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Electrosynthesis of dibenzonaphthyridine derivatives from 2,2-(2-nitrobenzyl)-2-substituted-acetonitriles

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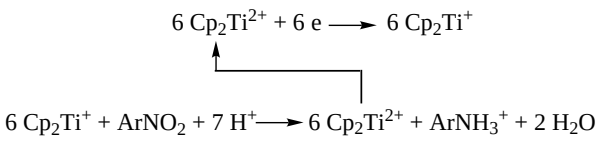
Abstract—An indirect electrochemical procedure involving an ex-cell two-phase process is proposed to produce dibenzonaphthyridine derivatives from 2,2-(2-nitrobenzyl)-2-substituted-acetonitriles in dichloromethane. The selective reduction of both nitro groups into amino groups using Cp_2Ti^+ in aqueous acidic medium avoids a cyclization of hydroxylamine intermediates as observed by direct electrolysis. © 2002 Elsevier Science Ltd. All rights reserved.

Electrochemistry has been currently used to prepare nitrogen-containing heterocycles from nitro compounds suitably substituted at the *ortho*-position.[1] It is well known that two steps leading to nucleophilic centers are generally observed during direct electrolysis of aromatic nitro compounds in acidic media. The first one, a four-electron reduction, affords hydroxylamines, the second one, a two-electron reduction, gives amines at a more cathodic potential. In this paper, we wish to report a new synthesis of dibenzonaphtyridine derivatives via diamino compounds produced by indirect electrolysis of easily available 2,2-(2-nitrobenzyl)-2-substituted-acetonitriles **1a**–**e**.[2] To our knowledge, only few studies about the reduction of similar dinitro compounds have been published. Reissert[3] studied the chemical reduction of 2,2-(2-nitrobenzyl)acetic acid and observed the formation of a dibenzonaphthyridine derivative. On the other hand, Leuch and Katinsky[4] obtained a spiro compound from the chemical reduction of 2,2-(2-nitrobenzyl)diethylmalonate.



Scheme 1.

Polarograms of **1a**–**c** and **1e** were performed in acidic medium (aqueous 2.5 M sulfuric acid–acetone, 1:4 v/v) and showed two cathodic waves. The first one corresponds to an eight-electron reduction of the two nitro groups into hydroxylamino groups. The second one, which corresponds to a four-electron reduction into the diamino derivatives, is a broad shoulder near the front of solvent. Cyclic voltammograms (scan rates 0.1 V s^{-1}) of **1a**–**c** and **1e** in the same medium were obtained at a glassy carbon electrode, and displayed a cathodic peak corresponding to the formation of hydroxylamino compounds. After potential reverse, an anodic wave attributed to the oxidation of the two hydroxylamino groups into the corresponding nitroso groups was only observed for **1e**. The absence of this wave for **1a**–**c** provided evidence for rapid chemical reactions between the hydroxylamino functions and the electrophilic nitrile centers.

Generally, when a macroscale electrolysis of a nitro aromatic compound is performed in acidic medium, at a potential close to hydrogen evolution, the whole of the substrate which is present at the electrode surface is not totally converted into the corresponding amino derivative. The intermediate hydroxylamine escapes from the cathode, so that secondary chemical reactions can take place in the bulk. Consequently, a selective reduction of **1a**–**c** into the corresponding diamino derivatives cannot be realized in a batch-cell fitted with a mercury or a glassy carbon cathode. Moreover, the solubility of **1a**–**e** in an aqueous-organic solution is low.

We initially investigated the indirect electrolysis of nitrobenzenes in organic solvent, using bis-(cyclopenta-

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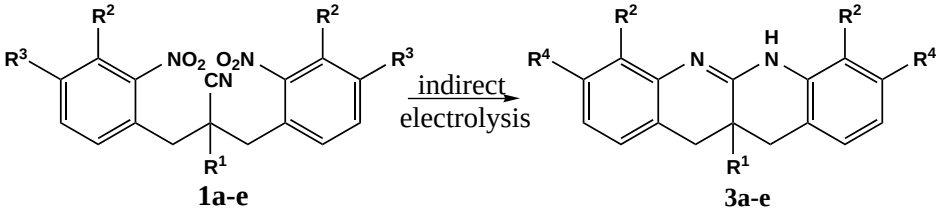
dienyl)titanium cation as mediator in an acidic aqueous medium, as depicted in Scheme 1.[5] Because of a total selectivity in the reduction of the nitro group into an amino group, side reactions which occur at the hydroxylamine step were avoided.

Typical procedure: 1 g of dinitro compounds **1a–c** and **1e–f** or tetranitro compound **1d** in 200 ml of dichloromethane in the presence of 0.5 g of titanocene dichloride dissolved in 200 ml of 1 M sulfuric acid were added in the flow system used to perform indirect electrolysis.[5a] The active form of mediator in aqueous medium was continuously regenerated at constant current intensity (0.15 A) by flowing the aqueous solution (6 ml mn^{-1}) through a graphite felt cathode until complete disappearance of the starting nitro compound. After completion of the electrolysis, an aqueous solution of sodium carbonate was added to the heterogeneous mixture until pH>8, then the two phases were separated. The aqueous solution was extracted with 3×50 ml of dichloromethane and the organic solutions were combined, dried over magnesium sulfate and evaporated to dryness. After treatment and purification of the residue, the dibenzonaphthyridines **3a–e**[6–10] (Table 1) and the spirobiquinoline **3f**[11] were obtained from **1a–e** and from **1f**, respectively.

Taken together, these results indicate that several reactions occurred during the indirect electrolysis as shown in Schemes 2 and 3. One amino group of **2a–d** (Scheme 2) reacts with a cyano group giving a fused bicyclic ring system containing an amidine function. The second amino group condenses preferentially with the amidine group affording dibenzonaphthyridines **3a–d** with ammonia elimination. Furthermore, indirect electrolysis of **1d** (entry 4) affects the four nitro groups. Because of a weaker activation of cyano group in **2e** (entry 5), the primary attack of amino group to cyano group is slow and a mixture of diamino compound **2e** (69%) together with dibenzonaphthyridine **3e** (12%) was isolated after electrolysis. **3e** was obtained as the main product by heating the mixture in acetic acid.

The unsymmetrical spirobiquinoline **3f** results from a quasi selective primary reaction between amino group and ester group (Scheme 3). We can note that a by-product was isolated in a minute quantity (2–3%) by column chromatography. ^{1}H NMR of this latter is in

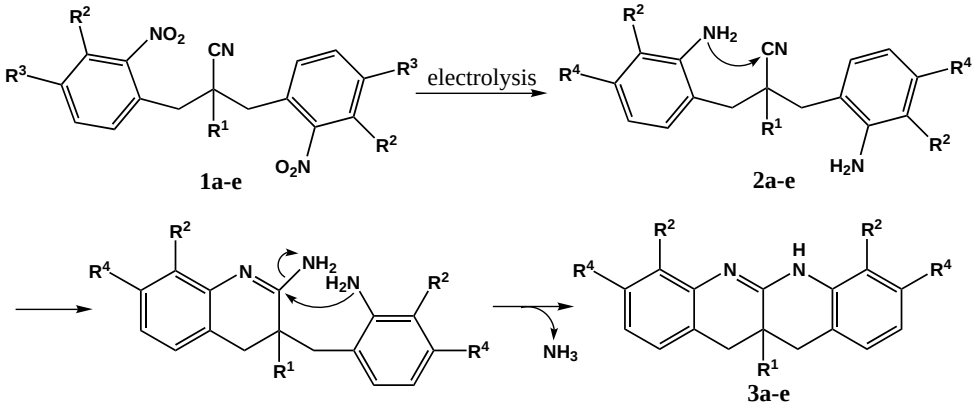
Table 1. Indirect electrolysis of 2,2-(2-nitrobenzyl)-2-substituted acetonitrile **1a–e**



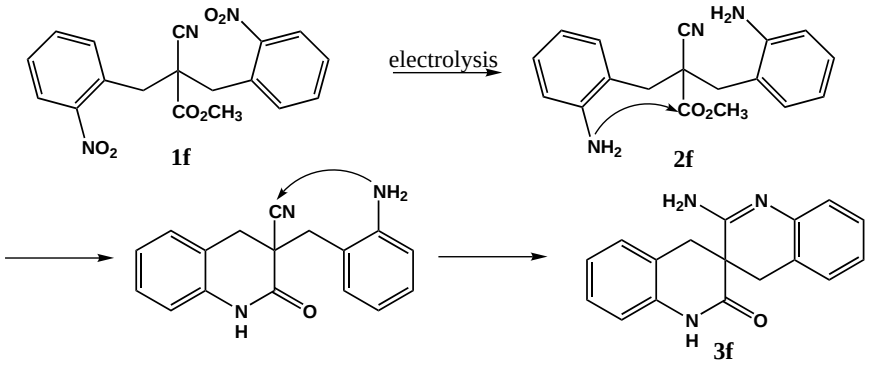
1a-e **3a-e**

Entry	Substrate				Product	Yield[a] %
	No.	R^1	R^2	R^3	R^4	
1	**1a**	CN	H	H	H	67
2	**1b**	CN	CO_2CH_3	H	H	65
3	**1c**	CN	H	CO_2CH_3	CO_2CH_3	70
4	**1d**	CN	H	NO_2	NH_2	55
5	**1e**	C_6H_5	H	H	H	65

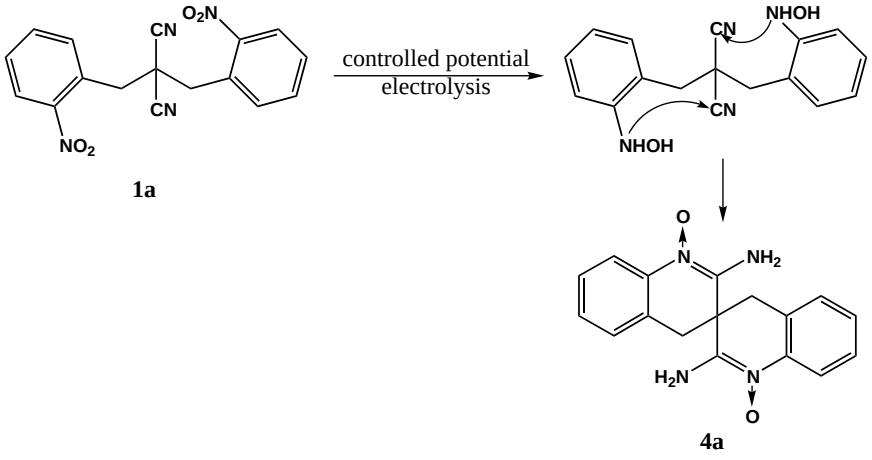
[a] Isolated after column chromatography and based on starting 2-nitrobenzyl bromides.



Scheme 2.



Scheme 3.



Scheme 4.

accordance with a dibenzonaphthyridine derivative resulting from an unfavored primary attack of amino group to cyano group.

It is worth noting that the direct electrolysis of **1a** in a mixture of 2.5 M sulfuric acid–acetone (1:4 v/v), at a mercury cathode maintained at a working potential corresponding to the first cathodic wave (–0.4 V versus SCE) afforded the symmetrical spiro compound **4a**[12] (Scheme 4).

In conclusion, we reported in this paper an efficient electrosynthesis of some dibenzonaphthyridine derivatives from readily available 2,2-(2-nitrobenzyl)-2-substituted acetonitriles. This result is consistent with a complete reduction of the two nitro groups into amino groups followed by chemical cyclizations involving only one nitrile function. However, the method cannot be used in the presence of an ester substituent at position 2.

Acknowledgements

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References

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2. The substrates **1a**–**f** were prepared from 2-nitrobenzyl bromides and, respectively, malonitrile for **1a**–**d**, benzyl cyanide for **1e** and ethyl cyanoacetate for **1f**. **1a**–**e** were obtained by phase transfer catalysis using NBu_4HSO_4 in a mixture dichloromethane/2.5 M aqueous NaOH. **1f** was prepared in ethanol containing solid sodium carbonate. 2-Nitrobenzyl bromides were obtained by refluxing overnight a mixture of 2-nitrotoluenes and *N*-bromosuccinimide in CCl_4 in the presence of catalytic amount of benzoyl peroxide. The crude substrates **1a**–**f** can be electrochemically reduced without further purification. Physical data for crystallized (dichloromethane/petroleum ether) **2,2-(2-nitrobenzyl)-malononitrile (1a)**: mp 168°C; ^{1}H NMR δ ($CDCl_3$) 4.15 (s, 4H), 7.75 (dd, 2H, $J=8.2$ Hz), 7.85–7.95 (m, 4H), 8.24 (dd, 2H, $J=8.2$ Hz); ^{13}C NMR δ 39.5, 41.1, 115.6, 126.7, 128.9, 131.3, 134.8, 134.9, 150.2; IR (KBr) $\nu_{CN}=2245$ cm^{-1}, $\nu_{NO_2}=1545$ and 1344 cm^{-1}. (**1e**) (Makosza, M.; Jagusztyn-Grochowska, J. M. *Rocz. Chem.* **1976**, *50*, 1859) and (**1f**) (Reissert, A. *Chem. Ber.* **1896**, *29*, 638) were previously described.

3. Reissert, A. *Chem. Ber.* **1894**, *27*, 2744.
4. Leuchs, H.; Katinsky, H. V. *Chem. Ber.* **1922**, *55*, 710.
5. (a) Floner, D.; Laglaine, L.; Moinet, C. *Electrochim. Acta* **1997**, *42*, 523; (b) Moinet, C.; Floner, D.; Jan, T. In *Novel Trends in Electroorganic Synthesis*; Torii, S., Ed.; Kodansha: Tokyo, 1995; p. 177; (c) Jan, T.; Floner, D.; Moinet, C. *Electrochim. Acta* **1998**, *44*, 201.
6. Compound **3a**: mp 218°C; ^{1}H NMR δ ($CDCl_3$) 3.40 (s, 4H), 6.97 (td, 2H, $J=7.4$ and 1.3 Hz), 7.03 (dd, 2H, $J=8$ and 1.1 Hz), 7.18–7.25 (m, 4H), 9.03 (s, 1H); ^{13}C NMR δ 36.2, 36.9, 119.7, 120.4, 122.0, 123.8, 128.7, 129.3, 142.4, 152.5; IR (KBr) $\nu_{NH}=3295$ cm^{-1}, $\nu_{CN}=2240$ cm^{-1}; MS (m/z) calcd for $C_{17}H_{13}N_3$: 259.1109. Found: 259.1113. Anal. Calcd: C, 78.74; H, 5.05; N, 16.20. Found: C, 78.62; H, 5.10; N, 16.27.
7. Compound **3b**: mp 210°C; ^{1}H NMR δ ($CDCl_3$) 3.30 (s, 4H), 3.90 (s, 6H), 6.94 (t, 2H, $J=8$ Hz), 7.20 (d, 2H, $J=8$ Hz), 7.70 (d, 2H, $J=8$ Hz), 10.70 (s, 1H); ^{13}C NMR δ 34.2, 36.7, 52.4, 117.7, 121.2, 122.8, 130.0, 131.7, 141.2, 150.7, 168.0; IR (KBr) $\nu_{NH}=3264$ cm^{-1}, $\nu_{CN}=2235$ cm^{-1}, $\nu_{CO}=1719$ cm^{-1}; MS (m/z) calcd for $C_{21}H_{17}N_3O_4$: 375.1219. Found: 375.1204.
8. Compound **3c**: mp>250°C; ^{1}H NMR δ ($CDCl_3$) 3.30 (s, 4H), 4.00 (s, 6H), 7.45 (d, 2H, $J=7.9$ and 1.3 Hz), 7.86 (d, 2H, $J=1.3$ Hz), 8.00 (dd, 2H, $J=7.9$ Hz); ^{13}C NMR δ 34.5, 36.1, 53.7, 119.7, 122.1, 124.6, 129.4, 131.4, 132.5, 154.6, 167.7; IR (KBr) $\nu_{NH}=3291$ cm^{-1}, $\nu_{CN}=2234$ cm^{-1}, $\nu_{CO}=1725$ cm^{-1}. MS (m/z) calcd for $C_{21}H_{17}N_3O_4$: 375.1219. Found: 375.1204.
9. Compound **3d**: mp>250°C; ^{1}H NMR δ ($CDCl_3$) 3.00 (s, 4H), 6.07 (dd, 2H, $J=7.9$ and 2 Hz), 6.16 (d, 2H, $J=2$ Hz), 6.72 (d, 2H, $J=7.9$ Hz), 9.95 (s, 1H); ^{13}C NMR δ 35.3, 36.3, 108.5, 108.9, 120.6, 126.9, 130.0, 142.3, 149.2, 152.1; IR (KBr) $\nu_{NH}=3220$ cm^{-1}, $\nu_{CN}=2234$ cm^{-1}, $\nu_{NH2}=3354$ and 3448 cm^{-1}; MS (m/z) calcd for $C_{17}H_{15}N_5$: 289.1317. Found: 289.1340.
10. Compound **3e**: mp 219°C; ^{1}H NMR δ ($CDCl_3$) 3.29 (AB, 2H, $J=15.6$ Hz), 3.47 (AB, 2H, $J=15.6$ Hz), 6.75–7.15 (m, 11H), 7.38 (dd, 2H, $J=8.2$ and 1.5 Hz), 10.08 (s, 1H); ^{13}C NMR δ 40.9, 44.3, 119.1, 122.6, 123.4, 126.2, 127.1, 127.7, 127.8, 128.7, 139.0, 141.7, 162.3; IR (KBr) $\nu_{CN}=$ 1626 cm^{-1}; MS (m/z) calcd for $C_{22}H_{18}N_2$: 310.1470. Found: 310.1473; Anal. Calcd: C, 85.13; H, 5.85; N, 9.02. Found: C, 85.11; H, 5.82; N, 9.00.
11. Compound **3f**: mp>250°C; ^{1}H NMR δ ($CDCl_3$) 3.05 (AB, 2H, $J=16$ Hz), 3.13 (AB, 2H, $J=15.9$ Hz), 6.98–7.42 (m, 8H), 7.92 (s, 1H), 9.51 (s, 1H), 10.01 (s, 1H); ^{13}C NMR δ 29.9, 31.9, 45.9, 116.6, 117.7, 118.3, 119.4, 126.3, 127.5, 129.1, 129.5, 129.6, 131.9, 134.0, 164.6, 170.4; IR (KBr) $\nu_{NH}=3191$, 3315, 3442 cm^{-1}, $\nu_{CO}=1685$ cm^{-1}; MS (m/z) calcd for $C_{17}H_{15}N_3O$: 277.1221. Found: 277.1215.
12. Compound **4a**: mp>250°C; ^{1}H NMR δ ($CDCl_3$) 3.04 (AB, 2H, $J=15.9$ Hz), 3.37 (AB, 2H, $J=15.9$Hz), 7.10 (d, 2H, $J=8.5$ Hz), 7.31 (t, 2H, $J=8.5$ Hz), 7.48 (t, 2H, $J=8.5$ Hz), 7.64 (d, 2H, $J=8.5$ Hz), 8.45 (s, 2H), 9.30 (s, 2H); ^{13}C NMR δ 30.4, 46.5, 115.8, 117.9, 128.7, 128.9, 130.2, 134.0, 158.3; IR (KBr) $\nu_{NH}=3162$ cm^{-1}; MS (m/z) calcd for $C_{17}H_{16}N_4O_2$: 308.1256. Found: 308.1273.