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Electrochemical Methoxylation of 1,2,3-Trisubstituted Azulenes

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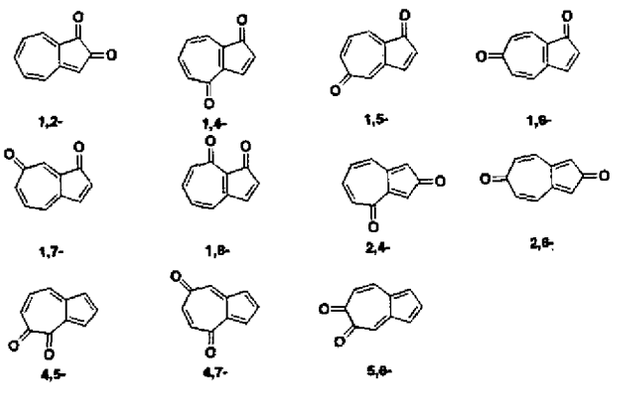
1,2,3-Trisubstituted azulene analogs **6a** and **6b** easily underwent methoxylation in position 4 or 6 of an azulene ring *via* an electrochemical oxidation. It is a simple, convenient and selective method for introducing a methoxy group into a 7-membered ring of azulene analogs when compared with traditional chemical methods. It could be useful in preparing 2,4- and 2,6-azuloquinone analogs.

INTRODUCTION

Azulenoids, a parent structure of bicyclo[5.3.0]decapentaene with 10 π-electrons, are a class of the fused bicyclic compounds, non-benzenoid hydrocarbons. The non-benzenoid hydrocarbons are useful as dye materials, medical treatment of inflammation and hypertension, and the development of liquid crystals.[1] Benzoquinones or quinones of polybenzenoid aromatic hydrocarbons have been known for a long time. Until 1980, Scott et al. reported the results of extensive theoretical calculations on the quinones of azulene and made predictions about their properties.[2] In the same time period, Morita et al. published a synthesis of the first unsubstituted azuloquinone, 1.2-AQ.[3] Recently, azuloquinones being found to reveal significant cytotoxicity in certain cell-culture screening test[4] were led to much attention. In the following years, synthetic attempts had been 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 (Scheme I).[4] Several chemical transformations for introduction of two *O*-containing functional groups in 5- and/or 7-membered ring of azulene analogs by using a series of chemical steps were developed.[5] In our continuous study for electrooxidation of azulene compounds,[6] this paper is reported herein to introduce a methoxy group in a 7-membered ring of 1,2,3-trisubstituted azulene analogs *via* electrooxidation.

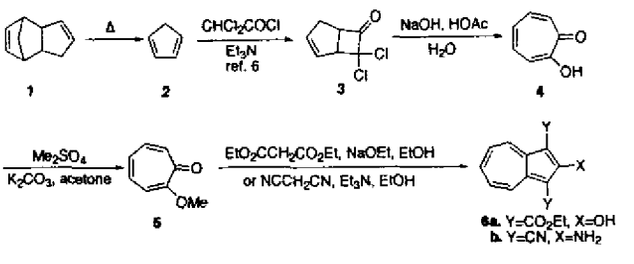
Scheme I



RESULTS AND DISCUSSION

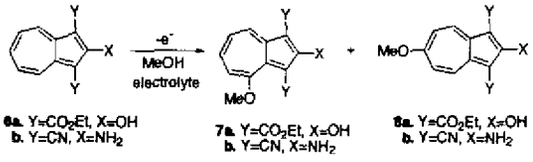
Diethyl 2-hydroxyazulene-1,3-dicarboxylate (**6a**) and 2-amino-1,3-dicyanoazulene (**6b**) were synthesized in the following manner (Scheme II). Cycloadduct **3** was prepared from dicyclopentadiene (**1**) according to procedures in the literature.[7] Tropolone (**4**) was obtained in 87% yield from the reaction of **3** with sodium acetate in aqueous acetic acid.[7] Methylation of **4** with dimethyl sulfate gave 2-methyltropone (**5**) in 74% yield.[8] 2-Methyltropone (**5**) underwent a base-catalyzed condensation with diethyl malonate to give diethyl 2-hydroxyazulene-1,3-dicarboxylate (**6a**) in 51% yield.[9] 2-Amino-1,3-dicyanoazulene (**6b**) was obtained from treatment of methyltropone (**5**) and malononitrile in the presence of triethylamine in 23% yield.[10]

Scheme II



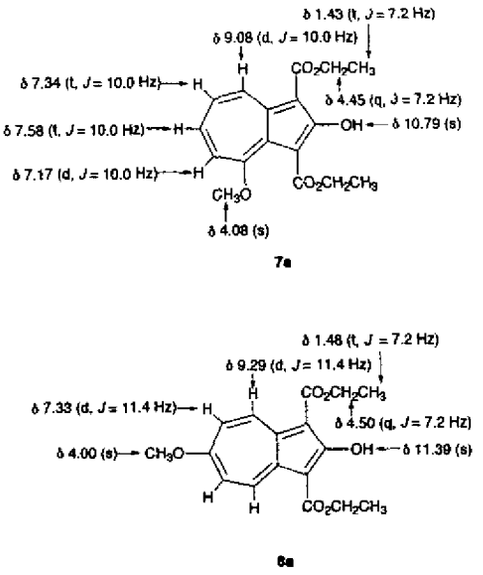
The anodic methoxylation of diethyl 2-hydroxyazulene-1,3-dicarboxylate (**6a**) was carried out in methanol by using an undivided cell with platinum-plate electrodes and with constant current to afford two products **7a** (yellow liquid) and **8a** (yellow crystal, mp 160-162 °C), as shown in Scheme III. As shown in Table 1, the yields of anodic

Scheme III



methoxylation of **6a** seemed to be affected by the supporting electrolytes. The products formed in the reaction condition of Et_4NOTs/MeOH/Pt were 1.6% of **7a** and 11.2% of **8a** (Entry 1). But the desired products **7a** and **8a** were not produced in the following reaction conditions: NaOMe/MeOH/Pt and NaOMe/Et_4NOTs/MeOH/Pt. The molecular formulas of compounds **7a** and **8a** were the same, $C_{17}H_{18}O_6$, from their mass spectra. The ^1H NMR spectrum of **7a** showed a singlet at δ 4.08 (3H) for a methoxy group at the position 4 of an azulene ring, two doublets at δ 7.17 (1H, J = 10.0 Hz) and δ 9.08 (1H, J = 10.0 Hz) for the protons at the positions 5 and 8 and two triplets at δ 7.34 (1H, J = 10.0 Hz) and δ 7.58 (1H, J = 10.0 Hz) for the protons at the positions 7 and 6 of an azulene ring and a singlet at δ 10.79 (1H) for an OH group (Scheme IV). The ^{13}C NMR spectrum (DEPT) of **7a** showed an additional peak at 56.6 ppm for a methoxy group in comparison with that of **6a**. The ^1H NMR of **8a** also had a singlet at δ 4.00 (3H) for a methoxy group at the position 6 of an azulene ring, two doublets at δ 7.33 (2H, J = 11.4 Hz) and δ 9.29 (2H, J = 11.4 Hz) for the protons at the positions 4, 5, 7 and 8 of an azulene ring and a singlet at δ 11.39 (1H) for an OH group (Scheme IV). Since analog **6b** can not be completely dissolved in methanol, the cosolvents of methanol with acetone or tetrahydrofuran were used in the electrolysis. Similarly, the anodic methoxylation of 2-amino-1,3-dicyanoazulene (**6b**) gave 4- and 6-methoxy azulene analogs (Scheme III). As shown in Table 1, the reaction condition of Et_4NOTs/MeOH:Acetone (1:1)/Pt afforded higher yield of products **7b** (10.0%) and **8b** (16.4%) (Entry 4). The proposed mechanism for anodic methoxylation of diethyl 2-hydroxyazulene-1,3-dicarboxylate **6a** was shown in Scheme V. The key intermediate cation **III** was formed

Scheme IV



from **6a** by losing two electrons and a proton of hydroxyl group.[11] The cation **III** was coupled with methanol at the positions 4 or 6 of an azulene ring to give two isomeric ketocarboxylates **IV** and **V**, which subsequently lost a proton to yield diethyl 2-hydroxy-4-methoxyazulene-1,3-dicarboxy-

Scheme V

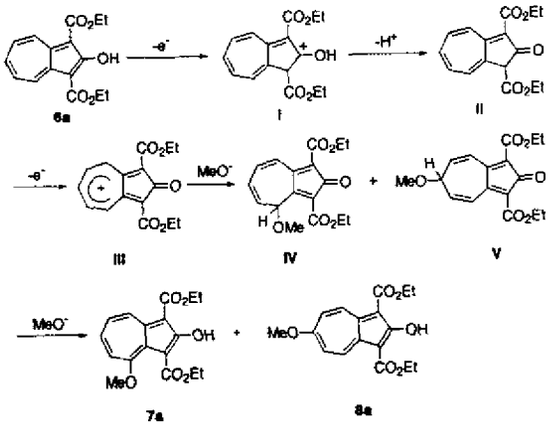


Table 1. Reaction Conditions and Yields for Anodic Methoxylation of **6a** and **6b**

Entry	Reactant	Reaction Condition	Products:Yields %
1	**6a**	Et_4NOTs/MeOH/Pt, 7.5F/mol	**7a**:1.6, **8a**:11.2
2	**6a**	$NaClO_4$/MeOH, 6F/mol	**7a**:3.1, **8a**:2.8
3	**6a**	NH_4NO_3/MeOH, 10F/mol	**7a**:1.1, **8a**:3.4
4	**6b**	Et_4NOTs/MeOH:Acetone(1:1)/Pt, 24F/mol	**7b**:10.0, **8b**:16.4*
5	**6b**	Et_4NOTs/MeOH:THF(1:1)/Pt, 59F/mol	**7b**:6.1, **8b**:16.2*
6	**6b**	NH_4NO_3/MeOH:THF(1:1)/Pt, 36F/mol	**7b**:10.3, **8b**:14.6*

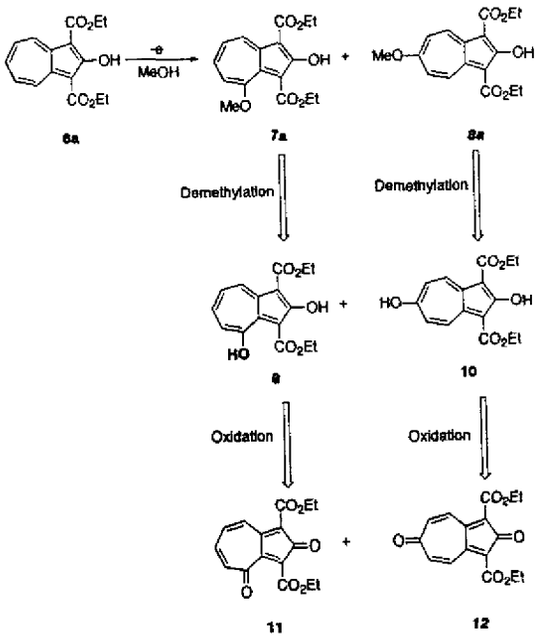
* The yields of products were determined by using ^1H NMR.

late **7a** and diethyl 2-hydroxy-6-methoxyazulene-1,3-dicarboxylate **8a**, respectively.

CONCLUSION

1,2,3-Trisubstituted azulene analogs **6a** and **6b** easily underwent methoxylations in position 4 or 6 of an azulene ring *via* an electrochemical oxidation, which is a simple, convenient and selective method for introducing a methoxy group into a 7-membered ring of azulene analogs. Azuloquinones have been found to exhibit significant antitumor activity, especially in cytotoxicity which is similar to benzoquinones.[4] The products **7a** and **8a** could possibly be prepared through demethylation[12] and oxidation[5f,13] to give the corresponding 2,4- and 2,6-azuloquinone, respectively (Scheme VI).

Scheme VI



EXPERIMENTAL SECTION

General

The melting points were measured without correction on a Yanagimoto Micromelting Point Apparatus. Infrared spectra were recorded on a Nicolet 550 FT-IR spectrophotometer. Absorption spectra were recorded on a Hewlett Packed HP8452A photodiode-array spectrophotometer. ^{1}H and ^{13}C nuclear magnetic resonance spectra were measured on a Varian VXR-300 and Bruker ACF-300 spectrometers. Mass spectra were determined on a VG Quattro GC/MS/MS DS spectrometer. Elemental analyses were measured on a Heraeus CHN-O-Rapid Analyzer. Cyclic voltammograms were measured on a BAS 100B/W cyclic voltammeter. Tetraethylammonium 4-toluenesulfonate (Et_4NOTs), sodium methoxide (NaOMe) and sodium perchlorate ($NaClO_4$) were purchased from Janssen Chemia Co. and used without further purification. Dicyclopentadiene, dichloroacetyl chloride, triethylamine, dimethyl sulfate and diethyl malonate were purchased from Merck Co. and purified by distillation before use. Sodium ethoxide and ammonium nitrate were obtained from Aldrich Co. without further purification.

Tropolone (4)

Cycloadduct (**3**) (15.0 g, 0.085 mol) was added to a solution of glacial acetic acid (85 mL), sodium hydroxide (16 g, 0.4 mol) and water (10 mL) in a 250 mL flask. The reaction solution was refluxed for 7 h at 130 °C in an oil bath. After cooling to room temperature, 100 mL of water was added. The solution was neutralized to pH 4-6 by sodium hydroxide. Then the solution was extracted with 300 mL of chloroform four times. The chloroform layer was washed with brine, dried over sodium sulfate and evaporated to give the residue which was recrystallized from *n*-hexane to give a light-yellow crystal (**4**) (9.0 g, 87% yield) with mp 47-50 °C. UV (CCl_4, nm): 258 (ε 6.31 × 10^4), 294 (ε 2.35 × 10^4), 306 (ε 2.62 × 10^4), 320 (ε 2.33 × 10^4), 342 (ε 1.51 × 10^4), 356 (ε 1.78 × 10^4), 374 (ε 1.54 × 10^4); ^{1}H NMR ($CDCl_3$, 300 MHz): 7.02-7.08 (m, 2H), 7.32-7.44 (m, 3H), 9.15 (br, 1H); ^{13}C NMR ($CDCl_3$, 75.43 MHz): 123.9, 128.2, 137.7, 171.8; MS (EI, 70 eV): *m/z* (%) 122 (M^+, 62), 94 (100).

2-Methoxytropone (5)

Tropolone (**4**) (30 g, 0.246 mol) was added to a solution of potassium carbonate (101.8 g, 0.738 mol), dimethyl sulfate (37 g, 0.295 mol) and 200 mL of 90% acetone aqueous solution in a 500 mL two-neck flask. After refluxing for 3 h in a water bath, the reaction solution was stirred at room temperature overnight. The solution was filtered and the residue was washed with acetone. The combined filtrate was washed with water, dried over sodium sulfate and evaporated to remove the solvent. The residue was distillated under reduced pressure to yield 2-methoxytropone (**5**) (24.77 g, 74% yield) with bp 128 °C/5 torr. UV (CCl_4, nm): 260 (ε 1.26 × 10^5), 280 (ε 5.68 × 10^5); IR (CCl_4, cm^{-1}): 2920, 1627, 1590, 1549, 1469, 1275, 1226, 1165, 1077, 989, 947; ^{13}C NMR ($CDCl_3$, 75.43 MHz): 55.2, 112.1, 127.3, 132.3, 135.8; MS (EI, 70 eV): *m/z* (%) 136 (M^+, 77), 106 (100).

Diethyl 2-Hydroxyazulene-1,3-dicarboxylate (6a)

A solution of 2-methoxytropone (**5**) (13.6 g, 0.1 mol), diethyl malonate (480 g, 0.3 mol), sodium ethoxide (34.0 g, 0.5 mol) and ethanol (300 mL) in a 500 mL flask was stirred for 40 h at room temperature. To the reaction solution was added 500 mL of water and then filtered. The precipitate was dissolved in 100 mL of glacial acetic acid, diluted with 100 mL of water and then extracted with 100 mL of chloroform four times. The organic layer was evaporated to remove the solvent. The residue was recrystallized from ethanol to give an orange-yellow crystal (**6a**) (14.8 g, 51% yield) with mp 101-102 °C. UV (CCl_4, nm): 280 (ε 5.74×10^5); IR (KBr, cm^{-1}): 3470, 3055, 2925, 2805, 1673, 1636, 1595, 1529, 1472, 1431, 1378, 1281, 1181, 1180, 1127, 1033, 794, 732; ^{1}H NMR ($CDCl_3$, 300 MHz): 1.50 (t, J = 7.2 Hz, 6H), 4.52 (q, J = 7.2 Hz, 4H), 7.72-7.74 (m, 3H), 9.36-9.40 (m, 2H), 11.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.43 MHz): 14.5, 60.5, 108.0, 132.4, 134.7, 136.1, 137.0, 143.3, 172.2; MS (EI, 70 eV): *m/z* (%) 288 (M^+, 13), 242 (24), 197 (44), 170 (100).

2-Amino-1,3-dicyanoazulene (6b)

A solution of malononitrile (19.4 g, 0.294 mol), triethylamine (29.7 g, 0.294 mol) and ethanol (300 mL) in a 500 mL flask was stirred for 4 h at room temperature. The reaction mixture was filtered. The precipitate was washed by using ethanol, water and acetone subsequently to give 2-amino-1,3-dicyanoazulene (**6b**) (23% yield). IR (KBr, cm^{-1}): 3340, 3205, 2185, 1664, 1546, 1505, 1424, 740; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.58-7.70 (m, 3H), 7.96-7.99 (m, 2H), 8.08 (br, 2H); ^{13}C NMR ($CDCl_3$, 75.43 MHz): 81.5, 115.3, 128.9, 133.1, 133.9, 146.5, 160.4.

Typical Anodic Methoxylation of Diethyl 2-Hydroxyazolene-1,3-dicarboxylate (6a)

Anodic methoxylation of **6a** (100.0 mg, 0.35 mmol) was carried out in a 40 mL undivided cell equipped with platinum-plate electrodes (2 × 2 cm). The solution contained 20 mL of methanol and Et_4NOTs (0.603 g, 2.0 mmol) used as supporting electrolytes. After 7.5 F/mol of electricity was passed with constant current of 10 mA under the condition of external cooling (-10 °C), the reaction solution was poured into 20 mL of water and extracted with chloroform (30 mL) 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 gel 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 (**7a**) (1.8 mg, 1.6% yield) and a yellow crystal (**8a**) (12.4 mg, 11.2% yield, mp 160-162 °C); **7a**: IR (CCl_4, cm^{-1}): 3440, 2920, 2850, 1720, 1645, 1530, 1456, 1374, 1250, 1179; ^{1}H NMR ($CDCl_3$, 300 MHz): 1.43 (t, J = 7.2 Hz, 3H), 1.49 (t, J = 7.2 Hz, 3H), 4.08 (s, 3H), 4.45 (q, J = 7.2 Hz, 2H), 4.49 (q, J = 7.2 Hz, 2H), 7.17 (d, J = 10.0 Hz, 1H), 7.34 (t, J = 10.0 Hz, 1H), 7.58 (t, J = 10.0 Hz, 1H), 9.08 (d, J = 10.0 Hz, 2H), 10.79 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.43 MHz): 14.5, 56.6, 60.5, 61.1, 97.3, 98.8, 113.2, 125.2, 133.6, 134.8, 161.3, 166.9; MS (EI, 70 eV): *m/z* (%) 318 (M^+, 14), 272 (34), 227 (35), 200 (100); Found: C, 63.78; H, 5.46%. Calcd for $C_{17}H_{18}O_6$: C, 64.13; H, 5.70%. **8a**: IR (KBr, cm^{-1}): 3445, 2940, 2830, 1666, 1620, 1530, 1530, 1470, 1450, 1344, 1286, 1210, 1183; ^{1}H NMR ($CDCl_3$, 300 MHz): 1.48 (t, J = 7.2 Hz, 6H), 4.00 (s, 3H), 4.50 (q, J = 7.2 Hz, 4H), 7.33 (d, J = 11.4 Hz, 2H), 9.29 (d, J = 11.4 Hz, 2H), 11.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.43 MHz): 14.6, 56.2, 60.3, 101.4, 119.0, 134.5, 138.3, 166.1, 166.8, 169.4; MS (EI, 70 eV): *m/z* 318 (M^+, 21), 272 (54), 227 (43), 200 (100); Found: C, 63.82; H, 5.52%. Calcd for $C_{17}H_{18}O_6$: C, 64.13; H, 5.70%. **7b**: IR (KBr, cm^{-1}): 3341, 3207, 2950, 2835, 1660, 1524, 1500, 1420, 1247, 1040, 784, 754; ^{1}H NMR ($CDCl_3$, 300 MHz): 4.20 (s, 3H), 5.38 (br, 2H), 7.40 (d, J = 12.3 Hz, 1H), 7.61 (m, 1H), 8.16 (d, J = 12.3 Hz, 1H); Found: C, 69.33; H. 3.32; N, 12.14%. Calcd for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.60; N, 12.49%. **8b**: IR (KBr, cm^{-1}): 3340, 3212, 2952, 2815, 1661, 1514, 1505, 1422, 1243, 1030, 774, 744; ^{1}H NMR ($CDCl_3$, 3000 MHz): 4.00 (s, 3H), 5.28 (br, 2H), 7.64 (d, J = 11.7 Hz, 2H), 8.10 (d, J = 11.7 Hz, 2H). Found: C, 69.28; H, 3.27; N, 12.15%. Calcd for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.60; N, 12.49%.

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Key Words

Azulenes; Azuloquinone; Anodic Methoxylation.

REFERENCES

1. Muller, E. *Mothoden der Organishen Chemie*, Georg Thieme Verlag, Stuttgart, **1985**, pp 127-417.
2. Scott, L. T.; Rozeboom, M. D.; Houk, K. N.; Fukunaga,

T.; Lindner, H. J.; Hafner, K. *J. Am. Chem. Soc.* **1980**, *102*, 5169.

3. Morita, T.; Karasawa, M.; Takase, K. *Chem. Lett.* **1980**, 197.
4. (a) Coll, J. S.; Hazard, F.; Wood, H. B.; Goldin, A. *Cancer Chemther. Rep.* **1974**, *4(2)*, 1. (b) Driscoll, J. S.; Hazard, F.; Wood, H. B.; Goldin, A. *Cancer Chemther. Rep.* **1974**, *4(4)*, 1.
5. (a) Nozoe, T.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1149. (b) Morita, T.; Takase, K. *Chem. Lett.* **1977**, 513. (c) Morita, T.; Ise, F.; Takase, K. *Chem. Lett.* **1982**, 1303. (d) Scott, L. T. *Pure & Appl. Chem.* **1983**, *55*, 363. (e) Scott, L. T.; Grutter, P.; Chamberlain, R. E. *J. Am. Chem. Soc.* **1984**, *106*, 4853. (f) Scott, L. T.; Adams, C. M. *J. Am. Chem. Soc.* **1984**, *106*, 4857.
6. (a) Chen, A. H.; Yang, C. H.; Morita, T. *Chemistry (Chin. Chem. Soc.)* **1995**, *53*, 115. (b) Chen, A. H.; Nozoe, T. *Tetrahedron Lett.* **1998**, *39*, 7511. (c) Chen, A. H. *Proc. Natl. Sci. Counc. ROC(A)* **1999** (in press).
7. Stevens, H. C.; Reich, D. A.; Brandt, D. R.; Fountain, K. R.; Gaughan, E. J. *J. Am. Chem. Soc.* **1965**, *87*, 5257.
8. Tachibana, T. "Shin-jikkenkagaku-koza", 14, Ed. by Mukai. T. *Syntheses and Reaction of Organic Compounds II.* Maruzenshoten, Tokyo, **1975**, Takase, K., Chap. 4-5, pp 917.
9. Nozoe, T.; Takase, K.; Shimazaki, N. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 1644.
10. Nozoe, T.; Seto, S.; Matsumura, S.; Murase, Y. N. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1179.
11. (a) Lund, H.; Baizer, M. M. *Organic Electrochemistry*, Maecell Dekker, **1991**, pp 616-628. (b) Bailey, S. I.; Ritchie, I. M.; Hewgill, F. R. *J. Chem. Soc., Perkin Trans II* **1983**, 645. (c) Richards, J. A.; Whitson, P. E.; Evans, D. H. *J. Electroanal. Chem.* **1975**, *63*, 311. (d) Richards, J. A.; Evans, D. H. *J. Electroanal. Chem.* **1977**, *81*, 171. (e) Speiser, B.; Reiker, A. *J. Electroanal. Chem.* **1979**, *102*, 373. (f) Evans, D. H.; Jimenez, P. J.; Kelly, M. J. *J. Electroanal. Chem.* **1984**, *163*, 145.
12. (a) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761. (b) Vickery, E. H.; Pahler, L. F.; Eisenbraun, E. J. *J. Org. Chem.* **1979**, *44*, 4444.
13. Kasturi, T. R.; Jayaram, S. K.; Sattigeri, J. A.; Pragnacharyulu, P. V. P.; Row, T. N. G.; Renuka, K.; Venkatesan, K.; Begum, N. S.; Munirathinam, N. *Tetrahedron* **1993**, *49*, 7145.