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SHORT COMMUNICATION

Practical synthesis of 2,3-dimethoxy-5-hydroxymethyl-6-methyl-1,4-benzoquinone

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2,3-dimethoxy-5-hydroxymethyl-6-methyl-1,4-benzoquinone (*V*) was prepared with a 75 % yield by means of a reaction sequence starting from 2,3,4,5-tetramethoxytoluene via Blanc chloromethylation reaction, Kornblum oxidation, $NaBH_4$ reduction and ceric ammonium nitrate oxidation. The procedure is operationally simple and amenable to gram-scale synthesis.

Keywords: coenzyme Q, idebenone, Kornblum oxidation, ceric ammonium nitrate oxidation

2,3-Dimethoxy-5-methyl-1,4-benzoquinones are coenzyme Q (CoQ) analogues and have attracted considerable attention owing to their biological and pharmacological activities (Astolfi et al., 2013; Bentinger et al., 2007; Tsoukala & Bjørsvik, 2011). A number of synthetic CoQ analogues have shown significant biological activities related to their therapeutic effects (Jung et al., 2005; Okamoto et al., 1988). In particular, idebenone (Fig. 1) was successfully designed and synthesised as an clinical drug for the treatment of various cognitive defects such as Alzheimer's and Parkinson's diseases (Bentinger et al., 2007; Tsoukala & Bjørsvik, 2011). Idebenone was also shown to be a free radical scavenger for reactive oxygen species (ROS) (Tsoukala & Bjørsvik, 2011).

Many studies show that the C-6 position in some 2,3-dimethoxy-5-methyl-1,4-benzoquinones is substituted with small groups (alkyl) bearing strong antioxidant activity and anti-glycation activity (Jung et al., 2005; Okamoto et al., 1988). However, the methods

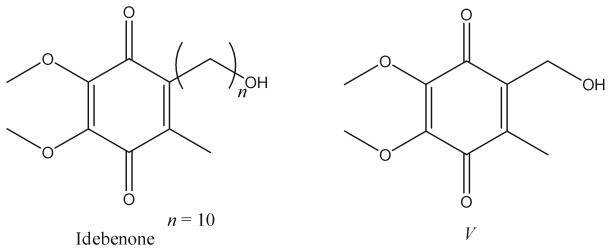

Fig. 1. Structure of idebenone and *V*.

published in the literature (Jung et al., 2005; Okamoto et al., 1988; Lipshutz et al., 2005) for preparing CoQ analogues have some drawbacks, such as low product yields, harsh reaction conditions, toxic reagents (titanium(IV) chloride, butyllithium, iodomethane), and difficult procedures. 2,3,4,5-tetramethoxy-6-methylbenzaldehyde (*III*) is a key intermediate for the synthesis of CoQ analogues, and several methods (Jung

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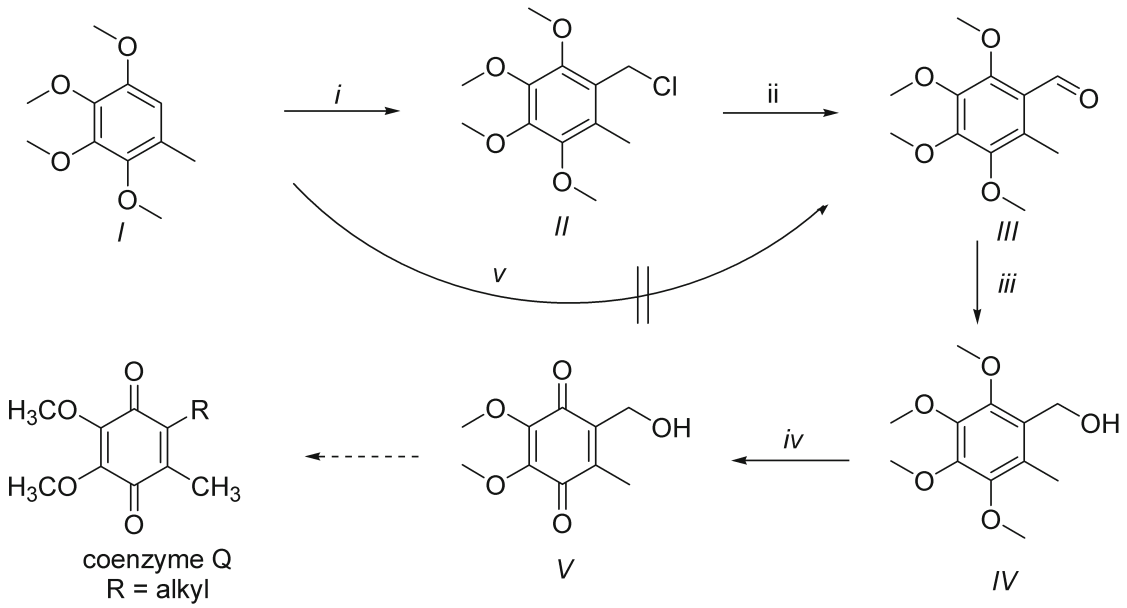

Fig. 2. Synthetic route to *V*: *i*) $(HCHO)n$, 37 % HCl, 40 °C 96 % ; *ii*) method 1 – $K_2Cr_2O_7$, H_2O, TBAB, 60 °C, 69 %; method 2 – $NaHCO_3$, DMSO, 80 °C, 87 %; *iii*) $NaBH_4$, CH_3OH, 25 °C, 97 %; *iv*) CAN, THF/H_2O, 0 °C, 92%; *v*) $POCl_3$, DMF, 80 °C.

et al., 2005; Nyland et al., 2010) have been reported for the synthesis of *III*. Usually, (Jung et al., 2005; Ma et al., 2011) the formyl group was introduced into the aromatic ring by using 1,1-dichloromethyl methyl ether (Cl_2CHOCH_3) and $TiCl_4$ under strict water-free conditions at 0 °C; however, the reagent $TiCl_4$ is easily hydrolysed by water to form a strong irritant gas (HCl), and the yield is not reproducible, which restricts the multi-gram synthesis of *III*. In view of the difficulties associated with the preparation of previous CoQ analogues (Jung et al., 2005; Okamoto et al., 1988; Lipshutz et al., 2005), the availability of 1-chloromethyl-2,3,4,5-tetramethoxy-6-methylbenzene (*II*) (Wang et al., 2010a, 2011a, 2011b) prompted the present initiative to devise a practical route to 2,3-dimethoxy-5-hydroxymethyl-6-methyl-1,4-benzoquinone (*V*) which is an analogue of idebenone. The current study details a convenient and practical method for the synthesis of *V*. The synthetic route is described in Fig. 2.

All reactions were monitored by TLC. NMR spectra data were recorded on a Bruker DRX 500 NMR spectrometer (Germany, 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR). TMS was used as an internal standard and chemical shift is given in δ relative to TMS, and for mass measurement a LC-MS (API) (Shimadzu 30& Triple QUAD 5500, Japan) mass spectrometer was used (mobile phase; A – water (0.1 vol. % trifluoroacetic acid (TFA)), B – acetonitrile (0.1 vol. % TFA), gradient – 5 %–95 % B in 1.2 min; flow-rate – 2.2 mL min^{-1}, column Poroshell 120 EC-C18 (Agilent, Japan) 4.6 mm × 30 mm × 2.7 μm). Ceric ammonium nitrate (CAN), $K_2Cr_2O_7$ and $NaBH_4$ were purchased from Adamas-beta (China).

2,3,4,5-Tetramethoxytoluene (*I*) and *II* were prepared by the method described previously (Wang et al., 2010a, 2011a, 2011b).

III was prepared using two methods; (i) to a mixture of *II* (5.20 g, 0.02 mol) and tetrabutylammonium bromide (0.64 g, 0.002 mol) in CH_2Cl_2 (10 mL) was added a solution of $K_2Cr_2O_7$ (7.0 g, 0.024 mol) in water (70 mL) at ambient temperature, then the reaction mixture was heated at 60 °C for 2 h, until the colour of the reaction solution changed from yellow to orange. The mixture was cooled to ambient temperature, diluted with water (30 mL), filtered to remove the solid (Cr_2O_3), then the filtrate was extracted with petroleum ether (3 × 50 mL) and the combined extracts were washed with brine. The solution was dried over anhydrous sodium sulphate and the solvent was removed under vacuum to afford a pure yellow oil *III* (3.3 g, 69 % yield); (ii) to a solution of *II* (2.60 g, 0.01 mol) in dry dimethylsulphoxide (5 mL) was added $NaHCO_3$ (1.26 g, 0.15 mol) at ambient temperature and maintained at 80 °C for 3 h. The mixture was then cooled to ambient temperature, water (50 mL) was added, the mixture was extracted with petroleum ether (3 × 40 mL) and the combined extracts were washed with brine. The solution was dried over anhydrous sodium sulphate and the solvent was removed under vacuum. The crude products were purified by silica-gel column chromatography (Adamas-beta; petroleum ether/EtOAc; φ_r = 5 : 1) to give a yellow oil *III* (2.10 g, 87 % yield). ^{1}H NMR data match the data in the literature (Ma et al., 2011); LC-MS: m/z =241(M^+ + H).

2,3,4,5-Tetramethoxy-6-hydroxymethyltoluene (*IV*) was prepared by adding $NaBH_4$ (0.38 g,

10 mmol) to a solution of *III* (2.4 g, 10 mmol) in methanol (10 mL) and the mixture was stirred at ambient temperature. The progress of the reaction was monitored by thin-layer-chromatography (TLC). Once the reaction was complete, the reaction mixture was extracted with three portions of CH_2Cl_2 (20 mL). The orange extracts were washed with brine until a neutral reaction was achieved, then dried over anhydrous Na_2SO_4 and concentrated under vacuum to give a yellow oil *IV* (2.3 g, 97 % yield). ^{1}H NMR data match the data in the literature (Ma et al., 2011); LC-MS: $m/z = 265$ ($M^+ + Na$).

V was prepared when the excess solution of ceric ammonium nitrate (11 g, 20 mmol) in water (11 mL) was added drop-wise to a solution of compound *IV* (1.6 g, 6.61 mmol) in tetrahydrofuran (10 mL) at 0 °C, then the mixture was stirred at ambient temperature and the progress of the reaction monitored by thin-layer-chromatography (petroleum ether/EtOAc; $\varphi_r = 4 : 1$). Once the reaction was complete, the crude product was extracted with three portions of CH_2Cl_2 (20 mL). The orange extracts were washed with brine until a neutral reaction was achieved, then dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude products were purified by silica-gel column chromatography (petroleum ether/EtOAc; $\varphi_r = 4 : 1$) to give a orange solid *V* (1.29 g, 92 % yield). M.p. 50–51 °C. 53–55 °C (Okamoto et al., 1985).

^{1}HNMR (500 MHz, $CDCl_3$), δ: 4.45 (s, 2H, CH_2OH), 3.92 (s, 6H, OCH_3), 2.92 (s, 1H, OH), 2.02 (s, 3H, CH_3).

^{13}CNMR (100 MHz, $CDCl_3$), δ: 184.9 (C═O), 184.5 (C═O), 144.6, 144.1, 140.6, 138.6, 61.1 (OCH_3), 56.5 (CH_2OH), 11.6 (CH_3).

Previously (Wang et al., 2010a, 2010b, 2011a, 2011b, 2012), a "green" and efficient synthesis of *II* was described and this synthetic methodology has now been extended to synthesise idebenone homologues. Fig. 2 shows that *I* using paraformaldehyde and 37 % HCl under solvent-free conditions provided *II* at 40 °C with a 96 % yield (Wang et al., 2010a, 2010b, 2011a, 2011b). Inspired by some reports (Jung et al., 2005; Nyland et al., 2010), a direct introduction of the aldehyde group into the aryl ring via Vilsmeier reaction employing $POCl_3$ and dimethylformamide was attempted; however, after many trials, only a trace amount of the desired compound *III* was obtained. It is assumed that the presence 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 *I*. Next, a treatment of *II* with $K_2Cr_2O_7$ and tetrabutylammonium bromide in water; modified as described by Freeman et al. (2007) was assayed. This time the desired aldehyde *III* was formed with a good yield without further purification with chromatography. An aldehyde is known to undergo further oxidation to a carboxylic acid under aqueous conditions; however, in this transformation only a trace amount of carboxylic acid was detected in the reaction product. Recently, a modified method (Xu et al., 2007) of direct transformation of *II* to *III* via Kornblum oxidation was improved utilising DMSO as a oxidant which avoids the toxic chromate oxidation; the yield for *II* to *III* was 87 % compared to 69 % when proceeding through *II* (Fig. 2). It is noted that Kornblum oxidation afforded some by-products of alcohol and acids, which required long-column chromatography to obtain the pure aldehyde *III*. The reduction reaction of *III* using $NaBH_4$ at ambient temperature afforded *IV*. Finally, the selective oxidation of *IV* employing CAN as a mild oxidant gave *V* with a good yield (92 %).

In summary, an operationally simple, efficient and practical procedure for the preparation of *V* was developed; this achieved an overall yield of 75 % based on *I*. Compounds *III* and *IV* may also be useful as starting materials for the synthesis of other CoQ analogues. Furthermore, compound *III* was successfully obtained by oxidation using DMSO as a mild oxidation reagent from benzyl halide *II* under mild conditions, thereby eliminating the use of large amounts of a dangerous oxidation reagent (dichromate). The advantages of these reactions are that they are operationally simple, readily processed, amenable to gram-scale synthesis and are carried out under mild reaction conditions. This procedure is also applicable to the preparation of a wide variety of biological idebenone analogues.

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