

NOVEL APPLICATIONS OF THE MODIFIED POLONOVSKI REACTION - IV¹
 PREPARATION OF (+)-HYGRINE AND (+)-N-METHYLRUSPOLINONE

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Abstract - Preparation of (+)-hygrine 5 and (+)-N-methylruspolinone 6 via N-methyl-2-cyanopyrrolidine 1 is described.

During our studies on the modified Polonovski (Polonovski-Potier) reaction¹⁻³ we became interested in applying the reaction in the pyrrolidine series, which, if successful, would permit the easy preparation of some pyrrolidine alkaloids (*vide infra*).

We first examined the possibility of preparing N-methyl-2-cyanopyrrolidines 1 and 2 (synthetically versatile iminium ion synthones) by methods recently developed in the piperidine series.¹⁻³

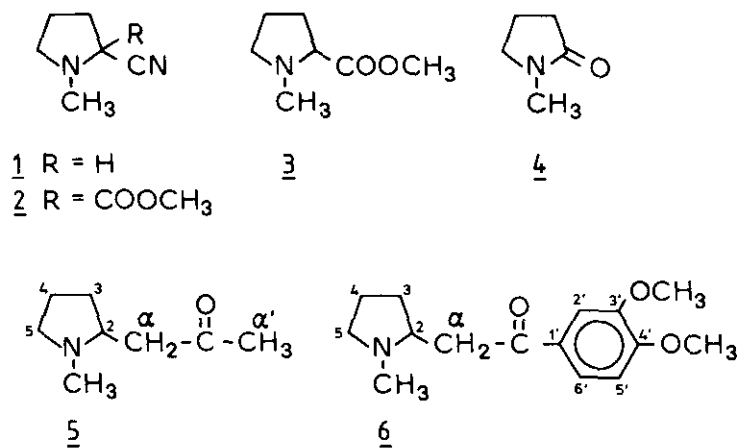
Treatment of N-methylproline methyl ester 3⁴ with aqueous H₂O₂ led to an N-oxide, which, when subjected to the modified Polonovski reaction conditions and CN⁻ trapping method⁵ (Polonovski-Potier-Husson reaction), furnished N-methyl-2-cyanopyrrolidine 1, albeit only in 25% yield.⁶

Alternatively, the m-CPBA-oxidation of N-methylproline methyl ester 3 in CH₂Cl₂, followed by the Polonovski-Potier-Husson reaction, gave N-methyl-2-cyano-2-methoxycarbonylpyrrolidine 2 in 88% yield.

We also investigated an alternative method⁷ for preparing N-methyl-2-cyanopyrrolidine 1. Reduction of N-methylpyrrolidone 4 with LAH in THF, followed by KCN treatment, afforded N-methyl-2-cyanopyrrolidine 1 in 57% yield.

With the versatile iminium ion synthon 1 in hand, we tested its usefulness to prepare two simple pyrrolidine alkaloids: (+)-hygrine 5⁸ and (+)-N-methylruspolinone 6⁹⁻¹¹. We found that the treatment of N-methyl-2-cyanopyrrolidine 1 with

ethyl acetoacetate and ethyl veratroacetate in aqueous NaOH solution led to (+)-hygrine 5 and (+)-N-methylruspolinone 6 in 20 and 25% yields, respectively.¹²



EXPERIMENTAL

N-Methylproline methyl ester 3.

Prepared from L-(-)-proline (Aldrich) according to Mohrle and Sieker.⁴ Yield 75%. Bp 39°C/1.2 mm. $[\alpha]_D -107.3^\circ$ (c = 1, CHCl₃). ¹H NMR (CDCl₃): δ 2.41 (3H, s, >N-CH₃), 3.74 (3H, s, -COOCH₃). ¹³C NMR (CDCl₃): δ 22.6 (t, C-4), 29.1 (t, C-3), 38.3 (q, >N-CH₃), 51.1 (q, -COOCH₃), 55.7 (t, C-5), 66.8 (d, C-2), 173.3 (s, -COOCH₃).

N-Methyl-2-cyanopyrrolidine 1.

a) From N-methylproline methyl ester 3.

A mixture of 1.6 g (11.2 mmol) of N-methylproline methyl ester 3, 10 ml of methanol, 10 ml of chloroform and 11.5 ml of 30% H₂O₂ was stirred at 50°C for 24 h. A small amount of Pd/C was added and the mixture allowed to stand overnight. After filtration the solvents were evaporated, the residue was dissolved in dry methanol and dried over Na₂SO₄. After evaporation of the solvent the residue was carefully dried in vacuo. It was then dissolved in 50 ml of dry CH₂Cl₂ and 10

mmol of TFAA (trifluoroacetic anhydride) was added dropwise during 30 min at 0°C. The mixture was stirred for 1 h and then allowed to reach room temperature. Aqueous solution of KCN [390 mg (6 mmol) in 20 ml of water] was added, followed by solid sodium acetate until the pH was 4-5. After stirring at room temperature for 45 min the mixture was basified with NaHCO₃, the organic layer separated, and the aqueous layer extracted with CH₂Cl₂. The combined organic phases were dried and evaporated. Yield 336 mg (25%). $[\alpha]_D \pm 0^0$ (c = 1, CHCl₃). IR (film): 2250 cm⁻¹ (w). ¹H NMR (CDCl₃): δ 2.48 (3H, s, >N-CH₃). ¹³C NMR (CDCl₃): δ 22.1 (t, C-4), 29.7 (t, C-3), 38.6 (q, >N-CH₃), 53.2 (t, C-5), 55.3 (d, C-2), 117.7 (s, CN). MS: m/z 110 (M⁺, 76%), 109 (100%), 84 (94%), 83 (50%).

b) From N-methyl-2-pyrrolidone 4.

To 9.90 g (100 mmol) freshly distilled N-methylpyrrolidone 4 in 100 ml of THF was added a suspension of 2 g of LAH in 20 ml of THF. The mixture was stirred for 2 h, during which it was refluxed for 45 min. Aqueous solution of KCN [13 g (200 mmol) in 30 ml of water] was added dropwise (caution) to the stirred mixture. The water phase was removed, the organic phase dried over MgSO₄ and the solvent evaporated. Yield 6.84 g (57%). IR, ¹H NMR, ¹³C NMR, MS as above.

N-Methyl-2-methoxycarbonyl-2-cyanopyrrolidine 2.

To 600 mg (4.2 mmol) of N-methylproline methyl ester 3 in 30 ml of CH₂Cl₂ was added 870 mg (5 mmol) of m-CPBA (m-chloroperbenzoic acid) at 0°C. The reaction mixture was stirred for 2.5 h and 1.68 g (8 mmol) of TFAA (trifluoroacetic anhydride) was added dropwise at 0°C. Stirring was continued for one more hour, after which 1.1 g (17 mmol) of KCN in 15 ml of water was added. After 1 h of stirring, the water layer was basified with NaHCO₃ and the phases were separated. After drying, the organic solvent was evaporated. Yield 619 mg (88%). IR (film): 2250 cm⁻¹. ¹H NMR (CDCl₃): δ 2.46 (3H, s, >N-CH₃), 3.87 (3H, s, -COOCH₃). ¹³C NMR (CDCl₃): δ 21.3 (t, C-4), 36.7 (q, >N-CH₃), 37.4 (t, C-3), 53.5 (q, -COOCH₃), 53.7 (t, C-5), 68.8 (s, C-2), 115.0 (s, CN), 167.5 (s, -COOCH₃). MS: m/z 168 (M⁺, 14%), 141 (15%), 110 (51%), 109 (100%).

(±)-Hygrine 5.

A mixture of 110 mg (1 mmol) of N-methyl-2-cyanopyrrolidine 1 and 130 mg (1 mmol) of ethyl acetoacetate in aqueous (2 N) NaOH solution was stirred for 24 h in the dark under argon. The mixture was extracted with chloroform, dried over Na₂SO₄ and the solvent evaporated under vacuum. The product was purified by PLC (silica gel; CHCl₃/MeOH; 90/10). Yield 26 mg (20%). ¹H NMR (CDCl₃): δ 2.18 (3H, s, α'-CH₃), 2.33 (3H, s, >N-CH₃). ¹³C NMR (CDCl₃): δ 21.9 (t, C-4), 30.7 (q, C-α'), 31.1 (t, C-3), 40.3 (q, >N-CH₃), 48.0 (t, C-α), 56.5 (t, C-5), 61.7 (d, C-2), 207.5 (s, C=O). MS: m/z 141 (M⁺, 24%), 84 (100%).

(±)-N-Methylruspolinone 6.

A mixture of 110 mg (1 mmol) of N-methyl-2-cyanopyrrolidine 1 and 252 mg (1 mmol) of ethyl veratroacetate in aqueous (2 N) NaOH solution was stirred for 24 h in the dark under argon. The mixture was extracted with chloroform, dried over Na₂SO₄ and the solvent evaporated under vacuum. The product was purified by PLC (silica gel; CHCl₃/MeOH; 90/10). Yield 64 mg (25%). ¹H NMR (CDCl₃): δ 2.40 (3H, s, >N-CH₃), 3.94 (3H, s, -O-CH₃), 3.95 (3H, s, -O-CH₃), 6.90 (1H, d, J = 8 Hz, aromatic), 7.54 (1H, s, aromatic), 7.62 (1H, d, J = 8 Hz, aromatic). ¹³C NMR (CDCl₃): δ 22.1 (t, C-4), 31.3 (t, C-3), 40.4 (q, >N-CH₃), 42.6 (t, C-α), 55.8 (q, 2 x -O-CH₃), 56.6 (t, C-5), 62.4 (d, C-2), 109.9 (d, C-2', C-5'), 122.6 (d, C-6'), 130.2 (s, C-1'), 148.8 (s, C-3'), 153.1 (s, C-4'), 197.4 (s, C=O). MS: m/z 263 (M⁺, 28%), 165 (86%), 84 (100%).

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