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ELECTROOXIDATIVE REARRANGEMENT OF TOSYLAMINO GROUP: FACILE SYNTHESIS OF α-AMINO ALDEHYDES FROM PRIMARY AMINES[1]

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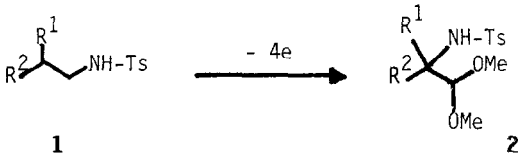
Abstract: Anodic oxidation of primary N-tosylamines in methanol containing halide ion gave α-(N-tosylamino) aldehyde dimethyl acetals, synthetically useful intermediates equivalent to α-amino aldehydes.

α-Amino aldehydes are versatile intermediates in the synthesis of nitrogen-heterocycles,[2] though their synthesis is not always easy.[3] We wish to report a facile synthetic method of α-tosylamino acetals **2**, equivalent to α-amino aldehydes, from primary N-tosylamines **1** utilizing anodic oxidation.

This novel method is interesting from not only a synthetic but also a mechanistic viewpoint, since the anodic oxidation involves a hitherto unknown oxidative rearrangement of tosylamino group as shown in eq. 1.



1 **2** (1)

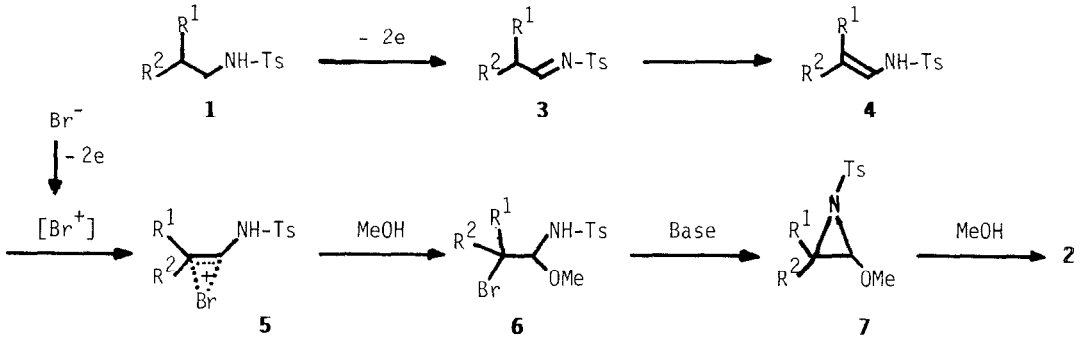
The anodic oxidation of **1** was carried out as follows: Into a cell equipped with a platinum anode (20 mm x 20 mm) and a carbon rod cathode (8 mmφ) was added a solution of **1** (1 mmol) in methanol (25 ml) containing KBr (0.5 mmol) and KOH (0.5 mmol). A constant current was passed through the solution externally cooled with a water bath. After 15-40 *F*/mol of electricity was passed, the solution was poured into water, and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ was evaporated *in vacuo* to give a residue. It was then subjected to column chromatography to give **2** in the yields shown in Table 1.

Although the exact mechanism is not yet clear, the following Scheme 1 reasonably explains the oxidative rearrangement of **1** to **2** (Scheme 1); anodic oxidation of **1** produces N-tosylimino derivatives **3**, which subsequently isomerize to α,β-unsaturated N-tosylamines **4**. The electrophilic attack of anodically generated bromine positive species $[Br^+]$[4] on **4** followed by the attack of methanol on the resulting bromonium ions **5** yields **6**. The final products **2** will be formed through aziridine intermediates **7** generated by the reaction of **6** with base.[5]

Table 1. Anodic Oxidation of **1** in the Presence of Bromide Ion[a]

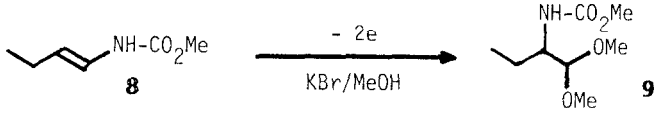
Run	Tosylamides **1** R^1	R^2	Electricity Passed (F/mol)	Products **2** R^1	R^2	Isolated Yields (%)
1	H	H	20	H	H	59
2	Me	H	20	Me	H	61
3	Et	H	20	Et	H	61
4	i-Pr	H	40	i-Pr	H	50
5	Et	Me	15	Et	Me	52

[a] Reaction conditions; **1** (1 mmol), KBr (0.5 mmol), KOH (0.5 mmol), MeOH (25 ml).



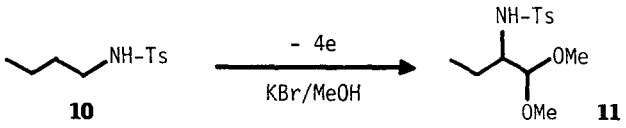
Scheme 1

Although the intermediates described in Scheme 1 were not able to be isolated, the proposed mechanism may be supported by the fact that the anodic oxidation of α,β-unsaturated N-methoxycarbonylamine **8**[6] under conditions similar to the electrochemical oxidation of **1** to **2** gave **9** (eq. 2).



(2)

The proposed mechanism is also supported by the results shown in Table 2 which indicates that the yield of **11** increased with the presence of base (run 2) and that halide ion, especially bromide ion, was essential for the satisfactory result.



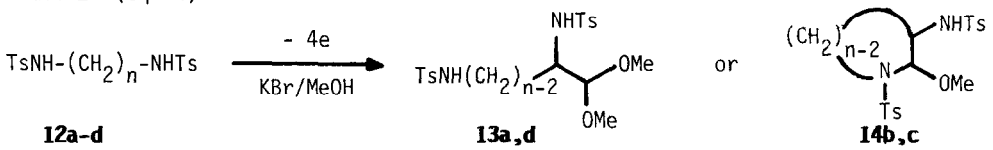
10 **11** (3)

Table 2. Effect of Supporting Electrolyte and KOH on the Yields of **11** from **10**[a,b]

Run	Supporting Electrolyte	With KOH (0.5 eq.)	Without KOH
1	KCl	14 (19)	—
2	KBr	65 (88)	38 (68)
3	KI	21 (100)	—
4	Et_4NOTs	0	0

[a] Figures in parenthesis indicate the yields based on consumed starting materials.
[b] Glc yields when 10 *F*/mol of electricity was passed.

This oxidative tosylamino group rearrangement was found to be applicable to α,ω-bistosylamides **12** (eq. 4).



(4)

12a-d

a; n=3
b; n=4
c; n=5
d; n=6

13a,d

13a; 62%
—
—
13d; 7%

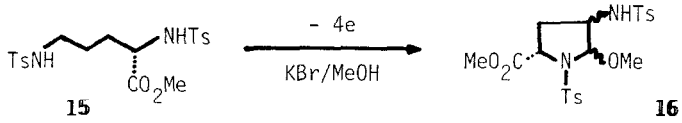
14b,c

—
14b; 91%
14c; 79%
—

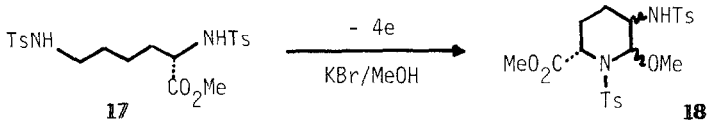
The anodic oxidation of **12a** and **12d** yielded oxidatively rearranged products (**13a** and **13d**), but **12b** and **12c** gave cyclized products (**14b** or **14c**).[7] However, **14b** and **14c** were also oxidatively rearranged products similar to **13a** and **13d**, since **14b** and **14c** were formed by intramolecular attack of the ω-tosylamino group on the acetal carbon.

The oxidative cyclization similar to the conversion of **12b** and **12c** to **14b** and **14c** appears to be common for α,ω-bistosylamides possessing four or five methylene units between two tosylamino groups. Thus, the anodic oxidation of an ornithine derivative **15** gave a mixture of stereoisomers of cyclic α-amino acid **16** with a ratio of 1:1 in 78% yield (eq. 5).[8] The stereoconfiguration of α-position of **15** was retained through this process, since optically active **15** yielded optically active **16**.[9]

Similarly, a mixture of stereoisomers of pipecolinic acid derivative **18**[10,11] was obtained with a ratio of 5:4 in 47% yield by the anodic oxidation of a lysine derivative **17** (eq. 6).[8]

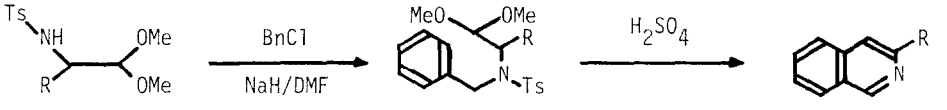


15 **16** (5)



17 **18** (6)

Although further studies may be required to calrify the exact mechanism of this oxidative rearrangement, this rearrangement seems to be synthetically worthwhile, since α-(N-tosyl-amino) aldehyde dimethyl acetals are easily preparable from simple primary amines by this method, and they are directly usable as α-amino aldehydes as exemplified by the synthesis of isoquinolines **21** and **22** from **19** and **20**, respectively (eq. 7).



19; R = H
20; R = Me

21; R = H 32%
22; R = Me 50%

(7)

References and Notes

1. Electroorganic Chemistry. 101.
2. For example;
   (a) M. A. Collins and F. J. Kernozek, *J. Heterocycl. Chem.*, **9**, 1437 (1972).
   (b) M. Maguet and R. Gugielmetti, *Bull. Soc. Chim. Fr.*, **1978**, 539.
3. The hitherto known methods of the synthesis of α-amino aldehydes; for example;
   (a) J. K. Lawson, Jr., *J. Am. Chem. Soc.*, **75**, 3398 (1953).
   (b) J. G. Erickson, W. H. Montgomery, and O. Rorso, *ibid.*, **77**, 6640 (1955).
   (c) Y. Hamada and T. Shioiri, *Chem. pharm. Bull.*, **30**, 1921 (1982).
4. [Br^+] denotes anodically generated bromine positive active species.
5. Intermediates similar to **6** have been described in the synthesis of N,N-dialkylated α-amino aldehydes from N,N-dialkylated enamines; I. Dyong and Q. Lam-Chi, *Angew. Chem., Int. Ed. Engl.*, **18**, 933 91979).
6. Since α,β-unsaturated N-tosyl amines **4** were not able to be prepared, the corresponding carbamate **8** was synthesized and used to support the mechanism. The synthesis of **8**; T. Shono, Y. Matsumura, K. Tsubata, Y. Sugihara, S. Yamane, T. Kanazawa, and T. Aoki, *J. Am. Chem. Soc.*, **104**, 6697 (1982).
7. The NMR spectra of **14b** (α-H, 4.89 ppm, J = 0 Hz) and **14c** (α-H, 4.62 ppm, J = 2.5 Hz) suggested that the stereochemistry with respect to the methoxy and tosylamino groups was predominantly trans.
8. The stereoconfiguration with respect to methoxy and tosylamino groups in **16** and **18** was assumed to be trans on the basis of the stereoconfiguration of **14b** and **14c**. Since each stereoisomer was not able to be separated, the optical rotation of each isomer was not measured.
9. The NMR spectrum of **16** obtained from racemic **15** had two signals corresponding to methoxy groups, but the two signals were changed to four signals by the addition of an optically active shift reagent (THFC-Eu). On the other hand, the two signals in the NMR spectrum of **16** obtained from optically active **15** were not changed by the addition of THFC-Eu. These results suggest that **16** prepared from optically active **15** is a mixture of two optically active stereoisomers.
10. These stereoisomers were not able to be separated.
11. The ratio of stereoisomers was estimated from the NMR spectrum.

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