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SHORT COMMUNICATIONS

3-Polyfluoroalkyl-1,5-diphenylpyrazoles in Suzuki Cross-Coupling Reactions

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Abstract—Suzuki cross-coupling was used for modification of 3-polyfluoroalkyl-1-phenylpyrazoles at the position C^4. The synthesized 4-bromo- and 4-phenyl derivatives showed antitubercular effect on pyrazinamide level.

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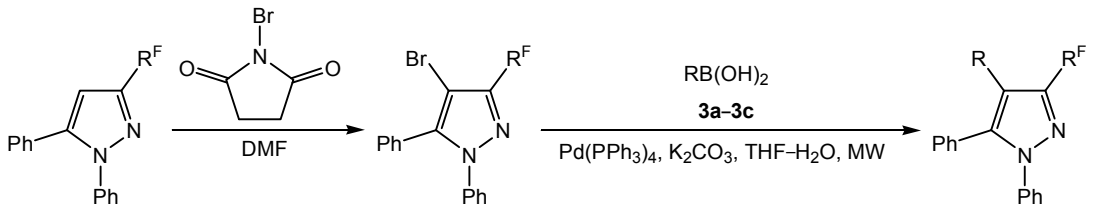
4-(Het)aryl-3-polyfluoroalkyl-1,5-diphenylpyrazoles were obtained from 3-polyfluoroalkyl-1,5-diphenylpyrazoles by Suzuki cross-coupling. Recently increased attention to pyrazoles chemistry is due to unique properties of their derivatives. The high significance of pyrazole ring was demonstrated in surveys [1–4]. Pyrazole structural motif is present in molecules demonstrating a wide spectrum of agrochemical and pharma-ceutical actions [1]. Besides that pyrazoles are on demand in supramolecular and polymer chemistry, and also as cosmetic dyes and UV stabilizers, a series of pyrazoles also possesses liquid-crystalline properties [5, 6].

In designing new drugs and agrochemicals good prospects are expected for fluoro-containing pyrazoles [7, 8]. In this series one of bestselling drugs may be mentioned, antiphlogistic medicine celebrex (celecoxib), veterinary antiarthritis drug mavacoxib (trocoxil), and also compounds in the stage of clinical tests SC-560 (anticancer activity), AS-136A (antiviral effect), razaxaban (anticoagulant activity) [9]. For preserving and increasing harvest in agriculture fungicide penthiopirad [10] and herbicide fluozolate [11] are applied. The range of pyrazoles biological activity is determined by the nature of peripheral surroundings of heterocyclic ring. In this connection development of methods of pyrazole scaffold modification is an actual task.

For modification of *N*-unsubstituted polyfluoroalkylpyrazoles reactions of alkylation [12–14] and ribosylation [15, 16] are effectively utilized; therewith the modulation of tuberculostatic [13], antibacterial [14], or antiviral [16] properties of new derivatives is possible. The alkylation and arylation of polyfluoroalkylpyrazoles, particularly those containing a halogen atom in the position *4*, occurs at competing atoms N^1 and N^2, while the center C^4 is not involved in these reactions [12–22].

In this study for modification in the position C^4 of polyfluoroalkyl containing pyrazoles **1a** and **1b** we applied arylation by Suzuki cross-coupling reaction. To this end from pyrazoles **1a** and **1b** first by reaction with *N*-bromosuccinimide 4-bromoderivatives **2a** and **2b** were prepared and further were brought into reactions with (het)arylboronic acids **3a–3c** in a microwave reactor at



1a, **1b** **2a**, **2b** **4a–4d**

1, **2**, $R^F = CF_3$ (**a**), HCF_2 (**b**); **3**, R = Ph (**a**), 4-$MeSC_6H_6$ (**b**), Th (**c**); **4**, R = Ph, $R^F = CF_3$ (**a**), HCF_2 (**b**); $R^F = CF_3$, R = 4-$MeSC_6H_4$ (**c**), Th (**d**).

135–155°C (250 W) that led to the formation of 4-(het)-aryl-substituted pyrazoles **4a–4d** in good yields.

1,4,5-Triphenyl-substituted pyrazole **4a** was obtained previously by Stille reaction [23] utilizing more expensive $ArSnR_3$ as arylating agent.

In tests *in vitro* on laboratory samples of $H_{37}Rv$ tuberculosis microbacteria tuberculostatic activity of 4-bromo- and 4-phenyl-substituted trifluormethylpyrazoles **2a** and **4a** was explored. As comparative preparation pyrazinamide was chosen, minimal inhibiting concentration (MIC) of which in the same experimental conditions was 12.5 μg/mL. Compounds **2a** and **4a** show moderate tuberculostatic activity at MIC 12.5 μg/mL.

Hence with Suzuki cross-coupling a modification of 3-polyfluoroalkyl-1-phenylpyrazoles at the position C^4 was performed. The synthesized 4-bromo- and 4-phenyl derivatives showed antitubercular effect on pyrazinamide level.

Pyrazoles **1a** and **1b** were synthesized by the method [24].

Pyrazoles (2a and 2b). A solution of 2.0 mmol of pyrazole **1a** and **1b** and 0.71 g (4.0 mmol) of *N*-bromosuccinimide in 10 ml of DMF was heated at 80°C for 10 h in an argon flow, then 50 mL of water was added and the mixture was extracted with CH_2Cl_2 (2 × 20 mL), the extract was dried with $MgSO_4$. The solvent was evaporated, reaction products **2a** and **2b** were purified by column chromatography, eluent hexane–ethyl acetate, 9 : 1.

4-Bromo-3-(trifluoromethyl)-1,4-diphenyl-1*H*-pyrazole (2a). Yield 79%, white powder, mp 100–102°C (102–104°C [23]).

4-Bromo-3-(tetrafluoroethyl)-1,4-diphenyl-1*H*-pyrazole (2b). Yield 78%, white powder, mp 103–105°C. IR spectrum, ν, cm^{-1}: 1108–1079 s (C–F). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.35 t.t [1H, $H(CF_2)_2$, $^2J_{H–F}$ 53.1, $^3J_{H–F}$ 4.8 Hz], 7.20–7.23 m (2H, H^o, Ph), 7.25–7.28 m (2H, H^o, Ph), 7.31–7.33 m (3H, $H^{m,p}$, Ph), 7.38–7.40 m (3H, $H^{m,p}$, Ph). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 25.10 t.d (2F, HCF_2, $^2J_{F–H}$ 53.1, $^3J_{F–F}$ 8.4 Hz), 47.55 d.t (2F, CF_2, $^3J_{F–H}$ 4.8, $^3J_{F–F}$ 8.3, $^2J_{F–F}$ 8.4 Hz). Found, %: C 51.03; H 2.73; N 7.17. $C_{17}H_{11}N_2F_4Br$. Calculated, %: C 51.15; H 2.78; N 7.02.

Compounds 4a–4d. To a mixture of 0.5 mmol of bromopyrazol **2a** or **2b**, 0.6 mmol of arylboronic acid **3a**, **3c** or **3b**, and 0.29 g (5 mol %) of $Pd(PPh_3)_4$ in 1.5 mL of THF was added a solution of 0.173 g (0.6 mmol) of K_2CO_3 in 2 mL of water. Argon was bubbled through obtained mixture and it was irradiated in a microwave reactor at 155°C (250 W) for 20 min, solvent was evaporated. The reaction product was purified by column chromatography, eluent hexane–ethyl acetate, 1 : 2 (**4a**), CH_2Cl_2 (**4b** and **4d**), CH_2Cl_2–hexane, 2 : 1 (**4c**).

3-(Trifluoromethyl)-1,4,5-triphenyl-1*H*-pyrazole (4a). Yield 85%, white powder, mp 162–164°C (159–161°C [23]).

3-(1,1,2,2-Tetrafluoroethyl)-1,4,5-triphenyl-1*H*-pyrazole (4b). Yield 93%, white powder, mp 171–173°C. IR spectrum, ν, cm^{-1}: 1103–1052 s (C–F). ^1H NMR spectrum [$(CD_3)_2SO$], δ, ppm: 6.92 t.t [1H, $H(CF_2)_2$, $^2J_{H–F}$ 52.1, $^3J_{H–F}$ 5.2 Hz], 7.12–7.14 m (2H, Ph), 7.22–7.33 m (10H, Ph), 7.39–7.41 m (3H, Ph). ^{19}F NMR spectrum [$(CD_3)_2SO$], δ, ppm: 25.61 t.d (2F, HCF_2, $^2J_{F–H}$ 52.1, $^3J_{F–F}$ 9.4 Hz), 53.66 d.t (2F, CF_2, $^3J_{F–H}$ 9.3, $^3J_{F–F}$ 9.2, $^2J_{F–F}$ 5.6 Hz). Found, %: C 69.68; H 4.12; N 7.19. $C_{23}H_{16}N_2F_4$. Calculated, %: C 69.69; H 4.07; N 7.07.

4-[(4-Methylsulfanyl)phenyl]-3-(trifluoromethyl)-1,5-diphenyl-1*H*-pyrazole (4c). Yield 86%, white powder, mp 181–183°C. IR spectrum, ν, cm^{-1}: 1179–1135 s (C–F). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.50 s (3H, Me), 7.21–7.42 m (12H, 2Ph, C_6H_4), 7.48–7.50 m (2H, C_6H_4). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 102.28 s (CF_3). Found, %: C 67.30; H 4.17; N 6.82. $C_{23}H_{17}F_3N_2S$. Calculated, %: C 67.18; H 4.13; N 6.75.

4-(Thiophen-2-yl)-3-(trifluoromethyl)-1,5-diphenyl-1*H*-pyrazole (4d). Yield 89%, white powder, mp 135–137°C. IR spectrum, ν, cm^{-1}: 1183–1132 s (C–F). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.00 d.d (1H, $H^{4'}$, *J* 5.1, 3.6 Hz), 7.04 d (1H, $H^{5'}$, *J* 3.3 Hz), 7.11 m (1H, $H^{3'}$), 7.22–7.43 m (10H, 2Ph). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: 99.51 s (CF_3). Found, %: C 64.73; H 3.52; N 7.51. $C_{20}H_{13}F_3N_2S$. Calculated, %: C 64.86; H 3.54; N 7.56.

Method of biological experiment.[1] Investigation of tuberculostatic activity consisted in determining the concentration inhibiting growth of the culture of laboratory strain MBT H37Rv, while growing in liquid medium Sotona and on dense yolky medium Novaya [25]. Culture of laboratory strain in an amount of 10 mg was placed in porcelain mortar, ground, and prepared as

[1] The antitubercular activity was tested in Ural Institute of Phthisiopulmonology of the Ministry of Health of Russia (Yekaterinburg) by the Candidate of biological sciences M.A. Kravchenko

suspension of culture by bacterial standard of turbidity 100 millions of microbe bodies in 1 mL (10 digits). The obtained suspension (0.2 mL) was seeded into test tubes with 5 mL of nutritive medium and the tested compound of an appropriate concentration. Test tubes were incubated at 37°C for 7–10 days. Three parallel tests were performed with each concentration.

NMR spectra were registered on a spectrometer Bruker Avance-500 [500 MHz, internal reference $SiMe_4$ (^1H), 470 MHz, reference C_6F_6 (^{19}F)]. IR spectra were recorded on a spectrometer Perkin Elmer Spectrum One with ATR method or by DRA. Melting points were measured in open capillaries on an apparatus for melting points measurement Stuart SMP30. Column chromatography was performed on silica gel 60 (0.063–0.02 mm). Elemental analysis (C, H, N) was carried out on analyzer Perkin Elmer PE 2400 series II. Microwave syntheses were performed in hermetic vials (35 mL) in UHF apparatus CEM Discover & Explorer with resulting power in the range 0–300 W. Temperature was monitored with IR detector. The content of the vial was mixed by a magnet with regulated rotation speed positioned under UHF cavity, and a Teflon magnetic stick inside the vial. Profiles of temperature and power were registered with software controlled by a computer.

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