

AZIRIDINE IN ALKALOID SYNTHESIS : A NOVEL SYNTHESIS OF SENDAVERINE

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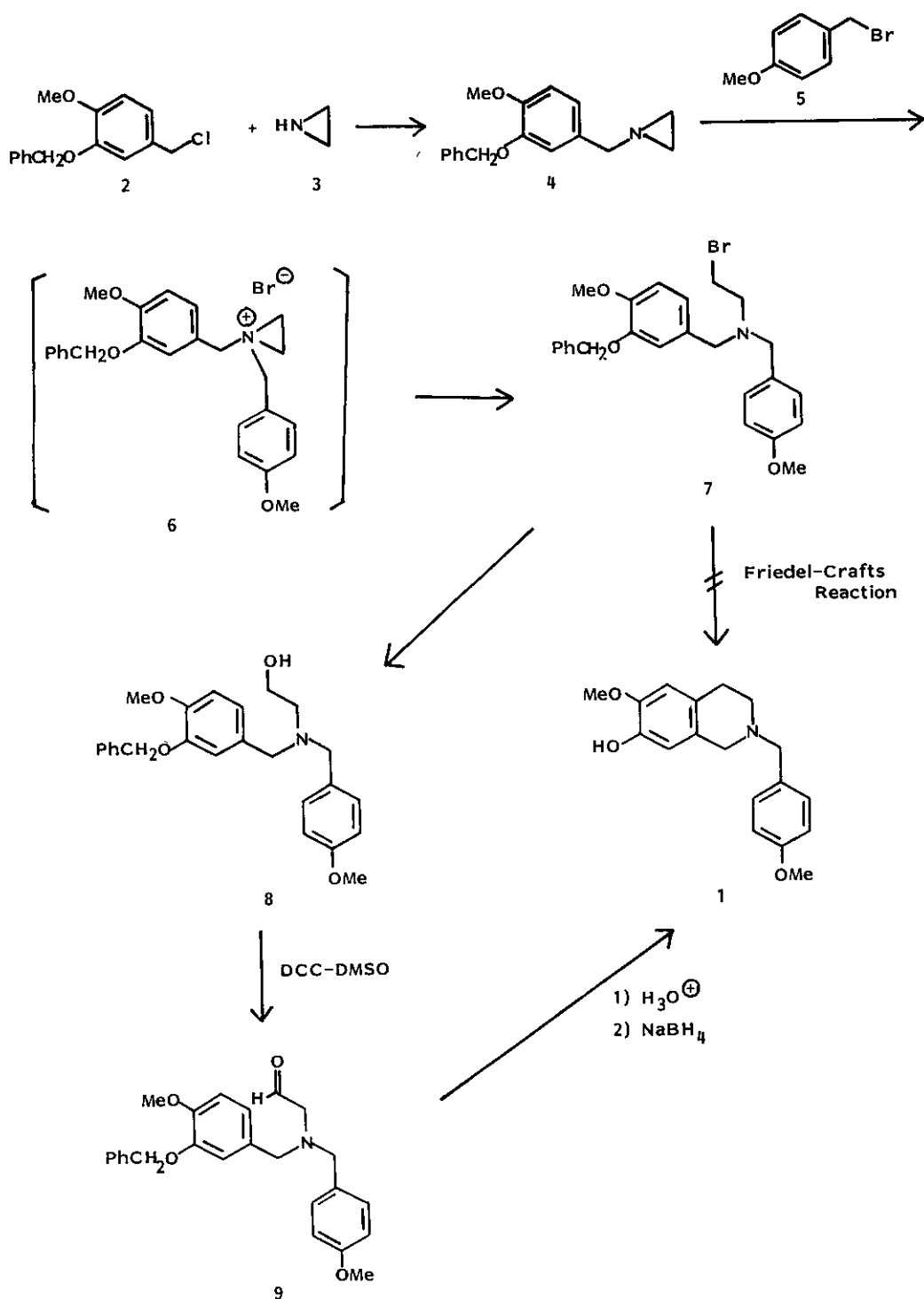
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Abstract — A facile synthesis of 2-benzylisoquinoline alkaloid, sendaverine, has been achieved by ring opening of aziridine derivative as a key reaction.

Aziridines and their quaternary salts¹ are easily attacked by nucleophiles² and electrophiles³ with the formation of ring-opened amines. We have already reported the synthesis of isopavine alkaloids⁴ and phthalide isoquinoline alkaloids⁵ by the application of this type of reaction. As an extension of this work, we have investigated the reaction of N-benzylaziridine with benzyl halide in the hope of obtaining a quaternary aziridinium salt, which may serve as a suitable precursor for a synthesis of 2-benzylisoquinoline by a subsequent cyclization reaction. Herein we wish to report a facile and novel synthesis of 2-benzylisoquinoline alkaloid, sendaverine (1).

3-Benzylloxy-4-methoxybenzyl chloride (2) was condensed with ethyleneimine (3) in benzene in the presence of potassium carbonate to afford the N-(3-benzylloxy-4-methoxybenzyl)aziridine (4) in 96 % yield. Treatment of 4 with 4-methoxybenzyl bromide (5) in refluxing acetone furnished the amino-bromide (7) via the formation of the quaternary aziridinium salt (6) and subsequent nucleophilic ring-opening reaction by bromide ion. Since a simple synthesis of the amino-bromide (7) has been accomplished, we focused our attention to its conversion into sendaverine. Since various attempted cyclization of 7 by Friedel-Crafts reaction resulted in failure, the bromide (7) was converted to the amino alcohol (8) by passing through alumina column with benzene. Oxidation of 8 with dicyclohexylcarbodiimide in dimethyl sulfoxide gave rise to the aldehyde (9) in quantitative yield. Heating 9 with 10 % aqueous hydrochloric acid in ethanol, followed by sodium borohydride reduction, afforded sendaverine (1), which was identical with an authentic specimen⁶.

Thus, the simple and novel synthesis of sendaverine has been achieved by using ring-opening of the quaternary aziridinium salt as a key reaction, and this type of reaction would provide a useful route to the synthesis of 2-alkylisoquinolines.



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