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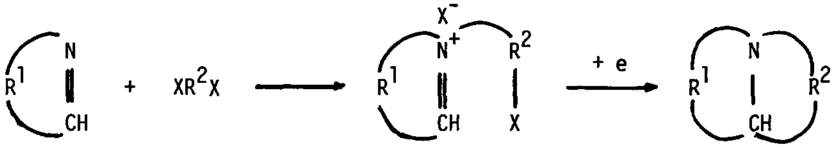
NOVEL ELECTROREDUCTIVE ANNELATION FORMING A HETERORING IN CERTAIN ALKALOID SYSTEMS[1]

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

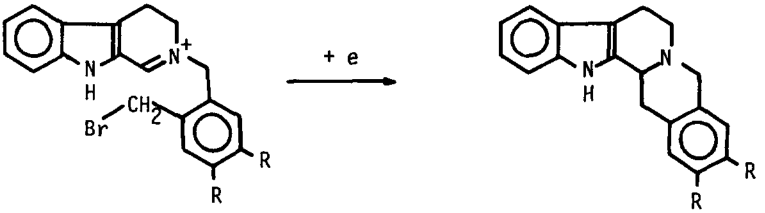
Synthesis of isoquinoline- and indole-alkaloids is undoubtedly one of the most interesting subjects in organic synthesis,[2] and has been studied extensively, while methods of formation of a heteroring by annelation are not necessarily established in alkaloid systems.[3]

We wish to describe herein a novel annelation forming a heteroring by electroreductive addition of alkyl halides to immonium salts.[4]



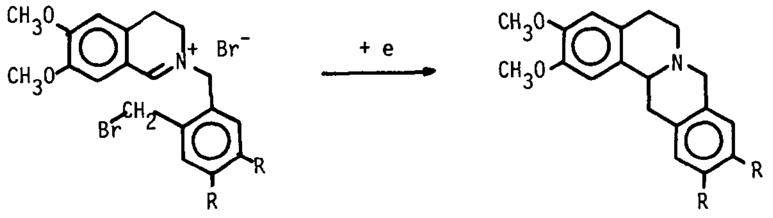
General reaction procedure is as follows: A solution of an immonium salt (30 mmol) in dimethylformamide (70 ml) was electroreduced at -1.8 V *vs.* SCE in a divided cell equipped with platinum electrodes and a plate of lead metal which may behave as a scavenger of halogen. After 3 *F*/mol of electricity was passed, the solvent was evaporated, and the residue was poured into aqueous potassium hydroxide (50 ml) followed by the extraction with three portions of ether (50 ml). The combined organic layer was dried over magnesium sulfate, and was evaporated. The residue was subjected to column chromatography(alumina, THF/hexane) to yield the cyclized product.[5]

Some results leading to the synthesis of indole- and isoquinoline-alkaloids are shown in the following schemes.



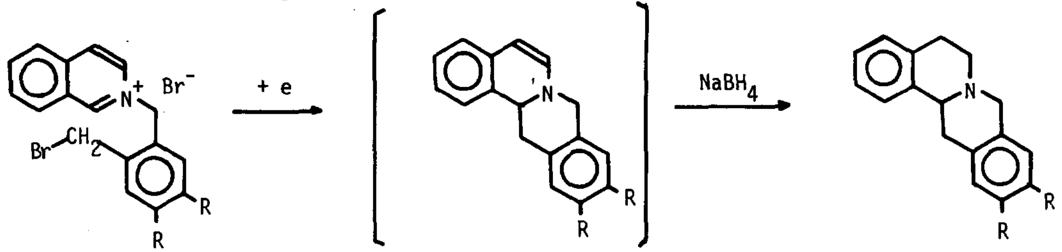
1a R = H
b R = OCH_3

2a, 60 %
b, 41 %



3a R = H
b R = OCH_3

4a, 35 %
b, 10 %

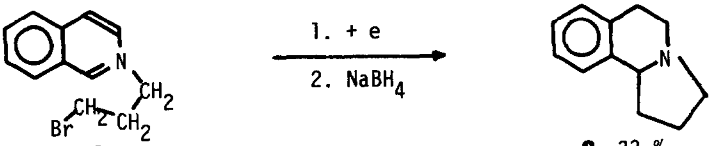


5a R = H
b R = OCH_3

6

7a, 67 %
b, 55 %

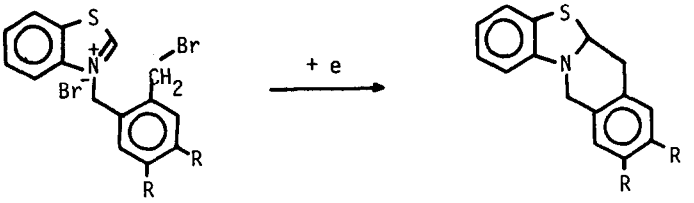
The first product **6** obtained by the electroreduction of the isoquinolinium salt **5** was reduced by sodium borohydride[7] without its isolation, since the product **6** was unstable because of its enamine structure.



8

9, 33 %

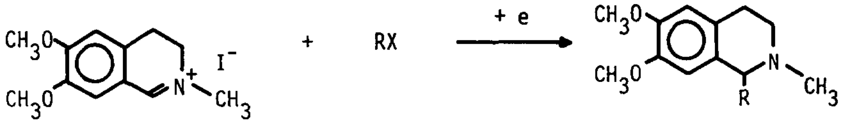
This electroreductive annelation was not limited to the heteroring possessing one heteroatom, but was successfully applicable to heterocycles with two heteroatoms such as the salt **10**. Synthesis of the compounds like **11** would not be facile by the conventional chemical methods.



10a R = H
b R = OCH_3

11a, 30 %
b, 36 %

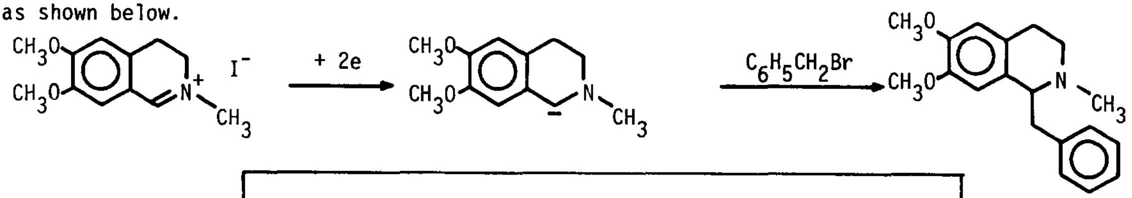
The intermolecular reductive addition of alkyl halides to immonium salts under similar reaction conditions as the annelation also gave good results leading to synthesis of alkaloids such as Laudanosine (**13c**), in good yields.



12

13a, RX = $C_6H_5CH_2Br$ 65 %
b, RX = $4\text{-}CH_3O\text{-}C_6H_4CH_2Br$ 73 %
c, RX = $3,4\text{-di-}CH_3O\text{-}C_6H_3CH_2Br$ 85 %
d, RX = CH_3I 35 %

The voltammetric reduction peak potentials of the immonium salt **12** and benzyl bromide are shown in Figure 1, and the relationship between yields and cathode potentials is summarized in Table 1. The fact that the reduction peak of immonium salt **12** was observed at more positive potential than that of benzyl bromide and the best yield was obtained when the cathode potential was between the reduction peak potentials of the immonium salt **12** and benzyl bromide suggests that the reaction was initiated by reduction of the immonium salt **12** to an anionic species as shown below.



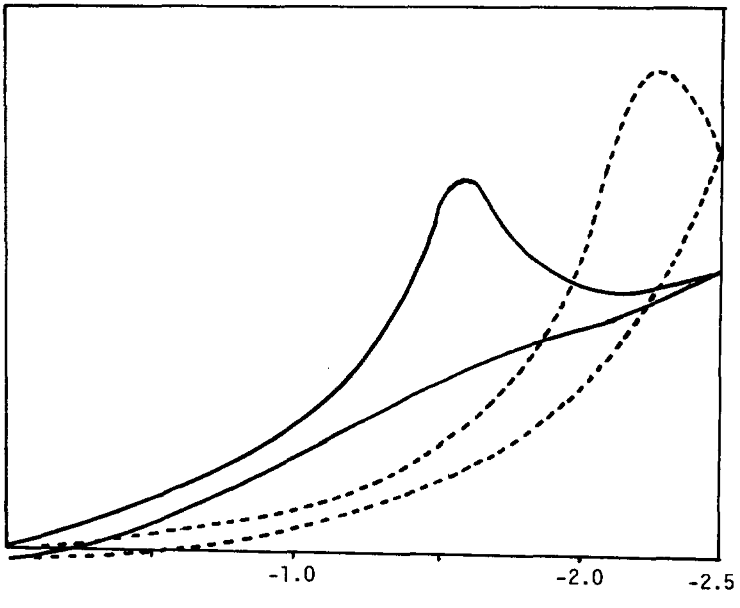


Figure 1. The cyclic voltammogram of the immonium salt **12** (solid line) and benzyl bromide (dashed line) in DMF, 0.1 M Tetraethyl ammonium *p*-toluenesulfonate at 100 mV/sec.

Table 1. The relationship between isolated yields and cathodic potentials

Reaction Potential (V *vs.* SCE)	Yield (%)
-2.0	45
-1.8	65
-1.6	35
-1.4	~0

Yields were determined at the time when 3 *F*/mol of electricity was passed.

Although the yields are still not satisfactory in certain cases, this new reaction may be remarkable in its mild reaction conditions, simplicity, and potentiality to yield heterocycles prepared difficultly by other multistage methods.

References and Notes

1. Electroorganic Chemistry. 36.
2. (a) R. Cottlieh and J. L. Neumeyer, *J. Am. Chem. Soc.*, **97**, 7108 (1976); (b) K. Nakanishi, T. Goto, S. Ito, S. Natori, and S. Nozoe, Ed., "Natural Products Chemistry", Vol. 2, Kodansha Ltd., Tokyo, 1975.
3. (a) D. W. Brown, S. F. Dyke, M. Sainslury, and W. G. D. Lugton, *Tetrahedron*, **26**, 4985 (1970); (b) T. Kametani, M. Kajiwara, T. Takahashi, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 737; (c) M. Kushmann, J. Gentry, and F. W. Dekow, *J. Org. Chem.*, **42**, 1111 (1977).
4. A solution of an imine (0.3 mol) and an alkyl halide (0.3 mol) in THF (50 ml) was stirred at room temperature until the precipitation of the immonium salt was completed. The immonium salt was washed with hexane and dried over calcium chloride.
5. All products were identified by the elemental and spectroscopic analyses and/or by the comparison with authentic samples.[6]
6. Compound **2a**: (a) S. Yamada and T. Kunieda, *Chem. Pharm. Bull.*, **15**, 499 (1967); (b) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, **1946**, 617. Compound **4a**: T. Kametani, T. Kato, and K. Fukumoto, *Tetrahedron*, **30**, 1043 (1974). Compound **4b**: C. -Y. Chen and D. B. Maclean, *Can. J. Chem.*, **46**, 2501 (1968). Compound **13b**: M. Tomita, T. Shingu, K. Fujitani, and H. Furukawa, *Chem. Pharm. Bull.*, **13**, 921 (1965). Compound **13c**: C. J. Pouchert and J. R. Campbell, "The Aldrich Library of NMR Spectra", Aldrich Chemical Co., Inc., Milwaukee, 1974. Compound **13d**: S. D. Brown, J. E. Hodgkins, J. L. Massingnill, Jr., and M. G. Reinecke, *J. Org. Chem.*, **37**, 1825 (1972).
7. The reduction by $NaBH_4$ was carried out according to the general method. For example, see J. H. Ager and E. L. May, *J. Org. Chem.*, **27**, 245 (1962).

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