APPLICATION OF ELECTRO-OXIDATIVE α-CYANATION OF AZA-RINGS TO THE SYNTHESIS OF GEPHYROTOXIN 223AB

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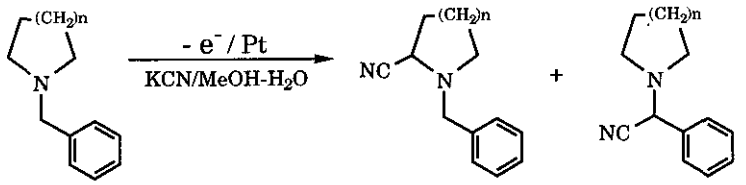
Abstract - Six and five-membered cyclic α-cyanoamines have been prepared efficiently from *N*-benzylpiperidine and *N*-benzylpyrrolidine. These α-cyanoamines were successfully used in the synthesis of gephyrotoxin 223AB.

The versatility of α-cyanoamines as synthons in the preparation of various nitrogenous compounds has attracted much attention recently.[1] The cyclic α-cyanoamines are extremely useful for the preparation of a variety of aza-rings including alkaloids. However, most of the methods for preparing cyclic α-cyanoamines suffer from low yields[2,3] or from limited sources.[4,5] Herein, we report a general and feasible methodology for making this type of compounds. Through regioselective electro-oxidative α-cyanation of aza-ring compounds,[6] we have obtained the cyclic α-cyanoamines, such as α-cyanopyrrolidine and α-cyanopiperidine, in good yields. Meanwhile, a typical 3, 5-disubstituted indolizidine alkaloids, gephyrotoxin 223AB,[7] was synthesized *via* this method.

The electro-oxidative α-cyanation was carried out in a beaker-type undivided cell, fitted with two platinum plate type electrodes. A typical electrolysis procedure (Entry 9 in Table 1) is described as follows. A solution of cyclic amine (**1b**) (2.0 mmol) in 25 ml of methanol and a solution of KCN (7.5 mmol) in 25 ml water was placed in a 100 ml beaker. To this mixture was charged with 3.50 Volt[8] of regulated dc-power through a larger platinum plate anode (8.0 x 5.0 cm) and a smaller platinum plate cathode (3.0 x 1.0 cm). The progress of the reaction was monitored with tlc and nmr spectroscopy, and the power was disconnected after 16 hours when the side products began to form.[9] The resulted mixture was concentrated *in vacuo* and the products were purified by column chromatagraphy. The results of this electro-oxidative substitution at the α-nitrogenous carbon under various conditions are summarized in Table 1.



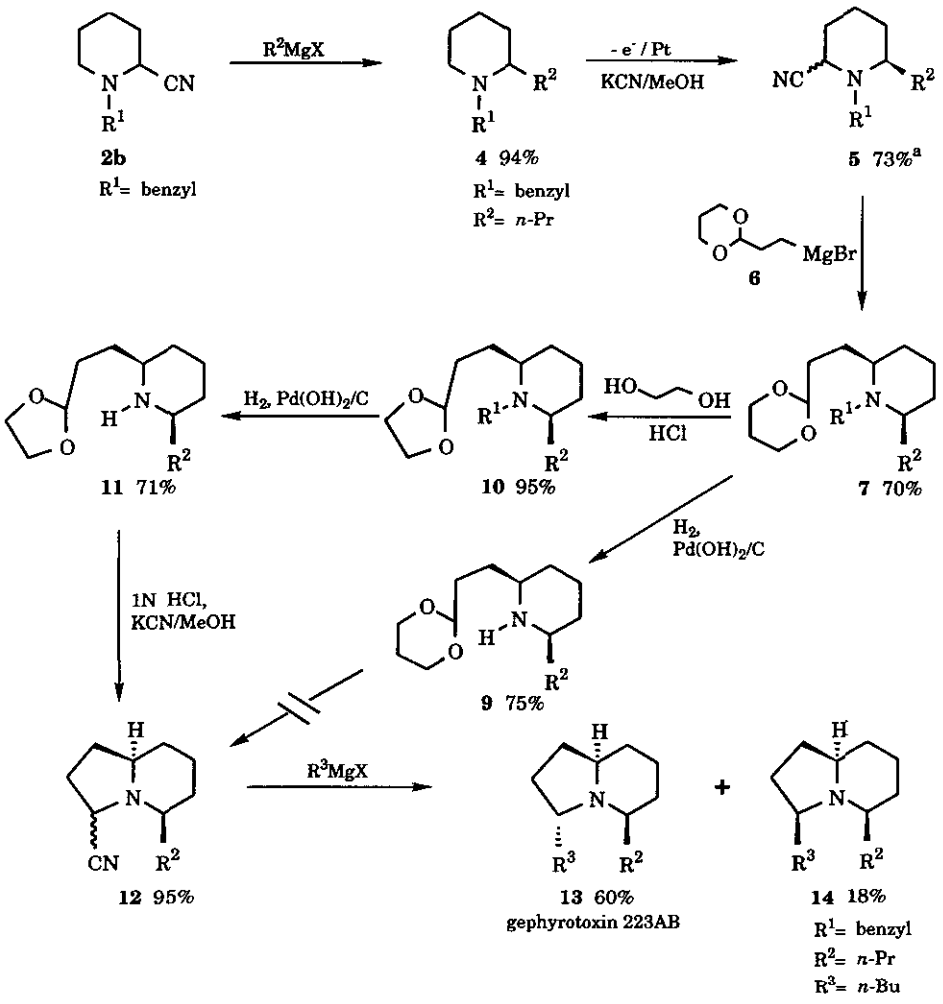
1a : n = 1 **2a** : n = 1 **3a** : n = 1
1b : n = 2 **2b** : n = 2 **3b** : n = 2

Table 1:

Entry	Amine(Conc.)	KCN	DC-Voltage	Reaction time(temperature)	α-Cyanomamines Yield% (2 / 3)
1	**1a**(0.10M)	0.15M	2.80V	34 h (0°C)	65 (4.0)
2	**1a**(0.10M)	0.15M	3.00V	23 h (0°C)	62 (4.8)
3	**1a**(0.10M)	0.15M	3.00V	17 h (ambient)	45 (7.0)
4	**1a**(0.10M)	0.15M	3.50V	15 h (0°C)	27 (8.3)
5	**1a**(0.10M)	0.15M	3.50V	9 h (ambient)	20 (6.0)
6	**1b**(0.10M)	0.15M	3.50V	5 h (ambient)	56 (3.0)
7	**1b**(0.10M)	0.15M	3.50V	16 h (ambient)	49 (4.0)
8	**1b**(0.10M)	0.15M	3.50V	36 h (ambient)	45 (5.5)
9	**1b**(0.04M)	0.15M	3.50V	16 h (ambient)	74 (3.0)
10	**1b**(0.04M)	0.15M	3.50V	36 h (ambient)	30 (9.0)

According to our observations, the electrolysis gave better chemical yield at lower dc-power voltage (Entry 1 vs. 2 vs. 4) or at lower reaction temperature(Entry 2 vs. 3). However, better regioselectivities (ratios of **2** to **3**) were observed at higher dc-voltage (Entry 1 vs. 2 vs. 4) or longer reaction time (Entry 6 vs. 7 vs. 8 and 9 vs.10). This is probably due to the further oxidation of α-cyanoamines (**2** and **3**) to form the corresponding multi-cyanated products, and between the two α-cyanoamines, **3** is more prone to undergo such reaction. Meanwhile, lowering the concentration of amine in the reaction mixture also gave better yield of α-cyanoamine (Entry 7 vs. 9), because at higher concentration the amine became oily and required much longer reaction time. The optimized condition to obtain high yield of α-cyanoamine (**2b**) (74%, Entry 9) is to charge a solution of 0.04 M of amine (**1**) and 0.15 M of KCN with 3.50 V dc at room temperature for 16 hours.

Scheme 1:



a· yield based on unrecovered starting material.

A demonstrative synthesis of indolizidine alkaloid, gephyrotoxin 223AB, is outlined in Scheme 1. In this synthesis, α-cyanoamine (**2b**) was allowed to react with *n*-propylmagnesium bromide in THF at ambient temperature to give amine (**4**) in 94% yield.[10] While amine (**4**) was subjected to the similar electrolysis conditions as Entry 9, regioselective generation of α-cyanoamines (**5**) in 60% yield was achieved as a mixture of *cis* and *trans* stereoisomers (based on 73% conversion of the starting amine (**4**)). Further substitution of α-cyanoamine (**5**) with Grignard reagent (**6**) in THF at 0°C produce the *cis*-2,6-alkyl disubstituted piperidine (**7**) in 71% yield

along with 8% of its *trans*-isomer (**8**).[11] A simple chromatographic purification gave the pure *cis*-piperidine (**7**) of which the benzyl protecting group was removed by hydrogenolysis in ethanol at 50 psi of H_2 over palladium hydroxide to give the secondary amine (**9**).[12] Unfortunately, we were unable to obtain α-cyanoamine (**12**) by acidic hydrolysis of the acetal (**9**) in the presence of KCN.[13] As an alternative, ethylene glycol was used to replace 1,3-propanediol to give 72% of 1,3-dioxolane (**10**)[14] of which the acetal functionality was hydrolyzed under milder conditions. Hydrogenolysis of *N*-benzylamine (**10**) in ethanol at 50 psi of H_2 over palladium hydroxide at ambient temperature gave secondary amine (**11**) in 71% yield. Finally, an intramolecular Strecker reaction and another substitution of α-cyanoamine (**12**) by Grignard reagent were executed based on a literature procedure[15] to give a 3.3 : 1 mixture of gephyrotoxin 223AB (**13**) (60%) and its epimer (**14**) (18%).[16]

In conclusion, the electro-oxidative α-cyanantion of cyclic amine offers an efficient route to the α-cyanopiperidine and α-cyanopyrrolidine, which can serve as an important precursor in the synthesis of alkaloids. An indolizidine alkaloids, gephyrotoxin 223AB, has been synthesized by this methodology.

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4. A dialdehyde and an alkylamine (or an aldehyde with an intramolecular amino group) are needed to form the α-cyanoamine through an iminium ion intermediate.For example see: C. Yue, J. Royer and H.-P. Husson, *J. Org. Chem.*, **1990**, *55*, 1140, J. Royer and H.-P. Husson, *Heterocycles*, **1993**, *36*, 1493.

5. A photocyanation of tertiary amine was reported by Santamaria in the demethylation process, however, it is not suitable for the α-cyanation of cyclic amine at α-carbon of heterocycles. see J. Santamaria, M. T. Kaddachi, and J. Rigaudy, *Tetrahedron Lett.*, **1990**, *31*, 4735.

6. (a) T. Shono, *Tetrahedron* , **1984**, *40*, 811. (b) D. K. Kyriacou, "Basics of Electroorganic Synthesis", Wiley-Interscience, **1981**, p. 60. (c) A. J. Fry, *Aldrichimica Acta*, **1993**, *26*, 3.

7. T. F. Spande, J. W. Daly, D. J. Hart, Y. M. Tsai, and T. L. Macdonald, *Experientia*, **1981**, *37* , 1242. For a recent synthesis of gephyrotoxin 223AB, see: A. Fleurant, J. P. Celerier, and G. L. Lhommet, *Tetrahedron : Asymmetry*, **1993**, *4*, 1429.

8. The reaction was carried out at 3.50 Volt without reference electrode. However, water was reduced at cathode during the electrolysis. Therefore, we assumed that the applied voltage was quite stable relative to reductive potential of water at cathode.

9. We found most of side products were decomposed during the chromatography and unable to identified.

10. (a) L. E. Overman and R. M. Burk, *Tetrahedron Lett.*, **1984**, *25*, 1635. (b) N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.*, **1957**, *79*, 5279.

11. M. Bonin, J. R. Romero, D. S. Grierson, and H. P. Husson, *J. Org. Chem.*, **1984**, *49*, 2392.

12. The use of Pd/C as the catalyst for the hydrogenolysis was unable to remove the benzyl protecting group. Please see P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals" Academic Press, New York, NY, **1967**, p. 464.

13. Treatment of acetal (**9**) with hydrochloric acid or *p*-toluenesulfonic acid in the presence of KCN gave very messy products with only trace amount of α-cyanoamine (**12**).

14. An attempt to prepare 2,6-disubstituted piperidine (**10**) by direct substitution of α-cyanoamine (**5**) with the Grignard reagent of 2-(2-bromoethyl)-1,3-dioxolane was unsuccessful. see J. C. Stowell, *J. Org. Chem.*, **1976**, *41*, 560.

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16. Gephyrotoxin 223AB (**13**): ^{13}C Nmr ($CDCl_3$, 75.4 MHz) δ 14.2, 14.6, 19.0, 23.0, 24.7, 25.1, 26.5, 29.2, 30.1, 31.0, 32.4, 35.9, 56.7, 58.6, 59.1; Exact mass calcd for $C_{15}H_{29}N$ 223.2302, found 223.2301.

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