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Synthesis of Racemic Cryptostylines I, II, and III by Radical Cyclization

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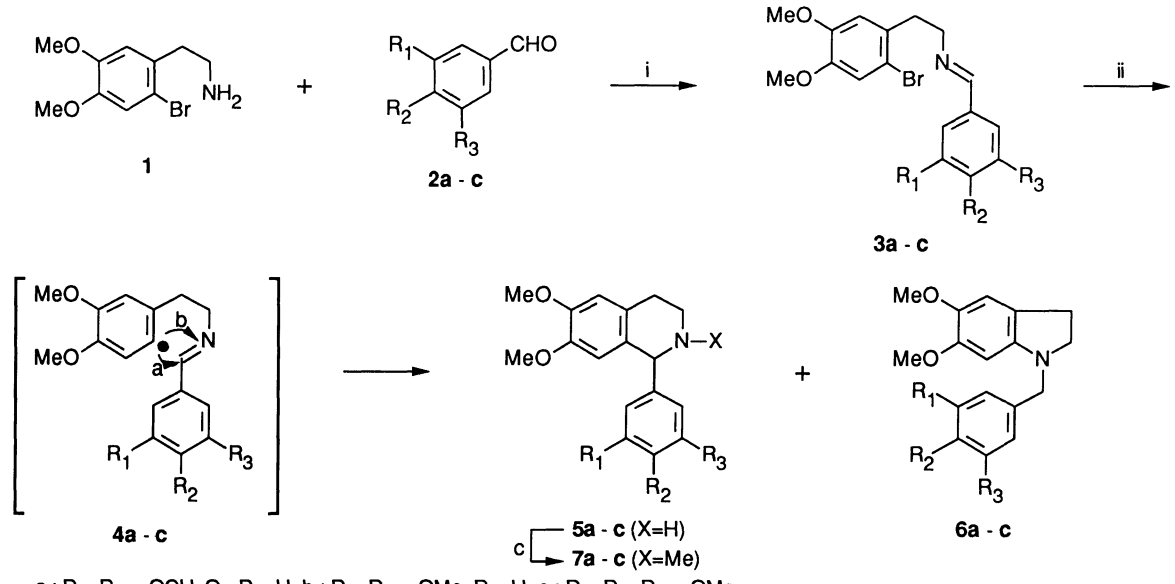
Three 1-phenyl-1,2,3,4-tetrahydroisoquinoline alkaloids, cryptostylines I, II, and III, have been synthesized in racemic forms via a aryl radical-initiated cyclization.

Although cyclization initiated by radical intermediates has been extensively exploited in the construction of heterocyclic frameworks, bond formation involving radical addition at either carbon atom or hetero atom of carbon-hetero atom multiple bond is not very common.[1] We report herein a synthesis of three 1-phenylisoquinoline alkaloids, cryptostylines I (**7a**), II (**7b**), and III (**7c**), found in the family of Orchidaceae plants,[2] employing the less common type of radical cyclization.[3]

On treatment with tri-n-butyltin hydride (2 equiv.) in boiling toluene, the Schiff's base (**3a**), prepared by condensing 2-bromo-4,5-dimethoxyphenylethylamine[4] (**1**) and 3,4-methylenedioxybenzaldehyde (**2a**), afforded two isomeric products in 56 and 9.7% yield, respectively, after purification by silica gel column chromatography. Based on spectroscopic data, the major compound was assigned to be the 1-aryltetrahydroisoquinoline (**5a**) generated via the aryl radical intermediate (**4**) by endo-cyclization mode[5] (route a), while the minor one to be the 1-benzylindoline



Scheme 1.

Reagents and conditions: i) benzene, reflux, ≈5 h; ii) n-Bu_3SnH (2.0 equiv.), AIBN (cat.), toluene, reflux, 1.5 - 2.0 h; iii) 30% formalin, $NaBH_4$, MeOH.

(**6a**) generated by exo-cyclization mode[5] (route b). Reductive methylation of the former with formalin and sodium borohydride furnished the known 1-phenylisoquinoline alkaloid, cryptostyline I[2] (**7a**), in 88.4% yield, whose physical and spectral data were identical with those reported.[2,3b]

Having established the structures of the cyclization products, we applied the present method to the synthesis of two other 1-phenylisoquinoline alkaloids isolated from the same family of the plants. Thus, on the same treatment, the Schiff's base (**3b**), obtained from the bromo-amine (**1**) and 3,4-dimethoxybenzaldehyde (**2b**), afforded the 1-aryltetrahydroisoquinoline (**5b**) and the 1-benzylindoline (**6b**) in yields of 51.4 and 8.9%, the former of which gave cryptostyline II[2] (**7b**) in 72.3% yield on the same reductive methylation above. Quite similarly, the Schiff's base (**3c**) obtained from **1** and 3,4,5-trimethoxybenzaldehyde (**2c**) afforded the isoquinoline (**5c**) (36.2%) and the indoline (**6c**) (5.6%). From the former cryptostyline III[2] (**7c**) could be obtained in 94.8% yield by the reductive methylation.

The present aryl radical-initiated cyclization, though lacking regioselectivity, may be noteworthy since facile reaction could occur at either carbon or nitrogen of carbon-nitrogen double bond.

References

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2) K. Leander and B. Luning, Tetrahedron Lett., 1968, 1393; K. Leander, B. Luning, and E. Ruusa, Acta Chem. Scand., 23, 244 (1969); J. Lundstrom, in "The Alkaloids," ed by A. Brossi, Academic Press, New York (1983), Vol. 21, p. 255.

3) Preceding synthesis of these alkaloids, see: a) Ref. 2; b) A. Brossi and S. Teitel, Helv. Chim. Acta, 54, 1564; c) A. P. Venkov and N. M. Mollow, Dokl. Bolg. Akad. Nauk., 32, 895 (1979).

4) J. Harley-Mason, J. Chem. Soc., 1953, 200.

5) Cf. A. L. J. Beckwith and C. H. Schiesser, Tetrahedron, 41, 3925 (1985); J. E. Baldwin, J. Chem. Soc., Chem. Commun., 1976, 734.

6) All the new products obtained gave satisfactory spectral data as follows:
5a: IR (film) ν 3250 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.96 (br.s, 1H, exchangeable with D_2O), 2.76-3.23 (m, 4H), 3.67 (s, 3H), 3.87 (s, 3H), 4.96 (s, 1H), 5.93 (s, 2H), 6.27 (s, 1H), 6.62 (s, 1H), 6.72 (s, 3H); MS (m/z) 313 (M^+), 192 (100%).
5b: IR (film) ν 3250 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.89 (br.s, 1H, exchangeable with D_2), 2.68-3.23 (m, 4H), 3.63 (s, 3H), 3.81 (s, 3H), 3.86 (s, 6H), 4.98 (s, 1H), 6.27 (s, 1H), 6.62 (s, 1H), 6.76-6.83 (m, 3H); MS (m/z) 329 (M^+), 192 (100%).
5c: IR (film) ν 3300 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.04 (br.s, 1H, exchangeable with D_2O), 2.87-3.22 (m, 4H), 3.68 (s, 3H), 3.81 (s, 6H), 3.05 (s, 3H), 4.98 (s, 1H), 6.31 (s, 1H), 6.49 (s, 2H), 6.63 (s, 1H); MS (m/z) 359 (M^+), 192 (100%).
6a: ^{1}H-NMR ($CDCl_3$) δ 2.87-2.95 (m, 2H), 3.13-3.33 (m, 2H), 3.81 (s, 6H), 4.09 (s, 2H), 5.95 (s, 2H), 6.23 (s, 1H), 6.78-6.79 (m, 3H), 6.90 (s, 1H); MS (m/z) 313 (M^+), 135 (100%).
6b: ^{1}H-NMR ($CDCl_3$) δ 2.57-2.88 (m, 2H), 3.10-3.33 (m, 2H), 3.73 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 4.13 (s, 2H), 6.26 (s, 1H), 6.78 (s, 1H), 6.89-6.97 (m, 3H); MS (m/z) 329 (M^+), 151 (100%).
6c: ^{1}H-NMR ($CDCl_3$) δ 2.78-3.17 (m, 2H), 3.18-3.24 (m, 2H), 3.81 (s, 6H), 3.87 (s, 6H), 3.96 (s, 3H), 4.12 (s, 2H), 6.23 (s, 1H), 6.63 (s, 2H), 6.77 (s, 1H); MS (m/z) 359 (M^+), 181 (100%).

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