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SHORT COMMUNICATIONS

Self-Assembling 3-[2-Pyridylamino(phenyl)methyl]imidazo-[1,2-*a*]pyridine from Phenylpropynal and 2-Aminopyridine

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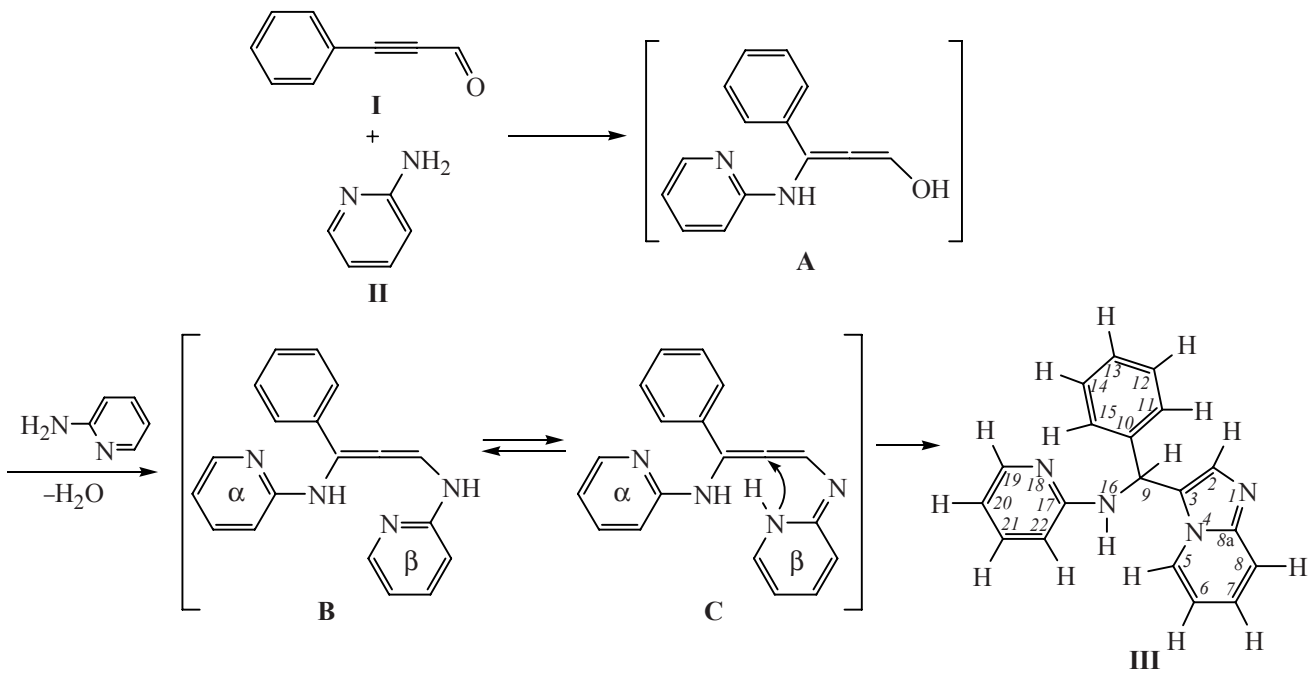
Phenylpropynal is known to be ambidente electrophile, and it can react with nucleophiles involving both reaction sites. However dominates the reaction at the carbonyl group giving the corresponding dithianes [1], acetals [2], dipyrrolylmethanes [3], Baylis–Hillman adducts [4], and 1,3-enynes by Horner–Emmons reaction [5]. Secondary amines selectively add to the β-carbon of the triple bond providing aminoenals [6]. Phenylpropynal is a specific, highly efficient, and irreversible inhibitor of typical β-lactamases [7]. The inhibition occurs by intramolecular crosslinking involving the primary amino groups of lysine forming a part of the protein composition building an amino-enimine fragment. This fact shows the possibility of the simultaneous addition of primary amines to the triple bond and the carbonyl group of the phenylpropynal undr the biomimetic conditions [8].

We unexpectedly discovered that under the conditions analogous to the formation of *N*-(2-pyridyl)-2-(trimethylsilylethynyl)-1,2-dihydropyridine-3,5-dicarbaldehyde [9] from trimethylsilylpropynal and 2-aminopyridine (**II**) (MeCN, 25°C, 5 mol% HCl) in event of phenylpropynal (**I**) occurred a self-assembling of previously unknown



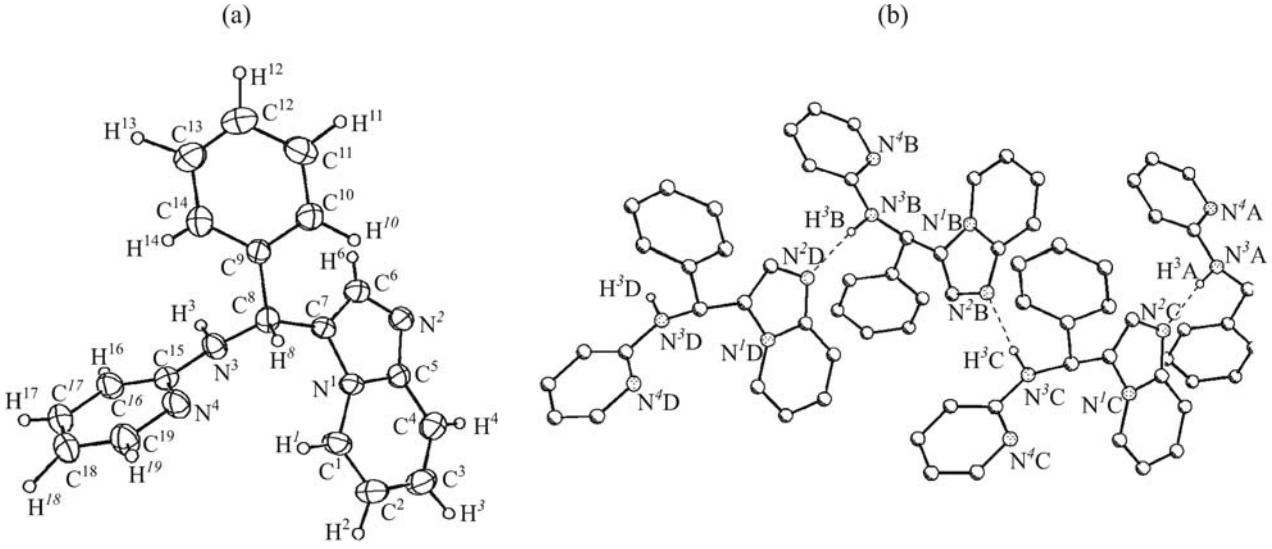
3-[2-pyridylamino(phenyl)methyl]imidazo[1,2-*a*]pyridine (**III**) in 61% yield.

According to NMR data imidazopyridine **III** formed as a racemic mixture of two enantiomers. The racemate obtained on crystallization from a mixture of $CHCl_3$ with hexane underwent spontaneous separation. This was revealed by the XRD study of one of single crystals which showed that the crystal was built up by the packing of the molecules of *R*-enantiomer contained in the initial racemic mixture. In the molecule of *R*-imidazo[1,2-*a*]-pyridine **III** (see the figure, *a*) the imidazo[1,2-*a*]-pyridine bicycle is planar and is located at angles of 71.1(1) and 61.2(1) deg to the planes of phenyl and pyridine rings. In the solid phase molecules **III** are linked into chains by hydrogen bonds (see the figure, *b*) of types N–H···N [N–H 0.93(5), H···N 2.11(5), N···N 3.043(5) Å, angle NHN 174(4)°].

We believe that the process of compound **III** formation consists in successive stages of the 1,4-nucleophilic addition of amine **II** to phenylpropynal (**I**), the substitution of the enol hydroxy group in allene intermediate **A** by the amino group of the second molecule of the 2-amino-pyridine, the enamino-imine tautomerism in the *b* fragment in intermediate **B**, and the cyclization of allene **C**. The succession of the stages fundamentally differs from that in the reaction of trimethylsilylpropynal with 2-aminopyridine thus indicating the significant influence of the nature of the substituent at the triple bond of α-acetylene aldehyde on the direction of hetero-cyclization in the reaction with the 2-aminopyridine under the conditions of acid catalysis.

The discovered self-assembling of compound **III** might be of fundamental importance for the development of purposeful synthesis of compounds from the imidazo-[1,2-*a*]pyridine series that are widely employed in pharmacology in treatment of diseases concerning the distortions of the brain blood supply, and also at allergic and respiratory illness [10–13].

3-[2-Pyridylamino(phenyl)methyl]imidazo[1,2-*a*]-pyridine. A mixture of 1.0 g (7.7 mmol) of phenyl-propynal, 0.7 g (7.7 mmol) of 2-aminopyridine, 0.05 ml of concn. HCl, and 5.0 ml of acetonitrile was kept at room temperature for 7 days; therewith gradually precipitated the crystals of the reaction product. The crystals were filtered off, washed with cold acetonitrile (2 ml), and dried in a vacuum. Yield 0.7 g (61% with respect to 2-aminopyridine), light-red crystalline substance, mp 198–199°C. IR spectrum (KBr), cm^{-1}: 1495, 1600 [ν(C=C, C=N)], 1575 [δ(NH)]. ^1H NMR spectrum, δ, ppm: 5.36 d (1H, NH, $^3J_{H^9H^{16}}$ 7.7 Hz), 6.41 d (1H, H^{22}, $^3J_{H^{21}H^{22}}$ 8.3 Hz), 6.50 d (1H, H^9, $^3J_{H^9H^{16}}$ 7.7 Hz), 6.58 d.d (1H, H^{20}, $^3J_{H^{19}H^{20}}$ 5.1, $^3J_{H^{20}H^{21}}$ 7.3 Hz), 6.72 d.d (1H, H^6, $^3J_{H^5H^6}$ 6.8, $^3J_{H^6H^7}$ 7.1 Hz), 7.12 s (1H, H^2), 7.14 d.d (1H, H^7, $^3J_{H^6H^7}$ 7.1, $^3J_{H^7H^8}$ 9.2 Hz), 7.32–7.37 m (3H, H^{12}, H^{13}, H^{14}), 7.35 d.d (1H, H^{21}, $^3J_{H^{20}H^{21}}$ 7.3, $^3J_{H^{21}H^{22}}$ 8.3 Hz), 7.41 d (2H, H^{11}, H^{15}), 7.56 d (1H, H^8, $^3J_{H^7H^8}$ 9.2 Hz), 7.99 d (1H, H^5, $^3J_{H^5H^6}$ 6.8 Hz), 8.03 d (1H, H^{19}, $^3J_{H^{19}H^{20}}$ 5.1 Hz). ^{13}C NMR spectrum, δ, ppm:



Structure of the molecule (a) and the way of chains formation through hydrogen bonds; (b) in the solid phase of 3-[2-pyridyl-amino(phenyl)methyl]imidazo[1,2-*a*]pyridine (**III**).

50.88 (C^{9}), 107.84 (C^{22}), 112.30 (C^{6}), 113.85 (C^{20}), 117.84 (C^{8}), 124.26 (C^{5}), 124.31 (C^{7}), 125.33 (C^{3}), 127.20 (C^{11}, C^{15}), 127.96 (C^{13}), 128.77 (C^{12}, C^{14}), 133.22 (C^{2}), 137.56 (C^{21}), 139.12 (C^{10}), 146.05 (C^{8a}), 148.16 (C^{19}), 157.63 (C^{17}). Found, %: C 75.56; H 5.60; N 18.61. $C_{19}H_{16}N_4$. Calculated, %: C 75.98; H 5.37; N 18.65.

X-ray diffraction study. For preparation of crystals of good quality 50 mg of imidazo[1,2-*a*]-pyridine **III** was dissolved in 10 ml of boiling $CHCl_3$. The solution obtained was filtered, kept in an open flask at 5єC till the volume of solution decreased to ~5 ml, and cautiously along the wall of the flask was added 5 ml of hexane. After 24 h the formed crystals were separated using a spatula, and then filtered off.

The array of reflections was obtained on a diffractometer Smart Apex CCD (Bruker AXS) (MoK_α, T 295 K), the extinction was accounted for by the program Bruker SADABS, version 2.10. The structure was solved by the direct method and refined in full-matrix least-mean-squares method in anisotropic approximation for all nonhydrogen atoms. The positions of hydrogen atoms were localized by difference synthesis of the electron density. All calculations for solving and refining the structure were performed using software Bruker SHELXTL Version 6.14. For *R*-imidazo[1,2-*a*]pyridine **III**: $C_{19}H_{16}N_4$, M 300.36, crystals monoclinic, space group $P2_1/c$, a 8.268(5), b 10.449(7), c 17.275(11) Å, β 96.554(13)°, V 1482.6(17) Å^3, Z 4, ρ_{calc} 1.346 g/cm^3, μ 0.083 cm^{-1}, 10028 measured reflections ($2.37 < \theta < 23.36°$, R_{int} 0.1103), among them 2111 with $I > 2\sigma(I)$, R_1 0.0829, wR_2 0.2074.

The crystallographic data of molecule **III** are deposited in the Cambridge Crystallographic Data Center under the number CCDC 668097.

IR spectrum was recorded on a spectrophotometer Specord 75IR. ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker DPX-400, internal reference HMDS, solvent $CDCl_3$. The melting point was measured on a heating block and was reported uncorrected.

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REFERENCES

1. Tseng, H.-R. and Luh, T.-Y., *J. Org. Chem.,* 1996, vol. 61, p. 8685.
2. Denmark, S.E. and Ghosh, S.K., *Angew Chem. Int. Ed*., 2001, vol. 40, p. 4759.
3. Milgrom, L.R. and Yahioglu, G., *Tetrahedron Lett*., 1996, vol. 37, p. 4069.
4. Krishna, P.R., Sekhar, E.R., and Kannan, V., *Tetrahedron Lett.,* 2003, vol. 44, p. 4973.
5. Deussen, H.-J., Jeppesen, L., Schдrer, N., Junager, F., Bentzen, B., Weber, B., Weil, V., Mozer, S.J., and Sauerberg, P., *Org. Proc. Res. Dev.,* 2004, vol. 8, no. 3, p. 363.
6. Wille, F. and Knorr, F., *Chem. Ber.,* 1952, vol. 85, p. 841.
7. Schenkein, D.P. and Pratt, R.F., *J. Biol. Chem.,* 1980, vol. 255, p. 45.
8. Grace, M.E., Schenkein, D.P., and Pratt, R.F., *J. Biol. Chem*., 1987, vol. 262, p. 16778.
9. Medvedeva, A.S., Mareev, A.V., Afonin, A.V., and Ushakov, I.A., *Zh. Org. Khim*., 2005, vol. 41, p. 478.
10. Fuchs, K., Fechteler, K., Mendla, K., Briem, H., and Romig, H., German Patent 10040016, 2002; *Chem. Abstr.,* 2003, vol. 136, 183824.
11. Maul, C., Hennies, H.-H., Sundermann, B., Grunenthal, G.H., German Patent 10117184, 2002; *Chem. Abstr.,* 2003, vol. 137, 294956.
12. Hennies, H.-H., Oberborsch, S., Sundermann, B., Sundermann, C., and Grunenthal, G.H., German Patent 10247269, 2004; *Chem. Abstr.,* 2004, vol. 140, 321366.
13. Pen, S., Wang, G., Schinazi, R.F., and Zhao, K., *Tetrahedron Lett.,* 1998, vol. 39, p. 8191.