

The Knoevenagel reaction in electrochemically activated solvents

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Abstract

The electrochemical activation of organic solvents HS (CH₃CN, CH₃CH₂CN, DMF, DMSO) containing Et₄NPF₆ as supporting electrolyte (i.e. their electrolysis under galvanostatic control) allows to induce in these solutions, in the absence of any catalyst, the Knoevenagel condensation between CH-acid CH₂(CN)₂ (**1**) and carbonylic substrates **2a–e**. Reaction products **3a–e** were isolated in good yields 97–48%. The progress of the Knoevenagel condensation is affected by *Q* (number of Faradays per mol of **1** supplied to the electrodes) and, moderately, by the nature of the solvents. The rates of the single steps were compared by elementary voltammetric analysis.

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1. Introduction

The set up of new and more efficient methodologies for C–C bond formation may be considered, in modern synthetic organic chemistry, an attractive target. In this context, considerable attention has been paid to processes carried out under mild and safe conditions and avoiding the use of toxic and dangerous chemicals and catalysts. The Knoevenagel condensation [1–5] of an aldehyde or ketone with an active methylene compound (to give the corresponding substituted alkene and H₂O) is one of the most useful and widely employed reaction for the C–C bond formation. Numerous applications of Knoevenagel reaction, in the synthesis of substituted alkenes as intermediates or end-products of a wide variety of fine chemicals (e.g. target molecules concerning pharmaceuticals, polymers, perfumes, etc.) have been reported.

The Knoevenagel reaction, carried out in organic solvents, is catalyzed by bases (ammonia, primary and secondary amines and their salts, sodium etoxide, etc.) [2,6–8] as well as by Lewis acids (CuCl₂, ZnCl₂, SmI₃, etc.) [9–11]. Recently, numerous acidic and basic heterogeneous systems (solid catalysts in organic solvents) have been reported [12,13]. The use of

insoluble catalysts (instead of hazardous and sometimes toxic homogeneous catalysts), which can be removed from the reaction mixture by filtration, allows easy work up of the reaction mixture and flexible recovery of the catalysts. The effect of the catalyst with the addition of ultrasounds [14–16] or microwaves [17–19] have been described.

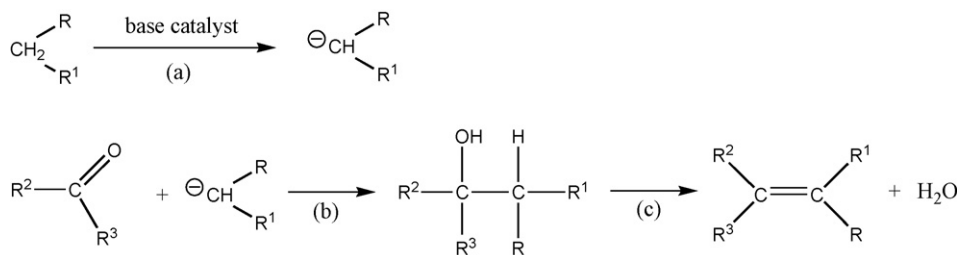
On the other hand, though many investigations were aimed at finding new and more effective catalysts, yet, as far as we know, no enough studies were carried out to establish the conditions allowing to avoid completely the addition of catalysts in the cases in which, in their absence, the Knoevenagel reaction would proceed at an extremely low rate.

In connection with what stated above, it is worth pointing out that the accepted mechanism for the base-catalyzed Knoevenagel reaction is related to: (a) the abstraction of a proton by the basic catalyst to yield the carbanion on the methylenic group; (b) the attack of the carbanion to the carbonyl group; (c) the protonation of the oxygen anion thus formed; (d) the elimination of the hydroxyl group to form the substituted alkenes and water [20] (Scheme 1).

According to this mechanism, the formation of carbanion [−]CHRR¹ has to be regarded as the necessary condition for the condensation of the CH-acid with the carbonylic compound.

On this subject, the electrochemical methodology is able to suggest effective alternative solutions. In fact, anionic intermediates can be obtained (selectively, in mild conditions and

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in the absence of catalysts) by direct cathodic reduction or by deprotonation, via EGB, of the CH_2RR^1 -acid.

The reduction (in DMSO as solvent, Pt cathode) of CH-acids, yielding conjugate bases and dihydrogen, was extensively described by Evans [21,22]. Therefore, when studying the electrogeneration of ethyl nitroacetate, it was discovered that attempts to generate anions by direct reduction of ethyl nitroacetate were quite inefficient due to the side reaction of the initially formed radical anion. Thus the efficient generation of ethyl nitroacetate anion required the deprotonation of ethyl nitroacetate via an electrogenerated base, superoxide anion $\text{O}_2^{\bullet-}$ [23].

The same authors reported the formation of the anion $^-\text{CH}_2\text{NO}_2$ via deprotonation of CH_3NO_2 by the electrogenerated base superoxide anion [24,25], as well as that one of the anion $^-\text{CH}(\text{CN})_2$ (formed along with dihydrogen) by cathodic direct reduction of $\text{CH}_2(\text{CN})_2$ [26,27] and the addition of the anions $^-\text{CH}_2\text{NO}_2$ and $^-\text{CH}(\text{CN})_2$ to carboxylic substrates.

Recently, we have reported that the deprotonation of CH- and NH-acids can be carried out by addition of these substrates to electrochemically activated solvent-supporting electrolyte systems (i.e. to solvents previously electrolyzed under galvanostatic conditions) [28–31]. According to this procedure, the deprotonation of NH- and CH-acids may be achieved avoiding the direct reduction of the substrates, or the peculiar addition of suitable probases to the solvent-supporting electrolyte system.

This prompted us to study the reactivity of the CH-acid $\text{CH}_2(\text{CN})_2$ (**1**) versus aldehydic substrates **2a–e** in electrochemically activated solvents HS (CH_3CN , $\text{CH}_3\text{CH}_2\text{CN}$, DMF, DMSO) containing TEAFP as supporting electrolyte (Scheme 2). Aim of this investigation was to assay the feasibility of the Knoevenagel condensation in electrochemically activated solvents. The products of the syntheses were isolated, identified and the yields evaluated. The progress of the overall reaction was studied and the rate of each chemical step compared by voltammetric analysis.

2. Experimental

2.1. Starting materials

Purifications of solvents and supporting electrolyte have been described elsewhere [32]. Compounds **1** and **2a–e** (commercial, Sigma–Aldrich) were used as received.

2.2. Instrumentation

GC–MS measurements were carried out on a SE 54 capillary column using a Fisons 8000 gas chromatograph coupled with a Fisons MD 800 quadrupole mass selective detector. ^1H and ^{13}C NMR spectra were recorded using a Bruker AC 200 spectrometer using CDCl_3 as internal standard.

Voltammetric measurements were performed with an Amel 552 potentiostat equipped with an Amel 566 function generator and an Amel 563 multipurpose unit in a three-electrode cell; the curves were displayed on an Amel 863 recorder. A 492/Pt/1 Amel microelectrode was employed, and a Pt counter electrode. The reference electrode was a modified saturated calomel electrode. Its potential was -0.07 V versus SCE.

Electrolyses under galvanostatic control were carried out with an Amel 552 potentiostat equipped with an Amel 721 integrator. A two-compartment cell was used; the cathode was a Pt spiral (apparent area 1.0 cm^2) and the counter electrode was a cylindrical platinum gauze (apparent area 1.3 cm^2). The anodic solution (MeCN or other solvent where specified- 0.1 mol dm^{-3} Et_4NPF_6) was separated from the cathodic compartment through a porous plug filled with methylcellulose in $\text{DMF}-1.0\text{ mol dm}^{-3}$ Me_4NClO_4 .

2.3. General procedure

Constant current electrolyses were carried out (using Pt electrodes and solvent-supporting electrolyte system described in the Tables) in solvent- 0.1 mol dm^{-3} supporting electrolyte solutions (30 ml) with continuous nitrogen bubbling, at room temperature ($I=20\text{ mA cm}^{-1}$). At the end of the electrolyses, compounds **1** (1.5 mmol) and **2a–e** (1.5 mmol) were added to the catholyte and the solution was analyzed by cyclic voltammetry. After 48 h, the solvent was evaporated under reduced pressure and the residue extracted with diethyl ether ($3 \times 20\text{ ml}$). When DMF and DMSO were used as solvent, the catholyte was poured into water (60 ml) and extracted with diethyl ether ($3 \times 20\text{ ml}$). The extracts were analyzed by thin layer chromatography, GC–MS and ^1H NMR; all products were purified by flash chromatography, using *n*-hexane-ethyl acetate 8:2 as eluent.

All compounds were identified by comparison of their spectral data with data reported in literature.

2.3.1. 2-(Phenylmethylene)malononitrile **3a** [33]

^1H NMR (CDCl_3), δ : 7.92–7.87 (m, 2H), 7.77 (s, 1H), 7.67–7.48 (m, 3H). ^{13}C NMR (CDCl_3), δ : 159.8, 134.5,

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