

3,5-Dibromo-1-(1,1-dioxothietanyl-3)-1,2,4-triazole, New Reagent for Preparation of Substituted Thietane 1,1-Dioxides

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Abstract—A new reagent, 3,5-dibromo-1-(1,1-dioxothietanyl-3)-1,2,4-triazole, was introduced for the synthesis of 3-substituted thietane 1,1-dioxides that were treated with sodium alcoholates and phenolates to prepare 3-alkoxy- and 3-aryloxythietane 1,1-dioxides.

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Derivatives of sulfur heterocycles found wide application in various industrial branches and in the medicine [1, 2]. However compounds containing a thietane ring are poorly studied because of their unavailability.

The published procedures for preparation of 3-alkoxy- and 3-aryloxythietane 1,1-dioxides consist in the oxidation of 3-aryloxythietanes [3, 4] and in the reaction of thietane 1,1-dioxide with nucleophilic reagents [5].

We developed a new method of synthesis of 3-substituted thietane 1,1-dioxides based on the study of chemical properties of 3,5-dibromo-1-(1,1-dioxothietanyl-3)-1,2,4-triazole (**I**). Initial dioxothietanyltriazole **I** was easily obtained by oxidation of a 3,5-dibromo-1-(thietanyl-3)-1,2,4-triazole with hydrogen peroxide [6].

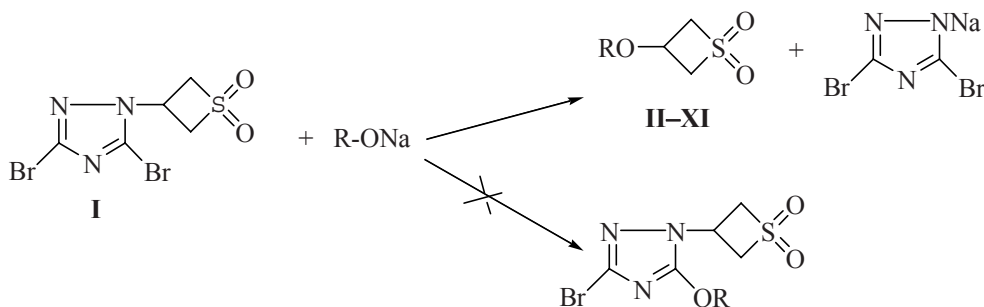
When investigating reactions of dioxothietanyltriazole **I** with sodium alcoholates we unexpectedly obtained

3-substituted thietane 1,1-dioxides instead of 5-substituted 3-bromo-1-(1,1-dioxothietanyl-3)-1,2,4-triazoles (Scheme 1).

It was established that 3-alkoxythietane 1,1-dioxides **II–VII** formed in 50–90% yields at heating compound **I** with an equimolar quantity of sodium alcoholate in the corresponding alcohol. The sodium alcoholate was prepared in situ by adding metallic sodium to the anhydrous alcohol. The reaction in benzene solution also led to 3-alkoxythietane 1,1-dioxides.

In the ^1H NMR spectra of compounds **II–VII** the signals of ring protons of the thietane dioxide are observed: the proton signals of one $\text{S}(\text{CH}_2)_2$ -group appear in the range 4.0–4.2 ppm, and the proton signals of the other $\text{S}(\text{CH}_2)_2$ -group overlap with the proton signals of the OCH -group and are registered in the region 4.2–4.4 ppm. The signals of the substituent in the position 3 are observed in appropriate regions.

Scheme 1.



R = CH_3 (**II**), C_2H_5 (**III**), $n\text{-C}_3\text{H}_7$ (**IV**), $iso\text{-C}_3\text{H}_7$ (**V**), $n\text{-C}_4\text{H}_9$ (**VI**), $iso\text{-C}_4\text{H}_9$ (**VII**), C_6H_5 (**VIII**), $\text{C}_6\text{H}_4\text{CH}_3$ -4 (**IX**), $\text{C}_6\text{H}_3(\text{CH}_3)_2$ -3,4 (**X**), $\text{C}_6\text{H}_3\text{CH}(\text{CH}_3)_2$ -2,2, CH_3 -5 (**XI**).

We also studied the reactions of compound **I** with sodium phenolates. Initial sodium phenolates were prepared in situ by adding sodium metal to the benzene solution of the corresponding phenol. It was established that the heating of equimolar amounts of compound **I** and an appropriate sodium phenolate in benzene provided 3-aryloxythietane 1,1-dioxides **VIII–XI** in 57–79% yields.

Performing the reaction with sodium phenolate in polar solvents endowed with nucleophilic properties (anhydrous ethanol and 1-butanol) also resulted in the formation of 3-phenoxythietane-1,1-dioxide but in lower yield.

We confirmed the structure of compound **VIII** by an independent synthesis from 2-chloromethylthiirane and phenol followed by oxidation of the 3-phenoxythietane with the hydrogen peroxide in the glacial acetic acid [3]. In the IR spectra of compound **VIII** prepared by the published procedure [3] and that obtained by our method the absorption bands completely coincided and also the position of signals and their intensity in the corresponding ^1H NMR spectra were identical.

In the ^1H NMR spectra of compounds **VIII – XI** the proton signals of one $\text{S}(\text{CH})_2$ -group of the thietane dioxide ring appear in the range 4.1–4.3 ppm, the proton signals of the other $\text{S}(\text{CH})_2$ -group are observed in the region 4.4–4.6 ppm, and the proton signal of the OCH-group, at 4.9–5.1 ppm. The proton signals from the phenol residue appear in the appropriate regions.

Therefore the developed preparation procedure is characterized by the simplicity of the reaction performance, high yields and easy isolation of the target products, and 3,5-dibromo-(1,1-dioxothietanyl-3)-1,2,4-triazole is a new reagent for the synthesis of 3-substituted thietane 1,1-dioxides.

EXPERIMENTAL

^1H NMR spectra were registered on a spectrometer Bruker AM-300 at operating frequency 300 MHz from solutions in deuteriochloroform. IR spectra were recorded on a spectrophotometer Infracum FT-02 from pellets with KBr. TLC was performed on Sorbfil plates, eluents hexane–ethanol (6:4) for compounds **II–VII**, ethanol–acetone (6 : 4) for compounds **VIII–XI**, development in iodine vapor.

3,5-Dibromo-1-(1,1-dioxothietanyl-3)-1,2,4-triazole (**I**) was obtained by procedure [6].

3-Alkoxythietane 1,1-dioxides II – VII. *a.* To 20 ml of an appropriate alcohol was added 0.11 g

(0.005 mol) of metallic sodium, and the reaction mixture was heated to the end of hydrogen bubbles liberation. Then 1.65 g (0.005 mol) of compound **I** was added, and the mixture was boiled for 30 min. The reaction mixture was evaporated in a vacuum. The residue was extracted with benzene, and the extract was evaporated.

3-Methoxythietane 1,1-dioxide (II). Yield 0.36 g (53%). mp = 63–64°C (hexane–acetone), R_f = 0.58. ^1H NMR spectrum, δ , ppm: 3.33 br.s (3H, CH_3O), 4.05–4.17 m (2H, $\text{S}(\text{CH})_2$), 4.18–4.28 m (1H, OCH), 4.29–4.42 m (2H, $\text{S}(\text{CH})_2$). IR spectrum, ν , cm^{-1} : 1143 and 1320 (SO_2). Found, %: C 35.25; H 5.81; S 25.58. Calculated, %: C 35.29; H 5.88; S 25.53.

3-Ethoxythietane 1,1-dioxide (III). *a.* Yield 0.47 g (63%). mp = 48–49°C, R_f = 0.59. ^1H NMR spectrum (CDCl_3), δ , ppm: 1.20 t (3H, J 6.90 Hz, CH_3), 3.45 q (2H, J 6.90 Hz, CH_2O), 4.00 – 4.20 m (2H, $\text{S}(\text{CH})_2$), 4.22–4.42 m (3H, $\text{S}(\text{CH})_2$, OCH). IR spectrum, ν , cm^{-1} : 1143 and 1320 (SO_2). Found, %: C 39.89; H 6.60; S 21.40. Calculated, %: C 39.95; H 6.66; S 21.30.

b. To 20 ml of benzene was added 0.69 g (0.015 mol) of anhydrous ethanol and 0.11 g (0.005 mol) of sodium metal, and boiling was continued till the end of gas liberation. Then 1.65 g (0.005 mol) of compound **I** was added, and the mixture was boiled for 2 h. The precipitate was filtered off, the benzene filtrate was evaporated in a vacuum. Yield 0.60 g (80%). mp = 48–49°C, R_f = 0.59. ^1H NMR spectrum, δ , ppm: 1.20 t (3H, J 6.90 Hz, CH_3), 3.45 q (2H, J 6.90 Hz, CH_2O), 4.00–4.20 m (2H, $\text{S}(\text{CH})_2$), 4.22–4.42 m (3H, $\text{S}(\text{CH})_2$, OCH). IR spectrum, ν , cm^{-1} : 1143 and 1320 (SO_2). The mixed sample with compound obtained by procedure *a* melted without melting point depression.

3-*n*-Propoxythietane 1,1-dioxide (IV). Yield 0.43 g (52%). n_D^{20} = 1.4684, R_f = 0.60. ^1H NMR spectrum, δ , ppm: 0.92 t (3H, J 7.38 Hz, CH_3), 1.53–1.74 m (2H, CH_2), 3.34 t (2H, J 6.45 Hz, CH_2O), 4.04–4.17 m (2H, $\text{S}(\text{CH})_2$), 4.24–4.41 m (3H, $\text{S}(\text{CH})_2$, OCH). Found, %: C 43.98; H 7.22; S 19.59. Calculated, %: C 43.90; H 7.32; S 19.51.

3-*iso*-Propoxythietane 1,1-dioxide (V). Yield 0.41 g (50%). mp = 50–51°C (hexane–acetone), R_f = 0.63. ^1H NMR spectrum, δ , ppm: 1.18 d (6H, J 6.13 Hz, 2CH_3), 3.61 m (1H, J 6.12 Hz, CHO), 4.04 – 4.15 m (2H, $\text{S}(\text{CH})_2$), 4.26–4.48 m (3H, $\text{S}(\text{CH})_2$, OCH). IR spectrum, ν , cm^{-1} : 1144 and 1320 (SO_2). Found, %: C 43.82; H 7.38; S 19.55. Calculated, %: C 43.90; H 7.32; S 19.51.

3-n-Butoxythietane 1,1-dioxide (VI). Yield 0.80 g (90%). $n_D^{20} = 1.4663$, $R_f = 0.58$. ^1H NMR spectrum, δ , ppm: 0.88 t (3H, J 7.38 Hz, CH_3), 1.27–1.41 m (2H, CH_2), 1.48–1.60 m (2H, CH_2), 3.35 t (2H, J 6.47 Hz, CH_2O), 4.01–4.13 m (2H, $\text{S}(\text{CH}_2)_2$), 4.22–4.38 m (3H, $\text{S}(\text{CH}_2)_2$, OCH). Found, %: C 47.11; H 7.75; S 17.91. Calculated, %: C 47.19; H 7.87; S 17.98.

3-iso-Butoxythietane 1,1-dioxide (VII). Yield 0.72 g (81%). mp = 44–45°C (hexane–acetone), $R_f = 0.73$. ^1H NMR spectrum, δ , ppm: 0.92 d (6H, J 6.67 Hz, 2CH_3), 1.80–1.98 m (1H, CH), 3.15 d (2H, J 6.45 Hz, CH_2O), 4.03–4.18 m (2H, $\text{S}(\text{CH}_2)_2$), 4.24–4.40 m (3H, $\text{S}(\text{CH}_2)_2$, OCH). IR spectrum, ν , cm^{-1} : 1144 and 1320 (SO_2). Found, %: C 47.27; H 7.76; S 17.95. Calculated, %: C 47.19; H 7.87; S 17.98.

3-Aryloxythietane 1,1-dioxides VIII–XI. *a.* To 20 ml of benzene was added 0.005 mol of an appropriate phenol and 0.11 g (0.005 mol) of sodium metal, and the mixture was boiled for 1 h. Then 1.65 g (0.005 mol) of compound **I** added and the mixture was boiled for 2 h. The precipitate was filtered off, the benzene filtrate was evaporated in a vacuum.

3-Phenoxythietane 1,1-dioxide (VIII). *a.* Yield 0.71 g (72%). mp = 129–130°C (acetone–hexane), $R_f = 0.75$. ^1H NMR spectrum, δ , ppm: 4.26–4.38 m (2H, $\text{S}(\text{CH}_2)_2$), 4.52–4.64 m (2H, $\text{S}(\text{CH}_2)_2$), 5.00–5.10 m (1H, OCH), 6.84 d (2H, J 8.40 Hz, 2CH_{arom}), 7.07 t (1H, J 7.36 Hz, CH_{arom}), 7.34 t (2H, J 7.77 Hz, 2CH_{arom}). IR spectrum, ν , cm^{-1} : 1143 and 1320 (SO_2). Found, %: C 54.43; H 5.11; S 16.10. Calculated, %: C 54.55; H 5.05; S 16.16.

b. To 20 ml of anhydrous ethanol was added 0.005 mol of phenol and 0.11 g (0.005 mol) of sodium metal. The reaction mixture was heated for 1 h. Then 1.65 g (0.005 mol) of compound **I** was added and the mixture was boiled for 1.5 h. On cooling the precipitate was filtered off, the filtrate was evaporated in a vacuum. Yield 0.45 g (45%). mp = 130–131°C, $R_f = 0.77$.

c. To a solution of 0.17 g (0.003 mol) of potassium hydroxide in 30 ml of 1-butanol was added 0.28 g (0.003 mol) of phenol and 0.99 g (0.003 mol) of compound **I**. The reaction mixture was boiled for 3 h. Then the reaction mixture was evaporated in a vacuum, water was added to the residue, and the precipitate was filtered off. Yield 0.30 g (51%). mp = 128–129°C, $R_f = 0.75$.

d. [3, 4]. Yield 0.49 g (50%). mp = 130–131°C, $R_f = 0.75$. The mixed samples with compounds obtained by procedures *a–c* melted without melting point depression.

3-(4-Methylphenoxy)thietane 1,1-dioxide (IX). Yield 0.60 g (57%). mp = 120–122°C (2-propanol), $R_f = 0.75$. ^1H NMR spectrum, δ , ppm: 2.27 s (3H, CH_3), 4.17–4.25 m (2H, $\text{S}(\text{CH}_2)_2$), 4.48–4.59 m (2H, $\text{S}(\text{CH}_2)_2$), 4.94–5.02 m (1H, OCH), 6.72 d (2H, J 8.62 Hz, 2CH_{arom}), 7.11 d (2H, J 8.75 Hz, 2CH_{arom}). IR spectrum, ν , cm^{-1} : 1143 and 1320 (SO_2). Found, %: C 56.67; H 5.56; S 15.01. Calculated, %: C 56.60; H 5.66; S 15.09.

3-(3,4-Dimethylphenoxy)thietane 1,1-dioxide (X). Yield 0.84 g (74%). mp = 121–122°C (2-propanol), $R_f = 0.75$. ^1H NMR spectrum, δ , ppm: 2.21 s (3H, CH_3), 2.25 s (3H, CH_3), 4.23–4.32 (2H, m, $\text{S}(\text{CH}_2)_2$), 4.49–4.59 m (2H, $\text{S}(\text{CH}_2)_2$), 4.97–5.05 m (1H, OCH), 6.55 d.d (1H, 3J 8.21 Hz, 4J 2.68 Hz, CH_{arom}), 6.66 d (1H, 4J 2.64 Hz, CH_{arom}), 7.06 d (1H, 3J 8.21 Hz, CH_{arom}). IR spectrum, ν , cm^{-1} : 1143 and 1320 (SO_2). Found, %: C 58.34; H 6.16; S 14.09. Calculated, %: C 58.41; H 6.19; S 14.16.

3-(2-iso-Propyl-5-methylphenoxy)thietane 1,1-dioxide (XI). Yield 1.00 g (79%), mp = 126–127°C (2-propanol), $R_f = 0.76$. ^1H NMR spectrum, δ , ppm: 1.21 d (6H, J 6.86 Hz, 2CH_3), 2.32 s (3H, CH_3), 3.09 m (1H, J 6.82 Hz, CH), 4.24–4.36 m (2H, $\text{S}(\text{CH}_2)_2$), 4.49–4.61 m (2H, $\text{S}(\text{CH}_2)_2$), 4.97–5.05 m (1H, OCH), 6.63 d (1H, J 9.30 Hz, CH_{ap}), 6.65 s (1H, CH_{arom}), 7.18 d (1H, J 9.30 Hz, CH_{arom}). IR spectrum, ν , cm^{-1} : 1143 and 1320 (SO_2). Found, %: C 61.41; H 7.08; S 12.62. Calculated, %: C 61.42; H 7.09; S 12.60.

REFERENCES

1. Block, E., *Comprehensive Heterocyclic Chemistry*, Katrietzky, A.R., Rees, C.W., and Scriven, E.F., Ed., New York: Pergamon, 1996, vol. 7, p. 410.
2. Mashkovskii, M.D., *Lekarstvennyye sredstva* (Drugs), Moscow: Mir, 2000, 278 p.
3. Tomashevskii, A.A., Sokolov, V.V., and Potekhin, A.A., *Zh. Org. Khim.*, 2003, vol. 39.
4. Sander, M., *Monatsch. Chem.*, 1965, vol. 96, p. 896.
5. *Heterocyclic Compounds with Three- and Four-Membered Rings*, Weissberger, A., Ed., New York: Wiley & Sons, Inc., 1964, p. 647.
6. Iskhakova, G.F., *Cand. Sci. (Pharm.) Dissertation*, Perm, 2004, 20 p.