Electrochemical Studies of β-Lactams; Part 2[1]. Electrosynthesis of β-Lactams via Bond Formation between C-3 and C-4

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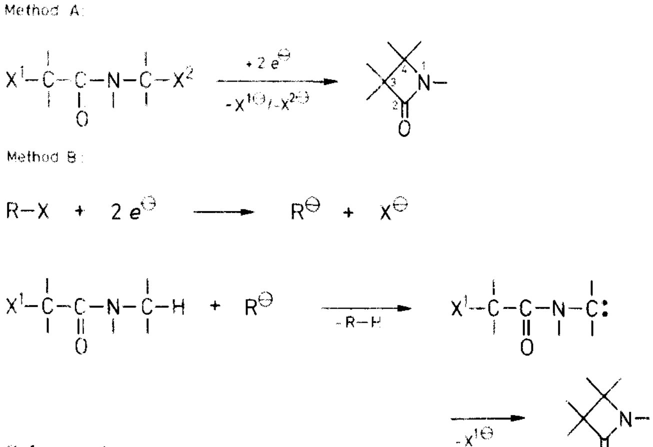
An electrochemical synthesis of β-lactams from readily available substituted haloacetamides is reported. The formation of an anionic site, which promotes cyclization by intramolecular nucleophilic substitution, occurs either directly on the substrate molecule by electrochemical reduction of a carbon-halogen bond, or following induction on the substrate itself by a base, also generated by electroreduction of a suitable probase. The procedure is characterized by high yields and versatility, and its compatibility with sensitive groups present in the substrate molecules.

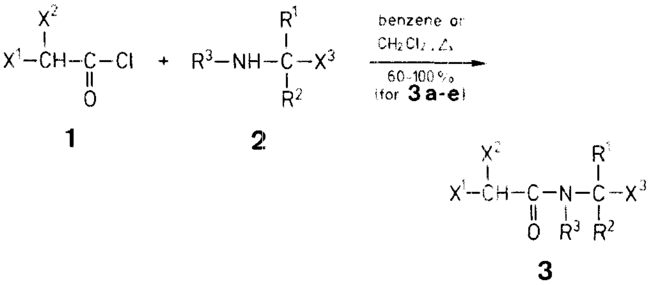
Several compounds, both natural and synthetic, containing the β-lactam nucleus are of clinical importance. The search for new products having broader or more selective pharmacological activities[2] has led to a considerable number of novel synthetic approaches to the β-lactam nucleus[3], with particular regard to regio- and stereoselectivity. However, to our knowledge no attempts have been performed to synthetize β-lactams by electrochemical methods, although it is known that regioselectivity is one of the distinguishing features of electroorganic syntheses. Thus, a given function can be selectively reduced or oxidized, even in the presence of complex functionalization of the molecule, providing that its reduction or oxidation potential differs by only ~ 200 mV from those of other electroactive groups[4]. Furthermore, electrosynthesis can be accomplished under mild experimental conditions (room temperature, aprotic solvent, neutral medium), thus not affecting many sensitive groups which may be present in the substrate molecule.

We have now attempted the electrosynthesis of β-lactams via bond formation between C-3 and C-4 of the azetidine ring (a typical chemical route to β-lactams[5]) using Methods A and B depicted in the general Scheme A.



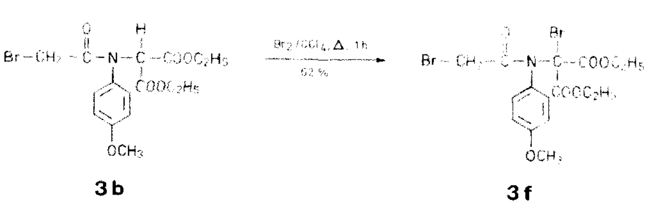
Scheme A

In Method A, a substituted acetamide having a halogen atom X^1 or X^2 and a suitable leaving group X^2 or X^1 is used as the starting material. Its electrochemical reduction leads to C-Hal bond cleavage to generate a carbanion which undergoes



1 2 3

3	X^1	X^2	X^3	R^1	R^2	R^3
a	Br	H	H	$-COOC_2H_5$	$-COOC_2H_5$	$-CH_2-COOC_2H_5$
b	Br	H	H	$-COOC_2H_5$	$-COOC_2H_5$	
c	Cl	H	H	$-COOC_2H_5$	$-COOC_2H_5$	
d	Cl	Cl	H	$-COOC_2H_5$	$-COOC_2H_5$	
e	Cl	H	H	$-COOCH_3$	H	$-CH_2-COOCH_3$
f	Br	H	Br	$-COOC_2H_5$	$-COOC_2H_5$	



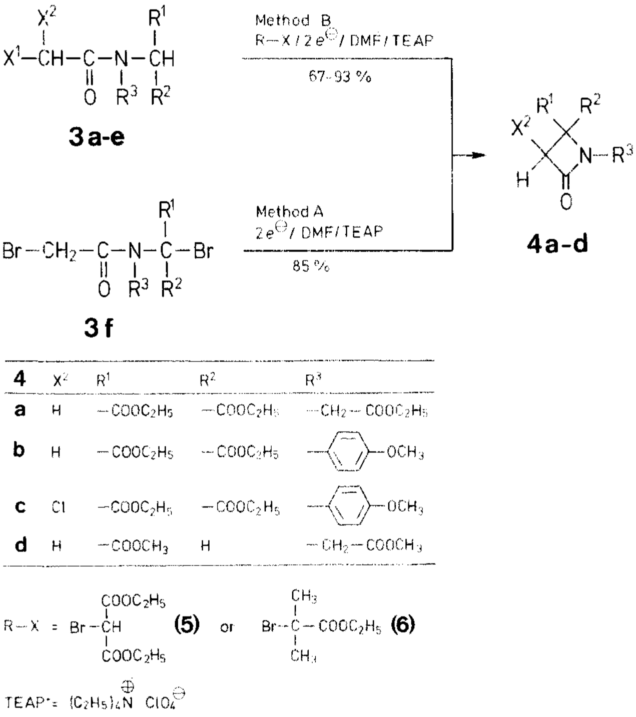
3b 3f

Scheme B

cyclization to the β-lactam by intramolecular nucleophilic substitution. The selectivity of the electrochemical reduction allows both X^1 and X^2 to be halogen atoms.

In Method B, the anionic site on the starting substituted acetamide (X^1 = leaving group) is generated by proton abstraction by a base $R^{\ominus}$ arising from the electrochemical reduction of a suitable probase R—X [6].

The substituted haloacetamides **3a–e** are prepared from halo- or dihaloacetyl chlorides **(1)** and suitable secondary amines (**2**, *N*-substituted aminomalonic esters or iminodiacetic esters); the substituted acetamide **3f** is obtained by bromination of **3b** (Scheme **B**). The electrolysis of compounds **3a–f** can be performed on a preparative scale whereby ring closure gives β-lactams **4a–d** in high to nearl quantitative yield (Scheme **C**).



Scheme C

The electrosynthesis of β-lactams **(4)** described here affords yields which are comparable to those obtained by the chemical route[5] and it has the advantage of being applicable to substrates such as **3c** having only one electron-withdrawing group at the C-atom pro-4 (with regard to azetidine numbering); substrates of this latter type have been found not to cyclise even in the presence of strong bases such as sodium alkoxide or ethanolic potassium hydroxide[7]. Therefore, our results show that electrochemical methods can be usefully employed in the synthesis of β-lactams.

Diethyl *N*-Bromoacetyl-*N*-ethoxycarbonylmethylaminomalonate (**3a**) is prepared according to Ref.[8].

Diethyl *N*-Haloacetyl-*N*-(4-methoxyphenyl)-aminomalonates 3b, c, d; General Procedure:

A mixture of diethyl 4-methoxyanilinomalonate[9] (2.0 g, 7.1 mmol) and bromoacetyl, chloroacetyl, or dichloroacetyl chloride (7.8 mmol) in anhydrous benzene (25 ml) is refluxed for 2 h, then cooled to room temperature, and shaken with saturated sodium hydrogen carbonate solution (50 ml). The organic layer is separated, and dried with sodium sulfate. The solvent is removed at reduced pressure to leave pure compound **3** as an oil. [Compound **3c** has already been prepared by an analogous procedure, but it was not fully characterized[9]].

Dimethyl *N*-Chloroacetyliminodiacetate (3e):

To a stirred mixture of dimethyl iminodiacetate hydrochloride (2.0 g, 10.1 mmol) and triethylamine (2.2 g, 22 mmol) in anhydrous dichloromethane (70 ml) is added dropwise chloroacetyl chloride (1.2 g, 10.6 mmol) and stirring is continued for 1 h at room temperature. The solvent is removed under reduced pressure, and the residue (2.1 g) purified by column chromatography on silica gel (Merck 70–230 mesh, 250 g) using benzene/ethyl acetate (1/1) as eluent. Compound **3e** is recovered from the first eluted fraction; yield: 1.45 g (60 %)

Diethyl *N*-Bromoacetyl-*N*-(4-methoxyphenyl)-aminobromomalonate (3f):

A stirred solution of compound **3b** (0.40 g, 1 mmol) in tetrachloromethane (2 ml) is maintained under reflux and irradiated with a 100 W lamp. Under these conditions, a solution of bromine (0.20 g, 1.1 mmol) in tetrachloromethane (10 ml) is added dropwise and stirring continued for 1 h. The solvent is removed under reduced pressure and the residue purified by column chromatography on silica gel (50 g) using benzene/ethyl acetate (9/1) as eluent. Compound **3f** (0.30 g) is recovered from the first eluted fraction.

Table 1. Substituted Haloacetamides (**3**) prepared

Product	Yield[a] [%]	Molecular formula[b]	M.S.[c] *m/e* (M⁺)	I.R. (Film)[d] ν[cm⁻¹]	¹H-N.M.R. ($CDCl_3/TMS_{int}$)[e] δ[ppm]
3b	100	$C_{16}H_{20}BrNO_6$ (402.25)	401	1760, 1745, 1680, 1610, 1590, 1510	7.5–7.3 (m, 2H_{arom}); 6.9–6.6 (m, 2H_{arom}); 5.30 (s, 1 H, CH); 4.12 (q, 4 H, 2OCH_2); 3.83 (s, 3 H, OCH_3); 3.65 (s, 2 H, $BrCH_2$); 1.20 (t, 6 H, 2CH_3)
3c	100	$C_{16}H_{20}ClNO_6$ (357.8)	357	1770, 1750, 1690, 1610, 1590, 1510	7.5–7.2 (m, 2H_{arom}); 6.9–6.6 (m, 2H_{arom}); 5.48 (s, 1 H, CH); 4.20 (q, 4 H, 2OCH_2); 3.87 (s, 2 H, $ClCH_2$); 3.80 (s, 3 H, OCH_3); 1.15 (t, 6 H, 2CH_3)
3d	100	$C_{16}H_{19}Cl_2NO_6$ (392.2)	391	1770, 1750, 1700, 1610, 1590, 1510	7.6–7.4 (m, 2H_{arom}); 7.0–6.8 (m, 2H_{arom}); 5.90 (s, 1 H, Cl_2CH); 5.30 (s, 1 H, N—CH); 4.20 (q, 4 H, 2OCH_2); 3.85 (s, 3 H, OCH_3); 1.20 (t, 6 H, 2CH_3)
3e	60	$C_8H_{12}ClNO_5$ (237.6)	237	1750, 1670	4.30 (s, 2 H, N—CH_2); 4.25 (s, 2 H, N—CH_2); 4.15 (s, 2 H, $ClCH_2$); 3.85 (s, 3 H, OCH_3); 3.80 (s, 3 H, OCH_3)
3f	62	$C_{16}H_{19}Br_2NO_6$ (481.15)	479	1770, 1740, 1700, 1610, 1590, 1510	7.4–7.2 (m, 2H_{arom}); 6.9–6.7 (m, 2H_{arom}); 4.10 (q, 4 H, 2OCH_2); 3.83 (s, 3 H, OCH_3); 3.60 (s, 2 H, $BrCH_2$); 1.20 (t, 6 H, 2CH_3)

[a] Yield of pure, isolated products.

[b] Satisfactory microanalyses obtained: C, ±0.40; H, ±0.20; N, ±0.15.

[c] Recorded at 70 eV on a Hewlett-Packard 5980 A low-resolution mass spectrometer. The *m/e* values refer to the most abundant isotope of the halogen. Correct patterns for isotopic abundances are observed.

[d] Recorded on a Perkin-Elmer model 177 spectrophotometer

[e] Recorded on a Varian EM-390 spectrometer.

Table 2. β-Lactams (**4**, 2-Oxoazetidines) prepared

Product[a]	Substrate	Method	R–X[b]	E[c] [Volt]	Yield[d] [%]	Molecular Formula[e]	M.S.[f] m/e (M^+)	I.R. (film)[f] ν[cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[f] δ[ppm]
4a	3a	B	**5**	−0.45	90	Ref.[8]			
4b	3b	B[h]	**5**	−0.45	88	$C_{16}H_{19}NO_6$ (321.3)	321	1775, 1745, 1615, 1590, 1520	7.6–7.4 (m, 2H_{arom}); 6.9–6.7 (m, 2H_{arom}); 4.30 (q. 4H, 2x OCH_2); 3.75 (s, 3H, OCH_3); 3.17 (s, 2H. 3-H); 1.23 (t, 6H, 2CH_3)
	3c	B	**5**	−0.5	93				
	3f	A	–	−0.45	85				
4c	3d	B	**5**	−0.5	84	$C_{16}H_{18}ClNO_6$ (355.8)	355	1790, 1750, 1610, 1590, 1520	7.6–7.3 (m, 2H_{arom}); 7.0–6.7 (m, 2H_{arom}); 5.48 (s, 1H, 3-H); 4.40 (q. 2H, OCH_2); 4.30 (q. 2H, OCH_2); 3.76 (s. 3H, OCH_3); 1.30 (t, 3H, CH_3); 1.20 (t, 3H, CH_3)
4d	3e	B	**6**	−1.0	67	$C_8H_{11}NO_5$ (201.2)	201	1780, 1750	4.48 (dd, 1H, $J_{4,3cis}$ = 6 Hz, $J_{4,3trans}$ = 3 Hz, 4-H); 4.31 (d, 1H, J_{gem} = 18 Hz, N—CH_2); 3.87 (d, 1H, N—CH_2); 3.78 (s, 3H, OCH_3); 3.73 (s, 3H, OCH_3); 3.38 (dd, 1H, $J_{3,3}$ = 15 Hz, 3-H); 3.05 (*dd*, 1H, 3-H)

[a] Oils.
[b] **5** = diethyl bromomalonate; **6** = ethyl 2-bromo-2-methylpropanoate.
[c] versus SCE.
[d] Isolated, pure product.
[e] Satisfactory microanalyses obtained: C. ±0.22; H. ±0.13; N, ±0.14.
[f] For recording of spectra, see Table 1.
[g] The synthesis of **4b** has been reported without characterization of the product[9].
[h] In acetonitrile.

Electrocyclization of Substituted Acetamides 3 to β-Lactams (4); General Procedure:

Electrolysis Cell: as described in Ref.[10].

Reference electrode: Calomel-type as described in Ref.[11]; its potential: −0.029 V vs. SCE (does not change during the experiment). All potential values are referred to this electrode.

Cathode: Mercury pool cathode, maintained under nitrogen.

Catholyte: Dimethylformamide containing tetraethylammonium perchlorate at a concentration of 0.1 molar. The catholyte is deaerated before use and pre-electrolyzed at the experiment potential; temperature of cathode and catholyte: 20° ± 0.1 °C. [Other aprotic solvents such as acetonitrile can be used in place of dimethylformamide, the course and the yield of the electrolysis not being affected]. The solvent and the supporting electrolyte are purified as described in Ref.[10].

Performance:

Method A: The electrolysis is carried out by the stepwise addition of a solution of compound **3f** (0.48 g, 1 mmol) in dimethylformamide (10 ml) to the catholyte (50 ml). Each portion (2 ml) is added when the current value has dropped to that mesured at the end of the pre-electrolysis. At the end of the electrolysis, the catholyte solution is separated, the solvent removed at 40–45 °C under reduced pressure, and the residue extracted with ether (5 × 50 ml). The precipitate is filtered off, and the filtrate evaporated to constant weight under vacuum. Column chromatography of the residue (0.32 g) on silica gel (30 g) using benzene/ethyl acetate (9/1) as eluent gives **4b**; yield: 0.27 g (85%).

Method B: The electrolysis is carried out by the stepwise addition of a solution of the probase R—X [diethyl bromomalonate (**5**) or ethyl 2-bromo-2-methylpropanoate (**6**); 1.1–2 molar equivalents] in dimethylformamide (5 ml) to a solution of the haloacetamide **3** (1–2 mmol) in the catholyte (50 ml). Each portion (1 ml) is added when the current has dropped to that measured at the end of the pre-electrolysis. At the end of the electrolysis, the catholyte solution is separated, the solvent removed at 40–45 °C under reduced pressure, and the residue extracted with ether (5 × 50 ml). The precipitate is filtered off, and the filtrate evaporated to constant weight under vacuum. The residue is column-chromatographed on silica gel (100 g/1 g of residue) using benzene/ethyl acetate (9/1) as eluent to give the β-lactam **4** as an oily product.

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