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DIOXOTHIETANYLATION OF HETEROCYCLES

1. *N*-(1,1-DIOXOTHIETAN-3-YL)-1,2,4-TRIAZOLES

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3,5-Substituted 1-(1,1-dioxothietan-3-yl)-1,2,4-triazoles have been prepared by treating NH-1,2,4-triazole sodium salts with 3,5-dibromo-1-(1,1-dioxothietan-3-yl)-1,2,4-triazole (a novel dioxothietanylating reagent). The reactions occur regioselectively at the position 2 for 5-bromo-1,2,4-triazoles containing ethoxy-, isopropoxy-, or phenoxy groups at the position 3 and at position 1 for 3-methylsulfanyl-1,2,4-triazole. The reaction occurs nonselectively at positions 1 and 2 in the case of 3-methylsulfonyl-1,2,4-triazole and 5-bromo-3-(piperidin-1-yl)-1,2,4-triazole, to give the isomeric 3-R-5-R^1- and 5-R-3-R^1-1-(1,1-dioxothietan-3-yl)-1,2,4-triazoles.

Keywords: thietane 1,1-dioxide, 1,2,4-triazole, dioxothietanylation.

Methods have been reported in the literature for the preparation of *N*-(1,1-dioxothietan-3-yl)-1,2,4-triazoles by oxidative reactions of *N*-(thietan-3-yl)- and *N*-(1-oxothietan-3-yl)-1,2,4-triazoles [1], inferring a preliminary alkylation of 1,2,4-triazoles by 2-chloromethylthiirane and subsequent nucleophilic substitution [2-4].

In continuation of our studies [5], we propose a novel method for the introduction of a thietane-1,1-dioxide ring into 3,5-substituted NH-1,2,4-triazoles, which is based on the use of 3,5-dibromo-1-(1,1-dioxothietan-3-yl)-1,2,4-triazole (**1**) as the dioxothietanylating reagent [6].

It was found that reaction of the NH-1,2,4-triazoles **2a-g** with compound **1** in *tert*-butanol in the presence of sodium *tert*-butoxide gave the ***N***-dioxothietanylation products *N*-(1,1-dioxothietan-3-yl)-1,2,4-triazoles **3-9** in 39-64% yields. Evidently the reaction of the 3,5-dibromo-1-(1,1-dioxothietan-3-yl)-1,2,4-triazole (**1**) with sodium *tert*-butoxide occurs with elimination of thietane 1,1-dioxide, which takes part in a Michael addition of the NH-1,2,4-triazoles. It is known that thietane 1,1-dioxides are used as Michael acceptors and readily add ethanol, hydrogen sulfide, thiophenol and amines in the presence of bases to give high yields of 3-substituted thietane 1,1-dioxides [7].

The composition and structure of compounds **3-9** were confirmed from elemental analysis data, IR and ^{1}H NMR spectroscopy, and also by a counter synthesis.

The reactions of compound **1** with the sodium salts of unsymmetrical 1,2,4-triazoles can occur at the positions 1, 2, and 4 of the triazole ring. In the reaction of 3,5-dibromo-1-(1,1-dioxothietan-3-yl)-1,2,4-triazole (**1**) with the unsubstituted 1,2,4-triazole (**2a**), addition occurs at the N-1 atom to give 1-(1,1-dioxothietan-3-yl)-1,2,4-triazole (**3**). The product of dioxothietanylation at the N-4 atom was not observed [5].

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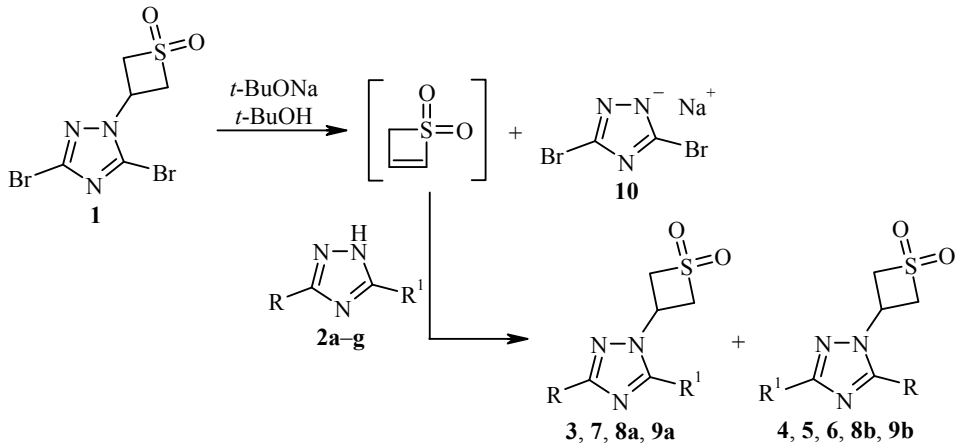

2a, **3** R = R^1 = H; **2b**, **4** R = OEt, R^1 = Br; **2c**, **5** R = O(Pr-*i*), R^1 = Br; **2d**, **6** R = OPh, R^1 = Br; **2e**, **7** R = SMe, R^1 = H; **2f**, **8a**,**b** R = SO_2Me, R^1 = H; **2g**, **9a**,**b** R = piperidin-1-yl, R^1 = Br

In the case of the 5-bromo-3-ethoxy- (**2b**), 5-bromo-3-isopropoxy- (**2c**), and 5-bromo-3-phenoxy-1,2,4-triazoles (**2d**) reactions occur regioselectively at the position 2, giving the 3-bromo-1-(1,1-dioxothietan-3-yl)-5-ethoxy- (**4**), 3-bromo-1-(1,1-dioxothietan-3-yl)-5-isopropoxy- (**5**), and 3-bromo-1-(1,1-dioxothietan-3-yl)-5-phenoxy-1,2,4-triazoles (**6**), respectively. Compounds **4-6** did not depress the melting points when mixed with those samples obtained by known methods [1, 4] *via* oxidation of 3-bromo-1-(thietan-3-yl)-5-ethoxy-, 3-bromo-5-isopropoxy-1-(thietan-3-yl)- and 3-bromo-1-(thietan-3-yl)-5-phenoxy-1,2,4-triazoles. Their IR spectra were also in full agreement.

Reaction of compound **1** with 3-methylsulfanyl-1,2,4-triazole (**2e**) gave only the 1-(1,1-dioxothietan-3-yl)-3-methylsulfanyl-1,2,4-triazole (**7**) in 63% yield. The ^{1}H NMR spectrum of compound **7** showed signals in the regions typical for the thietanedioxide ring [8] and methylsulfanyl residue protons. The singlet for the =CH proton of the triazole ring was observed at 8.16 ppm, confirming the formation of the 3-methylsulfanyl isomer [9].

Dioxothietanylation of the 3-methylsulfonyl-1,2,4-triazole (**2f**) gave a mixture of two compounds: 1-(1,1-dioxothietan-3-yl)-3-methylsulfonyl- (**8a**) and 1-(1,1-dioxothietan-3-yl)-5-methylsulfonyl-1,2,4-triazoles (**8b**). In the ^{1}H NMR spectrum of the isomer mixture the 5-methylsulfonyl isomer has triazole ring =CH proton singlet at 9.05 ppm, while the singlet for the 3-methylsulfonyl isomer is found at lower field at 9.65 ppm, which is in agreement with literature data [9, 10]. The ratio of 3-methylsulfonyl- and 5-methylsulfonyl isomers **8a** and **8b** was judged to be 1:2 from the integrated intensities of the NCH group proton signals.

The reaction of compound **1** with 5-bromo-3-(piperidin-1-yl)-1,2,4-triazole (**2g**) leads to a mixture of isomeric 5-bromo-1-(1,1-dioxothietan-3-yl)-3-(piperidin-1-yl)- (**9a**) and 3-bromo-1-(1,1-dioxothietan-3-yl)-5-piperidin-1-yl)-1,2,4-triazoles (**9b**). Doubling of the ^{1}H NMR signals for the thietanedioxide ring and the piperidine residue in the mixture of compounds **9a** and **9b** led us to conclude that they are formed in a 2:1 ratio (according to the integrated intensities). The assignment of the proton signals to the 3- and 5-isomers was made on the basis of ^{1}H NMR spectrum of the 5-piperidinyl isomer **9b** synthesized earlier by treating 3,5-dibromo-1-(1,1-dioxothietan-3-yl)-1,2,4-triazole with piperidine [1, 9].

Hence the dioxothietanylation occurs regioselectively at the position 2 for the 5-bromo-1,2,4-triazoles containing ethoxy-, isopropoxy- or phenoxy groups in position 3, but at position 1 of the triazole ring for the 3-methylsulfanyl-1,2,4-triazole. Reactions of 3-methylsulfonyl-1,2,4-triazole and 5-bromo-3-(piperidin-1-yl)-1,2,4-triazole with 3,5-dibromo-1-(1,1-dioxothietan-3-yl)-1,2,4-triazole occur nonselectively at the positions 1 and 2, to yield the isomeric 3-R-5-R^1- and 5-R-3-R^1-1-(1,1-dioxothietan-3-yl)-1,2,4-triazoles. The ratio of isomers depends on the nature of the substituents at positions 3 and 5 of the triazole ring.

EXPERIMENTAL

IR spectra were recorded on an Infralum FT-02 instrument for KBr pellets. ^{1}H NMR spectra were recorded on a Bruker AM-300 instrument (300 MHz) with the residual solvent signals as standard (7.26 ppm for $CDCl_3$ and 2.50 ppm for DMSO-d_6). Elemental analysis was performed on a Euro3000 Hekatech CHNS-analyzer. Melting points were determined on a PTP instrument.

3,5-Dibromo-1-(1,1-dioxothietan-3-yl)-1*H*-1,2,4-triazole (**1**) was prepared by method [1] and 1-(1,1-dioxothietan-3-yl)-1*H*-1,2,4-triazole (**3**) by method [5].

Preparation of Compounds 4-7, 9a,b (General Method). Sodium metal (0.08 g, 3.3 mmol) was added to *t*-BuOH (30 ml) and heated until evolution of gas bubbles ceased. Compound **2a-g** (3.0 mmol) and 3,5-dibromo-1-(1,1-dioxothietan-3-yl)-1*H*-1,2,4-triazole (**1**) (0.99 g, 3.0 mmol) were then added. The reaction mixture was refluxed for 2 h, the solvent was evaporated to dryness *in vacuo*, and water was added to the residue. The precipitate was filtered off and dried.

3-Bromo-1-(1,1-dioxothietan-3-yl)-5-ethoxy-1*H*-1,2,4-triazole (4). Yield 0.57 g (64%); mp 169-170ºC (EtOH) (mp 166-167ºC [1]). The spectroscopic data agreed with the literature [1].

3-Bromo-1-(1,1-dioxothietan-3-yl)-5-isopropoxy-1*H*-1,2,4-triazole (5). Yield 0.36 g (39%), mp 154-155ºC (EtOH) (mp 150-151.5ºC [1]). IR spectrum, ν, cm^{-1}: 1295, 1493, 1551 (C=N), 1143, 1342 (SO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J,* Hz): 1.41 (6H, d, *J* = 6.2, $CH(C\underline{H}_3)_2$); 4.40-4.58 (2H, m) and 4.64-4.81 (2H, m, CH_2SCH_2); 4.96-5.20 (2H, m, OCH, NCH).

3-Bromo-1-(1,1-dioxothietan-3-yl)-5-phenoxy-1*H*-1,2,4-triazole (6). A. Yield 0.48 g (46%); mp 246-248ºC (*n*-BuOH). IR spectrum, ν, cm^{-1}: 1292, 1487, 1528 (C=N, C=C), 1142, 1323 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 4.69-4.89 (4H, m, CH_2SCH_2); 5.35-5.47 (1H, m, NCH); 7.28-7.35 (1H, m, H Ph); 7.38-7.43 (2H, m, H Ph), 7.45-7.51 (2H, m, H Ph). Found, %: C 38.45; H 2.81; N 12.18. $C_{11}H_{10}BrN_3O_3S$. Calculated, %: C 38.39; H 2.93; N 12.21.

B. A 37% solution of H_2O_2 (2.76 g, 30 mmol) was added to a solution of the 3-bromo-1-(thietan-3-yl)-5-phenoxy-1,2,4-triazole [4] (0.94 g, 3.3 mmol) in glacial acetic acid (7 ml). The reaction mixture was refluxed for 2 hours and then cooled. The precipitate formed was filtered off and dried. Yield 0.65 g (57%), mp 249-250ºC (*n*-BuOH). The spectroscopic data agreed with that for compound **6** prepared by method A.

1-(1,1-Dioxothietan-3-yl)-3-methylsulfanyl-1*H*-1,2,4-triazole (7). Yield 0.41 g (63%); mp 147-148ºC (EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.62 (3H, s, SCH_3); 4.56-4.66 (2H, m) and 4.74-4.83 (2H, m, CH_2SCH_2); 5.15-5.25 (1H, m, NCH); 8.16 (1H, s, H-5). Found, %: C 32.87; H 4.19; N 19.33. $C_6H_9N_3O_2S_2$. Calculated, %: C 32.86; H 4.14; N 19.16.

5-Bromo-1-(1,1-dioxothietan-3-yl)-3-(piperidin-1-yl)-1*H*-1,2,4-triazole (9a) and 3-Bromo-1-(1,1-dioxothietan-3-yl)-5-(piperidin-1-yl)-1*H*-1,2,4-triazole (9b). Yield 0.53 g (53%) as a mixture of compounds **9a** and **9b** (isomer ratio 2:1); mp 160-162ºC (EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.55-1.78 (6H, m, 3,4,5-CH_2 piperidine (**9a**+**9b**)); 3.01-3.12 (1.32H, m, 2,6-CH_2 piperidine (**9b**)); 3.32-3.45 (2.68H, m, 2,6-CH_2 piperidine (**9a**)); 4.41-4.55 (2H, m) and 4.75-4.91 (2H, m, CH_2SCH_2 (**9a**+**9b**)); 4.96-5.06 (0.33H, m, NCH (**9b**)); 5.10-5.21 (0.67H, m, NCH (**9a**)). Found, %: C 35.90; H 4.55; N 16.69. $C_{10}H_{15}BrN_4O_2S$. Calculated, %: C 35.83; H 4.51; N 16.71.

1-(1,1-Dioxothietan-3-yl)-3-methylsulfonyl-1*H*-1,2,4-triazole (8a) and 1-(1,1-Dioxothietan-3-yl)-5-methylsulfonyl-1*H*-1,2,4-triazole (8b). Sodium metal (0.08 g, 3.3 mmol) was added to *t*-BuOH (40 ml) and heated until evolution of gas bubbles ceased. 3-Methylsulfonyl-1*H*-1,2,4-triazole (**2f**) (0.44 g, 3 mmol), 3,5-dibromo-1-(1,1-dioxothietan-3-yl)-1*H*-1,2,4-triazole (**1**) (0.99 g, 3 mmol) and DMF (25 ml) were added, and the mixture was refluxed for 2 h. The solution was evaporated to dryness *in vacuo*, and the residue was treated with water. The precipitate was filtered off and dried. Yield 0.34 g (45%) as a mixture of compounds **8a** and **8b** (isomer ratio 1:2); mp 163-167ºC (*n*-BuOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.38 (0.67H, s, SO_2CH_3 (**8b**)); 3.55 (0.33H, s, SO_2CH_3 (**8a**)); 4.65-4.94 (4H, m, CH_2SCH_2 (**8a**+**8b**)); 5.40-5.51 (0.33H, m, NCH

(**8a**)); 5.51-5.63 (0.67H, m, NCH (**8b**)); 9.05 (0.67H, s, H-3 (**8b**)); 9.65 (0.33H, s, H-5 (**8a**)). Found, %: C 28.62; H 3.65; N 16.67. $C_6H_9N_3O_4S_2$. Calculated, %: C 28.68; H 3.61; N 16.72.

REFERENCES

1. F. A. Khaliullin and E. E. Klen, *Zh. Org. Khim.*, **45**, 138 (2009).
2. E. E. Klen, F. A. Khaliullin, and G. F. Iskhakova, *Zh. Org. Khim.*, **41**, 1881 (2005).
3. E. E. Klen, I. L. Nikitina, F. A. Khaliullin, G. F. Iskhakova, E. K. Alekhin, and O. A. Ivanova, *Vopr. Biol. Med. i Farm. Khim.*, No. 7, 42 (2010).
4. E. E. Klen, N. N. Makarova, F. A. Khaliullin, E. K. Alekhin, I. L. Nikitina, O. A. Ivanova, and R. A. Gabidullin, *Bashk. Khim. Zh.*, **15**, No. 4, 112 (2008).
5. E. E. Klen, N. N. Makarova, and F. A. Khaliullin, *Khim. Geterotsikl. Soedin.*, 625 (2011). [*Chem. Heterocycl. Compd.*, **47**, 519 (2011)].
6. F. A. Khaliullin, E. E. Klen, and N. N. Makarova, *Zh. Org. Khim.*, **44**, 1729 (2008).
7. A. N. Butkevich, V. V. Sokolov, A. A. Tomashevskii, and A. A. Potekhin, *Khim. Geterotsikl. Soedin.*, 655 (2007). [*Chem. Heterocycl. Compd.*, **43**, 544 (2007)].
8. E. Block, in: A. R. Katritzky and C. W. Rees (editors), *Comprehensive Heterocyclic Chemistry II*, Vol. 7, Elsevier, Oxford, New York (1997), p. 403.
9. E. E. Klen and F. A. Khaliullin, *Zh. Org. Khim.*, **46**, 694 (2010).
10. V. V. Saraev, T. P. Kanakina, M. S. Pevzner, E. L. Golod, B. I. Ugrak, and V. V. Kachala, *Khim. Geterotsikl. Soedin.*, 1078 (1996). [*Chem. Heterocycl. Compd.*, **32**, 928 (1996)].