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A New Anodic C-N Bond Forming Reaction Useful to Formation of Aziridine, Azetidine, and Pyrrolidine Rings[1)]

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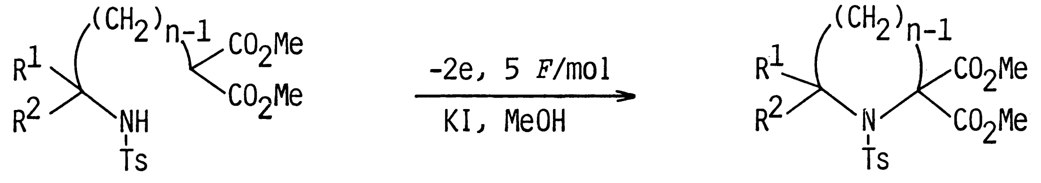
Aziridine, azetidine, and pyrrolidine rings were formed in high yields by anodic oxidation of the corresponding dimethyl α-(ω-tosylaminoalkyl)malonates in methanol containing KI as a mediator.

In our continuing studies on anodic oxidation using halogen ions as mediators,[2)] we have shown that these mediatory systems have the potentiality of providing a new method for the C-N bond formation.

We wish to report herein our new findings that the intramolecular C-N bond forming reaction between a tosylamino group (-NHTs) and an active methyne group ($-CH(CO_2Me)_2$) is promoted by using iodide as the mediator provided that one, two, or three carbons are located between these two functional groups (Eq. 1).



1a-e 2a-e (1)

a; n = 2, $R^1 = R^2 = H$	2a; 100%
b; n = 2, $R^1 = Me$, $R^2 = H$	2b; 96%
c; n = 2, $R^1 = R^2 = Me$	2c; 100%
d; n = 3, $R^1 = R^2 = H$	2d; 85%
e; n = 1, $R^1 = Et$, $R^2 = H$	2e; 46%

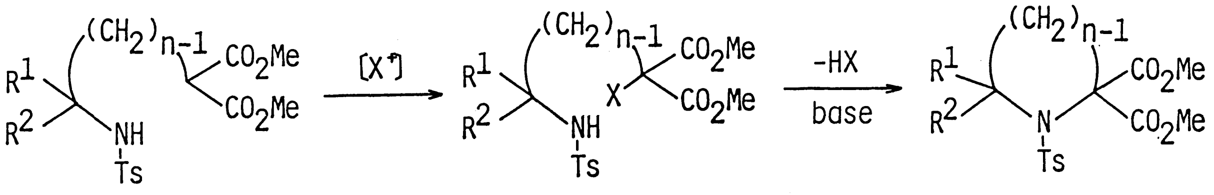
This new C-N bond forming reaction seems worthwhile from synthetic point of view since the procedure is simple, the yields are high, and the products are easily convertible to cyclic α-amino acids such as proline and α-azetidinecarboxylic acid.

A typical procedure for the C-N bond forming reaction exemplified by the synthesis of 2a is described below.

Into an electrolysis cell equipped with a platinum anode (2 cm x 2 cm), a carbon rod cathode (8 mmϕ) and a magnetic bar was added a solution of 1a (0.658 g, 2 mmol) and potassium iodide (0.166 g, 1 mmol) in 20 ml of methanol, and then anodic oxidation was carried out under conditions of constant current (0.05 A/cm^2) at a terminal voltage of about 10 V. After 5 *F*/mol of electricity was passed, the solution was poured into 30 ml of aqueous sodium thiosulfate containing sodium bicarbonate, the organic portion was extracted with three portions of methylene chloride (90 ml), and the combined organic solution was dried on magnesium sulfate successively. The residue obtained by evaporation of the solvent was subjected to column chromatography to give 2a in quantitative yield. The anodic oxidations of 1b-e under the similar conditions gave 2b-e in the yields shown in Eq. 1.

In this anodic C-N bond forming reaction, the supporting electrolyte was used as the mediator and hence it gives a remarkable effect on the yields of 2. This effect is typically shown in the anodic oxidation of 1a (Table 1). Namely, the cyclization of 1a to 2a was achieved in a quantitative yield by using iodide (KI or NaI) as the supporting electrolyte (run 1), while the yields of 2a were decreased in order of I$^-$ > Br$^-$ > Cl$^-$ (runs 1-3), and the cyclization did not occur in the case using a tosylate (run 4).

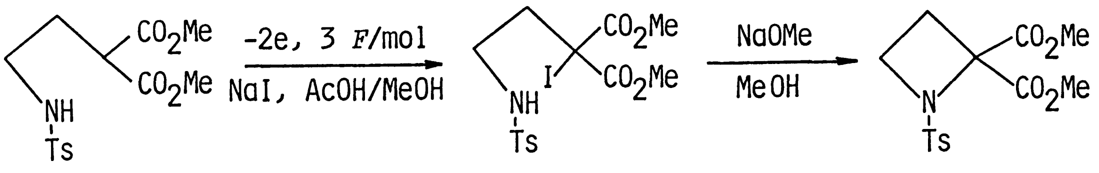
These results clearly indicate that this C-N bond formation was brought by the indirect oxidation in which the anion part of supporting electrolyte played as the mediator. Thus, the halogen active species, [X$^+$] generated anodically from X$^-$ 3) attacked on 1 to afford 3 and the latter was converted to 2 by the action of base generated in situ4) (Scheme 1).



1 3 2

Scheme 1.

The intermediary formation of 3 was supported by the facts that the anodic oxidation of a methanolic solution of 1a containing NaI (1.0 equiv.) and acetic acid (1.0 equiv.) gave 3a (87% yield), and it was converted to 2a by treatment with NaOMe (100% yield) (Eq. 2).5)



(2)

1a 3a 2a

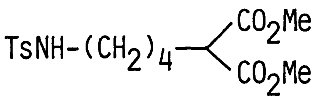
Table 1. Effect of Supporting Electrolyte on the Yield of 2a

Run	Supporting electrolyte[a]	Yield/% of 2a[b]
1	KI or NaI	≈ 100
2	KBr or NaBr	74 — 76
3	KCl or NaCl	14 — 15
4	NaOTs	0[c]

a) The amount of supporting electrolyte was 0.5 equiv. to 1a.
b) Electricity passed was 5 *F*/mol.
c) Starting material 1a was recovered.

The proposed mechanism is not contradictory to the fact that 0.5 equiv. of KI was enough to complete the C-N bond formation. The difference of activity as the mediator among the halide ions ($I^- > Br^- > Cl^-$) is not necessarily explainable, but *difference of the oxidation potential may be one of the factors.*[6]

The chain length between tosylamino and malonate moieties was also found to show a remarkable effect on the C-N bond forming reaction. Namely, compounds 1a-e which possess one, two or three carbons chain between the two moieties gave the corresponding cyclized products as descrived above, while the starting commound 4 which has four carbons chain gave a complicated mixture of products. Similar intermolecular C-N bond forming reaction between N-alkylsulfonamides 5 and dimethyl malonates 6 was also unsuccessful.

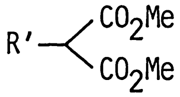


4

TsNH-R

5

R = alkyl

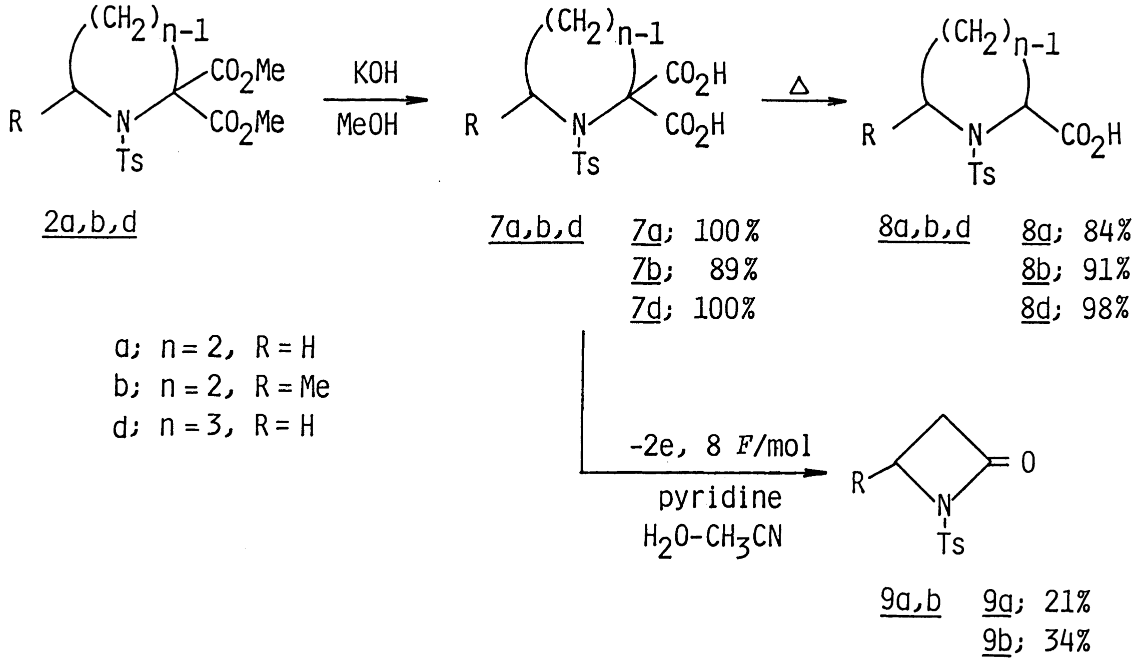


6

R′ = H or alkyl

The cyclized products 2 can easily be converted to some cyclic α-amino acids such as α-azetidinecarboxylic acids 8a,b and proline 8d. Namely, hydrolysis of 2a,b,d with KOH/MeOH gave dicarboxlic acids 7a,b,d, and decarboxylation by heating of 7a,b,d at 150 °C for 5 min without using solvents gave 8a,b,d (Eq. 3).

The products 7a,b may be transformed to the corresponding β-lactams by oxidative elimination of the α,α-biscarboxyl group.[7] In fact, the anodic oxidation of 7a,b in an aqueous solution of a mixture of pyridine and acetonitrile gave 9a,b in 21% and 34% yields respectively (Eq. 3). Although the yields are low and not optimized at present, this would be a new route for the synthesis of β-lactams.



(3)

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2) T.Shono, "Electroorganic Chemistry as a New Tool in Organic Synthesis," Springer-Verlag, Berlin (1984); T.Shono, Y.Matsumura, and K.Inoue, J. Am. Chem. Soc., 106, 6075 (1984); T.Shono, Y.Matsumura, S.Katoh, K.Inoue, and Y.Matsumoto, Tetrahedron Lett., 27, 6083 (1986).
3) $[X^+]$ denotes an anodically generated positive halogen species.
4) T.Shono, O.Ishige, H.Uyama, and S.Kashimura, J. Org. Chem., 51, 546 (1986).
5) The cyclization of 1a-e to 2a-e can also be achieved by treatment of 1a-e with iodine and NaOMe, though one equivalent of iodine and NaOMe were required; yield of 2a, 95%; 2b, 92%; 2c, 92%; 2d, 99%, 2e, 42%.
6) K.Yoshida, "Electrooxidation in Organic Chemistry," Wiley-Interscience, New York (1983), p.87.
7) Oxidation with lead tetraacetate: J.Meinwald, J.J.Tufariello, and J.J.Hurst, J. Org. Chem., 29, 2914 (1964); Anodic oxidation: J.Nokami, T.Yamamoto, M.Kawada, M.Izumi, N.Ochi, and R.Okawara, Tetrahedron Lett., 1979, 1047.

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