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Electrogenerated acetonitrile anion induced selective N-alkylation of bifunctional compounds

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ABSTRACT

The simple galvanostatic reduction of a solution of MeCN-0.1 M Et_4NPF_6 leads to the formation of acetonitrile anion, whose counter-ion is the Et_4N^+ cation, which leaves the anion 'naked'. This enhances the reactivity of acetonitrile anion, which reveals to be selective in the N-monoalkylation of bifunctional compounds (cycloserine, β-amino alcohols, 2-substituted anilines) obtaining high yields. *N*,*N*-bis-alkylation has never been observed, indicating that the electrochemical methodology is highly regioselective.

Electrogenerated acetonitrile anion has revealed to be a powerful reagent in organic chemistry, due to its counter-ion, a tetraalkylammonium cation, which leaves it a 'naked' anion, and so extremely reactive.[1] It has been, in fact, employed successfully in many reactions as a nucleophile (e.g., in the synthesis of β-hydroxynitriles or 2-aminothiophenes)[2] or as a base (in the synthesis of oxazolidin-2-ones, β-lactams, butenolides, Knoevenagel reaction, etc.).[3] Besides its particular reactivity, acetonitrile anion has also the advantage of leaving no side product, as the acid–base reaction leads to the formation of a molecule of solvent.

The electrochemical generation of acetonitrile anion is easily achieved by cathodic galvanostatic reduction of a solution of acetonitrile containing a tetraalkylammonium salt as supporting electrolyte (Scheme 1).

$$CH_3CN / Et_4N\text{-}PF_6 \xrightarrow{+\ e^-} Et_4\overset{+}{N}\ \overset{-}{C}H_2CN$$

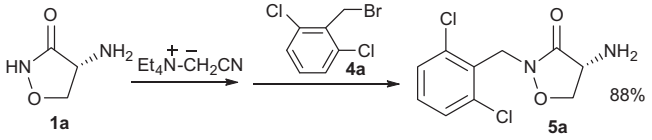
Scheme 1. Electrogeneration of acetonitrile anion.

The mechanism of this reduction is still uncertain, but it has generally assumed that in solution of acetonitrile/tetraalkylammonium salts the cathodic limit is due to the reduction of the tetraalkylammonium cation[4]; the reduction of R_4N^+ has been reported by Peters[5] as consisting in many steps, with the final formation of an alkyl anion that can behave as strong base, deprotonating the solvent. If the solvent is acetonitrile, an acetonitrile anion is formed, whose counter-ion is a tetraalkylammonium cation (Scheme 2).

$$R_4N^+ + e^- \longrightarrow R_4N\cdot$$
$$R_4N\cdot \longrightarrow R\cdot + R_3N$$
$$R\cdot + e^- \longrightarrow R^-$$
$$R^- + HA \longrightarrow RH + A^-$$

Scheme 2. Electrochemical reduction of tetraalkylammonium cation.[6]

As some of us are involved in a research concerning the biological effects of derivatives of cycloserine, an organic compound containing two nitrogen atoms (amine and oxyamide N-atoms), we have envisaged the possibility of discriminating between the two different functionalities in an alkylation reaction by means of electrogenerated anion. In fact, the high nucleophilicity of the amine group and the acidity of the oxyamide one result often in a mixture of products and/or in



Scheme 3. Selective alkylation of D-cycloserine.

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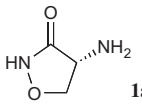
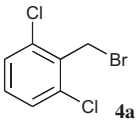
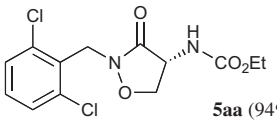
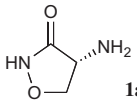
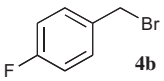
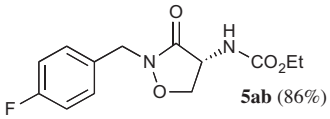
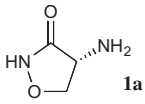
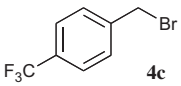
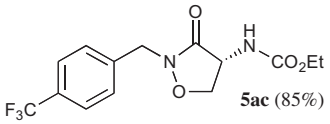
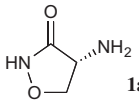
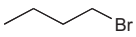
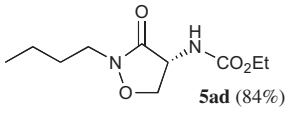
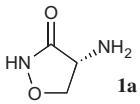
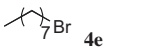
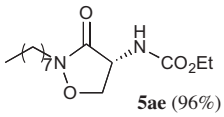
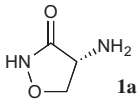
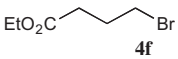
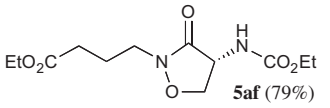
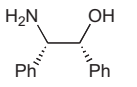
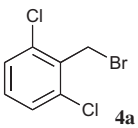
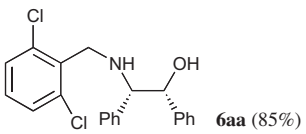
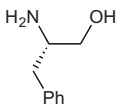
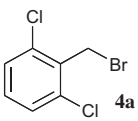
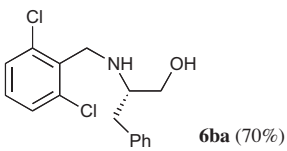
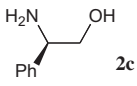
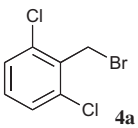
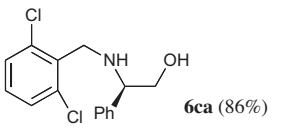
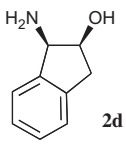
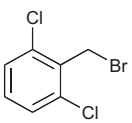
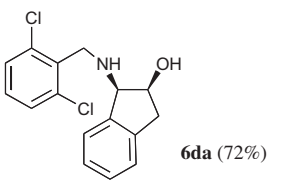
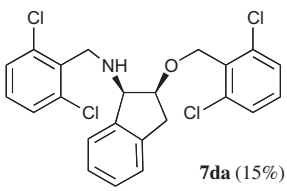
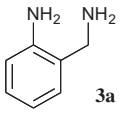
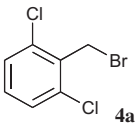
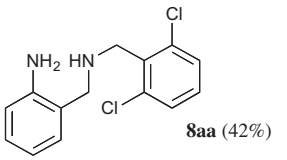
low yields and usually the selective oxyamide N-alkylation is carried out having the previously protected amine moiety (e.g., as Cbz- or Boc-derivative or as imine).[7]

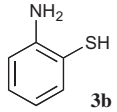
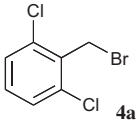
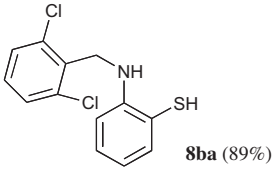
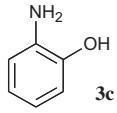
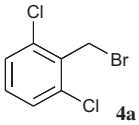
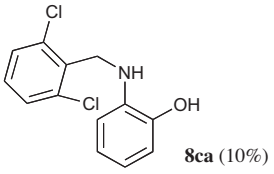
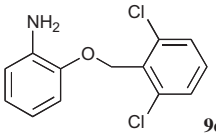
Following this idea, we have subjected cycloserine to reaction with electrogenerated acetonitrile anion. After the production of acetonitrile anion[8] (by galvanostatic reduction of MeCN-0.1 M tetraethylammonium hexafluorophosphate (TEAHFP), 145 C), D-cycloserine **1a** (1 mmol) was added to the catholyte and, after 15 min at room temperature, 1 mmol of 2-(bromomethyl)-1,3-dichlorobenzene as alkylating agent was added. The reaction was

Table 1
Alkylation reaction using electrogenerated acetonitrile anion in MeCN-0.1 M TEAHFP, rt, 2 h[a]

Entry	Substrate	Alkylating reagent	Products (Yields)
1[b]	 **1a**	 **4a**	 **5aa** (94%)
2[b]	 **1a**	 **4b**	 **5ab** (86%)
3[b]	 **1a**	 **4c**	 **5ac** (85%)
4[b]	 **1a**	 **4d**	 **5ad** (84%)
5[b]	 **1a**	 **4e**	 **5ae** (96%)
6[b]	 **1a**	 **4f**	 **5af** (79%)
7	 **2a**	 **4a**	 **6aa** (85%)
8	 **2b**	 **4a**	 **6ba** (70%)
9	 **2c**	 **4a**	 **6ca** (86%)
10	 **2d**	 **4a**	 **6da** (72%)  **7da** (15%)
11	 **3a**	 **4a**	 **8aa** (42%)

(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate	Alkylating reagent	Products (Yields)	
12	 **3b**	 **4a**	 **8ba** (89%)	
13	 **3c**	 **4a**	 **8ca** (10%)	 **9ca** (88%)

[a] The reduction was conducted under galvanostatic conditions (20 mA cm^{-2}), on Pt electrodes in a divided cell at rt, on 20 ml MeCN-0.1 M TEAHFP solution containing 1 mmol of substrate. At the end of the electrolysis, 1 mmol of alkylating agent was added. After 2 h at rt, usual workup gave the products.
[b] Cycloserine was added to the catholyte at the end of the electrolysis. At the end of the alkylation reaction, the crude was treated with ethyl chloroformate/$NaHCO_3$.

completely selective for the oxyamide moiety and the yield in product **5a** was quite high (Scheme 3).

Unfortunately, in a short period of time the alkylated cycloserine **5a** was subjected to degradation, probably to the cycloserine dimer, piperazinedione; this dimerization is reported to occur even in the solid state and it requires the free amino group.[9] So, in order to avoid the degradation of the alkylated product, the amino group was transformed into carbamate by reaction with ethyl chloroformate after the alkylation reaction (to avoid altering the selectivity of the electrochemical reaction). In this case, 94% yield in product **5aa** was achieved (Table 1, entry 1).

Very good yields in 2-alkylated cycloserine were obtained using various benzyl or alkyl bromides, with no racemization[10] (Table 1, entries 1–6). With all bromides used, the selectivity is complete versus the oxyamide nitrogen atom, thus confirming the regioselectivity of this electrochemical methodology.

Following this information, we have subjected 1,2-amino alcohols to an alkylation reaction, induced by acetonitrile anion deprotonation, hoping to obtain a nitrogen-selective mono alkylation in the presence of a hydroxy moiety.

The selective N-monoalkylation of β-amino alcohols is usually achieved by the reaction with an aldehyde and subsequent reduction of the corresponding adduct,[11] as the direct action of a base and of an alkylating agent can lead to low yields and low selectivity and requests long reaction times or/and high temperature.[12] Very good results (in yields and selectivity) have been reached by Kol and Bar-Haim, using the chelation to 9-BBN prior to deprotonation and alkylation of amino alcohols.[13]

As 1,2-amino alcohols **2a–d** are neither electroactive nor degradable, we have added them to the catholyte prior to the cathodic reduction. 2-(Bromomethyl)-1,3-dichlorobenzene was used as alkylating agent and the results are reported in Table 1, entries 7–10. The N-monoalkylated amino alcohols **6aa–6ca** were selectively obtained in good yields (Table 1, entries 7–9)[14] with no byproducts due to bis-alkylation or O-alkylation. Only in the case of 1-amino-2,3-dihydro-1*H*-inden-2-ol **2d** (entry 10) 15% of N,O-bis-alkylation product **7da** has been isolated, indicating that the first deprotonation/alkylation affects the nitrogen atom and only in a second time the reaction interests the oxygen.

Then, we have exploited this reaction using different amines. When the alkylation reaction is carried out on the substrates containing simultaneously a benzylamine and aniline nitrogens (substrate **3a**, Table 1, entry 11), the alkylation is much less effective (42%), but selective on the benzyl nitrogen atom. On the other hand, the reactivity of aniline nitrogen atom in this reaction is strongly dependent on the other functional group present on the aromatic ring.

In fact, if a thiol group is present (substrate **3b**, Table 1, entry 12), the selective N-alkylation in good yield (89%) is obtained, while when a hydroxy group is present (substrate **3c**, Table 1, entry 13), the reaction is prevalent on the oxygen atom, probably because of the higher acidity of the phenol moiety. On the other hand, selective O-alkylation of aminophenols has been achieved only protecting the aniline group as imine and then performing the alkylation.[15] These last three results evidence that this reaction is influenced by both the nucleophilicity and the acidity of the functional groups.

In conclusion, electrogenerated acetonitrile anion has confirmed to be a selective reagent in the N-alkylation of bifunctional substrates (cycloserine, β-amino alcohols, α-substituted anilines). The main advantages in the use of this base are the easiness of generation and the complete absence of metallic cations, which could inhibit its reactivity.

In no case *N*,*N*-bis-alkylation has been obtained, rendering this methodology really competitive with the current chemical methodologies for the monoalkylation of amines.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.038.

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