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Cathodic Synthesis of 2-Amino-2-propene-1-ones Electrolytical Studies on Vinylazides, VII.

Dierk Knittel* and **V. Suryanarayana Rao****

Institut für Physikalische Chemie, Universität Hamburg,
D-2000 Hamburg, Federal Republic of Germany

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The cathodic preparation of enamino ketones from enazidoketones has been generalised to include heteroaromatic and aliphatic derivatives. Mechanistically the role of different sites of protonation, either on N^1 of the N_3-group or on carbonyl depending on electrolysis potential and acid strength, apparent by product distribution, is clarified. Aldehydic groups are preferentially reduced compared to the vinylazide part. Purely aliphatic azidoketones yield conjugated dienes under reductive acetylation, which might be useful for cycloaddition reactions.

[Keywords: Enazidoketones; Enaminoketones; 2-Acetoxy-3-amino-dienes-(2,4); Cathodic reduction mechanism]

Elektrolytische Untersuchungen an Vinylaziden, 7. Mitt.: Kathodische Synthese von 2-Amino-2-propen-1-onen

Die kathodische Synthese von Enaminoketonen aus ungesättigten Azidoketonen wurde auf heteroaromatisch substituierte und auf rein aliphatische Derivate übertragen. Zum Reduktionsmechanismus wurde der Einfluß verschiedener Stellen der Protonierung (am N^1 der N_3-Gruppe bzw. an der Carbonylgruppe), abhängig von Potential und Säurestärke, untersucht. Aldehydische Gruppen als weitere funktionelle Gruppen im Enazid werden leichter als die Vinylazide reduziert. Die rein aliphatischen Enazidoketone ergeben bei reduktiver Acylierung konjugierte Diene.

Introduction

The successful cathodic preparation of enamino-carbonyl compounds from azidochalcones (1,3-diaryl-2-azido-propene-2-ones) as described in

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* Present address: Deutsches Textilforschungszentrum Nord-West, Institut für textile Meßtechnik, D-4150 Krefeld, Federal Republic of Germany.

** Present address: Department of Chemistry, University of Anantapur, 515003 (AP), India.

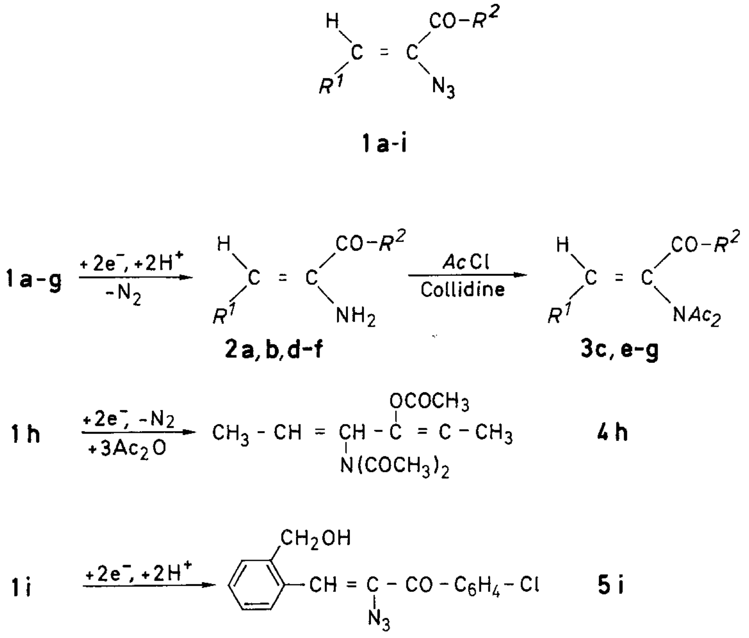
a previous paper [1] prompted us to include sensitive heteroaromatic substituents into the starting azido compounds and to investigate more clearly the role of protons in the course of reaction. From a preparative point, any type of enazidocarbonyl compound, even pure aliphatic ones, should be tested as precursor of enamines.

Results and Discussion

Electrolysis at the First Reduction Potential

A survey of compounds studied in electrolysis at the first reduction potential is given in Scheme 1.

Scheme 1. Products of cathodic reduction of enazidoketones



1a	R^1 = 4-Tolyl	R^2 = 4-Cl—C_6H_4
1b	4-Anisyl	4-Cl—C_6H_4
1c	4-F—C_6H_4	4-Cl—C_6H_4
1d	2-Furyl	4-Cl—C_6H_4
1e	2-Thienyl	4-Tolyl
1f	3-Indolyl	4-Cl—C_6H_4
1g	4-Cl—C_6H_4	Methyl
1h	Ethyl	Methyl
1i	2-Formylphenyl	4-Cl—C_6H_4

Table 1. *Reaction conditions and products in electrolysis of enazidoketones in the presence of proton donors at the first reduction potential*

Substrate	E_{p1}[a]	E_{p2}[a]	E_{el}[b]	Charge per mol	Products (% yield, HPLC)	
					of enamines	of diacylenamines
1 a	− 1.21	− 1.65[r]	− 1.25	2.5	2 a (85)	—
1 b	− 1.05	− 1.73[r]	− 1.25	4.3	2 b (90)	—
1 c	− 1.12	− 1.54	− 1.11	2.2	2 c (80)[s]	3 c (52)
1 d	− 1.09	− 1.36	− 1.11	2.0	2 d (70)	—
1 e	− 1.15	− 1.73	− 1.17	2.5	2 e (75)	3 e (55)
1 f	− 1.32	− 1.71	− 1.35	2.1	2 f (90)[s]	3 f (65)
1 g	− 1.05	− 1.85	− 1.35	2.4	2 g (88)[s]	3 g (60)
1 h	− 1.77	—	− 1.80	2.7	4 h (10)	
1 i	− 1.15	− 1.56	− 1.20	1.2	5 i (50) (enazide)	

[a] Peak potential in CV: *AN*/*TEAB*/*Ac*OH, 50 mVs^{-1} on Hg vs. SCE
[b] Potential of electrolysis, totally 5 m*M* of **1 a–i**
[r] Quasi-reversible
[s] In solution only

In most cases the enazido system is reduced with loss of N_2 in the first reduction step whereas compounds bearing an additional aldehydic function like **1 i** are reduced preferential to the carbinol stage (**5 i**) the N_3-group remaining uneffected.

Generally the reduction under protic conditions at the first reduction potential runs as an ECCEC-mechanism:

$$RN_3 \rightarrow (+e^-/-N_2/+H^+/+e^-+H^+) \rightarrow RNH_2$$

The details of preparative results are shown in Table 1.

Electrolysis at the Second Reduction Potential

To clarify the following discussion on the reduction of azidochalcones a cyclic voltammogramm of 1-(4-chlorophenyl-)-azido-1-(4-anisyl-)-propene-2-one-1 (**1 b**) in the presence of scavengers for anonic intermediates (*Ac*$_2$O or *Ac*OH) is presented in Fig. 1. Since no stringent anhydrous conditions may be prevailing at the electrode even using the anhydride as additional reagent the voltammogram is discussed best in terms of the dominating presence of protons.

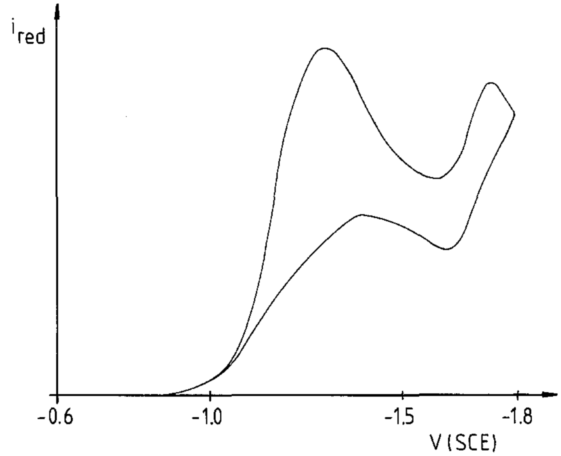
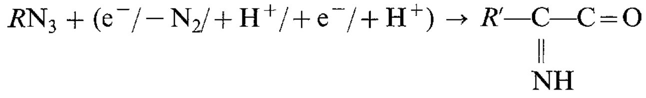


Fig. 1. CV of the reduction of azidochalcone **1b** in *AN/TEAB* at Hg, 50 mVs^{-1}

In the preceeding paper [1] the unusual features of the reduction of azidochalcones, i.e., a totally irreversible reduction peak followed by a quasireversible reduction process at more negative values have been discussed in terms of an ECCEC-mechanism with a different course of protonation, i.e.,



$$RN_3 + (e^-/-N_2/+H^+/+e^-/+H^+) \rightarrow R'\text{—}\underset{\underset{\text{NH}}{\|}}{\text{C}}\text{—C=O}$$

leading to structures like a ketone-imine, which might be reducible reversibly in the potential range mentioned (c.f. [2a, b]). If this interpretation would be correct, electrolysis at the second reduction potential in the presence of protons would lead to the saturated α-aminoketone consuming four electrons per mole of azide.

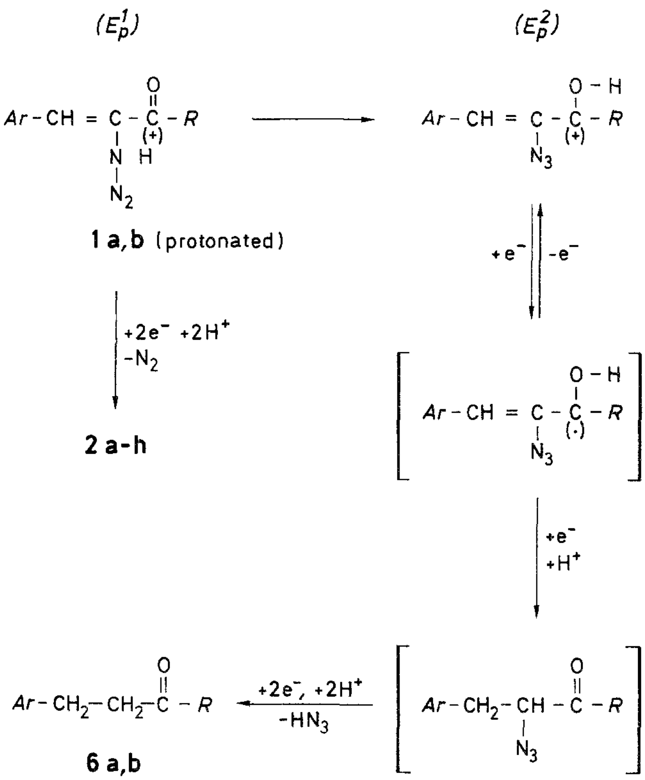
In order to check this hypothesis, preparative electrolyses have been performed at negative values, resulting in high yields of the simple saturated ketones (**6a, b**), free of any nitrogen function (only a very weak release of N_2-bubbles can be observed under these conditions; less than 5% of nitrogen containing byproducts can be found).

To trace the fate of the N-functions quantitative analyses of the catholyte with respect to N_3^--ions have been performed at the end of the electrolysis, which gave a yield of about 3% N_3^-. This low value may be due to losses of hydrazoic acid due to its reducibility. The standard redox potential for the reduction of HN_3 to NH_4^+ and N_2 in aqueous solution lies at very positive value of 1.96 V [3] (solvent effects may contribute for a shift of 1 V, other shifts will be due to the kinetics of the reduction on Hg), experimentally the reduction of a solution of HN_3 in *A*N starts as a drawn-out wave at -1.5 V vs. SCE.

These reductions proceed with a consumption of almost exactly four electrons per mole of substrate. Since any reduction going through keto-imino structures and splitting off of the third nitrogen atom afterwards, would require six electrons per mole, another explanation for the occurrence of the quasi-reversible peak in azidochalcone-reduction has to be thought.

The results can best be rationalized by the following situation at the electrode interphase. An equilibrium, which might be potential dependent, exists between the N-protonated azido group and the protonated carbonyl function. The $C=OH^+$ group is reduced reversibly on the time scale of the CV-experiments, ultimately yielding, after a second electron

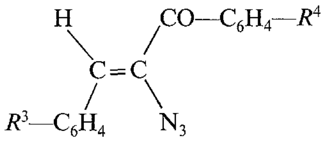
Scheme 2. Protonated forms of azidochalcones and their reduction at different potentials E_p^1 and E_p^2



transfer and protonation, a saturated α-azidoketone. Saturated azidoketones are known to loose N_3^- on reduction under protic conditions [4]. The overall reduction by this path requires only four electrons per mole as found experimentally. The peak heights in the voltammograms reflect roughly the equilibrium composition of the two protonated species, if as a first approximation the kinetics of protonation are neglected (Scheme 2).

Table 2. *Selected peak potentials of 4,4′-substituted azidochalcones* (*AN*/*TEAB*/*Ac*$_2$O; 50 mVs^{-1})

R^3	R^4	E_{p1}	E_{p2}	$E_{p2}{}^a$
—H	—H	− 1.28	− 1.78	—
—CH_3	—Cl	− 1.21	− 1.68	− 1.60
—OCH_3	—Cl	− 1.05	− 1.73	− 1.61
—CH_3	—Br	− 1.27	− 1.42	− 1.30
—Cl	—CH_3	− 1.35	− 1.55	—
—Cl	—Cl	− 1.39	− 1.63	—
—OH	—CH_3	− 1.50	− 1.76	—



[a] Potential of the anodic peak

In order to get some insight in the homogeneous protonation behaviour some IR-measurements [5] of compound **1 a** in $CHCl_3$ in the presence of trifluoroacetic acid have been made. A preferential protonation on nitrogen (37% decrease of intensity of the N_3-band compared to only 25% decrease of the C=O-band) is thereby indicated. Another position for protonation might be the β-carbon atom, which should only be discussed in very strongly acidic solutions [6].

As can be seen in Table 2 only those azidochalcones bearing an electron donating substituent in the ring at C^3 together with an electron withdrawing substituent in the aromatic part of C^1 show reversible behaviour at the second potential. Any other combinations of substituents at the aromatic parts are reduced irreversibly at both peak potentials, thus reflecting the stabilization of the intermediate radicals on the time scale of the CV-experiments by a push-pull effect.

The details of this protonation reaction, heterogeneously or homogeneously, will be subject to further investigations in due course.

Experimental

All electrolyses were performed in a cell as described in [7]. Usually 20 cm^3 of *AN* (dried over alumina Woelm Super B1) and 2 cm^3 of *Ac*OH, containing 0.1*M* *TEAB*, are pre-electrolyzed at the working potential chosen (usually 0.1 V more negative than the peak potential in CV; all values vs. SCE) until the residual current had fallen to about 5 mA. Substrate is added in portions of 0.5 to 1.0 m*M* resulting in electrolysis currents ranging from 300 to 800 mA. New material is added after the current of the previous addition has fallen to about 10% of the initial value. The progress of a synthesis is monitored by HPLC-analysis after each interval (7 μm silica). Work up of the reaction mixtures, i.e. evaporation, neutralization, extraction and flash-chromatography (40 μm, Baker) follows the way described in the previous paper unless otherwise noted (*EE* = ethyl acetate, *PE* = petrolether, DIP = diisopropylether). In cases, where the enamines **2** obtained are sensitive to work up, the reaction mixture, after removal of *AN*, is chemically acetylated by using collidine/*Ac*Cl in CH_2Cl_2 at room temperature and the N,N-diacetylated compounds (**3**) have been characterized.

IR-spectra are recorded in KBr, ^{1}H-NMR-spectra (60 MHz and 270 MHz) in $CDCl_3$/*TMS*, mass spectra are taken at 70 eV ionization energy.

Starting azidochalcones have been prepared according to [8]. The properties of newly synthetized ones are given below.

4-(4-Chlorophenyl-)-3-azido-butene-3-one-2 (**1 g**)

From 4-chlorobenzaldehyde und azidoacetone in 56% yield as yellow crystals.

$C_{10}H_8ClN_3O$ (221.65). Mp. 114–120 °C (dec., *Me*OH). ^{1}H-NMR: δ 7.52 (A_2B_2), 6.63 (s, —CH=), 2.50 (s, 3 H). MS [*m*/e, %] (35 Cl): 221 (M^+, 2), 193 (2), 178 (2), 151 (21), 123 (9), 116 (10), 85 (15), 43 (100). IR: 2 100, 2 080, 2 070 (N_3), 1 675 (C=O) cm^{-1}.

3-Azido-hexene-3-one-2 (**1 h**)

From porpionaldehyde and azidoacetone in 60% yield as pale yellow oil.

$C_6H_9N_3O$ (139.16). Bp. 37 °C (0.4 mm Hg). ^{1}H-NMR: δ 5.88 (t, —CH=, $J = 8$ Hz), 2.28 (q, 2 H, $J = 8$ Hz), 1.23 (s, 3 H), 1.05 (t, 3 H, $J = 8$ Hz). MS [*m*/e, %]: 96 (M^+-acetyl, 1, 689), 57 (10), 54 (15), 43 (100). IR: 2 130 (N_3), 1 685 (C=O), 1 615 cm^{-1}.

1-(4-Chlorophenyl-)-2-azido-3-(2-formylphenyl-1)-propene-2-one-1 (**1 i**)

White crystals in 60% yield by condensation of *o*-phthalaldehyde with 4-chloro-α-azidoacetophenon.

$C_{16}H_{10}ClN_3O_2$ (311.73). Mp. 107–109 °C (dec., *Me*OH). ^{1}H-NMR: δ 9.25 (s, CHO), 7.73 (mc, 9 H). MS [*m*/e, %] (^{35}Cl): 311 (M^+, 1), 285 (M^+-N_2, 3), 141 (36), 139 (100), 113 (18), 111 (48), 75 (25). IR: 2 100, 1 700 cm^{-1}.

Electrolysis at the First Reduction Potential

Procedure and data of the conversion of azide **1 a** to enamine **2 a** have been described previously [1].

1-(4-Chlorophenyl-)-2-amino-3-(4-anisyl-)-propene-2-one-1 (**2 b**)

Electrolysis of azide **1 b** at − 1.3 V using only stoichiometric amounts of HO*Ac* yields the enamine **2 b** in 80% of the theoretical amount as yellow crystals.

$C_{16}H_{14}ClNO_2$ (287.75). Mp. 209–211 °C (*EE*/*DIP*). ^{1}H-NMR: δ 7.39 (A_2B_2), 7.17 (A_2B_2), 7.03 (—CH=), 3.88 (s, 3 H), 3.75 (NH_2). MS [*m*/e, %] (^{35}Cl): 287 (M^+, 58), 285 (44), 270 (15), 250 (6), 174 (5), 158 (12), 148 (50), 139 (86), 121 (100), 111 (48). IR: 3 300, 1 630, 1 610, 1 540, 1 505 cm^{-1}.

1-(4-Chlorophenyl-)-2-(N,N-diacetylamino-)-3-(4-fluorophenyl-)-propene-2-one-1 (**3c**)

White crystals by electrolysing azide **1c** followed by chemical acetylation.

$C_{19}H_{15}ClFNO_3$ (359.78). Mp. 130–132 °C (sublim., 0.3 mm Hg). ^{1}H-NMR: δ 7.67 (A_2B_2), 7.25 (A_2B_2), 7.12 (—H=), 2.30 (s, 6 H). MS [*m*/e, %] (^{35}Cl): 359 (M^+, 2.6), 317 (35), 275 (75), 258 (4), 240 (10), 139 (21), 136 (28), 111 (17), 43 (100). IR: no NH, no OH, 1 780, 1 605, 1 590, 1 510 cm^{-1}.

1-(4-Chlorophenyl-)-2-amino-3-(2-furyl-)-propene-2-one-1 (**2d**)

Yellow crystals in 70% yield from azide **1d**.

$C_{13}H_{10}ClNO_2$ (247.68). Mp. 105–107 °C (*DIP*). ^{1}H-NMR: δ 7.43 (mc, 7 H), 5.77 (—CH=), 4.93 (—NH_2). MS [*m*/e, %] (^{35}Cl): 247 (M^+, 100), 139 (68), 111 (32), 108 (54), 81 (46), 43 (80). IR: 3 250 (NH), 1 760, 1 700 (C=O) cm^{-1}.

1-(4-Tolyl-)-2-amino-3-(2-thienyl-)-propene-2-one-1 (**2e**)

Yellow, very air-sensitive crystals by electrolysing azide **1e** under protic conditions in 75% yield.

$C_{14}H_{13}NOS$ (243.33). Mp. 125–127 °C (*DIP*). ^{1}H-NMR: δ 7.27 (mc, 7 H), 6.36 (—CH=), 4.5 (NH_2), 2.43 (s, 3 H). MS [*m*/e, %]: 243 (M^+, 100), 124/52, 119 (71), 97 (57), 91 (55). IR: 3 250, 1 700 cm^{-1}.

1-(4-Tolyl-)-2-(N,N-diacetylamino-)-3-(2-thienyl-)-propene-2-one-1 (**3e**)

By acylation of the enamine **2e** containing catholyte in 55% overall yield.

$C_{18}H_{17}N_3OS$ (327.40). Mp. 133–135 °C (*EE*/*DIP*). MS [*m*/e, %]: 327 (M^+, 3), 285 (23), 243 (39), 190 (16), 119 (88), 91 (50), 43 (100). IR: 1 650 cm^{-1}.

1-(4-Tolyl-)-2-amino-3-(3-indolyl-)-propene-2-one-1 (**2f**)

From azide **1f** at − 1.35 V as crude and labile oil.

$C_{18}H_{16}N_2O$ (276.24). MS [*m*/e, %]: 276 (M^+, 1.2), 236 (15), 144 (62), 130 (100), 91 (25). IR: 3 300 (NH), 1 650 cm^{-1}.

1-(4-Tolyl-)-2-(N,N-diacetylamino-)-3-(N′-acetyl-3-indolyl-)-propene-2-one-1 (**3f**)

White crystals starting from azidochalcone **1f** in 65% yield (after chemical acetylation with collidine/*Ac*Cl of the amine **2f** containing catholyte).

$C_{24}H_{22}N_2O_4$ (402.43). Mp. 155–158 °C (*DIP*/*Me*OH). ^{1}H-NMR: δ 7.43 (mc, 1 OH), 2.67 (s, 6 H), 2.50 (s, 3 H), 2.43 (s, 3 H). MS [*m*/e, %]: 402 (M^+, 17), 360 (29), 318 (35), 276 (41), 130 (43), 119 (78), 91 (49), 43 (100). IR: 1 700, 1 550 cm^{-1}.

1-(4-Chlorophenyl-)-2-(N,N-diacetylamino-)-butene-2-one-1 (**3g**)

White crystals starting from azide **1g** (after acetylation with AcCl/collidine) in 60% overall yield.

$C_{14}H_{14}ClNO_3$ (279.72). Mp. 157–159 °C (*DIP*). ^{1}H-NMR: δ 7.58 (—CH=), 7.35 (mc, 4 H), 2.55 (s, 3 H), 2.28 (s, 6 H). MS [*m*/e, %] (^{35}Cl): no M^+, 237 (M^+-ketene, 29), 195 (31), 160 (7), 152 (13), 43 (100). IR: no NH, no OH, 1 720, 1 700, 1 675, 1 635, 1 510 cm^{-1}.

2-Acetoxy-3-(N,N-diacetylamino-)-hexadiene-2,4 (**4h**)

Yellow oil in 10% yield electrolysing azide **1h** at − 1.65 V using *Ac*$_2$O as scavenger as the vinylogue enolacetate of 3-(N,N-diacetylamino-)-hexene-3-one-2 (**3h**).

$C_{12}H_{17}NO_4$ (239.24). ^{1}H-NMR: δ 6.27 (d, 1 H, $J = 15$ Hz), 5.60 (dt, 1 H, $J = 7$ Hz, $J = 15$ Hz), 2.32 (s, 6 H), 2.08 (s, 3 H, C^1), 1.80 (d, 3 H, $J = 7$ Hz, C^6). MS [*m*/e, %] (^{35}Cl): 239 (M^+, 2.7), 197 (7), 180 (1.4), 155 (13), 137 (30), 113 (76), 112 (50), 94 (7), 68 (11), 43 (100). IR: no NH, no OH, 1 745, 1 700 cm^{-1}.

1-(4-Chlorophenyl-)-2-azido-3-(o-methylolphenyl-)-propene-2-one-1 (**5i**)

Yellow crystals separating in 50% yield during electrolysis of the aldehydic azido compound **1i**.

$C_{16}H_{12}ClN_3O_2$ (313.74). Mp. 165 °C (dec., *PE*/*Me*OH). ^{1}H-NMR: δ 7.60 (A_2B_2), 7.15 (mc, 5 H), 5.01 (d, 1 H), 3.51 (d, 2 H). MS [*m*/e, %] (^{35}Cl): 285 (M^+-N^2, 0.8), 270 (3.4), 238 (14), 204 (10), 139 (100), 111 (35), 91 (26). IR: 3 475 (OH), 2 100 (N_3), 1 660 cm^{-1}.

Calc.: C 61.25, H 3.82, Cl 11,31, N 13.49.
Found: C 61.05, H 3.81, Cl 11.55, N 13.21.

1-(4-Chlorophenyl-)-3-(4-tolyl-)-propane-2-one-1 (**6a**)

By electrolysing azide **1a** in the presence of *Ac*OH at − 1.8 V in 65% yield. Identified by MS-data and comparison with an authentic sample.

MS [*m*/e, %] (^{35}Cl): 258 (M^+, 48), 139 (100), 119 (38), 111 (35), 105 (50), 91 (18).

1-(4-Chlorophenyl-)-3-(4-anisyl-)-propane-2-one-1 (**6b**)

By electrolysing compound **1b** at − 1.8 V in 60% yield. Less than 5% of nitrogen containing materials are found as byproducts.

$C_{16}H_{15}ClO_2$ (274.7). Mp. 68–70 °C (*DIP*). ^{1}H-NMR: δ 7.67 (A_2B_2), 6.96 (A_2B_2), 3.76s, 3 H), 3.22 (t, 2 H, $J = 7$ Hz), 2.99 (t, 2 H, $J = 7$ Hz). MS [*m*/e, %] (^{35}Cl): 274 (M^+, 22), 243 (0.8), 156 (2), 139 (27), 135 (11), 121 (100), 110 (18), 108 (16), 91 (10), 43 (26).

Determination of N_3^-

Since even in the presence of large amounts of *Ac*OH no hydrazoic azid could be swept out by a stream of nitrogen from the *AN*-solutions during electrolysis, the catholyte, after conversion of 3 m*M* of azidochalcone, was set alkaline by addition of NaOH and the solvent evaporated. After dilution by water all organic material was removed by extraction with ether. The residual water phase was analyzed according to *Franco* et al. [9] by using the absorbance at 321 nm of the $CN_3S_2^-$-species formed with CS_2.

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