

Selective one-pot synthesis of various phenols from diarylethanes†

Ryota Nakamura, Yasushi Obara and Yasutaka Ishii*

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Various substituted phenols were selectively synthesized by a one-pot reaction through the NHPI-catalyzed aerobic oxidation of 1,1-diarylethanes followed by treatment with dilute sulfuric acid.

Phenols are very important raw materials for the synthesis of phenol resins, dyes, pharmaceuticals, antioxidants *etc.* In 2003, worldwide production of phenol amounted to 7.2 megatons and is still growing.¹ Although several methods are known for the synthesis of phenols, most phenols are currently synthesized by the cumene method developed by Hock and Lang.² Previously, we reported an efficient carbon radical generation method from saturated hydrocarbons by using *N*-hydroxyphthalimide (NHPI) as a catalyst.³ The NHPI-catalyzed reactions provide convenient methodologies for oxygenation,⁴ nitration,⁵ and sulfonation⁶ of alkanes and phenol synthesis from cumene⁷ and cyclohexylbenzene.^{8,9} In recent years, an efficient hydroarylation of styrenes with benzenes leading to 1,1-diarylethanes is explored by using common Lewis acids like FeCl₃,¹⁰ BiCl₃,¹¹ and Bi(OTf)₃¹² in good yields. The FeCl₃-catalyzed reaction is particularly important, because various substituted 1,1-diarylethanes are easily prepared from cheap starting materials such as styrene and substituted benzenes.

The easy access to a variety of 1,1-diarylethanes by the hydroarylation prompts us to attempt a selective synthesis of phenols, which are difficult to obtain by conventional methods, from 1,1-diarylethanes. We report here the first successful approach to various substituted phenols by the NHPI-catalyzed aerobic oxidation of 1,1-diarylethanes.

A strategy of the present phenol synthesis is depicted in Scheme 1.

The aerobic oxidation of 1,1-diarylethane (**1**) under the influence of NHPI is expected to furnish a hydroperoxide (**2**) on which subsequent treatment with sulfuric acid would produce a pair of cleaved products, Ar¹OH (**3**) and Ar²(CO)Me (**4**) and/or Ar²OH (**3'**) and Ar¹(CO)Me (**4'**) through the degradation *via* a *path a* and/or a *path b*, respectively. Therefore, it is interesting to clarify the influence of the aryl moiety on the degradation course, *path a* and/or *path b*, of the generating hydroperoxides.

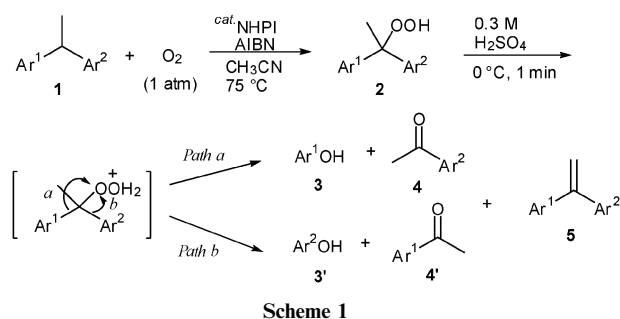
Various 1,1-diarylethanes were used as starting materials prepared by Beller¹⁰ methods and allowed to react with O₂ (1 atm) in the presence of catalytic amounts of NHPI and AIBN in acetonitrile at 75 °C followed by treatment with dilute sulfuric acid at 0 °C for 1 min, giving the corresponding phenols and acetophenones in good selectivities at a satisfactory conversion.

To elucidate an optimum reaction condition, 1-(4-methoxyphenyl)-1-phenylethane (**1a**) was allowed to react under various conditions (Table 1).

The oxidation of **1a** (3 mmol) was examined under O₂ (1 atm) in the presence of AIBN (3 mol%) and NHPI (10 mol%) in MeCN (3 mL) at 75 °C for 15 h, and then the resulting mixture was treated with 0.3 M H₂SO₄ (1 mL) at 0 °C for 1 min to give both 4-methoxyphenol (**3a**) and acetophenone (**4a**) in 61% yield (97% selectivity) at 63% conversion of **1a** (entry 1). Surprisingly, the degradation of hydroperoxide (**2a**) with sulfuric acid took place selectively through the *path a* to lead to a pair of products, **3a** and **4a**, exclusively, without formation of **3'a** and **4'a**, even though there are two degradation courses from **2a** to phenols as shown in Scheme 1. This indicates that the difference in electron state of the two aromatic rings in **1a** is crucial to determine the degradation course. Therefore, the present method would provide a very useful synthetic tool for the selective synthesis of substituted phenols as well as acetophenones which can be recycled as the starting styrenes after hydrogenation followed by dehydration.

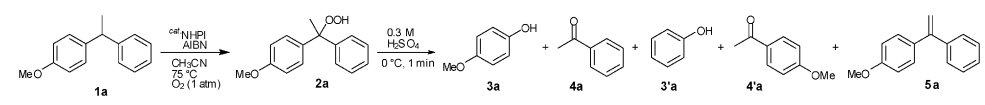
The reaction for 6 h under these conditions afforded phenol **3a** in 54% yield (96% selectivity) (entry 2). When both AIBN and NHPI were halved, the yield of **3a** was slightly decreased but the selectivity was kept in high (entries 3 and 4). Removal of the AIBN from the reaction system resulted in a slight decrease of the conversion of **1a** (entry 5).

By treating the reaction mixture with triphenylphosphine (900 mg) followed by treatment with 0.3 M H₂SO₄ (5 mL) at 75 °C, 1-(4-methoxyphenyl)-1-phenylethylene (**5a**) was formed in 60% yield (97% selectivity) without formation of phenols (entry 6).¹³



Department of Chemistry and Material Engineering, Faculty of Chemistry, Materials and Bioengineering & High Technology Research Center, Kansai University, Suita, Osaka, 564-8680, Japan.
E-mail: ishii@ipcku.kansai-u.ac.jp; Fax: +81-6-6339-4026;
Tel: +81-6-6368-0793

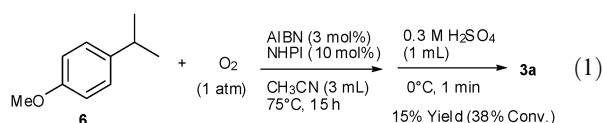
† Electronic supplementary information (ESI) available: Experimental and compound characterization data (¹H, ¹³C NMR, IR and MS) and spectra data of **1**, **3**, **4**, **5** and **9**. See DOI: 10.1039/b804055a

Table 1 Synthesis of 4-methoxyphenol (**3a**) from 1-(4-methoxyphenyl)-1-phenylethane (**1a**) under various conditions^a


Entry	AIBN (mol%)	NHPI (mol%)	Time/h	Conv. (%)	Yield (selectivity) (%) ^b				
					3a	4a	3'a	4'a	5a
1	3	10	15	63	61(97) [52]	61(97) [54]	—	—	1
2	3	10	6	56	54(96)	55(98)	—	—	1
3	1.5	5	6	38	37(97)	37(97)	—	—	1
4	1.5	5	15	54	51(94)	51(94)	—	—	2
5	0	10	15	50	48(96)	48(96)	—	—	1
6 ^c	3	10	15	62	—	—	—	—	60(97) [54]

^a **1a** (3 mmol) was allowed to react in the presence of AIBN (1.5 or 3 mol%) and NHPI (5 or 10 mol%) under O₂ (1 atm) in CH₃CN (3 mL) at 75 °C for 6–15 h followed by treatment with 0.3 M H₂SO₄ (1 mL) at 0 °C for 1 min. ^b Yields based on GC analysis. Numbers in square brackets show isolated yields. ^c Treatment of the reaction mixture with PPh₃ (900 mg) at 75 °C for 1 h followed by treatment with 0.3 M H₂SO₄ at 75 °C for 1 h.

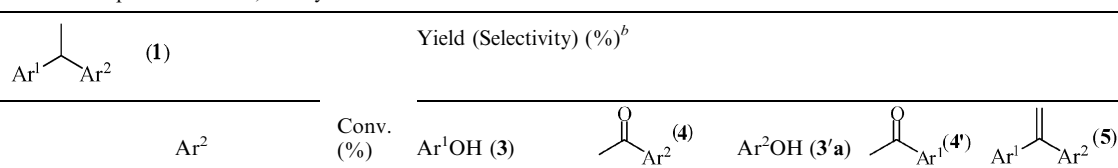
In order to reveal the usefulness of the present method, the synthesis of **3a** from 4-isopropylanisole (**6**) was examined (eqn (1)).



The oxidation of **6** under the same condition as entry 1 in Table 1 followed by treatment with sulfuric acid gave **3a** in low yield (15%) at 38% conversion. This indicates that **1a** is much more reactive than **6** for the aerobic oxidation. Therefore, 1,1-diarylethanes are thought to be new valuable phenol sources which are difficult to prepare by conventional method, because a variety of the starting 1,1-diarylethanes are now synthesized in good yields from cheap raw materials.

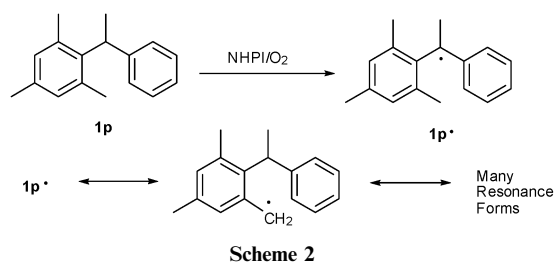
Thus, various diarylethanes were prepared and converted into the corresponding phenols by means of this synthetic approach (Table 2).

1,1-Diphenylethane (**1b**) afforded phenol (**3b**) in 53% yield (90% selectivity) (entry 1). From the reaction of 1-phenyl-1-(4-tolylethane (**1c**), *p*-cresol (**3c**) was obtained in relatively good yield (63%) and selectivity (82%) (entry 2), while the reaction of 1-phenyl-1-(3-tolylethane (**1d**) gave a mixture of *m*-cresol (**3d**) (40%) and phenol (**3d'**) (21%) (entry 3). 1-Phenyl-1-(3,4-xylyl)ethane (**1e**), 1-(4-chlorophenyl)-1-(3,4-xylyl)ethane (**1f**), and 1,1-di(3,4-xylyl)ethane (**1g**) gave rise to 3,4-dimethylphenol (**3e–g**) in 70%, 71%, and 79% yields, respectively (entries 4–6). From **1c**, **1e**, and **1f**, small amounts of a counter part of phenols, **3'e**, **3'f** and **3'g** were obtained *via* the *path b*. Under these reaction conditions, 1-(4-ethylphenyl)-1-phenylethane (**1h**), 1-phenyl-1-(4-propylphenyl)ethane (**1i**), and 1-(4-*tert*-butylphenyl)-1-phenylethane (**1j**) afforded 4-ethylphenol (**3h**), 4-propylphenol (**3i**), and

Table 2 Synthesis of substituted phenols from 1,1-diarylethanes^a


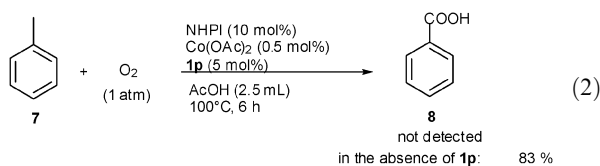
Entry	Ar ¹	Ar ²	Conv. (%)	Yield (Selectivity) (%) ^b				
				Ar ¹ OH (3)	Ar ² OH (3'a)	Ar ¹ -C(Ar ²)=Ar ² (5)		
1	1b Ph	Ph	59	53(90) [45] (3b)	—	4		
2 ^c	1c 4-CH ₃ C ₆ H ₄	Ph	77	63(82) [50] (3c)	—	4		
3	1d 3-CH ₃ C ₆ H ₄	Ph	70	40(57) [37] (3d)	21 (3d')	4		
4	1e 3,4-(CH ₃) ₂ C ₆ H ₃	Ph	82	70(85) [62] (3e)	7	3		
5	1f 3,4-(CH ₃) ₂ C ₆ H ₃	4-ClC ₆ H ₄	81	71(88) [61] (3f)	3	5		
6	1g 3,4-(CH ₃) ₂ C ₆ H ₃	3,4-(CH ₃) ₂ C ₆ H ₃	88	79(90) [71] (3g)	—	5		
7	1h 4-C ₂ H ₅ C ₆ H ₄	Ph	63	49(78) [41] (3h)	5	2		
8	1i 4-C ₃ H ₇ C ₆ H ₄	Ph	62	54(87) [48] (3i)	2	5		
9 ^c	1j 4- <i>tert</i> -C ₄ H ₉ C ₆ H ₄	Ph	59	50(85) [41] (3j)	4	1		
10	1k 3,4-(CH ₃ O) ₂ C ₆ H ₃	Ph	76	60(79) [53] (3k)	nd	1		
11	1l 4-CH ₃ OC ₆ H ₄	4-CH ₃ C ₆ H ₄	53	50(94) [41] (3l)	1	1		
12	1m 4-CH ₃ OC ₆ H ₄	4-ClC ₆ H ₄	58	56(97) [50] (3m)	nd	2		
13	1n 3,5-(CH ₃) ₂ -4-(CH ₃ O)C ₆ H ₂	Ph	73	68(93) [65] (3n)	nd	4		
14	1o 2,5-(CH ₃) ₂ C ₆ H ₃	Ph	1	nd	nd	trace		
15	1p 2,4,6-(CH ₃) ₃ C ₆ H ₂	Ph	< 1	nd	nd	trace		

^a **1** (3 mmol) was allowed to react under the same conditions as entry 1 in Table 1. ^b Yields and selectivity based on GC analysis. Numbers in square brackets show isolated yields. ^c NHPI (20 mol%) and AIBN (6 mol%) was used at 80 °C for 24 h.



4-*tert*-butylphenol (**3j**) in 49%, 54% and 50% yields, respectively, with good selectivities (78–87%) (entries 7–9). Furthermore, the oxidation of 1-(3,4-dimethoxyphenyl)-1-phenylethane (**1k**) gave 3,4-dimethoxyphenol (**3k**) (60% yield, 79% selectivity). From 1-(4-methoxyphenyl)-1-(4-tolyl)ethane (**1l**) and 1-(4-chlorophenyl)-1-(4-tolyl)ethane (**1m**), the same phenol **3a** was formed in high selectivity (entries 11 and 12). From 1-(3,5-dimethyl-4-methoxyphenyl)-1-phenylethane (**1n**), 3,5-dimethyl-4-methoxyphenol (**3n**) (68% yield, 93% selectivity) was obtained (entry 13). The results presented in Table 2 indicate that the 1,2-aryl shift is a nucleophilic process on the electron deficient oxygen atom and the degradation of hydroperoxides was selectively induced to give more electron-rich phenols in high selectivities.

It is interesting to note that 1,1-diarylethanes bearing alkyl substituents on their *ortho*-positions like 1-phenyl-1-(2,5-xylyl)ethane (**1o**) and 1-mesityl-1-phenylethane (**1p**) were reluctant for the aerobic oxidation (entries 14–15). We thought that **1o•** and **1p•** generated from **1o** and **1p** are sterically hindered stable radicals which can serve as inhibitors in the radical chain-transfer reaction. In particular, the **1p•** is a very stable radical which can take many resonance forms (Scheme 2). Therefore, these diarylethanes can act as chain-transfer inhibitors for the aerobic oxidation of alkanes. Thus, we examined the aerobic oxidation of toluene in the presence or absence of **1p** (eqn (2)). Toluene (**7**) was efficiently oxidized by NHPI combined with Co(OAc)₂ to give benzoic acid (**8**) in 83% yield, but no oxidation of **7** was observed in the presence of a small amount of **1p** (5 mol%) (eqn (2)).



Phenol and amine derivatives are well-known to serve as radical inhibitors, however, the autoxidation is rarely inhibited by a simple aromatic hydrocarbon such as **1p**. Therefore, **1p** is a particular interesting compound as a new class of inhibitor not involving amino or phenol group.

In conclusion, we have developed a new selective synthetic approach to phenols by aerobic oxidation of 1,1-diarylethanes using NHPI as a key catalyst. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas “Advanced Molecular Transformation of Carbon Resources” from the Ministry of Education, Culture, Sports, Science and Technology, Japan, “High-Tech Research Center” Project for Private Universities: matching fund subsidy from the Ministry of Education, Culture, Sports, Science and Technology, 2005–2009, and Research Association for Ishii Oxidation Technology.

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- Treatment of the reaction mixture with PPh₃ formed 1-(4-methoxy-phenyl)-1-phenylethanol (**9**) exclusively. However, the alcohol **9** could not be detected by GC analysis due to thermal conversion of **9** to **5a** during the GC measurement. Therefore, we performed further treatment of the reaction mixture with 0.3 M H₂SO₄ to produce **5a** as a product (in entry 6, Table 1).