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Electrochemical Reduction of 2,2-Dibromoacetophenone

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Dedicated to Professor Henning Lund on the occasion of his 70th birthday.

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The cathodic reduction of 2,2-dibromoacetophenone in aprotic medium DMF–$LiClO_4$ yields (*E*)-4,4-dibromo-1,3-diphenyl-2,3-epoxybutan-1-one as the major product and *trans*-1,2,3-tribenzoylcyclopropane through an ionic or carbene route, respectively. When the electrolysis is carried out under highly dilute conditions, together with these products, (*E*)-4-bromo-1,3-diphenyl-2,3-epoxybutan-1-one and (*Z*)-4-bromo-1,3-diphenyl-2,3-epoxybutan-1-one are obtained.

The cathodic reduction of phenacyl bromides has allowed the synthesis of several interesting organic products. Reduction of phenacyl bromide in DMF–$LiClO_4$ at a mercury cathode has afforded 2,4-diarylfurans in good yield.[1] This reaction is strongly dependent on the concentration of substrate in the cell. However, when the electrolyses were carried out under highly dilute conditions no furans were observed. In this case, a mixture of acetophenone and (*E*)-4-bromo-1,3-diphenyl-2,3-epoxybutan-1-one was obtained.[2] Under the same dilute conditions 4-aryl-2-methylfurans were produced[3] when dry acetone was used as the solvent. Cathodic reduction of the same substrates in the presence of methyl chloroformate using dry dichloromethane–tetrabutylammonium tetrafluorborate as a solvent-supporting-electrolyte (SSE) gave 1-arylethenyl methyl carbonates in a regioselective *O*-acylation process.[4]

In this paper we describe the cathodic reduction of 2,2-dibromoacetophenone (**1**) at a mercury cathode, and in DMF–$LiClO_4$ as SSE. The electrolysis was performed for two different substrate concentrations: (a) 5×10^{-3} mol of **1** in the cathodic compartment afforded (*E*)-4,4-dibromo-1,3-diphenyl-2,3-epoxybutan-1-one as the major product (61%) and *trans*-1,2,3-tribenzoylcyclopropane (27%) as a secondary compound; (b) 5×10^{-3} mol of **1** slowly added to the cathodic compartment yielded a mixture of keto epoxides and *trans*-1,2,3-tribenzoylcyclopropane.

Formation of keto epoxides and *trans*-1,2,3-tribenzoylcyclopropane involves the production of electrogenerated anions and carbenes, respectively.

Results and discussion

In previous work we have studied the behavior of the electrogenerated enolate in the cathodic reduction of phenacyl bromide. This behavior is highly dependent on the substrate concentration. The generated enolate, formed after reduction of phenacyl bromide at a mercury electrode, attacks the carbonyl group of another substrate molecule adsorbed onto the electrode (adsorption onto platinum is so strong that reduction at this electrode cannot be performed), to give 2,4-diarylfurans.[1] Nevertheless, when the reaction was carried out under highly dilute conditions, the electrogenerated anion could not find another molecule of adsorbed starting material. The anion, then, was desorbed into the solution where it acted as a hard base abstracting a proton from another added substrate molecule yielding acetophenone and a brominated enolate. Owing to the withdrawing effect of the bromine atom, this brominated enolate is a softer base than the electrogenerated enolate, and upon attack of the carbonyl group of phenacyl bromide gives (*E*)-4-bromo-1,3-diphenyl-2,3-epoxybutan-1-one.[2]

In the electrochemical reduction of 2,2-dibromoacetophenone, the formation of (*E*)-4,4-dibromo-1,3-diphenyl-2,3-epoxybutan-1-one, *trans*-1,2,3-tribenzoylcyclopropane and a small amount of (*E*)-4-bromo-1,3-diphenyl-2,3-epoxybutan-1-one (9%) can be explained as follows. In the first step, the cathodic reduction of one of the carbon–halogen bonds takes place to give the corresponding monobrominated enolate (**I**), which adds to the carbonyl group of another molecule of substrate giving the intermediate **II**. The negatively charged oxygen of **II** then regioselectively attacks the C–Br bond on the secondary carbon leading to a 2,3-epoxide (**2**) after displacement of a bromide anion (see Scheme 1).

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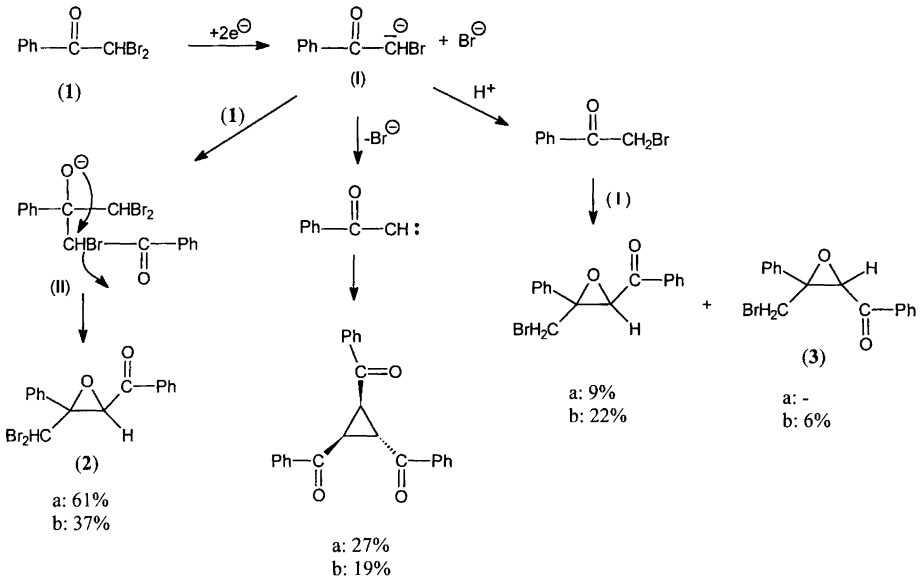

Scheme 1. a, 5 mmol of substrates in cell; b, highly dilute conditions.

No traces of 3,4-epoxide were detected. This result can be explained by the well-known high reactivity of α-halogenated ketones versus the S_N2 substitution.

As the electrolysis progresses, the concentration of adsorbed substrate decreases, reducing the possibility of addition to the adsorbed phenacyl bromide of freshly generated enolate. For this reason **I** can lose a bromide anion to afford the carbene precursor of *trans*-1,2,3-tribenzoylcyclopropane or react with traces of water to form phenacyl bromide [phenacyl bromide is not reduced at a working potential of −0.35 V (vs. SCE) but it can be attacked by another molecule of **I** affording the monobrominated keto epoxides]. This pathway was confirmed by running the reaction in DMF with a higher water content. In this case, the yield of monobrominated keto epoxides was increased.

When the cathodic reduction of 2,2-dibromoacetophenone was carried out under highly dilute conditions, a solution of electroactive substrate was added dropwise to the cathodic compartment, but each new drop was added only when the current fell to zero. The dibrominated keto epoxide (**2**) was again obtained as the major product but the yield, 37%, was lower than in the reaction performed with all the substrate in the cell. *trans*-1,2,3-Tribenzoylcyclopropane (19%), (*E*)-4-bromo-1,3-diphenyl-2,3-epoxybutan-1-one (22%), (*Z*)-4-bromo-1,3-diphenyl-2,3-epoxybutan-1-one (6%) and phenacyl bromide (9%) were obtained as side-products.

These results are explained as follows. The intermediate **I** is now electrogenerated under highly dilute conditions in which it is difficult to encounter another molecule of substrate (on the mercury surface or at the electrical interface) to undergo the addition reaction. In this case **I** is desorbed to the solution, where it acts as a soft base, (**I** is also formed in the reduction of phenacyl bromide in highly dilute homogeneous media) attacking the soft center of a new substrate molecule yielding **2** [instead of abstracting a proton (hard center) from **1**]. No traces of the tribrominated keto epoxide was detected. The yield of **2** is lower than that obtained with the whole substrate in the cell, because the intermediate **I** in the bulk solution reacts with traces of water giving phenacyl bromide. In parallel to this, the increase of phenacyl bromide concentration in the catholyte enables reaction with **I**, to form the monobrominated keto epoxides. Electroreduction of **1** at high dilution produces both isomers (*E* and *Z*), although the yield of *E*-isomer is higher. Production of *trans*-1,2,3-tribenzoylcyclopropane is decreased owing to the low probability of three carbene species, or two carbenes and one **I** molecule undergoing a successful encounter.

Experimental

The electrolyses were 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, for samples as dispersions in KBr, on a Perkin-Elmer Model 583 spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded on a Varian Unity 300 apparatus with deuteriochloroform as an internal standard. The chemical shifts are given in ppm. Melting points were determined on a Reichert Thermovar micro-hot-stage apparatus, and are uncorrected. Elemental analyses were performed on a Perkin-Elmer Model 240-B analyzer. Polarography was carried out on a Metrohm apparatus Model 663 VA Stand and a Scanner 626 Polarecord. The potential values are given in volts. Analytical HPLC was performed on a Hewlett-

Packard 5033 instrument, using a reversed phase column and 80% ethanol–water as the eluent. The products were purified by silica gel 60 chromatography (230–400 mesh) using toluene as the eluent.

The electroactive 2,2-dibromoacetophenone (**1**) was prepared from acetophenone (6.18 g, 5.15×10^{-2} mol) and bromine (74.64 g, 46.6×10^{-2} mol) in glacial acetic acid as solvent. The reaction was carried out by adding the bromine to the acetophenone solution rapidly enough to cause reflux until the solution was not decolorized. AcONa (7 g, 0.085 mol) was then added and then further Br_2. The mixture was stirred for two days. When the reaction was finished the excess of bromine and the solvent were evaporated off under vacuum. The crude product obtained was extracted with ether water and the ethereal fraction dried with magnesium sulfate. The expected 2,2-dibromoacetophenone (96% yield) was obtained when the ether was evaporated off. Physical and spectroscopical properties were identical with those described in literature.[5]

General electrochemical procedure. The electrochemical reduction was carried out using the following conditions. Anode: platinum. Anolyte: lithium perchlorate (0.56 g, 5.26×10^{-3} mol) in DMF (10 ml). Cathode: mercury pool. Catholyte: lithium perchlorate (1.4 g, 0.013 mol) in DMF (25 ml) and 2,2-dibromoacetophenone (1.396 g, 5×10^{-3} mol). 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 sodium carbonate (2 g, 1.42 mmol) was added to the anodic compartment for '*in-situ*' neutralization of the perchloric acid generated. Solid sodium thiosulfate (1 g, 6.32 mmol) was added to the anodic compartment to avoid bromine generation.

A constant cathodic potential of −0.35 V (vs. SCE) was applied. The reaction time was around 1.5 h and at the end of this period the cathodic solution was poured over ice-water. After 12 h the precipitated solid was filtered off and dried under reduced pressure. The crude product obtained was washed with ether after which a white solid was isolated and characterized by its spectroscopic properties[6] as *trans*-1,2,3-tribenzoylcyclopropane (0.16 g, 4.52×10^{-4} mol) (27%).

The ethereal solution was chromatographed on a silica gel (25 × 3 cm) column, using toluene as the eluent, to isolate the following compounds:

(E)-4,4-Dibromo-1,3-diphenyl-2,3-epoxybutan-1-one (0.61 g, 1.53×10^{-3} mol) (61% yield).

(E)-4-Bromo-1,3-diphenyl-2,3-epoxybutan-1-one[2] (0.072 g, 2.26×10^{-4} mol) (9% yield).

The compound (*E*)-4,4-dibromo-1,3-diphenyl-2,3-epoxybutan-1-one (**2**) is described now for the first time by its physical and spectroscopical properties.

(E)-4,4-Dibromo-1,3-diphenyl-2,3-epoxybutan-1-one (**2**). 61% yield; m.p. 108–109 °C. IR (KBr): 3063, 2992, 1684, 1588, 1444, 1227, 1167, 1020, 934, 851, 759, 704 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.77 (s, 1 H, $CHBr_2$), 5.84 (s, 1 H), 7.2–7.64 (m, 8 H_{Ar}), 7.96 (m, 2 H_{Ar}). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 46.14 ($CHBr_2$), 65.61 (Ph–CO–*C*H–O), 67.53 [Ph–*C*($CHBr_2$)–O], 127.5, 128.0, 128.47, 128.74, 128.98, 129.78 (*ipso*), 133.07, 134.7 (*ipso*), 190.6 (C=O). MS *m/z* (rel. int.): 233 ($M^+ - CHBr_2$, 100), 105 (83), 77 (87), 51 (35). Anal. Calc. for $C_{16}H_{12}Br_2O_2$: C, 48.48; Br, 40.40; H, 3.03. Found: C, 48.18; Br, 40.59; H, 3.13.

Electrolysis under highly dilute conditions. The electrochemical reduction was carried out under the same conditions described before, only the applied potential and the initial concentration of substrate in the cell were modified: 2,2-dibromoacetophenone (1.396 g, 5×10^{-3} mol) in 15 ml SSE was added to the cathodic compartment over 12 h. The constant cathodic potential was −0.35 V (vs. SCE). The crude product of the electrolysis was processed as detailed before. In this case, the product distribution was as follows:

(E)-4,4-Dibromo-1,3-diphenyl-2,3-epoxybutan-1-one (0.333 g, 8.42×10^{-4} mol) (37% yield).

trans-*1,2,3-Tribenzoylcyclopropane* (0.1 g, 2.86×10^{-4} mol) (19% yield).

(E)-4-Bromo-1,3-diphenyl-2,3-epoxybutan-1-one (0.16 g, 5.07×10^{-4} mol) (22% yield).

(Z)-4-Bromo-1,3-diphenyl-2,3-epoxybutan-1-one (0.044 g, 1.39×10^{-4} mol) (6% yield).

Phenacyl bromide (8.6 mg, 4.36×10^{-4} mol) (9% yield).

(Z)-4-Bromo-1,3-diphenyl-2,3-epoxybutan-1-one (**3**). 6.1% yield; m.p. 122–123 °C. IR (KBr): 3056, 1678, 1592, 1448, 1396, 1332, 1226, 1012, 916, 762, 710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.76 (d, 1 H, CH_2Br, J = 11.3 Hz), 3.9 (d, 1 H, CH_2Br, J = 11.3 Hz), 4.53 (s, 1 H), 7.10–7.14 (m, 3 H_{Ar}), 7.22–7.28 (m, 2 H_{Ar}), 7.34 (m, 2 H_{Ar}), 7.46 (m, 1 H_{Ar}), 7.8 (m, 2 H_{Ar}). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 36.37 (CH_2Br), 65 (Ph–CO–*C*H–O), 67.0 [Ph–*C*($CHBr_2$)–O], 126.8, 127.9, 128.31, 128.37, 132.6 (*ipso*), 133.4, 135 (*ipso*), 191.2 (C=O). MS *m/z* (rel. int.): 223 ($M^+ - CH_2Br$, 55) 105 (100), 77 (49), 51 (12). Anal. Calc. for $C_{16}H_{13}BrO_2$: C, 60.57; Br, 25.24; H, 4.1. Found: C, 60.37; H, 4.25; Br, 25.0.

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