Organic Process Research & Development **2010**, *14*, 1379–1384

A Switchable Oxidation Process Leading to Two Various Versatile Pharmaceutical Intermediates

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Abstract:

An efficient high-yielding and environmentally benign switchable oxidation process that can selectively produce two different versatile synthetic intermediates is disclosed. One of the two intermediates, 2,3-dimethoxy-5-methylcyclohexa-2,5-diene-1,4-dione (coenzyme Q_0), is obtained by means of a telescoped two-step synthetic protocol that in the first step involves treatment of the substrate (1,2,3-trimethoxy-5-methylbenzene) with hydrogen peroxide in acetic acid with *p*-toluene sulphonic acid present as a Brønsted acid catalyst, succeeded by a telescoped second step that entails treatment with fuming nitric acid to achieve the target molecule in an excellent isolated yield (88%). If the substrate is treated directly with nitric acid (65%) in glacial acetic acid two different products can be obtained, namely acetic acid 3,4,5-trimethoxybenzyl ester in a superb isolated yield (93%) or, under slightly altered reaction conditions, 1,2,3-trimethoxy-5-(nitromethyl)benzene in a moderate to low yield (35%) and low selectivity. The two pathways leading to the two different products in the nitric acid oxidation protocol were investigated by means of DFT calculations as an aid to elaborate a proposal for the reaction mechanism.

Introduction

Methoxy- and methyl-substituted phenyl moieties constitute integral parts of a vast number of natural products, biological active compounds, and pharmaceutical chemicals within a variety of therapeutic areas. A few examples include amoproxan (antiarrhythmic),[1] fedotozine (gastroprokinetic),[2] hexobendine (coronary vasodilator),[3] pirozadil (antilipemic),[4] trimebutine (antispasmodic),[5] trimethoprim (antibacterial),[6] and trimetozine (anxiolytic).[7]

A long-term project in our group is dedicated to the design, development, investigation, and optimization of new efficient green processes for the preparation of such methyl- and methoxy-substituted arenes suitable as building blocks for the preparation of various antioxidants, pharmaceutical chemicals, and compounds used in nutraceuticals. In this context, different oxidation processes for the production of methyl- and methoxy-substituted phenols and their corresponding hydroquinones and benzoquinones have been of particular interest. Previous disclosures from our group include a novel process for direct hydroxylation of the aromatic ring of methyl- and methoxy-substituted benzenes[8] and a process for the preparation of 2-methoxy-3-methyl-[1,4]benzoquinone in a two-step, one-pot telescoped oxidation process.[9]

A current research activity in our laboratory is dedicated to the development of new total syntheses of coenzyme Q_{10}[10] and the synthetic analogue idebenone,[11] see Chart 1. In this context we wanted to develop a new process for the preparation of 2,3-dimethoxy-5-methylcyclohexa-2,5-diene-1,4-dione (coenzyme Q_0), **1**,[12] that functions as a key intermediate in the two syntheses. For this purpose we assumed that our previously developed process for 2-methoxy-3-methyl-[1,4]benzoquinone[9] could be used for the preparation of coenzyme Q_0, **1**, whose reaction conditions constitute a green and environmentally benign alternative compared to formerly reported oxidation methods whereof several make use of environmentally unfriendly stoichiometric reagents.[13−17]

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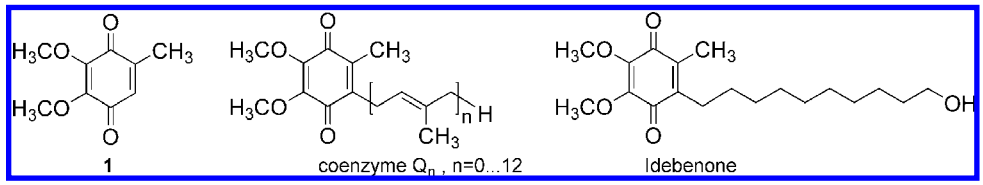
10.1021/op100185x
Published on Web 10/05/2010

Chart 1



During the introductory work related to the synthesis of coenzyme Q_0 **1**, we observed two side products that must have been formed through another reaction mechanism that spurred us to undertake further investigation that led us to a simple protocol for the preparation of acetic acid 3,4,5-trimethoxybenzyl ester, **4**, in excellent yield.

Methods and Results

Our previously disclosed two-step telescoped oxidation process[9] was here used to oxidize 1,2,3-trimethoxy-5-methylbenzene **2** with the goal to produce 2,3-dimethoxy-5-methyl-[1,4]benzoquinone, **1**. In addition to the expected target molecule **1** (44%), two additional unexpected products were produced, namely 1,2,3-trimethoxy-5-(nitromethyl)benzene, **3** (14%), and acetic acid 3,4,5-trimethoxybenzyl ester, **4** (12%), respectively, see Scheme 1.

During our earlier investigations of the two-step oxidation protocol[9] we have previously revealed that the type of Brønsted acid used as catalyst was fundamental for the selectivity of the oxidation process. Thus, in a new experiment we treated 1,2,3-trimethoxy-5-methylbenzene, **2**, with hydrogen peroxide in glacial acetic acid with the presence of *p*-toluene sulfonic acid (in the place of HNO_3 dissolved in glacial acetic acid) as the Brønsted acid catalyst, step (a), Scheme 2, but without altering the other reaction conditions. The desired product 2,3-dimethoxy-5-methyl-[1,4]benzoquinone, **1**, was achieved in a yield of >95% with quantitative conversion of the substrate **2**. During a simple and additional workup and purification step, the target product **1** was isolated in a yield of 88%. The underlying reaction mechanism of this process involves the formation of 2,3,4-trimethoxy-6-methylphenol (Scheme 2). Detailed discussions related to the reaction mechanism regarding the direct hydroxylation of the aromatic ring are previously reported.[8,9]

The acetoxylated compound **4** achieved as a byproduct during the introductory experiments (Scheme 1) titillated our curiosity. With the simultaneous formation of the two products **3** and **4**, there was little doubt that there is an underlying radical mechanism, but could it be conceivable to fine-tune and optimize the procedure so that one could approach a protocol providing the highly valuable compound **4** with high selectivity and yield?

Prior disclosures regarding acetoxylation of methylarenes include gas-phase reactions for the conversion of toluene to the corresponding acetic acid benzyl ester. A tiny scratch in the huge body of reports regarding acetoxylation of toluene reveals that such processes are conducted in gas phase and demand high temperature and often complex composite catalysts, for example Pd−Cu−TiO_2,[18] Pd−Sb−Bi/TiO_2,[19] TiO_2 supported K−Sn−Pd,[20] or Pd−Sb−TiO_2.[21] Several previous works are also reported for reactions performed in liquid phase; for example Jullien and co-workers[22] demonstrated via a multistep synthesis the preparation of 3-acetoxymethyl-4-nitrobenzoic acid from 3-methyl-4-nitrobenzoic acid methyl ester, a synthesis that involved bromination with NBS, succeed by reacting the benzyl bromide with acetic acid anhydride. Several studies concerning the use of metal/bromide-catalyzed autoxidation processes have been reported; see for example ref 23 and references therein. However, a common drawback of several of these processes is the often harsh and complex reaction conditions.

As indicated in Scheme 2 and thoroughly discussed in previously disclosed reports,[8,9] the function of hydrogen peroxide in the telescoped oxidation process is to initially produce the corresponding phenol of the substrate whereupon the added nitric acid acts as an oxidant of the phenol that results in the benzoquinone framework. Concurrently, a hitherto previously undescribed oxidation process take place, namely the nitric acid oxidation of the methyl of an arene (3,4,5-trimethoxy-5-methyl benzene, **2**).

We thought, therefore, to exclude hydrogen peroxide from the oxidation protocol, starting directly with the oxidation step that involves nitric acid.

Concentrated nitric acid (1.6 M) in acetic acid was added over a period of 30 min to a solution of compound **2** in acetic acid. During the course of the reaction, several samples were withdrawn in order to monitor the quantity profiles of the compounds **2**, **3**, **4**, and **6**. See Scheme 3 and Figure 1.

A significant higher yield (35%) of **4** was achieved, although the quantity of the nitrated compound 1,2,3-trimethoxy-5-(nitromethyl)benzene, **3**, was as much as 27% with a conversion of 67% of substrate **2**. From the graphics (Figure 1), the reaction appears to terminate after a reaction time of $t \approx 30$ min. This suggests that the nitric acid is consumed at a relatively high rate and that nitric acid is mandatory for the operation of the

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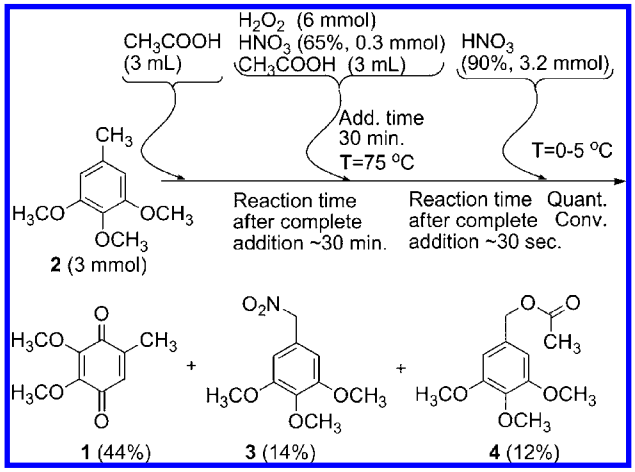
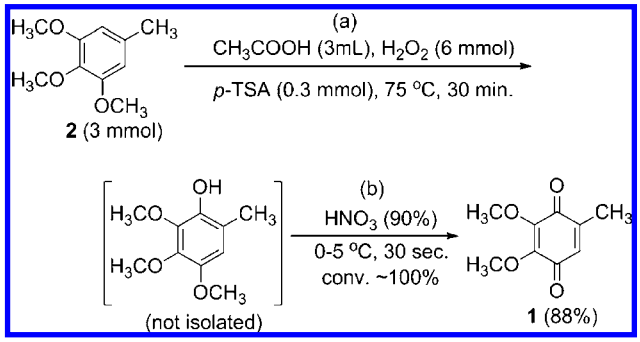
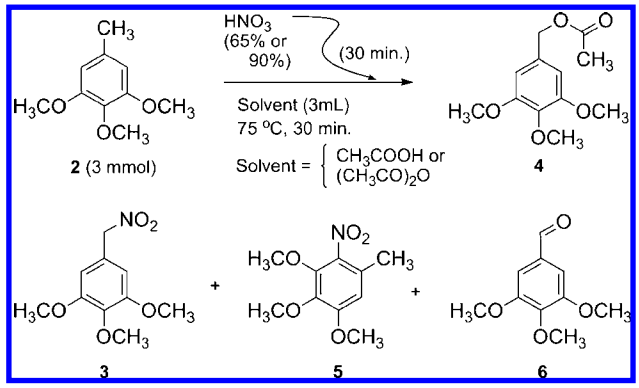
Scheme 1. **Screening experiment with the goal to produce 2,3-dimethoxy-5-methyl-[1,4]benzoquinone, 1, provided two unexpected byproducts 3 and 4**



Scheme 2. **Telescoped oxidation process**



Scheme 3



reaction. Additional nitric acid did not augment the yield. An experiment where the whole quantity of nitric acid was added in one portion at the start of the reaction was also conducted that, however, proved to be detrimental for the oxidation process.

Acetic acid anhydride was also tested as reaction medium, which showed up to be detrimental for the process. Only a low yield of **4** (~27%) were observed along with a small quantity (~11%) of 1,2,3-trimethoxy-5-methyl-4-nitrobenzene, **5**. The observation may be due to formation of larger quantities of 1-nitrooxyethanone (produced by reaction between acetic acid anhydride and nitric acid) that can operate as a nitration

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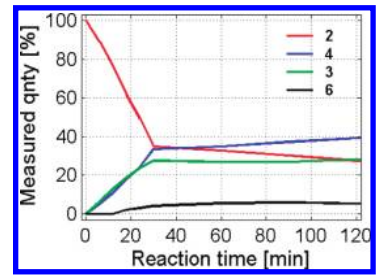

Figure 1. **By means of a syringe-pump, HNO_3 (65%, 3.2 mmol, $[HNO_3] = 1.6$ M) in acetic acid (2 mL) was added over a period of 30 min. ($r_{add}^{HNO_3} = 4$ mL h^{-1}) to a solution of 1,2,3-trimethoxy-5-methylbenzene (3 mmol), 2, in acetic acid (5 mL). After that, the reaction mixture was stirred at 20 °C for another 30 min. A yield of 35% of 2,3,4-trimethoxy-6-methylphenyl ester, 4, was achieved after a reaction time of $t \approx 60$ min.**

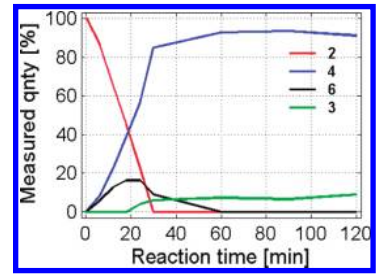

Figure 2. **By means of a syringe-pump, HNO_3 (65%, 3.2 mmol, $[HNO_3] = 0.32$ M.) in acetic acid (10 mL) was added over a period of 30 min. ($r_{add}^{HNO_3} = 20$ mL h^{-1}) to a solution of 1,2,3-trimethoxy-5-methylbenzene (3 mmol), 2, in acetic acid (5 mL). After that, the reaction mixture was stirred at 20 °C for another 30 min. A yield of 93% of acetic acid 3,4,5-trimethoxybenzyl ester, 4, was achieved after a reaction time of $t \approx 60$ min.**

reagent,[24] suggested by the fact that the nitro compound **5** was formed in more than minute quantities.

The relative high quantity of nitrated compound **3** and **5** in the two previous experiments suggested a reduction in the quantity or a more diluted solution of nitric acid in the oxidation protocol, as well as keeping acetic acid as reaction medium. Thus, a solution (0.32 M) of nitric acid (65%) in acetic acid was added over a period of 30 min to a solution of substrate **2** dissolved in acetic acid. During the course of the reaction, several samples were withdrawn in order to monitor the quantity profiles of the compounds **2**, **3**, and **4**. As Figure 2 shows, the experiment provided an excellent result, namely a quantitative conversion of substrate **2** to achieve the ester **4** in an excellent yield (>93%). In addition to the products **3**, **4**, and **6** (Figure 2) the oxidation process produced a reddish brown gas, which we assumed to be nitrous gases. An identical experiment was repeated under argon atmosphere in order to verify if an autoxidation mechanism intervened. The unaltered result revealed that the oxidation proceeded without any influence of autoxidation.

Scaling up this procedure was attempted (10-g scale of the substrate **2**). The reaction was conducted in a cylindrical flat-bottomed glass reactor with no baffles ($D = 78$ mm, $H = 140$ mm, $V \approx 500$ mL). The reactor was equipped with a radial turbine stirrer (flat blades, 50 mm, and stirrer rate ≈ 200 turns × min^{-1}). The experiment was run for 1 h 30 min to provide a yield of ~80% of desired product **4**, which is somewhat lower than in the original scale (93%). The lower yield is first of all due to

Scheme 4. **Proposal of a reaction mechanism that is constituted by a series of radical processes leading to the compounds 3 and 4; green pathways are initiation steps, the blue are the propagation steps, and the red ones are the termination steps that also lead to the two products 3 and 4**

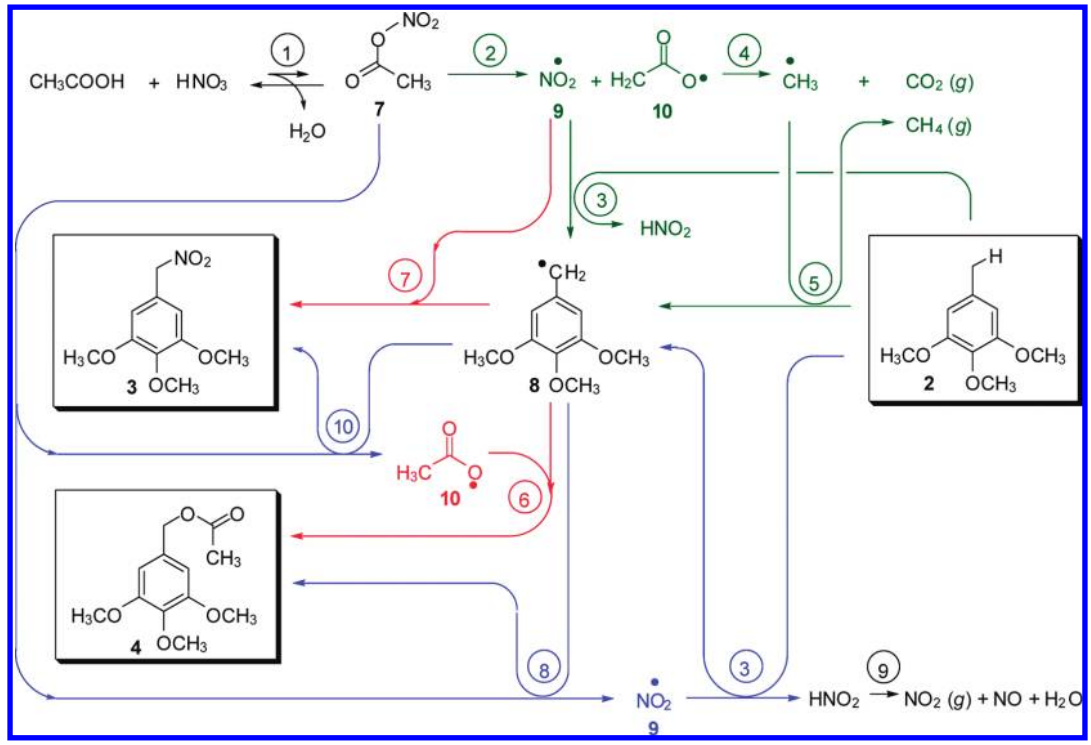

Table 1. **Thermodynamic data (in gas phase) obtained through DFT calculations[25,26] for the reaction pathways outlined in reaction Scheme 3**

path	$\Delta H_{298.15\ K}$ kcal mol^{-1}	$\Delta G_{298.15\ K}$ kcal mol^{-1}	$\Delta S_{298.15\ K}$ cal mol^{-1} K^{-1}
1	8.7	8.5	0.6
2	23.4	11.8	38.9
3	11.4	12.2	−2.7
4	−12.7	−21.9	30.7
5	−16.6	−15.0	−5.4
6	−63.8	−51.1	−42.4
7	−42.7	−30.7	−40.3
8	−40.3	−39.3	−3.4
9	3.0	−1.9	16.4
10	−19.3	−18.9	−1.4

a lower conversion of the substrate (9% was identified in the final reaction mixture) and also because a byproduct was produced, most probably a nitro compound. These problems can probably be solved by using better tailored equipment both for the mixing and dosage of oxidation reagent.

A series of radical reactions that can take place under the utilized reaction conditions are outlined in Scheme 4, which result in the production of compounds **3** and **4**. The green-colored pathway constitutes the initiation steps, the blue-colored pathway the propagation steps, and finally the red-colored pathways illustrates the termination steps.

Table 1 provides the thermodynamic data for the gas-phase reactions obtained through DFT calculations.[25,26] Nitric acid and acetic acid can react to provide, at equilibrium ($\Delta H = 8.7$ kcal mol^{-1}, $\Delta G = 8.5$ kcal mol^{-1}), minute quantities of 1-nitrooxyethanone **7**, see path (1) of Scheme 4. 1-Nitrooxyethanone **7** can undergo an endothermic homolytic cleavage, where the N−O(CO) bond is cleaved, pathway (2), a reaction that produces the radicals NO_2• and CH_3COO• both involved in the initiation steps, pathways (3) and (4 + 5), which result in the production of the benzyl radical **8.**

(25) **Computational details:** Geometry optimizations have been performed using the implementation of density functional theory (DFT) in the Gaussian 03 suite of programs with the B3LYP functional for closed shell systems and UB3LYP for open shell systems. The 6-311+G(d,p) basis set with contractions [3s,1p] for H atoms and [5s,4p,1d] for carbon and oxygen atoms have been used for both the geometry optimizations and the energy evaluations. The spin expectation values ⟨S2⟩ for the investigated radicals were found to be very close to 0.75 (pure doublet state), indicating a negligible spin contamination. Thermochemical corrections to obtain zero-point energies, enthalpies, Gibbs free energies, and entropy were computed within the harmonic-oscillator, rigid-rotor, and ideal-gas approximations using the same method and basis set as in the geometry optimizations, and all of the stationary geometries were characterized as minima (no imaginary frequencies).

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The reaction **7** + **8** → **4,** path (8**),** produces in addition the radical species NO_2• that subsequently is used in path (3) for the production of the benzyl radical **8**. The two pathways (3) and (8) thus constitute a radical chain process that results in the production of compound **4**, a process that furthermore is highly exothermic ($\Delta H = -28.9$ kcal mol^{-1}, $\Delta G = -27.1$ kcal mol^{-1}) and thus represents the most likely main route to acetic acid 3,4,5-trimethoxybenzyl ester, **4**. In addition a free energy contribution is obtained through the decomposition of the side product HNO_2 (path 3), namely: $HNO_2 \rightarrow 0.5\ NO_2 + 0.5\ NO + 0.5\ H_2O$, ($\Delta G = -1.9$ kcal mol^{-1}), path 9 of Scheme 4. Moreover, the benzyl radical **8** can react with 1-nitrooxyethanone **7** to give 1,2,3-trimethoxy-5-(nitromethyl)benzene, **3**, path (10), plus the radical CH_3COO• (**10**). Thus, the two pathways (3) and (10) constitute a second radical chain process that leads to the secondary product **3**. Path 10 ($\Delta G = -18.9$ kcal mol^{-1}) in agreement with the obtained experimental yields of **3** and **4** is predicted to be less favored than path 8 ($\Delta G = -39.3$ kcal mol^{-1}). Finally, the main termination steps of the radical chain process appear to comprise two radical−radical coupling reactions that also lead to **3** (path 7) and **4** (path 6). Again, the formation of the main product **4** (path 6) is predicted to be favored with respect to **3** (path 7), see Table 1.

DFT calculations suggest that the production of the benzyl radical **8**, in principle, can follow the alternative pathway involving the paths (2)+(4)+(5), which also is energetically comparable ($\Delta H = -6.0$ kcal mol^{-1}, $\Delta G = -25.2$ kcal mol^{-1}) to the radical chain involving the paths (3)+(8) ($\Delta H = -28.9$ kcal mol^{-1}, $\Delta G = -27.1$ kcal mol^{-1}). This competitive pathway involves on the other hand production of three equivalents of gaseous products, namely NO_2, CO_2, and CH_4 that also explains the large entropic contribution to the free energy (Table 1). From our experimental observations, this pathway appears not to be the major one, since such a gas production would have been macroscopically evident, which however was absent in our experiments. At room temperature, the endothermic homolytic cleavage of the N−O(CO) bond of **7** [path (2)] appears to be absent, since any evident production of NO_2 (reddish-brown gas) or any other gases (CO_2, CH_4) is observed when HNO_3 is mixed with acetic acid. However with the presence of the substrate **2**, it is clearly evident that a reddish-brown gas evolvement takes place in the reaction mixture.

With the purpose to evaluate the new radical oxidation protocol's properties as a general *O*-acetylation method, a series of different substituted toluenes (see Supporting Information) were submitted for the oxidation conditions. Surprisingly, only the most activated substrate, namely 1,2,3-trimethoxy-5-methylbenzene **2** that has been described hitherto was oxidized according to the protocol revealed herein, which however provided an excellent yield (≥93%) of the *O*-acetylated product. Any other activated substrates do not react, or are only nitrated on the aromatic ring.

Initially these results were very unanticipated, but in light of the achieved results from the development and optimization study performed for compound **1**, summarized in Schemes 1 and 2 and Figure 1, it was in fact evident that it is of paramount importance that the reaction conditions are fine-tuned for the particular compound. Otherwise, both nitration of the aromatic ring and of the methyl group and the partial oxidation of the methyl group (producing the aldehyde group) proceed in the place of the desired *O*-actylation of the methyl group.

Conclusion

In summary we have developed two expedite high-yielding and selective synthetic protocols for the preparation of 2,3-dimethoxy-5-methyl-[1,4]benzoquinone (coenzyme Q_0), **1**, and acetic acid 3,4,5-trimethoxybenzyl ester, **4**, from the cheap and readily available 1,2,3-trimethoxy-5-methylbenzene, **2**. Supported by DFT calculations, a reaction mechanism is proposed for the acetoxylation reaction. Both of the compounds **1** and **4** can serve as key intermediates for the synthesis of a vast number of pharmaceutical chemicals that are used in a number of therapy categories.[2−7]

Experimental Section

General Methods. GLC analyses were performed on a capillary gas chromatograph equipped with a fused silica column (*L* 25 m, 0.20 mm i.d., 0.33 μm film thickness) from at a helium pressure of 200 kPa, split less/split injector and flame ionization detector.

Mass spectra were acquired on a GC−MS instrument, using a gas chromatograph equipped with fused silica column (*L* 30 m, 0.25 mm i.d., 0.25 μm film thickness) and He as carrier gas.

Structure controls were conducted by means of ^{1}H NMR spectra recorded on a NMR spectrometer operating at 400 MHz. Chemical shifts were referenced to internal TMS.

Optimized Procedure to 2,3-Dimethoxy-5-methyl-[1,4]benzoquinone 1 [605-94-7]. 1,2,3-Trimethoxy-5-methylbenzene **2** (0.547 g, 3 mmol) and acetic acid (3 mL) was added to a round-bottom flask (20 mL) equipped with a reflux condenser. *p*-Toluene sulfonic acid monohydrated (57 mg, 0.3 mmol) and the oxidant hydrogen peroxide (30%, 0.65 mL, 6 mmol) were then added. The reaction mixture was stirred and heated at 75 °C for 30 min, after which the mixture was cooled at 0 °C. HNO_3 (90%, 1.5 mmol) was then added dropwise. The cold reaction mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined and washed with water (2 × 80 mL) in order to remove residues of acetic acid and then dried over anhydrous sodium sulfate and filtered; finally, the solvent was evaporated under reduced pressure to achieve the crude as a dark-red oil (0.528 g).

Purification. The crude product was dissolved in boiling hexane (70 mL) and filtered. The solvent was removed under reduced pressure to provide the pure coenzyme Q_0 (0.480 g, 88% isolated yield) as red-colored needles.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 [d, 3H, $J = 1.6$ Hz, Me], 4.00 [s, 3H, OMe], 4.02 [s, 3H, OMe], 6.43−6.44 [q, 1H, $J = 1.6$ Hz]. ^{13}C NMR (400 MHz, $CDCl_3$): δ 15.4, 31.1, 61.2, 131.3, 144.0, 144.9, 145.1, 184.1, 184.4. MS *m*/*z* (%): 182 (85), 167 (32), 153 (13), 137 (100), 121 (6), 111 (23), 96 (12), 83 (67), 69 (31), 53 (15).

Acetic Acid 3,4,5-Trimethoxybenzyl Ester 4 [72092-48-9]. 1,2,3-Trimethoxy-5-methylbenzene **2** (0.547 g, 3 mmol) and acetic acid (5 mL) were transferred to a two-necked round-bottom flask equipped with a reflux condenser and a septum.

Nitric acid (65%, 3.2 mmol, 0.222 mL) in acetic acid (10 mL) was then added by means of a syringe installed in a syringe pump (addition rate = 20 mL h^{-1}) over a period of 30 min at 20 °C. After complete addition of the nitric acid, the reaction mixture was continuously stirred for further 30 min.

Workup and Purification. The reaction mixture was treated with anhydrous sodium sulfate (anhydrous conditions are of paramount importance for the workup), and with charcoal for 10 min. The solids were filtered off followed by removal of the solvent under reduced pressure to provide the title compound **4** as a beige-colored viscous oil (0.745 g, 93% yield).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.17 [s, 3H], 3.83 [s, 3H], 3.86 [s, 6H], 5.03 [s, 2H], 6.59 [s, 2H]. ^{13}C NMR (200 MHz, $CDCl_3$, ppm): δ 21.0, 56.1, 60.8, 66.6, 105.6, 131.4, 138.0, 153.3, 170.9. MS *m*/*z* (%): 240 (100), 225 (3), 198 (40), 181 (68), 169 (16), 155 (7), 148 (7), 138 (6), 123 (10), 109 (3), 95 (7), 77 (4), 43 (13).

Scaled Up Reaction Protocol. 1,2,3-Trimethoxy-5-methylbenzene **2** (10 g, 55 mmol) was transferred to a cylindrical flat-bottomed glass reactor with no baffles (D = 78 mm, H = 140 mm, $V \approx$ 500 mL) that was equipped with a radial turbine stirrer (flat blades, 50 mm, and stirrer rate $\approx$ 500 turns $\times$ min^{-1}). The substrate **2** was dissolved in acetic acid (90 mL). A solution of nitric acid (4 mL, 65%) in acetic acid (185 mL) was added with the syringe pump over a period of t = 30 min. (corresponding to addition rate of 390 mL h^{-1}). After complete addition of the nitric acid solution, the reaction mixture was continuously stirred for further 60 min.

Workup. The reaction mixture was then treated with anhydrous sodium sulfate and then stirred with charcoal for a period of 10−15 min. The solids was filtered off, and the solvent was removed under reduced pressure to provide a crude product of 10.6 g. ^{1}H NMR analysis of the isolated crude product revealed a yield of 80% of desired product **4,** nonconverted substrate **1** (9%) and a nonidentified byproduct (11%).

Acknowledgment

Economic support to the project from the EC Marie Curie Actions (to the InSolEx project), Denomega AS (A.T.) and from the University of Bergen and CPU resources granted through the NOTUR supercomputing program are gratefully acknowledged.

Supporting Information Available

^{1}H NMR and ^{13}C NMR spectra of compounds **1** and **4**; additional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review June 30, 2010.

OP100185X