AZIRIDINE IN ALKALOID SYNTHESIS : A NOVEL SYNTHESIS OF SENDAVERINE

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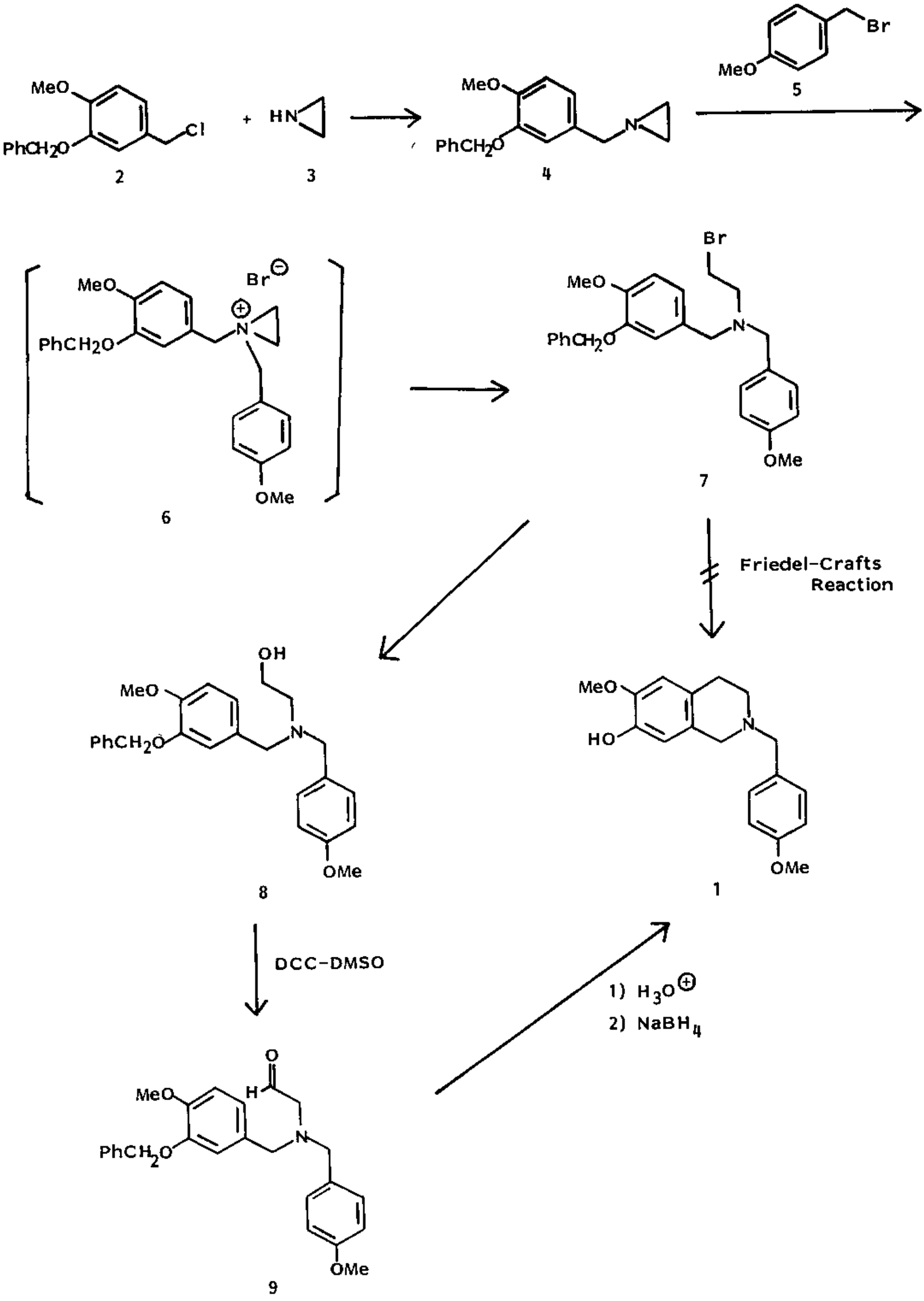
Abstract —— A facile synthesis of 2-benzylisoquinoline alkaloid, sendaverine, has been achieved by ring opening of aziridine derivative as a key reaction.

Aziridines and their quaternary salts[1] are easily attacked by nucleophiles[2] and electrophiles[3] with the formation of ring-opened amines. We have already reported the synthesis of isopavine alkaloids[4] and phthalide isoquinoline alkaloids[5] 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-Benzyloxy-4-methoxybenzyl chloride (2) was condensed with ethyleneimine (3) in benzene in the presence of potassium carbonate to afford the N-(3-benzyloxy-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 nuclephilic 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 attemped 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 specimen[6].

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.


MeO
PhCH2O
Cl
HN
2
3
4
Br
MeO
5
Br⊖
⊕
OMe
6
7
Friedel-Crafts Reaction
OH
HO
8
1
DCC-DMSO
1) H3O⊕
2) NaBH4
O
H
9

REFERENCES

1 D. R. Crist and N. J. Leonard, *Angew. Chem.*, 1969, **81**, 953.

2 N. J. Leonard and K. Jann, *J. Am. Chem. Soc.*, 1962, **84**, 4806.

3 W. Nagata, S. Hirai, T. Okamura, and K. Kawata, *J. Am. Chem. Soc.*, 1968, **90**, 1650.

4 T. Kametani, S. Hirata, and K. Ogasawara, *J. Chem. Soc. Perkin I*, 1973, 1466.

5 T. Kametani, T. Honda, H. Inoue, and K. Fukumoto, *J. Chem. Soc. Perkin I*, 1976, 1221.

6 T. Kametani and K. Ohkubo, *Chem. and Pharm. Bull. (Japan)*, 1967, **15**, 608.

Received, 19th November, 1981