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A Novel Base-Promoted Oxidative Rearrangement Of 2-Methyl-4-Substituted Phenols To 1,2-(Methylenedioxy)-4-Substituted Benzenes

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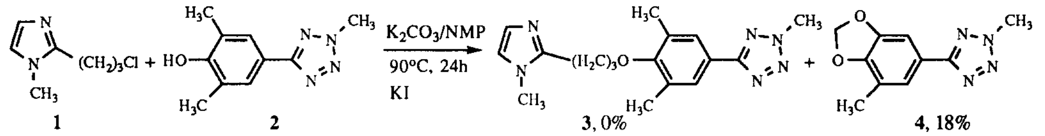
Abstract: Several 2-methyl-4-substituted phenols **5** were oxidatively rearranged to 1,2-(methylenedioxy)-4-substituted benzenes **6** in the presence of base and air. A mechanism was proposed. © 1997 Elsevier Science Ltd.

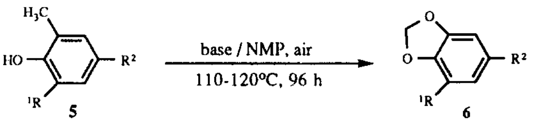
The oxygenation of phenolates generally leads to a complex reaction mixture. The oxidizability of phenolates depends on the nature of the substituents on the aromatic ring. Electron-donating substituents accelerate the reaction whereas electron-withdrawing substituents retard it.[2] We now report a novel base-promoted oxidative rearrangement reaction of 2-methyl-4-substituted phenols to 1,2-methylenedioxy-4-substituted benzenes while the 4-substituent is a electron-withdrawing group.[3]

As part of the antiviral program,[4] we were interested in the preparation of the tetrazol **3**. Surprisingly, an attempt to alkylate the phenol **2**[4] with the chloride **1**, we did not obtain the product **3** but isolated an unknown compound in 18% yield (mp. 126-128°C). Combustion analysis data coupled with ^1H & ^{13}C NMR and mass spectrum established its structure as **4**.[5] In an effort to explore this unprecedented reaction, it was found that both base and molecular oxygen were necessary. In the absence of K_2CO_3, treatment of the phenol **2** with either air or $NaIO_4$ did not lead to any of the product **4**. After many trials of the reaction conditions,[6] we were pleased to find out that Cs_2CO_3 gave the best yield of **4** (80%).[7] We then examined the scope of the 4-substitution groups. The results were summarized in Table 1. 4-Methyl phenyl substitution also gave the rearrangement product[5] although

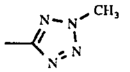


1 2 3, 0% 4, 18%

Table 1.



5 6

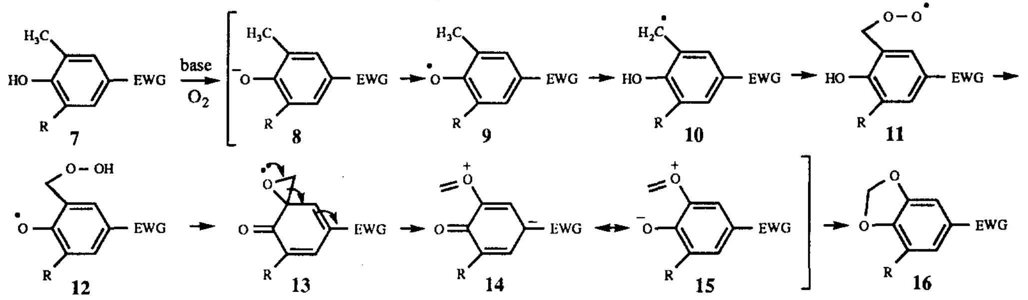
Entry	R^1	R^2	Base	Yield[a]
1	CH_3		Cs_2CO_3	80
2	H	4-methyl phenyl	Cs_2CO_3	22
3	CH_3	2-pyridyl	Cs_2CO_3	48
4	CH_3	CN	K_2CO_3[b]	25
5	CH_3	NO_2	Cs_2CO_3	0
6	H	tert-Butyl	Cs_2CO_3	0

a: All reactions were run in 0.5 mmol scale. b: Cs_2CO_3 hydrolyzed CN to $CONH_2$ more severely than K_2CO_3

in lower yield (22%, entry 2). Replacement with a better electron-withdrawing group improved the yield (48%, entry 3). Direct substitution with the base labile electron-withdrawing groups resulted in either low yield (25%, entry 4) or no product (entry 5). Electron-donating group also failed to produce any rearrangement product (entry 6).

To rationalize the formation of **6**, we tentatively proposed a mechanism[8] as illustrated in Scheme 1. The anion **8** was converted into the radical **9** by its oxidation with oxygen.[9] The radical **9** abstracted a hydrogen atom to give the benzylic radical **10**[10] which captured oxygen to give the hydroperoxide **12**.[9,11] Homolytic decomposition of **12** might lead to the epoxy ketone **13**.[12] The preferred ionization of the carbon-carbon bond[13] of the epoxide **13** might be due to the energy gained from the stabilization of the negative charge by the electron-withdrawing group in **14** and, this might explain why the better electron-withdrawing group gave higher yield (entry 3 vs. entry 2) whereas the electron-donating substitution gave no product (entry 6).

Scheme 1



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5. All new compounds gave satisfactory spectral data, elemental analysis and/or high resolution mass spectra.
6. Various temperatures (60°C, 90°C, 110°C-120°C, 140°C) and different bases (K_2CO_3, Cs_2CO_3, NaOH, KOH) were tried. **4** was obtained in 42% yield if KOH was used. Replacing NMP with DMF also gave the product although in lower yield (15% lower).
7. In a larger scale preparation (40 mmol), **4** was obtained in < 5%. However, if oxygen was bubbled through the reaction mixture, **4** was obtained in 47% in less than 10 hours.
8. We thank Professor Paul Helquist, Professor Tom Hoye and Dr. Lawrence Kruse for the discussions of the mechanism.
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