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A NEW SYNTHETIC METHOD OF NITROGEN HETEROCYCLES THROUGH A NOVEL ANNULATION

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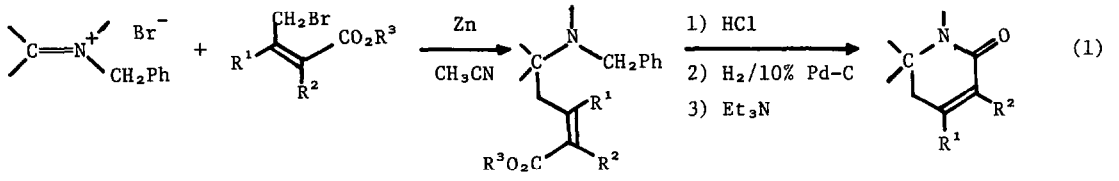
A new zinc promoted coupling reaction of iminium salts with alkyl halides gave a variety of nitrogen heterocycles through a novel annulation process.

We describe herein a new synthetic method of nitrogen heterocycles through a novel annulation using iminium salts and bromo esters[1] as starting materials and zinc as a promotor.



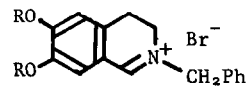
(1)

1 - 3 **4 - 8** **9** **10**

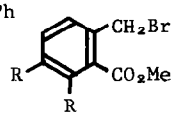
The first step of the reaction is promoted by zinc and an alkyl group is introduced into an iminium salt.[2] Thus, the treatment of a mixture of an iminium salt **1 - 3** and an alkyl halide **4 - 8** with zinc[3] in acetonitrile afforded an alkylated product **9** in good yield.[4] The annulated product **10** was obtained from the hydrochloride of **9** by debenzylation through Pd catalyzed hydrogenolysis followed by the aminolysis with Et_3N. Table I (run a - c) shows the results of the synthesis of berberine derivatives **1a - c** using *o*-bromomethylbenzoates **4,5** and iminium salts **1,2**. The C_4-annulation was also feasible by the coupling of iminium slats **1,3** and bromocrotonate derivatives **6 - 8**. The results are summarized in Table I (run d - g).

Table I.

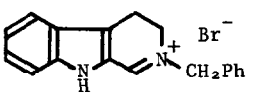
run	Iminium Salt	Alkyl Bromide	**9**	Yield (%)	**10**	Yield (%)
a	**1**	**4**	**9a**	93	**10a**	89
b	**1**	**5**	**9b**	93	**10b**	88
c	**2**	**5**	**9c**	99	**10c**	93
d	**1**	**6**	**9d**	98	**10d**	95
e	**1**	**7**	**9e**	91	**10e**	82
f	**1**	**8**	**9f**	85	**10f**	88
g	**3**	**6**	**9g**	85	**10g**	90



1, R=Me
2, R+R=-CH_2-



4, R=H
5, R=OMe



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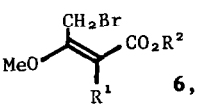
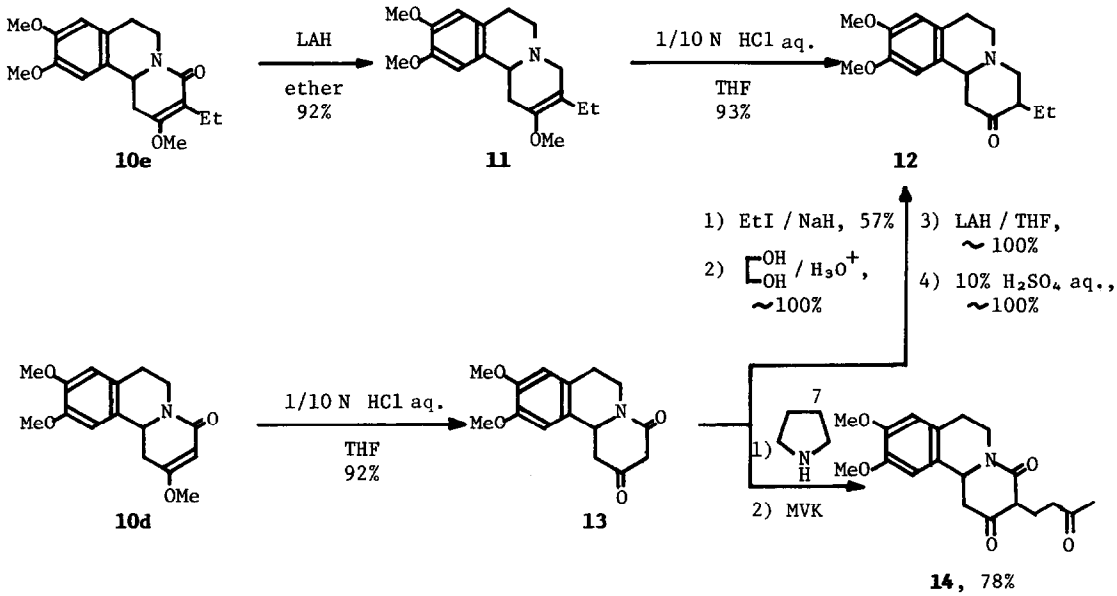


6, R^1=H, R^2=Me
7, R^1=R^2=Et
8, R^1=CH_2CO_2Et, R^2=Et

These products are useful in the synthesis of alkaloids in the following points. First, the carbonyl group of the product **10d** was reducible by $LiAlH_4$ to afford amino vinyl ether, which was hydrolyzable into keto amine. The precursor **12** for emetine[5] was yielded by the same procedure from **10e**, which was prepared using ethyl 4-bromo-2-ethyl-3-methoxy-crotonate (**7**) as the alkyl halide. Secondly, the product **10d** was easily hydrolyzed into 1,3-dicarbonyl compound **13**,[6] to which the alkylation at the active methylene group was easily achievable to yield several alkaloid precursors **12**,**14** as shown in the following scheme.



Thus, it is noteworthy that this novel annulation can afford a variety of useful nitrogen heterocycles in good yield under very simple and mild conditions.

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References and Notes

1) Electroreductive coupling has been reported by us. T. Shono, Y. Usui, T. Mizutani, and H. Hamaguchi, *Tetrahedron Lett.*, **21**, 3073 (1980).
2) Introduction of several alkyl groups into iminium salts by zinc was accomplished by us. Details will be reported elsewhere.
3) Commercial 99.9% zinc powder (Institute of High Purity Chemicals, Saitama, Japan) was used without any activation.
4) Typical procedure is as follows: To a solution of an iminium salt **1** (2.01 mmol, 0.73 g) and an alkyl halide **6** (6.02 mmol, 1.26 g) in acetonitrile (20 ml) was added zinc powder[3] (10.7 mmol, 0.70 g) at - 15 °C under an atmosphere of nitrogen. After stirring for two days at room temperature, the reaction mixture was poured into 10% aqueous KOH (20 ml) and extracted with CH_2Cl_2. After drying with $MgSO_4$ and evaporation of solvents, the residue was subjected to column chromatography (silica gel, *n*-hexane—AcOEt) to get the alkylated amine **9d** (1.96 mmol, 0.81 g), the yield being 98%.
5) Cs. Szántay, L. Töke, and P. Kolonita, *J. Org. Chem.*, **31**, 1447 (1966).
6) W. Schneider, E. Kämmerer, and K. Schilken, *Pharmazie*, **21**, 26 (1966).
7) A. A. Akhrem and Yu G. Chernov, *Synthesis*, **1980**, 996.

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