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Electrochemical Cyclization of o-Trichloroacetylanilides: Preparation of 4H-3,1-Benzoxazin-4-ones and 3,3-Dichloroquinolin-4-ones.

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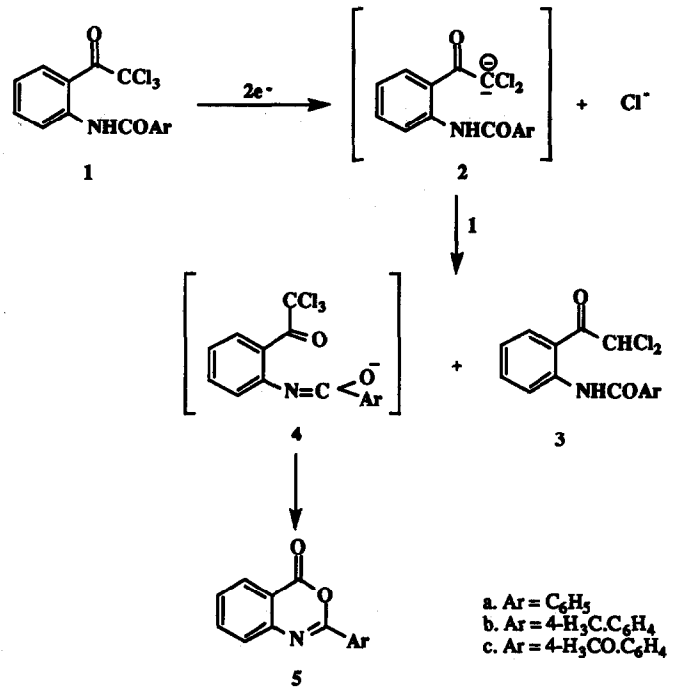
Abstract: The electrochemical reduction of several o-trichloromethylanilides and their imidoyl chloride derivatives on mercury pool in acetonitrile, yields 4H-3,1-benzoxazin-4-ones and 3,3-dichloroquinolin-4-ones respectively.

Electrochemical methods can be usefully employed in organic synthesis when a single group present in polyfunctional molecules must be selectively modified by selecting the applied potential. This fact makes the electrochemical methods a very attractive alternative to conventional procedures for achieving a high degree of regio- and / or chemoselectivity. In this context, several studies on the synthetic applications of electrodic cleavage of the carbon-halogen bond have been undertaken and exhaustively reviewed[1]. To our knowledge, however, there have been no reports dealing with synthetic aspects of the electrochemical reduction of gem-trihalocompounds. It has only been mentioned[2] that compounds possesing the trichloromethyl moiety can be electrolytically converted into their less chlorinated analogs. We wish to report here that α,α,α–trichloroacetophenones bearing either one o-amido or one o-imidoyl chloride substituent undergo an electrochemical reductive dehalogenation process to give 4H-3,1-benzoxazin-4-ones or 3,3-dichloroquinolin-4-ones respectively. Thus, an acetonitrile solution of o-trichloroacetylanilide **1**, available from o-acetylanilides by reaction with thionyl chloride in the presence of triethylamine, was electrolyzed[3] at room temperature at controlled cathodic potential of -1.1V *versus* SCE, up to 1 Faraday / mol of **1**. The dehalogenated amide **3** (38-46%) together the 2-aryl-4H-3,1-benzoxazin-4-one **5** (40-45%) was obtained after column chromatography separation[4].

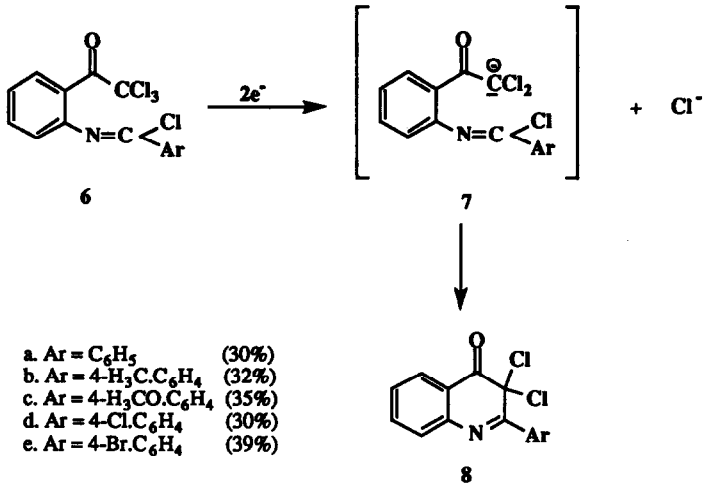
It has been described that the cathodic reduction of α-halocarbonyl compounds leads to the generation of the intermediate anions, which may function as electrogenerated bases[5] (EGBs). According to Scheme 1, the substrate **1** itself behaves as a proton donor towards the electrogenerated anion **2** rendering the dehalogenated amide **3** and the conjugated base **4** electroinactive at the working potential, so that only half of the substrate undergoes the desired two-electron reduction. Intermediate **4** eventually undergoes cyclization with concomitant elimination of trichloromethyl anion to give **5**.



Scheme 1

The competition between the cleavage of a carbon-chlorine bond belonging to a trichloromethyl group *versus* an imidoyl chloride substituent was examined in the case of compounds **6**, readily available in good yields either from **1** or directly from o-acetylanilides by reaction with thionyl choride. When an acetonitrile solution of **6** was electrolyzed at room temperature under controlled cathodic potential at -1.4 V *versus* SCE up to 2 Faradays / mol of **6**, the previously unreported 2-aryl-3,3-dichloroquinolin-4-ones **8** was obtained after column chromatography separation in moderate yields (30-39%). Attempts to improve the yield of **8** were unsuccessful because during the work-up these compounds undergo hydrolytic ring-opening even under mild conditions to give **3**. The structure of compounds **8** was confirmed by microanalytical and spectral data. The EI-mass spectra show the expected M^+, M^++2 and M^++4 ion peaks (100: 64: 10) and in the ^{13}C-NMR spectra the C-3 carbon atom appears at 104 ppm as a quaternary carbon atom[6]. Polarographic studies on model compounds indicate that the trichloromethyl group ($E_{1/2}$=-0.32 V *vs* ECS) is more easily reduced than the imidoyl chloride ($E_{1/2}$=-1.55 *vs* ECS) one. Taking into account this fact, the proposed mechanism for the conversion **6** → **8**, outlined in Scheme 2, involves an initial two-electron reduction process to give the electrogenerated anion **7** electroinactived at the working potential which undergoes cyclization by nucleophilic attack of the carbon atom on the imidoyl group with elimination of chloride anion.

The findings of the present study show, once again, that electrochemical methods should be considered for the selective transformation of polyfuntional molecules. Furthermore, they can allow the preparation of compounds of valuable biological interest e. g. chloro-substituted quinolin-4-ones[7].



Scheme 2

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3. Electrolyses were carried out in a concentric cylindrical cell equipped with a magnetic stirrer, with two compartments separated by a porous glass diaphragm. The solvent-supporting electrolyte system (SSE) was acetonitrile 0.02M in lithium perchlorate. A mercury pool (diameter 5 cm) was used as the cathode and a platinum plate as the anode. The reference electrode was a SCE. Electrolyses were performed under controlled cathodic potential using an Amel 557 potentiostat and the amount of electricity was measure with and Amel 558 coulometer integrator coupled to the potentiostat. The values of the initial currents were about 100mA and the electrolyses were continued until the current decreases to less than 1% of the starting value. The cell temperature was controlled at 25°C and nitrogen was bubbled through the catholyte solution for 10 min. prior to electrolysis and above it during the experiment. For prevention of the accumulation of electrogenerated acid in the anode compartment anhydrous sodium carbonate (1 gr) was placed in the glass diaphragm. The cathode solution was separated from the mercury by decantation, and then evaporated to dryness under reduced pressure. The crude reaction product was chromatographed on a silica gel column using ethyl acetate / n-hexane (1:3) as eluent.
4. Compound **3a** (Ar= C_6H_5). ^{1}H-n.m.r. (300 MHz, $CDCl_3$) δ 6.90 (s, 1H), 7.17 (dt, 1H, ^3J = 8.0 Hz, ^4J = 0.8 Hz),

7.50-7.56 (m, 3H), 7.68 (dt, 1H, ^3J = 8.0 Hz, ^4J = 1.3 Hz), 7.96-8.06 (m,3H), 9.02 (dd, 1H, ^3J = 8.0 Hz, ^4J= 0.8 Hz), 12.05 (broad, 1H). ^{13}C-n.m.r. (75 MHz, $CDCl_3$) δ 67.88 (CH), 116.72 (q), 121.63, 122.55, 127.47, 128.93, 130.97, 132.33, 134.33 (q), 137.02, 143.33 (q), 166.06 (CONH), 189.50 (CO).

Compound **3b** (Ar = 4-H_3C-C_6H_4). ^{1}H-n.m.r. (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 6.92 (s, 1H), 7.18 (t, 1H, ^3J = 8.4 Hz), 7.33 (d, 2H, ^3J = 8.1Hz), 7.70 (t, 1H, ^3J = 8.4 Hz), 7.94-8.02 (m, 3H), 9.04 (d, 1H, ^3J = 8.4 Hz), 12.05 (broad, 1H). ^{13}C-n.m.r. (75 MHz, $CDCl_3$) δ 21.53 (CH_3), 67.91 (CH), 116.64 (q), 121.61, 122.39, 127.52, 129.61, 130.94, 131.54 (q), 136.99, 142.99 (q), 143.50(q), 166.07 (CONH), 189.45 (CO).

Compound **3c** (Ar= 4-H_3CO-C_6H_4). ^{1}H-n.m.r. (300 MHz, $CDCl_3$) δ 3.89 (s, 3H), 6.94 (s, 1H), 7.03 (d, 2H, ^3J=7.0 Hz), 7.18 (dt, 1H, ^3J=8.0 Hz, ^4J=0.7 Hz), 7.70 (dt, 1H, ^3J=8.0 Hz, ^4J=1.4 Hz), 8.07-7.98 (m, 3H), 9.04 (dd, 1H, ^3J=8.0 Hz, ^4J=0.7 Hz), 12.04 (broad, 1H). ^{13}C-n.m.r. (75 MHz, $CDCl_3$) δ 55.56 (CH_3O), 67.97 (CH), 114.20, 116.54 (q), 121.57, 122.36, 126.60 (q), 129.55, 131.02, 137.14, 143.73 (q), 162.96 (q), 165.68 (CONH), 189.54 (CO).

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6. Compound **8a** (Ar=C_6H_5). ^{1}H-n.m.r. (300 MHz, $CDCl_3$) δ 7.23 (t, 1H, ^3J =7.0 Hz), 7.05-7.36 (m, 5H), 8.17-8.19 (m, 3H). ^{13}C-n.m.r. (75 MHz, $CDCl_3$) δ 104.26 (q), 118.82 (q), 125.81, 126.46, 127.16, 128.08, 128.46, 130.33 (q), 131.26, 132.13, 140.18 (q), 141.97 (q), 154.28 (CO). m/z (%) 293 (M^++4, 6), 291 (M^++2, 37), 289(M^+, 58), 76 (100). i.r. (Nujol) 1647 cm^{-1}.

Compound **8b** (Ar=4-H_3C-C_6H_4). ^{1}H-n.m.r. (300 MHz, $CDCl_3$) δ 2.43 (s, 3H), 7.25-7.30 (m, 3H), 7.37-7.46 (m, 2H), 8.11 (d, 2H, ^3J = 8.4 Hz), 8.24 (dd, 1H, ^3J = 8.1 Hz, ^4J = 1.5 Hz). ^{13}C- n.m.r. (75 MHz, $CDCl_3$) δ 21.65 (CH_3), 104.09 (q), 118.77 (q), 125.79, 126.31, 126.91, 127.55 (q), 128.08, 129.21, 131.21, 140.35 (q), 142.02 (q), 142.77 (q), 154.46 (CO). m/z (%) 307 (M^++4, 4), 305 (M^++2, 25), 303 (M^+, 40), 110 (100). i.r. (Nujol) 1647 cm^{-1}.

Compound **8c** (Ar = 4-H_3CO-C_6H_4). ^{1}H-n.m.r. (300 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.96 (d, 2H, ^3J=8.9 Hz), 7.24 (dt, 1H, ^3J=7.2 Hz, ^4J=2.0 Hz), 7.36-7.41 (m, 2H), 8.13-8.22 (m, 3H). ^{13}C-n.m.r. (75 MHz, $CDCl_3$) δ 55.40(CH_3O), 103.93 (q), 113.88, 118.62 (q), 122.71 (q), 125.80, 126.15, 126.65, 130.23, 131.22, 140.53 (q), 142.10 (q), 154.27 (q), 162.90 (q). m/z (%) 323 (M^++4, 10), 321 (M^++2, 64), 319 (M^+, 100). i.r. (Nujol) 1645 cm^{-1}.

Compound **8d** (Ar= 4-Cl-C_6H_4). ^{1}H-n.m.r. (300 MHz, $CDCl_3$) δ 7.29 (dt, 1H,^3J=7.6 Hz, 4J=1.5 Hz), 7.46-7.36 (m, 4H), 8.14 (d, 2H, ^3J=8.4 Hz), 8.23 (d, 1H, ^3J=7.6 Hz). ^{13}C-n.m.r. (75 MHz, $CDCl_3$) δ 104.55 (q), 118.79 (q), 121.81 (q), 125.89, 126.51, 127.41, 128.83, 129.38, 131.37, 138.49 (q), 139.94 (q),141.85 (q), 153.42 (CO). m/z (%) 329 (M^++6, 4), 327 (M^++4, 36), 325 (M^++2, 99), 323 (M^+, 100). i.r. (Nujol) 1649 cm^{-1}.

Compound **8e** (Ar= 4-Br-C_6H_4). ^{1}H-n.m.r. (300 MHz, $CDCl_3$) δ 7.47-7.24 (m, 3H), 7.59 (d, 2H, ^3J=8.5 Hz), 8.05 (d, 2H, ^3J=8.5 Hz), 8.21 (d, 1H, ^3J=7.9 Hz). ^{13}C-n.m.r. (75 MHz, $CDCl_3$) δ 104.21 (q), 118.50 (q), 125.62, 126.30, 126.77 (q), 127.23, 129.06 (q), 129.26, 131.15, 131.53, 139.66 (q), 141.60 (q), 153.13 (CO). m/z (%) 373 (M^++6, 5), 371 (M^++4, 36), 369 (M^++2, 78), 367 (M^+, 50), 123 (100). i.r. (Nujol) 1650 cm^{-1}.

7. Satisfactory ^{1}H, ^{13}C-n.m.r., mas spectra and elemental analyses were obtained for all new compounds.

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