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SYNTHESIS OF [1,4]DITHIINO[2,3-*d*]PYRIMIDINE-6-CARBONITRILE DERIVATIVES *VIA* THE REACTION OF 2-[(4-CHLOROPYRIMIDIN-5-YL)SULFANYL]ACETONITRILES WITH CARBON DISULFIDE

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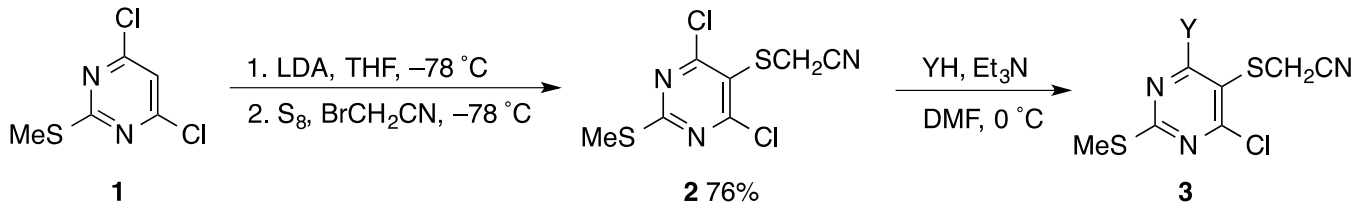
Abstract – An efficient procedure has been developed for the preparation of 7-(alkylsulfanyl)[1,4]dithiino[2,3-*d*]pyrimidine-6-carbonitrile derivatives from 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP). 2-{[4-Chloro-2-(methylsulfanyl)pyrimidin-5-yl]sulfanyl}acetonitriles are prepared *via* the reaction of the 5-lithio derivative of DCSMP with sulfur and then 2-bromoacetonitrile. These can be converted into the desired products on treatment with carbon disulfide in the presence of sodium hydride followed by alkyl halides. This is the first construction of the [1,4]dithiino[2,3-*d*]pyrimidine structure.

Recently, we developed several new methods to achieve the preparation of pyrimidine-fused heterocyclic systems of potential biological importance starting with 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) (**1**) under mild and operationally easy conditions.[1] Herein, we wish to report a facile method for the synthesis of 7-(alkylsulfanyl)[1,4]dithiino[2,3-*d*]pyrimidine-6-carbonitrile derivatives (**6**). It is based on the reaction of 2-{[4-chloro-2-(methylsulfanyl)pyrimidin-5-yl]sulfanyl}acetonitriles (**2**), (**3**) and (**5**), easily prepared by sequences based on successive treatment of the corresponding 5-lithio derivatives

of DCSMP (**1**) or 4-chloro-6-methoxy-2-(methylsulfanyl)pyrimidine (**4**) with sulfur and 2-bromoacetonitrile, with carbon disulfide in the presence of sodium hydride followed by alkyl halides. [1,4]Dithiino[2,3-*d*]pyrimidine is a novel heterocyclic system that has not been reported previously in the literature, though the preparation of a compound involving this heterocyclic system, 2,4,6,8-tetrachloro[1,4]dithiino[2,3-*d*:6,5-*d*']dipyrimidine, has been recorded.[2]

The synthesis of 2-{[4-chloro-2-(methylsulfanyl)pyrimidin-5-yl]sulfanyl}acetonitriles (**2**) and (**3**) from DCSMP (**1**) was carried out according to the sequence outlined in Scheme 1. To prepare the 2-{[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]sulfanyl}acetonitrile (**2**), DCSMP (**1**) was treated with LDA in THF at –78 ˚C as described previously[1a] and the resulting 5-lithiated derivative was allowed to react successively with sulfur and 2-bromoacetonitrile at the same temperature to give the desired product in 76% yield. This compound was efficiently transformed into 4-dialkylamino derivatives (**3a**) and (**3b**) in good yields on treatment with secondary amines in DMF at 0 ˚C in the presence of triethylamine. Similarly, 4-alkyl(or aryl)sulfanyl derivatives (**3c**) and (**3d**) were obtained in fair yields using thiols in place of secondary amines. These results are shown in Table 1. However, when compound (**2**) was treated with methanol under these reaction conditions, the starting material was quantitatively recovered. The reaction of **2** with sodium methoxide resulted in the formation of an intractable mixture of products. After all, 4-methoxy derivative (**5**) was prepared in 57% yield by a successive treatment of 4-chloro-6-methoxy-2-(methylsulfanyl)pyrimidine (**4**) with LDA,[1a] sulfur, and 2-bromoacetonitrile, as shown in Scheme 2.



1 **2** 76% **3**

Scheme 1

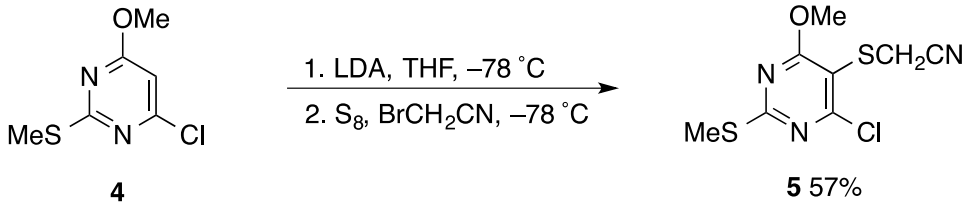
Table 1. Preparation of 2-[(pyrimidin-5-yl)sulfanyl]acetonitrile derivatives (**3**)

Entry	Y	**3**	Yield/%[a]
1	Me_2N	**3a**	78
2	piperidin-1-yl	**3b**	82
3	EtS	**3c**	70
4	PhS	**3d**	60

[a] Yields of isolated products.

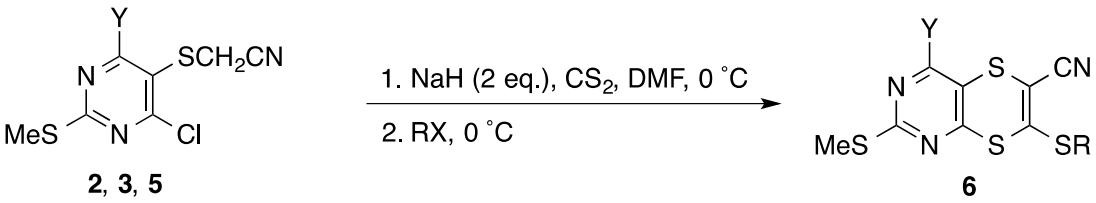
With 2-{[4-chloro-2-(methylsulfanyl)pyrimidin-5-yl]sulfanyl}acetonitriles (**2**), (**3**), and (**5**) in hand, we examined the reactions with carbon disulfides in the presence of a base. The reaction of these precursors

with excess carbon disulfide in the presence of two equivalents of sodium hydride followed by treatment with alkyl halides in DMF at 0 ˚C afforded, after aqueous work up and the subsequent purification of the crude products by column chromatography on silica gel, 4-substituted 7-(alkylsulfanyl)-2-(methylsulfanyl)[1,4]dithiino[2,3-*d*]pyrimidine-6-carbonitriles (**6**), as depicted in Scheme 3.



4 **5** 57%

Scheme 2



2, **3**, **5** **6**

Scheme 3

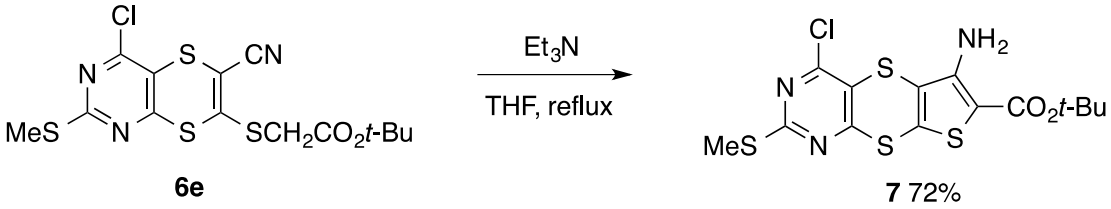
Table 2. Preparation of [1,4]dithiino[2,3-*d*]pyrimidine derivatives (**6**)

Entry	**2**, **3**, or **5**	Y	RX	**6**	Yield/%[a]
1	**2**	Cl	MeI	**6a**	88
2	**2**	Cl	CH_2=$CHCH_2Br$	**6b**	69
3	**2**	Cl	BnBr	**6c**	62
4	**2**	Cl	$PhCOCH_2Br$	**6d**	50
5	**2**	Cl	*t*-$BuOCOCH_2Br$	**6e**	56
6	**2**	Cl	$NCCH_2Br$	**6f**	39
7	**2**	Cl	$PhSCH_2Cl$	**6g**	18
8	**3a**	Me_2N	MeI	**6h**	58
9	**3b**	piperidin-1-yl	MeI	**6i**	62
10	**3c**	EtS	MeI	**6j**	60
11	**3d**	PhS	BnBr	**6k**	43
12	**5**	MeO	MeI	**6l**	76

[a] Yields of isolated products.

The results are summarized in Table 2. It indicates that phenacyl bromide and *tert*-butyl 2-bromoacetate are usable in the present reaction to afford the corresponding products (**6d**) and (**6e**) in moderate yields (Entries 4 and 5, respectively). Unfortunately, however, it was found that when 2-bromoacetonitrile was employed, a rather lower yield of the desired product was obtained (Entry 6). This may be due to the higher acidity of an α-hydrogen of this halide than those of phenacyl bromide and *tert*-butyl

2-bromoacetate. Chloromethyl phenyl sulfide is also usable to give the corresponding product (**6g**), albeit in a low yield (Entry 7). It should be noted that a non-activated halo alkane, such as 1-bromobutane, did not work well in the present reaction; no more than a trace amount of the expected product was obtained. Subsequently, one of compounds (**6**) was further transformed into a novel tricyclic heterocycle system as outlined in Scheme 4. Thus, compound (**6e**) was treated with an equivalent of triethylamine in refluxing THF to afford a thieno[3',2':5,6][1,4]dithiino[2,3-*d*]pyrimidine derivative (**7**) in a relatively good yield.



Scheme 4

The above-mentioned results demonstrate that the sodium hydride-mediated reaction of 2-{[4-chloropyrimidin-5-yl]sulfanyl}acetonitriles, derived easily from 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP), with carbon disulfide followed by alkyl halides provides a facile approach for the synthesis of a novel class of heterocycles, [1,4]dithiino[2,3-*d*]pyrimidines. Major advantages of the present method are that the starting materials are readily available and that the operations are very simple, and it may offer interesting pharmacophores.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded as KBr disks with a PerkinElmer Spectrum 65 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 and 125 MHz, respectively. High-resolution MS spectra were measured by a Thermo Scientific Exactive spectrometer (DART, positive or ESI, negative) or a JEOL JMS-T100GCV (FI, TOF; 2100V) spectrometer. Elemental analyses were performed with an Elementar Vario EL II instrument. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. 4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidine (**4**) was prepared according to the reported procedure.[1a] *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of Compounds (2) and (5). 2-{[4,6-Chloro-2-(methylsulfanyl)pyrimidin-5-yl]sulfanyl}acetonitrile (2). To a stirred solution of LDA (3.0 mmol), generated by the standard method from *i*-Pr_2NH and *n*-BuLi (1.6 M in hexane), in THF (9 mL) at –78 ˚C was added a solution of **1** (0.59 g, 3.0 mmol) in THF (2.5 mL) dropwise. After 15 min, a solution of S_8 (96 mg, 0.38 mmol) in THF (9.5 mL) and $BrCH_2CN$ (0.36 g, 3.0 mmol) was successively added. Stirring was continued for an additional 10 min before addition of saturated aqueous NH_4Cl (25 mL). The mixture was warmed to rt and extracted with AcOEt (3 × 20 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 (Et_2O/hexane 1:3) to give **2** (0.60 g, 76%); a pale-yellow solid; mp 111–113 ˚C (hexane/CH_2Cl_2); IR 2249, 1526 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60 (s, 3H), 3.67 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.7, 19.5, 114.9, 118.6, 166.6, 175.0. Anal. Calcd for $C_7H_5Cl_2N_3S_2$: C, 31.59; H, 1.89; N, 15.79; S, 24.09. Found: C, 31.46; H, 1.65; N, 15.69; S, 23.97.

2-{[4-Chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]sulfanyl}acetonitrile (5): a white solid; mp 114–116 ˚C (hexane/CH_2Cl_2); IR 2243, 1545 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.57 (s, 3H), 3.59 (s, 2H), 4.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 14.5, 19.0, 55.8, 105.3, 115.6, 164.5, 169.1, 173.6. Anal. Calcd for $C_8H_8ClN_3OS_2$: C, 36.71; H, 3.08; N, 16.05. Found: C, 38.76; H, 2.99; N, 16.18.

Typical Procedure for the 6-Dialkylaminated or 6-Sulfanylated Compounds (3). 2-{[4-Chloro-6-(dimethylamino)-2-(methylsulfanyl)pyrimidin-5-yl]sulfanyl}acetonitrile (3a). To a stirred solution of **2** (0.11 g, 0.40 mmol) in DMF (2.5 mL) containing Et_3N (40 mg, 0.40 mmol) at 0 ˚C was added Me_2NH (50% in water; 36 mg, 0.40 mmol). The mixture was warmed to rt and stirring was continued for 10 min before addition of saturated aqueous NH_4Cl (10 mL). The mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with H_2O (3 × 15 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was recrystallized to give **3a** (85 mg, 78%); a beige solid; mp 141–143 ˚C (hexane/CH_2Cl_2); IR 2240, 1558 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (s, 3H), 3.31 (s, 6H), 3.43 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.3, 21.2, 42.1, 100.0, 115.6, 164.7, 166.7, 171.3. Anal. Calcd for $C_9H_{11}ClN_4S_2$: C, 39.34; H, 4.04; N, 20.39. Found: C, 39.19; H, 4.03; N, 20.35.

2-{[4-Chloro-2-(methylsulfanyl)-6-(piperidin-1-yl)pyrimidin-5-yl]sulfanyl}acetonitrile (3b): a white solid; mp 175–177 ˚C (hexane/CH_2Cl_2); IR 2239, 1534 cm^{-1}; ^1H NMR (THF-d_8) δ 1.50 (br s, 6H), 2.24 (s, 3H), 3.36 (br s, 4H), 3.45 (s, 2H); ^{13}C NMR (THF-d_8) δ 13.3, 19.5, 24.9, 25.6, 50.0, 103.5, 115.7, 165.7, 166.2, 171.2. Anal. Calcd for $C_{12}H_{15}ClN_4S_2$: C, 45.78; H, 4.80; N, 17.80; S, 20.37. Found: C, 45.41; H, 4.77; N, 18.07; S, 20.41.

2-{[4-Chloro-6-(ethylsulfanyl)-2-(methylsulfanyl)pyrimidin-5-yl]sulfanyl}acetonitrile (3c): a white solid; mp 106–108 ˚C (hexane/CH_2Cl_2); IR 2246, 1514 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (t, J = 7.4 Hz, 3H),

2.55 (s, 3H), 3.15 (q, *J* = 7.4 Hz, 2H), 3.59 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 13.8, 14.5, 18.7, 26.0, 114.9, 115.1, 164.1, 173.8, 177.5. Anal. Calcd for $C_9H_{10}ClN_3S_3$: C, 37.04; H, 3.45; N, 14.40. Found: C, 36.97; H, 3.41; N, 14.46.

2-{[4-Chloro-2-(methylsulfanyl)-6-(phenylsulfanyl)pyrimidin-5-yl]sulfanyl}acetonitrile (3d): a pale-yellow solid; mp 83–85 ˚C (hexane/CH_2Cl_2); IR 2246, 1508 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3H), 3.70 (s, 2H), 7.42–7.47 (m, 3H), 7.53 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 19.1, 113.9, 115.0, 128.2, 129.2, 129.9, 136.1, 164.2, 173.5, 178.0. Anal. Calcd for $C_{13}H_{10}ClN_3S_3$: C, 45.94; H, 2.97; N, 12.36; S, 28.30. Found: C, 45.85; H, 2.84; N, 12.16; S, 28.45.

Typical Procedure for the Preparation of Dithiinopyrimidines (6). 4-Chloro-2,7-bis(methylsulfanyl)[1,4]dithiino[2,3-*d*]pyrimidine-6-carbonitrile (6a). To a stirred solution of **2** (0.14 g, 0.52 mmol) and freshly distilled CS_2 (0.20 g, 2.6 mmol) in DMF (4 mL) at 0 ˚C was added NaH (60% in mineral oil; 25 mg, 1.0 mmol) in several portions and stirring was continued for 1 h at the same temperature. MeI (73 mg, 0.52 mmol) was then added and 15 min later the resulting mixture was worked up as described for the preparation of **1a**. The residue was purified by column chromatography on SiO_2 (AcOEt/hexane 1:13) to give **6a** (0.14 g, 88%); a pale-yellow solid; mp 133–135 ˚C (hexane/CH_2Cl_2); IR 2211, 1509 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H), 2.68 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 14.6, 18.7, 95.7, 113.6, 119.5, 156.3, 157.6, 165.6, 172.7. HR-MS (DART). Calcd for $C_9H_7ClN_3S_4$ (M+H): 319.9211. Found: *m*/*z* 319.9208. Anal. Calcd for $C_9H_6ClN_3S_4$: C, 33.80; H, 1.89; N, 13.14. Found: C, 34.05; H, 1.69; N, 13.20.

4-Chloro-2-(methylsulfanyl)-7-[(prop-2-enyl)sulfanyl][1,4]dithiino[2,3-*d*]pyrimidine-6-carbonitrile (6b): a yellow solid; mp 80–82 ˚C (hexane/CH_2Cl_2); IR 2214, 1635, 1523 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H), 3.76 (d, *J* = 6.9 Hz, 2H), 5.16 (d, *J* = 10.3 Hz, 1H), 5.23 (d, *J* = 16.6 Hz, 1H), 5.75–5.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.6, 38.8, 100.3, 113.5, 119.2, 120.3, 131.3, 153.1, 157.5, 165.6, 172.8. HR-MS (DART). Calcd for $C_{11}H_9ClN_3S_4$ (M+H): 345.9368. Found: *m*/*z* 345.9362. Anal. Calcd for $C_{11}H_8ClN_3S_4$: C, 38.20; H, 2.33; N, 12.15. Found: C, 38.04; H, 2.09; N, 12.15.

4-Chloro-2-(methylsulfanyl)-7-[(phenylmethyl)sulfanyl][1,4]dithiino[2,3-*d*]pyrimidine-6-carbonitrile (6c): a yellow solid; 119–121 ˚C (hexane/CH_2Cl_2); IR 2207, 1511 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.58 (s, 3H), 4.32 (s, 2H), 7.23–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.6, 40.5, 101.3, 113.4, 118.8, 128.1, 128.7, 129.3, 134.5, 152.7, 157.5, 165.9, 172.8. HR-MS (DART). Calcd for $C_{15}H_{11}ClN_3S_4$ (M+H): 395.9524. Found: *m*/*z* 395.9518. Anal. Calcd for $C_{15}H_{10}ClN_3S_4$: C, 45.50; H, 2.55; N, 10.61. Found: C, 45.34; H, 2.29; N, 10.66.

7-[(Benzoylmethyl)sulfanyl]-4-chloro-2-(methylsulfanyl)[1,4]dithiino[2,3-*d*]pyrimidine-6-carbonitrile (6d): a pale-yellow solid; mp 117–119 ˚C (hexane/CH_2Cl_2); IR 2210, 1690, 1517 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 4.62 (s, 2H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.92 (d, *J* = 7.4 Hz,

2H); ^{13}C NMR ($CDCl_3$) δ 14.6, 41.9, 100.2, 113.3, 119.1, 128.5, 129.0, 134.3, 134.9, 152.6, 157.6, 165.6, 172.9, 191.8. HR-MS (DART). Calcd for $C_{16}H_{11}ClN_3OS_4$ (M+H): 423.9473. Found: *m*/*z* 423.9467. Anal. Calcd for $C_{16}H_{10}ClN_3OS_4$: C, 45.33; H, 2.38; N, 9.91; S, 30.25. Found: C, 45.06; H, 2.24; N, 9.66; S, 30.24.

1,1-Dimethylethyl 2-{[4-Chloro-6-cyano-2-(methylsulfanyl)[1,4]dithiino[2,3-*d*]pyrimidin-7-yl]sulfanyl}acetate (6e): a pale-yellow solid; mp 103–105 ˚C (hexane/CH_2Cl_2); IR 2216, 1733, 1513 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 2.56 (s, 3H), 3.78 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.6, 27.8, 37.7, 83.4, 100.2, 113.2, 119.2, 152.6, 157.6, 165.6, 166.2, 173.0. HR-MS (DART). Calcd for $C_{14}H_{15}ClN_3O_2S_4$ (M+H): 419.9735. Found: *m*/*z* 419.9725. Anal. Calcd for $C_{14}H_{14}ClN_3O_2S_4$: C, 40.04; H, 3.36; N, 10.01. Found: C, 40.05; H, 3.39; N, 9.97.

4-Chloro-6-[(cyanomethyl)sulfanyl]-2-(methylsulfanyl)[1,4]dithiino[2,3-*d*]pyrimidine-6-carbonitrile (6f): a yellow solid; mp 153–155 ˚C (hexane/CH_2Cl_2); IR 2254, 2223, 1516 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H), 3.87 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.7, 20.7, 105.5, 112.5, 114.0, 118.2, 147.4, 157.7, 164.4, 173.6. HR-MS (DART). Calcd for $C_{10}H_6ClN_4S_4$ (M+H): 344.9164. Found: *m*/*z* 344.9152. Anal. Calcd for $C_{10}H_5ClN_4S_4$: C, 34.83; H, 1.46; N, 16.25. Found: C, 35.02; H, 1.44; N, 16.12.

4-Chloro-2-(methylsulfanyl)-7-{[(phenylsulfanyl)methyl]sulfanyl}[1,4]dithiino[2,3-*d*]pyrimidine-6-carbonitrile (6g): a yellow solid; mp 82–84 ˚C (hexane/CH_2Cl_2); IR 2214, 1514 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.58 (s, 3H), 4.53 (s, 2H), 7.18–7.23 (m, 3H), 7.50 (dd, *J* = 7.4, 1.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.6, 43.0, 101.2, 113.3, 118.6, 128.4, 129.0, 132.0, 133.4, 151.2, 157.3, 165.3, 172.8. HR-MS (FI). Calcd for $C_{15}H_{10}ClN_3S_5$ (M): 426.9167. Found: *m*/*z* 426.9163. Anal. Calcd for $C_{15}H_{10}ClN_3S_5$: C, 42.09; H, 2.36; N, 9.82. Found: C, 42.07; H, 2.24; N, 9.78.

4-(Dimethylamino)-2,7-bis(methylsulfanyl)[1,4]dithiino[2,3-*d*]pyrimidine-6-carbonitrile (6h): a beige solid; mp 148–150 ˚C (hexane/CH_2Cl_2); IR 2207, 1543 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 2.68 (s, 3H), 3.30 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 14.3, 18.9, 41.0, 95.9, 101.6, 114.5, 160.2, 161.4, 166.8, 169.9. HR-MS (DART). Calcd for $C_{11}H_{13}N_4S_4$ (M+H): 329.0023. Found: *m*/*z* 329.0007. Anal. Calcd for $C_{11}H_{12}N_4S_4$: C, 40.22; H, 3.68; N, 17.06. Found: C, 40.13; H, 3.65; N, 17.11.

2,7-Bis(methylsulfanyl)-4-(piperidin-1-yl)[1,4]dithiino[2,3-*d*]pyrimidine-6-carbonitrile (6i): a pale-yellow solid; mp 86–88 ˚C (hexane/CH_2Cl_2); IR 2214, 1534 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.71 (br s, 6H), 2.49 (s, 3H), 2.68 (s, 3H), 3.72 (br s, 4H); ^{13}C NMR ($CDCl_3$) δ 14.3, 18.8, 24.3, 25.8, 49.3, 95.6, 103.4, 114.5, 160.7, 160.8, 166.2, 170.2. HR-MS (DART). Calcd for $C_{14}H_{17}N_4S_4$ (M+H): 369.0336. Found: *m*/*z* 369.0329. Anal. Calcd for $C_{14}H_{16}N_4S_4$: C, 45.63; H, 4.38; N, 15.20; S, 34.80. Found: C, 45.62; H, 4.28; N, 15.32; S, 35.10.

4-(Ethylsulfanyl)-2,7-bis(methylsulfanyl)[1,4]dithiino[2,3-*d*]pyrimidine-6-carbonitrile (6j): a pale-yellow solid; mp 154–156 ˚C (hexane/CH_2Cl_2); IR 2213, 1508 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (t, J = 7.4 Hz, 3H), 2.56 (s, 3H), 2.66 (s, 3H), 3.23 (q, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.4, 18.7, 25.1, 95.7, 113.9, 116.5, 157.2, 162.4, 168.8, 171.1. HR-MS (DART). Calcd for $C_{11}H_{12}N_3S_5$ (M+H): 345.9635. Found: *m*/*z* 345.9628. Anal. Calcd for $C_{11}H_{11}N_3S_5$: C, 38.24; H, 3.21; N, 12.16; S, 46.40. Found: C, 37.96; H, 3.02; N, 12.21; S, 46.06.

2-(Methylsulfanyl)-7-[(phenylmethyl)sulfanyl]-4-(phenylsulfanyl)[1,4]dithiino[2,3-*d*]pyrimidine-6-carbonitrile (6k): a pale-yellow solid; mp 152–154 ˚C (hexane/CH_2Cl_2); IR 2214, 1518 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (s, 3H), 4.32 (s, 2H), 7.23–7.29 (m, 5H), 7.43–7.48 (m, 3H), 7.52 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 40.6, 100.5, 113.8, 115.0, 126.9, 128.0, 128.7, 129.2, 129.3, 130.0, 134.7, 136.1, 154.1, 163.4, 168.7, 171.3. HR-MS (DART). Calcd for $C_{21}H_{16}N_3S_5$ (M+H): 469.9948. Found: *m*/*z* 469.9944. Anal. Calcd for $C_{21}H_{15}N_3S_5$: C, 53.70; H, 3.22; N, 8.95. Found: C, 53.59; H, 3.09; N, 8.88.

4-Methoxy-2,7-bis(methylsulfanyl)[1,4]dithiino[2,3-*d*]pyrimidine-6-carbonitrile (6l): a pale-yellow solid; mp 149–151 ˚C (hexane/CH_2Cl_2); IR 2204, 1532 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.55 (s, 3H), 2.65 (s, 3H), 4.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 14.4, 18.6, 55.2, 96.5, 106.4, 114.0, 156.4, 163.9, 164.5, 172.0. HR-MS (DART). Calcd for $C_{10}H_{10}N_3OS_4$ (M+H): 315.9706. Found: *m*/*z* 315.9701. Anal. Calcd for $C_{10}H_9N_3OS_4$: C, 38.08; H, 2.88; N, 13.32; S, 40.65. Found: C, 38.00; H, 2.69; N, 13.39; S, 40.60.

1,1-Dimethylethyl 6-Amino-4-chloro-2-(methylsulfanyl)thieno[3',2':5,6][1,4]dithiino[2,3-*d*]pyrimidine-2-carboxylate (7). A solution of **6e** (84 mg, 0.20 mmol) in THF (5 mL) containing Et_3N (20 mg, 0.20 mmol) was refluxed for 8h. After cooling the resulting solution was concentrated by evaporation. The residual solid was recrystallized to give **7** (60 mg, 72%); a pale-yellow solid; mp 170–172 ˚C (hexane/CH_2Cl_2); IR 3472, 3359, 1674 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (s, 9H), 2.55 (s, 3H), 5.53 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.5, 28.4, 81.8, 105.0, 117.4, 119.7, 132.5, 148.7, 157.2, 162.9, 167.7, 171.0. HR-MS (ESI). Calcd for $C_{14}H_{13}ClN_3O_2S_4$ (M–H): 417.9579. Found: *m*/*z* 417.9592. Anal. Calcd for $C_{14}H_{14}ClN_3O_2S_4$: C, 40.04; H, 3.36; N, 10.01. Found: C, 39.76; H, 3.42; N, 9.86.

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