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Lewis acid mediated cyclisation of β-phenylethylamides with an unactivated benzene ring: an efficient preparation of dihydroisoquinolines

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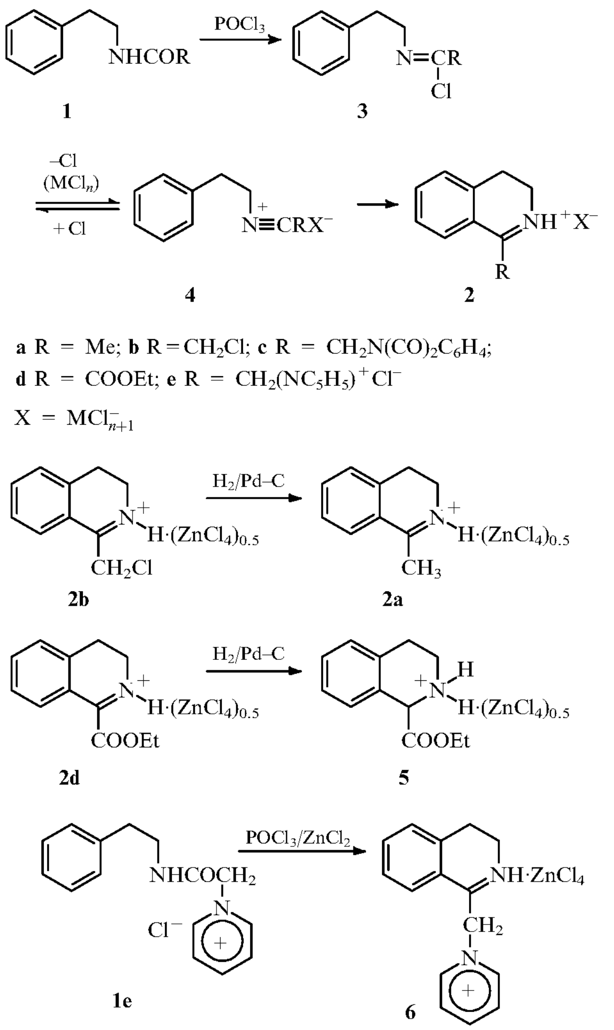
The efficient Lewis acid assisted cyclisation of β-phenylethylamide into dihydroisoquinolines was optimised in relation to metal chloride catalyst, and by X-ray crystallography a new type of non-bonded interaction in the cyclic systems was demonstrated: face coordination of the Cl-anion and an electron deficient pyridinium π-system.

Although there are numerous literature examples of Bischler–Napieralski dihydroisoquinoline syntheses, in practically all known cases the aromatic ring of the starting β-phenylethylamines contain one or several electron-donating activating substituents. When no activating group is present, under the standard conditions for ring closure ($POCl_3$, P_2O_5, polyphosphoric acid or its trimethylsilyl ether[1]), the yields of cyclic products are unsatisfactory and the separation of end products is a time and reagent consuming operation.

In this communication we report a simple protocol for dihydroisoquinoline ring formation from type **1** amides which is suitable for the large-scale preparation of some important drug intermediates. The main focus of our attention was primarily on Lewis acid optimisation in relation to maximum



a R = Me; **b** R = CH_2Cl; **c** R = $CH_2N(CO)_2C_6H_4$;
d R = COOEt; **e** R = $CH_2(NC_5H_5)^+Cl^-$
X = MCl_{n+1}^-

Scheme 1

yields in the transformation **1**→**2** (Scheme 1).

The solvent in all cases was $POCl_3$ as preliminary experiments had demonstrated the superiority of this solvent-reagent. Moreover, $POCl_3$ is easily recoverable for repeated use and excellently dissolves metal chlorides. With regard to the mechanistic function of $POCl_3$, our speculation is along the generally accepted line that the first step in the conversion **1**→**2** is the formation of imidoyl chloride **3**.[2] When the aromatic ring has an activating substituent the following step **3**→**2** does not require any catalyst. Otherwise, the electophilicity of **3** is not sufficient for ring closure and the conversion of **3** into the more powerful electrophile **4**[3] is a substantial mechanistic step. Thus, the efficiency of Lewis acids in transformation **1**→**2** may be related to the complex anion stability and, as a result, with the equilibrium shift **3**→**4**. For the particular amide **1c**, the evaluation of several Lewis acids is presented in Table 1. As can be seen, several metal salts are comparitively active in promoting reaction **1**→**2**. Surprisingly, $AlCl_3$ with its strong Lewis acidity is not effective in this case. Probably, the low yields and tarring of the reaction mixture are associated with the phthalyl function of **1c**. With **1a** $AlCl_3$ gives a good yield of **2a**. Practical considerations, however, make $ZnCl_2$ the most attractive of all the tested salts by virtue of its ability to facilitate the separation of product **2** as a complex with 0.5 mole $ZnCl_2$. A typical procedure for the **1b**→**2b** transformation demonstrates this unique property of $ZnCl_2$. To a suspension of 2.3 g (0.09 mol) of $ZnCl_2$ (dried by boiling with $SOCl_2$) in 42 ml (0.4 mol) $POCl_3$ is added 16.0 g (0.08 mol) of **1b** and the mixture is stirred at 90–95 °C for 1.5 h. After that period HCl evolution subsides (bubble counter) and from the solution thus formed the excess of $POCl_3$ is evaporated off using a rotary evaporator. The oily residue is dissolved in 100 ml of EtOAc and after 2–3 h at room temperature, the precipitated solid is filtered off, washed with 80 ml of the same solvent and dried. The yield of **2b**·HCl·0.5 $ZnCl_2$ is 22.3 g (97%). *Caution: this salt is an extremely strong skin irritant even in trace quantities!* mp 156–157 °C; ^{1}H NMR in TFA 3.2 (t, 2H, $ArCH_2$), 4.17 (t, 2H, NCH_2), 5.20 (s, 2H, CH_2Cl), 7.70 (m, 4H, ArH). The double bond of this Zn-complex resists saturation and when hydrogenated over Pd–C at atmospheric pressure and room temperature gives only the dechlorinated product **2a**. HCl·0.5 $ZnCl_2$, mp 200–201 °C; ^{1}H NMR in TFA, 2.23 (s, 3H, CH_3), 2.47 (t, 2H, $ArCH_2$), 3.50 (t, 2H, NCH_2), 7.14 (m, 4H, ArH); ^{13}C NMR, (δ, D_2O), 19.91 (t, CH_3), 24.36 (t, $ArCH_2$), 41.36 (t, NCH_2), 126.48 (q, ArC), 137.24 (t, C=N). The same product is obtained from **1a** with $POCl_3$–$ZnCl_2$, yield 90%. In the above procedure the ratio of $ZnCl_2$ to starting amide is 1:1. This excessive ratio of Lewis acid is not critical as the reaction proceeds to completion with a 0.5:1 proportion but precipitation of the end product is invariably more complete with a molar equivalent of $ZnCl_2$. Analogously, from ethyloxalate and β-phenylethylamine in dioxane the compound **1d** can be prepared, mp 55–56 °C; ^{1}H NMR in [$^2H_6$]acetone, 1.33 (t, 3H, CH_3), 2.85 (t, 2H, $ArCH_2$), 3.53 (q, 2H, NCH_2), 4.30 (q, 2H, OCH_2), 7.22 (m, 6H, ArH, NH), which gives **2d**·HCl·0.5 $ZnCl_2$, yield 87%, mp, 158–160 °C (EtOH); ^{1}H NMR in CD_3OD, 1.45 (t, 3H, CH_3), 7.83 (m, 4H, ArH). Hydrogenation of the **2d** Zn-complex in EtOH over Pd–C proceeds normally and gives **5** (Scheme 1), in 93% yield, mp 204–205 °C; ^{1}H NMR in CD_3OD, 0.25 (t, 3H, CH_3), 3.15 (t, 2H, $ArCH_2$), 4.30 (t, 2H, OCH_2), 5.49 (s, 1H, CH), 7.27 (m,

Table 1 Valuation of Lewis acids in the Bischler–Napieralski cyclization of **1c**.

Entry	Lewis acid	Reaction temperature (°C)	Time/h	Yield (%) of **2c**[a]
1	LiCl	90–95	0.5	60
2	$MgCl_2$	90–95	1.5	80
3	$CaCl_2$	104–106	0.5	30
4	$ZnCl_2$	90–95	0.5	95
5	$ZnSO_4$	90–95	0.5	0[b]
6	$CuSO_4$	90–95	0.5	60
7	CuCl	90–95	0.5	60–70
8	$TiCl_4$	104–106	5	90
9	$AlCl_3$	104–106	5	0[c]

[a] As a free base, after aqueous NaOH treatment. [b] Salt is insoluble in POCl. [c] Excessive tar formation.

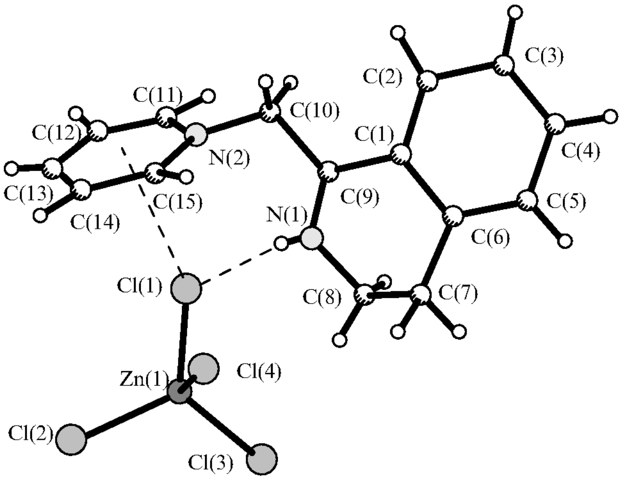


Figure 1 Molecular view of the complex **6** with selected distances and angles: Zn–Cl(1) 2.301(2) A, Zn–Cl(2) 2.241(3) A, Zn–Cl(3) 2.282(2) A, Zn–Cl(4) 2.240(3) A, N(1)–C(8) 1.48(1) A, N(1)–C(9) 1.30(1) A, N(2)–C(10) 1.44(1) A, Cl(1)···N(1) 3,188(7) A, Cl(1)···(Py ring centroid) 3.347 A, N(1)–H(1)···Cl(1) 164(6)°.

ArH). Amide **1b** with pyridine in MeCN gives the pyridinium salt **1e** (mp 175–178 °C, yield 84%), ring closure of which gives the pyridinium salt **4**, in 89% yield (after crystallisation from water), mp 237–238 °C; ^{1}H NMR in [^{2}H$_6$]DMSO, 3.4 (s, 2H, ArCH$_2$), 4.1 (s, 2H, NCH$_2$), 7.06 (s, 2H, N$^+$-CH$_2$), 8.83 (m, 9H, ArH).

The crystal structure[†] of **6** is of special interest (see Figure 1). The unusual proximity of one chlorine atom of $ZnCl_4^{2-}$ anion to the centre of the pyridinium fragment [angle between the normal to the plane of Py$^+$-ring and the vector (Py$^+$-centroid)–Cl(1) is 7.8°][‡] indicates a charge-transfer interaction between the Cl-atom and the electron deficient pyridinium cation. Here, the electron-rich complex anion interacts with the electron deficient π-system of the pyridinium cation. The opposite type of phenomenon, *i.e.* cation–π interaction between the Me$_3$N$^+$ moiety and the aromatic ring has recently received considerable attention as a new type of binding force that is important in biological systems.[4]

[†] *Crystal data for* **6**. A single X-ray quality crystal of **6** of dimensions 0.1×0.3×0.5 mm was obtained from a water solution at room temperature and mounted on an Enraf-Nonius CAD-4 diffractometer interfaced to a IBM-PC/286 computer and equipped with a graphite monochromator and Mo K_α radiation source. An orthorhombic unit cell was derived by least-squares refinement of 24 of the strongest reflections with 2θ angles in the range of 32–36°. The space group $P2_12_12_1$ was assumed and then confirmed by the successful solution and refinement of the structure; $C_{15}H_{16}N_2Cl_4Zn$, $M = 431.5$, $a = 7.131(1)$, $b = 14.070(3)$, $c = 17.666(4)$ A, $V = 1772(1)$ A^3, $Z = 4$, $d_c = 1.62$ g cm^{-3}, $m = 2.02$ mm^{-1}, $F(000) = 872.0$.

Crystal and/or instrumental instability was monitored by the intensity of three reference reflections (1 3 13), (2 10 5) and (5 1 8) measured every 2 h, and two standard reflections were used as orientation control and checked every 200 reflections. The reference reflection underwent fading during data collection up to 17% of its initial value. The net intensities of the collected data were corrected for the fading and for Lorentz and polarization effects. The structure was solved by a direct method and refined by full-matrix least squares (NP = 250) to give a final $R = 0.065$ and $R_w = 0.064$ [$w = 1/s^2(F)$] for 2223 unique reflections with $I > 2\sigma(I)$. All non-hydrogen atoms were refined in anisotropic approximation of thermal parameters. Hydrogen atoms were obtained from difference Fourier syntheses and were refined with fixed displacement parameters, $U_{iso} = 0.06$. All calculations were carried out on an IBM-PC/Pentium computer with programs SHELX76, SHELXS86 and locally written programs for the calculation of geometrical data. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC), see Notice to Authors, *Mendeleev Commun.*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 1135/8.

[‡] The projection of the chlorine atom on the plane of the Py$^+$-ring is shifted slightly from the centre of the ring to the nitrogen atom and thus could be close to a centre of electron deficiency of the Py$^+$-ring.

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