Notes

A Novel and Convenient Electrochemical Synthesis of 3,7-Diaryl-2*H*-imidazo[2,1-*b*][1,3,4]oxadiazines

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It is well known that the cathodic reduction of phenacyl bromides in aprotic media leads in very good yields to the formation of 2,4-diarylfurans.[1] This occurs via the cleavage of the carbon–bromine bond, giving an anion[2,3] that adds to the carbonyl group of another molecule of substrate adsorbed on the surface of the electrode (mercury pool). However this reaction is highly dependent on the substrate concentration in the reaction medium. At very low concentrations of substrate, the reaction takes a different course. The electrogenerated anion desorbs from the electrode surface and, in solution, acts as a base.[4,5] On the other hand, if the carbonyl group of the phenacyl bromide is protected by formation of the corresponding semicarbazone, production of the dimeric semicarbazone takes place by cathodic reduction, in almost quantitative yield.[6]

As part of our recent investigations, we have carried out the cathodic reduction of semicarbazones of phenacyl bromides at very low concentrations of substrate. Under these conditions a facile and clean synthesis of 3,7-diaryl-2*H*-imidazo[2,1-*b*][1,3,4]oxadiazines has been achieved (Scheme I).

The [1,3,4]oxadiazines have proven to be of great utility. They are used in shampoos,[7] hair and skin cosmetics,[8] polycarbonate foams,[9] and in pharmaceutical preparations such as cardiotonics,[10] antihypertensives,[10,11] inhibitors of platelet aggregation activity,[11] anticholesteremics,[12] etc. Some of them have bactericidal or antiviral activity.[13–16] Limited general synthetic methods exist in the literature for the preparation of 3,7-diaryl-2*H*-imidazo[2,1-*b*][1,3,4]-oxadiazines.[17,18] Therefore, we report our findings.

Results and Discussion

The electrochemical reduction of **1a–f** using DMF–$LiClO_4$ as system-solvent–electrolyte-support, on a mercury cathode gives 3,7-diaryl-2*H*-imidazo[2,1-*b*] [1,3,4]-oxadiazines **3a–f**. The assignment of the product structures was made based on their spectral properties. No carbonyl bands were observed in the IR spectra. The analysis of the ^1H, ^{13}C, and DEPT NMR spectra (for **3a–f**) in combination with direct ^1H–^{13}C correlation (HETCOSY) NMR experiments (only for **3a**, Figure 1) pointed to the structures of new compounds **3b–f**. The structure of **3a** was confirmed by its physical properties, already described in the literature.[18]

The chemistry of the transformation involves the transfer of two electrons to the substrate **1**, as determined by coulometric measurement, with cleavage of the C–Br bond and formation of an anion **2** . The anion **2** is electrogenerated under high dilution conditions by the slow addition of **1** into the cathodic compartment. This anion then desorbs from the electrode surface and adds to the carbonyl group of another molecule of the substrate to give, after intramolecular cyclization, the imidazooxadiazine **3**.

The advantages of this synthetic method include the unambiguous positioning of the substituents, good yields, and the ready availability of the starting materials.

The process can be summarized as outlined in Scheme II.

Experimental Section

The electrolysis was carried out using an Amel potentiostat Model 552 with an electronic integrator Amel Model 721. Mass spectra (EI, ionizing voltage 70 eV) were determined using a Hewlett-Packard Model 5988A mass-selective detector equipped with a Hewlett-Packard MS Chem Station. IR spectra were obtained, as dispersions in KBr, on a Perkin-Elmer Model 583 spectrometer. ^1H NMR (300 MHz) and ^{13}C NMR(75.4 MHz) spectra were recorded on a Varian-Unity 300 apparatus with TMS (^1H) or deuteriochloroform (^{13}C) as internal standard. Melting points were determined on a Reichter Thermovar microhot stage apparatus and are uncorrected. Elemental analysis was performed on a Perkin-Elmer Model 240-B analyzer. Analytical HPLC was performed on a Hewlett-Packard 5033 instrument, using a reverse-phase column and 80% methanol/water as the eluent. All products were purified by silica gel 60 (230–400 mesh ASTM) using 10% ethanol/chloroform as the eluent.

General Electrolysis Procedure. The preparation of the semicarbazones was as previously described.[6] The electrochemical reductions were carried out using the following conditions. Anode: Platinum. Anolite: lithium perchlorate (0.42 g, 4 mmol) in DMF (dried over anhyd $MgSO_4$) (10 mL). Cathode: mercury pool. Catholyte: lithium perchlorate (1.5 g, 14 mmol) in dry DMF (40 mL). Electrolysis cell: divided cell equipped with a magnetic stirrer containing a piece of glass tubing with a glass frit of medium porosity at one end (anodic compartment). Solid

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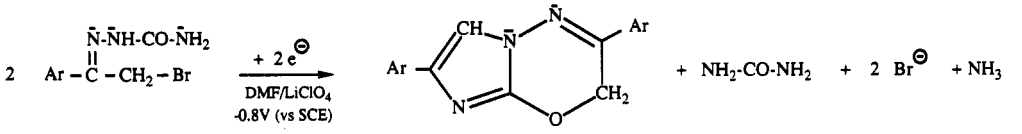
Scheme I



1 (a-f) 3 (a-f)

a: Ar= C_6H_4
b: Ar= 4-OMe-C_6H_4
c: Ar= 4-Me-C_6H_4
d: Ar= 4-Cl-C_6H_4
e: Ar= 4-Br-C_6H_4
f: Ar= 4-Ph-C_6H_4

sodium carbonate (2.0 g, 1.42 mmol) was added to the anodic compartment for "in situ" neutralization of the perchloric acid generated.

A solution of the semicarbazone (2 mmol in 20 mL of dry DMF) was dropped slowly onto the cathodic compartment, and a constant cathodic potential of −0.8 V (vs SCE) was applied. A new drop was added when the current approached zero. The reaction time was about 8 h and at the end of this period the cathodic solution was poured over ice–water. After 12 h the precipitated solid was filtered and dried under reduced pressure. The crude product was chromatographed on a silica gel (18 × 2.5 cm) column, using 9:1 $CHCl_3$/EtOH as eluent. A crystalline pale yellow compound was obtained after recrystallization from CH_3CN.

3,7-Diphenyl-2*H*-imidazo[2,1-*b*][1,3,4]oxadiazine (3a): 75% yield; mp 199–200 °C; IR (KBr) 3149, 3051, 2923, 1604, 1598, 1458, 1375, 1338, 1168, 1075, 739, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (s, 2H), 7.32 (s, 1H), 7.22–7.3 (m, 1H), 7.34–7.42 (m, 2H), 7.51 (m, 1H), 7.52 (m, 2H), 7.74–7.8 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 64.35, 109.3, 124.6, 125.98, 127.11, 128.53, 129.11, 131.5, 131.6, 133.21, 135.34, 143.61, 149.76; MS *m/e* (rel inten) 275 (M^+, 29.6), 172 (7.03), 145 (10.42), 116 (100), 103 (48.47), 77 (38.63), 51 (11.05). Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.18; H, 4.72; N, 15.27. Found: C, 74.23; H, 4.8; N, 15.07.

3,7-Bis(4-methoxyphenyl)-2*H*-imidazo[2,1-*b*][1,3,4]-oxadiazine (3b): 71% yield; mp 217–220 °C; IR (KBr) 3134, 3010, 2957, 1593, 1515, 1379, 1254, 1173, 1028, 833 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 3.87 (s, 3H), 5.28 (s, 2H), 6.89–6.99 (m,

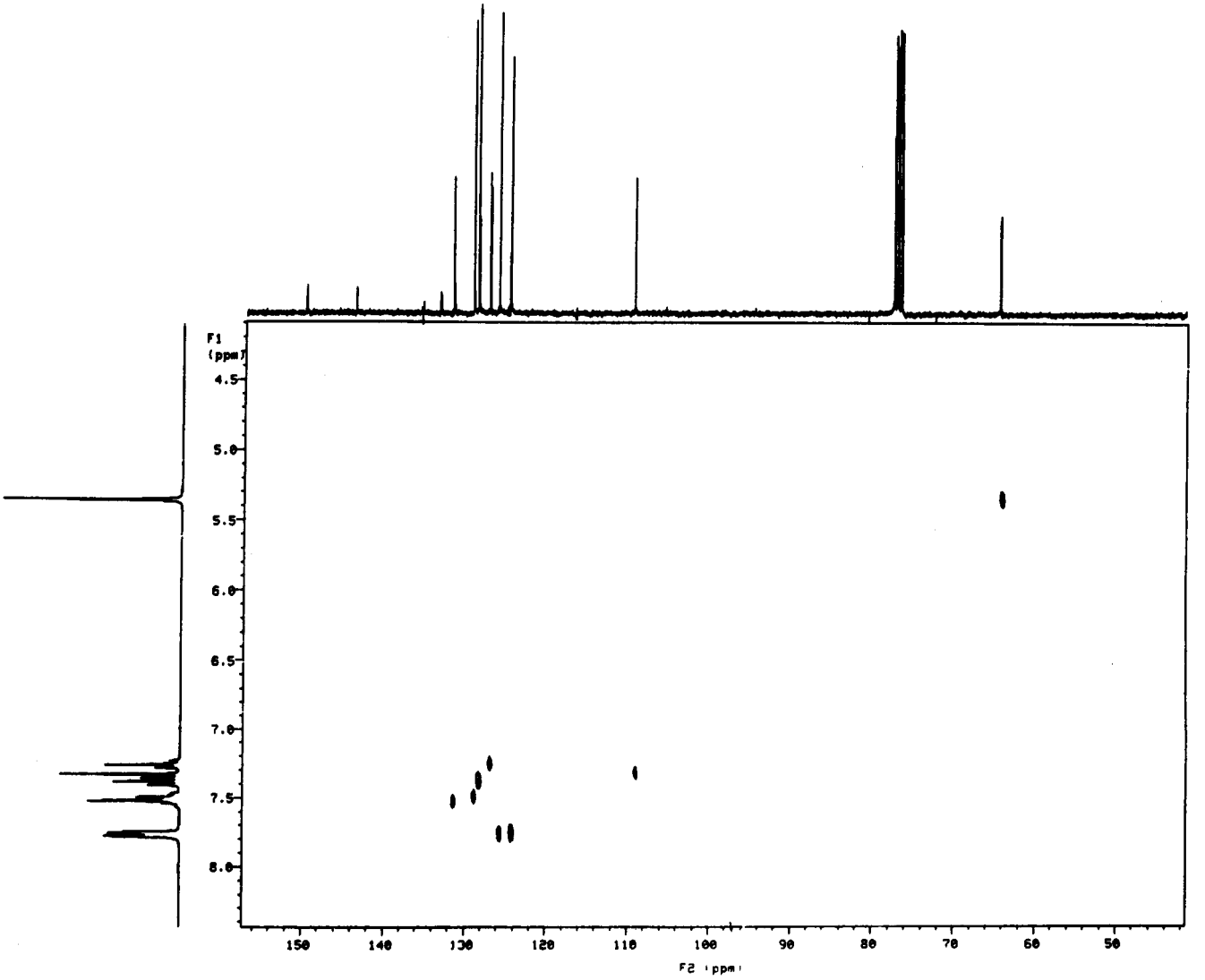
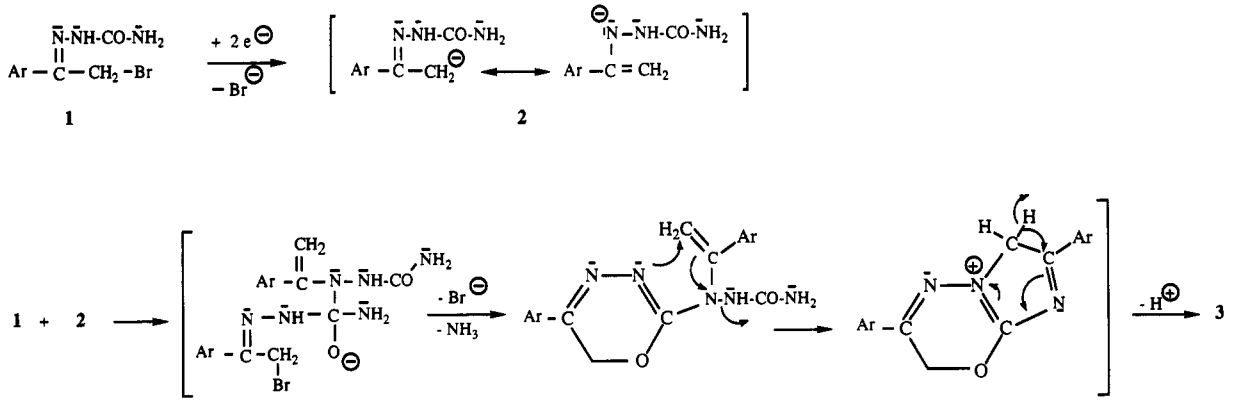


Figure 1.

Scheme II



4H), 7.2 (s, 1H), 7.65–7.72 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 54.95, 55.12, 63.8, 107.7, 113.65, 114.18, 123.68, 125.4, 126.07, 127.29, 127.8 , 135.17, 137.1, 143.2, 148.7; MS *m/e* (rel inten) 335 (M^+, 5.74), 175 (11.47), 147 (32.7), 146 (52.12), 133 (100), 132 (36.84), 103 (46.51), 90 (46.06), 89 (42.42), 77 (37.94), 76 (22.73), 63 (24.65), 51 (9.67). Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.06; H, 5.07; N, 13.43. Found: C, 68.21; H, 5.01; N, 13.32.

3,7-Bis(4-methylphenyl)-2*H*-imidazo[2,1-*b*][1,3,4]-oxadiazine (3c): 60% yield; mp 197–200 °C; IR (KBr) 3148, 2919, 1614, 1591, 1459, 1378, 1340, 1171, 1049, 823, 747, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 2.4 (s, 3H), 5.29 (s, 2H), 7.27 (s, 1H), 7.1–7.32 (m, 4H), 7.6–7.8 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.22, 29.38, 63.93, 108.46, 124.14, 125.56, 128.64, 128.90, 129.48, 129.75, 130.33, 136.4, 141.82, 143.38, 149.21; MS *m/e* (rel inten) 303 (M^+, 17.53), 276 (18.68), 249 (9.88), 202 (7.22), 130 (17.52), 117 (55.93), 116 (62.54), 115 (100), 91 (74.12), 65 (17.3), 51 (6.28). Anal. Calcd for $C_{19}H_{17}N_3O$: C, 75.24; H, 5.61; N, 13.86. Found: C, 74.98; H, 5.47; N, 14.02.

3,7-Bis(4-chlorophenyl)-2*H*-imidazo[2,1-*b*][1,3,4]-oxadiazine (3d): 74% yield; mp 227–230 °C; IR (KBr) 3151, 2926, 1594, 1400, 1172, 1093, 998, 830, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.32 (s, 2H), 7.28 (s, 1H), 7.31–7.34 (m, 2H), 7.45–7.49 (m, 2H), 7.65–7.72 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 64.11, 109.47, 125.83, 127.23, 128.72, 129.47, 129.9, 131.84, 132.75, 134.68, 137.99, 143.57, 148.68; MS *m/e* (rel inten) 347 (M^+ + 4, 3.09), 345 (M^+ + 2, 16.84), 343 (M^+, 28.16), 316 (3.07), 209 (21.71), 195 (14.96), 193 (16.54), 179 (19.52), 152 (42.2), 150 (100), 137 (92.38), 111(37), 102 (56.0), 75 (43.64), 51 (7.21). Anal. Calcd for $C_{17}H_{11}N_3OCl_2$: C, 59.30; H, 3.2; N, 12.20. Found: C, 59.51; H, 3.21; N, 12.17.

3,7-Bis(4-bromophenyl)-2*H*-imidazo[2,1-*b*][1,3,4]-oxadiazine (3e): 54% yield; mp 233–235 °C; IR (KBr) 3137, 1605, 1586, 1399, 1073, 1006, 825, 739, 641 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.32 (s, 2H), 7.30 (s, 1H), 7.46–7.64 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 63.71, 109.19, 125.8, 127.04, 129.27, 131.32, 131.96, 132.11, 132.61, 134.2, 137.8, 143.22, 148.7; MS *m/e* (rel inten) 435 (M^+ + 4, 5.58), 433 (M^+ + 2, 15.92), 431 (M^+, 6.68), 390 (10.34), 255 (21.83), 202 (56.3), 199 (56.93), 183 (100), 157 (30.15), 155 (27.97), 102 (70.46), 75 (26.67), 51 (14.47). Anal. Calcd for $C_{17}H_{11}N_3OBr_2$: C, 47.11; H, 2.54; N, 9.70. Found: C, 47.05; H, 2.49; N, 9.98.

3,7-Bis(4-phenylphenyl)-2*H*-imidazo[2,1-*b*][1,3,4]-oxadiazine (3f): 48% yield; mp 285–288 °C; IR (KBr) 3142, 2924, 2854, 1605, 1484, 1404, 1172, 1078, 840, 762, 737, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.4 (s, 2H), 7.28 (s, 1H), 7.3–8.27 (m, 18H); MS *m/e* (rel inten) 427 (M^+, 1.85), 296 (8.76), 251 (64.11), 235 (30.56), 208 (30.22), 179 (100), 178 (77.6), 152 (85.57), 127 (9.58), 77 (8.22), 58 (9.23), 51 (5.48). Anal. Calcd for $C_{29}H_{21}N_3O$: C, 81.5; H, 4.92; N, 9.84. Found: C, 81.28; H, 4.8; N, 9.93.

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