Supporting Information

Mild and Catalyst-free Microwave-assisted Synthesis of 4,6-Disubstituted 2-Methylthiopyrimidines – Exploiting Tetrazole as an Efficient Leaving Group

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Instrumentation for routine analysis

NMR spectra were recorded on a Bruker Avance AV 300 or a Bruker DRX 500. The residual proton, \(^1\)H, or carbon \(^{13}\)C resonances of the >99 % deuterated solvents were used for internal reference of all spectra acquired. (CDCl\(_3\) \(^1\)H 7.260 ppm, \(^{13}\)C 77.16 ppm; DMSO-\(d_6\), \(^1\)H 2.500 ppm, \(^{13}\)C 39.52 ppm).

Electrospray ionization (ESI) mass spectrometry were recorded with a Surveyor LC system MSQ electrospray mass spectrometer LC-MS couple (ThermoFisher, Dreieich, Germany) by use of an acetonitrile/water gradient in positive mode (+), if not indicated otherwise. 0.1% TFA was added if necessary.

Analytical and Experimental Data

\(IH\)-Tetrazole:

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H \\
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N \end{array}
\]

Sodium azide (0.2 mol, 13 g), ammonium chloride (0.2 mol, 10.7 g) and ethyl orthoformate (0.6 mol, 89 g) were charged in a round bottom flask. Glacial acid (0.8 mol, 46 ml) was added slowly at room temperature. After addition, the mixture was stirred at 80°C for 16 hrs. The reaction mixture was evaporated to dryness in dynamic vacuum (at 40°C) and the resulting colorless residue was resuspended in boiling acetone and filtered hot (G4 glass frit). The acetone was removed \textit{in vacuo} and the colorless residue was recrystallized from ethyl acetate to yield \(IH\)-tetrazole as colorless needles (7.1 g, 51%).

ESI-MS(-): m/z 68.9 [M-H]⁻

\(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 9.38\) ppm (s, 1 H)

\(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta = 143.2\) ppm
General Procedure for the synthesis of compounds 2-24:

1 equivalent of starting material (either compound 1 (for cmpds 2-24) or 4,6-dichloro-2-thiomethylpyrimidine (for cmpds 1, 17op)) was dissolved in the solvent indicated in Table 3 or 4. The reactant (for equivalents see Table 3 or 4) and 1 equivalent of base was added at once and the mixture was stirred in a capped vial in a CEM Discover SP microwave oven connected to a CEM Explorer SP 12S autosampler for the indicated time and temperature (see Table 3 and 4). Isolation and purification of the desired compounds was achieved either by addition of water and subsequent filtration (2, 3, 5-8, 13-20, 22) or by column chromatography (4, 9-12, 21, 23, 24).

Compound 2:

![Chemical Structure of Compound 2]

ESI-MS(+): m/z 210.0 [M-N$_2$+H]$^+$

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 10.12$ (s, 1 H), 6.88 (s, 1 H), 3.20 (br. s, 6 H), 2.54 ppm (s, 3 H)

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta = 171.1, 162.4, 151.9, 141.8, 86.9, 86.6, 13.0$ ppm

Compound 3:

![Chemical Structure of Compound 3]

ESI-MS(+): m/z 196.0 [M-N$_2$+H]$^+$

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 10.10$ (s, 1 H), 8.07 (d, $J$=4.1 Hz, 1 H), 6.73 (s, 1 H), 2.91 (d, $J$=4.6 Hz, 3 H), 2.54 ppm (s, 3 H)

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta = 172.5, 163.8, 151.0, 142.1, 90.0, 27.5, 14.1$ ppm
Compound 4:

ESI-MS(+): m/z 182.0 [M-N2+H]^+

$^1$H NMR (300 MHz, DMSO-$d_6$) $\delta = 10.10$ (s, 1H), 7.59 (br. s., 2H), 6.73 (s, 1H), 2.52 (s, 3H)

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta = 171.8, 164.9, 151.7, 141.6, 141.4, 13.4$ ppm

Compound 5:

ESI-MS(+): m/z 299.9 [M+H]^+, 271.9 [M-N2+H]^+

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 10.09$ (s, 1H), 8.62 (t, $J=5.3$ Hz, 1H), 7.16-7.50 (m, 5 H), 6.86 (s, 1H), 4.64 (d, $J=5.5$ Hz, 2H), 2.41 - 2.51 ppm (m, 3 H)

$^{13}$C NMR (300 MHz, DMSO-$d_6$): $\delta = 172.4, 163.3, 152.0, 143.4, 139.2, 129.6, 128.3, 127.1, 90.6, 44.4, 14.0$ ppm
**Compound 6:**

![Chemical structure of Compound 6](image)

ESI-MS(+): m/z 236.0 [M-N₂+H]^+

^1H NMR (300 MHz, CHLOROFORM-d): δ = 9.45 (s, 1 H), 6.65 (s, 1 H), 3.71 (t, J=6.6 Hz, 2 H), 3.46 (t, J=6.6 Hz, 2 H), 2.55 (s, 3 H), 1.85-2.24 ppm (m, 4 H)

^13C NMR (75 MHz, CHLOROFORM-d): δ = 116.1, 111.8, 108.0, 102.9, 80.8, 64.2, 55.9, 55.5, 51.3 ppm

**Compound 7:**

![Chemical structure of Compound 7](image)

ESI-MS(+): m/z 251.8 [M-N₂+H]^+

^1H NMR (300 MHz, CHLOROFORM-d): δ = 9.39 (s, 1 H), 6.81 (s, 1 H), 3.42-4.07 (m, 8 H), 2.48 ppm (s, 3 H)

^13C NMR (75 MHz, CHLOROFORM-d): δ = 172.8, 162.6, 152.9, 140.3, 86.3, 66.3, 44.5, 14.2 ppm
Compound 8:

![Chemical structure of Compound 8]

ESI-MS(+): m/z 278.2 [M+H]^+, 251.2 [M-N₂+H]^+

^1H NMR (300 MHz, CHLOROFORM-d): δ = 9.45 (s, 1 H), 6.88 (s, 1 H), 3.73 (br. s, 4 H), 2.54 (s, 3 H), 1.62-1.79 ppm (m, 6 H)

^13C NMR (75 MHz, CHLOROFORM-d): δ = 172.5, 162.0, 152.8, 140.4, 140.2, 45.7, 25.6, 24.4, 14.2 ppm

Compound 9:

![Chemical structure of Compound 9]

ESI-MS(+): m/z 232.9 [M-N₂+H]^+

^1H NMR (300 MHz, DMSO-d6): δ = 10.35 (s, 1 H), 8.87 (s, 1 H), 8.22 (s, 2 H), 7.22 (s, 1 H), 2.71 ppm (s, 3 H)

^13C NMR (75 MHz, DMSO-d6): δ = 173.3, 156.8, 154.1, 142.3, 136.2, 131.2, 116.8, 93.8, 14.0 ppm
Compound 10:

![Chemical Structure of Compound 10](image)

ESI-MS: a signal for the molecular ion was not found

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 10.28$ (s, 1 H), 7.04 (s, 1 H), 2.62 ppm (s, 3 H)

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta = 173.0$, 162.4, 153.3, 142.5, 90.8, 14.2 ppm

FT-IR (cm$^{-1}$): 3107, 2936, 2732, 2288, 2235, 2185, 1626, 1588, 1523, 1474, 1439, 1391, 1347, 1332, 1294, 1238, 1186, 1139, 1100, 1081, 1013, 980, 966, 936, 822, 793, 763, 723, 773

pK$_a$ = 3.17 ± 0.05

Compound 11:

![Chemical Structure of Compound 11](image)

ESI-MS(+): m/z 197.0 [M-N$_2$+H]$^+$

$^1$H NMR (300 MHz, CHLOROFORM-$d$): $\delta = 9.48$ (s, 1 H), 7.08 (s, 1 H), 4.09 (s, 3 H), 2.64 ppm (s, 3 H)

$^{13}$C NMR (75 MHz, CHLOROFORM-$d$): $\delta = 173.9$, 171.0, 153.4, 140.3, 92.6, 91.2, 14.2 ppm
Compound 12:

![Chemical Structure](image)

ESI-MS(+): m/z 239.1 [M+H]^+, 211.1 [M-N_2+H]^+

_1^H NMR (500 MHz, CHLOROFORM-d): δ = 9.48 (s, 1 H), 7.04 (s, 1 H), 4.53 (q, J=7.1 Hz, 2 H), 2.57 (s, 3 H), 1.44 ppm (t, J=7.1 Hz, 3 H)

_1^3C NMR (126 MHz, CHLOROFORM-d): δ = 173.7, 170.6, 153.4, 140.2, 92.0, 64.0, 14.2, 14.2 ppm

Compound 13:

![Chemical Structure](image)

ESI-MS(+): m/z 258.9 [M-N_2+H]^+

_1^H NMR (300 MHz, CHLOROFORM-d): δ = 9.43 (s, 1 H), 7.40 (d, J=7.7 Hz, 2H), 6.97-7.31 (m, 4H), 2.42 (s, 3H)

_1^3C NMR (75 MHz, CHLOROFORM-d): δ = 174.4, 170.9, 154.3, 151.9, 140.3, 129.8, 126.4, 121.4, 91.5, 14.2
Compound 14:

![Chemical Structure]

ESI-MS(+): m/z 227.1 [M+H]⁺, 255.1 [M-N₂+H]⁺

¹H NMR (300 MHz, CHLOROFORM-d): δ = 9.42 (s, 1 H), 7.43 (s, 1 H), 3.20 (q, J=7.4 Hz, 2 H), 2.55 (s, 3 H), 1.36 ppm (t, J=7.4 Hz, 3 H)

¹³C NMR (75 MHz, CHLOROFORM-d): δ = 174.5, 173.2, 151.0, 140.3, 102.2, 102.1, 24.5, 14.2 ppm

Compound 15:

![Chemical Structure]

ESI-MS(+): m/z 283.2 [M+H]⁺, 255.1 [M-N₂+H]⁺

¹H NMR (300 MHz, CHLOROFORM-d): δ = 9.41 (s, 1 H), 7.38 (s, 1 H), 2.55 (s, 3 H), 1.60 ppm (s, 9 H)

¹³C NMR (75 MHz, CHLOROFORM-d): δ = 175.6, 173.0, 150.8, 140.2, 103.0, 49.8, 30.3, 14.5 ppm
Compound 16:

![Chemical Structure of Compound 16](image)

ESI-MS(+): m/z 317.2 [M+H]^+, 289.1 [M-N_2+H]^+

^1^H NMR (300 MHz, CHLOROFORM-d): \(\delta = 9.40 (s, 1 \text{ H}), 7.44 (s, 1 \text{ H}), 6.99-7.39 (m, 5 \text{ H}), 4.44 (s, 2 \text{ H}), 2.53 \text{ ppm (s, 3 H)}\)

^13^C NMR (75 MHz, CHLOROFORM-d) \(\delta = 173.7, 173.4, 151.1, 140.4, 140.2, 136.0, 128.9, 128.8, 127.7, 102.1, 102.0, 34.2, 14.3\)

Compound 17/17op:

![Chemical Structure of Compound 17/17op](image)

ESI-MS(+): m/z 303.1 [M+H]^+, 275.1 [M-N_2+H]^+

^1^H NMR (300 MHz, CHLOROFORM-d): \(\delta = 9.38 (s, 1 \text{ H}), 7.32-7.73 (m, 5 \text{ H}), 7.07 (s, 1 \text{ H}), 2.38 \text{ ppm (s, 3 H)}\)

^13^C NMR (75 MHz, CHLOROFORM-d) \(\delta = 176.9, 173.3, 152.1, 140.4, 140.2, 135.9, 130.9, 130.2, 126.6, 14.2 \text{ ppm}\)
Compound 18:

![Chemical Structure]

ESI-MS(+) : m/z 337.3 [M+H]^+, 309.1 [M-N2+H]^+

$^1$H NMR (300 MHz, CHLOROFORM-d): $\delta$ = 9.36 (s, 1 H), 7.29-7.60 (m, 4 H), 7.12 (s, 1 H), 2.33 ppm (s, 3 H)

$^{13}$C NMR (75 MHz, CHLOROFORM-d): $\delta$ = 175.7, 173.5, 152.0, 140.4, 140.1, 137.4, 137.1, 130.3, 125.0, 14.2 ppm

Compound 19:

![Chemical Structure]

ESI-MS(+) : m/z 305.0 [M-N2+H]^+

$^1$H NMR (300 MHz, CHLOROFORM-d): $\delta$ = 9.46 (s, 1 H), 7.54 (d, $J$=8.1 Hz, 2 H), 6.87-7.18 (m, 3 H), 3.82-4.00 (m, 3 H), 2.51 ppm (s, 3 H)

$^{13}$C NMR (75 MHz, CHLOROFORM-d): $\delta$ = 178.1, 173.1, 161.7, 152.1, 140.3, 137.4, 116.9, 115.8, 100.3, 55.5, 14.2 ppm
Compound 20:

![Chemical structure image]

ESI-MS(+) : m/z 289.0 [M+H]<sup>+</sup>

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta =$ 10.22 (s, 1 H), 7.66 (d, $J$=7.5 Hz, 1 H), 7.48-7.59 (m, 2 H), 7.34 - 7.45 (m, 1 H), 7.05 (s, 1 H), 2.44 (s, 3 H), 2.37 ppm (s, 3 H)

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta =$ 174.5, 172.2, 152.1, 142.8, 142.0, 136.8, 131.4, 131.3, 127.6, 125.6, 100.7, 20.3, 13.6 ppm

Compound 21:

![Chemical structure image]

ESI-MS(+) : m/z 187.0 [M+H]<sup>+</sup>

$^1$H NMR (300 MHz, CHLOROFORM-$d$): $\delta =$ 5.73 (s, 1 H), 3.92 (s, 6 H), 2.56 ppm (s, 3 H)

$^{13}$C NMR (75 MHz, CHLOROFORM-$d$): $\delta =$ 171.1, 170.9, 85.3, 54.0, 14.0 ppm
**Compound 22:**

![Chemical Structure of Compound 22]

ESI-MS(+): m/z 343.0 [M+H]^+

$^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ = 7.33-7.46 (m, 10H), 5.72 (s, 1H), 2.32 (s, 3H)

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ = 172.0, 170.8, 136.3, 135.8, 130.9, 130.5, 126.8, 107.2, 13.9 ppm

**Compound 23:**

![Chemical Structure of Compound 23]

ESI-MS(+): m/z 340.0 [M+H]^+

$^1$H NMR (300 MHz, CHLOROFORM-$d$): $\delta$ = 7.46 (d, $J$=7.2 Hz, 2 H), 7.28-7.39 (m, 3 H), 7.15-7.26 (m, 3 H), 7.09 (d, $J$=7.3 Hz, 2 H), 5.33 (s, 1 H), 5.00 (s, 1 H), 4.28 (br. s., 2 H), 2.34 ppm (s, 3 H)

$^{13}$C NMR (126 MHz, CHLOROFORM-$d$): $\delta$ = 170.8, 161.4, 135.8, 129.6, 129.5, 128.7, 128.6, 127.4, 127.3, 45.2, 13.9 ppm
Compound 24:

![Compound 24](image)

ESI-MS(+): m/z 258.8 [M+H]^+

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 8.71$ (t, $J=1.0$ Hz, 2 H), 8.07 (t, $J=1.4$ Hz, 2 H), 7.90 (s, 1 H), 7.22 (dd, $J=1.6$, 0.8 Hz, 2 H), 2.64 ppm (s, 3 H)

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta = 172.8$, 156.3, 135.8, 131.0, 130.8, 116.6, 90.3, 13.6 ppm

Crystallization of compound 1:

10 mg of 1 was dissolved in a minimum amount of hot methanol (~800µl). The clear solution was allowed to cool down to room temperature and left standing open to atmosphere for slow evaporation. Colorless, needle shaped crystals formed after 2 days.

CCDC Number 1052351 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

SI Table 1. Conditions tried to obtain N,N-dimethyl-2-(methylthio)-6-(1H-tetrazol-1-yl)pyrimidin-4-amine starting from 6-chloro-N,N-dimethyl-2-(methylthio)pyrimidin-4-amine

<table>
<thead>
<tr>
<th>Method</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heating</td>
<td>DMF, TEA, 60-140°C, 1-2 eq tetrazole, 24 hrs[a]</td>
</tr>
<tr>
<td>Microwave</td>
<td>DMF, TEA, 60-140°C, 1-2 eq tetrazole, 1 hr[a]</td>
</tr>
<tr>
<td>Heating</td>
<td>Neat, 2 eq tetrazole, 130°C, 24 hrs[a]</td>
</tr>
</tbody>
</table>

[a] TLC showed no conversion of starting material
Determination of the pK$_a$ of compound 10:

The pK$_a$ of 10 was measured using the SiriusT3 automatic titration system (Sirius Analytical Ltd, Forest Row, UK) and the software supplied with the machine for the refinement of the experimental data. Standard solutions of hydrochloric acid 0.5 M and potassium hydroxide 0.5 M in Millipore water were used as acid and base titrant, respectively. The ionic strength of the water used for dissolving the samples was adjusted adding potassium chloride obtaining a 0.15 M solution. A solution of 50 % acetonitrile – 50 % Millipore water was prepared and potassium chloride was added in it for obtaining a final mixture 50 % acetonitrile with 0.15 M KCl. In each experiment 10 was titrated three times in acetonitrile – water solution (first titration in 42 %, second titration in 35 % and third titration in 27 % of acetonitrile) from basic to acidic pH. Three independent experiments were performed per each compound at room temperature. The pK$_a$ was obtained by linear extrapolation of the psK$_a$ of each experiment resulting in a pK$_a$ = 3.17 ± 0.05 and in a acceptable coefficient of determination ($R^2$ = 0.8927).