ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 1, pp. 135–138. © Pleiades Publishing, Ltd., 2009.
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Thietane Ring as a Novel Protecting Group

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Received February 18, 2008

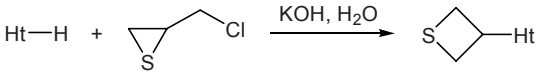
Abstract—A novel protecting group for NH functionality of heterocycles, a thietane ring, was proposed. It can be readily introduced by alkylation of NH-heterocycles with 2-chloromethylthiirane. Removal of the thietane protecting group is performed via oxidation to thietane 1,1-dioxide with hydrogen peroxide in acetic acid and subsequent treatment with sodium alkoxide.

DOI: 10.1134/S1070428009010187

Protecting groups are widely used in many fields of modern organic chemistry, specifically for selective modification of particular functional groups in heterocyclic compounds. For example, the 7-NH group in xanthines is protected with a benzyl group [1], and the 1-NH group in 1,2,4-triazoles, with an 3-oxobutyl [2], benzyl [3], or diphenylmethyl group [4].

We propose to protect NH functionality in heterocycles via introduction of a thietane ring by alkylation with 2-chloromethylthiirane in aqueous medium in the presence of alkali. The reaction is accompanied by thiirane–thietane rearrangement with formation of the corresponding N-(thietan-3-yl)-substituted heterocycle **IIa**–**IId** [5, 6] (Scheme 1).

Scheme 1.



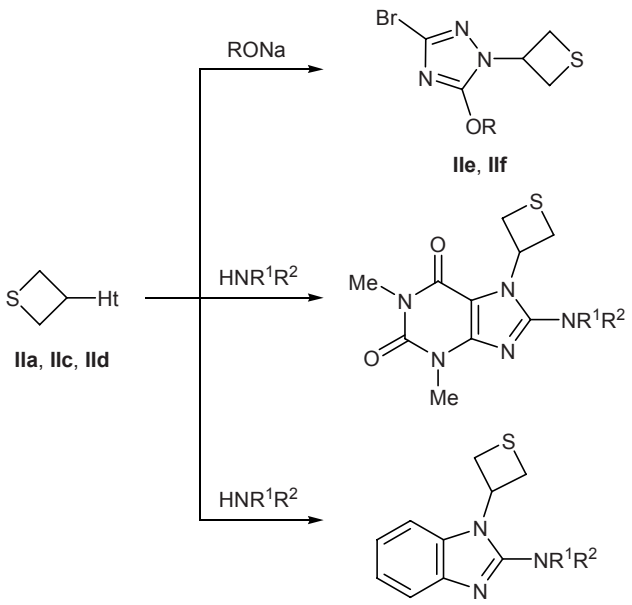
Ia–Id **IIa–IId**

I, **II**, Ht = 3,5-dibromo-1*H*-1,2,4-triazol-1-yl (**a**), 8-bromo-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl (**b**), 8-bromo-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl (**c**), 2-chloro-1*H*-benzimidazol-2-yl (**d**).

N-(Thietan-3-yl)indoles were also reported [7]. Thietane ring is resistant to the action of acids, bases, nucleophiles, and electrophiles, so that further modification of N-(thietan-3-yl)-substituted heterocycles becomes possible.

For example, 3,5-dibromo-1-(thietan-3-yl)-1*H*-1,2,4-triazole (**IIa**) reacted with sodium alkoxides to give the corresponding 5-alkoxy derivatives **IIe** and **IIf** as a result of nucleophilic replacement of one bromine atom (Scheme 2). Nucleophilic substitution of halogen atoms as readily departing groups by amines was also studied, and amino-substituted *N*-(thietan-3-yl)xanthines [8] and *N*-(thietan-3-yl)benzimidazoles [9] were thus obtained (Scheme 2).

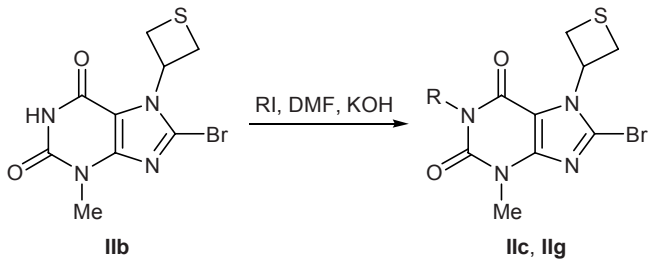
Scheme 2.



II, R = Et (**e**), *i*-Pr (**f**).

The thietane protection does not hamper electrophilic substitution. An example is electrophilic alkylation of 8-bromo-3-methyl-7-(thietan-3-yl)xanthine (**IIb**) at the N^1 atom by the action of an equimolar amount of methyl iodide or propyl iodide in dimethylformamide in the presence of potassium hydroxide (Scheme 3). As a result, 8-bromo-1,3-dimethyl- and

Scheme 3.

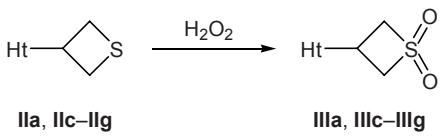


R = Me (**c**), Pr (**g**).

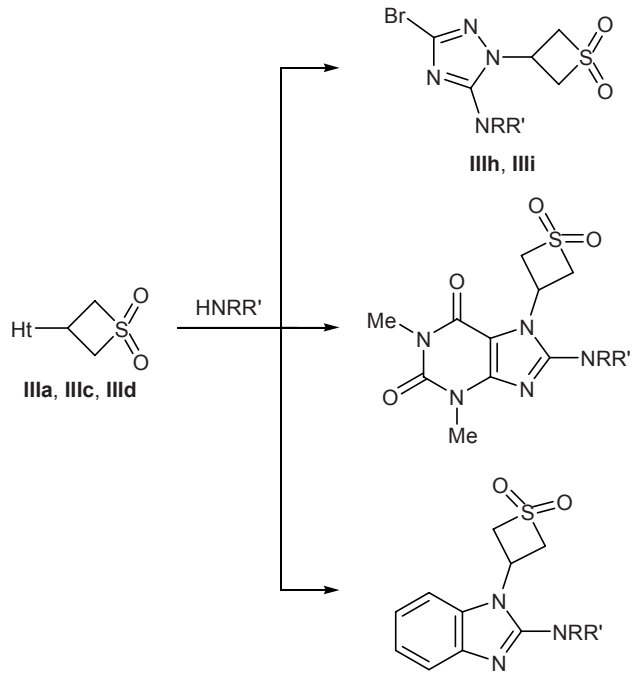
8-bromo-3-methyl-1-propyl-7-(thietan-3-yl)xanthines **IIg** and **IIh** were isolated. The physical constants of compound **IIc** obtained in such a way coincided with published data, and no depression of the melting point was observed on mixing with a sample prepared by alkylation of 8-bromo-1,3-dimethylxanthine with 2-chloromethylthiirane.

Before deprotection, the thietane ring should be oxidized to thietane 1,1-dioxide by the action of excess hydrogen peroxide in acetic acid (Scheme 4).

Scheme 4.



Scheme 5.

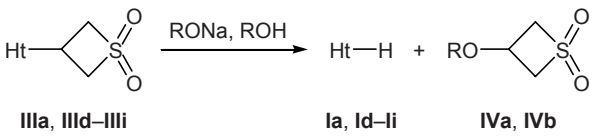


R = H, R′ = $PhCH_2$ (**h**), RR′N = piperidino (**i**).

Thietane 1,1-dioxides are stable toward some nucleophilic and electrophilic reagents, so that further modification of protected heteroring may be performed. For example, the reaction of 3,5-dibromo-1-(1,1-dioxo-λ^6-thietan-3-yl)-1*H*-1,2,4-triazole (**IIIa**) with amines was not accompanied by elimination of the thietane dioxide ring. Nucleophilic replacement of one bromine atom leads to the formation of 5-amino-*N*-(dioxothietanyl)triazoles **IIIh** and **IIIi** (Scheme 5). Likewise, we previously synthesized 8-amino-substituted 1,3-dimethyl-7-(1,1-dioxo-λ^6-thietan-3-yl)xanthines and 2-amino-1-(1,1-dioxo-λ^6-thietan-3-yl)benzimidazoles [9].

Thietane 1,1-dioxide ring can be removed by treatment with sodium alkoxide in the corrresponding alcohol (Scheme 6). Presumably, the reaction is favored by strong electron-withdrawing properties of the sulfonyl group. The products of this reaction are 3-alkoxy-λ^6-thietane 1,1-dioxide **IVa** or **IVb** and the corresponding heterocycle sodium salt. The latter is converted into NH-heterocycle **Ia** or **Id**–**Ii** by acidification of its aqueous solution to pH 3–4.

Scheme 6.



IV, R = Et (**a**), *i*-Pr (**b**).

Thus the thietane ring can be readily introduced into molecules of NH heterocycles, ensures their further modification, and can be readily removed, i.e., it can be used as protecting group.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer from samples dispersed in mineral oil. The ^1H and ^{13}C NMR spectra were measured on a Bruker AM-300 instrument at 300 and 75 MHz, respectively. The chemical shifts were determined relative to the corresponding sovent signals. The purity of the isolated compounds was checked by thin-layer chromatography on Silufol plates using hexane–ethanol (8:2) (**I**, **III**) and chloroform–ethanol (3:1) (**II**) as eluents; spots were visualized by treatment with iodine vapor.

Compound **IIa** was synthesized according to the procedure described in [5], and compounds **IIb**–**IId** were prepared as reported in [6].

3-Bromo-5-ethoxy-1-(thietan-3-yl)-1*H*-1,2,4-triazole (IIe). Metallic sodium, 0.12 g (5 mmol), was dissolved in 10 ml of anhydrous ethanol, a solution of 1.50 g (5 mmol) of compound **IIa** in 15 ml of anhydrous ethanol was added, and the mixture was heated for 1 h under reflux (on a water bath) and filtered while hot. The filtrate was cooled, and the precipitate was filtered off, washed with water, and recrystallized from hexane. Yield 75%, mp 120–121°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.45 t (3H, CH_3, J = 7.1 Hz), 3.20–3.32 m (2H, SCH_2), 3.95–4.08 m (2H, SCH_2), 5.39–5.54 m (1H, NCH), 4.47 q (2H, OCH_2, J = 7.1 Hz). Found, %: C 31.75; H 3.80; N 15.88. $C_7H_{10}BrN_3OS$. Calculated, %: C 31.83; H 3.82; N 15.91.

3-Bromo-5-isopropoxy-1-(thietan-3-yl)-1*H*-1,2,4-triazole (IIf) was synthesized in a similar way using isopropyl alcohol as solvent. The reaction mixture was concentrated to 1/6 of the original volume, and the precipitate was filtered off, washed with water, and recrystallized from hexane. Yield 51%, mp 64–66°C. Found, %: C 34.50; H 4.38; N 15.09. $C_8H_{12}BrN_3OS$. Calculated, %: C 34.54; H 4.35; N 15.11.

1-Alkyl-8-bromo-3-methyl-7-(thietan-3-yl)-1*H*-purine-2,6(3*H*,7*H*)-diones IIc and IIg (*general procedure***).** Potassium hydroxide, 0.34 g (6 mmol), was dissolved in 5 ml of water, 1.59 g (5 mmol) of 8-bromo-3-methyl-7-(thietan-3-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione (**IIb**), 50 ml of DMF, and 6 mmol of methyl iodide or propyl iodide were added, and the mixture was stirred for 4 h at room temperature. The precipitate was filtered off, washed with water, and recrystallized from ethanol.

8-Bromo-1,3-dimethyl-7-(thietan-3-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione (IIc). Yield 66%, mp 220–221°C. The product showed no depression of the melting point on mixing with an authentic sample prepared according to the procedure described in [6].

8-Bromo-3-methyl-1-propyl-7-(thietan-3-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione (IIg). Yield 84%, mp 155–156°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.98 t (3H, CH_3, J = 7.0 Hz), 1.63–1.78 m (2H, CH_2), 3.28–3.37 m (2H, SCH_2), 3.55 s (3H, 3-CH_3), 4.00–4.07 m (2H, NCH_2), 4.36–4.46 m (2H, SCH_2), 5.94–6.09 m (1H, NCH). Found, %: C 40.20; H 4.25; N 15.55. $C_{12}H_{15}BrN_4O_2S$. Calculated, %: C 40.12; H 4.21; N 15.60.

N*-(1,1-Dioxo-λ^6-thietan-3-yl)azoles IIIa and IIIe–IIIg (general procedure***).** Compound **IIa** or **IIe**–**IIg**, 5 mmol, was dissolved in 20 ml of glacial acetic acid on heating, 1.70 g (50 mmol) of 37% hydrogen peroxide was added in one portion, and the mixture was heated for 1 h under reflux. The mixture was cooled, and the precipitate was filtered off, washed with water, and dried.

3,5-Dibromo-1-(1,1-dioxo-λ^6-thietan-3-yl)-1*H*-1,2,4-triazole (IIIa). Yield 65%, mp 223–224°C (from *i*-BuOH). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 4.66–4.98 m (4H, $SCH)_2$), 5.55–5.75 m (1H, NCH). Found, %: C 18.09; H 1.58; N 12.67. $C_5H_5Br_2N_3O_2S$. Calculated, %: C 18.14; H 1.52; N 12.70.

3-Bromo-5-ethoxy-1-(1,1-dioxo-λ^6-thietan-3-yl)-1*H*-1,2,4-triazole (IIIe). Yield 85%, mp 166–167°C (from *i*-PrOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.46 t (3H, CH_3, J = 7.0 Hz), 4.42–4.58 m (4H, SCH_2, OCH_2), 4.67–4.83 m (2H, SCH_2), 4.98–5.15 m (1H, NCH). Found, %: C 28.29; H 3.45; N 14.15. $C_7H_{10}BrN_3O_3S$. Calculated, %: C 28.39; H 3.40; N 14.19.

3-Bromo-5-isopropoxy-1-(1,1-dioxo-λ^6-thietan-3-yl)-1*H*-1,2,4-triazole (IIIf). Yield 59%, mp 150–151.5°C (from *i*-PrOH). Found, %: C 30.76; H 3.96; N 14.10. $C_8H_{12}BrN_3O_3S$. Calculated, %: C 30.98; H 3.90; N 13.55.

8-Bromo-3-methyl-1-propyl-7-(1,1-dioxo-λ^6-thietan-3-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione (IIIg). Yield 56%, mp 252°C (decom., from ethanol). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.95 t (3H, CH_3, J = 7.42 Hz), 1.60–1.75 m (2H, CH_2), 3.55 s (3H, 3-CH_3), 3.96–4.05 m (2H, NCH_2), 4.33–4.44 m and 5.19–5.30 m (2H each, SCH_2), 5.54–5.69 m (1H, NCH). Found, %: C 36.94; H 3.90; N 14.38. $C_{12}H_{15}BrN_4O_4S$. Calculated, %: C 36.84; H 3.86; N 14.32.

5-Benzylamino-3-bromo-1-(1,1-dioxo-λ^6-thietan-3-yl)-1*H*-1,2,4-triazole (IIIh). Benzylamine, 4.20 g (39 mmol), was added to a solution of 4.25 g (13 mmol) of compound **IIIa** in 50 ml of butanol, and the mixture was heated for 5 h under reflux. The mixture was evaporated under reduced pressure, the oily residue was ground with water, and the precipitate was filtered off, washed with water, and recrystallized from isopropyl alcohol. Yield 43%, mp 175–176°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.42 d (2H, NCH_2, J = 5.6 Hz), 4.52–4.74 m (4H, SCH_2), 4.70–4.90 m (1H, NH), 5.18–5.34 m (1H, NCH), 7.26–7.40 m (5H, C_6H_5), 7.58 t (1H, NH, J = 5.6 Hz). Found, %: C 40.29; H 3.76; N 15.70. $C_{12}H_{13}BrN_4O_2S$. Calculated, %: C 40.35; H 3.67; N 15.68.

3-Bromo-1-(1,1-dioxo-λ^6-thietan-3-yl)-5-piperidino-1*H*-1,2,4-triazole (IIIi). Piperidine, 4.25 g

(50 mmol), was added to a solution of 3.31 g (10 mmol) of compound **IIIa** in 80 ml of butanol, and the mixture was heated for 3 h under reflux. The mixture was cooled, and the precipitate was filtered off, washed with water, and recrystallized from isopropyl alcohol. Yield 68%, mp 224–226°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.50–1.90 m (6H, CH_2), 2.95–3.22 m (4H, NCH_2), 4.40–4.68 m and 4.70–4.90 m (2H each, SCH_2), 4.92–5.15 m (1H, NCH). Found, %: C 35.70; H 4.60; N 16.64. $C_{10}H_{15}BrN_4O_2S$. Calculated, %: C 35.83; H 4.51, N 16.71.

NH-Heterocycles Ia and Id–Ii and 3-alkoxy-λ^6-thietane 1,1-dioxides IVa and IVb (*general procedure***).** A solution of 0.11 g (5 mmol) of metallic sodium and 5 mmol of the corresponding N-(dioxothietanyl)-substituted heterocyclic compound in 20 ml of ethanol (*a*) or isopropyl alcohol (*b*) was heated for 30 min under reflux. The mixture was evaporated under reduced pressure, and the oily residue was washed with 45 ml benzene. The undissolved material was dissolved in water, the solution was acidified to pH 3–4 with dilute acetic or hydrochloric acid, and the precipitate was filtered off and washed with water to isolate compound **Ia** or **Id**–**Ii**. The benzene solution was evaporated, and the residue was dried and purified by reprecipitation from acetone with hexane. We thus isolated compound **IVa** or **IVb**.

3,5-Dibromo-1*H*-1,2,4-triazole (Ia). Yield 75% (*a*), mp 210–212°C (from water). The product showed no depression of the melting point on mixing with an authentic sample prepared by bromination of 1,2,4-triazole.

2-Chlorobenzimidazole (Id). Yield 80% (*a*), mp 180–181°C (from aqueous ethanol). IR spectrum, ν, cm^{-1}: 2800–3100 (NH); 1548, 1724 (C=C, C=N). Found, %: C 55.10; H 3.30; N 18.36. $C_7H_5ClN_2$. Calculated, %: C 55.14; H 3.28; N 18.30.

3-Bromo-5-ethoxy-1*H*-1,2,4-triazole (Ie). Yield 59% (*a*), mp 96–98°C (from ethanol–hexane). Found, %: C 24.96; H 3.09; N 21.95. $C_4H_6BrN_3O$. Calculated, %: C 25.02; H 3.15; N 21.88.

3-Bromo-5-isopropoxy-1*H*-1,2,4-triazole (If). Yield 45% (*a*), mp 68–70°C (from ethanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.30 t (6H, CH_3, J = 6.17 Hz), 4.90 m (1H, OCH, J = 6.17 Hz). Found, %: C 29.80; H 3.56; N 19.87. $C_5H_8BrN_3O$. Calculated, %: C 29.15; H 3.91; N 20.39.

8-Bromo-1-methyl-3-propyl-1*H*-purine-2,6(3*H*,7*H*)-dione (Ig). Yield 84% (*b*), mp 233–235°C (decomp., from ethanol). Found, %: C 37.70; H 3.77; N 19.34. $C_9H_{11}BrN_4O_2$. Calculated, %: C 37.65; H 3.86; N 19.51.

5-Benzylamino-3-bromo-1*H*-1,2,4-triazole (Ih). Yield 88% (*a*), mp 210.5–212°C (from *i*-PrOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.32 d (2H, NCH_2, J = 6.4 Hz), 7.21–7.36 m (5H, C_6H_5), 7.43 t (1H, NH, J = 5.7 Hz). Found, %: C 42.58; H 3.67; N 22.31. $C_9H_9BrN_4$. Calculated, %: C 42.71; H 3.58; N 22.14.

3-Bromo-5-piperidino-1*H*-1,2,4-triazole (Ii). Yield 84% (*a*), mp 216–218°C (from water). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.55–2.00 m (6H, CH_2), 3.10–3.70 m (4H, NCH_2), 11.33 br.s (1H, NH). Found, %: C 36.29; H 4.69; N 24.30. $C_7H_{11}BrN_4$. Calculated, %: C 36.38; H 4.80; N 24.24.

3-Ethoxy-λ^6-thietane 1,1-dioxide (VIa). Yield 63%, mp 48–49°C. IR spectrum, ν, cm^{-1}: 1143, 1320 (SO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.20 t (3H, CH_3, J = 6.90 Hz), 3.45 q (2H, CH_2O, J = 6.90 Hz), 4.00–4.20 m (2H, SCH_2), 4.22–4.42 m (3H, SCH_2, OCH). Found, %: C 39.89; H 6.60; S 21.40. Calculated, %: C 39.95; H 6.66; S 21.30.

3-Isopropoxy-λ^6-thietane 1,1-dioxide (VIb). Yield 94%, mp 50–51°C. IR spectrum, ν, cm^{-1}: 1144, 1320 (SO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.18 d (6H, CH_3, J = 6.13 Hz), 3.61 m (1H, CHO, J = 6.12 Hz), 4.04–4.15 m (2H, SCH_2), 4.26–4.48 m (3H, SCH_2, OCH). Found, %: C 43.82; H 7.38; S 19.55. Calculated, %: C 43.90; H 7.32; S 19.51.

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