

## Efficient synthesis of 1-alkyl-2,3,4,5-tetramethoxy-6-methylbenzene: key intermediate for preparing coenzyme Q analogues

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### Abstract

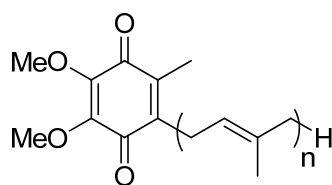
This paper described a convenient and efficient route for the synthesis of 1-alkyl-2, 3, 4, 5-tetramethoxy-6-methylbenzene, which are the key intermediate for the synthesis of C-6 substituted Coenzyme Q analogues. All the reactions are operationally simple and amenable to gram-scale synthesis.

**Keywords:** Coenzyme Q, Kornblum oxidation, one-pot tandem reaction, aromatic nitrile

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### Introduction

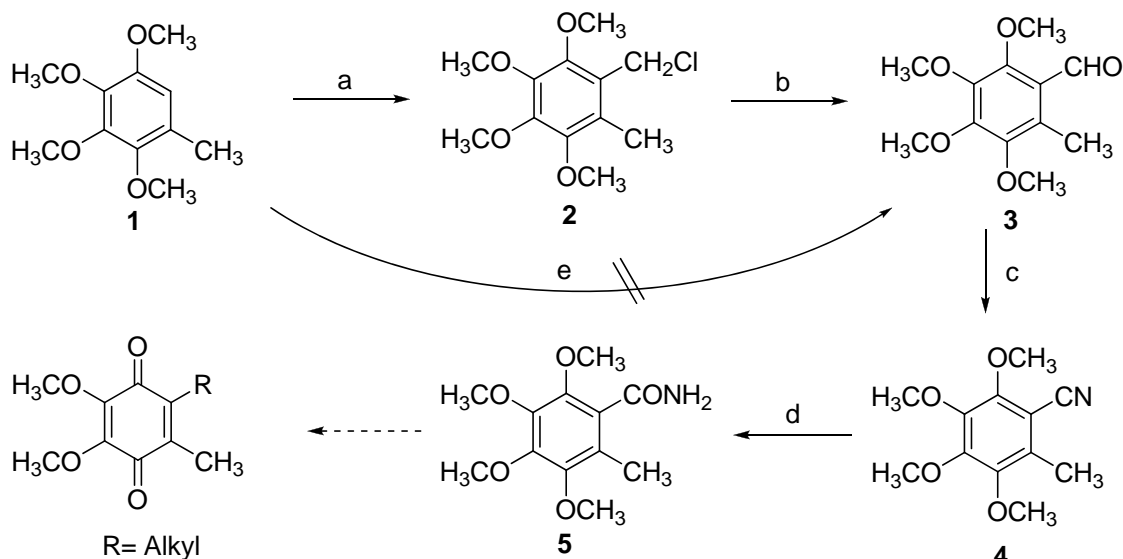
Coenzyme Q (CoQ, or CoQn) (Figure 1), also known as ubiquinone, occurs naturally in the inner mitochondrial membrane, which plays pivotal role in the mitochondrial respiratory chain.<sup>1-2</sup> CoQ acts as a mobile electron carrier in the energy-transducing membranes of mitochondria and distributes the electrons between the various dehydrogenases and the cytochrome segments of the respiratory chain.<sup>3-6</sup> CoQ<sub>10</sub> (contains 10 isoprenyl units), the main homologue of CoQ existing in humans, is one of the most effective lipid-soluble antioxidants. CoQ<sub>10</sub> is widely used in the treatment of cardiovascular disease, hepatitis and cancer. CoQ<sub>10</sub> is also sold as a drug or dietary supplement in many countries, and there is an increasing market demand.<sup>3-14</sup>



Coenzyme Q<sub>n</sub>  
(ubiquinones;  $n \leq 12$ )

**Figure 1.** Coenzyme Q.

Many researches<sup>3-14</sup> have shown that some metabolites of CoQ<sub>10</sub>, and a number of synthetic CoQ analogues exhibit significant biological activities, such as inhibition of mitochondrial complex I, lipid peroxidation activity and blood platelet aggregation. Especially, some CoQ analogues with heterocyclic substituents could be developed as drugs,<sup>12-15</sup> so to find a simple and efficient synthetic route for its preparation is considerable incentive. However, previously published methods<sup>3-6, 12-15</sup> for the preparation of these CoQ analogues with heterocyclic substituents have some significant drawbacks such as long reaction time, low yields of the products and difficult work-up. Herein we report a convenient and efficient method to synthesize **5** which has the potential to be a key intermediate for preparing CoQ analogues bearing heterocyclic substituents. The synthetic route is shown in Scheme 1.



**Scheme 1.** Reagents and conditions: (a) (HCHO)<sub>n</sub>, 37% HCl, 40 °C, 98 %; (b) KHCO<sub>3</sub>, DMSO, 80 °C, 92 %; (c) I<sub>2</sub>, 28 % NH<sub>3</sub> · H<sub>2</sub>O, 25 °C, 100%; (d) 30% NaOH, 30% H<sub>2</sub>O<sub>2</sub>, 75 °C, 98 %; (e) POCl<sub>3</sub>, DMF, 80 °C, no reaction.

## Results and Discussion

As shown in **Scheme 1**, Firstly, chloromethylation of **1** with paraformaldehyde and conc. HCl under catalyst-free conditions provided **2** in an excellent yield.<sup>7-11</sup> Secondly, we initially tried to introduce the aldehyde group into the aryl ring *via* Vilsmeier-Haack reaction by employing POCl<sub>3</sub> and DMF,<sup>19</sup> but we got none of the desired compound **3** after many trials, we speculated that the effects of four electron-donor methoxy groups in the aromatic ring made it more difficult for the Vilsmeier reagent to attack the C-6 position of compound **1**. Recently, we developed a new method which could direct transformation of **2** to **3** via Kornblum oxidation by utilizing DMSO as an oxidant.<sup>16</sup> In the present case, treatment of **2** with DMSO in the presence of KHCO<sub>3</sub> furnished **3** in good yield. Thirdly, direct transformation of aldehyde **3** to nitrile **4** was achieved by using iodine in ammonia water instead of liquid ammonia or ammonia gas in alcohol solvents.<sup>17,20</sup> It was noteworthy that this transformation was completed in aqueous media by one-pot tandem reaction within a short period (10 minutes) at room temperature in 100% yield. Finally, partial hydrolysis of **4** by using 30% H<sub>2</sub>O<sub>2</sub> in the solution of 30% NaOH afforded **5** in 98% yield.

## Conclusions

A convenient and efficient route for the synthesis of the key intermediate **5** had been achieved in an overall 88% yield. Furthermore, we developed a simple, efficient, and environmentally procedure for the preparation of nitrile **4** which is a viable precursor for the preparation of a variety of nitrogen-containing functional compounds. We have explored a new methodology using one-pot tandem reaction for the direct conversion of aldehyde **3** to nitrile **4** via iodine in ammonia water at room temperature, and the desired product **4** was obtained without further purification. This method can also circumvent the problem in prior preparation of nitrile compounds from halides and toxic cyanides. In addition, all the compounds **2**, **3**, and **4** are useful intermediates for the synthesis of other CoQ analogues. These experimentally simple approaches could also be useful for the synthesis of other biological CoQ analogues with heterocyclic substituents.

## Experimental Section

**General.** All reactions were monitored by TLC, IR spectra were recorded on an Impact 400 FT-IR instrument. NMR and mass spectra were recorded on a Bruker DRX NMR and a ZAB-2F Mass spectrometers, respectively. All reagents (DMSO, paraformaldehyde, 30% H<sub>2</sub>O<sub>2</sub>) were purchased from Adamas-beta, P. R. China, and used without further purification. Compounds (**1**) and (**2**) were synthesized according to our previous procedures.<sup>7-10, 21-24</sup>

**2,3,4,5-Tetramethoxy-6-methylbenzaldehyde (3).**<sup>18</sup> To a solution of **2** (2.60 g, 0.01 mol) in anhydrous DMSO (8 mL) was added  $\text{KHCO}_3$  (1.50 g, 0.015 mol), then the reaction mixture was intensely stirred at 80 °C for another 3 hours. The mixture was cooled to room temperature, water was added and the mixture was extracted with petroleum ether, and the combined extracts were washed with brine. The solution was dried over anhydrous sodium sulfate and solvent was removed in vacuo. The residue was purified by a silica-gel column chromatography (petroleum ether : ethyl acetate = 5:1) to give a yellow oil **3** (2.2 g, 92% yield). IR ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1700 (Ar-CHO);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  10.35 (s, 1H, CHO), 3.96 (s, 3H,  $\text{OCH}_3$ ), 3.88 (s, 3H,  $\text{OCH}_3$ ), 3.84 (s, 3H,  $\text{OCH}_3$ ), 3.69 (s, 3H,  $\text{OCH}_3$ ), 2.38 (s, 3H,  $\text{CH}_3$ ). Literature<sup>18</sup>:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  3.99-4.02 (s, 12H, 4 ×  $\text{OCH}_3$ ), 2.25 (s, 3H,  $\text{CH}_3$ ), 10.45 (s, 1H, CHO).

**2,3,4,5-Tetramethoxy-6-methylbenzotrile (4).** To a solution of aldehyde **3** (1.3 g, 5.4 mmol) and iodine (1.4 g, 5.4 mmol) in THF (6 mL), ammonia water (5 mL of 28% solution) was added dropwise over a period of 10 minutes, then the mixture was stirred at room temperature for 10 minutes. The dark solution became colorless at the end of reaction. Quenched with saturated  $\text{Na}_2\text{SO}_3$  solution and extracted with petroleum ether, and the combined extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo to give a yellow oil **4** (1.28 g, 100% yield). IR ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 2229 (Ar-CN);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  3.98 (s, 3H,  $\text{OCH}_3$ ), 3.97 (s, 3H,  $\text{OCH}_3$ ), 3.87 (s, 3H,  $\text{OCH}_3$ ), 3.78 (s, 3H,  $\text{OCH}_3$ ), 2.36 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  152.3 (Ph), 151.8 (Ph), 147.8 (Ph), 144.6 (Ph), 130.9 (Ph), 115.2 (CN), 102.5 (Ph), 61.8 ( $\text{OCH}_3$ ), 61.4 ( $\text{OCH}_3$ ), 61.2 ( $\text{OCH}_3$ ), 60.8 ( $\text{OCH}_3$ ), 14.0 ( $\text{CH}_3$ ); ESI-MS:  $m/z = 238$   $[\text{M}+\text{H}]^+$ , Calcd for  $\text{C}_{12}\text{H}_{16}\text{NO}_4$ : 238.1079. Found: 238.1077.

**2,3,4,5-Tetramethoxy-6-methylbenzamide (5).** To a mixture of **4** (1.3 g, 5.4 mmol), tetrabutyl ammonium bromide (0.2 g, 0.62 mmol) and 30% NaOH solution (2 mL) in ethanol (5 mL), 30% hydrogen peroxide (5 mL, 5.4 mmol) was added dropwise over a period of 10 minutes, then the mixture was stirred at 75 °C for another 5 hours. Then water (20 mL) was added and the reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$ , the combined extracts were washed with brine and water, dried over anhydrous sodium sulfate and concentrated in vacuo to give a yellow oil **5** (1.25 g, 98% yield). IR ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1650 (Ar- $\text{CONH}_2$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  5.89 (s, 2H,  $\text{NH}_2$ ), 3.92 (s, 3H,  $\text{OCH}_3$ ), 3.90 (s, 3H,  $\text{OCH}_3$ ), 3.87 (s, 3H,  $\text{OCH}_3$ ), 3.78 (s, 3H,  $\text{OCH}_3$ ), 2.24 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  169.4 ( $\text{CONH}_2$ ), 148.3 (Ph), 147.9 (Ph), 146.2 (Ph), 144.7 (Ph), 126.3 (Ph), 124.5 (Ph), 62.1 ( $\text{OCH}_3$ ), 61.2 ( $\text{OCH}_3$ ), 61.0 ( $\text{OCH}_3$ ), 60.6 ( $\text{OCH}_3$ ), 12.4 ( $\text{CH}_3$ ); ESI-MS:  $m/z = 278$   $[\text{M}+\text{Na}]^+$ , Calcd for  $\text{C}_{12}\text{H}_{17}\text{NNaO}_5$ : 278.1004. Found: 278.1002.

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## References

1. Lenaz, G.; Genova, M.L. *Biochim. Biophys. Acta.* **2009**, *1787*, 563.
2. Bentinger, M.; Brismar, K.; Dallner, G. *Mitochondrion.* **2007**, *7*, S41.  
<http://dx.doi.org/10.1016/j.mito.2007.02.006>
3. Jung, Y. S.; Joe, B. Y.; Cho, S. J.; Konishi, Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1125.  
<http://dx.doi.org/10.1016/j.bmcl.2004.12.029>
4. Duveau, D. Y.; Arce, P. M.; Schoenfeld, R. A.; Raghav, N.; Cortopassi, G. A.; Hecht, S. M. *Bioorg. Med. Chem.* **2010**, *18*, 6429.  
<http://dx.doi.org/10.1016/j.bmc.2010.06.104>
5. Tsoukala, A.; Bjørsvik, H.-R. *Org. Process Res. Dev.* **2011**, *15*, 673.  
<http://dx.doi.org/10.1021/op200051v>
6. Lipshutz, B. H.; Lower, A.; Berl, Schein, V. K.; Wetterich, F. *Org. Lett.* **2005**, *7*, 4095.  
<http://dx.doi.org/10.1021/ol051329y>
7. Wang, J.; Yang, J.; Yang, B.; Hu, X.; Sun, J.Q.; Yang, T. *J. Chem. Res.* **2010**, *34*, 717.  
<http://dx.doi.org/10.3184/030823410X12857507693437>
8. Wang, J.; Yang, J.; Yang, B.; Sun, J.Q.; Yang, T. *J. Chem. Res.* **2010**, *34*, 724.  
<http://dx.doi.org/10.3184/030823410X12857507693464>
9. Wang, J.; Yang, J.; Zhou, R. G.; Yang, B.; Wu Y.S. *J. Chem. Res.* **2011**, *35*, 431.  
<http://dx.doi.org/10.3184/174751911X13099411630089>
10. Wang, J.; Yang, J.; Zhou, R. G.; Yang, B.; Wu Y.S. *J. Chem. Res.* **2011**, *35*, 428.  
<http://dx.doi.org/10.3184/174751911X13099377293263>
11. Wang, J.; Zhou, R.G.; Wu, T.; Yang, T.; Qin, Q.X.; Li, L.; Yang, Bo.; Yang, J. *J. Chem. Res.* **2012**, *36*, 121.  
<http://dx.doi.org/10.3184/174751912X13285269293913>
12. Okamoto, K.; Watanabe, M.; Kawada, M.; Goto, G.; Imada, I.; Morimoto, H. *Chem. Pharm. Bull.* **1982**, *30*, 2797.  
<http://dx.doi.org/10.1248/cpb.30.2797>
13. Goto, G.; Okamoto, K.; Okutani, T.; Imada, I. *Chem. Pharm. Bull.* **1985**, *33*, 4422.  
<http://dx.doi.org/10.1248/cpb.33.4422>
14. Okamoto, K.; Matsumoto, M.; Watanabe, M.; Kawada, M.; Imamoto, T.; Imada, I. *Chem. Pharm. Bull.* **1985**, *33*, 3745.  
<http://dx.doi.org/10.1248/cpb.33.3745>
15. Yabunaka, H.; Kenmochi, A.; Nakatogawa, Y.; Sakamoto, K.; Miyoshi, H. *Biochim. Biophys. Acta.* **2002**, *1556*, 106.  
[http://dx.doi.org/10.1016/S0005-2728\(02\)00341-9](http://dx.doi.org/10.1016/S0005-2728(02)00341-9)
16. Xu, G.; Wu, J. P.; Ai, X. M.; Yang, L.R. *Chin. Chem. Lett.* **2007**, *18*, 643.  
<http://dx.doi.org/10.1016/j.ccllet.2007.04.003>
17. Shie, J.J.; Fang, J.M. *J. Org. Chem.* **2003**, *68*, 1158.  
<http://dx.doi.org/10.1021/jo026407z>

18. Ma, W.; Li, D.W.; Sutherland, T.C.; Li, Y.; Long, Y.T.; Chen, H.Y. *J. Am. Chem. Soc.* **2011**, *133*, 12366.  
<http://dx.doi.org/10.1021/ja204014s>
19. Rajput, A.P.; Girase, P.D. *Int. J. Pharm.chem.-Bio. Sci.* **2012**, *3*, 25.
20. Luo, Q.L.; Nan, W.H.; Li, Yu.; Chen, X. *Arkivoc.* **2014**, (iv), 350.  
<http://dx.doi.org/10.3998/ark.5550190.p008.707>
21. Wang, J.; Hu, X.; Yang, J. *Synthesis.* **2014**, *46*, 2371.  
<http://dx.doi.org/10.1055/s-0033-1338643>
22. Wang, J.; Li, S.; Hu, X.; Yang, J. *Org. Prep. Proced. Int.* **2014**, *46*, 469.  
<http://dx.doi.org/10.1080/00304948.2014.944409>
23. Wang, J.; Li, S.; Yang, T.; Yang, J. *Eur. J. Med. Chem.* **2014**, *86*, 710.  
<http://dx.doi.org/10.1016/j.ejmech.2014.09.042>
24. Wang, J.; Li, S.; Yang, T.; Yang, J. *Tetrahedron.* **2014**, *70*, 9029.  
<http://dx.doi.org/10.1016/j.tet.2014.10.017>