The First Synthesis of [1,2]oxaphosphinino[6,5-c]pyrazoles by Thiophosphorylation of 6-Aminopyrano[2,3-c]pyrazole-5-Carbonitriles †

Victor V. Dotsenko 1,2,3,*, Vladimir A. Dushenko 1, Nikolai A. Aksenov 3, Inna V. Aksenova 3 and Evgeniy E. Netreba 4

1 Department of Chemistry and High Technologies, Kuban State University, 149 Stavropolskaya str, Krasnodar 350040, Russia; 1guft1@gmail.com
2 ChemEx Lab, Vladimir Dal’ Lugansk National University, 20A/7 Molodezhny, Lugansk 91034, Russia
3 Department of Chemistry, North Caucasus Federal University, 1a Pushkin St., 355009 Stavropol, Russia; radioanimation@rambler.ru (N.A.A.); inna-aksenova00@rambler.ru (I.V.A.)
4 Taurida Academy of V.I. Vernadsky Crimean Federal University, 4 Prospekt Vernadskogo, 295007 Simferopol, Russia; evgtnu@gmail.com
* Correspondence: victor_dotsenko_@mail.ru
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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]).

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 P2S10 or Lawesson reagent (LR,
2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane) was reported to afford 1,3,2\(\lambda^5\)-diaza phosphinanes [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, 1,3,2\(\lambda^5\)-diaza phosphinanes 2–4 [12–14] or 1,3,2\(\lambda^5\)-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-pyra ns with P_{4}S_{10} or Lawesson reagent](image)

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 pyranopyrazoles 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. Dinitrile 10 then was thiophosphorylated at oxygen atom with P$_2$S$_5$ × 2 C$_5$H$_5$N 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]oxaphosphino[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$_2$C$_6$H$_3$).

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 \( ^1H \), 162 MHz–\( ^31P \), 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]oxazaphosphinino[6,5-c]pyrazole le-2(6H)-thiolate (9a), a solution of \( \text{P}_2\text{S}_5 \text{O} \) (1.11 g, 2.5 mmol) in absolute pyridine (20 mL), was refluxed for 2 h to form a clear solution of the adduct \( \text{P}_2\text{S}_5 \times 2 \text{C}_5\text{H}_5\text{N} \). 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, \( \nu \), cm\(^{-1} \) is as follow: 3417, 3202 (N–H), 2237 (C=\( \equiv \)N) in DMSO-\( d_6 \).

\( ^1H \) NMR spectrum (400 MHz), \( \delta \), ppm (J, Hz): 1.44 s (3H, \( \alpha \)), 4.56 d (1H, \( \beta \)), \( J_{\alpha -\beta } = 4.7 \) Hz, 7.53 d (1H, H\( ^6 \) Ar, \( J_{\alpha -\beta } = 8.6 \) Hz), 7.57 dd (1H, H\( ^6 \) Ar, \( J_{\alpha -\beta } = 1.7 \) Hz), 7.83 d (1H, H\( ^7 \) Ar, \( J_{\alpha -\beta } = 1.7 \) Hz), 8.00-8.04 m (2H, H\( ^3 \), H\( ^5 \) Py), 8.54 AB-pattern (1H, H\( ^6 \) Py, \( J_{\alpha -\beta } = 7.7 \) Hz), 8.90 d (2H, H\( ^2 \), H\( ^6 \) Py, \( J_{\alpha -\beta } = 5.6 \) 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-\( d_6 \), \( \delta \), 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-\( d_6 \), \( \delta \), ppm is as follows: 10.9* (\( CH_3 \)), 41.5* br.s (C\( \equiv \)H), 49.2 d (C\( \equiv \)), \( J_{\beta -C } = 35.2 \) Hz), 95.5 d (C\( =\)N, \( J_{\beta -C } = 26.4 \) Hz), 114.0 d (C\( =\)N, \( J_{\beta -C } = 32.3 \) Hz), 127.0* (C\( \equiv \)), 128.1* (C\( \equiv \)), 129.4* (C\( \equiv \)), 132.2* (C\( \equiv \)), 132.7 d (C\( =\)Ar, \( J_{\beta -C } < 7.3 \) Hz), 134.2 (C\( =\)Ar), 134.9 (C\( =\)Ar), 136.7 (C\( =\)Ar), 142.8* (C\( =\)C, H\( =\)C\( \equiv \)), 145.6* (C\( =\)C), 155.0 4 (C\( =\)C, \( J_{\beta -C } = 5.9 \) Hz).

*Opposite signals.

References
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