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Activation of Elemental Sulfur by Electrogenerated Cyanomethyl Anion: Synthesis of Substituted 2-Aminothiophenes by the Gewald Reaction

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Abstract: The activation of elemental sulfur (S_8) has been achieved by means of electrogenerated cyanomethyl anion [easily obtained by galvanostatic reduction from acetonitrile/tetraethylammonium hexafluorophosphate ($MeCN-Et_4NPF_6$)]. The "activated" sulfur reacted with ylidenemalononitriles to give substituted 2-aminothiophenes in very high yields. This variation of the Gewald reaction has been carried out using only catalytic amounts of electricity and supporting electrolyte. A proposed mechanism for the interaction between S_8 and cyanomethyl anion is described.

Keywords: 2-aminothiophenes; electrogenerated cyanomethyl anion; elemental sulfur; Gewald reaction; ylidenemalononitriles

Introduction

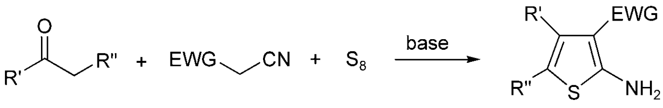
Substituted 2-aminothiophenes are attractive molecules, largely used in the industry due to their applications in pharmaceuticals, agriculture, pesticides and dyes.[1] They are, in fact, potent inhibitors of JNK2 and JNK3 kinases,[2] allosteric enhancers of A_1-adenosine receptor[3] and glucagon receptor antagonists.[4] They also show antimicrobial activity against various Gram(+) and Gram(−) bacteria and fungi,[5] antibacterial activity against *S. aureus*, *B. subtilis* and *E. coli*,[6] as well as antioxidant and anti-inflammatory activity.[7] Moreover, these molecules are dyes[8] and precursors of azo dispersed dyes.[9]

Many are the routes to this kind of product (such as, for example, the cyclization of thioamides and their *S*-alkylates),[1] but usually they involve difficult preparation of the starting materials, multistep synthesis and do not produce high yields. The most facile, versatile and important reaction leading to 2-aminothiophenes with electron-withdrawing substituents (such as cyano, ethoxycarbonyl, carboxamido, etc.) is the Gewald reaction[10] and its variations.

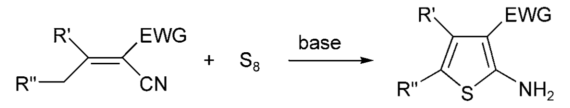
The Gewald reaction is a three-component condensation reaction in which an α-methylene carbonyl compound, elemental sulfur and a cyanomethylene containing an electron-withdrawing group condense in the presence of an organic base to yield a thiophene system (Scheme 1).

In the first version of this reaction, an α-mercaptoaldehyde or an α-mercaptoketone is treated with an activated nitrile (bearing an electron-withdrawing group, EWG) in the presence of a basic catalyst (usually an amine) at 50 °C; this reaction uses starting materials that are unstable and difficult to prepare.[11]

The second version of the Gewald reaction is the most elegant and consists of a one-pot condensation of the three reactants (see Scheme 1) at room temperature, in the presence of an amine, but in this case in 0.5–1.0 molar equivalent amounts; the yields are higher than in the first version[10] (82–99% yields with cyclohexanone derivatives[4,12]).



Scheme 1.



Scheme 2.

The third version is the reaction of an α,β-unsaturated nitrile (prepared by a Knoevenagel condensation) with sulfur and an amine (Scheme 2). This two-step version gives the highest yields in short times and allows the reaction of alkyl aryl ketones, which are unreactive under the one-pot conditions.[13]

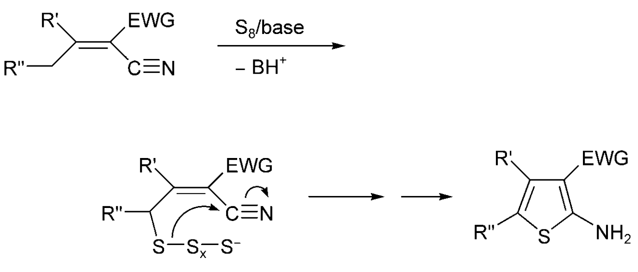
During the last decade, many papers have been published concerning improvements in both version 2 and version 3 of the Gewald reaction.[14]

In particular, as regards the one-pot synthesis, the reaction has been carried out on a solid support,[15] in ionic liquids,[16] with microwave-assistence;[17] while, as concerns the two-step synthesis, a method to obtain 4-alkylthiophenes (instead of the mainly obtained 5-alkyl ones) has been depicted,[18] and the use of an inorganic base in THF/water allows the suppression of by-product formation.[19]

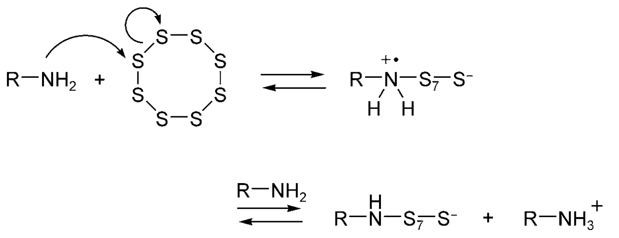
The mechanism of this reaction is not fully clear; in fact the reaction of addition of elemental sulfur to the nitrile group is not known in detail. Some authors report that the Knoevenagel product is thiolated at the methylene group with elemental sulfur, followed by ring closure (Scheme 3).[1,18,20] In this version, the methylene group is deprotonated and then thiolated.

However, it is sure that S_8 has to be activated to react with the Knoevenagel product. This activation can be achieved therefore by using a base, but also by electrochemical means. In fact, it is reported in the literature (and not related to the Gewald reaction) that elemental sulfur reacts with amines to yield polysulfide anions (Scheme 4),[21] that can behave as nucleophiles:

On the other hand, the electrochemical activation of sulfur has been reported by Le Guillanton and coworkers:[22] as sulfur S_8 is electroactive, it has been incorporated in a carbon electrode (to have sufficient electric conductivity) and used as a sacrificial cathode at a potential of –0.9 V (*vs.* SCE) to yield $S_3^{\bullet-}$, $S_8^{\bullet-}$ and S_4^{2-} species, that can act as reducing species and nucleophiles. When this methodology was applied to the synthesis of 2-aminothiophenes, high yields (61–91%) were obtained.[23]



Scheme 3.



Scheme 4.

In recent papers, we showed the ability as a base of electrogenerated cyanomethyl anion in the synthesis, acylation and alkylation of oxazolidin-2-ones, in the synthesis of organic carbamates and β-lactams.[24] As the generation of this base is very simple and this anion ($^-CH_2CN$) is highly reactive, due to the fact that its counter-ion is a tetraalkylammonium cation, we envisaged the possibility to use electrogenerated cyanomethyl anion as the basic species necessary to activate S_8 in the Gewald reaction.

Results and Discussion

Cyanomethyl anion was generated by galvanostatic reduction ($I = 25\ \mathrm{mA\,cm^{-2}}$) of a solution of acetonitrile/0.1 M tetraethylammonium hexafluorophosphate (TEAHFP, as supporting electrolyte), in a two-compartment cell (catholyte and anolyte separated by a glass frit filled with a gel containing DMF and TEAHFP), on a Pt cathode at room temperature under an inert atmosphere. At the end of the electrolysis (Q = 0.5 F/mol **1a**), elemental sulfur and 2-(4-phenylcyclohexylidene)malononitrile **1a** (taken as a model compound) were added to the catholyte, and the solution was allowed to stand under stirring for 1 hour. Usual work-up (see experimental) gave the corresponding 2-aminothiophene in 85% yield (see Scheme 5 and Table 1, entry 2).

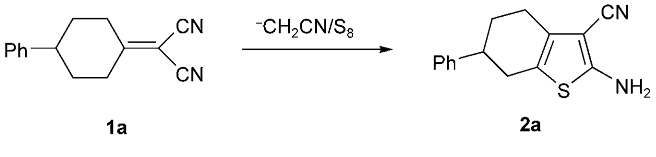
In this reduction the electroactive species should be the tetraethylammonium cation and not MeCN,[24c]

$$Et_4N^+ + e^- \longrightarrow Et_4N^\bullet$$

$$Et_4N^\bullet \longrightarrow Et^\bullet + Et_3N$$

$$Et^\bullet + e^- \longrightarrow Et^-$$

$$Et^- + CH_3CN \longrightarrow EtH + {}^-CH_2CN$$



Scheme 5.

Table 1. Electrochemical generation of cyanomethyl anion, followed by its reaction with S_8 and 2-(4-phenylcyclohexylidene)malononitrile **1a** to yield 2-aminothiophene **2a** (see Scheme 5).[a]

Entry	Catholyte	Q (F/mol **1a**)[b]	Recovered **1a**	**2a**[c]
1	MeCN/ Et_4NPF_6	–	100%	–
2[d]	MeCN/ Et_4NPF_6	0.50	13%	85%
3	MeCN/ Et_4NPF_6	0.50	12%	83%
4[e]	MeCN/ Et_4NPF_6	0.50	–	65%
5	MeCN/ Et_4NPF_6	0.25	–	98%
6	MeCN/ Et_4NPF_6	0.10	–	>99%
7	MeCN	0.25	–	>99%
8	MeCN	0.10	–	98%
9	MeCN	0.05	10%	83%
10[f]	MeCN	0.10	100%	–
11[g]	MeCN	0.10	92%	–

[a] Catholyte in a two-compartment cell (~2 mL), Pt electrodes, room temperature, N_2 bubbling, galvanostatic conditions (I=25 mA cm^{-2}). At the end of the electrolysis S_8 (1 mmol) was added to the catholyte followed, after 1 min, by **1a** (1 mmol). The mixture was allowed to stand at room temperature, under stirring, for 1 h and then, after work-up, thiophene **2a** was isolated.

[b] Amount of electricity (with respect to reagent **1a**) flown through the cell.

[c] Isolated yields.

[d] In this case, S_8 and **1a** were added simultaneously to the catholyte.

[e] Workup of the catholyte after 12 h. In this case, a 29% of 4-phenylcyclohexanone was recovered.

[f] A one-compartment cell was used.

[g] In this case, starting material was not **1a**, but its precursors, 4-phenylcyclohexanone and malononitrile.

and cyanomethyl anion is formed by deprotonation.[25,26]

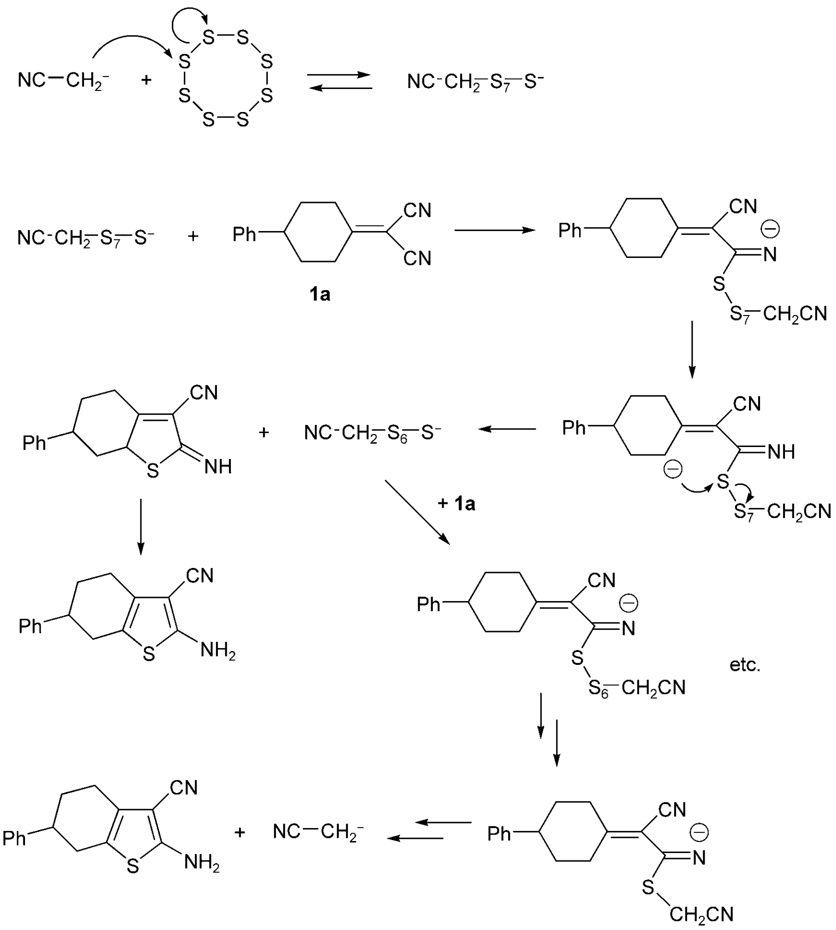
This encouraging result permits us to define the electrogenerated cyanomethyl anion as a good catalyst in the Gewald reaction; in fact, when this reaction was carried out in the same experimental conditions, but in the absence of electricity (i.e., in the absence of cyanomethyl anion), no product **2a** was isolated (see Table 1, entry 1).

To better understand the reaction pathway, the addition of elemental sulfur to the catholyte was done before the addition of **1a** (about 1 min); work-up of the solution gave **2a** in the same yield (83%, Table 1, entry 3). The interaction between $^{-}CH_2CN$ and S_8 is proved by the change in the colour of the catholyte (from pale yellow at the end of the electrolysis to dark red-brown after the addition of S_8). This colour suggests the presence of anions and/or radical anions of sulfur.[27] Any attempt to isolate the intermediate due to the interaction of cyanomethyl anion and elemental sulfur failed and when the mixture $^{-}CH_2CN/S_8$ was allowed to react with BuI, only the presence of Bu–S–S–Bu and Bu–S–S–S–Bu was evidenced; the same result has been obtained by Jonczyk by treating alkyl halides with S_8/NaOH/DMSO.[28] This seems to suggest a behaviour of $^{-}CH_2CN$ similar to that of amines (Scheme 4). Moreover, when the ylidenemalononitrile **1a** was added to a solution of cyanomethyl anion in the absence of S_8, no change in the colour of the catholyte was obtained, while when S_8 and **1a** were added to the catholyte simultaneously, the solution become dark red-brown, the same colour as obtained after the addition of only S_8. From these results, it can be evinced that cyanomethyl anion reacts with S_8 also in the presence of ylidenemalononitrile **1a**, thus starting the Gewald reaction. The interaction of cyanomethyl anion and S_8 is also supported by the voltammetric curves of sulfur in MeCN in the absence and in the presence of cyanomethyl anion: S_8 in MeCN gives rise to two reduction peaks (Pt cathode), the first of which related to the direct cathodic reduction of S_8;[29] when $^{-}CH_2CN$ is added to a solution of MeCN containing S_8, all the peaks disappear, showing that no S_8 (or its reduction products) is now present in the solution and excluding an electron transfer between the two species (no oxidation peak is present).[30] An hypothesis for the mechanism is depicted in Scheme 6, by analogy with the behaviour of sulfur with amines reported in Scheme 4. The "activated" sulfur could then give nucleophilic attack to the CN triple bond of the ylidenemalononitrile, leading to the formation of the thiophene ring.[31]

As can be seen from Scheme 6, cyanomethyl anion exits (last reaction) from the first cycle of reactions (in which all eight sulfur atoms of an S_8 molecule are used to build the thiophene ring) and can reenter in another cycle of activation (first reaction).

As reported in Table 1, entries 2 and 3, the reaction to give **2a** is not complete (12–13% of starting material was recovered), so the next step was to prolong the reaction time to let the reaction go to termination. If the reaction was allowed to stand for 12 h before work-up, the yield in product **2a** was lowered to 65%, while 4-phenylcyclohexanone was obtained in 29% (Table 1, entry 4); it is hence clear that prolonged times in the presence of a base lead to the decomposition of the product into its precursors.

As the chosen amount of electricity was arbitrary (the Gewald reaction is formally base-catalyzed, but sometimes a stoichiometric amount of base is necessary) and starting from the results of experiment of entries 2 and 3, we tried to lower the amount of base (thus lowering the amount of electricity flowing through the electrolysis cell). When 0.25 F/mol of **1a**



Scheme 6.

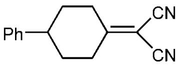
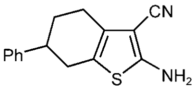
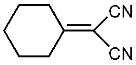
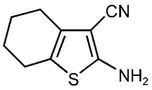
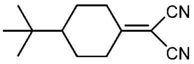
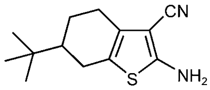
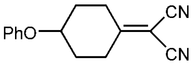
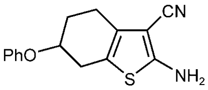
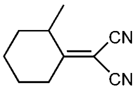
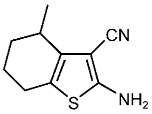
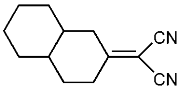
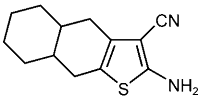
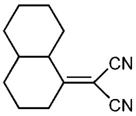
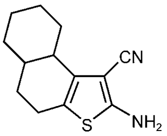
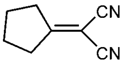
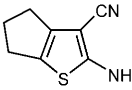
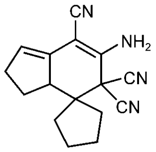
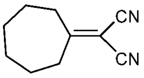
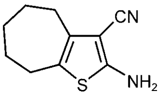
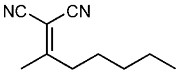
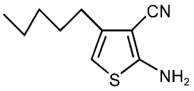
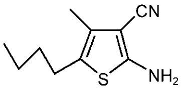
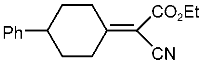
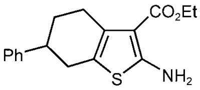
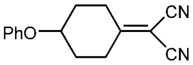
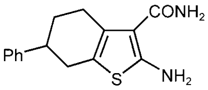
were used, the yield of **2a** raised to 98%, while with 0.10 F/mol the yield was quantitative (Table 1, entries 5 and 6). Having obtained such good results, our next step was to simplify the methodology, trying to avoid the use of the supporting electrolyte Et_4NPF_6 in the catholyte, but mantaining the one in the gel of separation as only a small amount of electricity is necessary (and the salt in the gel could be enough to carry out the electrolysis). The results are reported in Table 1, entries 7–9. As can be seen, the yields of **2a** depend on the amount of electricity, the highest (99 and 98%) being with 0.25 and 0.1 F/mol, while using a value of 0.05 F/mol 10% of starting material was recovered, along with 83% of product. Further simplifications were to use a one-compartment cell (no separation gel, entry 10) and to add 4-phenylcyclohexanone and malononitrile instead of the Knoevenagel product (attempting an one-pot synthesis, entry 11), but both led to a quantitative recovery of starting materials.

Choosing the experimental conditions reported in Table 1, entry 8 as the optimum, we extended our investigation to other alkylidenemalononitriles **1b–j**, as reported in Table 2. All the cyclohexylidenemalononitriles taken into account (**1a–g**) gave very high yields (90–99%) in aminothiophenes (Table 2, entries 1–7), irrespective of the substituents and their position on the cyclohexane ring (only in the case of compound **1g**, derived from the hindered 1-oxodecaline, is the yield slightly lower, 90%), as well as cycloheptylidenemalononitrile **1i** (entry 9, 99%). In the case of compound **1j/1j′** (Table 2, entry 10), two products are possible, 2-amino-4-pentylthiophene-3-carbonitrile and 2-amino-5-butyl-4-methylthiophene-3-carbonitrile; according to what is reported in the literature,[18] the major isomer was the 4,5-disubstituted one (50%), while the 4-substituted was obtained in 18% yield.

When the reagent was cyclopentylidenemalononitrile **1h** (Table 2, entry 8), the yield in the corresponding 2-aminothiophene was 58%. This was due to the concomitant formation of the dimer **3h** in 41% yield. The reaction that leads to this compound is a base-catalyzed dimerization that probably starts with the deprotonation of the methylene in the α-position to the double bond, followed by the addition of a second molecule of ylidenemalononitrile, as depicted in Scheme 7.[32]

The different reactivity of cyclopentylidenemalononitrile, with respect to the cyclohexylidene analogue,

Table 2. Electrochemically induced Gewald reaction. Experimental conditions as in Table 1, entry 8.

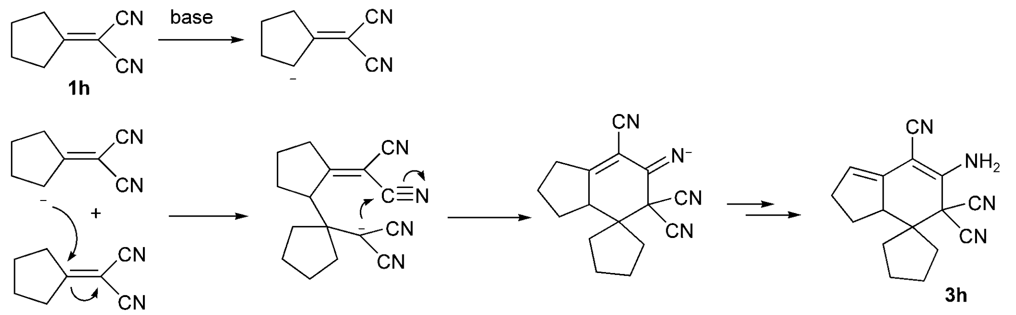
Entry		Reagent		Product	Yield [%]
1[a]	**1a**		**2a**		98
2	**1b**		**2b**		>99
3	**1c**		**2c**		>99
4	**1d**		**2d**		>90
5	**1e**		**2e**		97
6	**1f**		**2f**		96
7	**1g**		**2g**		90
8	**1h**		**2h + 3h**	 + 	58 and 41
9	**1i**		**2i**		99
10	**1j**		**2j + 2j′**	 + 	18 and 50
11[b]	**1k**		**2k**		>99
12[b]	**1l**		**2l**		94

[a] Same result reported in Table 1, entry 8.

[b] These electrolyses were carried out on an MeCN-Et_4NPF_6 solution, Q = 0.2 F/mol. After the addition of S_8 and **1k** or **1l**, the solution was allowed to stand al 50 °C for 120 min.

is probably due to the higher internal strain of the cyclohexylidenemalononitrile ring, that renders the *sp*^{2} ring atom more reactive towards its tetrahedralization.[33]

When an EWG group different from CN is present in the starting molecule (i.e., CO_2Et or $CONH_2$, see Table 2, entries 11 and 12), the reactivity of the molecule decreases and, to obtain high yields on the corresponding 2-aminothiophene, the reaction protocol has been slightly changed: the electrosynthesis of $^-CH_2CN$ was carried out from a solution of MeCN-Et_4NPF_6 (thus enhancing the current efficiency) and, after the addition of S_8 and **1k** or **1l**, the cathodic solution was allowed to stand at 50 °C for 3 h. This variation of methodology permitted us to obtained products **2k** and **2l** in very high yields (99 and 94%, respectively).



Scheme 7.

Conclusions

In conclusion, this paper describes the efficient activation of elemental sulfur by electrogenerated cyanomethyl anion and the application of this “activated” reagent to the synthesis of substituted 2-aminothiophenes, molecules that are largely used in the pharmaceutical, agricultural and dye industries. The product yields are very high and the procedure is simple (galvanostatic reduction of a solution of MeCN-Et_4NPF_6).

Experimental Section

General Procedure

A constant current electrolysis was carried out (I = 25 mA cm^{-2}) in MeCN (2 cm^3) as catholyte (anolyte: 2 cm^3), at room temperature, under a nitrogen atmosphere, in a divided glass cell separated through a porous glass plug filled up with a layer of agar gel (i.e., methyl cellulose 0.5% vol dissolved in DMF-Et_4NPF_6 1.0 mol dm^{-3}); Pt spirals (apparent area 0.8 cm^2) were used both as anode and cathode. After 10 C were passed, the current was switched off and S_8 (1 mmol) was added to the catholyte, followed, after 1 min, by 1 mmol of ylidenemalononitrile **1a–j**. The mixture was allowed to stand at room temperature under stirring and the reaction followed by thin layer chromatography. After about 1 hour, the solvent was evaporated under reduced pressure and the solid analyzed by GC-MS and ^{1}H NMR; when necessary the residue was washed with a small portion of MeCN or purified by flash chromatography (*n*-hexane/ethyl acetate, 7/3 as eluent). The yields in 2-aminothiophenes are reported in Table 2.

In the case of compounds **1k** and **1l**, the catholyte was MeCN/0.1 mol dm^{-3} Et_4NPF_6 and, after the addition of the reagents, the cathodic solution was allowed to stand at 50 °C for 3 h.

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[31] In the cases in which the reduction potential of the ylidenemalononitrile is more negative of the first reduction potential of S_8, it is possible to obtain the Gewald product by potentiostatic reduction of a solution of solvent-supporting electrolyte containing S_8 and the ylidenemalononitrile. We have carried out the selective electrochemical reduction of S_8 in the presence of **1b**, in a MeCN/Et_4NPF_6 0.1 mol dm^{-3} solution, at room temperature, under an N_2 atmosphere, on a Pt cathode, at a potential of -0.8 V *vs.* SCE. After 0.4 F/mol of **1b**, the electrolysis was stopped and, after 1 hour at room temperature, the usual work-up gave **2b** in a quantitative yield. This methodology, that is, the direct cathodic reduction of elemental sulfur, is slightly more complicated with respect to the one described in this paper, as a reference electrode and the supporting electrolyte are necessary.

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