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Multigram scale synthesis of 3,4- and 3,6-dihydro-2*H*-thiopyran 1,1-dioxides and features of their NMR spectral behavior

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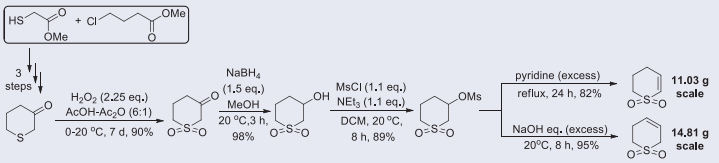
ABSTRACT

A new four-step synthesis of 3,4- and 3,6-dihydro-2*H*-thiopran-1,1-dioxides from dihydro-2*H*-thiopyran-3(4*H*)-one is reported. The title compounds are synthesized starting with oxidation of the ketone with a 30% aqueous solution of hydrogen peroxide in a mixture of AcOH-Ac_2O. The keto group is then reduced by sodium borohydride followed by mesylation and elimination of methanesulfonic acid under basic conditions (pyridine for 3,4-isomer and aqueous NaOH for 3,6-isomer). This sequence is simpler, than previously known methods, uses cheaper and more readily available reagents, and leads to 2*H*-thiopran-1,1-dioxides on multigram scale with 64% and 74% total yields, respectively. The structure and purity of the compounds were confirmed by 2D NMR and GCMS methods. The proposed method expands the means to access functionalized cyclic sulfones as building blocks in the synthesis of combinatorial libraries of new biologically active compounds.

GRAPHICAL ABSTRACT



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2D NMR; cyclic sulfones; oxidation; reduction; thiopyrans

Introduction

The cyclic sulfone motif is present in a large number of bioactive molecules and found broad application in organic synthesis.[1–4] The aim of this paper is the development of more practical method for the synthesis of 3,4- and 3,6-dihydro-2H-thiopyran-1,1-dioxides **1** and **2**, which can be used as building blocks for the synthesis of plant growth regulators, herbicides, pesticides, pharmaceutical products, and drug-like compounds.

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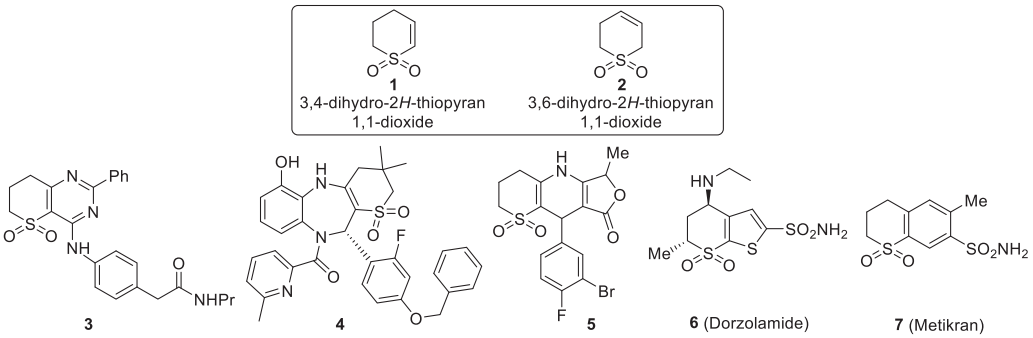
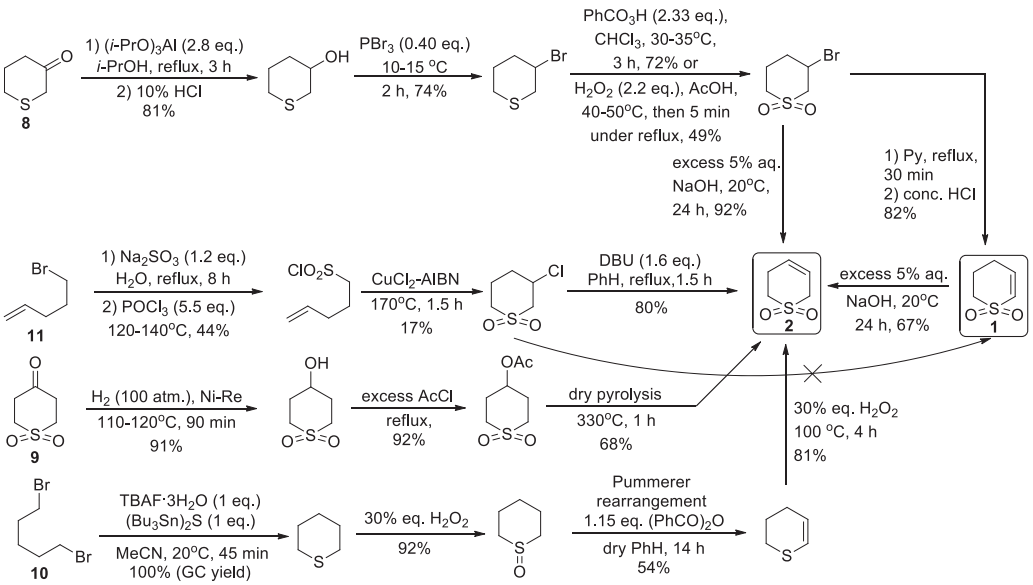
Depending on the substitution pattern of the core thiopyran ring, this class of compounds has demonstrated a diverse range of biological activities ranging from anti-inflammatory and antiviral to ATP-sensitive potassium channel (KATP) openers (e.g. compounds **3–5**).[5–7] Antiglaucoma agent Dorzolamide **6** and diuretic Metikran **7** even became marked drugs (Scheme 1).[8]

Dihydrothiopyran dioxides **1** and **2** were previously obtained from dihydro-2*H*-thiopyran-3(4*H*)-one **8** in four steps with total yields of 35 and 40%, respectively (Scheme 2).[9] Besides, it was shown that sulfone **1** can be isomerized into **2** under basic conditions. Following this method,[9] ketone **8** is reduced by large excess of aluminum isopropoxide, and the resulting alcohol is then brominated by phosphorus tribromide (described yield is 74%, but in our hands it did not exceed 50% at three fold repeat). Thiopyran ring is further oxidized to thiopyran dioxide by peroxybenzoic acid (usage of



Scheme 1. Structures of 3,4- and 3,6-dihydro-2*H*-thiopyran 1,1-dioxides **1**, **2** and selected thiopyran-based biologically important compounds **3-7**.



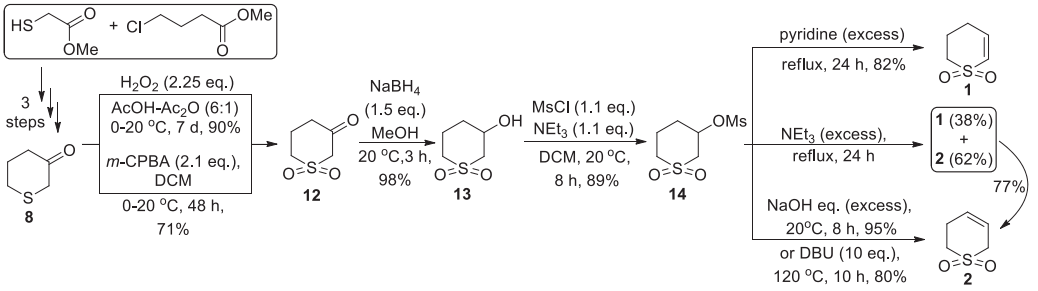
Scheme 2. Known methods for the synthesis of 3,4- and 3,6-dihydro-2*H*-thiopyran 1,1-dioxides **1**, **2**.

the cheaper hydrogen peroxide gives 49% yield only) followed by elimination of hydrogen bromide under basic conditions. The main disadvantage of this protocol is low total yield of target sulfones **1**, **2**, reproducibility of some synthetic steps, and usage of caustic, expensive, and highly toxic reagents (PBr_3, $PhCO_3H$). Authors[10,11] proposed alternative methods for the synthesis of **2** from ketosulfone **9** (total yield after three steps is 57%) and 1,5-dibromopentane **10** (total yield after four steps is 40%). The least practical route is the synthesis of compound **2** from 5-brompent-1-ene **11** (total yield is 6% only).[12]

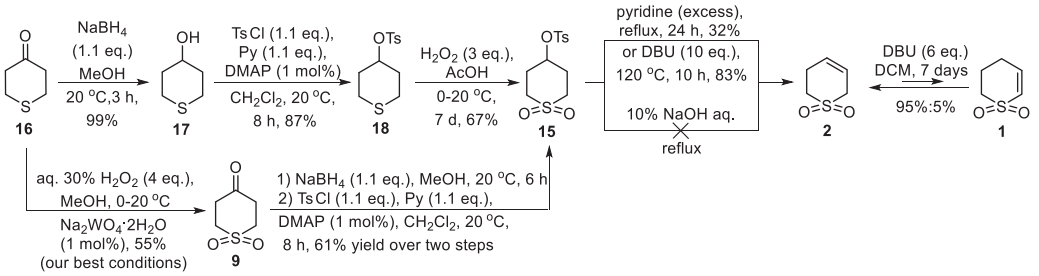
Results and discussion

When developing a more convenient method for the synthesis of 3,4- and 3,6-dihydro-2H-thiopyran-1,1-dioxides **1** and **2**, as the first step we performed oxidation of ketone **8** to ketosulfone **12** using the mixture of aq. H_2O_2-AcOH-Ac_2O (method A, see experimental part). *m*-Chloroperoxybenzoic acid is a slightly worse variant giving the yield of 71% (method B, see experimental part). The second step is reduction of keto-group by sodium borohydride in methanol. Interaction of the obtained alcohol **13** with mesyl chloride almost quantitatively gives the corresponding mesylate **14** (the average yield at each step is at least 90%). Elimination of methanesulfonic acid from mesylate **14** under basic conditions leads to target sulfones **1**, **2** with good yields on decagram scale (Scheme 3). It is found that the nature of base plays the key role in regioselectivity of this elimination. The use of NaOH aqueous solution gives Δ^3-isomer **2** exclusively, and on the other hand, reflux in pyridine leads to Δ^2-isomer **1**. The reaction with triethylamine provides the mixture of isomers **1**, **2** which can be easily turned into pure Δ^3-isomer **2** by the treatment with 5% aqueous solution of NaOH at room temperature (r.t.) (yield 77%). So, the reported method leads to the target compounds **1**, **2** in decagram scale with total yields of 64% and 74%, respectively.

As another possible variant for the synthesis of sulfone **2**, we performed detosylation of the compound **15** in different conditions. It seems to be more convenient method, but refluxing in 10% NaOH aqueous solution leads to the starting material only, and heating with pyridine gives **2** in dramatically low yield of 32% on 9.10 g scale. In this case, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gives much better results on NMR scale (Scheme 4). It was also found that treatment of the resulted sulfone **2** (analytically pure sample, 1 mmol) with excess of DBU in DCM solution at r.t. for 7 days afforded mixture of isomers **1** and **2** in ratio 5:95% accordingly (GCMS data). This means that



Scheme 3. New scalable method for the synthesis of 3,4- and 3,6-dihydro-2*H*-thiopyran-1,1-dioxides **1**, **2**.



Scheme 4. An alternative method for the synthesis of sulfone **2**.

sulfone **2** is much more thermodynamically favored product than **1**. Thus, above-described methods for the synthesis of **1** and **2** from mesylate **14** are significantly more effective.

The tosylate **15** was synthesized from commercially available ketone **16** via compounds **17** and **18** or via ketosulfone **9**. We failed to obtain ketone **9** by oxidation with a 30% aqueous solution of hydrogen peroxide (2.1 eq.) in an AcOH or mixture of AcOH-Ac_2O at 0–20 °C (according to ^{1}H NMR, no desired ketosulfone **9** in crude product was observed). Ultimately we synthesized product **9** in methanolic solution using larger excess of hydrogen peroxide and Na_2WO_4 as the catalyst. Transformation **9** to **15** was achieved as a one-pot two-step procedure without purification of the intermediate alcohol. So, we obtained tosylate **15** from two different routes from ketone **16** in 58 and 34% overall yields as depicted on the Scheme 4.

It is worth noting that NMR spectra for compound **1** published in works[12,13] are completely different. Sulfone **2** does not have published NMR spectra at all. Therefore, for the detailed investigation of spectral behavior of sulfones **1**, **2**, we measured their ^{1}H, ^{13}C, COSY, and HSQC spectra (Figures S1–S4, see Supplemental data). Apart from discrepancies in NMR data, mass spectrum for Δ^2-isomer **1** given in works[12] is the same in detail as our mass spectrum for Δ^3-isomer **2** (Figures S5, see Supplemental data). Consequently, according to our set of spectral data, authors[12] made an incorrect conclusion regarding the regioselectivity of the HCl elimination from the molecule of 3-chlorotetrahydro-2*H*-thiopyran-1,1-dioxide by the treatment with DBU. In this case, Δ^3-isomer **2** is formed, but not Δ^2-isomer **1** stated in papers (Scheme 2). Studying of peculiarities of NMR spectral behavior of compounds **1**, **2** shows the following observations:

(a) $H^{2,3}$ nuclei of unsaturated fragment of Δ^2-isomer **1** have predictably larger chemical shift in relation to similar nuclei $H^{3,4}$ of the compound **2** ($\Delta\delta$ 0.63 ppm) and a higher mutual equivalence ($\Delta\delta$ $H^{2,3}$ 0.05 ppm for **1** and $\Delta\delta$ $H^{3,4}$ 0.23 ppm for **2**);
(b) since there is no doubt in mutual assignment of protons $H^{2,3}$ in olefin fragment of compound **1**, from COSY spectrum a weak long range interaction of H^3 and H^6 ($^5J_{3,6}$), H^2 and H^4 nuclei ($^4W_{2,4}$, allylic coupling) are clearly observed, as well as many vicinal interactions $^3J_{2,3}$, $^3J_{3,4}$, $^3J_{4,5}$, and $^3J_{5,6}$;
(c) according to the COSY spectrum of compound **2**, mutual arrangement of nuclei $H^{3,4}$ is as follows: $H^3 < H^4$, that is, nucleus of proton H^3, which is localized close to the electron-withdrawing SO_2 group, uncommonly resonates in a stronger

field. Such arrangement correlates well with the logical assumption that $^3J_{2,3} > W_{2,4}$. Besides, in the COSY spectrum a weak long range interaction of H^2 and H^5 ($^5J_{2,5}$, homoallylic coupling), H^2 and H^4 ($W_{2,4}$, allylic coupling), H^2 and H^6 ($W_{2,6}$), H^3 and H^5 ($W_{3,5}$, allylic coupling) nuclei are clearly observed, as well as many vicinal interactions $^3J_{2,3}$, $^3J_{3,4}$, $^3J_{4,5}$ and $^3J_{5,6}$;

(4) position of the chemical shift of ^{1}H and ^{13}C nuclei in C^6H_2 methylene group of both isomers is rather close: 3.17 ppm for **1** and 3.08 ppm for **2**; 50.69 ppm for **1** and 47.43 ppm for **2**.

Detailed NMR data obtained in the course of our work will be useful for the identification of related sulfone derivatives.

Conclusion

New four-step method for the synthesis of 3,4- and 3,6-dihydro-2H-thiopyran-1,1-dioxides **1** and **2** from dihydro-2*H*-thiopyran-3(4*H*)-one **8** has been developed. According to this method, ketone **8** was oxidized by hydrogen peroxide, and keto group was then reduced by sodium borohydride followed by mesylation and elimination of the methanesulfonic acid under basic conditions. The reported method uses readily available reagents and leads to the target thiopyran-1,1-dioxides **1**, **2** in decagram scale with total yields of 64% and 74%, respectively. Features of the NMR spectral behavior of the above mentioned compounds allowed to make reliable assignment of the chemical shifts of ^{1}H, ^{13}C nuclei and to correctly identify Δ^2- and Δ^3-isomers, and related compounds. The proposed synthetic protocol expands the means to access similar functionalized cyclic sulfones for the elaboration of combinatorial libraries of biologically active substances.

Experimental

Solvents were dried and distilled immediately prior to use. Melting points were determined in open capillary tubes and reported uncorrected. ^{1}H, ^{13}C, COSY, and HSQC spectra were measured using Bruker spectrometers (400 and 500 MHz for ^{1}H nuclei) at r.t. in appropriate solvents. Chemical shifts (δ) are reported in parts per million (ppm) with respect to the solvent residual signal ($CDCl_3$ ^{1}H: $\delta = 7.26$ ppm, ^{13}C: $\delta = 77.16$ ppm; DMSO-d_6 ^{1}H: $\delta = 2.50$ ppm, ^{13}C: $\delta = 39.52$ ppm). Coupling constants (J) are reported in Hertz (Hz), and multiplicities are given as s (singlet), d (doublet), t (triplet), dd (doublet of doublets), and m (multiplet). Purity of the synthesized compounds was checked by the gas chromatography mass spectrometry using Shimadzu GCMS-QP2010 instrument: column Restek Rxi-5ms (Crossbond® 5% diphenyl/95% dimethylpolysiloxane), length 30 m, diameter 0.25 mm, thickness 0.25 µm, carrier gas helium, flow rate 1 ml/min, injection mode split, injection temperature 250 °C, column temperature from 50 to 300 °C with gradient 15 °C/min then isothermally at 300 °C for 5 min. Low resolution mass spectra of compounds **1**, **2** were recorded in electron impact ionization mode (EI) at the energy of 70 eV in the range of *m/z* 25–400. Thin layer chromatography (TLC) was performed on Silufol UV-254 plates in ethyl acetate and its mixtures with hexane. The plates were visualized with potassium permanganate

stain. The elemental analysis (C, H, S) was performed using Carlo Erba analyzer. The analytical results were within ±0.4% of the theoretical values. Starting dihydro-2*H*-thiopyran-3(4*H*)-one **8** was synthesized from methyl thioglycolate and methyl-4-chlorobutyrate as published,[9] and ketone **16** was purchased from Enamine Ltd.

Typical experimental procedures for the key compounds

3 ,4-Dihydro-2H-thiopyran-1,1-dioxide (1)

The solution of mesylate **14** (27.00 g, 0.118 mol) in dry pyridine (100 mL) was stirred at 120 °C in oil bath for 24 hours. After cooling to r.t., water (200 mL) was slowly added to the reaction mixture with cooling in the ice bath and then concentrated HCl (∼95 mL) to the pH∼2. The product was extracted with dichloromethane (4 × 200 mL). Water layer was saturated with crystalline sodium chloride, and product was additionally extracted with ethyl acetate (3 × 100 mL). Combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to oily residue which was distilled under vacuum at 123–126 °C (1.5 mm Hg). Yield of the crude product 12.80 g (82%, purity by GCMS 89.3%). The product was further purified by recrystallization from 400 ml mixture of heptane : ethyl acetate (∼3:1) at overcooling to minus 30 °C. Yield: 11.03 g (long transparent needles, purity by GCMS 98.0%), mp 46–46.5 °C (44–46 °C[9]), R_f 0.21 (ethyl acetate: hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (1H, d, $^3J_{2,3}$ = 11.2 Hz, H-2), 6.38 (1H, d, $^3J_{2,3}$ = 11.2 Hz, H-3), 3.20–3.14 (2 H, m, H-6), 2.36–2.30 (4H, m, H-4,5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.71 (C-2), 130.10 (C-3), 50.69 (C-6), 24.81 (C-4), 20.72 (C-5). Mass spectrum (EI, 70eV), *m/z* ($I_{rel.}$, %): 132 (M*, 18), 103.0 (88), 87.0 (78), 83.1 (71), 67.1 (56), 55.1 (56), 41.1 (65), 39.1 (100). The same method was used for the synthesis of sulfone **2** from tosylate **15** (66.0 g, 0.217 mol) in dry pyridine (200 mL). Yield 11.0 g of the crude product (purity by GCMS 82.9%), after recrystallization 9.10 g (purity by GCMS 96.7%, 32% yield).

3 ,6-Dihydro-2H-thiopyran-1,1-dioxide (2)

To an 5% aqueous solution of sodium hydroxide (200 mL), mesylate **14** (27.00 g, 0.118 mol) was added and the reaction mixture stirred at 20 °C for 8 hours. The product was extracted with dichloromethane (4 × 200 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to oily residue which was recrystallized from methyl *tert*-butyl ether (500 mL). Yield: 14.81 g (95%, purity by GCMS 94.5%), mp 67–69 °C (68–72 °C (cyclohexane),[10] 65–69 °C[9]), R_f 0.29 (ethyl acetate: hexane, 1:1). The product should be stored at 4 °C! ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (1H, d, $^3J_{3,4}$ = 10.7 Hz, H-4), 5.65 (1H, d, $^3J_{3,4}$ = 10.7 Hz, H-3), 3.66–3.60 (2 H, m, H-2), 3.11–3.05 (2 H, m, H-6), 2.80–2.74 (2H, m, H-5). ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.83 (C-4), 119.42 (C-3), 50.79 (C-2), 47.43 (C-6), 25.80 (C-5).[12] ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.80 (1H, d, $^3J_{3,4}$ = 10.7 Hz, H-4), 5.61 (1H, d, $^3J_{3,4}$ = 10.7 Hz, H-3), 3.71–3.65 (2 H, m, H-2), 3.18–3.12 (2 H, m, H-6), 2.63–2.57 (2H, m, H-5). ^{13}C NMR (100 MHz, DMSO-d_6) δ 126.21 (C-4), 119.96 (C-3), 49.95 (C-2), 46.46 (C-6), 25.62

(C-5). Mass spectrum (EI, 70eV), *m/z* ($I_{rel.}$, %): 131.9 (M*, 1), 68.0 (22), 67.1 (100), 53.0 (24), 39.0 (21), 41.0 (14).

Disclosure statement

No potential conflict of interest was reported by the authors.

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