NOVEL APPLICATIONS OF THE MODIFIED POLONOVSKI REACTION - IV[1]
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) reaction[1-3] 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]

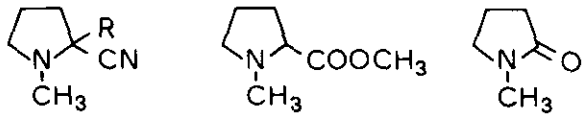
Treatment of N-methylproline methyl ester 3[4] with aqueous H_2O_2 led to an N-oxide, which, when subjected to the modified Polonovski reaction conditions and CN^- trapping method[5] (Polonovski-Potier-Husson reaction), furnished N-methyl-2-cyanopyrrolidine 1, albeit only in 25% yield.[6]

Alternatively, the m-CPBA-oxidation of N-methylproline methyl ester 3 in CH_2Cl_2, followed by the Polonovski-Potier-Husson reaction, gave N-methyl-2-cyano-2-methoxycarbonylpyrrolidine 2 in 88% yield.

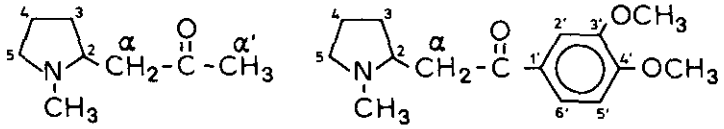
We also investigated an alternative method[7] for preparing N-methyl-2-cyanopyrrolidine 1. Reduction of N-methylpyrrolidone 4 with LAH in THF, followed by KCN treatment, afforded N-methyl-2-cyanopyrrolidine 1 in 57% yield.

With the versatile iminium ion synthon 1 in hand, we tested its usefulness to prepare two simple pyrrolidine alkaloids: (±)-hygrine 5[8] and (±)-N-methylruspolinone 6[9-11]. 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]



1 R = H
2 R = $COOCH_3$



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° (c = 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.41 (3H, s, >N-CH_3), 3.74 (3H, s, -$COOCH_3$). ^{13}C NMR ($CDCl_3$): δ 22.6 (t, C-4), 29.1 (t, C-3), 38.3 (q, >N-CH_3), 51.1 (q, -$COOCH_3$), 55.7 (t, C-5), 66.8 (d, C-2), 173.3 (s, -$COOCH_3$).

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% H_2O_2 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 Na_2SO_4. After evaporation of the solvent the residue was carefully dried in vacuo. It was then dissolved in 50 ml of dry CH_2Cl_2 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. Aquoues 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 $NaHCO_3$, the organic layer separated, and the aqueous layer extracted with CH_2Cl_2. The combined organic phases were dried and evaporated. Yield 336 mg (25%). $[\alpha]_D \pm 0^0$ (c = 1, $CHCl_3$). IR (film): 2250 cm^{-1} (w). ^1H NMR ($CDCl_3$): δ 2.48 (3H, s, >N-CH_3). ^{13}C NMR ($CDCl_3$): δ 22.1 (t, C-4), 29.7 (t, C-3), 38.6 (q, >N-CH_3), 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 $MgSO_4$ and the solvent evaporated. Yield 6.84 g (57%). IR, ^1H NMR, ^{13}C 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 CH_2Cl_2 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 $NaHCO_3$ and the phases were separated. After drying, the organic solvent was evaporated. Yield 619 mg (88%). IR (film): 2250 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.46 (3H, s, >N-CH_3), 3.87 (3H, s, -$COOCH_3$). ^{13}C NMR ($CDCl_3$): δ 21.3 (t, C-4), 36.7 (q, >N-CH_3), 37.4 (t, C-3), 53.5 (q, -$COO\underline{C}H_3$), 53.7 (t, C-5), 68.8 (s, C-2), 115.0 (s, CN), 167.5 (s, -$\underline{C}OOCH_3$). 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 Na_2SO_4 and the solvent evaporated under vacuum. The product was purified by PLC (silica gel; $CHCl_3$/MeOH; 90/10). Yield 26 mg (20%). ^1H NMR ($CDCl_3$): δ 2.18 (3H, s, α'-CH_3), 2.33 (3H, s, >N-CH_3). ^{13}C NMR ($CDCl_3$): δ 21.9 (t, C-4), 30.7 (q, C-α'), 31.1 (t, C-3), 40.3 (q, >N-CH_3), 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 Na_2SO_4 and the solvent evaporated under vacuum. The product was purified by PLC (silica gel; $CHCl_3$/MeOH; 90/10). Yield 64 mg (25%). ^1H NMR ($CDCl_3$): δ 2.40 (3H, s, >N-CH_3), 3.94 (3H, s, -O-CH_3), 3.95 (3H, s, -O-CH_3), 6.90 (1H, d, J = 8 Hz, aromatic), 7.54 (1H, s, aromatic), 7.62 (1H, d, J = 8 Hz, aromatic). ^{13}C NMR ($CDCl_3$): δ 22.1 (t, C-4), 31.3 (t, C-3), 40.4 (q, >N-CH_3), 42.6 (t, C-α), 55.8 (q, 2 x -O-CH_3), 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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8. For earlier syntheses of (±)-hygrine 5, see inter alia, G.A. Swan, An Introduction to the Alkaloids, Blackwell Scientific Publications, Oxford, 1967. See also E. Leete, J. Am. Chem. Soc., 1967, 89, 7081, and M.L. Rueppel and H. Rapoport, J. Am. Chem. Soc., 1971, 93, 7021.

9. Strictly speaking N-methylruspolinone 6 is not an alkaloid but the N-methyl derivative of the known alkaloid ruspolinone.[10]

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11. For earlier syntheses of alkaloids of ruspolinone type, see R.B. Herbert, F.B. Jackson and I.T. Nicolson, J. C. S. Chem. Comm., 1976, 450; See also R.B. Herbert and P.C. Wormald, J. Chem. Research (S), 1982, 299.

12. The use of silver ion, e.g. silver trifluoroacetate, in THF to enhance the leaving ability of the cyano group, in the manner employed by Husson et al.[5] for dihydropyridine nitriles, resulted in a mixture of polar compounds, apparently dimeric and trimeric in nature.[13]

13. G.A. Swan and J.D. Wilcock, J. C. S. Chem. Comm., 1974, 885.

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