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Electrochemical Oxidation of Dihydroindoloquinazoline and Dihydroquinazoline Derivatives

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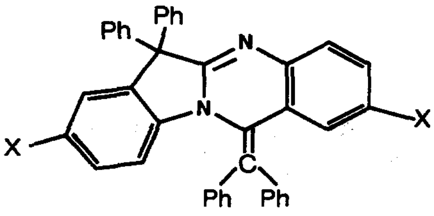
Abstract: The electrochemical properties of tetracyclic dihydroindoloquinazoline and bicyclic dihydroquinazoline derivatives of type **1** and **2** have been studied in dichloromethane, both on Pt and glassy carbon anodes. Cyclic voltammetric results are discussed in terms of substituent and steric effects on the first and second anodic peak potentials. Anodic oxidation of type **1** compounds yields purple solutions (presumably cation radical species), regardless of the nature of the substituent. Exposure of the purple solutions to both light and air results in the formation of decomposition products: benzophenone and cyclic amides of type **4** (the X-ray crystal structure of **4c** has been determined). On anodic oxidation, both **2b** and **2c** undergo mostly ring-closure to form the tetracyclic derivatives **1b** and **1c** , respectively, whereas **2d**, which does not undergo cyclization, yields the bicyclic amide **5d**. The mechanism of the formation of products is discussed.

INTRODUCTION

Recently we have investigated[1] the anodic oxidation of aryl-substituted ketene imines of type $(XC_6H_4)N{=}C{=}CPh_2$. The effect of substituent on their redox properties (by cyclic voltammetry) and the outcome of preparative anodic oxidation have been discussed[2] in terms of both electronic and steric factors. In general, they undergo unique intermolecular cyclization processes to form bi- and tetracyclic dimeric heterocycles (**1** and **2**, respectively), as well as trimeric tricyclic carbocation salts.[3] The major products (~70%) obtained from ketene imines with X=H, *p*- Me or *p*- OMe are the tetracyclic dihydroindoloquinazolines of type **1**, while for those with electron-withdrawing substituents (X= *p*- NO_2, *m*- NO_2 or *p*- CN), the bicyclic dimers of type (**2**), containing the quinazoline skeleton, become predominant. It is noteworthy, that the chemical synthesis of both types of heterocycles is unknown and they are not naturally occurring compounds. However, each individual moiety in the fused system in **1**, namely quinazoline and indole, is found in alkaloids and biologically active drugs.[4]

The present paper describes the electrochemical properties and results obtained from anodic oxidation of compounds of type **1** and **2** (formerly the products from ketene imines electrochemical oxidation [1,2]), which lead to new cyclic amides (*vide infra*, **4** and **5**).



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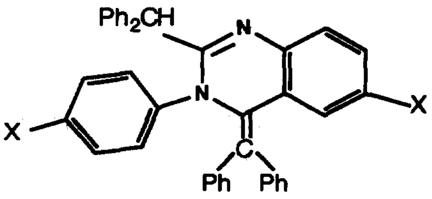

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RESULTS AND DISCUSSION

Cyclic voltammetry and MO calculation

Table 1 shows cyclic voltammetric data of heterocycles of type **1** and **2**. All derivatives studied afford two oxidation waves, except for the nitro compound, **1e**. Also, all first oxidation waves (Ep_{ox}^1) are reversible and all the second ones (Ep_{ox}^2) are irreversible.

Table 1. Cyclic Voltammetric Data^a for **1** and **2**

Substrate (substituent)	Ep_{ox}^1 (V)^{b,c}	Ep_{ox}^2 (V)^{b,d}
1a (H)	0.77 (0.83)	1.22 (1.25)
1b (p-Me)	0.75 (0.70)	1.22 (1.18)^e
1c (p-OMe)	0.62 (0.73)	1.20 (1.30)^e
1d (p-Br)	0.90 (0.95)	1.18 (1.23)
1e (p-NO_2)	1.22 (1.24)	- (-)
2b	0.53 (0.70)	1.07 (1.13)
2c	0.51 (0.68)	1.13 (1.23)
2d	0.75 (0.90)	1.17 (1.20)
2e	1.02 (1.05)	1.25 (1.23)
2f (p-CN)	0.95 (0.98)	1.22 (1.24)

[a] [substrate]=1 mM; electrolyte: 0.1M tetrabutylammonium fluoroborate in CH_2Cl_2. All potentials are recorded at Pt *vs* Ag/AgCl reference electrode. Scan rate: 50 mV/s.

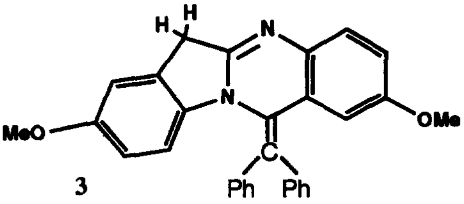
[b] Values in parentheses represent results glassy carbon working electrode.

[c] Reversible waves even under oxygen atmosphere.

[d] Irreversible waves

[e] Quasi-reversible

Since it is not clear *a priori* which site in **1** or **2** is susceptible for the first oxidation (e.g., C=C or C=N bond, or aryl group), and in order to shed light on this issue, Extended Hueckel calculations[5] have been conducted for a model molecule, **3**, using the coordinates obtained by X-ray diffraction of **1c**. The results show that the HOMO mainly involves the 'p' orbitals of the olefinic C=C bond, the lone pairs of the two nitrogens, and to a smaller extent, the two aryl groups. The calculated 'reduced charge' on the exocyclic C=C



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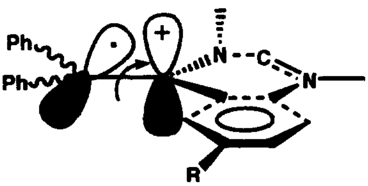
bond is: $Ph_2C(0.5320)$=$C(0.2168)$. The contribution of the two phenyl groups in **3** is negligible because their planes are not co-planar with the plane of the C=C bond. Therefore, it seems likely that the initial anodic step involves the oxidation of this double bond of which the charge density is directly affected by the neighbouring aryl group, and thus by the nature of the substituent attached to it.

Table 1 also shows that electron-donating groups reduce the first peak potential (Ep_{ox}^1) while electron-withdrawing groups increase it. Furthermore, only the first peak potentials are linearly dependent on the substituents, as shown by the Hammett plots in the Figure 1. However, the second oxidation waves are quite similar (~1.1-1.2V) and independent on the nature of the substituent. The almost independence of the second oxidation wave on the nature of the substituent may indicate that once a cation-radical is formed, the 'p' orbital which contains the unpaired electron is no longer conjugated with the π system of the adjacent aryl ring. Meeting such a hypothesis requires that the unpaired electron will be localized at the 'p' orbital of the 'exocyclic' carbon (Ph_2C), and not co-planar with the heterocyclic moiety, as is demonstrated in the following scheme:



It is noteworthy, that the first oxidation peak potentials (Ep_{ox}^1) of the bicyclic derivatives **2** are smaller than the corresponding derivatives of **1**, namely the former are easier to oxidize than the latter ones. For instance, the corresponding first oxidation potentials of **2b-2e** are 0.53, 0.51, 0.75 and 0.95V, compared with 0.75, 0.62, 0.90 and 1.22V for **1b-1e**, respectively. At least two explanations could account for this behavior: a) Each derivative of type **2** possesses a benzylic hydrogen and the oxidation of the activated benzylic carbon (followed by a loss of proton) could take place at less positive potentials than for the C=C bond, and therefore compete favorably with the latter, and b) The rigidity of molecules of type **1** causes the C=C bond in them to be more sterically hindered than that in **2**, and as a consequence they approach the electrode surface more difficult. It seems to us that explanation (b) is preferred over (a) on the following grounds: (1) No peak potentials/substituent dependence is anticipated if the benzylic carbon in **2** is firstly oxidized, and as mentioned earlier, this is not the case; and (2) There are precedents in the literature[6] which indicate that steric hindrance causes an increase in oxidation potentials.

Anodic oxidations

All three tetracyclic dimers (**1a**-**1c**) and three of the four (**2b**-**2e**) bicyclic derivatives studied afford purple color (except for **2e**, entry 10 in Table 2), regardless of the nature of the substituent, when they are oxidized anodically. However, electrolysis (e.g., of **1c**, entry 5 in Table 2) in the presence of equimolar amount of water avoids the formation of the purple color. The conversion percentage of the substrate and hence the intensity of the purple color and the yield of products are dependent on the amount of electricity consumed.

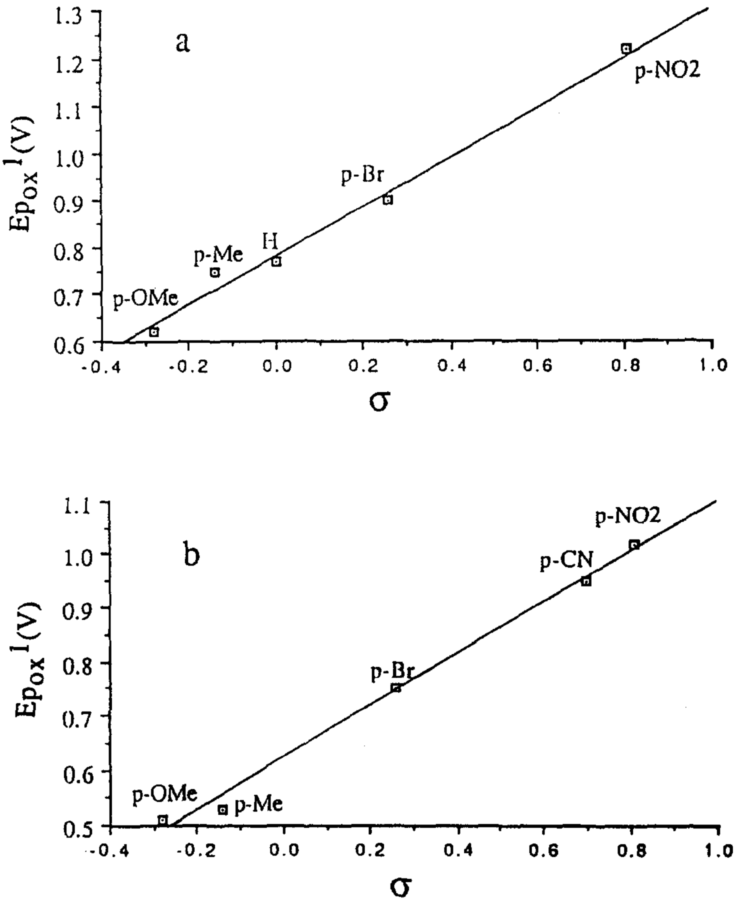


Figure 1. Hammett plots for first anodic peak potentials (Ep_{ox}^1) of: (a) **1** (correlation coefficient=0.994) ; (b) **2** (correlation coefficient=0.988)

Table 2. Products from Anodic Oxidation of 1 and 2 Beyond their Second Oxidation Wave[a]

	Substrate	Conc. (mM)	F/mol	E(V)	% Substrate recovered	UV-Vis of purple solns. (λ_{max} nm(ε))[b]	% Products (isolated)
1.	**1a**	4.7	2.1	1.2	56	540 (2700); 315 (sh)	**4a** (43)
2.	**1b**	4.4	3.6	1.2	15	540 (2650); 320 (sh)	**4b** (80)
3.	**1c**	4.2	2.6	1.2	50	560 (2565); 325 (sh)	**4c** (41)
4.	**1c**	4.2	3.6	1.2	19		**4c** (80)
5.	**1c**[c]	4.2	3.5	1.2	32	*d*	**4c** (8)[e]
6.	**1c**	4.2	3.9	0.7	24		**4c** (50)
7.	**2b**	17.7	0.7[f]	0.6	30	*g*	**1b** (30)[e]
8.	**2c**	19.5	0.7[f]	0.7	30	*g*	**1c** (20)[e]
9.	**2d**	4.3	3.8	1.2	20	540 (2858); 337 (sh)	**5d** (78%)
10.	**2e**	3.7	4.0	1.2	28	*d*	*e*

[a] In CH_2Cl_2-0.1M Et_4NBF_4, using Pt anode *vs* Ag wire quasi-reference electrode.
[b] In CH_2Cl_2.
[c] 0.4% water was added prior to electrolysis.
[d] No purple color is observed.
[e] Other unidentified products were formed.
[f] No more electricity could be passed through the solution.
[g] Purple color was observed but disappeared fast.

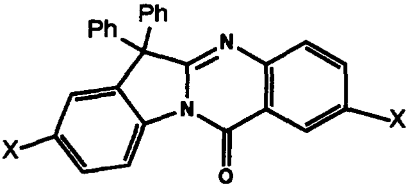
For instance, by comparing entries 3 and 4 in Table 2, the yield in the former increases form 41% to 80% upon consuming 2.6 and 3.6 F/mol, respectively. Oxidation around the first anodic peak potential results in lower yield of products (entry 6 vs. 4), or low concentration of the purple color due to low electricity consumption (entries 7 and 8).

Attempts to characterise any of the purple solutions generated from the anodic oxidation of **1** or **2**, by means of e.p.r. measurements have been unsuccessful, so far, for unforeseen reasons. Surprisingly, only in one arbitrary occasion, an e.p.r. signal was detected (from the oxidation of **1c**), with no hyperfine structure, which may hint of the presence of organic radical species.[7] However, an indirect evidence for the existence of cation radical species, which is based on the results published by Nelsen and co-workers[8,9] could be considered. The latter authors already demonstrated, that stable cation radicals could be generated electrochemically from olefins (e.g., the cation radical from adamantyl adamantylidene absorbs at λ=530nm). It is noteworthy, that the color of cation radicals of olefins[10] and thianthrene[11], are also purple and absorb at similar wave lengths. It has been suggested that the absorption in the visible region could be attributed to electrons' transition from a σ orbital to a partially filled SOMO. In our opinion, although there is no direct proof in hands, it is likely that the purple color, with a characteristic absorption at 540-560nm (Table 2), stems from cation radical species which are electrogenerated by the anodic oxidation of both the tetracyclic dimers of type **1** and the bicyclic dimers of type **2**. It should be pointed out, that in the latter case, the possibility that **2** could first cyclize to **1** and then get further oxidized to $\mathbf{1}^{+\cdot}$, cannot be ruled out, especially because such electrochemical conversion, although not quantitative, has been previously[1] demonstrated in the case of **2c**.

It is quite surprising that when the anodic oxidation takes place beyond the second oxidation wave (~1.2 V), schematically to form dicationic species, the purple color does not disappear. Also, Table 2 shows that starting material was always left (15-56%) at the end of electrolysis, under these conditions. These last two results may indicate that possibly a conproportionation reaction takes place, as follows:

$$2^{++} + 2 \rightleftharpoons 2\,(2^{+})$$

The purple mixture generated after the end of electrolysis, was found to be persistent to color change upon water addition. However, when it was exposed to air and ordinary light for few days, the color faded and turned to bright yellow. Work-up of each of the yellow solution of **1a-1c** afforded two products: benzophenone and quinazolinone derivatives of type **4**. The electrochemical oxidation of the bicyclic compounds **2b** and **2c**, resulted in partial formation of the corresponding tetracyclic products **1b-1c**, in 30% and 20% yield, respectively, among other unidentified products. However, that of **2d** yielded benzophenone and **5d**. The reaction mixture of **2e** contains, after work-up, three unidentified products and ~28% of unreacted **2e**. The spectral data for the isolated products, **4a-4c**, are described in Table 3. ORTEP drawing and STEREO view of **4c** are shown in Figure 2.



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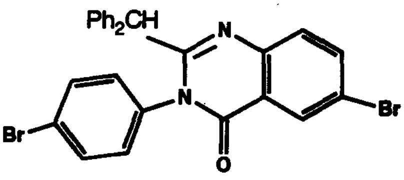


5d

Table 3. Spectral Data of Products

	IR(cm^{-1}) (C=N);(C=O)	^{1}H-nmr (CDCl$_3$, δ,ppm)	M.S.(%)
4a	1630;1680	6.61(d,1H,J=8.3Hz); 6.72(d,1H,J=8.3Hz); 7.11-7.67(m,12H); 7.74(d,2H,J=3Hz); 8.43(d,1H,J=8.1Hz); 8.72(d,1H,J=7.8Hz)	CI:387(MH$^+$,35) EI:386(M$^+$,66),385(100) 359(57),309(26)
4b	1635;1680	2.31 (s,3H); 2.42 (s, 3H); 6.73-7.00(m,3H); 7.07-7.61(m,11H); 8.13(s,1H); 8.50 (d,1H,J=7.5Hz)	CI:415(MH$^+$,100) EI:414(M$^+$,61),413(100) 399(4),337(33),321(16)
4c	1630;1680	3.81(s,3H); 3.94(s,3H); 6.89(d,1H,J= 2.6Hz);6.97 (d,1H,J=2.6Hz); 7.00 (d,1H, J= 2.6Hz);7.26-7.34(m,10H); 7.67 (d,1H,J=8.8Hz);7.78 (d,1H,J=2.6Hz); 8.63 (d,1H,J=8.8Hz)	CI:447(MH$^+$,100) EI:446(M$^+$,29),445(30) 369(14),354(3),211(17) 183(15),167(15),149(8), 116(60),105(32),84(100)
5d	1630;1680	5.08(s,1H); 6.85(d,2H, J=7.5Hz); 7.05-7.50(m,15H);	CI:MH$^+$:549(46) 547(100), 545(52) EI:548(M$^+$,42),546(100), 544(41),381(72),379(49), 183(26),168(44),167(40)

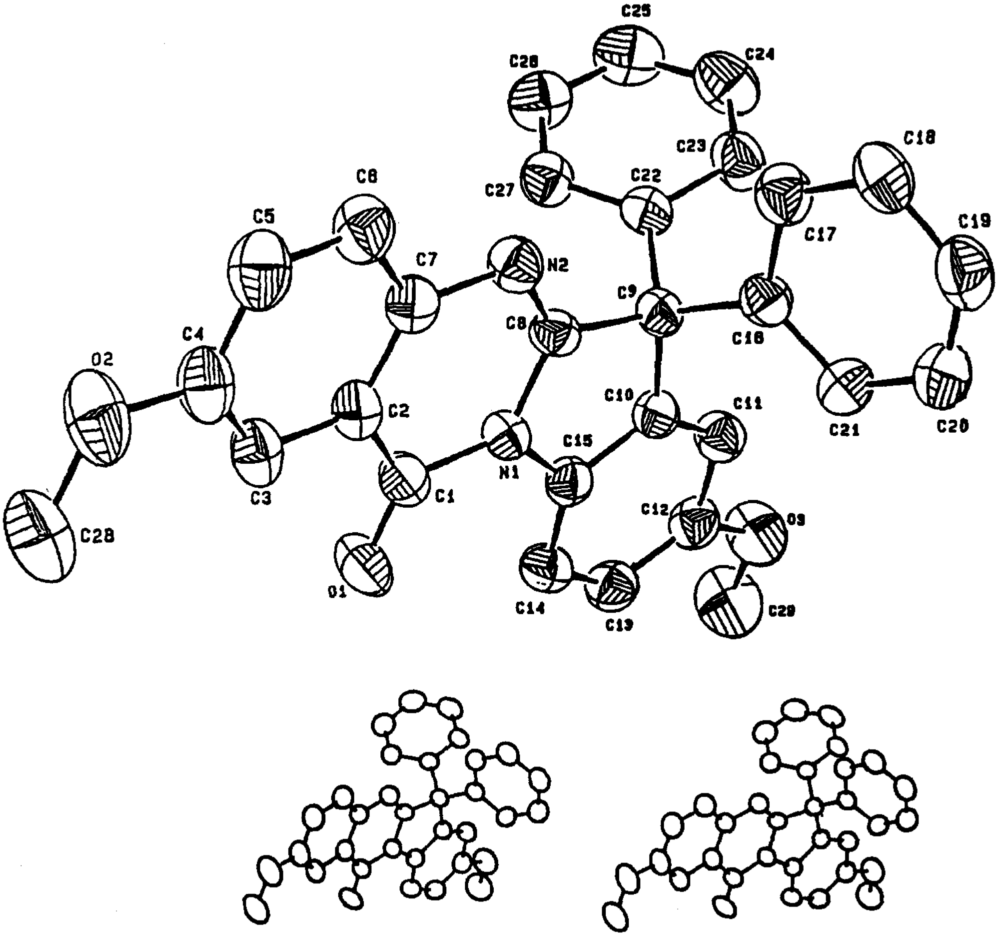
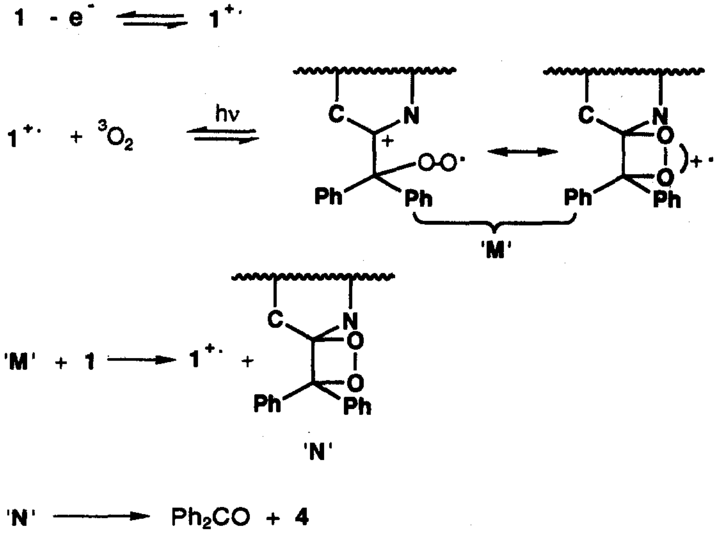


Figure 2. ORTEP and STEREO drawings of the X-ray crystal structure of 4c

MECHANISM

The reaction of triplet oxygen ($^3O_2$) with cation radicals of olefins[8,12], dienes[13] and acetylenes[14] have been studied extensively. Therefore, it seems likely that the oxidation of compounds 1 and 2 takes place at the olefinic bond in the 'Ph$_2$C=C' moiety. This assumption is also supported by our MO computations mentioned earlier. Nelsen and coworkers[10] suggested that initially formed cation radicals react with oxygen to afford peroxy cation radicals (M), followed by formation of dioxetanes (N), and decomposition to final products according to the following scheme:



CONCLUSION

Cyclic voltammetry data of new one-pot electrogenerated heterocycles, which are neither naturally occurring nor chemically synthesized, namely, tetracyclic dihydroindoloquinazoline (**1**) and bicyclic dihydroquinazoline (**2**) derivatives, afford two oxidation waves in dichloromethane, of which the first is reversible. The results indicate that while the first anodic peak potential is dependent on the substituent, the second one is not. This behavior is explained in terms of localization of the unpaired electron in a specific 'p' orbital which is not conjugated with the aryl rings. Also, Extended Hueckel computations on a model compound supports the suggestion that the site of initial oxidation is the double bond in the Ph$_2$C=C moiety.

Anodic oxidation of type **1** compounds yield purple solutions (presumably cation radical species), regardless the nature of substituent. Exposure of the purple solutions to both light and air results in the formation of decomposition products: benzophenone and cyclic amides of type **4**. The X-ray crystal structure of derivative **4c** has been determined.

Unlike the results from the oxidation of type **1** derivatives, those of **2b** and **2c** shows that they undergo mostly ring-closure to form the tetracyclic derivatives **1b** and **1c** , respectively, whereas **2d**, which does not undergo cyclization, yields the cyclic amide **5d**.

EXPERIMENTAL SECTION

Materials

Cyclic compounds of type **1** and **2** were prepared according to the electrochemical procedure described before.[1] Tetraethylammonium tetrafluoroborate (TEABF$_4$, supporting electrolyte) was purchased from Aldrich (>99%) and used after vacuum drying (~2mmHg) at 120°C for ~30h. Commercially available Ag/AgCl (from Bioanalytical Systems) was used as a reference electrode. HPLC grade CH_2Cl_2 (distilled from CaH_2) was used for preparative electrolyses.

Spectral Instruments

The following instruments have been used for spectral measurements: Nicolet 5ZDX: FT-IR spectrometer; Perkin-Elmer Lambda 5 UV-VIS spectrometer; Brukner WP200SY NMR spectrometer, and Finnigan 4020 Quadruple or V.G. Model 7035 mass spectrometers.

Electrochemistry

For cyclic voltammetry measurements, a Princeton Applied Research (PAR) potentiostat Model 173, a PAR Universal Programmer Model 175 and Yokogawa XY-recorder Model 3036, were utilized. A glass cylinder closed at one end, containing 1-5mM substrate in 5-10ml solution was used for cyclic voltammetry, employing Pt button ($3x10^{-3}$ cm^2) (or glassy carbon, ~$3x10^{-2}$ cm^2) working electrode, surrounded by Pt net cylinder auxiliary electrode. All potentials were measured vs. Ag/AgCl reference electrode. For controlled potential electrolysis, an 'H' type three-compartment cell equipped with medium glass frit as a membrane, a polished silver wire quasi-reference electrode, immersed in a glass cylinder with fine glass frit at its end and containing electrolyte solution, were used in these experiments. Typically, the anodic compartment contains 0.08-0.1 mmol of ketene-imine dissolved in 20 ml of CH_2Cl_2-0.1M Et_4NBF_4. Supporting electrolyte was previously dried in vacuum (~2mmHg) at 120°C for 30h. The solvent was distilled from CaH_2. The solvent-electrolyte solution was stored over molecular sieves (4Å) which was previously heated to 150°C under vacuum for ~30h, before electrolysis. Experiments were carried out under nitrogen atmosphere. The nitrogen gas was passed through oxygen trap (V^{2+}/Zn-Hg) and moisture trap (dry molecular sieves), before entering the electrolysis cell. Electrolyses were terminated when no ketene-imine was detected by TLC. The electrolysis mixture was left in the open till the purple color faded to yellowish one. The work-up involved stripping of the solvent followed by water addition and extraction into diethyl ether (in which TEABF$_4$ electrolyte is insoluble). After phase separation, drying over $MgSO_4$ and filtration, the solution was concentrated to ~2ml and column separated by Chromatotron (Harrison) Model 7924T, using 2mm thick silica gel (PF-254 with $CaSO_4$, from Merck) round plates. Products were separated by gradual elution with 20% 80/20 PE/CH_2Cl_2 to pure CH_2Cl_2.

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