Tetrahedron Vol. 49, No. 23, pp. 5091-5098, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Aryl Halides as Precursors of Electrogenerated Bases. Utilization in Coupling Reactions of Acetonitrile with various Electrophilic Compounds.

Rachid Barhdadi, Jacques Gal, Monique Heintz, Michel Troupel* and Jacques Périchon.

Laboratoire d'Electrochimie, Catalyse et Synthèse Organique (UMR 28), C.N.R.S. - Université Paris 12 Val de Marne, 2, rue Henri Dunant, 94320 Thiais, France.

(*Received in Belgium* 15 *March* 1993)

Key Words: Cyanomethylation | Electrogenerated bases | Aryl halides as probases

Abstract: An electrochemical alternative to classical cyanomethylation is possible by using electrogenerated bases (EGBs), obtained by electroreduction of aryl halides in an undivided cell fitted with a cadmium coated cathode and a sacrificial magnesium anode. Acetonitrile is used both as solvent and as hydrogen-active compound. A coupling reaction with various electrophilic compounds was carried out. When the electrophilic compound was present from the beginning of the electrolysis, the expected coupling product with the cyanomethyl anion was obtained. If the electrophilic compound was added only after complete electrolysis of the aryl halide, dimerization of the cyanomethyl anion and a coupling reaction between the dimer anion and the electrophilic compound were observed.

Introduction

Cyanomethylation is a very common reaction which has been widely used for the synthesis of numerous compounds[1]. In this reaction, acetonitrile is coupled with an electrophilic compound in the presence of a strong basic reagent.

In a previous publication[2], we reported the effective synthesis of β-oxonitriles or β-oxoesters from the coupling of active-hydrogen compounds (AH) with esters. These reactions result from the deprotonation of AH by means of electrogenerated bases (EGBs) produced by the electroreduction of substrates called probases. Acetonitrile is a polar solvent commonly used in electrochemistry. Its utilization both as an active-hydrogen compound and as a solvent in which EGB would be produced can be considered an electrochemical alternative to the classical cyanomethylation.

Among the substances which can be used as probases, aryl halides e.g. bromobenzene and iodobenzene, proved to be very convenient since their electroreduction yields a very strong base. When carried out at a cathode coated with an electrolytic deposit of cadmium, the electroreduction of PhBr or PhI occurs at a much less negative potential (-1.9 and -1.6 V *vs* SCE respectively) i.e. 0.3 to 0.6V higher than at an uncoated cathode[3]. This widens the scope of this method as the feasibility of the reaction depends on the fact that the reduction of the probase must occur rather than that of the active-hydrogen and/or electrophilic compound when the reaction is performed in a one-pot procedure. A further advantage of aryl halides is that no side reaction can occur from nucleophilic attack of Ph^- and/or A^- on the probase.

We report here new syntheses promoted by EGBs in which acetonitrile is coupled with various electrophiles.

Results and discussion

Acetonitrile containing a small amount of Bu_4NBF_4 (4.10^{-2} mol.l^{-1}) as supporting electrolyte was used both as the solvent and as the active hydrogen compound. Bromobenzene ($6.2.10^{-1}$ mol.l^{-1}) was the probase.

All the syntheses were conducted under simple and mild conditions. Electrolyses were carried out, at room temperature, at constant current (1 A.dm^{-2}), in an undivided cell fitted with a sacrifical magnesium anode and a nickel grid cathode freshly coated with a small deposit of cadmium obtained by electroreduction of $CdBr_2$.

a) One-pot procedure

In the one-pot procedure, an electrophilic compound E (carbonyl compound, ester or alkyl halide), (6.10^{-1}mol.l^{-1}) was added to the solution before the electrolysis was started. The reactions then occuring are:

Anodic process:	Mg	⟶	Mg^{2+} + 2e
Cathodic process:	PhBr + 2e	⟶	Ph^- + Br^-
In solution:	Ph^- + CH_3CN	⟶	PhH + $\bar{C}H_2CN$
Then:	$\bar{C}H_2CN$ + E	⟶	Product

The last step depends on the nature of the electrophile and can be a nucleophilic substitution or a nucleophilic addition, followed in some cases by an elimination reaction.

Results obtained with various electrophilic compounds are given in Table 1.

When the electrophilic compound is an aldehyde or a ketone, the nucleophilic attack of the electrogenerated $^-CH_2CN$ on the carbonyl leads to the formation of a β-hydroxynitrile. Such electrosyntheses were previously realized by BELLAMY[4] and DEGRAND[5], using a divided cell. These authors noted a further transformation of the formed β-hydroxynitrile, presumably through a dehydration followed by the reduction of the resultant α,β-unsaturated nitrile. We did not observe such a transformation and we think that, under our conditions, the product of the coupling reaction may be stabilized by the Mg^{2+} ions resulting from the magnesium anode oxidation in the form of an alkoxide magnesium salt. The β-hydroxynitrile is obtained through acidic hydrolysis, after the electrolysis is complete.

b) Two steps procedure

Though the one-pot synthesis proved quite suitable with numerous electrophilic compounds, it cannot be used when the latter are reduced more easily than PhBr. So we attempted to realize condensations by introducing the electrophilic compound only after complete electrolysis of the probase. The results obtained with various electrophile compounds are given in Table 2.

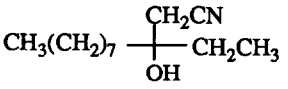
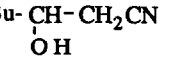
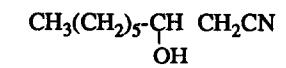
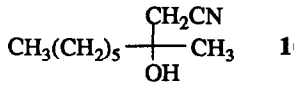
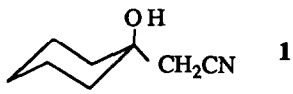
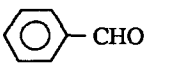
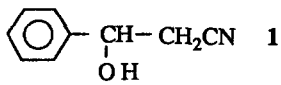
Electrophilic compound	Products		Yield[a]
t - $BuCO_2Me$	*t* - $BuCOCH_2CN$	**1**	60
$PhCO_2Me$	$PhCOCH_2CN$	**2**	83
4-$CF_3C_6H_4CO_2Me$	4-$CF_3C_6H_4COCH_2CN$	**3**	78
2-Thienyl-CO_2Me	2-Thienyl-$COCH_2CN$	**4**	70
$PhCF_2CO_2Me$	$PhCF_2COCH_2CN$	**5**	60
$CH_3(CH_2)_6CO_2Me$	$CH_3(CH_2)_6COCH_2CN$	**6**	66
$CH_3(CH_2)_7COCH_2CH_3$		**7**	52
t -Bu- CHO		**8**	65
$CH_3(CH_2)_5CHO$		**9**	74
$CH_3(CH_2)_5COCH_3$		**10**	56
		**11**	68
		**12**	55*
$CH_3(CH_2)_6Cl$	$CH_3(CH_2)_6CH_2CN$	**13**	32

Table 1: Condensation, in a one-pot procedure, of acetonitrile with various electrophilic compounds, using PhBr as a probase.

[a] : isolated products in percent *vs* initial electrophilic compound.

* : Probase = PhI.

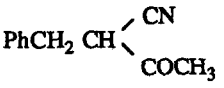
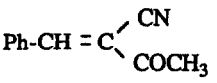
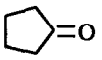
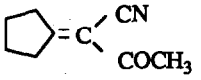
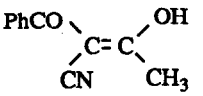
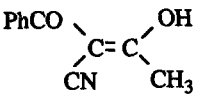
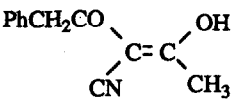
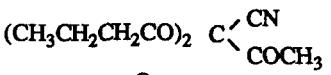
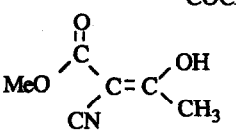
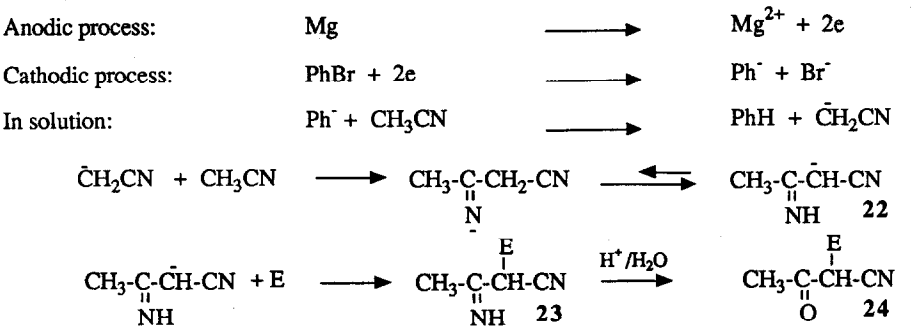
Electrophile	Product		Yield
$PhCH_2Cl$		**14**	60[a]
PhCHO		**15**	50[a]
		**16**	20[a]
$PhCO_2Me$		**17**	48[a]
PhCOCl		**17**	57[a]
$PhCH_2COCl$		**18**	55[a]
CH_3COCl	$(CH_3CO)_3CCN$	**19**	88[b]
$CH_3CH_2CH_2COCl$		**20**	75[b]
$ClCO_2Me$		**21**	81[a]

Table 2 : Condensation of acetonitrile with some electrophilic compounds introduced after complete electrolysis of the probase PhBr.

[a] : isolated products in percent *vs* initial electrophile compound

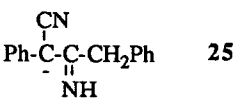
[b] : isolated products in percent *vs* PhBr.

In these conditions, simple cyanomethylation products are not obtained. We interpret these results as follows. The electroreduction of PhBr generates the cyanomethyl anion $^{-}CH_2CN$ which is not stable in the solution at room temperature. It undergoes a Thorpe-like reaction with a second molecule of acetonitrile, yielding the stable dimer anion **22** which reacts with the electrophilic compound E introduced after completion of the electrolysis. The imino group of the product thus obtained is finally turned into a cabonyl group through acidic hydrolysis. The reaction pathway can be represented by the following scheme:



Products **23** (and **24**) depend on the nature of the electrophile (E), since the coupling reaction can be a nucleophilic substitution or a nucleophilic addition followed in some cases by an elimination reaction.

We tried to demonstrate this mechanism through direct hydrolysis of **22**, without addition of E. This proved difficult because the product resulting from the hydrolysis of this anion cannot be easily isolated under our conditions. We therefore carried out electrolysis of PhBr in $PhCH_2CN$ instead of acetonitrile, which would yield the dimer anion **25**.



25

After removal of the solvent and hydrolysis, the expected Thorpe reaction product $PhC(CN)=C(OH)CH_2Ph$ **26** was obtained in 73% yield.

The formation of products **15** and **16** can be explained by the above mechanism. In both cases, product **24**, which is both a β-hydroxyketone and a β-hydroxynitrile having one H α to both carbonyl and nitrile groups, undergoes a dehydration in the acidic medium used for the hydrolysis. An elimination occuring from **23** directly in the bulk of the electrolytic solution, which is strongly basic, could also explain the formation of **15** and **16**.

The formation of **19** and **20** implicates the coupling of two molecules of E with the dimer anion. This could be explained if one assumes that the first coupling reaction is followed by an acid-base exchange between **23** and **22** acting as a basic agent, but no direct evidence has been obtained so far.

Conclusion

When performed in an undivided cell fitted with a magnesium anode and a cadmium coated cathode, the electroreduction of bromobenzene or iodobenzene proved to be an efficient way to carry out syntheses which implicate the anion Ph^- as an EGB. Cyanomethyl anion was then produced through the deprotonation of acetonitrile, used as the solvent. When electrophilic compounds were added before electrolysis, cyanomethylation products were obtained in high yields. This electrochemical method then offers an interesting alternative to the classical cyanomethylation, avoiding the preparation and use of strong bases.If the electrophilic compounds were added only after complete reduction of the probase, the products obtained resulted from an original reaction where the electrophile coupled with the dimer anion of acetonitrile, presumably stabilized by Mg^{2+} cations resulting from the oxidation of the scrificial magnesium anode.

We thank the *Société Nationale des Poudres et Explosifs*, and the *Electricité de France* for financial support.

Experimental

All the chemicals used were of reagent grade quality and used without preliminary purification except for tetrabutylammonium tetrafluoroborate (Fluka^R) and cadmium bromide (Aldrich^R) which were dried by heating overnight at 70°C in vacuo.

Electrolysis

Electrolysis was performed in an undivided cell described elsewhere[6] and fitted with a nickel grid cathode and a SCE as a reference electrode. All potentials are given *vs* SCE. Argon bubbling was maintained during the electrolysis.

Cadmium coating of the cathode is achieved by electrolysing a strirred solution of $CdBr_2$ (5.10^{-2} mol.l^{-1}) in DMF, a cadmium anode being used in order to maintain a constant concentration of Cd^{2+} ions. A constant current of 0.2 A was applied during 17 min. The solution of $CdBr_2$ was removed from the cell which was then rinsed with acetonitrile.

To 40 ml of acetonitrile containing 500 mg of Bu_4NBF_4 was added 2 ml of PhBr (0.19 mol.l^{-1}) and the electrophilic compound (carbonyl compound, aliphatic halide, acyl chloride or ester) in a molecular ratio of 0.9:1 versus PhBr. This solution was introduced to the electrochemical cell fitted with the cadmium coated cathode, an SCE as reference and a magnesium anode. Electrolysis was achieved under argon bubbling, applying a constant current of 0.2 A. Reaction progress during electrolysis was checked by GC analysis of 200µl samples of the solution and the electrolysis was stopped after complete consumption of PhBr.

Recovery of the products

After electrolysis, most of the solvent was evaporated under vacuo. The residue was acidified with 6 mol.l^{-1} aqueous hydrochloric acid (50 ml) and extracted twice with diethylether or methylene chloride (50 ml). The extracts were washed with aqueous sodium hydrogencarbonate, dried over magnesium sulfate and then evaporated in vacuo. The products were isolated by column chromatography on silica gel with pentane/Et_2O mixtures as eluent. Analysis of the products was achieved by GC, ^1H NMR, and mass spectroscopy.

Characteristics of the compounds obtained are given below.

4,4-dimethyl-3-oxo-pentanenitrile (**1**) : ^{1}H NMR ($CDCl_3$, 200MHz) δ 1.2 (s, 9H), 3.7 (s, 2H) ; MS m/z, (relative intensity) 126 (M+1), 68, 57 (100) ; Registry number [59997-51-2].

3-oxo-3-phenylpropanenitrile (**2**) : ^{1}H NMR ($CDCl_3$, 200MHz) δ 4.1 (s, 2H), 7.5 (m, 5H) ; MS m/z, (relative intensity) 145 (M), 105 (100), 77 ; Registry number [614-16-4].

3-oxo-3-[4-trifluoromethylphenyl]propanenitrile (**3**) : ^{1}H NMR ($CDCl_3$, 200MHz) δ 4.2 (s, 2H), 7,65 (dd, 4H) ; ^{19}F NMR ($CDCl_3$) δ -63.3 (s) ; MS m/z, (relative intensity) 213 (M), 173 (100), 145 ; Registry number [71682-94-5].

3-oxo-3-[2-thienyl]propanenitrile (**4**) : ^{1}H NMR ($CDCl_3$, 200MHz) δ 3.95 (s, 2H), 7-8 (m, 3H); MS m/z, (relative intensity) 151 (M), 111 (100) ; Registry number [33898-90-7].

4,4-difluoro-3-oxo-4-phenylbutanenitrile (**5**) : ^{1}H NMR ($CDCl_3$, 200MHz) δ 3.8 (s, 2H), 7.4 (m, 5H) ; ^{19}F NMR ($CDCl_3$) δ -104 (s) ; MS m/z, (relative intensity) 196 (M+1), 176, 168 (100).

3-oxo-decanenitrile (**6**) :^{1}H NMR ($CDCl_3$, 200MHz) δ 3,6 (s, 2H), 2,2 (t, 2H), 1,5 (m, 13H) MS m/z, (relative intensity) 167 (M^+, 14,6), 152 (6,54), 127 (42,8), 99 (100), 84 (25,4).

3-ethyl-3-hydroxyundecanenitrile (**7**) : ^{1}H NMR ($CDCl_3$, 200MHz) δ 3.2 (s,1H), 2.35 (s, 2H), 0.7-1.6 (m, 22H) ; MS m/z, (relative intensity) 182 (M-29), 57 (100).

4,4-dimethyl-3-hydroxypentanenitrile (**8**) : ^{1}H NMR ($CDCl_3$, 200MHz) δ 3.4 (s, 1H), 3.1 (t,1H), 2.5 (d, 2H), 0.85 (s, 9H) ; MS, m/z, (relative intensity) 128 (M+1), 103 (100).

3-hydroxynonanenitrile (**9**) : ^{1}H NMR ($CDCl_3$, 200MHz) δ 3.35 (s, 1H), 2.5 (d, 2H), 0.65-1.45 (m, 14H) ; MS m/z, (relative intensity) 137 (M-18), 43 (100) ; Registry number [30683-75-1]

3-hydroxy-3-methylnonanenitrile (**10**) : ^{1}H NMR ($CDCl_3$, 200MHz) δ 3.3 (s, 1H), 2.4 (s, 2H), 0.7-1.5 (m, 16H) ; MS m/z, (relative intensity) 170 (M+1), 152, 44 (100)

1-cyanomethylcyclohexan-1-ol (**11**) : ^{1}H NMR ($CDCl_3$, 200MHz) δ 3.1 (s, 1H), 2.2 (s, 2H), 1-1.5 (m, 10H) ; MS m/z,(relative intensity) 122 (M-17), 81 (100) ; Registry number [14368-55-9]

3-hydroxy-3-phenylpropanenitrle (**12**): ^{1}H NMR ($CDCl_3$, 200MHz) δ 7,1 (m, 5H), 4,3 (t, 1H, J =11Hz), 3,2 (d, 2H, J =11Hz) ; MS m/z, (relative intensity) 147 (M^+, 3,41), 129 (100), 103 (43,12), 77 (51,13).

nonanenitrile (**13**) : ^{1}H NMR ($CDCl_3$, 200MHz) δ 2,1 (t, 2H, J =10Hz), 1,8 - 0,8 (m, 15H,) ; MS m/z, (relative intensity) 139 (M^+, 3,60), 124 (8,45), 113 (33,3), 110 (12,05), 96 (100).

2-acetyl-3-phenylpropanenitrile (**14**) : ^{1}H NMR ($CDCl_3$, 200MHz) δ 7.2 (m, 5H), 3.6 (t, 1H), 3.05 (d, 2H), 2.2 (s, 3H) ; MS m/z, (relative intensity) 173 (M, 0.88), 91 (16), 43 (100) ; Registry number [84831-51-6]

2-acetyl-3-phenylprop-2-enenitrile (**15**) : 1H NMR ($CDCl_3$, 200MHz) δ 7.2 (m, 5H), 2.25 (s, 3H), 2.25 (s, 1H) ; MS m/z, (relative intensity) 172 (M+1, 32.4), 157 (M-Me, 100)

2-cyclopentylidene-3-oxobutanenitrile (**16**) : ^1H NMR ($CDCl_3$, 200MHz) δ 1.8-2.4 (m, 8H), 2.2 (s, 3H); MS m/z, (relative intensity) 150 (M+1, 88), 135 (M+1-Me, 11), 80 (100)

2-acetyl-3-oxo-3-phenylpropanenitrile (**17**)[a] : ^1H NMR ($CDCl_3$, 200MHz) δ 7.3-7.6 (m, 5H), 6.8 (s, 1H), 2.2 (s, 3H) ; MS m/z, (relative intensity) 187 (M, 1.25), 186 (M-1, 8.15), 105 (100) ; Registry number [75279-86-6]

2-acetyl-3-oxo-4-phenylbutanenitrile (**18**)[a] : ^1H NMR ($CDCl_3$, 200MHz) δ 7.2 (m, 5H), 6.1 (s, 1H), 3.8 (s, 2H), 2.1 (s, 3H) ; MS m/z, (relative intensity) 201 (M, 4.2), 109 (100)

triacetylacetonitrile (**19**) : ^1H NMR ($CDCl_3$, 200MHz) δ 2.25 (s, 9H) ; MS m/z, (relative intensity) 167 (M, 3.3), 124 (M - "$COCH_3$", 48), 43 (100)

2-acetyl-3-oxo-2-[1-oxobutyl]-hexanenitrile (**20**) : ^1H NMR ($CDCl_3$, 200MHz) δ 2.7 (t, 2H), 2.68 (s, 3H), 2.4 (t, 2H), 1.45-1.76 (m, 4H), 0.9 (t, 6H) ; MS m/z, (relative intensity) 223 (M, 2.04), 222 (M-1, 13.6), 71 (100)

2-cyano-3-oxobutanoic acid, methyl ester (**21**)[a] : ^1H NMR ($CDCl_3$, 200MHz) δ 5.8 (s, 1H), 3.7 (s, 3H), 2.23 (s, 3H) ; MS m/z, (relative intensity) 141 (M, 8.9), 109 (M-OMe, 100) ; Registry number [3288-52-6]

3-oxo-2,4-diphenylbutanenitrile (**26**) : ^1H NMR ($CDCl_3$, 200MHz) δ 7.05-7.3 (m, 10H), 5.0 (s, 1H), 3.65 (s, 1H), 2.95 (s, 1H) ; MS m/z, (relative intensity) 235 (M, 32), 234 (M-1, 100), 217 (16), 91 (25)

[a] : For compounds **17**, **18** and **21** the names are given for their carbonyl form, ^1H NMR spectra indicate that they are recovered in their enolic form.

References

1. Arseniyadis, S.; Kyler, K.S.; Watt, D.S.: Addition and Substitution Reactions of Nitrile-Stabilized Carbanions. In Organic Reactions (vol.31); Eds John Wiley and Sons : New York, 1984.

2. Barhdadi, R.; Gal, J.; Heintz, M.; Troupel, M. J.C.S. Chem. Commun., 1992, 50.

3. Saboureau, C.; Troupel, M.; Sibille, S.; d'Incan, E.; Périchon, J. J.C.S. Chem. Commun., 1989, 896.

4. Bellamy, A.J.;Howatt, G.; Mac Kirdy, L.S. J. Chem. Soc. Perkin II, 1977, 786.

5. Degrand, C.; Compagnon, P.L.; Gasquez, F. J. Org. Chem., 1983, 61, 2581.

6. Chaussard, J.; Folest, J.C.; Nedelec, J.Y.; Périchon, J.; Sibille, S.; Troupel, M. Synthesis, 1990, 5, 369.