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ELECTROCHEMICAL STUDIES ON ß-LACTAMS. PART 3.[1] ELECTROSYNTHESIS OF ß-LACTAMS *via* N-C_4 BOND FORMATION

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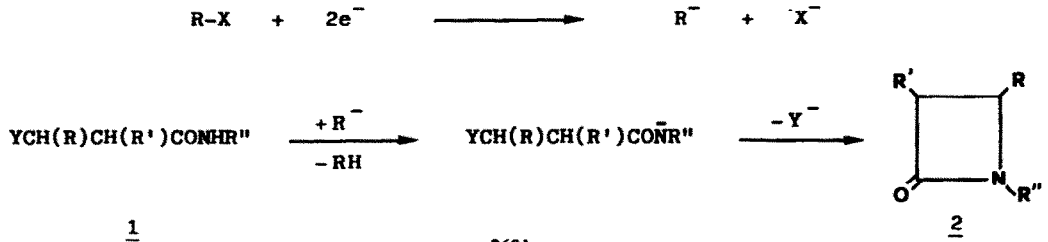
Abstract. Electrochemically promoted cyclization of propionamides or propionohydroxamates 1 affords ß-lactams 2 through N-C_4 bond formation. Very high yields and stereochemical control are remarkable features of this new synthetic methodology.

A widely used approach to the ß-lactam nucleus involves the ring closure through the N-C_4 bond formation. Earlier works on the subject have been performed using 3-halopropionamides as the substrate and strong bases as the ionizing agent.[2] More recently, the use of hydroxamates has been proposed as more acidic substrates than the corresponding amides, which allow the cyclization to be carried out under milder conditions.[3] For example, propionohydroxamates bearing a leaving group at the ß position, were found to afford ß-lactams in very high yield and without competitive formation of undesired α,ß-unsaturated products.[3,4] The synthetic utility of this procedure, has been established for a number of ß-lactams, including a formal total synthesis of the biologically important Aztreonam.[4]

We have previously shown that electrochemical methods can be usefully exploited in the field of ß-lactam chemistry, taking advantage of their peculiar features (regio- and stereoselectivity, mild experimental conditions, etc.).[5] In particular, the electrosynthesis of ß-lactams was accomplished in good to very high yields, *via* bond formation between C-3 and C-4, using readily available, substituted acetamides as starting materials.[1] We wish now to report an extension of such studies to the electrosynthesis of ß-lactams *via* N-C_4 bond formation, carried out according to the Scheme:



1 2

where RX is a suitable probase (PB), whose cathodic reduction yields the electrogenerated base (EGB) R^-. Acid-base reaction between the EGB and the substrate gives rise to a nitrogen anion, which undergoes cyclization to ß-lactam via intramolecular nucleophilic substitution. A prerequisite of the method is that 1 must be electroinactive at the working potential, corresponding to the plateau of the reduction wave of the PB. Both propionamides and propionohydroxamates 1, bearing a leaving group at the position 3 and further substituted at the position 3 and/or 2 (Table 1), prepared by conventional chemical routes (see Experimental), were used as the substrates. Ethyl 2-bromo-2-methylpropanoate (EBMP) ($E_{1/2}$=-0.87V vs SCE) or diethyl bromomalonate (DBM) ($E_{1/2}$=-0.25V vs SCE), whose reduction potential is sufficiently more positive than that of the substrates to ensure their electroinactivity,[6] were employed as the PB. Controlled-potential electrolyses have been carried out at a mercury pool cathode for N,N-dimethylformamide (DMF) solutions containing tetraethylammonium perchlorate (TEAP) as supporting electrolyte. Work-up of the reduction mixture allowed the isolation of the corresponding ß-lactam in poor to very high yields (Table 1).

Table 1. Products and yields of the electrochemically promoted cyclization of 1

Entry	Substrate	Y	R	R'	R''	PB	ß-lactam (% yield)
1	1a	Br	H	H	$CH_2C_6H_5$	DBM	....[a]
2	1a	Br	H	H	$CH_2C_6H_5$	EBMP	2a (70)
3	1b	Br	H	H	$C_6H_4OCH_3$(p)	EBMP	2b (54)
4	1c	Br	H	Pht	$C_6H_4OCH_3$(p)	EBMP	2c (10)
5	1d	Br	H	Pht	$OCH_2C_6H_5$	EBMP	2d (36)
6	1d	Br	H	Pht	$OCH_2C_6H_5$	DBM	2d (96)
7	1e	Br	CH_3	Pht	$OCH_2C_6H_5$	DBM	2e (93)[b]
8	1f	OMs	CH_3	Pht	$OCH_2C_6H_5$	DBM	2e (82)[c]
9	1e	Br	CH_3	Pht	$OCH_2C_6H_5$	EBMP	2e (65)[d]

Pht = Phtalimido; Ms = Mesyl

[a]Unchanged 1a was quantitatively recovered; [b]cis-isomer; [c]trans-isomer; [d]2:1 mixture of trans-/cis-isomers.

In our case as well, the yield of ß-lactam strongly depends on the acidity of both the NH group and the CH adjacent to the carbonyl group. In addition, the basicity of the EGB plays an essential role on the course of the reaction. In the case of amide-type substrates (1a-c), the lower acidity of the NH group requires the use of the stronger EGB derived from EBMP for the reaction to take place (cfr. entries 1

and 2). If an activating group is present at pro-3 carbon atom, the yield of ß-lactam sharply decreases, probably due to the competitive dehydrohalogenation reaction (cfr.entries 3 and 4). In the case of hydroxamates-type substrates (1d-f), the stronger acidity of the NH group allows its ionization to be promoted as well, and more selectively, by the EGB derived from DBM. In fact, the yield of ß-lactam increases considerably by changing the PB from EBMP to DBM (cfr.entries 5 and 6), attaining very high values with the latter.

Some considerations about the mechanism of the ring-closure reaction can be drawn from the stereochemical outcome of the cyclization of threonine derivatives 1e,f. If the EGB arising from DBM is used to promote ring closure, only one, stereochemically pure ß-lactam is formed, according to a typical S_N2 mechanism (cfr.entries 7 and 8).[7] On the other hand, if the ionizing agent is the EGB derived from EBMP the cyclization occurs without stereochemical control and a mixture of two stereoisomeric ß-lactams cis-2e and trans-2e is obtained (entry 9). Clearly, in this case a different reaction pathway, probably an elimination-addition sequence, must also be involved. This would therefore represent the first example at our knowledge of ß-lactam synthesis through intramolecular, Michael-type addition involving $N-C_4$ bond formation.[8]

EXPERIMENTAL

Electrochemical apparatus as well as the cell and reference electrode used in controlled-potential electrolyses have been already described.[5] Melting points were taken upon a Tottoli apparatus, and are uncorrected. IR spectra were recorded for Nujol mulls on a Perkin Elmer 281B grating spectrophotometer. NMR spectra were recorded for solution in CD_3COCD_3 (unless otherwise stated), using a Varian EM-390 spectrometer and the chemical shift values are reported relative to Me_4Si as internal standard. Column chromatography (c.c.) was carried out on Merck silica gel 60 (70-230 mesh). Preparative layer chromatography (p.l.c.) was performed on Merck silica gel 60 pre-coated plates (layer thickness 2 mm). High-performance liquid chromatography (h.p.l.c.) analyses were carried out on a Perkin Elmer system made up from a Series 4 LC, an LC 85B spectrophotometric detector, an LC Autocontrol, and a Sigma 15 chromatography data station using a Merck Hibar RT-250-4 Lichrosorb Si 60 (7 m) column and a mixture hexane/ethyl acetate 9:1 as eluant. All new compounds gave satisfactory elemental analyses.

N-Benzyl-3-bromopropionamide (1a), m.p. 97-99°C (lit.,[9] m.p.102-104°C) and 3-Bromo-N-(4-methoxyphenyl)propionamide (1b), m.p. 107-109°C (lit.,[10] m.p.111-112°C) have been prepared according to standard procedures.

Compounds 1a-e have been synthesized from the corresponding amino acid via N-protection, amide bond formation and bromination.

N-Phtaloyl-DL-serine, m.p.148-150°C (lit.,[11] m.p.152°C) and N-Phtaloyl-L-threonine, m.p. 135-137°C; IR: $\bar{\nu}$ 3520, 3420, 1775, 1760, 1720, 1700 and 1610 cm^{-1}; NMR: δ 7.95 (s, 4H, aromatic) 4.85 (d, 1H, CH-N), 4.65 (m, 1H, CH-OH) and 1.39 ppm (d, 3H, CH_3), have been prepared as already described.[12]

Amide bond formation has been accomplished with carbodiimide method in the presence of 1-hydroxybenzotriazole.

3-Hydroxy-N-(4-methoxyphenyl)-2-phtalimidopropionamide, m.p.151-153°C; IR: $\bar{\nu}$ 3500, 3260, 1770, 1730, 1710, 1660 and 1600 cm^{-1}; NMR: δ 9.5-9.3 (bs, 1H, NH, disappears on deuteration), 7.90 (s, 4H, aromatic), 7.6-7.4 (m, 2H, aromatic), 7.0-6.8 (m, 2H, aromatic), 5.03 (t, 1H, CH-N), 4.6-4.2 (group of signals, 3H, CH_2-OH) and 3.75 ppm (s, 3H, OCH_3).

Benzyl 3-Hydroxy-2-phtalimidopropionohydroxamate, m.p.90-92°C; IR: $\bar{\nu}$ 3320, 1770, 1710, 1660 and 1620 cm^{-1}; NMR: δ 10.7-10.4 (bs, 1H, NH, disappears on deuteration), 7.90 (s, 4H, aromatic), 7.6-7.3 (m, 5H, aromatic), 5.1-4.8 (m, 1H, CH-N), 4.90 (s, 2H, CH_2Ph) and 4.5-4.1 ppm (group of signals, 3H, CH_2OH).

Benzyl (2S,3R)-3-Hydroxy-2-phtalimidobutyrohydroxamate, m.p.120-121°C; IR: $\bar{\nu}$ 3530, 3310, 1760, 1700 and 1690 cm^{-1}; NMR: δ 10.7-10.5 (bs, 1H, NH, disappears on deuteration) 7.90 (s, 4H, aromatic), 7.6-7.2 (m, 5H, aromatic), 4.90 (s, 2H, CH_2Ph),4.9-4.5 (group of signals, 2H, CH-CH), 4.25 (d, 1H, OH, disappears on deuteration) and 1.23 ppm (d, 3H, CH_3).

The bromination reaction has been accomplished with the adduct Ph_3P-Br_2, according to the literature.[13]

3-Bromo-N-(4-methoxyphenyl)-2-phtalimidopropionamide (1c), m.p.133-137°C (dec.); IR: $\bar{\nu}$ 3300, 1780, 1720, 1650 and 1600 cm^{-1}; NMR: δ 9.6-9.2 (bs, 1H, NH, disappears on deuteration), 7.97 (s, 4H, aromatic), 7.6-7.4 (m, 2H, aromatic), 7.0-6.8 (m, 2H, aromatic), 5.27 (t, 1H, CH-N, J=6Hz), 4.33 (d, 2H, CH_2Br, J=6Hz) and 3.75 ppm (s, 3H, OCH_3).

Benzyl 3-Bromo-2-phtalimidopropionohydroxamate (1d), m.p. 128-130°C; IR: $\bar{\nu}$ 1770, 1720 and 1650 cm^{-1}; NMR: δ 11.1-10.7 (bs, 1H, NH, disappears on deuteration), 7.90 (s, 4H, aromatic) 7.6-7.2 (m, 5H, aromatic), 5.3-5.0 (m, 1H, CH-N), 4.85 (s, 2H, CH_2Ph) and 4.4-4.1 ppm (m, 2H, CH_2Br).

Benzyl (2S,3S)-3-Bromo-2-phtalimidobutyrohydroxamate (1e), m.p.135-137°C; IR: $\bar{\nu}$ 3260, 1760, 1710, 1690 and 1670 cm^{-1} ; NMR ($CDCl_3$): δ 9.6-9.4 (bs, 1H, NH), 8.0-7.7 (m, 4H, aromatic), 7.5-7.2 (m, 5H, aromatic), 5.4-4.8 (group of signals, 2H, CH-CH), 4.93 (s, 2H, CH_2Ph) and 1.65 ppm (d, 3H, CH_3).

Compound 1f has been prepared from the corresponding 3-hydroxy derivative according to the literature.[4]

Benzyl (2S,3R)-3-Mesyloxy-2-phtalimidobutyrohydroxamate (1f), IR: $\bar{\nu}$ 1770, 1710 and 1610 cm^{-1}; NMR ($CDCl_3$): δ 8.0-7.7 (m, 4H, aromatic), 7.7-7.2 (m, 5H, aromatic), 5.60 (m, 1H, CH-OMs), 5.0-4.7 (s+d, 3H, CH_2Ph + CH-N), 2.87 (s, 3H, CH_3S) and 1.40 ppm (d, 3H, CH_3).

ELECTROSYNTHESIS OF ß-LACTAMS 2

General procedure. Preparative controlled-potential electrolyses have been carried out by stepwise addition of a DMF solution of the PB to 50 ml of a DMF - 0.1 M TEAP solution of the substrate. The molar ratio PB/substrate was 1.5:1, and the applied potential was -1.1V vs SCE in the case of bromopropanoate and -0.5V vs SCE in the case of bromomalonate. The electrolyses were stopped when the current had dropped from its initial value of 0.2A to 10mA. At the end of the electrolysis, the cathode was discarged and the solvent removed at 40-45°C under reduced pressure. The residue was extracted with Et_2O (5x50 ml), the insoluble solid was dissolved in H_2O and extracted with $CHCl_3$ (3x50 ml). The combined organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by p.l.c. or c.c. Parameters concerning the various electrolyses and analytical data of the synthesized ß-lactams are given below.

1-Benzyl-2-azetidinone (2a). The reduction of EBMP was carried out in the presence of 1a (0.30g). P.l.c. of the residue from the work-up of the reduction mixture using $CHCl_3$/AcOEt 9:1 as eluant afforded 2a[9] (0.14g, 70% yield). If DBM was used instead of EBMP no reaction occurred.

1-(4-Methoxyphenyl)-2-azetidinone (2b). The reduction of EBMP was carried out in the presence of 1b (0.51g). C.c. of the residue (0.6g) from the work-up of the reduction mixture using $CHCl_3$/AcOEt 9:1 as eluant afforded 2b (0.19g, 54% yield), m.p.100-101°C (lit.,[10] m.p.98-99°C).

1(4-Methoxyphenyl)-3-phtalimido-2-azetidinone (2c). The reduction of EBMP was carried out in the presence of 1c (0.46g).C.c. of the residue (0.44g) from the work-up of the reduction mixture using $CHCl_3$/Me_2CO 95:5 as eluant afforded 2c (0.036g, 10% yield); m.p.215-218°C; IR: $\bar{\nu}$ 1775, 1760 and 1710 cm^{-1}; NMR ($CDCl_3$): δ 8.1-7.7 (m, 4H, aromatic), 7.6-7.3 (m, 2H, aromatic), 7.1-6.9 (m, 2H, aromatic), 5.60 (t, 1H, H-3, J=4Hz), 4.05 (d, 2H, H-4, J=4Hz) and 3.85 ppm (s, 3H, OCH_3).

1-Benzyloxy-3-phtalimido-2-azetidinone (2d). **A)** The reduction of EBMP was carried out in the presence of 1d (0.55g). C.c. of the residue (0.31g) from the work-up of the reduction mixture using $CHCl_3$/Me_2CO 9:1 as eluant afforded 2d (0.16g, 36%); m.p.106-108°C; IR: $\bar{\nu}$ 1780, 1720 and 1610 cm^{-1}; NMR: δ 7.85 (s, 4H, aromatic), 7.6-7.3 (m, 5H, aromatic), 5.23 (dd, 1H, H-3), 5.10 (s, 2H, CH_2Ph) and 4.0-3.7 ppm (m, 2H, H-4).

B) The reduction of DBM was carried out in the presence of 1d (0.30g). Purification of the residue (0.34g) as above afforded 2d (0.23g, 96% yield).

1-Benzyloxy-4-methyl-3-phtalimido-2-azetidinone (2e) **A)** The reduction of DBM was carried out in the presence of 1e (0.16g). C.c. of the residue (0.22g) from the work-up of the reduction mixture using $CHCl_3$/Me_2CO 95:5 as eluant afforded cis-2e (0.12g, 93%); m.p.84-86°C (cyclohexane). IR: $\bar{\nu}$ 1770 and 1720 cm^{-1}; NMR: δ 7.95 (s, 4H, aromatic), 7.7-7.3 (m, 5H, aromatic), 5.20 (d, 1H, H-3, J=4.5 Hz), 5.10 (s, 2H, CH_2Ph), 4.4-4.1 (m, 1H, H-4) and 1.10 ppm (d, 3H, CH_3).

B) The reduction of DBM was carried out in the presence of 1f (0.22g). C.c. of the residue (0.25g) from the work-up of the reduction mixture using $CHCl_3$/Me_2CO 9:1 as

eluant afforded trans-2e (0.14g, 82% yield); m.p.94-96°C (cyclohexane); IR: $\bar{\nu}$ 1780, 1770 and 1720 cm^{-1}; NMR: δ 7.90 (s, 4H, aromatic), 7.7-7.3 (m, 5H, aromatic), 5.12 (s, 2H, CH_2Ph), 4.75 (d, 1H H-3, J=2 Hz), 4.4-4.2 (m, 1H, H-4) and 1.30 ppm (d, 3H, CH_3).

C) The reduction of EBMP was carried out in the presence of 1e (0.36g). H.p.l.c. analysis of the residue (0.28g) from the work-up of the reduction mixture showed the presence of a 2:1 mixture of trans-2e/cis-2e, in 65% overall yield.

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