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Synthesis of β-Lactams by 4-*exo-tet* Cyclization Process Induced by Electrogenerated Cyanomethyl Anion, Part 2:[1] Stereochemical Implications

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Abstract: An efficient electrochemically induced synthesis of chiral *cis* β-lactams has been described, *via* deprotonation of chiral amides containing an acidic methylene group and a bromine atom as leaving group and bearing a chiral auxiliary or amine function. The electrogenerated base – cyanomethyl anion – is easily obtained by galvanostatic reduction of acetonitrile-tetraethylammonium hexafluorophosphate solutions under very mild conditions. The yields are high and the *cis*-diastereoselection complete. The use of starting chiral amides has allowed in many cases the preparation of the most abundant isomer in a pure form.

Keywords: cathodic reduction; 4-*exo-tet* cyclization; electrogenerated cyanomethyl anion; electrosynthesis; *cis*-β-lactams

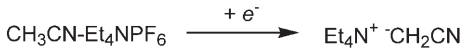
Introduction

Natural and synthetic β-lactams are compounds of great interest due to their well known pharmacological activities.[2] Moreover, they are used also as synthons for biologically important compounds.[3] It is thus obvious that organic chemists are interested in finding newer and newer syntheses of these compounds that are stereoselective, easy, proceed with high yields and, possibly, are green.

There are two main pathways for the synthesis of the azetidin-2-one ring: [2+2]cycloaddition and cyclization reactions. Among the [2+2]cycloadditions, the Staudinger reaction between an imine and a ketene[4] is the most common, due to the predictability of the stereochemical output, but also a [2+2]cycloaddition between an olefin and an isocyanate is used.[3] The cyclization reaction can be due to an N–C-2, an N–C-4, or a C-3–C-4 bond formation. This method has a less predictable stereochemical output and it is therefore less used. The stereochemistry of the products is, in fact, very important as it is well known that the spatial structure of the molecules has often a determining influence on their biological activity. Thus, there is a necessity to develop β-lactam syntheses with a clearly defined stereochemical outcome. In particular, the C-3–C-4 cyclization synthesis of β-lactams has been carried out using a radical pathway and an ionic one. The radical synthesis led to *trans*-isomers[5] and, when a chiral amine was used, some *trans*-diastereoselection was obtained. When an oxidative coupling of dianions was used to obtain β-lactams, a mixture of isomers was attained, with a predominance of the *cis* ones.[6] In particular, a good *cis*-diastereoselection was obtained. The ionic pathway, starting from ethyl *N*-2-iodopropionyl-*N*-allyl glycinate (after reaction with *t*-BuOK in THF) led to the pair of *cis*-isomers.[7]

In recent years, the author and collaborators have established an electrochemical method for the synthesis of azetidin-2-one ring by a cyclization reaction, at first following an N–C-4 bond formation path,[8] subsequently following a C-3–C-4 one.[1,9] In both cases, a very mild methodology has been used, consisting of deprotonation and intramolecular halide displacement to form the four-membered ring. The base used for the deprotonation is the electrogenerated cyanomethyl anion (an electrogenerated base, EGB[10]), easily obtained by galvanostatic cathodic reduction, at room temperature, of a solution of acetonitrile–0.1 mol dm^{-3} Et_4NPF_6 (Scheme 1) at a platinum electrode.[11]

This electrogenerated base has a high reactivity, being a naked anion as its counterion is a tetraalkylammonium cation. It can deprotonate a nitrogen

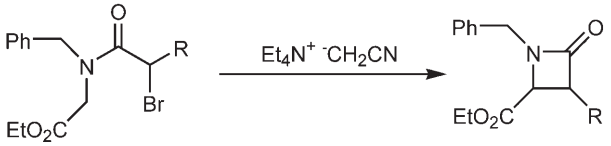


Scheme 1. Electrochemical generation of cyanomethyl anion.

atom (starting the N–C-4 pathway), or a carbon atom (starting the C-3–C-4 one).

In particular, the deprotonation of a suitable bromoamide by electrogenerated cyanomethyl anion led to the formation of a β-lactam predominantly as the *cis*-isomer in good yields (Scheme 2, *cis*/*trans* ratio from 87/13 to 93/07).[1,9]

Of course, the starting amide being a racemic com-



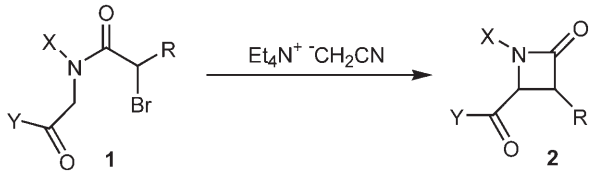
Scheme 2. Electrochemically induced synthesis of β-lactams by C-3–C-4 bond formation.

pound, a pair of *cis*-enantiomers was obtained and, obviously, it was not possible to separate them by ordinary means. Starting from these, however, encouraging results and as a logical continuation of the previous work, I wanted to further study the stereochemical outcome of this electrochemically induced cyclization of amides to β-lactams. As in the reaction reported in Scheme 2, we obtained a pair of *cis*-enantiomers as main products, I thought to incorporate a chiral auxiliary or a chiral reagent into the starting amide, attempting in this way to obtain a diastereomeric mixture in which the two *cis*-β-lactams could be separated with ordinary means. This work was divided in two parts, the first concerning the diastereoselectivity of this cyclization related to the control of C-4 configuration (substrates **1a–e**, Table 1), the second concerning the diastereoselectivity related to the configuration of both C-3 and C-4 atoms (substrates **1f–j**, Table 2) with particular reference to the *cis/trans*-diastereoselection.

Results and Discussion

Considering the structure of the amide used in the previous paper,[1] I recognized two positions with which a chiral reagent could be linked (see Scheme 3): the nitrogen atom (X is in this case a chiral group) and the carbonyl group in the β-position to the nitrogen atom (Y is a chiral auxiliary).

The choice of the chiral reagent or auxiliary has been done in view of an easy removal. In fact, when a



Scheme 3. General reaction Scheme for the electrochemically induced synthesis of β-lactams.

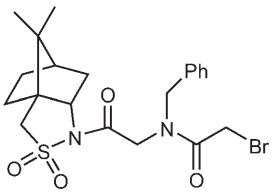
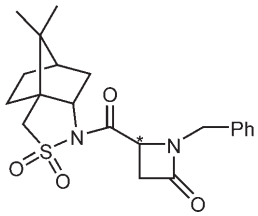
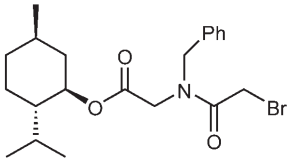
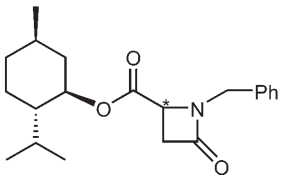
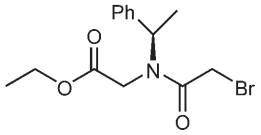
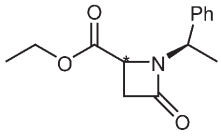
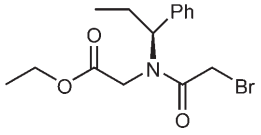
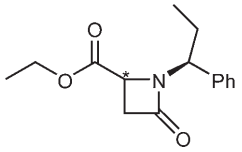
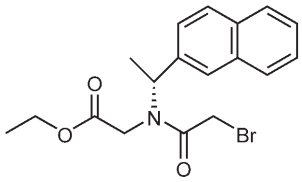
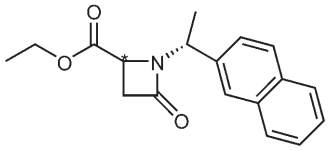
chiral auxiliary (like Oppolzer's camphor sultam or menthol) is used in the Y position, the deprotection of the produced β-lactam **2** (for example, by hydrolysis) would be quite easy; besides, if a chiral benzylamine is used in the synthesis of the starting amide **1** (X position), the resulting β-lactam **2** (due to a 4-*exo-tet* cyclization) would incorporate this chiral part as a protective group that could be removed (due to the reactivity of the benzyl group) by many means: using potassium persulfate,[12,13] lithium[14] or sodium in liquid ammonia.[8] Moreover, chiral benzylamines are readily available and relatively cheap, and their use in the synthesis of β-lactams has been suggested by some authors.[13]

I have taken into account both possibilities (X and Y chiral, but not at the same time), not being able to predict which of these two ways would lead to the best asymmetric induction. At first, substrates **1a–e** (Scheme 3, R = H) have been taken into consideration to evaluate the aymmetric induction at the C-3 position (Table 1).

The cyanomethyl anion was generated by galvanostatic electrochemical reduction of a solution of acetonitrile, containing tetraethylammonium hexafluorophosphate as supporting electrolyte, at 0 °C[15] and under a nitrogen atmosphere. The electrolysis was carried out in a two-compartment cell with a sintered glass/agar gel separator, equipped with platinum anode and cathode, and was stopped after two equivalents of electricity (2 Faradays per mol of amide)[16] had passed through the solution. Amide **1** (as a sum of two rotamers) was then added and the mixture stirred at 0 °C for 3 h. Usual work-up gave the corresponding β-lactam **2**. The results are reported in Table 1 and are consistent with a reaction pathway involving deprotonation of the acidic methylene in the α-position to the nitrogen atom, followed by internal halide displacement with a 4-*exo-tet* cyclization.

As can be seen from Table 1, the yields in β-lactams **2** are generally good (69 to 79 %), irrespective of the position of the chiral part of the molecule. Moreover, except for the case of amide **1b**, the two diastereomeric β-lactams are obtained with a fairly good diastereoselection [from 35/65 to 23/77, this last result being achieved with the more hindered 1-(2-naphthyl)-ethylamine]. Unfortunately, any attempt to separate the diastereoisomers with ordinary means failed. In

Table 1. Electrochemically promoted diastereoselective synthesis of monosubstituted β-lactams.

Entry	Reagent	Product[a]		Yield[b]	*dr*[c]
1		**1a**		**2a**	79%	33/67
2		**1b**		**2b**	71%	50/50
3		**1c**		**2c**	71%	26/74
4		**1d**		**2d**	69%	35/65
5		**1e**		**2e**	76%	23/77

[a] As sum of two epimers at the asterisked position.
[b] Yields in isolated product, as sum of two epimers at the asterisked position.
[c] Diastereomeric ratio between the two diastereoisomeric products. The first number of the ratio refers to the diastereoisomer in which the proton marked with the asterisk resonates at a lower field with respect to the corresponding proton of the other diastereoisomer in the ^{1}H NMR spectrum.

the case of amide **1b** (entry 2), the bulky isopropyl group of the chiral auxiliary is perhaps too far from the reaction centre and it fails to influence the stereochemical output of the reaction (attaining a 50/50 diastereomeric ratio).

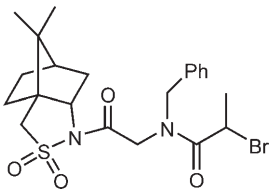
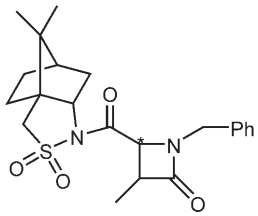
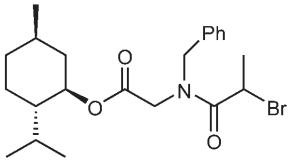
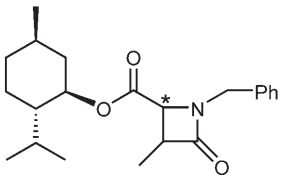
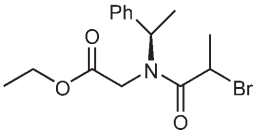
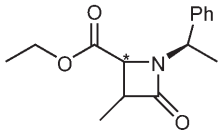
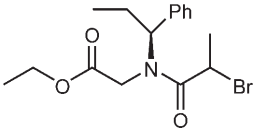
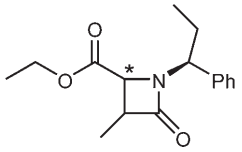
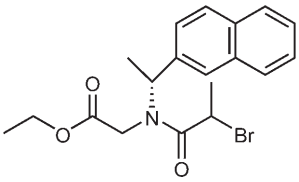
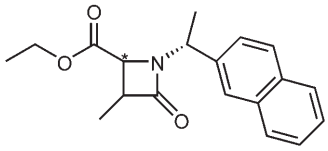
β-Lactam **2c** has been previously synthesized by Cordero and co-workers[17] in 61% yield as an inseparable 1:1 mixture of isomers starting from a 1:1 mixture of chiral spiro[cyclopropane-1,5′-isoxazolidine] isomers treated with *p*-TsOH in CH_3CN at 50°C (we have synthesized this β-lactam in 71% yield with a diastereomeric ratio of 26/74).

A similar reaction was carried out by González-Muñiz and co-workers[18] starting from a halogenated amide **1** (Scheme 3, in which R = H, X = *p*-methoxybenzyl, Y = OCH_3 and Cl instead of Br) in MeCN as solvent and using Cs_2CO_3 as base; in this case the reaction took 10 days to obtain the corresponding β-lactam **2** in 54% yield. This fact confirms the validity of our electrogenerated cyanomethyl anion as a highly reactive base.

Having obtained good results in yields and diastereoselection with these substrates, we have introduced a methyl group (R = CH_3 in Scheme 3) to try to reproduce the good *cis*-diastereoselectivity obtained in our previous work with racemic amides (Scheme 2). The same chiral reagents or auxiliaries reported in Table 1 have been used (in this case, starting amides **1** are used as mixtures of diastereoisomers and rotamers) and the results are reported in Table 2.

The two main features of this Table are the high yields (except for amide **1f**, entry 1, in which the chiral auxiliary is Oppolzer's camphor sultam[19]), between 78 and 83%, obtained under very mild conditions, and the complete *cis*-diastereoselection of the produced β-lactams **2f–j**. In fact, in no case the *trans*-isomers of **2f–j** have been detected.

Table 2. Electrochemically promoted diastereoselective synthesis of *cis*-disubstituted β-lactams.

Entry	Reagent	Product[a]	Yield[b]	*dr*[c]
1	 **1f**	 **2f**	52%	50/50
2	 **1g**	 **2g**	79%	49/51
3	 **1h**	 **2h**	78%	46/54
4	 **1i**	 **2i**	80%	47/53
5	 **1j**	 **2j**	83%	42/58

[a] As sum of two *cis*-diastereoisomers.

[b] Yields in isolated product, as sum of two *cis*-diastereoisomers. The *cis*-configuration was established on the basis of the coupling constant (in the ^{1}H NMR spectrum) of the proton marked with the asterisk, as reported in the literature. See, for example, ref.[6]

[c] Diastereomeric ratio between the two *cis*-diastereoisomeric products. The first number of the ratio refers to the diastereoisomer in which the proton marked with the asterisk resonates at a lower field with respect to the corresponding proton of the other diastereoisomer in the ^{1}H NMR spectrum.

The two isomers of each *cis*-β-lactam have been obtained in a nearly equimolar amount (from 42/58 to 50/50); nevertheless, in the cases of compounds **2f** and **2h–j** they could be separated and one of the two diastereoisomers isolated in a pure form (see Supporting Information, again L-menthol – entry 2 – seems an unsuitable chiral auxiliary for this kind of reaction).

β-Lactam **2h** has been previously synthesized by Shibasaki and co-workers[20] in 86% yield using an N−C-2 pathway, starting from a *cis*-β-amino-thiol ester, in more drastic conditions and with a transition metal reagent [Cu(I)OTf, $CaCO_3$, toluene, reflux]; in this case (contrary to our method) the stereochemical outcome of the reaction was innate in the *cis* nature of the reagent, as the 3 and 4 positions are not touched during the reaction.

Conclusions

In conclusion, I have described an easy and convenient electrochemical strategy to promote the *cis*-stereoselective synthesis of chiral β-lactams in high yields by 4-*exo-tet* cyclization of suitable bromo amides bearing a chiral auxiliary or chiral protective group. The base (cyanomethyl anion) is obtained in a stoichiometric amount by simple galvanostatic electrolysis of a solution of acetonitrile/tetraethylammonium hexafluorophosphate. This is a very reactive base, as its counterion is a tetraalkylammonium cation, so it can be considered a naked ion. This very efficient electrochemical synthesis leads to a complete diastereoselection in the products, as only the *cis*-isomers are obtained. In most cases, the most abundant *cis*-lactam could be isolated in pure form.

Experimental Section

General Procedure for Electrochemically Promoted Diastereoselective Synthesis of β-Lactams

A constant current electrolysis was carried out (I= 75 mA cm^{-2}) in an MeCN-Et_4NPF_6 0.1 mol dm^{-3} (20 cm^3) solution as catholyte (anolyte: 5 cm^3), at 0 °C, under an argon atmosphere, 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_4NClO_4 1.0 mol dm^{-3}); Pt spirals (apparent areas 0.8 cm^2) were used both as cathode and anode. After 193 C were passed, the current was switched off and amide **1** (1 mmol) was added to the catholyte and the solution was allowed to stand under stirring at 0 °C for 3 h. The solvent was then evaporated under reduced pressure and the residue extracted with diethyl ether (3 × 30 cm^3). 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 7:3 as eluent. The two β-lactams produced are named β^1 and β^2, β^1 being the first isomer reported in the *dr* in Table 1 and Table 2, and β^2 the second one.

Acknowledgements

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[14] D. A. Evans, E. B. Sjogren, *Tetrahedron Lett.* **1985**, *26*, 3783–3786 and 3787–3790.
[15] Electrolyses carried out at a lower temperature (−20 °C) led to lower chemical yields in β-lactams, with no improvement in the *dr.*
[16] An increase in the number of Faradays per mol had no effect, see ref.[1]
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[19] The low yield in *cis*-β-lactam **2f** can be due both to the high steric hindrance of this chiral auxiliary and to the fact that under these experimental conditions part of the auxiliary is removed (either from starting amide **1f** or from product **2f**). In fact, from the cathodic solution Oppolzer's camphor sultam has been isolated.
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