Enantioselective Synthesis of Some Nicotiana Alkaloids

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A modified approach to myosmine (6) via a silyl enol ether of 3-acetylpyridine (1) is described. Chiral reduction of 6 with N-(benzyloxycarbonyl)-L-proline/NaBH₄ and formylation leads to (R)-N-formylnornicotine (8) (35 % ee) which in turn is converted to (R)-nornicotine (11) and (R)-nicotine (10).

Various methods for the synthesis of nicotiana alkaloids as racemates are reported, inter alia. We here describe a modified approach to myosmine (6) and strategies for chiral syntheses of nicotine derivatives.

Methyl-arylketones react with Böhme-Eschenmoser-salt to the pertinent Mannich bases (type 4) which in turn are converted to the 3-oxo-3-arylbutyronitriles (type 5). Partial hydrogenation with concomitant ring closure leads to 2-aryl-1-pyrrolines (type 6). This method gives very low yields with methyl-arylketones having low C-H-acidity of the methyl group as we recognized in our synthesis of Preininger's alkaloid. So we adapted Danishefsky's idea of activating the methyl group via its pertinent silyl enol ether: 3-acetylpyridine (1) was silylated in 95 % yield with CH₃-S-O-Si(CH₃)₃ to 2; 2 reacted with dimethyl-methylene-immonium iodide to give 3, which was hydrolyzed to the Mannich base 4. 4-HCl was treated with CN⁻ to afford the nitrile 5, the overall yield 2 to 5 is 72–75 %. Partial hydrogenation of 5 with Raney-Ni in EtOH/NH₃ led to myosmine (6). An exceeding hydrogenation to racem. nornicotine is prevented by our conditions (cf. Experi. Part) (Scheme 1).

Chiral reduction generates a centre of chirality at C-1 of the former pyrroline group.

Chiral reductions of imines being part of indol and isoquinoline alkaloids with Iwakuma's reagent are known. In our hands usual cleavage of the N-borane adduct as described does not give any defined product. Therefore, we used our work-up procedure with simultaneous N-acylation, leading to the rotamers of (+)-(R)-N-formylnornicotine (8) in 35 % ee and 90 % chemical yield. Routine procedures give rise to (+)-(R)-nicotine (10) and (+)-(R)-nornicotine (11) of equal optical purity (Scheme 2).
Use of acetyl anhydride instead of the mixed anhydride H-CO-O-CO-CH_3 during work-up after chiral reduction affords the racemate of N-acetyl-nornicotinic (9)11 with the enantiomer R-9 being enriched.

Experimental part

General remarks: lit10. – Kugelrohr distillations were performed in a Büchi apparatus with at least 5 bulbs and twofold cooling with dry ice. The external temp. is cited.

1-Trimethylsilyloxy-1-(3-pyridyl)-ethene (2)

To 6.05 (0.05 mol) 3-acytelypyridine (1)1 in 80 ml absol. benzene and 6 g Et_3N were added drop by drop 23.05 g F_3C-CH=Si(OCH_3)_3 then the mixture was refluxed for 3 h. The upper phase (benzene) was evaporated i. vac. and the residue sublimated under the condition of Kugelrohr distillation (50–60 °C, 0.05 mm Hg): White crystals (9.18 g, 95%), m. p. > 200 °C.

2-Cyano-1-(3-pyridyl)-propan-1-one (5)

7.73 g (0.04 mol) 2 were dissolved in 20 ml absol. CH_2Cl_2 under purified N_2. Then 8.14 g (10% excess) dimethylmethyleniminium iodide14 was added at 0 °C in one portion under purified N_2. After addition cooling is removed and after 1 h CH_2Cl_2 is evaporated i. vac. under N_2. The residue (colourless oil 3; the structure of 3 is deduced from Danishefsky’s publication9) was dissolved at 0 °C in 2N HCl, excess HCl was evaporated i. vac. leaving a colourless oil 4. In the hood dry KCN (3.90 g, 50% excess) was added in one portion under N_2 followed by 400 ml water of 40 °C. After stirring under N_2 at this temp. until 4 had disappeared (tlc control; Al_2O_3/ethyl acetate or Al_2O_3/HCl); CH_2Cl_2), Chromatography (CC) (Al_2O_3/ethyl acetate) afforded 4.60 g (72%) 5; m. p. 66 °C (Et_2O, lit.3: 66–67 °C). – IR (KBr): 2264 cm^−1 (C=N), 1700 cm^−1 (C=0). – 'H-NMR: 8 (ppm) = 3.07 (3H, s; CH_3); 7.43–8.40 (2H, aromat.).

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Myosine (6)

Contrary to Leete5 we hydrogenated 5 at atmospheric pressure and 40–50 °C. – To 2.92 (20 mmol) 5 in 100 ml absol. EtOH were added 3 ml of abs. EtOH which was saturated with NH_3 at 0 °C. and 1.5 g Raney-Ni. – The reaction was controlled by tlc (Al_2O_3/ethyl acetate or Al_2O_3/Et_3O) in order to prevent further reduction of the C=N double bond. When 5 had been converted completely, the mixture was filtered and evaporated and the residue was purified (short column; Al_2O_3; CH_2Cl_2) to obtain 6 as a colourless pure residue (NMR). Kugelrohr distillation at 95 °C/0.05 mm Hg: 10 mg (93%) colourless oil.

(+)-(R)-N-Formylnornicotine (8)

Modifying Ikawaka’s procedure his reagent was prepared as follows: 1.98 g (7.98 mmol) N-benzoylcarbonyl-L-proline were added in portions to a suspension of 79.44 mg (2.10 mmol) NaH in 13 ml absol. THF at 5 °C under N_2 and stirring. Stirring at this temp. was continued until development of H_2 had ceased. After 3 h at room temp. THF was evaporated at 10 °C under N_2, the residue was dried at 20 °C, 0.05 mmg Hg, and dissolved in 4 ml absol. CH_2Cl_2 at 0 °C under N_2. – To this solution 219.3 mg (1.5 mmol) 6 in 4 ml absol. CH_2Cl_2 were added at 0 °C under N_2. After 10 h at 0 °C and stirring for 3 d at room temp. the solution was divided into two fractions (about 1.5 and 6.5 ml, respectively). Both solutions were evaporated separately (faint yellow oils). The major part was reacted at 0 °C with 6 ml acetic formic anhydride, previously cooled to 0 °C. The mixture was stirred for 30 min at room temp. then 30 min at 40–50 °C, followed by evaporation of the excess of anhydride. To the residue was added HClO_4 (70%) at 0 °C. After 30 min at 0 °C and 30 min at room temp. the mixture was neutralized with NaOH at 0 °C and rapidly extracted with CH_2Cl_2. After drying and CC (Al_2O_3; CH_2Cl_2/H_2CCN 9:1) 8 was purified by Kugelrohr distillation (95–100 °C; 0.05 mm Hg): 195.4 mg (91%) colourless oil. – 1R (film): 1665 cm^−1 (CO). – 1H-NMR: 8 (ppm) = 1.75–2.15 (m; 3H, pyrrolidine), 2.25–2.60 (m; 1H, pyrrolidine), 3.47–3.97 (m; 2H, pyrrolidine), 4.85–5.20 (m; 1H, pyrrolidine), 7.27–7.54 (m; 2H, aromat.), 8.39 (s; 0.35 H, N-CH=0), 8.15 (s; 0.65 H, N-CH=0), 8.67–8.80 (m; 2H, aromat.). Because 8 was not separated on ChirasilR the ee was determined at the stage of N-acetyl-nornicotinate (9).

The minor fraction was processed analogously but instead of the mixed anhydride mentioned above 3 ml acetic anhydride was used. Neutralization at −5 °C; CC with CHCl_3; Kugelrohr distillation at 95 °C/0.05 mm Hg: 49.75 mg (93%) colourless oil.

The ee was determined as described10.11: 35.4% (+)-(R)-9. - IR (film): 1660 cm^−1 (CO). – 1H-NMR: 8 (ppm) = 1.70–2.70 (m; 4H, pyrrolidine), 1.82 (s; 3H, CO-CH_3), 3.48–3.85 (m; 2H, pyrrolidine), 4.83–5.28 (m; 1H, pyrrolidine), 7.40–7.58 (m; 2H, aromat.), 8.35–8.85 (m; 2H, aromat.). – The ms revealed the fragment ions described11 in similar rel. int.

References


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7 3-Acetylpyridine from EGA-Chemie, D-7900 Steinheim.