Pergamon

Tetrahedron Letters, Vol. 37, No. 21, pp. 3765-3768, 1996
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0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00677-6

A Novel *m*-CPBA Oxidation: *p*-Quinols and Epoxyquinols from Phenols

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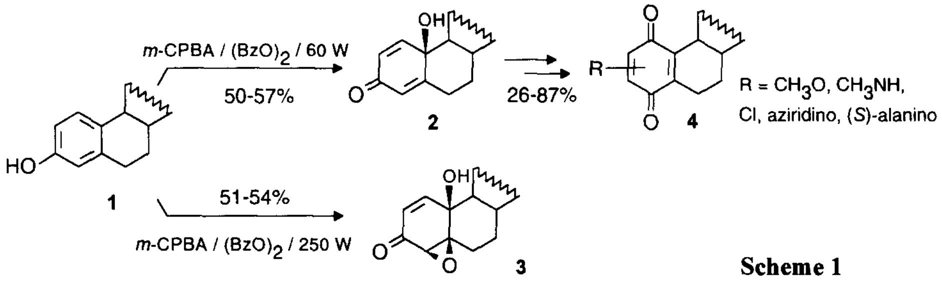
Abstract: Steroidal quinols were obtained on large scale in 50-57% yield, together with *syn*-epoxyquinols. The reaction conditions can be adjusted to afford only the corresponding steroidal epoxyquinol in 51-54% yield. Copyright © 1996 Elsevier Science Ltd

Extensive studies[1] of the reactivity and biological activity of quinone / hydroquinone couples, including our own,[2] and also of the antitumor activity of certain types of estrogens,[3] prompted our search for an optimal synthesis of A-ring substituted steroidal estrane-type quinones **4** and their biological evaluation.[4]



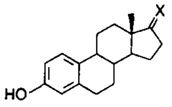
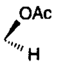
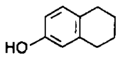
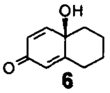
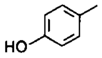
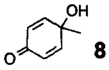
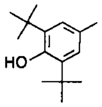
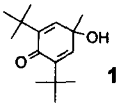
Scheme 1

Although steroidal quinols can be obtained in a 42-50% yield directly from the corresponding phenols,[5,6] no method was found suitable on a higher (10-50 g) scale. In order to find an alternative system for the desired transformation, we examined several peroxyacids as potential reagents for phenol-to-quinol oxidation starting either from estrone (**1a**) or estradiol 17-acetate (**1b**). Peroxyacetic acid, Mg-monoperoxyphtalate and *m*-CPBA were tested on **1a** and 6-hydroxy-1,2,3,4-tetrahydronaphtalene (**5**) under the reaction conditions described below. With peroxyacetic acid no reaction took place, while Mg-monoperoxyphtalate afforded only 11-15% of *p*-quinols.

We found *m*-CPBA / $(BzO)_2$ / hν as a good oxidising reagent for the desired transformation (Scheme 1; **1a** → **2a**, 57%).[7] In order to gain a deeper insight into this novel reaction, several simple *p*-substituted phenols (**5**, **7**, **9**) were treated with this system and selected examples are given in Table 1.

Using phenol **5**, we found catalytic amount of initiator and irradiation by daylight 60 W bulb necessary for reaction to proceed. Benzoyl peroxide was much more effective than AIBN (Runs 9 and 11), and the reactions advanced well with 0.05-0.1 equiv of $(BzO)_2$ (with respect to substrate). Although pure acetone is not

TABLE 1. Oxidation of Phenols to Quinols with *m*-CPBA / $(BzO)_2$ / hν system

Run	Substrate	Method (Solvent)	Reaction Time (h)	Yield of Quinol (%)[a]	
1	 **1a**: X = O	**A** CH_2Cl_2 / acetone (4:1)	3.5	**2a** **3a**	(57) (15)
2	**1a**	**B** CH_2Cl_2 / acetone (4:1)	24	**2a** **3a**	(54) (18)
3	**1a**	**C** CH_2Cl_2 / acetone (4:1)	24	**3a**	(51)
4	**1b**: X = 	**A** CH_2Cl_2 / acetone (4:1)	6	**2b** **3b**	(50) (15)
5	**1b**	**B** CH_2Cl_2 / acetone (4:1)	48	**2b** **3b**	(50) (15)
6	**1b**	**C** CH_2Cl_2 / acetone (4:1)	36	**3b**	(54)
7	 **5**	**A** CH_2Cl_2	5	 **6** ref. 6a	(55)
8		CH_2Cl_2 / acetone (4:1)	5		(44)
9		**B** CH_2Cl_2	24		(49)
10		acetone	24		(20)
11		**D** CH_2Cl_2	2.5		(28)
12	 **7**	**A** CH_2Cl_2	24	 **8** refs. 6a, 6b	(35)
13		CH_2Cl_2 / acetone (4:1)	24		(26)
14	 **9**	**A** CH_2Cl_2	24	 **10**	(30)
15		CH_2Cl_2 / acetone (4:1)	24		(22)

A: *m*-CPBA (85%) / $(BzO)_2$ (3 : 0.1 equiv. per 1 equiv. of substrate), 60 W, rfl.; **B**: *m*-CPBA (85%) / $(BzO)_2$ (2 : 0.1), 60 W, rfl.; **C**: *m*-CPBA (85%) / $(BzO)_2$ (3 : 0.1), 250 W, rfl.; **D**: *m*-CPBA (85%) / AIBN (2 : 0.1).

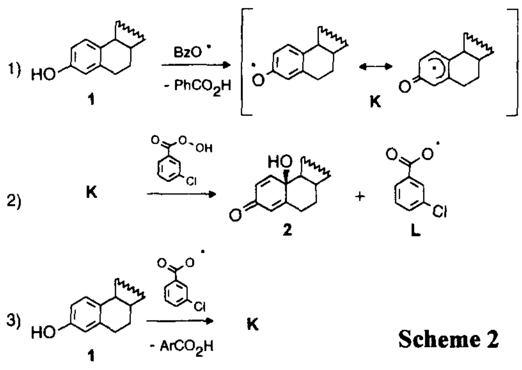
a. Yield of isolated compounds.

the solvent of choice (Runs 9 and 10), for solubility reasons we found CH_2Cl_2 / acetone mixture a suitable solvent for this transformation. Under described reaction conditions, no competitive Baeyer-Villiger process occurs either from acetone[8] or from estrone.

The effect of concentration of *m*-CPBA on oxidation of phenols **1** was examined with 100%, 85% and 65% *m*-CPBA,[9] always yielding the corresponding quinols **2** and the epoxyquinol side products **3**. With model substrate **5** (as well as with **7** and **9**) no epoxyquinol was detected. Since the best results were obtained with 85% *m*-CPBA, in Table 1 only the results using this reagent are presented.

Upon irradiation of *m*-CPBA (85%) in the presence of 5% $(BzO)_2$ for 24 h we recovered 21% of peroxyacid, while under the same conditions 90% of benzoyl peroxide decomposes. This is in accordance with our findings that at least 2 equivalents of 85% *m*-CPBA were necessary for completion of phenol oxidation (the educts were isolated with 1.5 equiv). The effect of increasing concentration of *m*-CPBA (1.5 → 5 equiv, with $(BzO)_2$ in 2.5-5% range) indeed resulted in reaction time shortening (Runs 1 and 2, 4 and 5, 7 and 9). Best results were obtained using 3 and 2 equiv of peroxyacid (Table 1) with slightly better yields of quinols by applying method A.

According to our preliminary results, it can be speculated that this oxidation takes place *via* radical intermediates since the reaction occurs only in the presence of light and the initiator, and can be stopped by passing oxygen through the reaction mixture. Isolation of *m*-CBA in 96% yield indicates that aryloxy radicals **L** propagate the reaction (Scheme 2).



Scheme 2

Epoxyquinols **3a** and **3b** could be obtained as main products directly from the corresponding phenols, in 51% (**3a**) and 54% (**3b**) yield (Runs 3 and 6; method C), simply by replacing 60 W lamp with 250 W. The preparation of **3a** and **3b** from the corresponding phenols may also be achieved from quinols **2a** and **2b** by epoxidation using reaction conditions A, in 58% and 62% yield, respectively. It is interesting to note that *m*-CPBA oxidation of quinols **2a** and **2b** affords only one epoxyquinol regioisomer and not the mixture of two as it was recently shown to occur with $Ti(OPr^i)_4$ and $VO(acac)_2$.[6b] Also, we demonstrated the advantage of *m*-CPBA / $(BzO)_2$ / hν system over previous two by the one-pot phenol-to-epoxyquinol transformation of estrone (**1a**) and estradiol 17-acetate (**1b**). The oxygen transfer probably also proceeds *via* radical pathway and the epoxidation occurring only in the presence of light, and not accompanied by lactone formation.[6b]

The results of further investigation of this reaction on other systems, and of conversion of **2a** and **2b** into the corresponding quinoid compounds, and of the biological activity of the obtained products will be published elsewhere.

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7. In a typical experiment, estrone (**1a**; 15.00 g, 55.5 mmol), *m*-CPBA (33.80 g, 165.5 mmol; 85% Jansen Chimica) and $(BzO)_2$ (1.34 g, 5.6 mmol) in 3 L mixture of CH_2Cl_2 / Me_2CO (4 / 1) was heated to reflux for 3.5 h while irradiated with 60 W tungsten lamp under argon. The reaction mixture was then evaporated to dryness, diluted with water and extracted with CH_2Cl_2. Combined organic extracts were washed with sat. $NaHCO_3$, and dried over anh. Na_2SO_4, the residue was chromatographed on SiO_2 column to afford **2a** (9.06 g, 57%) and **3a** (2.52 g, 15%). Acidification of chilled water layer with conc. HCl and crystallisation of crude product from H_2O / EtOH gave 22.89 g (96%) of *m*-CBA. **2a:** mp = 219-221°C; $[\alpha]_{546}$= +62, $[\alpha]_{578}$= +68 (c = 1.32, chl). **3a:** mp = 203-205°C ; $[\alpha]_{546}$= +317, $[\alpha]_{578}$ = +283 (c = 1.04, chl). 10β-Orientation of hydroxy group in **2a** was confirmed using 2D NMR techniques (COSY, HETCOR and NOE DIFF). When irradiating **1a** with 250 W tungsten lamp for 24 h, under the same conditions and using the same work-up procedure as above, epoxyquinol **3a** was isolated in a 51% yield.
8. GS-MS analysis of crude reaction mixture, and mixed probes with authentic sample proved the absence of methyl acetate.
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(*Received in UK* 17 *January* 1996; *revised* 3 *April* 1996; *accepted* 12 *April* 1996)