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PREPARATIVE ELECTROCHEMISTRY I. A NOVEL ELECTROCHEMICAL OXIDATION OF A 1,2,3,4-TETRAHYDROCARBAZOLE TO A CARBAZOLE DERIVATIVE[†]

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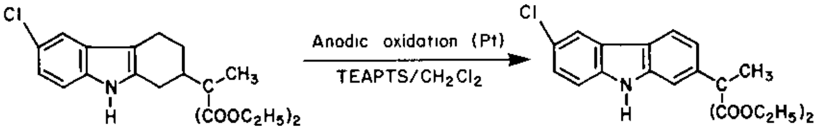
Abstract - Diethyl(6-chloro-1,2,3,4-tetrahydro-2-carbazolyl)methyl malonate can be oxidized via a four electron process at a platinum electrode in 0.1 M tetraethylammonium p-toluenesulfonate in methylene chloride to diethyl(6-chloro-2-carbazolyl)methyl malonate in 15% yield.

A commercial synthesis of Rimadyl® [(d,l)-6-chloro-α-methylcarbazole-2-acetic acid] involves the chemical oxidation of diethyl(6-chloro-1,2,3,4-tetrahydro-2-carbazolyl)methyl malonate (1) to diethyl(6-chloro-2-carbazolyl)methyl malonate (2). The electrochemical oxidation of (1) has now been investigated as a possible alternate route for the synthesis of the intermediate (2).



(1) (2)

The electrochemical oxidation of (1) was carried out in a divided cell, equipped with a platinum gauze anode, platinum wire cathode, and a silver-silver chloride saturated potassium chloride reference electrode [with a bridge of 1.1 M tetrabutylammonium perchlorate (Bu_4NClO_4) in acetonitrile[1]] . The pulsed voltage of +1.40 v, 0.67 Hz and 66.7% duty cycle was originated from a Princeton Applied Research (PAR) Universal Programmer, Model 175, and fed to a PAR Model 173/179 Potentiostat set at +0.10 volts. Thus, the applied voltage was +1.50 v (pulsed), and the current density was 3.75 mA/cm^2. One hundred forty ml of 0.1 M tetraethylammonium p-toluenesulfonate (TEAPTS) in methylene chloride (30.1 g in 1 liter of methylene chloride) was used as anolyte, and 25 ml as a catholyte. The electrolyte was deaerated, pre-electrolyzed for 30 min at +1.70 volts and switched off, modulation applied and 5.1 grams of (1) were fed into the anode compartment. Immediately, the current rose to 6 mA and stayed at this level for 6 h. Then it steadily dropped to 3.8 mA over a period of 24 h. No further change in the UV spectrum of the reaction mixture was observed.

The anolyte was stripped down to a thick oil (about 35 g). This residue was loaded on a 1 inch diameter silica gel column (210 g of silica gel, 76-230 mesh, E. Merck Reagent, in 300 ml of a 9:1 mixture of toluene/ethyl acetate), and was eluted with the same mixture. Two 200 ml cuts were taken, followed by twenty-three 50 ml cuts. The desired material started eluting in cut #15, and appeared pure by TLC (Rf = 0.25 in 9:1, toluene/ethyl acetate)

[†] Dedicated to the memory of Dr. Willy Leimgruber, deceased July 8, 1981.

through cut #19. The solvent was stripped on a rotory evaporator and after a few min under high vacuum, the residue crystallized, giving 224 mg of pure product. An additional 100 mg of (2) was isolated from cuts 20-29. The highest isolated yield was about 15%. The product was confirmed by comparison of the physical data with those of the authentic sample. Elemental analysis: C 64.39 (64.26), H 5.44 (5.39), N 3.67 (3.75) and Cl 9.32 (9.48). UV (isopropanol) λ max 239, 262, 301, 335 and 339 nm, ϵ = 46,300; 21,900; 22,800; 3,630 and 2,930. IR ($CHCl_3$) 3470 cm^{-1} (NH), 1725 cm^{-1} (C=O). NMR ($CDCl_3$) ppm 1.24 (6H), 1.96 (3H), 4.26 (4H), 6.99-7.71 (6H), 8.30 (1H).

After cut #25, the eluate was replaced with toluene/ethyl acetate 1:1 v/v and the eluted material was a mixture of various products by TLC and NMR (various dimers of (1) and (2) etc.).

The electrochemical experiments (summarized in Table I) have shown that the reaction paramters for this anodic oxidation procedure are quite critical. This would explain why, up to now, no successful electrochemical procedure to oxidize 1,2,3,4-tetrahydrocarbazole to carbazole has been reported, although such attempts have been made[2,3,4]. Willis[2] reported that the anodic oxidation of tetrahydrocarbazole yielded the 1,9' dimer as the only isolable product. Furthermore, it has been stated in the literature[3] that the ring substituted carbazole cation radicals (generated via anodic oxidation) are extremely reactive, especially at positions C-3, C-6 and N-9.

TABLE I. Summary of Experimental Parameters of Anodic Oxidation of (1) to (2)

Electrolyte	Electrode	+E[a]/V	Yield
0.1 M TEAPTS[b]/CH_2Cl_2	Pt	1.70	30% (2)[c], 50% (1)
0.1 M TEAPTS/CH_2Cl_2	Pt	1.50	15% (2)[d]
0.1 M TEAPTS/CH_2Cl_2	Pt	1.90	44% (2)[c], dimers of (1), no (1)
0.1 M TEAPTS/CH_2Cl_2 (dry)	Pt	1.50	60% (2)[c]
0.1 M Bu_4NBF_4/CH_2Cl_2	Pt	1.65	No (2) detected
0.1 M $LiClO_4$/CH_3CN	Pt	0.90	Mainly dimers of (1)
0.1 M $LiClO_4$/CH_3CN	*Pt*	*1.70*	*No (1) or (2) detected*
0.1 M TEAPTS/CH_2Cl_2	Carbon	1.30	No (1) or (2), various dimers
0.1 M TEAPTS/CH_2Cl_2	Ti	1.60	No. (2), various dimers

[a] V vs/Ag/AgCl electrode. [b] Tetraethylammonium p-toluenesulfate. [c] Total yield of various oxidized products: (2) plus various dimers of (2), based on UV spectral data. [d] Yield of isolated purified material.

The highest yields of (2) were obtained when the oxidation was carried out in 0.1 M TEAPTS/methylene chloride at a platinum gauze electrode at +1.5 to +1.9 volts. Applying a carbon anode, mainly dimers of (1) were formed and no (2). Also using 0.1 M Bu_4NBF_4/methylene chloride or 0.1 M $LiClO_4$/acetonitrile instead of 0.1 M TEAPTS/methylene chloride produced mainly dimers of (1) and (2) and no (2).

Two major problems exist. The first one is the formation of dimers of several types. No experiments were performed to identify the exact structures of the dimers or their mode of formation. The second problem involves the absorption of the oxidation products at the anode leading to large drops of current ("electrode fouling"). This phenomenon makes it difficult to obtain complete conversion of the starting material although current pulsing minimizes the absorption problem and increases the yield.

The initially observed high yields of (2) (60%) were based on the TLC, NMR, and UV data of the crude. Isolation and purification of the material showed that the highest isolated yield of (2) is about 15%. It was found that the crude batches contain not only various dimers of (2) [spectral properties similar to those of (2)] but also some dimers (or high polymers) of (1).

It is possible that with a systematic study of the reaction parameters, such as nature of electrode material, temperature, voltage, supporting electrolyte, etc., the yield of the anodic oxidation of (1) to (2) could be raised so that this technique could become of synthetic utility.

Preliminary experiments have also indicated that other tetrahydro structures can be oxidized. Unsubstituted 1,2,3,4-tetrahydroisoquinoline and 1,2,3,4-tetrahydronaphthalene can be oxidized electrochemically to the corresponding aromatic compounds, although the initial yields have been low (2-4%).

REFERENCES

1. An intermediary bridge of 1.1 M tetrabutylammonium perchlorate (Bu_4NClO_4) in acetonitrile was used as a matter of convenience (used in our laboratory with a variety of organic solvents). Instead of Bu_4ClO_4, the bridge could consist of TEAPTS in acetonitrile, but not in CH_2Cl_2: a possible slight aqueous bleeding from the aqueous reference electrode can create two liquid phases which has been observed in our laboratory to create some crusting at the fitted interface.
2. J. P. Willis, Diss. Abstr. Int. B., 34, 76 (1978).
3. J. F. Ambrose, L. L. Carpenter and R. F. Nelson, J. Electrochem. Soc., 122, 876 (1978).
4. During this investigation, an electrochemical oxidative decarboxylation of tetrahydro-β-carboline carboxylic acids to β-carboline has been reported by J. M. Bobbitt and J. P. Willis, J. Org. Chem., 45, 1978 (1980).

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