Electrodic Cleavage of the N–S Bond in *N*-Tosylcarboxamides. A New Entry to *N*-Unsubstituted Lactams

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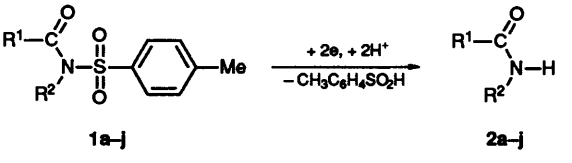
The electrochemical reduction of different types of *N*-tosylcarboxamides under various experimental conditions has been investigated. It has been found that in all instances the N–S bond is selectively cleaved with respect to the N–C bond, thus providing a new method for the deblocking of the tosyl group from such substrates. As a consequence, a two-step electrochemical synthesis for *N*-unsubstituted lactams is now available, which has been simplified to a one-pot procedure in the case of synthetically important azetidin-2-ones.

Electrochemical methods can be usefully employed in organic synthesis when a single group present in polyfunctional molecules must be selectively modified. In fact, among the peculiar features of these methods are the demand for very mild reaction conditions and high regio- and/or chemo-selectivity, the latter being easily achieved by simply changing the applied potential. These characteristics make electrochemical methods a very attractive alternative to conventional procedures, for example in the deprotection stage of protection–deprotection sequences of complex and/or chiral molecules. Several studies on this topic have been undertaken and exhaustively reviewed.[1,2] In particular, the electrochemical removal of the tosyl group by direct reduction at the cathode and/or homogeneous phase redox catalysis from sulfonylated alcohols,[3] phenols,[3e] and amines[3a,3e,4,5] has been investigated. To our knowledge, however, no studies have been carried out on *N*-tosylcarboxamides, even if sulfonamides and carboxamides have been investigated and found to display very similar cathodic behaviour.[4]

In connection with other work, we were interested in the selective deblocking of the tosyl group from *N*-tosyl lactams, whose electrosynthesis from ω-bromo-*N*-tosylalkanamides we have recently disclosed,†[,6] to the corresponding, synthetically important *N*-unsubstituted lactams. Although the available data[4] were discouraging, as the usual chemical methods of cleavage of the N–S bond can hardly be considered expedient in solving the problem, we have verified the possibility of performing such cleavage electrochemically. In addition to tosyllactams, representative examples of other classes of *N*-tosylcarboxamides have also been taken into account (Scheme 1), which have established the scope and generality of this new electrochemical deblocking method.



1a–j **2a–j**

a $R^1 = CH_3(CH_2)_3$, $R^2 = H$
b $R^1 = CH_3(CH_2)_3$, $R^2 = Me$
c $R^1 = CH_3(CH_2)_2$, $R^2 = H$
d $R^1 = Et$, $R^2 = H$
e $R^1 = Me$, $R^2 = H$
f $R^1 = Ph$, $R^2 = H$
g $R^1 = Ph$, $R^2 = Me$
h $R^1R^2 = (CH_2)_2$
i $R^1R^2 = (CH_2)_3$
j $R^1R^2 = (CH_2)_4$

Scheme 1

Results and discussion

Compounds **1a**, **1b** and **1h** were selected as model compounds of secondary, tertiary and cyclic amides for voltammetric and coulometric measurements as well as for establishing the optimum electrolysis conditions. All three substrates show a single reduction peak which occurs in the range −2.0 to −2.2 V (*vs.* SCE) (Table 1). This is a significantly less negative value than that measured in the case of tosylamides[3a,3e,4,5] and results in a useful simplification of the electrochemical procedure. The addition of CH_3CO_2H as proton donor leads to no change in the peak potential value for any substrate, whereas although the current intensity value is unchanged for the secondary amide **1a** it is doubled for the tertiary (**1b**) and cyclic (**1h**) derivatives, as is the n_{app} value (number of Faraday per mol of substrate) measured for all three substrates. As a whole, these data point to a two-electron process responsible for the reduction peak involving, when no exogenous acid is added, an autoprotonation reaction of anionic intermediates by the starting material. Some aspects of the electrochemical behaviour of the substrates under study, if compared with that of sulfonamides,[4,5] must be explained. In fact, Kossai[5] showed that, contrary to our findings with tertiary tosylcarboxamides, *N*,*N*-disubstituted tosylamides undergo two-electron cleavage of the N–S bond without intervention of

Table 1 Voltammetric and coulometric data for solutions of **1a**, **1b** and **1h** in DMF–0.1 mol dm^{-3} TEAP (c 5 × 10^{-3} mol dm^{-3}, v 0.2 V s^{-1}, Hg cathode)

Substrate	$-E_p$/V	i_p/μA	i_p^a/μA	n_{app}	n^a_{app}
1a	2.19	20.8	20.9	1.0	2.0
1b	2.07	27.7	58.0	1.1	2.1
1h	2.02	24.8	52.8	0.9	2.0

[a] Value measured after addition of equimolar amount of acetic acid.

† The synthesis of *N*-tosyl-β-lactams through halogen-induced oxidative cyclization of *N*-tosyl-β,γ-dehydrocarboxamides has also been reported.[7]

Table 2 Electrochemical reduction of *N*-tosylamides **1a**, **1b**, **1h**

Entry	Substrate	Cathode	Solvent	Potential (V) or current density (mA cm^{-2})	Yield of **2** (%)[a]
1	**1a**	Hg	DMF	−2.3	50
2	**1a**	Hg	DMF–H_2O	−2.3	48
3	**1a**	Hg	DMF–CH_3CO_2H	−2.3	98
4	**1a**	Hg	DMF–CH_3CO_2H	10	73[b]
5	**1a**	Hg	CH_3CN–CH_3CO_2H	10	80[b]
6	**1a**	C	DMF–CH_3CO_2H	−2.3	50
7	**1a**	C	DMF–CH_3CO_2H	10	47[b]
8	**1a**	Cu	DMF–CH_3CO_2H	10	4[b]
9	**1a**	Ni	DMF–CH_3CO_2H	10	11[b]
10	**1a**	Pb	DMF–CH_3CO_2H	10	67[b]
11	**1a**	Pb[c]	DMF–CH_3CO_2H	10	52[b]
12	**1a**	C[c]	DMF–CH_3CO_2H	10	45[b]
13	**1b**	Hg	DMF	−2.3	47
14	**1b**	Hg	DMF–CH_3CO_2H	−2.3	98
15	**1b**	Hg	DMF–CH_3CO_2H	10	70[b]
16	**1h**	Hg	DMF–CH_3CO_2H	−2.2	95
17	**1h**	Hg	DMF–CH_3CO_2H	10	89[b]
18	**1h**	Hg	DMF–CH_3CO_2H	15	84[b]
19	**1h**	Hg	DMF–CH_3CO_2H	20	82[b]
20	**1h**	C	DMF–CH_3CO_2H	10	36[b]

[a] GC analysis. [b] Analysis after 2 F mol^{-1}. [c] Undivided cell, Mg anode.

Table 3 Electrodeprotection of *N*-tosylamides **1a–j** in DMF–0.1 mol dm^{-3} TEAP, containing CH_3CO_2H (2 mol per mol of substrate); Hg cathode, I = 10 mA cm^{-2}

Substrate	Yield of **2** (%)[a]
1a	73
1b	70
1c	65
1d	68
1e	78
1f	37[b]
1g	92[b]
1h	89
1i	86
1j	96

[a] GC analysis after 2 F mol^{-1}. [b] HPLC analysis after 2 F mol^{-1}.

an autoprotonation reaction in aprotic medium as well, so that the addition of proton donors promotes no change in either the current intensity or n_{app} values. The different behaviour can be ascribed to the presence of acidic hydrogens at the α-position with respect to the amide carbonyl group in both **1b** and **1h**, which make their autoprotonation in aprotic medium possible. On the other hand, the addition of proton donors increases (or doubles) the i_p and n_{app} values of *N*-substituted tosylamides, whereas only the n_{app} (but not i_p) value of **1a** is modified by addition of acetic acid. It appears that in the reduction of **1a** the protonation by the exogenous acid cannot compete effectively with the autoprotonation reaction at the electrode surface (as shown by voltammetry) as it does instead in the bulk of the solution (as shown by coulometry). This behaviour is not surprising since a pK_a of approximately 2.5 has been measured in the case of α-amino-*N*-tosylcarboxamides.[13]

As mentioned, **1a**, **1b** and **1h** were also used to establish the optimum electrolysis conditions (Table 2). According to the voltammetric and coulometric data, controlled-potential reduction of **1a** in aprotic medium gives deprotected amide **2a** in only 50% yield. The remainder of starting material **1a**, together with toluene-*p*-sulfinic acid formed by the cleavage of N–S bond, is recovered unchanged after acidic work-up. Clearly, the substrate itself behaves as a proton donor rendering the conjugated base electroinactive at the working potential, so that only half of the substrate undergoes the desired two-electron reduction. Water is unable to compete with the substrate as proton donor (entry 2), whereas the addition of acetic acid raises the yield of **2a** to 98% (entry 3). If the electrolysis is carried out under constant current conditions, the yield of **2a** is still good using either DMF or CH_3CN as solvent (entries 4,5). The effectiveness of solid electrodes as cathode in both controlled-potential and constant current electrolysis was also tested and a sharp effect depending on the nature of the electrode material on the course of the cleavage reaction was found. Lead and vitreous carbon were still efficient, whereas unsatisfactory yields of deprotected amide were obtained using nickel and copper electrodes (entries 6–10). A similar trend in the effectiveness of the electrode material was found by Iwasaki[5] in the deblocking of *N*-tosyl derivatives of amino acids and peptides. To further simplify the system, the electrolysis was also performed in diaphragmless cells, using magnesium as sacrificial anode and lead or vitreous carbon as cathode (entries 11, 12). In both cases, the faradaic yield decreases, but the small difference is surely compensated by the remarkable simplicity of the apparatus used. Quite similar results were obtained in the case of tertiary tosylamide **1b**: as for **1a**, the conversion ceased at 50% if acetic acid was not added to the solution and the yield of **2b** was still good with constant current electrolysis (entries 13–15).

The deprotection of β-lactam **1h** was then checked using the best conditions found for **1a**, **b** (entries 16, 17). Owing to the synthetic interest in such classes of compounds, additional runs were also performed on **1h**. At higher current densities, the yield of **2h** is still quite good at 20 mA cm^{-1}, which is an acceptable value for industrial scale processes (entries 18, 19). On the contrary, the use of vitreous carbon as cathode failed to give satisfactory results (entry 20).

The electrodeprotection procedure was extended to a number of representative *N*-tosyl-amides and -lactams to establish the generality of the method. Compounds **1a–j** were electrolysed under conditions considered to be a good compromise between simplicity of operation and product yields (Table 3). All compounds, except **1f**,* undergo detosylation in good to

* The low conversion yield of **1f** must be ascribed to the ineffectiveness of acetic acid as proton donor toward this substrate, as ascertained by the recovery of starting **1f** (48%) from acidic work-up of the reduction mixture.

excellent yields, showing that the electrochemical cleavage of the sulfonyl group can be advantageously applied to a large variety of tosylcarboxamides.

Finally, a 'two-step, one-pot' procedure for the synthesis of **2h** has been attempted (see Experimental section). Two-electron reduction of diethyl bromomalonate affords the electrogenerated base (EGB) diethyl malonate anion. Following acid–base reaction with the EGB and intramolecular nucleophilic displacement of bromine, 3-bromo-*N*-tosylpropanamide cyclizes to **1h**. The electrodeprotection of the latter to **2h** can be carried out *in situ* after addition of a proton donor by simply switching the value of the applied potential. The overall yield of **2h** (84%) appears very promising for a preparative scale application of the process.

Conclusions

In spite of the quite similar cathodic behaviour of carboxamides and sulfonamides, the electrochemical reduction of *N*-tosylcarboxamides promotes selective two-electron cleavage of the N–S bond to afford deprotected carboxamides and toluene-*p*-sulfinic acid. The method has been attempted for a number of tosylcarboxamides, including synthetically important lactams and appears to have wide generality. Provided that a suitable proton donor is added, high yields of amide can be attained (except for aromatic secondary derivatives) even under experimental conditions suitable for preparative scale synthesis. Azetidin-2-one can be prepared in 84% overall yield from the readily available 3-bromo-*N*-tosylpropionamide through an electrochemical 'two-step, one-pot' procedure. The findings of the present study show, once again, that electrochemical methods should be considered for the selective transformation of polyfunctional molecules. Furthermore, they can allow different reaction pathways, with respect to conventional chemical methods, thus widening the synthetic strategies available to the organic chemist.

Experimental

General.—Voltammetric measurements were carried out at an Amel 498 sessile mercury drop electrode or an Amel vitreous carbon microelectrode with an Amel 471 multipolarograph. Coulometry and controlled-potential electrolysis were carried out with an Amel 552 potentiostat equipped with an Amel 721 integrator. Three-compartment cells of the type previously described[8] were used for these techniques; the cathode was a mercury pool or a disk of the appropriate solid material (area 12 cm^2), the counter electrode was a cylindrical platinum gauze, and the reference electrode was of the calomel type described by Fujinaga;[9] its potential was −0.040 V *vs.* SCE (saturated calomel electrode). Constant current electrolyses were carried out with the same apparatus using divided or diaphragmless cells; in the latter case a magnesium rod (φ 0.8 cm, *h* 3 cm) was used as anode. *N*,*N*-Dimethylformamide (DMF; Riedel de Häen spectranal) and tetraethylammonium perchlorate (TEAP; Fluka) were purified as previously described;[8] CH_3CN (Erba RS) was used without further purification. All the experiments were carried out at 20.0 ± 0.1 °C. HPLC analyses were carried out on a Perkin-Elmer system made up of a Series 4 LC, an LC 85B spectrophotometric detector, an LC Autocontrol and a Sigma 15 chromatography data station, using a Merck LiChrocart RP-18 (250–4, 7 μm) column and a mixture H_2O–CH_3CN as eluent in linear gradient from 9:1 to 2:8 in 25 min at a flow rate of 1 cm^3 min^{-1}. GC analyses were carried out with a Perkin-Elmer 8500 GC using a J and W fused silica megabore DB-WAX (30 m) column in the temperature range 130–160 °C, depending on the nature of the amide. Quantitative HPLC and GC analyses were performed with the internal standard method. M.p.s were taken with a Tottoli apparatus, and were uncorrected. IR spectra were recorded with a Perkin Elmer 281B grating spectrophotometer as Nujol mulls; ^1H NMR spectra were recorded for solution in $CDCl_3$ using a Varian EM-390 spectrometer and the chemical shifts were reported relative to Me_4Si as internal standard. All reaction products were identified by comparison with authentic samples. All new compounds gave satisfactory elemental analyses (C ± 0.3%; H ± 0.2%; N ± 0.2%).

Chemistry.—Compounds **1a**, **c–f** were prepared from the correspondent acid anhydride and toluene-*p*-sulfonamide, according to the literature.[10]

N-*Tosylvaleramide* **1a**: m.p. 87–88 °C (AcOEt–cyclohexane); ν_{max}/cm^{-1} 3290, 1695 and 1590; δ_H 0.86 (3 H, t, CH_3), 1.8–1.0 (4 H, m, 2 × CH_2), 2.30 (2 H, t, CH_2CO), 2.46 (3 H, s, CH_3), 7.40 (2 H, d, aromatic), 8.10 (2 H, d, aromatic) and 9.7–8.5 (1 H, br s, NH).

N-*Tosylbutyramide* **1c**: m.p. 82–83 °C (lit.,[10] m.p. 82–83 °C).

N-*Tosylpropionamide* **1d**: m.p. 110–111 °C (lit.,[10] m.p. 111–112 °C).

N-*Tosylacetamide* **1e**: m.p. 136–137 °C (lit.,[11] m.p. 137 °C).

N-*Tosylbenzamide* **1f**: m.p. 145–146 °C (lit.,[10] m.p. 147 °C).

N-*Methyl*-N-*tosylvaleramide* **1b**. A mixture of **1a** (1 g, 3.9 mmol), CH_3I (4.3 g, 30 mmol) and Na_2CO_3 (0.9 g, 8 mmol) in CH_3CN (40 cm^3) was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, water was added to the residue and the mixture extracted with $CHCl_3$ (3 × 50 cm^3). Removal of the solvent from the combined organic layers left **1b**, m.p. 37–39 °C; ν_{max}/cm^{-1} 1695 and 1590; δ_H 0.86 (3 H, t, CH_3), 1.8–1.0 (4 H, m, 2 × CH_2), 2.46 (3 H, s, CH_3), 2.70 (2 H, t, CH_2CO), 3.36 (3 H, s, NCH_3), 7.40 (2 H, d, aromatic) and 7.87 (2 H, d, aromatic). N-*Methyl*-N-*tosylbenzamide* **1g** was prepared by treating *N*-methyltosylamide with benzoyl chloride according to the literature.[12] M.p. 59–60 °C (lit.,[12] m.p. 58 °C). Lactams **1h–j** were prepared by electrochemically induced cyclization of the corresponding ω-bromo-*N*-tosylalkanamides.[6] All reaction products were either commercially available or synthesized by usual methods.

Electrochemistry.—Typically, the electrodeprotection was carried out on solutions (60–80 cm^3) of the depolarizer (0.8–1.0 g) in DMF (or CH_3CN) containing TEAP (0.1 mol dm^{-3}) as supporting electrolyte and, if required, water (5% v/v) or acetic acid (2 mol per mol of substrate). Representative procedures for reductions carried out both at controlled-potential and constant current are as follows.

Controlled-potential electrolysis of **1a** *at* Hg *pool cathode.* The electrolysis was carried out by addition of **1a** (1.0 g, 3.9 mmol) in five aliquots to DMF–0.1 mol dm^{-3} TEAP (60 cm^3) containing CH_3CO_2H (0.47 g, 7.8 mmol), previously de-gassed and pre-electrolysed at the working potential (−2.3 V). Each portion was added when the value of the current had dropped to the value measured at the end of the pre-electrolysis.

At the end of the electrolysis, the catholyte was separated from the cathode and a sample taken for HPLC and/or GC analysis. The solvent was removed at 40–45 °C under reduced pressure, water (100 cm^3) was added to the residue and the mixture was extracted with $CHCl_3$ (5 × 50 cm^3). The combined organic layers were dried (Na_2SO_4), and the solvent evaporated to constant weight under vacuum to give **2a** (0.38 g, 98% yield). The aqueous layer was acidified (1 mol dm^{-3} H_2SO_4) and extracted with $CHCl_3$ (3 × 50 cm^3). The combined organic layers were dried (Na_2SO_4), and the solvent evaporated to constant weight under vacuum to give toluene-*p*-sulfinic acid (0.52 g, 85% yield). GC analysis of the crude reduction mixture confirmed the yield of **2a**.

Constant current electrolysis of **1a** *at* Hg *pool cathode.* A

previously de-gassed solution of **1a** (1.0 g, 3.9 mmol) in DMF–0.1 mol dm^{-3} TEAP (60 cm^3) containing CH_3CO_2H (0.47 g, 7.8 mmol) was electrolysed under a constant current flow (I = 10 mA cm^{-2}). After 2 F mol^{-1} had been expended, the catholyte was separated and worked-up as before. The NMR spectrum of the residue from $CHCl_3$ extracts showed the presence of **2a** and **1a** in 7:2 molar ratio. The yields determined by GC (**2a**) and HPLC (**1a**) analysis of the crude reduction mixture were: **2a** 73% and **1a** 21%. The residue from $CHCl_3$ extracts of the acidified aqueous solution was toluene-*p*-sulfinic acid (0.39 g, 64% yield).

One-pot synthesis of azetidin-2-one **1h**. A solution of 3-bromo-*N*-tosylpropionamide[6] (0.21 g, 0.7 mmol) in DMF–0.1 mol dm^{-1} TEAP (70 cm^3), previously de-gassed and maintained under N_2, was pre-electrolysed at –0.7 V at a Hg pool cathode. Diethyl bromomalonate (0.17 g, 0.7 mmol) was added to the catholyte and the electrolysis carried out at the same potential until the current had dropped to the value measured at the end of the pre-electrolysis. Acetic acid (0.09 g, 1.5 mmol) was added to the catholyte, the potential adjusted to −2.2 V, and the electrolysis carried out until the current had again dropped to the value measured at the end of the pre-electrolysis. GC analysis of the reduction mixture shows the presence of **1h** (84% yield).

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