

An Unusual Anodic Methoxylation: 3,4-Dimethoxyacetophenone

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Abstract: The electrolysis of 3,4-dimethoxyacetophenone in methanol at a platinum anode gives a high yield of 1-acetyl-4,5,5,6-tetramethoxycyclohexa-1,3-diene, whose structure is proven by ¹H and ¹³C NMR.

Anodic nuclear methoxylation of a variety of aromatic compounds is a well established method and widely used.¹ Its mechanism was rationalized by Dolson and Swenton² as an *EEC_r-C_p* process which, for 1,2-dimethoxyaromatic compounds predicts 1,2-addition products. This was recently shown³ for methyl eugenol where 1,2- and 1,4-addition products were isolated as intermediates in the electrochemical preparation of γ -asarone, a case where a different addition product had been suggested previously.⁴

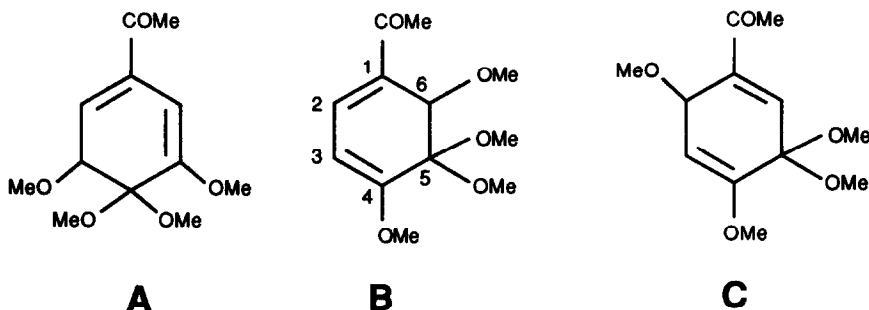
Here we report unexpected results from the anodic oxidation of 3,4-dimethoxyacetophenone at a platinum anode in alkaline methanol solution and under controlled current conditions. When the acetophenone derivative was electrolyzed (4.5 Fmol⁻¹) compound **1**, the major product (71%), was isolated after silica gel chromatography as a yellowish oil with u.v. data $\lambda_{\max} = 270$ nm and $\log \epsilon = 4.14$. The same product was detected in the ¹H NMR spectrum of the reaction mixture prior to chromatography and therefore it does not result from a rearrangement during the isolation procedure. Accurate mass measurement of the molecular ion in the mass spectrum of **1** gave the molecular formula C₁₂H₁₈O₅. Aromatisation of **1** in methanolic HCl afforded **2**, identified as 2,3,4-trimethoxyacetophenone by ¹H (cf. reported data by Anthonsen⁵) and ¹³C NMR (cf. reported data by Makriyannis and Knittel⁶).

The ¹H and ¹³C NMR spectra of **1** are summarised in Scheme 1, and the interproton couplings between

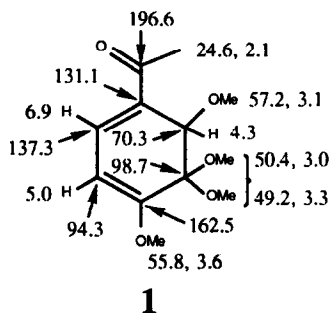
Scheme 1

δ ¹ H ppm		δ ¹³ C ppm
2.1 (3H,s)	—————	24.6 (q)
3.3 (3H,s)	—————	49.2 (q)
3.0 (3H,s)	—————	50.4 (q)
3.6 (3H,s)	—————	55.8 (q)
3.1 (3H,s)	—————	57.2 (q)
4.3 (1H, d, J = 1.0 Hz)	—————	70.3 (d)
5.0 (1H, d, J = 6.7 Hz)	—————	94.3 (d)
		98.7 (s)
		131.1 (s)
6.9 (1H, dd, J = 1.0, 6.7 Hz)	—————	137.3 (d)
		162.5 (s)
		196.6 (s)

the resonances at 4.3, 5.0 and 6.9 ppm were confirmed by a ^1H 2-D COSY spectrum. These data are consistent with a basic cyclohexadiene structure with one acetyl and four methoxyl substituents. The aromatisation reaction then involves the elimination of methanol from the molecule. The one-bond ^{13}C - ^1H connectivities found in the 2-D ^{13}C - ^1H heteronuclear chemical shift correlation experiment are shown in Scheme 1 by solid lines, and the ^{13}C - ^1H multiplicities ($-\text{CH}_3 = \text{q}$, $>\text{CH}- = \text{d}$, $>\text{C} = \text{s}$) were determined with aid of DEPT ^{13}C spectra. The 2-D ^{13}C - ^1H long range (2 & 3 bond) coupling correlation gave the methoxyl proton \rightarrow carbon connectivities; 3.0 and 3.3 ppm \rightarrow 98.7 ppm (i.e. a geminal dimethoxyl grouping); 3.1 ppm \rightarrow 70.3 ppm ($>\text{CHOMe}$); 3.6 ppm \rightarrow 162.5 ppm (possibly enol methyl ether $=\text{COMe}$). A number of structures which incorporate these features are possible but considering the starting material and its plausible anodic methoxylation products, three structures (A - C) are candidates for **1**.

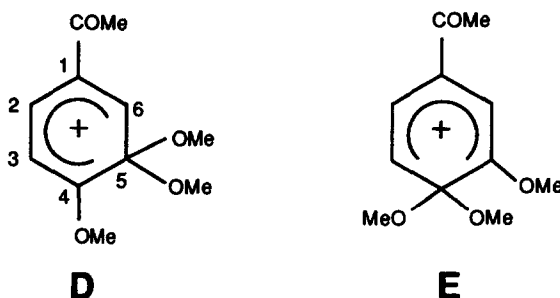


The u.v. maximum (270 nm) is most consistent with **A**; **B** and **C** are predicted to absorb at longer and shorter wavelengths respectively. To distinguish unambiguously between these possibilities the ^{13}C 2-D INADEQUATE experiment was performed on **1**. The correlations shown by this experiment (see Figure) are the 1-bond ^{13}C - ^{13}C couplings. Starting with the resonance at 70.3 ppm, this carbon is directly bonded to that with the resonance at 98.7 ppm, which in turn is directly bonded to that with the resonance at 162.5 ppm. Therefore **1** includes the fragment $-\text{CH}(\text{OMe})-\text{C}(\text{OMe})_2-\text{C}(\text{OMe})=$. Two of the three possible structures include this fragment, **A** and **B**. Further inspection of the INADEQUATE spectrum (Figure) showed that the resonance at 70.3 ppm is correlated with that at 131.1 ppm (s), which in turn is correlated with that at 137.3 (d), thence to 94.3 (d) and 162.5 ppm (s). Only one structure (**B**) is consistent with this. Additionally the carbonyl resonance at 196.6 ppm correlates with that at 131.1 ppm and the methyl resonance at 24.6 ppm. Therefore the final ^1H and ^{13}C assignments may be summarised as:



This structure should be fully consistent with all the remaining NMR data. The ^{13}C - ^1H long range coupling 2-D correlation gave the methoxyl proton correlations referred to above. Additional $^1\text{H} \rightarrow ^{13}\text{C}$ long range correlations were: 6.9 ppm \rightarrow 70.3, 162.5 and 196.6 ppm; 5.0 ppm \rightarrow 98.7 and 131.1 ppm; 4.3 ppm \rightarrow 57.2, 98.7, 131.1 and 162.5 ppm. These data are all consistent with the proposed structure, the observed correlations being *via* 2- and 3-bond ^{13}C - ^1H couplings. Finally we consider the spatial proximities indicated by the ^1H homonuclear 2-D Overhauser experiment (NOESY). The following strong correlations were found: 6.9 ppm \rightarrow 2.1 and 5.0 ppm; 5.0 ppm \rightarrow 3.6 ppm; 4.3 ppm \rightarrow 3.1 and 3.3 ppm; 3.3 ppm \rightarrow 3.0 ppm; 2.1 ppm \rightarrow 3.0 and 3.3 ppm. Inspection of a molecular model shows that all these spatial correlations are accommodated with the proposed structure. Taken together these NMR spectral data point to the unambiguous assignment of the structure of **1** as 1-acetyl-4,5,5,6-tetramethoxycyclohexa-1,3-diene **B**.

The EEC_rC_p mechanism involves two electrochemical oxidations, a coupling of the anodically generated aromatic radical cation to methoxy radical, and a reaction of the resulting cation with methanol. In our case the formation of two cations, **D** and **E**, is possible by the EEC_rC_p mechanism:



None of the expected reaction products of **E** with methanol was observed, which points to the preferential formation of **D**. Cation **E** should be less stable than **D** because the electron-withdrawing effect of the acetyl group should be more important in **E**. The lack of formation of a significant amount of a 1,2-tetramethoxy derivative, one of the methoxylation products from the anodic oxidation of methyl eugenol, is surprising as its formation could occur *via* **D** or **E**. No obvious explanation for this is available at present. We conclude that compound **1** results from reaction of methanol with **D** at the 6-position rather than the 2-position as the former gives the thermodynamically favoured cyclohexa-1,3-diene.

Typical procedure: The electrolysis was performed in an undivided cell using a Pt foil anode (2.5 x 3.5 cm) and a W wire as cathode. A solution of 3,4-dimethoxyacetophenone (0.075 M) in MeOH (130 ml) containing NaClO_4 (0.2 M) and NaOCH_3 (0.2 M) was electrolyzed at room temperature (435 mA, 0.050 A cm^{-2} , 4.5 F mol^{-1}). After completion, MeOH was removed under reduced pressure. Water was added to the residue and the mixture extracted with methylene chloride. After concentration under reduced pressure the product was isolated by column chromatography (SiO_2 , Et_2O -petroleum ether 1:1).

^1H and ^{13}C NMR Data: The ^1H and ^{13}C NMR experiments (^{13}C DEPT, ^1H 2-D COSY, ^1H 2-D NOESY, ^{13}C - ^1H 2-D shift correlation, and ^{13}C 2-D INADEQUATE) are all standard experiments described, for example, by Sanders and Hunter.⁷ With the exception of the INADEQUATE spectrum all ^1H and ^{13}C spectra of **1** were measured on samples in CDCl_3 solution contained in 5 mm o.d. tubes at 200 and 50.3 MHz respectively using a Bruker AC-200 spectrometer. The ^{13}C INADEQUATE spectrum was measured at 100.6 MHz using a Bruker AMX-400 spectrometer. The mixing time for the NOESY experiment was 0.5 s

and the ^{13}C - ^1H long range coupling 2-D shift correlation assumed a ^{13}C - ^1H coupling = 6 Hz for calculating the critical pulse sequence delay time. In the INADEQUATE pulse sequence a delay corresponding to a 1-bond ^{13}C - ^{13}C coupling of 65 Hz was assumed. The sample used for INADEQUATE contained *ca.* 350 mg of **1** in 0.5 ml CDCl_3 with 6 mg $\text{Cr}(\text{acac})_3$ added as relaxation reagent. The recycle delay between successive scans was 1.1 s, and the total experiment measurement time was 38 h.

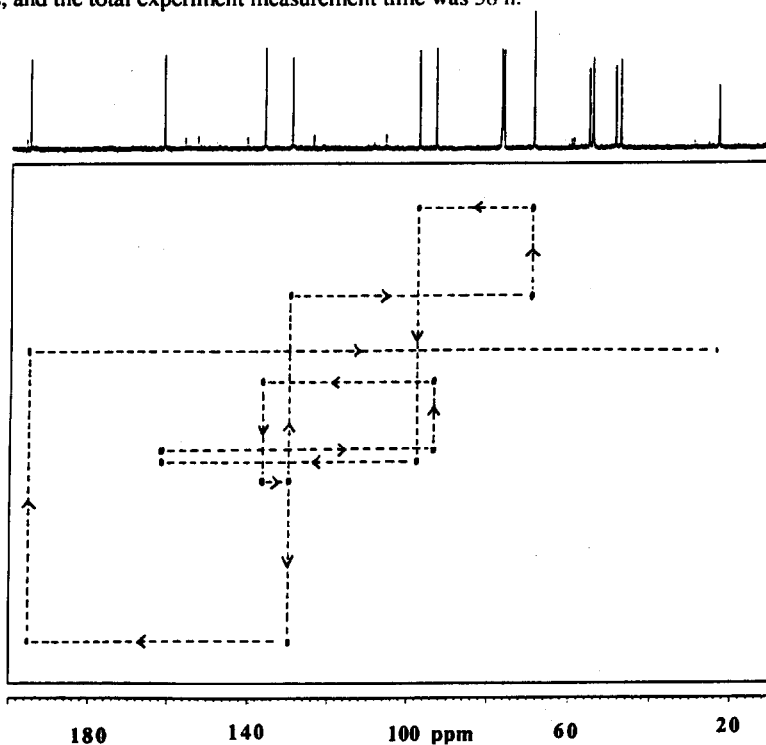


Figure. ^{13}C 2-D INADEQUATE spectrum of **1**. Broken lines show the ^{13}C - ^{13}C connectivities.

Acknowledgements

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References

1. Torii, S. *Electroorganic Synthesis: Methods and Applications, Part 1: Oxidations*. Monographs in Modern Chemistry, vol. 15; Kodansha, Tokyo, and VCH Weinheim, 1985.
2. Dolson, M.G.; Swenton, J.S. *J. Am. Chem. Soc.* **1981**, *103*, 2361-2371.
3. Wang, S.; Swenton, J.S. *Tetrahedron Lett.* **1990**, *31*, 1513-1516.
4. Vargas, R.R.; Pardini, V.L.; Viertler, H. *Tetrahedron Lett.* **1989**, *30*, 4037-4040.
5. Anthonson, T. *Acta Chem. Scand.* **1968**, *22*, 352-355.
6. Makriyannis, A.; Knittel, J.J. *Tetrahedron Lett.* **1979**, *20*, 2753-2756.
7. Sanders, J.K.M.; Hunter, B.K. *Modern NMR Spectroscopy*; Oxford University Press, Oxford, 1987, pp 100-111, 121-124, 167-172, 253-256.