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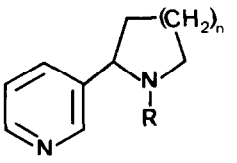
SYNTHESIS OF TOBACCO ALKALOIDS VIA TERTIARY AZIDES

Gilles F. ALBERICI, Jean ANDRIEUX*, Gérard ADAM and Michel M. PLAT

Laboratoire de Pharmacie Chimique II. E.R.A. 317
Faculté de Pharmacie - Université de PARIS XI
11, rue Jean-Baptiste Clément
92290 CHATENAY-MALABRY - FRANCE

Abstract: A convenient new synthesis of different tobacco alkaloids, such as nicotine and anabasine is described, using as key step the SCHMIDT reaction applied to tertiary alcohols.

Many syntheses of pyridine alkaloids substituted in the -3 position like nicotine 4a and anabasine 3b have been proposed during the last century (1, 2) and more recently (3, 4).



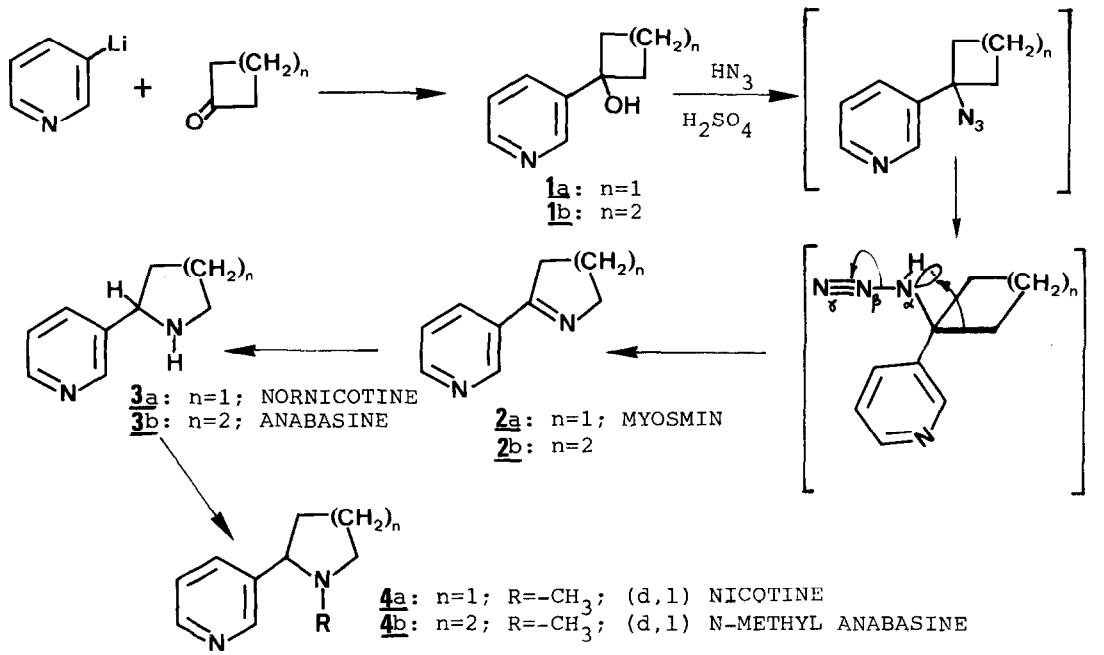
4a: nicotine n = 1, R = CH_3

3b: anabasine n = 2, R = H

Recently, a new stereoselective synthesis has been published using L-proline as starting material (5). The yields of these methods are generally poor because either the intermediates are too numerous, or there is, in the synthetic pathway, a limiting step.

During previous works, we have shown that the acid catalysed breakdown of tertiary azides gives the same products as those obtained by applying the SCHMIDT reaction (HN_3-H_2SO_4) to tertiary alcohols or trisubstituted olefins. This is important when the intermediary azides cannot be obtained and these two reactions lead easily and directly to heterocycle imines substituted on the carbon atom in the α-position relative to nitrogen, and, according to this route, simple disubstituted pyridine alkaloids have been prepared (6). In benzocyclanic series, acid catalysed breakdown of tertiary azides leads, in a regioselective manner, to heterocycles in which only benzylic bond migration has been observed. So, indoles (7), 3,4-dihydro 5H benzo (b) azepines (8) and 3,4-dihydro quinolines (9) has been prepared with good yields. This regioselectivity is not encountered when the SCHIMDT reaction is applied to benzocyclanic ketones (10).

This method is now extended to the preparation of some tobacco alkaloids, according to the following scheme:



Scheme 1

The condensation of 3-pyridyl lithium (prepared from n-butyl lithium and 3-bromopyridin at -78°C (11)) with cyclobutanone leads to 1-(3-pyridyl) cyclobutanol 1a with a 80 % yield (I.R.: ν (OH): 3380 cm^{-1}; N.M.R. ^1H (δ ppm/T.M.S.-$CDCl_3$): (-CH_2-2-3 and -4): from 1,40 to 2,65, m, 6H; (-OH-1): 5,80, s, 1H; (-H-5'): 7,20, dd, 1H; (-H-4') 7,85, td, 1H; (-H-6'): 8,30, dd, 1H; (-H-2') 8,60, d, 1H; N.M.R.^{13}C (δppm/TMS-$CDCl_3$): C_1: 74,2, s; M.S.: M^+ m/e = 149).

The same reaction on cyclopentanone allows the preparation of 1-(3-pyridyl) cyclopentanol 1b (I.R.: ν (OH): 3280 cm^{-1}; N.M.R. ^1H: (-CH_2-2, -3, -4 and -5) from 1,65 to 2,20, m, 8H; (-OH-1): 4,40, s, 1H; (-H-5'): 7,10, dd, 1H; (-H-4'): 7,80, td, 1H; (-H-6') 8,25, dd, 1H; (-H-2'): 8,55, d, 1H; N.M.R. ^{13}C: C_1: 80,7, s; M.S.: M^+ m/e = 163). Attempts to isolate tertiary azides in treating alcohols 1a and 1b with hydrazoic acid and boron trifluoride etherate in benzene were infructuous because of complexation of the pyridin: nitrogen atom with the Lewis acid (12). These results explain why, in this work, we have used the SCHMIDT reaction directly.

Treatment of alcohol 1a *at 0°C with a solution of hydrazoic acid (in dichloromethane) and concentrated* sulfuric acid leads to the imine 2a with a yield of 65 % (I.R.: ν (C=N): 1615 cm^{-1}; N.M.R. ^1H: (-CH_2-4):

from 1,85 to 2,35, m, 2H; (-CH_2-5): from 2,75 to 3,05, m, 2H; (-CH_2-3): from 3,85 to 4,25, m, 2H; (-H-5'): 7,30, dd, 1H; (-H-4'): 8,15, td, 1H; (-H-6'): 8,65, dd, 1H; (-H-2'): 8,97, d, 1H; N.M.R. ^{13}C: C_2: 170,5, s; M.S.: M^+ m/e = 146). The imine 2a is identical to an authentic sample of myosmin. In a similar manner, the alcohol 1b, treated in the same experimental conditions gives the imine 2b with a good yield (75 %). (I.R.: ν (C=N): 1630 cm^{-1}; N.M.R. ^1H: (-CH_2 -4 and -5) from 1,40 to 2,15, m, 4H; (-CH_2-3) from 2,45 to 2,85, m, 2H; (-CH_2 -6) from 3,75 to 4,05), m, 2H; (-H-5') 7,25, dd, 1H; (-H-4') 8,05, td, 1H; (-H-6') 8,60, dd, 1H; (-H-2') 8,95, d, 1H; N.M.R. ^{13}C: C_2: 163,5, s; M.S.: M^+ m/e = 160).

These results show that migration of the pyridyl substituent does not occur since the exocyclic imine formed in this way would have led, by hydrolysis in these experimental conditions, to a mixture of 3-aminopyridine and starting ketone. This can be explained by the fact that, in acid medium, protonation of the pyridinic nitrogen atom reverses its electronic effect in such a way that the cyclanic bonds are more able to migrate onto an electron-deficient system. To this electronic effect are added, firstly, the decrease of ring strains already seen in other examples (7,13) and secondly, the preferential migration of acyclic bonds (C_1-C_2) transantiperiplanar relative to the azido group which, in this position, has the maximum overlap with the sp_x orbital of the free doublet of nitrogen atom N_α (8). These facts are therefore in accordance with an exo position of the azido-group, i.e. oriented in the less hindered half space (14) (see scheme I).

Reduction of myosmin 2a by sodium cyanoborohydride in methanol (15) leads with a 68 % yield to (d,l) nor -nicotine 3a which appears as pale yellow oil further purified by column chromatography (SiO_2; CH_2Cl_2-MeOH) (I.R.: ν (NH): 3240 cm^{-1}; N.M.R. ^1H: (-CH_2-3 and -4): from 1,30 to 2,40, m, 4H; (-NH-1): 2,85, 5, 1H exchangeable with D_2O; (-CH_2-5): 3,20, m, 2H; (-H-2): 3,80, m, 1H; (-H-5'): 7,25, dd, 1H; (-H-4'): 7,75, td, 1H; (-H-6'): 8,40, dd, 1H; (-H-2): 8,60, d, 1H; N.M.R. ^{13}C: C_2: 59,7, d: M.S.: M^+ m/e = 148). The reduction of the imine 2b gives (d,l) anabasine 3b (yield: 95 %; I.R.: ν (NH): 3360 cm^{-1}; N.M.R. ^1H: (-CH_2-3, -4, -5 and -6) from 1,20 to 3,40, m, 8H; (-NH-1): 2,20, s, 1H exchangeable with D_2O; (-H-2): 3,67, m, 1H; (-H-5') 7,20, dd, 1H; (-H-4') 7,80, td, 1H; (-H-6'): 8,40, dd, 1H; (-H-2'): 8,55, d, 1H; N.M.R. ^{13}C: C_2: 59,1, d; M.S.: M^+ m/e = 162). This reduction may also be completed by catalytic hydrogenation with Pd/C. Nor-nicotine 3a and anabasine 3b may be methylated according to ESCHWEILER-method leading to (d,l) nicotine 4a (16) and, (d,l) N-methyl-anabasine 4b respectively (N.M.R. ^1H: (-N-CH_3) 2,03, s, 3H; (-CH_2 -3, -4, -5 and -6): from 1,45 to 2,60, m, 8H; (-H-2): 3,10, m, 1H; (-H-5'): 7,20, dd, 1H; (-H-4'): 7,80, td, 1H); (-H-6'): 8,35, dd, 1H; (-H-2'): 8,40, d, 1H; N.M.R. ^{13}C: (N-CH_3): 36,4, q; C_2: 67,3, d,; M.S.: M^+ m/e = 176).

So, this synthetic method allows the preparation of the desired alkaloïds in only four steps with an almost 40 % yield in relation to cyclanones used as starting materials. This method involves an intermediary imine which may eventually permit the preparation of optically active nicotine and anabasine by using transition metals bearing chiral ligands as reductive agents (17). The convertion of myosmin to nor-nicotyrine is also possible using a known oxidative method (18).

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