A NOVEL REDUCTIVE AMINO CYCLIZATION METHOD AND ITS APPLICATION FOR THE SYNTHESES OF PYRROLIDINE AND PIPERIDINE NUCLEUS

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Abstract ——— A novel synthetic method for pyrrolidine and piperidine derivatives is developed. Its versatility is proved by the syntheses of 6a,9a-cis-6,6a,7,8,9,9a-hexahydro-2H-isooindolo[4,5,6-cd]indole and cactus alkaloid, (±)-lophocerine.

In the previous paper, we have reported a novel intramolecular reductive amino cyclization reaction of nitro-olefin and its application to the ergot alkaloid synthesis culminating in the simple total synthesis of (±)-aurantioclavine. In an effort to extend the scope of this reaction, we have now succeeded in finding a novel construction method for pyrrolidine and piperidine nucleus.

I. Synthesis of Pyrrolidine Nucleus

In our synthetic study directed toward α-cyclopiazonic acid (1), we prepared an important key intermediate, 6a,9a-cis-7,7-dimethyl-6,6a,7,8,9,9a-hexahydro-2H-isooindolo[4,5,6-cd]indole (2). One serious problem facing us in the synthesis is a laborious long pathway and poor overall yield of 2 for pursuing further synthetic efforts. We now applied the amino cyclization method in the hope of developing an effective synthetic method for 2.

First, 4-ido-3-(2-nitrovinyl)indole (4), prepared from 3-indolecarbaldehyde (3) in two steps with 69% overall yield, was subjected to the improved Heck reaction with 3-buten-2-ol using an excess amount of triethylamine and N,N-dimethylformamide to produce a 2:1 mixture of 3,4-cis- (5c) and 3,4-trans-acetyl-3-nitromethyl-1,3,4,5-tetrahydrobenz[b]indole (5t) in 48% yield (Chart 1). This interesting one step conversion of 4 to 5 can be explained by the initial formation of a carbonyl compound (6), followed by base catalyzed intramolecular Michael addition reaction as...
illustrated in Chart 1. Successive Wittig reaction of a mixture of 5c and 5t with methylenetriphenylphosphorane afforded an inseparable 4:1 mixture of 7c and 7t in 63% yield as reported previously. When the mixture of 7c and 7t was subjected to the aminocyclization method with zinc amalgam and hydrochloric acid in methanol, the desired pyrrolidine derivative (2) was produced in 10% yield in addition to the corresponding amines, (8c) and (8t), in 23% and 5% yields, respectively. Although optimization is not made, we thus succeeded in finding a short step and simple synthetic method for 2.

II. Synthesis of Piperidine Nucleus

Heck reaction of 6-bromoveratraldehyde (9a) with 2-methyl-3-buten-2-ol in the presence of triphenylphosphine, a catalytic amount of palladium acetate, and triethylamine afforded 2-(3-hydroxy-3-methyl-1-buten-1-yl)-4,5-dimethoxybenzaldehyde (10a, mp 76-78°C) in 74% yield (Chart 2). Under the same reaction conditions, 6-bromo-4-benzyl-3-methoxybenzaldehyde (9b) afforded the corresponding olefinated compound (10b, mp 91-92°C) in 73% yield. Aldol condensation reaction of 10a and 10b with nitromethane by the action of ammonium acetate produced 11a (mp 142-143°C) and 11b (mp 184-186°C) in 76% and 78% yields, respectively. Subsequent reduction of these compounds with sodium borohydride in methanol yielded 12a (mp 99-100°C) and 12b (mp 102-103°C) in 74% and 81% yields, respectively.

Reductive amino cyclization method was successfully applied for 12a and 12b by the treatment with zinc in refluxing methanolic hydrochloric acid to give the desired 1-(2-methyl-1-propen-1-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13a, mp 53.5-55°C) and the corresponding 7-benzyl-3oxy compound (13b, mp 112-114°C) in 67%
The structure of isoquinoline was confirmed unequivocally by leading 13b into the cactus alkaloid, lophocerine (16). Thus, treatment of 13b with methyl chloroformate in methylene chloride and triethylamine afforded the corresponding N-methoxy-carbonyl compound (14, oil) in 99% yield. Reduction of 14 with lithium aluminum hydride in dry tetrahydrofuran gave N-methyl compound (15, oil) in 86% yield. Catalytic hydrogenation of double bond and debenzylation over 10% Pd/C in methanol produced (1)-lophocerine (16, oil) in 39% yield, which was identical with the sample prepared according to the procedures described in the literature.

In conclusion, we could realize a general reaction represented in Chart 3. In its intramolecular examples, the method proved to be versatile for the preparation of pyrrolidine and piperidine derivatives. We believe that under the acidic reaction conditions the cyclization occurs in the hydroxylamine stage. Further extension of the reaction to ene-oximes and related compounds is in progress.
REFERENCES AND NOTES


8. Intramolecular cyclization of olefinated hydroxylamines is reported:


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