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Dimerization of phenols and naphthols using an aqueous sodium hypochlorite

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ABSTRACT

The observation of an unusual dimerization of phenols and naphthols using a sodium hypochlorite (NaOCl) in an aqueous solution is reported. NaOCl is an environmentally friendly and less expensive reagent than previously used reagents for dimerization. The yield of the dimer is moderate to high at ambient temperature.

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1. Introduction

The synthesis of symmetrical biaryl compounds is a challenging and continuously evolving field in organic chemistry. Symmetrical biaryl compounds are frequently found in natural products chemistry and in drug development.[1] Recently, there has been numerous reports in this area, particularly with respect to the dimerization of phenols and naphthol via an oxidative coupling of monomers using stoichiometric oxidants as well as relatively complex homogeneous and heterogeneous Lewis acid type catalysts.[2–4] The use of Cu(II)–amine complexes,[5] Cu(II)–amine complexes with AgCl,[6] CuCl(OH), TMEDA,[7] $CuSO_4(Al_2O_3)$,[8] $K_3[Fe(CN)_6]$,[9] $Mn(acac)_3$,[10,11] and oxovanadium complexes[12] are some notable examples for a catalytic oxidative coupling of 2-naphthols into 1,1′-bi-2-naphthols. The dimerization has also been reported in (a) enzymes such as horseradish peroxidase[13] and laccase[14] catalyzed dimerizations and (b) chloramine induced oxidative dimerization.[15]

Currently, there are several methods available for the synthesis of dimers. However, these methods have limitations and disadvantages, such as (1) use of expensive oxidants, (2) use of hazardous organic solvents, and (3) not suitable for scale-up. Thus, the replacement of known synthetic routes by environmentally benign reaction conditions is one of the major goals of Green Chemistry, which presents both economic and environmental advantages. Such an attempt, to evolve a novel synthesis route utilizing inexpensive and eco-friendly reagent, brought an aqueous sodium hypochlorite (NaOCl) to the researcher's attention.[16–21] NaOCl have been widely used in organic synthesis, including, N-chlorination of indole,[22] intramolecular oxidative coupling of brominated 2,4′-dihydroxy-diarylmethanes, biogenetic synthesis of thelepin,[23] and chlorination of various aromatic systems.[24] NaOCl has been successfully used as a reagent for various synthetic conversions, however, there are no reports of this reagent being used for dimerization of aromatic systems. In this Letter, we report the dimerization of various phenol derivatives and naphthol using an aqueous NaOCl at high yields using ambient conditions. All the reactions reported were carried out with a short reaction time at room temperature.

2. Results and discussion

Hopkins and Chisholm[24] reported the synthesis of 5-chloro-2-hydroxy-4-methoxybenzaldehyde by chlorination of 2-hydroxy-4-methoxybenzaldehyde using NaOCl in the presence of 4% aqueous NaOH. Under the same reaction conditions, we attempted to synthesize 3-chloro-2-hydroxy-4-methoxybenzaldehyde by chlorination of 2-hydroxy-5-methoxybenzaldehyde. However, the reaction did not proceed to afford the expected product. Instead, the 2-hydroxy-5-methoxybenzaldehyde underwent an unusual dimerization to produce compound **2a** (Scheme 1). Mass spectrometry and NMR confirmed the dimer.[25,26] The ^1H NMR results of dimer **2a** showed a doublet of doublet at δ 7.07 (d, J = 3.0 Hz, 1H) and δ 7.25 (d, J = 3.3 Hz, 1H) and the occurrence of doublets to *meta*

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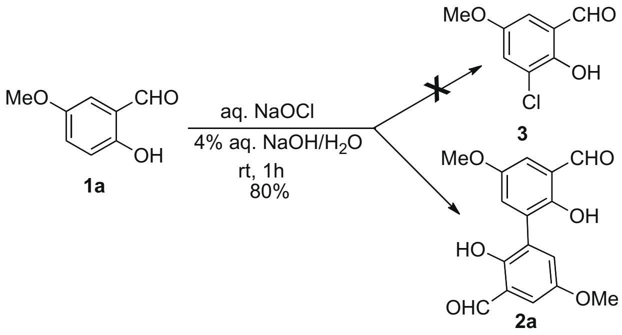


Scheme 1.

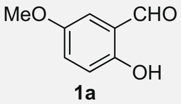
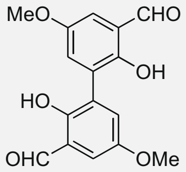
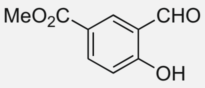
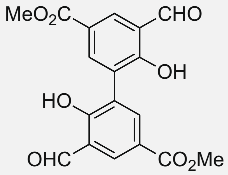
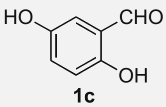
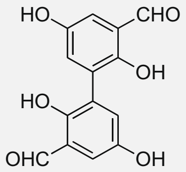
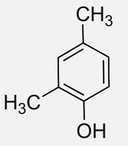
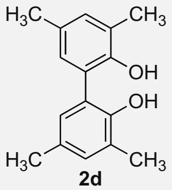
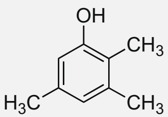
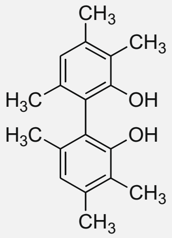
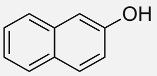
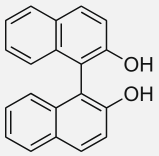
hydrogen–hydrogen can be assigned to the *ortho–ortho* coupling. The structures of starting material, product, and reaction conditions are shown in Scheme 1. The product yield was remarkably high (80%).

Pending further investigations to the mechanism of dimer formation in aqueous NaOCl, a plausible mechanism for the formation of the *ortho–ortho* coupling is depicted in Scheme 2. The mechanism could follow the formation of carbanion intermediate **4** under basic NaOCl condition followed by electrophilic chlorination to give intermediate **5**. As a final step in mechanism, both the intermediates **4** and **5** might have undergone an oxidative coupling to form the dimerized product **2a**.[26] In order to investigate the carbanion formation, we performed the reaction of 2,4-dimethylphenol and 2-chloro-4,6-dimethylphenol in 4% aqueous NaOH solution. The reaction was monitored for several hours using HPLC.[27] This reaction has not produced a dimer suggesting that the basic condition alone cannot be the reason for the dimerization and needs the presence of NaOCl.

In order to explore the generality and scope of the reaction condition, a variety of substrates with electron-donating and electron-withdrawing substituents were tested. The results are summarized in Table 1. The reactivity of substrates varied with electron-donating and electron-withdrawing groups substituted at the 5-position. In general, the substrates with the electron-donating group gave a better yield than the substrates with the electron-withdrawing substituent. This information is insufficient to evolve a mechanism. All reactions were completed within 1–5 h and gave an exclusively *ortho–ortho* coupling product. The final product was isolated by filtration.

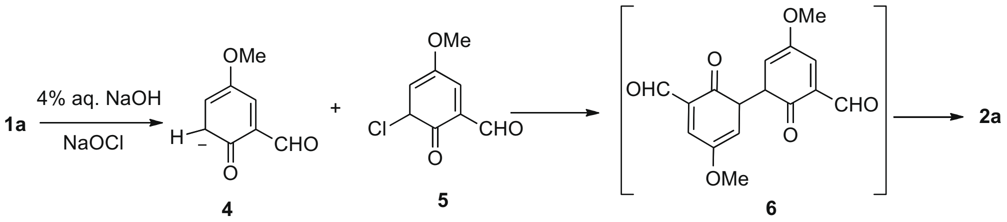
We note that by adopting aqueous NaOCl reaction conditions, dimerization occurs, not only for dimethyl-substituted phenols like 2,4-dimethylphenol but also for trimethyl-substituted phenols like 2,3,5-trimethylphenol (Table 1, products **2d** and **2e**). The discovery and development of a more effective and eco-friendly means of synthesizing compounds is useful and important. Here we have developed the means to synthesize 1,1′-binaphthalene-2,2′-diol, as well as a limited family of other diols, which produces a good yield in the presence of sodium hypochlorite and aqueous sodium hydroxide, as an effective alternative to the currently available methods for synthesizing 1,1-bi-2-naphthol from 2-naphthol.

Table 1
Dimerization of phenols and 2-naphthol using an aqueous sodium hypochlorite

Entry	Substrate	Time (h)	Product[25]	Yield (%)
1	 **1a**	1	 **2a**	80
2	 **1b**	4	 **2b**	47
3	 **1c**	3	 **2c**	56
4	 **1d**	5	 **2d**	72
5	 **1e**	4	 **2e**	78
6	 **1f**	2	 **2f**	58

Compounds **2d**–**f** were characterized according to data reported in Refs. 8,10b,c.

In conclusion, a simple, yet effective aqueous condition has been created to demonstrate the dimerization of phenol derivatives and naphthol in moderate to high yields.



Scheme 2.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.173.

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25. *Typical experimental procedure for* **2a**: To a stirred solution of 2-hydroxy-5-methoxybenzaldehyde (1.0 g, 7.0 mmol) in water (10.0 mL) and 4% aqueous NaOH (4.0 mL), aqueous NaOCl (4.0 mL) was slowly added at room temperature and stirred for 1 h. Upon acidifying with dil. HCl (10.0 mL), a precipitate formed was filtered and dried ($CaCl_2$). (0.79 g, 80%); mp152–156 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 3H), 7.07 (d, $J = 3$ Hz, 1H), 7.25 (d, $J = 3.3$ Hz, 1H), 9.90 (s, 1H, CHO), 10.99 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.78, 115.80. 118.25, 126.03, 126.67, 152.25, 153.53, 196.23. HRMS calcd for $C_{16}H_{14}O_6$: 302.0790. Found: 302.0799.
26. HPLC conditions: Column: Phenomenex Prodigy 250 × 4.60 mm, 5 micron. Eluent: 50% Acetonitrile/50% (0.1 M) Ammonium formate. Flow rate: 2.0 mL/min; pressure: 2970 Psi. Scheme 1 was monitored continuously. Retention times 3.883 and 6.692 min were corresponding to 2-hydroxy-5-methoxybenzaldehyde **1a** and dimer **2a**, respectively.
27. Reaction of 2,4-dimethylphenol and 2-chloro-4,6-dimethylphenol in an aqueous NaOH solution was monitored continuously. The HPLC condition was similar to that of Ref. 26. Retention times 4.655 and 8.480 min were corresponding 2,4-dimethylphenol and 2-chloro-4,6-dimethylphenol, respectively. Even after 16 h of stirring at room temperature, the content failed to produce the dimer **2d**, which was known to elute at 2.807 min.