Stereoselective Synthesis of all-*trans*-Isomers of 1,2,3,4-Tetrahydropyridines and Piperidines from Hantzsch-Type 1,4-Dihydropyridines

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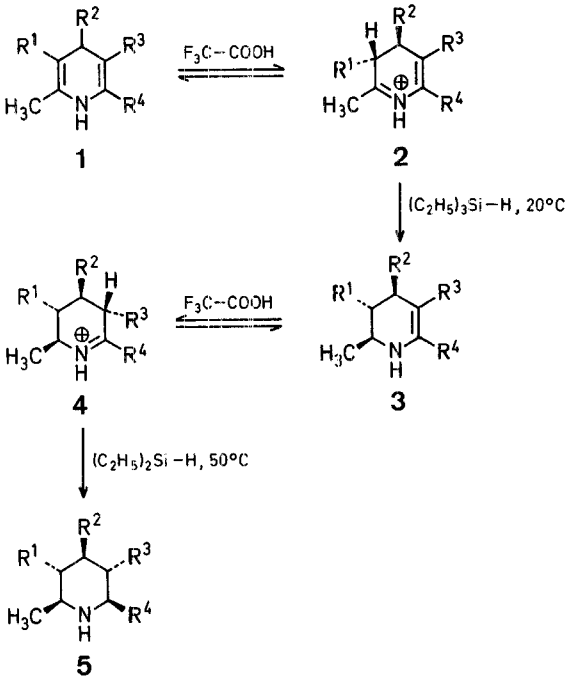
1,4-Dihydropyridines obtained by Hantzsch synthesis[1,2] can be reduced to the corresponding 1,2,3,4-tetrahydropyridines and piperidines by either electrochemical reduction[3,4] or catalytic hydrogenation[5,6]. These methods are however incompatible with the presence of numerous functional groups such as nitro, keto, cyano or olefinic double bonds.

In this communication we report a practical synthesis of stereochemically pure 1,2,3,4-tetrahydropyridines (**3**) and piperidines (**5**) from 1,4-dihydropyridines (**1**) that tolerates the presence of a broad variety of functional groups. The reductions are carried out in trifluoroacetic acid with triethylsilane[7] as a hydride donating agent. 1,2,3,4-



1 **2** **3** **4** **5**

1-5	R^1	R^2	R^3	R^4
a	H_3COOC		$COOCH_3$	CH_3
b	H_3COOC		$COCH_3$	CH_3
c	H_3COOC		$COCH_3$	CH_3
d	$H_3C–CO–$		$–CO–CH_3$	CH_3
e	H_3COOC		$–CN$	CH_3
f	C_2H_5OOC		$COOC_2H_5$	$COOC_2H_5$

Tetrahydropyridines (**3**) are obtained selectively with 1 equivalent of triethylsilane at room temperature (Table 1). Use of 3 equivalents of triethylsilane at ~ 50 °C yields the piperidine derivatives **5** (Table 2).

The stepwise, stereoselective reduction is explained by the following mechanism. Reversible protonation of a double bond in **1** gives the thermodynamically more stable *trans*-configuration of the 3,4-substituents in **2**. The resulting, highly reactive, vinylogous *N*-acyliminium species **2** is reduced by triethylsilane to the thermodynamically most stable all-*trans*-configurated product **3**. Protonation of **3** gives an immonium salt **4** of lower reactivity (as compared to **2**) which reacts with triethylsilane only at higher temperature.

The reaction of the educt **1f** is an exception. Since the intermediate immonium salt **4f** ($R^4 = COOC_2H_5$) is sufficiently activated, product **5f** is formed by reaction with triethylsilane at 20 °C.

Table 1. 1,2,3,4-Tetrahydropyridines (**3**) prepared

Product	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
3a	58	67–73°	$C_{17}H_{21}NO_4$ (303.3)	3340, 1735, 1670, 1595, 1510	1.08 (d, J = 7 Hz, 3H); 2.30 (s, 3H); 2.51 (t, J = 10 Hz, 1H); 3.25 (s, 3H); 3.53 (s, 3H); 3.56 (dq, J = 10 Hz, J = 7 Hz, 1H); 4.10 (s, 1H); 4.15 (d, J = 10 Hz, 1H); 7.05–7.33 (m, 5H)
3b	66	157–160°	$C_{17}H_{20}N_2O_6$ (348.4)	3430, 1740, 1690, 1600, 1530	1.20 (d, J = 7 Hz, 3H); 2.31 (s, 3H); 2.68 (t, J = 10 Hz, 1H); 3.25 (s, 3H); 3.61 (dq, J = 10 Hz, J = 7 Hz, 1H); 3.65 (s, 3H); 4.13 (s, 1H); 4.65 (d, J = 10 Hz, 1H); 7.23–7.39 (m, 2H); 7.48 (t, J = 8 Hz, 1H); 7.69 (d, J = 8 Hz, 1H)
3c	69	126°	$C_{18}H_{20}F_3NO_4$ (371.4)	3320, 1740, 1670, 1580, 1570, 1530	1.11 (d, J = 7 Hz, 3H); 2.34 (s, 3H); 2.58 (t, J = 10 Hz, 1H); 3.23 (s, 3H); 3.55 (s, 3H); 3.65 (dq, J = 10 Hz, J = 7 Hz, 1H); 4.13 (s, 1H); 4.53 (d, J = 10 Hz, 1H); 7.23 (t, J = 7 Hz, 1H); 7.35 (t, J = 7 Hz, 1H); 7.45 (t, J = 7 Hz, 1H); 7.56 (d, J = 7 Hz, 1 Hz)
3d	64	175–180°	$C_{17}H_{20}N_2O_4$ (316.4)	3270, 1705, 1630, 1530, 1500	1.08 (d, J = 7 Hz, 3H); 1.84 (s, 3H); 1.88 (s, 3H); 2.35 (s, 3H); 2.78 (t, J = 9 Hz, 1H); 3.54 (dq, J = 9 Hz, J = 7 Hz, 1H); 4.34 (d, J = 9 Hz, 1H); 4.60 (s, 1H); 7.34–7.56 (m, 2H); 7.98–8.13 (m, 2H)
3e	63	202–204°	$C_{16}H_{17}N_3O_4$ (315.3)	3300, 2180, 1730, 1600, 1500	1.20 (d, J = 7 Hz, 3H); 2.13 (s, 3H); 2.35 (t, J = 11 Hz, 1H); 3.49 (s, 3H); 3.54 (dq, J = 11 Hz, J = 7 Hz, 1H); 3.98 (d, J = 11 Hz, 1H); 6.59 (s, 1H); 7.45–7.58 (m, 2H); 8.01 (s, 1H); 8.06–8.15 (m, 1H)

[a] Satisfactory microanalysis obtained: C ±0.31, H ±0.13, N ±0.13.

Table 2. Piperidines (**5**) prepared

Product	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
5a	55	122–124°	$C_{17}H_{23}NO_4$ (305.4)	1725, 1710	1.13 (d, J = 7 Hz, 6H); 2.36 (dd, J = 11 Hz, J = 10 Hz, 2H); 3.12 (dq, J = 10 Hz, J = 7 Hz, 2H); 3.26 (t, J = 11 Hz, 1H); 3.39 (s, 6H); 7.10–7.33 (m, 5H)
5b	94	142°	$C_{17}H_{22}N_2O_6$ (350.4)	1740, 1730, 1520	1.14 (d, J = 7 Hz, 6H); 2.35 (dd, J = 11 Hz, J = 10 Hz, 2H); 3.14 (dq, J = 11 Hz, J = 10 Hz, 2H); 3.48 (s, 6H); 3.95 (t, J = 11 Hz, 1H); 7.28–7.39 (ddd, J = 7 Hz, J = 6 Hz, J = 3 Hz, 1H); 7.50–7.65 (m, 3H)
5c	56	70°	$C_{18}H_{22}F_3NO_4$ (373.4)	1740, 1730	1.13 (d, J = 7 Hz, 6H); 2.38 (t, J = 11 Hz, 2H); 3.21 (dq, J = 11 Hz, J = 7 Hz, 2H); 3.39 (s, 6H); 3.65 (t, J = 11 Hz, 1H); 7.30–7.38 (m, 1H); 7.54–7.61 (m, 3H)
5d	60	138°	$C_{17}H_{22}N_2O_4$ (318.4)	1700, 1540, 1520	1.13 (d, J = 7 Hz, 6H); 1.76 (s, 6H); 2.63 (dd, J = 11 Hz, J = 10 Hz, 2H); 3.06 (dq, J = 10 Hz, J = 7 Hz, 2H); 3.33 (t, J = 11 Hz, 1H); 7.36–7.50 (m, 2H); 8.03–8.11 (m, 2H)
5e	89	112°	$C_{16}H_{19}N_3O_4$ (317.4)	2250, 1740, 1530	1.12 (d, J = 7 Hz, 3H); 1.39 (d, J = 7 Hz, 3H); 2.38 (dd, J = 11 Hz, J = 10 Hz, 1H); 2.45 (dd, J = 11 Hz, J = 10 Hz, 1H); 3.06 (dq, J = 10 Hz, J = 7 Hz, 1H); 3.12 (dq, J = 10 Hz, J = 7 Hz, 1H); 3.29 (t, J = 11 Hz, 1H); 3.44 (s, 3H); 7.48–7.61 (m, 2H); 8.10–8.20 (m, 2H)
5f[b]	72	110°	$C_{21}H_{28}N_2O_8$ (436.5)	1730, 1710, 1530	0.88 (t, J = 7 Hz, 3H); 0.91 (t, J = 7 Hz, 3H); 1.20 (d, J = 7 Hz, 3H); 1.25 (t, J = 7 Hz, 3H); 2.36 (dd, J = 11 Hz, J = 10 Hz, 1H); 2.73 (dd, J = 11 Hz, J = 10 Hz, 1H); 3.14 (dq, J = 10 Hz, J = 7 Hz, 1H); 3.41 (t, J = 11 Hz, 1H); 3.73–3.98 (m, 5H); 4.2 (q, J = 7 Hz, 2H); 7.43 (m, 2H); 8.08–8.18 (m, 2H)

[a] Satisfactory microanalysis obtained: C ±0.17, H ±0.07, N ±0.09. [b] Reaction carried out at room temperature.

1,2,3,4-Tetrahydropyridines (3) from 1,4-Dihydropyridines (1); General Procedure:
To a stirred solution of the appropriate 1,4-dihydropyridine (**1**; 0.1 mol) in trifluoroacetic acid (100 ml) is added triethylsilane (15.9 ml, 0.1 mol). Slight warming occurs after the mixture becomes homogenous. After standing at room temperature for 30 min the mixture is evaporated in vacuo and the resultant oily residue taken up in ethyl acetate (200 ml). The ethyl acetate solution is extracted with 1 normal sodium hydroxide solution (2 × 100 ml), dried with anhydrous sodium sulfate, and evaporated to dryness. The residue is crystallized from ether (**3a, b, d, e**) or petroleum ether (**3c**).

Piperidines (5) from 1,4-Dihydropyridines (1); General Procedure:
To a stirred solution of the appropriate 1,4-dihydropyridine (**1**; 0.1 mol) in trifluoroacetic acid (100 ml) is added triethylsilane (47.7 ml, 0.3 mol). The mixture is stirred for 3 h at 50 °C. After cooling the mixture is evaporated in vacuo, the resulting oily residue taken up in ethyl acetate (200 ml) and extracted with 1 normal sodium hydroxide solution (2 × 100 ml). The organic layer is dried with anhydrous sodium sulfate and evaporated. If the product does not crystallize spontaneously, the oily residue is heated at 60 °C and 1 mbar (to remove excess triethylsilane). The residue is crystallized from ether.

Received: July 6, 1984

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