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Efficient and Green Telescoped Process to 2-Methoxy-3-methyl-[1,4]benzoquinone

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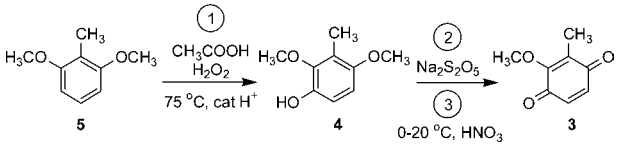


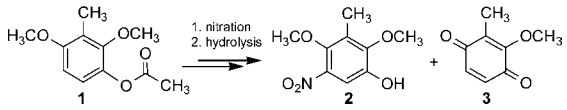
A telescoped process for the preparation of 2-methoxy-3-methyl-[1,4]benzoquinone is disclosed. When this novel process is compared to the prevailing method that utilizes $Na_2Cr_2O_7$ as the oxidant, the novel process represents a high yielding (95%), green, and environmentally benign alternative with H_2O_2 and HNO_3 as the oxidants and CH_3COOH as the reaction medium.

Introduction

Methoxy- and methyl-substituted [1,4]benzoquinone and phenolic derivatives constitute important classes of building blocks because such moieties are found in a wide range of biologically active compounds. Thus, they are essential basic building blocks for natural product synthesis.

An example of such a compound is 2-methoxy-3-methyl-[1,4]benzoquinone, which is found as a molecular moiety in several classes of natural products that exhibit a plethora of biological activities. Examples of such compounds are the antitumor antibiotic mitomycin,[1] the antibiotic mimosamycin,[2] the marine diterpenoid elisabethin A,[3,4] the allelochemical sorgoleone,[5] the diterpenes colombiasin A[6] and elisapterosin B,[7] and the small molecular mimetic of insulin demethylasterriquinone B1.[8] The synthetic processes toward such compounds require normally several advanced and ingenious synthetic steps. However, the synthetic chemist often ignores the challenge related to the synthesis of the basic starting compounds, which very often thus results in synthetic paths involving environmentally atrocious and noxious reagents. For example, Cr^{VI} salts (dichromate) have for years been known to be carcinogenic; nevertheless, they are still utilized for oxidation purposes in organic synthesis and are frequently employed in reaction protocols for the preparation of [1,4]benzoquinone derivatives. The popularity of the dichromate protocol for the preparation of benzoquinones is probably a result of the high selectivity and yield that in general is achieved. A protocol disclosed by Vliet[9] more than 70 years ago gently provides [1,4]benzoquinone from hydroquinone with high selectivity and yield (86−92%). Other lengthy protocols involving cerium diammonium hexanitrate[10] as the oxidant were also disclosed for the purpose of preparing [1,4]-benzoquinone derivatives. There have also been some attempts to develop green chemistry protocols for the synthesis of benzoquinones. Notably, Orita and co-workers[11] disclosed a method using hydrogen peroxide and formic acid as the oxidative system, but despite high conversion observed in most of their examples, only low yields and selectivity were achieved.

SCHEME 1



Methods and Results

For a project in progress in our laboratory we needed access to 2,4-dimethoxy-3-methyl-5-nitrophenol **2** as an intermediate in the synthesis of carbazomycines G and H.[12] During our initial tests and adaptation of the reaction conditions for the nitration of acetic acid 2,4-dimethoxy-3-methylphenyl ester **1**, it was found that significant quantities of the title compound **3** had formed as well (Scheme 1).

We associated this finding with an incomplete protection of the hydroxyl group of compound **1** that thus allowed a nitric acid oxidation of the free hydroxyl group. This spurred us to investigate the possibility of performing an oxidation of 2,4-dimethoxy-3-methyl-phenol **4** to 2-methoxy-3-methyl-[1,4]benzoquinone **3** by treatment with concentrated nitric acid. The oxidation experiment was conducted under similar conditions as for the nitration.[13] The anticipated oxidation reaction

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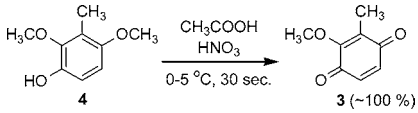
SCHEME 2



proceeded instantaneously with a quantitative conversion of the phenol **4** to the title compound **3** (see Scheme 2). The nitric acid oxidation of phenols into the corresponding [1,4]benzoquinones has been known for a century. Nakao and co-workers[14] used such a protocol in the synthesis of antileukemic agents on the basis of 2,5-disubstituted [1,4]benzoquinones, and such a protocol was used by Cohen and co-workers[15] in a total synthesis of vitamin E (tocopherol), but the nitric acid oxidation protocol has to the best of our knowledge never been reported for the preparation of the title compound **3**.

Encouraged by this result, we wanted to expand the process to include the oxidation of the commercially available 1,3-dimethoxy-2-methyl benzene **5**. Recently, we disclosed a process that permits the direct oxidation of compound **5** to **4**[16] by means of in situ generated peracid. 1,3-Dimethoxy-2-methyl benzene **5** is treated with hydrogen peroxide in glacial acetic acid with the presence of *p*-toluene sulfonic acid (pTSA) as the acid catalyst at a slightly elevated temperature. During the investigations of step **5** → **4**, traces of compound **3** were observed as a byproduct, an observation that spurred us to perform a thorough investigation of the importance of the different experimental variables for the oxidizing system. Table 1 reveals results from trials using various Brønsted acids as catalysts (cat. H^+). As Table 1 shows, the selectivity toward the phenol **4** and the [1,4]-benzoquinone **3** varies significantly with the different acids. Entries 2−4 show the results when various solid acids are utilized. Even though a low yield (12%) is achieved when Nafion 117 (entry 2, Table 1) is utilized as the catalyst, 2-methoxy-3-methyl-[1,4]benzoquinone **3** is achieved with a selectivity of ≈100%. In contrast, the previously disclosed procedure utilizing pTSA as the acid catalyst (entry 1) gives high yield (85%) with excellent selectivity (>99%) toward **4**.

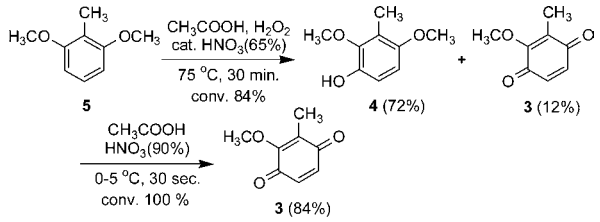
Except for Nafion 117, all of the investigated Brønsted acids (Table 1) provide medium to high conversion of **5** during a relatively short reaction time (15−180 min). Prolonged reaction times lead to the degradation of products **3** and **4**. In addition to Nafion 117, the application of concentrated sulfuric acid as a catalyst provides the title compound **3** in an elevated quantity (28%), although with a selectivity of only 39%. A useful result from the acid catalyst screening is that nitric acid (entry 8) provides a comparable conversion and yield, as when pTSA is used (entry 1) as the acid catalyst. Although an inferior selectivity is achieved with HNO_3 (65%), the final result will approach similar values because the byproduct achieved with

TABLE 1. Oxidation of 5 to 4 and 3 with Various Acid Catalysts Present[a]

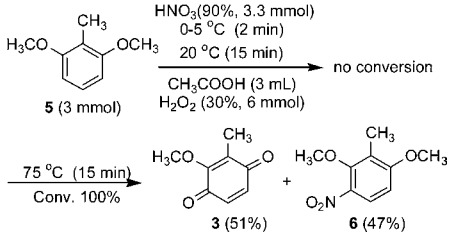
entry	cat. H^+	time [min]	conv. **5** [%]	selec. **4** [%]	yield **4** [%]	selec. **3** [%]	yield **3** [%]
1	4-CH_3−$C_6H_4SO_3H$	60	85	>99	85	<1	<1
2	Nafion 117 solution	30	10	60	6	40	4
		60	12	33	4	67	8
		180	12			100	12
3	Amberlite IR 120	30	56	91	51	9	5
		60	d.i.[b]				
4	Amberlyst 15	30	52	65	34	35	18
		60	d.i.[b]				
5	CF_3COOH[c]	60	64	93	60	7	4
		120	70	93	65	7	5
6	CF_3SO_3H	15	72	89	64	11	8
		30	d.i.[b]				
7	H_2SO_4[d] (95−97%)	15	71	61	43	39	28
		30	d.i.[b]				
8	HNO_3 (65%)	15	76	86	65	14	11
		30	84	86	72	14	12
		60	d.i.[b]				
9	HCl (37%)	30	69	84	58	14	11
		60	85	87	74	14	12
		120	d.i.[b,c]				
10	H_3PO_4 (85%)	15	39	100	39		
		30	43	100	43		
		75	66	100	66		
		120	76	∼100	∼76		traces
		240	81	∼100	∼81		traces

[a] Conditions: To a solution of **5** (3 mmol, 0.456 g) in CH_3COOH (3 mL) were added cat. H^+ (0.3 mmol) and H_2O_2 (30%, 6 mmol, 0.65 mL), which was heated at 75 °C for a period of 15−180 min. [b] d.i. = decomposition initiated. The reaction was thus concluded. [c] CF_3COOH in the amount of 1.3 mmol (0.1 mL) was used. [d] Mean values of two experiments. [e] Slow decomposition rate. At 180 min, <2% of **2** was decomposed.

SCHEME 3



SCHEME 4



HNO_3 as the catalyst is the target product **3**. These results can with advantage be utilized to simplify the protocol with respect to the number of required reagents.

The two oxidation steps, **5** → **4** and **4** → **3**, were then combined in an attempt to establish a telescoped oxidation process[17] (Scheme 3). This experiment provided target product **3** in high yield (≈85%) and excellent selectivity (≈100%).

Further contraction of the oxidation process was attempted by adding the whole quantity of nitric acid along with hydrogen peroxide from the start of the reaction, Scheme 4. Similar to the nitration procedure, the nitric acid was added at a temperature of 0 °C.[18] After a period of 15 min at room temperature, no conversion of the toluene **5** was observed. When the reaction

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temperature was raised to 75 °C for 15 min, a complete conversion of the starting toluene **5** was achieved. However, the selectivity was poor, yielding compounds **3** and **6** in the ratio 51:47.

The title compound **3** was obtained in an excellent yield (87%) by means of a similar protocol but at a slightly elevated temperature (20 °C) for the nitric acid addition. The nitric acid oxidation itself was then conducted at a temperature of 35 °C for a period of 4 h. The only byproduct that was determined was the nitro compound **6** in a quantity of 10%. This experiment was monitored over the course of the reaction, and the quantity profiles of compounds **3**−**6** are exhibited in Figure 1a, as determined by GC using an internal standard method. The various concentration profiles show clearly that the side product **6** begins to form at the point of time where the formation of the phenol **4** ceases, that is, at $t \approx 120$ min. At the same time, the formation of target product **3** stops. The consumption profile of the starting material **5** and the profile for the formation of compound **6** mirror each other, which suggests that, from the same point of time, only the nitration of **5** takes place.

Attempts to utilize a less-concentrated nitric acid (65%) with otherwise similar conditions in the second step, that is, the nitric acid oxidation step, failed to provide the title compound **3**.

Figure 1b shows a similar experiment as in Figure 1a, but a further quantity of hydrogen peroxide was added at the discovered critical point of time (Figure 1a) where the concentration profile of the phenol **4** starts descending. Moreover, an additional portion of HNO_3 was added toward the end of the oxidation profile. Those two actions influenced the course of the reaction to provide an even higher yield, namely, an increase from 86 to 93%.

The knowledge gained in the preceding experiments was further used for an experimental setup where the two oxidizing steps were performed in sequence, Figure 2. First, the transformation of the dimethoxytoluene **5** (3 mmol) into the corresponding phenol **4** was performed by the addition of hydrogen peroxide (30%, 6 mmol) as the oxidant. The reaction mixture was then left stirring at 75−80 °C for a short period of time (15 min), after which an extra portion of H_2O_2 (30%, 3 mmol) was added. After an additional period of time of heating and stirring (total reaction time of 40 min), the remaining H_2O_2 was quenched by adding $Na_2S_2O_5$ (3 mmol). The reaction mixture was then cooled at 0 °C over a period of 10 min upon which HNO_3 (90%, 3 mmol) was added to perform the second partial step of the telescoped process, the **4** → **3** transformation. This strategy was very successful, as the reaction approached the final stage after only 65 min and provided a yield of 95% of the target benzoquinone **3**. No nitration products were detected and, except for **3**, only starting material **5** remained after the reaction was stopped.

Synthesis of Other Benzoquinones. In an attempt to utilize the nitric acid oxidation for the preparation of other useful benzoquinone derivatives, trials were conducted to prepare 2,5-dimethoxy-[1,4]benzoquinone **10**. Efforts to convert 1,4-dimethoxybenzene into 2,5-dimethoxyphenol **9** by means of our direct hydroxylation protocol failed.[19] The phenol **9** was thus

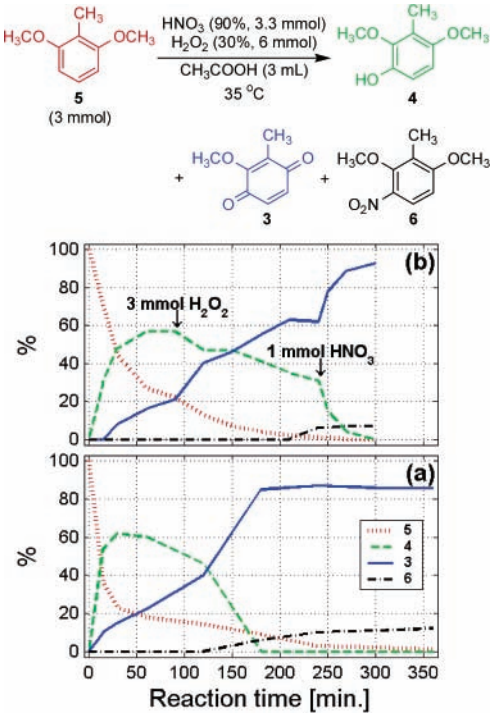

FIGURE 1. Course of the telescoped oxidation process **5** → **4** → **3**. (a) At $t = 120$ min, formation of **6** is initiated (dot-dashed line). At $t \approx 360$ min, a yield of 86% of **3** was achieved. (b) At $t \approx 90$ min, H_2O_2 (30%, 3 mmol) was added, and at $t = 240$ min, HNO_3 (90%, 1 mmol) was added. Yield of **3** was 93% at $t \approx 300$ min.

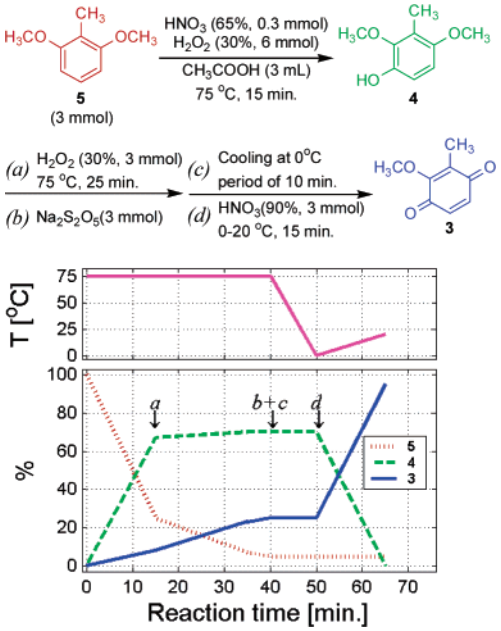

FIGURE 2. Course of the telescoped oxidation process **5** → **4** → **3**. Yield of **3** was 95% at $t \approx 65$ min.

prepared by subjecting 1-(2,5-dimethoxyphenyl)-ethanone **7** to a Baeyer−Villiger oxidation[20] to achieve 2,5-dimethoxyphenyl ester **8** in a yield of 97%. Subsequent hydrolysis of the ester **8**

(17) A telescoped process implies that two or more steps are conducted without isolation or workup of the intermediate synthesized compounds. Such methodology is of great importance for industrial processes as a result of the (1) impact on the throughput, (2) implication of less handling of solvents and, thus, a more environmentally friendly process, and (3) lack of material loss as a result of intermediate product workup, and so on.

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(19) The direct hydroxylation using H_2O_2 with pTSA as the acid catalyst in CH_3COOH was used for the oxidation of 1,4-dimethoxybenzene. After a period of 40 min, only a small quantity (≈3%) of 2,5-dimethoxy-[1, 4]-benzoquinone **10** was detected with a conversion of 55%. After another 80 min, a conversion of 80% was observed, but still only a small quantity of **10** was present.

SCHEME 5

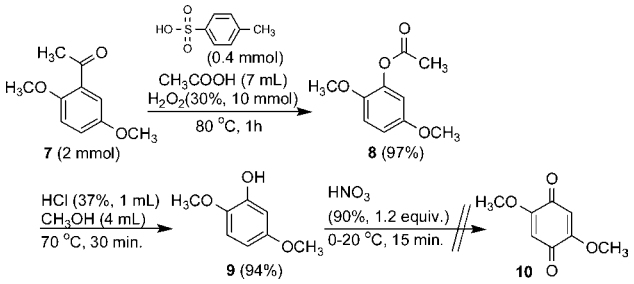
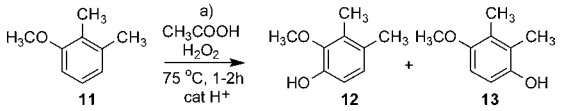


TABLE 2. Oxidation of 11 with Various Acid Catalysts Present[a]



entry	cat. H^+	time [min]	conv. **11** [%]	selec. **12** [%]	yield **12** [%]	selec. **13** [%]	yield **13** [%]
1	4-CH_3−$C_6H_4SO_3H$	30	68	>99	68		
		60	73	>99	73		
2	HNO_3[b] (65%)	15	42	73	31	27	11
		30	63	75	47	25	16
		120	77	92	71	8	6
3	H_2SO_4 (95−97%)	30	44	>99	44		
		60	57	>99	57		

[a] Conditions: Compound **11** (3 mmol, 0.42 mL) was added to acetic acid (3 mL) and nitric acid (65%, 0.3 mmol). H_2O_2 (30%, 6 mmol, 0.65 mL) was then added, and the mixture was heated at 75−80 °C. [b] More H_2O_2 (30%, 3 mmol, 0.33 mL) was added after 15 min.

provided the corresponding phenol **9** (94%), which was subjected to the nitric acid oxidation. A quantitative conversion of the phenol **9** was achieved, but only traces of target molecule 2,5-dimethoxy-[1,4]benzoquinone **10** were detected (Scheme 5).

The complete telescoped oxidation protocol was also applied to the oxidation of 1-methoxy-2,3-dimethylbenzene **11** in the hope of generating 2,3-dimethyl-[1,4]benzoquinone as the final product.

Such a process required 4-methoxy-2,3-dimethylphenol **13** as the first partial oxidation step intermediate product. The results from the oxidation experiments using various Brønsted acid catalysts in an attempt to produce the required phenol **13** are provided in Table 2. Nitric acid as the acid catalyst affords the needed intermediate product **13**,[21] although only in a very low quantity. The major product was the phenol **12**,[22−24] which, however, is another important phenolic compound that can be used in the synthesis of various biologically active compounds, such as the antibiotics carbazomycine B and C[25] and 4,5-diacyloxybenzofurans, which are valuable leukotriene inhibitors.[26]

Conclusion

2-Methoxy-3-methyl-[1,4]benzoquinone **3** is produced in high yield (95%) and selectivity by a single-pot telescoped oxidation process that is composed of three partial steps: (1) oxidation using hydrogen peroxide and in the presence of a Brønsted acid (e.g., HNO_3) as a catalyst, (2) elimination of excess oxidant using sodium metabisulfite, and then (3) oxidation using concentrated nitric acid. When this method is compared to previous methods that make use of sodium dichromate as an oxidant, this disclosed telescoped process constitutes a green and environmentally benign alternative that also should be suitable for large-scale use.

Experimental Section

Telescoped Oxidation Procedure 5 → 4 → 3. To a round-bottom flask (20 mL) equipped with a reflux condenser was added glacial acetic acid (3 mL) followed by **5** (3 mmol, 0.456 g) and HNO_3 (65%, 0.3 mmol) as the catalyst. The oxidant H_2O_2 (30%, 6 mmol, 0.65 mL) was then added. The reaction mixture was stirred and heated at 75−80 °C for 15 min, whereas further H_2O_2 (30%, 3 mmol, 0.33 mL) was added. At a reaction time of 40 min, sodium metabisulfite ($Na_2S_2O_5$, 3 mmol, 0.570 g) was added to quench the remaining H_2O_2. The reaction mixture was then cooled on an ice bath for 10 min. HNO_3 (90%, 3 mmol) was then added dropwise over a period of 1−2 min, the ice bath was removed, and the reaction mixture was left under stirring for another 15 min at 20 °C. The oxidation was quenched by adding water (50 mL). The diluted reaction mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (2 × 100 mL), dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure to achieve the target product **3** as a dark red oil (0.450 g, 94.3% yield, and 96% purity by GC).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.72−6.67 (d, 1H), 6.62−6.57 (d, 1H), 4.03 (s, 3H), 1.95 (s, 3H). ^{13}C NMR (200 MHz, $CDCl_3$, ppm): δ 188.7, 183.6, 136.6, 135.0, 129.4, 61.2, 9.0. MS *m*/*z* (%): 152 (100), 137 (5), 122 (35), 109 (23), 94 (6), 82 (25), 66 (29), 53 (32).

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Supporting Information Available: General experimental information and ^{1}H and ^{13}C NMR spectra for compounds **1**−**4**, **8, 9**, **12**, and **14** are available free of charge via the Internet at http://pubs.acs.org.

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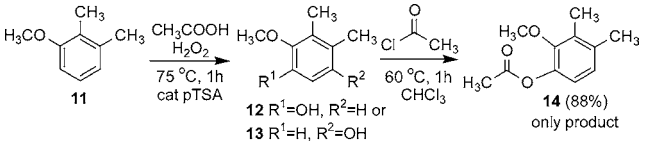
(22) A sample from an oxidation experiment of **11** was analyzed by ^{1}H NMR and ^{13}C NMR. The ^{1}H NMR signals were: δ 6.83−6.79 (d, 1H), 6.73−6.69 (d, 1H), 5.05 (s, 1H), 3.76 (s, 3H), 2.19 (s, 6H). Previously published ^{1}H NMR signals for the 4-methoxy-2,3-dimethylphenol **13** (ref 21) were: δ 6.49 (s, 2H), 5.40 (s, 1H), 3.72 (s, 3H), 2.13 (s, 6H). The δ 6.49 ppm singlet is due to the two hydrogen atoms at the phenyl ring of **13**. The two doublets at δ 6.83−6.79 and δ 6.73−6.69 ppm correspond to the two phenyl protons of compound **12**. The recorded ^{1}H NMR spectrum from the oxidation of **11** confirmed the structure assigned to be the phenol **12**. Moreover, a sample from the oxidation of **11** was treated with acetyl chloride to produce the corresponding acetic acid phenyl ester **14**. ^{1}H NMR, ^{13}C NMR, and MS data obtained for this product were coincident with the literature data for acetic acid 2-methoxy-3,4-dimethylphenyl ester **14** (ref 20), which thus represent a supplemental confirmation for the oxidation product of **11** to be the phenol **12** (2-methoxy-3,4-dimethylphenol).



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