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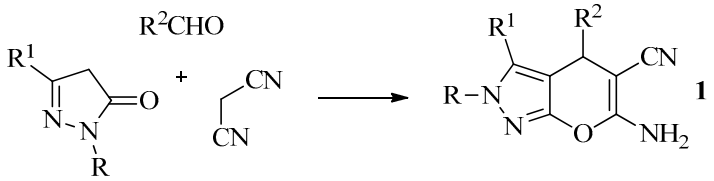
Abstract: The reaction of 6-amino-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles with phosphorus sulfide in boiling pyridine leads to the formation of the unexpected [1,2]oxaphosphinino[6,5-c]pyrazoles. The structure of the products was confirmed with 2D Nuclear Magnetic Resonance (NMR) spectroscopy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

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

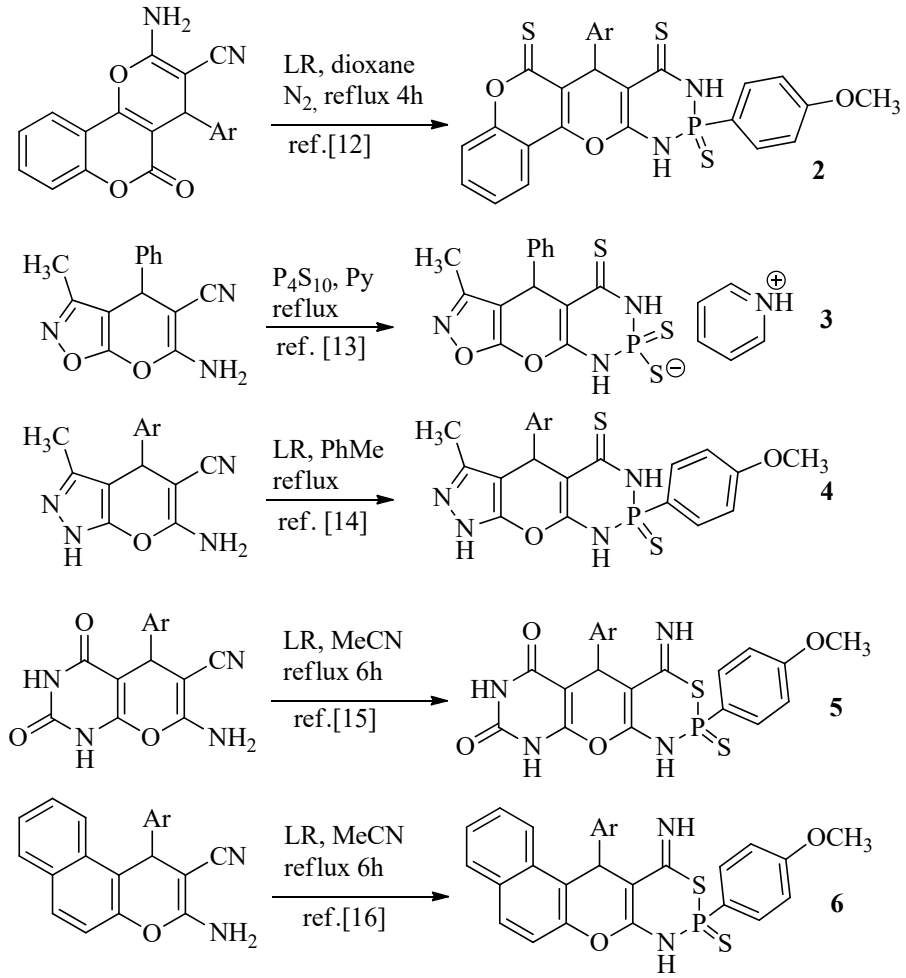
6-Amino-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles **1**, which is easily available using three-component condensation of aldehydes with malononitrile and pyrazole-5-ones (Scheme 1), attract attention due to their exceptional availability and simple preparation. This class of compounds and their 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. Synthesis of 6-Amino-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles **1**

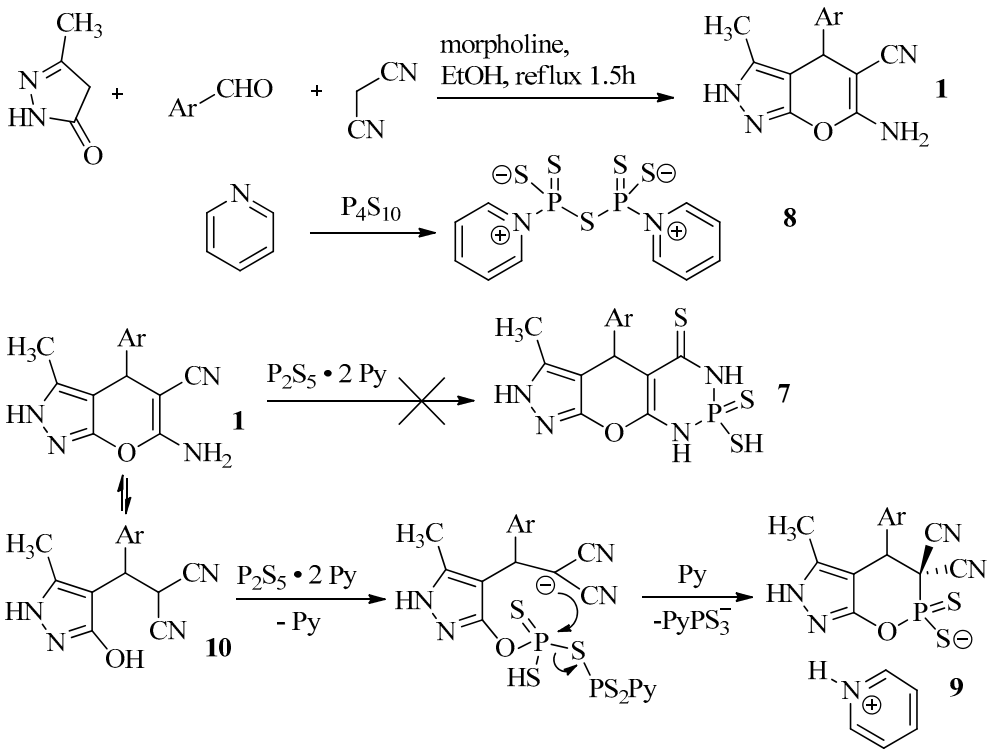
However, despite the availability, the reactions of compounds **1** are relatively poorly studied [1]. Meanwhile, the presence of an enaminonitrile fragment in molecule **1** makes this class of compounds a promising substrate for further transformations. Thiophosphorylation of enaminonitriles (*ortho*-aminocarbonitriles) 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 1,3,2λ⁵-diazaphosphinanes [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, 1,3,2λ⁵-diazaphosphinanes **2–4** [12–14] or 1,3,2λ⁵-thiaazaphosphinanes **5**,**6** [15] were prepared through the thiophosphorylation (Scheme 2). It is noteworthy that compound **6** possess promising fungicidal activity [16], while compounds **2** possess antitumor activity and are tyrosinase inhibitors [12].



Scheme 2. The reactions of 2-amino-3-cyano-4H-pyrans with P_4S_{10} or Lawesson reagent

In continuation of our studies of diazaphosphinanes' chemistry [17], 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 $P_2S_5 \times 2\ C_5H_5N$ **8**, and then added pyranopyrazols **1** to the solution of the adduct **8**. The analysis of the Nuclear Magnetic Resonance (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)-thiolate s **9** (Scheme 3).



Scheme 3. The possible mechanism of the formation of **9**

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. It is noteworthy that 1,2-oxaphosphinines are a relatively poorly studied heterocyclic system and [1,2]oxaphosphinino[6,5-c]pyrazoles were not described in the literature to date.

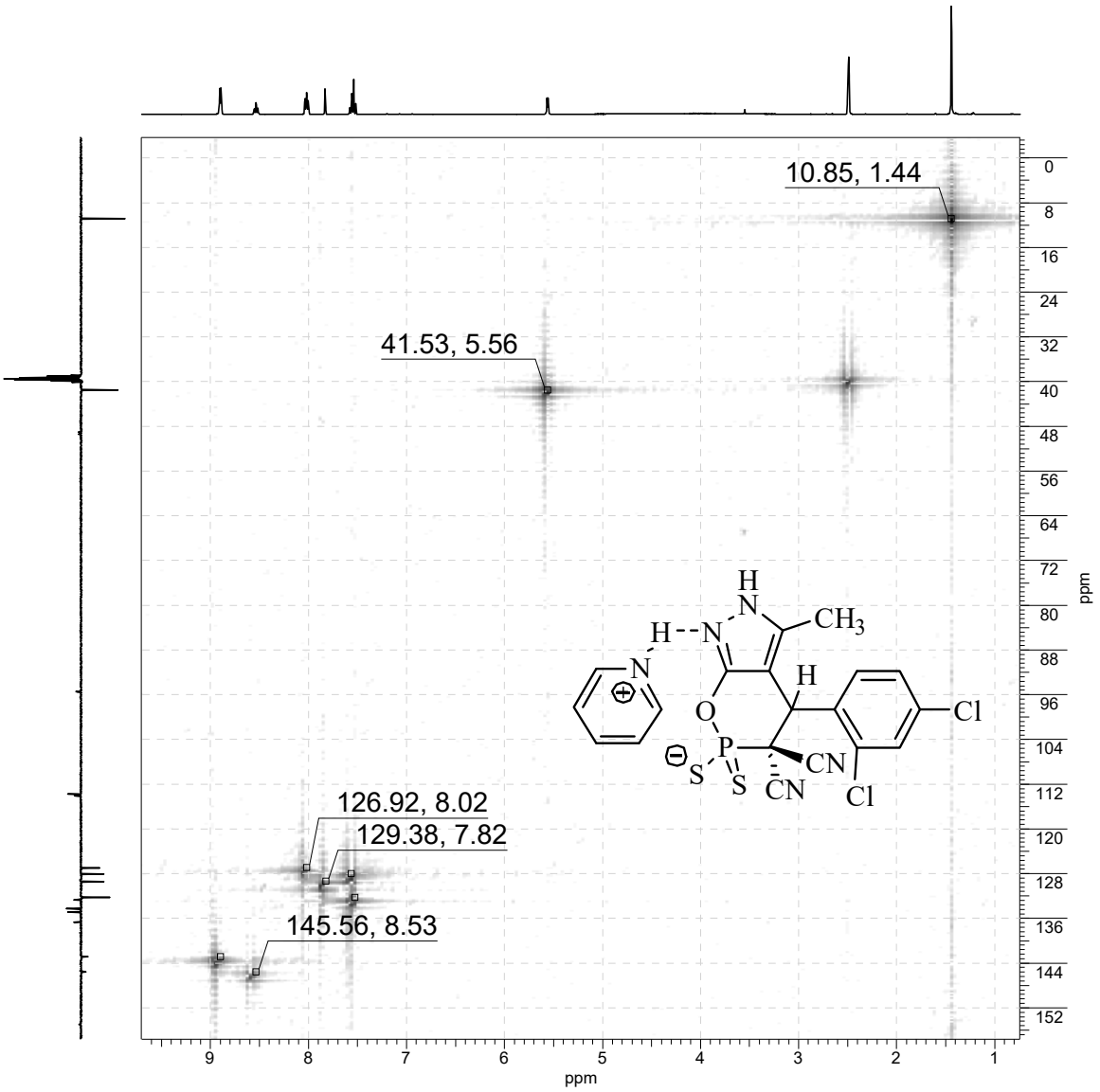


Figure 1. HSQC (Heteronuclear single quantum correlation) ^{1}H–^{13}C Nuclear Magnetic Resonance (NMR) experiment (400/101 MHz, DMSO-d_6) spectrum of **9** (Ar = 2,4-$Cl_2C_6H_3$).

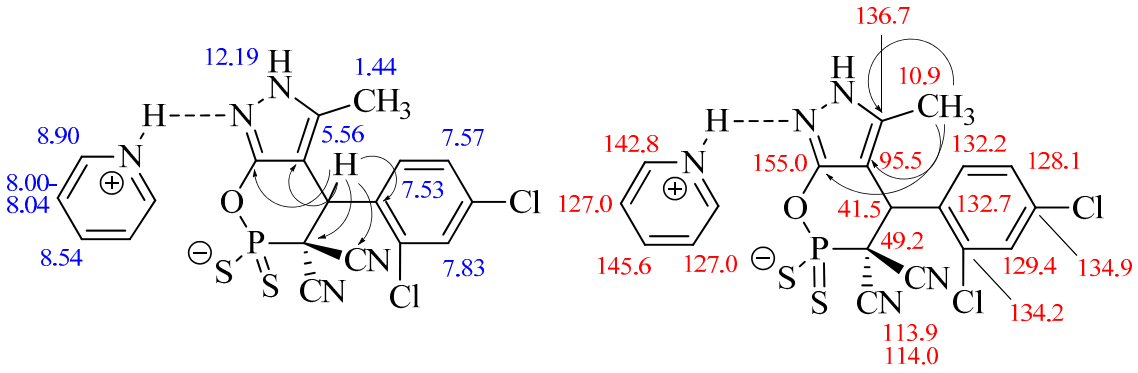


Figure 2. The chemical shifts in the ^{1}H NMR (**left**) and ^{13}C NMR (**right**) spectra of **9a**.

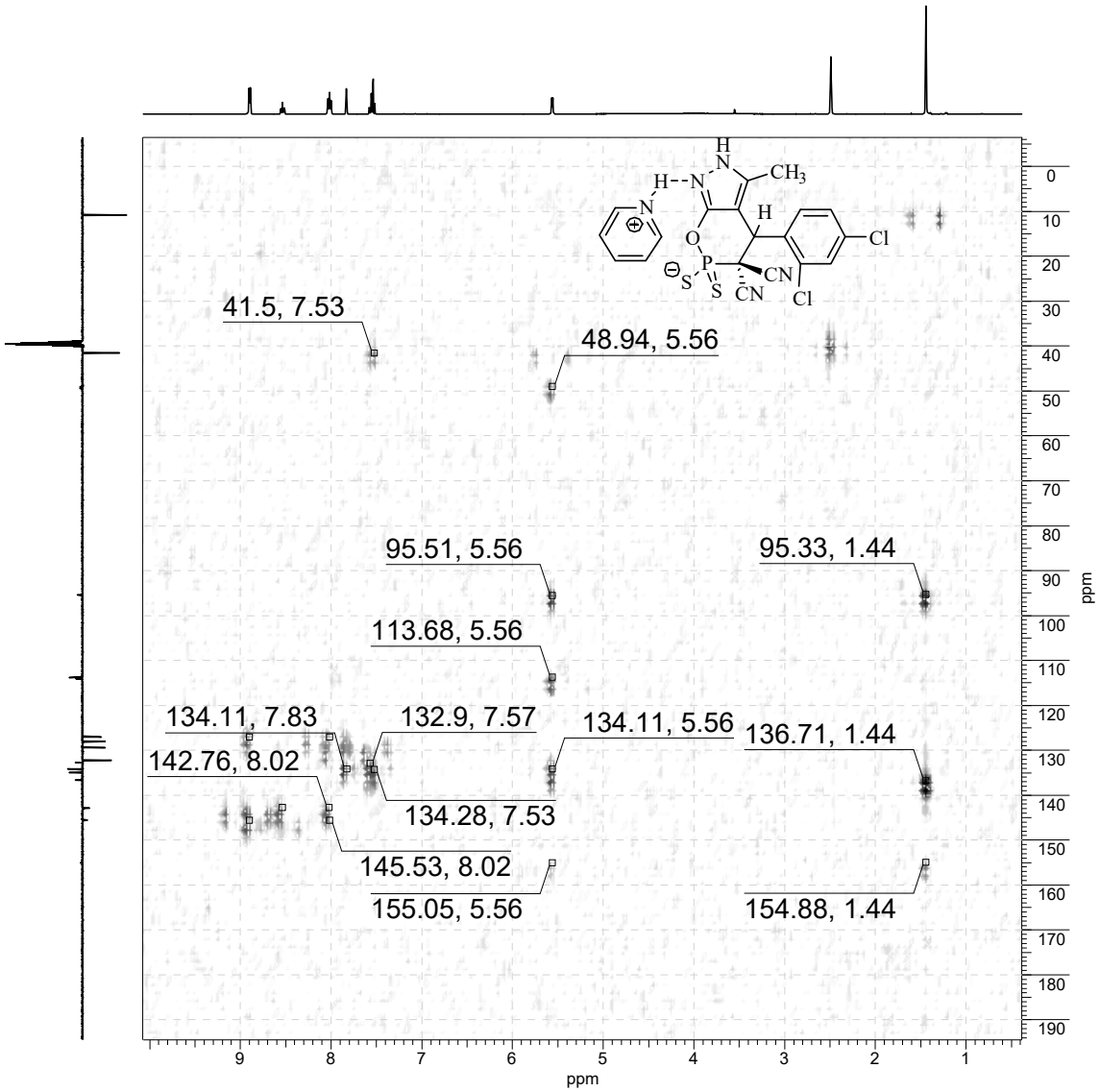


Figure 3. HMBC (Heteronuclear Multiple Bond Correlation) $^{1}H–^{13}C$ NMR experiment (400/101 MHz, DMSO-d_6) spectrum of **9a**.

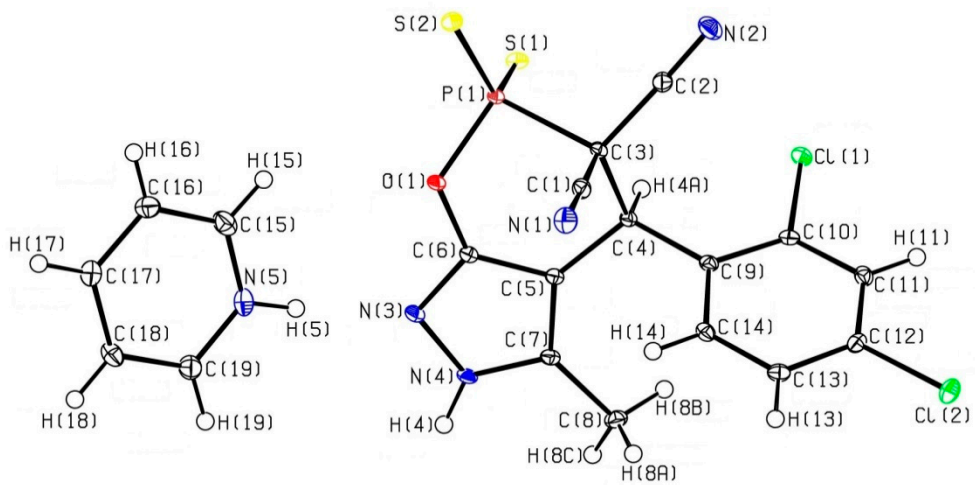


Figure 4. Single crystal X-ray of compound **9a**.

Experimental

Infrared (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 h to form a clear solution of the adduct $P_2S_5 \times 2\ C_5H_5N$. 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 (thin layer chromatography) 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} is as follow: 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, $^3J_{P\text{-}H}$ 4.7 Hz), 7.53 d (1H, H^6 Ar, ^3J 8.6 Hz), 7.57 dd (1H, H^5 Ar, ^3J 8.6 Hz, ^4J 1.7 Hz), 7.83 d (1H, H^3 Ar, ^4J 1.7 Hz), 8.00-8.04 m (2H, H^3, H^5 Py), 8.54 AB_2-pattern (1H, H^4 Py, ^3J 7.7 Hz), 8.90 d (2H, H^2, H^6 Py, ^3J 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 is as follows: 99.47.

^{13}C NMR DEPTQ (distorsionless enhancement by polarization transfer including the detection of quaternary nuclei) spectrum (101 MHz, DMSO-d_6), δ_C, ppm is as follows: 10.9* (C$\underline{H}_3$), 41.5* br.s ($\underline{C}^4$H), 49.2 d(C^3, $^1J_{P\text{-}C}$ 35.2 Hz), 95.5 d (C^{4a}, $^3J_{P\text{-}C}$ 7.3 Hz), 113.9 d (C≡N, $^2J_{P\text{-}C}$ 26.4 Hz), 114.0 d (C ≡ N, $^2J_{P\text{-}C}$ 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, $^3J_{P\text{-}C}$ 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}, $^3J_{P\text{-}C}$ 5.9 Hz). *Opposite signals.

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