The first synthesis of [1,2]oxaphosphinino[6,5-c]pyrazoles by thiophosphorylation of 6-aminopyrano[2,3-c]pyrazole-5-carbonitriles

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Abstract

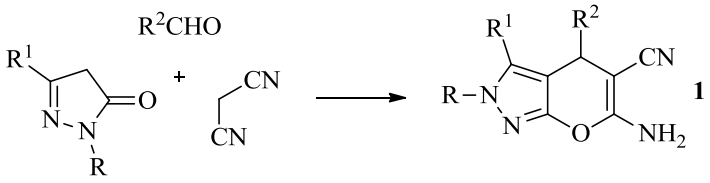
The reaction of 6-amino-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles with phosphorus sulfide in boiling pyridine leads to the formation of the unexpected [1,2]oxaphosphinino[6,5-c]pyrazoles. The structure of the products was confirmed by means of 2D NMR spectroscopy and X-ray analysis.

Keywords

Thiophosphorylation, phosphorus (V) sulfide, pyrano[2,3-c]pyrazoles, 1,2-oxaphosphinine, X-ray structural analysis.

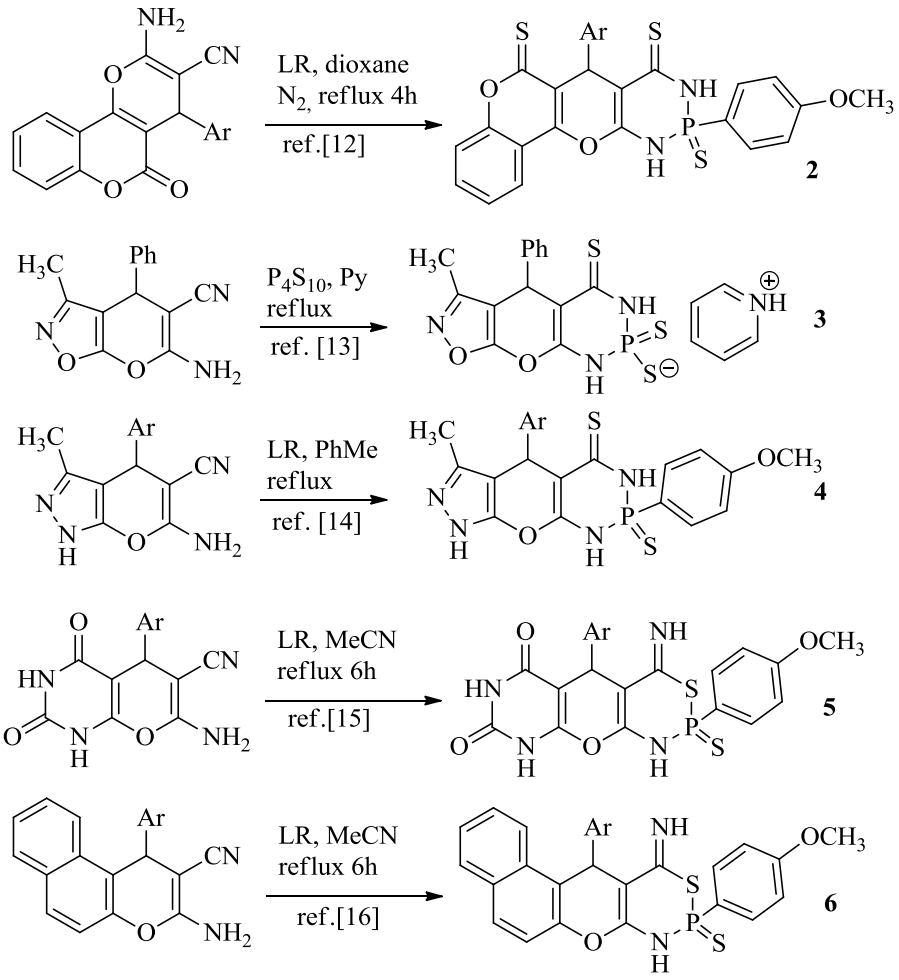
6-Amino-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles **1**, easily available by three-component condensation of aldehydes with malononitrile and pyrazole-5-ones (Scheme 1), attract the attention due to their exceptional availability and simplicity to prepare. This class of compounds and their analogs of 2-amino-3-cyano-4H-pyran and -chromene series have an interesting profile of biological activity (for reviews, see [1-4]).

Scheme 1



However, despite the availability, the reactions of compounds **1** are relatively poorly studied [1]. Meanwhile, the presence of an enaminonitrile fragment in molecule **1** makes this class of compounds a promising substrate for further transformations. Thiophosphorylation of enaminonitriles (*ortho*-aminocarbonitriles) using P_4S_{10} or Lawesson reagent (LR, 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane) was reported to afford 1,3,2λ^5-diazaphosphinanes (for example, see refs. [5-11]). For 2-amino-3-cyano-4H-pyran and chromenes, such reactions have been described in only a few recent papers; Thus, according to the known data, 1,3,2λ^5-diazaphosphinanes **2-4** [12-14] or 1,3,2λ^5-thiaazaphosphinanes **5,6** [15, were prepared through the thiophosphorylation (Scheme 2). Noteworthy that compounds **6** possess promising fungicidal activity [16], while compounds **2** possess antitumor activity and are tyrosinase inhibitors [12].

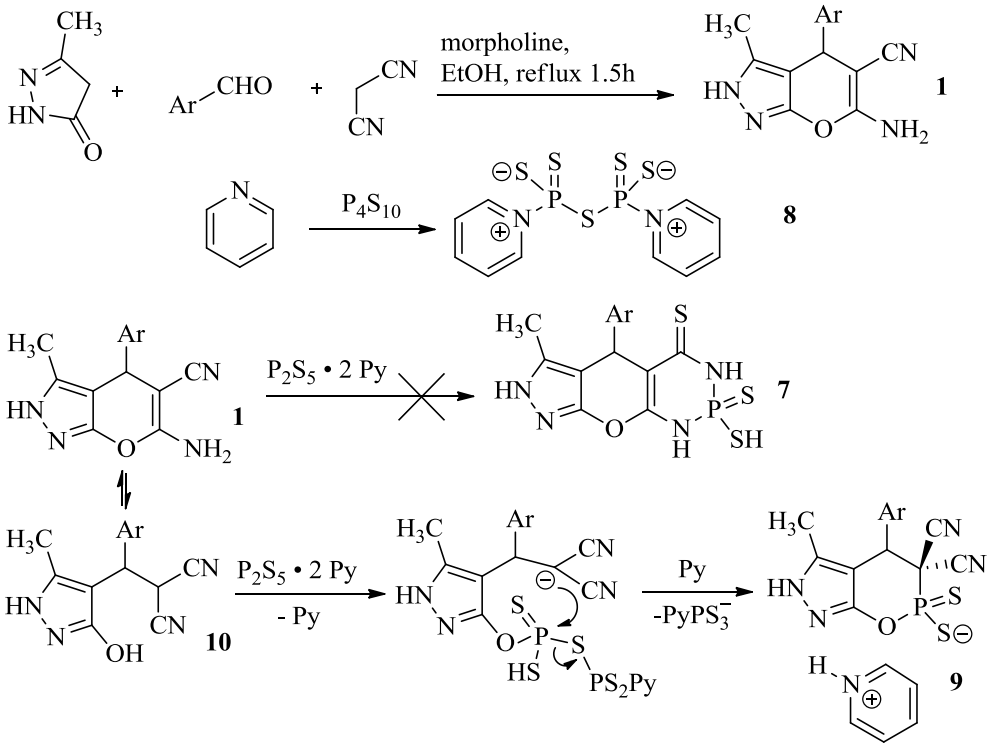
Scheme 2



In continuation of our studies in the chemistry of diazaphosphinanes [17], herein we report the reaction of 6-amino-4-aryl-3-methyl-2,4-

dihydropyrano[2,3-c]pyrazole-5-carbonitriles with phosphorus sulfide. Aiming to obtain pyrazolo[4',3': 5,6]pyrano[2,3-d][1,3,2]diazaphosphinanes **7** (Scheme 3), we first reacted phosphorus sulfide with boiling pyridine to form the adduct P_2S_5 × 2 C_5H_5N **8**, and then added pyranopyrazols **1** to the solution of the adduct **8**. The analysis of the NMR spectra as well as the X-ray diffraction data of the prepared compounds allowed us to conclude that the products of the reactions are not diazaphosphinanes, but pyridinium 4-aryl-3,3-dicyano-5-methyl-2-thioxo-3,4-dihydro[1,2]oxaphosphinino[6,5-c]pyrazole-2(6H)-thiolates **9** (Scheme 3).

Scheme 3



The proposed mechanism for the formation of compounds **9** probably involves the formation of dinitrile **10**, an acyclic tautomer of the starting pyranopyrazole **1**. Dinintrile **10** then was thiophosphorylated at oxygen atom with P_2S_5 × 2 C_5H_5N **8**. The subsequent intramolecular nucleophilic attack of the dicyanomethyl anion on a phosphorus atom resulted in the closure of 1,2-oxaphosphinine ring. Noteworthy that 1,2-oxaphosphinines are relatively poorly studied heterocyclic system and [1,2]oxaphosphinino[6,5-c]pyrazoles were not described in the literature to date.

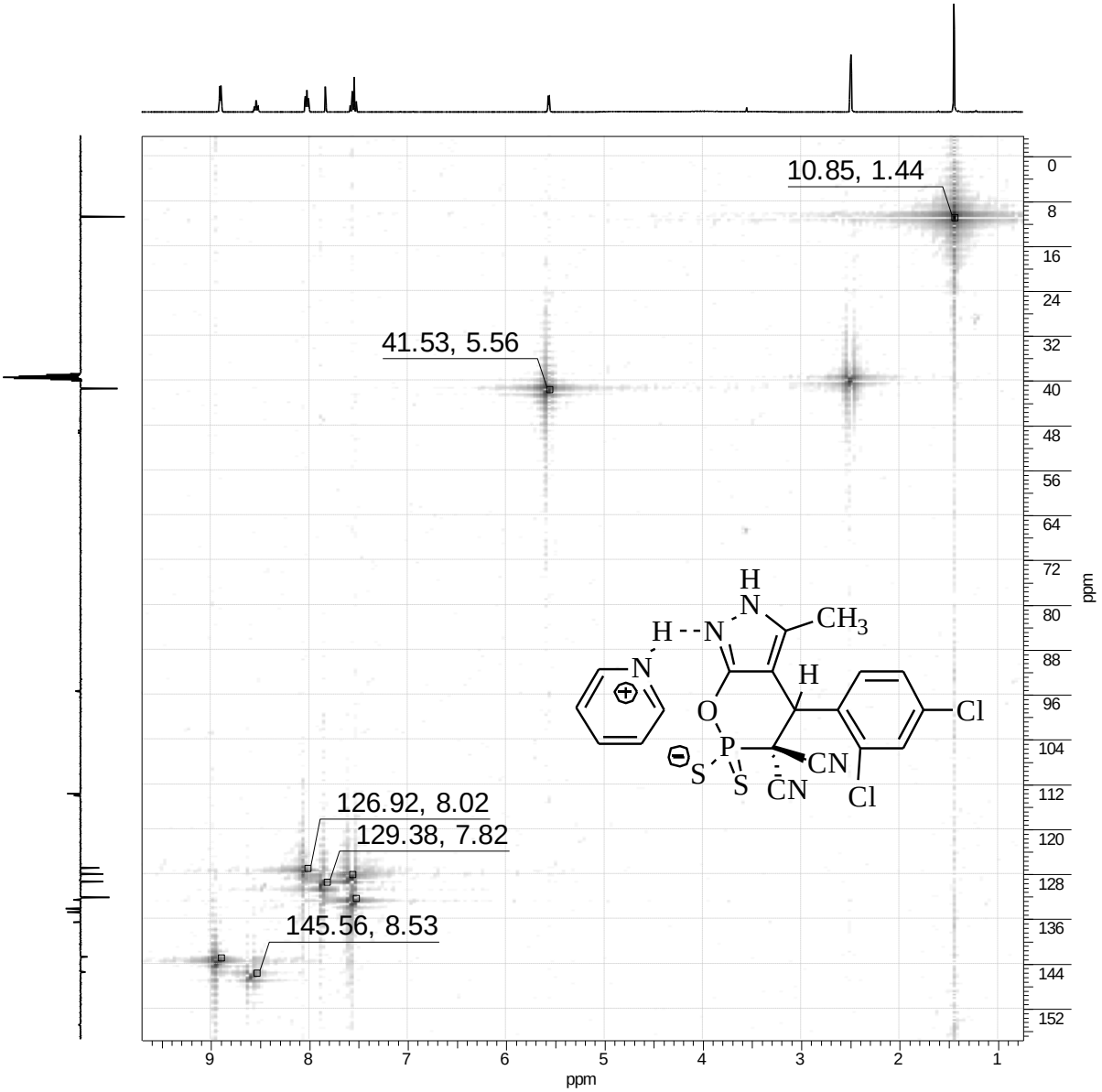


Fig. 1. HSQC ^{1}H–^{13}C NMR (400/101 MHz, DMSO-d_6) spectrum of **9** (Ar = 2,4-$Cl_2C_6H_3$).

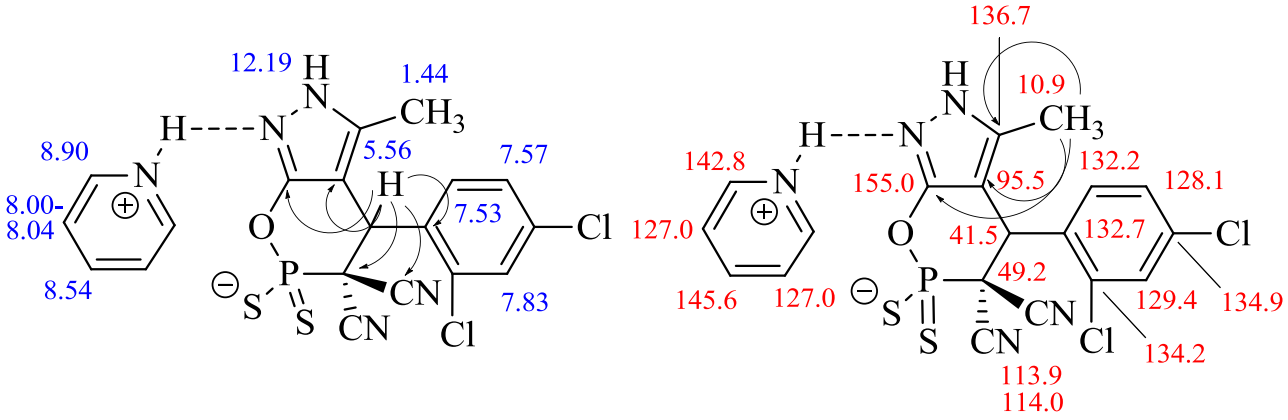


Fig. 2. The chemical shifts in the ^{1}H NMR (left) and ^{13}C NMR (right) spectra of **9a**.

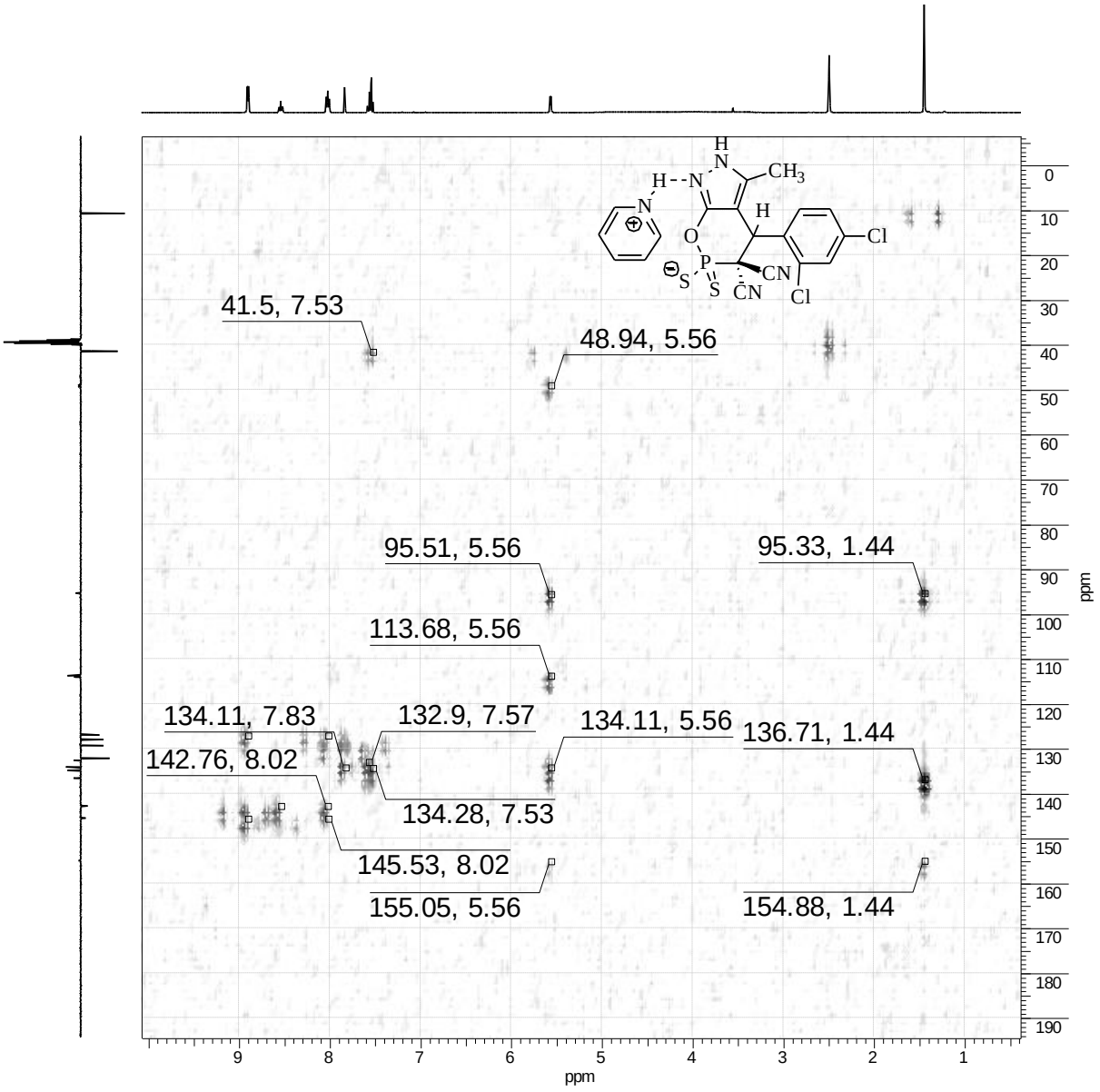


Fig. 3. HMBC $^{1}H–^{13}C$ NMR (400/101 MHz, DMSO-d_6) spectrum of **9a**.

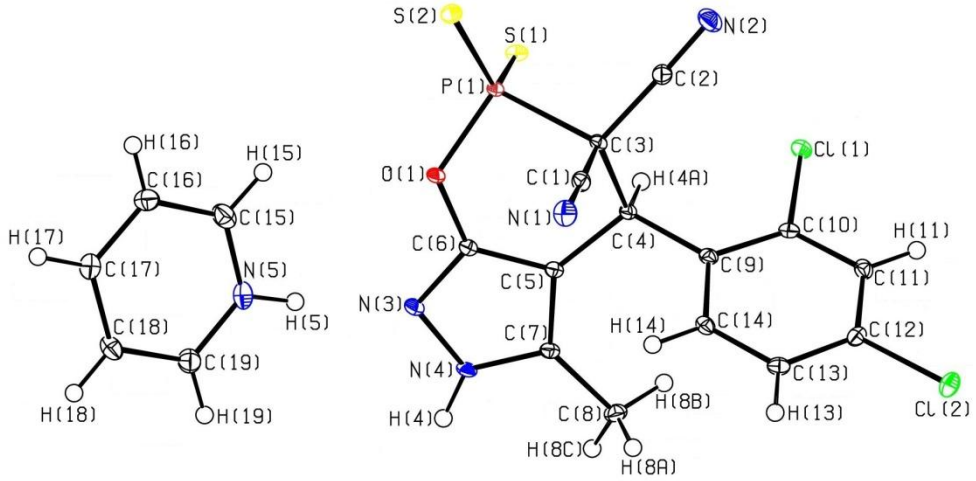


Fig. 4. Single crystal X-ray of compound **9a**.

Experimental

IR spectra were recorded on a Bruker Vertex 70 spectrometer. NMR spectra were recorded on a Bruker Avance III HD (400 MHz for ^{1}H, 162 MHz – ^{31}P, 101 MHz for ^{13}C) in DMSO-d_6. Selected experimental procedure (synthesis of **9a**) is given.

Pyridinium 4-(2,4-dichlorophenyl)-3,3-dicyano-5-methyl-2-thioxo-3,4-dihydro[1,2]oxaphosphinino[6,5-c]pyrazole-2(6H)-thiolate (9a). A solution of P_4S_{10} (1.11 g, 2.5 mmol) in absolute pyridine (20 ml) was refluxed for 2 hours to form a clear solution of the adduct P_2S_5 × 2 C_5H_5N. To the resulting solution of the adduct, a solution of pyrano[2,3-c]pyrazole **1a** (0.8 g, 2.5 mmol) in 10 ml of absolute pyridine was added, and the mixture then was refluxed for another 6 h (TLC control). After cooling, the reaction mixture was poured into ice water and carefully adjusted with 5% HCl to pH 5. The precipitate formed was filtered off, washed with water and recrystallized from absolute dioxane. The yield of compound **9a** was 11%, yellow powder. For X-ray analysis, a pale yellow monocrystalline material was prepared from an acetonic solution by slow evaporation.

IR spectrum, ν, cm^{-1}: 3417, 3202 (N–H), 2237 (C≡N), 1634, 1582 (C=N, C=C).

^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 1.44 s (3H, C$\underline{H}_3$), 4.56 d (1H, H^4, $^{3}J_{P\text{-}H}$ 4.7 Hz), 7.53 d (1H, H^6 Ar, ^{3}J 8.6 Hz), 7.57 dd (1H, H^5 Ar, ^{3}J 8.6 Hz, ^{4}J 1.7 Hz), 7.83 d (1H, H^3 Ar, ^{4}J 1.7 Hz), 8.00-8.04 m (2H, H^3, H^5 Py), 8.54 AB_2-pattern (1H, H^4 Py, ^{3}J 7.7 Hz), 8.90 d (2H, H^2, H^6 Py, ^{3}J 5.6 Hz), 12.19 br.s (1H, NH). The signal of NH$^+$ was not detected probably due to H-D exchange.

^{31}P NMR spectrum (162 MHz, DMSO-d_6), δ, ppm: 99.47.

^{13}C NMR DEPTQ spectrum (101 MHz, DMSO-d_6), δ_C, ppm: 10.9* ($\underline{C}H_3$), 41.5* br.s ($\underline{C}^4$H), 49.2 d(C^3, $^{1}J_{P\text{-}C}$ 35.2 Hz), 95.5 d (C^{4a}, $^{3}J_{P\text{-}C}$ 7.3 Hz), 113.9 d (C≡N, $^{2}J_{P\text{-}C}$ 26.4 Hz), 114.0 d (C≡N, $^{2}J_{P\text{-}C}$ 32.3 Hz), 127.0* (C^3, C^5 Py), 128.1* (C^5 Ar), 129.4* (C^3 Ar), 132.2* (C^6 Ar), 132.7 d (C^1 Ar, $^{3}J_{P\text{-}C}$ 7.3 Hz), 134.2 (C^2 Ar), 134.9 (C^4 Ar), 136.7 (C^5), 142.8* (C^2,C^6 Py), 145.6* (C^4 Py), 155.0 д (C^{7a}, $^{3}J_{P\text{-}C}$ 5.9 Hz). *Opposite signals.

References

1. Myrboh B., Mecadon H., Rohman M.R., Rajbangshi M., Kharkongor I., Laloo B.M., Kharbangar I., Kshiar B. // Org. Prep. Proced. Int. 2013. Vol. 45. N 4. P. 253. DOI: 10.1080/00304948.2013.798566.

2. Sharanin Yu.A., Goncharenko M.P., Litvinov V.P. // Russ. Chem. Rev. 1998. Vol. 67. N 5. P. 393. DOI: http://dx.doi.org/RC980393.

3. Shestopalov A.M., Emeliyanova Yu.M. in Selected methods for synthesis and modification of heterocycles. Vol. 2 / Ed. V.G. Kartsev, Moscow: IBS Press, 2003, P. 363 (in Russian).

4. Litvinov Yu.M., Shestopalov A.M. in Advances in heterocyclic chemistry, Vol. 103 / Ed. A.R. Katritzky, Oxford: Academic Press, 2011, P. 175.

5. Kozachenko A.P., Shablykin O.V., Gakh A.A., Rusanov E.B., Brovarets V.S. // Heteroatom Chem. 2010. Vol. 21. N 7. P. 492. DOI: https://doi.org/10.1002/hc.20638.

6. Khalladi K., Touil S. // J. Sulfur Chem. 2012. Vol. 33. N 1. P. 27. DOI: https://doi.org/10.1080/17415993.2011.639021.

7. Allouche F., Chabchoub F., Salem M., Kirsch, G. // Synthetic Commun. 2011. Vol. 41. N 10. P. 1500. DOI: https://doi.org/10.1080/00397911.2010.486516.

8. Nilov D.B., Kadushkin A.V., Solov'eva N.P., Sheinker Y.N., Granik V.G. // Chem. Heterocycl. Compds. 2004. Vol. 40. N 1. P. 106. DOI: https://doi.org/10.1023/B:COHC.0000023777.35950.cd.

9. Nilov D.B., Kadushkin A.V., Solov’eva N.P., Sedov A.L., Granik, V.G. // Mendeleev Commun. 1996. Vol. 6. N 5. P. 191. DOI: 10.1070/MC1996v006n05ABEH000640.

10. Nilov D.B., Kadushkin A.V., Granik V.G. // Pharm. Chem. J. 2004. Vol. 38. N 8. P. 451. DOI: https://doi.org/10.1023/B:PHAC.0000048910.45523.b7.

11. Elgazwy A.S.S.H., Soliman D.H. // Open Conf. Proc. J. 2013. Vol. 4. P.77. DOI: 10.2174/2210289201304010077.

12. Gardelly M., Trimech B., Belkacem M.A., Harbach M., Abdelwahed S., Mosbah A., Bouajila J., Jannet H.B. // Bioorg. Med. Chem. Lett. 2016. Vol. 26. N 10. P. 2450. DOI: 10.1016/j.bmcl.2016.03.108.

13. Ali T.E., Assiri M.A., Abdel-Kariem S.M., Yahia I.S. // J. Sulfur Chem. 2018. DOI: 10.1080/17415993.2018.1455837.

14. Mohamed N.R., Khaireldin N.Y., Fahmy A.F., El-Sayed A.A. // J. Heterocycl. Chem. 2013. Vol. 50. N 6. P. 1264. DOI: 10.1002/jhet.884.

15. Younes S.H.H., Mohamed S.K., Albayati M.R. // Arch. Pharm. 2013. Vol. 346. N 10. P. 727. DOI: 10.1002/ardp.201300171

16. Younes S.H., Mohamed S.K., Abdelhamid A.A., Ghattas A.-B.A.G. // Int. J. Pharm. Sci. Rev. Res. 2013. Vol. 23. N 2. P. 81. Avail. URL: http://globalresearchonline.net/journalcontents/v23-2/15.pdf

17. Dotsenko V.V., Krivokolysko S.G. // Chem. Heterocycl. Compds. 2012. Vol. 48. N. 12. P. 1863. DOI: 10.1007/s10593-013-1220-6.