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A One-Pot Synthesis of (±) Cryptostylines I, II, III

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ABSTRACT

A one-pot synthesis of cryptostylines I, II, III, via the Pictet–Spengler reaction is reported.

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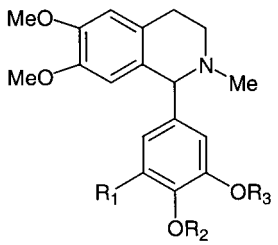
Cryptostylines I, II, III, are rare 1-aryltetrahydroisoquinoline alkaloids which have been isolated from *Cryptostylis fulva*[1] and *Cryptostylis erythroglosa*.[2] Several asymmetric syntheses[3] and racemic syntheses[1,4] of the cryptostylines have been reported, all involving multi-steps with discreet operations. In continuation with our interest in the application of the Pictet–Spengler reaction for the synthesis of alkaloids,[5] we report our work on the application of this reaction to the one-pot synthesis of cryptostyline I, cryptostyline II, and cryptostyline III in this article.

The Pictet–Spengler reaction[6] is a classical reaction involving the electrophilic substitution of activated aromatic compounds with an iminium intermediate. The reaction is commonly used for the synthesis of 1,2,3,4-tetrahydroisoquinoline and carboline alkaloids. Recent investigations have applied the reaction to the stereospecific synthesis[7] of these compounds as well as to solid phase synthesis.[8] The reaction has also recently been extended to the synthesis of other related compounds.[9] Normally the Pictet–Spengler reaction requires acids as the condensing agent, but in some special cases the reaction proceeds under neutral conditions. Recently it was shown that cyclization reactions for carboline formation can also be performed with hypervalent iodine compounds.[10]

The Pictet–Spengler reaction has also been applied to the synthesis of a 1-phenyltetrahydroisoquinoline intermediate, in which dopamine can be condensed with benzaldehyde in the presence of dilute hydrochloric acid, whereas for a similar cyclization in the case of homoveratrylamine, phosphoric acid was required.[11]



Cryptostyline I $R_1 = H$, $R_2+R_3 = CH_2$
Cryptostyline II $R_1 = H$, $R_2=R_3 = Me$
Cryptostyline III $R_1 = OMe$, $R_2=R_3 = Me$

We found that formic acid could conveniently be employed as both acid and solvent for the condensation of 3,4-dimethoxyphenylethylamine (homoveratrylamine) with aromatic aldehydes to yield the corresponding 1-aryltetrahydroisoquinoline derivatives. Condensation of homoveratrylamine with piperonal in formic acid at an oil bath temperature of 110°C for 7 h gave the required product, norcryptostyline I, in 58% yield after purification by crystallization of the oxalate salt. Having successfully effected the required cyclization by the action of formic acid, we then investigated the "one pot" synthesis of cryptostylines I, II, III. Since cyclization could be effected by **formic acid** and *N*-methylation by formaldehyde and **formic acid** is well documented[12] we anticipated that by adding formaldehyde to the above cyclization reactionn we would be able to effect both the cyclization and *N*-methylation in sequence to produce the required compound in one pot.

The above prediction was realized by heating homoveratrylamine with piperonal in formic acid at 110°C for 7 h then adding 37% formaldehyde and continuing heating the reaction mixture for a further 4 h. After work-up and purification by preparative layer chromatography, cryptostyline I was isolated in 61% yield. Similarly, cryptostylines II and III could be synthesized by heating homoveratrylamine with veratraldehyde and 3,4,5-trimethoxybenzaldehyde in formic acid followed by *N*-methylation with formaldehyde in 69 and 79% yield respectively after purification by preparative layer chromatography.

In conclusion, the above synthesis fits with one of the criteria of the ideal synthesis[13] requiring that consecutive reactions should be carried out in the same medium. Due to environmental concerns, use of less solvent is very much favored. We have found that formic acid, as the solvent, serves as an excellent acid for the Pictet–Spengler reaction and also acts as a good reducing agent in the further methylation of the intermediate so obtained.

EXPERIMENTAL

Representative Procedure

A mixture of 2-(3,4-dimethoxyphenyl) ethylamine (0.362 g, 2.00 mmol) and 3,4-methylenedioxybenzaldehyde (0.360 g, 2.40 mmol) in 99% formic acid (4 mL) was heated in an oil bath at 110°C for 7 h,

then 2 mL of 37% formaldehyde was added and the mixture was further heated for 4 h. The excess of formic acid and formaldehyde was removed by distillation and the mixture was then cooled and made basic with 1 M sodium carbonate. The solution was extracted twice with methylene chloride. The organic extracts were combined, washed with water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness to give brown solid which was recrystallized from ether to give the product (0.399 g) as a white solid.

Cryptostyline I (61%): M.p. 117–118°C (ether) (Lit.[1] 117–118°C); IR (KBr) 2949, 1609, 1511, 1369, 1245, 1217, 1140, 1036 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 2.25 (s, 3H, NCH_3), 2.59 (dt, 1H, $J = 4.0$, 11.0 Hz), 2.72 (dt, 1H, $J = 3.3$, 15.6 Hz), 3.12 (m, 2H), 3.62, 3.85 (s, 3H, OCH_3), 4.12 (s, 1H, C*H*), 5.93 (d, 2H, $J_{AB} = 0.7$ Hz, OCH_2O), 6.17 (s, 3H, Ar*H*), 6.59 (s, 3H, Ar*H*), 6.71 (s, 3H, Ar*H*), 6.76 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 28.9, 44.1, 52.1, 55.7, 55.8, 70.6, 100.9, 107.4, 109.3, 110.7, 111.4, 122.8, 126.5, 130.2, 137.7, 146.8, 147.0, 147.4, 147.8; MS (EI) m/z 327 (M^+, 28), 206 (100).

Cryptostyline II (69%): M.p. 101–102°C (ether) (Lit.[1] 103–104°C); IR (KBr) 2894, 1465, 1355, 1220, 1190, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H, N*H*), 2.60 (dt, 1H, $J = 4.0$, 11.1 Hz), 2.76 (m, 1H), 3.14 (m, 2H), 3.58 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.11 (s, 1H, C*H*), 6.14 (s, 1H, Ar*H*), 6.60 (s, 1H, Ar*H*), 6.76 (d, 1H, $J = 1.7$ Hz), 6.82 (s, 1H, Ar*H*), 6.83 (d, 1H, $J = 1.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 28.8, 44.2, 52.4, 55.6, 55.7, 55.8, 70.9, 110.3, 110.6, 111.4, 122.0, 126.3, 130.4, 136.0, 146.9, 147.4, 148.3, 149.0; MS (EI) m/z 343 (M^+, 17), 206 (100).

Cryptostyline III (79%): M.p. 140–141°C (EtOH) (Lit.[1] 141–142°C); IR (KBr) 2948, 1463, 1360, 1220, 1182, 812 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H, NCH_3), 2.59 (m, 1H), 2.72 (m, 1H), 3.12 (m, 2H), 3.61 (s, 3H, OCH_3), 3.82 (s, 6H, $2 \times$ OCH_3), 3.85 (s, 6H, $2 \times$ OCH_3), 4.06 (s, 1H, C*H*), 6.17 (s, 1H, Ar*H*), 6.59 (s, 1H, Ar*H*), 4.50 (s, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 28.8, 44.4, 52.5, 55.7, 55.9, 56.1, 60.8, 71.6, 106.4, 110.7, 111.4, 126.4, 130.1, 137.2, 139.4, 146.9, 147.5, 153.0; MS (EI) m/z 373 (M^+, 13), 206 (100).

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REFERENCES

1. Leander, K.; Luning, B.; Ruusa, E. Acta Chem. Scand. **1969**, *23*, 244.
2. Agurell, S.; Granelli, I.; Leander, K.; Luning, B.; Rosenblom, J. Acta Chem. Scand. **1974**, *28*, 239.
3. Munchhof, M.J.; Meyers, A.I. J. Org. Chem. **1995**, *60*, 7086; Suzuki, H.; Aoyagi, S.; Kibayashi, C. Tetrahedron Lett. **1995**, *36*, 6709; Yamato, M.; Hashigaki, K.; Qais, N.; Ishikawa, S. Tetrahedron **1990**, *46*, 5909; Polniaszek, R.P.; Dillard, L.W. Tetrahedron Lett. **1990**, *31*, 797.
4. Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. Chem. Lett. **1990**, 315; Tamao, K.; Kodama, S.; Nakajima, I.; Kumada, M.; Minato, A.; Suzuki, K. Tetrahedron **1982**, *38*, 3347; Venkov, A.; Lukanov, L.; Mollov, N. Synthesis **1982**, 486; Brossi, A.; Teitel, S. Helv. Chim. Acta **1971**, *54*, 1564–1571; Leander, K.; Luning, B. Tetrahedron Lett. **1968**, 1393.
5. Ruchirawat, S.; Chaisupakitsin, M.; Patranuwatana, N.; Cashaw, J.L.; Davis, V.E. Synth. Commun. **1984**, *14*, 1221.
6. Cox, E.D.; Cook, J.M. Chem. Rev. **1995**, *95*, 1797; Whaley, W.M.; Govindachari, T.R. *Organic Reactions*; Adams, R., et al., Eds.; John Wiley & Sons: New York, 1951; Vol. 6, pp. 151–206.
7. Rozwadowska, M.D. Heterocycles **1994**, *39*, 903; Gremmen, C.; Willemse, B.; Wanner, M.J.; Koomen, G.J. Org. Lett. **2000**, *2*, 1955.
8. Lorsbach, B.A.; Kurth, M. J. Chem. Rev. **1999**, *99*, 1549.
9. Merriman, G.H.; Fink, D.M.; Freed, B.S.; Kurys, B.E.; Pavlek, S.; Varriano, J.; Paulus, E.F. Synlett **2000**, 137.
10. Papadopoulou, D.; Papoutsis, I.; Spyroudis, S.; Varvoglis, A. Tetrahedron Lett. **1998**, *39*, 2865.
11. Sarges, R. J. Heterocyclic Chem. **1972**, *11*, 599.
12. Eschweiler, W. Chem. Ber. **1905**, *38*, 880; Clarke, H.T.; Gillespie, H.B.; Weishaus, S.Z. J. Am. Chem. Soc. **1933**, *55*, 4571; Icke, R.N.; Moore, M.L. Org. Reactions **1945**, *5*, 31; Wisegarver, B.B.; Alles, G.A. Org. Syn. Coll. Vol. 3 **1955**, 723.
13. Turner, S. *The Design of Organic Synthesis*; Elsevier Scientific Publishing Company: Amsterdam–Oxford–New York, 1976.

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