

NMR AND X-RAY INVESTIGATION OF NEW DIHYDROIMIDAZO-, TETRAHYDROIMIDAZOPYRIDINES

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Abstract. The synthesized dihydroimidazo- and tetrahydroimidazopyridines were investigated by NMR and X-Ray methods. Obtained results have demonstrated the presence of an intramolecular distribution of free electron pair of nitrogen in dihydroimidazopyridine cycles.

Keywords: pyridine, electron pair, broadening, conjugated, NMR, X-Ray.

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1. Introduction

Pyridine ring, a privileged structural core in heterocyclic chemistry, is present in many natural products such as nicotinic acid, nicotinamide and vitamin B₆, which play important roles in metabolism. In addition, functionalized pyridines have been shown to exhibit a broad range of biological activities including antimicrobial, antiulcer, anti-cancer, antipyretic and anti-inflammatory activities (Goda *et al.*, 2004; Xiao *et al.*, 2014; Abadi *et al.*, 2010; Eissa *et al.*, 2009; Rupert *et al.*, 2003).

Due to all these attractive features of pyridine-containing compounds, numerous synthetic methods that enable the construction of substituted pyridines have been developed (Wu *et al.*, 2015; Wan *et al.*, 2016; Bagdi *et al.*, 2015; Hilf *et al.*, 2016; Huang *et al.*, 2016; Fu *et al.*, 2016; Zhang *et al.*, 2015; Kour *et al.*, 2016; Garmroodi *et al.*, 2015; Allahabadi *et al.*, 2017; Mobinikhaledi *et al.*, 2016; Naghiyev *et al.*, 2018; Naghiyev *et al.*, 2020, 2020; Mamedova *et al.*, 2020).

In containing the synthesized compounds there are nitrogen, chlorine, bromine atoms in pyridine, amine, nitrile, aromatic fragments. The behavior of such pharmaceutical potential like functionalized conjugated molecules in solution and solid-state as well as the presence or absence of dynamic processes are of considerable theoretical and practical interest (Pal *et al.*, 2015; Oikonomou *et al.*, 2015; Mamedov *et al.*, 2010a,b,c, 2012, 2013a,b, 2015a,b, 2016, 2017; Maharramov *et al.*, 2008). To get insight into dynamics behaviors of these systems, we have applied NMR and X-Ray methods to functionalized imidazopyridines.

2. Experimental

Materials and instrumentation

All the chemicals were obtained from commercial sources (Aldrich) and used as received.

1D/2D NMR experiments have been performed on a BRUKER FT NMR spectrometer (UltraShield™ Magnet) AVANCE 300 (300.130 MHz for ^1H and 75.468 MHz for ^{13}C) with a BVT 3200 variable temperature unit in 5 mm sample tubes using Bruker Standard software (TopSpin 3.1). The ^1H and ^{13}C chemical shifts were referenced to internal tetramethylsilane (TMS); the experimental parameters for ^1H : digital resolution = 0.23 Hz, SWH = 7530 Hz, TD = 32 K, SI = 16 K, 90° pulse-length = 10 μs , PL1 = 3 dB, ns = 1, ds = 0, d1 = 1 s; for ^{13}C : digital resolution = 0.27 Hz, SWH = 17985 Hz, TD = 64 K, SI = 32 K, 90° pulse-length = 9 μs , PL1 = 1.5 dB, ns = 100, ds = 2, d1 = 3 s. ^{13}C DEPT 90 and 135, HMQC, HMBC NMR spectra were performed by the Bruker Standard software (Figure S1-S8). NMR-grade DMSO- d_6 (99.7 %, containing 0.3% H_2O), was used for the solutions of **4a-d** and **6 g, h**.

X-Ray structure determination

The crystals of **4b**, **4c**, and **6h** were immersed in cryo-oil, mounted in a Nylon loop, and the intensity data were collected at 296 K on a Smart Apex II diffractometer using Mo $K\alpha$ radiation ($\lambda = 0.71073$ E). The diffraction experiments were carried out on a Bruker APEX II CCD diffractometer. The program SHELXTL was used for collecting frames of data, indexing reflections, and for the determination of the lattice parameters, SAINTP-for integration of the intensity of reflections and scaling, SADABS-for absorption correction, and SHELXTL-for the space group and structure determination, least-squares refinements on F^2 . The crystallographic details are summarized in Table (Figure S7, 8).

Electrospray mass spectra of **4a**, **4d** and **6g** were run with an ion-trap instrument (Esquire 6000 Ion Trap Mass Spectrometer) equipped with an electrospray (ESI) ion source. For electrospray ionization, the drying gas and flow rate were optimized according to the particular sample with 35 p.s.i. nebulizer pressure. Scanning was performed from m/z 100 to 1200 in methanol solution. The compounds were observed in the positive mode (capillary voltage = 80–105 V).

The purity of the synthesized compounds was confirmed by thin-layer chromatography (TLC) on commercial aluminum-backed plates of silica gel (60 F254), iodine vapor was used as a visualizing agent, eluent- 5:2 hexane/ethyl acetate.

Melting points were measured on an Electrothermal 9100 apparatus without correction.

Synthesis of 4a-d

A mixture of benzylidenemalononitriles (5.1 mmol) and malononitrile (5.1 mmol) was dissolved in 25 mL of methyl alcohol and stirred for 5-7 minutes. Ethylenediamine (5.1 mmol) was added to the mixture with vigorous stirring. The progress of the reaction was monitored by TLC (EtOAc/n-hexane, 2:1). The reaction mixture was stirred for 48-72 hours. When the solvent was evaporated, crystals sedimented. Crystals were filtered by filter paper and recrystallized from a mixture of ethanol-water (Scheme 1) (Naghiyev *et al.*, 2018).

5-Amino-7-phenyl-2,3-dihydroimidazo[1,2-a]pyridine-6,8-dicarbonitrile (4a)

Yellow powder; mp 325°C ; ^1H NMR (300.130 MHz, DMSO- d_6 , δ): 8.14 (s, 2H, H-8); 7.62-7.39 (m, 5H, arom.); 3.97 (s, 4H, H-1,2); ^{13}C NMR (75.468 MHz, DMSO- d_6 , δ): 160.09, 154.37, 152.71, 135.60, 130.36, 128.98, 128.34, 117.27, 117.04, 80.09, 72.01, 52.76, 46.77; MS (ESI): 261.10 $[\text{M}+\text{H}]^+$

5-Amino-7-(p-tolyl)-2,3-dihydroimidazo[1,2-a]pyridine-6,8-dicarbonitrile**(4b)**

White powder; mp 347°C; ^1H NMR (300.130 MHz, DMSO- d_6 , δ): 8.09 (s, 2H, H-8); 7.37-7.31 (s, 4H, arom.); 3.94 (s, 4H, H-1,2); 2.38 (s, 3H, H-15). ^{13}C NMR (75.468 MHz, DMSO- d_6 , δ) 160.01, 154.99, 152.25, 140.07, 133.21, 129.91, 128.46, 117.12, 117.27, 81.02, 72.24, 53.87, 47.04, 21.84.

5-Amino-7-(4-methoxyphenyl)-2,3-dihydroimidazo[1,2-a]pyridine-6,8-dicarbonitrile (4c)

Green powder; mp 286°C; ^1H NMR (300.130 MHz, DMSO- d_6 , δ): 8.00 (s, 2H, H-8); 7.39 (d, 2H, $J = 7.9$, H-12); 7.05 (d, 2H, $J = 7.9$, H-13); 3.91 (s, 4H, H-1,2); 3.81 (s, 3H, H-15). ^{13}C NMR (75.468 MHz, DMSO- d_6 , δ) 160.94, 159.75, 154.43, 152.89, 130.10, 127.51, 117.50, 117.31, 114.27, 55.73, 52.73, 49.07, 46.75.

5-Amino-7-(4-(dimethylamino)phenyl)-2,3-dihydroimidazo[1,2-a]pyridine-6,8-dicarbonitrile (4d)

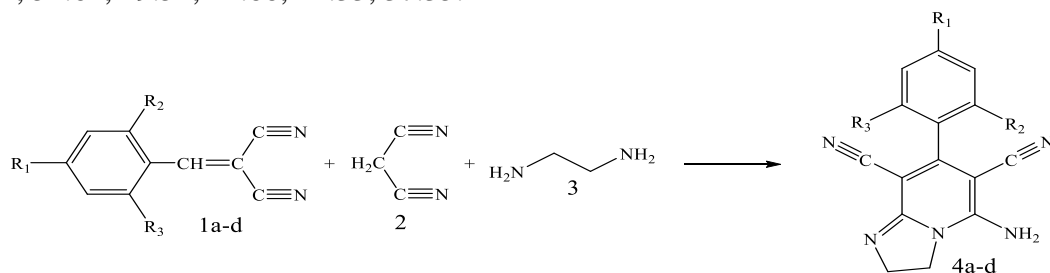
Yellow powder; mp 367°C; ^1H NMR (300.130 MHz, DMSO- d_6 , δ): 7.95 (s, 1H, H-8); 7.29 (d, 2H, $J = 6.9$, H-12); 6.77 (d, $J = 6.9$, 2H, H-13); 3.91 (s, 4H, H-1,2); 3.6 (s, 1H, H-8). ^{13}C NMR (75.468 MHz, DMSO- d_6 , δ): 159.61, 154.09, 151.33, 129.26, 121.44, 117.46, 117.31, 111.14, 52.03, 46.23, 40.31; MS (ESI): 339.01 [M+H] $^+$

5-Amino-7-(2,4-dichlorophenyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6,8-dicarbonitrile (6g)

Brown powder; mp 254°C; ^1H NMR (300.130 MHz, DMSO- d_6 , δ): 7.50 (s, 1H, H-1); 7.50-7.35 (m, 3H, arom.); 6.41 (s, 2H, H-9); 4.74 (s, 1H, H-6); 3.84 (t, 2H, $J = 7.8$, H-3); 3.51 (t, 2H, $J = 7.8$, H-2). ^{13}C NMR (75.468 MHz, DMSO- d_6 , δ): 154.33, 151.63, 142.84, 132.94, 132.39, 129.07, 128.43, 121.66, 121.10, 55.10, 52.11, 45.11, 42.37, 37.63; MS (ESI): 295.06 [M+H] $^+$

5-Amino-7-(2,6-dichlorophenyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6,8-dicarbonitrile (6h)

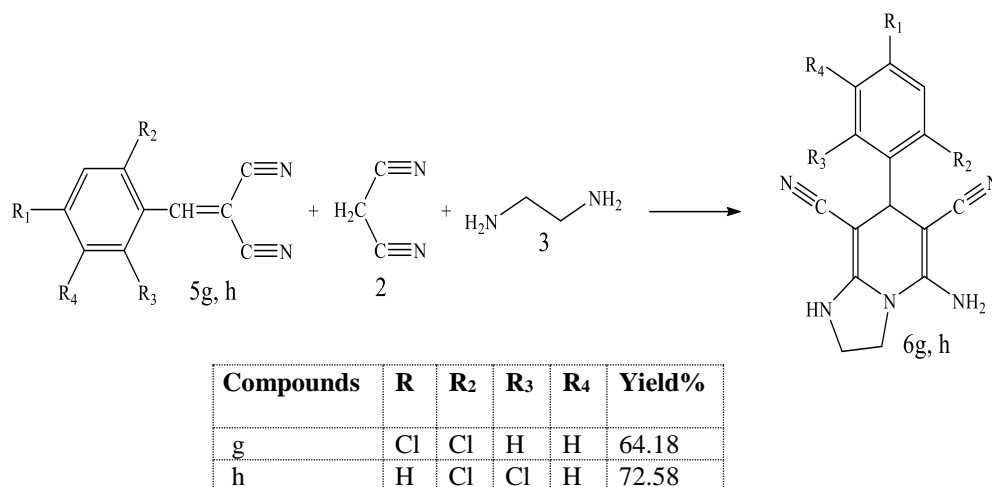
Brown powder; mp 265°C; ^1H NMR (300.130 MHz, DMSO- d_6 , δ): 7.50 (s, 1H, NH); 7.43 (d, 2H, $J = 7.8$, H-14); 7.27 (m, 1H, H-15); 6.37 (s, 2H, H-9); 5.36 (s, 1H, H-6); 3.86 (t, 2H, $J = 7.7$, H-3); 3.51 (t, 2H, $J = 7.7$, H-2). ^{13}C NMR (75.468 MHz, DMSO- d_6 , δ): 155.03, 152.31, 138.06, 136.29, 134.78, 131.26, 129.60, 128.79, 121.58, 121.02, 52.61, 49.52, 44.88, 42.33, 37.35.



Compounds	R ₁	R ₂	R ₃	Yield%
<i>a</i>	H	H	H	51.5
<i>b</i>	CH ₃	H	H	66.15
<i>c</i>	OCH ₃	H	H	65.87
<i>d</i>	Br	H	H	61.78

Scheme 1. The synthesis of compounds **4a-d**

This procedure was followed for the synthesis of products **6g, h** (Scheme 2).



Scheme 2. The synthesis of compounds **6g, h**

3. Results and discussion

In our previous work about the synthesis of new dihydroimidazopyridines had been informed (Naghiyev *et al.*, 2018). Reporting work devoted to comparing of NMR and X-Ray investigation of dihydroimidazo- and tetrahydroimidazopyridines.

Initially, we carried out NMR investigation of dihydroimidazopyridines (**4a-d**) (Scheme 1).

At ^{13}C NMR spectra of all synthesized dihydroimidazopyridines (**4a, b, d**) were observed broadening of carbon signals (number of carbons, 4 and 6 in formulas), which connected $\text{C}\equiv\text{N}$ groups at 22°C . To get insight into dynamics behaviors of these systems, ^{13}C NMR spectra were obtained at $+22^\circ\text{C} \div +90^\circ\text{C}$ and observed narrowing of indicated carbon signals for the **4a, b, d** (Figure S1, S2 and S4) at 90°C , but as a result of more broadening for the compound **4c** were not observed signals for the carbons 4 and 6 at room temperature and determinate traces at 90°C (Figure S3). The melting point for DMSO- d_6 is 20.2°C and our compounds have good solubility only in DMSO. By this reason, we can't carry out investigation below 20°C

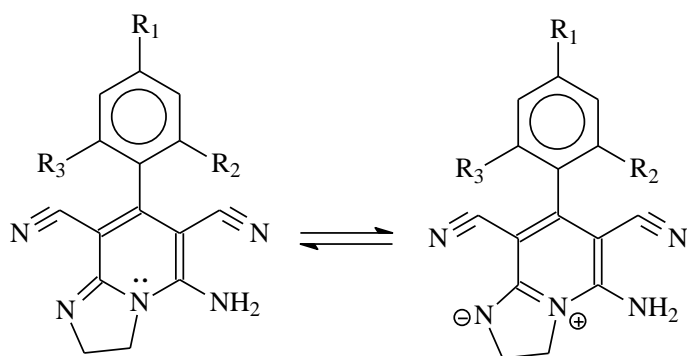
At ^1H NMR of indicated compounds were observed one singlet instead of two different signals at 3.9 ppm for the two CH_2 groups of five-member cycle, as a result of presences of dynamic transitions in molecules. In DMSO- d_6 solution, the proton integral intensity of NH_2 protons at 8 ppm decreases continuously in the range of $+25^\circ\text{C} \div +90^\circ\text{C}$, with rising temperature as a result of the fast proton exchange with residual water.

Besides above the presents, in the crystal structure of investigated compounds (**4a, b, d**) were observed deviation of C-C, C=C, C=N bond lengths in six-member cycle (normal values are accordingly 1.54, 1.34, 1.38 Å), please see Figure S7.

For the comparing of influencing of double bond place to the ^{13}C NMR spectra were investigated new tetrahydroimidazopyridines (**6g, h**) (Scheme 2). In this case were observed normal ^{13}C signals without broadening (Figure S5, S6, and S8) and signals of two CH_2 groups have been split into two different triplets. Obtained results confirm the absence of any dynamic transitions in molecules **6g, h** and their structural stability in solutions.

On the based NMR and X-Ray results we can note, that broadening of ^{13}C NMR signals (carbon numbers 4 and 6 in formulas) of six-member cycle (which connected $\text{C}\equiv\text{N}$ groups), probably connected by the presence of intramolecular distribution of free electron pair of nitrogen in dihydroimidazopyridine cycles in solutions.

Finally, demonstrated the probability of the distribution of the free electron pair of nitrogen between the conjugated five and six-member cycles of dihydroimidazopyridines in solutions.



4. Conclusions

In this work NMR and X-Ray investigation of synthesized dihydroimidazo- and tetrahydroimidazopyridines were reported. On the basis of obtained NMR and X-Ray results were demonstrated the presence of an intramolecular distribution of free electron pair of nitrogen in dihydroimidazopyridine cycles.

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