

The Electrogenerated Cyanomethyl Anion in Organic Synthesis

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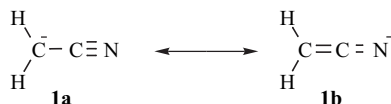
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Abstract: Suitable electrochemical methodologies for the generation of cyanomethyl anion and some electrochemically induced cyanomethylation reactions of electrophilic substrates are described and discussed. In addition, the electrochemical syntheses of carbamates and chiral oxazolidin-2-ones (under mild conditions and avoiding the use of hazardous chemicals), *via* a new carboxylating reagent ($\text{CH}_2\text{CN}^-/\text{CO}_2$), are reported in this article.

Keywords: Cyanomethyl anion, organic electrosyntheses, cyanomethylation reactions, chiral oxazolidinones, carbamates, carboxylating reactions.

INTRODUCTION

Carbanions stabilised by electron-withdrawing groups are frequently utilised in organic synthesis to affect carbon-carbon bond formation reactions [1]. In this regard, several convenient methods for the generation of cyanomethyl anions (**1**) have been described and the reactivity of these nitrile-stabilized carbanions carefully evaluated (Scheme 1).



Scheme 1.

Accordingly, several cyanomethylation reactions (i.e. the reaction of cyanomethyl anion with electrophilic substrates) such as alkylation, arylation and acylation reactions as well as addition reactions to aldehydes, ketones, imines, etc. and Michael-type addition reactions have been extensively studied. At present, many synthetic processes involving new carbon-carbon bonds formation, are carried out *via* cyanomethylation reactions [2].

Deprotonation of acetonitrile ($\text{pK}_a = 31.3$) [1] by suitable bases constitutes the most widely practiced method for generating cyanomethyl anion. Different bases are utilised: alkali metal hydrides, sodium amide, lithium diethylamide, sodium bis(trimethylsilyl)amide, sodium hydroxide under phase-transfer conditions, *n*-butyllithium, potassium *tert*-butoxide, sodium methylsulfinylmethide and lithium diisopropylamide. The selection of the appropriate base (according to the considered reaction and the considered substrate) may ensure high yields and avoid the presence of by-products.

In addition to the deprotonation of acetonitrile, several synthetically useful alternatives for the generation of CH_2CN^- anion were reported: among them, chemical reduction of α , β -unsaturated nitriles, transmetalation of α -(trialkylstannyl)nitriles, reduction of α -thioalkoxynitriles or α , α -dibromonitriles, and conjugate addition of nucleophiles

to either α , β -unsaturated nitriles or cyclopropane-carbonitriles. Finally, some suitable electrochemical methodologies for the generation of CH_2CN^- were described by several authors.

ELECTROCHEMICAL GENERATION OF CYANOMETHYL ANION

In recent years, non-conventional synthetic processes which make use of intermediates obtained through the electrochemical reduction or oxidation of suitable depolarisers were set up [3]. In a classical paper, Evans [4] summarised the versatility of the electrochemical method in organic synthesis: "the electrochemical method offers the unique possibility of generating at the cathode, a wide variety of organic anions under very mild conditions and without the stoichiometric addition of a chemical base. The main advantage of this approach is that it is very easy to control of both the solvent and the counterion, which can be very useful because the nucleophilic reactivity of anion depends strongly on these factors. The cathodic generation of anions is most useful for strongly nucleophilic anions". In this context, particular attention was dedicated to the study of the reactivity of electrogenerated cyanomethyl anion CH_2CN^- towards electrophilic substrates (cyanomethylation reactions) or acidic substrates (acid-base reactions). In fact, interesting results (as regards the development of new synthetic methodologies) were obtained by simple addition of non-electroactive substrates to solutions containing the electrogenerated cyanomethyl anion.

Cyanomethyl anions are electrogenerated by:

- i) Electrochemical reduction of cyanomethyl derivatives (cyanomethyl triphenylphosphonium or arsonium cations and phenylsulphonyl acetonitrile) or chloroacetonitrile in dry dimethylformamide, which involves reductive cleavage of P-C, As-C, S-C or C-Cl bonds.
- ii) Electrolyses of CH_3CN solutions containing suitable probases (PBs) [5] such as azobenzene, aromatic ketones and aldehydes, aryl halides, diphenyl selenide etc. The cathodic reduction of the probases affords bases (EGBs: electrochemically generated bases)

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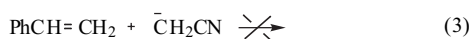
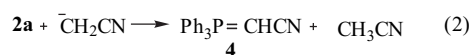
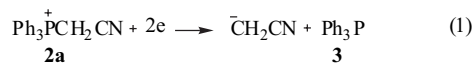
strong enough to deprotonate the solvent CH₃CN yielding its conjugate base CH₂CN⁻.

- iii) Cathodic reduction of CH₃CN-Bu₄NBF₄ or CH₃CN-LiClO₄ systems on a Pt electrode (E = -3.38 V vs. Ag/Ag⁺ reference electrode).
- iv) Electrolyses under galvanostatic control of CH₃CN-Et₄NClO₄ (TEAP) solutions.

Several authors have extensively investigated the reactivity of the electrogenerated CH₂CN⁻ as nucleophilic reagent as well as strong base. Here below we wish to summarise the results of these studies highlighting the possible utilisations of the CH₂CN⁻ anion in organic electrosynthesis.

ELECTROGENERATED CYANOMETHYL ANION: A NUCLEOPHILIC AGENT

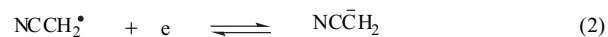
An early example of electrogeneration of cyanomethyl anion was reported by Vagenknecht and Baizer [6]. They studied the reactivity of styrene with the intermediates produced by cathodic cleavage of certain cyanoalkylphosphonium compounds [(C₆H₅)₃P(CH₂)_nCN]⁺Br⁻ (n = 1, 2, 3). The polarogram of bromo(triphenylphosphoranylidene)acetonitrile (n = 1) (**2**) in dimethylsulfoxide-tetrabutylammonium bromide (DMSO/TBAB) (0.2 mol dm⁻³) showed three reductions waves. The first wave was related to a two-electron reduction of (C₆H₅)₃P⁺CH₂CN (**2a**) to triphenylphosphine (**3**) and CH₂CN⁻ (Scheme 2, eq. 1). A pseudo one-electron reduction was measured; in fact the electrogenerated CH₂CN⁻ attacks the parent ion **2a** to form CH₃CN and (triphenylphosphoranylidene)acetonitrile (**4**) (Scheme 2, eq. 2) thus engaging two molecules of starting material in reaction with two electrons.



Scheme 2.

Large-scale electrolyses, carried out at a potential corresponding to the first reduction wave of **2** in the presence of styrene (**5**), yielded **3** and triphenylphosphine oxide (**6**) but none of the coupling products with styrene were observed. In the author's opinion, styrene was unable to compete with **2** to capture the electrogenerated CH₂CN⁻ formed by reductive cleavage (Scheme 2, eq. 3). The compound **4** apparently formed (Scheme 2, eq. 2) reacts with water during the work-up to form acetonitrile actually observed.

Recently, the reactivity of cyanomethyl anion (obtained by cathodic reduction of chloroacetonitrile; Scheme 3, eq. 1 and 2) towards carbon dioxide was studied [7]. Cyclic voltammetry and controlled potential electrolysis of DMF and CH₃CN solutions of chloroacetonitrile were performed. Aim of this investigation was to set-up electrochemical methodologies for the synthesis of cyanoacetic acid, a useful starting material in many industrial processes [8].



Scheme 3.

Cyanoacetic acid was isolated, as coupling product between CH₂CN⁻ and CO₂, at the end of electrolyses carried out in CO₂ saturated solutions containing chloroacetonitrile (Scheme 3, eq. 3).

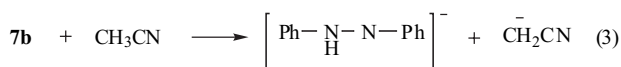
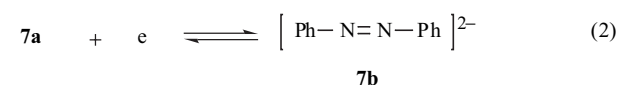
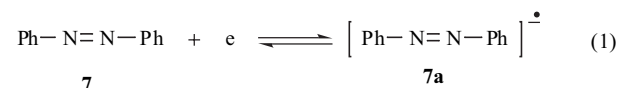
The effect of the electrolysis conditions on the yield of cyanoacetic acid was considered. The electrolyses were performed in DMF or CH₃CN solutions saturated with CO₂ using a two compartment cell with a Pt anode separated from the cathodic compartment by a medium porosity glass frit or an undivided cell with a sacrificial Al anode. Hg or graphite cathodes were adopted. Very good results (93% yields) were obtained when the electrolyses were carried out in CH₃CN solutions using undivided cells and an Al sacrificial anode. In addition, the catalytic reduction of chloroacetamide *via* [Ni^I(salen)]⁻ or aromatic radical anion was proposed (Scheme 4). Nevertheless, the use of these catalytic systems does not offer appreciable advantages over direct cathodic reduction of chloroacetamide. In fact, low yields of cyanoacetic acid and low turnover number were achieved.



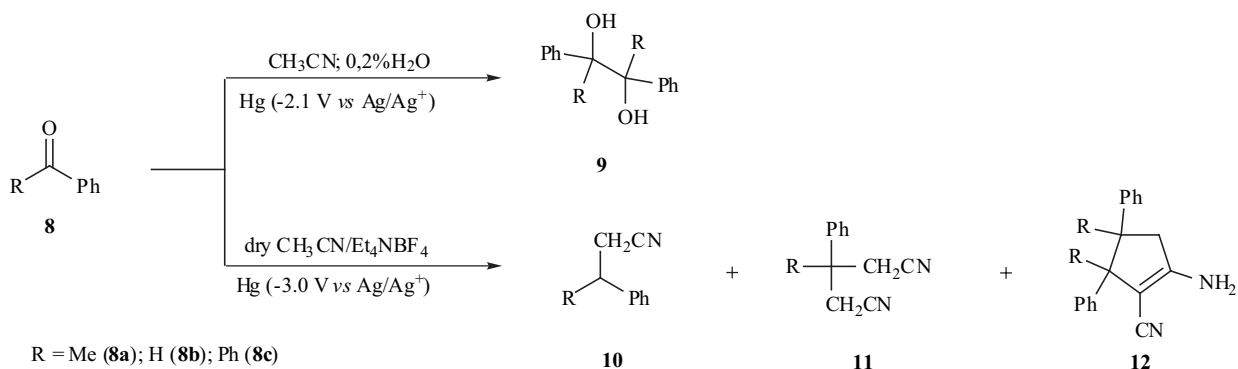
A: Catalyst

Scheme 4.

Other authors evidenced the presence of CH₂CN⁻ in the cathodic compartment, at the end of electrolyses of CH₃CN-TEAP solutions containing azobenzene (**7**) [9]. The electrochemical reduction of azobenzene in acetonitrile involves two one-electron transfer steps yielding mono- and di-anions (Scheme 5, eq. 1 and 2). Both electron-transfer steps are reversible and the observed irreversibility of the second polarographic wave is due to the very fast irreversible protonation of the dianion (**7b**) (Scheme 5, eq. 3).



Scheme 5.



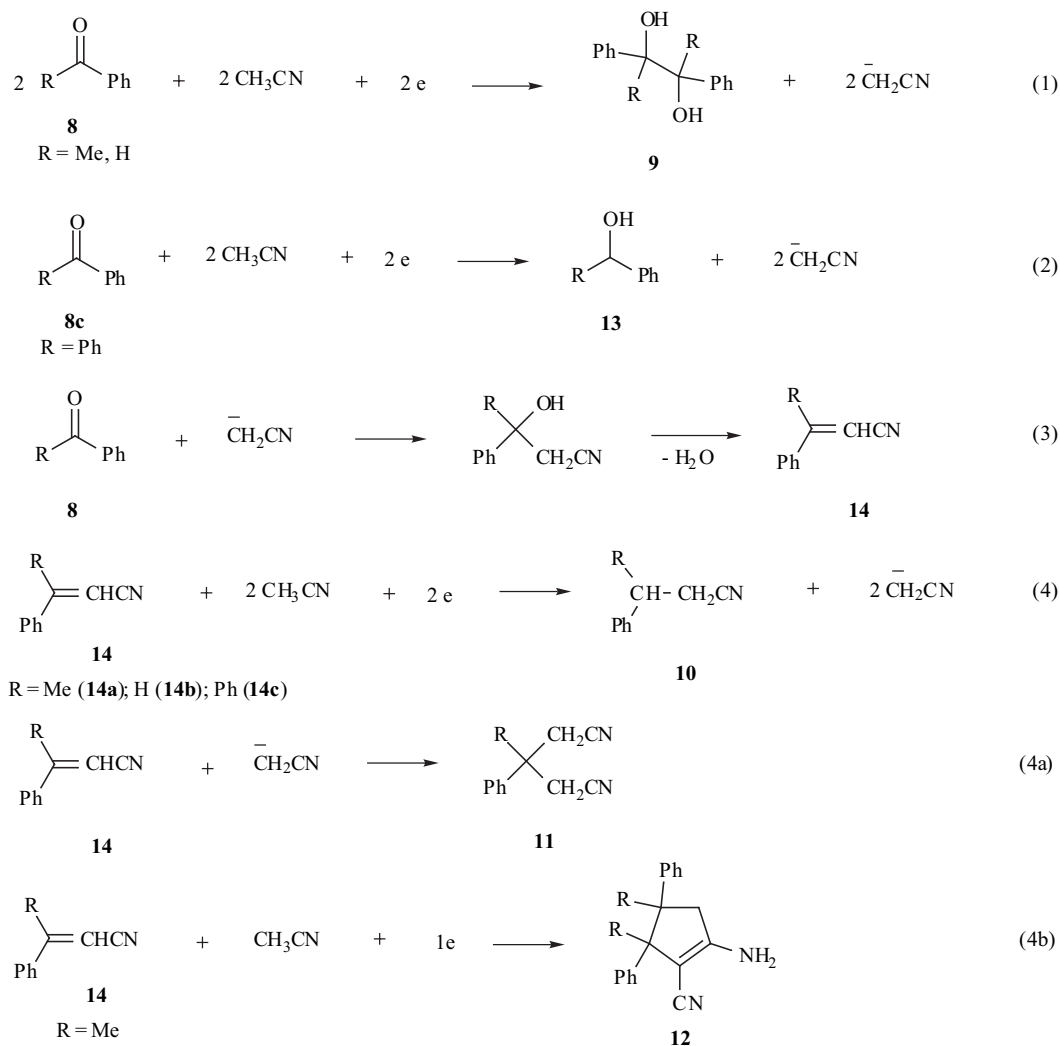
Scheme 6.

It was reported [10] that the preparative cathodic reduction of acetophenone (8a), carried out in water containing (0.2%) acetonitrile solutions at a controlled potential of $-2.1 \text{ V vs. Ag/Ag}^+$ ($\text{CH}_3\text{CN}-0.1 \text{ mol dm}^{-3} \text{ AgNO}_3$), afforded the corresponding pinacol (9a) (95% of yield) as the only product (Scheme 6).

On the contrary [11a,b] electrolyses of acetophenone (8a), benzaldehyde (8b) and benzophenone (8c), carried out at on a Hg cathode ($E = -3.0 \text{ V}$ or $-2.5 \text{ V vs. Ag/Ag}^+$ $\text{CH}_3\text{CN}-0.1$

$\text{mol dm}^{-3} \text{ AgNO}_3$) in dry CH_3CN ($<100 \text{ ppm water}$) containing Et_4NBF_4 (1.0 mol dm^{-3}) as supporting electrolyte, gave significant yields of cyanomethylation products (10, 11, 12) via reaction of the electrogenerated cyanomethyl anion CH_2CN^- with the carbonyl compounds (8) (Scheme 6). Only small amounts of diol 9 were detected.

The initial formation of cyanomethyl anion (CH_2CN^-) may be related to the reduction of carbonyl compound (8) to diol (9) and carbinol (13) (Scheme 7, eq. 1 and 2). In



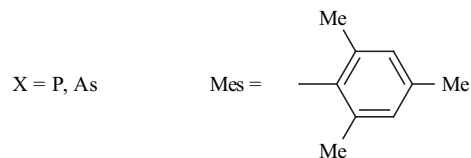
Scheme 7.

addition, CH_2CN^- was generated during the cathodic reduction of **14** to **10** (Scheme 7, eq. 4). Moreover, it was observed [11b] that, once CH_2CN^- was formed, the subsequent cyanomethylation processes (Scheme 7 eq. 3 and 4) continue to regenerate the CH_2CN^- via the deprotonation of the solvent. Consequently, the overall process may be considered as a catalytic process. The effects of the nature of the substituent R and of the electrolysis conditions (controlled potential or controlled current conditions, water concentration in the solution, temperature, cathodic material, etc.) on the products yield were also discussed. For the reported conditions, the generation of CH_2CN^- by direct or indirect reduction of the solvent was excluded [12].

Bellamy studied, by through an electrochemical methodology, the rate of addition of the electrogenerated CH_2CN^- to various electrophiles (carbonyl compounds, α,β -unsaturated nitriles etc.) [13a-d]. The cyanomethyl anion was generated, in the presence of carbonyl compounds or α,β -unsaturated nitriles, *via*:

- Cathodic reduction of azobenzene (or azopyridines or phenylazopyridines) [13e] in CH_3CN , through two or one-electron transfer step followed by rapid protonation of the dianion by way of the solvent CH_3CN (Scheme 5);
- Cathodic reduction of (cyanomethyl)(triphenyl) phosphonium ($\text{Ph}_3\text{P}^+\text{CH}_2\text{CN}$), (cyanomethyl)(triphenyl) arsonium ($\text{Ph}_3\text{As}^+\text{CH}_2\text{CN}$), (cyanomethyl)(trimesityl)phosphonium ($\text{Mes}_3\text{P}^+\text{CH}_2\text{CN}$) cations or (phenylsulphonyl)acetonitrile ($\text{PhSO}_2\text{CH}_2\text{CN}$) in super-dry DMF through the reductive cleavage of C–X bond (X = P, As, S) (Scheme 8).

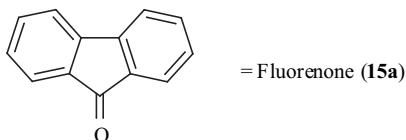
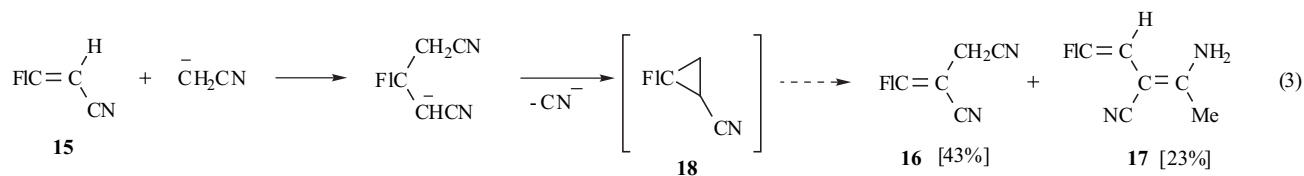
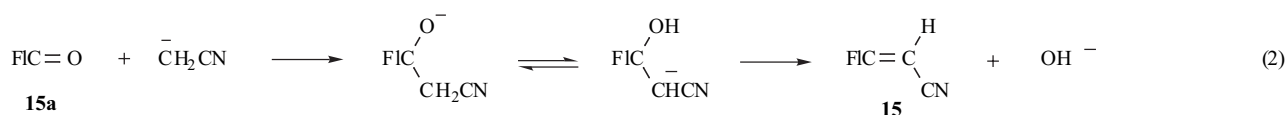
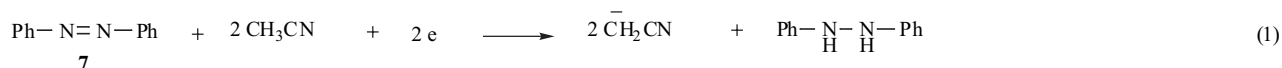
The use of $\text{Ph}_3\text{P}^+\text{CH}_2\text{CN}$ or $\text{Ph}_3\text{As}^+\text{CH}_2\text{CN}$ as a source of electrogenerated cyanomethyl anion may be complicated by the deprotonation of the parent cation operated by CH_2CN^- . The rate of this deprotonation reaction would be considerably reduced in the case of $\text{Mes}_3\text{P}^+\text{CH}_2\text{CN}$ anion (the methylene group is more sterically crowded).



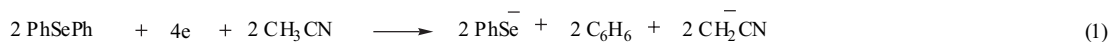
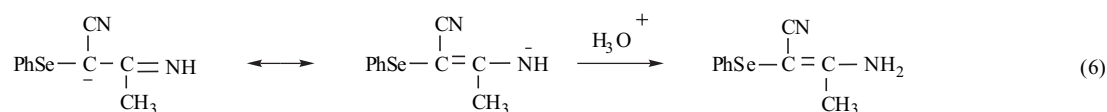
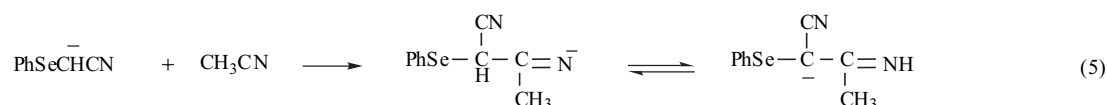
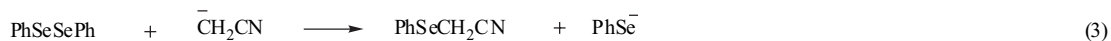
Scheme 8.

The voltammetric curves of carbonyl compounds and unsaturated nitriles were recorded in the absence and in the presence of a more reducible compound (azobenzene, $\text{Ph}_3\text{P}^+\text{CH}_2\text{CN}$, $\text{Ph}_3\text{As}^+\text{CH}_2\text{CN}$, etc.) which generated, directly or indirectly, CH_2CN^- close to the electrode. In the presence of CH_2CN^- , carbonyl compounds and unsaturated nitriles were converted into the corresponding addition products. Consequently, the current peak of the first voltammetric peak of these substrates decreased. The magnitude of this decrease was used to evaluate the rate constant of the addition reaction of the CH_2CN^- to carbonyl compounds and α,β -unsaturated nitriles.

The reactivity of the electrogenerated CH_2CN^- towards fluorenone (**15a**) (as well as towards its Schiff bases) was studied by Degrand [14a-c]. The cyanomethyl anion was generated *via* cathodic reduction of azobenzene to its dianion using CH_3CN as solvent. In a typical procedure, a CH_3CN -DMF (1:10) 0.1 mol dm^{-3} in Bu_4NPF_6 solution containing azobenzene (**7**) (2.0 mmol dm^{-3}) was electrolysed on Hg pool cathode at -2.0 V vs. SCE (Saturated Calomel Electrode), under argon atmosphere. After the consumption of 2.0 F mol^{-1} of azobenzene, fluorenone was added to the



Scheme 9.

**19****20****Scheme 10.**

catholite and the mixture was left for 2-3 h. Two main products were identified after column chromatography: **16** (43 %) and **17** (23 %) (Scheme 9).

It was suggested that nucleophilic addition of CH_2CN^- to fluorenone derivative **15** (or to its Schiff bases) led to an unstable key intermediate (**18**), which was further transformed to (**16**) and (**17**) (Scheme 9).

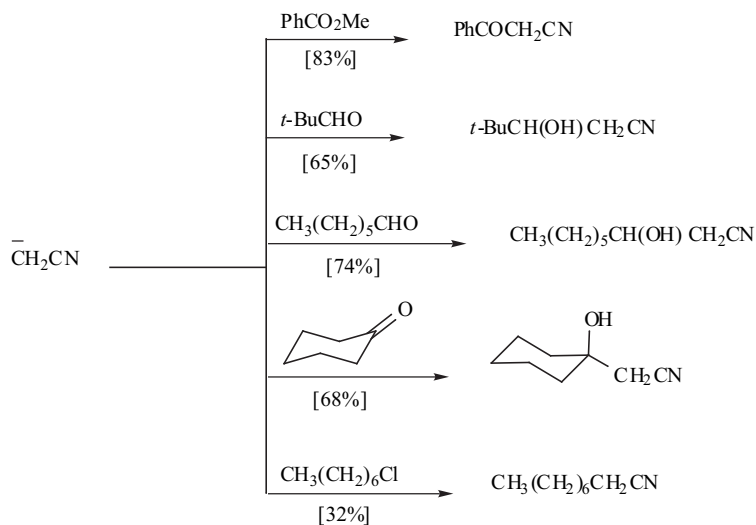
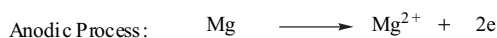
Cyanomethyl anion CH_2CN^- may be obtained *via* deprotonation of CH_3CN operated by Ph^- anion. It was reported that the electrochemical reduction of diphenyl selenide (**19**), carried out in CH_3CN 0.1 mol dm^{-3} Bu_4NPF_6 solutions (Pt as cathode and anode, $E = -2.0 \div -2.7$ V vs. SCE) led to the formation of PhSe^- and Ph^- [14d]. These anions were protonated by molecules of solvent and so CH_2CN^- anions were generated. By addition of air, PhSe^- was further oxidised to PhSe-SePh , which reacted with the

CH_2CN^- anions, giving 1-phenylseleno-1-cyano-2-aminopropene (**20**) (Scheme 10).

The synthesis of **20** from diphenyldiselenide and CH_2CN^- was also confirmed by reaction of electrogenerated CH_2CN^- (obtained by reduction of azobenzene in CH_3CN solution) with diphenyldiselenide (Scheme 11).

An electrochemical alternative to the classical cyanomethylation of carbonyl compounds, esters or alkyl halides was reported by Troupel [15]. Acetonitrile was used both as solvent and as hydrogen-active compound. The deprotonation of acetonitrile to cyanomethyl anion was carried out *via* EGB, i.e. Ph^- obtained by electroreduction of suitable probases (bromobenzene or iodobenzene) in an undivided cell fitted with cadmium coated cathode and a sacrificial magnesium anode. Moderate to high yields (32-83%) of the coupling products between cyanomethyl anion and the electrophilic substrates were isolated (Scheme 12).

**Scheme 11.**

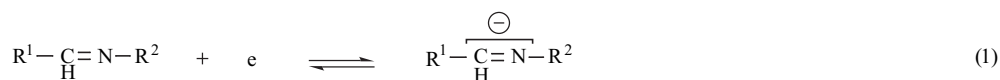


Scheme 12.

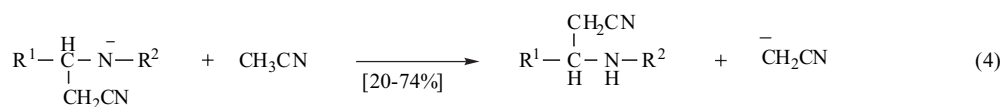
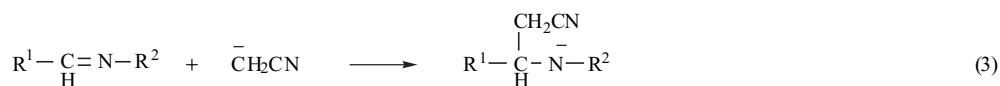
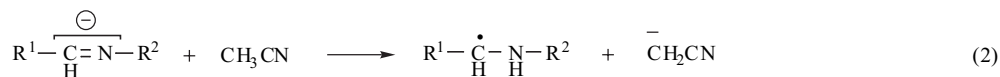
These electrochemically-induced cyanomethylation reactions may be carried out either by a one-pot procedure (the substrate was added to the solution before the beginning of the electrolysis) or by a two-step procedure (the electrophilic substrate was added at the end of the electrolysis). The cathodic reduction of PhBr or PhI at a cathode coated with an electrolytic deposit of cadmium occurs at -1.9 V (PhBr) or at -1.6 V (PhI) (vs. SCE) i.e. 0.3-

0.6 V higher than the reduction at an uncoated cathode. Accordingly, the cathodic reduction of the probase, rather than the electrophilic substrates, should occur.

Hydrocyanomethylation of *N*-heteroaryl-substituted azomethines *via* electrogenerated CH_2CN^- was proposed by Hess [16]. β -Aminonitriles (**21**) were isolated (yields 20-74 %) from the cathodic compartment at the end of electrolyses



22



21

$\text{R}^1 =$ pirid-4-yl; pirid-3-yl; pirid-2-yl; quinoline-4-yl; quinoline-3-yl.

$\text{R}^2 =$ C_6H_5 ; 4-Cl- C_6H_4 ; 4- CH_3 - C_6H_4 ; 4F- C_6H_4 ; 4- $\text{CH}_3\text{OC}_6\text{H}_4$.

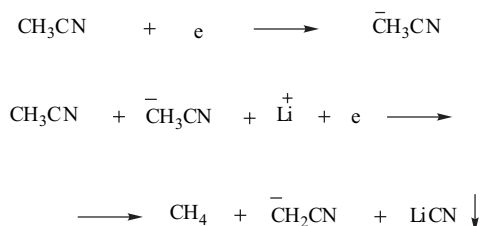
Scheme 13.

The electrochemically-induced hydrocyanomethylation of **22** consumed only a catalytic amount of current (0.1-0.2 F mol⁻¹) according to a chemical regeneration of CH₂CN⁻ (Scheme 13, eq. 3, 4).

Recently, the electrochemical synthesis of 3-phenylcinnamionitrile (**24**) (yield: 55% with 50 % of theoretical circulated charge) by reduction of benzophenone (**8c**) in acetonitrile was reported [17]. The electrolyses were carried out under galvanostatic or potentiostatic control, in CH₃CN-Et₄NCl or in CH₃CN-Bu₄NBF₄ solutions containing **8c**. Divided cells, Hg or Pt cathode and Pt anode were used. In the above reported electrolyses conditions benzophenone was reduced to its radical-anion (**23**). The radical-anion **23** was strong enough base to abstract a proton from the solvent yielding the nucleophile CH₂CN⁻. The electrogenerated cyanomethyl anion reacted with benzophenone, according to a father-son like mechanism, yielding 3-phenylcinnamionitrile (**24**) (Scheme 14).

During the electrolyses of CH₃CN-supporting electrolyte solutions, the cathodic behaviour of acetonitrile was strongly affected by the experimental conditions adopted (cathodic material, supporting electrolyte, work potential, etc.). In the absence of a proton donor, the carbanion CH₂CN⁻ was produced [18]. Electrolyses of *t*-Bu₄NBF₄ (0.1 mol dm⁻³) or LiClO₄ (0.1 mol dm⁻³) in CH₃CN solutions were carried out at -3.30 V with respect to an Ag/Ag⁺ (AgNO₃ 0.1 mol dm⁻³) reference electrode (Pt anode and cathode, divided cell). The authors reported that the electrochemical behaviour of CH₃CN-*t*-Bu₄NBF₄ was consistent with the evolution of hydrogen and the formation of an active hydride intermediate which was able to deprotonate the solvent to CH₂CN⁻ (Scheme 15, eq. 1, 5). The formation of CH₂CN⁻ was evidenced by its following reaction with isobutyraldehyde (suitably added to the solution) to give 3-hydroxy-4-methylvaleronitrile (**25**) (Scheme 15, eq. 6). The anion CH₂CN⁻ reacted with acetonitrile to give 3-iminobutyronitrile (**26**) and 3-aminocrotonitrile (**27**) (Scheme 15, eq. 7). The formation of trimers **28** and **29** by reaction of the dimer anions with acetonitrile was also proved (Scheme 15, eq. 8 and 9).

The electrochemical behaviour of CH₃CN-LiClO₄ solutions was consistent with a direct electron transfer to the acetonitrile molecule (Scheme 16). Dimer **26**, **27** and trimer **28**, **29** were isolated from the catholyte at the end of the electrolyses.



Scheme 16.

ELECTROGENERATED CYANOMETHYL ANION: A STRONG BASE

In the previously summarised articles, the reactivity of the electrogenerated CH₂CN⁻ as nucleophilic agent towards

carbonyl compounds, Schiff bases, esters, alkyl halides, carbon dioxide etc. was discussed. Recently, the reactivity of the electrogenerated cyanomethyl anion as base and the possible utilisation of the CH₃CN-CH₂CN⁻ acid-based system in organic syntheses induced by strong bases was considered. In this connection, the reactivity of the electrogenerated CH₂CN⁻ towards amines and amino alcohols in CO₂ saturated CH₃CN solutions was examined. Aim of this investigation was to set up new methodologies for the electrogenerated CH₂CN⁻ induced synthesis of carbamates and chiral oxazolidin-2-ones *via* carboxylation of amines and amino alcohols under mild conditions. Likewise, a possible electrochemical acylation of chiral oxazolidin-2-ones was considered.

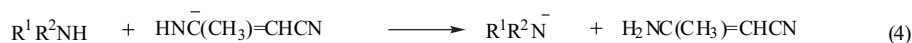
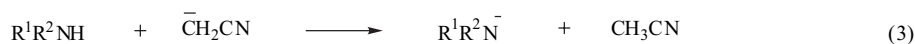
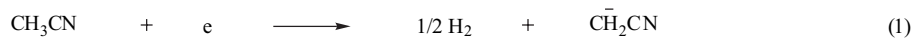
Cyanomethyl anion generated by electrolyses of CH₃CN-TEAP (0.1 mol dm⁻³) solutions was used as base. The electrolyses were carried out under galvanostatic conditions (I = 16 mA cm⁻²) on a Pt (or Pd, Cu, C, Ni, Zn) cathode and on a Pt anode in a divided cell, at rt, with continuous N₂ bubbling. Accordingly to the presence of cyanomethyl anion in the electrolysed CH₃CN-TEAP solutions, products related to the nucleophilic attack of CH₂CN⁻ to the parent molecule CH₃CN (i.e. **26-29**; Scheme 15, eq. 7-9) were isolated from the catholyte at the end of the electrochemical procedure.

Organic carbamates are compounds of remarkable interest because of their applications as protective groups for the aminic function of amino acids in peptide chemistry. Notable, is their role in the syntheses of pharmaceutical and agricultural chemicals and in chemical industry [19]. Chiral oxazolidin-2-ones (Evans' chiral auxiliaries) [20a,b] were used in a wide range of reactions directed to the stereoselective synthesis of natural products, antibiotics and pharmaceuticals [20c].

The classical syntheses of carbamates [21] as well as of oxazolidin-2-ones [22] usually involve toxic and hazardous reagents (phosgene or its derivatives) and/or drastic reaction conditions (strong bases, very high temperature and pressure) or catalytic reactions. In order to avoid the use of harsh reaction conditions, many efforts were devoted to the development of phosgene-free routes to carbamates [23] and chiral oxazolidin-2-ones [24]. Syntheses of carbamates [25] and of chiral oxazolidin-2-ones [22d,e] carried out using CO₂ (a safe, cheap and abundant reagent) as a replacement of phosgene or its derivatives, were described by several authors. Recently, phosgene-free electrochemical methodologies for the synthesis of carbamates and chiral oxazolidin-2-ones *via* i) electrogenerated O₂^{•-}/CO₂ system [26], ii) EGBs/CO₂ systems [27] and iii) direct cathodic reduction of CO₂ [28] were described.

Electrogenerated CH₂CN⁻/CO₂ System: A New Carboxylating Reagent

Recently, a new carboxylating reagent (CH₂CN⁻/CO₂) was obtained by bubbling CO₂ in a CH₃CN-TEAP solution previously electrolysed under galvanostatic control as above described. Organic carbamates or chiral oxazolidin-2-ones were isolated from these solutions after addition of amines and of an alkylating agent or by addition of amino alcohols and TsCl, respectively.



Scheme 17.

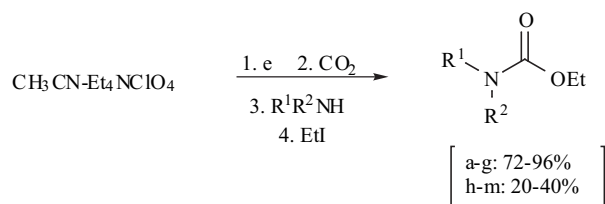
Synthesis of Carbamates [29] (Scheme 17, 18)

Carbamates were not obtained by mere bubbling of CO_2 and addition of amine and of an alkylating agent in: i) a non-electrolysed CH_3CN -TEAP solution or ii) in a DMF-TEAP solution previously electrolysed under galvanostatic control. Consequently, the activation of the amines towards CO_2 may be related to the modification of the chemical properties of CH_3CN -TEAP solutions as a consequence of the presence of the electrogenerated $\bar{\text{C}}\text{H}_2\text{CN}^-$ anion and the derived 3-aminocrotonitrile anion (see above). In CO_2 saturated CH_3CN -TEAP solutions containing amines, the cyanomethyl and the 3-aminocrotonitrile anions constitute basic systems strong enough to deprotonate the NH group of the amines yielding acetonitrile and 3-aminocrotonitrile respectively and carbamate anion (Scheme 17). In fact, 3-aminocrotonitrile was isolated, in addition to carbamate, from the catholyte at the end of the electrochemical procedure. These results suggest a double behaviour of $\bar{\text{C}}\text{H}_2\text{CN}^-$ anion: as a base towards the aminic substrates yielding, in the presence of CO_2 , the carbamate ion; as a nucleophile towards the parent molecule yielding the 3-aminocrotonitrile anion.

The yields of carbamates were affected by: i) the number of Faradays (Q) per mole of amine supplied to the electrode, ii) the nature of the anion and of the cation of the supporting electrolyte, iii) the cathodic material. The highest yields were obtained when Pt or Cu cathode was used and 2.0-3.0 F per mole of amine were consumed. In these conditions, carbamates were isolated from primary and secondary aliphatic amines in high to excellent yields (76-92 %) and from aromatic amines in moderate yields (20-40 %) depending on the nucleophilicity of the nitrogen atom (Scheme 18).

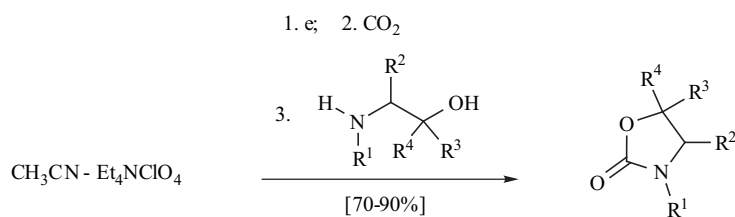
Synthesis of Chiral Oxazolidin-2-ones from Chiral Aminoalcohols [30] (Scheme 19)

The yields of chiral oxazolidin-2-ones were affected by the number (Q) of Faradays per mole of amino alcohols supplied to the electrode. The best efficiency was obtained when 4.0 F mol^{-1} of amino alcohol were consumed. The nature of both the amino groups (primary or secondary) and the substituent on the carbon atom in the α -position to the nitrogen atom may affect the yields of oxazolidin-2-ones. In addition, the reaction occurs, in all cases examined, with



	R ¹	R ²
a	C ₆ H ₁₁	H
b	C ₅ H ₉	H
c	C ₇ H ₁₃	H
d	C ₆ H ₁₁ CH ₂	H
e	CH ₂ =CHCH ₂	H
f	PhCH ₂	H
g	PhCH ₂	CH ₃
h	Ph	H
i	4-NO ₂ -Ph	H
j	4-Cl-Ph	H
k	3-Cl-Ph	H
l	2-Cl-Ph	H
m	Ph	Ph

Scheme 18.



R ¹	R ²	R ³	R ⁴
H	Ph	H	H
H	Bn	H	H
H	Ph	Ph	H
H	Me	Ph	H
H	Me	Ph	Ph
H	Et	H	H
H	i-Pr	H	H
H	Me ₂ CH ₂ CH	H	H
H	C ₆ H ₁₁ CH ₂	H	H
H	MeOCH ₂	Ph	H
Bn	Ph	H	H

Scheme 19.

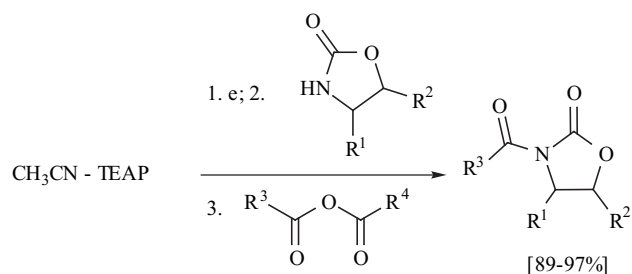
total retention of the absolute configuration of all the chiral atoms. Besides, *N*-tosylamino alcohols were isolated as by-products from the reaction mixture (Scheme 19).

Therefore, electrolysis of CH₃CN-TEAP solutions carried out under galvanostatic control yields, after addition of CO₂, a new carboxylating reagent: cyanomethyl anion/carbon dioxide. As previously reported in the electrochemically induced syntheses of carbamates and chiral oxazolidin-2-ones, this reagent, was able to carboxylate amines and amino alcohols opportunely added to the solutions. In comparison with the classical syntheses, carbamates and chiral oxazolidin-2-ones were obtained in remarkable yields, under mild conditions, without any peculiar addition of bases or probases and avoiding the use of toxic, polluting or hazardous chemicals.

The frequent utilisation, in asymmetric synthesis, of chiral *N*-acyl oxazolidin-2-ones spurred many authors to investigate new methodologies for the *N*-acylation of chiral oxazolidin-2-ones. Classical acylation of oxazolidin-2-ones were carried out by addition of an acylating agent (acyl chlorides or anhydrides) to oxazolidinones in the presence of bases. The bases (*n*-BuLi or triethylamine and 4-(*N,N*-dimethylamino)pyridine) are strong enough to deprotonate the substrate yielding *N*-oxazolidinone anion [31]. On this subject, the electrochemical methodology is able to suggest effective alternative solutions. In fact, the electrochemical acylation of chiral oxazolidin-2-ones *via* EGBs (as 2-pyrrolidone anion) was reported [32]. Recently, *N*-acyloxazolidin-2-ones were isolated, after addition of chiral oxazolidin-2-ones and an acylating agent [33]. (Scheme 20) to CH₃CN-TEAP solutions electrolysed under galvanostatic control (see above).

The almost quantitative yields (89-97%) involve very high current efficiencies (Q = 1.0; where Q represent the number of Faradays per mole of oxazolidin-2-one supplied

to the electrode). In addition, in all the examined cases the acylation reaction occurred with total retention of the absolute configuration of all the chiral carbon atoms and any possible epimerisation was avoided.



R ¹		R ²		Acylating Agent	
R ¹	R ²	R ³	R ⁴	R ³	R ⁴
Ph	H	Me	Me	Me	Me
Me	Ph	Ph	Ph	Ph	Ph
Ph	Ph	Ph(CH ₂) ₂	Ph(CH ₂) ₂	Ph(CH ₂) ₂	Ph(CH ₂) ₂
i-Pr	H	PhCH=CH	PhCH=CH	PhCH=CH	PhCH=CH
Bu	H	PhCH=CH	Cl	PhCH=CH	Cl
		PhCH ₂ CH ₂	Cl	PhCH ₂ CH ₂	Cl
		ClCH ₂	ClCH ₂	ClCH ₂	ClCH ₂

Scheme 20.

ELECTROCHEMICALLY GENERATED CYANOMETHYL ANIONS: FURTHER CRITICAL NOTES

Cyanomethyl anions can be obtained (selectively, under mild conditions and avoiding the use of chemical

deprotonating or reducing reagents) by cathodic reduction of suitable depolarisers. A lot of electrochemical methodologies have been set up, but none can be considered of general use. Indeed, the choice of the method strongly depends both on the nature of the substrate and on the type of reaction involving the cyanomethyl anion and the substrate (i.e. cyanomethylation or acid-base reaction).

Cyanomethyl anions may be produced by cathodic cleavage of P-C, As-C, S-C or Cl-C bonds carried out *via* controlled-potential electrolyses of solutions containing both the source of CH_2CN^- and the substrate. As concerns this method, some drawbacks (low yields, undesirable by-products) arise from possible competing reactions between the electrogenerated cyanomethyl anion and its source (mother-son reactions).

However, so far, the most frequently used electrochemical way to generate CH_2CN^- seems to be the protonation of reduced species (such as aromatic ketone radical anions or azobenzene dianions etc.) by means of acetonitrile, the latter being used also as solvent. This procedure is not affected by the drawback present in the previously examined methodology, namely deprotonation of the source of CH_2CN^- by the same cyanomethyl anion. Nevertheless, an important limitation to the use of azobenzene should be taken in account; it is relative to the high negative potential required to generate its dianion. Consequently, in the investigations concerning the reactivity of electrogenerated CH_2CN^- versus electroactive substrates, the use of azobenzene as probase, is strongly restricted. In order to overcome this limitation, the use of the more easily reducible azopyridines was investigated by some authors.

Finally, cyanomethyl anions were generated by electrolyses of acetonitrile-supporting electrolyte solutions carried out under potentiostatic or galvanostatic control. By employing these methods, cyanomethyl anions have been obtained without any addition of probases or sources of CH_2CN^- to the electrolysed solutions. Accordingly: i) a reduced solution is obtained which is less complex than by other methods; ii) it is possible to avoid the formation of undesired by-products; iii) the synthesis product can be more easily isolated.

CONCLUSION

The frequent utilisation of the cyanomethyl anion in organic synthesis in order to effect carbon-carbon bonds formation spurred many authors to study new methods able to obtain CH_2CN^- avoiding the preparation and the use of strong bases. As regards the electrochemical methodology, CH_2CN^- was generated by:

- i) Electrolyses of CH_3CN solutions containing suitable probases;
- ii) Electrochemical reduction of cyanomethyl anion derivatives;
- iii) Cathodic reduction, under potentiostatic control, of CH_3CN - Bu_4NBF_4 solutions;
- iv) Electrolyses, under galvanostatic control, of CH_3CN -TEAP solutions.

The reactivity of the electrogenerated cyanomethyl anion towards nucleophilic and acid substrates (styrene, carbon dioxide, carbonyl compounds, fluorenone and its Schiff bases, esters, alkyl halides, amines, aminoalcohols) was also evaluated. In addition, the electrochemical syntheses of carbamates and chiral oxazolidin-2-ones (under mild conditions and avoiding the use of toxic and hazardous chemicals) *via* a new carboxylating reagent ($\text{CH}_2\text{CN}^-/\text{CO}_2$) were set up.

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