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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 8517–8519

Electrogenerated cyanomethyl anion in organic synthesis: a simple diastereoselective synthesis of *cis*-3-alkyl-1-benzyl-4-ethoxycarbonyl-β-lactams

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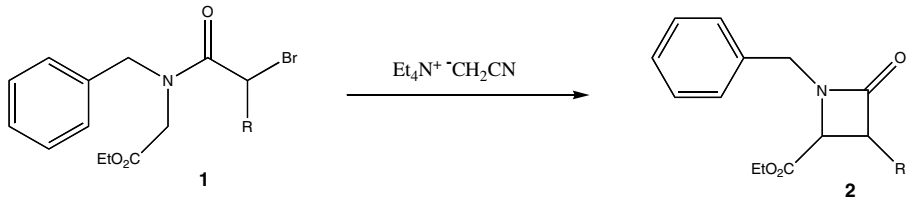
Received 6 July 2005; revised 3 October 2005; accepted 5 October 2005
Available online 21 October 2005

Abstract—A ready diastereoselective synthesis of *cis*-3-alkyl-1-benzyl-4-ethoxycarbonyl-β-lactams has been developed by galvanostatic electrolysis of MeCN–Et_4NPF_6 solutions and subsequent addition of a *N*-(ethoxycarbonyl)methyl-*N*-benzyl-2-bromoalkylcarboxamide. The yields in β-lactams are very high and the cis isomers have been obtained in a large excess, the cis/trans ratios varying from 87/13 to 93/07.

β-Lactams are known to be of high clinical importance.[1] For this reason, many methods of synthesis of β-lactams have been developed.[2] Among them, electrochemical approaches are of interest because of mild reaction conditions and elimination of the use of toxic and harmful chemicals. Thus β-lactams have been synthesized by electrochemical cyclization involving intramolecular displacement of a halide by a nitrogen anion (N–C4 bond formation) or by a carbanion (C3–C4 bond formation). The cyclization of bromoamides (N–C4 cyclization) involved electrogenerated bases,[3] whereas C3–C4 cyclization was accomplished either by the reduction of a 1,4-dibromoamide[4] or by electrochemically induced deprotonation of a *N*-aryl-*N*-(diethoxycarbonyl)methyl-2-haloalkylcarboxamide.[4,5]

In our laboratory, we have developed new methodologies of electroorganic synthesis based on EGBs to obtain electrogenerated bases by simple galvanostatic reduction of solvent-supporting electrolyte.[6] In continuation of our studies, we report the use of electrogenerated cyanomethyl anion for a highly diastereoselective synthesis of 3,4-disubstituted β-lactams **2** from *N*-(ethoxycarbonyl)methyl-*N*-benzyl-2-bromoalkylcarboxamides



R = CH_3 (**1, 2a**), CH_2CH_3 (**1, 2b**), $CH(CH_3)_2$ (**1, 2c**), $(CH_2)_3CH_3$ (**1, 2d**), *c*-C_5H_9 (**1, 2e**), *c*-C_6H_{11} (**1, 2f**)

Scheme 1.

Keywords: β-Lactams; Electrogenerated cyanomethyl anion; Electrosynthesis; Cathodic reduction.
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doi:10.1016/j.tetlet.2005.10.008

Table 1. Cyclization of *N*-(ethoxycarbonyl)methyl-*N*-benzyl-2-bromoalkyl-carboxamides **1** by electrogenerated cyanomethyl anion[a]

Entry	R[b]	F/mol[c]	β-Lactam **2**, yield (%)[d]	cis/trans ratio[e]
1	$(CH_3)_2CH$	1	33[f]	75/25
2	$(CH_3)_2CH$	2	75	87/13
3	$(CH_3)_2CH$	3	76	85/15
4	CH_3	2	84	91/09
5	CH_3CH_2	2	90	90/10
6	$CH_3(CH_2)_3$	2	85	93/07
7	*c*-C_5H_9	2	57	90/10
8	*c*-C_6H_{11}	2	63	91/09

[a] Reaction conditions: MeCN–Et_4NPF_6 as solvent-supporting electrolyte, Pt anode and cathode, two-compartment cell, $I = 75$ mA cm^{-2}, rt, N_2 bubbling. At the end of the electrolysis, 0.5 mmol of amide was added to the cathodic solution and the mixture was stirred at rt for 16 h under N_2.
[b] See Scheme 1.
[c] Number of Faradays per mol of amide supplied to the electrodes.
[d] Isolated yields based on the starting amide.
[e] The cis/trans ratio was determined by ^{1}H NMR of the crude product.
[f] 61% of recovered starting material.

1 (Scheme 1). The advantage of this approach comes from the high reactivity of the naked cyanomethyl anion, the counter ion being a tetraalkylammonium cation.

The cyanomethyl anion was generated by galvanostatic electrochemical reduction of a solution of acetonitrile containing a tetraalkylammonium salt, Et_4NPF_6, as supporting electrolyte at room temperature and under a nitrogen atmosphere. The electrolysis was carried out at constant current in a two-compartment cell with a sintered glass/agar gel separator, and a platinum cathode and anode, and was stopped after the desired quantity of electricity was reached. The *N*-(ethoxycarbonyl)methyl-*N*-benzyl-2-bromoalkylcarboxamide **1** was then added and the mixture stirred at room temperature under nitrogen overnight.[7] The results are reported in Table 1.

In entries 1–3, the effect of the charge passed is illustrated with the *N*-(ethoxycarbonyl)methyl-*N*-benzyl-2-bromoalkylcarboxamide **1c** ($R = (CH_3)_2CH$) as substrate. Complete conversion of the substrate required two moles of electrons per mole of substrate (2 F/mol) (entry 2). An equimolar amount of electrogenerated base (1 F/mol) was not sufficient to ensure complete conversion of substrate (entry 1), whereas the use of a larger excess of electrogenerated base (3 F/mol) had no noticeable effect (entry 3).[8] So the reactions in entries 4–8 were carried out with two equivalents of electricity (2 F/mol) to ascertain the efficiency and generality of this method.

The two mean features of Table 1 are (i) the high yields of β-lactams **2a**–**d** (R = linear alkyl group, 75–90%) and the good yields of β-lactams **2e**–**f** (R = cyclic alkyl group, 57–63%), obtained under very mild and convenient conditions (electrolysis under constant current at room temperature, no manipulation of strong bases, easy work-up procedure); and (ii) the high cis/trans ratios (87/13 to 93/07), irrespective of the nature of the R group. Such high cis/trans ratios were quite unexpected considering (i) the most probable mechanism of cyclization (intramolecular S_N2 displacement of the bromide by the ester enolate generated by proton abstraction at C-2 of carboxamide **1**) and (ii) the fact that the ester enolate is naked or not strongly associated with a metallic cation. Indeed, Kawabata, Minami and Hiyama[9] have reported a highly diastereoselective synthesis of *cis*-3,4-disubstituted β-lactams by treating the dianion of *N*-[(*tert*-butoxycarbonyl)methyl]-*N*-(4-methoxyphenyl)butanamide with *N*-iodosuccinimide (NIS). To explain the high *cis* diastereoselectivity, they propose that the conformation of the dianion is fixed by intramolecular association of the two oxygen atoms of the dianion with a lithium cation. The conformation would be retained in the 2-iododerivative resulting from the reaction of the dianion with NIS for the S_N2 displacement of the iodide. Since, in our case, no such strong coordination can be invoked, other factors must be responsible for the *cis* diastereoselectivity. This aspect is the subject of a separate study. When the electrolysis was carried out using a sacrificial anode (Mg), in a one compartment cell, only the starting amide was recovered (in quantitative yield); this unfavourable result may be related to the presence of electrogenerated Mg^{2+} cations, that strongly coordinate the cyanomethyl anion, thus inhibiting its reactivity.

In conclusion, we have described a novel and simple method of cyclization of *N*-(ethoxycarbonyl)methyl-*N*-benzyl-2-bromoalkylcarboxamides under mild conditions using electrogenerated cyanomethyl anion. The method is easy to apply (constant current electrolysis, facile work-up) and allow to avoid the manipulation of strong bases. Unexpectedly, a high cis/trans ratio was obtained with all the substrates.

Acknowledgements

The authors wish to thank Mr. M. Di Pilato for his contribution to the experimental part of this work. This work was supported by research grants from MURST (Prin 2004) and CNR, Roma, Italy.

Supplementary data

In this file, the syntheses of starting amides and of β-lactams are reported, along with their spectral data. Supplementary data associated with this article can be

found, in the online version, at doi:10.1016/j.tetlet.2005.10.008.

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7. *Typical experimental procedure*: The constant current electrolyses were carried out (using Pt electrodes, $I = 75\ \text{mA cm}^{-2}$) in MeCN–0.1 mol dm^{-3} Et_4NPF_6 solutions (25 ml), at room temperature and with continuous nitrogen bubbling. At the end of the electrolyses, bromoamides (0.5 mmol) were added to the catholyte and the solution was allowed to stand under stirring for 16 h. The solvent was then evaporated under reduced pressure and the residue extracted with diethyl ether (3×30 ml). The extracts were analyzed by thin layer chromatography, GC–MS and ^{1}H NMR; all products were purified by flash chromatography, using *n*-hexane–ethyl acetate 95:5 to 8:2 as eluent. *cis*-1-Benzyl-4-ethoxycarbonyl-3-isopropyl-2-azetidinone. ^{1}H NMR ($CDCl_3$) δ: 7.33–7.16 (5H, m), 4.82 (1H, d, $J = 14.9$ Hz), 4.17 (2H, q, $J = 7.2$ Hz), 4.02 (1H, d, $J = 14.9$ Hz), 3.96 (1H, d, $J = 5.6$ Hz), 3.14 (1H, dd, $J = 9.9$, 5.6 Hz), 2.07–1.89 (1H, m), 1.24 (3H, t, $J = 7.2$ Hz), 1.11 (3H, d, $J = 6.6$ Hz), 0.87 (3H, d, $J = 6.5$ Hz). ^{13}C NMR ($CDCl_3$) δ: 169.78, 168.28, 135.02, 128.76, 128.46, 127.78, 61.41, 61.26, 54.81, 44.92, 26.17, 21.56, 20.18, 14.04. EIMS, *m*/*z* (%): ($M^{+\cdot}$ absent), 247 ($M^{+\cdot}$-CO, 5), 202 ($M^{+\cdot}$-CO_2Et, 6), 143 (32), 115 (30), 91 (100). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69, N, 5.09. Found: C, 69.15; H, 8.09; N, 4.80.
8. To evaluate this electrochemical approach to the synthesis of β-lactams (via $^-CH_2CN$ induced cyclization of 2-bromocarboxamides), the reactivity of **1c** versus a classical organic base has been carried out (LDA in THF, −78 °C). β-Lactam **2c** was not isolated and **1c** was quantitatively recovered. See also Ref. 9.
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