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The reaction of thioesters with nitriles. A new synthetic approach to the preparation of substituted 4-alkylthio- and 4-arylthiopyrimidine derivatives

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Abstract—*S*-Alkyl and *S*-aryl thioesters react with nitriles in the presence of triflic anhydride to form substituted 4-alkylthio- and 4-arylthiopyrimidines. However, when methyl thiocyanate is used as nitrile, dithioimidocarbonates are formed. A mechanism to explain these differences is postulated.

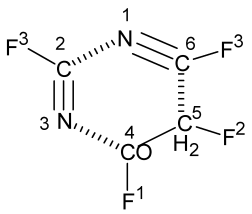
1. Introduction

The pyrimidine ring system is present in many natural products, pharmaceuticals, agrochemicals, etc. Thus, there is a continuous quest for efficient methods of synthesis of pyrimidine derivatives.[1,2] Among these substances, alkylthio and arylthiopyrimidines are compounds of great interest. Alkylthiopyrimidines are widely used as agrochemicals. Particularly, 4-alkylthiopyrimidine derivatives have shown excellent broad spectrum herbicidal activity in transplanted paddy rice.[3] Alkylthiopyrimidones are precursors for the preparation of anilinopyrimidones, which are useful as insecticidal and acaricidal agents capable of controlling pest of agrohorticultural plants.[4] 2-Alkylthiopyrimidine derivatives have also found application as agrochemical fungicides.[5,6] Herbicidal compositions based on 5-alkylthiopyrimidines are used as postemergence herbicides for cereals.[7,8] Recent investigations have demonstrated that substituted 6-methylthiopyrimidines present antimicrobial activity against pathogenic bacterial agents including *Mycobacterium tuberculosis*.[9] The worldwide resurgence of tuberculosis caused by multiresistant strains of this bacteria has made this application significant. Cephalosporin compounds which have 3-[(aminopyridiniumyl)thio]methyl substituents show high antimicrobial activity against various bacterial species including *Pseudomonas aeruginosa*.[10] Alkylthio analogs of dihydroalkoxybenzyloxopyrimidines (DABOs) are 10-fold more potent than their parent compounds in inhibiting the multiplication of HIV-1 in vitro.[11]

In the field of synthetic organic chemistry, alkylthio and arylthiopyrimidines are useful intermediates in the preparation of highly substituted pyrimidines by nucleophilic substitution reactions.[12] 2-Methylthiopyrimidines are particularly reactive substrates toward the palladium-catalyzed cross-coupling reaction with benzylic reagents.[13]

Many methods for preparing alkylthio- and arylthiopyrimidines are described in the literature.[1] In spite of their importance, only a few procedures for the preparation of these compounds do not involve multiple step sequences.

The cocyclization of ketones and aliphatic and aromatic nitriles promoted by Tf_2O is a versatile route to substituted alkyl and arylpyrimidines.[14] The pyrimidine ring is formed by a cyclization reaction of two nitrile units and one unit of the corresponding carbonyl compound. The two cyano carbons become C2, C6 (or C4 depending on the IUPAC nomenclature rules) of the pyrimidine ring while the alpha and carbonyl carbons become C5, C4 (or C6), respectively (Scheme 1).



Scheme 1.

Keywords: thioesters; triflic anhydride; alkylthiopyrimidines; arylthiopyrimidines.
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Substitution at the α position of the carbonyl compound leads to 5-F[2] substituted pyrimidines. Direct functionalization F[1] at the carbonyl group leads to 4-substituted pyrimidines. In this regard, application of this reaction to α-haloketones[15] or aliphatic esters[16] provided a convenient route to 5-halopyrimidines and 4-alkoxypyrimidines respectively. On the other hand, the use of functionalized nitriles permits the introduction of both functions F[3] at positions 2 and 6 of the pyrimidine ring. As a consequence, the use of methylthiocyanate as nitrile produces 2,4-bis(methylthio)pyrimidines.[17]

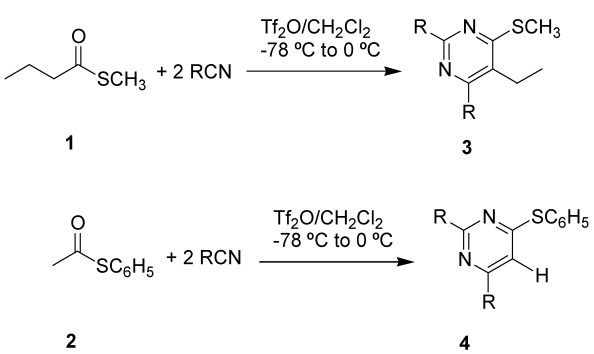
The preparation of monothioalkyl or monothioaryl substituted pyrimidines requires the use of a carbonyl compound bearing the thioalkyl or thioaryl moiety. The introduction of this functionality should afford a direct approach to the synthetically interesting intermediates 4-thiosubstituted pyrimidines. The easy nucleophilic replacement of the 4-alkylthio or 4-arylthiogroup permits the introduction of a range of functionalities.

We report here the reaction of *S*-alkyl and *S*-arylthioesters with nitriles in the presence of triflic anhydride. The reaction easily produces 4-alkylthio and 4-arylthiopyrimidines in good yields. The results can be explained by the general mechanism proposed for the reaction of ketones, nitriles and triflic anhydride.[14,18]

The use of nitriles of lower nucleophilic character such as thiocyanates leads to rearranged dithioiminocarbonates. Experiments were carried out to clarify these reactivity differences and to determine the origin of the rearrangement.

2. Results and discussion

4-Alkylthio substituted pyrimidines **3** and 4-arylthio substituted pyrimidines **4** are easily obtained from the simpler starting materials *S*-methyl butanethioate **1** and *S*-phenyl ethanethioate **2**. Thus, the reaction of these thioesters with various aliphatic and aromatic nitriles in the presence of triflic anhydride leads to the formation of the target pyrimidines in moderate to good yield and high purity. The process and results are presented in Scheme 2 and Table 1. The relatively high reactivities of the thioesters require low temperatures for their reactions with nitriles and triflic anhydride. It is noteworthy that the use of *S*-aryl



Scheme 2.

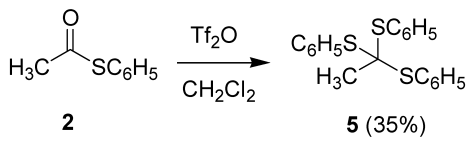
Table 1. Substituted 4-alkylthio- **3** and 4-arylthiopyrimidines **4** prepared

Entry	R	Product	Yield[a]
1	CH_3-	**3a**	92
2	$CH_3(CH_2)_7-$	**3b**	60
3	C_6H_5-	**3c**	53
4	$4\text{-}CH_3C_6H_4-$	**3d**	86
5	$4\text{-}ClC_6H_4-$	**3e**	87
6	$3,4\text{-}(CH_3O)_2C_6H_3-$	**3f**	64
7	$C_6H_5CH_2-$	**3g**	80
8	$4\text{-}CH_3C_6H_4CH_2-$	**3h**	50
9	$4\text{-}ClC_6H_4CH_2-$	**3i**	41
10	CH_3-	**4a**	43
11	C_6H_5-	**4b**	53
12	$4\text{-}CH_3C_6H_4-$	**4c**	48
13	$3,4\text{-}(CH_3O)_2C_6H_3-$	**4d**	56

[a] % Yield of isolated product.

thioesters leads to the preparation of pyrimidines with the C5 position unsubstituted.

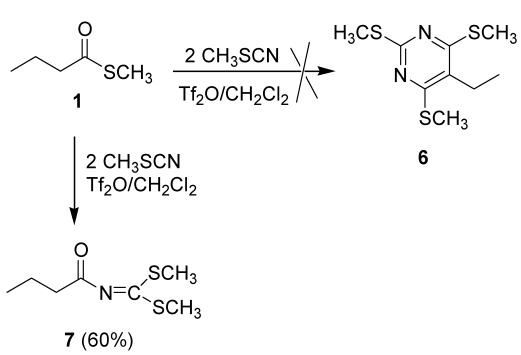
When the reaction was carried out with *S*-phenyl ethanethioate **2**, the corresponding substituted 4-arylthiopyrimidines **4** were isolated together with the corresponding ortho ester **5**. The formation of **5** could be explained by an ortho esterification process induced by the triflic anhydride. To test this side reaction, the treatment of **2** with Tf_2O in the same reaction conditions employed for the preparation of **4** produces the ortho ester **5**. Thus, the yields obtained in the synthesis of **4** were reduced by the formation of **5** (Scheme 3). The ortho esterification process did not takes place when alkylthioesters were used as starting materials.



Scheme 3.

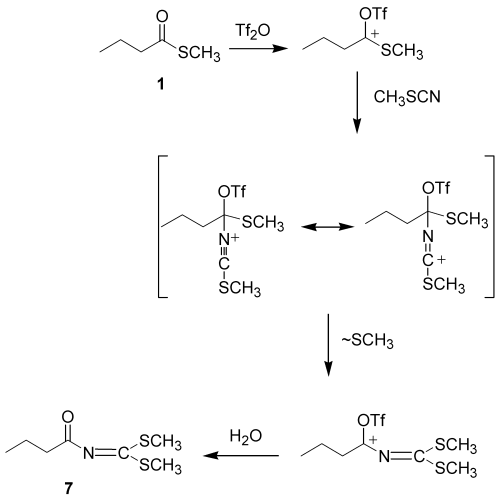
Substituted 4-alkylthiopyrimidines **3** and substituted 4-arylthiopyrimidines **4** were easily obtained using alkyl, aryl and benzyl nitriles.

To extend this synthetic procedure to the preparation of tris(alkylthio)pyrimidines, intermediates desired for their synthetic potential, we investigated the reaction between thioesters and methylthiocyanate. When the latter reacts with *S*-methyl butanothioate **1** in the presence of triflic anhydride, a new product **7** was isolated instead the anticipated 2,4,6-trimethylthiopyrimidine **6** (Scheme 4).



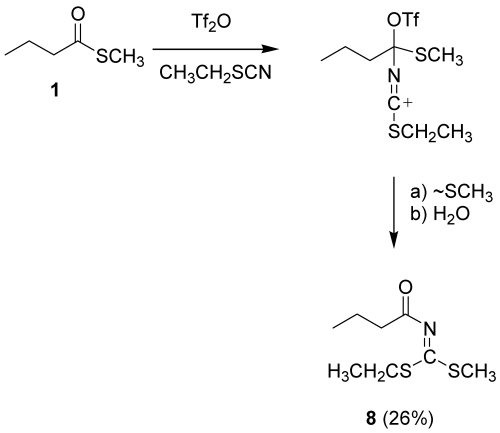
Scheme 4.

The formation of **7** can be explained by the relatively low nucleophilic character of the methylthiocyanate compared to aliphatic and aromatic nitriles. The trifliloxycarbenium ion formed initially (Scheme 5) is not attacked by a second molecule of methylthiocyanate. Instead, this intermediate rearranges with migration of one of the methylthio groups. After hydrolysis the imidocarbonate **7** is formed.



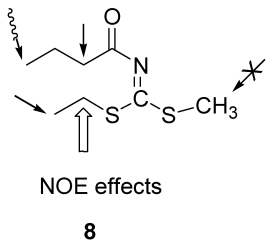
Scheme 5.

To identify the migrating thioalkyl group (from methylthiocyanate or from methylthioester) and to test the postulated mechanism, we investigated this reaction using ethylthiocyanate. The obtained product corresponds to the ethyl methyl butyryldithioimidocarbonate **8**, indicating that the thioalkyl group which rearranges comes from the starting thioester (Scheme 6).



Scheme 6.

In order to determine the stereochemical relationship of the substituents attached at the C=N bond in **8**, we carried out NOE experiments. Thus, the selective irradiation of the methyl protons of the butyl group appearing at δ 0.96 produced a clear NOE effect on the signal corresponding to the methylene protons of the thioethyl moiety. Moreover, smaller enhancements of the signals for the CH_3 protons of the thioethyl group and the CH_2CO protons were observed. The total absence of the NOE effect on the SCH_3 signal confirms the structure



Scheme 7.

(Scheme 7). The complete assignment of the ^1H and ^{13}C NMR signals of **8** was carried out from a 2D HMQC spectrum.

This result shows clearly that carbonyl and thioethyl groups are *cis* to each other. Because only one of the possible isomers was detected, the reaction involves a stereoselective rearrangement process.

We conclude that thioesters react with aliphatic and aromatic nitriles in the presence of triflic anhydride yielding substituted 4-alkylthio and 4-arylthiopyrimidines. When the reaction is carried out using thiocyanates as nitriles, a new process takes place yielding substituted dithioimidocarbonates.

3. Experimental

3.1. General

All reagents were commercial grade and were used as received unless otherwise indicated. Triflic anhydride was prepared from triflic acid[19] and redistilled twice prior to use. TLC analyses were performed on silica gel $60F_{250}$ plates and flash chromatography was carried out on silica gel 60 (70–230 mesh). Melting points were measured on a Gallenkamp apparatus and are uncorrected. Infrared spectra were taken on a Shimadzu FTIR 8300. Sample pellets were produced with spectroscopic grade potassium bromide. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 300 at 300 MHz for ^1H and 75.47 MHz for ^{13}C. The chemical shifts (δ_H and δ_C) are assigned to residual $CHCl_3$ (7.26 and 77.0 ppm, respectively). Coupling constants (J) are given in Hz. Mass spectra were carried out on a HP 5989A quadrupole instrument at 70 eV (EI) with a source temperature of 250°C. Electrospray mass spectra (ESI) were obtained on a Bruker Esquire-LC™ using 3500 V as the ionization voltage, nitrogen as nebulizer gas and methanol as solvent. Elemental analyses: Perkin–Elmer 2400 CHN.

3.2. Preparation of substituted 4-alkylthiopyrimidines (3a–i) and substituted 4-arylthiopyrimidines (4a–d): general procedure

A mixture of *S*-methyl butanethioate **1** (1 g, 8.4 mmol) or *S*-phenyl ethanethioate **2** (1 g, 6.5 mmol) and the corresponding nitrile (33.6 mmol) dissolved in 30 mL of CH_2Cl_2 was cooled at −78°C. Triflic anhydride (3.55 g, 12.6 mmol) in 20 mL of CH_2Cl_2 is added dropwise. The reaction mixture is allowed to stand at 0°C and stirred at this temperature during 4 days. The reaction can be monitored

by TLC. The reaction mixture was hydrolyzed by careful addition of saturated aqueous solution of sodium hydrogen carbonate until was basic (pH>8). The organic layer was separated, washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue purified by flash chromatography using hexane/ethyl acetate 7:3 as eluent. The crude product was distilled (**3a**–**b**, **3g**) or recrystallized.

3.2.1. 5-Ethyl-2,4-dimethyl-6-(methylthio)pyrimidine 3a. Purification of crude product by flash chromatography affords 1.4 g (92%) of a yellow liquid, bp 150°C/0.3 Torr, (kugelrohr); ν (film): 2968, 2930, 1701, 1541, 1433, 858 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.14 (t, 3H, J=7.6 Hz, CH_3), 2.41 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 2.63 (c, 2H, J=7.6 Hz, CH_2) ppm; ^{13}C NMR ($CDCl_3$) δ: 11.70 (CH_3CH_2), 12.46 (CH_3S), 20.47 (CH_3), 20.96 (CH_2), 25.09 (CH_3), 127.99, 160.41, 163.29, 168.0 (arom.) ppm; *m/z* (EI, 70 eV): 182 ($M^{+\cdot}$,8), 167 (20), 149 (13), 71 (45), 57 (40), 43 (100). Anal. calcd for $C_9H_{14}N_2S$: C 59.30, H 7.74, N 15.37, S 17.59, found C 58.97, H 7.23, N 15.55, S 16.85.

3.2.2. 5-Ethyl-4-(methylthio)-2,6-dioctylpyrimidine 3b. Purification of crude product by flash chromatography affords 1.89 g (60%) of a yellow liquid, bp 150°C/0.5 Torr (kugelrohr); ν (film): 2957, 2926, 1537, 1466, 1402 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.83–0.98 (m, 6H, CH_3), 0.99 (t, 2H, J=7.4 Hz, CH_2), 1.16 (t, 3H, CH_2, J=7.4 Hz), 1.25–1.40 (m, 18H, CH_2), 1.57–1.82 (m, 4H, CH_2), 2.53 (s, 3H, CH_3S), 2.63 (c and t overlapped, 4H, J=7.4 Hz, CH_2), 2.82 (t, 2H, J=7.4 Hz, CH_2) ppm; ^{13}C NMR ($CDCl_3$) δ: 12.56, 12.79, 13.99 (CH_3), 20.81, 22.57, 22.58, 28.37, 29.15, 29.19, 29.35, 29.42, 29.71, 31.77, 31.82, 34.11, 38.97 (CH_2), 127.55, 164.73, 167.07, 167.65 (arom.) ppm; *m/z* (EI, 70 eV): 378 ($M^{+\cdot}$,7), 363 (24), 293 (27), 280 (42), 265 (100). Anal. calcd for $C_{23}H_{42}N_2S$: C 72.96, H 11.18, N 7.40, S 8.47, found C 73.18, H 10.89, N 6.93, S 8.75.

3.2.3. 5-Ethyl-4-(methylthio)-2,6-diphenylpyrimidine 3c. Purification of crude product by column chromatography affords 1.35 g (53%) of a white solid, mp 96–97°C (MeOH); ν (KBr): 2959, 2922, 1527, 1391, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.19 (t, 3H, J=7.5 Hz, CH_3), 2.72 (c, 2H, J=7.5 Hz, CH_2), 2.74 (s, 3H, CH_3S), 7.44–7.55 (m, 8H, Ar-H), 8.49 (m, 2H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 13.04, 13.09 (CH_3), 21.71 (CH_2), 128.07, 128.21, 128.29, 128.64, 128.98, 130.22, 137.87, 138.98, 160.30, 162.82, 169.6 (arom.) ppm; *m/z* (EI, 70 eV): 306 ($M^{+\cdot}$,63), 305 (100), 291 (22), 273 (32). Anal. calcd for $C_{19}H_{18}N_2S$: C 74.47, H 5.92, N 9.14, S 10.46, found C 73.85, H 5.01, N 9.25, S 10.39.

3.2.4. 5-Ethyl-2,4-bis(4-methylphenyl)-6 (methylthio)-pyrimidine 3d. Purification of crude product affords 2.41 g of a white solid, mp 104–105°C (MeOH); ν (KBr): 1528, 1506, 1391 cm^{-1}; ^1H NMR ($CDCl_3$) ν: 1.19 (t, 3H, J=7.7 Hz, CH_3), 2.42 (s, 3H, CH_3S), 2.44 (s, 3H, CH_3), 2.72 (c, 2H, J=7.7 Hz, CH_2), 2.73 (s, 3H, CH_3), 7.24–7.31 (m, 4H, Ar-H), 7.46–7.50 (m, 2H, Ar-H), 8.39–8.43 (m, 2H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) ν: 13.13 (CH_3CH_2), 21.33 (CH_2), 21.47 (CH_3-Ar), 21.74 (CH_3S), 128.10, 128.66, 128.91, 129.03, 135.22, 136.18, 138.58, 140.35, 160.33, 162.75, 169.40 (arom.) ppm; *m/z* (EI, 70 eV): 334 ($M^{+\cdot}$,59), 333 (100), 319 (47), 301 (37). Anal. calcd for $C_{21}H_{22}N_2S$: C 75.41, H 6.63, N 8.38, S 9.59, found C 76.09, H 6.03, N 7.97, S 9.22.

3.2.5. 2,4-Bis(4-chlorophenyl)-5-ethyl-6-(methylthio)-pyrimidine 3e. Purification of crude product by chromatography affords 2.73 g (87%) of a white solid, mp 151–152°C (MeOH); ν (KBr): 1524, 1487, 1389 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.19 (t, 3H, J=7.5 Hz, CH_3), 2.70 (c, 2H, J=7.5 Hz, CH_2), 2.72 (s, 3H, CH_3S), 7.40–7.49 (m, 6H, Ar-H), 8.41–8.45 (m, 2H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 12.99 (CH_3CH_2), 13.16 (CH_3S), 21.70 (CH_2), 128.56, 129.17, 129.41, 130.08, 134.99, 136.23, 136.54, 137.26, 159.47, 161.63, 170.16 (arom.) ppm; *m/z* (EI, 70 eV): 374 ($M^{+\cdot}$,62), 373 (100), 359 (16), 341 (30). Anal. calcd for $C_{19}H_{16}Cl_2N_2S$: C 60.80, H 4.30, N 7.46, S 8.54, found C 61.01, H 4.11, N 7.39, S 8.95.

3.2.6. 2,4-Bis(3,4-dimethoxyphenyl)-5-ethyl-6-(methylthio)pyrimidine 3f. Purification of crude product by column chromatography affords 2.29 g (64%) of a white solid, mp 141–142°C (MeOH); ν (KBr): 1508, 1387, 1269 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.23 (t, 3H, J=7.5 Hz, CH_3), 2.73 (s, 3H, CH_3S), 2.75 (c, 2H, J=7.5 Hz, CH_2), 3.94–3.98 (broad s, 12H, OCH_3), 6.94–7.16 (m, 4H, Ar-H), 8.10–8.18 (m, 2H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 13.03 (CH_3CH_2), 13.18 (CH_3S), 21.78 (CH_2), 55.87, 55.89, 55.94 (OCH_3), 110.67, 110.76, 110.95, 112.29, 121.38, 121.43, 128.15, 130.90, 131.74, 148.68, 148.73, 149.54, 151.05, 159.93, 162.29, 169.36 (arom.) ppm; *m/z* (EI, 70 eV): 426 ($M^{+\cdot}$,99), 425 (100), 411 (46), 393 (30). Anal. calcd for $C_{23}H_{26}N_2O_4S$: C 64.77, H 6.14, N 6.57, S 7.52, found: C 64.11, H, 6.39, N 6.11, S, 7.98.

3.2.7. 2,4-Dibenzyl-5-ethyl-6-(methylthio)pyrimidine 3g. Purification of crude product by column chromatography affords 2.24 g (80%) of a yellow liquid, bp 200°C/0.4 Torr (kugelrohr); ν (film): 2968, 2928, 1537, 1393, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.00 (t, 3H, J=7.5 Hz, CH_3), 2.47 (s, 3H, CH_3S), 2.60 (c, 2H, J=7.5 Hz, CH_2), 4.07 (s, 2H, Ar-CH_2-Ar), 4.19 (s, 2H, Ar-CH_2-Ar), 7.17–7.40 (m, 10H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 12.19 (CH_3CH_2), 12.75 (CH_3S), 21.02 (CH_2), 40.65, 45.57 (Ar-CH_2-Ar), 126.18, 126.33, 128.12, 128.37, 128.65, 128.81, 129.36, 138.34, 138.83, 162.85, 165.54, 168.92 (arom.) ppm; *m/z* (EI, 70 eV): 334 ($M^{+\cdot}$,66), 319 (100), 301 (30), 91 (34). Anal. calcd for $C_{21}H_{22}N_2S$: C 75.41, H 6.63, N 8.38, S 9.59, found C 75.03, H 6.12, N 8.45, S 9.89.

3.2.8. 5-Ethyl-2,4-bis(4-methylbenzyl)-6-(methylthio)-pyrimidine 3h. Purification of the crude product affords 1.52 g of an undistillable oil; ν (film): 2970, 2928, 1539, 1514, 908 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.01 (t, 3H, J=7.5 Hz, CH_3), 2.30 (s, 3H, Ar-CH_3), 2.33 (s, 3H, Ar-CH_3), 2.49 (s, 3H, CH_3S), 2.59 (c, 2H, J=7.5 Hz, CH_2), 4.03 (s, 2H, Ar-CH_2Ar), 4.15 (s, 2H, Ar-CH_2-Ar), 7.07–7.34 (m, 8H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 12.19 (CH_3CH_2), 12.70 (CH_3S), 20.93, 20.95 (Ar-CH_3), 20.98 (CH_2), 40.24, 45.16 (Ar-CH_2-Ar), 128.48, 128.65, 128.79, 129.02, 129.17, 135.26, 135.75, 135.80, 163.04, 165.61, 168.77 (arom) ppm; *m/z* (EI, 70 eV): 362 ($M^{+\cdot}$,53), 347 (100), 329 (18). Anal. calcd for $C_{23}H_{26}N_2S$: C 76.20, H 7.23, N 7.73, S 8.84, found C 75.75, H 6.91, N 7.00, S 8.21.

3.2.9. 2,4-Bis(4-chlorobenzyl)-5-ethyl-6-(methylthio)-pyrimidine 3i. Purification of crude product affords 1.38 g (41%) of an undistillable oil; ν (film): 2970, 2932, 2253, 1541, 1491, 1391, 908, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.03 (t, 3H, J=7.6 Hz, CH_3), 2.47 (s, 3H, CH_3S), 2.60 (c, 2H, J=7.6 Hz, CH_2), 4.01 (s, 2H, Ar-CH_2-Ar), 4.13 (s, 2H, Ar-CH_2-Ar), 7.08–7.34 (m, 8H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 12.35 (CH_3CH_2), 12.87 (CH_3S), 21.09 (CH_2), 39.80, 44.76 (Ar-CH_2-Ar), 128.17, 128.43, 128.77, 129.98, 130.66, 132.05, 132.20, 136.70, 137.11, 162.34, 165.14, 169.21 (arom) ppm; m/z (EI, 70 eV): 402 ($M^{+\cdot}$,56), 387 (100), 369 (23). Anal. calcd for $C_{21}H_{20}Cl_2N_2S$: C 62.53, H 5.00, N 6.94, S 7.95, found C 62.11, H 4.37, N 6.01, S 7.28.

3.2.10. 2,4-Dimethyl-6-(phenylthio)pyrimidine 4a. Purification of crude product affords 0.70 g (43%) of a white solid, mp 52–54°C (MeOH); ν (KBr): 2218, 1560, 1541, 908, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.31 (s, 3H, CH_3), 2.64 (s, 3H, CH_3S), 6.37 (s, 1H,), 7.48–7.64 (m, 5H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ: 23.86, 25.55 (CH_3), 112.67, 128.05, 129.72, 129.84, 135.51, 165.81, 166.77, 172.51 (arom.) ppm; m/z (EI, 70 eV): 216 ($M^{+\cdot}$,58), 215 (100), 201 (17), 176 (31). Anal. calcd for $C_{12}H_{12}N_2S$: C 66.64, H 5.55, N 12.95, S 14.82, found C 66.39, H 5.03, N 12.83, S 15.01.

3.2.11. 2,4-Diphenyl-6-(phenylthio)pyrimidine 4b. Purification of crude product by column chromatography affords 1.18 g (53%) of a white solid, mp 104–106°C (MeOH); ν (KBr): 1553, 1520, 1369, 745, 689 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.13 (s, 1H), 7.47–7.56 (m, 9H), 7.71–7.76 (m, 2H), 8.01–8.06 (m, 2H), 8.49–8.54 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ: 110.34, 127.14, 128.34, 128.45, 128.50, 128.77, 129.71, 129.89, 130.73, 135.78, 136.81, 136.97, 137.38, 163.06, 163.67, 172.82 (arom) ppm; m/z (EI, 70 eV): 340 ($M^{+\cdot}$,71), 339 (100), 263 (9), 236 (21). Anal. calcd for $C_{22}H_{16}N_2S$: C 77.62, H 4.74, N 8.23, S 9.42, found C 77.01, H 4.49, N 7.85, S 9.07.

3.2.12. 2,4-Bis(4-methylphenyl)-6-(phenylthio)pyrimidine 4c. Purification of crude product by column chromatography affords 1.16 g (48%) of a white solid, mp 150–152°C (MeOH); ν (KBr): 1545, 1516, 1504, 1367, 1321 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.41 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.06 (s, 1H), 7.25–7.28 (m, 4H), 7.51–7.54 (m, 3H), 7.69–7.74 (m, 2H), 7.89–7.93 (m, 2H), 8.36–8.40 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ: 21.39, 21.48 (CH_3), 109.73, 127.04, 128.41, 128.71, 129.07, 129.46, 129.64, 129.77, 134.28, 134.79, 135.76, 140.88, 141.01, 162.99, 163.69, 172.44 (arom.) ppm; m/z (EI, 70 eV): 368 ($M^{+\cdot}$,67), 367 (100), 277 (5), 250 (10). Anal. calcd for $C_{24}H_{20}N_2S$: C 78.23, H 5.47, N 7.60, S 8.70, found C 77.77, H 5.11, N 7.85, S 8.99.

3.2.13. 2,4-Bis(3,4-dimethoxyphenyl)-6-(phenylthio)-pyrimidine 4d. Purification of crude product by column chromatography affords 1.69 g (56%) of a white solid, mp 165–166°C (MeOH); ν (KBr): 1556, 1512, 1258, 1232 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.92 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.92–6.97 (m, 2H), 7.08 (s, 1H), 7.49–7.56 (m, 4H), 7.69–7.73 (m, 3H), 7.92 (m, 1H), 8.10–8.14 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 55.77, 55.84, 55.89, 55.96 (OCH_3), 109.15, 109.99, 110.60, 110.96, 111.00, 120.15, 121.66, 128.75, 129.44, 129.56, 129.71, 130.34, 135.96, 148.66, 149.17, 151.34, 151.41, 162.30, 163.11, 171.72 (arom.) ppm; m/z (EI, 70 eV): 460 ($M^{+\cdot}$,100), 459 (78), 445 (15), 429 (7), 414 (16). Anal. calcd for $C_{26}H_{24}N_2O_4S$: C 67.81, H 5.25, N 6.08, S 6.96, found C 67.75, H 5.39, N 5.91, S, 7.07.

3.2.14. {[1,1-bis(phenylthio)ethyl]thio}benzene 5. Triflic anhydride (3.7 g, 13.14 mmol) in 20 mL of CH_2Cl_2 was added to a solution containing 1 g (6.57 mmol) of *S*-phenyl ethanethioate **2** in 30 mL of CH_2Cl_2. The reaction mixture is allowed to stand at 0°C during one week. The reaction mixture was hydrolyzed by addition of saturated aqueous solution of sodium hydrogen carbonate. The organic layer was separated, dried and the solvent removed under reduced pressure. The crude solid was purified by column chromatography affording 0.81 g (35%) of a yellow solid, mp 140–141°C (EtOH); ν (KBr): 1464, 754, 704 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.41 (s, 3H, CH_3), 7.34–7.41 (m, 9H), 7.65–7.69 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ: 29.23 (CH_3), 70.55 (C), 128.52, 129.40, 132.31, 136.84 (arom.) ppm; m/z (ESI): 377 $[M+Na]^+$. Anal. calcd for $C_{20}H_{18}S_3$: C 67.75, H 5.12, S 27.13, found C 67.59, H 5.05, S 26.89.

3.2.15. Dimethyl butyryldithioimidocarbonate 7. Following the general procedure for the preparation of substituted 4-alkylthiopyrimidines, when *S*-methyl butanethioate was reacted with methyl thiocyanate, purification of the crude product by chromatography affords 0.96 g of a colorless liquid, bp 100°C/0.5 Torr (kugelrohr); ν (film): 2962, 2928, 1691, 1578, 1460, 1153 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.96 (t, 3H, J=7.5 Hz, CH_3), 1.68 (hex, 2H, J=7.5 Hz, CH_2), 2.48 (t, 2H, J=7.5 Hz, CH_2), 2.48 (s, 6H, 2 SCH_3) ppm; ^{13}C NMR ($CDCl_3$) δ: 13.63 (CH_3), 15.29 (CH_3S), 18.08, 40.48 (CH_2), 170.12 (C=N), 184.78 (C=O) ppm; m/z (ESI): 230 $[M+K]^+$, 214 $[M+Na]^+$, 192 $[M+H]^+$. Anal. calcd for $C_7H_{13}NOS_2$: C 43.95, H 6.85, N 7.32, S 33.52, found C 43.75, H 6.33, N 7.01, S 33.01.

3.2.16. Ethyl methyl butyryldithioimidocarbonate 8. Following the general procedure for the preparation of substituted 4-alkylthiopyrimidines, when *S*-methyl butanethioate was reacted with ethyl thiocyanate, purification of the crude product by chromatography affords 0.44 g of a colorless liquid, bp 75°C/0.4 Torr (kugelrohr); ν (film): 1670, 1578, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.96 (t, 3H, J=7.5 Hz, CH_3CH_2), 1.32 (t, J=7.5 Hz, 3H, CH_3CH_2S), 1.68 (hex., 2H, J=7.5 Hz, $CH_3CH_2CH_2$), 2.46 (t, 2H, J=7.5 Hz, CH_2CO), 2.46 (s, 3H, SCH_3), 3.05 (c, 2H, J=7.5 Hz, CH_2S) ppm; ^{13}C NMR ($CDCl_3$) δ: 13.78 (CH_3), 14.00 (CH_3CH_2S), 15.39 (CH_3S), 18.21 ($CH_3CH_2CH_2$), 26.88 (CH_2S), 40.41 (CH_2CO), 168.78 (C=N), 184.77 (C=O) ppm; m/z (ESI): 228 $[M+Na]^+$, 206 $[M+H]^+$. Anal. calcd for $C_8H_{15}NOS_2$: C 46.80, H 7.36, N 6.82, S 31.23, found C 46.39, H 7.11, N 6.51, S 30.29.

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