A facile synthesis of 2, 3-dimethoxy-5-methyl-1, 4-benzoquinones

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Several 2, 3-dimethoxy-5-methyl-1, 4-benzoquinones substituted at the C-6 position with alkoxy methyl groups were prepared by a reaction sequence starting from 2, 3, 4, 5-tetramethoxytoluene (alkoxy methyl) via a Blanc chloromethylation reaction, Williamson reaction and oxidation. The method provided a good yield of 2, 3-dimethoxy-5-methyl-1, 4-benzoquinones and is suitable for the synthesis of other benzoquinone analogues.

Keywords: coenzyme Q, idebenone, Blanc chloromethylation reaction, Williamson reaction

2, 3-Dimethoxy-5-methyl-1, 4-benzoquinones are Coenzyme Q analogues and have attracted considerable attention owing to their biological and pharmacological activities.[1,2] Synthetic benzoquinones have protocollagen-proline hydroxylase inhibiting activity, collagen biosynthesis inhibitory activity and 5-lipoxygenase suppressant activity, and are useful for the prevention and treatment of such disease as hepatocirrhosis, arteriosclerosis, Alzheimer's disease, Parkinson's disease, urticaria, etc.[1–5] Hence, several researchers have focused on the development of new methods for the synthesis of these useful compounds.

Among the quinone derivatives synthesised previously, 6-(10-hydroxydecyl)-2, 3-dimethoxy-5-methyl-1, 4-benzoquinone (idebenone), Fig. 1, was found to improve neurological symptoms in stroke-prone spontaneously hypertensive rats with experimental cerebral ischaemia and to show beneficial effects on the physiological and neurological symptoms in patients with cerebral vascular diseases.[3,8] Furthermore, 6-alkyl-2, 3-dimethoxy-5-methyl-1, 4-benzoquinones showed effects on mitochondrial succinate and on reduced nicotinamide adenine dinucleotide oxidase systems.[2,3,6–8] Among the compounds which have been reported those which had a different length of the side chain at the C-6 position showed strong anti-oxidant activity[7] and anti-glycation activity[2]. We synthesised several idebenone homologues (**4a, 4b, 4c**) in preparation for studies on structural effects on redox functions.

In general, coenzyme Q_0[1,2,9] has been frequently employed as starting material for benzoquinone synthesis. However, quinones have been used sparingly because they are much less nucleophilic than phenols and their ether derivatives.[2] The published syntheses of benzoquinones have significant drawbacks such as long reaction times, low yields of the products, harsh reaction conditions, difficult work-up, and the use of expensive and environmentally toxic catalysts, reagents, or media.[1,2,6,7,8,9] The development of simple and efficient methods for the synthesis of 2, 3-dimethoxy-5-methyl-1, 4-benzoquinones is therefore desirable.

Recently,[4,5] we described a green and efficient synthesis of 1-chloromethyl-2, 3, 4, 5-tetramethoxy-6-methylbenzene (**2**) and we have now extended this synthetic methodology to synthesise idebenone homologues. Herein we report a facile synthesis of 2, 3-dimethoxy-5-methyl-1, 4-benzoquinones substituted at the C-6 position with alkoxy methyl groups starting from 2, 3, 4, 5-tetramethoxytoluene (**1**) via a Blanc chloromethylation reaction, Williamson reaction and oxidation.

Results and discussion

As shown in Scheme 1, chloromethylation of 2, 3, 4, 5-tetramethoxytoluene **1** using paraformaldehyde and 37%

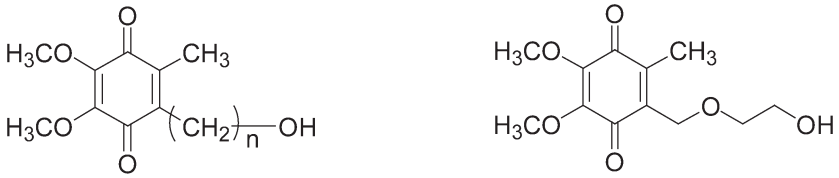
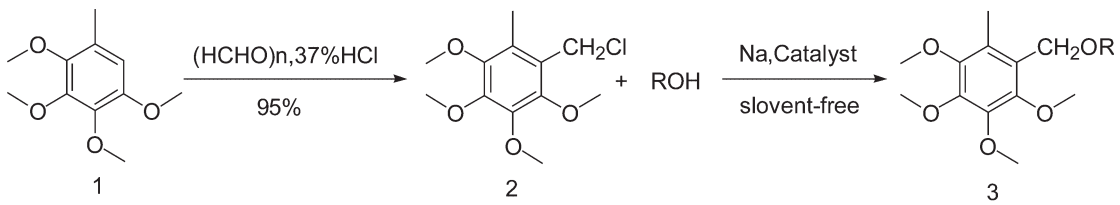


Fig. 1



Scheme I

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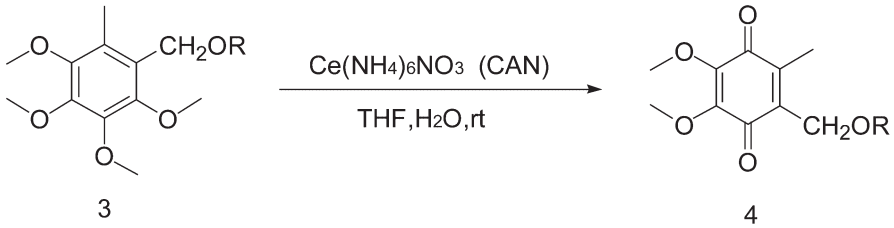
Table 1 Williamson reaction catalysed by KI under solvent-free conditions

Entry	R	Catalyst	Catalyst load/g	Reaction temp./°C	Time/h	Product	Yield/%
1	CH_3	KI	0.1	Reflux	0.5	**3a**	99
2	CH_3CH_2	KI	0.1	Reflux	0.5	**3b**	98
3	CH_2CH_2OH	KI	0.1	70	1	**3c**	94



3 4

Scheme 2

HCl under solvent-free conditions provided **2** at 40 °C in an excellent yield (95%).[4] A direct method for converting **2** to the ether **3** is by the Williamson reaction. We considered that the electron-donating effect of four methoxy groups in **2** favoured a Williamson reaction. Treatment of **2** and the alcohol with Na catalysed by KI under solvent-free conditions provided **3** in nearly quantitative yields[11–12] (as shown in Table 1).

Finally, As shown in Scheme 2, the ethers **3** were oxidised with cerricammoniumnitrate (CAN) to afford the benzoquinones **4** in good yield.[10] A summary of the results is given in Table 2.

In conclusion, the electron-donating effect of methoxy and methyl groups enhanced the Blanc chloromethylation reaction and Williamson reaction. 37% HCl and ROH were employed as both reagent and solvent. An approach based on the reaction with 2, 3, 4, 5-tetramethoxytoluene (**1**) as a starting material is promising for the synthesis of 1, 4-benzoquinones affording an efficient reaction for the preparation of 2, 3-dimethoxy-5-methyl-1, 4-benzoquinones of potential synthetic and pharmacological interest. We believe that this experimentally simple approach could be a useful addition to reported methods.[1,2,6–9]

Experimetal

All reactions were monitored by TLC, Melting points were measured on a YRT-3 temp apparatus and are uncorrected. IR spectra were recorded on an Impact 400 FT-IR instrument. ^{NMR} spectra data were recorded on a Bruker DRX 500 NMR spectrometer and a ZAB-2F mass spectrometer, respectively.

2, 3, 4, 5-Tetramethoxytoluene (**1**) and 1-chloromethyl-2, 3, 4, 5-tetramethoxy-6-methylbenzene (**2**) were prepared by the literature method.[4]

Synthesis of compounds (**3**)*; general procedure*

Freshly cut sodium (0.5 g, 0.022mol) was dissolved in the dry ROH (10 mL). The catalyst KI (0.1 g) and 1-chloromethyl -2, 3, 4, 5-tetramethoxy-6-methylbenzene **2** (0.7g, 2.69mmol) were added under a N_2 atmosphere .The mixture was refluxed for 1 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and water (50 mL) were added and then neutralized to pH 7 with 1% aqueous HCl. The mixture was extracted with CH_2Cl_2 (4 × 30 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the desired compounds **3**.

Table 2 Synthesis of 2, 3-dimethoxy-5-methyl-1, 4-benzoquinones **(4)**

Compound	R	Yield/%	Colour
4a	CH_3	88	Orange
4b	CH_3CH_2	76	Orange
4c	CH_2CH_2OH	68	Orange

Synthesis of 2, 3-dimethoxy-5-methyl-1, 4-benzoquinones (**4**)*; general procedure*

A solution of compounds **3** (2.5 mmol) in THF (10 mL) was diluted with water (5 mL), and an excess solution of cerric ammonium nitrate (CAN) (3.9g, 7 mmol) in 10 mL water was added at 0 °C. The mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the THF was removed under a vacuum at 40 °C, and the crude mixture was extracted with three portions of CH_2Cl_2 (20 mL). The orange extracts were washed with brine until neutrality, then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude products were purified by a silica-gel column chromatography with petroleum ether and EtOAc as eluent to give the desired benzoquinones (**4**).

Previously reported materials were characterised by comparison of their m.p., IR, ^{1}H NMR, and MS data with those of authentic samples. All new compounds gave satisfactory spectral data in accordance with their proposed structures.

1, 2, 3, 4-Ttetramethoxy-5-(methoxymethyl)-6-methylbenzene (**3a**): Colourless oil; IR (KBr/cm^{-1}):2930, 2865, 1470, 1412, 1354, 1282, 1204, 1113, 1055; ^{1}H NMR (500 MHz, DMSO-d_6):4.34 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H), 3.67 (s, 3H), 3.30 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, C_5D_5N-d_5):148.4, 147.5, 146.6, 144.1, 126.7, 124.5, 65.5, 61.1, 60.4, 60.3, 59.8, 57.5, 10.7; MS (EI): *m/z* = 256 (M^+). HRMS-EI: *m/z* (M^+) Calcd for $C_{13}H_{20}O_5$: 256.1311. Found:256.1315.

1-(Ethoxymethyl)-2, 3, 4, 5-tetramethoxy-6-methylbenzene (**3b**): Colourless oil; IR (KBr/cm^{-1}):2962, 2858, 1477, 1412, 1353, 1269, 1198, 1120, 1055; ^{1}H NMR (500MHz, $CDCl_3$):4.48 (s, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 3.62–3.56 (q, *J* = 8.8 Hz, 2H), 2.26 (s, 3H), 1.26–1.23 (t, *J* = 8.8 Hz, 3H); ^{13}C NMR (125 MHz, MeOD):148.7, 147.9, 146.9, 127.1, 125.1, 65.8, 64.0, 61.8, 60.9, 60.8, 60.4, 15.2, 11.2.

2-(2, 3, 4, 5-Tetramethoxy-6-methylbenzyloxy)ethanol (**3c**): Colourless oil; IR (KBr/cm^{-1}): 3506, 3434, 2960, 2876, 1467, 1415, 1369, 1109, 1045; ^{1}H NMR (500 MHz, C_5D_5N-d_5): 4.40 (s, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.63 (s, 3H), 3.56 (s, 2H), 3.46–3.45 (m, 2H), 3.14 (brs, 1H), 2.11 (s, 3H); ^{13} C NMR (125 MHz, MeOD): 148.7, 147.8, 146.9, 144.4, 127.1, 124.6, 71.5, 64.4, 61.6, 61.4, 60.9, 60.8, 60.4, 11.3; MS (ESI): *m/z* = 285 (M^--H). HRMS-ESI: *m/z* (M^--H) Calcd for $C_{14}H_{21}O_6$: 285.1338. Found:285.0396.

2, 3-Dimethoxy-5-(methoxymethyl)-6-methylcyclohexa-2, 5-diene-1, 4-dione (**4a**): Orange solid; m.p. 33–34 °C (lit.[8]36 °C);IR (KBr/cm^{-1}): 3520, 3300, 2923, 2852, 1665, 1613, 1464, 1269, 1114, 1049; ^{1}H NMR (500 MHz, $CDCl_3$): 4.30 (s, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 3.35 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (125 MHz, MeOD):184.3, 183.2, 144.4, 144.2, 143.0, 136.5, 64.0, 61.0, 60.9, 58.6, 11.9; MS (ESI): *m/z* = 225 (M^--H).HRMS-ESI: *m/z* (M^--H) Calcd for $C_{11}H_{13}O_5$: 225.0762. Found: 225.0759.

2-(Ethoxymethyl)-5, 6-dimethoxy-3-methylcyclohexa-2, 5-diene-1, 4-dione (**4b**): Orange oil; IR (KBr/cm^{-1}): 3300, 2982, 2949, 2878, 1665, 1606, 1457, 1282, 1113, 1036; ^{1}H NMR (500 MHz, $CDCl_3$): 4.33 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H), 3.55-3.50 (m, 2H), 2.09 (s, 3H), 1.19–1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):

184.5, 183.3, 144.5, 144.4, 143.1, 136.9, 66.6, 62.2, 61.1, 61.1, 15.1, 12.0; MS (ESI): *m/z* = 263 (M^+ + Na). HRMS-ESI: *m/z* (M^+ + Na) Calcd for $C_{12}H_{16}O_5Na$: 263.0895. Found:263.0892.

2-[(2-Hydroxyethoxy)methyl]-5, 6-dimethoxy-3-methylcyclohexa-2, 5-diene-1, 4-dione (**4c**): Orange oil; IR (KBr/cm^{-1}): 3389, 3265, 2967, 1765, 1674, 1454; ^{1}H NMR (500 MHz, C_5D_5N-d_5): 4.31 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.62–3.61 (m, 2H), 3.51–3.50 (m, 2H), 2.80 (brs, 1H), 2.01 (s, 3H); ^{13} C NMR (125 MHz, MeOD):184.2, 183.4, 144.3, 144.1, 143.0, 136.4, 72.0, 62.6, 61.3, 61.0, 60.9, 11.9; MS (ESI): *m/z* = 255 (M^--H).HRMS-ESI: *m/z* (M^--H) Calcd for $C_{12}H_{15}O_6$: 255.0868. Found: 255.0869

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