Synthesis of Isomeric Enamine Derivatives of Fused Cycloalkeno Thieno[2,3-d]pyrimidin-4(3H)-ones. Stereoelectronic Effect on the Regioselectivity

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Abstract: A regioselective synthesis of enamine and enamino derivatives of fused cycloalkeno thieno[2,3-d]pyrimidin-4(3H)-ones is reported. The enamine versus enamino product in the condensation reaction with N,N-dimethylformamide dimethylacetal (DMFDMA) was shown to depend on the conformation of the cycloalkeno ring fused to the pyrimidinone moiety. The ring conformation and the stereoelectronic effect of the amidine α-protons were studied by X-ray crystallography. In deuterium exchange experiments, the amidine-ketene–N,N-acetal tautomerism was shown to be prohibited with larger (n = 3–4) ring systems consequently yielding the enamino products.

Key words: regioselectivity, electrophilic additions, imines, ketones, tautomerism

In this study we report a stereoselective synthesis of enamine and enamino derivatives of fused cycloalkeno thieno[2,3-d]pyrimidin-4(3H)-ones. The reaction product and the regioselectivity in the condensation reaction with N,N-dimethylformamide dimethylacetal (DMFDMA) was shown to depend on the conformation of the cycloalkeno ring fused to the pyrimidinone moiety. These tetracyclic compounds are currently of interest in our studies on nonsteroidal 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) inhibitors.1

DMF dialkyl acetals2 are mostly known for their alkylation and formylation reactions, which proceed mainly via azaoxo-stabilized carbenium ions. Activated methyl and methylene groups, for example in carbonyl compounds and imines, can react with DMF acetals in a condensation reaction sometimes referred to as aminomethylation. We visualize the reaction as proceeding via an electrophilic attack of the carbencium ion to form a carbon–carbon bond and a subsequent elimination of respective alkanols to form enamines (Scheme 1). Alternatively, under truly basic conditions the reaction could proceed via the anion of the amidine. DMFDMA is often the reagent of choice owing to its low price and commercial availability.

The thermal condensation of DMFDMA with carbonyl compounds produces enamines, versatile building blocks for the synthesis of various nitrogen containing heterocycles,3 for example, pyrazoles,4 oxazoles,5 pyrimidines,6 pyridones,7 and pyroles.8 Enaminones have also been employed in the synthesis of Mannich bases, where the condensation of DMF acetals with ketones and esters followed by reduction with LiAlH4 is non-acidic and regioselective method.9 Imines are known to react with DMFDMA to produce 4-dimethylamino-2-azabutadiene type structures, which can be subsequently converted to azoles, thiazoles, or imidazoles.10

Activated methylene groups in heterocyclic compounds, for example, in 2-methylimidazoles,11 6-methyluracils,12 and 2-alkyl amides13 are also known to give the corresponding enamines in the reaction with DMF dialkyl acetals. Similarly activated arylmethyl groups can be converted into corresponding aldehydes by periodate cleavage of enamines.14

In a condensation reaction related to that with DMF dialkylacetals, Vilsmeier reagent (POCl3/DMF) has been reported to furnish C9 enamines from 6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones.15 This paper demonstrates the finely tuned regioselectivity of the thermal condensation of DMFDMA with fused tricyclic and tetracyclic cycloalkeno thieno[2,3-d]pyrimidin-4(3H)-ones possessing both amidine and carbonyl functionality. In addition, the synthesis and characterization of several thieno[2,3-d]pyrimidin-4(3H)-one derivatives are reported.

In connection with our 17β-HSD1 inhibition studies, cyclization of ethyl 2-amino-4,5,6,7-tetrahydrobenzenes
zo[b]thiophene-3-carboxylate (1) with N-methylacetamide or with five- to eight-membered lactams was carried out in the presence of POCl₃ to afford fused tricyclic and tetracyclic (di)cycloalkeno thiendo[2,3-α]pyrimidin-4(3H)-ones 2a–e in good yields. The subsequent oxidation of 2a–e with an excess of PCC/Celite afforded 3a–e as the only isolable products in reasonable yields (Scheme 2).

Scheme 2

The condensation reaction of 3a–c with four equivalents of DMFDMA in DMF proceeded in high yield and selectivity, producing the corresponding conjugated enamines 4a–c (Scheme 3). Interestingly, no reaction was observed when 3d and 3e, with seven- or eight-membered cycloalkeno rings fused to the pyrimidinone moiety, were exposed to the same reaction conditions. Under harsher conditions of elevated temperature and prolonged reaction time, the products formed instead were the corresponding enamines 5a and 5b (Scheme 3). With 3d and 3e no reaction at the amidine α-position could be observed. Best overall yield of 5a and purity of the crude product was obtained when toluene was used as the solvent.

To investigate possible factors underlying the remarkable regioselectivity, the degree of the required amidine-ketene–N,N-acetal tautomerism was studied. Ring size is known to affect the imine-enamine tautomerism in cyclic lactim ethers.¹⁶ The H/D isotope exchange at the amidine α-position was measured by refluxing compounds 2a–e in MeOD in the presence of a catalytic amount of triethylamine for two days. With 2a and 2c, approximately 75%, and with 2b 68% of the amidine α-protons were exchanged to deuteriums as calculated from the ¹H NMR spectra. Under the same reaction conditions, the amidine α-protons in 2d and 2e were not exchanged indicating that tautomerism does not operate in the compounds with a fused larger cycloalkeno ring. The X-ray crystal structures of 3b–e were resolved to determine possible conformational biases in the fused ring systems to explain the differences in the regioselectivity and in the amidine-ketene–N,N-acetal tautomerism (Table 1). For the amidine α-proton abstraction to occur and thus the condensation and deuteration reactions to proceed, the α-C–H bond must be able to adopt an orientation approximately parallel to the amidine bond p orbitals. In the crystal structures of 3b and a chloride salt of 3c the two amidine α-protons (Hₐ and Hₙ) are positioned out of the plane of the ring with respect to the amidine double bond with dihedral angles between 44–73° (Table 2), suggesting favorable p orbital interactions. In the tricyclic derivative 3a, the amidine α-methyl group rotates freely and hence the required conformation for the tautomerism should be obtained readily. In the crystal structures of 3d and 3e with larger fused cycloalkeno rings, the amidine α-proton deviations from 90° dihedral angle become much larger, leading to an unpropitious stereoelectronic effect of the α-C–H bonds thus prohibiting the amidine-ketene–N,N-acetal tautomerism which is crucial for the condensation reaction with DMFDMA (Figure 1). In these compounds, even at elevated temperatures, the carbonyl α-position was more activated than the amidine α-position, and enamino became the favored product.

The configuration of the double bond was E for both the enamine and enamimone compounds as determined by NOESY¹⁷ NMR experiments. For the tetracyclic 4b,c and 5a,b clear NOE was found between the vinylic proton and the N-methyl groups, but no correlation could be seen for the ring protons. Compound 4b was the only one in which the allylic trans coupling (J = 1.7 Hz) could be observed. According to ¹H NMR spectrum, the 2-(dimethylamino)
moiety in the tricyclic derivative 4a does not rotate freely and the compound had two rotamers at 27 °C temperature. A coalescence temperature (Tc) of 31 °C was determined for the two N-methyl resonances of compound 4a by variable temperature 500 MHz 1H NMR measurements. The difference in the separated N-methyl resonance frequencies δν at –15 °C was 134.8 Hz. An energy barrier ΔG of 60 kJ was estimated between the rotamers with the aid of the Tc and δν (Equation 1).

\[
\Delta G^\ddagger = RT_c \left[ 22.06 - \ln \left( \frac{T_c}{\delta \nu} \right) \right] \text{J mol}^{-1}
\]

\[
\Delta G^\ddagger = 60 \text{ kJ}
\]

Equation 1 Estimation of the energy barrier for the rotamers of 4a

Figure 1 The superimposed crystal structures of 3b (green) and 3d (orange) demonstrating the different conformational orientations of the amidine α-protons. The superimposition (RMSD = 0.021 Å) was made by using the thiophene ring as a template.

Table 1 Crystallographic Data for Compounds 3b–e

<table>
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<tr>
<th>Parameters</th>
<th>3b</th>
<th>3c HCl salt</th>
<th>3d</th>
<th>3e</th>
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<td>C13H12CIN2O2S</td>
<td>C14H16N2O2S</td>
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<td>Molecular weight</td>
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<td>310.79</td>
<td>288.36</td>
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<tr>
<td>Crystal system</td>
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<tr>
<td>T (K)</td>
<td>173(2)</td>
<td>173(2)</td>
<td>173(2)</td>
<td>173(2)</td>
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<td>Space group</td>
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<td>P 2/1/c</td>
<td>P 2/1/c</td>
<td>P 2/1/c</td>
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<tr>
<td>a (Å)</td>
<td>18.729(3)</td>
<td>9.283(2)</td>
<td>13.569</td>
<td>7.349(2)</td>
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<tr>
<td>b (Å)</td>
<td>18.729(3)</td>
<td>12.008(2)</td>
<td>7.266</td>
<td>9.884(2)</td>
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<tr>
<td>c (Å)</td>
<td>7.0070(10)</td>
<td>12.364(3)</td>
<td>17.507</td>
<td>19.726(4)</td>
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<td>90.24(3)</td>
<td>128.24</td>
<td>93.78(3)</td>
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<td>V (Å³)</td>
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<td>1378.2(5)</td>
<td>1355.6</td>
<td>1429.7(6)</td>
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<tr>
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<td>1.498</td>
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<td>F(000)</td>
<td>1112</td>
<td>648</td>
<td>608</td>
<td>640</td>
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<tr>
<td>μ (mm⁻¹)</td>
<td>0.262</td>
<td>0.431</td>
<td>0.242</td>
<td>0.233</td>
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<td>Crystal size (mm)</td>
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<td>0.3 × 0.04 × 0.04</td>
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<tr>
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<td>Independent reflections (Rint)</td>
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<td>2414 (0.1337)</td>
<td>2520 (0.0740)</td>
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<td>2144/0/181</td>
<td>2520/0/181</td>
<td>3285/18/217</td>
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<td>Full-matrix least-squares on F²</td>
<td>Full-matrix least-squares on F²</td>
<td>Full-matrix least-squares on F²</td>
<td>Full-matrix least-squares on F²</td>
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<tr>
<td>Goodness-of-fit on F²</td>
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<td>1.070</td>
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<td>0.0561, 0.1081</td>
<td>0.0676, 0.1601</td>
<td>0.0367, 0.0804</td>
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<tr>
<td>Minimum and maximum residual density (e/Å³)</td>
<td>–0.348 and 0.410</td>
<td>–0.537 and 0.413</td>
<td>–0.491 and 0.662</td>
<td>–0.250 and 0.256</td>
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In conclusion, we have shown that the regioselectivity in the reaction of DMFDMA with tricyclic and tetracyclic cycloalkeno thieno[2,3-d]pyrimidin-4(3H)-ones is controlled by stereoelectronic effects at the amidine α-site. The reaction product is the corresponding conjugated enamine when the amidine α-protons are forced to the amidine α-site close to 90°. Large deviation from the favorable constrained orientation of the amidine α-protons was prevented by H/D-exchange experiments in compounds with a seven- or eight-membered cycloalkeno ring fused to the pyrimidinone moiety under conditions mimicking the DMFDMA condensation.

The NMR spectra were measured with Varian Mercury 300 MHz (proton frequency) or Inova 500 MHz spectrometers at 27 °C. Variable temperature spectra were measured using 500 MHz instrument with 5 mm 1H(X) indirect detection probe incorporating z-gradient coil. NOESY experiments (CDCl3, 500 MHz): for 5a relaxation time 1 s, mixing time 0.4 s, number of increments 256, spectral width 5115 Hz, acquisition time 0.256 s, number of transients 16; and for 4b, as above except number of transients 64, number of increments 128. The melting points were measured with Büchi B-545 melting point apparatus and are corrected. The IR spectra were recorded with PerkinElmer Spectrum One FT-IR -spectrometer. The HRMS were measured with Bruker MicroToF-q(c) (ESI) on the positive mode using Agilent ESI Tunemix as a calibration solution. Crystal data were collected on a Nonius KappaCCD diffractometer. Silica gel and TLC plates of 0.040–0.063 mm were purchased from Merck. Crystal 1 was measured on a PerkinElmer FT-IR spectrometer. The IR spectra were recorded. HRMS (ESI): m/z calc'd for C12H15N2OS [M + H]+: 235.0900; found: 235.0900.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Bond angle (°)</th>
<th>Dihedral angle (°)</th>
<th>Product</th>
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<tr>
<td>3b</td>
<td>96.7</td>
<td>62.4</td>
<td>4b</td>
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<tr>
<td>3c</td>
<td>98.3</td>
<td>43.9</td>
<td>4c</td>
</tr>
<tr>
<td>3d</td>
<td>80.0</td>
<td>127.5</td>
<td>5a</td>
</tr>
<tr>
<td>3e</td>
<td>129.3</td>
<td>139.8</td>
<td>5b</td>
</tr>
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</table>

*The dihedral and bond angles measured from the crystal structures.

*The H/D percentage of exchange of the amidine α-protons after 2-day refluxing in MeOD with Et3N.

Compound 2a was synthesized as described above using N-methylacetamide as the starting material; yield: 85%; white crystals; mp 144.6–146.2 °C (EtOH).

Compound 2b was synthesized as described above using N-methylacetamide as the starting material; yield: 85%; white crystals; mp 144.6–146.2 °C (EtOH).


Yield: 90%; white crystals; mp 153.2–153.6 °C (EtOH) [Lit.\(^{20}\) mp 150–152 °C (EtOH), Lit.\(^{20b}\) mp 150–151 °C (CH\(_2\)Cl\(_2\)–hexane)].

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.16–1.88\) (m, 10 H), 2.75–2.77 (m, 2 H), 2.99–3.03 (m, 4 H), 4.33–4.37 (m, 2 H).

\(^1\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 22.4, 23.0, 25.22, 25.25, 25.6, 27.8, 29.6, 37.5, 42.1, 120.3, 131.6, 131.7, 158.6, 159.2, 161.8.

HRMS (ESI): \(m/z\) calcd for C\(_4\)H\(_8\)N\(_2\)O\(_5\)S [M + H]\(^+\): 275.0845; found: 275.0840.

2,3,8,9,10,11,12-Decahydro-14H-[1]benzothieno[2,3-d][pyrimidin-4(3H)]-ones

Yield: 54%; white crystals; mp 196.3–196.4 °C (MeOH) [Lit.\(^{21}\) mp 199–200 °C].

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 1.74\) (br s, 2 H), 1.78–1.82 (m, 4 H), 2.13–2.18 (m, 2 H), 2.57–2.60 (m, 2 H), 2.99–3.00 (m, 2 H), 3.19–3.21 (m, 2 H), 4.28–4.30 (m, 2 H).

\(^1\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 24.0, 25.0, 25.8, 27.6, 29.6, 37.8, 38.3, 42.5, 120.2, 132.2, 150.4, 158.9, 163.3, 168.0, 192.6.

HRMS (ESI): \(m/z\) calcd for C\(_6\)H\(_{14}\)N\(_2\)O\(_2\)S [M + H]\(^+\): 289.1005; found: 289.1007.

2,3,9,10,11,12-Hexahydro-8H-[1]benzothieno[2,3-d][pyrimido[1,2-a]pyrimidine-4,8(3H,7H)-dione (3e)

Yield: 56%; white crystals; mp 182.1–182.2 °C (MeOH).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.40–1.45\) (m, 2 H), 1.55–1.63 (m, 2 H), 1.84–2.01 (m, 4 H), 2.19–2.27 (m, 2 H), 2.63–2.68 (m, 2 H), 2.99–3.03 (m, 2 H), 3.28 (app t, \(J = 6.1\) Hz, 2 H), 4.30 (br s, 2 H).

\(^1\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 24.0, 24.3, 25.9, 26.2, 28.9, 30.7, 36.0, 38.3, 43.0, 120.4, 132.1, 134.0, 158.8, 161.4, 186.2.

HRMS (ESI): \(m/z\) calcd for C\(_6\)H\(_{14}\)N\(_2\)O\(_2\)S [M + H]\(^+\): 303.1162; found: 303.1159.

Enamines; 6,7-Dihydro-2-[2-(dimethylamino)ethenyl]-1H-benzothieno[2,3-d][pyrimidin-4(3H,7H)-dione (4a); Typical Procedure

DMFDMA (0.321 mL, 286 mg, 2.40 mmol) was added to compound 3a (151 mg, 0.610 mmol) in anhyd DMF (7.5 g, 8.0 mL), and the mixture was heated to 70 °C for 3 h. After cooling, the mixture was evaporated to dryness by water aspirator vacuum distillation. The residue was dissolved in CH\(_2\)Cl\(_2\) (50 mL) and the organic layer was washed with H\(_2\)O (3 × 15 mL) and dried (Na\(_2\)SO\(_4\)). After filtration, the solvent was evaporated. The crude product was purified with flash chromatography (10% MeOH–CH\(_2\)Cl\(_2\)); yield: 93%; yellow powder; mp 271.6–271.9 °C (MeCN) (dec.).

IR (neat): 1663, 1643, 1627, 1517, 1506 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 2.15–2.23\) (m, 2 H), 2.59–2.63 (m, 2 H), 2.8–3.25 (br s, 6 H, NCH\(_3\)), 3.23 (app t, \(J = 6.1\) Hz, 2 H), 3.51 (s, 3 H), 4.88 (d, \(J = 11.9\) Hz, 1 H), 8.13 (d, \(J = 11.9\) Hz, 1 H).

\(^1\)C NMR (500 MHz, CDCl\(_3\)): \(\delta = 28.9\) (NCH\(_3\), s, 3 H), 3.25 (NCH\(_3\), s, 3 H), other resonances as above.

\(^1\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 23.9, 25.9, 29.2, 37.5\) (br s), 38.1, 45.5 (br s), 85.1, 115.9, 127.7, 151.6, 153.4, 158.7, 159.8, 170.1, 192.3.

\(^1\)C NMR (125 MHz, –15 °C, CDCl\(_3\)): \(\delta = 37.3\) (NCH\(_3\), s), 45.5 (NCH\(_3\), s), other resonances as above.

HRMS (ESI): \(m/z\) calcd for C\(_{16}\)H\(_{18}\)N\(_2\)O\(_2\)S [M + H]\(^+\): 304.1114; found: 304.1128.

3-[[(Dimethylamino)methylene]-2,3,8,9-tetrahydro-1H-benzothiophen-2,3-d][pyrrole[1,2-a]pyrimidine-6,10(1H,7H)-dione (4b)

Compound 3b was used as the starting material; yield: 95%; yellow powder; mp 286–287 °C (toluene) (dec.).

IR (neat): 1664, 1636, 1535, 1520 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 2.15–2.23\) (m, 2 H), 2.59–2.63 (m, 2 H), 3.13 (s, 6 H), 3.16–3.26 (m, 4 H), 4.06–4.12 (m, 2 H), 7.46 (t, \(J = 1.73\) Hz, 1 H).
\^13\text{C} NMR (75 MHz, CDCl\_3): \( \delta = 23.6, 24.0, 25.8, 38.1, 42.3, 43.7, 95.0, 117.4, 128.1, 144.5, 150.9, 158.7, 162.4, 172.6, 192.3. 

HRMS (ESI): \text{m/z calc for C}_{19}\text{H}_{28}\text{N}_3\text{O}_2\text{S} [\text{M + H}]^+ : 316.1114; \text{found: 316.1105.}

5-[(Dimethylamino)methylene]-4,10,11-triydroxy-2H-1-benzo-thiencino[2,3-d]pyrido[1,2-a]pyrimidin-8,12(3H,9H)-dione (4c)

Compound 3c was used as the starting material; yield: 84%; yellow powder; mp 245.7–246.2 °C (EtOAc) (dec.).

IR (neat): 1662, 1648, 1606, 1497, 1463 cm\(^{-1}\).

HRMS (ESI): \text{m/z calc for C}_{19}\text{H}_{28}\text{N}_3\text{O}_2\text{S} [\text{M + H}]^+ : 316.1105; \text{found: 316.1105.}

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Acknowledgment

References


(19) Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 643240 (3b), CCDC 643241 (3c), CCDC 643242 (3d), and CCDC 643243 (3e). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
