Electrocatalytic transformation of malononitrile and cycloalkylidenemalononitriles into spirobicyclic and spirotricyclic compounds containing 1,1,2,2-tetracyanocyclopropane fragment

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Electrolysis of malononitrile and cycloalkylidenemalononitriles in EtOH in an undivided cell in the presence of NaBr affords spirobicyclic compounds containing a 1,1,2,2-tetracyanocyclopropane fragment in 50—88% yields.

Key words: electrolysis, electrocatalytic transformation, malononitrile, cycloalkylidenemalononitriles, mediators, spirobicyclic compounds.

Malononitrile is a commonly known and widely used reagent in the synthesis of pharmaceuticals, pesticides, fungicides, solvatochromic dyes, and organic semiconductors.[1]

The unique reactivity of malononitrile promotes more extensive and diverse applications of this reagent in organic chemistry even compared to the use of other known CH-acids such as malonic and cyanoacetic esters.

Nevertheless, little is known about the electrochemical transformations of malononitrile. Although electrooxidation of the malonic ester anion was performed back in the 19th century,[2] no studies devoted to electrooxidation, electroreduction, or any other electrochemical transformation of malononitrile is mentioned in the monographs or reviews on electroorganic chemistry[3,4] or reviews on the use of malononitrile in organic chemistry.[5,6]

As far as we know, apart from the studies performed by our research group, only one relevant publication can be mentioned, namely, one dealing with electrochemical anodic arylation of malononitrile.[7]

The use of alkylidenemalononitriles, which contain an activated double bond together with the reactive CN group (see reviews[8,9]), is also quite common in organic synthesis. These reagents are usually prepared from malononitrile and carbonyl compounds by the Knoevenagel reaction.[10] Known reactions in the electrochemistry of alkylidenemalononitriles include cathodic hydrogenation[11] and cyclodimerization of arylidenemalononitriles,[12] and cathodic addition of alkylidenemalononitriles to acrylonitrile and methyl acrylate.[13]

In recent decades, mediators and mediator systems have been successfully used for electroreduction and electrooxidation of organic compounds. Among numerous mediators, the halide anion—halogen redox system is one of the most promising for the use in organic synthesis.

Previously, in our studies dealing with electrocatalytic oxidation of organic compounds in the presence of alkali metal halides as mediators, we performed electrochemical transformations of aldehydes and malononitrile[14] or cyanoacetic acid[15] to functionally substituted cyclopropanes and the transformation of ketones and malononitrile to 3,3-disubstituted tetracyanocyclopropanes.[16,17]

The last-mentioned reaction is an electrochemical analog of the Wideqvist reaction, *i.e.*, the reaction of bromomalononitrile with ketones in the presence of stoichiometric amounts of sodium iodide.[18] In the electrochemical version, bromomalononitrile is replaced by malononitrile and catalytic amounts of sodium bromide, which is fully regenerated during the process. However, to prepare large amounts of tetracyanocyclopropanes in the electrochemical Wideqvist reaction, one should employ a three- to four-fold excess of the ketone. In addition, it was found unexpectedly that in the case of cyclohexanone, this electrochemical process cannot be stopped after the formation of tetracyanocyclopropane; co-electrolysis of cyclohexanone and malononitrile under these conditions furnishes 2-amino-1,5-dicyano-4,4-diethoxy-6,6-pentamethylene-3-azabicyclo[3.1.0]hex-2-ene (**1**)[17] in 62% yield (Scheme 1).

Recently, we proposed a new approach to the synthesis of functionally substituted cyclopropanes, namely, co-electrolysis of CH-acids with activated olefins[19,20] (Scheme 2).

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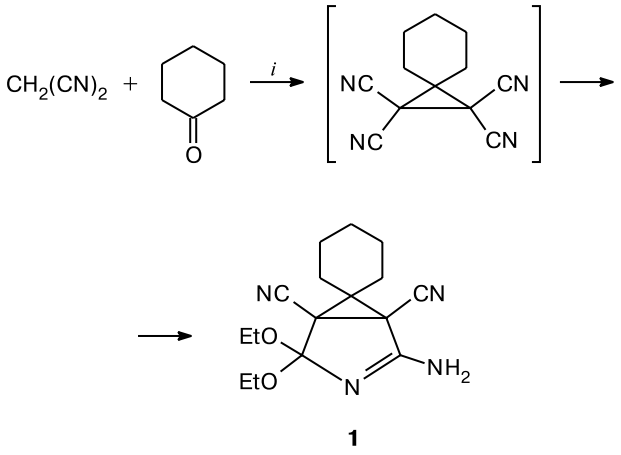
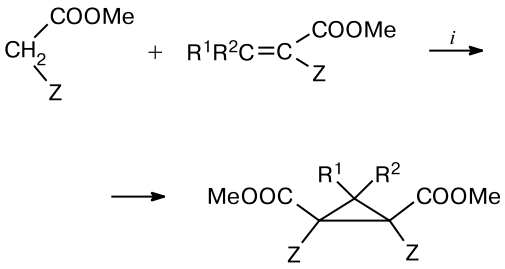
Scheme 1



i. Electrolysis, NaBr, EtOH.

Scheme 2

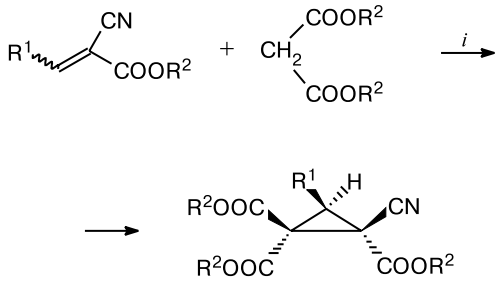


Z = COOMe, CN

i. Electrolysis, NaHal, MeOH; Hal = Br, I.

The co-electrolysis of alkylidenecyanoacetic and malonic esters carried out within the framework of this approach resulted in stereoselective synthesis of (*E*)-isomers of trialkyl 3-substituted-2-cyanocyclopropane-1,1,2-tricarboxylates[21] (Scheme 3).

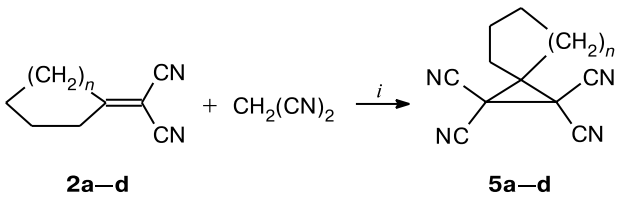
Scheme 3



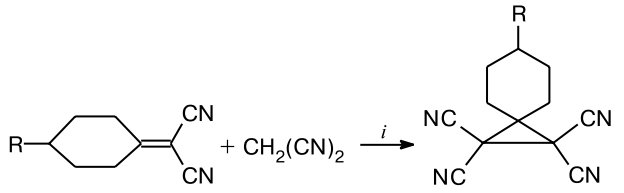
i. Electrolysis, NaBr, R^2OH.

In this study, we used this approach to prepare tetracyano-substituted spirobicyclic and spirotricyclic compounds containing a cyclopropane fragment from cycloalkylidenemalononitriles **2a—d**, **3a—c**, and **4a**,**b** and malononitrile. Compounds of this type are also promising for the synthesis of natural biologically active products[22,23] and up-to-date drugs[24] (Scheme 4).

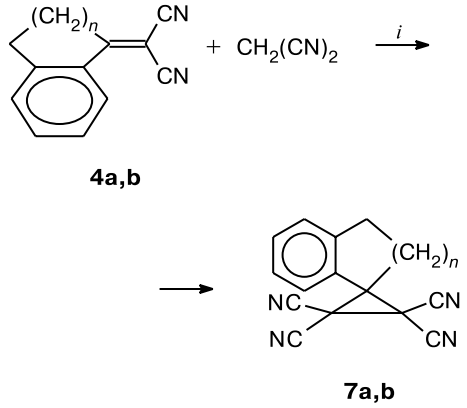
Scheme 4



n = 1 (**a**), 2 (**b**), 3 (**c**), 8 (**d**)



R = Me (**a**), Ph (**b**), Bu^t (**c**)



n = 1 (**a**), 2 (**b**)

i. Electrolysis, NaBr, EtOH.

The first phase included development of a method for the preparation of 3,3-pentamethylene-1,1,2,2-tetracyanocyclopropane **5b** from cyclohexylidenemalononitrile **2b** and malononitrile (Table 1). It is noteworthy that electrolysis of malononitrile in the presence of excess cyclohexanone yielded tricyclic compound **1** as the only product.[17]

Table 1. Co-electrolysis of malononitrile and cyclohexylidenemalononitrile[a]

Run	Q[b] /F mol^{-1}	T/°C	**2b**/malononitrile, mol/mol	Cyclopropane **5b**, yield (%)[c]
1	2.0	5	1 : 1	51
2	2.0	20	1 : 1	65
3	2.5	20	1 : 1	48
4[d]	2.2	20	2 : 3	69
5[d]	2.5	20	2 : 3	84
6[d]	3.0	20	2 : 3	93 (82)[e]

Note: [a] 10 mmol of malononitrile, 10 mmol of **2b**, 5 mmol of NaBr, 20 mL of EtOH, Fe cathode, C anode, current density 100 mA cm^{-2}.
[b] Quantity of electricity.
[c] According to ^{1}H NMR data.
[d] 15 mmol of malononitrile.
[e] Relative to isolated **5b**.

Table 2. Co-electrolysis of malononitrile and cycloalkylidenemalononitriles

Cycloalkylidenemalononitrile	n	R	Q[a] /F mol^{-1}	Cyclopropane, yield (%)[b]
2a	1	—	3	**5a**, 65
2b	2	—	3	**5b**, 82
2c	3	—	3	**5c**, 87
2d	8	—	3	**5d**, 69
3a	—	Me	3	**6a**, 63
3b	—	Ph	3	**6b**, 61
3c	—	Bu^t	3	**6c**, 88
4a[c]	1	—	4	**7a**, 57
4b[c]	2	—	4	**7b**, 51

Note: [a] Quantity of electricity.
[b] The yield is related to the isolated cyclopropane.
[c] The cycloalkylidenemalononitrile/malononitrile ratio = 1 : 2.

It follows from the data of Table 1 that a decrease in the temperature to 5 °C entails some decrease in the yield of compound **5b**. With the use of an equimolar **2b**/malononitrile ratio, passing a quantity of electricity exceeding the theoretical value (2 F/mol) results in a decrease in the yield of compound **5b** (see Table 1, run *3*); in addition, tricyclic pyrroline **1** is formed (yield 17%) together with **5b**. As shown by NMR analysis of the reaction mixtures obtained in runs *2* and *3* (see Table 1), at the instant of full conversion of malononitrile, the degree of conversion of **2b** is only 60—65%. Therefore, the subsequent experiments (see Table 1, runs *4*—*6*) were carried out with a 1.5-fold excess of malononitrile. Under the optimal conditions, tetracyanocyclopropane **5b** was obtained in 93% yield at full conversion of **2b** and 95% conversion of malononitrile.

Under the conditions of choice for the preparation of tetracyanocyclopropane **5b** from malononitrile and **2b** (see Table 1, run *6*), we carried out co-electrolysis of cycloalkylidenemalononitriles **2a—d**, **3a—c**, **4a,b**, and malononitrile (Table 2).

It follows from the data of Table 2 that the electrolysis conditions optimal for **2b** are also applicable to cycloalkylidenemalononitriles **2a,c,d** with various ring size and to substituted cyclohexylidenemalononitriles **3a—c**.

In the case of compounds **4a,b** containing a fused benzene ring, for obtaining cyclopropanes **7a,b** in a substantial yield, the amount of malononitrile needs to be increased to a two-fold excess and the quantity of electricity, to 4 F mol^{-1}.

Relying on the above results (and the data on the mechanism of the electrochemical version of the Wideqvist reaction[15,17]), we propose a mechanism for the electrochemical transformation of malononitrile and cycloalkylidenemalononitriles into spirobicyclic and -tricyclic compounds containing a 1,1,2,2-tetracyanocyclopropane fragment.

The reactions that take place at the electrodes during the joint electrochemical transformation of malononitrile and cycloalkylidenemalononitriles are the usual reactions for the mediator system involved (bromide anion—molecular bromine), which include the formation of bromine at the anode and hydrogen evolution at the cathode with generation of ethoxide ions

$$\text{anode: } 2\,Br^- - 2e \longrightarrow Br_2,$$

$$\text{cathode: } 2\,EtOH + 2e \longrightarrow 2\,EtO^- + H_2.$$

The ethoxide ion reacts with malononitrile in the solution to give the malononitrile anion:

$$CH_2(CN)_2 + EtO^- \longrightarrow \bar{C}H(CN)_2 + EtOH.$$

The reaction of the malononitrile anion with bromine results in bromomalononitrile:

$$\bar{C}H(CN)_2 + Br_2 \longrightarrow CH(Br)(CN)_2 + Br^-.$$

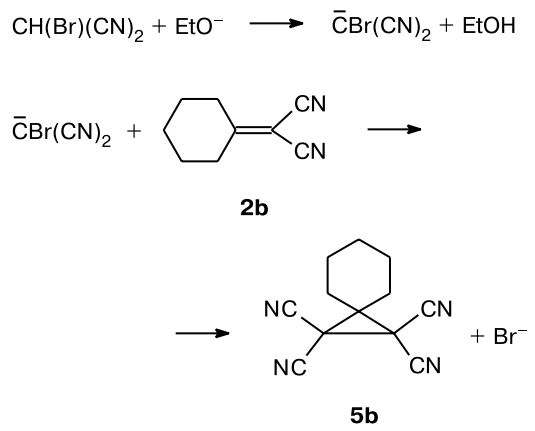
The subsequent processes that take place in the solution were considered in relation to the co-electrolysis of malononitrile and cyclohexylidenemalononitrile **2b**.

The bromomalononitrile anion generated under the action of the ethoxide ion adds to the double bond of nitrile **2b** to give cyclopropane **5b** (pathway *A*, Scheme 5):

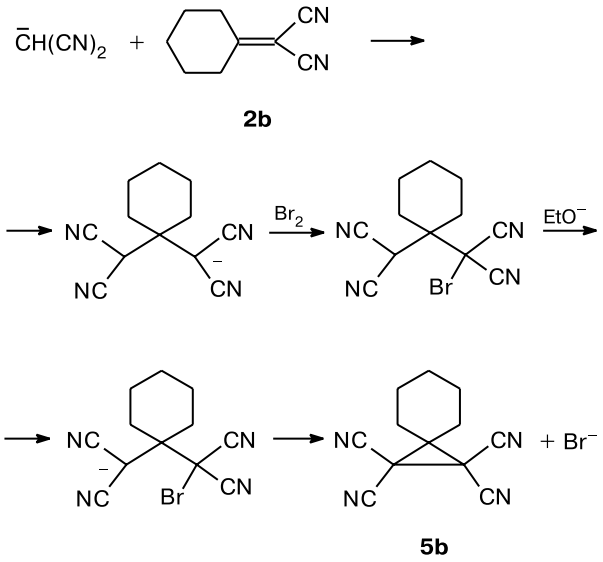
Cyclopropane **5b** can also be produced *via* a different reaction pathway *B*, namely, the Michael addition of the malononitrile anion to **2b** and the subsequent bromination and cyclization (Scheme 6).

Reaction pathway *B* is embodied in the co-electrolysis of malonic and alkylidenemalonic esters[19] or malonic and alkylidenecyanoacetic esters.[21] When the quantity of electricity passed was insufficient for completion of the pro-

Scheme 5



Scheme 6



cess, the reaction mixtures were found to contain the corresponding Michael adducts.

When co-electrolysis of malononitrile and unsaturated nitrile **2b** was carried out under conditions of run *6* (see Table 1) with 0.5, 1.0, and 2.0 $F\ mol^{-1}$ of electricity, the corresponding Michael adduct, namely, 2-(1-dicyanomethylcyclohexyl)malononitrile, was not detected in the electrolysis products. Only the starting compounds and cyclopropane **5b** were found in the reaction mixture in 21, 35, and 68% yields, respectively. These results suggest that occurrence of the reaction by pathway *B* is unlikely.

It should be emphasized that excess malononitrile in the reaction mixture prevents the subsequent electrocatalytic transformation of cyclopropane **5b** into bicyclic pyrroline **1** by decreasing the current concentration of ethoxide ions. As a consequence, unlike the electrocatalytic version of the Wideqvist reaction,[17] in the case of co-electrolysis of malononitrile and compound **2b**, cyclopropane **5b** was prepared in a yield of more than 90%.

Thus, co-electrolysis of malononitrile and cyclic alkylidenemalononitriles carried out in an undivided cell in the presence of a mediator provided a one-step synthesis of spirobicyclic and spirotricyclic compounds containing a 1,1,2,2-tetracyanocyclopropane fragment. Using techniques of classical organic chemistry, this transformation could be accomplished only as a two-step process comprising (i) halogenation of malononitrile and (ii) addition of halomalononitrile to the double bond of cyclic alkylidenemalononitrile followed by cyclization.[25]

The only electrochemical analog of this process is electrochemical transformation of ketones and malononitrile into substituted tetracyanocyclopropanes.[17] However, this requires a considerable excess of ketone, which is a significant drawback, especially in those cases where the ketone is a more expensive chemical than malononitrile. In addition, in some cases, electrolysis performed in an excess of a ketone cannot be stopped after the formation of tetracyanocyclopropane.

The electrocatalytic transformation of malononitrile and cyclic alkylidenemalononitriles into spirobicyclic and spirotricyclic compounds containing a 1,1,2,2-tetracyanocyclopropane fragment was accomplished within the framework of development of a new approach to the synthesis of functionally substituted cyclopropanes by co-electrolysis of CH-acids and activated olefins.[19—21]

The electrochemical route we developed for the transformation of malononitrile and cyclic alkylidenemalononitriles into spirobicyclic and spirotricyclic compounds containing a 1,1,2,2-tetracyanocyclopropane fragment is convenient and economic. The use of common and readily available reagents, inexpensive equipment, and undivided cells are advantages of this method. The procedures of electrolysis and product isolation are facile and convenient when implemented both in the laboratory and on a pilot scale.

Experimental

^1H NMR spectra were recorded on Bruker WM-250 and Bruker AM-300 instruments operating at 250 and 300 MHz, respectively, for solutions in $CDCl_3$. The NMR chemical shifts are given in the δ scale and referred to Me_4Si. The malononitrile used was a commercial preparation (Aldrich).

Cyclohexylidenemalononitriles were prepared by Knoevenagel condensation of appropriate ketones (commercial preparations, Merck and Aldrich) with malononitrile.[26]

Cyclopentylidenemalononitrile (2a),[25] yield 78%, b.p. 142—145 °C (16 Torr).

Cyclohexylidenemalononitrile (2b),[25] yield 86%, b.p. 160—162 °C (18 Torr).

Cycloheptylidenemalononitrile (2c),[27] yield 75%, b.p. 169—172 °C (16 Torr).

Cyclododecylidenemalononitrile (2d),[28] yield 76%, b.p. 218—219 °C (11 Torr).

4-Methylcyclohexylidenemalononitrile (3a),[29] yield 85%, b.p. 163—166 °C (18 Torr).

4-Phenylcyclohexylidenemalononitrile (3b), yield 92%, m.p. 101—103 °C. Found (%): C, 79.84; H, 6.13, N, 12.38. $C_{15}H_{14}N_2$. Calculated (%): C, 81.05; H, 6.35; N, 12.60. ^{1}H NMR ($CDCl_3$), δ: 1.78, 2.29, 2.55 (all m, each 2 H); 2.92 (m, 1 H); 3.21 (m, 2 H); 7.18—7.50 (m, 5 H, Ph).

4-*tert*-Butylcyclohexylidenemalononitrile (3c), yield 83%, m.p. 84—85 °C (Ref. 30: m.p. 82—83 °C).

2,3-Dihydro-1*H*-inden-1-ylidenemalononitrile (4a), yield 72%, m.p. 147—149 °C (Ref. 25: m.p. 147—150 °C).

3,4-Dihydro-2*H*-naphthalen-1-ylidenemalononitrile (4b), yield 65%, m.p. 107—108 °C (Ref. 25: m.p. 108—109 °C).

Electrolysis (general procedure). A solution of malononitrile (10—20 mmol), cycloalkylidenemalononitrile (10 mmol), and NaBr (5 mmol) in 20 mL of EtOH was subjected to electrolysis in an undivided cell equipped with a C anode and a Fe cathode (the electrode area was 5 cm^2) at 20 °C and at a constant current density equal to 100 mA cm^{-2}; the quantities of electricity passed are given in Tables 1 and 2. The tetracyanocyclopropane precipitate was filtered off and washed with cold EtOH. The filtrate was concentrated and extracted with chloroform. Chloroform was evaporated and the residue (Table 1, runs *1—6*) was analyzed by ^{1}H NMR spectroscopy and crystallized from an acetone—hexane mixture to isolate an additional amount of tetracyanocyclopropane from the reaction mixture.

1,1,2,2-Tetracyanospiro[2.4]heptane (5a), m.p. 250—251 °C (Ref. 17: m.p. 250—251 °C). ^{1}H NMR (DMSO-d_6), δ: 1.90, 2.05 (both m, 4 H).

1,1,2,2-Tetracyanospiro[2.5]octane (5b), m.p. 178—180 °C (Ref. 25: m.p. 177—179 °C). ^{1}H NMR (DMSO-d_6), δ: 1.51 (m, 2 H); 1.67, 1.89 (both m, 4 H each).

1,1,2,2-Tetracyanospiro[2.6]nonane (5c), m.p. 169—170 °C (Ref. 17: m.p. 170—171 °C). ^{1}H NMR (DMSO-d_6), δ: 1.60, 1.81, 2.01 (all m, 4 H each).

1,1,2,2-Tetracyanospiro[2.10]tetradecane (5d), m.p. 200—202 °C (Ref. 25: m.p. 197—200 °C). ^{1}H NMR (DMSO-d_6), δ: 1.39 (m, 14 H); 1.65, 1.88 (both m, 4 H each).

1,1,2,2-Tetracyano-6-methylspiro[2.5]octane (6a), m.p. 166—167 °C. Found (%): C, 69.81; H, 5.63; N, 24.75. $C_{13}H_{12}N_4$. Calculated (%): C, 69.62; H, 5.39; N, 24.98. ^{1}H NMR (DMSO-d_6), δ: 0.98 (d, 3 H, Me, J = 7 Hz); 1.25 (m, 2 H); 1.50—1.70 (m, 3 H); 1.88; 2.23 (both m, 2 H each). ^{13}C NMR (DMSO-d_6), δ: 20.7 (Me); 25.6, 27.8 (C); 28.7 (CH_2); 29.9 (CH); 30.8 (CH_2); 45.5 (C); 109.5, 109.6 (CN).

1,1,2,2-Tetracyano-6-phenylspiro[2.5]octane (6b), m.p. 171—173 °C. Found (%): C, 75.72; H, 5.03; N, 19.41. $C_{18}H_{14}N_4$. Calculated (%): C, 75.51; H, 4.93; N, 19.57. ^{1}H NMR ($CDCl_3$), δ: 1.83, 2.15 (both m, 2 H each); 2.41 (m, 4 H); 2.84 (m, 1 H); 7.25—7.52 (5 H, Ph). ^{13}C NMR (DMSO-d_6), δ: 26.2, 28.1 (C); 29.4 (CH_2); 30.1 (CH_2); 41.6 (C); 44.9 (CH); 109.9, 110.0 (CN); 126.3, 127.0, 128.3, 145.1 (all Ph).

1,1,2,2-Tetracyano-6-*tert*-butylspiro[2.5]octane (6c), m.p. 177—179 °C. Found (%): C, 72.34; H, 6.93; N, 20.88. $C_{16}H_{18}N_4$. Calculated (%): C, 72.15; H, 6.81; N, 21.04. ^{1}H NMR (DMSO-d_6), δ: 0.89 (s, 9 H, Me); 1.21 (m, 2 H); 1.25 (m, 1 H); 1.66, 1.97, 2.24 (all m, each 2 H). ^{13}C NMR (DMSO-d_6), δ: 24.2 (CH_2); 25.9 (C); 27.3 (CH_3); 28.1 (C); 29.5 (CH_2); 32.1 (C); 45.7 (CH); 109.7, 109.9 (CN).

1,1,2,2-Tetracyano-4,5-benzospiro[2.4]heptane (7a), m.p. 198—200 °C. Found (%): C, 73.94; H, 3.43; N, 22.83. $C_{15}H_8N_4$. Calculated (%): C, 73.76; H, 3.30; N, 22.94. ^{1}H NMR (DMSO-d_6), δ: 2.65 (t, 2 H, J = 7 Hz); 3.20 (t, 2 H, J = 7 Hz); 7.35—7.60 (m, 4 H, Ar). ^{13}C NMR (DMSO-d_6), δ: 27.5 (C); 29.1 (CH_2); 31.9 (CH_2); 52.1 (C); 109.4, 110.0 (CN); 122.8, 125.4, 125.6, 130.7, 131.6, 148.2 (all Ar).

1,1,2,2-Tetracyano-4,5-benzospiro[2.5]octane (7b), m.p. 173—175 °C (Ref. 25: m.p. 167—170 °C). ^{1}H NMR ($CDCl_3$), δ: 2.15, 2.42, 3.03 (all m, 2H each); 7.20—7.60 (m, 3 H); 7.85 (m, 1 H). ^{13}C NMR (DMSO-d_6), δ: 18.7 (CH_2); 27.6 (C); 28.5, 30.2 (CH_2); 45.5 (C); 109.9, 110.0 (CN); 124.8, 125.9, 126.9, 129.5, 129.9, 141.1 (all Ar).

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