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Electromethoxylation of Diethyl 2-Hydroxyazulene 1,3-Dicarboxylate and 2-Amino-1,3-Dicyanoazulene

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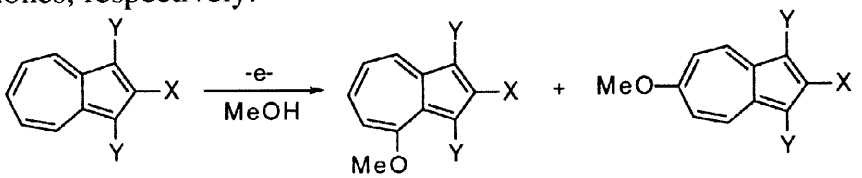
Abstract: A simple new method for methoxylation of 7-membered ring of 1,2,3-trisubstituted azulenes via electrooxidation is reported. It could be useful in preparing 2,4- and 2,6-azuloquinone analogs. © 1998 Elsevier Science Ltd. All rights reserved.

Azulenoids, non-benzenoid hydrocarbons, are essentially used for the dye materials, the medical treatment of inflammation and hypertension and the development of liquid crystals[1]. Recently, azuloquinones being found to reveal significant cytotoxicity in a certain cell-culture screening test[2] were led to much attention. With the theoretical predictions[3], the synthetic attempts had achieved for preparations of six species, i.e. 1,2-, 1,4-, 1,5-, 1,6-, 1,7- and 2,6-AQs of the eleven possible azuloquinones[4]. Several chemical transformations via being introduced two O-containing functional groups in 5- and/or 7-membered ring of azulene analogs were developed. In our continuous study for electrooxidation of azulene compounds[5], this communication describes introduction of methoxy group in 7-membered ring of azulene analogs via electrooxidation, not ordinary chemical methods[4b~g].

First, diethyl 2-hydroxyazulene-1,3-dicarboxylate **1a** and 2-amino-1,3-dicyanoazulene **1b** were synthesized in according to the literatures[6]. The anodic methoxylation of analog **1a** was carried out in methanol solvent by using an undivided cell equipped with platinum-plate electrodes and with constant current[7]. Since analog **1b** can not be completely dissolved in methanol, the cosolvents of methanol with acetone or tetrahydrofuran were used in electrolysis. After electrolysis, the methoxylated products were isolated and were identified by spectroscopies[8](Scheme 1). The results are summarized in Table 1. Analogs **1a** and **1b** were easily undergone methoxylations in position 4 or 6 of azulene ring. The yields of their products seemed to be affected by the supporting electrolytes, better for tetraethylammonium 4-toluene sulfonate as a supporting electrolyte in both cases. The products **2a** and **3a** could be followed through demethylation and oxidation to be converted into the corresponding 2,4- and 2,6-azuloquinones, respectively.



1a. Y=CO_2Et, X=OH
b. Y=CN, X=NH_2

2a. Y=CO_2Et, X=OH
b. Y=CN, X=NH_2

3a. Y=CO_2Et, X=OH
b. Y=CN, X=NH_2

Scheme 1

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Table 1. Reaction conditions and yields for anodic methoxylation of **1a** and **1b**

Reactant	Reaction condition	Products:yields %
1a	Et_4NOTs/MeOH/Pt, 7.5F/mol	2a:1.6, 3a:11.2
1a	$NaClO_4$/MeOH, 6F/mol	2a:3.1, 3a:2.8
1a	NH_4NO_3/MeOH, 10F/mol	2a:1.1, 3a:3.4
1b	Et_4NOTs/MeOH:acetone(1:1)/Pt, 24F/mol	2b:10.0, 3b:16.4
1b	Et_4NOTs/MeOH:THF(1:1)/Pt , 59F/mol	2b:6.1, 3b:16.2
1b	NH_4NO_3/MeOH:THF(1:1)/Pt, 36F/mol	2b:10.3, 3b:14.6

In conclusion, anodic methoxylation is a simple, convenient and selective method for introducing methoxy group into 7-membered ring of azulene analogs when compared to the traditional chemical methods[4b-g].

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7. Typical Electrolysis Procedure: Anodic methoxylation of **1a**(100.0mg, 0.35mmol) was carried out in a 40ml undivided cell equipped with platinum-plate electrodes(2x2cm). Solvent was 20ml of methanol containing Et_4NOTs(0.603g, 2.0mmol) as supporting electrolytes. After 7.5F/mol of electricity was passed with constant current of 10mA under the condition of external cooling(-10°C), the reaction solution was poured into 20ml of water and extracted with chloroform(30ml) twice. The combined organic layer was washed with brine, dried over sodium sulfate and evaporated to remove the solvent. The residue was separated by a silica flash chromatography with an eluent of n-hexane/ethyl acetate(5/1) and a thin-layer chromatography with a developing solvent of n-hexane/ethyl acetate(5/1) four times to give a yellow liquid **2a**(1.8mg, 1.6%) and a yellow crystal **3a**(12.4mg, 11.2%, m.p.160-162°C).
8. **2a**:^{1}HNMR($CDCl_3$, 300MHz): 1.43(t, J=7.2, 3H), 1.49(t, J=7.2, 3H), 4,08(s, 3H), 4.45(q, J=7.2, 2H), 4.49(q, J=7.2, 2H), 7.17(d, J=10.0, 1H), 7.34(t, J=10.0, 1H), 7.58(t, J=10.0), 9.08(d, J=10.0, 2H), 10.79(s, 1H); ^{13}CNMR($CDCl_3$, 75.43MHz): 14.53, 56.65, 60.57, 61.11, 97.36, 98.81, 113.29, 125.20, 133.60, 134.80, 161.39, 166.92; MS(IE, 70ev): m/z(%) 200(100.0), 227(35.0), 272(33.9), 318(M^+, 14.6). **3a**: ^{1}HNMR($CDCl_3$, 300MHz): 1.48(t, J=7.2, 6H), 4.00(s, 3H), 4.50(q, J=7.2, 4H), 7.33(d, J=11.4, 2H), 9.29(d, J=11.4, 2H), 11.39(s, 1H); ^{13}CNMR($CDCl_3$, 75.43MHz): 14.60, 56.23, 60.31, 101.43, 119.08, 134.50, 138.39, 166.19, 166.84, 169.45; MS(EI, 70ev): m/z(%) 200(100.0), 227(42.9), 272(53.5), 318(M^+, 21.1);