Direct metallation of thienopyrimidines using a mixed lithium-cadmium base and antitumor activity of functionalized derivatives

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X-ray diffraction analysis

The sample was studied with graphite monochromatized Mo$_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). X-ray diffraction data were collected at $T = 100(2)$ K using APEXII Bruker-AXS diffractometer. The structure was solved by direct methods using the SIR97 program,$^1$ and then refined with full-matrix least-square methods based on F$^2$ (SHELX-97)$^2$ with the aid of the WINGX program.$^3$ All non-hydrogen atoms were refined with anisotropic thermal parameters. H atoms were finally included in their calculated positions. Except N-linked hydrogen that was introduced in the structural model through Fourier difference maps analysis, H atoms were finally included in their calculated positions. The molecular diagram was generated by ORTEP-3 (version 1.08).$^4$

ORTEP figure

Crystal data

10a: C$_{12}$H$_6$ClIN$_2$S; $M_r = 372.60$; $T = 100(2)$ K; $\lambda = 0.71073$ Å; orthorhombic; space group $P c a b$, $a = 5.8116(2)$ Å, $b = 16.7820(6)$ Å, $c = 24.6525(9)$ Å, $V = 2404.36(15)$ Å$^3$; $Z = 8$; $D_c = 2.059$ g cm$^{-3}$; $\mu = 3.035$ mm$^{-1}$; $F(000) = 1424$; crystal size = 0.22 x 0.08 x 0.06 mm; $\theta$ range for data collection: 3.52-27.46°, limiting indices: $-7 \leq h \leq 7$, $-21 \leq k \leq 19$, $-31 \leq l \leq 30$; 27353 reflections collected; 2743 reflections unique ($R_{int} = 0.0587$); $R_1$(I>$2\sigma$(I))= 0.0252; $wR_2$(I>$2\sigma$(I))= 0.0495; Crystallographic data were deposited in CSD under CCDC registration number 729714.

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NMR data

Methyl 3-benzoylaminothiophene-2-carboxylate. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 3.88 (s, 3H), 7.51 (m, 4H), 7.99 (m, 2H), 8.27 (d, 1H, J = 5.4 Hz), 11.1 (s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 52.1, 110.4, 122.3, 127.4, 128.9, 131.9, 132.3, 133.6, 145.2, 164.1, 165.2.

2-Phenyl-3$H$-thieno[3,2-$d$]pyrimidin-4-one. $^1$H NMR ((CD$_3$)$_2$SO, 300 MHz): $\delta$ 7.48 (d, 1H, J = 5.2 Hz), 7.57 (m, 3H), 8.13 (m, 3H), 8.22 (d, 1H, J = 5.2 Hz), 12.7 (br s, 1H); $^{13}$C NMR ((CD$_3$)$_2$SO, 75 MHz): $\delta$ 121.2, 125.4, 127.8, 128.6, 131.3, 132.5, 135.4, 154.3, 157.9, 158.5.

4-Chloro-2-phenylthieno[3,2-$d$]pyrimidine (2). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.51 (m, 3H), 7.62 (d, 1H, J = 5.5 Hz), 8.02 (d, 1H, J = 5.2 Hz), 8.52 (m, 2H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 125.2, 128.3, 128.5, 128.7, 130.9, 136.7, 136.8, 154.9, 161.7, 162.8.

4-Chloro-2-phenylthieno[2,3-$d$]pyrimidine (3). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.42 (d, 1H, J = 6.0 Hz), 7.50 (m, 3H), 7.54 (d, 1H, J = 6.0 Hz), 8.52 (m, 2H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 119.9, 127.4, 127.5, 128.6, 128.7, 131.1, 136.3, 155.1, 160.0, 169.7.

4-Methoxythieno[2,3-$d$]pyrimidine (4). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 4.12 (s, 3H), 7.35 (d, 1H, J = 6.0 Hz), 7.37 (d, 1H, J = 6.0 Hz), 8.64 (s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 54.1, 118.6, 119.2, 124.8, 153.4, 164.3, 168.5.

4-Methoxy-2-phenylthieno[2,3-$d$]pyrimidine (6). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 4.22 (s, 3H), 7.31 (d, 1H, J = 6.0 Hz), 7.35 (d, 1H, J = 6.0 Hz), 7.50 (m, 3H), 8.55 (m, 2H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 53.6, 117.1, 118.5, 124.1, 128.3, 130.3, 137.5, 159.7, 163.8, 169.4.

4-(Pyrazol-1-yl)thieno[2,3-$d$]pyrimidine (5). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.26 (s, 1H), 8.26 (d, 1H, J = 6.0 Hz), 8.59 (s, 1H), 9.15 (d, 1H, J = 6.0 Hz), 9.50 (d, 1H, J = 2.7 Hz), 9.57 (s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 108.7, 119.2, 123.4, 126.4, 129.0, 144.3, 151.0, 152.4, 171.7.

4-(Morpholin-4-yl)-2-phenylthieno[2,3-$d$]pyrimidine (7). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 3.88 (m, 4H), 3.97 (m, 4H), 7.24 (d, 1H, J = 6.0 Hz), 7.31 (d, 1H, J = 6.0 Hz), 7.45-7.48 (m, 3H), 8.46 (m, 2H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 47.3, 66.7, 114.9, 120.2, 121.9, 128.2, 128.3, 130.1, 138.0, 158.7, 158.8, 170.7.

4-Chloro-6-iodothieno[2,3-$d$]pyrimidine (8). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.70 (s, 1H), 7.80 (s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 82.2, 129.4, 131.3, 152.7, 152.8, 172.8.

6-Iodo-4-methoxythieno[2,3-$d$]pyrimidine (9). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 4.10 (s, 3H), 7.60 (s, 1H), 8.56 (s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 54.4, 77.2, 121.1, 128.5, 153.5, 162.4, 172.5.
4-Chloro-6-iodo-2-phenylthieno[3,2-d]pyrimidine (10a). \(^1^H\) NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.49 (m, 3H), 7.83 (s, 1H), 8.47 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 92.2, 128.5, 128.7, 131.1, 133.3, 134.9, 136.3, 152.6, 162.0, 163.0.

4-Chloro-6-iodo-2-phenylthieno[2,3-d]pyrimidine (11). \(^1^H\) NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.50 (m, 3H), 7.68 (s, 1H), 8.48 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 80.9, 128.6, 128.7, 129.2, 129.5, 131.3, 135.9, 152.8, 159.9, 173.5.

4-Chloro-6,7-diiodo-2-phenylthieno[3,2-d]pyrimidine (10b). \(^1^H\) NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.48 (m, 3H), 8.54 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 98.7, 101.3, 128.7, 128.8, 131.4, 132.8, 135.9, 153.1, 162.0, 162.7.

6-Iodo-4-methoxy-2-phenylthieno[2,3-d]pyrimidine (12). \(^1^H\) NMR (CDCl\(_3\), 300 MHz): \(\delta\) 4.21 (s, 3H), 7.48 (m, 3H), 7.60 (s, 1H), 8.49 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 53.9, 76.1, 119.0, 128.4, 128.4, 128.5, 130.6, 137.2, 159.7, 162.1, 173.3.

6-Iodo-4-(morpholin-4-yl)-2-phenylthieno[2,3-d]pyrimidine (13). \(^1^H\) NMR (CDCl\(_3\), 300 MHz): \(\delta\) 3.89 (t, 4H, \(J = 4.5\) Hz), 4.00 (t, 4H, \(J = 4.3\) Hz), 7.48 (m, 3H), 7.55 (s, 1H), 8.44 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 46.5, 65.9, 76.1, 116.2, 127.7, 128.4, 130.3, 130.6, 137.0, 156.3, 157.3, 173.4.

4-(Morpholin-4-yl)-2-phenyl-6-(pyridin-2-yl)-thieno[2,3-d]pyrimidine (14). \(^1^H\) NMR (CDCl\(_3\), 300 MHz): \(\delta\) 3.93 (m, 4H), 4.06 (m, 4H), 7.23 (ddd, 1H, \(J = 2.0, 4.9\) and \(6.0\) Hz), 7.48 (m, 3H), 7.73 (m, 2H), 7.88 (s, 1H), 8.47 (m, 2H), 8.64 (dt, 1H, \(J = 1.2\) and \(4.6\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 47.3, 66.8, 116.2, 117.5, 119.6, 122.7, 128.3, 128.3, 130.2, 136.8, 138.0, 139.3, 149.8, 151.8, 158.7, 159.3, 171.2.

(S)-3-Phenyl-2-(2-phenylthieno[3,2-d]pyrimidin-4-ylamino)propanoic acid (15). \(^1^H\) NMR (CD\(_3\)SO, 300 MHz): \(\delta\) 3.34 (AB part of an ABX system, 2H, \(J_{AX} = 3.7\) Hz, \(J_{BX} = 8.9\) Hz and \(J_{AB} = 13.6\) Hz), 4.99 (m, 1H), 7.06 (t, 1H, \(J = 7.0\) Hz), 7.15 (t, 2H, \(J = 7.2\) Hz), 7.29 (d, 2H, \(J = 7.2\) Hz), 7.44 (m, 4H), 7.76 (br s, 1H), 8.06 (d, 1H, \(J = 5.3\) Hz), 8.39 (m, 2H); \(^{13}\)C NMR (CD\(_3\)SO, 75 MHz): \(\delta\) 37.0, 56.3, 113.4, 124.6, 125.8, 127.7, 127.8, 128.1, 129.2, 129.7, 132.9, 138.4, 139.1, 156.5, 159.5, 160.2, 173.7.

(S)-2-(6-Iodo-2-phenylthieno[3,2-d]pyrimidin-4-ylamino)-3-phenylpropanoic acid (16). \(^1^H\) NMR (CD\(_3\)SO, 300 MHz): \(\delta\) 3.26 (AB part of an ABX system, 2H, \(J_{AX} = 4.0\) Hz, \(J_{BX} = 9.9\) Hz and \(J_{AB} = 13.6\) Hz), 4.90 (m, 1H), 7.10 (t, 1H, \(J = 7.2\) Hz), 7.18 (t, 2H, \(J = 7.3\) Hz), 7.31 (d, 2H, \(J = 7.2\) Hz), 7.43 (m, 3H), 7.71 (s, 1H), 8.10 (br s, 1H), 8.33 (m, 2H); \(^{13}\)C NMR (CD\(_3\)SO, 75 MHz): \(\delta\) 36.7, 56.3, 89.3, 118.3, 126.0, 127.7, 128.0, 128.2, 129.1, 129.9, 133.9, 137.9, 138.8, 155.0, 159.7, 160.9, 174.4.

(S)-2-(6,7-Diiodo-2-phenylthieno[3,2-d]pyrimidin-4-ylamino)-3-phenylpropanoic acid (17). \(^1^H\) NMR (CD\(_3\)SO, 300 MHz): \(\delta\) 3.20 (m, 2H), 4.85 (m, 1H), 7.07 (t, 1H, \(J = 7.2\) Hz), 7.15 (t, 2H, \(J = 7.3\) Hz), 7.71 (s, 1H), 8.06 (d, 1H, \(J = 5.3\) Hz), 8.39 (m, 2H); \(^{13}\)C NMR (CD\(_3\)SO, 75 MHz): \(\delta\) 37.0, 56.3, 113.4, 124.6, 125.8, 127.7, 127.8, 128.1, 129.2, 129.7, 132.9, 138.4, 139.1, 156.5, 159.5, 160.2, 173.7.
Hz), 7.26 (br d, 2H, J = 7 Hz), 7.47 (m, 3H), 7.96 (br s, 1H), 8.40 (m, 2H); $^{13}$C NMR ((CD$_3$)$_2$SO, 75 MHz): $\delta$ 36.7, 56.3, 99.9, 103.7, 125.8, 127.8, 127.9, 128.2, 129.1, 129.4, 130.2, 137.7, 139.1, 159.6, 160.6, 173.9.

(S)-3-Phenyl-2-(2-phenylthieno[2,3-d]pyrimidin-4-ylamino)propanoic acid (18). $^1$H NMR ((CD$_3$)$_2$SO, 300 MHz): $\delta$ 3.29 (AB part of an ABX system, 2H, J$_{AX}$ = 3.8 Hz, J$_{BX}$ = 10 Hz and J$_{AB}$ = 13.4 Hz), 3.71 (br s, 1H), 5.00 (m, 1H), 7.08 (t, 1H, J = 7.1 Hz), 7.17 (t, 2H, J = 7.3 Hz), 7.33 (d, 2H, J = 7.3 Hz), 7.43 (m, 3H), 7.49 (d, 1H, J = 5.9 Hz), 7.71 (d, 1H, J = 5.9 Hz), 8.17 (d, 1H, J = 7.0 Hz), 8.36 (m, 2H); $^{13}$C NMR ((CD$_3$)$_2$SO, 75 MHz): $\delta$ 37.1, 56.3, 114.8, 119.7, 122.3, 125.9, 127.7, 127.9, 128.2, 129.1, 129.9, 137.9, 139.0, 156.5, 158.5, 166.7.

(S)-2-(6-Iodo-2-phenylthieno[2,3-d]pyrimidin-4-ylamino)-3-phenylpropanoic acid (19). $^1$H NMR ((CD$_3$)$_2$SO, 300 MHz): $\delta$ 3.23 (AB part of an ABX system, 2H, J$_{AX}$ = 4.5 Hz, J$_{BX}$ = 10.3 Hz and J$_{AB}$ = 13.7 Hz), 4.92 (m, 1H), 7.13 (t, 1H, J = 7.2 Hz), 7.23 (t, 2H, J = 7.3 Hz), 7.35 (br d, 2H, J = 7.1 Hz), 7.43 (m, 3H), 8.06 (s, 1H), 8.30 (m, 3H); $^{13}$C NMR ((CD$_3$)$_2$SO, 75 MHz): $\delta$ 36.6, 55.9, 75.8, 116.7, 126.2, 127.8, 128.1, 128.3, 129.0, 129.1, 130.2, 137.4, 138.4, 154.9, 158.5, 170.7, 173.8.

(S)-2-[(6-Iodo-2-phenylthieno[2,3-d]pyrimidin-4-yl)(methyl)amino]-3-phenylpropanoic acid (20). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 3.12 (s, 3H), 3.40 (AB part of an ABX system, 2H, J$_{AX}$ = 4.4 Hz, J$_{BX}$ = 9.9 Hz and J$_{AB}$ = 14 Hz), 5.11 (br s, 1H), 7.14 (m, 5H), 7.39 (m, 4H), 8.28 (br d, 2H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 29.7, 34.6, 73.2, 116.6, 126.8, 128.2, 128.4, 128.6, 128.9, 130.4, 130.7, 136.9, 137.0, 137.4, 156.0, 158.1, 174.5.

(S)-1-(6-Iodo-2-phenylthieno[2,3-d]pyrimidin-4-yl)pyrrolidine-2-carboxylic acid (22). $^1$H NMR ((CD$_3$)$_2$SO, 300 MHz): $\delta$ 1.86-2.27 (m, 4H), 3.95 (m, 2H), 4.69 (m, 1H), 7.41 (m, 3H), 7.80 (s, 1H), 8.31 (m, 2H); $^{13}$C NMR ((CD$_3$)$_2$SO, 75 MHz): $\delta$ 21.1, 24.7, 24.8, 28.4, 31.1, 49.3, 61.5, 63.1, 74.7, 116.0, 127.8, 128.3, 130.3, 130.6, 137.2, 157.6, 174.0.
Copies of NMR spectra

$^1$H - CDCl$_3$ - 300 MHz

$^{13}$C - CDCl$_3$ - 75 MHz
$^1$H - (CD$_3$)$_2$SO - 300 MHz

$^{13}$C - (CD$_3$)$_2$SO - 75 MHz
$^{1}H$ - CDCl$_3$ - 300 MHz

$^{13}C$ - CDCl$_3$ - 75 MHz
$^{1}H$ - (CD$_3$)$_2$SO - 300 MHz

$^{13}$C - (CD$_3$)$_2$SO - 75 MHz