# Unusual Tandem Oxidative C–C Bond Cleavage and Acetalization of Chalcone Epoxides in the Presence of Iodine in Methanol

Balaso G. Jadhav, Shriniwas D. Samant\*

Department of Chemistry, Institute of Chemical Technology, Matunga, Mumbai 400019, India Fax +91(22)33611020; E-mail: samantsd@yahoo.com; E-mail: sd.samant@ictmumbai.edu.in *Received: 16.03.2014; Accepted after revision: 28.04.2014* 

**Abstract:** An unusual reaction of chalcone epoxides is observed where chalcone epoxides on heating with iodine in methanol leads to  $\alpha,\alpha$ -dimethoxyacetophenones, through C–C bond cleavage followed by acetalization of the formyl group. The process occurs through ring opening of the chalcone epoxide by methanol to form  $\beta$ -methoxy alcohol, cleavage of the C–C bond in the latter to form  $\alpha$ -ketoaldehyde, and acetalization of the formyl group to give the product. The protocol provides direct access to  $\alpha,\alpha$ -dimethoxyacetophenones from chalcone epoxides.

Key words: oxidative cleavage, chalcone epoxides, iodine,  $\alpha$ , $\alpha$ -dimethoxyacetophenones, acetals,  $\alpha$ -ketoaldehydes

Reactions of epoxides are interesting due to the presence of a strained oxirane ring in them. The most common reactions involve opening of the oxirane ring to form 1,2disubstituted compounds.<sup>1</sup> Another type of reaction involves breaking of the C–O bond of epoxides followed by rearrangement of the skeleton to form carbonyl compounds with the same number of carbons as epoxides.<sup>1</sup> On the other hand, cleavage of the C–C bond in epoxides followed by oxidation, that is, oxidative cleavage of epoxides, is not that common and reported to require uncommon reagents and drastic conditions. However, this process has a potential to serve as an effective and selective alternative to oxidative cleavage of olefins which employs very hazardous reagents like OsO<sub>4</sub>, ozone, etc.

Oxidative cleavage of epoxides has been attempted using  $HIO_4^2$  or  $H_5IO_6^{,3}$  Pb(OAc)<sub>4</sub>,<sup>4</sup> CAN,<sup>5</sup> Na<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>·2H<sub>2</sub>O,<sup>6</sup> PyCrO(O<sub>2</sub>)<sub>2</sub>,<sup>7</sup> PyMoO(O<sub>2</sub>)<sub>2</sub>,<sup>8</sup> alkaline H<sub>2</sub>O<sub>2</sub>,<sup>9</sup> NaIO<sub>4</sub>,<sup>10</sup> and

hypervalent iodine reagents.<sup>11</sup> A few catalytic systems have also been described for the cleavage. For example, molecular  $O_2/DMSO$  with bismuth(III) ligands<sup>2</sup> affords carboxylic acids, instead of aldehydes and ketones. Only one method of cleavage of  $\alpha$ -methyl styrene epoxides using sodium molybdate/H<sub>2</sub>O<sub>2</sub>,<sup>8</sup> with HMPT or TDPT in a biphasic system of dichloromethane and acidified water, affords the corresponding aldehydes. The reaction has been reported electrochemically.<sup>2</sup> Literature survey shows that epoxides which are used for the oxidative cleavage are those bearing hydrogen, alkyl, or aryl on the oxirane ring.<sup>2</sup> However, such a C–C bond cleavage of  $\alpha$ , $\beta$ -epoxyketones is not reported, though it may provide  $\alpha$ -keto aldehydes which are difficult to prepare by other methods.

Herein we report our serendipitous observation of oxidative cleavage of  $\alpha,\beta$ -epoxy ketones (chalcone epoxides) to  $\alpha,\alpha$ -dimethoxy acetophenones using iodine in refluxing methanol. To our surprise  $\alpha,\alpha$ -dimethoxy acetophenones were the sole products in the reaction. The reaction proceeded through ring opening of the chalcone epoxide by methanol to form  $\beta$ -methoxy alcohol, cleavage of the C– C bond in the latter to form  $\alpha$ -ketoaldehyde, and acetalization of the formyl group to give the product. Chalcone epoxides were prepared from chalcones using hydrogen peroxide and sodium hydroxide in methanol.<sup>12</sup>

We were interested in the reaction of trifunctional derivative **2**, which can be obtained from **1** through methanolysis (Scheme 1). While attempting to prepare **2a** ( $R^1 = R^2 = R^3 = H$ ) in good yield, without any side product, **1a** ( $R^1 =$ 



Scheme 1 Oxidative cleavage of chalcone epoxides to  $\alpha, \alpha$ -dimethoxyacetophenones using iodine in methanol

*SYNLETT* 2014, 25, 1591–1595 Advanced online publication: 03.06.2014 DOI: 10.1055/s-0033-1339134; Art ID: st-2014-b0231-l © Georg Thieme Verlag Stuttgart · New York  $R^2 = R^3 = H$ ) was reacted with excess of pure methanol. The reaction did not take place in the absence of any catalyst. While attempting different catalysts, particularly Lewis acids, we found that a catalytic amount of iodine was highly beneficial, and **2a** was obtained in excellent yield. The reaction was studied in detail using different quantities of iodine (Table 1). The reaction of **1a** with 5 mol% of iodine in excess of methanol at room temperature provided **2a** in 95% yield in two hours. Compound **2a** was characterized by <sup>1</sup>H NMR spectroscopy which showed a 3:1 *syn/anti* ratio in accordance with the literature.<sup>13</sup> Increase in quantity of iodine resulted only in the decrease in the reaction time with no effect on the yield or the *syn/anti* ratio of **2a**.

Table 1Effect of Concentration of Iodine on the Methanolysis ofChalcone Epoxide 1a to  $\beta$ -Methoxy Alcohol 2a<sup>a</sup>

Entry I	odine (mol%)	Time (h)	Yield of <b>2a</b> (%) <sup>b</sup>	syn/anti
1	5	2	95	3:1
2 1	0	1.2	95	3:1
3 2	20	0.5	95	3:1

<sup>a</sup> Reaction conditions: **1a** (1 mmol), I<sub>2</sub>, MeOH (3 mL), 25 °C. <sup>b</sup> Isolated yield.

Surprisingly, we noticed that when **1a**, in boiling methanol, was treated with a larger quantity of iodine (0.5 equiv), it underwent an unusual reaction and gave **4a** (20%) along with **2a** (70%; Table 2, entry 4). Compound **4a** was separated by column chromatography and was identified as  $\alpha, \alpha$ -dimethoxyacetophenone by HRMS and IR and <sup>1</sup>H NMR spectroscopy.

**Table 2** Reaction of 1a in Methanol in the Presence of IncreasingAmounts of Iodine<sup>a</sup>

Entry	Iodine (mol%)	Time (h)	Yield of <b>4a</b> (%) <sup>b</sup>	Yield of <b>2a</b> (%) <sup>b</sup>
1	5	12	_	95
2	10	12	_	95
3	20	12	_	95
4	50	12	20	70
5	100	12	50	40
6	150	12	70	20
7	200	10	85	_
8	250	12	85	_
9	300	12	85	_

<sup>a</sup> Reaction conditions: **1a** (1 mmol), I<sub>2</sub>, MeOH (3 mL), reflux. <sup>b</sup> Isolated yield. The effect of the quantity of iodine on the reaction is given in Table 2. Maximum yield of **4a** was obtained with 2.0 equivalents of iodine; increasing the time did not increase the yield of **4a** further. The reaction was also carried out in EtOH as solvent in the presence of iodine (2.0 equiv) at reflux for nine hours. The reaction took place in the same manner and gave the expected product ( $\alpha$ , $\alpha$ -diethoxy acetophenone) in 85% yield. However, other alcohols, 1-propanol and 2-propanol, afforded a mixture of products from which we could not isolate the desired products.

A plausible mechanism of the formation of  $\alpha, \alpha$ -dimethoxyacetophenones 4 from chalcone epoxides 1 is given in Scheme 2. In excess of methanol the epoxide ring in 1 is opened, in the presence of iodine functioning as a Lewis acid, to form  $\beta$ -methoxy alcohol 2. Such a kind of ring opening of epoxides is known.<sup>13</sup> Alcohols are known to react with bromine and iodine to form hypobromites and hypoiodites.<sup>14</sup> Iodine, present in 2.0 equivalents, may react with the hydroxyl group in 2 to form a hypoiodite 5. The I-O bond in the hypoiodite is very weak and undergoes homolysis. The hypoiodite 5 may undergo homolysis with iodine radical to form oxyradical 6 which would undergo C–C bond cleavage to form  $\alpha$ -keto aldehyde 3 and radical 7. The latter may form benzyl methyl ether 8 through hydrogen abstraction from HI. To support the mechanism we treated 2a separately with 2.0 equivalents of iodine in excess methanol. In this reaction 4a was formed. Thus, the reaction goes through the intermediate 2.



**Scheme 2** Proposed mechanism of the formation of  $\alpha$ , $\alpha$ -dimethoxy-acetophenones from chalcone epoxides via  $\beta$ -methoxy alcohols

In order to test the generality of the reaction, chalcone epoxides substituted on either ring were subjected to the oxidative cleavage (Table 3).

The most striking observation was that the substituents present on the phenyl ring adjacent to the epoxide had a profound effect on the course of the reaction. As one extreme, the electron-withdrawing CN group at the *para* position gave only the  $\beta$ -methoxy alcohol **2b**<sup>16</sup> and no further reaction took place. On the other hand, the electron-donating OMe group (Table 3, entry 10) at the *para* 

position was favorable for the expected reaction; the reaction was fast, and **4a** was obtained within two hours in 75% yield. The halogen like Cl at the *para* position was slightly helpful (Table 3, entry 9). These observations supported the mechanism proposed. As the reaction involves initial complexation of iodine with the epoxide ring, the group on the adjacent phenyl ring may exert substantial effect on this complexation. The group may also affect the stability of the C–C bond, which breaks and forms the product.

Table 3 Oxidative Cleavage of Chalcone Epoxides 1 to  $\alpha, \alpha$ -Dimethoxy Acetophenones 4<sup>a</sup>

Entry	Chalcone epoxide 1	Product 4	Time (h)	Yield of $4 (\%)^{b}$
1		OMe	10	85
	1a	4a		
2	Br	Br	8	85
	1b	4b		
3		OMe	14	75
	1c	4c		
4	MeO	MeO OMe	12	75
	1d	4d		
5	Med d	OMe	11	75
	1e	4e		
6	CI O O	CI O OMe OMe	24	75
	1f	4f		
7		OMe	8	75
	1g	4g		
8		OMe	13	75
	1h	4h		

**Table 3** Oxidative Cleavage of Chalcone Epoxides 1 to  $\alpha, \alpha$ -Dimethoxy Acetophenones 4<sup>a</sup> (continued)



<sup>a</sup> Reaction conditions: chalcone epoxide **1** (1 mmol), I<sub>2</sub> (2.0 mmol), MeOH (3 mL), reflux. <sup>b</sup> Isolated yield.

The minor effect exhibited by the substituent present on the phenyl ring adjacent to carbonyl group may be explained on the basis of participation of the carbonyl oxygen in the complexation of iodine with the epoxy oxygen. The 2,4-disubstituted phenyl ring took longer time for completion (Table 3, entry 6). This reaction has a potential to generate key intermediates  $\alpha,\alpha$ -dimethoxy acetophenones which find application in the synthesis<sup>15</sup> of chiral cyanohydrins, nicotine derivatives, chiral sulfoxides,  $\alpha$ -hydroxy acetals, chiral 1,2-diols, and myretnalderived chiral auxillaries.

We have reported an unusual observation of oxidative cleavage of the C–C bond in chalcone epoxides followed by acetalization with methanol to form  $\alpha,\alpha$ -dimethoxy-acetophenones, when chalcone epoxides are reacted with iodine in methanol. To the best of our knowledge, no such tandem C–C bond cleavage and acetalization is reported earlier. The reaction goes through  $\beta$ -methoxy alcohol formation. The reaction takes place under very mild conditions. The reaction is an equivalent of a retro-Darzen reaction. The products are synthetically important intermediates.

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**Supporting Information** for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/ 10.1055/s-00000083.

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- (16) General Procedure for Oxidative Cleavage of Chalcone Epoxides to α,α-Dimethoxy Acetophenones To a solution of an appropriate chalcone epoxide (1.0 mmol) in MeOH (3 mL) was added iodine (2.0 mmol) in one

portion. The reaction mixture was refluxed for the appropriate time (monitored by TLC and visualized with 2,4-dinitrophenyl hydrazine stain). The reaction mixture was cooled to r.t. MeOH was evaporated under reduced pressure to obtain an oily residue that was purified by column chromatography (silica gel, 60–120 mesh size) using 5–10% EtOAc in PE as an eluent to obtain pure products. Pure products were identified by IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR spectroscopy and HRMS.

### Analytical Data of New Compounds

**1-(2,4-Dichlorophenyl)-2,2-dimethoxyethanone (4f)** Yield 75%; oil. FTIR (neat): 2939, 2833, 1707 (s), 1583, 1456, 1276, 1193, 867, 750 cm<sup>-1</sup>. HRMS: *m/z* calcd for  $C_{10}H_{10}ClO_3Na [M + Na]^+$ : 270.9967; found: 271.0039, 273.0010, 274.9986. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 3.46 (s, 6 H), 5.16 (s, 1 H), 7.29–7.52 (m, 2 H), 7.63 (d, 1 H, *J* = 8.1 Hz). <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 54.5, 103.4, 127.0, 130.4, 131.1, 133.0, 134.2, 137.8, 195.3.

## 4-(2-Hydroxy-1-methoxy-3-oxo-3-phenylpropyl)benzonitrile (2b)

Yield 95%; white solid; mp 87–89 °C. FTIR (neat): 3369, 2941, 2823, 2230, 1674 (s), 1597, 1448, 1224, 1114, 830, 736, 690 cm<sup>-1</sup>. DI-MS:  $m/z = 282.1 \text{ [M + H]}^+$ . <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 3.24$  (s, 3 H), 3.62 (d, 1 H, J = 7.5 Hz), 4.53 (d, 1 H, J = 4.5 Hz), 5.35–5.38 (m, 1 H), 7.24 (d, 2 H, J = 8.7 Hz), 7.45–7.66 (m, 5 H), 7.84 (d, 2 H, J = 7.2 Hz). <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 57.6$ , 76.6, 85.0, 112.0, 118.5, 128.2, 128.6, 128.8, 131.8, 134.2, 134.6, 142.0, 199.0.

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