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Hydrogenation of plant polyalkoxybenzene derivatives: convenient access to coenzyme Q_0 analogues

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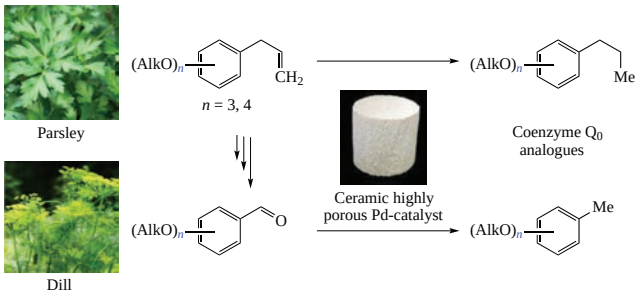
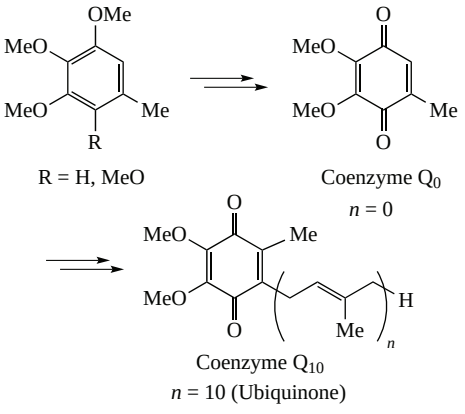
A technologically advanced protocol has been developed for converting plant allyl(polyalkoxy)benzenes to methyl- and propyl(polyalkoxy)benzenes being intermediates in the syntheses of coenzyme Q_0 analogues. The key stage of allyl and benzaldehyde moieties hydrogenation was carried out in a periodical autoclave mode on highly porous ceramic block Pd-catalysts. These catalysts possess large surface area, low hydraulic resistance, significant thermal and mechanical stabililty, multiple cycling and easy regeneration, which can dramatically reduce Pd consumption.



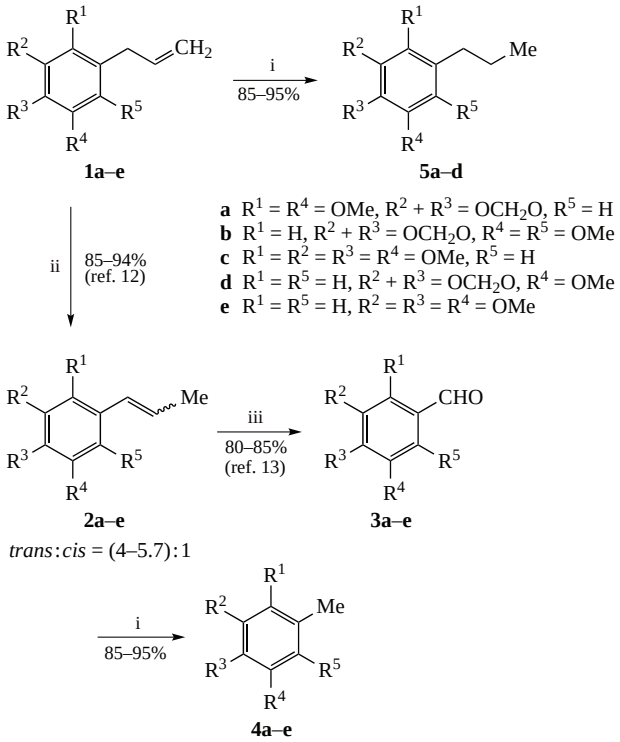
Keywords: coenzyme Q_0, antioxidants, ceramic block catalysts, palladium catalysts, hydrogenation, alkyl(polyalkoxy)benzenes.

The family of coenzymes in the organisms of mammals and plants is part of the mitochondrial respiratory chain. They have strong antioxidant activity and regulate the permeability of mitochondrial membranes. The synthesis of numerous analogues of coenzymes Q_0–Q_{15} with various lengths of the isoprenoid chain (n = 0–15) and alkoxy/alkyl substituents in the quinonoid ring (Scheme 1) has been the subject of several thousand publications. 2,3-Dimethoxy-5-methyl-1,4-benzoquinone (coenzyme Q_0)[1,2] is the main synthon for their preparation.

Recently, compound Q_0 was found to possess antitumor properties, in particular, it inhibits the metastasis of breast,[3] skin (melanoma)[4] and ovarian[5] cancer in mice. The original synthesis of Q_0 comprised a multistage scheme starting from gallic acid.[6] More efficient schemes involved the oxidation and demethylation of 1-methyl-2,3,4,5-tetramethoxytoluene **4c** (Scheme 2)[7] or 1-methyl-3,4,5-trimethoxytoluene **4e**,[8] which were in turn



Scheme 1



Scheme 2 *Reagents and conditions*: i, H_2 (20 atm), 5% Pd/6% α-Al_2O_3/γ-Al_2O_3, MeOH, 20 °C, 2–6 h; ii, KOH, 100 °C, 40 min; iii, O_3, $CHCl_3$–MeOH–pyridine (80 : 20 : 3 v/v), –15 °C, 1–2 h.

obtained by selective hydrogenation of the corresponding benzaldehydes on 10% Pd/C.[9] However, the majority of alkylbenzenes and benzaldehydes with four alkoxy substituents

had previously to be obtained from trimethoxybenzene derivatives, while direct oxidation of **4e** to coenzyme Q_0 was complicated by side processes.[8]

In this work, we suggest a facile source for synthesizing the intermediates of Q_0 and its analogues with methoxy, methylenedioxy, methyl and alkyl substituents in the ring based on allylpolymethoxybenzenes **1a–e** (see Scheme 2) that are easily isolated in large quantities from CO_2 extracts of parsley and dill seeds.[11] The isomerization of allylbenzenes to propenylbenzenes **2a–e** in alkaline media and the consequent ozonolysis to aldehydes **3a–e** that we developed earlier[12,13] occur in high yields even in large (50–100 g) scale.

It is important to note that the starting allylbenzenes **1** and their methyl- (**4**) and propyl-containing (**5**) analogues have an antitumor effect as well. In fact, methyl derivative of apiole (**4a**, referred to as SY-1 in the literature) and coenzyme Q_0 were isolated from the Chinese parasite fungus *Antrodia camphorata*. They are the main components responsible for the antitumor activity.[14] The extracts of mycelium and spores of this fungus have long been used in the traditional Chinese medicine.[15] Compound **4a** not only inhibits the growth of various cancer lines (breast, prostate, liver), but also has a synergistic effect – namely, it enhances the effect of taxol on prostate cancer.[14] Rather recently, data on the inhibition of colon cancer cells COLO 205 appeared for apiole **1a**, dihydroapiole **5a**, and a number of other derivatives.[17,18] The chemico-prophylactic anticancer properties of myristicin **1d** and dihydromyristicin **5d** were described.[19]

The key stage of the synthesis (see Scheme 2) involves the hydrogenation of allylbenzenes and benzaldehydes on highly porous ceramic block palladium catalysts in a periodical autoclave mode. Previously, catalysts of this type were successfully used for the hydrogenation of nitrobenzenes,[20] benzaldoximes,[21] and Schiff bases.[21] Such catalysts have a number of advantages, namely, a wide range of block designs and sizes, large surface area, low hydraulic resistance, high thermal and mechanical resistance. The possibility of repeated regeneration (30–40 times)[20] without activity loss reduces the consumption of the Pd-catalyst. Moreover, the reaction mixture can be removed without the need for filtering devices, which greatly simplifies the procedure. In our hands, the reaction was well reproducible at various concentrations and loads of the starting compounds **1** and **3** (2–5%, 1–5 g). Varying the hydrogen pressure did not affect the composition of the final product but affected the reaction time (6–8 h at 2 atm and 2–4 h at 20 atm for allylbenzenes; 24–28 h at 5 atm and 4–6 h at 20 atm for aldehydes). In the hydrogenation of compound **3a** as the example of benzaldehydes **3**, the formation of the intermediate benzylic alcohol was detected by TLC, HPLC, and mass spectrometry. If an equimolar amount of hydrochloric acid was added to the reaction mixture, benzyl methyl ether, which further turned to methylbenzene **4a**, was detected by mass spectrometry. These observations agree with the published data on the hydrogenation of aldehydes on Pd/C.[9] It was found that compounds without substituents at the *ortho* position relative to the hydrogenated group (**1d**, **3d**, **3e**) react faster than those containing an *ortho* methoxy group (for example, **1d** is consumed within 2 h while **1b** within 4 h). The application of catalysts with different Pd concentrations (0.6–5%) did not affect the purity of the final product, however, the reaction time decreased significantly with a decrease in the catalyst concentration (for example, 4–8 h at 5% Pd and 20 h at 0.6% Pd for benzaldehydes **3**).[†] According to the reported data,[9] the hydrogenation of benzaldehydes on Pd/C often results in product mixtures (the corresponding alcohols and methyl ethers[9]). The selective formation of methylbenzenes (Pd/C, 5 wt%) is observed upon addition of strong acids such as HCl or CF_3COOH, which complicates the further purification of the products.[9] In our experiments, only trace amount of impurities were found after hydrogenation on block Pd-catalyst in the absence of acids in pure methanol.

After unloading the reaction solution, the block catalyst can be used up to 40 times in the next syntheses after regeneration, while hydrogenation can be carried out at a 2.5 times higher concentration of aldehydes (5 wt%) than in the case of Pd/C.[9] For this reason, the production and isolation of products are faster and cheaper, while the consumption of palladium per 1 mol of the product becomes many times smaller because nothing of fresh catalyst should be added.

The spatial structure of natural compound **4a** (SY-1) that is necessary for further studies of the antitumor and antioxidant properties of its analogues was confirmed by single-crystal X-ray analysis (Figure 1).[‡]

Except for the hydrogen and C(8) atoms, the molecule of **4a** is almost planar (the rms deviation is 0.037 Å). The methoxy group at the C(3) carbon atom is slightly twisted by 3.18(19)° relative to the bicyclic plane, apparently due to steric reasons.

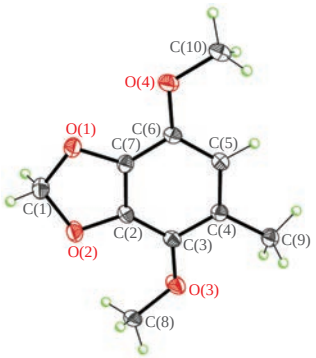


Figure 1 Molecular structure of **4a** (50% ellipsoids).

[†] *General procedure for the hydrogenation of allylbenzenes* **1a–d** *and benzaldehydes* **3a–e**. A solution of allylbenzene **1a–d** or benzaldehyde **3a–e** (23 mmol) in methanol (100 ml) was loaded into a stainless steel autoclave with fluoroplastic insert, and a regenerated block highly porous ceramic catalyst cylinder was fixed. Hydrogenation was carried out at 20 bar at room temperature for 2–4 h (for allylbenzenes) or 4–8 h (for benzaldehydes) with HPLC and/or TLC monitoring. After the starting reactant disappeared, the reaction solution was poured out of the autoclave, the block catalyst was washed with methanol (3 × 30 ml), and the combined solutions were filtered from mechanical impurities. The solvent was evaporated to afford analytically pure aromatic alkyl(polyalkoxy)-benzenes **4a–e** or **5a–d**.

[‡] *Crystal data for* **4a**. The crystal of **4a** ($C_{10}H_{12}O_4$, M = 196.20) is hexagonal, space group $P21/c$, at T = 100 K: a = 6.9251(7), b = 18.0537(17) and c = 7.2902(7) Å, V = 902.79(15) Å^3, Z = 4, d_{calc} = 1.444 g cm^{-3}, $F(000)$ = 416, μ = 0.112 mm^{-1}. X-ray diffraction data were collected on a three-circle Bruker D8 QUEST PHOTON-III CCD diffractometer [λ(MoKα)-radiation, T = 100 K, graphite monochromator, φ and ω scan mode] and corrected for absorption using the SADABS program.[27] The data were indexed and integrated using the SAINT program.[28] For details, see Online Supplementary Materials, Table S1. The structure was determined by direct methods and refined by full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. The hydrogen atoms were placed in calculated positions and refined within the riding model with fixed isotropic displacement parameters [U_{iso}(H) = 1.5U_{eq}(C) for the Me groups and 1.2U_{eq}(C) for the other groups]. All calculations were carried out using the SHELXTL program suite.[29]

CCDC 1997755 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

The two methoxy groups are arranged *trans* relative to each other [the C(8)–O(3)···O(4)–C(10) torsion angle is 166.45(12)°]. The molecules of **4a** in a crystal are packed in stacks along the crystallographic axis *a* and arranged at Van der Waals distances.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.09.015.

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