OXIDATIVE CYCLIZATION OF 3-ANILINO-CYCLOHEX-2-ENONES TO TETRAHYDROCARBAZOLES[+1]

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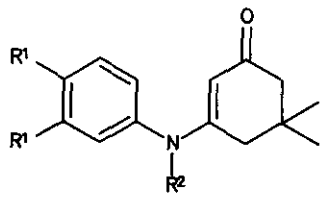
Abstract- 3-Anilino-cyclohex-2-enones 1a-1c are prepared from anilines and 5,5-dimethyl-1,3-cyclohexanedione. Anodic oxidation of 1a affords the *p*-benzoquinone monoimine dimethyl acetal 4, that is cyclized with CF_3CO_2H to the tetrahydrocarbazole 6. Lead tetraacetate oxidation of 1c leads directly to the tetrahydrocarbazole 9.

Enaminones can be dimerized at the anode to 3,4-diketopyrroles[2]. Similarly aryl ethers can be coupled to biaryls[3]. We were interested to find out, whether the combined electrophores can be anodically coupled to afford heterocyclic compounds[4]. Here we report on the cyclization of 3-anilino-cyclohex-2-enones to tetrahydrocarbazoles. N-2-Haloaryl substituted enaminones can be cyclized to tetrahydrocarbazoles by photolysis[5] or copper(I)-catalysis[6]. N-Arylenaminones without a halo substituent cyclize photochemically to hexahydrocarbazoles[7a] or by subsequent dehydrogenation to carbazoles[7b].

The 3-anilino-cyclohex-2-enones 1a,b were prepared according to ref.[8] from 5,5-dimethyl-1,3-cyclohexanedione and 3,4-dimethoxyaniline or aniline in 85% or 65% yield, respectively. Enone 1c was obtained in 81% yield by methylation of 1a with sodium hydride and methyl iodide in toluene.

+ HJS wishes to dedicate this paper to Sir Derek Barton on the occasion of his 70th birthday.

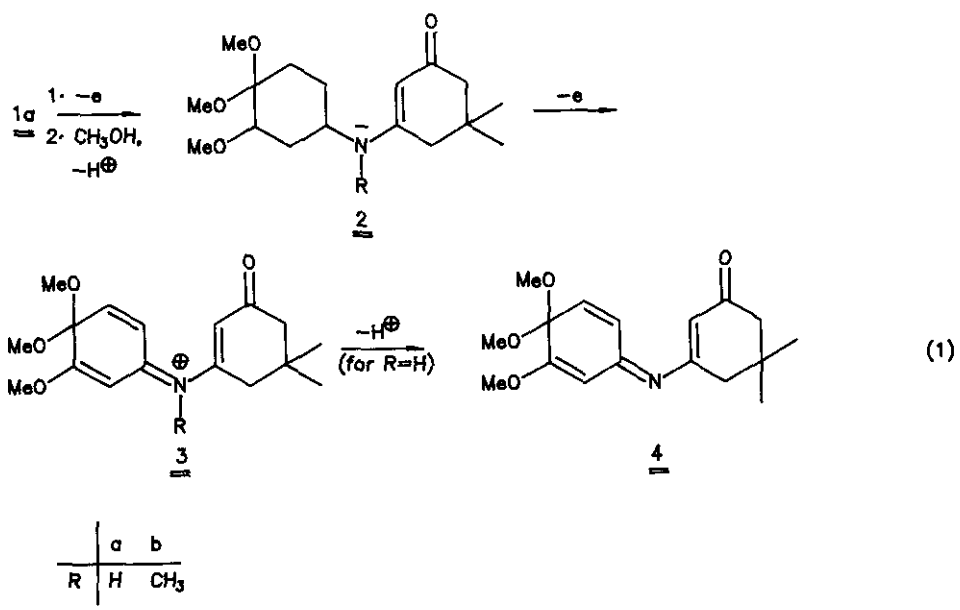


	R^1	R^2
a	MeO	H
b	H	H
c	MeO	Me

1

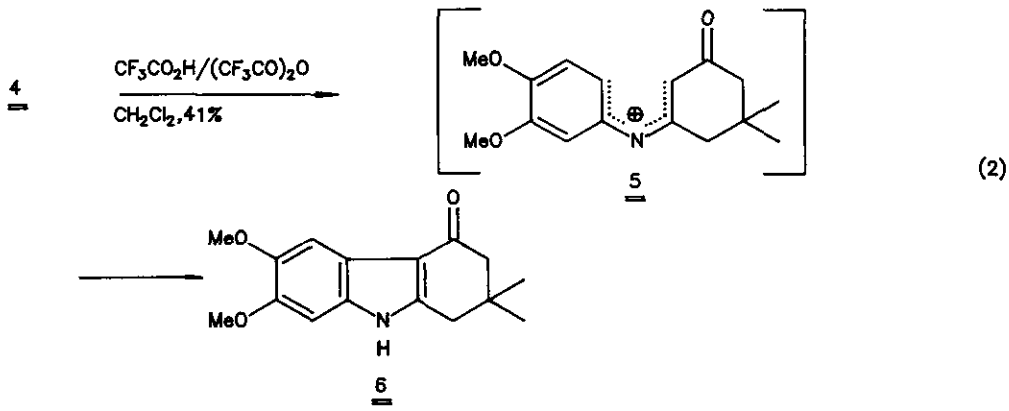
In cyclic voltammetry (glassy carbon anode, 0.1 M $NaClO_4$ in MeOH) **1a** exhibits three irreversible oxidation peaks at E_p = 0.90, 1.07 and 1.60 V (vs. SCE). Those of **1c** are found at E_p = 1.00, 1.25 and 1.65 V (SCE), whilst those of **1b** appear at potentials of 1.50 V and higher. More anodic oxidation potentials for **1b** are reasonable as here the two electrondonating methoxy groups of **1a,c** are missing.

Controlled potential electrolysis (cpe) of **1a** at 1.00 V (SCE) at a graphite anode in an undivided cell at 10°C afforded after current consumption of 2.5 F/Mol and the total conversion of **1a** in 72% yield the imino acetal **4**, which exhibits in its cyclovoltammogram three oxidation peaks at E_p = 1.38, 1.63 and 1.86 V (SCE). At the applied anode potential of 1.00 V (SCE) it is thus inert against further oxidation. The imine **4** is probably formed by oxidation of **1a** to the radical cation, its methanolysis to **2a**, further oxidation of **2a** to the cation **3** and deprotonation to **4** (eq. 1).



(1)

	a	b
R	H	CH_3

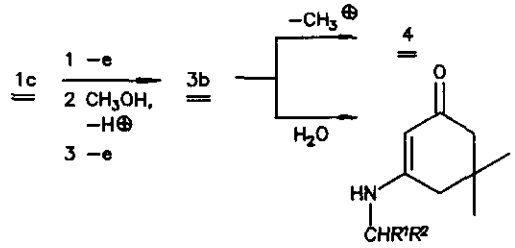


(2)

The intermediate radical cation $1a^{+\cdot}$ did not undergo the expected cyclization, presumably because it was trapped by methanolysis prior to the cyclization. The imine **4**, however, seemed to be a good precursor to form with acids a azapentadienyl cation **5**, that could undergo an electrocyclic ring closure to the tetrahydrocarbazol **6** (eq. 2), analogous to the cyclization of pentadienyl cations[9].

When **2** was treated in methylene dichloride at -35^{0}C with a catalytic amount of $CF_3CO_2H/(CF_3CO)_2O$ (20:1) **41%** of the tetrahydrocarbazole **6** was yielded. Side products were polymers of unknown structure. Other acids, as *p*-toluenesulfonic acid did not increase the yield of **6**, BF_3 etherate led to tars.

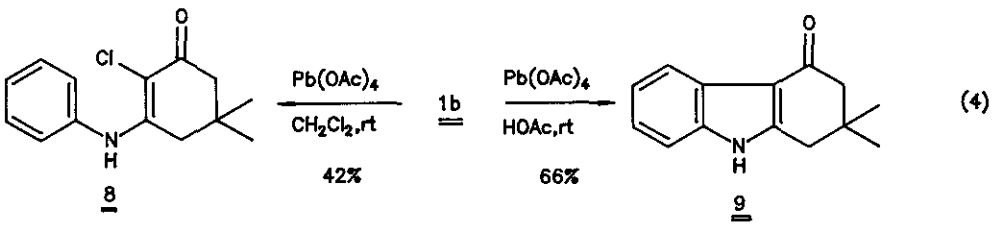
The enone **1c** was chosen as the next substrate, because here the deprotonation at nitrogen, which perhaps prevented the cyclization of the radical cation of **1a**, was not possible. When **1c** was electrolyzed under similar conditions as **1a** after consumption of 6 F/Mol and total conversion of **1c** the compounds **4** (16%), **7a** (39%), **7b** (6%) and **7c** (6%) were found. The formation of the products can be rationalized the following way (eq. 3). The radical cation of **1c** reacts to **3b** that undergoes demethylation to **4**[10] or hydrolysis to **7a**. The enaminoketone **7a** is further oxidized at the methyl group to **7b** and **7c**[11].



(3)

	R¹	R²
a	H	H
b	H	MeO
c	MeO	MeO

Controlled potential electrolysis of **1b** at 1.50 V (SCE) in methanol led to an unseparable product mixture, possibly at this potential the products are further oxidized. The oxidation with lead tetraacetate proved to be more successful, although the oxidation in methylene dichloride was not encouraging, because chlorination to **8** (eq. 4) was found. However, in acetic acid within 3 h at room temp 66% tetrahydrocarbazole **9** was obtained. The yield is two- to threefold higher than this found with the more expensive palladium acetate[8].



(4)

The anodic cyclizations of N-benzyl- and N-2-phenethylenaminones[4] are published in a separate paper.

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EXPERIMENTAL

Equipment for cyclovoltammetry (CV) and preparative electrolyses[12].

Preparative electrolyses were conducted in methanol (0.1 M $NaClO_4$) in an undivided cell (anode: 105 cm^2 graphite cyclinder [P 127, Sigri-Meitingen, FRG], cathode: graphite rod) at 10°C. For work-up the electrolyte was rotaevaporated in the cold, the residue extracted with CH_2Cl_2 (5x50 ml), insoluble supporting electrolyte was filtered off, the CH_2Cl_2-solution dried ($MgSO_4$) and the crude product was purified by chromatography [high pressure liquid chromatography (HPLC) on silica gel Si 60, 7µm (Merck)].

3-Anilino-5,5-dimethylcyclohex-2-enone (**1b**): A solution of aniline (3.00 g, 32.3 mmol), 5,5-dimethyl-1,3-cyclohexanedione (4.51 g, 32.25 mmol) and 2 drops of conc. sulfuric acid in 200 ml of abs. toluene were heated 6 h in a Dean-Stark trap. After concentrating the solution and recrystallization (acetone : hexane, 1:1) **1b** (4.5 g, 20.96 mmol, 65%) was obtained, mp 181-182°C (lit.[13] mp 181°C). Ir (CH_2Cl_2) ν 3390, 1610, 1575, 1500 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ(ppm) 1.04 (s, 6H), 2.18 (s, 2H), 2.37 (s, 2H), 4.56 (s, 1H), 7.09-7.29 (m, 5H), 7.81 (s, 1H); ms (70eV) m/z (%) 215 (M^+, 82), 198 (18), 159 (100).

3-(3,4-Dimethoxyanilino)-5,5-dimethylcyclohex-2-enone (1a): 3,4-Dimethoxyaniline (1.00 g, 6.53 mmol) and 5,5-dimethyl-1,3-cyclohexanedione (0.951 g, 6.53 mmol) in 150 ml of abs. toluene yielded as above after recrystallization (n-hexane:acetone, 1:1) 1a (1.52 g, 5.55 mmol, 85%) in yellow needles, mp 203-204°C. Ir (KBr) ν 3400, 1610, 1580, 1500; uv (ethanol) $\lambda_{max}(\varepsilon)$ 310 (19098), 236 (8368); ^{1}H-nmr($CDCl_3$) δ 1.11 (s, 6H), 2.20 (s, 2H), 2.34 (s, 2H), 3.83 (s, 3H), 3.88 (s, 3H), 5.42 (s, 1H), 6.40 (s, 1H), 6.70-6.83 (m, 3H); ms (70eV) m/z (%) 276 (M^++1, 20), 275 (M^+, 100). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.68; N, 5.08. Found: C, 69.70; H, 7.75; N, 5.00.

3-(N-Methyl-3,4-dimethoxyanilino)-5,5-dimethylcyclohex-2-enone (1c): A solution of 1b (0.50 g, 1.81 mmol) in 100 ml of abs. toluene was heated with sodium hydride (48 mg, 2 mmol) for 1 h at reflux. After addition of methyl iodide (0.26 g, 1.81 mmol) in 10 ml of abs. toluene and refluxing for 2 h, 50 ml of ice water was added, the organic layer was separated, the aqueous layer was extracted with chloroform (3x50 ml) and the combined organic layers were dried ($MgSO_4$). Chromatography of the crude product (HPLC, methylene dichloride : ethyl acetate : methanol, 4:4:2) yielded 1c (0.42g, 1.46 mmol, 81%) as a light yellow oil. Ir (CH_2Cl_2) ν 2880, 1610, 1550, 1500; ^{1}H-nmr($CDCl_3$) δ 1.25 (s, 6H), 2.16 (s, 2H), 2.25 (s, 2H), 3.30 (s, 3H), 3.93 (s, 3H), 3.97 (s, 3H), 5.35 (s, 1H), 6.65-6.90 (m, 3H); ms (70eV) m/z (%) 289 (100), 272 (98). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.44; H, 8.07; N, 4.94.

Electrolysis of 1b: 1b (0.30 g, 1.09 mmol) was electrolyzed in 90 ml of methanol (0.1 M $NaClO_4$) at a graphite anode at 1.00 V (SCE) until 2.5 F/Mol and all of 1b (DC-control) was consumed. After work-up and HPLC-purification (methylene dichloride : ethyl acetate : methanol, 4:4:2) N-1-(5,5-dimethylcyclohex-1-en-3-one)-1,1,2-trimethoxy-2,5-cyclohexadien-4-imine (4) (0.239g, 0.78 mmol, 72%) was obtained as a brown oil. Ir (CH_2Cl_2) ν 2900, 2820, 1645, 1590; uv (ethanol) λ_{max}(e) 265 (12910): ^{1}H-nmr($CDCl_3$) δ 1.17 (s, 6H), 2.3 (s, 2H), 2.33 (s, 2H), 3.32 (s, 6H), 3.78 (s, 3H), 5.36 (s, 1H), 5.68 (s, 1H), 6.34 (d, 1H, J=12Hz), 6.55 (d, 1H, J=12Hz); ms (70eV) m/z (%) 305 (M^+, 20), 290 (40), 274 (84). M^+ (MS) Calcd for $C_{17}H_{23}NO_4$: 305.1626. Found: 305.1617.

Conversion of 4 into 6: 4 (0.10g, 0.32 mmol) in 35 ml of methylene dichloride was stirred for 2 h at -35°C under nitrogen with 0.1 ml of trifluoroacetic acid/trifluoroacetic anhydride (20:1). The brown-black solution was then neutralized to pH ~8 with a saturated sodium bicarbonate solution. Work-up and chromatography (HPLC, methylene dichloride : ethyl acetate : methanol, 4:4:2) yielded 2,3-dihydro-6,7-dimethoxy-2,2-dimethylcarbazol-4(1H)-one (6) (35 mg, 0.13 mmol, 41%) as a yellow oil. Ir (CH_2Cl_2)ν 3430, 1640, 1590 cm^{-1}; ^{1}H-nmr($CDCl_3$) δ 1.16 (s, 6H), 2.45 (s, 2H), 3.88 (s, 3H), 3.95 (s, 3H), 6.86 (s, 1H), 7.68 (s, 1H), 8.68 (s, 1H); ms (70eV) m/z (%) 273 (M^+, 100), 258 (30), 217 (29). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.30; H, 7.00; N, 5.12. Found: C, 70.40; H, 7.04; N, 5.19.

Electrolysis of 1c: 1c (150 mg, 0.519 mmol) was electrolyzed, as **1b**, until 6 F/Mol was consumed. Usual work-up and chromatography yielded three fractions: a) 4 (23 mg, 0.077 mmol, 15%); b) 15 mg of a 1:1-mixture of 3-(N-methoxymethylamino)-5,5-dimethylcyclohex-2-enone (**7b**) [Gc/Ms (70eV)) m/z (%) 184 (M^+, 10), 169 (70), 153 (100)] and 3-(N-dimethoxymethylamino)-5,5-dimethylcyclohex-2-enone (**7c**) [Gc/Ms(70eV) m/z (%) 230 (M^+, 6), 215 (20), 199 (100)]; c) 31 mg (0.2 mmol, 39%) of 5,5-dimethyl-3-methylaminocyclohex-2-enone (**7a**); mp 153-154°C (lit.[14] mp 153-164°C); ir (CH_2Cl_2)ν 3440, 2880, 1585, 1530 cm^{-1}; ^{1}H-nmr($CDCl_3$) δ 1.08 (s, 6H), 2.18 (s, 3H), 2.80 (s, 2H), 2.82 (s, 2H), 4.90 (s, 1H), 5.09 (s, 1H); ms (70eV) m/z (%) 154 (M^++1, 6), 153 (M^+, 55).

$Pb(OAc)_4$-oxidation of 1b:

a: In methylene dichloride: **1b** (0.50 g, 2.32 mmol) in 50 ml of methylene dichloride was stirred under nitrogen at 0°C for 12 h with lead tetraacetate (2.00 g, 4.64 mmol). Neutralization with a sodium bicarbonate solution, work-up and chromatography (HPLC, methylene dichloride : ethyl acetate, 1:1) yielded 2-chloro-3-anilino-5,5-dimethylcyclohex-2-enone (**8**) (0.24 g, 0.97 mmol, 42%) as white prisms (acetone : hexane, 1:1), mp 183°C; ir (CH_2Cl_2) ν 3350, 1630, 1565, 1370; ^{1}H-nmr($CDCl_3$) δ 1.05 (s, 6H), 2.43 (s, 2H), 2.44 (s, 2H), 7.31 (s, 1H), 7.12-7.45 (m, 5H); ms (70eV) m/z (%) 251 (M^+, 35), 249 (M^+, 100). Anal. Calcd for $C_{14}H_{16}NOCl$: C, 67.33; H, 6.45; N, 14.19; Cl, 5.60. Found: C, 67.21; H, 6.57; N, 14.29; Cl, 5.47. Furthermore **1b** (0.174 g, 0.81 mmol, 35%) was eluted.

b: In acetic acid: **1b** (50 mg, 0.23 mmol) in 25 ml of acetic acid was stirred with lead tetraacetate (0.154 g, 0.34 mmol) for 3.5 h, when **1b** was nearly consumed. After neutralization (aqueous $NaHCO_3$) and usual work-up by chromatography (HPLC, methylene dichloride : ethyl acetate, 3:2) 2,3-dihydro-2,2-dimethylcarbazol-4(1H)-one (**9**) (32 mg, 0.15 mmol, 66%) was obtained; mp 208-209°C (lit.[5] mp 209-211°C); ir (CH_2Cl_2) ν 3440, 1640 cm^{-1}; ^{1}H-nmr($CDCl_3$) δ 1.21 (s, 6H), 2.52 (s, 2H), 2.88 (s, 2H), 7.22-8.20 (m, 4H); ms (70eV) m/z (%) 214 (M^++1, 10), 213 (M^+, 78), 157 (100). - Furthermore **1b** (5 mg, 0.025 mmol, 11%) was eluted.

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