



# Photoinduced transformation of $\alpha,\beta$ -epoxyketones to $\beta$ -hydroxyketones by Hantzsch 1,4-dihydropyridine

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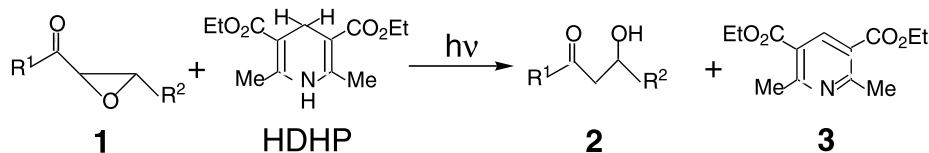
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**Abstract**—Irradiation ( $\lambda > 300$  nm) of Hantzsch 1,4-dihydropyridine with aromatic  $\alpha,\beta$ -epoxyketones in acetonitrile selectively breaks the C $\alpha$ –O bond of the epoxides giving the corresponding  $\beta$ -hydroxyketones in excellent yields. © 2002 Elsevier Science Ltd. All rights reserved.

The selective transformation of  $\alpha,\beta$ -epoxyketones to  $\beta$ -hydroxyketones has long been a subject of interest in synthetic organic chemistry<sup>1</sup> since it allows not only formation of acyclic  $\beta$ -hydroxyketones, but also of a variety of cyclic  $\beta$ -hydroxyketones which are key intermediates in the construction of numerous natural products. Diverse reducing reagents, such as samarium diiodide,<sup>1a</sup> aluminium amalgam,<sup>1b</sup> lithium,<sup>1c</sup> sodium hydrogen telluride<sup>1d</sup> and benzenselenolate,<sup>1e</sup> have been used to achieve this transformation. Recent work includes the use of lithium naphthalenide<sup>2</sup> and titanocene chloride<sup>3</sup> to induce the reaction. In addition, photochemical approaches have been developed in the last decade by exciting  $\alpha,\beta$ -epoxyketones in the presence of tributyltin hydride,<sup>4</sup> triethylamine<sup>5</sup> and 1,3-dimethyl-2-phenyl-benzimidazoline (DMPBI).<sup>6</sup> However, photoexcitation of a ketone inevitably brings about side reactions, hence lowering the yield of the expected  $\beta$ -hydroxyketones.<sup>4–6</sup> Since two electrons and two protons are required for converting  $\alpha,\beta$ -epoxyketones to  $\beta$ -hydroxyketones it is expected that photoexcitation of electron donors which could afford two electrons and two protons (or their equivalent) would also accomplish the transformation, offering an alternative photochemical approach.

Hantzsch 1,4-dihydropyridine (HDHP), a well-known model compound of co-enzyme NADH, has been extensively studied from both a mechanistic and synthetic points of view.<sup>7</sup> In our research program on photoinduced electron transfer reactions<sup>8</sup> we found that photoexcited HDHP was a very good electron and hydrogen donor that could reduce carbon tetrachloride.<sup>8a</sup> In this reaction HDHP was oxidized to the corresponding pyridine derivative by sequential transfer of an electron, a proton and a hydrogen atom. Therefore, photoexcited HDHP should also be able to induce reductive cleavage of  $\alpha,\beta$ -epoxyketones. We report herein a selective C $\alpha$ –O cleavage reaction of aromatic  $\alpha,\beta$ -epoxyketones by photoexcited HDHP that produces the corresponding  $\beta$ -hydroxyketones in excellent yields.

A solution of  $\alpha,\beta$ -epoxyketones **1** (1 mmol) and HDHP (1 mmol) in 10 mL of anhydrous acetonitrile was irradiated with a 500 W high pressure mercury lamp in a Pyrex bottle ( $\lambda > 300$  nm) under an argon atmosphere at ambient temperature. The reaction was monitored by thin layer chromatography and the solvent was removed under reduced pressure after the reaction was



## Scheme 1.

**Keywords:** photoinduced electron transfer;  $\alpha,\beta$ -epoxyketone;  $\beta$ -hydroxyketone; Hantzsch ester.

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**Table 1.** Photochemical reactions between **1** and HDHP

Substrate	R <sup>1</sup>	R <sup>2</sup>	E <sub>red</sub> (V versus SCE)	ΔG (kJ/mol)	t (h)	Conversions (%)	Yields <sup>a</sup> (%)
<b>1a</b> <sup>b</sup>	Ph	Ph	−1.70 <sup>4a</sup>	−81.0	1	100	<b>2a</b> (92)
<b>1b</b> <sup>b</sup>	Ph	4-Cl-C <sub>6</sub> H <sub>4</sub>	−1.73 <sup>5a</sup>	−78.1	1	100	<b>2b</b> (94)
<b>1c</b> <sup>b</sup>	Ph	4-MeO-C <sub>6</sub> H <sub>4</sub>	−1.73 <sup>5a</sup>	−78.1	1.5	95	<b>2c</b> (88)
<b>1d</b> <sup>b</sup>	Ph	<i>i</i> -Pr	−1.76 <sup>5a</sup>	−75.2	1.5	100	<b>2d</b> (91)
<b>1e</b> <sup>b</sup>	Ph	Me			1	100	<b>2e</b> (92)
<b>1f</b>	4-Cl-C <sub>6</sub> H <sub>4</sub>	Ph	−1.60 <sup>c</sup>	−90.6	1	100	<b>2f</b> (91)
<b>1g</b>	4-Cl-C <sub>6</sub> H <sub>4</sub>	<i>i</i> -Pr			1	100	<b>2g</b> (93)
<b>1h</b>	4-MeO-C <sub>6</sub> H <sub>4</sub>	Ph	−1.86 <sup>4a</sup>	−85.5	1.5	98	<b>2h</b> (92)
<b>1i</b>	4-MeO-C <sub>6</sub> H <sub>4</sub>	<i>i</i> -Pr			1.5	98	<b>2i</b> (90)
<b>1j</b>	4-CN-C <sub>6</sub> H <sub>4</sub>	Ph	−1.39 <sup>4a</sup>	−110.9	1.5	100	<b>2j</b> (95)
<b>1k</b>	Me	Ph	−2.40 <sup>5b</sup>	−13.5	1.5	33	<b>2k</b> (0)

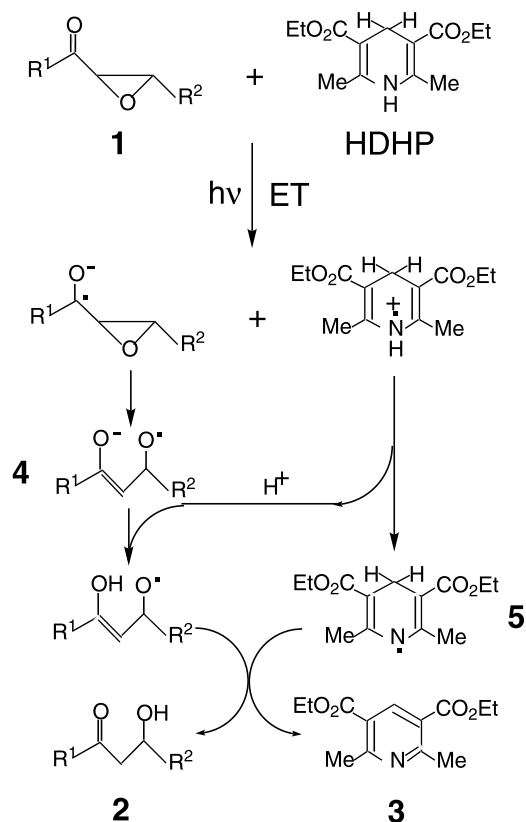
r &gt;

<sup>a</sup> Isolated yields.<sup>b</sup> Reaction conducted in the presence of 1 mmol of anhydrous Mg(ClO<sub>4</sub>)<sub>2</sub>.<sup>c</sup> Estimated from the Hammett plot based on the reduction potentials of **1a**, **1h** and **1k**.

complete. The products were easily isolated by silica gel column chromatography and identified by <sup>1</sup>H NMR and mass spectroscopy as β-hydroxyketones **2** and the pyridine derivative **3**<sup>9</sup> (Scheme 1). The results are summarized in Table 1.

It was found that although compounds **1a–e** showed no reaction under the experimental conditions, addition of anhydrous magnesium perchlorate (1 mmol) to the reaction system made the reaction proceed smoothly. Compounds **1f–j** reacted in the absence of Mg(ClO<sub>4</sub>)<sub>2</sub>, while **1k** gave no β-hydroxyketone even in the presence of Mg(ClO<sub>4</sub>)<sub>2</sub>, but did give decomposition products. All of these compounds showed no reaction with HDHP and Mg(ClO<sub>4</sub>)<sub>2</sub> in the dark even at 60°C for 3 h. Since the wavelength of the incident light was longer than 300 nm only HDHP (λ<sub>max</sub> = 360 nm) was excited. Therefore, a photoinduced electron transfer mechanism can be proposed, as shown in Scheme 2. In Scheme 2, photoinduced electron transfer between the excited HDHP and the aryl epoxy ketone **1** produces the radical cation of HDHP and the radical anion of **1**. It is well-known that the bond dissociation energy (BDE) of radical ions are much lower than their parent molecules,<sup>10</sup> hence radical ions undergo facile bond cleavage.<sup>8a,c</sup> Maslak and co-workers<sup>11</sup> have termed the unimolecular fragmentation of radical ions as mesolytic cleavage and demonstrated the acceleration of bond cleavage due to mesolytic processes. In the present reaction the anionic mesolysis selectively breaks the Cα–O bond of the epoxide, forming the enolate alkoxy radical **4**, and the cationic mesolysis of HDHP<sup>+</sup> exudes a proton, forming the HDHP radical **5**. Protonation of the enolate **4** and hydrogen abstraction from **5** gives the final products **2** and **3**. It is clear that aromatization of HDHP also affords a driving force for the reaction.

Our results suggest that this reaction is controlled by both thermodynamic and kinetic factors. All the aryl ketones (**1a–j**) gave excellent yields of **2**, while the alkyl ketone **1k** did not react. This is understandable in view of the thermodynamics of the photoinduced electron transfer process between **1** and HDHP. The free energy change, ΔG, of the reactions, as listed in Table 1, can be

**Scheme 2.**

calculated using the Rehm–Weller equation,<sup>12</sup> taking the oxidation potential of HDHP as 0.72 V (versus SCE)<sup>7b</sup> and the excitation energy of 3.2 eV, as determined from the fluorescence spectrum.<sup>13</sup> Some reduction potentials of **1**<sup>4a,5</sup> are also listed in Table 1. It can be seen from Table 1 that the reduction potentials of the aryl epoxy ketones are in the range of −1.3 ~ −1.9 V which makes their electron transfer with HDHP highly exothermic (ΔG = −70 ~ −110 kJ mol<sup>−1</sup>) giving a thermodynamically feasible reaction, while the ΔG for the alkyl ketone **1k** is a very small negative value (−13.5 kJ mol<sup>−1</sup>) making the reaction difficult to occur. The sub-

stituent R<sup>2</sup> on the epoxy side exerts a small effect on the reduction potential and the reactivity.

It is worth noting that although the reactions of **1a–e** are thermodynamically feasible they did not react in the absence of magnesium perchlorate. This suggests that kinetic factors may also contribute to the reaction. Metal ion-catalyzed reduction of carbonyl compounds by HDHP and other NADH model molecules has been extensively studied previously.<sup>7</sup> It was suggested that magnesium ions coordinate to carbonyls and may lower the activation energy of the initial single electron transfer step, hence catalyzing the electron transfer process.<sup>7b</sup>

In conclusion, this work affords a new, facile approach for the selective transformation of  $\alpha,\beta$ -epoxy aryl ketones to the corresponding  $\beta$ -hydroxy ketones with high yields and using long wavelength irradiation. The crucial difference of this approach from the photochemical cleavage of  $\alpha,\beta$ -epoxy ketones reported previously<sup>4–6</sup> is excitation of the electron and proton donor (HDHP) rather than excitation of the  $\alpha,\beta$ -epoxy ketone. In the latter case, side reactions from the excited triplet ketones were observed, making the reaction less clean and not as efficient as the present one. Extension of this approach to  $\alpha,\beta$ -epoxy alkyl ketones and other photochemical reduction reactions is underway in this laboratory.

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- Spectral data for some typical products. **2a**: <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>/TMS),  $\delta$  (ppm) 3.39 (d,  $J=6.0$  Hz, 2H, CH<sub>2</sub>), 5.37 (t,  $J=6.0$  Hz, 1H, CH), 7.30–8.01 (m, 10H, 2 $\times$ PhH), MS ( $m/z$ , %) 226 (M<sup>+</sup>, 12), 208 (M<sup>+</sup>–18, 27), 105 (M<sup>+</sup>–121, 100); **2d**: <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>/TMS),  $\delta$  (ppm) 1.02 (d,  $J=5.7$  Hz, 6H, 2 $\times$ CH<sub>3</sub>), 1.83 (m, 1H, CH), 3.09 (d,  $J=5.6$  Hz, 2H, CH<sub>2</sub>), 4.01 (m, 1H, CH), 7.35–8.04 (m, 5H, PhH), MS ( $m/z$ , %) 192 (M<sup>+</sup>, 2), 174 (M<sup>+</sup>–18, 32), 105 (M<sup>+</sup>–87, 100); **2e**: <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>/TMS),  $\delta$  (ppm) 1.27 (d,  $J=6.5$  Hz, 3H, CH<sub>3</sub>), 3.07 (d,  $J=5.9$  Hz, 2H, CH<sub>2</sub>), 3.40 (s, 1H, OH), 4.46 (m, 1H, CH), 7.33–7.96 (m, 5H, PhH), MS ( $m/z$ , %) 164 (M<sup>+</sup>, 4), 146 (M<sup>+</sup>–18, 13), 105 (M<sup>+</sup>–59, 100); **3**: <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>/TMS),  $\delta$  (ppm) 1.42 (t,  $J=7.1$  Hz, 6H, 2 $\times$ CH<sub>3</sub>), 2.87 (s, 6H, 2 $\times$ CH<sub>3</sub>), 4.41 (q,  $J=7.1$  Hz, 4H, 2 $\times$ CH<sub>2</sub>), 7.60 (s, 1H, ArH); MS ( $m/z$ , %) 252 (M<sup>+</sup>, 100).
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- The fluorescence spectrum of HDHP was determined in acetonitrile giving the absorption and emission maximum at 360 and 430 nm, respectively, corresponding to the  $E_{0,0}$  of 3.2 eV.