Diarylthiopyrimidines And Pyridines: Synthesis And Biological Activity

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Prior work with diarylethers of pyrimidine, pyridine, and benzene showed encouraging antitumor results. As an extension of that work the synthesis of diarylthio derivatives of pyrimidine and pyridine has been accomplished. The synthetic scheme employed the nucleophilic displacement of chlorines from trichloropyrimidine, **1**, dichloropyrimidines **4** and **6**, and 2,6-dichloropyridine **8** using the anion of thiophenols **2**. Antitumor evaluation by the National Cancer Institute showed no useful activity.

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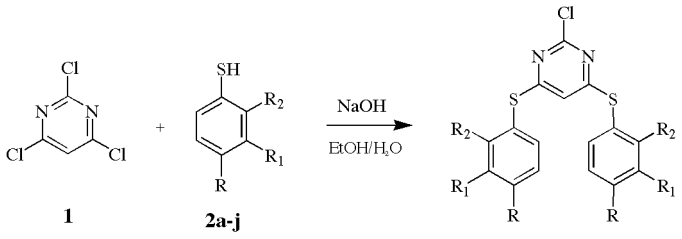
Previous work in our laboratories involved the synthesis of diarylether derivatives of pyrimidine, pyridine, and benzene [1,2]. Several of these compounds exhibited modest antitumor activity [3]. We were interested in exploiting this observation by preparing a series of sulfur-based analogs, a logical extension of the oxygen-bridged derivatives.

The literature has shown very little work in which halogenated heterocycles such as pyrimidines and pyridines have been subjected to nucleophilic displacement reactions by sulfur nucleophiles. For example, treatment of 2,4,6-trichloropyrimidine **1** with potassium hydrogen sulfide affords the corresponding trithiol in 55% yield [4]. Other halogenated pyrimidines have been subjected to reaction with a variety of sodium or potassium salts of alkylthiols and sodium salts of thiophenols [5].

Based on the earlier observation that a pyrimidine containing two 4-substituted phenoxy groups had antitumor activity that warranted further testing, the current goal was to maintain the theme of bis-4-substitutedphenyl derivatives with the oxygen bridge being replaced by a sulfur atom. We describe in this report a synthesis of 2,4- and 4,6-diarylthiopyrimidines and 2,6-diarylthiopyridines. Results of their biological screening as potential antitumor agents are also provided.

Our initial focus was on the nucleophilic displacement of two chlorine atoms from **1** (Scheme 1). Earlier results from the reaction of phenolate ions [2] with **1** suggested that a similar substitution pattern would be seen when the thiophenolate ions **2** were employed. So we were not surprised when the only disubstituted products obtained were those in which the 4- and 6- chloro groups were replaced to give **3**. No evidence of a 2,4-disubstituted product was observed. The initial evidence for this assignment was obtained from the ^{1}H nmr spectra of all of the products, **3**. Only one set of signals attributable to the phenyl ring was observed indicating the symmetrical 4,6-disubstitution pattern rather than the unsymmetrical 2,4-disubstitution pattern. To confirm this initial assignment the X-ray determination of the structure of **3d** was obtained. The x-ray crystallographic analysis of **3d** provided confirmation [6] that the substitution pattern was indeed at the 4- and 6-positions (Figure 1).

Scheme 1



Compound	R	R^1	R^2	Compound	R	R^1	R^2
a	H	H	H	**f**	CH_3O	H	H
b	CH_3	H	H	**g**	H	NH_2	H
c	CH_3	H	CH_3	**h**	Cl	H	H
d	H	H	CH_3O	**i**	NO_2	H	H
e	H	CH_3	H	**j**	CN	H	H

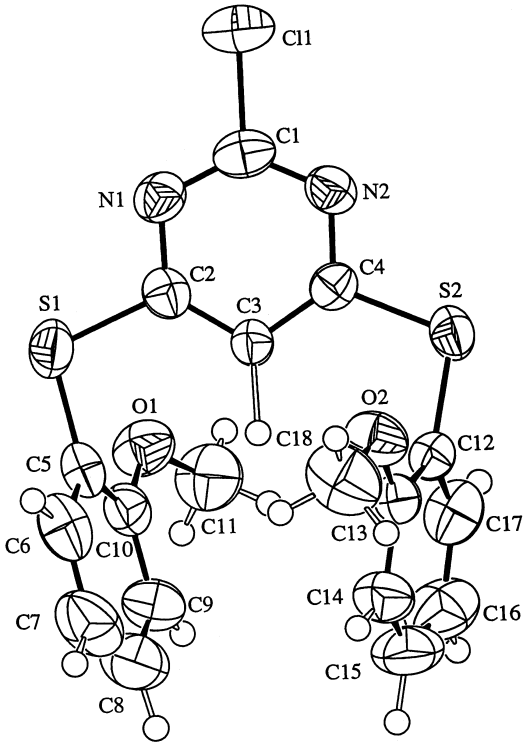
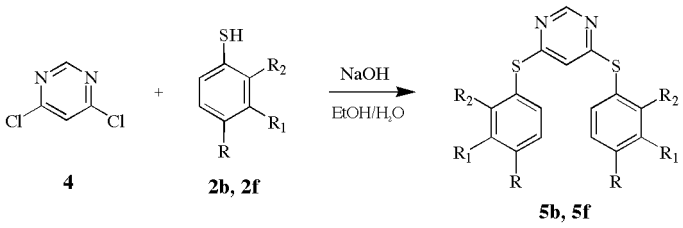


Figure 1. ORTEP drawing of **3d**.

In a typical reaction the thiophenol is treated with one equivalent of sodium hydroxide in ethanol. Complete solution of the sodium hydroxide was achieved by prior heating with subsequent cooling to room temperature prior to addition of **2**. When the thiophenol **2** is added to the ethanolic base the resulting solution is allowed to stir for approximately one to two hours at room temperature. After addition of **1** and workup, the 4,6-disubstituted derivatives **3** were obtained. As seen in the experimental section yields of **3** under these conditions averaged 30 percent, ranging from 2 percent to 57 percent. No effort was made to heat these reactions because of a concern that solvolysis could occur at one or more of the chloro groups. We have seen such solvolyses occur when extensive heating in ethanol was employed during the attempted replacement of the chlorine atoms in **1** by anilines [7]. There does not appear to be any trend in yields as a function of the electronic or steric attributes of the substituent. We have no good explanation for the particularly poor yield of **3f**. One obvious explanation for the mediocre yields may be the inefficient deprotonation of the thiophenols under the conditions employed.

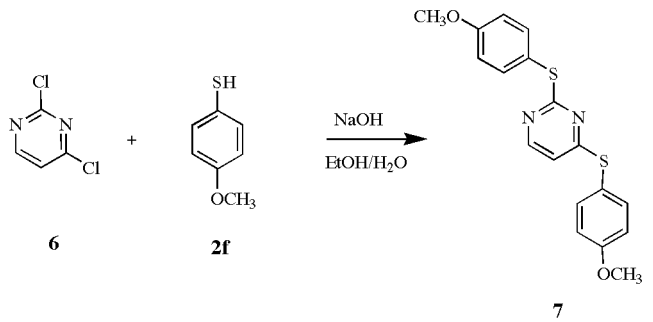
In an effort to ascertain the biological effect of the unreplaced chlorine in **3**, 4,6-dichlorpyrimidine **4** was treated with two equivalents of the thiophenoxy anions **2b** and **2f** (Scheme 2) and afforded the expected disubstituted products **5b** and **5f**. 2,4-Dichloropyrimidine **6** was similarly treated with two equivalents of the thiophenoxy anion of **2f** (Scheme 3) providing the corresponding disubstituted pyrimidine **7**. Of course in each of these cases the position of the arylthio groups is unambiguous.

Scheme 2



4 **2b, 2f** **5b, 5f**

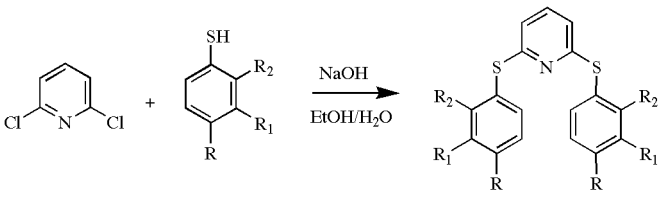
Scheme 3



6 **2f** **7**

In a similar way the pyridine derivatives **9e** and **9k** were derived from 2,6-dichlorpyridine **8** and two equivalents of the anions of the corresponding thiophenols **2e** and **2k** (Scheme 4).

Scheme 4



8 **2e, 2k** **9e, 9k**

All of the compounds in this study were transmitted to the National Cancer Institute and screened in their standard panel of approximately 60 tumor cell lines that has been previously described [8]. Initially, compound **3f** exhibited useful preliminary activity with values for Log_{10}GI50 (-5.15), Log_{10} TGI (-4.75), and Log_{10}LC50 (-4.37). Values lower than approximately -4.00 are considered active in this screen. Since this was a 4-substitutedphenyl derivative and the substituent represented the more active donor group in the collection we sought to ascertain the importance of the position of the substituent. Consequently **3d** and **3e** were prepared which provided positional isomers of **3f**. We also prepared **3g**, a 3-aminophenylsubstituted compound. Only **3g** gave positive results in the initial National Cancer Institute screen. The values obtained were –4.15 for Log_{10} GI50, -4.37 for Log_{10} TGI, and –4.09 for Log_{10} LC50.

Compounds **3f** and **3g** were submitted for further testing in the *in vivo* mouse hollow fiber assay [9]. Unfortunately neither of these compounds proved to be sufficiently active to justify further testing.

Compounds **5f** and **7** were designed to assess the importance of the chloro substituent on the pyrimidine ring. Neither compound possessed a value below -4.00 to warrant further exploration.

Finally, the pyridine derivatives **9c** and **9k** were synthesized to test the original central ring in biological importance. These, too, failed to demonstrate any preliminary activity, as defined above.

EXPERIMENTAL

General Conditions.

Melting points are uncorrected and were determined in open capillary tubes using either a Thomas Hoover or MelTemp instrument. The ^{1}H nmr (at 300 MHz) spectra were recorded on a QE-300 NMR Spectrometer in deuteriochloroform, deuterioacetonitrile, or dimethylsulfoxide-d_6, with tetramethylsilane as the internal standard. All values are reported in ppm relative to tetramethylsilane. Mass spectra were measured on a Hewlett Packard 5995A GC/MS instrument, using a direct insertion probe.

2-Chloro-4,6-bis(phenyl)sulfanylpyrimidine (**3a**).

To an ethanolic solution containing sodium hydroxide (0.335 g; 8.38 mmol) was added thiophenol **2a** (1.07 g; 9.37 mmol). This mixture was allowed to stir at room temperature for two hours. 2,4,6-Trichloropyrimidine **1** (1.83 g; 10 mmol) was added slowly and the mixture stirred for an additional 10 minutes.

Upon removal of the solvent under vacuum a solid residue was obtained. This solid was washed with water and recrystallized from acetonitrile to give pure **3a**, mp 156-8 °C (34 %); ^{1}H nmr (dimethylsulfoxide-d_6): δ 7.40 (d, 4H), 7.32 (d, 4H), 7.28 (t, 2H), 5.80 (s, 1H); ms (m/z): 332 (44), 331 (60), 330 (100), 329 (87), 221 (38), 160 (56), 138 (43).

Anal Calcd for $C_{16}H_{11}ClN_2S_2$: C, 58.08; H, 3.35; N, 8.47. Found: C, 57.83, H, 3.47, N, 8.47.

2-Chloro-4,6-bis-((4-methyl)phenyl)sulfanylpyrimidine (**3b**).

The crude product, obtained as for **3a**, was recrystallized from acetonitrile to give pure **3b**, mp 129-31 °C (23 %); ^{1}H nmr (dimethylsulfoxide-d_6): δ 7.30 (d, 4H), 7.20 (d, 4H), 5.86 (s, 1H), 2.32 (s, 6H); ms (m/z): 360 (56), 359 (71), 358 (100), 234 (33), 174 (31).

Anal Calcd for $C_{18}H_{15}ClN_2S_2$: C, 60.24; H, 4.21; N, 7.80. Found: C, 60.35, H, 4.27, N, 7.83.

2-Chloro-4,6-bis-((2,4-dimethyl)phenyl)sulfanylpyrimidine (**3c**).

The crude product, obtained as for **3a**, was recrystallized from acetonitrile to give pure **3c**, mp 132-4 °C (40 %); ^{1}H nmr (deuteriochloroform): δ 7.25 (d, 2H), 6.97 (s, 2H), 6.92 (d, 2H), 5.50 (s, 1H), 2.40 (s, 6H), 2.20 (s, 6H); ms (m/z): 388 (22), 387 (12), 386 (55), 355 (42), 354 (26), 353 (100).

Anal Calcd for $C_{20}H_{19}ClN_2S_2$: C, 62.08; H, 4.95; N, 7.24. Found: C, 62.11, H, 5.04, N, 7.27.

2-Chloro-4,6-bis-((2-methoxy)phenyl)sulfanylpyrimidine (**3d**).

The crude product, obtained as for **3a**, was recrystallized from acetonitrile to give pure **3d**, mp 145-6 °C (32 %); ^{1}H nmr (deuteriochloroform): δ 7.40 (m, 4H), 6.92 (t, 2H), 6.75 (d, 2H), 5.74 (s, 1H), 3.60 (s, 6H); ms (m/z): 390 (11), 361 (43), 360 (21), 359 (100).

Anal Calcd for $C_{18}H_{15}ClN_2O_2S_2$: C, 55.31; H, 3.87; N, 7.17. Found: C, 55.44, H, 3.91, N, 7.17.

2-Chloro-4,6-bis-((3-methoxy)phenyl)sulfanylpyrimidine (**3e**).

The crude product, obtained as for **3a**, was recrystallized from hexane to give pure **3e**, mp 115-8 °C (21 %); ^{1}H nmr (deuteriochloroform): δ 7.25 (t, 2H), 6.95 (m, 6H), 5.80 (s, 1H), 3.80 (s, 6H); ms (m/z): 392 (46), 391 (60), 390 (100), 389 (92).

Anal Calcd for $C_{18}H_{15}ClN_2O_2S_2$: C, 55.31; H, 3.87; N, 7.17. Found: C, 55.26, H, 3.92, N, 7.15.

2-Chloro-4,6-bis-((4-methoxy)phenyl)sulfanylpyrimidine (**3f**).

The crude product, obtained as for **3a**, was recrystallized from acetonitrile to give pure **3f**, mp 122-4 °C (2 %); ^{1}H nmr (dimethylsulfoxide-d_6): δ 7.26 (d, 4H), 6.90 (d, 4H), 5.70 (s, 1H), 3.81 (s, 6H); ms (m/z): 392 (45), 391 (36), 390 (100), 389 (34).

Anal Calcd for $C_{18}H_{15}ClN_2O_2S_2$: C, 55.31; H, 3.87; N, 7.17. Found: C, 55.23, H, 3.91, N, 7.13.

2-Chloro-4,6-bis-((3-amino)phenyl)sulfanylpyrimidine (**3g**).

The crude product, obtained as for **3a**, was recrystallized from toluene to give pure **3g**, mp 140 °C dec (44 %); ^{1}H nmr (deuteriochloroform/deuterioacetonitrile): δ 7.11 (t, 2H), 6.72 (m, 6H), 5.99 (s, 1H), 3.50 (br s, 4H); ms (m/z): 362 (33), 361 (44), 360 (100), 359 (43), 327 (39).

Anal Calcd for $C_{16}H_{13}ClN_4S_2$: C, 53.25; H, 3.63; N, 15.52. Found: C, 53.56, H, 3.70, N, 15.16.

2-Chloro-4,6-bis-((4-chloro)phenyl)sulfanylpyrimidine (**3h**).

The crude product, obtained as for **3a**, was recrystallized from acetonitrile to give pure **3h**, mp 166-8 °C (57 %); ^{1}H nmr (dimethylsulfoxide-d_6): δ 7.49 (s, 8H), 5.98 (s, 1H); ms (m/z): 402 (37), 401 (37), 400 (100), 399 (76), 398 (78), 397 (61), 256 (35), 254 (40).

Anal Calcd for $C_{16}H_9Cl_3N_2S_2$: C, 48.07; H, 2.27; N, 7.01. Found: C, 47.92, H, 2.26, N, 7.03.

2-Chloro-4,6-bis-((4-nitro)phenyl)sulfanylpyrimidine (**3i**).

The crude product, obtained as for **3a**, was recrystallized from acetonitrile to give pure **3i**, mp 226-8 °C (24 %); ^{1}H nmr (dimethylsulfoxide-d_6): δ 8.22 (d, 4H), 7.82 (d, 4H), 6.61 (s, 1H); ms (m/z): 422 (38), 421 (44), 420 (100), 385 (20), 300 (46).

Anal Calcd for $C_{16}H_9ClN_4O_4S_2$: C, 45.66; H, 2.16; N, 13.31. Found: C, 45.68, H, 2.13, N, 13.28.

4,6-Bis-((4-methyl)phenyl)sulfanylpyrimidine (**5b**).

The crude product, obtained as for **3a**, was recrystallized from acetonitrile to give pure **5b**, mp 118-9 °C (40 %); ^{1}H nmr (dimethylsulfoxide-d_6): δ 7.30 (d, 4H), 7.19 (d, 4H), 5.95 (s, 1H), 2.34 (s, 6H); ms (m/z): 344 (57), 323 (100), 171 (19).

Anal Calcd for $C_{18}H_{16}N_2S_2$: C, 66.63; H, 4.97; N, 8.63. Found: C, 66.75, H, 5.11, N, 8.72.

4,6-Bis-((4-methoxy)phenyl)sulfanylpyrimidine (**5f**).

The crude product, obtained as for **3a**, was recrystallized from acetonitrile to give pure **5f**, mp 116-8 °C (21 %); ^{1}H nmr (dimethylsulfoxide-d_6): δ 8.52 (s, 1H), 7.30 (d, 4H), 6.90 (d, 4H), 5.80 (s, 1H), 3.75 (s, 6H); ms (m/z): 356 (86), 355 (100).

Anal Calcd for $C_{18}H_{16}N_2O_2S_2$: C, 60.65; H, 4.52; N, 7.86. Found: C, 60.54, H, 4.62, N, 7.77.

2,4-Bis-((4-methoxy)phenyl)sulfanylpyrimidine (**7**).

The crude product, obtained as for **3a**, was recrystallized from acetonitrile to give pure **7**, mp 100-1 °C (31 %); ^{1}H nmr (dimethylsulfoxide-d_6): δ 8.18 (d, 1H), 7.45 (dd, 4H), 6.99 (dd, 4H), 6.51 (d, 1H), 3.56 (s, 6H); ms (m/z): 357 (31), 356 (100), 355 (79), 217 (38).

Anal Calcd for $C_{18}H_{16}N_2O_2S_2$: C, 60.65; H, 4.52; N, 7.86. Found: C, 60.76, H, 4.58, N, 7.77.

2,6-Bis-((3-methoxy)phenyl)sulfanylpyridine (**9e**).

The crude product, obtained as for **3a**, was recrystallized from acetonitrile to give pure **9e**, mp 138-40 °C (27 %); ^{1}H nmr (deuteriochloroform): δ 7.30 (t, 2H), 7.18 (overlapping signals, 5H), 6.94 (m, 2H), 6.58 (d, 2H), 2.83 (s, 6H); ms (m/z): 356 (36), 355 (100), 354 (91).

Anal Calcd for $C_{19}H_{17}NO_2S_2$: C, 64.20; H, 4.82; N, 3.94. Found: C, 63.97, H, 4.80, N, 3.93.

2,6-Bis-((4-cyano)phenyl)sulfanylpyridine (**9k**).

The crude product, obtained as for **3a**, was recrystallized from acetonitrile to give pure **9k**, mp 236-9 °C (42 %); ^{1}H nmr (dimethylsulfoxide-d_6): δ 7.77 (d, 4H), 7.67 (t, 1H), 7.55 (d, 4H), 7.15 (d, 2H); ms (m/z): 345 (15), 344 (20), 301 (20), 283 (56), 171 (100).

Anal Calcd for $C_{19}H_{11}N_3S_2 \cdot 0.25H_2O$: C, 65.21; H, 3.31; N, 12.01. Found: C, 65.34, H, 3.27, N, 12.14.

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[6] Crystallographic data (excluding structural factors) for compound **3d** have been deposited with the Cambridge Crystallographic Data Centre with the supplementary publication number 163859. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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