NOVEL APPLICATIONS OF THE MODIFIED POLONOVSKI REACTION - II[1]

REGIOCONTROLLED IMINIUM ION FORMATION

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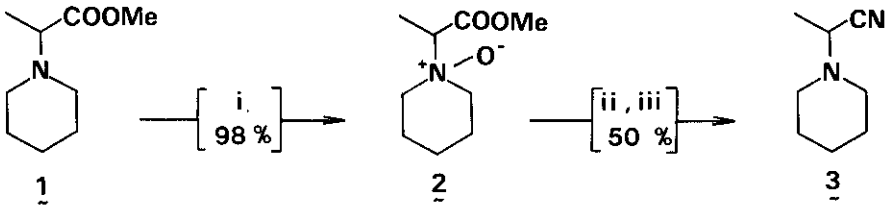
Abstract – Suitably substituted α-piperidinoacetic esters can be transformed to either the corresponding endocyclic or exocyclic α-amino nitriles. The latter case is accompanied with decarboxylation.

Masked iminium compounds can easily be generated from the corresponding N-oxides *via* the Polonovski-Potier (modified Polonovski) reaction[2-4] followed by trapping the intermediate iminium ion according to the procedure described by Husson[5].

Generation of an exocyclic iminium double bond on a piperidine ring has been indicated by Potier *et al.*[6] and recently we[1] have shown that when the intermediate exocyclic iminium compound is subjected to the Husson cyanide-trapping conditions[5], the decarboxylated α-aminonitrile 3[1] can be isolated in fair yield.

Further experimentation on this reaction has allowed us to develop a selective method to generate the iminium equivalent either exocyclic (as in 3) or endocyclic (as in 4) from the same starting compound 1 simply by a slight change of reaction conditions.
When the oxidation of 1 is performed with H_2O_2 (method A) and the isolated N-oxide 2 subjected to the Polonovski-Potier reaction conditions[2-4] followed by cyanide-trapping[5], only the decarboxylated exocyclic aminonitrile 3[1] is generated. An alternative m-CPBA- oxidation of 1 *in situ* and subsequent Polonovski-Potier-Husson reaction (method B) as above gives the endocyclic aminonitrile 4 as the only isolable product.

Method A



1 2 3

REAGENTS: i H_2O_2; ii TFAA, CH_2Cl_2, 0°, then r.t.; iii KCN / H_2O - CH_2Cl_2, r.t., pH 5.

Method B

1 4

REAGENTS: i mCPBA, CH_2Cl_2, 0°; ii TFAA, CH_2Cl_2, - 15°; iii KCN / H_2O - CH_2Cl_2, r.t., pH 5.

Our procedure thus constitutes a highly selective method to control the formation of the iminium equivalent either exo- or endocyclic at will. The ease of operation, selective formation of either type of product depending only on the method chosen and the ease of purification make these two complementary reactions extremely versatile for several synthetic problems.

Further work on the application of these methods, especially on the synthesis of sarpagine type indole alkaloids, is in progress.

Typical experimental procedures are given below:

Method A: Compound 1 (1.71 g, 10 mmol) was dissolved in 1:1 $CHCl_3$:EtOH (150 ml) to which 30 % H_2O_2 (2.5 ml) was added. The mixture was stirred at 68°C for 21 h and then 10 % Pd/C (200 mg) was added. After stirring for another 1 h at 68°C, Pd/C was filtered and the solution was taken to dryness *in vacuo*. The residue was dissolved in dry CH_2Cl_2 (50 ml), the solution dried twice with Na_2SO_4 and evaporated *in vacuo*. After final drying for 5 h in vacuum pump, the N-oxide 2 was obtained as a pale yellow semisolid oil (1.84 g, 98 %).
The N-oxide 2 was dissolved in dry CH_2Cl_2 (25 ml) and stirred at 0°C under argon. To this solution, trifluoroacetic anhydride (3.0 ml, 2.5 eq) was added *via* syringe over a period of 15 min, the mixture stirred for 1 h at 0°C and 15 min at r.t. It was then concentrated *in vacuo*, redissolved in CH_2Cl_2 (7 ml) and reacted with an aqueous solution of KCN (1.0 g, 1.5 eq)

in H_2O (5 ml) (pH of the aqueous layer was adjusted to 5 by the addition of solid NaOAc) for 15 min. After basification (10 % aq Na_2CO_3), extractive work-up and chromatographic purification (alumina, 1:1 CH_2Cl_2:hexane) gave 3[1] (0.69 g, 50 %) as a colorless oil.
IR: 2220 cm^{-1} (w) (CN).
^{1}HNMR ($CDCl_3$, 60 MHz) δ: 1.45 (d, J = 7.3 Hz, 3 H), 1.4 - 1.95 (m, 6 H), 2.51 (m, 4 H), 3.63 (q, J = 7.3 Hz, 1 H).
^{13}CNMR ($CDCl_3$, 15 MHz) δ: 17.0 (q, $\underline{C}H_3$-CH), 23.9 (t, C-4), 25.5 (t, C-3 and C-5), 50.5 (t, C-2 and C-6), 52.8 (d, N-$\underline{C}$H-CH_3), 117.4 (s, $\underline{C}$N).
MS m/z (rel. int.): 138 (M^+), 123 (100 %), 111, 110, 96, 82, 69, 55.

Method B: To a cooled (0°C) stirred solution of 1 (2.57 g, 15 mmol) in dry CH_2Cl_2 (50 ml) under argon, m-CPBA (80 %) (2.85 g, 1.1 eq) in dry CH_2Cl_2 (30 ml) was added *via* syringe. The mixture was stirred at 0°C for 1.5 h and then cooled to - 15°C. Trifluoroacetic anhydride (4.2 ml, 2.3 eq) was added *via* syringe over a period of 15 min and stirring was continued for another 1 h at - 15°C. The solution was then rapidly concentrated to a volume of about 15 ml and thereafter reacted with aq KCN as in method A. Usual extractive work-up and column chromatographic (alumina) purification gave 4 (1.16 g, 40 %) as a pale yellow oil.

IR: 2280 cm^{-1} (w) (CN), 1745 cm^{-1} (s) (COOMe).
^{1}HNMR ($CDCl_3$, 60 MHz) δ: 1.34 (d, J = 7 Hz, 3 H), 1.3 - 2.1 (m, 6 H), 2.55 - 2.95 (m, 2 H), 3.48 (q, J = 7 Hz, 1 H), 3.73 (s, 3 H), 3.90 (m, 1 H).
^{13}C NMR ($CDCl_3$, 15 MHz) δ: 14.22 and 14.87 (q, $\underline{C}H_3$-CH), 20.00 and 20.32 (t, C-4), 24.67 (t, C-5), 28.83 and 29.41 (t, C-3), 45.52 and 46.02 (t, C-6), 49.80 and 50.19 (d, C-2), 50.97 (q, O-$\underline{C}H_3$), 60.64 and 61.49 (d, N-$\underline{C}$H-CH_3), 116.16 and 117.07 (s, CN), 171.86 and 172,32 (s, $\underline{C}OOCH_3$).
MS m/z (rel. int.): 196 (2, M^+), 181 (100), 166 (25), 113 (50).

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