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Reactions of Thiiranes with NH Heterocycles: II[1]. *C*-Bromo/Nitro-1-(thietan-3-yl)pyrazoles as Convenient Synthons for Substituted 1-(Thietan-3-yl)pyrazoles

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Abstract—Reactions of 2-(chloromethyl)thiirane with symmetrically substituted *C*-bromo/nitropyrazoles in water in the presence of bases were accompanied by thiirane–thietane rearrangement to afford 4-bromo(nitro)- and 3,5-dibromo-4-bromo(nitro)-1-(thietan-3-yl)-1*H*-pyrazoles as convenient intermediate products for further transformations. Possible modifications of the title compounds via oxidation to 1-(1-oxo-λ^4-thietan-3-yl)- and 1-(1,1-dioxo-λ^6-thietan-3-yl)pyrazoles, reactions with oxygen and nitrogen nucleophiles with the formation of thietane-containing 5-methoxy- and 5-(morpholin-4-yl)-1*H*-pyrazoles, and reduction to 4-amino-3-bromo-5-(morpholin-4-yl)-1-(thietan-3-yl)-1*H*-pyrazole have been demonstrated.

Keywords: pyrazole, thiirane, thietane, alkylation, sulfoxide, sulfone, amines, alcohols, reduction

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INTRODUCTION

Polyfunctional heterocycles possessing several reaction centers are currently used in the directed design of new biologically active compounds [2, 3]. Such heterocycles are 1-substituted pyrazoles containing bromo and/or nitro substituents at the carbon atoms, for which nucleophilic substitution with the formation of 5- [4–8] and 4-amino derivatives [9, 10], cross-coupling to produce 3,4,5-triarylpyrazoles [11–13] and 5-methylpyrazoles [14], reduction [15–17], and cyclizations to afford fused heterocyclic compounds [1, 18, 19] have been reported. Scheme 1 shows some reactions of 1-substituted *C*-bromo/nitro pyrazoles.

RESULTS AND DISCUSSION

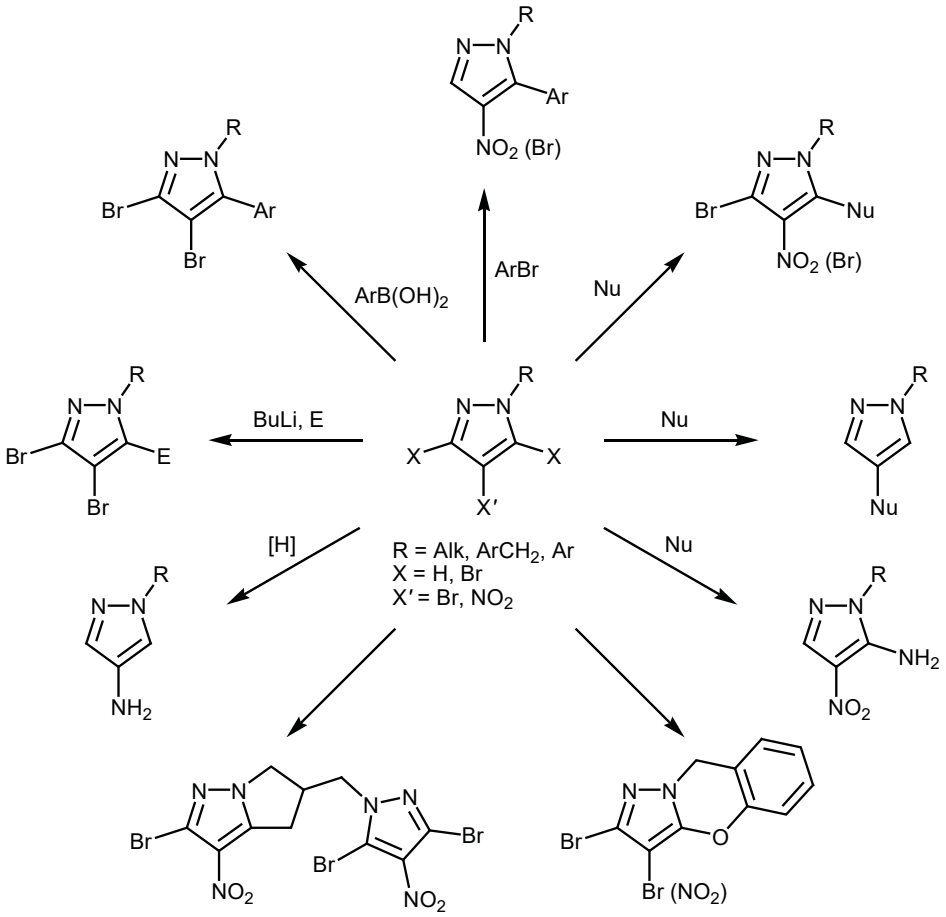
Pyrazoles containing halogen atoms and nitro groups at the endocyclic carbons and products of their further transformations are used as medicines (Fig. 1). For example, sulfaphenazole obtained from 5-amino-1-phenyl-1*H*-pyrazole exhibits antibacterial activity, and 5-piperazinylpyrazole derivative teneligliptin inhibits dipeptidyl peptidase 4 and is used in the therapy of diabetes [20]. Anti-inflammatory activity is typical of 1,5-diphenylpyrazoles (e.g., celecoxib) [20]. 4-Bromopyrazole derivative nelotanserin was proposed for the treatment of dementia [21]. Fused pyrazoles are used for cancer therapy (larotrectinib) and to treat erectile dysfunction (sildenafil) [20].

1-Substituted *C*-halo/nitropyrazoles are generally synthesized by alkylation and arylation of *N*-unsubstituted pyrazoles [22–26], but mixtures of isomeric N^1- and N^2-substituted products are often formed. This problem can be solved by using as substrates readily available symmetrical 4-bromo-, 4-nitro-, 3,4,5-tribromo-, and 3,5-dibromo-4-nitropyrazoles which give rise to only N^1-substituted derivatives.

Therefore, synthesis of new symmetrical 1-substituted *C*-bromo/nitro pyrazoles and study of their reactivity are among important problems of modern organic and medicinal chemistry.

[1] For communication I, see [1].

Scheme 1.



Herein, we describe methods of synthesis of 4-bromo/nitro- and 3,5-dibromo-4-bromo/nitro-1-(thietan-3-yl)-1*H*-pyrazoles and some ways of their further modification.

We previously found [1] that 3,5-dibromo-4-nitropyrazole (**1a**) reacts with 1.2 equiv of 2-(chloromethyl)thiirane (**2**) in water in the presence of potassium hydroxide to give thietanylpyrazole **3a** (Scheme 2). In continuation of this studies, we carried out reactions of 3,4,5-tribromo-, 4-nitro-, and 4-bromopyrazoles **1b**–**1d** with 2-(chloromethyl)thiirane (**2**) under similar conditions. In all cases, the reactions involved thiirane–thietane rearrangement to afford 25–47% of 1-(thietan-3-yl)pyrazoles **3b**–**3d** (Scheme 2). The formation of thietane ring was confirmed by the presence in the ^{1}H and ^{13}C NMR spectra of **3b**–**3d** of three multiplet proton signals at δ 3.3–3.4, 3.9–4.1 [$S(CH)_2$], and 5.5–5.7 ppm (NCH) and carbon signals at δ_C 33–35 ppm [$S(CH_2)_2$] and 56–58 ppm (NCH) [27].

The thietane ring of pyrazoles **3a**–**3d** was subjected to oxidation. As shown in [28, 29], thietanyl-substituted azoles can be oxidized to the corresponding sulfoxides and sulfones using accessible hydrogen peroxide in acetic acid. 1-(1-Oxothietan-3-yl)pyrazoles **4a**–**4d** were synthesized by oxidation of **3a**–**3d** with 2 equiv of hydrogen peroxide at 25°C (Scheme 2). Sulfoxides **4a**–**4d** were formed in up to 92% yield as mixtures of two diastereoisomers (Fig. 2), as followed from the presence of a double set of signals in their ^{1}H and ^{13}C NMR spectra. In the case of compounds **4a**–**4c**, the fraction of the *trans* isomer was about 90% for **4a** and **4c** and 80% for **4b**, whereas the *cis* isomer predominated for **4d** (23% of the *trans* isomer).

In the ^{1}H NMR spectra of **4a**–**4d**, methylene protons of the thietane ring of the *cis* isomer resonated in the regions δ 3.6–3.9 and 4.1–4.2 ppm, while the corresponding signals of the *trans* isomer appeared at δ 3.6–3.7 and 3.9 ppm. The NCH proton of the *trans* isomer is spatially close to the sulfoxide oxygen atom, and its multiplet signal is shifted downfield by 0.7–1.4 ppm relative to the NCH signal of the *cis* isomer [30]. A reliable criterion for the assignment of signals to particular isomers is the position of the NCH carbon signal of the thietane ring in the ^{13}C NMR spectrum. In

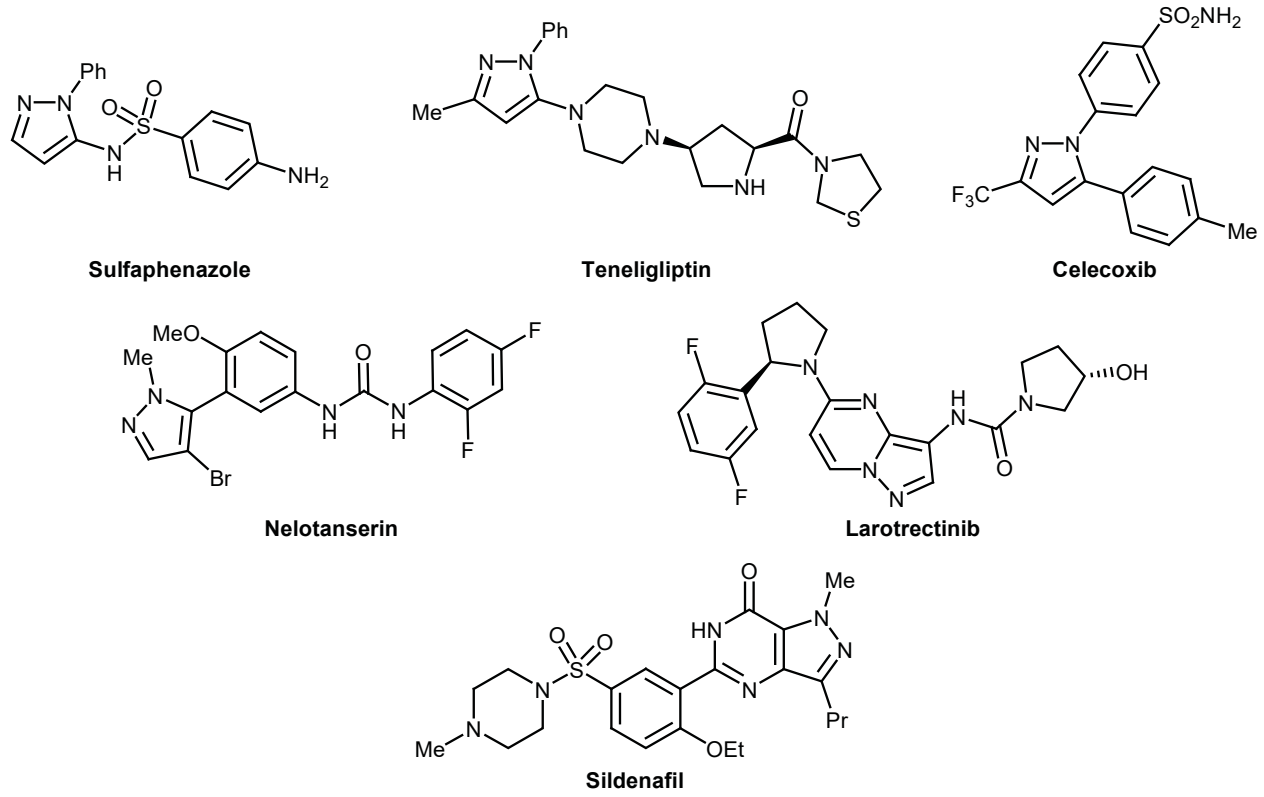


Fig. 1. Marketed drugs containing a pyrazole ring.

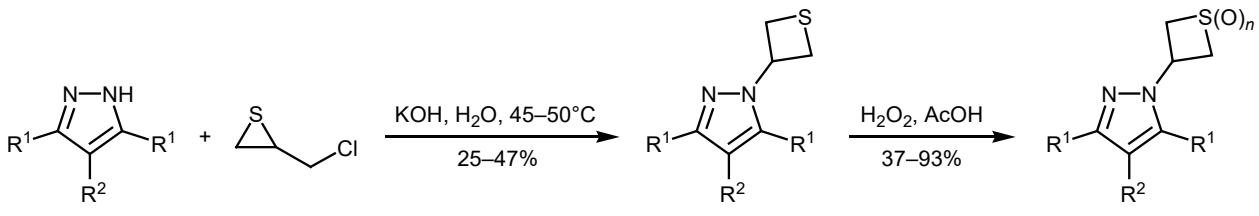
keeping with the data of [31], the C^3 signal of the thietane 1-oxide ring of *cis* isomers is located 6.3–9.9 ppm upfield from that of the corresponding *trans* isomers. In the ^{13}C NMR spectra of **4a**–**4d**, the NCH signal of the *cis* isomer was observed at δ_C 44–45 ppm against δ_C 54 ppm for the *trans* isomer.

The IR spectra of **4a**–**4d** showed a strong narrow peak at 1042–1065 cm^{-1} due to stretching vibrations of the S=O group.

To obtain sulfones **5a**–**5d**, the amount of hydrogen peroxide was increased to 10 equiv, and the reactions were carried out under reflux for 30–45 min (Scheme 2). Sulfones **5a**–**5d** were formed in 67–83% yields. In the ^1H NMR spectra of **5a**–**5d**, the $S(CH)_2$ signals shifted downfield by 0.5 and 0.9–1.1 ppm, and the NCH signal shifted upfield by 0.6 ppm, relative to the corresponding signals of initial thietanylpyrazoles **3a**–**3d**. The ^{13}C NMR spectra of sulfones **5a**–**5d** also displayed expected downfield shift of the $S(CH_2)_2$ signal by 37 ppm and upfield shift of the NCH group by 15 ppm. Unlike the initial thietanes, the IR spectra of **5a**–**5d** contained strong narrow absorption peaks due to stretching vibrations of the sulfonyl group at 1133–1146 and 1305–1332 cm^{-1}.

Pyrazoles **3a** and **5a** were used as substrates in reactions with O- and N-nucleophiles. The reaction of **3a** with an equimolar amount of sodium methoxide in methanol at room temperature afforded 77% of 5-methoxypyrazole (Scheme 3). According to literature data [4–6], 1-alkyl-3,5-dibromo-4-nitropyrazoles

Scheme 2.



4, n = 1; **5**, n = 2; R^1 = Br, R^2 = NO_2 (**a**), R^1 = R^2 = Br (**b**), R^1 = H, R^2 = NO_2 (**c**), R^1 = H, R^2 = Br (**d**).

readily react with amines on heating in ethanol. Pyrazole **3a** was reacted with morpholine at a molar ratio of 1:3 in boiling ethanol (Scheme 3). As a result, 5-morpholinopyrazole **6b** was obtained in 85% yield. Likewise, sulfone **5a** reacted with morpholine under similar conditions to produce 96% of 5-morpholino derivative **6c**. The ^{1}H NMR spectra of **6a**–**6c** showed signals for protons of the thietane ring, as well as a signal of methoxy protons (**6a**) or two multiplets for protons of the morpholine fragment (**6b**, **6c**). In the ^{13}C NMR spectra of **6a**–**6c**, the C^5 signal of the pyrazole ring was observed at lower field (by 31–35 ppm).

4-Nitropyrazole **6a** was reduced with iron in the presence of ammonium chloride [17]. The yield of the resulting 4-aminopyrazole **7** was 65% (Scheme 3). In the IR spectrum of **7**, stretching vibrations of the amino group appeared at 3323.3 and 3401.5 cm^{-1}, and its ^{13}C NMR spectrum displayed upfield shifts of signals from the pyrazole carbon atoms by 4–9 ppm relative to the corresponding signals of **6a**.

EXPERIMENTAL

The IR spectra were recorded in KBr on an Infralyum FT-02 spectrometer with Fourier transform (Russia). The ^{1}H and ^{13}C were accorded on a Bruker Avance III spectrometer (USA) at 500.13 and 125.47 MHz, respectively, using a 5-mm *Z*-gradient PABBO probe maintained at 298 K; the chemical shifts were measured relative to TMS as internal standard or residual proton and carbon signals of the deuterated solvents. Signals in the ^{13}C NMR spectra were assigned using DEPT-90 and DEPT-135 experiments.

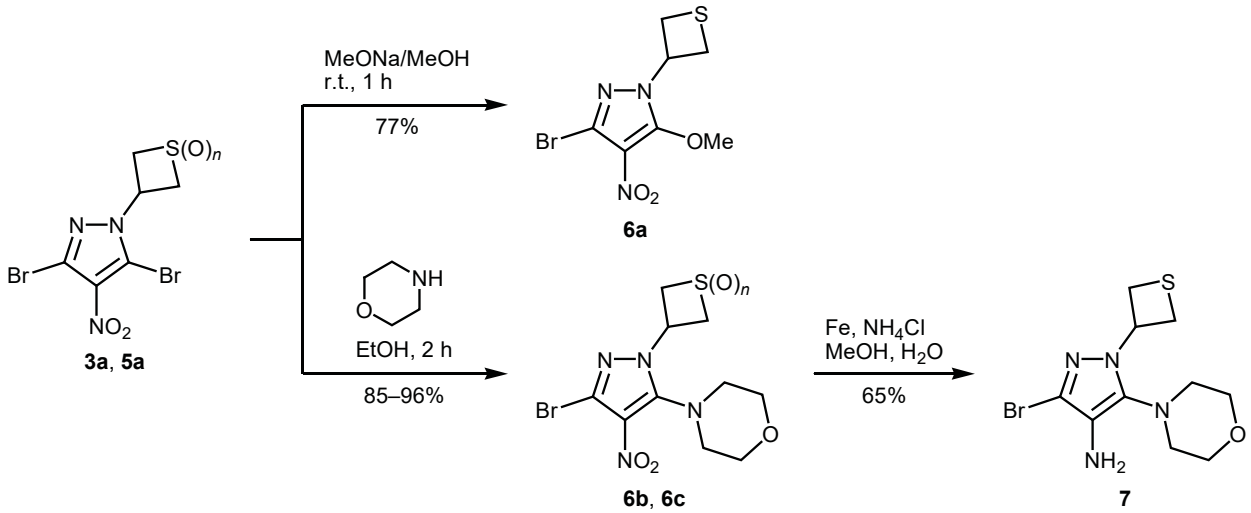
Fig. 2. *cis* and *trans* Isomers of compounds **4a**–**4d**.

Elemental analysis was performed with a Hekatech Euro3000 analyzer (Germany). The melting points were determined on a Stuart SMP30 melting point apparatus (UK). The progress of reactions and the purity of the isolated compounds were monitored by TLC on Sorbfil P-A-UF plates (Russia); visualization was done by treatment with iodine vapor and under UV light.

Compound **3a** was synthesized previously [1]. Commercially available reagents with a purity of no less than 96% were used.

1-(Thietan-3-yl)pyrazoles 3a–3d (*general procedure***).** Pyrazole **1a**–**1d**, 40 mmol, was added to a solution of 2.69 g (48 mmol) of potassium hydroxide in 100 mL of water, and the mixture was heated to 45°C with stirring. 2-(Chloromethyl)thiirane (**2**), 5.20 g (48 mmol), was then added, and the mixture was stirred at 45–50°C for 1–1.5 h and cooled to room temperature. The precipitate of **3a**–**3c** was filtered off, washed with 5% aqueous potassium hydroxide and water, and dried. In the synthesis of **3d**, the mixture was made alkaline to pH 9.0–10.0 and extracted with chloroform (3×15 mL). The combined extracts were washed with water, dried over magnesium sulfate, and evaporated to dryness under reduced pressure. The oily residue was crystallized from hexane.

Scheme 3.



3a, **6a**, **b**, **7,** $n = 0$; **5a**, **6c**, $n = 2$.

3,5-Dibromo-4-nitro-1-(thietan-3-yl)-1*H*-pyrazole (3a). Yield 13.72 g (40%), white powder, mp 143.0–144.6°C (from *i*-PrOH). IR spectrum, ν, cm^{-1}: 1524.7, 1319.0 (NO_2), 1462.9, 1447.9, 1428.7, 1398.5 (C–N, C=C, C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.31–3.34 m and 4.09–4.13 m [2H each, $S(CH)_2$], 5.79–5.86 m (1H, NCH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 56.0 (NCH), 33.1 [$S(CH_2)_2$], 114.4, 124.3. Found, %: C 21.04; H 1.43; N 12.18; S 9.30. $C_6H_5Br_2N_3O_2S$. Calculated, %: C 21.01; H 1.47; N 12.25; S 9.35.

3,4,5-Tribromo-1-(thietan-3-yl)-1*H*-pyrazole (3b). Yield 7.05 g (47%), white powder, mp 120.2–122.5°C (from *i*-PrOH). IR spectrum, ν, cm^{-1}: 1483.0, 1447.1, 1356.4, 1248.2 (C–N, C=C, C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.28–3.31 m and 4.06–4.10 m [2H each, $S(CH)_2$], 5.66–5.73 m (1H, NCH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 33.9 [$S(CH_2)_2$], 56.1 (NCH), 100.4, 115.0, 128.91. Found, %: C 19.01; H 1.29; N 7.33; S 8.61. $C_6H_5Br_3N_2S$. Calculated, %: C 19.12; H 1.34; N 7.43; S 8.51.

4-Nitro-1-(thietan-3-yl)-1*H*-pyrazole (3c). Yield 2.62 g (35%), white powder, mp 72.1–74.1°C (from hexane). IR spectrum, ν, cm^{-1}: 1524.1, 1310.5 (NO_2), 1503.0, 1405.0, 1133.4 (C–N, C=C, C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.42–3.45 m and 3.94–3.98 m [2H each, $S(CH)_2$], 5.52–5.59 m (1H, NCH), 8.11 s and 8.22 s (1H each, 3-H, 5-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 33.7 [$S(CH_2)_2$], 58.2 (NCH), 126.7 and 136.1 (C^3, C^5). Found, %: C 38.79; H 3.88; N 22.58; S 17.42. $C_6H_7N_3O_2S$. Calculated, %: C 38.91; H 3.81; N 22.69; S 17.31.

4-Bromo-1-(thietan-3-yl)-1*H*-pyrazole (3d). Yield 2.16 g (25%), white powder, mp 65.4–67.4 °C (from hexane). IR spectrum, ν, cm^{-1}: 1450.6, 1386.8, 1265.2 (C–N, C=C, C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.37–3.40 m and 3.91–3.95 m [2H each, $S(CH)_2$], 5.46–5.53 m (1H, NCH), 7.50 s and 7.51 s (1H each, 3-H, 5-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 34.5 [$S(CH_2)_2$], 57.8 (NCH), 93.7 (C^4), 127.6 and 140.4 (C^3, C^5). Found, %: C 32.75; H 3.29; N 12.68; S 14.73. $C_6H_7BrN_2S$. Calculated, %: C 32.89; H 3.22; N 12.79; S 14.63.

3-(1*H*-Pyrazol-1-yl)-1λ⁴-thietan-1-ones 4a–4d (*general procedure*). Pyrazole **3a**–**3d**, 3.1 mmol, was dissolved in 10 mL of glacial acetic acid, 0.59 g (6.2 mmol) of 36% hydrogen peroxide was added, and the mixture was stirred at 25°C for 1.5 h. The mixture was cooled to 15°C and neutralized to pH 8.0 with ammonia. The precipitate was filtered off, washed with water, and dried.

3-(3,5-Dibromo-4-nitro-1*H*-pyrazol-1-yl)-1λ⁴-thietan-1-one (4a). Yield 0.82 g (74%), yellowish powder, decomp. point 212.5°C (from *i*-BuOH). IR spectrum, ν, cm^{-1}: 1522.9, 1329.7 (NO_2), 1515.8, 1461.2, 1400.1 (C–N, C=C, C=N), 1056.9 (S=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.56–3.61 m [2H, $S(CH)_2$, *cis*], 3.67–3.72 m [2H, $S(CH)_2$, *trans*], 3.93–3.96 m [2H, $S(CH)_2$, *trans*], 4.21–4.24 m [2H, $S(CH)_2$, *cis*], 5.26–5.32 m (1H, NCH, *cis*), 5.92–5.97 m (1H, NCH, *trans*). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 45.3 (NCH, *cis*), 53.6 (NCH, *trans*), 56.4 [$S(CH_2)_2$, *trans*], 59.0 [$S(CH_2)_2$, *cis*], 119.2, 124.7, 132.1. Found, %: C 19.92; H 1.46; N 11.62; S 8.71. $C_6H_5Br_2N_3O_3S$. Calculated, %: C 20.07; H 1.40; N 11.71; S 8.93.

3-(3,4,5-Tribromo-1*H*-pyrazol-1-yl)-1λ⁴-thietan-1-one (4b). Yield 1.13 g (93%), white powder, mp 170.2–171.9°C (from EtOH–H_2O). IR spectrum, ν, cm^{-1}: 1480.4, 1430.6, 1360.9, 1246.4 (C–N, C=C, C=N), 1065.0 (S=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.54–3.58 m [2H, $S(CH)_2$, *trans*], 3.90–3.98 m [2H, $S(CH)_2$, *cis*, *trans*], 4.10–4.14 m [2H, $S(CH)_2$, *cis*], 4.75–4.82 m (1H, NCH, *cis*), 6.03–6.09 m (1H, NCH, *trans*). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 44.0 (NCH, *cis*), 53.8 (NCH, *trans*), 56.1 [$S(CH_2)_2$, *trans*], 59.2 [$S(CH_2)_2$, *cis*], 101.1, 116.3, 129.9. Found, %: C 18.45; H 1.21; N 7.20; S 8.07. $C_6H_5Br_3N_2OS$. Calculated, %: C 18.34; H 1.28; N 7.13; S 8.16.

3-(4-Nitro-1*H*-pyrazol-1-yl)-1λ⁴-thietan-1-one (4c). Yield 0.23 g (37%), yellowish powder, mp 187.2–188.9°C (from EtOH). IR spectrum, ν, cm^{-1}: 1541.6, 1309.4 (NO_2), 1512.6, 1414.2, 1139.7, 1064.4 (C–N, C=C, C=N), 1042.2 (S=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.62–3.70 m [2H, $S(CH)_2$, *cis*, *trans*], 3.89–3.93 m [2H, $S(CH)_2$, *trans*], 4.22–4.26 m [2H, $S(CH)_2$, *cis*], 4.99–5.07 m (1H, NCH, *cis*), 5.79–5.84 m (1H, NCH, *trans*), 8.39 s and 8.99 s (1H each, 3-H, 5-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 45.1 (NCH, *cis*), 54.4 (NCH, *trans*), 57.0 [$S(CH_2)_2$, *trans*], 59.5 [$S(CH_2)_2$, *cis*], 131.0 (C^3 or C^5), 135.6 (C^4), 136.9 (C^5 or C^3). Found, %: C 35.70; H 3.59; N 20.77; S 16.01. $C_6H_7N_3O_3S$. Calculated, %: C 35.82; H 3.51; N 20.89; S 15.93.

3-(4-Bromo-1*H*-pyrazol-1-yl)-1λ⁴-thietan-1-one (4d). Yield 0.36 g (49%), white powder, mp 150.1–152.0°C (from EtOH). IR spectrum, ν, cm^{-1}: 1447.1, 1388.7, 1265.9 (C–N, C=C, C=N), 1048.3 (S=O).

^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.56–3.64 m [2H, S(CH)$_2$, *cis*, *trans*], 3.82–3.85 m [2H, S(CH)$_2$, *trans*], 4.18–4.22 m [2H, S(CH)$_2$, *cis*], 4.87–4.92 m (1H, NCH, *cis*), 5.59–5.73 m (1H, NCH, *trans*), 7.68 s (1H, 3-H or 5-H, *trans*), 7.70 s (1H, 3-H or 5-H, *cis*), 8.10 s (1H, 3-H or 5-H, *trans*), 8.14 s (1H, 3-H or 5-H, *cis*). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 45.0 (NCH, *cis*), 53.4 (NCH, *trans*), 57.5 [S(CH$_2$)$_2$, *trans*], 60.2 [S(CH$_2$)$_2$, *cis*], 92.8 (C^4), 130.4 (C^3 or C^5, *cis*), 130.7 (C^3 or C^5, *trans*), 140.7 (C^3 or C^5). Found, %: C 30.48; H 3.09; N 12.01; S 13.44. $C_6H_7BrN_2OS$. Calculated, %: C 30.65; H 3.00; N 11.92; S 13.64.

3-(1*H*-Pyrazol-1-yl)-1λ^6-thietane-1,1-diones 5a–5d (*general procedure*). Pyrazole **3a**–**3d**, 2.5 mmol, was dissolved in 10 mL of glacial acetic acid, 2.36 g (25 mmol) of 36% hydrogen peroxide was added, and the mixture was refluxed for 30–45 min. The mixture was cooled, and the precipitate was filtered off, washed with water, and dried.

3-(3,5-Dibromo-4-nitro-1*H*-pyrazol-1-yl)-1λ^6-thietane-1,1-dione (5a). Yield 0.70 g (75%), white powder, mp 219.9–220.2°C (from *i*-BuOH). IR spectrum, ν, cm^{-1}: 1522.5, 1328.6 (NO_2), 1466.2, 1402.9, 1223.9 (C–N, C=C, C=N), 1328.6, 1145.8 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.75–4.85 m [4H, S(CH)$_2$], 5.53–5.59 m (1H, NCH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 41.9 (NCH), 71.0 [S(CH$_2$)$_2$], 120.3, 124.0, 132.5. Found, %: C 18.93; H 1.54; N 11.01; S 8.28. $C_6H_5Br_2N_3O_4S$. Calculated, %: C 19.22; H 1.34; N 11.21; S 8.55.

3-(3,4,5-Tribromo-1*H*-pyrazol-1-yl)-1λ^6-thietane-1,1-dione (5b). Yield 0.85 g (83%), white powder, mp 236.1–237.2°C (from BuOH). IR spectrum, ν, cm^{-1}: 1488.4, 1454.3, 1361.4, 1219.1 (C–N, C=C, C=N), 1313.8, 1142.2 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.69–4.73 m [2H, S(CH)$_2$], 4.76–4.81 m [2H, S(CH)$_2$], 5.41–5.47 m (1H, NCH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 41.6 (NCH), 71.2 [S(CH$_2$)$_2$], 100.8, 119.0, 128.4. Found, %: C 17.28; H 1.44; N 6.63; S 7.58. $C_6H_5Br_3N_2O_2S$. Calculated, %: C 17.62; H 1.23; N 6.85; S 7.84.

3-(4-Nitro-1*H*-pyrazol-1-yl)-1λ^6-thietane-1,1-dione (5c). Yield 0.39 g (72%), white powder, mp 209.9–211.4°C (from EtOH). IR spectrum, ν, cm^{-1}: 1532.6, 1304.9 (NO_2), 1498.7, 1412.7, 1223.4 (C–N, C=C, C=N), 1304.9, 1132.9 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.71–4.75 m [2H, S(CH)$_2$], 4.79–4.84 m [2H, S(CH)$_2$], 5.39–5.45 m (1H, NCH), 8.41 s and 9.07 s (1H each, 3-H, 5-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 43.0 (NCH), 71.3 [S(CH$_2$)$_2$], 131.4 (C^3 or C^5), 135.8 (C^4), 136.9 (C^5 or C^3). Found, %: C 32.96; H 3.32; N 19.13; S 14.58. $C_6H_7N_3O_4S$. Calculated, %: C 33.18; H 3.25; N 19.35; S 14.76.

3-(4-Bromo-1*H*-pyrazol-1-yl)-1λ^6-thietane-1,1-dione (5d). Yield 0.42 g (67%), white powder, decomp. point 236.4°C (from MeCN). IR spectrum, ν, cm^{-1}: 1452.5, 1390.3, 1271.3 (C–N, C=C, C=N), 1316.1, 1144.6 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.62–4.65 m [2H, S(CH)$_2$], 4.73–4.78 m [2H, S(CH)$_2$], 5.30–5.34 m (1H, NCH), 7.70 s and 8.17 s (1H each, 3-H, 5-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 42.0 (NCH), 71.3 [S(CH$_2$)$_2$], 93.1 (C^4), 131.0 and 140.8 (C^3, C^5). Found, %: C 28.59; H 2.88; N 11.06; S 12.66. $C_6H_7BrN_2O_2S$. Calculated, %: C 28.70; H 2.81; N 11.16; S 12.77.

3-Bromo-5-methoxy-4-nitro-1-(thietan-3-yl)-1*H*-pyrazole (6a). Metallic sodium, 0.048 g (2.1 mmol), was added to 12 mL of methanol, and the mixture was stirred until gas no longer evolved. Pyrazole **3a**, 0.65 g (1.9 mmol), was added, and the mixture was stirred at room temperature for 1 h, treated with 80 mL of water, and cooled. The precipitate was filtered off, washed with water, and dried. Yield 0.43 g (77%), white powder, mp 73.2–73.7°C (from EtOH–H_2O, 6:1). IR spectrum, ν, cm^{-1}: 1561.5, 1345.9 (NO_2), 1463.7, 1401.8, 1254.6 (C–O, C–N, C=C, C=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.23–3.27 m [2H, S(CH)$_2$], 4.03–4.07 m [2H, S(CH)$_2$], 4.20 s (3H, OCH_3), 5.59–5.66 m (1H, NCH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 33.2 [S(CH$_2$)$_2$], 52.4 (NCH), 63.9 (OCH_3), 122.8, 149.8. Found, %: C 28.69; H 2.69; N 14.37; S 10.85. $C_7H_8BrN_3O_3S$. Calculated, %: C 28.58; H 2.74; N 14.29; S 10.90.

4-[3-Bromo-4-nitro-1-(thietan-3-yl)-1*H*-pyrazol-5-yl]morpholine (6b). Morpholine, 0.65 g (7.5 mmol), was added to 0.86 g (2.5 mmol) of pyrazole **3a** in 35 mL of ethanol, and the mixture was refluxed for 2 h. The mixture was treated with 35 mL of water and cooled, and the precipitate was filtered off, washed with water, and dried. Yield 0.74 g (85%), yellowish powder, mp 155.7–157.1°C (from EtOH). IR spectrum, ν, cm^{-1}: 1540.2, 1345.4 (NO_2), 1494.7, 1427.3, 1257.6 (C–O, C–N, C=C, C=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.08–3.17 m [4H, N(CH$_2$)$_2$], 3.21–3.27 m [2H, S(CH)$_2$], 3.81–3.90 m [4H, O(CH$_2$)$_2$], 4.06–4.12 m [2H, S(CH)$_2$], 5.79–5.88 m (1H, NCH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 33.6 [S(CH$_2$)$_2$], 49.5 [N(CH$_2$)$_2$], 52.5 (NCH), 66.7 [O(CH$_2$)$_2$], 123.5, 127.4, 145.9. Found, %: C 34.26; H 3.70; N 16.14; S 9.25.

$C_{10}H_{13}BrN_4O_3S$. Calculated, %: C 34.39; H 3.75; N 16.04; S 9.18.

3-[3-Bromo-5-(morpholin-4-yl)-4-nitro-1*H*-pyrazol-1-yl]-1λ⁶-thietane-1,1-dione (6c) was synthesized as described above for **6b** from 0.45 g (1.2 mmol) of pyrazole **5a** and 0.31 g (3.6 mmol) of morpholine. Yield 0.44 g (96%), yellowish powder, mp 192.2–194.0°C (from EtOH). IR spectrum, ν, cm^{-1}: 1547.5, 1331.9 (NO_2), 1499.0, 1433.6, 1258.8, 1222.4, 1107.9 (C–O, C–N, C=C, C=N), 1331.9, 1146.9 (SO_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.07–3.09 m [4H, $N(CH_2)_2$], 3.71–3.73 m [4H, $O(CH_2)_2$], 4.69–4.74 m [2H, $S(CH)_2$], 4.79–4.84 m [2H, $S(CH)_2$], 5.50–5.56 m (1H, NCH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 38.3 (NCH), 49.0 [$N(CH_2)_2$], 66.6 [$O(CH_2)_2$], 71.0 [$S(CH_2)_2$], 123.0, 127.2, 148.3. Found, %: C 31.20; H 3.66; N 14.42; S 8.23. $C_{10}H_{13}BrN_4O_5S$. Calculated, %: C 31.51; H 3.44; N 14.70; S 8.41.

4-[4-Amino-3-bromo-1-(thietan-3-yl)-1*H*-pyrazol-5-yl]morpholine (7). Pyrazole **6b**, 1.01 g (2.9 mmol), was added to 50 mL of methanol, a solution of 0.78 g (14.5 mmol) of ammonium chloride in 13 mL of water and 0.80 g (14.5 mmol) of iron shavings were then added, and the mixture was refluxed for 6 h. The mixture was cooled and filtered, the filtrate was evaporated under reduced pressure, and the residue was treated with a mixture of methylene chloride and methanol at a volume ratio of 10:1. The mixture was filtered, the filtrate was evaporated under reduced pressure, the residue was ground with water, and the precipitate was filtered off and dried. Yield 0.60 g (65%), brownish powder, mp 169.8–171.1°C (from *i*-BuOH). IR spectrum, ν, cm^{-1}: 3401.5, 3323.3 (NH_2), 1622.9, 1582.8, 1485.0, 1466.6, 1395.2, 1261.3, 1107.2 (C–O, C–N, C=C, C=N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.97 br.s [4H, $N(CH_2)_2$], 3.24–3.27 m [2H, $S(CH)_2$], 3.65–3.68 m [4H, $O(CH_2)_2$], 3.75–3.78 m [2H, $S(CH)_2$], 5.58–5.65 m (1H, NCH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 34.3 [$S(CH_2)_2$], 50.2 [$N(CH_2)_2$], 52.0 (NCH), 67.1 [$O(CH_2)_2$], 119.2, 122.5, 136.3. Found, %: C 37.35; H 4.78; N 17.35; S 9.92. $C_{10}H_{15}BrN_4OS$. Calculated, %: C 37.62; H 4.74; N 17.55; S 10.04.

CONCLUSIONS

The reaction of 2-(chloromethyl)thiirane with *C*-bromo/nitro pyrazole afforded *C*-bromo/nitro-1-(thietan-3-yl)-1*H*-pyrazoles as promising intermediate products for the synthesis of new biologically active compounds.

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CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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