Rearrangement of 2-amino-1-aryl-1,4-dihydropyridines

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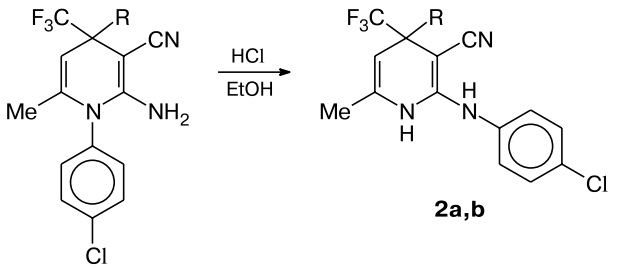
Heating of 2-amino-1-aryl-1,4-dihydropyridines in acidic aqueous media gives 2-arylamino-1,4-dihydropyridines. The reaction formally involves the migration of the aryl substituent from the endo- to exocyclic N atom.

Key words: 1,4-dihydropyridines, rearrangement, recyclization, 2-arylamino-1,4-dihydropyridines, X-ray diffraction analysis.

At present, methods for the synthesis of polyfunctionalized pyridines are under intensive development.[1] Various 2-amino-3-cyano-1,4-dihydropyridines as potential insecticides have been synthesized.[2—4] It is important to search for new transformations in the series of these compounds and study their chemical properties.

We have found that 2-amino-1-aryl-1,4-dihydropyridines[2] (**1**) undergo an earlier unknown rearrangement to give 2-arylamino-1,4-dihydropyridines (**2**). Compounds **1a** and **1b** were quantitatively (TLC data) converted into compounds **2a** and **2b**, respectively, by heating in boiling ethanol in the presence of HCl (Scheme 1).

Scheme 1



1a,b

R = CO_2Et (**1a**, **2a**), CF_3 (**1b**, **2b**)

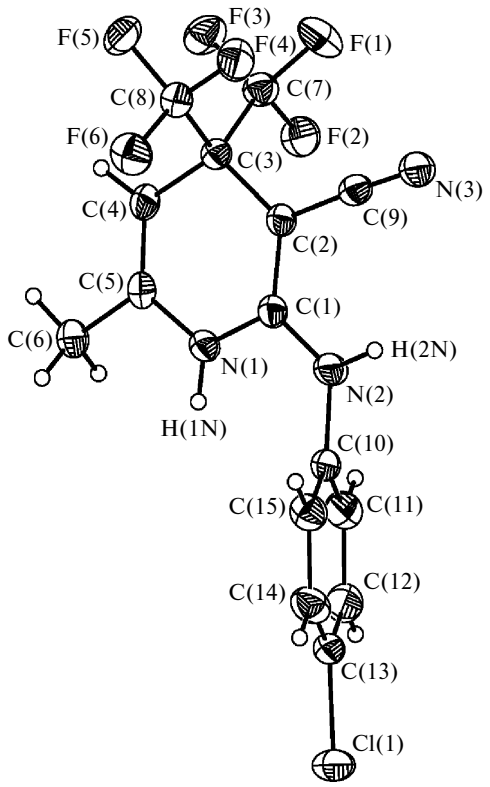


Fig. 1. Structure **2b**.

The closest analogy to this reaction is the base-catalyzed Dimroth rearrangement[5] in the pyridine series, which is driven by an energy gain resulting from aromatization of the final product. In our case, the aryl substituent formally migrates from the endocyclic to exocyclic N atom with retention of the double bond distribution (aromatization is impossible because two substituents are in position 4). The structures of compounds **2** were completely proven by NMR spectroscopy, as well as by the X-ray diffraction analysis of product **2b** (Fig. 1).

A comparison of the geometries of compounds **1** (see Ref. 2) and **2b** revealed that the bond lengths and angles in the pyridine rings are almost equal. The largest discrepancy was observed for the N(1)—C(5) bond length (1.417(2) and 1.397(2) Å, respectively). In both the structures, the heterocycle was found to be virtually planar.

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A B3LYP/6-31G** calculation showed that the bond length distribution in compounds **1b** and **2b** in the isolated state is also virtually identical. The calculated energy difference was only 4.3 kcal mol^{-1}. As expected, the energy of compound **1b** is slightly higher, which correlates with the direction of the rearrangement.

Thus, we discovered a rearrangement in the series of 2-amino-1-aryl-1,4-dihydropyridines. The starting compounds **1** have been patented[6] as efficient insecticides, which can make this new transformation of topical interest.

Experimental

^{1}H and ^{19}F NMR spectra were recorded on a Bruker AMX-400 instrument (400.13 and 376.47 MHz, respectively) with Me_4Si as the internal standard for ^{1}H and with CF_3COOH as the external standard for ^{19}F.

Ethyl 2-(4-chlorophenylamino)-3-cyano-6-methyl-4-trifluoromethyl-1,4-dihydropyridine-4-carboxylate (2a). Concentrated HCl (2 drops) was added to a solution of compound **1a** (50 mg, 13 mmol) in ethanol (5 mL). The resulting solution was refluxed for 4 h and neutralized with triethylamine. Volatile substances were removed in a rotary evaporator. The residue was extracted with ether, the extract was dried over Na_2SO_4 and concentrated in a rotary evaporator, and the crystals obtained were dried. The yield of compound **2a** was 45 mg (90%), colorless crystals, m.p. 144 °C. ^{1}H NMR (DMSO-d_6), δ: 1.30 (t, 3 H); 1.85 (s, 3 H); 4.25 (q, 2 H); 4.47 (s, 1 H); 7.00, 7.21 (both d, 2 H each, Ar); 8.59, 9.00 (both s, 1 H each, NH). ^{19}F NMR (DMSO-d_6), δ: 4.60 (s, 3 F).

2-(4-Chlorophenylamino)-6-methyl-4,4-bis(trifluoromethyl)-1,4-dihydropyridine-3-carbonitrile (2b) was obtained analogously. The yield of compound **2b** was 90%, gray crystals, m.p. 130—131 °C. ^{1}H NMR (DMSO-d_6), δ: 1.86 (s, 3 H); 4.61 (s, 1 H); 7.0 (d, 2 H, Ar); 7.32 (d, 2 H, Ar); 8.95 (s, 1 H, NH); 9.41 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 6.46 (s, 3 F).

X-ray diffraction analysis of compound 2b. $C_{15}H_{10}ClF_6N_3$, M = 381.71. At 120 K, the crystals are monoclinic, space group $P2_1/c$, a = 6.821(1) Å, b = 12.788(2) Å, c = 18.434(4) Å, β = 97.002(4)°, V = 1595.9(5) Å^3, Z = 4, μ = 3.07 mm^{-1}. Reflections were collected on a SMART CCD diffractometer. The number of measured reflections was 14 598. Independent reflections (3482, R_{int} = 0.0201) were used to interpret and refine the structure. Final residuals were $R(F)$ = 0.0427 (for 2979 observed reflections) and $wR(F^2)$ = 0.1037.

The crystallographic parameters of compound **2b** and a summary of data collection have been deposited with the Cambridge Crystallographic Data Center (CCDC # 279620)*.

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* These data are free available upon request to: CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 (1223) 336033. E-mail: deposit@ccdc.cam.ac.uk).