



A convenient and efficient one-pot way to synthesize α,β -epoxy ketones directly from acetophenones and arylaldehydes

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ABSTRACT

A convenient and efficient one-pot way to synthesize α,β -epoxy ketones directly from ketones and aldehydes has been described. Reactions were carried out at room temperature and the corresponding α,β -epoxy ketones were isolated in moderate to excellent yields.

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α,β -Epoxy ketones have played a pivotal role in many organic reactions because they could be readily transformed into various synthetically useful intermediates, such as α - and β -hydroxy carbonyls, α,β -epoxy alcohols and 1,3-diols.¹

The Darzens reaction² is a well-known synthetic method for generating α,β -epoxy ketones from α -halo carbonyl compounds and aldehydes directly. However, the limitation of Darzens reaction is the inconvenience in the preparation of α -halo carbonyl compounds.

Epoxidation of α,β -unsaturated ketones is another general way to synthesize α,β -epoxy ketones.³ This method usually requires nucleophilic oxidation under basic conditions. However, various α,β -unsaturated ketones should be obtained from the aldol reaction of ketones and aldehydes firstly, which made this synthetic method to be more complicated. What is more, sometimes the preparation of α,β -unsaturated ketones from ketones and aldehydes is troublesome according to the procedures reported before.⁴ For example, subjecting 1.0 equiv of 2-prop-2-ynyloxybenzaldehyde **1a** and 2.0 equiv of 1-(4-chlorophenyl)ethanone **2a** into the aqueous NaOH solution without any other solvents, we could only get product **3a** rather than the corresponding enone (Scheme 1). Only after the aldol reaction product **3a** was dissolved in MeOH with further addition of NaOH upon a prolonged reaction time, the corresponding enone was then finally obtained. Further experiments revealed that the formed enone could also be partially hydrolyzed to **3a** under either weak acidic or weak basic conditions, causing some trouble to obtain pure enone for further use. Therefore, we envisaged that if the formed enone could be directly used for further epoxidation without isolation to synthesize α,β -epoxy ketone from ketone and aldehyde in a one-pot manner, these problems would be easily resolved.

In this Letter, we wish to report a convenient and efficient method using ketones and aldehydes as raw materials to synthe-

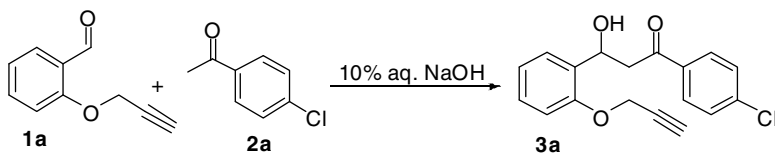
size α,β -epoxy ketones directly in a one-pot manner for the first time. This synthetic protocol involves two steps: (i) formation of enone from ketone and aldehyde; (ii) epoxidation of enone with H_2O_2 (Scheme 2).

The reaction was initially carried out using equimolar amounts of ketone **1a** and aldehyde **2a** in the presence of catalytic amount of 10% aqueous NaOH (0.3 equiv) under solvent free conditions. When the starting materials were consumed completely, 1.0 mL of 30% H_2O_2 was slowly added to the above system at 0 °C. To our disappointment, the reaction gave a very poor result. However, it was found that when the reaction was carried out in methanol, the reaction outcome could be improved significantly. The foregoing experiment showed that 1.0 equiv of base was the best choice to the reaction. It should be noted that if the solubility of the formed α,β -unsaturated ketone in methanol was poor, the more amount of solvent should be required.

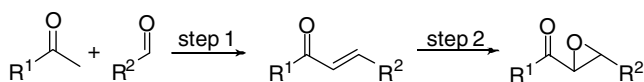
After a series of careful examination of the reaction conditions, we found that subjecting equimolar amounts of ketone **1a**, aldehyde **2a**, and aqueous NaOH solution in methanol at room temperature resulted in the production of α,β -unsaturated ketone exclusively without the formation of the corresponding aldol product **3a**. Then, adding excess amounts of 30% hydrogen peroxide slowly afforded α,β -epoxy ketone **4a** immediately as white solid in good yield.

This simple and efficient reaction procedure could be successfully extended to a variety of ketones and aldehydes.⁵ The results of these studies are listed in Table 1. Treating 1-(4-chlorophenyl)ethanone **2a** with aryl aldehydes such as **1a** and **1b** produced the corresponding α,β -epoxy ketones **4a** and **4b** in moderate yields (Table 1, entries 1 and 2), although when aliphatic aldehyde was used into this reaction, no desired product was obtained along with the recovery of 54% of **2a** (Table 1, entry 3). Conducting other ketones such as **2b** and **2c** with various aldehydes under the standard conditions afforded the corresponding α,β -epoxy ketones in moderate to good yields (Table 1, entries 4–9). As for the aldehyde **1h** bearing two strongly electron-donating

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Scheme 1. Aldol reaction between 2-Prop-2-ynyloxybenzaldehyde **1a** and 1-(4-Chlorophenyl)ethanone **2a** in the aqueous NaOH solution.



Scheme 2. Protocol for the one-pot synthesis of α,β -epoxy ketones.

methoxy groups on the aromatic ring, no reaction occurred (Table 1, entry 10). The best results were obtained by using one electron-

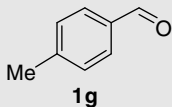
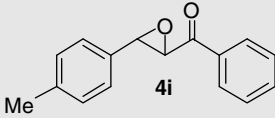
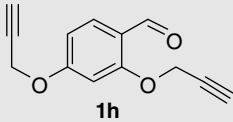
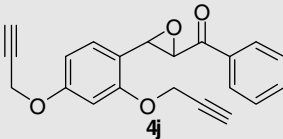
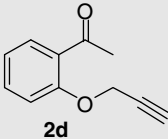
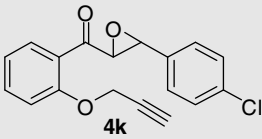
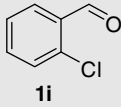
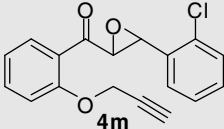
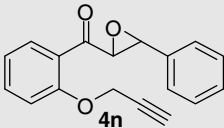
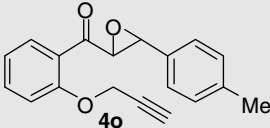
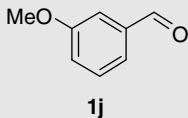
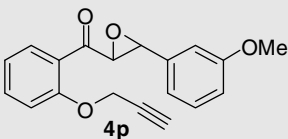
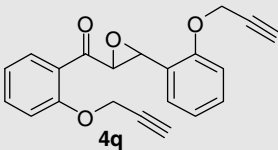
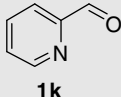
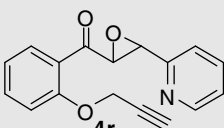
donating group substituted acetophenones **2d**, **2e**, and **2f** as the substrate to react with various aryl aldehydes, affording the desired products in good to excellent yields (Table 1, entries 11–20).

Further examination of the scope and limitations of the reaction surprisingly revealed that treatment of 3-phenylpropenal **1i** and 1-phenylethanone **2c** under the optimized conditions only afforded 1-phenyl-3-(3-phenyloxiranyl)propenone **5** in 35% yield rather than the corresponding α,β -epoxy ketone (Scheme 3). Moreover, using 2-butenal **1m** as the substrate under identical conditions

Table 1
Scope of the one-pot reaction for the synthesis of α,β -epoxy ketones from ketones and aldehydes

Entry	Aldehyde	Ketone	Product	Yield ^a (%)
1				78
2		2a		68
3 ^b		2a		—
4	1a			71
5				56
7	1b	2c		60
8		2c		62

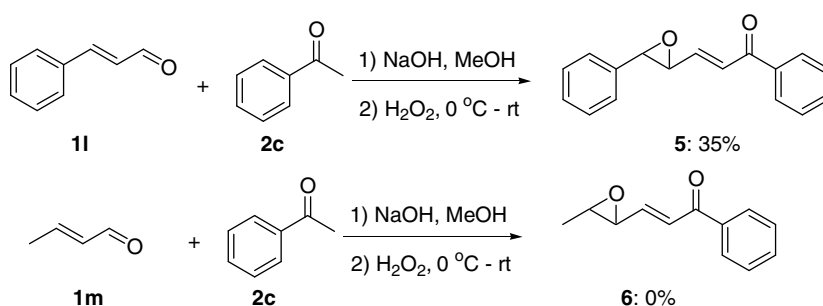
Table 1 (continued)

Entry	Aldehyde	Ketone	Product	Yield ^a (%)
9		2c		62
10		2c		—
11	1b			78
13		2d		91
14	1d	2d		80
15	1g	2d		77
16		2d		87
17	1a	2d		75
18		2d		54

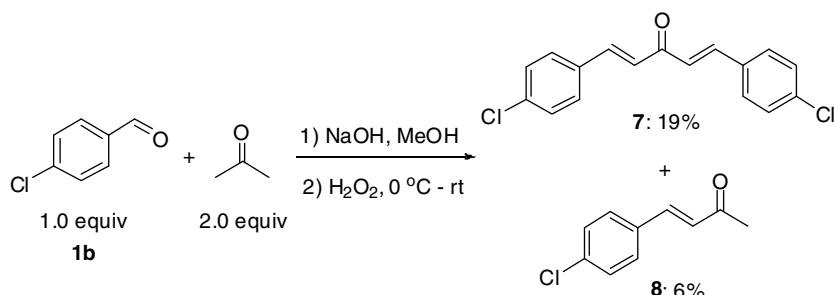
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Table 1 (continued)

Entry	Aldehyde	Ketone	Product	Yield ^a (%)
19	1a	2e	4s	92
20	1b	2f	4t	90

^a Isolated.^b 54% of 1-(4-chlorophenyl)ethanone **2a** was recovered.

Scheme 3. One-pot synthesis of 1-phenyl-3-(3-phenyloxiranyl)propenone.



Scheme 4. One-pot reaction between 4-chlorobenzaldehyde and acetone under the optimized reaction procedure.

did not result in the formation of product **6**. Compared with the synthetic methods reported before, our new synthetic procedure is very simple to produce these kinds of products.⁶

We have also attempted the one-pot synthesis of α,β -epoxy ketone from 4-chlorobenzaldehyde **1b** and acetone under the similar reaction conditions. But, it was found that products **7** and **8** were obtained in 19% yield and in 6% yield, respectively, rather than the corresponding α,β -epoxy ketone (Scheme 4).

Inspired by the above results, we next examined the reaction of benzaldehyde with nitroethane under identical conditions. To our disappointment, complex product mixtures were formed without the formation of the desired product.

In conclusion, we have developed a one-pot synthetic approach to synthesize α,β -epoxy ketones from aldehydes and acetophenones in moderate to excellent yields. Compared with the previously reported methods, our approach has several advantages, for example, easily available starting materials (aldehydes and ketones), mild reaction conditions, simple procedures, and highly improved yields. The scope and limitations of this one-pot procedure are still under progress in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.110.

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5. *Typical reaction procedures:* 2-Prop-2-ynyloxybenzaldehyde **1a** (3.0 mmol, 480 mg) and 1-(4-chlorophenyl)ethanone **2a** (3.0 mmol, 462 mg) were dissolved in 10 mL of MeOH, and then 1.2 mL of 10% aqueous NaOH (3.0 mmol, 120 mg) solution was added at room temperature. The reaction was monitored by TLC. When the starting materials were consumed completely, 1.0 mL of 30% hydrogen peroxide (16.7 mmol) was slowly added at 0 °C. The reaction was returned to room temperature. After the reaction completed on the basis of TLC examination, the mixture was extracted with EtOAc and the combined organic layers were washed with water for several times to remove MeOH, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a viscous oil, which was purified by chromatography on silica gel (EtOAc/PE = 1:10) to give **4a** as a white solid (0.74 g, 78%). Compound **4a**: Mp. 109–111 °C; IR (NaCl) ν 3295, 3068, 3042, 2924, 2870, 1917, 1694, 1589, 1492, 1456, 1444, 1289, 1239, 1092, 1009 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz, TMS) δ 2.50 (1H, t, J = 2.4 Hz), 4.12 (1H, d, J = 1.8 Hz), 4.36 (1H, d, J = 1.8 Hz), 4.73 (2H, d, J = 2.4 Hz), 7.02–7.07 (2H, m), 7.31–7.38 (2H, m), 7.46 (2H, d, J = 8.4 Hz), 8.01 (2H, d, J = 8.4 Hz); ¹³C NMR (CDCl₃, 75 MHz, TMS) δ 55.6, 55.8, 60.4, 75.9, 78.0, 111.8, 121.7, 124.6, 125.7, 129.1, 129.6, 129.8, 133.7, 140.3, 155.8, 192.4; MS (EI) m/z 111 (M^+ –218, 49.6), 113 (M^+ –199, 17.4), 139 (M^+ –173, 100.0), 141 (M^+ –171, 32.7), 191 (M^+ –122, 14.9), 193 (M^+ –120, 5.0), 312 (M^+ , 1.6); Anal. Calcd for C₁₈H₁₃ClO₃: C, 69.13; H, 4.19. Found: C, 69.08; H, 4.25.
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