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New method of zinc activation by electrochemistry: synthetic applications to the Blaise reaction

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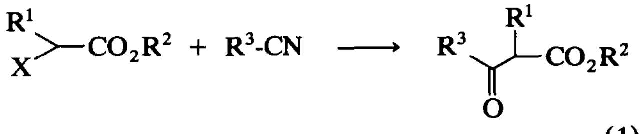
Abstract

A new electrochemical zinc metal activation method based on the cathodic reduction of a catalytic amount of zinc bromide in the presence of a zinc anode is described. This procedure is applied to the coupling of α-bromoesters with nitriles, and affords β-ketoesters in good yield.

1. Introduction

The use of zinc metal as a reducing agent for the condensation of activated halides (allyl bromides, α-bromoesters) with electrophilic substrates has received much attention [1]. The zinc-mediated electrochemical coupling of allyl halides or α-haloesters with carbonyl compounds in the presence of a nickel catalyst has also been reported [2]. One of the major problems related to the use of zinc metal is the special care needed in preparing the active zinc or other zinc/metal complex necessary to initiate the reactions. The preparation of active zinc by reaction of zinc chloride with alkali metals such as Li or K, or with C_8K has been described [3], and needs high temperatures and/or long reaction times. Activation by ultrasound techniques in the presence of lithium metal has also been reported [4].

We present here a new, simple and efficient electrochemical method for zinc metal activation. This procedure was applied to the Blaise reaction [5], the cross-condensation of Reformatsky-type reagents and organic nitriles (eqn. (1)).



(1)

(X = Br or I)

In conventional methods, the addition of zinc Reformatsky reagents to nitriles generally needs for acceptable yields, an excess of bromoester, long reaction times and use of THF or benzene at reflux temperatures [6].

The use of nitriles as electrophiles in electrochemical reactions has not been examined, except by Schäfer, who reported electrochemical acylation of aryl olefins by various nitriles [7]. Most electrochemical reactions involving nitriles (essentially CH_3CN, used as the solvent) lead to reductive decyanation [8], reduction to the corresponding amines [9], or, in some cases, cyanomethylation of carbonyl compounds by the electrogenerated CH_2CN^- anion [10].

2. Results and discussion

2.1. General electrochemical method of zinc activation

The method is based on the use of a commercial zinc rod as anodic material in an undivided cell, and involves the reduction of a catalytic amount of Zn^{2+}. In a typical procedure, a benzonitrile or acetonitrile solution containing tetrabutylammonium tetrafluoroborate (0.4 mmol) as the supporting electrolyte and anhydrous $ZnBr_2$ (2 mmol) was electrolyzed in a single-compartment cell fitted with a zinc anode and a gold cathode, at -0.5 to -0.9 V *vs.* SCE with the passage of 200 Coulombs intake. This amount of electricity allows the reduction of 1 mmol of Zn^{2+}, *i.e.* half of the $ZnBr_2$ present. A grey zinc deposit on the surface of the cathode was observed. This zinc deposit (active zinc,

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Zn^*) was achieved within a few minutes at room temperature.

The reactions occurring at the electrodes can be expressed as follows

Anode: $Zn \longrightarrow Zn^{2+} + 2e$

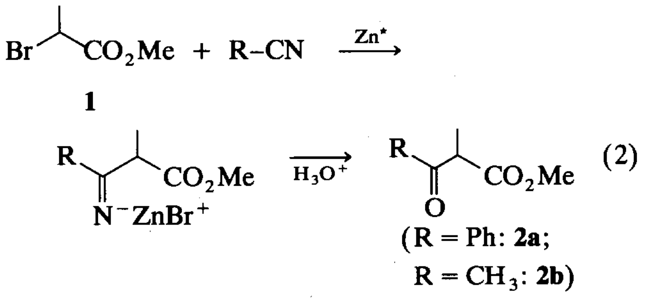
Cathode: $ZnBr_2 + 2e \longrightarrow Zn^* + 2Br^-$

(* deposited on the cathode surface)

Without any further electrolysis, the addition of methyl-2-bromopropionate (**1**) (10 mmol), to the solution caused the immediate disappearance of the zinc deposit. After 1 h, the halide consumption was 80%, and 75% of coupling product **2** was formed (eqn. (2)). The reaction was complete in 2 h. The Blaise reductive coupling reaction was carried out using only a catalytic amount of electricity. Thus, with a pre-electrolysis of the solution equivalent to 1 mmol of $ZnBr_2$, up to tenfold bromide reacted (and the reaction can proceed further up to 40–50 mmol bromide). The reductive coupling was therefore mediated by the zinc rod of the anode. When the zinc rod was removed from the solution after the pre-electrolysis, the coupling reaction did not occur beyond the amount of initial electricity used (corresponding to 1 mmol of **1**).

2.2. *Optimization of the conditions for an effective zinc electroactivation*

The coupling of α-bromoester **1** with benzonitrile or acetonitrile (the solvent) was the model reaction (eqn. (2)) used to examine the influence of the nature of the electrodes, the amount and the rate of the metal deposit, and the nature of the solvent on the reactivity of the activated Zn^*.



(R = Ph: **2a**;
R = CH_3: **2b**)

A zinc anode was found to be essential for the reaction; magnesium or aluminium anodes were not effective and did not yield any coupling product.

Using a zinc anode and the general procedure, several cathodic materials were examined (Table 1).

Gold and zinc cathodes were the most effective for the condensation. Moreover, a zinc cathode was found to accelerate the reaction, with reaction times of 20–30 min for conversion of 10 mmol of **1** with a zinc cathode, compared to 1.5 to 2 h with a gold cathode.

TABLE 1. Influence of the cathode material on the electro-assisted Blaise reaction (eqn. (2)) [a]

Cathode	% Yield [b]	
	2a	**2b**
Gold	86	90
Nickel foam	70	70
Carbon fibre	60	50
Inox	0	0
Zinc	80	95

[a] PhCN (40 ml); $(NBu_4)(BF_4)$ (0.4 mmol); $ZnBr_2$ (2 mmol); Zn-anode; constant potential electrolysis (−0.8 V/SCE) with 200 Coulombs intake; addition of **1** (10 mmol).
[b] Yields determined by GC.

The amount of electrolyzed $ZnBr_2$ in CH_3CN before the addition of **1** (10 mmol) was changed from 0 to 6 mmol. The consumption of **1** after 30 min without further electrolysis is presented in Table 2. Without preliminary electrolysis of $ZnBr_2$, the zinc anode shows no activity towards bromoester **1**. An optimal reactivity was found with the electrolysis of 1 mmol of $ZnBr_2$. Greater pre-electrolysis (always catalytic with respect to **1**) did not increase the bromoester consumed within 30 min. However, in all cases, **1** was completely consumed within 2 h, and the yields of **2a** were in the range of 80–90%.

The density of current to generate the active Zn^* in benzonitrile reactions (for 1 mmol deposit) was raised from 5 to 7.5 mA cm^{-2}. After 30 min, **1** was consumed in 65% and 35% respectively. In each case (and also with different amounts of electrolyzed $ZnBr_2$, Table 2), the Zn^* deposit looked different: a light grey colour was observed with 0.5–2 mmol $ZnBr_2$ deposit at low current density, and a dark grey colour was obtained when a thicker deposit was formed.

TABLE 2. Influence of the amount of pre-deposited zinc on the coupling of **1** in benzonitrile [a]

$ZnBr_2$ electrolyzed (mmol)	Conversion of **1** after 30 min (mmol)
0	0
0.5	2.5
1.0	6.5
2.0	5.2
3.0	5.0
4.0	5.0
6.0	5.0

[a] PhCN (40 ml); $(NBu_4)(BF_4)$ (0.4 mmol); $ZnBr_2$ (x mmol); Zn-anode; gold cathode; constant potential electrolysis (−0.8 V/SCE); **1** (10 mmol) added after electrolysis of various amounts of $ZnBr_2$.

The zinc deposition can be carried out at controlled potential (−0.5 to −0.9 V *vs.* SCE) or at constant current intensity of 100 mA (corresponding to a working cathodic potential of −0.5 to −0.7 V *vs.* SCE). Constant current conditions are easier to arrange.

The synthesis was carried out with good yields in both benzonitrile and acetonitrile. The yields are better in dichloromethane in the presence of RCN, than in *N*,*N*-dimethylformamide.

2.3. Electro-assisted Blaise reaction

Following the general procedure (zinc deposit of 1 mmol at 100 mA), several β-ketoesters were prepared with benzonitrile or acetonitrile as the solvent. The results are given in Table 3.

Secondary and tertiary bromides reacted with good yields in either CH_3CN or PhCN. However, acetonitrile was more reactive towards primary halides such as methyl-2-bromoacetate. For this halide in benzonitrile an 80% yield of coupling product could be obtained by keeping electrolysis at constant 20–30 mA throughout the reaction (4 h). In order to generalize the electrochemical Blaise reaction to other nitriles (used as reagents and not solvents) experiments were run in other solvents, such as DMF, CH_2Cl_2. In DMF, and even with an excess of nitrile, only very low yields of ketoester could be obtained (< 20%). In contrast dichloromethane was an effective solvent for this reaction. Despite the poor solubility of $ZnBr_2$ in CH_2Cl_2–$(NBu_4)(BF_4)$ solutions, the addition of nitriles such as n-C_4H_9CN, $Cl(CH_2)_3CN$, PhCN, and CH_3CN enhanced its solubility and facilitated the electrochemical reduction of $ZnBr_2$. With nitriles enhancing the solubility of $ZnBr_2$, the zinc deposit was prepared as usual, and the coupling reaction was carried out with the yields shown in Table 4.

Aliphatic long chain nitriles can be used. Functionalized 4-chloro- and 5-chloro-nitriles gave the chloroketoesters expected without any further cyclization. 2-Methylacrylonitrile yielded the unsaturated ketoester in 65% yield. An excess of bromide is not always necessary under our conditions, in contrast to other examples in the literature [6].

TABLE 3. Electroassisted Blaise reaction [a]

α-Bromoester	RCN	Cathode	Reaction time	β-Ketoester (%)
$BrCH(CH_3)CO_2Me$	CH_3CN	Au	2 h	90
$BrCH_2CO_2{}^tBu$	CH_3CN	Zn	20 min	95
$BrCH_2CO_2{}^tBu$	CH_3CN	Au	3 h	80
$BrCH_2CO_2Me$	CH_3CN	Au	2 h	55
$BrCH(CH_3)CO_2Me$	PhCN	Au	2 h	86
$BrCH(CH_3)CO_2Me$	PhCN	Zn	20 min	80
$BrCH_2CO_2Me$	PhCN	Au	5 h	10 [b]
$BrC(CH_3)_2CO_2Me$	PhCN	Au	3 h	70

[a] RCN (40 ml); (NBu_4) (BF_4) (0.4 mmol); $ZnBr_2$ (2 mmol); Zn anode; α-bromoester (10 mmol).

[b] The yield was raised to 80% with the electrolysis kept at 20–30 mA throughout the reaction.

TABLE 4. Electroassisted Blaise reaction of methyl-2-bromopropionate, **1** with various nitriles in CH_2Cl_2 as the solvent, at 20°C [a]

Nitrile	Nitrile/1 ratio	Cathode	Reaction time (h)	Isolated yield of β-ketoester [b]
CH_3CN	2/1	Au	2	72
CH_3CH_2CN	2/1	Au	2	84
$CH_3(CH_2)_4CN$	1/1	Au	5	40
$CH_3(CH_2)_4CN$	1/1	Zn	3	52 [c]
$CH_3(CH_2)_2CN$	1/1	Au	4	50 [c]
$CH_2{=}C(CH_3)CN$	4/1	Au	3	65 [c]
$CH_2{=}C(CH_3)CN$	1/1	Zn	2	33
$Cl(CH_2)_3CN$	1/1	Zn	5	56
$Cl(CH_2)_4CN$	1/1	Zn	5	57

[a] CH_2Cl_2 (40 ml); (NBu_4) (BF_4) (0.4 mmol); $ZnBr_2$ (2 mmol); RCN (10 mmol-40 mmol); Zn-anode; constant current 50 mA with 200C intake; addition of **1** (10 mmol).

[b] Isolated yield of distilled product.

[c] Yield calculated by ^1H NMR and by GC with internal standard.

Other nitriles, such as 2-chloroacetonitrile or p-trifluoromethylbenzonitrile did not solubilize $ZnBr_2$ enough for its efficient electroreduction, and no coupling products were formed.

2.4. Mechanistic considerations

For the electrochemical Blaise reaction, we propose a mechanism in which the first step is the electrochemical two-electron reduction of $ZnBr_2$ in the presence of the nitrile, either as solvent or as reagent. The nitrile was shown to be essential for the stabilization of the Zn^* species formed upon reduction. In the presence of the α-bromoester, R'Br, the activated Zn^*–RCN species may form an R'ZnBr–RCN intermediate by oxidative addition. This intermediate should then be chemically reduced by the zinc anode [11 *].

The need for the further R'ZnBr reduction step becomes evident for less reactive primary halides. The reducing power of the zinc anode did not then allow the reduction of the R'ZnBr intermediate, and continuous electrolysis was necessary to effect the coupling (see Table 3).

We further found that once the active (catalytic) zinc species Zn^* (prepared by pre-electrolysis of $ZnBr_2$) was present, the zinc anode could be replaced by zinc powder added to the solution without any previous purification, and the coupling reaction for the more reactive halides kept efficient.

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* Reference number with asterisk indicates a note in the list of references.

3. Conclusion

We describe a new method of activation of zinc metal by electro-reduction of a catalytic amount of a $ZnBr_2$ solution in the presence of a commercial zinc anode. Nitriles stabilize the electrogenerated Zn^0 species, and condensation with α-bromoesters was carried out in good yields under mild conditions.

4. Experimental details

Benzonitrile, acetonitrile, and dichloromethane were reagent grade (Janssen, SDS) used without further purification.

The supporting electrolyte and zinc bromide were dried under vacuum (0.1 mmHg) at 50°C before use. α-Bromoesters were used as supplied.

4.1. General procedure

The three electrode single-compartment electrochemical cell was similar to that described previously [12]. The anode was a cylindrical rod of zinc (diameter 1.3 cm) surrounded by a gold gauze or zinc sheet cathode (apparent surface 40 cm^2). A solution of RCN (R = Me or Ph) (40 ml) of $ZnBr_2$ (2 mmol) containing $(NBu_4)(BF_4)$ (0.4 mmol) was electrolyzed under argon until 200 Coulombs had passed, either at $i = 100$ mA or at $E = -0.8$ V *vs.* SCE. Once the electrolysis was stopped, the α-bromoester (10 mmol) was added and the solution stirred at room temperature until complete consumption of the halide (monitored by GLC, 0.3–4 h).

The solution was hydrolyzed with 1 N HCl, extracted with Et_2O, and the organic layer washed with H_2O, dried over $MgSO_4$ and taken to dryness. The crude products were purified by distillation or by column chromatography (normal or flash on silica gel) with pentane/Et_2O as eluent. All compounds have corrected analytical and spectroscopic data.

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11 The inertness of the zinc anode alone towards promoting cross-coupling (as mentioned) and its complementary action with the active R'Zn*Br, RCN species formed at the cathode was emphasized in two cases: (a) when the cathode recovered with the deposit was removed from the reaction medium before R'–Br addition, only traces of product were detected; (b) when the cathode was removed as soon as product appeared after R'–Br addition, cross-coupling continued.

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