Reaction of hydrazine and hydroxylamine derivatives with pyrimidinoacetic acid esters and lactones

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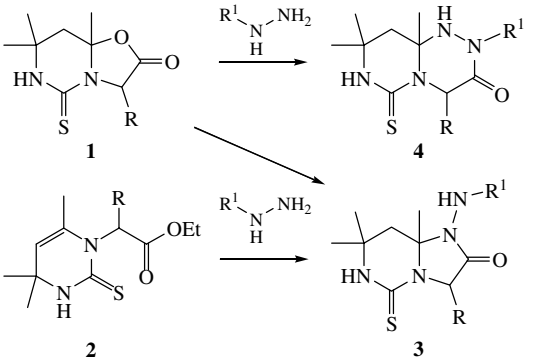
The reaction of hydrazine derivatives with the esters and lactones of pyrimidinoacetic acid gives new five- and six-membered bicyclic heterocyclic systems.

The synthesis and properties of pyrimidinethione lactones have been studied by Zigeuner *et al.*[1] The anti-inflammatory and anti-tumour activity of bicyclic pyrimidinethione derivatives is well known.[2–5] α-Alkyl-substituted lactones **1** gave 1-aminohexahydroimidazo[1,2-*c*]pyrimidin-2-ones on heating in butanol with hydrazine hydrate.[6,7]

We obtained new bicyclic products **3**–**5** in a reaction of hydrazine and hydroxylamine derivatives with esters and lactones of pyrimidinoacetic acids. The yields and structures of the reaction products strongly depend on the nature of both substituent R in the lactone and substituent R^1 in hydrazine. The reaction with hydrazine hydrate in ethanol starts at room temperature; prolonged refluxing does not necessarily increase the yield of the target product, since prolonged heating results in destruction of the pyrimidine ring. Substituted hydrazines react with lactones and esters less efficiently, and we were able to isolate cyclic products **3e**–**g** only in the case of lactone **1a**.



1a R = H
1b R = Me
1c R = Ph
1d R = CH_2Ph
2a R = H
2b R = Me

3a R = R^1 = H
3b R = Me, R^1 = H
3c R = Ph, R^1 = H
3d R = CH_2Ph, R^1 = H
3e R = H, R^1 = Ph
3f R = H, R^1 = C_6H_4COOH
3g R = H, R^1 = $C(O)C_6H_4OMe$

4a R = R^1 = H
4b R = H, R^1 = Me

Scheme 1

We found that refluxing pyrimidinoacetates **2a**,**b** with hydrazine in ethanol results in corresponding 1-aminohexahydroimidazo[1,2-*c*]pyrimidin-2-ones **3a**,**b**.

The reaction is more complex for lactone **1a** (R = H), which also gives products **3e**–**f** on treatment with hydrazines [R^1 = Ph, C_6H_4COOH, $C(O)C_6H_4OMe$], whereas for R^1 = H, Me or Ac, condensation with hydrazine derivatives results in 8,8,9a-trimethyl-6-thioxohexahydro-4*H*-pyrimido[6,1-*c*][1,2,4]triazin-3(6*H*)-one **4a**.

The acetyl derivative was not isolated in the case of acetohydrazide since the acetyl fragment was eliminated during the synthesis, and compound **4a** was formed as the end product. Refluxing aromatic hydrazides with lactone **1a** in ethanol (4–8 h) results in a mixture of products that undergo complete cyclisation on refluxing in toluene (1–2 h) to give, *e.g.*, compound **3g**.

Both lactone **1a** and ester **2a** react with hydroxylamine to give product **5**. The structure of compound **5** was confirmed by ^{1}H NMR and IR spectroscopy (stretching vibrations of the OH group at 3373 cm^{-1})† and the HMBC spectrum.

No cyclic products were isolated for the other esters and lactones.

The structures of compounds **3** and **4** were determined using NMR spectroscopy. The ^{1}H NMR spectra of compounds **3a**–**d**

† IR spectra were measured on a Bruker IFS-88 spectrometer in the range 700–4000 cm^{-1} using suspensions in Vaseline oil.

NMR spectra were recorded on a Bruker DRX-500 instrument using solutions in [$^2H_6$]DMSO at 30 °C. Signals of residual protons of the solvent in ^{1}H NMR spectra (δ_H 2.50 ppm) or the signal of [$^2H_6$]DMSO in ^{13}C NMR spectra (δ_C 39.5 ppm) were used as references for chemical shift measurements. Two-dimensional spectra were recorded using standard techniques provided by Bruker. HMBC experiments were optimised for the coupling constant $J_{H,C}$ 8 Hz.

Starting compounds **1** and **2** were synthesised using the procedures reported previously.[1]

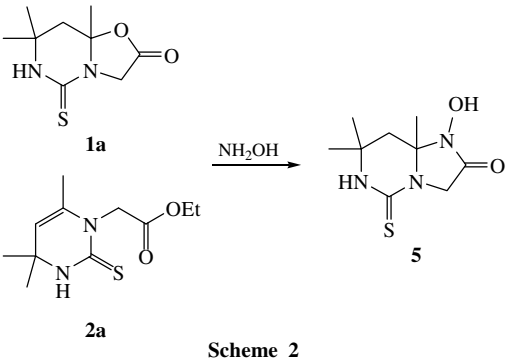
General procedure for the synthesis of compounds **3**–**5**. A suspension of a lactone or ester (0.01 mol), hydrazine (0.015 mol) (the salts were first neutralised with an equimolar amount of sodium hydrocarbonate) in ethanol (30 ml) was refluxed for 2–8 h with TLC monitoring and then diluted with water (50 ml). The precipitate formed was filtered off, washed with water and recrystallised from ethanol–DMF (3:1).

1-Amino-7,7,8a-trimethyl-5-thioxohexahydroimidazo[1,2-c]pyrimidin-2(3H)-one **3a**, yield 74%, mp 205–208 °C. IR (ν/cm^{-1}): 3321, 3285, 3237, 3184, 1710, 1643, 1530, 1274, 1206, 1194, 1090, 945. ^{1}H NMR, δ: 8.40 (s, 1H, NH), 4.65 (s, 2H, NH_2), 4.51 (d, 1H, *J* 18.0 Hz), 3.92 (d, 1H, *J* 18.0 Hz), 2.32 (d, 1H, 8-H, *J* 13.7 Hz), 1.73 (d, 1H, 8-H, *J* 13.7 Hz), 1.45 (s, 3H, 8a-Me), 1.32 (s, 3H, 7-Me), 1.26 (s, 3H, 7-Me). Found (%): C, 47.33; H, 7.10; N, 24.50; O, 7.05; S, 14.02. Calc. for $C_9H_{16}N_4OS$ (%): C, 47.35; H, 7.06; N, 24.54; O, 7.01; S, 14.04.

1-Amino-3,7,7,8a-tetramethyl-5-thioxohexahydroimidazo[1,2-c]pyrimidin-2(3H)-one **3b**: yield 71%, mp 216–218 °C. IR (ν/cm^{-1}): 3321, 3285, 3234, 3217, 3184, 1711, 1643, 1529, 1206, 1194, 1089, 944. ^{1}H NMR, δ: 8.49 (s, 1H, NH), 4.75 (s, 2H, NH_2), 4.55 (q, 1H, *J* 7.4 Hz), 2.30 (d, 1H, 8-H, *J* 13.7 Hz), 1.63 (d, 1H, 8-H, *J* 13.7 Hz), 1.52 (s, 3H, 8a-Me), 1.47 (d, 3H, 3-Me, *J* 7.4 Hz), 1.30 (s, 3H, 7-Me), 1.28 (s, 3H, 7-Me). Found (%): C, 49.54; H, 7.51; N, 23.10; O, 6.62; S, 13.23. Calc. for $C_{10}H_{18}N_4OS$ (%): C, 49.56; H, 7.49; N, 23.12; O, 6.60; S, 13.23.

1-Amino-7,7,8a-trimethyl-3-phenyl-5-thioxotetrahydroimidazo[1,2-c]-pyrimidin-2(3H)-one **3c**: yield 65%, mp 264–266 °C. ^{1}H NMR, δ: 8.75 (s, 1H, NH), 7.48 (d, 2H, Ph, *J* 8.0 Hz), 7.26 (t, 2H, Ph, *J* 8.0 Hz), 7.24 (t, 1H, Ph, *J* 8.0 Hz), 5.82 (s, 1H, 3-H), 4.81 (s, 2H, NH_2), 2.34 (d, 1H, 8-H, *J* 12.5 Hz), 1.78 (d, 1H, 8-H, *J* 12.5 Hz), 1.52 (s, 3H, 8a-Me), 1.31 (s, 3H, 7-Me), 1.27 (s, 3H, 7-Me). Found (%): C, 59.16; H, 6.64; N, 18.40; O, 5.27; S, 10.53. Calc. for $C_{15}H_{20}N_4OS$ (%): C, 59.18; H, 6.62; N, 18.41; O, 5.26; S, 10.53.

1-Amino-3-benzyl-7,7,8a-trimethyl-5-thioxohexahydroimidazo[1,2-c]-pyrimidin-2(3H)-one **3d**: yield 68%, mp 275–276 °C (decomp.). ^{1}H NMR, δ: 8.15 (s, 1H, NH), 7.30 (d, 2H, Ph, *J* 7.4 Hz), 7.22 (t, 2H, Ph, *J* 7.4 Hz), 7.14 (t, 1H, Ph, *J* 7.4 Hz), 4.65 (dd, 1H, 3-H, *J* 8.5 Hz, *J* 2.4 Hz), 4.32 (s, 2H, NH_2), 3.78 (dd, 1H, CH_2, *J* 8.5 Hz, *J* 13.4 Hz), 3.24 (dd, 1H, CH_2, *J* 2.4 Hz, *J* 13.4 Hz), 2.25 (d, 1H, 8-H, *J* 12.8 Hz), 1.62 (d, 1H, 8-H, *J* 12.8 Hz), 1.54 (s, 3H, 8a-Me), 1.31 (s, 3H, 7-Me), 1.27 (s, 3H, 7-Me). Found (%): C, 60.33; H, 6.99; N, 17.60; O, 5.02; S, 10.07. Calc. for $C_{16}H_{22}N_4OS$ (%): C, 60.35; H, 6.96; N, 17.59; O, 5.02; S, 10.07.



Scheme 2

7,7,8a-Trimethyl-1-phenylamino-5-thioxohexahydroimidazo[1,2-c]-pyrimidin-2-one **3e**: yield 68%, mp 278–280 °C (decomp.). IR (ν/cm^{-1}): 3256, 3147, 3092, 1714, 1600, 1530, 1281, 1151, 749. ^{1}H NMR, δ: 8.58 (s, 1H, NH), 8.21 (s, 1H, NH), 7.16 (d, 2H, Ph, J 8.0 Hz), 6.75 (m, 3H, Ph), 4.55 (d, 1H, 3-H, J 17.5 Hz), 4.08 (s, 2H, 3-H, J 17.5 Hz), 2.23 (d, 1H, 8-H, J 12.9 Hz), 1.95 (d, 1H, 8-H, J 12.9 Hz), 1.58 (s, 3H, 8a-Me), 1.31 (s, 3H, 7-Me), 1.27 (s, 3H, 7-Me). Found (%): C, 59.16; H, 6.64; N, 18.41; O, 5.26; S, 10.53. Calc. for $C_{15}H_{20}N_4OS$ (%): C, 59.18; H, 6.62; N, 18.41; O, 5.26; S, 10.53.

4-[7,7,8a-Trimethyl-2-oxo-5-thioxohexahydroimidazo[1,2-c]pyrimidin-1(5H)-yl]aminobenzoic acid **3f**: yield 68%, mp 282–286 °C (decomp.). IR (ν/cm^{-1}): 3612, 3222, 3127, 1724, 1708, 1607, 1526, 1175, 1095, 994, 777. ^{1}H NMR, δ: 12.3 (s, 1H, OH), 8.84 (s, 1H, NH), 8.58 (s, 1H, 6-NH), 7.76 (d, 2H, 2′-H, 6′-H, J 8.2 Hz), 6.88 (d, 2H, 3′-H, 5′-H, J 8.2 Hz), 4.60 (d, H, 3-H$_e$, J 15.6 Hz), 4.11 (d, H, 3-H$_a$, J 15.6 Hz), 4.6 (d, H, 3-H$_e$, J 15.6 Hz), 2.20 (d, H, 8-H$_e$, J 13.7 Hz), 2.04 (d, H, 8-H$_a$, J 13.7 Hz), 1.58 (s, 3H, 8a-Me), 1.29 (s, 3H, 7-Me$_e$), 1.26 (s, 3H, 7-Me$_a$). ^{13}C NMR, δ: 173.99 (C=S), 167.72 (COOH), 167.06 (C-2), 151.65 (C-4′), 130.81 (C-2′, C-6′), 121.23 (C-1′), 111.63 (C-3′, C-5′), 75.97 (C-8a), 50.82 (C-7), 49.03 (C-3), 42.75 (C-8), 32.27 (7-Me$_e$), 28.93 (7-Me$_a$), 23.39 (8a-Me). Found (%): C, 55.18; H, 5.76; N, 16.06; O, 13.79; S, 9.21. Calc. for $C_{16}H_{20}N_4O_3S$ (%): C, 55.16; H, 5.79; N, 16.08; O, 13.78; S, 9.20.

*4-Methoxy-*N*-(7,7,8a-trimethyl-2-oxo-5-thioxohexahydroimidazo[1,2-c]-pyrimidin-1-yl)benzamide* **3g**: yield 68%, mp 280–285 °C (decomp.). IR (ν/cm^{-1}): 3328, 3175, 1718, 1676, 1609, 1578, 1284, 1256, 1175, 1023. ^{1}H NMR, δ: 10.53 (s, 1H, N*H*Ac), 8.67 (s, 1H, 6-NH), 7.90 (d, 2H, 2′-H, 6′-H, J 9.1 Hz), 7.07 (d, 2H, 3′-H, 5′-H, J 9.1 Hz), 4.62 (d, H, 3-H$_e$, J 17.1 Hz), 4.16 (d, H, 3-H$_a$, J 17.1 Hz), 4.6 (d, H, 3-H$_e$, J 15.6 Hz), 3.84 (s, 3H, OMe), 2.29 (d, H, 8-H$_e$, J 13.4 Hz), 1.99 (d, H, 8-H$_a$, J 13.4 Hz), 1.57 (s, 3H, 8a-Me), 1.29 (s, 3H, 7-Me$_e$), 1.26 (s, 3H, 7-Me$_a$). Found (%): C, 56.32; H, 6.13; N, 15.45; O, 13.25; S, 8.85. Calc. for $C_{17}H_{22}N_4O_3S$ (%): C, 56.33; H, 6.12; N, 15.46; O, 13.24; S, 8.85.

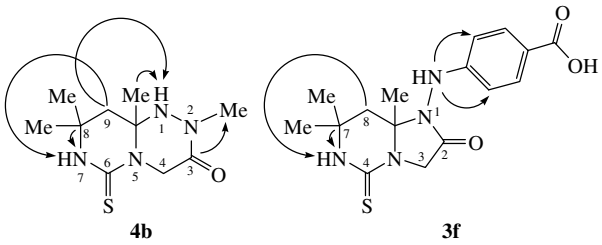
*8,8,9a-Trimethyl-6-thioxohexahydro-4*H*-pyrimido[6,1-c][1,2,4]triazin-3(6*H*)-one* **4a**: yield 64%, mp 262–265 °C (decomp.). IR (ν/cm^{-1}): 3225, 3178, 3070, 1676, 1531, 1279, 1195, 1165, 906. ^{1}H NMR, δ: 9.30 (s, 1H, 2-NH), 8.32 (s, 1H, 7-NH), 6.28 (s, 1H, 1-NH), 4.69 (d, 1H, 4-H$_a$, J 17.8 Hz), 4.11 (d, 1H, 4-H$_e$, J 17.8 Hz), 2.97 (s, 3H, NMe), 2.04 (d, 1H, 9-H$_a$, J 13.8 Hz), 1.72 (d, 1H, 9-H$_e$, J 13.8 Hz), 1.36 (s, 3H, 9a-Me), 1.28 (s, 3H, 8-Me), 1.22 (s, 3H, 8-Me). Found (%): C, 47.32; H, 7.12; N, 24.45; O, 7.10; S, 14.01. Calc. for $C_9H_{16}N_4OS$ (%): C, 47.35; H, 7.06; N, 24.54; O, 7.01; S, 14.04.

*2,8,8,9a-Tetramethyl-6-thioxohexahydro-2*H*-pyrimido[6,1-c][1,2,4]-triazin-3(4*H*)-one* **4b**: yield 44%, mp 252–255 °C (decomp.). IR (ν/cm^{-1}): 3276, 3183, 1650, 1512, 1278, 1191, 867. ^{1}H NMR, δ: 8.32 (s, 1H, 7-NH), 6.28 (s, 1H, 1-NH), 4.69 (d, 1H, 4-H$_a$, J 17.7 Hz), 4.11 (d, 1H, 4-H$_e$, J 17.7 Hz), 2.97 (s, 3H, NMe), 2.04 (d, 1H, 9-H$_a$, J 13.4 Hz), 1.72 (d, 1H, 9-H$_e$, J 13.4 Hz), 1.36 (s, 3H, 9a-Me), 1.28 (s, 3H, 8-Me), 1.22 (s, 3H, 8-Me). ^{13}C NMR, δ: 173.99 (C=S), 166.29 (C-3), 69.73 (C-9a), 49.85 (C-8), 49.07 (C-4), 43.37 (C-9), 36.17 (N-Me), 31.87 (9a-Me), 29.06 (8-Me$_a$), 21.56 (8-Me$_e$). Found (%): C, 49.53; H, 7.52; N, 23.10; O, 6.62; S, 13.21. Calc. for $C_{10}H_{18}N_4OS$ (%): C, 49.56; H, 7.49; N, 23.12; O, 6.60; S, 13.23.

*1-Hydroxy-7,7,8a-trimethyl-5-thioxohexahydroimidazo[1,2-c]pyrimidin-2(3*H*)-one* **5**: yield 71%, mp 243–245 °C. IR (ν/cm^{-1}): 3373, 3268, 1694, 1661, 1528, 1320, 1283, 1212, 1166, 1140, 1081. ^{1}H NMR, δ: 9.87 (s, 1H, OH), 8.39 (s, 1H, NH), 4.49 (d, 1H, 3-H, J 16.5 Hz), 3.90 (d, 1H, 3-H, J 16.5 Hz), 2.30 (d, 1H, 8-H, J 13.5 Hz), 1.79 (d, 1H, 8-H, J 13.5 Hz), 1.53 (s, 3H, 8a-Me), 1.38 (s, 3H, 7-Me), 1.31 (s, 3H, 7-Me). Found (%): C, 47.15; H, 6.58; N, 18.34; O, 13.95; S, 13.98. Calc. for $C_9H_{15}N_3O_2S$ (%): C, 47.14; H, 6.59; N, 18.33; O, 13.96; S, 13.98.

contain a typical signal of the NH_2 group in the region of δ 4.3–4.8; therefore, their structures should not be doubted. The spectrum of compound **4a** contains three different signals of the NH group that match the six-membered bicyclic structure. In the case of substituted hydrazines, ^{1}H NMR data are insufficient. A detailed study was carried out using two compounds with principally different structures, **3f** and **4b**, which were confirmed by two-dimensional (H–H) and (H–C) spectroscopy.

The HMBC spectrum of compound **3f** contains a correlation peak of interaction between aromatic carbon atoms C-3′/5′ with the N–H proton, which suggests that the N–H group is not located at the ring. The decisive feature for determining the structure of compound **4b** is the correlation interaction peak of the carbonyl carbon atom and the protons of the N–Me group.



Scheme 3 Main interactions in HMBC spectra of compounds **4b** and **3f**.

Based on the above data, it can be concluded that formation of the six-membered bicyclic system is possible in the condensation of lactone **1** with hydrazine hydrate and alkyl-substituted hydrazines. Five-membered bicycles are formed from esters of pyrimidinoacetic acids. Five- and six-membered rings are distinguished based on the carbonyl signal in IR spectroscopic data: it is short-wave (1676–1649 cm^{-1}) for six-membered rings and long-wave (1710–1694 cm^{-1}) for five-membered rings.

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