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A Simple and Convenient Route to 1,2,3,4,5,6,7,8-Octahydro-1,6-naphthyridines

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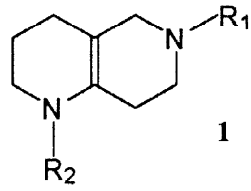
Abstract: A simple and convenient synthetic approach to the new series of 1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridines **1a-j** has been developed. This was achieved *via* a one-pot process combining metalated 4-piperidinonimine alkylation and intramolecular cyclization.

1-Substituted 1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridines **1** are practically unknown in the literature.[1,2] Nevertheless, these molecules seem to be interesting targets since they represent convenient building blocks and also may be precursors to biologically active compounds. Indeed, using the PASS programme[3] we have predicted that these compounds may possess psychotropic, neuroleptic, spasmolytic and analgesic activities.



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In this report, we describe the simple and convenient conversion of 4-piperidinonimines into 1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridines **1**.

The route we have choosen was based on the combination of two methodologies examined in detail by us[4] and by D.A. Evans.[5] The first methodology involves alkylation of metalated 4-piperidinonimines by alkyl halides followed by hydrolysis of the crude product on silica which affords the corresponding 3-substituted 4-piperidinones on a preparative scale.[4] The second methodology involves Evans's two-step annelation sequence allowing for the synthesis of a variety of cyclic enamines from structurally diverse imine anions.[5]

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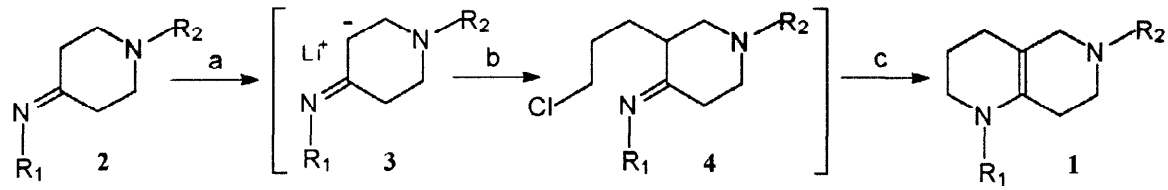
Thus, the combination of the two methodologies mentioned above offered a convenient route to the desired 1-substituted 1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridines **1a-d** (Scheme 1). This methodology has also been applied for the synthesis of optically active 1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridines **1e-j** containing the (*S*)-1-phenylethyl group at N(1).



a: $R_1 = C_6H_5$, $R_2 = CH_3$; b: $R_1 = C_6H_5$, $R_2 = CH_2C_6H_5$; c: $R_1 = CH_2C_6H_5$, $R_2 = CH_2C_6H_5$;
d: (dl)-$CH(CH_3)C_6H_5$, $R_2 = CH_2C_6H_5$; e: R_1 = (S)-$CH(CH_3)C_6H_5$, $R_2 = CH_2C_6H_5$;
f: R_1 = (S)-$CH(CH_3)C_6H_5$, $R_2 = CH_3$; j: R_1 = (S)-$CH(CH_3)C_6H_5$, $R_2 = COC_6H_5$

Scheme 1 Reagents and conditions: a) LDA or $(C_2H_5)_2NLi$, THF, -30°C, 30 min; b) $Cl(CH_2)_3Br$, -78°C to rt; c) reflux 4 h

Imines **2a-d** and optically active examples **2e-j**[4b] were prepared from corresponding 1-substituted 4-piperidinones and amines following the usual methodology (toluene, Dean-Stark trap for imines **2a,b**[6] or benzene, anhydrous $MgSO_4$ for imines **2c-j**[7]) in 80-100% yields. Metalation of imines **2a-j** was readily accomplished using an excess of lithium diisopropyl amide (LDA) or lithium diethylamide. Alkylation of the lithio derivatives **3a-j** by 1,3-bromochloropropane and subsequent intramolecular cyclization of the resulting chloroalkyl imines **4a-j**[8] directly afforded the endocyclic enamines **1a-j**.[9] All compounds were characterized by 400 MHz ^1H NMR, IR and mass spectrometry.[10]

In conclusion, 1-substituted 1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridines **1a-j** can be made readily available by a simple and convenient approach. Further studies directed towards the preparation of optically active decahydro-1,6-naphthyridine derivatives *via* asymmetric transformation of the endoenamine function in **1e-j** are under way.

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8. Hydrolysis of the crude alkylated imine **3b** on a silica gel column gave 1-benzyl-3-(3-chloropropyl)-4-piperidinone in 70% yield. Colourless oil. TCL (silica gel 60 F_{254}, Merck, benzene - acetone, 6:1) R_f 0.75. IR: ν_{max} (film) 1720 cm^{-1} (C=O). m/z 263, 265 $[M]^+$ 100%, 220 (15) $[M-43]^+$, 187 (15) $[M-76]^+$, 172 (15) $[M-91]^+$, 146 (15) $[M-117]^+$, 133 (15) $[M-130]^+$, 120 (15) $[M-143]^+$, 117 (15) $[M-146]^+$, 91(100) $[M-172]^+$. ^1H NMR (C_6D_6, 400 MHz), δ: 1.35 (m, 1H, 7H), 1.78 (m, 5a, 5e, 7H'), 2.30 (dd, 1H, 2a, J_{gem}=11.4, $J_{2a,3a}$=10.0 Hz), 2.34 (m, 1H, 6a), 2.60 (m, 3a, 8H, 8H'), 3.10 (m, 2H, 2e, 6e), 3.52 (m, 2H, 9-$C\underline{H}_2Cl$), 3.62 (AB q, 2H, J_{gem}=13.3 Hz, $C\underline{H}_2C_6H_5$), 7.20 (m, 5H, $CH_2C_6\underline{H}_5$). Chloroalkyl imines **4a-j** were used directly in the next step without isolation.
9. ***General Procedure for the Preparation of Compounds* 1a-j**: All reactions were carried out using syringe techniques under an argon atmosphere. To a solution 0.22 g (2.18 mmol) of diisopropylamine in 20 ml of anhydrous THF was added at -10 °C 1.09 ml (2.50 mmol) of 2M solution of *n*-BuLi in hexane. After 10 min, the mixture was cooled to -30 °C and 0.50 g (1.89 mmol) of **2b** in anhydrous THF (3 ml) was added. After 30 min, the deep red solution was cooled to -78 °C and 0.36 g (2.27 mmol) of 1,3-bromochloropropane in anhydrous THF (2 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature over a period of 2 h and then refluxed for 4 h. The solution was evaporated *in vacuo*, diluted with brine (10 ml), made basic with solid K_2CO_3 (pH 9-10) and extracted with ether (7 x 5 ml). The organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on alumina with 10% ethyl acetate/pentane to yield 0.42 g (73%) of pure product **1b**.

   The crude enamines **1a-j** were obtained in 70-90% yields according to analysis by ^1H NMR. However, isolated yields of enamines **1c-j** containing benzyl and (*S*)-1-phenylethyl groups at N(1) after SiO_2 or

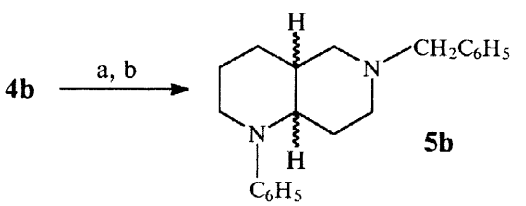
alumina column purification were reduced to 30-40%. Therefore, endocyclic enamines **1** should be used directly without purification.

Selected physical and spectral data:

1b: 73%. Colourless oil. TCL (silica gel, 60 F_{254}, Merck, benzene - acetone, 2:1) R_f 0,63. IR: ν_{max} (film) 1695 cm^{-1} (N-C=C). m/z 304 (M^+, 50%), 275 (2) $[M-29]^+$, 213 (20) $[M-91]^+$, 198 (6) $[M-106]^+$, 184 (21) $[M-120]^+$, 170 (4) $[M-134]^+$, 156 (3) $[M-148]^+$, 144 (1) $[M-160]^+$, 130(3) $[M-174]^+$, 118 (3) $[M-186]^+$, 106 (4) $[M-198]^+$, 91(49) $[M-213]^+$. ^1H NMR (C_6D_6, 400 MHz), δ 1.43 (m, 2H, 3-$C\underline{H}_2$), 1.68 (m, 2H, 4-$C\underline{H}_2$), 2.23 (m, 2H, 8-$C\underline{H}_2$), 2.47 (m, 2H, 7-$C\underline{H}_2$), 2.93 (m, 2H, 5-$C\underline{H}_2$), 3.28 (m, 2H, 2-$C\underline{H}_2$), 3.48 (c, 2H, $C\underline{H}_2C_6H_5$), 7.35 (m, 10H, $C_6\underline{H}_5$ and $CH_2C_6\underline{H}_5$).

1e: 35%. Yellow oil. TCL (silica gel, 60 F_{254}, Merck, benzene - acetone, 2:1) R_f 0.63. $[\alpha]_D^{24}$ - 26.8° (*c* 4.10, benzene). IR: ν_{max} (film) 1675 cm^{-1} (N-C=C). m/z 332 (M^+, 53%), 331 (100) $[M-1]^+$, 303 (4) $[F_1-28]^+$, 241 (18) $[M-91]^+$, (F_1), 227 (21) $[M-105]^+$, 212 (24) $[F_1-119]^+$, 105 (55) $[M-227]^+$, 91 (44) $[M-241]^+$. 1H NMR (C_6D_6, 400 MHz), δ 1.21 (d, 3H, J = 7.00 Hz, $CH(C\underline{H}_3)C_6H_5$), 1.48 (m, 2H, 3-$C\underline{H}_2$), 1.74 (m, 2H, 4-$C\underline{H}_2$), 2.18 (m, 2H, 8-$C\underline{H}_2$), 2.48 (m, 1H, 7-$C\underline{H}_2$), 2.64 (m, 3H, 7-$C\underline{H}'_2$, 2-$C\underline{H}_2$), 2.85 (d, 1H, J = 14.40 Hz, $\underline{H}$-5*a*), 3.02 (d, 1H, J = 14.40 Hz, $\underline{H}$-5*e*), 3.50 and 3.52 (AB q, 2H, J = 14.40 Hz, $C\underline{H}_2C_6H_5$), 4.55 (q, 1H, J = 7.00 Hz, $C\underline{H}(CH_3)C_6H_5$), 6.90 - 7.5 (m, 10H, $CH(CH_3)C_6\underline{H}_5$ and $CH_2C_6\underline{H}_5$).

10. Usually the isolated enamines are rather unstable and all attempts to obtain analytical samples have failed. Therefore 6-benzyl-1-phenyl-1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridine **1b** was analysed as the decahydro derivative **5b** (Scheme 2).



Scheme 2 Reagents and conditions: a) HCl/C_2H_5OH; b) $NaBH_4$, 3 eq., -78 °C

5b: 69%. Colorless oil. The mixture of *cis* and *trans* isomers. TCL (silica gel, 60 F_{254}, Merck, benzene - acetone, 2:1) R_f 0·50 and 0·35. m/z 306 ($[M]^+$, 17%), 215 (85) $[M-91]^+$, (F_1), 186 (59) $[F_1-29]^+$, 173 (5) $[F_1-42]^+$, 172 (21) $[M-134]^+$, 158 (9) $[M-148]^+$, 134 (5) $[M-172]^+$, 91 (100) $[M-215]^+$. ^1H NMR (CD_2Cl_2, 400 MHz), δ 1.10 (m, 1H); 1.30 (m, 1H); 1.50 (m, 1H); 1.70 (m, 6H); 1.95 (m, 1H); 2.25 (m, 1H); 2.75 (m, 2H); 3.19 (m, 1H); 3.50 (m, 2H); 7.00 - 7.20 (m, 10H, Ar). Anal. Calcd for $C_{21}H_{26}N_2$: C 82.31; H 8.55; N 9.14; found C 82.22; H 8.51; N 8.86.