On the nature of the intermediate in the Lewis acid-promoted synthesis of dihydroisoquinolines from nitriles and β-phenylethyl chloride

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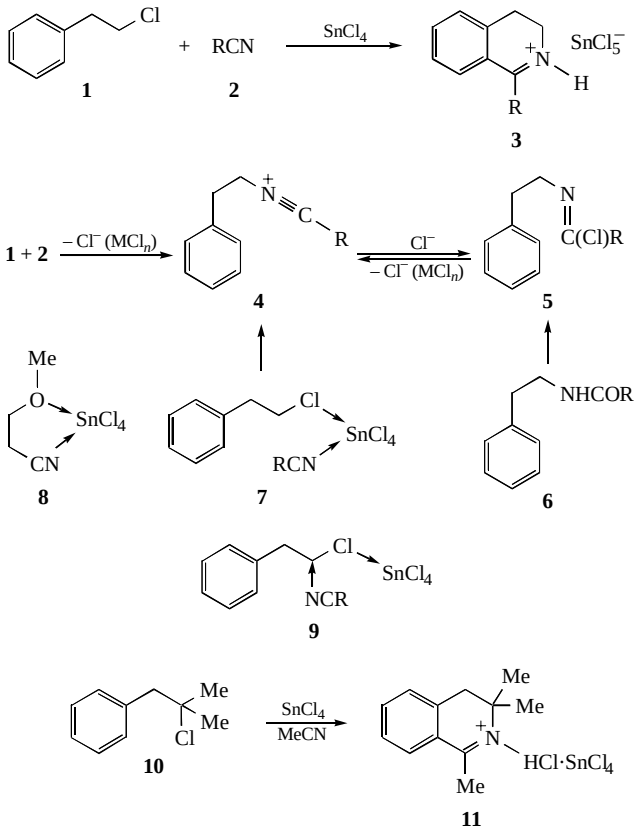
In addition to Lewis acidity, the ability to co-ordinate both reactants is a prerequisite for catalyst activity in the cyclisation reaction of β-phenylethyl chloride and alkyl- or aryl nitriles to dihydroisoquinolines.

The known cyclisation reaction of β-phenylethyl chloride to dihydroisoquinolines with nitriles and $SnCl_4$ presents a useful synthetic method.[1] In this communication we present our efforts to elucidate the connection between the structure of the nitrile component and the nature of the Lewis acid. Based on the experimental evidence, an attempt is made to rationalize some mechanistic aspects of the reaction, namely, the nature of the intermediate.

Two variants of the experimental conditions were used to obtain the results presented below.† (*A*) Low-boiling acetonitrile was used as excess reactant and solvent and (*B*) the solvent was phosphorus oxychloride for high-boiling nitriles. As shown in preliminary experiments, the literature procedure for **1** → **3** conversion is more convenient when run in the solvent $POCl_3$ (Scheme 1). Apart from the ease of end product separation this solvent significantly activates the Lewis acid and may be recovered for repeated use. The results are presented in Table 1.

So, the acidity of Lewis catalysts is not directly related to the yield of cyclized products. To explain why some moderately strong acids are active and give cyclic products (entries 1, 2 and 5), but some do not (entries 3, 4, 6) — including the strongest of the acids tested $AlCl_3$ — it is helpful also to consider the specific structure of the 'reactive' (entries 1 and 2) and 'unreactive' (entries 3 and 4) nitriles. To the same end, also informative are the mechanistic considerations of another synthetic approach to dihydroisoquinolines *via* β-phenylethylamines (Bishler–Napiralski procedure, Scheme 1, **1** → **4** → **3** and **6** → **5** → **4** → **3**).[2] Obviously, it may be assumed that both synthetic pathways have the same intermediate, nitrilium cation **4**, which originates either by dechlorination of imidoyl chloride or alkylation of alkyl nitrile on nitrogen. But this assumption is an oversimplification of the actual process. In fact, in this line of reasoning the best catalyst for conversion of **1** and **2** to nitrylium **4** should be the strongest Lewis acid $AlCl_3$, which, if it bound chlorine to complex anion $AlCl_4$ and thus facilitated the formation of carbonium ion intercepted by nitrile, would immediately give the cyclized product.



a R = Me
b R = CH_2Ph
c R = CH_2Cl
d R = CH_2CH_2OMe

Scheme 1

Table 1 The yield of isoquinoline as a function of nitrile structure and Lewis acid.

Entry	Nitrile	Lewis acid	Products[a]	Yield (%)
1	**2a**	$SnCl_4$	**3a** x = $SnCl_5$	85
2	**2b**	$SnCl_4$	**3b** x = $SnCl_5$	80
3	**2c**	$SnCl_4$	—	0[b]
4	**2d**	$SnCl_4$	—	0[b]
5	**2a**	$TiCl_4$	**3a** x = $TiCl_{4+n}$	60
6	**2a**	$ZnCl_2$	—	0[b]
7	**2a**	$SbCl_5$	**3a** x = $SbCl_6$	60[c]
8	**2a**	$AlCl_3$	—	0[b]

[a] x is the anion in the complex salt. [b] No organic basic fraction was isolated after aqueous work-up. [c] Extensive chlorination of the end product and intermolecular condensation of the starting chloride are the main side reactions.

† *Method A*. To 20 ml of acetonitrile was added $SnCl_4$ (0.04 mol) gradually with cooling followed by chloride **10** (0.04 mol). After heating at 60–70 °C for 6 h and overnight at room temperature, the reaction mixture was decomposed by water with cooling (40 ml). Pentane was added (40 ml) and then, with cooling, the aqueous layer was saturated with solid KOH. The organic extract (after drying over KOH, filtration through Al_2O_3 and evaporation) was converted into chloride by the action of 5 ml of trimethyl chlorosilane in 5 ml Bu^iOH and 10 ml ethyl acetate. After filtration and washing with 10×2 ml of EtOAc the recovered yield was 6.67 g (79%) of **11** as the hydrochloride,[2] mp 176–177 °C. ^1H NMR (D_2O) δ: 1.58 (s, 6H, *gem* Me), 2.90 (s, 3H, Me), 3.28 (s, 2H, CH_2), 7.55–8.13 (m, 4H, aromatic).

Method B. To a mixture of 1.16 mol β-phenylethyl chloride (163.5 g, 150 ml) and 1.16 mol acetonitrile (47.6 g, 61 ml) was added 1.16 mol of $POCl_3$ (177.5 g, 105 ml) and, gradually with cooling, 1.16 mol (303.2 g, 133 ml) $SnCl_4$. After gentle reflux for 5 h and overnight at room temperature, 300 ml of ethyl acetate was added. The complex salt was filtered off and washed with 500 ml of the same solvent and 100 ml of diethyl ether. Yield was 465.4 g (95%); to a suspension of this complex in 800 ml of water was added, with cooling, 800 ml of 10 M sodium hydroxide. The base after extraction with diethyl ether and drying over solid NaOH was distilled, bp 100–105 °C/5 mmHg, yield 104.6 g (62%). Chloride mp 198–200 °C. ^1H NMR (base, $CDCl_3$) δ: 2.23 (s, 3H, Me), 2.47 (t, 2H, Ar–CH_2), 3.50 (t, 2H, N–CH_2), 7.14 (m, 4H, aromatic); ^{13}C NMR ($CDCl_3$) δ: 19.19 (t, Me), 24.87 (t, Ar–CH_2), 40.78 (t, N–CH_2), 128.57 (q, Ar–C), 136.76 (t, C=N).

In reality, this catalyst is completely inactive and the starting chloride **1** may be recovered almost quantitatively after standard work-up. At the same time, $AlCl_3$ smoothly converts amide **6a** into isoquinoline **3a**, presumably *via* **4**. Thus, it is not only the Lewis acidity of the catalyst which is of importance, but also some other intrinsic property of the metal chlorides used for **1** → **3** conversion. We believe that this crucial factor is the metal coordination number and the ease of ligand exchange in the transition complex. A logical assumption is that all components of the reaction, *i.e.*, nitrile and chloride, are incorporated into the inner sphere of the metal (**7**, Scheme 1).

Within such a framework, the aluminium chloride complex with nitrile is unable to add another ligand, β-phenyethyl chloride, or to exchange it for one of the chlorides. Also, following the same line of reasoning, the unreactivity of nitrile **2d** may be explained by coordination as in **8** or **9**. Nitrile **2c** is inactive (see entry 3) also by virtue of this 'wrong' coordination (on chlorine) or not coordinating at all (reduced nucleophilicity of nitrogen). Interestingly, if the two important parts of the isoquinoline molecule are assembled together as in **4**, aluminium chloride and all the other chlorides in Table 1 are effective as cyclisation catalysts.

References

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