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Electrochimica Acta 50 (2005) 2029–2036
ELECTROCHIMICA Acta
www.elsevier.com/locate/electacta

An electrochemical alternative strategy to the synthesis of β-lactams via N–C4 bond formation

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Received 4 June 2004; received in revised form 13 August 2004; accepted 13 September 2004
Available online 22 October 2004

Abstract

A simple electrochemical synthesis of β-lactams has been developed using constant current electrolysis in a suitable solvent-supporting electrolyte solutions, with subsequent addition of bromoamides. The regio- and stereo-selectivity of the electrochemically-induced cyclization of bromoamides to β-lactams, via N─C4 bond formation, has been evidenced. This synthesis avoids any addition of bases and probases and gives β-lactams in high yields.

Keywords: β-Lactams; Cyclization; Bromoamides; Stereoselectivity; Organic electrosynthesis

1. Introduction

Several natural and synthetic compounds, containing the β-lactam nucleus, are of clinical importance due to their high antibiotic activity [1]; however, their extensive use has promoted the development of many resistant strains of bacteria [2]. Therefore, the need for new β-lactamic structures, capable of overcoming the increasingly efficient defence mechanisms of bacteria, has been continuously growing. This need has promoted a great deal of work, both for the synthesis of new β-lactams and for working out new and efficient routes for the synthesis of the β-lactamic ring, or improving those already available. The interest in this field has been also stimulated by the recent extensive use of β-lactams as chiral building blocks in organic synthesis [3]. The most commonly employed methodologies for the synthesis of this nucleus involve two possible strategies: (a) cycloaddition via ketene–imine reaction (Staudinger reaction); and (b) cyclization of suitable substrates (aminoacids, aminoesters, etc.) [3a,4].

As regards the latter methodology, the base promoted (NaH, Et_3N, Cs_2CO_3, etc.) cyclization of β-amino acids (activated by $PhP(O)Cl_2$)) [5], β-amino acid-amides [6], and chloro acetyl amino acid derivatives [7] has been recently proposed. In addition, the stereoselectivity of the base-promoted cyclization to β-lactams of *N*-alkyl-*N*-chloroacetyl amino acid [8] and β-hydroxy-α-thioalkyl ester derivatives [9] has been exstensively discussed. The electrochemically promoted cyclization to β-lactams of propionamides and propionohydroxamates, bearing a leaving group at the position 3, has been reported [10]. According to this methodology, the acid–base reaction between an electrogenerated base (EGB) and the amidic substrate gives rise to a nitrogen anion, which undergoes cyclization to β-lactams via intramolecular nucleophilic substitution (N–C4 bond formation). The EGB's were obtained by potentiostatically-controlled electrolyses of DMF–TEAP solutions, initially containing both the probase (PB: ethyl 2-bromo-2-methylpropanoate or diethyl bromomalonate) and the amidic substrates. This elec-

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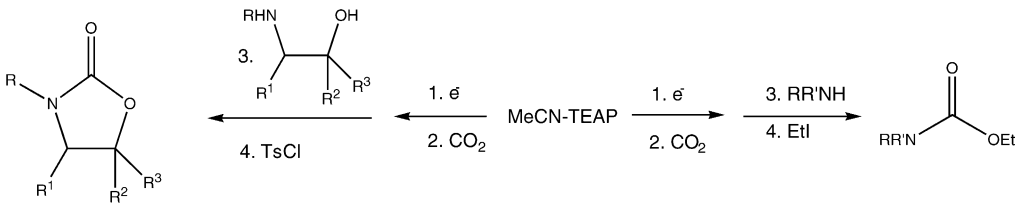
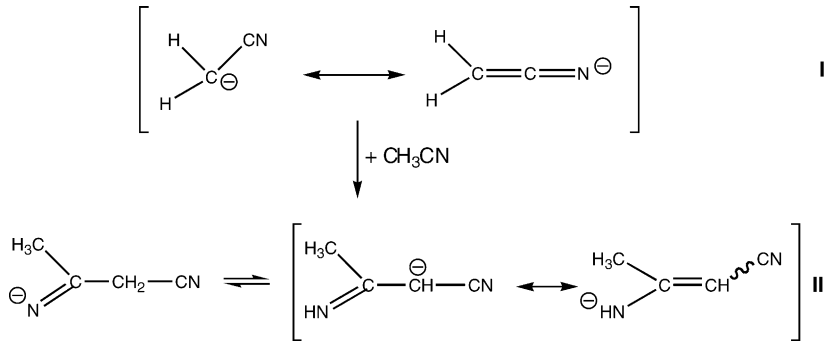
doi:10.1016/j.electacta.2004.09.011



Scheme 1.



Scheme 2.

trochemical approach has some limitations. Due to the fact that both the substrate and the PB are present in the electrolytic solution, the electrolyses have to be carried out under potentiostatic control and the substrate must be electroinactive at a potential at which the base can be electrogenerated from the PB. Furthermore, undesired byproducts are often formed by reaction of the EGB's, which are generally strong bases (e.g., the 2-methylpropanoate anion), with the parent PB, with the solvent, or with the supporting electrolyte.

We are engaged in examining some electrochemical procedures to seek new and simpler synthetic methodologies. Recently, we have shown that electrolyses under galvanostatic control of MeCN–TEAP solutions yield a basic system which enables, via deprotonation of the N–H group, the carboxylation of primary and secondary amines, and of amino alcohols yielding organic carbamates [11] and oxazolidin-2-ones [12], respectively. Amines and amino alcohols were added to the cathodic solution at the end of the electrolyses (Scheme 1).

During the electrolyses of MeCN–TEAP solutions, cyanomethyl (**I**) and 3-amino-crotonitrile (**II**) anions may be produced (Scheme 2). These anions show, in MeCN–TEAP solutions, i.e., in the presence of a large counter-ion as TEA^+, a remarkable reactivity as bases [12,13]. The mechanism of formation of cyanomethyl anion (via an active hydride intermediate or via a direct electron transfer to an acetonitrile molecule [14]) has been reported. 3-Amino-crotonitrile anion (**II**) is formed by a nucleophilic attack of $^-CH_2CN$ on the parent molecule. The ratio between cyanomethyl and 3-amino-crotonitrile anions and the reactivity of these basic intermediates can be strongly affected by the experimental conditions, i.e., divided or undivided cell, electrolyses carried out under potentiostatic or galvanostatic control, cathodic material and supporting electrolyte, etc.

We have studied the reactivity of bromoamides **1a–i** in electrolyzed MeCN-supporting electrolyte solutions, i.e., in the presence of cyanomethyl and other derived anions. The reactivity of bromoamides **1** has also been investigated in other electrolyzed solvent-supporting electrolyte systems.

The purpose of this study is the development of a new methodology for the electrochemically-induced synthesis of β-lactams via cyclization of bromoamides under mild condition (Scheme 3).

2. Experimental

2.1. Starting material

MeCN was distilled twice from P_2O_5 and CaH_2; EtCN and $MeNO_2$ were distilled before use; *N*,*N*-dimethylformamide (DMF) was distilled from activated alumina under reduced pressure; dimethylsulphoxide (DMSO) was used without any purification. Tetraethylammonium perchlorate (TEAP) was crystallized twice from water and then dried under high vacuum at 45 °C for 48 h [15]; tetramethylammonium perchlorate (TMAP), tetraethylammonium chloride (TEACl), tetrabutylammonium chloride (TBACl), tetraethylammonium hexafluorophosphate (TEAFP) and tetrabutylammonium hexafluorophosphate (TBAFP) were dried under high vacuum at 45 °C for 24 h. Compounds **1a–i** were synthesized following the procedure described in the literature [16]; the spectral data of known compounds were in accord with those reported: **1a** [17], **1b** [18], **1d** [19], **1f** [18], **1g** [18], **1h** [18], and **1i** [19]. Compound **1j** was