DOI 10.1007/s10593-024-03329-9
Chemistry of Heterocyclic Compounds **2024**, *60*(5/6), 251–256

A one-pot synthesis of 3-nitro-2*H*-thiopyrans and their selective reduction to 3-nitro-3,4-dihydro-2*H*-thiopyrans

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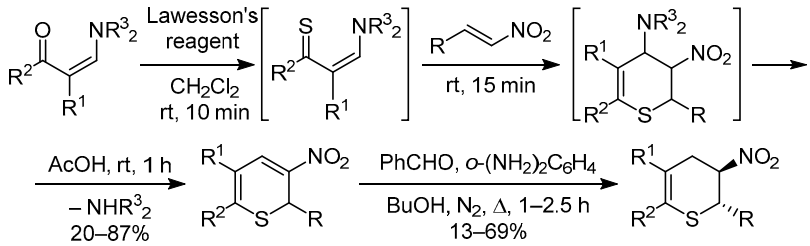
Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2024, *60*(5/6), 251–256

Submitted June 13, 2024
Accepted after revision July 17, 2024



R = Ph, 4-ClC$_6$H$_4$, 4-*t*-BuC$_6$H$_4$, β-styryl; R^1 = H, Me; R^2 = Ph, 4-Py; NR$^3_2$ = NMe$_2$, *N*-pyrrolidinyl

A one-pot method for the synthesis of 3-nitro-2*H*-thiopyrans starting from enamin-3-ones was developed. Reduction of the obtained 3-nitro-2*H*-thiopyrans with the benzaldehyde/*o*-phenylenediamine system in butanol led to 3-nitro-3,4-dihydro-2*H*-thiopyrans.

Keywords: Lawesson's reagent, β-nitrostyrenes, 2-phenylbenzimidazoline, one-pot synthesis, reduction of 2*H*-thiopyrans, synthesis of 2*H*-thiopyrans.

2*H*-Thiopyrans and 3,4-dihydro-2*H*-thiopyrans are of interest as potential biologically active substances. Recent reviews have presented the spectrum of biological activity of thiopyrans.[1] In particular, annulated 3-nitrothiopyrans exhibit antibacterial and antifungal activity[2] and also serve as precursors for the synthesis of 3-aminothiopyrans, which act as agonists of dopamine D1 receptors.[3]

A general method for the synthesis of annulated 3-nitro-2*H*-thiopyrans is the reaction of nitroalkenes with 2-mercaptoarylaldehydes[3a] or their synthetic analog, such as *o*-mercaptoarylimines[4] or *S*-carbamoyl-2-mercapto-arylaldehydes.[3b] This approach also includes the one-pot reaction of nitroalkenes, 2-haloarylaldehydes, and NaHS.[5] The subject of the reduction of 3-nitro-2*H*-thiopyrans to 3-nitro-3,4-dihydro-2*H*-thiopyrans is very poorly represented in the literature and is limited to only two sources. Thus, it is known that annulated 3-nitrothiopyrans are reduced to 3,4-dihydro derivatives by $NaBH_4$ in 15–30% yields.[6] The chemistry of unannulated 3-nitro-2*H*-thiopyrans also remains relatively poorly studied. It is known that 3-nitro-2*H*-thiopyrans can be obtained by the hetero-Diels–Alder reaction of enamine-3-thiones with unsaturated nitro compounds.[7]

In continuation of the study of the synthetic potential of our recently developed one-pot method for the synthesis of 2*H*-thiopyrans by the hetero-Diels–Alder reaction of enamine-3-thiones with electron-deficient dienophiles,[8] we demonstrated in the present study the possibility of using nitroalkenes as dienophiles in a one-pot procedure (Scheme 1). By thionation of enamin-3-ones **1a**,**b** with Lawesson's reagent followed by introduction of the obtained thiones **2a**,**b** into the hetero-Diels–Alder reaction with β-nitro-styrenes **3a**–**c**, we succeeded in obtaining 3-nitro-2*H*-thiopyrans **5a**–**d** in 20–87% yields (Table 1).

All steps of the process were carried out at room temperature. The cycloaddition step was completed within 10 min (TLC control), but attempts to isolate relatively unstable adducts **4a**–**d** were complicated by their slow

Scheme 1

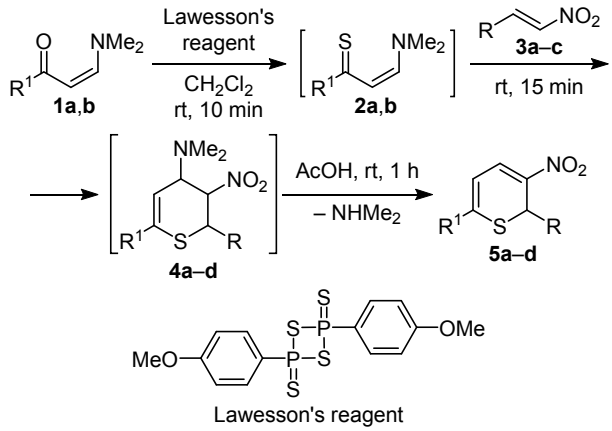


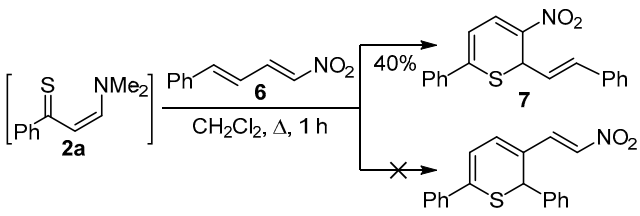
Table 1. The yields of 3-nitro-2*H*-thiopyrans **5a–d**

Product	R	R^1	Yield, %
5a	Ph	Ph	87
5b	4-ClC_6H_4	Ph	71
5c	4-*t*-BuC_6H_4	Ph	77
5d	Ph	4-Py	20

deamination to final thiopyrans **5a–d**. Complete deamination of intermediates **4a–d** occurred after acidification of the reaction mixture with AcOH.

In the case of using cinnamylidene nitromethane (**6**) as the dienophile, cycloaddition with thione **2a** did not occur at room temperature; when the mixture was heated under reflux, the reaction proceeded selectively at position 1 or 2 of the nitrodiene, resulting in product **7** being isolated in 40% yield (Scheme 2). Under these conditions, deamination occurred spontaneously without the use of acid catalysis.

Scheme 2



The structure of compounds **5a–d**, **7** was established based on ^1H and ^{13}C NMR spectra; the signals were assigned on the basis of two-dimensional ^1H–^{13}C HSQC and ^1H–^{13}C HMBC spectra. In the ^1H NMR spectra, doublets were present in the 6.69–6.84 and 7.90–8.05 ppm ranges, which corresponded to the protons at the C-5 and C-4 atoms of the thiopyran ring, respectively (J = 7.3–7.4 Hz). The signal of the proton at the C-2 atom in the ^1H NMR spectra of compounds **5a–d** could be observed in the range of 5.70–5.76 ppm (for compound **7** – at 5.31 ppm). In the ^{13}C NMR spectra, the signals of carbon atoms C-2, C-3, C-4, C-5, and C-6 were in the 38.5–40.0, 136.0–139.1, 130.1–131.1, 113.6–116.2, and 147.0–150.4 ppm ranges,

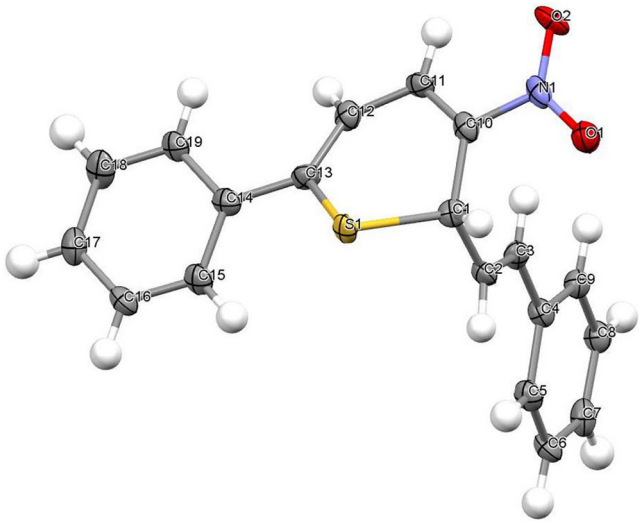
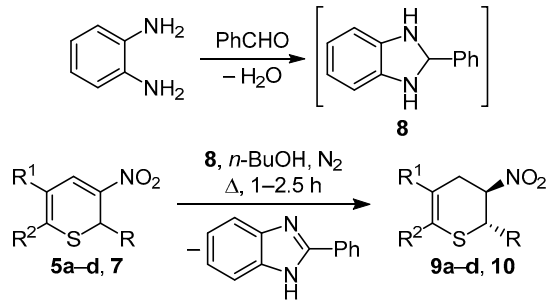


Figure 1. The molecular structure of compound **7** with atoms represented as thermal vibration ellipsoids of 50% probability.

respectively. The spatial structure of product **7** was confirmed by X-ray structural analysis (Fig. 1).

The properties of unannulated 3-nitro-2*H*-thiopyrans have hardly been studied. We found that these compounds can be selectively reduced to 3-nitro-3,4-dihydro-2*H*-thiopyrans **9a–e**, **10** by the benzaldehyde/*o*-phenylenediamine system in 13–69% yields (Scheme 3).

Scheme 3



The direct reducing agent in this case is 2-phenylbenzimidazoline (**8**) formed *in situ* as a result of the reaction of benzaldehyde with *o*-phenylenediamine.[9] The double bond in the α,β-positions to the nitro group was selectively hydrogenated, which is consistent with literature data.[10]

Due to the difficulty of purifying 5-methyl-containing thiopyran **5e**, it was introduced into the reduction reaction without analysis (Scheme 4). The yields of products **9a–e**, **10** are presented in Table 2.

The mechanism of reduction of 3-nitro-2*H*-thiopyrans using 2-phenylbenzimidazoline (**8**) (Scheme 5), proposed on the basis of literature data,[10] involved the transfer of a hydride ion from 2-phenylbenzimidazoline (**8**) to the starting material with the formation of intermediate **11** and subsequent proton transfer from it to intermediate **12**, the carbanion center of which is stabilized by a nitro group, leading to the formation of the final dihydrothiopyran.

Scheme 4

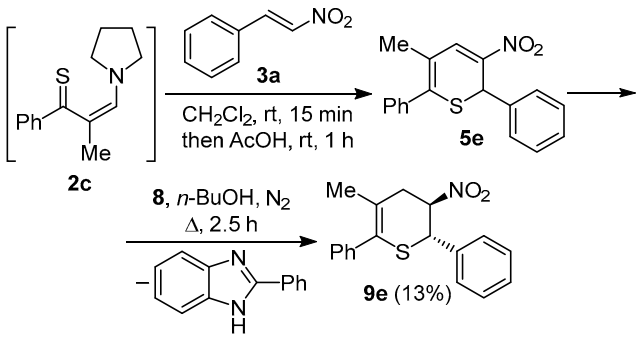


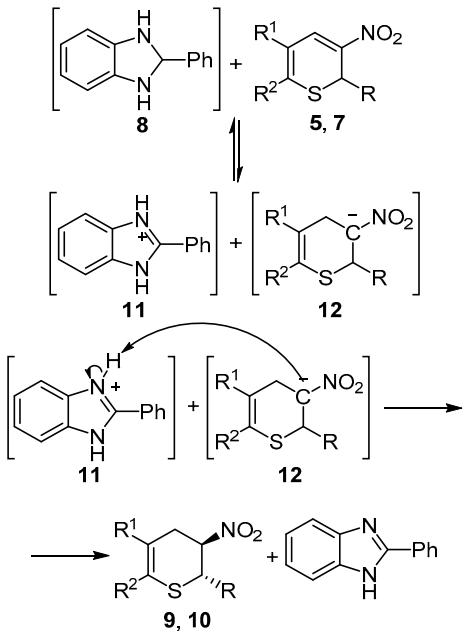
Table 2. The yields of 3-nitro-3,4-dihydro-2*H*-thiopyrans **9a**–**e**, **10**

Product	R	R^1	R^2	Yield, %
9a	Ph	H	Ph	69
9b	4-ClC_6H_4	H	Ph	29
9c	4-*t*-BuC_6H_4	H	Ph	61
9d	Ph	H	4-Py	23
9e	Ph	Me	Ph	13*
10	β-Styryl	H	Ph	45

* Yield based on starting enaminone **1c**.

A necessary condition for the reaction to occur is the presence of a strong electron-withdrawing group.[10] Thus, we demonstrated that imides of 2*H*-thiopyran-2,3-dicarboxylic acid did not undergo hydrogenation under the same conditions, apparently due to the insufficient electron-withdrawing effect of the imide group. It should be noted that this is the first example of the use of 2-phenylbenzimidazoline (**8**) for the reduction of thiopyrans. However, its use is known for the hydrogenation of α,β-unsaturated dinitriles,[11] nitroalkenes,[12] coumarins,[13] and 4-(arylmethylene)-1,2-azol-5-ones.[14]

Scheme 5



The structure of compounds **9a**–**e**, **10** was elucidated based on ^{1}H and ^{13}C NMR spectra as well as two-dimensional ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC spectra. The ^{1}H NMR spectra exhibited a doublet in the region of 4.79–4.82 ppm (in the case of compound **10**, a triplet at 4.46 ppm), which corresponded to the proton at the 2-CH atom of the thiopyran ring (J = 9.9–10.2 Hz). The signal of the 3-CH proton at ~5.2–5.4 ppm appeared as a triplet of doublets (J = 9.9–10.5 and 5.1–5.5 Hz). The pseudoaxial (ax.) and pseudoequatorial (eq.) protons at the 4-CH_2 atom appeared as a doublet of doublets (J = 17.9–18.4, 10.2, and 3.3–3.5 Hz) and a doublet of triplets (J = 17.9–18.4 and 5.5–5.6 Hz), respectively. The vicinal coupling constants of ~10 Hz correspond to the *trans* configuration of the 2-CH and 3-CH protons relative to each other;[7c,d] thus, compounds **9a**–**e**, **10** present (2*R**,3*S**)-isomers. In the ^{13}C NMR spectra of compounds **9a**–**e**, **10**, the signals of carbon atoms C-2, C-3, C-4, C-5, and C-6 were present in the 43.3–48.7, 85.2–87.4, 30.1–37.3, 114.9–122.2, and 137.4–145.0 ppm ranges, respectively.

To conclude, we have developed a one-pot method for the synthesis of 3-nitro-2*H*-thiopyrans and their reduction with the benzaldehyde/*o*-phenylenediamine system, selectively yielding previously undescribed nonannulated 4-unsubstituted 3-nitro-3,4-dihydro-2*H*-thiopyrans. The use of such a reaction sequence substantially extends the scope of our previously developed method for the synthesis of 3,4-dihydro-2*H*-thiopyrans based on a one-pot reaction of α,β-unsaturated ketones, Lawesson's reagent, and dienophiles,[15] and makes it possible to obtain nitro products that are inaccessible by the latter method.[16]

Experimental

IR spectra were registered on a PerkinElmer Spectrum Two FT-IR Fourier transform spectrometer with an ATR accessory. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance 400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$, with the residual solvent signals serving as internal standard. High-resolution mass spectra were recorded on a Bruker maXis instrument, electrospray ionization, capillary voltage 4.5 kV, in the positive ion registration mode, 100–1000 Da mass scanning range. Melting points were determined on an Electrothermal IA 9300 Series instrument. TLC was performed on Sorbfil PTLC-P-V-UV plates. Macherey-Nagel Kieselgel 60 0.063–0.2 mm silica gel was used for preparative column chromatography.

Lawesson's reagent was obtained using a known method.[17]

Synthesis of 2-methyl-1-phenyl-3-(pyrrolidin-1-yl)-prop-2-en-1-one (1c). α-Formylpropiophenone (0.5 g, 3 mmol) was dissolved in PhMe (10 ml). AcOH (0.15 ml, 2.68 mmol) and pyrrolidine (0.25 ml, 3 mmol) were added to the resulting solution. The resulting mixture was heated under reflux in a flask equipped with a Dean–Stark trap until the separation of H_2O ceased (for 1.5 h). The reaction mixture was cooled to room temperature, washed with

saturated aqueous Na_2CO_3 (2×25 ml). The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product was cooled to –10°C. Yield 605 mg (90%), brown crystals, mp 36–38°C. IR spectrum, ν, cm^{-1}: 1628 (C=O), 1578 (Ar), 1557, 1378, 1302. ^{1}H NMR spectrum, δ, ppm: 1.81–1.94 (4H, m, $C\underline{H}_2CH_2NCH_2C\underline{H}_2$); 2.13 (3H, s, CH_3); 3.47–3.55 (4H, m, $CH_2C\underline{H}_2NC\underline{H}_2CH_2$); 7.07 (1H, s, NCH=); 7.29–7.38 (3H, m, H Ar); 7.38–7.45 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 10.6 (CH_3); 25.0 ($\underline{C}H_2CH_2NCH_2\underline{C}H_2$); 51.2 ($CH_2\underline{C}H_2N\underline{C}H_2CH_2$); 106.2 ($\underline{C}CH_3$); 127.4 (C-3,5); 127.8 (C-2,6); 128.4 (C-6); 141.8 (C-1); 152.7 (NCH=); 196.3 (C=O). Found, *m*/*z*: 238.1204 $[M+Na]^+$. $C_{14}H_{17}NNaO$. Calculated, *m*/*z*: 238.1202.

Synthesis of 3-nitro-2*H*-thiopyrans 5a–d (General method). Lawesson's reagent (0.135 g, 0.336 mmol) was added with stirring to a solution of enaminone **1a**–**c** (0.67 mmol) in CH_2Cl_2 (3.2 ml). The resulting mixture was stirred at room temperature for 10 min, then β-nitrostyrene **3a**–**c** (0.67 mmol) was added, and stirring at room temperature was continued for 15 min. Then, AcOH (2 ml) was added, and the resulting mixture was stirred at room temperature for 1 h (monitoring by TLC). The solvent was then removed, the residue was dissolved in CH_2Cl_2, and the product was isolated by column chromatography on silica gel, eluent CH_2Cl_2. The oily product was triturated with hot petroleum ether until crystallization (in the case of thiopyran **5d**, the product was dissolved in a minimal amount of *n*-BuOH, the solution was cooled to –10°C, and the resulting precipitate was filtered off).

3-Nitro-2,6-diphenyl-2*H*-thiopyran (5a). Yield 172 mg (87%), red powder, mp 93–95°C (mp 85°C[7a]). IR spectrum, ν, cm^{-1}: 1623 (C=C), 1520 (ν asymm. NO_2), 1490, 1303 (ν symm. NO_2), 766, 698 (δ CH Ar monosubstitution). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.76 (1H, s, 2-CH); 6.71 (1H, d, *J* = 7.4, 5-CH); 7.36–7.50 (8H, m, H Ph); 7.56–7.64 (2H, m, H Ph); 8.05 (1H, d, *J* = 7.4, 4-CH). ^{13}C NMR spectrum, δ, ppm: 40.0 (2-CH); 114.2 (5-CH); 126.6 (2CH); 128.2 (2CH); 128.6 (CH); 128.9 (4CH); 130.9 (CH); 131.1 (4-CH); 136.0 (C-3); 137.3 (C); 139.7 (C); 147.4 (C-6). Found, *m*/*z*: 318.0562 $[M+Na]^+$. $C_{17}H_{13}NNaO_2S$. Calculated, *m*/*z*: 318.0559.

2-(4-Chlorophenyl)-3-nitro-6-phenyl-2*H*-thiopyran (5b). Yield 157 mg (71%), red powder, mp 110–112°C. IR spectrum, ν, cm^{-1}: 1624 (C=C), 1545 (ν asymm. NO_2), 1489, 1307 (ν symm. NO_2), 1088 (C–Cl), 824 (δ CH Ar 1,4-disubstitution), 766, 700 (δ CH Ar monosubstitution). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.70 (1H, s, 2-CH); 6.70 (1H, d, *J* = 7.3, 5-CH); 7.25–7.37 (4H, m, H Ar); 7.37–7.51 (3H, m, H Ar); 7.54–7.61 (2H, m, H Ar); 8.03 (1H, d, *J* = 7.3, 4-CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 39.0 (2-CH); 113.7 (5-CH); 127.5 (2CH); 127.8 (2CH); 128.5 (2CH); 128.7 (2CH); 130.6 (CH); 130.9 (4-CH); 134.1 (C); 135.4 (C); 136.5 (C-3); 137.8 (C); 146.9 (C-6). Found, *m*/*z*: 352.0177 $[M+Na]^+$. $C_{17}H_{12}ClNNaO_2S$. Calculated, *m*/*z*: 352.0169.

2-(4-*tert*-Butylphenyl)-3-nitro-6-phenyl-2*H*-thiopyran (5c). Yield 181 mg (77%), red powder, mp 120–121°C. IR spectrum, ν, cm^{-1}: 2967 (ν CH_3), 1629 (C=C), 1524 (ν asymm. NO_2), 1505, 1487, 1309 (ν symm. NO_2), 732, 688 (monosubstitution Ar). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.29 (9H, s, $C(CH_3)_3$); 5.72 (1H, s, 2-CH); 6.69 (1H, d, *J* = 7.4, 5-CH); 7.25–7.36 (4H, m, H Ar); 7.36–7.51 (3H, m, H Ar); 7.55–7.65 (2H, m, H Ar); 8.01 (1H, d, *J* = 7.4, 4-CH). ^{13}C NMR spectrum, δ, ppm: 30.8 ($C(\underline{C}H_3)_3$); 34.2 ($\underline{C}(CH_3)_3$); 39.2 (2-CH); 113.6 (5-CH); 125.4 (2CH); 125.9 (2CH); 127.8 (2CH); 128.5 (2CH); 130.4 (CH); 130.5 (4-CH); 135.7 (C); 136.3 (C-3); 137.0 (C); 147.1 (C-6); 151.2 (*C*-*t*-Bu). Found, *m*/*z*: 374.1189 $[M+Na]^+$. $C_{21}H_{21}NNaO_2S$. Calculated, *m*/*z*: 374.1185.

3-Nitro-2-phenyl-6-(pyridin-4-yl)-2*H*-thiopyran (5d). Yield 39.7 mg (20%), red powder, mp 116–118°C. IR spectrum, ν, cm^{-1}: 1627 (C=C), 1489 (ν asymm. NO_2), 1407, 1311 (ν symm. NO_2), 1294, 801, 712 (δ CH Ar monosubstitution). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.76 (1H, s, 2-CH); 6.84 (1H, d, *J* = 7.2, 5-CH); 7.30–7.40 (5H, m, H Ar); 7.45 (2H, d, *J* = 5.2, H-3,5 Py); 8.03 (1H, d, *J* = 7.2, 4-CH); 8.67 (2H, d, *J* = 5.2, H-2,6 Py). ^{13}C NMR spectrum, δ, ppm: 39.5 (2-CH); 116.2 (5-CH); 121.6 (2CH); 126.5 (2CH); 128.9 (CH); 129.1 (2CH); 130.1 (4-CH); 138.8 (C); 139.1 (C); 143.1 (C); 143.6 (C-6); 150.4 (2CH). Found, *m*/*z*: 297.0695 $[M+H]^+$. $C_{16}H_{13}N_2O_2S$. Calculated, *m*/*z*: 297.0698.

Synthesis of 3-nitro-6-phenyl-2-(β-styryl)-2*H*-thiopyran (7). Lawesson's reagent (0.577 g, 1.4 mmol) was added with stirring to a solution of *N*,*N*-dimethylamino-1-phenylprop-2-en-1-one (**1a**) (0.5 g, 2.8 mmol) in CH_2Cl_2 (14 ml). The resulting mixture was stirred for 10 min, then cinnamylidenenitromethane (**6**) (0.6 g, 2.8 mmol) was added, and the resulting mixture was heated under reflux for 1 h. After cooling the mixture to room temperature, the solvent was evaporated. The residue was dissolved in CH_2Cl_2, and the product was isolated by column chromatography on silica gel, eluent CH_2Cl_2. After evaporation of the eluent, the residue was treated with Et_2O. Yield 367 mg (40%), red powder, mp 152–153°C. IR spectrum, ν, cm^{-1}: 1625 (C=C), 1490 (ν asymm. NO_2), 1443, 1296 (ν symm. NO_2), 960 (δ CH HC=CH *trans*), 745 (δ CH Ar monosubstitution). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.31 (1H, d, *J* = 7.6, 2-CH); 6.22 (1H, dd, *J* = 15.7, *J* = 7.6, C<u>H</u>=CHPh); 6.57 (1H, d, *J* = 15.7, CH=C<u>H</u>Ph); 6.73 (1H, d, *J* = 7.3, 5-CH); 7.22–7.39 (6H, m, H Ph); 7.41–7.53 (3H, m, H Ph); 7.65–7.72 (2H, m, H Ph); 7.90 (1H, d, *J* = 7.3, 4-CH). ^{13}C NMR spectrum, δ, ppm: 38.5 (2-CH); 114.4 (5-CH); 123.3 (PhCH=<u>C</u>H); 126.8 (C-2,6 PhCH=CH); 128.3 (3C); 128.6 (C-3,5 PhCH=CH); 128.9 (3,5-CH 6-Ph); 130.5 (4-CH); 130.9 (6-CH 6-Ph); 132.3 (Ph<u>C</u>H=CH); 135.8 (<u>C</u>CH=CH); 136.2 (<u>C</u>–C-6); 136.3 (C-3); 147.0 (C-6). Found, *m*/*z*: 344.0719 $[M+Na]^+$. $C_{19}H_{15}NNaO_2S$. Calculated, *m*/*z*: 344.0716.

Synthesis of 3-nitro-3,4-dihydro-2*H*-thiopyrans 9a–d, **10** (General method). *o*-Phenylenediamine (0.1 g, 0.907 mmol) was added under a nitrogen atmosphere to a mixture of thiopyran **5a**–**d** (0.34 mmol), *n*-BuOH (2 ml), and benzaldehyde (0.1 ml, 0.91 mmol). The mixture was heated under reflux under a nitrogen atmosphere for 2.5 h (in the case of product **9d** – 1 h; monitoring by TLC), then cooled to room temperature, and the resulting precipitate was filtered off.

(2*R,3*S**)-3-Nitro-2,6-diphenyl-3,4-dihydro-2*H*-thiopyran (9a)**. Yield 61.4 mg (69%), white powder, mp 128–130°C. IR spectrum, ν, cm^{-1}: 1630 (C=C), 1545 (ν asymm. NO_2), 1436 (δ CH_2),1370 (ν symm. NO_2), 1337, 754, 742, 696 (δ CH Ar monosubstitution). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.06 (1H, dt, *J* = 18.0, *J* = 5.6, 4-CH eq.); 3.15 (1H, ddd, *J* = 18.0, *J* = 10.2, *J* = 3.3, 4-CH ax.); 4.80 (1H, d, *J* = 10.2, 2-CH); 5.30 (1H, td, *J* = 10.2, *J* = 5.4, 3-CH); 6.06 (1H, dd, *J* = 5.7, *J* = 3.3, 5-CH); 7.30–7.54 (10H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 31.7 (4-CH_2); 47.6 (2-CH); 86.2 (3-CH); 115.0 (5-CH); 126.0 (2CH); 127.9 (2CH); 128.2 (2CH); 128.4 (CH); 128.7 (3CH); 134.5 (C); 134.9 (C); 137.4 (C-6). Found, *m*/*z*: 320.0719 $[M+Na]^+$. $C_{17}H_{15}NNaO_2S$. Calculated, *m*/*z*: 320.0716.

(2*R,3*S**)-2-(4-Chlorophenyl)-3-nitro-6-phenyl-3,4-dihydro-2*H*-thiopyran (9b)**. Yield 32.6 mg (29%), white powder, mp 127–128.5°C. IR spectrum, ν, cm^{-1}: 1620 (C=C), 1552, 1541 (ν asymm. NO_2), 1492, 1444 (δ CH_2), 1372 (ν symm. NO_2), 1092 (CCl), 854 (δ CH Ar 1,4-disubstitution), 754, 697 (δ CH Ar monosubstitution). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.03–3.22 (2H, m, CH_2); 4.79 (1H, d, *J* = 10.2, 2-CH); 5.25 (1H, td, *J* = 10.2, *J* = 5.6, 3-CH); 6.08 (1H, dd, *J* = 5.6, *J* = 3.3, 5-CH); 7.33–7.43 (7H, m, H Ar); 7.44–7.52 (2H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 32.0 (4-CH_2); 47.3 (2-CH); 86.5 (3-CH); 115.5 (5-CH); 126.5 (2CH); 128.7 (2CH); 128.9 (4-CH Ar); 129.4 (2CH); 129.7 (2CH); 133.5 (C); 135.1 (2C); 137.7 (C-6). Found, *m*/*z*: 332.0504 $[M+H]^+$. $C_{17}H_{15}ClNO_2S$. Calculated, *m*/*z*: 332.0507.

(2*R,3*S**)-2-(4-*tert*-Butylphenyl)-3-nitro-6-phenyl-3,4-dihydro-2*H*-thiopyran (9c)**. Yield 74.6 mg (61%), white powder, mp 159–161°C. IR spectrum, ν, cm^{-1}: 2964 (ν CH_3), 1632 (C=C), 1549 (ν asymm. NO_2), 1370 (ν symm. NO_2), 1338, 752, 703 (δ CH Ar monosubstitution). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.31 (9H, s, $C(CH_3)_3$); 3.06 (1H, dt, *J* = 17.9, *J* = 5.5, 4-CH eq.); 3.14 (1H, ddd, *J* = 17.9, *J* = 10.2, *J* = 3.3, 4-CH ax.); 4.79 (1H, d, *J* = 10.2, 2-CH); 5.30 (1H, td, *J* = 10.2, *J* = 5.5, 3-CH); 6.06 (1H, dd, *J* = 5.5, *J* = 3.3, 5-CH); 7.29–7.42 (7H, m, H Ar); 7.43–7.52 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 30.8 ($C(\underline{C}H_3)_3$); 31.8 (4-CH_2); 34.2 ($\underline{C}(CH_3)_3$); 47.2 (2-CH); 86.2 (3-CH); 115.0 (5-CH); 125.7 (2CH); 126.0 (2CH); 127.6 (2CH); 128.2 (2CH); 128.3 (4-CH Ar); 131.3 (C); 135.0 (C); 137.5 (C-6); 151.7 (<u>C</u>-*t*-Bu). Found, *m*/*z*: 376.1345 $[M+Na]^+$. $C_{21}H_{23}NNaO_2S$. Calculated, *m*/*z*: 376.1342.

(2*R,3*S**)-3-Nitro-2-phenyl-6-(pyridin-4-yl)-3,4-dihydro-2*H*-thiopyran (9d)**. Yield 23.2 mg (23%), white powder, mp 146–147°C. IR spectrum, ν, cm^{-1}: 1624 (C=C), 1594, 1547 (ν asymm. NO_2), 1408, 1371 (ν symm. NO_2), 744, 696 (δ CH Ar monosubstitution). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.11 (1H, dt, *J* = 18.4, *J* = 5.5, 4-CH eq.); 3.20 (1H, ddd, *J* = 18.4, *J* = 10.0, *J* = 3.5, 4-CH ax.); 4.81 (1H, d, *J* = 10.0, 2-CH); 5.30 (1H, td, *J* = 10.0, *J* = 5.5, 3-CH); 6.30 (1H, dd, *J* = 5.5, *J* = 3.5, 5-CH); 7.38–7.45 (7H, m, H Ar); 8.62 (2H, d, *J* = 5.3, H-2,6 Py). ^{13}C NMR spectrum, δ, ppm: 31.8 (4-CH_2); 47.7 (2-CH); 85.9 (3-CH); 118.4 (5-CH); 120.6 (2CH); 128.3 (2CH); 129.2 (2CH); 129.3 (4-CH Ar); 133.2 (C); 134.5 (C); 145.0 (C-6); 150.2 (2,6-CH Py). Found, *m*/*z*: 299.0848 $[M+H]^+$. $C_{16}H_{15}N_2O_2S$. Calculated, *m*/*z*: 299.0849.

(2*R,3*S**)-3-Nitro-6-phenyl-2-(β-styryl)-3,4-dihydro-2*H*-thiopyran (10)**. Yield 49.5 mg (45%), white powder, mp 138–139°C. IR spectrum, ν, cm^{-1}: 1621 (C=C), 1552 (ν asymm. NO_2), 1491, 1443 (δ CH_2), 1370 (ν symm. NO_2), 966 (CH=CH *trans*), 746 (δ CH Ar monosubstitution), 688. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.98 (1H, dt, *J* = 18.1, *J* = 5.5, 4-CH eq.); 3.11 (1H, ddd, *J* = 18.1, *J* = 9.9, 3.3, 4-CH ax.); 4.46 (1H, t, *J* = 9.4, 2-CH); 4.98 (1H, td, *J* = 9.9, *J* = 5.5, 3-CH); 6.02 (1H, dd, *J* = 5.5, *J* = 3.3, 5-CH); 6.12 (1H, dd, *J* = 15.6, *J* = 9.4, C<u>H</u>=CHPh); 6.77 (1H, d, *J* = 15.6, CH=C<u>H</u>Ph); 7.24–7.42 (8H, m, H Ph); 7.44–7.51 (2H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 30.1 (4-CH_2); 45.9 (2-CH); 85.2 (3-CH); 114.9 (5-CH); 121.4 (PhCH=<u>C</u>H); 126.1 (2CH); 126.5 (2CH); 128.2 (3CH); 128.3 (3CH); 133.7 (C); 135.1 (<u>C</u>CH=CH); 136.2 (Ph<u>C</u>H=CH); 137.6 (C-6). Found, *m*/*z*: 346.0882 $[M+Na]^+$. $C_{19}H_{17}NNaO_2S$. Calculated, *m*/*z*: 346.0872.

Synthesis of (2*R,3*S**)-5-methyl-3-nitro-2,6-diphenyl-3,4-dihydro-2*H*-thiopyran (9e)**. Lawesson's reagent (135 mg, 0.336 mmol) was added with stirring to a solution of enaminone **1c** (0.145 g, 0.67 mmol) in CH_2Cl_2 (3.2 ml). The resulting mixture was stirred at room temperature for 10 min, then β-nitrostyrene (**3a**) (0.125 g, 0.67 mmol) was added, and stirring at room temperature was continued for 15 min. Then, AcOH (2 ml) was added, and the resulting mixture was stirred at room temperature for 1 h (monitoring by TLC). The solvent was then removed, the residue was dissolved in CH_2Cl_2, and the product was isolated by column chromatography on silica gel, eluent CH_2Cl_2. The oily product was triturated with hot petroleum ether until crystallization (in the case of thiopyran **5d**, the product was dissolved in a minimal amount of *n*-BuOH, the solution was cooled to –10°C, and the resulting precipitate was filtered off). The solvent was evaporated, *n*-BuOH (2 ml), benzaldehyde (0.1 ml, 0.91 mmol), and *o*-phenylenediamine (0.1 g, 0.907 mmol) were added to the residue under a nitrogen atmosphere. The resulting mixture was heated under reflux under nitrogen atmosphere for 2.5 h, cooled to room temperature, and the resulting precipitate was filtered off. Yield 20.9 mg (13%), white powder, mp 139.5–141.5°C. IR spectrum, ν, cm^{-1}: 2909 (ν CH_3), 1636 (C=C), 1550, 1535 (ν asymm. NO_2), 1489, 1441 (δ CH_2), 1374 (ν symm. NO_2), 1344, 731, 697 (δ CH Ar monosubstitution). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.78 (3H, s, CH_3); 2.93 (1H, dd, *J* = 17.4, *J* = 5.1, 4-CH eq.); 3.09 (1H, dd, *J* = 17.4, *J* = 10.5, 4-CH ax.); 4.82 (1H, d, *J* = 10.5, 2-CH); 5.38 (1H, td, *J* = 10.5, *J* = 5.1, 3-CH); 7.32–7.45 (10H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.3 (CH_3); 37.3 (4-CH_2); 48.7 (2-CH); 87.4 (3-CH); 122.2 (C-5); 127.8 (C); 128.1 (CH); 128.3 (2CH); 128.4 (2CH); 129.0 (3CH); 129.4 (2CH); 134.9 (C); 137.5 (C-6). Found, *m*/*z*: 312.1052 $[M+H]^+$. $C_{18}H_{18}NO_2S$. Calculated, *m*/*z*: 312.1053.

X-ray structural analysis of compound 7. Single crystals of compound **7** were grown by slow evaporation from a Me_2CO solution. X-ray structural analysis of single crystals was performed on a SuperNova diffractometer, Single source at offset/far, HyPix3000. Using the Olex2

software package,[18] the structure was solved by the direct method in the SHELXS program[19] and refined by the least squares method as implemented in the SHELXL program.[20] The main crystallographic data for compound **7** are presented in the Supplementary information file. The full set of X-ray structural parameters was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2310879).

Supplementary information file containing ^{1}H and ^{13}C NMR and high-resolution mass spectra of compounds **1c**, **5a–d**, **7**, **9a–e**, **10**, as well as ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC spectra of compounds **7**, **10** and X-ray structural analysis data for **7** is available at the journal website http://link.springer.com/journal/10593.

Analysis of synthesized compounds was carried out using the Saint Petersburg State University resource centers "Magnetic Resonance Research Centre", "Centre for X-ray Diffraction Studies", and "Chemical Analysis and Materials Research Centre".

References

1. (a) Laxmikeshav, K.; Kumari, P.; Shankaraiah, N. *Med. Res. Rev.* **2022**, *42*, 513. (b) Pathania, S.; Narang, R. K.; Rawal, R. K. *Eur. J. Med. Chem*. **2019**, *180*, 486.
2. Kassab, N.; Abdallah, S.; Ead, H. A. R.; Zaki, D. *Z. Naturforsch.*, *B*: *J. Chem. Sci.* **1976**, *31*, 376.
3. (a) Clark, A. H.; McCorvy, J. D.; Watts, V. J.; Nichols, D. E. *Bioorg. Med. Chem*. **2011**, *19*, 5420. (b) Cueva, J. P.; Chemel, B. R.; Juncosa, J. I., Jr.; Lill, M. A.; Watts, V. J.; Nichols, D. E. *Eur. J. Med. Chem*. **2012**, *48*, 97.
4. Weißenfels, M.; Pulst, M.; Greif, D. *J. Prakt. Chem./Chem.-Ztg.* **1992**, *334*, 147.
5. (a) Singh, S.; Samanta, S. *Chin. J. Chem*. **2015**, *33*, 1244. (b) Le, T. T. H.; Youhei, C.; Le, Q. H.; Nguyen, T. B.; Mac, D. H. *Org. Biomol. Chem*. **2019**, *17*, 6355.
6. (a) Luo, N.; Fang, X.; Su, M.; Zhang, X.; Li, D.; Li, H.; Li, S.; Zhao, Z. *Chin. J. Chem*. **2021**, *39*, 115. (b) Li, J.; Zhao, W.; Zhao, Z.; Li, D.; Fang, X. CN Patent 110372663A.
7. (a) Baruah, P. D.; Mukherjee, S.; Mahajan, M. P. *Tetrahedron* **1990**, *46*, 1951. (b) Dietrich, U.; Feindt, A.; Pulst, M.; Weißenfels, M.; Greif, D.; Cao, W. *J. Prakt. Chem./Chem.-Ztg.* **1994**, *336*, 434. (c) Bogdanowicz-Szwed, K.; Budzowski, A. *Monatsh. Chem*. **2001**, *132*, 947. (d) Bogdanowicz-Szwed, K.; Budzowski, A. *Z. Naturforsch.*, *B*: *J. Chem. Sci.* **2002**, 57, 637.
8. Karpov, I. D.; Ovchinnikov, K. L.; Kolobov, A. V. *Russ. Chem. Bull*. **2023**, *72*, 1279.
9. Chikashita, H.; Nishida, S.; Miyazaki, M.; Morita, Y.; Itoh, K. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 737.
10. Chikashita, H.; Miyazaki, M.; Itoh, K. *J. Chem. Soc.*, *Perkin Trans. 1* **1987**, 699.
11. Bobal, P.; Bobalova, J. *Molecules* **2013**, *18*, 2212.
12. Chikashita, H.; Morita, Y.; Itoh, K. *Synth. Commun*. **1985**, *15*, 527.
13. Risitano, F.; Grassi, G.; Foti, F.; Bilardo, C. *Heterocycles* **2001**, *55*, 1311.
14. Risitano, F.; Grassi, G.; Caruso, F.; Foti, F. *Tetrahedron* **1996**, *52*, 1443.
15. (a) Merkulova, E. A.; Kolobov, A. V.; Ovchinnikov, K. L. RF patent 2670977. *Byull. Izobret.* **2018**, (30). (b) Merkulova, E. A.; Kolobov, A. V.; Ovchinnikov, K. L. *Russ.Chem. Bull.* **2019**, *68*, 606. (c) Merkulova, E. A.; Kolobov, A. V.; Ovchinnikov, K. L.; Khrustalev, V. N.; Nenajdenko, V. G. *Chem. Heterocycl. Compd*. **2021**, *57*, 245. (d) Merkulova, E. A.; Kolobov, A. V.; Ovchinnikov, K. L.; Belyaeva O. A.: Plakhtinskii, V. V.; Nenajdenko, V. G. *Chem. Heterocycl. Compd*. **2021**, *57*, 837.
16. Merkulova, E. A. *Extended Abstract of PhD (Chemistry.) Thesis*; Moscow, 2023. https://www.rudn.ru/storage/media/science_dissertation/052186ac-d744-4f18-ae28-e9eb3aa077bd/merkulova_avtoreferat_ final3.pdf
17. Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.
18. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Crystallogr*. **2009**, *42*, 339.
19. Sheldrick, G. M. *Acta Crystallogr.*, *Sect. A*: *Found. Adv.* **2008**, *A64*, 112.
20. Sheldrick, G. M. *Acta Crystallogr.*, *Sect. C*: *Struct. Chem.* **2015**, *C71*, 3.