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Synthesis of 3-aryl-6a-methyl-6-nitro-1-phenyl-hexahydrothieno[2,3-*d*]pyrazole 4,4-dioxides

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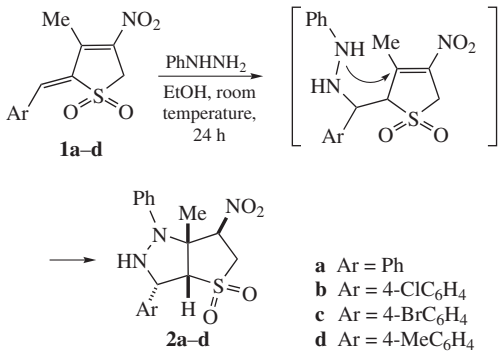
Reaction of 2-benzylidene-3-methyl-4-nitro-3-thiolene 1,1-dioxides and phenylhydrazine affords 3-aryl-6a-methyl-6-nitro-1-phenyl-hexahydrothieno[2,3-*d*]pyrazole 4,4-dioxides in moderate yields.

Functionalized thiolene and thiolane 1,1-dioxides are widely used for constructing substances with valuable properties.[1–4] Condensed polycyclic derivatives of sulfolane can serve as anthracycline antibiotics, inhibitors of influenza virus neuraminidase, and a variety of natural compounds precursors.[5–7] *s-trans*-Fixed 2-benzylidene-3-methyl-4-nitro-3-thiolene 1,1-dioxides turned to be efficient substrates for creating polynuclear structures.[8] Their reaction with dihydroresorcinol proceeding as Michael addition–cyclization affords tricyclic structures comprising condensed cycles of hexahydrochromene and sulfolane.[9]

The current work describes the reaction of 2-benzylidene-3-methyl-4-nitro-3-thiolene 1,1-dioxides **1a–d** with phenylhydrazine. This reaction proceeds in ethanol at room temperature and completes within 24 h to give colourless crystal 3-aryl-6a-methyl-6-nitro-1-phenylhexahydrothieno[2,3-*d*]pyrazole 4,4-dioxides **2a–d**.† According to ^{1}H NMR data they are formed as mixtures of two diastereomers (~10:1), the major one being isolated by crystallization.

The probable reaction pathway consists of two consequent Michael addition processes (see Scheme 1 and *cf.* ref. 9).



Scheme 1

† *General procedure for the synthesis of compounds* **2a–d**. Freshly distilled phenylhydrazine (0.21 g, 2 mmol) was added to the suspension of 2-benzylidene-3-methyl-4-nitro-3-thiolene 1,1-dioxide **1a–d** (1 mmol) in ethanol (10 ml). The mixture was stirred at room temperature for 24 h. After that the obtained precipitate was filtered off and dried at ambient temperature.

(3S,3aR*,6aR*,6S*)-6a-Methyl-6-nitro-1,3-diphenylhexahydrothieno[2,3-*d*]pyrazole 4,4-dioxide* **2a**. The colourless crystals (0.15 g, 40%) of the diastereomeric mixture (10:1) were obtained. The major diastereomer was isolated by crystallization from propan-2-ol. Yield, 0.13 g (35%), colourless crystals, mp 148–150 °C (propan-2-ol). IR (ν/cm^{-1}): 1126, 1320 (SO_2), 1364, 1565 (NO_2), 3262 (NH). ^{1}H NMR, δ: 1.30 (s, 3H, Me), 3.89 (dd, 1H, C^{5}H′, $^2J_{H'H''}$ 14.7 Hz, $^3J_{H'C^6H}$ 6.7 Hz), 3.96 (dd, 1H, C^{5}H″, $^2J_{H'H''}$ 14.7 Hz, $^3J_{H''C^6H}$ 6.1 Hz), 4.54 (d, 1H, C^{3a}H, $^3J_{HC^3C^{3a}H}$ 4.9 Hz), 5.09 (dd, 1H, C^{3}H, $^3J_{HC^3C^{3a}H}$ 4.9 Hz, $^3J_{HC^3NH}$ 14.0 Hz), 5.53 (d, 1H, NH, $^3J_{HC^3NH}$ 14.0 Hz), 5.75 (dd, 1H, C^{6}H, $^3J_{H'C^6H}$ 6.7 Hz, $^3J_{H''C^6H}$ 6.1 Hz), 6.99–7.04 (m, 1H, Ph–N), 7.25–7.29 (m, 4H, Ph–N), 7.32–7.47 (m, 5H, Ph–C). ^{13}C NMR, δ: 19.29 (Me), 54.75 (C^5), 62.30 (C^3), 74.81 (C^{3a}), 77.38 (C^{6a}), 89.17 (C^6), 120.86, 123.07, 126.47, 127.65, 128.51, 128.76, 134.40, 147.21 (Ph, Ar). Found (%): C, 57.83; H, 5.11; N, 11.35. Calc. for $C_{18}H_{19}N_3O_4S$ (%): C, 57.90; H, 5.13; N, 11.25. For the minor diastereomer, ^{1}H NMR, δ: 1.25 (s, 3H, Me), 4.05–4.20 (m, 2H, C^{5}H$_2$), 5.86–5.88 (m, 1H, C^{6}H), signals of other protons virtually coincide with those for the major diastereomer.

*3-(4-Chlorophenyl)-6a-methyl-6-nitro-1-phenylhexahydrothieno[2,3-*d*]pyrazole 4,4-dioxide* **2b**. Yield, 0.11 g (28%), colourless crystals, mp 149–153 °C. IR (ν/cm^{-1}): 1119, 1323 (SO_2), 1366, 1556 (NO_2), 3274 (NH). ^{1}H NMR, δ: 1.29 (s, 3H, Me), 3.89 (dd, 1H, C^{5}H′, $^2J_{H'H''}$ 14.8 Hz, $^3J_{H'C^6H}$ 6.7 Hz), 3.95 (dd, 1H, C^{5}H″, $^2J_{H'H''}$ 14.8 Hz, $^3J_{H''C^6H}$ 5.8 Hz), 4.55 (d, 1H, C^{3a}H, $^3J_{HC^3C^{3a}H}$ 4.9 Hz), 5.12 (dd, 1H, C^{3}H, $^3J_{HC^3C^{3a}H}$ 4.9 Hz, $^3J_{HC^3NH}$ 14.0 Hz), 5.55 (d, 1H, NH, $^3J_{HC^3NH}$ 14.0 Hz), 5.74 (dd, 1H, C^{6}H, $^3J_{H'C^6H}$ 6.7 Hz, $^3J_{H''C^6H}$ 5.8 Hz), 6.99–7.03 (m, 1H, Ph), 7.26–7.29 (m, 4H, Ph), 7.41 (d, 2H, C_6H_4, $^3J_{HH}$ 8.9 Hz), 7.45 (d, 2H, C_6H_4, $^3J_{HH}$ 8.9 Hz). ^{13}C NMR, δ: 19.28 (Me), 54.71 (C^5), 61.82 (C^3), 74.77 (C^{3a}), 77.49 (C^{6a}), 89.13 (C^6), 120.86, 123.15, 128.24, 128.48, 128.77, 132.95, 133.33, 147.06 (Ph, Ar). Found (%): C, 53.30; H, 4.41; N, 10.42. Calc. for $C_{18}H_{18}ClN_3O_4S$ (%): C, 53.01; H, 4.45; N 10.30.

*3-(4-Bromophenyl)-6a-methyl-6-nitro-1-phenylhexahydrothieno[2,3-*d*]pyrazole 4,4-dioxide* **2c**. Yield, 0.13 g (31%), colourless crystals, mp 149–151 °C (propan-2-ol). IR (ν/cm^{-1}): 1120, 1329 (SO_2), 1364, 1559 (NO_2), 3273 (NH). ^{1}H NMR, δ: 1.29 (s, 3H, Me), 3.89 (dd, 1H, C^{5}H′, $^2J_{H'H''}$ 14.7 Hz, $^3J_{H'C^6H}$ 6.7 Hz), 3.96 (dd, 1H, C^{5}H″, $^2J_{H'H''}$ 14.7 Hz, $^3J_{H''C^6H}$ 6.1 Hz), 4.54 (d, 1H, C^{3a}H, $^3J_{HC^3C^{3a}H}$ 4.9 Hz), 5.06 (dd, 1H, C^{3}H, $^3J_{HC^3C^{3a}H}$ 4.9 Hz, $^3J_{HC^3NH}$ 13.7 Hz), 5.53 (d, 1H, NH, $^3J_{HC^3NH}$ 13.7 Hz), 5.75 (dd, 1H, C^{6}H, $^3J_{H'C^6H}$ 6.7 Hz, $^3J_{H''C^6H}$ 6.1 Hz), 6.99–7.03 (m, 1H, Ph), 7.27–7.29 (m, 4H, Ph), 7.38 (d, 2H, C_6H_4, $^3J_{HH}$ 8.5 Hz), 7.56 (d, 2H, C_6H_4, $^3J_{HH}$ 8.5 Hz). ^{13}C NMR, δ: 19.36 (Me), 54.79 (C^5), 61.94 (C^3), 74.79 (C^{3a}), 77.57 (C^{6a}), 89.19 (C^6), 120.92, 121.07, 123.21, 128.60, 128.83, 131.54, 133.88, 147.12 (Ph, Ar). Found (%): C, 47.63; H, 4.15; N, 9.53. Calc. for $C_{18}H_{18}BrN_3O_4S$ (%): C, 47.80; H, 4.01; N, 9.29.

*6a-Methyl-6-nitro-1-phenyl-3-*p*-tolylhexahydrothieno[2,3-*d*]pyrazole 4,4-dioxide* **2d**. Yield: 0.11 g (38%), colourless crystals, mp 150–154 °C (propan-2-ol). IR (ν/cm^{-1}): 1120, 1329 (SO_2), 1364, 1557 (NO_2), 3275 (NH). ^{1}H NMR, δ: 1.29 (s, 3H, Me), 2.33 (s, 3H, *Me*Ar) 3.87 (dd, 1H, C^{5}H′, $^2J_{H'H''}$ 14.7 Hz, $^3J_{H'C^6H}$ 6.7 Hz), 3.94 (dd, 1H, C^{5}H″, $^2J_{H'H''}$ 14.7 Hz, $^3J_{H''C^6H}$ 6.1 Hz), 4.52 (d, 1H, C^{3a}H, $^3J_{HC^3C^{3a}H}$ 4.9 Hz), 5.08 (dd, 1H, C^{3}H,

The structure of new compounds **2a–d** was confirmed by elemental analysis, IR and NMR (^{1}H, ^{13}C, HMQC, HMBC) spectroscopy.‡ IR spectra of these compounds contain vibrational bands of nonconjugated nitro (1556–1565, 1364–1366 cm^{-1}), sulfonyl (1320–1329, 1120–1126 cm^{-1}) and NH (3262–3274 cm^{-1}) groups. ^{1}H NMR spectra of compounds **2a–d** fully correlate with their structures. For example, the spectrum of compound **2a** contains a singlet of methyl protons at 1.30 ppm. Methylene protons C^{5}H and nitromethine proton C^{6}H manifest an ABX spin system as a double doublets at 3.89 and 3.96 ppm ($^2J_{H'H''}$ 14.7 Hz, $^3J_{H'C^6H}$ 6.7 Hz, $^3J_{H''C^6H}$ 6.1 Hz) and a multiplet at 5.75 ppm. Methine protons at C^{3a} and C^3 and a proton at the nitrogen atom form an AMX system at 4.54 (d), 5.09 (dd), 5.53 (d) ppm ($^3J_{HC^3C^{3a}H}$ 4.9 Hz, $^3J_{HC^3NH}$ 14.0 Hz). The low field contains signals of benzene rings (6.99–7.47 ppm).

X-ray diffraction of single crystal **2a**§ reveals its monoclinic $P2_1/c$ space group. Pyrazolidine and sulfolane rings are *cis*-oriented, which supports the stereo efficient orientation of the substituents at bond C(3a)–C(6a) (frozen conformation). Each cycle has an envelope conformation. Atom C(3a) is out of the plane by 0.6 Å in the pyrazolidine cycle. In the sulfolane cycle, atom C(6a) is out of the plane by 0.5 Å. The nitro group is *trans*-oriented towards the pyrazolidine cycle [torsion angle N(1)C(6a)C(6)N(21), 170.4(1)°]. The angles between an average plane of the sulfolane cycle and bonds S=O(19) and S=O(20) are 29.3(1)° and 33.6(1)°, respectively. The bicyclic structure is also dependent on an intramolecular hydrogen bond between atom O(20) of the sulfonyl group and the hydrogen atom at atom N(2) [S–O(20)···H–N(2), 3.041 Å]. Chiral centers in molecule **2a**, C(3), C(3a), C(6a), C(6), have configurations *S*, *R*, *R*, *S*, respectively.

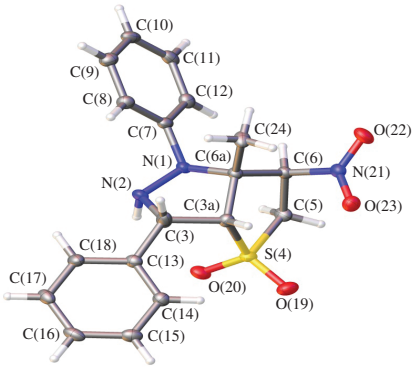


Figure 1 X-ray crystal structure of **2a**.

Thus, we have developed a convenient procedure for preparing new condensed bicyclic structures containing pyrazolidine and sulfolane rings from nitrothiolene 1,1-dioxides and phenylhydrazine. The new compounds have potential in medicinal chemistry.

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References

1 M. G. Brant and J. E. Wulff, *Org. Lett.*, 2012, **14**, 5876.
2 A. A. Eid, A. Koubeissi, R. Bou-Mjahed, N. Al Khalil, M. Farah, R. Maalouf, N. Nasser and K. H. Bouhadir, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 174.
3 A. Kiriazis, G. B. af Gennas, V. Talman, E. Ekokoski, T. Ruotsalainen, I. Kylanlahti, T. Ruffer, G. Wissel, H. Xhaard, H. Lang, R. K. Tuominen and J. Yli-Kauhaluoma, *Tetrahedron*, 2011, **67**, 8665.
4 B. Li, R. A. Buzon and B. Hritzko, *Synlett.*, 2012, **23**, 131.
5 S. S. Y. Wong, M. G. Brant, C. Barr, A. G. Oliver and J. E. Wulff, *Beilstein J. Org. Chem*, 2013, **9**, 1419.
6 G. A. Tolstikov, E. E. Shul'ts, G. F. Vafina and L. V. Spirikhin, *Russ. J. Org. Chem.*, 1992, **28**, 157 (*Zh. Org. Khim.*, 1992, **28**, 192).
7 G. A. Tolstikov, E. E. Shul'ts, G. F. Vafina, L. V. Spirikhin and A. A. Panasenko, *J. Org. Chem. USSR (Engl. Transl.)*, 1989, **25**, 1109 (*Zh. Org. Khim.*, 1989, **25**, 1231).
8 V. M. Berestovitskaya, *Russ. J. Gen. Chem.*, 2000, **70**, 1419 (*Zh. Obshch. Khim.*, 2000, **70**, 1512).
9 V. M. Berestovitskaya, M. V. Selivanova, M. I. Vakulenko, I. E. Efremova and G. A. Berkova, *Russ. J. Org. Chem.*, 2009, **45**, 1814 (*Zh. Org. Khim.*, 2009, **45**, 1818).
10 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 2008, **64**, 112.
11 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339.
12 *CrysAlisPro, Version 1.171.36.32*, Agilent Technologies, 2013.

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$^3J_{HC^3C^{3a}H}$ 4.9 Hz, $^3J_{HC^3NH}$ 14.0 Hz), 5.52 (d, 1H, NH, $^3J_{HC^3NH}$ 14.0 Hz), 5.75 (dd, 1H, C^{6}H, $^3J_{H'C^6H}$ 6.7 Hz, $^3J_{H''C^6H}$ 6.1 Hz), 6.99–7.03 (m, 1H, Ph), 7.26–7.29 (m, 4H, Ph), 7.21 (d, 2H, C_6H_4, $^3J_{HH}$ 8.2 Hz), 7.34 (d, 2H, C_6H_4, $^3J_{HH}$ 8.2 Hz). ^{13}C NMR, δ: 19.35 (Me), 20.58 (*Me*Ar), 54.80 (C^5), 62.19 (C^3), 74.92 (C^{3a}), 77.38 (C^{6a}), 89.25 (C^6), 120.88, 123.07, 124.43, 128.79, 129.12, 131.29, 137.51, 147.29 (Ph, C_6H_4). Found (%): N, 11.16. Calc. for $C_{19}H_{21}N_3O_4S$ (%): N, 10.84.

‡ Physico-chemical studies were performed at the Center for Collective Use of A. I. Herzen State Pedagogical University of Russia. ^{1}H, ^{13}C{^{1}H} NMR, ^{1}H–^{13}C HMQC, and ^{1}H–^{13}C HMBC spectra were recorded with a Jeol JNM ECX400A spectrometer operating at 399.78 (^{1}H) and 100.53 MHz (^{13}C) in CD_3CN solution; the signals of the residual nondeuterated solvents were used as internal standard. IR spectra were recorded with a Shimadzu IR-Prestige-21 Fourier spectrometer in KBr. Elemental analysis was performed with an Eurovector EA 3000 (CHN Dual mode) analyzer.

§ For single crystal X-ray diffraction experiment, crystal of **2a** was fixed on a micro mount placed on an Agilent Technologies SuperNova Atlas diffractometer and measured at 100 K using microfocused monochromated CuKα radiation. The unit cell parameters (monoclinic, space group $P2_1/c$, a = 12.2376(3), b = 11.5358(2) and c = 13.4551(3) Å, β = 117.030(3)°, V = 1691.99(8) Å^3, Z = 4) were refined by least square techniques using 14520 reflections in the 2θ range of 8.11–144.98°. The structure was solved by the direct methods and refined R_1 = 0.040 (wR_2 = 0.101) for 2996 unique reflections with $|F_0| \geqslant 4\sigma_F$ by means of the SHELXL-97 program[10] incorporated in the OLEX2 program package.[11] The carbon and nitrogen-bound H atoms were placed in calculated positions and were included in the refinement in the 'riding' model approximation, with U_{iso}(H) set to 1.5U_{eq}(C) and C–H 0.96 Å for Me groups, U_{iso}(H) set to 1.2U_{eq}(C) and C–H 0.97 Å for CH_2 groups, U_{iso}(H) set to 1.2U_{eq}(C) and C–H 0.93 Å for CH groups, U_{iso}(H) set to 1.2U_{eq}(C) and C–H 0.98 Å for tertiary CH groups and U_{iso}(H) set to 1.2U_{eq}(N) and N–H 0.86 Å for NH groups. Empirical absorption correction was applied in CrysAlisPro[12] program complex using spherical harmonics implemented in SCALE3 ABSPACK scaling algorithm.

CCDC 1011950 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.