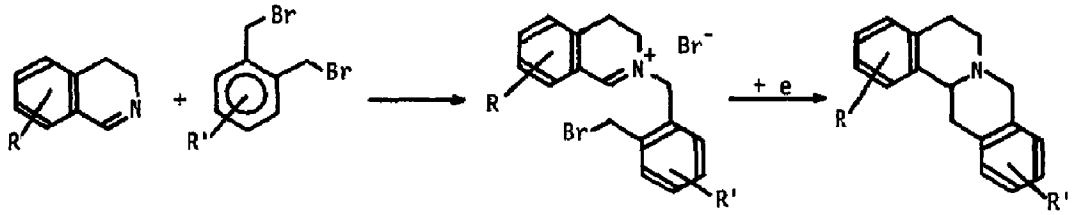
Tetrahedron Letters Vol. 21, pp 3073 - 3076 0040-4039/80/0901-3073$02.00/0

A NEW ELECTROREDUCTIVE ANNELLATION USEFUL IN SYNTHESIS OF ALKALOIDS[1]

Tatsuya Shono,* Yoshihiro Usui, Tadashi Mizutani, and Hiroshi Hamaguchi
Department of Synthetic Chemistry, Faculty of Engineering,
Kyoto University, Yoshida, Sakyo, Kyoto 606, Japan

Controlled potential reduction of immonium salts in the presence of bromo esters such as *o*-bromomethyl benzoates has afforded annellated products. The method is applicable to the synthesis of berbine alkaloids.

Because of its potentiality in synthesis of natural products, exploiting a novel pattern of cyclization is undoubtedly one of the most interesting subjects.[2] We have previously reported a new electroreductive annellation reaction which is applicable to the synthesis of berbine type compounds (eq. 1).[3] Although the method is simple, it is disadvantageous in the following two points. First, in the annellation shown in equation 1, the immonium salts prepared from imines and α,α'-dibromo-*o*-xylenes are mixtures of isomers in principle when two bromomethyl groups on α,α'-dibromo-*o*-xylenes are made regionally unequal by the presence of substituents on their nucleus. Secondly, yields of the annellation are not always satisfactory.

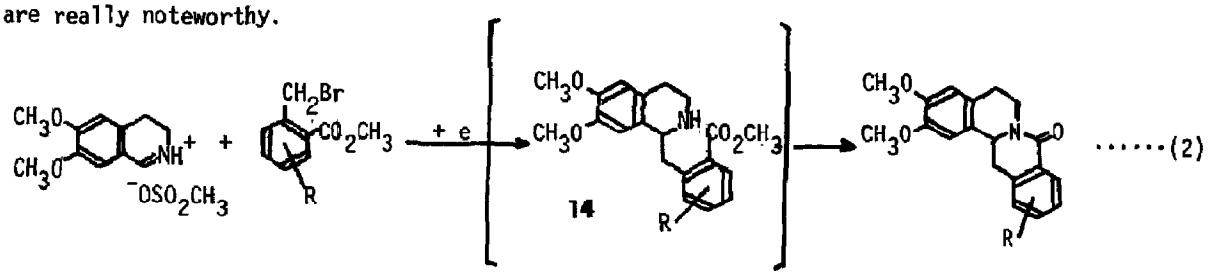


.....(1)

In the present study, we have exploited a new and facile electroreductive method of annellation which can give the cyclized products in high yields without contamination with isomers. Thus, electroreduction of mixtures of immonium salts **1-3**[4] and methyl *o*-bromomethylbenzoates **6a-d**[6] afforded cyclized amides **8-10** in high yields without forming isomers. The results are summarized in Table I. The reaction probably proceeds through reduction of immonium salts to anionic species[9] followed by the attack of the anions on the bromomethyl group of the methyl *o*-bromomethyl esters and subsequent intramolecular aminolysis of amino esters **14** yielding δ-lactams as exemplified in equation 2.

Formation of the intermediates like compound **14** was not always confirmed, but they were identified in some particular cases. For example, electroreduction of a mixture of benzalanilinium methanesulfonate (**4**) and **6a** gave an amino ester **11** as a sole product. The reaction of a noncyclizable *N*-methyl iodide **5** with bromo esters **6a** or **7** is also feasible, the products being

amino esters **12** or **13** as shown in Table I. High yields and versatility of this new annellation are really noteworthy.



A typical procedure is as follows. A solution of 3,4-dihydro-6,7-dimethoxyisoquinolinium methanesulfonate (**1**) (2 mmol), methyl 2,3-dimethoxy-6-bromomethylbenzoate (**6b**) (4 mmol), and methanesulfonic acid (3 mmol)[11] in DMF (40 ml) was used as catholyte, whereas anolyte was a solution of tetraethylammonium *p*-toluenesulfonate (3 g) in DMF (5 ml). The reaction was carried out at room temperature under the conditions of controlled potential (- 1.8 V *vs.* SCE) using platinum electrodes. The presence of a lead plate in the reaction system was desirable, though its role was not clear but assumed to be a scavenger of bromide ion or any other active bromine species. After 4 *F*/mol of electricity was passed through the cell, the solvent was removed by evaporation. To the residue, dilute aqueous hydrochloric acid was added, and extracted with three portions of methylene chloride (100 ml), and the combined organic layer was dried over magnesium sulfate. After it was filtered, solvent was evaporated, and the residue was subjected to column chromatography (Silica Gel $CHCl_3/CH_3OH$) to get the product 8-oxo-tetrahydropalmatine (**8b**) (2 mmol).

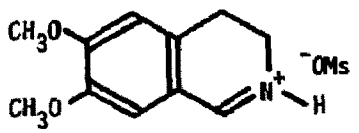
Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.09; H, 6.33; N, 3.77. IR (KBr): 2835, 1685, 1610, 1573, and 1107 cm^{-1}. NMR ($CDCl_3$ 70%, CCl_4 30%): δ 2.60-3.10 (5H, m, C-5, C-6, and 13 H's), 3.83 (9H, s, 3-OCH_3's), 3.96 (3H, s, -OCH_3), 4.40-5.11 (2H, m, C-6 and C-13aH's), 6.59 (2H, s, C-1 and C-4 H's), 6.87 (2H, s, C-11 and C-12 H's). m.p. 170-171 °C recrystallized from methanol-ether.

Table I. Reaction of Immonium Salts with Bromo Esters.

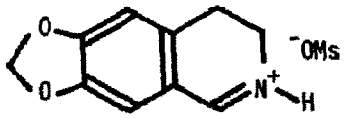
Immonium Salts	Bromo Esters	Products[a]	Yields[b] (%)	Immonium Salts	Bromo Esters	Products[a]	Yields[b] (%)
1	**6a**	**8a**[10]	83	**2**	**6c**	**9c**	85
1	**6b**	**8b**	~100	**3**	**6a**	**10a**	85
1	**6c**	**8c**	71	**3**	**6d**	**10d**	91
1	**6d**	**8d**[10]	94	**4**	**6a**	**11**	62
2	**6a**	**9a**	80	**5**	**6a**	**12**	64
2	**6b**	**9b**	92	**5**	**7**	**13**	93

a) Identified by NMR, IR and/or elemental analysis.

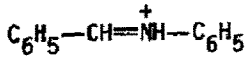
b) Isolated yield with column chromatography.



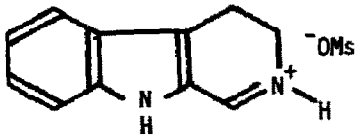
1



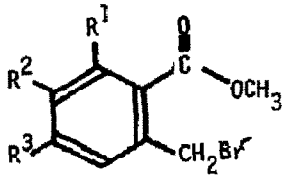
2



4



3



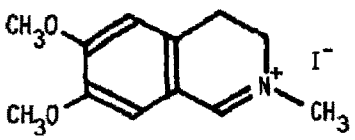
6

6a: $R^1=R^2=R^3=H$

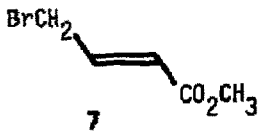
b: $R^1=R^2=OCH_3$, $R^3=H$

c: $R^1 + R^2=OCH_2O$, $R^3=H$

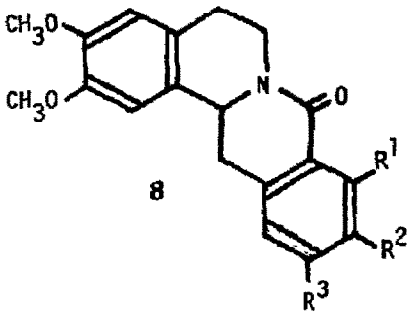
d: $R^1=H$, $R^2=R^3=OCH_3$



5



7



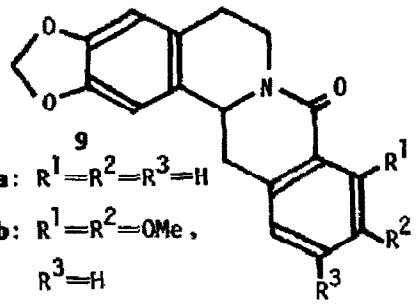
8

8a: $R^1=R^2=R^3=H$

b: $R^1=R^2=OMe$, $R^3=H$

c: $R^1 + R^2=OCH_2O$, $R^3=H$

d: $R^1=H$, $R^2=R^3=OMe$

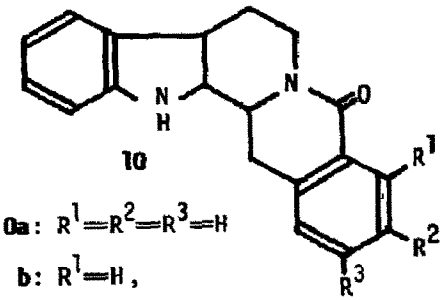


9

9a: $R^1=R^2=R^3=H$

b: $R^1=R^2=OMe$, $R^3=H$

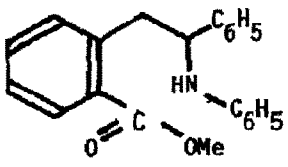
c: $R^1 + R^2=OCH_2O$, $R^3=H$



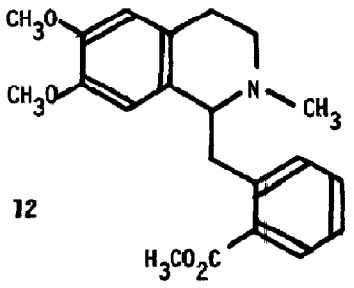
10

10a: $R^1=R^2=R^3=H$

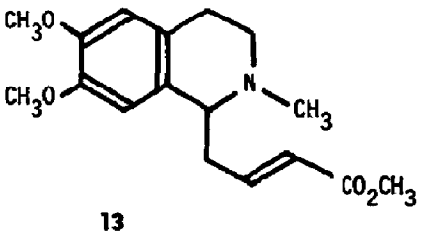
b: $R^1=H$, $R^2=R^3=OCH_3$



11



12



13

References and Notes

1) Electroorganic Chemistry. 45.
2) a) Steven M. Weinreb, Nazir A. Kharti, and Jayant Shringarpure, *J. Am. Chem. Soc.*, **101**, 5073 (1979).
   b) Gilbert Stork and D. J. Morgans, Jr., *ibid.*, **101**, 7110 (1979). References cited therein.
3) T. Shono, K. Yoshida, K. Ando, Y. Usui, and H. Hamaguchi, *Tetrahedron Lett.*, **1978**, 4819.
4) Immonium salts were prepared by dissolving imines[5] to a solution of methanesulfonic acid in THF. The solution was stirred overnight and filtered. The precipitated salts were washed with *n*-hexane several times and dried under vacuum.
5) a) Wilson M. Whaley and Tuticorin R. Govindachari, "Organic Reactions", John Wiley & Sons, Inc., New York, Ed. by Roger Adams.
   b) N. J. Whittaker, *J. Chem. Soc.*, **C**, 85 (1969).
6) Methyl *o*-bromomethylbenzoate (**6a**) was prepared according to the reported method.[7] Other derivatives of bromomethylbenzoate **6c-d** were synthesized by the similar method. Compound **6b** was prepared by treatment of methyl 6-chloromethyl-2,3-dimethoxybenzoate[8] with LiBr in DMF. Details of syntheses will be reported elsewhere.
7) Ernest L. Eliel and Donald E. Rivard, *J. Org. Chem.*, **17**, 1252 (1952).
8) Richard T. Dean and Henry Rapoport, *J. Org. Chem.*, **43**, 2115 (1978).
9) The reduction peak potential of compound **6a** is - 1.92 V *vs.* SCE, while that of compound **1** is - 1.52 V *vs.* SCE. Controlled potential electrolysis was carried out at - 1.8 V *vs.* SCE, at which potential the former compound is hardly reducible.
10) a) I. Ninomiya, T. Naito, and H. Takasugi, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1720.
    b) G. R. Lenz, *J. Org. Chem.*, **39**, 2846 (1974).
11) The role of methanesulfonic acid is to keep the reaction mixture always acidic, which is essential to avoid the formation of by-products. Details will be reported elsewhere.

(Received in Japan 14 May 1980)