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Thietanyl Protection in the Synthesis of 1-Alkyl-8-amino-3-methyl-3,7-dihydro-1*H*-purine-2,6-diones

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Abstract—1-Alkyl-8-bromo-3-methyl-7-(1,1-dioxo-1λ^6-thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-diones reacted with amines to give the corresponding 1-alkyl-8-amino-3-methyl-7-(1,1-dioxo-1λ^6-thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-diones which were treated with sodium alkoxide to remove thietanyl protecting group with formation of 1-alkyl-8-amino-3-methyl-3,7-dihydro-1*H*-purine-2,6-diones possessing no substituent on N^7.

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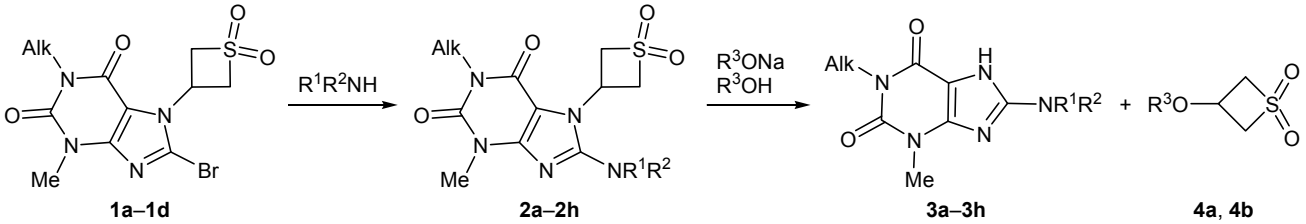
We previously described [1] the use of thietanyl protecting group in the synthesis of 7-unsubstituted 1-alkyl-8-bromo-3-methyl-3,7-dihydro-1*H*-purine-2,6-diones. In this work we followed an analogous approach to synthesize 1-alkyl-8-amino-3-methyl-3,7-dihydro-1*H*-purine-2,6-diones having no substituent on N^7. These compounds are difficultly accessible since direct alkylation of N^1 in 8-substituted 3-methyl-3,7-dihydro-1*H*-purine-2,6-diones is impossible due to higher reactivity of N^7 [2]. Moreover, 7-unsubstituted 1-alkyl-8-halo-3-methyl-3,7-dihydro-1*H*-purine-2,6-diones react with amines only under harsh conditions (under pressure or using the amine as reaction medium) [3]. Both these difficulties could be overcome by blocking the 7-position with a thietanyl protecting group.

Initial 1-alkyl-8-bromo-3-methyl-7-(1,1-dioxo-1λ^6-thietan-3-yl)-3,7-dihydro-1*H*-purine-2,6-diones **1a**–**1d** were synthesized as described in [1] via introduction of a thietanyl protecting group, alkylation of N^1, and oxidation of the thietane ring to thietane 1,1-dioxide. The reactions of **1a**–**1d** with amines were carried out by heating the reactants in boiling ethanol or DMF for 1–5 h. The corresponding 8-amino derivatives **2a**–**2h** were formed in 76–91% yield (Scheme 1).

The ^{1}H NMR spectra of **2a**–**2h** contained signals from protons in the alkyl substituents on N^1 and N^3, multiplet signals typical of thietane 1,1-dioxide ring, and signal of the corresponding amine residues in the 8-position. For example, compound **2c** displayed multiplets at δ 3.15–3.23 and 3.83–3.91 ppm due to CH_2NCH_2 and CH_2OCH_2 protons in the morpholine fragment. In the IR spectra of **2a**–**2h** we observed strong absorption bands due to stretching vibrations of sulfonyl group at 1133–1148 and 1309–1321 cm^{-1}.

The thietane protection was removed by treatment of **2a**–**2h** with sodium ethoxide or isopropoxide in the corresponding alcohol (30 min under reflux). 1-Alkyl-8-amino-3-methyl-3,7-dihydro-1*H*-purine-2,6-diones **3a**–**3h** were thus isolated in 59–98% yield, and the

Scheme 1.



1, Alk = Et (**a**), Pr (**b**), Bu (**c**), C_5H_{11} (**d**); **2**, **3**, Alk = Et, R^1 = H, R^2 = $PhCH_2$ (**a**); Alk = Pr, R^1R^2N = piperidin-1-yl (**b**), morpholin-4-yl (**c**), azepan-1-yl (**d**); Alk = Bu, R^1R^2N = piperidin-1-yl (**e**), morpholin-4-yl (**f**); Alk = C_5H_{11}, piperidin-1-yl (**g**), morpholin-4-yl (**h**); **4**, R^3 = Et (**a**), *i*-Pr (**b**).

yield of the other product, 3-alkoxy-1λ^6-thietane 1,1-dioxide **4a** or **4b** ranged from 84 to 94%. The properties of the latter were consistent with published data [4].

The ^{1}H NMR spectra of **3a**–**3h** showed signals belonging to alkyl substituents on N^1 and N^3 and amine residues on C^8 and a singlet at δ 11.15–11.88 ppm due to N^7H, while no signals assignable to thietane 1,1-dioxide ring were present. The N^7–H stretching vibration band was observed in the region 3000–3300 cm^{-1} of the IR spectra of **3a**–**3h**.

Thus, thietanyl protection of N^7 ensures successful synthesis of difficultly accessible 1-alkyl-8-amino-3-methyl-3,7-dihydro-1*H*-purine-2,6-diones having no substituent on N^7.

EXPERIMENTAL

The IR spectra were recorded in KBr on an Infralyum FT-02 spectrometer. The ^{1}H NMR spectra were measured on Bruker AM-300 (**2a**, **2c**–**2h**) and Bruker AM-500 spectrometers (**2b**) at 300 and 500 MHz respectively, using the residual proton signal of the deuterated solvent as reference. The purity of the isolated compounds was checked by TLC on Silufol plates (butan-1-ol–acetic acid–water, 4:1:2; development with iodine vapor).

Compounds **1a**, **1c**, **1d** [1], **1b**, **4a**, and **4b** [4] were synthesized according to known methods.

8-(Benzylamino)-7-(1,1-dioxo-1λ^6-thietan-3-yl)-1-ethyl-3-methyl-3,7-dihydro-1*H*-purine-2,6-dione (2a). Benzylamine, 0.96 g (9 mmol), was added to a solution of 1.13 g (3 mmol) of compound **1a** in 25 mL of DMF, and the mixture was heated for 1 h under reflux. The mixture was cooled and diluted with 50 mL of water, and the precipitate was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 1.10 g (91%), mp 232–234°C. IR spectrum, ν, cm^{-1}: 1690, 1646, 1613 (C=C, C=N, C=O), 1133, 1311 (SO_2). ^{1}H NMR spectrum, δ, ppm: 1.22 t (3H, CH_3, J = 7.0 Hz), 3.52 s (3H, 3-CH_3), 4.05 q (2H, C**H**$_2$CH$_3$, J = 7.0 Hz), 4.46–4.56 m (2H, SCH_2), 4.67 d (2H, PhC**H**$_2$, J = 5.1 Hz), 4.84–4.94 m (CH_2S), 5.69–5.82 m (1H, 7-CH), 6.00 t (1H, NH, J = 5.1 Hz), 7.27–7.45 m (5H, C_6H_5). Found, %: C 53.79; H 5.47; N 17.54. $C_{18}H_{21}N_5O_4S$. Calculated, %: C 53.59; H 5.25; N 17.36.

7-(1,1-Dioxo-1λ^6-thietan-3-yl)-3-methyl-8-(piperidin-1-yl)-1-propyl-3,7-dihydro-1*H*-purine-2,6-dione (2b). Piperidine, 1.02 g (12 mmol), was added to a solution of 1.56 g (4 mmol) of compound **1b** in 35 mL of ethanol, and the mixture was heated for 5 h under reflux. The mixture was cooled, and the precipitate was filtered off, washed with water, and dried. Yield 1.20 g (76%), mp 204–205°C (from EtOH). IR spectrum, ν, cm^{-1}: 1703, 1643, 1604, (C=C, C=N, C=O), 1319, 1134 (SO_2). ^{1}H NMR spectrum, δ, ppm: 0.94 t (3H, CH_3, J = 7.4 Hz), 1.62–1.77 m [8H, CH_2, $(CH_2)_3$], 3.12–3.16 m [4H, $N(CH_2)_2$], 3.52 s (3H, 3-CH_3), 3.97–4.01 m (2H, 1-CH_2), 4.26–4.31 m (2H, SCH_2), 5.07–5.22 m (3H, SCH_2, 7-CH]. Found, %: C 51.49; H 6.47; N 17.74. $C_{17}H_{25}N_5O_4S$. Calculated, %: C 51.63; H 6.37; N 17.71.

Compounds **2c**–**2h** were synthesized in a similar way.

7-(1,1-Dioxo-1λ^6-thietan-3-yl)-3-methyl-8-(morpholin-4-yl)-1-propyl-3,7-dihydro-1*H*-purine-2,6-dione (2c). Yield 82%, mp 234–236°C (from EtOH). IR spectrum, ν, cm^{-1}: 1710, 1691, 1667, 1614 (C=C, C=N, C=O), 1139, 1317 (SO_2). ^{1}H NMR spectrum, δ, ppm: 0.94 t (3H, CH_3, J = 7.4 Hz), 1.59–1.74 m (2H, CH_2), 3.15–3.23 m [4H, $N(CH_2)_2$], 3.53 s (3H, 3-CH_3), 3.83–3.91 m [4H, $O(CH_2)_2$], 3.96–4.05 m (2H, 1-CH_2), 4.25–4.37 m (2H, SCH_2), 5.12–5.28 m (3H, SCH_2, 7-CH). Found, %: C 48.68; H 5.91; N 17.40. $C_{16}H_{23}N_5O_5S$. Calculated, %: C 48.35; H 5.83; N 17.62.

8-(Azepan-1-yl)-7-(1,1-dioxo-1λ^6-thietan-3-yl)-3-methyl-1-propyl-3,7-dihydro-1*H*-purine-2,6-dione (2d). Yield 77%, mp 199–201°C (from EtOH). IR spectrum, ν, cm^{-1}: 1695, 1647, 1605 (C=C, C=N, C=O), 1321, 1135 (SO_2). ^{1}H NMR spectrum, δ, ppm: 0.95 t (3H, CH_3, J = 7.4 Hz), 1.61–1.92 m [10H, CH_2, $(CH_2)_4$], 3.42–3.48 m [4H, $N(CH_2)_2$], 3.51 s (3H, 3-CH_3), 3.95–4.03 m (2H, 1-CH_2), 4.18–4.28 m (2H, SCH_2), 4.98–5.12 m (1H, 7-CH), 5.16–5.26 m (2H, SCH_2). Found, %: C 52.69; H 6.37; N 17.24. $C_{18}H_{27}N_5O_4S$. Calculated, %: C 52.79; H 6.65; N 17.10.

1-Butyl-7-(1,1-dioxo-1λ^6-thietan-3-yl)-3-methyl-8-(piperidin-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2e) was synthesized from compound **1c**. Yield 78%, mp 191–193°C (from EtOH). IR spectrum, ν, cm^{-1}: 1694, 1655, 1611 (C=C, C=N, C=O), 1309, 1133 (SO_2). ^{1}H NMR spectrum, δ, ppm: 0.95 t (3H, CH_3, J = 7.3 Hz), 1.32–1.46 m (2H, CH_2), 1.57–1.81 m [8H, CH_2, $(CH_2)_3$], 3.11–3.19 m [4H, $N(CH_2)_2$], 3.53 s (3H, 3-CH_3), 4.00–4.08 m (2H, 1-CH_2), 4.25–4.35 m (2H, SCH_2), 5.06–5.26 m (3H, SCH_2, 7-CH). Found, %: C 52.91; H 6.68; N 17.32. $C_{18}H_{27}N_5O_4S$. Calculated, %: C 52.79; H 6.65; N 17.10.

1-Butyl-7-(1,1-dioxo-1λ^6-thietan-3-yl)-3-methyl-8-(morpholin-4-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2f) was synthesized from compound **1c**. Yield 90%, mp 203–205°C (from EtOH). IR spectrum, ν, cm^{-1}: 1699, 1662, 1613 (C=C, C=N, C=O), 1320, 1138 (SO_2). ^{1}H NMR spectrum, δ, ppm: 0.92 t (3H, CH_3, J = 7.3 Hz), 1.29–1.42 m (2H, CH_2), 1.55–1.66 m (2H, CH_2), 3.15–3.24 m [4H, $N(CH_2)_2$], 3.52 s (3H, 3-CH_3), 3.83–3.91 m [4H, $O(CH_2)_2$], 3.97–4.06 m (2H, 1-CH_2), 4.25–4.39 m (2H, SCH_2), 5.12–5.27 m (3H, SCH_2, 7-CH). Found, %: C 49.82; H 6.29; N 17.10. $C_{17}H_{25}N_5O_5S$. Calculated, %: C 49.62; H 6.12; N 17.02.

7-(1,1-Dioxo-1λ^6-thietan-3-yl)-3-methyl-1-pentyl-8-(piperidin-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2g) was synthesized from compound **1d**. Yield 85%, mp 177–179°C (from EtOH). IR spectrum, ν, cm^{-1}: 1699, 1655, 1615 (C=C, C=N, C=O), 1317, 1148 (SO_2). ^{1}H NMR spectrum, δ, ppm: 0.90 t (3H, CH_3, J = 6.3 Hz), 1.28–1.40 m [4H, $(CH_2)_2$], 1.57–1.81 m [8H, CH_2, $(CH_2)_3$], 3.09–3.18 m [4H, $N(CH_2)_2$], 3.53 s (3H, 3-CH_3), 3.97–4.06 m (2H, 1-CH_2), 4.24–4.35 m (2H, SCH_2), 5.07–5.26 m (3H, SCH_2, 7-CH). Found, %: C 53.97; H 6.78; N 16.38. $C_{19}H_{29}N_5O_4S$. Calculated, %: C 53.88; H 6.90; N 16.54.

7-(1,1-Dioxo-1λ^6-thietan-3-yl)-3-methyl-8-(morpholin-4-yl)-1-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (2h) was synthesized from compound **1d**. Yield 80%, mp 163–165°C (from EtOH). IR spectrum, ν, cm^{-1}: 1698, 1655, 1610 (C=C, C=N, C=O), 1313, 1142 (SO_2). ^{1}H NMR spectrum, δ, ppm: 0.89 t (3H, CH_3, J = 6.4 Hz), 1.18–1.40 m [4H, $(CH_2)_2$], 1.57–1.69 m (2H, CH_2), 3.15–3.23 m [4H, $N(CH_2)_2$], 3.53 s (3H, 3-CH_3), 3.83–3.91 m [4H, $O(CH_2)_2$], 3.97–4.06 m (2H, 1-CH_2), 4.24–4.39 m (2H, SCH_2), 5.13–5.28 m (3H, SCH_2, 7-CH). Found, %: C 51.02; H 6.29; N 16.39. $C_{18}H_{27}N_5O_5S$. Calculated, %: C 50.81; H 6.40; N 16.46.

1-Alkyl-8-amino-3-methyl-3,7-dihydro-1*H*-purine-2,6-diones 3a–3h and 3-alkoxy-1λ^6-thietane 1,1-dioxides 4a and 4b (*general procedure*). Metallic sodium, 0.14 g (6 mmol), was dissolved in 25 mL of ethanol or propan-2-ol, 5 mmol of compound **2b**, **2c**, or **2e**–**2h** (EtOH) or **2a** or **2d** (*i*-PrOH) was added, and the mixture was heated for 30 min under reflux. The mixture was evaporated under reduced pressure, the residue was dissolved in 15 mL of water, and the solution was extracted with benzene (3×15 mL). The aqueous phase was adjusted to pH 3 by adding 8% aqueous HCl, and the precipitate (compound **3a**–**3h**) was filtered off, washed with water, and dried. The benzene extract was evaporated, and the residue (compound **4a** or **4b**) was dried.

8-(Benzylamino)-1-ethyl-3-methyl-3,7-dihydro-1*H*-purine-2,6-dione (3a). Yield 72%, mp 233–235°C (from EtOH). IR spectrum, ν, cm^{-1}: 3400–3000 (NH), 1698, 1655, 1629 (C=C, C=N, C=O). ^{1}H NMR spectrum, δ, ppm: 1.10 t (3H, CH_3, J = 7.0 Hz), 3.53 s (3H, 3-CH_3), 3.94 q (2H, 1-CH_2, J = 7.0 Hz), 4.70 d (2H, CH_2, J = 5.9 Hz), 5.24 t (1H, 8-NH, J = 5.9 Hz), 7.18–7.37 m (5H, C_6H_5), 11.88 s (1H, 7-H). Found, %: C 59.89; H 5.57; N 23.57. $C_{15}H_{17}N_5O_2$. Calculated, %: C 60.19; H 5.72; N 23.40.

3-Methyl-8-(piperidin-1-yl)-1-propyl-3,7-dihydro-1*H*-purine-2,6-dione (3b). Yield 59%, mp 261–263°C (from EtOH). IR spectrum, ν, cm^{-1}: 3300–3000 (NH), 1699, 1653, 1615 (C=C, C=N, C=O). ^{1}H NMR spectrum, δ, ppm: 0.94 t (3H, CH_3, J = 7.4 Hz), 1.62–1.74 m [8H, CH_2, $(CH_2)_3$], 3.54 s (3H, 3-CH_3), 3.61–3.69 br.s [4H, $N(CH_2)_2$], 3.89–3.98 m (2H, 1-CH_2), 11.46 s (1H, 7-H). Found, %: C 57.52; H 7.47; N 23.88. $C_{14}H_{21}N_5O_2$. Calculated, %: C 57.71; H 7.27; N 24.04.

3-Methyl-8-(morpholin-4-yl)-1-propyl-3,7-dihydro-1*H*-purine-2,6-dione (3c). Yield 63%, mp 317–319°C (from EtOH. IR spectrum, ν, cm^{-1}: 3300–3050 (NH), 1703, 1656, 1627 (C=C, C=N, C=O). ^{1}H NMR spectrum, δ, ppm: 0.96 t (3H, CH_3, J = 7.4 Hz), 1.60–1.74 m (2H, CH_2), 3.55 s (3H, 3-CH_3), 3.67–3.76 m [4H, $N(CH_2)_2$], 3.78–3.87 m [4H, $O(CH_2)_2$], 3.88–3.96 m (2H, 1-CH_2), 11.68 s (1H, 7-H). Found, %: C 53.28; H 6.29; N 23.72. $C_{13}H_{19}N_5O_3$. Calculated, %: C 53.23; H 6.53; N 23.88.

8-(Azepan-1-yl)-3-methyl-1-propyl-3,7-dihydro-1*H*-purine-2,6-dione (3d). Yield 67%, mp 243–244°C (from EtOH). IR spectrum, ν, cm^{-1}: 3300–3050 (NH), 1705, 1663, 1624 (C=C, C=N, C=O). ^{1}H NMR spectrum, δ, ppm: 0.94 t (3H, CH_3, J = 7.4 Hz), 1.52–1.88 m [10H, CH_2, $(CH_2)_4$], 3.65–3.76 m [4H, $N(CH_2)_2$], 3.55 s (3H, 3-CH_3), 3.88–3.97 m (2H, 1-CH_2), 11.15 s (1H, 7-H). Found, %: C 59.29; H 7.47; N 23.04. $C_{15}H_{23}N_5O_2$. Calculated, %: C 59.00; H 7.59; N 22.93.

1-Butyl-3-methyl-8-(piperidin-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (3e). Yield 85%, mp 231–233°C (from EtOH). IR spectrum, ν, cm^{-1}: 3300–3050 (NH), 1701, 1653, 1622 (C=C, C=N, C=O). ^{1}H NMR spectrum, δ, ppm: 0.94 t (3H, CH_3, J = 7.3 Hz), 1.29–1.43 m (2H, CH_2), 1.57–1.72 m [8H, CH_2, $(CH_2)_3$], 3.55 s (3H, 3-CH_3), 3.61–3.68 br.s [4H, $N(CH_2)_2$], 3.94–4.02 m (2H, 1-CH_2), 11.43 s (1H, 7-H). Found, %: C 59.22; H 7.73; N 22.84. $C_{15}H_{23}N_5O_2$. Calculated, %: C 59.00; H 7.59; N 22.93.

1-Butyl-3-methyl-8-(morpholin-4-yl)-3,7-dihydro-1*H*-purine-2,6-dione (3f). Yield 98%, mp 263–265°C (from EtOH). IR spectrum, ν, cm^{-1}: 3230–3050 (NH), 1703, 1651, 1620 (C=C, C=N, C=O). ^{1}H NMR spectrum, δ, ppm: 0.95 t (3H, CH_3, J = 7.3 Hz), 1.29–1.43 m (2H, CH_2), 1.54–1.68 m (2H, CH_2), 3.55 s (3H, 3-CH_3), 3.66–3.75 m [4H, N(CH_2)$_2$], 3.77–3.86 m [4H, O(CH_2)$_2$], 3.89–3.98 m (2H, 1-CH_2), 11.70 s (1H, 7-H). Found, %: C 54.82; H 6.69; N 22.72. $C_{14}H_{21}N_5O_3$. Calculated, %: C 54.71; H 6.89; N 22.79.

3-Methyl-1-pentyl-8-(piperidin-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (3g). Yield 85%, mp 218–219°C (from EtOH). IR spectrum, ν, cm^{-1}: 3300–3100 (NH), 1700, 1656, 1624 (C=C, C=N, C=O). ^{1}H NMR spectrum, δ, ppm: 0.90 t (3H, CH_3, J = 6.4 Hz), 1.25–1.40 m [4H, (CH_2)$_2$], 1.58–1.75 br.s [8H, CH_2, (CH_2)$_3$], 3.54 s (3H, 3-CH_3), 3.60–3.70 br.s [4H, N(CH_2)$_2$], 3.92–4.01 m (2H, 1-CH_2), 11.39 s (1H, 7-H). Found, %: C 60.27; H 7.83; N 22.14. $C_{16}H_{25}N_5O_2$. Calculated, %: C 60.17; H 7.89; N 21.93.

3-Methyl-8-(morpholin-4-yl)-1-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (3h). Yield 86%, mp 243–245°C (from EtOH). IR spectrum, ν, cm^{-1}: 3300–3050 (NH), 1706, 1650, 1624 (C=C, C=N, C=O). ^{1}H NMR spectrum, δ, ppm: 0.90 t (3H, CH_3, J = 6.6 Hz), 1.24–1.43 m [4H, (CH_2)$_2$], 1.57–1.69 m (2H, CH_2), 3.55 s (3H, 3-CH_3), 3.67–3.76 m [4H, N(CH_2)$_2$], 3.78–3.87 m [4H, O(CH_2)$_2$], 3.89–3.98 m (2H, 1-CH_2), 11.66 s (1H, 7-H). Found, %: C 56.04; H 6.99; N 22.02. $C_{15}H_{23}N_5O_3$. Calculated, %: C 56.06; H 7.21; N 21.79.

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