CCA-1885

Electrochemical Synthesis of Heterocyclic Compounds. Part 21.[1] Anodic Oxidation of 1-Arylmethylenesemicarbazides in Methanol

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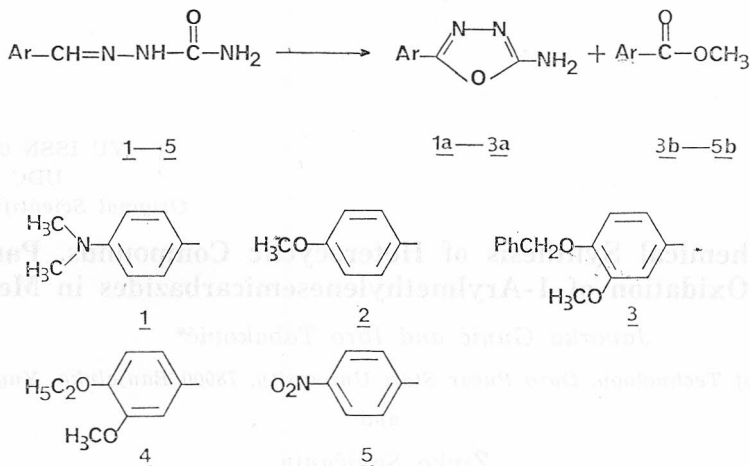*Medical Faculty, Đuro Pucar Stari University, 78000 Banjaluka, Yugoslavia*

Anodic oxidation of 1-arylmethylenesemicarbazides (*1—5*) was performed in methanol-tetraethylammonium perchlorate electrolyte solution by constant-current electrolysis. As a result of anodic oxidation, the corresponding oxadizoles (*1a—3a*) were isolated in good yields, ranging from 51 to 65%. The anodic oxidation represents a novel efficient conversion of an aromatic aldehyde to an aromatic methyl ester (*3b—5b*) through oxidation of its semicarbazones.

We have shown[2-7] in previous investigations that the anodic oxidation of compounds having an azomethine function led to different products depending on the structure of the starting compounds and solution conditions. Hammerich and Parker[8] reported anodic cyclization of 1-arylmethyelene-semicarbazides to the corresponding oxadiazoles in high yield by using canstant current electrolysis in acetic acid-sulphuric acid media. However, in our hands this reaction resulted in a mixture of at least four products (TLC) and the oxadiazoles were isolated in 10—20% yield. Having in mind that anodic oxidation of hydrazones in the presence of nucleophiles gave different reaction products[9], we examined in the present research anodic oxidation of 1-arylmethylenesemicarbazides in methanol as a nucleophilic solvent.

RESULTS AND DISCUSSION

Anodic oxidations of 1-arylmethylenesemicarbazides (*1—5*) was typically performed in a methanol solution containing tetraethylammonium perchlorate (0.1 M). Constant-current electrolysis was carried out until all starting 1-aryl-methylenesemicarbazide was consumed, as determined by TLC. All electrochemical syntheses were performed in a divided cell at Pt-gauze anode and Ni cathode to high yield of oxadiazoles (*1a—3a*) and/or aromatic methyl esters (*3b—5b*) according to Scheme 1.

$$Ar-CH=N-NH-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2 \longrightarrow Ar-\langle\overset{N-N}{\underset{O}{\bigcirc}}\rangle-NH_2 + Ar-\overset{\overset{\displaystyle O}{\|}}{C}-OCH_3$$

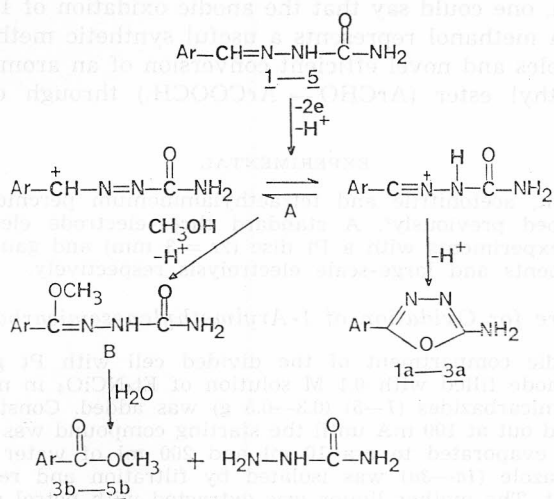1—5   1a—3a   3b—5b

Scheme 1

Voltametric and preparative data for the anodic oxidation of 1-aryl-methylenesemicarbazides (1—5) are given in Table I. Cyclic voltammograms showed irreversible waves for sweep rates from 0.02 to 1.0 Vs^{-1}. The value of the peak potential changes in a manner consistent with donor or acceptor capability of the substituted aryl group. The current functions, $i_p/v^{1/2} C$, were constant with sweep rates and showed two-electron behaviour by comparison of the values of the current function with that obtained for tris-(4-bromo-phenyl)amine, a compound known to undergo one electron oxidation[10]. Coulometry at 0.7V vs. SCE of 1 in acetonitrile —0.1 M tetraethylammonium perchlorate solution shows that the overall electrode reaction is a two-electron oxidation. The oxidation product (1a) precipitated during the reaction and was isolated by filtration in 60% yield. All other preparative oxidations were carried out under constant-current electrolysis in methanol —0.1 M tetraethylammonium perchlorate solution and the results are presented in Table I. All product were verified by IR, NMR and MS spectral analysis.

TABLE I

Electroanalytical and Preparative Data

Compound	E_p [a] (V vs. SCE)	Yield of products/%		Current yield/%
		Oxadiazole 1a—3a	Methyl ester 3b—5b	
1	0.72	52	—	71
2	1.16	65	—	75
3	1.30	51	38	95
4	1.25	—	80	90
5	1.78	—	55	96

[a] Sweep rate, 0.1 V/s, concentration of 1-arylmethylenesemicarbazides, 10^{-3} M; CH_3CN-0.1 M Et_4NClO_4; Pt electrode.

Oxidation of 1-arylmethylenesemicarbazides is initiated by the rapid formation of cation A through two electron and one proton loss (Scheme 2.).

$$Ar-CH=N-NH-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2$$
$$\underline{1-5}$$
$$\downarrow \begin{array}{c} -2e \\ -H^+ \end{array}$$

$$\overset{+}{Ar-CH}-N=N-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2 \rightleftharpoons Ar-C\equiv\overset{+}{N}-\overset{\overset{\displaystyle H}{|}}{N}-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2$$
$$A$$

$$CH_3OH$$ $$-H^+$$ $$-H^+$$

$$\overset{\overset{\displaystyle OCH_3}{|}}{Ar-C}=N-NH-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2 \qquad Ar\underset{O}{\overset{N-N}{<}}NH_2$$
$$B \qquad\qquad 1a-3a$$

$$\downarrow H_2O$$

$$Ar-\overset{\overset{\displaystyle O}{\|}}{C}-OCH_3 + H_2N-NH-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2$$
$$3b-5b$$

Scheme 2.

Deprotonation of cation A should enhance cylization to oxadizole through the formation of the dipolar ion, as postulated by Scott and coworkers[11]. Such a mechanism was ruled out by Hammerich and Parker[8]. It is well established that the oxidation of hydrazones in neutral, acid and basic solution occurs also through the formation of the cation as an intermediate and not through the dipolar nitrilimine.[9]. Hammerich and Parker concluded that the intramolecular cyclization of cation A is a very rapid reaction. They offered an alternative pathway which might be expected to favour the formation of oxadizole by nucleophilic attack of water on cation A, which is followed by cyclization. In order to test this possibility, we ran the cyclic voltammetry of 1 in the presence of activated alumina[12], e. g. under super dry conditions in $CH_3CN-Et_4NClO_4$ solution, but cyclic voltammetry failed to show any reduction peak due to the formation of A. This experiment is in line with the conclusion that the oxadiazoles (1a—3a) are formed through intramolecular cyclization of cation A.

Cation A is liable to nucleophilic attack by the methanol present, leading to semicarbazide B, which is hydrolyzed by water, leading to loss of the semicarbazide, which was detected by TLC, and aromatic methyl esters (3b—5b).

The reaction selectivity of the anodic oxidation of 1-arylmethylenesemicarbazides in methanol, e. g. the formation of oxadiazole vs. aromatic methyl esters, remains unsettled at present. It seems that the stability and/or suitable conformation of cation A in solution might play the main role if the reaction occurs through intramolecular or intermolecular nucleophilic attack. Similar differences in the oxidation of 1-arylmethylenesemicarbazide with lead tetraacetate on the formation of the reaction products, depending on the donating capability of the substituents on aryl group, were observed[13].

Further work on the anodic oxidation of 1-arylmethylenesemicarbazides in the presence of heteroaromatic basis is in progress in our laboratory.

In conclusion, one could say that the anodic oxidation of 1-arylmethylene-semicarbazides in methanol represents a useful synthetic method for the synthesis of oxadiazoles and novel efficient conversion of an aromatic aldehyde to an aromatic methyl ester (ArCHO → ArCOOCH$_3$) through oxidation of its semicarbazone.

EXPERIMENTAL

The equipment, acetonitrile and tetraethylammonium perchlorate purification have been described previously[9]. A standard three-electrode electrochemical cell was used for all experiments with a Pt disc (2r = 3 mm) and gauze (3 × 5 cm) for analytical experiments and large-scale electrolysis respectively.

General Procedure for Oxidation of 1-Arylmethylenesemicarbazides (1—5)

Into the anodic compartment of the divided cell with Pt gauze (3 × 5 cm) anode and Ni cathode filled with 0.1 M solution of Et$_4$NClO$_4$ in methanol (100 ml) 1-arylmethylenesemicarbazides (1—5) (0.3—0.5 g) was added. Constant-current electrolysis was carried out at 100 mA until the starting compound was consumed (TLC). The solution was evaporated to cca 10 ml and 200 ml of water was added. The precipitated oxadiazole (1a—3a) was isolated by filtration and recrystallized from appropriate solvent. The mother liquor was extracted with petrol ether (3 × 40 ml). The extracts were washed several times with water. After drying (MgSO$_4$), the (3b—5b) which was recrystalized from appropriate solvent.

2-Amino-5-(4-N,N-dimethylamino)phenyl-1,3,4-oxadiazole, 1a

m. p. 277—279° (acetonitrile); IR (KBr) 3300, 3095, 1645, 1600, 1375, 1205, 1030, 955, 815 cm^{-1}; NMR (DMSO-d$_6$) 3.0 (s, 6H, (CH$_3$)$_2$N); 6.75 (s, 2H, NH$_2$); 6.95 and 7.25 (AA'BB' system, 8H, Ar) ppm; MS, m/e (relative intensity) 204(100), 161(9.5), 160(20.1), 149(54), 145(13.5), 132(14), 118(6.5), 105(4.5), 91(4), 77(6.5).

Anal. for C$_{10}$H$_{12}$N$_4$O (204.23) calc'd.: C 58.81, H 5.92, N 27.43%
found: C 58.95, H 5.98, N 27.01%.

2-Amino-5-(4-methoxy)phenyl-1,2,4-oxadiazole, 2a

m. p. 250—251° (ethyl acetate). lit.[14] m. p. 251—253°; IR (KBr) 3300, 3105, 1650, 1600, 1500, 1295, 1260, 1185, 1030, 840 cm^{-1}; NMR (CDCl$_3$) 3.8 (s, 3H, CH$_3$O); 7.2 (s, 2H, NH$_2$); 7.10 and 7.75 (AA'BB' system, 8H, Ar) ppm; MS, m/e (relative intensity) 191(100), 162(4), 149(4.5), 148(26), 135(38), 133(71), 107(13), 105(27), 92(18), 77(23.5).

2-Amino-5-(3-methoxy-4-benzyloxy)phenyl-1,3,4-oxadiazole, 3a

m. p. 214—215° (benzene); IR (KBr) 3320, 3050, 2940, 1650, 1580, 1300, 1280, 1250, 1225, 1150, 1085 cm^{-1}; NMR (CDCl$_3$) 3.55 (s, 3H, CH$_3$O); 5.2 (s, 2H, CH$_2$), 6.9 (s, 2H, NH$_2$); 7.1—7.6 (m, 8H, Ar) ppm; MS, m/e (relative intensity) 297(6), 206(12), 163(4), 92(10), 91(100), 77(5), 74(6), 65(16).

Anal for C$_{16}$H$_{15}$N$_3$O$_3$ (297.31) calc'd.: C 64.64, H 5.05, N 14.48%
found: C 64.55, H 5.11, N 14.27%.

Methyl 3-methoxy-4-bezyloxybenzoate, 3b

m. p. 69—71° (benzene); IR (KBr) 2920, 1700, 1585, 1500, 1340, 1295, 1270, 1215, 1180, 990, 880, 855, 765, 750, 700 cm^{-1}; NMR (CDCl$_3$) 3.90 (s, 3H, CH$_3$O); 3.95 (s, 3H, CH$_3$O); 5.25 (s, 2H, CH$_2$); 7.25—7.75 (m, 8H, Ar) ppm; MS, m/e (relative intensity) 272(15), 257(5), 111(5), 97(15), 91(100), 83(10), 69(9), 65(7).

Anal. for C$_{16}$H$_{16}$O$_4$ (272.28) calc'd.: C 70.58, H 5.92%
found: C 70.31, H 5.72%.

Methyl 3-methoxy-4-ethoxybenzoate, 4b

m.p. 78—79° (methanol); IR (KBr) 2930, 1700, 1590, 1505, 1435, 1340, 1290, 1260, 1220, 1180, 1130, 1030, 875, 825, 780, 765 cm^{-1} NMR (CDCl$_3$) 1.5 (t, 3H, CH$_3$); 3.9 (s, 3H, CH$_3$O); 3.95 (s, 3H, CH$_3$O); 4.17 (q, 2H, CH$_2$) 6.75—7.75 (m, 3H, Ar) ppm; MS, *m/e* (relative intensity) 210(78), 183(6), 182(55), 179(14), 167(9), 151(100), 123(8), 79(2).

Anal. for C$_{11}$H$_{14}$O$_4$ (210.22) calc'd.: C 62.85; H 6.71%
found: C 62.53, H 6.48%.

Methyl 4-nitrobenzoate, 5b

m. p. 86—88° (methanol); lit.[15] m.p. 96°; IR (KBr) 1710, 1600, 1520, 1435, 1350, 1275, 1105, 830 cm^{-1}; NMR (CDCl$_3$) 4.0 (s, 3H, CH$_3$O); 8.2 and 8.65 (AA'BB' system, 4H, Ar); MS, *m/e* (relative intensity) 181(53), 166(5), 164(8), 150(100), 135(8), 120(19), 104(21), 92(16), 76(21).

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SAŽETAK

Elektrokemijska sinteza heterocikličkih spojeva. Dio 21. Anodna oksidacija 1-arilmetilensemikarbazida u metanolu

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Anodna oksidacija 1-arilmetilensemikarbazida (*1—5*) izvršena je u elektrolitskoj otopini metanol-tetraetilamonijev perhlorat pri konstantnoj gustini struje. Kao rezultat anodne oksidacije izolirani su odgovarajući oksadiazoli (*1a—3a*) u dobrom iskorištenju od 51 do 65%. Anodna oksidacija predstavlja novu i efikasnu konverziju aromatskih aldehida u aromatske metilestere (*3b—5b*) oksidacijom njihovih semikarbazona.