Letters in Organic Chemistry, 2018, *15*, 878-882

RESEARCH ARTICLE

Synthesis of Substituted Phenols *via* Hydroxylation of Arenes Using Hydrogen Peroxide in the Presence of Hexaphenyloxodiphosphonium Triflate

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ARTICLE HISTORY

Received: August 11, 2017
Revised: April 11, 2018
Accepted: April 19, 2018

DOI:
10.2174/1570178615666180430121524

Abstract: A mild and efficient protocol for the synthesis of phenols from arenes has been developed using aqueous hydrogen peroxide as an oxidizing agent and hexaphenyloxodiphosphonium triflate as a promoter. The reactions were carried out with the simple procedure in EtOH-H_2O at room temperature in short reaction times.

Keywords: Substituted phenols, hexaphenyloxodiphosphonium triflate, hydroxylation, hydrogen peroxide, arene.

1. INTRODUCTION

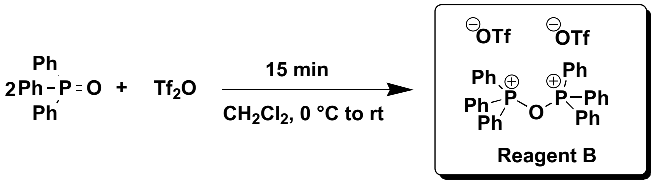
Phenol and its derivatives are important chemical intermediates in manufacturing pharmaceuticals, natural products, polymers, and dyes [1]. Classical methods for preparation of such phenols involve nucleophilic substitution of aryl halides and copper-catalyzed transformation of diazoarenes [2]. However, strict electron-rich requirements, incompatibilities with many functional groups, and harsh reaction conditions lead in limitations in its application. Impressive progress in the transition-metal-catalyzed synthesis of phenols from aryl halides has been achieved [3-9]. Transformation of arylboronic acids to the corresponding phenols with metal-catalyst under air conditions was reported [10]. In addition, some investigations indicate that arylboronic acids can be converted into phenols under metal-free conditions by using air as oxidant [11]. Other oxidants including H_2O_2 [12], ozone [13], MCPBA [14] or *N*-oxides [15] used for this transformation, have been reported. Some of these approaches have disadvantages including the use of ligand/base [10], the use of toxic chlorinated solvents [12d, 16] and require longer reaction times [11, 12]. The direct aromatic oxygenation reaction of arenes to phenols has attracted much attention due to its importance in commercial point in phenol production. This method has been chosen as an alternative route using environmentally benign oxidant such as O_2 or H_2O_2 [17-22].

The direct introduction of OH group into the aromatic C-H bond with such oxidants is challenging due to low product selectivity which made by overoxidation of phenols and low reactivity of aromatic C-H bond [23, 24].

Thus, the development of catalytic systems or promoters that are readily accessible, air and moisture stable, and that can promote these reactions with high selectivity and good product yields under mild reaction conditions are still desirable.

Among the oxidants, hydrogen peroxide is an economically and environmentally benign oxidant which is widely used as an electrophilic reagent and can react with many functional groups. It has a simple process, and water is the only by-product.

Trifluoromethanesulfonic anhydride, Tf_2O, is known for its utility for the conversion of an OH group into an OTf leaving group [25]. Tf_2O reacts exothermically with Ph_3PO in CH_2Cl_2 to give a white precipitate of hexaphenyloxodiphosphonium triflate (Reagent B) (Scheme **1**) [26].



Scheme (1). Synthesis of hexaphenyloxodiphosphonium triflate.

This reagent, commonly called Hendrickson`s reagent, was shown to be a powerful dehydrating agent and promoter, and promising reagent for some organic reactions [26-28].

2. RESULTS AND DISCUSSION

As part of our ongoing efforts to develop electrophilic aromatic substitution reaction using Tf_2O or the Tf_2O deriva-

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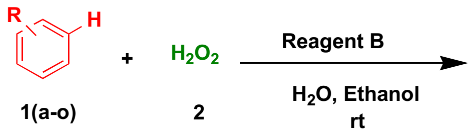
1875-6255/18 $58.00+.00

tives [29], we wish to report hydroxylation of arenes using Reagent B/H_2O_2 system in H_2O-EtOH at room temperature (Scheme **2**).



Scheme (2). Hydroxylation of arenes using Reagent B/H_2O_2 system.

Table 1. Hydroxylation of mesitylene using Reagent B/H_2O_2 system in different solvents at room temperature.

Entry	Solvent	Time (min)	Yield (%)^b
1	H_2O-Ethanol (1:1)	50	70
2	H_2O-Ethanol (1:2)	35	80
3	H_2O-Ethanol (1:3)	60	75
4	H_2O-Ethanol (2:1)	50	50
5	Ethanol	60	70
6	H_2O	95	50
7	CH_2Cl_2	90	40
8	MeCN	95	45
9	$CHCl_3$	95	40

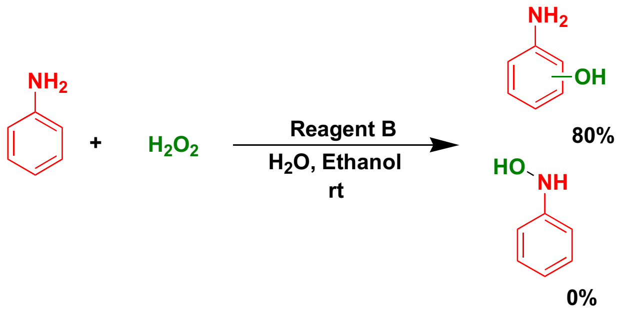
^{a}Mesitylene (1 mmol, 0.138 mL), H_2O_2 (4 mmol, 0.4 mL), Reagent B (1 mmol, 0.814 g) in 3 mL H_2O-EtOH: 1:2 at room temperature. ^{b} isolated yield.

As a starting point for optimization of the reaction conditions, mesitylene was chosen as a model substrate for investigation. The reaction initiated in a H_2O-EtOH (1:1) solution using H_2O_2 as the oxidant in the presence of Reagent B as a promoter. The result was promising, and the product produced in 70% yield (Table **1**, entry 1). Increasing the amount of EtOH in the EtOH-H_2O solution led to a higher yield of product (80%, Table **1**, entry 2). However, a further increase of ethanol (Table **1**, entry 3) or increase of water (Table **1**, entry 4), resulted in a decreased yield of the corresponding product. Pure ethanol (Table **1**, entry 5) or pure water (Table **1**, entry 6) as a solvent was also examined and the results indicated that the yield of the corresponding product reduced. This observation showed that the reaction reactivity was depended on the ratio of EtOH/H_2O. Investigation of the effect of other solvents including CH_2Cl_2, CH_3CN and $CHCl_3$ resulted in a lower yield of the product. The effect of amount of Reagent B on the reaction was also examined and it was found that 1 mmol of Reagent B was the best choice. When 1.2 and 1.4 mmol of Reagent B were used, the results did not show any noticeable differences with respect to the yield and reaction time. Therefore, the optimized reaction conditions for this reaction are Reagent B (1 equiv) in H_2O-EtOH (1:2) at room temperature. A control experiment conducted without Reagent B indicated that the reaction did not take place, and the mesitylene remained unreacted at the end of the reaction.

To study the generality of this procedure, we examined the reaction using several arenes under the optimized reaction conditions (Table **2**). The arenes with electron releasing groups react with shorter reaction times and good yields, while the reactions of arenes with electron withdrawing groups carried out with longer reaction times and lower yields. The rate differences between electron rich and poor arenes are so low, it may be due to the high reactivity of Reagent B.

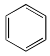
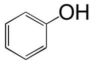
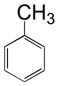
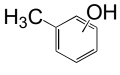
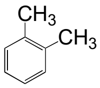
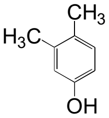
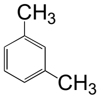
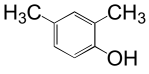
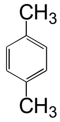
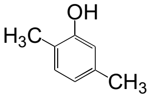
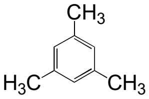
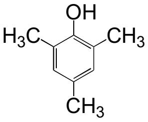
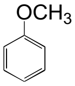
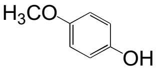
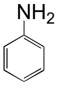
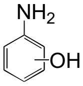
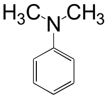
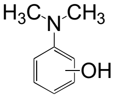
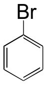
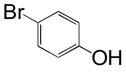
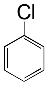
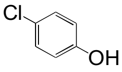
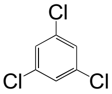
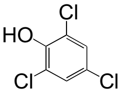
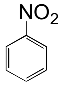
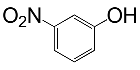
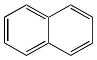
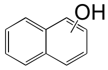
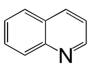
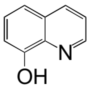
The hydroxylation of **1a** was carried out under the reaction conditions, and **3a** was obtained in 65% yield (Table **2**, entry 1). The overoxidation product, benzoquinone, was not produced. In addition, no polyhydroxylation product was observed. The reaction of **3a** under the same reaction conditions was accompanied by the formation of several by- products, and efforts to obtain the corresponding phenols were not successful.

The arene **1b** with an electron donor group reacted with H_2O_2 under the same reaction conditions and the mixture of isomeric products of **3b** was obtained in 55% yield (Table **2**, entry 2). The hydroxylation of **1c-1e** afforded the corresponding products **3c-3e** in 70, 78 and 75% yields, respectively due to having two methyl groups (Table **2**, entries 3, 4 and 5). The compound **1f** with three methyl groups reacted with H_2O_2 to give **3f** in 80% yield (Table **2**, entry 6). The reaction of **1g** with the moderate electron donor group was carried out with high regioselectivity to afford **3g** in 75% yield (Table **2**, entry 7). Hydroxylation of **1h** with the strong electron releasing group was performed to give a mixture of *o*- and *p*-isomers of **3h** with ratio 31:69 in 80% yield (Table **2**, entry 8). In this case, the C-hydroxylation product was obtained and no *N*-hydroxylation produced. The reason for this observation may have arisen from this fact that there is a hard-soft interaction between the nitrogen of **1h** and $^+$OH of H_2O_2. This hard-soft interaction intensifies the nucleophilic ability of carbon of **1h** in comparison with its nitrogen; so the carbon of **1h** reacted rapidly with H_2O_2 and it did not allow nitrogen to react (Scheme **3**).



Scheme (3). Hydroxylation of **1h** on carbon using Reagent B /H_2O_2 system.

Table 2. **Hydroxylation of arenes with H_2O_2 using Reagent B.**

Entry	ArH	Product	Time (min)	Yield[a] (%)
1	 **1a**	 **3a**	55	65
2	 **1b**	 **3b**	55	70
3	 **1c**	 **3c**	40	70
4	 **1d**	 **3d**	40	78
5	 **1e**	 **3e**	40	75
6	 **1f**	 **3f**	35	80
7	 **1g**	 **3g**	44	75
8	 **1h**	 **3h**	40	80[b]
9	 **1i**	 **3i**	60	55
10	 **1j**	 **3j**	45	60
11	 **1k**	 **3k**	50	65
12	 **1l**	 **3l**	50	70
13	 **1m**	 **3m**	60	50
14	 **1n**	 **3n**	50	68[c]
15	 **1o**	 **3o**	60	55

[a] Isolated yield.

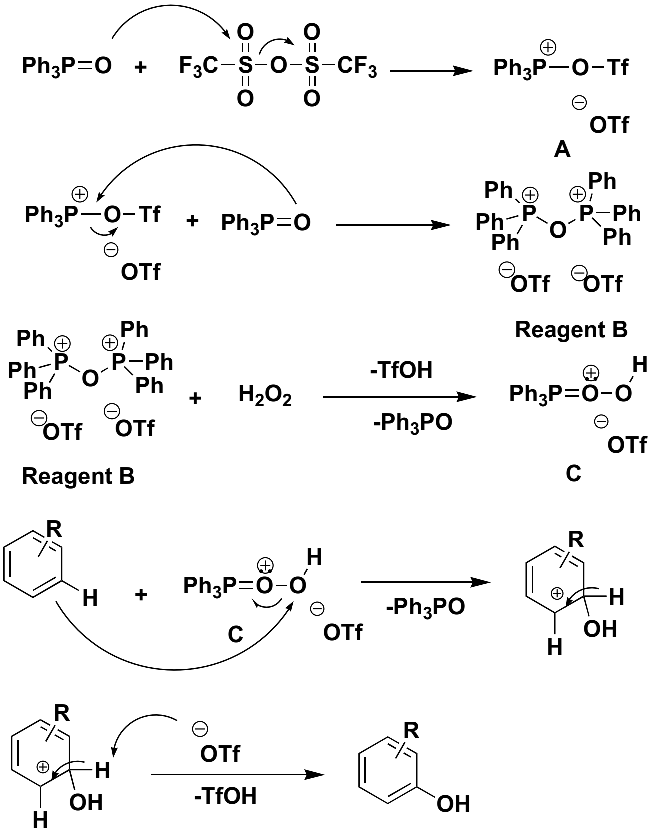
[b] The ratio of ortho:para was determined with ^{1}H NMR. Ratio = 69:31.

[c] The ratio of α:β was determined with ^{1}H NMR. Ratio = 62:38.

The substrate **1i** was also reacted with H_2O_2 and the corresponding mixture of products **3i** was obtained in 55% yield (Table **2**, entry 9).

Hydroxylation of **1j** and **1k** with electron withdrawing groups under the present reaction conditions also occurred with high regioselectivity and the *p*-isomers of **3j** and **3k** were obtained as sole products (Table **2**, entries 10 and 11). **1l** also reacted with H_2O_2 to afford the corresponding product **3l** in 70% yield (Table **2**, entry 12). The arene **1m** with strong electron withdrawing group reacted to give **3m** in 50% yield (Table **2**, entry 13).

The reaction of **1n** and H_2O_2 gave a mixture of isomers of **3n** with ratio 62:38 in 68% yield (Table **2**, entry 14). It was found that over oxidations in these reactions did not occur since no quinones were observed. The hydroxylation of **1o** occurred with high regioselectivity and **3o** was obtained as the only product in 55% yield (Table **2**, entry 15). It is interesting to note that for substrate bearing oxidizable nitrogen including **1i** and **1o**, no *N*-oxide product was found in the products. Unfortunately, the reactions of benzaldehyde led to producing several by-products, and efforts to obtain the desired phenol was useless. In addition, hydroxylation reaction of benzyl alcohol was also unsuccessful.



Scheme (4). Proposed reaction mechanism.

As a result of this observation, the above mechanism indicated in Scheme **4** was proposed for the synthesis of phenols promoted by Reagent B. This reagent was prepared via a two-step process at low temperature [28]. The produced phosphonium cation (**Reagent B**) accepts a nucleophilic compound and the triflate leaving group exits simultaneously [29d and 29e]. Replacement of triflate with the oxygen of H_2O_2 generates intermediate **C**. The intermediate **C** was characterized by FT-IR and NMR spectra (Supporting information). The presence of this intermediate might be confirmed by the observation of ^1H NMR peaks at 10.3 ppm attributed to the hydroxyl proton, and 7-9 ppm ascribed to the phenyl protons. The ^{13}C NMR spectrum of intermediate **C** also shows the peaks of the phenyl carbons. Furthermore, FT-IR peak at 3340 cm^{-1} related to the stretching vibrations of hydroxyl group. Thus, the resulting intermediate was used for successful hydroxylation of arene *via* an ordinary electrophilic aromatic substitution reaction.

3. EXPERIMENTAL SECTION

3.1. General Information

All the chemicals were obtained from Merck Company and used as received. All products are known and characterized by comparison of spectral (^1H NMR, ^{13}C NMR) data with those reported in the literature. All yields refer to isolated products. NMR spectra were recorded on Brucker Avance spectrophotometer (400 MHz) in $CDCl_3$ using TMS as an internal standard.

3.2. General Procedure for the Hydroxylation of Arenes

In a 25 mL flask, to a solution of Reagent B (0.814 g, 1 mmol) in 3 mL of H_2O/ethanol (1:2), H_2O_2 (4 mmol, 0.4 mL) was added and the mixture allowed stirring for 15 min at room temperature. Then, arene (1 mmol) was added and the reaction mixture allowed stirring for the appropriate time (Table **2**). Upon completion of the reaction, the crude product was purified by a column chromatography using ethyl acetate/n-hexane to afford the corresponding phenol. The products are all known compounds.

CONCLUSION

In conclusion, we have developed a salt-promoted, clean, mild, rapid, and efficient method for direct aromatic oxygenation reaction of arenes to phenols. The protocol uses readily available aromatic compounds as the substrates, inexpensive hydrogen peroxide as a hydroxylation agent, Reagent B as a promoter, and a mixture of water/ethanol as the solvent. This method could tolerate various functional groups and performed at room temperature without formation of by-products.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

We thank the Razi University for generous financial support of this work.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article. Experimental detail, ^{1}H and ^{13}C NMR spectra of compounds are given in supporting information.

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