J. Org. Chem. 1990, 55, 3270-3272

Electrochemical Methoxylation of Allyl and Propenyl Derivatives of Phenol and Phenol Ethers

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Received August 3, 1989

Anodic oxidation of a methanolic solution of a number of phenols and phenol ethers (anethole, estragole, safrole, isosafrole, eugenol, and isoeugenol) in a single cell at constant current, with use of sodium methoxide or sodium methoxide-sodium perchlorate as the supporting electrolyte, afforded substitution and addition products, some of them not described previously in the literature.

We report the anodic methoxylation of anethole, estragole, safrole, isosafrole, eugenol, and isoeugenol in MeOH/NaMeO or MeOH/NaMeO/$NaClO_4$, carried out under constant current. We were interested in these reactions for the following reasons: (i) Electronically, phenols and their methyl ethers differ little from each other, and this is reflected in the similarity of the reversible oxidation potentials[1] or gas-phase ionization potentials.[2] (ii) In some cases, cyclohexadienone derivatives are formed. These dienones are reactive and polyfunctional and should be useful as intermediates for the synthesis of complex molecules.[3] (iii) In previous works some of the substrates[4] were electrolyzed in methanol, but at controlled potential.[5,6] In our case the electrolyses were at constant current. This method is more simple technically and can be translated easily to large-scale reactions. (iv) These starting materials were readily available and useful in perfume and flavor industry together with some of their derivatives.[7]

Results and Discussion

Anodic methoxylation of anethole yielded *p*-anisaldehyde dimethyl acetal (**1**) and *p*-anisaldehyde methyl orthoester (**2**), products of the electrooxidative bond cleavage of the carbon-carbon double bond and side-chain substitution. Its acidic hydrolysis gave *p*-anisaldehyde and methyl *p*-methoxybenzoate, respectively, which were identified by comparison with authentic samples.

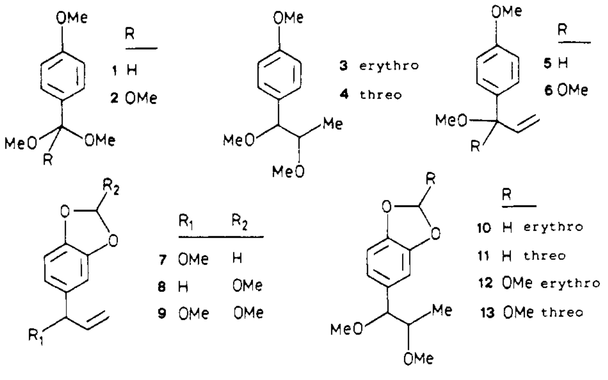
Moreover, new compounds **3** and **4**, products of the addition of methoxy groups to the double bond, were obtained. The ^1H NMR spectrum of compound **3** showed the methyl protons at lower field than those in compound **4**. Comparison of these data with those of the erythro and threo forms of 1,2-disubstituted 1-arylpropanes[8] let us assign for compound **3** the erythro form and for compound **4** the threo one.

Anodic methoxylation of estragole gave, apart the above mentioned compounds **1** and **2**, the side-chain substitution product **5**.[9] Compound **5** undergoes further anodic oxidation to give the new ketal **6**. This point has been verified because compound **6** increased its yield at the same rate that compound **5** decreased it as long as the reaction went on.

Table I. Yields of the Isolated Compounds

	compd	reaction time, min	yield, %
anethole	**1**	30	38
	2	45	11
	3	15	13
	4	15	17
estragole	**1**	15	7
	2	30	3
	5	15	44
	6	30	34
safrole	**7**	15	14
	8	15	2 (10)[a]
	9	15	8
isosafrole	**10**	15	10
	11	15	14
	12	15	3
	13	15	3
eugenol	**14**	20	15
	15	20	5
	16	20	4
isoeugenol	**17**	30	10
	18	30	10
	19	30	5

[a] Using NaMeO as electrolyte.



In the electroodixation of safrole, polymerization on the surface of the anode occurred, with decrease of the current intensity. The reaction afforded the known safrole derivative **7**[10] and the new compounds **8** and **9**.

The ^1H NMR spectrum of compound **8** showed the absence of the characteristic protons of the methylenedioxy group in the 1,3-benzodioxole system; this fact, and the presence of a singlet of a methoxy group, suggested the structure depicted for **8**. Moreover, acidic hydrolysis of compound **8** with concentrated HCl gave 4-allylcatechol, its correspondent hydroquinone, identified by comparison

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0022-3263/90/1955-3270$02.50/0

Table II. Spectral Data of New Compounds[a]

compd	IR ν_{max}, cm^{-1}	^{1}H NMR [δ (ppm), J (Hz)]	EIMS m/z [rel. int. (%)]
3	3060, 2920, 2820, 1600, 1240, 1160, 1080, 1020, 830, 760	7.23 (2 H, d, J = 9), 6.87 (2 H, d, J = 9), 4.10 (1 H, d, J = 5), 3.80 (3 H, s), 3.30 (1 H, m), 3.27 (3 H, s), 3.23 (3 H, s), 1.10 (3 H, d, J = 6)	210 (2), 151 (100), 136 (6), 135 (12), 121 (3), 108 (4)
4		7.20 (2 H, d, J = 9), 6.83 (2 H, d, J = 9), 4.03 (1 H, d, J = 7), 3.80 (3 H, s), 3.40 (3 H, s), 3.33 (1 H, m), 3.03 (3 H, s), 0.90 (3 H, d, J = 6)	
6	3060, 2920, 2820, 1600, 1230, 1160, 1070, 1050, 1020, 920, 820	7.40 (2 H, d, J = 9), 6.83 (2 H, d, J = 9), 5.70 (2 H, m), 5.23 (1 H, dd, J = 9 and 4), 3.80 (3 H, s), 3.13 (6 H, s)	208 (13), 181 (12), 177 (100), 151 (7), 145 (24), 135 (46), 107 (8)
8	3060, 2940, 2820, 1600, 1480, 1440, 1250, 1200, 1090, 1030, 910, 800	6.77 (4 H, m), 5.93 (1 H, m), 5.23–4.87 (2 H, m), 3.40 (3 H, s), 3.30 (2 H, br d, J = 7)	192 (80), 161 (100), 149 (12), 131 (37), 103 (43)
9	3060, 2920, 2820, 1600, 1480, 1430, 1240, 1200, 1080, 1030, 920, 800	6.87 (4 H, m), 5.93 (1 H, m), 5.33–5.10 (2 H, m), 4.53 (1 H, br d, J = 6), 3.40 (3 H, s), 3.30 (3 H, s)	222 (61), 195 (38), 191 (43), 161 (15), 131 (100), 119 (23), 103 (79)
10	3060, 2900, 2820, 1600, 1480, 1430, 1240, 1180, 1030, 930, 810	6.80 (3 H, m), 5.97 (2 H, s), 4.03 (1 H, d, J = 5), 3.33 (1 H, m), 3.30 (3 H, s), 3.23 (3 H, s), 1.13 (3 H, d, J = 6)	224 (5), 165 (100), 150 (16), 149 (12)
11		6.80 (3 H, m), 5.97 (2 H, s), 4.00 (1 H, d, J = 7), 3.47 (1 H, m), 3.40 (3 H, s), 3.23 (3 H, s), 0.90 (3 H, d, J = 6)	
12 and 13			254 (3), 223 (8), 195 (100), 151 (12), 135 (5)

[a] All compounds gave satisfactory combustion analyses.

of its spectral data with those of an authentic sample.

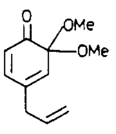
Compound **9** gave a ^{1}H NMR spectrum similar to that of compound **7**, but the signal of the methylenedioxy group was not present and signals of two methoxy groups were present. All this data, and the molecular ion displayed at the mass spectrum, supports the proposed structure for compound **9**.

The reaction of isosafrole afforded the new isomeric addition products **10** and **11**. The erythro and threo isomers were identified in the same way as indicated above for compounds **3** and **4**.

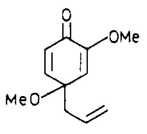
In this reaction were also detected through gas chromatography/mass spectrometry the new compounds **12** and **13**. Their identical mass spectra suggested that these compounds were isomeric erythro and threo forms like compounds **10** and **11** but with another methoxy group. The mass spectral fragmentation pattern supports for compounds **12** and **13** the structure depicted.

The formation of compounds **8**, **9**, **12**, and **13**, involves methoxylation of methylenedioxy units in an uncommon type of anodic methoxylation.

In the anodic methoxylation at constant current of eugenol and isoeugenol, polymerization on the surface of the anode was observed. Oxidation of eugenol gave ketones **14** and **15**, wich were identified by comparison of their ^{1}H NMR spectral data with those of the literature.[5] Also, in the extract of this reaction was isolated the dimeric phenol **16**, which was identified through its melting point and mass spectral data.[5,11]



14



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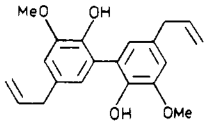
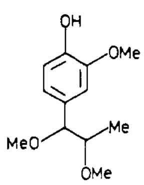


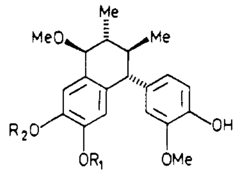
16

The obtention of ketones **14** and **15** could be explained through a classical sequence ECEC,[12] involving the formation of phenoxyl radicals followed by anodic oxidation to phenoxylium ions and methoxide ion trapping. A more recent proposal by Swenton and co-workers[13] for the anodic methoxylation of aromatic methoxylated compounds favors a sequence involving methoxy radical attack on the aryl radical cation, followed by a polar reaction with a methoxide ion (EEC$_r$C$_p$ mechanism).

Reaction with isoeugenol afforded the erythro and threo forms **17** and **18** and the dimeric compound **19**, wich were identified by comparison of their spectral properties with literature data.[6]



17 erythro
18 threo ,



19

R$_1$=H, R$_2$=Me or R$_1$=Me, R$_2$=H

The works of Iguchi and co-workers[5,6] with eugenol and isoeugenol, carried out under chronoamperometric conditions and using LiClO$_4$ as the supporting electrolyte, led to a major proportion of dimeric products. In our case, without accurate potential control, the presence of NaMeO favors a higher proportion of methoxylated products.

We only have obtained dimeric compounds when the substrates were eugenol and isoeugenol. The observation of anodic coupling has been well documented in the literature,[12,14] and different pathways have been proposed. The formation of compounds like **16** is probably due to the dimerization of the anodically generated phenoxy

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radicals. For compound **19**, a mechanistic proposal[6] favors the presence of a dimeric intermediate via C–C bond formation at the side chain in the initial stage.

In Table I are summarized the maximum yield of each compound obtained and the reaction time, and Table II shows the spectral data of the new compounds.

Experimental Section

Apparatus. A Promax generator with a maximum output of 60 V and 2 A was used. GLC analyses were performed on a HP-5890 instrument (OV-101, 25 m × 0.22 mm column) equipped with a flame-ionization detector with N_2 as the carrier gas. Melting points were measured on a Reichert Thermovar hot-stage microscope. IR spectra were obtained on a PYE UNICAM spectrophotometer using films on NaCl crystals. ^1H NMR spectra were recorded on a Varian EM360L (60 MHz) spectrometer; data were obtained from solutions in $CDCl_3$. Chemical shifts are reported as δ values relative to tetramethylsilane as internal reference. Mass spectra were recorded on a HP-5988A GLC/MS instrument at 70 eV (EI).

General Procedure. Electrolyses were carried out in cylindrical, water-refrigerated cells without separate compartments. The temperature was controlled at 30 °C, and stirring was magnetic. A carbon-paste plate was used as the anode and a stainless-steel plate as the cathode. Reactions were carried out under constant current at an anodic current density of 57 mA cm^{-2}. The solvent was always dry methanol (70 mL), and the electrolyte was, in the electrolyses of anethole and estragole sodium methoxide (0.2 g) and in the electrolyses of safrole, isosafrole, eugenol, and isoeugenol, a mixture of sodium methoxide and sodium perchlorate (0.05 g + 0.15 g). Estragole, anethole (3.3×10^{-3} mol), safrole, isosafrole (3×10^{-3} mol), eugenol, or isoeugenol (3.1×10^{-3} mol) was then added.

At the end of each electrolysis the solution was worked up by evaporation of the solvent to dryness under reduced pressure. The brown extract was suspended in 100 mL of water and extracted with ethylic ether (3 × 30 mL). The combined organics were dried with anhydrous Na_2SO_4, and the ether was evaporated at reduced pressure.

Products were isolated by flash chromatography (Merck, SiO_2 60, 9385) using ethyl acetate–hexane (2:98 v/v) as eluent for the extracts from the electrolyses of anethole, estragole, safrole, and isosafrole, and ethyl acetate–hexane (5:95 v/v) for the extracts from eugenol and isoeugenol. Yields were calculated from gas chromatography using cyclohexanone as the internal standard.

Stereoselective Obtention of *trans*-3,6-Dimethoxy-1,3,6-trimethylcyclohexa-1,4-diene by Anodic Methoxylation of Pseudocumene

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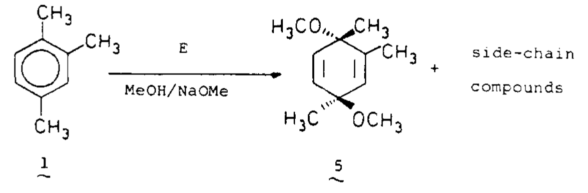
Received October 30, 1989

Anodic oxidation of a methanolic solution of pseudocumene (**1**) in a single-cell apparatus at constant current using sodium methoxide as the supporting electrolyte afforded *trans*-3,6-dimethoxy-1,3,6-trimethylcyclohexa-1,4-diene (**5**). This is the first time that 1,4-addition stereoselectivity has been observed in the anodic oxidation of alkylbenzenes. A rationale is provided.

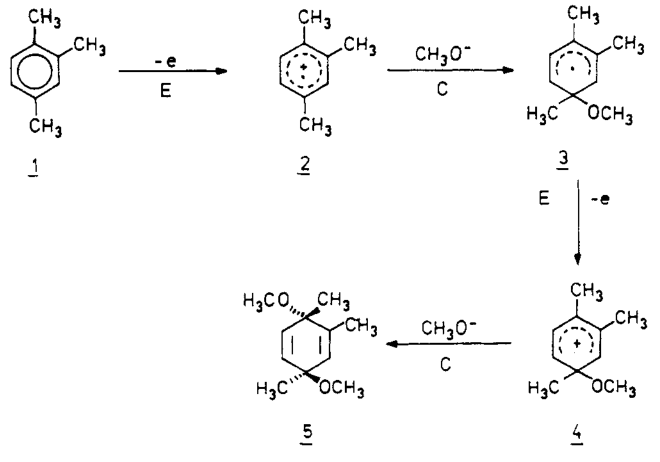
The anodic oxidation of alkylbenzenes in methanol usually gives side chain methoxylated products as well as nuclear-addition products.[1-5]

We have recently studied[1-5] the electrooxidative methoxylation of a series of alkylbenzenes and have found that nuclear-addition products are obtained from unactivated substrates which do not stabilize the cation radical (**2**) electrogenerated (Scheme I). In the substrates previously studied a mixture of the two possible cis, trans isomers was obtained.

Unexpectedly, the anodic methoxylation of pseudocumene (1,2,4-trimethylbenzene) (**1**) afforded only the trans isomer **5**. The structure was assigned by using ^1H NMR data and was supported by chemical mass spectrometry.



Scheme I



Results and Discussion

The anodic oxidation of pseudocumene (**1**) in methanol–sodium methoxide was carried out under constant current intensity. *trans*-3,6-Dimethoxy-1,3,6-trimethylcyclohexa-1,4-diene (**5**) was isolated as the major product (30%), while 4-(dimethoxymethyl)-1,2-dimethylbenzene (7%), 1-(dimethoxymethyl)-2,4-dimethylbenzene (14%), 1,2-dimethyl-4-(trimethoxymethyl)benzene (5%), and 2,4-dimethyl-1-(trimethoxymethyl)benzene (8%) were isolated as side products in a parallel process of side-chain

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