Aryl Halides as Convenient Precursors of Electrogenerated Bases. Efficient Syntheses of β-Oxo Nitriles or Esters by Coupling Active-hydrogen Groups with Esters

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In an undivided cell fitted with a sacrificial anode and a nickel cathode on which cadmium had been deposited, the electroreduction of aromatic halides affords a strong base which allows the effective synthesis of β-oxo nitriles or β-oxo esters from the coupling of active-hydrogen compounds with esters.

The highly versatile synthetic utility of β-oxo nitriles and β-oxo esters is reflected in the large number of publications and patents devoted to their preparation and utilisation. Among the various possibilities, a general method for their synthesis is a Claisen-type condensation with an ester of a nitrile (or an ester) containing an α-hydrogen. However, the choice of experimental conditions and particularly the nature of the deprotonating agent may have a crucial influence on the selectivity and the yield of the reaction. Depending on the starting materials, alkali metals and various bases such as alkoxide, amide, hydride ions or Grignard reagents have been used.

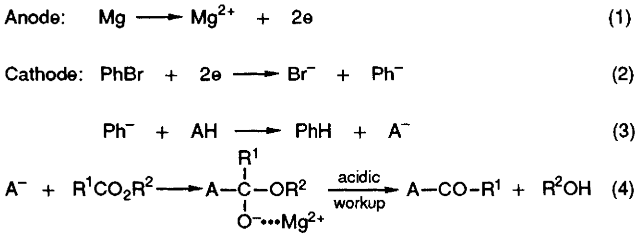
An alternative route for reactions requiring basic agents is the involvement of electrogenerated bases (EGBs)[1] produced by the electroreduction of a substrate commonly called a probase. For synthetic applications, such an electrochemical process should prove to be attractive, provided that the synthesis can be efficiently achieved under cheap and simple conditions.

We report here a new type of synthesis mediated by EGBs which affords good results under simple and mild conditions. The electrochemical device, described elsewhere,[2] is an undivided cell fitted with a sacrificial magnesium anode, and a nickel grid cathode freshly coated with a small deposit of cadmium obtained by electroreduction of a cadmium salt, *e.g.* $CdBr_2$. *N,N*-Dimethylformamide (DMF) containing a small amount of Bu_4NBF_4 (4×10^{-2} mol dm^{-3}) as supporting electrolyte was used as solvent. The solution contained the ester (0.6–1 mol dm^{-3}), the active-hydrogen compound (nitrile or ester, denoted AH; 0.6 mol dm^{-3}) and an aromatic halide, for instance PhBr (0.62 mol dm^{-3}), as the probase. An exception is the case of acetonitrile which was used both as solvent and acidic compound. The one-pot electrolysis was then carried out at 20–50 °C at a constant current (1 A dm^{-2}) until the consumption of the probase which was achieved with a 90–95% faradaic yield. Final products were obtained upon standard work-up (solvent evaporation and acidic hydrolysis) and recovered in a pure form by suitable extraction and chromatography on a silica-gel column.

Various β-oxo nitriles and β-oxo esters were synthesised by the reactions in Scheme 1. Results are presented in Table 1 when AH was acetonitrile and in Table 2 for the other syntheses which were carried out in DMF.†

Previous papers have described EGB-promoted reactions using halogenated compounds as probase: α-bromoesters,[3] alkyl bromides[4] or carbon tetrachloride.[5] To our knowledge, this is the first example with an aromatic halide, *e.g.* PhBr, a cheap material which yields a very strong base on electroreduction. A further advantage of aryl halides is that no side reaction can occur from nucleophilic attack of the carbanions Ph^- and/or A^- on the probase.

The success of the reaction depends significantly on the nature of the cathode. We have already reported that the electrochemical behaviour of organic halides is modified when using a cathode coated with an electrolytic deposit of cadmium (or another metal).[6] Indeed, compared with what may be observed when a classical solid metal electrode is used, the electroreduction signal of an organic halide is then observed at a much less negative potential (0.3 to 0.6 V higher) and exhaustive electrolyses do not give the same results. This fact was also verified for the reactions presented here. The synthesis of 4,4-dimethyl-3-oxo-pentanenitrile was attempted from acetonitrile and methyl pivalate by electroreduction of bromobenzene at a nickel grid either uncoated or coated with



$$\text{Anode:}\quad Mg \longrightarrow Mg^{2+} + 2e \qquad (1)$$

$$\text{Cathode:}\quad PhBr + 2e \longrightarrow Br^- + Ph^- \qquad (2)$$

$$Ph^- + AH \longrightarrow PhH + A^- \qquad (3)$$

$$A^- + R^1CO_2R^2 \longrightarrow A\text{—}\underset{O^-\cdots Mg^{2+}}{\overset{R^1}{C}}\text{—}OR^2 \xrightarrow[\text{workup}]{\text{acidic}} A\text{—CO—}R^1 + R^2OH \qquad (4)$$

Scheme 1

Table 1 Electrosyntheses of β-oxo nitriles from acetonitrile[a]

Ester	Isolated product	Yield (% *vs.* ester)
Bu^tCO_2Me	Bu^tCOCH_2CN **1**	60
$PhCO_2Me$	$PhCOCH_2CN$ **2**‡	83
$4\text{-}CF_3C_6H_4CO_2Me$	$4\text{-}CF_3C_6H_4COCH_2CN$ **3**	78
$2\text{-Thienyl}CO_2Me$	$2\text{-Thienyl}COCH_2CN$ **4**	70
$PhCF_2CO_2Me$[b]	$PhCF_2COCH_2CN$ **5**	60

[a] Solvent MeCN + Bu_4NBF_4 (4×10^{-2} mol dm^{-3}) + ester (0.6 mol dm^{-3}) + PhBr (0.62 mol dm^{-3}), anode Mg, cathode Ni/Cd. [b] Prepared by electrocarboxylation of $PhCF_3$.[8]

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† *Selected spectroscopic data* (^{19}F NMR: δ *vs.* $CFCl_3$; ^{1}H NMR: $CDCl_3$, 200 MHz unless noted otherwise): **1**: ^{1}H NMR, δ 1.2 (s, 9H) and 3.7 (s, 2H); *m/z* 126 (M + 1), 68 and 57 (base). **2**: ^{1}H NMR, δ 4.1 (s, 2H) and 7.5 (m, 5H); *m/z* 145 (M), 105 (base) and 77. **3**: ^{1}H NMR, δ 4.2 (s, 2H), 7.65 (d, *J* 8 Hz, 2H) and 7.9 (d, *J* 8 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −63.3 (s); *m/z* 213 (M), 173 (base) and 145. **4**: ^{1}H NMR, δ 3.95 (s, 2H) and 7–8 (m, 3H); *m/z* 151 (M) and 111 (base). **5**: ^{1}H NMR, δ 3.8 (s, 2H) and 7.4 (m, 5H); ^{19}F NMR ($CDCl_3$) δ −104 (s); *m/z* 196 (M + 1), 176 and 168 (base). **9a**: ^{1}H NMR (CD_3SOCD_3), δ 4.6 (s, 1H), 7.85 (s, 1H, disappears with D_2O), 8 (s, 1H, disappears with D_2O) and 7.5 (m, 5H); ^{19}F NMR (CD_3COCD_3) δ −78 (s); *m/z* 213 (M − 18), 116 (base) and 69. **9d** (*Z* + *E*): ^{1}H NMR δ 2.1 and 2.3 (s + s, 3H) and 7.5 (m, 5H); ^{19}F NMR ($CDCl_3$) δ −66.5 and −63.5 (s + s); *m/z* 256 (M + 1, base), 214 and 116 for one isomer; 256 (M + 1), 214 (base) and 116 for the other. **10**: ^{1}H NMR, δ 1.3 (s, 3H) and 7.2 (m, 5H); ^{19}F NMR ($CDCl_3$), δ −79 (s); *m/z* 227 (M), 208 and 130 (base). **11** ^{1}H NMR, δ 1.4 (s, 1H), 3.6 (s, 3H) and 7.3 (m, 5H); ^{19}F NMR ($CDCl_3$), δ −85 (s); *m/z* 247 (M + 1), 215 and 91 (base). **12**: ^{1}H NMR δ 1.2 (t, *J* 10 Hz, 3H), 4 (q, *J* 10 Hz, 2H), 4.2 (s, 1H) and 7–7.2 (m, 3H); ^{19}F NMR ($CDCl_3$) δ −83 (s); *m/z* 247 (M − 19), 183 and 169 (base). **13**: ^{1}H NMR, δ 4.4 (s, 1H) and 7.2–7.6 (m, 10H); ^{19}F NMR ($CDCl_3$), δ −105 (s); *m/z* 272 (M + 1), 252 and 127 (base).

‡ $PhCOCH_2CN$ has also been prepared by potentiostatic electroreductive coupling of $PhCO_2Me$ and MeCN (solvent) in a divided cell. The ester itself or azobenzene was used as probase. The yield was 45%.[7]

Table 2 Electrosyntheses of β-oxo nitriles or esters in DMF[a]

Active-hydrogen compound	Ester	Isolated product	Yield (% *vs*. AH)
$MeCH_2CN$	Bu^tCO_2Me	$Bu^tCOCH(Me)CN$ **6**	55
$PhCH_2CN$	Bu^tCO_2Me	$Bu^tCOCH(Ph)CN$ **7**	50
$PhCH_2CN$	$EtCO_2Me$	$EtCOCH(Ph)CN$ **8**	70
$PhCH_2CN$	CF_3CO_2Me	$CF_3C(OH)_2$-$CH(Ph)CN$ **9a** $CF_3COCH(Ph)CN$ **9b** $CF_3C(OH){=}C(Ph)CN$ **9c**	95[c]
$PhCH(Me)CN$	CF_3CO_2Me	$CF_3COC(Ph)(Me)CN$ **10**	35
$PhCH_2CO_2Me$	CF_3CO_2Me	$CF_3COCH(Ph)$-CO_2Me **11**	40
3-Thienyl-CH_2CO_2Et	CF_3CO_2Me	3-Thienyl-$CH(CO_2Et)COCF_3$ **12**	50
$PhCH_2CN$	$PhCF_2CO_2Me$[b]	$PhCF_2COCH(Ph)CN$ **13**	83

[a] Anode Mg, cathode Ni/Cd, probase PhBr ($0.62\ mol\ dm^{-3}$). [b] Prepared by electrocarboxylation of $PhCF_3$.[8] [c] Standard work-up affords a mixture of **9a**, **b** and **c**. The main product **9a** disappears after desiccation yielding **9b** and **9c** in equilibrium. Evidence was obtained by treating the mixture **9b** + **9c** with acetyl chloride which gives the acetylated product **9d** $CF_3C(OCOMe){=}C(Ph)CN$ ($Z + E$).

Table 3 Electrosynthesis of Bu^tCOCH_2CN under various conditions[a]

Electrolytic coating[b]	E_c[c]/V *vs*. SCE	GC yield (% *vs*. ester)
Cadmium	−1.8 to −2	85–80[d]
Lead	−1.8 to −2.3	60
Tin	−2.4 to −2.9	40
Copper	−2.1 to *	20
None	−2.3 to *	20
Cadmium[e]	−2.5 to −2.7	60
Cadmium[f]	−1.6 to −1.8	85

[a] Solvent MeCN + Bu_4NBF_4 ($4 \times 10^{-2}\ mol\ dm^{-3}$) + Bu^tCO_2Me ($0.6\ mol\ dm^{-3}$) + PhBr ($0.62\ mol\ dm^{-3}$) (except *e* and *f*), Mg anode (except *d*), nickel grid cathode. [b] For the method see ref. 6. [c] Working potential of the cathode during exhaustive electrolyses. * Indicates a drastic passivation ($E_c \ll -3$ V *vs*. SCE). SCE = saturated calomel electrode. [d] Al anode. [e] Probase = PhCl ($0.62\ mol\ dm^{-3}$). [f] Probase = PhI ($0.62\ mol\ dm^{-3}$).

various metallic deposits. The results presented in Table 3 clearly indicate the significant role of the nature of the electrode. Further work is needed to explain this behaviour.

Similar results were obtained from the electroreduction of other aromatic halides. Iodobenzene, 1,4-dibromobenzene and 4-bromoanisole were successfully tested as probases. Even chlorobenzene was reduced at about −2.6 V (*vs*. SCE) at a cadmium coated electrode, and so may be used, provided that the other reactants are not reduced more easily.

In conclusion, the synthesis of β-oxo nitriles or β-oxo esters is easily achieved by an electrochemically induced coupling of an active-hydrogen group with an ester as electrophile. Preliminary experiments showed that our method is also quite suitable for related reactions with other acidic and electrophilic compounds. For instance, esters, alcohols or alkylation products can be obtained by an EGB-mediated coupling with dialkyl carbonates, carbonyl derivatives or alkyl halides as electrophiles.

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References

1 For reviews see: M. M. Baizer, *Tetrahedron*, 1984, **40**, 935; T. Shono, *Electroorganic Chemistry as a New Tool in Organic Synthesis*, Part 3-3, Springer-Verlag, Berlin, Heidelberg, New York, Tokyo, 1984.

2 J. Chaussard, J. C. Folest, J. Y. Nedelec, J. Périchon, S. Sibille and M. Troupel, *Synthesis*, 1990, **5**, 369.

3 M. A. Casadei, A. Gessner, A. Inesi, W. Jugelt, H. Liebezeit and F. Micheletti Moracci, *Bull. Soc. Chim. Fr.*, 1989, **5**, 650.

4 J. C. Folest, S. Guibe, J. Y. Nedelec and J. Périchon, *J. Chem. Res.*, 1990, (*S*) 258; A. Curulli, A. Inesi and E. Zeuli, *Electrochim. Acta*, 1987, **32**, 1117.

5 S. T. Nugent, M. M. Baizer and R. D. Little, *Tetrahedron Lett.*, 1982, 1339.

6 C. Saboureau, M. Troupel, S. Sibille, E. d'Incan and J. Périchon, *J. Chem. Soc., Chem. Commun.*, 1989, 896.

7 L. Kistenbrügger, P. Mischke, J. Voss and G. Wiegand, *Liebigs Ann. Chem.*, 1980, 461.

8 C. Saboureau, M. Troupel, S. Sibille and J. Périchon, *J. Chem. Soc., Chem. Commun.*, 1989, 1139.