Note

OXIDATION OF ELECTRON-RICH ARENES USING HFIP-UHP SYSTEM

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KEYWORDS: Green oxidation, Quinones, Fluorinated alcohol, Arenes, Water peroxide

ABSTRACT

The straightforward oxidation of electron-rich arenes, namely phenols, naphthols and anisole derivatives under mild reaction conditions is described by means of the use of environmentally benign HFIP-UHP system. The corresponding quinones or hydroxylated arenes, were obtained in moderate to good yields.

Quinone derivatives constitute an important class of organic compounds present in several natural products that exhibit a wide range of applications in medicinal chemistry or biochemistry,[1] also playing an important role in some biological redox processes.[2] For example, some of these derivatives exhibit a demonstrated biological activity as it is the case of those representative examples shown in Figure 1.

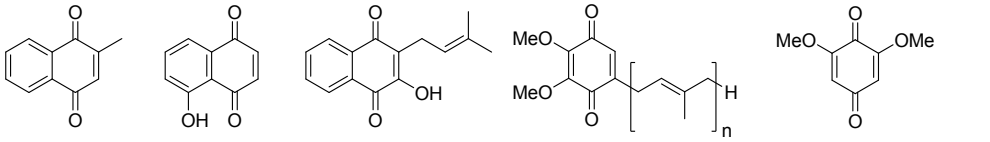


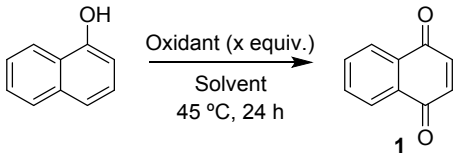
Figure 1. Representative examples of biologically active quinones.

Among different strategies employed for the synthesis of quinones, the most simple and straightforward method is the oxidation of arenes and/or phenols.[3] This fundamental organic reaction has been largely studied and therefore a myriad of synthetic procedures are nowadays available in the literature in order to carry out this transformation. However, in the majority of them, the use of oxidants such as organic peroxides,[4] hypervalent iodine compounds[5,6] or organic/inorganic salts is required,[7] hence generating a stoichiometric amount of waste in a low atom-economy process.[3] Consequently, the use of more environmentally benign oxidation methods that minimize such drawbacks would be desirable. In this regard, the employment of H_2O_2 and O_2 as oxidants has emerged as a green alternative methodology due to the high atom-economy achieved, reducing not only the amount but also the environmental impact of such waste.[8] Thus, despite the great progress already achieved in the use of these oxidants for the synthesis of quinones, the presence of a catalyst (metal-based or Lewis acids) is still necessary for the reaction to happen.[9]

Continuing with our studies in the use of fluorinated alcohols as solvents and mediators of reactions,[10] being able to replace metal catalysts,[11] and inspired by a pioneer study by Neumann group describing the electrophilic activation of H_2O_2 by means of these alcohols,[12,13] we decided to test the oxidation of phenols, naphthols and other electron-rich arenes using this combination. The results of this study are herein disclosed.

Firstly, the search for the optimal conditions was performed by using 1-naphthol as model substrate (Table 1). As oxidizing agents, H_2O_2 (30% aqueous solution) or UHP (urea-H_2O_2 adduct), which is considered a water-free source of H_2O_2, easier to handle and more stable than hydrogen peroxide solution, were used indistinctly in order to evaluate their performance in different solvents. Thus, the reaction barely worked after 24 hours at 45 ºC when both oxidants were employed in H_2O and 2-propanol. The use of 2,2,2-trifluoroethanol (TFE) also gave low conversions (Table 1, entries 1 and 2). However, when 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was the solvent of choice, modest conversions were observed for the formation of naphthoquinone (**1**) (Table 1, entries 3 and 5). Increasing the amount of oxidant up to 5 or 7.5 equiv. resulted in a substantial amelioration of the results when UHP was the oxidant employed (Table 1, entry 6 and 8). However, no improvement was observed with H_2O_2 (Table 1, entry 4). The reaction carried out in absence of solvent produced low conversion (Table 1, entry 7).

Table 1. Optimization of the reaction parameters[a]



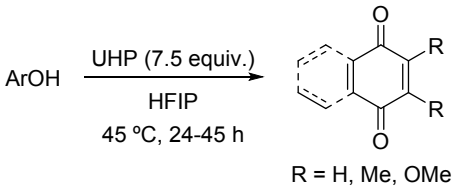
Entry	Solvent	Oxidant (equiv.)	Conv. (%)[b]
1	TFE	H_2O_2 (3)	10
2	TFE	UHP (3)	5
3	HFIP	H_2O_2 (3)	37
4	HFIP	H_2O_2 (5)	30
5	HFIP	UHP (3)	43
6	HFIP	UHP (5)	71
7	Neat	H_2O_2 (5)	18

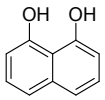
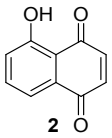
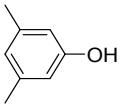
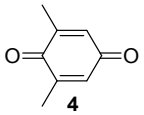
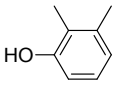
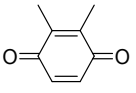
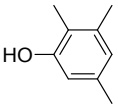
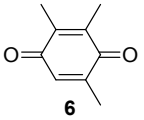
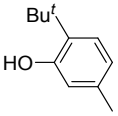
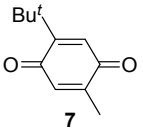
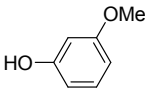
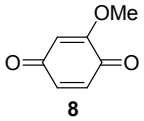
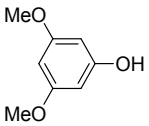
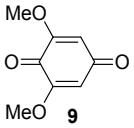
8	***HFIP***	***UHP (7.5)***	***>95 (87)[c]***

[a] All reactions were carried out using 0.15 mmol of 1-naphthol and the corresponding amount of oxidant in 150 μL of the solvent at 45 ºC for 24 h. [b] Conversion towards formation of 1, determined by GC-MS. [c] Isolated yield after preparative TLC.

With the optimal conditions in hand, HFIP as solvent and UHP (7.5 equiv.) as oxidant, different phenols and naphthols were essayed (Table 2). Good yield was obtained in the oxidation of 1-naphthol to the corresponding naphthoquinone (**1**) (Table 2, entry 1). However, when 2-naphthol was essayed, a complex mixture of oxidation compounds was obtained observing that no starting material remained unreacted by GC-MS neither by NMR (Table 2, entry 2). Better results were achieved when the reaction was performed with 8-hydroxy-1-naphthol, obtaining juglone (**2**) in high yields (Table 2, entry 3). Next, phenol derivatives were taken into account. Thus, when hydroquinone and 3,5-dimethylphenol were tested good yields were obtained in benzoquinones **3** and **4** (Table 2, entry 4 and 5). However, 2,3-dimethylphenol and 2-*tert*-butyl-5-methylphenol rendered the corresponding quinones (**5** and **7**) in low conversions (Table 2, entry 6 and 8). The yield increased up to 76% when 2,3,5-trimethylphenol was the substrate (Table 2, entry 7). Finally, phenols containing electron-donating groups (MeO) were selected as substrates. Thus, whereas 3-methoxyphenol gave low conversion towards the formation of quinone **8** (Table 2, entry 9), to our delight, high yield was obtained when the more electron-rich 3,5-dimethoxyphenol was employed (Table 2, entry 10). It is also worth mentioning that other aromatic alcohols, such as phenol, catechol, resorcinol, phloroglucinol or guaiacol were essayed too, however no reaction was observed.

Table 2. Oxidation of naphthols and phenols.[a]



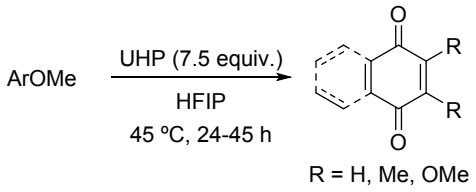
Entry	ArOH	Product	%Yield[b]
1	1-Naphthol	Naphthoquinone (**1**)	87
2	2-Naphthol	Unidentified products	> 95% conv.[c]
3		 **2**	83
4	Hydroquinone	1,4-Benzoquinone (**3**)	62
5		 **4**	67
6		 **5**	15[d]
7		 **6**	76
8		 **7**	18[d]
9		 **8**	17[d]
10		 **9**	84

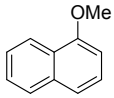
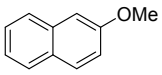
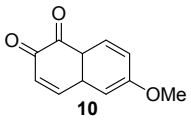
[a] All reactions were carried out using 0.15 mmol of arene and 7.5 equiv of UHP in 150 μL of the solvent at 45 ºC for 24-45 h. [b] Yield of the isolated compound after preparative TLC. [c] No starting material

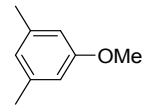
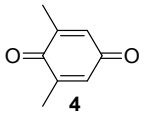
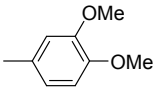
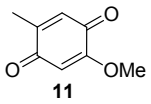
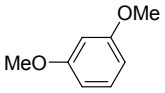
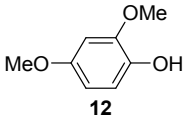
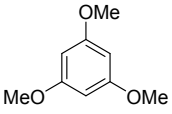
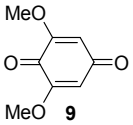
was observed by GC-MS. [d] Conversion towards formation of quinone, determined by GC-MS.

Next, anisole derivatives were also taken into account (Table 3). Thus, 1-methoxynaphthalene was firstly tested, obtaining naphthoquinone (**1**) in good yield (Table 3, entry 1). As in the previous case the reaction performed with 2-methoxynaphthalene produced a complex mixture of oxidation products, identifying 1,2-naphthoquinone derivative **10** among them (Table 3, entry 2). *p*-Methoxyanisole was next examined observing a very low conversion towards the formation of benzoquinone (**3**) by GC-MS (Table 3, entry 3). The same situation was found when 4-methyl-1,2-dimethoxybenzene was tested (Table 3, entry 5). However, better results were reached when 3,5-dimethylanisole was employed (Table 3, entry 4). Modest conversions were only achieved when *m*-dimethoxybenzene was checked, not observing the formation of the quinone, but the corresponding phenol **12** (Table 3, entry 6). Finally, to our delight 1,3,5-trimethoxybenzene rendered the quinone **9** in 87% isolated yield (Table 3, entry 7). Other methoxy containing benzenes, such as anisol, *p*-methoxyanisole, 2-methoxy-4-methylanisole, 2,6- and 5,6-dimethylanisole, were also tested but did not produced satisfactory results.

Table 3. Oxidation of anisole derivatives.[a]



Entry	ArOMe	Product	%Yield[b]
1		Naphthoquinone (**1**)	63[c]
2		 **10**	>95% conv. (30%)[d]

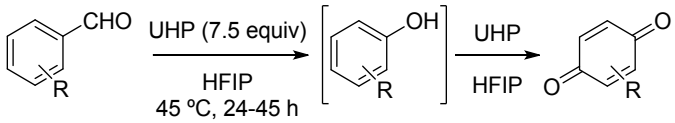
3	*p*-Methoxyanisole	1,4-Benzoquinone (**3**)	10[e]
4		 **4**	57[c]
5		 **11**	16[e]
6		 **12**	43[c,e]
7		 **9**	83

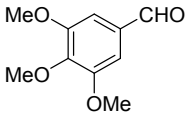
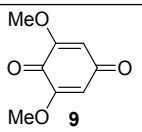
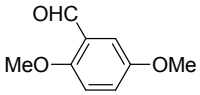
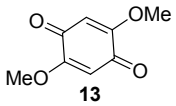
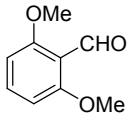
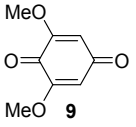
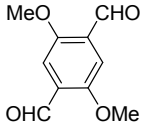
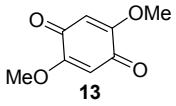
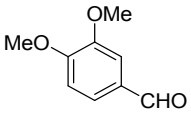
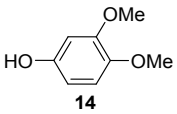
[a] All reactions were carried out using 0.15 mmol of arene and 7.5 equiv of UHP in 150 μL of the solvent at 45 ºC for 24-45 h. [b] Yield of the isolated compound after preparative TLC. [c] 10 equiv. of UHP were used. [d] No starting material was observed by GC-MS. [e] Conversion towards formation of quinone, determined by GC-MS.

Finally, taking advantage of the UHP-mediated Dakin oxidation described by Varma group, for the obtention of phenols from benzaldehydes,[14] we envisioned the possibility of performing a Dakin reaction-oxidation of phenols sequence obtaining the corresponding quinones directly from benzaldehydes (Table 4). Firstly, 3,4,5-trimethoxybenzaldehyde was submitted to the optimized oxidation conditions obtaining quinone **9** in high yields (Table 4, entry 1). Next, 2,5- and 2,6-dimethoxybenzaldehyde were also tested. Whereas 67% yield was achieved for compound **13**, quinone **9** was again isolated in high yield (Table 4, entry 2 and 3). 2,5-Dimethoxyterephthalaldehyde was also essayed, obtaining product **13** with a modest yield (Table 4, entry 4). Unfortunately, 3,4-dimethoxybenzaldehyde and *ortho*- and *para*-methoxybenzaldehyde did not produce the corresponding quinone and only the corresponding phenols were isolated in excellent yields (Table 4, entry 5, 6 and 7). These results are in agreement with those observed when *ortho*- and *para*-guaicol were submitted to oxidation

reaction, not producing the desired quinone as mentioned above. Finally, benzaldehyde produced the corresponding benzoic acid (**17**) in excellent yield (Table 4, entry 8).

Table 4. Quinones through Dakin reaction-oxidation of phenols sequence.[a]



Entry	ArCHO	Product	%Yield[b]
1		 **9**	84
2		 **13**	67[c]
3		 **9**	76
4		 **13**	51[c]
5		 **14**	88
6	*p*-MeOPhCHO	*p*-Guaicol (**15**)	91
7	*o*-MeOPhCHO	*o*-Guaicol (**16**)	91
8	PhCHO	PhCOOH (**17**)	93

[a] All reactions were carried out using 0.15 mmol of aldehyde and 7.5 equiv of UHP in 150 μL of the solvent at 45 ºC for 24-45 h. [b] Yield of the isolated compound after preparative TLC. [c] Not purely isolated; estimated yield by H-NMR

Regarding the reaction mechanism and based on literature precedents, where the electrophilic activation of H_2O_2 by means of fluorinated solvents has been proposed, the reaction pathway

depicted in Figure 2 was conceived. Firstly, the nucleophilic attack of electron rich arene onto activated H_2O_2, in a S_EAr-type reaction, would take place giving rise to the formation of intermediate A, which is prone to be further oxidize rendering the corresponding quinone.

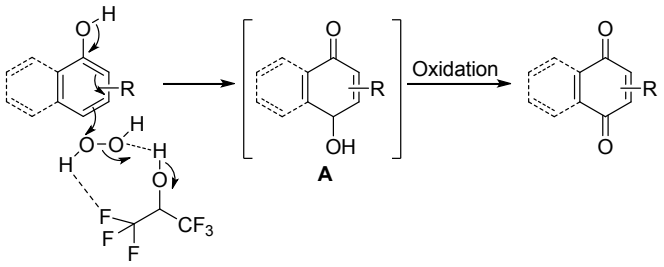
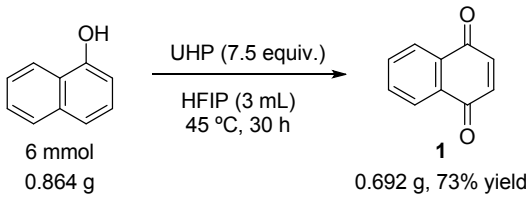


Figure 2. Proposed reaction mechanism.

Finally, to further demonstrate the applicability of this methodology, we decided to carry out a big-scale experiment (Scheme 1). A 6 mmol reaction was performed using 1-naphthol under the optimal reaction conditions but reducing the amount of HFIP. After 30 hours naphthoquinone (**1**) was obtained in a 73% yield. This result, although slightly inferior to the obtained previously, shows the feasibility of scaling-up the procedure.



Scheme 1. Big-scale reaction.

In conclusion, in this work we have developed a new straightforward and simple methodology for the synthesis of quinones through oxidation of electron-rich arenes. The oxidation protocol herein described is based on the use of UHP as source of H_2O_2 and HFIP as solvent and reaction promoter and its success relies on the electrophilic activation of H_2O_2 by means of the fluorinated alcohol. The whole process can be considered as environmentally benign since it avoids the use of metal and/or organic oxidants. In addition, it has a high atom economy and the

only by-products and waste formed (H_2O and urea) are considered biodegradable. In the majority of cases, the yields obtained vary from moderate to high. Although there is not a clear trend in reactivity, it can be asserted that naphthalene derivatives and highly substituted electron-rich arenes seems to perform better under the reaction conditions described. Additionally, it was observed that quinones bearing electron donating substituents on both double bonds were obtained with higher yields.

EXPERIMENTAL SECTION

General Remarks:

All reagents and solvents were obtained commercially and used without further purification.

NMR spectra were performed on a Bruker AV-300 or Bruker AV-400 (Bruker Corporation) using $CDCl_3$ as solvent and TMS as internal standard unless otherwise stated.

Low resolution mass spectra (MS) were recorded in the electron impact mode (EI, 70 eV, He as carrier phase) using an Agilent GC/MS 5973 Network Mass Selective Detector spectrometer apparatus equipped with a HP-5MS column (Agilent technologies, 30 m × 0.25 mm) and giving fragment ions in m/z with relative intensities (%) in parentheses. Low-resolution electron impact (EI) mass spectra were obtained at 70eV on Agilent GC/MS-5973N apparatus equipped with a HP-5MS column (Agilent technologies, 30 m × 0.25 mm).

Analytical TLC was performed on Merck silica gel plates and the spots visualized with UV light at 254 nm. Flash chromatography employed Merck silica gel 60 (0.040-0.063 mm). Silica gel 60 F254 containing gypsum was employed for preparative layer chromatography.

General procedure for the HFIP-UHP oxidation of electron-rich arenes.

In a capped tube, onto the corresponding arene (0.15 mmol), HFIP (150-200 μL) and UHP (7.5 equiv.) were added in one portion. The reaction was then stirred at 45 ºC (sand bath) for 24-45 hours, until the reaction was judged to be completed by GC-MS. After this time, the reaction mixture was filtered over silica/celite plug and then the solvent was evaporated and the crude material was directly purified by flash chromatography or preparative TLC.

For the big scale synthesis the general procedure was adapted: In a round-bottomed flask 1-naphthol (6 mmol, 0.864 g), UHP (7.5 equiv., 4.2 g) and 3 mL of HFIP were added in one portion. After heating the reaction at 45 ºC (sand bath) for 30 h, the crude mixture was filtered over silica/celite plug and then the solvent was evaporated and the residue was directly purified by flash chromatography to yield naphthoquinone (**1**) with 73% yield (0.692 g).

Spectroscopic and analytical data for isolated compounds are given below:

Naphthoquinone (**1**):[9h] Brown solid; purification by preparative TLC (hexane/ethyl acetate 8.5/1.5), Rf = 0.38, 20.5 mg, 87% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 8.11 (dd, *J* = 5.8, 3.3 Hz, 2H), 7.79 (dd, *J* = 5.8, 3.3 Hz, 2H), 7.01 (s, 2H) ppm; ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ_C = 185.0, 138.7, 133.9, 131.9, 126.4 pm; MS (EI): *m/z* 158 (M^+, 100%), 130 (27), 104 (31), 102 (31), 76 (21).

5-Hydroxy-1,4-naphthalenedione (Juglone) (**2**):[15] Orange solid; 21.6 mg, 83% yield, (without further purification), Rf = 0.41 (hexane/ethyl acetate 4/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 11.93 (s, 1H), 7.70 – 7.63 (m, 2H), 7.31 (dd, *J* = 7.4, 2.2 Hz, 1H), 6.98 (s, 2H) ppm; ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ_C = 190.3, 184.3, 161.4, 139.6, 138.6, 136.6, 131.7, 124.52, 119.18, 114.97 ppm; MS (EI): *m/z* 174 (M^+, 100%), 173 (25), 120 (19), 118 (29), 92 (16), 63 (13).

Benzoquinone (**3**):[17] Dark brown solid; purification by preparative TLC (hexane/ethyl acetate 9/1), Rf = 0.36, 10.1 mg, 62% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 6.81 (s, 4H) ppm; ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ_C = 187.2, 136.5 ppm; MS (EI): *m/z* 108 (M^+, 100%), 82 (32), 80 (25), 54 (55), 53 (14), 52 (16).

3,5-Dimethyl-p-benzoquinone (**4**):[9h] Dark orange solid; purification by preparative TLC (hexane/ethyl acetate 9/1), Rf = 0.46, 13.7 mg, 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 6.60 (q, *J* = 1.6 Hz, 2H), 2.04 (s, 3H), 2.04 (s, 3H) ppm; ^{13} C{H} NMR (101 MHz, $CDCl_3$): δ_C = 188.1, 145.8, 133.4, 15.5 ppm; MS (EI): *m/z* 136 (M^+, 100%), 108 (63), 107 (29), 96 (24), 80 (21), 79 (60), 77 (12), 68 (88).

2,3,5-Trimethyl-p-benzoquinone (**6**):[9h] Yellow oil, purification by preparative TLC (hexane/ethylacetate 9/1), Rf = 0.57, 17.1 mg, 76 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 6.75 – 6.40 (m, 1H), 2.06 (d, *J* = 1.6 Hz, 3H), 2.05 (t, *J* = 1.1 Hz, 3H), 2.03 (t, *J* = 1.1 Hz, 3H) ppm; MS (EI): *m/z* 150 (M^+, 100%), 122 (32), 121 (17), 107 (47), 79 (31), 68 (22), 54 (12).

2,6-Dimethoxy-p-benzoquinone (**9**):[16] Ochre-orange solid, purification by preparative TLC (hexane/ethyl acetate 4/1), Rf = 0.15, 22.0 mg, 87% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 5.88 (s, 2H), 3.84 (s, 6H) ppm; ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ_C = 186.9, 176.6, 157.4, 107.4, 56.4 ppm; MS (EI): *m/z* 168 (M^+, 74%), 138 (23), 125 (15), 97 (13), 80 (36), 69 (100), 59 (13), 53 (22).

2,5-Dimethoxy-p-benzoquinone (**13**):[16] Brown solid; purification by preparative TLC (hexane/ethyl acetate 9.0/1.0), Rf = 0.32, 16.8 mg, 67% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 5.89 (s, 2H), 3.87 (s, 6H) ppm; ^{13} C{H} NMR (126 MHz, $CDCl_3$): δ_C = 181.7, 159.6, 105.5, 56.6

ppm; MS (EI): *m/z* 168 (M^+, 13%), 155 (74), 153 (30), 149 (60), 139 (56), 127 (26), 122 (15), 112 (16), 95 (35), 69 (100), 59 (17), 53 (22).

3,4-Dimethoxyphenol (**14**):[14] Brown solid; purification by flash chromatography (hexane/ethyl acetate 4/1), Rf = 0.18, 20.3 mg, 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H =6.74 (d, *J* = 8.6 Hz, 1H), 6.49 (d, *J* = 2.8 Hz, 1H), 6.37 (dd, *J* = 8.6, 2.8 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H) ppm; ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ_C = 150.2, 149.8, 143.0, 112.4, 105.8, 100.6, 56.6, 55.8 ppm; MS (EI): *m/z* 154 (M^+, 100%), 139 (71), 111 (40), 93 (17), 69 (12), 65 (12), 55 (11).

4-Methoxyphenol (**15**):[14] White solid; 17.9 mg, 96% yield (without further purification), Rf = 0.23 (hexane/ethyl acetate 4/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 6.79 (s, 4H), 5.15 (s, 1H), 3.77 (s, 3H) ppm; ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ_C = 153.6, 149.5, 116.1, 114.9, 55.8 ppm; MS (EI): *m/z* 124 (M^+, 99%), 109 (100), 8 (42), 53 (14).

2-Methoxyphenol (**16**):[14] White solid; 17.0 mg, 91% yield (without further purification), Rf = 0.35 (hexane/ethyl acetate 4/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.05 – 6.84 (m, 4H), 5.71 (s, 1H), 3.91 (s, 3H) ppm; ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ_C = 146.6, 145.7, 121.5, 120.2, 114.6, 110.7, 55.8 ppm; MS (EI): *m/z* 124 (M^+, 93%), 109 (100), 81 (50).

Benzoic acid (**17**):[14] White solid; 17.0 mg, 93% yield (without further purification), Rf = 0.38 (hexane/ethyl acetate 3/2); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 12.02 (s, 1H), 8.21 – 8.10 (m, 2H), 7.70 – 7.59 (m, 1H), 7.51 (ddt, *J* = 8.2, 6.8, 1.0 Hz, 2H) ppm; ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ_C = 172.5, 133.8, 130.2, 129.3, 128.5 ppm; MS (EI): *m/z* 122 (M^+, 90%), 105 (100), 77 (62), 51 (22), 50 (13).

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge.

Copies of NMR spectra for all isolated compounds

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Notes

The authors declare no competing financial interest.

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TABLE OF CONTENTS