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A NEW SYNTHETIC METHOD OF 1-AZABICYCLO[4.n.0]SYSTEMS[1)]

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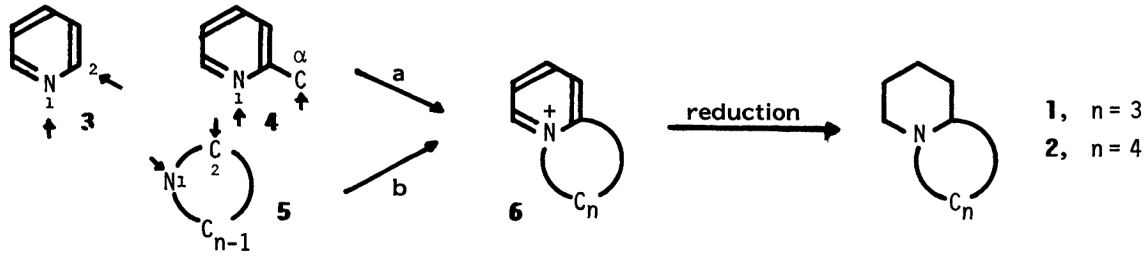
A new method for the synthesis of bicyclic pyridinium salts from alicyclic amines and reduction of the salts to 1-azabicyclo[4.n.0]systems has been exploited.

Since compounds possessing the skeletones of indolizidine **1** and quinolizidine **2** are widely found in a variety of physiologically important alkaloids, much effort has been devoted to the synthesis of such compounds.[2)] Among them, 1,2-annulation on the pyridine ring **3** and 1,α-annulation on the pyridine derivative **4** (route a in Scheme I) followed by reduction of the resulting pyridinium salts **6** seem to be convenient routes to prepare **1** and **2**,[3,4)] whereas multisteps often required in these routes, and the limited availability of the starting pyridine derivatives do not always allow the easy synthesis of **6** bearing functional groups on the desired positions.

Scheme I

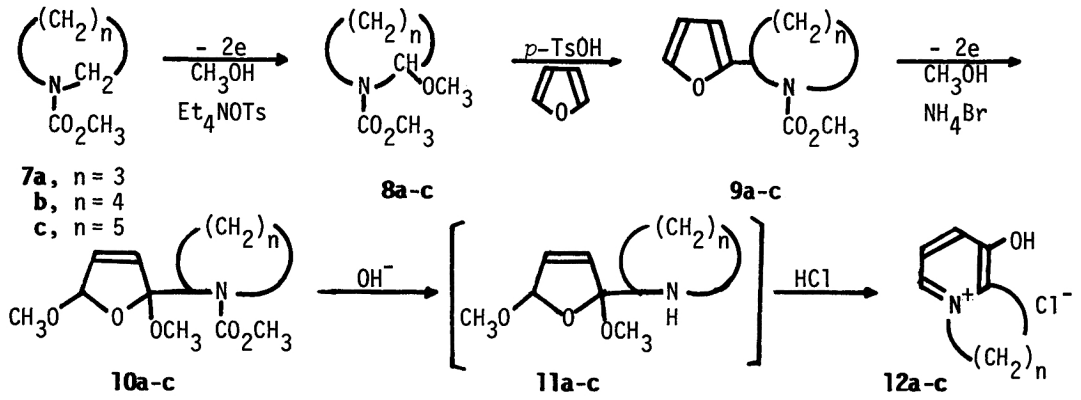


We describe herein a new synthetic method of **6**, which is characterized by formation of the pyridinium ring at the 1,2-positions of the starting cyclic secondary amines **5** (route b in Scheme I). The key reaction involved in the method is the conversion of dihydrofuran derivatives **10** to pyridinium salts **12**.[5)]

A typical procedure is exemplified by the preparation of 2,3-dihydro-8-hydroxy-1*H*-indolizinium chloride (**12a**). Anodic oxidation of 1-carbomethoxypyrrolidine **7a** followed by the acid-catalyzed coupling reaction of the resulting α-methoxylated carbamate **8a** with furan was carried out according to the reported procedure,[6)] the overall yield being 71%. Subsequent anodic oxidation of **9a** (30 mmol) in methanol (30 ml) containing ammonium bromide (20.4 mmol) gave 1-carbomethoxy-2-(2,5-dimethoxy-2,5-dihydrofuryl)pyrrolidine (**10a**) in 95% yield. After **10a** (6 mmol) was refluxed for 2 h in ethylene glycol (25 ml) containing potassium hydroxide (89mmol) and hydrazine hydrate (20.6 mmol), the mixture was cooled and extracted with methylene chloride to afford crude **11a**,

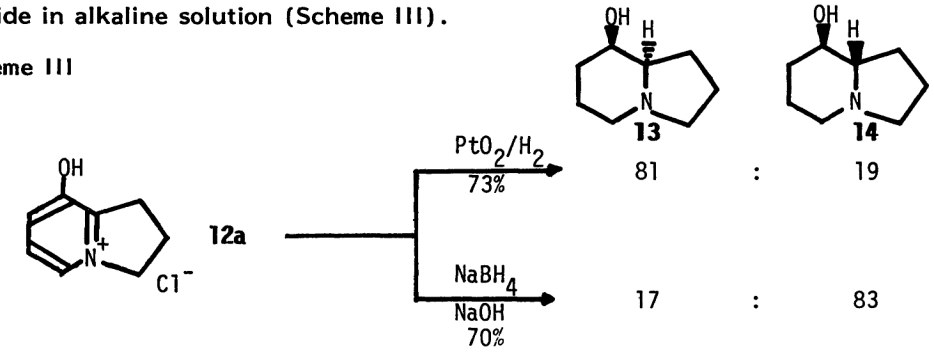
which was then heated without purification with 1N HCl (20 ml) followed by the removal of the solvent in vacuo to give **12a** (70% yield from **10a**). In a similar way, piperidine, hexamethyleneimine, and morphorine gave the corresponding pyridinium salts (**12b-d**) (Table 1).

Scheme II



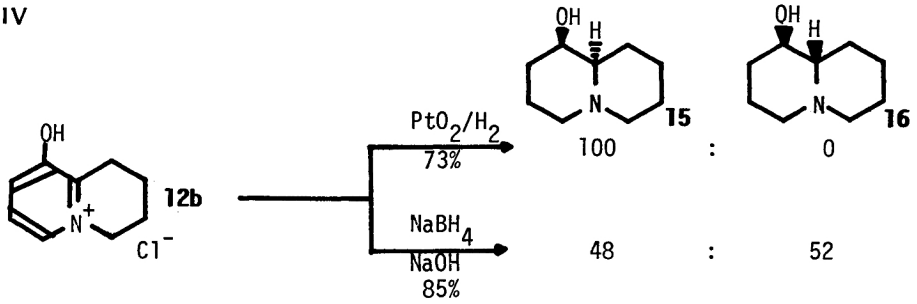
This method is advantageous for regioselective synthesis of substituted bicyclic pyridinium salts **12**. Thus, **12** possessing an alkyl substituent on the desired position of the rings can be regioselectively prepared as exemplified by the synthesis of 1,2,3,4-tetrahydro-9-hydroxy-6-methylquinolizinium chloride (**12e**) and 2,3-dihydro-8-hydroxy-5-methyl-1*H*-indolizinium chloride (**12f**). The former compound was obtained starting from α-pipecoline, and the latter was synthesized by the reaction of **8a** with methylfuran instead of furan. Also, the synthesis of hydroxyindolizidine and -quinolizidine from **12** was reasonably stereoselective. The catalytic hydrogenation of **12a** gave 8-hydroxyindolizidine (73% yield), in which the main isomer **13**[7] (distribution, 81%) has a trans configuration between the hydroxyl group and the bridgehead hydrogen. On the other hand, the predominant formation of epimer **14** was achieved by the reduction of **12a** with sodium borohydride in alkaline solution (Scheme III).

Scheme III



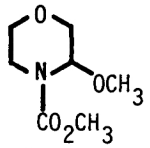
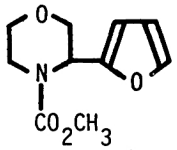
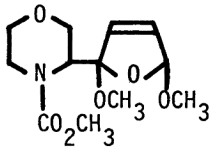
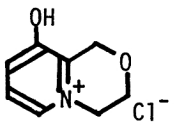
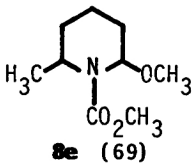
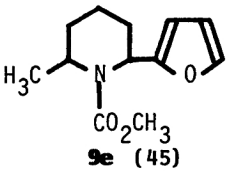
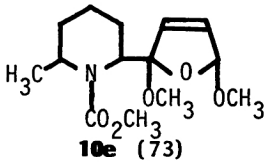
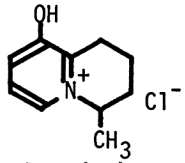
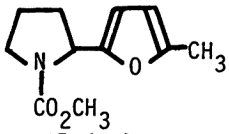
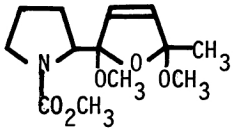
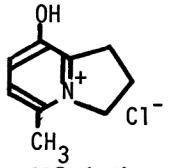
Furthermore, in the catalytic hydrogenation of **12b**, the compound **15**[8] was obtained as a sole product with indicating the perfect stereoselectivity of hydrogenation, while the reduction with sodium borohydride resulted in the formation of a mixture of **15** and its epimer **16** in a ratio of 48 : 52 (Scheme IV). The assignment of the stereochemistry of **13-16** was carried out by comparison of their physical and spectroscopic data with those of authentic samples which were prepared by the reduction of 8-ketoindolizidine[7] and 1-ketoquinolizidine.[8]

Scheme IV



Accordingly, our method described above provides a general route to synthesize 1-azabicyclo[4.n.0]system with high regio- and stereoselectivity. Application of this method to the synthesis of natural alkaloids is now in progress.

Table I. Preparation of Bicyclic Pyridinium Chlorides[a]

8 (Yield, %)	**9** (Yield, %)	**10** (Yield, %)	**12** (Yield, %)
8a (80)	**9a** (89)	**10a** (95)	**12a** (70)[b]
8b (86)	**9b** (72)	**10b** (83)	**12b** (66)
8c (72)	**9c** (65)	**10c** (80)	**12c** (54)
 **8d** (55)	 **9d** (79)	 **10d** (87)	 **12d** (70)[b]
 **8e** (69)	 **9e** (45)	 **10e** (73)	 **12e** (47)
8a	 **9f** (95)	 **10f** (96)	 **12f** (60)

[a] Spectroscopic data and elemental analyses of all compounds except **12a** and **d** were satisfactory for assigned structures.

[b] Because of their highly hygroscopic nature, satisfactory results were not obtained in the elemental analyses of **12a** and **d**, whereas their ir and nmr spectra were reasonable with the assigned structures. Also, the successful conversion of **12a** to the known **13** and **14** substantiates the structure of **12a**.

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