficient to give the desired Darzens adduct 3. In this reaction, aromatic aldehydes

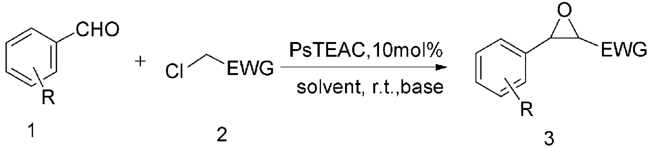
Table 1
Effect of various factors on the Darzens reactions

Entry	EWG	Solvent	Base	Time (h)	Yield (%)[a]	Cis:trans
1	2a: $-CO_2-Et$	THF	KOH	23	80 (3a)	6.5:1
2	2a: $-CO_2-Et$	Toluene	KOH	16	54 (3a)	3.1:1
3	2a: $-CO_2-Et$	CH_2Cl_2	KOH	24	41 (3a)	3.5:1
4	2a: $-CO_2-Et$	Et_2O	KOH	24	62 (3a)	5.3:1
5	2a: $-CO_2-Et$	THF	$LiOH \cdot H_2O$	48	13 (3a)	4.7:2
6	2a: $-CO_2-Et$	THF	KOH	70	17 (3a)	9.0:1
7	2b: –CN	THF	KOH	22	91 (3b)	Cis only
8	2b: –CN	THF	$LiOH \cdot H_2O$	48	42 (3b)	20:1
9	2a: $-CO_2-Et$	THF	KOH	24	43 (3a)[b]	10:1

[a] Isolated yield. Reaction conditions: 3.0 mmol of aldehyde, 3.6 mmol of α-chloroester or α-chloroaecetonitrile, 3.6 mmol of base, and 10 mmol% of Ps-PTC in THF (10 ml).

[b] Without PTC catalyst in this reaction.

Table 2
Investigations of the Darzens reactions with other aromatic aldehydes



Entry[a]	Aldehyde (R)	EWG	Time (h)	Yield (%)[b]	Cis:trans
1	1b: 4-Br	CO_2–Et	70	3c: 45	2.8:1
2	1c: 4-Me	CO_2–Et	23	3d: 73	0.7:1
3	1d: 2-OMe	CO_2–Et	23	3e: 19	1.4:1
4	1f: 4-NO_2	CO_2–Et	70	3f: 20	2.3:1
5	1b: 4-Br	CN	22	3g: 79	1.4:1
6	1c: 4-Me	CN	20	3h: 82	5.0:1
7	1d: 2-MeO	CN	16	3i: 54	1.4:1
8	1e: 4-MeO	CN	20	3j: 75	2.8:1
9	1f: 4-NO_2	CN	20	3k: 40	3.0:1

[a] Reaction conditions: 3.0 mmol of aldehyde, 3.6 mmol of α-chloroester or α-chloroaecetonitrile, 3.6 mmol of KOH, and 10 mmol% of Ps-PTC in THF (10 ml).

[b] Isolated yields.

Table 3
Efficiency of reused Ps-TEAC as a catalyst for 3b

Times	Yield (%)	Cis:trans
1	90	Cis only
2	87	Cis only
3	89	Cis only
4	86	Cis only
5	85	Cis only

with electron donating groups as CH_3- and Br-afforded higher yields, but those with withdrawing groups as CH_3O- and NO_2-afforded lower yields. The steric hindrance can also affect remarkably the chemical yields of 3i and 3j. It is known that the yield of 3j is higher than that of 3i because the steric hindrance of 2-OCH_3 substitutent is more serious than 4-OCH_3. The aromatic aldehydes react easier and faster with α-chloroaecetonitrile than ethyl chloroacetate. In this Ps-TEAC-catalyzed Darzen reaction, the diastereomeric ratio of three is satisfactory. Especially for 3b, only the cis-isomer was obtained in excellent yield (90%).

Reusability of Ps-TEAC in the reaction of benzyl aldehyde with α–chloroacetonitrile was examined five times. As shown in Table 3, the yield of 3b decreased slightly and the diastereomeric ratio kept invariable.

3. Conclusions

Polymer-supported phase-transfer catalysts (Ps-TEAC) act as quite effective PTCs in stead of THAB under mild reaction conditions to achieve high diastereoselectivities in the Darzens reaction using ethyl α-chloroacetate, chloroacetonitrile with aromatic aldehydes. Further investigations, such as mechanisms of Ps-PTC and new development in the fields of organic synthesis, are in progress.

4. Experimental

4.1. Preparation of the catalyst of Ps-TEAC

To a flask of 5.0 g chloromethyl resin (200–400 mesh, 3.5 mmol Cl/g) was added in 15 ml *N*,*N*-dimethylformamide, stirred for 2 h, and then, added 20 ml triethylamine. The mixture was refluxed at 80 °C for 24 h. The adduct was filtered under reduced pressure and washed with anhydrous ethanol. The residue was marinated in anhydrous ethanol and stirred for 12 h at 80 °C. Then, the product Ps-TEAC of the filtered residue was dried in vacuum. The concentration of onium ions, which is the same as chloride ions, was determinated by titration with silver nitrate.

4.2. Typical procedure of polymer supported PTC-catalyzed Darzens reaction

Synthesis of 3b: To a solution of 1a (318 mg, 3.0 mmol), 2b (272 mg, 3.6 mmol), and Ps-TEAC (300 mg, about 10 mol% for onium salt) in THF (10 ml), after 20 min stirring at room temperature, potassium hydroxide (200 mg, 3.6 mmol) was added. After stirring for 23 h at room temperature, the reaction was quenched with water and the mixture was extracted with ethyl acetate (15 ml × 3). The combined organic layer was washed with brine and solvent, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether:ethyl acetate = 50:1) exclusively gave 3b as a pale oil in good yield (396 mg, 91%).(Scheme 2). ^{1}H NMR ($CDCl_3$,400 MHz) δ_H (ppm): 3.39 (d, $J = 1.2$ Hz, 1H), 4.26 (d, $J = 1.6$ Hz, 1H), 7.25 (2H), 7.37(3H).

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