

An innovative strategy for electrochemically-promoted addition reactions

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Received (in Cambridge, UK) 5th May 2004, Accepted 23rd June 2004

First published as an Advance Article on the web 26th July 2004

A new strategy based on the catalytic release of the supporting electrolyte agent in the electrolysis medium proved to be effective for the direct electroactivation of suitable C–H acid-containing compounds vs. catalytic addition processes, under solvent-free conditions.

Over the last decades, electrosynthesis has emerged as a convenient tool to improve selectivity, cheapness and eco-friendliness of a wide variety of synthetic constructions, including catalytic C–C bond-forming processes. In this field, over a period of many years, a number of helpful electrochemical methods have enabled conjugate addition to activated unsaturated systems and nucleophile addition to carbonyl compounds.¹ Nevertheless, some downsides related to electrochemical techniques (specialized equipment for controlling the potential, trouble in scaling up the reactions, massive use of supporting electrolyte agents *etc.*) have resulted in little use of them to date in preparative organic synthesis.

To enhance the usefulness of the electrosynthetic methodology increasing efforts are being devoted to develop as easy as possible electrochemical reaction systems, mainly focused on the working out of constant current procedures. Still, a variety of synthetic targets have been conveniently obtained *via* electrogenerated bases (EGBs) and acids (EGAs). In our recent reports, *e.g.*, the EGB cyanomethyl anion² proved to be effective for a selective activation of amidic and aminic N–H as well as C–H bonds, successfully used in N–C and C–C bond-forming processes.³ On the other hand, the achievement of carb- and heteroanions by direct cathodic reduction of appropriate organic acids, avoiding any use of chemical or electrogenerated bases, certainly appears a much more attractive approach.⁴

In line with the demand for simplification, we here report a new strategy for the direct galvanostatic electrogeneration of carbon nucleophiles under solvent-free conditions characterized by a drastic slashing of the amount of supporting electrolyte in the electrolysis medium.

With this in mind and according to our previous investigations on electrochemically-promoted addition reactions,⁵ we checked for a direct electroactivation of the representative methylene-active compound **1a**, under several different electrolysis conditions (Table 1). The efficiency of the electrochemical activation systems was then tested in the conjugate addition to **2a**, chosen as a typical Michael acceptor (Scheme 1). As depicted in Fig. 1, all the experiments were performed using a two compartment cell equipped with a Pt anode and cathode, while a G3-glass diaphragm fitted up with a layer of agar gel† was used as separator septum. Furthermore, pure compound **1a** was used as catholyte, avoiding both the solvent and supporting electrolyte addition.

As summarized in Table 1, a set of experiments was performed to find the optimal electrochemical conditions by altering either the current quantity or the current intensity. As shown, under the optimised conditions (entry 4), Michael adduct **3a** was obtained in very good yield and selectivity. If compared to the electrogenerated cyanomethyl anion-catalysed procedure (entry 1), solventless electrolysis of **1a** allowed a significant improvement both in terms

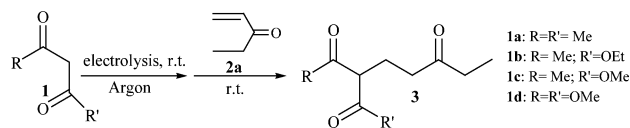
of chemical yield and chemoselectivity since, in this case, no double addition product was detected by ¹H NMR (as well as GC-MS) analyses of the crude mixtures.

As an extension of the methodology to other synthetically interesting β -dicarbonyl compounds, pure **1b–d** were electrolysed according to method B. At the end of the electrolysis ($I = 10 \text{ mA cm}^{-2}$, $Q = 0.1 \text{ F mol}^{-1}$), the Michael acceptor **2a** was added to the cathode compartment and the reaction was prolonged at room temperature for the time reported in Table 2. Surplus of starting materials **1b–d** was distilled under vacuum at room temperature and recovered for recycling with a glass trap cooled to $-78 \text{ }^\circ\text{C}$.

Table 1 Electrochemically-promoted Michael addition of **1a** under different electrolysis conditions

| Entry | Electrolysis method ^a | Current intensity (mA cm ⁻²) | Current quantity (F mol ⁻¹) ^b | Yield (%) ^c |
|-------|----------------------------------|--|--|------------------------|
| 1 | A | 10 | 0.1 | 76 (5) |
| 2 | B | 10 | 0.1 | 64 |
| 3 | B | 10 | 0.07 | 76 |
| 4 | B | 5 | 0.1 | 87 |

^a Method A: Anolyte: 0.1 M TEAP/DMF. Catholyte: 15 ml of 0.03 M TEAP/CH₃CN solution. At the end of the electrolysis **1a** (1 ml) and **2a** were added in sequence and the reaction was prolonged at room temperature for 2 h. Method B: electrolysis conditions being equal, except for the catholyte: (5 ml of pure **1a**). ^b The current quantity refers to the Michael acceptor **2a** (3 mmol scale), added to the catholyte at the end of the electrolysis. ^c The yields refer to isolated, chromatographically pure **3a** and are calculated on the starting material **2a**. Yield in brackets refers to double addition product.



Scheme 1

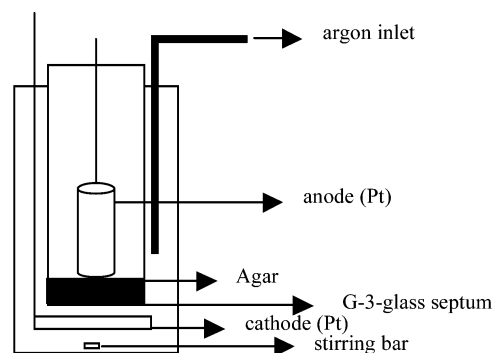


Fig. 1 Schematic depiction of the cell.

Crude mixtures yielded pure adducts **3** after simple filtration over silica gel.

As shown, the reaction proceeded with very satisfactory efficiency and selectivity with β -diketones, β -keto esters or malonate esters, affording the Michael adducts in good to excellent yields, under mild conditions and in short reaction times (Table 2, entries 1–3).

Finally, to test whether the method was applicable to different kinds of Michael acceptors, we considered the reactivity of the electrolysed compound **1d** towards the mono- and di-substituted olefins **2b–f**, bearing different EWG in conjugation with the double bond. The Michael addition again occurred with very good yields in nearly all the cases, using a catalytic amount of current; it is noteworthy that in spite of a slightly lower yield obtained for the acceptor **2e**, a total chemoselectivity in favour of the α -monoaddition products was always observed.

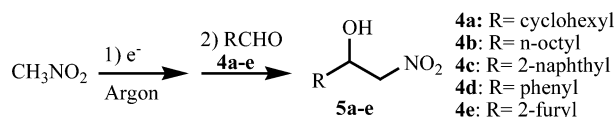
To further broaden the scope of this electrochemical methodology, we decided to investigate its effectiveness vs. other classes of catalytic nucleophilic additions. As a practical route to many important building blocks, the nitroaldol reaction is a main topic in this area. Concerning an electrosynthetic approach to the issue, Evans and co-workers reported a catalytic activation of nitromethane vs. Michael addition⁶ as well as Henry reaction,⁷ via superoxide anion as EGB. Actually, depending on the electrolysis procedure, the authors showed two different processes targeted at 2-nitroalcohols or 1,3-dinitro compounds.⁸

We have now found that, under the electrolysis conditions reported above (method B), the direct reduction of pure nitromethane, under an inert atmosphere, could be conveniently used for a selective synthesis of the 2-nitroalcohols **5** by addition of an aldehyde **4** to the cathode compartment at the end of the electrolysis (Scheme 2). As shown in Table 3, very good yields and selectivity

Table 2 Electrochemically-promoted Michael addition reactions under solvent-free conditions

| Entry | Donor 1 | Acceptor 2 | Product 3 | Reaction time (h) | Yield (%) ^a |
|------------------|----------------|-------------------|------------------|-------------------|------------------------|
| 1 | 1b | 2a | | 2 | 82 |
| 2 | 1c | 2a | | 4 | 83 |
| 3 ^b | 1d | 2a | | 2 | 93 |
| 4 ^b | 1d | 2b | | 12 | 87 |
| 5 ^b | 1d | 2c | | 12 | > 98 |
| 6 ^b | 1d | 2d | | 7 | 87 |
| 7 ^b | 1d | 2e | | 18 | 67 |
| 8 ^{b,c} | 1d | 2f | | 0.5 | 93 |

^a The yields refer to isolated, chromatographically pure products **3** and are calculated on the starting material **2**. ^b Electrolysis was performed under argon atmosphere, using a two-compartment cell, Pt anode and cathode with a G-5-glass separator septum. Catholyte: pure **1d** (5 ml); anolyte: 0.1 M TEAP/DMF solution. ^c The reaction was performed at -30 °C.



Scheme 2

Table 3 Electrochemically-promoted nitroaldol reactions under solvent-free conditions

| Entry | 4 | Current quantity (F mol ⁻¹) | Reaction time (h) | Yield (%) ^a |
|-------|-----------|---|-------------------|------------------------|
| 1 | 4a | 0.05 | 1 | 65 |
| 2 | 4a | 0.1 | 0.75 | 91 |
| 3 | 4b | 0.1 | 1 | 84 (12) |
| 4 | 4c | 0.1 | 1.5 | 60 (34) |
| 5 | 4c | 0.2 | 1.5 | 60 (36) |
| 6 | 4c | 1 | 1.5 | 31 (33) |
| 7 | 4d | 0.1 | 1.5 | 70 |
| 8 | 4e | 0.1 | 1 | 63 |

^a The yields refer to isolated, chromatographically pure 2-nitroalcohols **5** and are calculated on the starting aldehyde **4**. Yields in brackets refer to the recovered starting materials **4**.

were produced, for aromatic, heteroaromatic and aliphatic aldehydes. Thanks to the mild electrolysis conditions no by-products due to a concurrent α -elimination step on the products **5** were observed.

Unfortunately, attempts to improve the chemical yield for the substrate **4c**, by increasing the current quantity, the temperature or the reaction time, gave unsatisfactory results. In particular, the use of a stoichiometric amount of electricity (1 F mol⁻¹) compromised both the yield and the selectivity of the reaction (Table 3, entry 6).

In summary, we have demonstrated a new, convenient electrochemical strategy to promote the activation of C–H acid-containing compounds in a solventless environment, avoiding metal, basic or EGB catalysts. With respect to the traditional chemical methods, the electrochemical, metal-free conditions resulted in enhanced reactivity of the electrogenerated bare carbon-anion, so that the reactions with suitable acceptors were found to occur under mild conditions and in short reaction times. Furthermore, easy set-up and work-up procedures were established thanks to the minimised amount of the supporting electrolyte used.

The authors wish to thank MURST (Cofin 2002) for financial support.

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[†] Agar gel constituted methyl cellulose 0.5% vol. dissolved in 1 M TEAP/DMF solution.

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