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Electrochemically Induced Addition Reactions in the Absence of Solvent and Supporting Electrolyte

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Abstract: Solvent- and supporting electrolyte-free electrolysis in a two-compartment cell proved to be effective for the direct electroactivation of C–H acid-containing compounds vs. catalytic addition processes. Michael adducts (including quaternary carbon centres) and 2-nitroalkanols were obtained in very good yields and selectivity on application of a catalytic amount of electricity under galvanostatic conditions.

Keywords: electrogenerated enolates; electrosynthesis; Michael addition; nitroaldol reaction; solventless electrolysis

Introduction

The conjugate reaction of active methylene compounds[1] and nucleophilic addition to the carbonyl functionality are fundamental processes for the C–C bond construction, and the ever-increasing demand for selective, cheap and environmentally safe procedures still keeps on affording a number of new synthetic protocols.

Within the domain of the *green chemistry*, electrochemical technology can provide a valuable alternative to the use of conventional reagents for fine chemicals synthesis.[2] Thanks to the electron transfer between an electrode and the substrate molecules, the formation of highly reactive intermediates is achieved under mild conditions, avoiding reductive or oxidant agents as well as acids, bases and related waste byproducts.

Nevertheless, some drawbacks related to electrochemical techniques (specialised equipment for controlling the potential, trouble in scaling up the reactions, massive use of supporting electrolyte agents, etc.) have resulted, to date, in little use of them in preparative organic synthesis.

To bypass some of these disadvantages, much effort has been devoted to simplify the electrochemical reaction systems, e.g., by setting galvanostatic procedures. On the other hand, the design of specialised electrochemical apparatus has been proposed to avoid the use of supporting electrolytes in the electrolysis medium.[3,4]

In line with the demand for simplification, we here report a new strategy for the galvanostatic electrogeneration of carbon nucleophiles under solvent-free conditions avoiding the addition of a supporting electrolyte to the reaction medium.

In recent reports we widely showed the deprotonating ability of acetonitrile/tetraethylammonium perchlorate (TEAP) electrolysed solution towards several organic acids (amide and amine N–H as well as C–H bonds).[5,6] Nevertheless, the achievement of carb- and heteroanions generated by direct cathodic reduction of the appropriate organic acids certainly appears a much more attractive approach.[7]

Results and Discussion

With this in mind, and according to our investigation on the electrochemically-promoted Michael addition,[8] we checked for the electroactivation of the representative active methylene compound **1a** under several different electrolysis conditions (Table 1). The efficiency of the electrochemical activation system was then tested in the conjugate addition to pent-1-en-3-one (**2a**), chosen as a typical Michael acceptor (Scheme 1).

As summarised in Table 1, the direct electroactivation of **1a** can be conveniently performed under solvent-free conditions, without the addition of a supporting electrolyte to the catholyte. When compared to the cyanomethyl anion-catalysed procedures, under

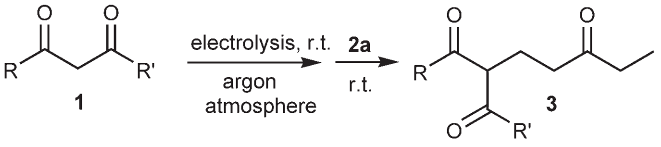
Table 1. Electroactivation of **1a** and Michael addition to **2a** under different electrolysis conditions.

Entry	Electrolysis Method[a]	Current Density [mA/cm^2]	Current Quantity[b] [F/mol]	Yield[c] [%]
1	A	10	0.1	76 (5)
2	B	10	0.1	73
3	C	10	0.1	54
4	C	5	0.1	60
5	D	10	0.1	64
6	D	10	0.07	76
7	D	5	0.1	87

[a] Method A: catholyte: **1a**/CH_3CN/TEAP. Method B: catholyte: **1a**/TEAP. Method C: catholyte: **1a**/CH_3CN. Method D: catholyte: pure **1a. 1a/2a** = 16. For a full account of the electrolysis condition and apparatus see the Experimental Section.

[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 **3** and are calculated on the starting material **2a**. Yield in brackets refers to the bis-addition product.



1a: R = R' = Me
1b: R = Me; R' =OEt
1c: R = Me; R' =OMe
1d: R = R' = OMe

Scheme 1.

optimised conditions (entry 7), solventless electrolysis allowed a significant improvement both in terms of yield and chemoselectivity.

Because of the high ratio **1/2** used in these preliminary experiments we become interested to carry out further investigations on this subject. A set of experiments was therefore performed by altering the molar ratio **1c/2a** (Scheme 2).

In spite of a very fast consumption of the starting material **2a**, reducing the **1c/2a** molar ratio resulted in a significant decrease in the chemoselectivity because of the formation of the bis-addition product. On the basis of these results, the general validity of the procedure was tested on different donors **1b–d** and acceptors **2a–f**, ensuring a large excess of donor. Therefore, pure **1b–d** were electrolysed according to the conditions reported in Table 1, entry 7. At the end of the electrolysis, the Michael acceptors **2** were added to the cathode compartment and the reaction was continued at room temperature for the time reported in Table 2.

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 short reaction times.

Although Michael addition of 1,3-dicarbonyl compounds is sensitive to steric and electronic effects, it is noteworthy that comparable results were obtained in the case of more hindered acceptors (entries 4 and 5) and less activated substrates, such as α,β-unsaturated esters and nitriles (respectively, entries 6 and 7).

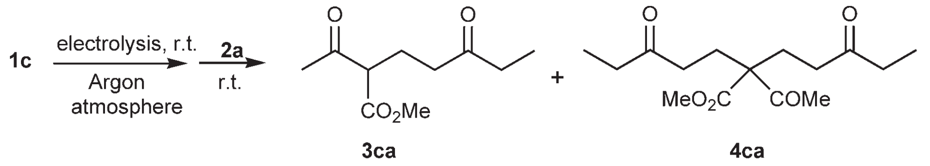
The attempt to extend the methodology to α,β-unsaturated aldehydes as acceptors proved to be unsuccessful both with acrolein and acrolein derivatives. After the usual electrolysis of pure **1d**, the addition of acrolein, or acrolein derivative [3-(furan-2-yl)acrylaldehyde] afforded complex mixtures of reaction.

On the other hand, the high reactivity of the directly electrogenerated enolates was further exploited for the construction of quaternary carbon centres (*QCC*s), starting from 2-alkylated 1,3-dicarbonyl compounds (Table 3).

The data listed in Table 3 show that the procedure proved to be effective, with very good yields and selectivity, for Michael acceptors and/or donors characterised by a considerable steric hindrance or by the presence of an additional functional group in the molecule (entry 5).

Positively, because of the presence of the substituents at the intercarbonyl carbon it was possible to avoid the previously required use of an excess of donor.

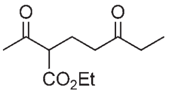
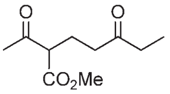
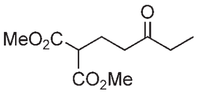
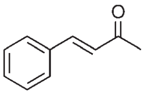
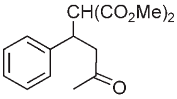
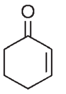
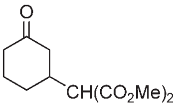
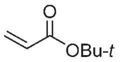
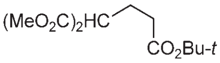
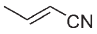
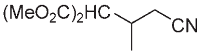
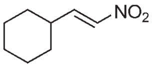
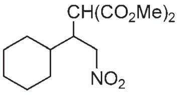
To further broaden the scope of this electrochemical methodology, we decided to investigate its effectiveness *vs.* other classes of catalytic nucleophilic additions. As a practical route to many important build-



1c/2a	3ca/4ca
12	8/1
9	5/1
4.5	3/1
1	1/1

Scheme 2.

Table 2. Electrochemically-promoted addition reaction of **1b–d** to various Michael acceptors.

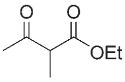
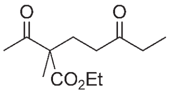
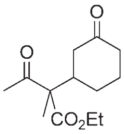
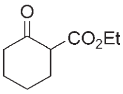
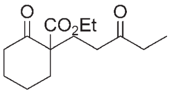
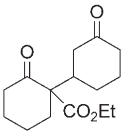
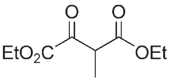
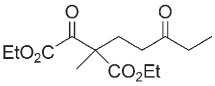
Entry	Donor **1**	Acceptor **2**		Product **3**		Reaction Time [h]	Yield[a] [%] of **3**
1	**1b**		**2a**		**3ba**	2	82
2	**1c**		**2a**		**3ca**	4	83
3[b]	**1d**		**2a**		**3da**	2	93
4[b]	**1d**		**2b**		**3db**	12	87
5[b]	**1d**		**2c**		**3dc**	12	>98
6[b]	**1d**		**2d**		**3dd**	7	87
7[b]	**1d**		**2e**		**3de**	18	67
8[b,c]	**1d**		**2f**		**3df**	0.5	93

[a] The yields refer to isolated, chromatographically pure **3** and are calculated on the starting material **2** (3 mmol scale).

[b] Electrolysis was performed using a two-compartment cell, Pt anode and cathode with a porous G-5 glass plug as separator septum. Catholyte: pure **1d**, anolyte: 0.1 M TEAP/DMF solution.

[c] The reaction was performed at −30 °C.

Table 3. Electrochemically-promoted construction of *QCC*s *via* Michael addition of **1e–g** to various Michael acceptors **2**.

Entry	Donor **1**		Acceptor **2**	Product **3**		Yield[a] [%]
1		**1e**	**2a**		**3ea**	81
2[b]		**1e**	**2c**		**3ec**	>98
3		**1f**	**2a**		**3fa**	82
4[b]		**1f**	**2c**		**3fc**	79
5		**1g**	**2a**		**3ga**	96

[a] The yields refer to isolated, chromatographically pure **3** and are calculated on the starting material **1** (20 mmol scale).

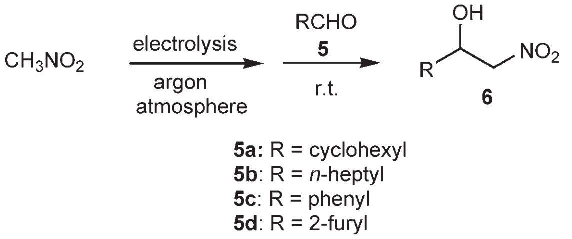
[b] No diastereoisomeric excess has been observed.

ing blocks, the Henry reaction is a main topic in this area.

Most of the chemical methods targeted at nitro alcohols involve the use of bases or metal catalysts.[9] Indeed, many different reagents have been tested to prevent concurrent reactions (retroaldolisation, dehydration, etc.) and/or the destruction of possible sensitive functionality in the reactant molecules.

An electrosynthetic approach to the issue previously reported by Evans and co-workers involved the catalytic activation of nitromethane *via* superoxide anion as electrogenerated base.[10,11] Actually, depending on the electrolysis procedure, the authors showed two different processes targeted at 2-nitro alcohols or 1,3-dinitro compounds.[12]

We have now found that, under the conditions reported above, the direct electrolysis of pure nitromethane, under an inert atmosphere, could be conveniently used for a selective synthesis of the 2-nitro alcohols **6** by addition of an aldehyde **5** to the cathode compartment at the end of the electrolysis (Scheme 3). As shown in Table 4, good yield and selectivity were produced for aromatic, heteroaromatic and aliphatic aldehydes.



Scheme 3.

Table 4. Electrochemically-promoted nitroaldol reactions of nitromethane to various aldehydes **5**.

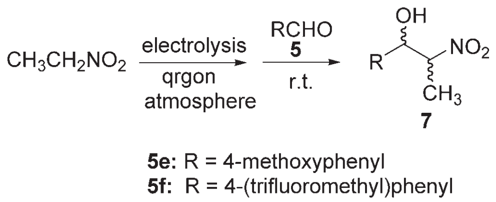
Entry	5	Product **6**	Molar Ratio CH_3NO_2/**5**	Current Quantity[a] [F/mol]	Reaction Time [h]	Yield[b] [%] of **6**
1	**5a**	**6a**	9	0.05	1	65
2	**5a**	**6a**	9	0.1	0.75	91
3	**5a**	**6a**	2.3	0.1	1	89
4	**5a**	**6a**	1.1	0.05	1	54 (27)
5	**5a**	**6a**	1.1	0.1	1	85
6	**5b**	**6b**	9	0.1	1	84 (12)
7	**5c**	**6c**	9	0.1	1.5	70
8	**5d**	**6d**	9	0.1	1	63

[a] The current quantity refers to the aldehyde **5**, added to the catholyte at the end of the electrolysis.

[b] The yields refer to isolated, chromatographically pure 2-nitroalchols **6** and are calculated on the starting aldehyde **5** (3 mmol scale). Yields in brackets refer to the recovered aldehydes **5**.

Since nitromethane is relatively inexpensive and easy to remove under vacuum, a large excess might be safely used to carry out the reactions with the best selectivity and chemical yield.

Anyway, in order to generalise the procedure, a more convenient stoichiometric ratio (1.1) was employed in a further development of the methodology to the Henry reaction of nitroethane (Scheme 4).



Scheme 4.

As shown in Table 5, in spite of the very reduced molar ratio nitroethane/**5**, the electrosynthesis of the respective 2-nitroaldols was accomplished in a very satisfactory way by addition of the aldehyde to the electrolysed pure nitroethane. Although the diastereoselectivity was usually modest, 2-nitro alcohols were obtained with total chemoselectivity, since no by-products arising from a concurrent elimination step on the product **7** or from a competing aldol condensation were observed. Unfortunately, attempts to improve the conversion of the starting materials **5c** and **5e** by increasing the current quantity, the temperature or the reaction time, gave unsatisfactory results.

Table 5. Electrochemically-promoted nitroaldol reactions of nitroethane to various aldehydes **5**.

Entry	5	Product **7**	Yield[a] [%] of **7**	**7** *syn/anti*[b]
1	**5a**	**7a**	76	55/45
2	**5b**	**7b**	91	60/40
3	**5c**	**7c**	71 (28)	67/33
4	**5e**	**7e**	81 (16)	73/27
5	**5f**	**7f**	93 (6)	68/32

[a] The yields refer to isolated, chromatographically pure **7** and are calculated on the starting aldehyde **5** (20 mmol scale). Yields in brackets refer to the recovered starting materials **5**.

[b] The diastereoisomeric ratios have been calculated by ^1H NMR analysis.

Conclusions

In conclusion, 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 with short reaction times. Furthermore, easy set-up and work-up procedures were established avoiding the addition of a supporting electrolyte in the electrolysis medium.

Experimental Section

General Remarks

Constant current electrolyses were performed under an argon atmosphere, using an Amel Model 552 potentiostat equipped with an Amel Model 572 integrator. Unless otherwise indicated, all the experiments were carried out in a divided glass cell separated through a porous glass plug filled up with a layer of agar gel (i.e., methyl cellulose 0.5% vol dissolved in DMF-Et$_4$NClO$_4$ 1.0 mol dm^{-3}); Pt spirals (apparent areas 0.8 cm^2) were used both as cathode and anode. Starting materials (1,3-dicarbonyl compounds or rather nitromethane and nitroethane) were used both as catholyte and anolyte.

Starting materials and all the others materials were purchased from Aldrich or Fluka and used without any further purification. Purification of the products were performed by flash chromatography column (silica gel, Merck). The IR spectra were recorded on an FT-IR instrument (Bruker Vector 22). The NMR spectra (Bruker DRX 400; ^{1}H 400 MHz; ^{13}C 100 MHz) were recorded as CDCl$_3$ solutions and referenced to residual CHCl$_3$ [7.26 ppm (^{1}H); 77.23 ppm (^{13}C)]. Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet); brs (broad singlet); d (doublet); dd (double doublet); t (triplet); q (quartet); m (multiplet). Coupling constants, J, are reported in Hz.

General Procedure for Electrochemically-Promoted Addition Reactions of 1a–d to Michael Acceptors 2a–f

Pure **1**, 5 mL, was electrolysed under galvanostatic control (I=5 mA cm^{-2}, Q=0.3 F, terminal voltage for **1b**=110 V) at room temperature. At the end of the electrolysis, the Michael acceptor **2** (3 mmol) was added to the cathode compartment and the reaction prolonged for the time reported in Table 2. Surplus starting materials was distilled under vacuum at room temperature and recovered for recycling in a glass trap cooled at −78 °C. Crude mixtures yielded pure adducts **3** (**3ba**: 0.53 g; **3ca**: 0.50 g; **3da**: 0.60 g; **3db**: 0.73 g; **3dc**: 0.68 g; **3dd**: 0.42 g; **3de**: 0.40 g, **3df**: 0.80 g) after simple filtration over silica gel. The isolated products **3da**,[13a] **3db**,[13b] **3dc**,[13c] **3dd**,[13d] **3de**[13e] and **3df**[13f] gave spectral and analytical data in accordance with those reported in the literature.

Ethyl 2-Acetyl-5-oxoheptanoate (3ba): ^{1}H NMR: δ=0.99 (t, 3H, J=7.1 Hz), 1.22 (t, 3H, J=7.0 Hz), 2.01–2.08 (m, 2H), 2.2 (s, 3H), 2.36 (q, 2H, J=7.4 Hz), 2.43 (q, 2H, J=7.1 Hz), 3.45 (t, 1H, J=7.2 Hz), 4.15 (q, 2H, J=7.1 Hz); ^{13}C NMR: δ=7.89, 14.23, 21.88, 29.18, 36.08, 39.23, 58.45, 61.61, 169.69, 203.14, 210.48.

Methyl 2-Acetyl-5-oxoheptanoate (3ca): ^{1}H NMR: δ=0.99 (t, 3H, J=7.2 Hz), 2.06–2.09 (m, 2H), 2.22 (s, 3H), 2.38 (q, 2H, J=7.4 Hz), 2.44 (q, 2H, J=7.2 Hz), 3.50 (t, 1H, J=7.2 Hz), 3.7 (s, 3H); ^{13}C NMR: δ=7.92, 21.95, 29.26, 36.12, 39.24, 52.65, 58.27, 170.20, 203.08, 210.45

General Procedure for Electrochemically-Promoted *QCCs* Construction *via* Michael Addition of 1e–g to Michael Acceptors 2

Pure **1**, 20 mmol, was electrolysed under galvanostatic control (I=5 mA cm^{-2}, Q=2 F, terminal voltage for **1c**=130 V) at 0 °C. At the end of the electrolysis, the Michael acceptor **2** (20 mmol) was added to the cathode compartment and the reaction prolonged for about 1 hour at room temperature. Crude mixtures yielded pure adducts **3** (**3ea**: 3.69 g, **3ec**: 4.80 g, **3fa**: 4.16 g, **3fc**: 4.20 g, **3ga**: 5.50 g) after simple filtration over silica gel. The isolated products **3ea**[14] gave spectral and analytical data in accordance with those reported in the literature.

Ethyl 2-Methyl-3-oxo-2-(3-oxocyclohexyl)butanoate (3ec) (1:1 mixture of two diastereoisomers): ^{1}H NMR: δ=1.24–1.29 (m, 6H), 1.32 (s, 3H), 1.35 (s, 3H), 1.33–1.51 (m, 2H), 1.59–1.84 (m, 2H), 2.06–2.12 (m, 4H), 2.14 (s, 3H), 2.15 (s, 3H), 2.18–2.28 (m, 4H), 2.39–2.43 (m, 3H), 2.58–2.62 (m, 3H), 4.15–4.24 (m, 4H); ^{13}C NMR; δ=13.80, 14.90, 14.97, 24.57, 24.69, 26.12, 26.27, 26.36, 26.75, 40.88, 41.48, 41.63, 42.80, 43.27, 61.32, 62.51, 171.03, 171.28, 203.88, 209.89.

Ethyl 2-Oxo-1-(3-oxopentyl)cyclohexanecarboxylate (3fa): ^{1}H NMR: δ=1.03 (t, 3H, J=8.0 Hz), 1.27 (t, 3H, J=6.8 Hz), 1.46–2.10 (m, 10H), 2.32–2.55 (m, 4H), 4.20 (q, 2H, J=6.8 Hz); ^{13}C NMR: δ=7.41, 13.91, 22.01, 27.14, 28.05, 35.43, 36.19, 36.96, 40.61, 59.59, 60.93, 171.58, 207.43, 209.90.

Ethyl 2-Oxo-1-(3-oxopentyl)cyclohexanecarboxylate (3fc) (1:1 mixture of two diastereoisomers): ^{1}H NMR: δ=1.29 (m, 3H), series of multiplets between 1.5–2.6 (17H), 4.2–4.6 (m, 2H); ^{13}C NMR: δ=13.47, 20.21, 21.83, 22.04, 24.28, 25.81, 26.44, 26.64, 31.17, 32.78, 40.50, 40.77, 42.26, 42.66, 59.52, 60.64, 62.50, 62.72, 169.82, 170.12, 205.35, 205.34, 209.67.

Diethyl 2-Methyl-3-oxo-2-(3-oxopenthyl)succinate (3ga): ^{1}H NMR: δ=0.94 (t, 3H, J=11.8 Hz), 1.19 (t, 3H, J=11.2 Hz), 1.28 (t, 3H, J=11.4 Hz), 1.34 (s, 3H), 2.05–2.15 (m, 2H), 2.25–2.45 (m, 2H), 4.07 (q, 2H, J=11.2 Hz), 4.22 (q, 2H, J=11.4 Hz); ^{13}C NMR: δ=6.81; 13.04 (2C), 18.79, 27.76, 34.83, 35.70, 54.63, 60.61, 61.63, 159.44, 170.74, 190.44, 208.41.

General Procedure for Electrochemically-Promoted Nitroaldol Reactions of Nitromethane to Aldehydes 5

Pure nitromethane, 5 mL, was electrolysed under galvanostatic control (I=10 mA cm^{-2}, Q=0.3 F) at 0 °C. At the end of the electrolysis, the aldehyde **5** (3 mmol) was added to the cathode compartment and the reaction prolonged, at room temperature, for the time reported in Table 4. Surplus nitromethane was evaporate under vacuum and the residue purified by flash chromatography to afford pure product **6** (**6a**: 0.47 g, **6b**: 0.47 g, **6c**: 0.35 g, **6d**: 0.29 g). The isolated products **6a**,[15a] **6c**,[15b] **6d**,[15c] gave spectral and analytical data in accordance with those reported in the literature.

1-Nitrononan-2-ol (6b): ^{1}H NMR: $\delta = 0.86$ (t, 3H, $J = 9.0$ Hz), 1.18–1.58 (m, 12H), 2.73 (brs, 1H), 4.25–4.45 (m, 3H); ^{13}C NMR: $\delta = 13.50$, 22.73, 25.32, 29.23, 29.38, 31.82, 33.85, 68.17, 80.83.

General Procedure for Electrochemically-Promoted Nitroaldol Reactions of Nitroethane to Aldehydes 5

Pure nitroethane (22 mmol), was electrolysed under galvanostatic control ($I = 37$ mA cm^{-2}, Q = 2 F) at 0 °C. At the end of the electrolysis, the aldehyde **5** (20 mmol) was added to the cathode compartment and the reaction prolonged, under stirring at room temperature. Once the TLC analysis showed the disappearance of **5**, the mixture was purified by flash chromatography to afford pure product **7** (**7a**: 2.842 g, **7b**: 3.694 g, **7c**: 2.570 g, **7e**: 3.418 g, **7f**: 4.631 g). The isolated products **7a**,[16a], **7b**[16b] **7c**,[16a] **7e**,[16a], **7f**[16a] gave spectral and analytical data in accordance with those reported in the literature.

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