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Synthesis of 3-(2,3,5,6-tetrafluoropyridinylthio)pyrazoles from 3-aminopyrazoles

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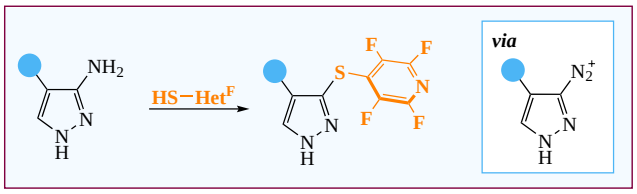
Pyrazoles bearing (2,3,5,6-tetrafluoropyridinyl)thio group were obtained from 3-aminopyrazoles. The reaction is performed by diazotization of starting amines followed by treatment of the intermediate diazonium salts with 2,3,5,6-tetrafluoropyridine-4-thiol and potassium carbonate. The method is best applied towards 4-substituted 3-aminopyrazoles.

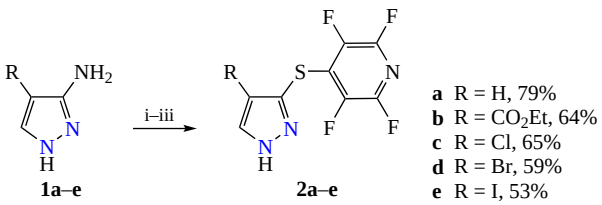


Keywords: pyrazoles, aminopyrazoles, sulfides, diazonium ions, organofluorine compounds, pyridines.

A variety of biologically active molecules used in practice contain pyrazole core.[1–5] These substances have found wide applications in the pharmaceutical and agrochemical industries. Indeed, they can exhibit analgesic, anti-inflammatory, antimicrobial, antiviral, and antitumor activities.[6–9] In this regard, the development of methods for the synthesis of new pyrazole derivatives is an important problem. Pyrazoles containing a fluorinated fragment have also been extensively evaluated due to their diverse biological activities.[10]

Recently, we have introduced (2,3,5,6-tetrafluoropyridin-4-yl)thio fragment (PyfS) as activating group in photocatalysis,[11,12] with the fluorinated pyridine playing a key role as electron acceptor.[13] Herein we report a method for the synthesis of pyrazoles bearing this fluorinated pyridinylthio group. The resulting 3-(2,3,5,6-tetrafluoropyridin-4-ylthio)-1*H*-pyrazoles are interesting not only in view of their potential biological activity, but also due to the possibility of their further involvement in subsequent transformations. In the literature, the diazotization of aminopyrazoles was used to introduce a halogen atom[14,15] and to perform cyclization reactions.[16,17] It was also described that arene diazonium salts may be coupled with thiols and disulfides leading to aromatic sulfides.[18–20] Accordingly, we decided to apply the diazotization reaction for the synthesis of arylthio-substituted pyrazoles.

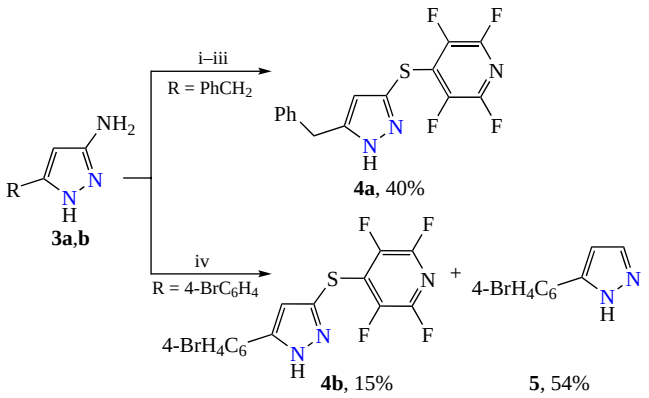
The diazotization of 4-substituted 3-aminopyrazoles **1a–e** was carried out by treatment with sodium nitrite and hydrochloric acid in a mixture of acetonitrile and water (4 : 1) at –5 °C (Scheme 1). The formation of the diazonium salts was accompanied by the characteristic appearance of the intense yellow color. Further addition of 2,3,5,6-tetrafluoropyridine-4-thiol (PyfSH), followed by the addition of potassium carbonate, and brief heating at 70 °C led to the formation of target products **2a–e**.



Scheme 1 *Reagents and conditions*: i, $NaNO_2$, HCl, $MeCN/H_2O$, –5 °C, 15 min; ii, PyfSH (1.3 equiv.), –5 °C to room temperature, 20 min; iii, K_2CO_3, 70 °C, 10 min.

We also briefly evaluated 5-susbtituted 3-aminopyrazoles (Scheme 2). Pyrazole **3a** bearing a benzyl group gave the expected sulfide **4a** under standard conditions, albeit with a moderate yield. At the same time, the reaction of substrate containing a 4-bromophenyl group was unsuccessful, and the target product was not formed. We decided to apply modified conditions when the aminopyrazole was combined with *tert*-butyl nitrite, the thiol, and the corresponding disulfide under blue light irradiation. The disulfide was used as an additive since the reaction of diazonium ions is supposed to proceed *via* aryl radicals, and this perfluorinated disulfide is known to be effective in transferring the PyfS-group towards radical species.[21] However, even under these conditions, target sulfide **4b** was formed in only 15% yield, along with deaminated compound **5** as a major product.

All obtained compounds were characterized by ^1H, ^{13}C, and ^{19}F NMR. It is worthy of note that in a series of 4-halogeno-



Scheme 2 *Reagents and conditions*: i, $NaNO_2$, HCl, $MeCN/H_2O$, –5 °C, 15 min; ii, PyfSH (1.3 equiv.), –5 °C to room temperature, 20 min; iii, K_2CO_3, 70 °C, 10 min; iv, Bu^tONO, Pyf_2S_2, PyfSH, MeCN, blue LED, 2 h.

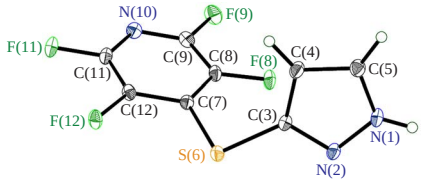
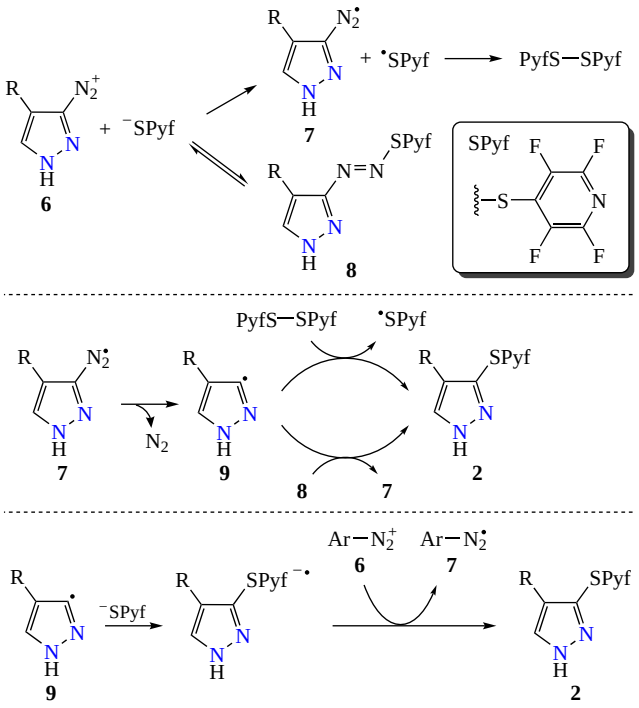


Figure 1 Crystal structure of compound **2a**.

substituted pyrazoles, in ^{13}C NMR, the C^4 signal shifts into the upfield region (112.9 ppm for chloro derivative **2c**, 101.0 ppm for bromo derivative **2d**, and 67.2 ppm for iodo derivative **2e**). The structure of compound **2a** was also verified by single crystal X-ray diffraction analysis (Figure 1).†

Concerning the mechanism, we believe that the reaction has a radical character, though several pathways may be operative (Scheme 3). First, diazonium ion **6** may be reduced *via* single electron transfer to generate the nitrogen-centered radical **7** and



Scheme 3

† *Crystal data for* **2a**. $C_8H_3F_4N_3S$ (M = 249.19), monoclinic, space group C_2/c, 99.9(3) K, a = 36.80852(18), b = 5.10856(3) and c = 29.71909(16) Å, β = 96.4108(5)°, Z = 24, d_{calc} = 1.788 g cm^{-3}, V = 5553.39(5) Å^3, μ(CuK$_\alpha$) = 3.545 mm^{-1}, F(000) = 2976. A total of 70617 reflections were collected (5881 independent reflections, R_{int} = 0.0509), GoF = 1.042, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0265 and wR_2 = 0.0668, R indices (all data): R_1 = 0.0275 and wR_2 = 0.0676, 446 refined parameters. X-ray diffraction data were collected on a four-circle Rigaku Synergy S diffractometer equipped with a HyPix6000HE area-detector (kappa geometry, shutterless ω-scan technique), using graphite monochromatized CuK$_\alpha$-radiation. The intensity data were integrated and corrected for absorption and decay by the CrysAlisPro program.[22] The structure was solved by direct methods using SHELXT[23] and refined on F^2 using SHELXL-2018[24] in the Olex2 program.[25] All non-hydrogen atoms were refined with individual anisotropic displacement parameters. The locations of hydrogen atoms H1A, H1B and H1C were found from the electron density-difference map; they were refined with individual isotropic displacement parameters. All other hydrogen atoms were placed in ideal calculated positions and refined as riding atoms with relative isotropic displacement parameters. The Olex2 program suite[25] was used for molecular graphics.

CCDC 2338434 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

the thiyl radical, which can readily dimerize to generate the disulfide. Alternatively, the thiolate anion may reversibly attack the nitrogen of the diazonium ion to give intermediate **8** featuring a nitrogen–sulfur bond. It is likely that the dissociation of **8** back to the diazonium and sulfide ions is favored at elevated temperatures. Radical intermediate **7** can easily expel the nitrogen molecule to generate pyrazolyl radical **9**, which can take the sulfide fragment either from the disulfide or from intermediate **8**. Another opportunity is the interaction of the pyrazolyl radical with the thiolate to give a radical anion, with subsequent rapid single electron oxidation by the diazonium ion.

In summary, the transformation of 3-aminopyrazoles into the corresponding fluorinated sulfides was investigated. The reaction works well with 4-susbtituted substrates, but aminopyrazoles bearing 5-positioned benzyl or aryl groups provide the corresponding sulfides in low yields.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.06.020.

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