Catalytic Ring Opening of α-Epoxyketones Using DDQ in Methanol Solution at Room Temperature and under Reflux Conditions in Excellent Yields

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Catalytic ring opening reactions of α-epoxyketones by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in methanol solution at r. t. and under reflux conditions resulted in the formation of α-hydroxy-β-methoxyketones through C_β–O bond cleavage in excellent yields. Whereas the type and nature of the additional substituent affects the rate of ring opening, the effect of temperature has an extreme influence on the rate of reactions. Cyclic voltammetric studies of DDQ at 15 °C and 33 °C support the increased electron-acceptor ability of DDQ by the increasing of temperature.

Key words: Ring Opening, α-Epoxyketones, 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

Introduction

It is known that 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is a versatile reagent. Its oxidation ability and relative stability cause it to be one of the most used reagents to perform several organic transformations such as dehydrogenation [1 – 5], oxidation [6 – 10] and deprotection [11 – 13]. Also DDQ is a well-known electron acceptor and its interaction with a variety of electron donors *via* the formation of charge-transfer (CT) complexes has been the subject of several investigations [14 – 19].

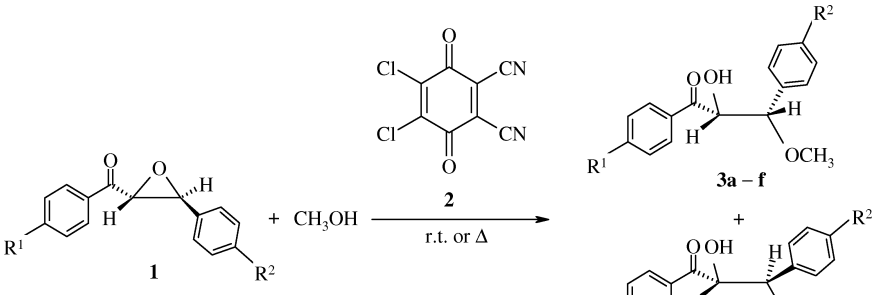
Ring opening reactions of α-epoxyketones have also attracted considerable interest from both synthetic and mechanistic standpoints. Such reactions have been recognized as important processes not only in thermal but also in photochemical transformations. Hasegawa and co-workers have extensively studied ring opening reactions of these compounds under different conditions [20 – 25]. Single electron transfer (SET) induced ring opening reactions of α-epoxyketones have demonstrated C_α–O and C_β–O bond cleavages through photocatalyzed electron transfer to 2,4,6-triphenylpyrylium tetrafluoroborate (TPT) [26 – 29] and *N*-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate (NBTPT) [30] or through electron transfer from triethylamine [20], tribenzylamine [20], 1,3-dimethyl-2-phenylbenzimidazoline [21 – 23], 2-hydroxyphenyl-1,3-dimethylbenzimidazoline [24], allyltributyltin (ATBT) [25] and tributyltin hydride (TBTH) [25] to the photoexcited α-epoxyketones. These reactions have also been observed through thermally induced electron transfer from AIBN/TBTH [25], AIBN/ATBT [25] and bis(cyclopentadienyl)titanium(III) chloride (Cp_2-TiCl) [31] to α-epoxyketones. Whereas in the case of C_α–O bond cleavage β-hydroxyketones were formed, the C_β–O bond cleavage followed by nucleophilic attack of methanol resulted in the formation of α-hydroxy-β-methoxyketones.

Now we wish to report on the thermal ring opening reactions of α-epoxyketones in the presence of DDQ as catalyst at r. t. and under reflux conditions in methanol solution to elucidate the effect of temperature on the rate and diastereoselectivity of the reaction.

Results and Discussion

In optimized reaction conditions, α-epoxyketones **1a** – **f** and DDQ (**2**) in a molar ratio of 10 : 1 in methanol solution were reacted at r. t. and under reflux conditions (Scheme 1). The reactions were followed by TLC until total disappearance of **1a** – **f** was observed. The results are summarized in Table 1.

These data indicate that the rate of the catalytic ring opening of α-epoxyketones **1a** – **f** depends on the nature and location of the substituent at the phenyl ring, and also on the temperature. In all cases, the



1 (R^1, R^2) = **a** (H, H); **b** (H, CH_3); **c** (CH_3, H); **d** (H, OCH_3); **e** (OCH_3, H); **f** (OCH_3, OCH_3).

Scheme 1.

Table 1. Ring opening reactions of **1a**–**f** catalyzed by **2** in methanol solution at room temperature (r. t.) and under reflux conditions (ΔT)[a].

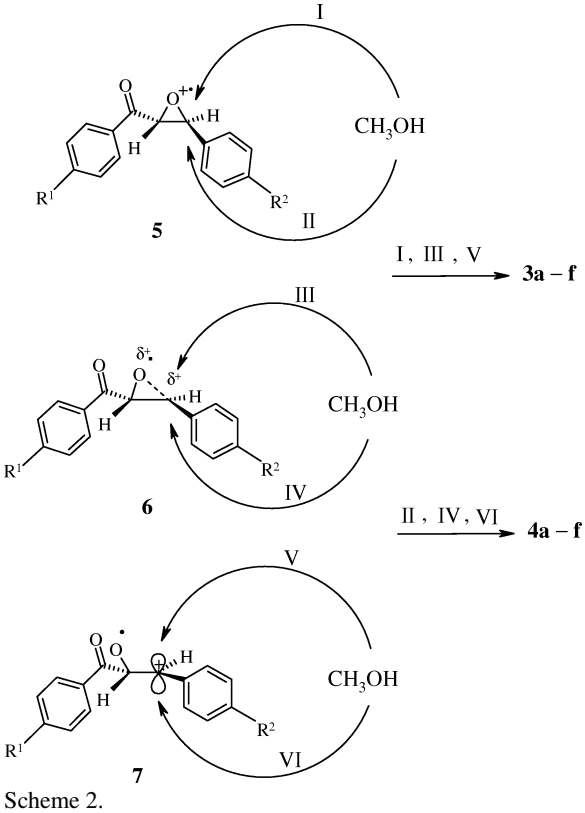
Compound	Time (h)	Yield (%)[b]	**4**/**3**[c]
1a (r. t.)	17	97	3.12 : 1
1a (ΔT)	3.5	98	2.57 : 1
1b (r. t.)	4	97	1 : 1.18
1b (ΔT)	0.5	98	1 : 1.25
1c (r. t.)	12.5	95	3.48 : 1
1c (ΔT)	2	98	2.68 : 1
1d (r. t.)	3.5	97	1 : 1.04
1d (ΔT)	0.5	98	1 : 1.10
1e (r. t.)	11	95	5.58 : 1
1e (ΔT)	2	97	2.97 : 1
1f (r. t.)	2.5	98	1.12 : 1
1f (ΔT)	0.5	98	1.09 : 1

[a] c(**1a**–**f**) = 0.04 M, c(**2**) = 0.004 M, corresponding to a molar ratio of 10 : 1; [b] based on consumed **1a**–**f**; [c] the ratios have been determined by comparison of the integral ratios of the hydrogen atoms at C-2.

ring opening proceeds faster at increased temperatures. Whereas electron donor groups such as *p*-methyl and *p*-methoxy on the phenyl ring directly attached to the epoxide ring (**1b**, **1d** and **1f**) facilitate the ring opening, the same substituents on the phenyl ring of the benzoyl moiety (**1c** and **1e**) have a smaller effect.

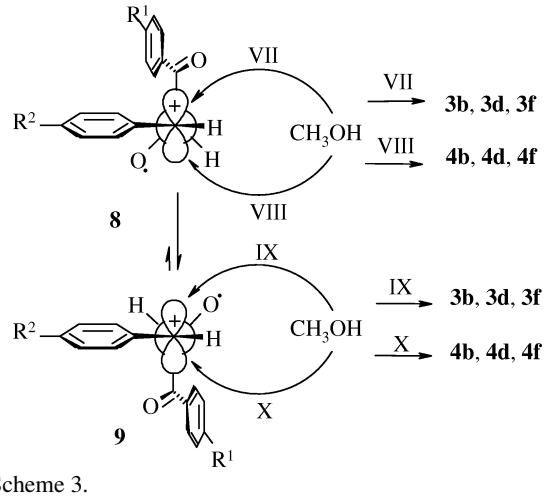
Regarding the proposed mechanism of the catalytic ring opening of α-epoxyketones, due to the electron transfer from **1a**–**f** to **2** three different intermediates **5**–**7** could be involved for the nucleophilic attack of methanol. The preferred participation of one of these intermediates in the reaction should be dependent on the ability of the additional electron-donating substituent to stabilize the involved intermediate (Scheme 2).

The interesting point in this reaction is that in the cases of **1b** and **1d**, the ratios of the diastereomeric products are reversed compared to the ratios obtained by reaction of **1a**, **1c**, **1e** and **1f**. This leads us to assume that the inductive effect of the *p*-methyl group (**1b**)



Scheme 2.

and also the resonance effect of the *p*-methoxy group (**1d** and **1f**) on the phenyl ring directly attached to the epoxide ring increase the contribution of the intermediates **6** and **7** because of the stabilization of carbocation or carbocation-like centers. Although the bond rotation between C-2 and C-3 can be the reason of the observed stereoselectivity of the reaction, the more stable conformer of the intermediate **7** may be formed through interaction of the lone pair at oxygen of the carbonyl group with the carbocation center (interme-



Scheme 3.

diates **8** and **9** in Scheme 3). In the case of C-2–C-3 bond rotation, the reaction temperature should influence the diastereomeric ratios, *i. e.*, due to faster bond rotation at higher temperatures the diastereomeric ratios obtained at r. t. and under reflux conditions are not necessarily the same. The results presented in Table 1 show that the diastereomeric ratios obtained by reaction with **1b** and **1d** under the two conditions are almost the same. Considering the steric hindrance of the substituents in both conformations **8** and **9**, participation of the conformation **9** in the reaction is more likely as compared with conformation **8**. On the basis of Cram's rule [32], the involvement of these intermediates leads to the preferred nucleophilic attack of methanol to the carbon atom at the less hindered site (VIII and IX) to form the diastereomeric products (Scheme 3).

These results also show that the diastereomeric ratios under reflux condition are getting closer to each other in comparison to the reaction at r. t. Two points should be suggested for these observations: (i) The enhanced ion mobility of donor-acceptor complexes at higher temperature makes the formation of the intermediates easier which are trapped by nucleophilic attack of methanol. On the other hand, the interaction of the intermediates with the counter ion is decreased upon heating and, therefore, the possibility of the nucleophilic attack of methanol from both sides becomes more probable, and (ii) the increased C-2–C-3 bond rotation depends on the applied temperature, as described above.

Cyclic voltammetry studies of DDQ at 15 °C and 33 °C support our experimental results obtained by the

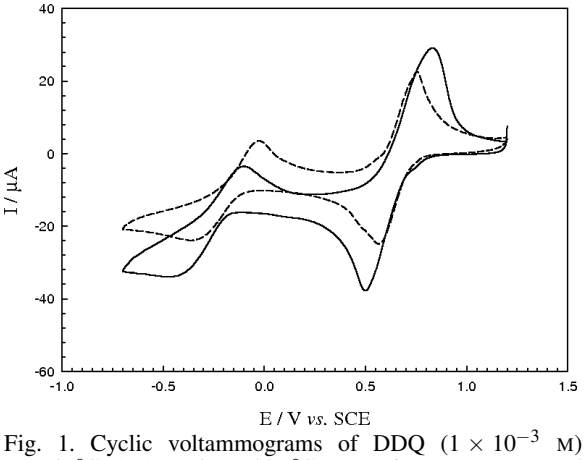


Fig. 1. Cyclic voltammograms of DDQ (1×10^{-3} M) at 15 °C (—) and at 33 °C (- - -) in argon saturated dichloromethane solutions containing tetrabutylammonium perchlorate (0.05 M) as the supporting electrolyte at a scan rate of 200 mVs^{-1} (SCE = standard calomel electrode).

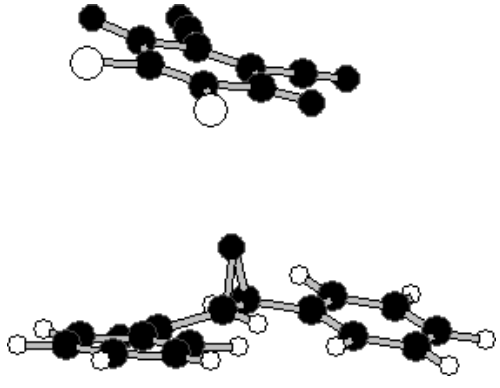


Fig. 2. Interaction of **1a** with DDQ according to semi-empirical PM3 calculations.

ring opening with DDQ at two different temperatures. These studies showed that DDQ at 33 °C is a better electron acceptor than at 15 °C, because the reduction potential of DDQ at 33 °C is more positive than the reduction potential of DDQ at 15 °C (Fig. 1). This observation could be due to enhanced molecular motion in the medium by increasing the temperature.

Finally, we compared the results of semi-empirical PM3 calculations on the complexes of **1a**–**f** + DDQ and on the α-epoxyketones **1a**–**f** alone (Fig. 2).

These results indicated that (i) the total dipole moments of the complexes of **1a**–**f** with DDQ are increased compared with the dipole moments of **1a**–**f** alone; (ii) a comparison between the electric charges of the epoxide ring atoms shows that electric charges

	1a – f				**1a – f** + DDQ			
	C-2 (C_α)	C-3 (C_β)	O	μ (D)	C-2 (C_α)	C-3 (C_β)	O	μ (D)
1a	−0.082	0.082	−0.229	2.852	−0.079	0.088	−0.252	6.081
1b	−0.083	0.084	−0.232	3.030	−0.083	0.093	−0.251	6.372
1c	−0.080	0.080	−0.231	3.000	−0.079	0.089	−0.254	6.749
1d	−0.084	0.089	−0.233	3.153	−0.084	0.098	−0.250	5.572
1e	−0.083	0.082	−0.232	3.731	−0.079	0.089	−0.256	6.879
1f	−0.083	0.088	−0.234	3.035	−0.081	0.097	−0.255	6.055

Table 2. Mulliken electric charges [33, 34] of epoxide ring atoms of **1a – f** and their total dipole moments (μ) and total dipole moments of the complexes of **1a – f** with DDQ obtained from quantum mechanical PM3 calculations.

at C-3 (C_β) (and oxygen) in complexes **1a – f** with DDQ are more positive (and more negative) than that in **1a – f** alone. The charges of C-3 (C_β) in the complexes of **1b**, **1d** and **1f** + DDQ are more positive than those in the complexes of **1c** and **1e** with DDQ. The increase of the charges of oxygen and C-3 (C_β) shows that the C_β–O bond in the complexes of **1a – f** with DDQ has a higher tendency for cleavage. This tendency for the complexes of **1b**, **1d** and **1f** with DDQ is increased by the presence of donor groups such as *p*-methyl and *p*-methoxy, because the nucleophilic attack of methanol to the C-3 (C_β) in these complexes is faster than in the others (Table 2).

In conclusion, the rate of ring opening of α-epoxyketones **1a – f** in the presence of DDQ as catalyst under reflux condition is faster than at r. t. The increase of the reaction temperature also affects the ratios of diastereomeric products. The rate of the disappearance of the α-epoxyketones **1a – f** was also increased depending on the nature of the additional substituents on the phenyl rings.

Experimental Section

All the α-epoxyketones **1a – f** were prepared according to literature procedures [35, 36]. ^{1}H NMR spectra of the mixtures of products were measured in $CDCl_3$ solutions containing tetramethylsilane (TMS) as internal standard on a Bruker spectrometer (300 MHz). The photoproducts are known and their spectroscopic data (IR, ^{1}H NMR, MS and elemental analyses) have been reported previously [26]. The cyclic voltammetric experiments were performed with an AUTOLAB 30 Potentiostat/Galvanostat. The electrochemical studies were conducted by using dichloromethane solutions containing tetrabutylammonium perchlorate under argon. A three-electrode system with a saturated calomel electrode (SCE) as reference, a platinium foil as the counter electrode and a platinium disk as the working electrode were used. Preparative layer chromatography (PLC) was carried out on 20×20 cm^2 plates coated with a 1 mm layer of Merck silica gel PF_{254} prepared by applying the silica as a slurry and drying in air. A mixture of petroleum ether/ethyl acetate = 10 : 1 was used as eluent for PLC.

*General procedure for thermal ring opening of α-epoxyketones **1a – f** at r. t. and under reflux conditions*

A solution of 0.8 mmol of **1a – f** in 20 mL of methanol (c = 0.04 M) and 0.08 mmol of **2** (c = 0.004 M) was stirred at r. t. and at reflux temperature for the periods of time given in Table 1. The solvent was evaporated and the products were isolated by PLC.

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