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SYNTHESIS OF 5,6-DISUBSTITUTED THIENO[2,3-*d*]PYRIMIDINES FROM 4-CHLOROPYRIMIDINES

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Abstract – Facile reaction sequences for the preparation of 5,6-disubstituted thieno[2,3-*d*]pyrimidines starting with 4-chloropyrimidines have been developed. 4-Chloro-6-methoxypyrimidines were aroylated at the 5-positions *via* lithiation with LDA and subsequent treatment with benzaldehyde or *N*-methoxy-*N*-methylbenzamides to give aryl(4-chloro-6-methoxypyrimidin-5-yl)methanones. These pyrimidinyl ketones were transformed in one-pot into 5,6-disubstituted 4-methoxythieno[2,3-*d*]pyrimidines by a successive treatment with sodium sulfide, $BrCH_2EWGs$, and sodium hydride. Lithiation of 4,6-dichloro-2-(methylsulfanyl)pyrimidine at the 5-position was followed by treatment with tertiary formamides to give 4-chloro-6-(dialkylamino)pyrimidine-5-carboxaldehydes, which could be transformed into 5,6-disubstituted 4-(dialkylamino)thieno[2,3-*d*]pyrimidines *via* aryl[4-chloro-6-(dialkylamino)-pyrimidin-5-yl]methanones using the same one-pot thiophene ring forming sequence.

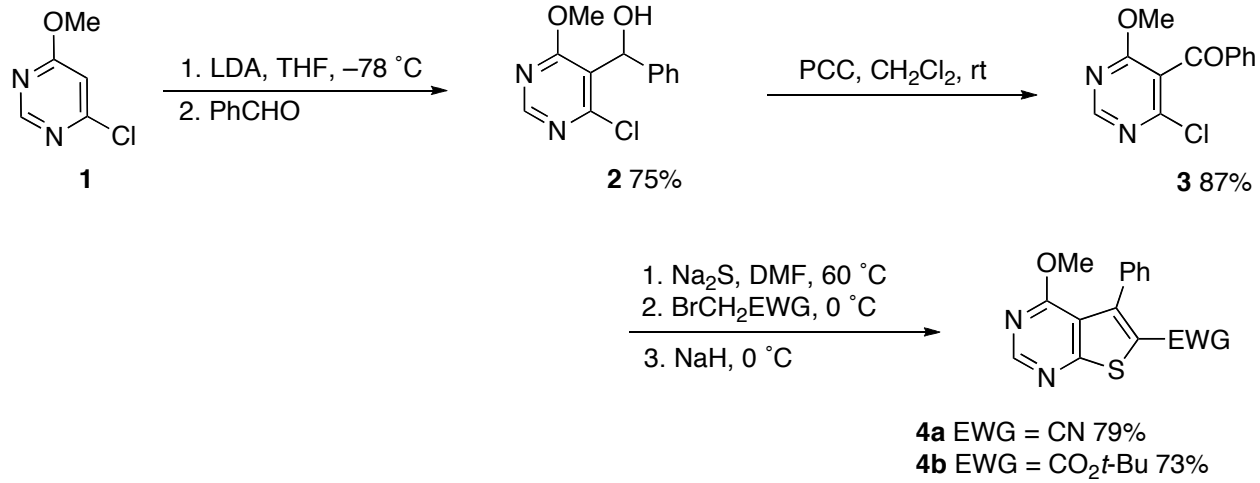
INTRODUCTION

We have previously reported that 2,3-disubstituted thieno[2,3-*b*]pyridines,[1] thieno[2,3-*c*]pyridines,[1] thieno[3,2-*c*]pyridines,[1] and 6,7-disubstituted thieno[2,3-*b*]pyrazines[2] can be prepared in one-pot from corresponding aryl(chloropyridinyl)methanones and aryl(2-chloropyrazin-3-yl)methanones by successive treatment with sodium sulfide, $BrCH_2EWGs$, and sodium hydride. As an extension of these syntheses to other thiophene-fused nitrogen heterocycles, we decided to synthesize 5,6-disubstituted

thieno[2,3-*d*]pyrimidines. We now report the results of our investigation, which provide convenient routes to 4-methoxy- (**4** and **7**) and 4-(dialkylamino)thieno[2,3-*d*]pyrimidines (**12**) starting with 4-chloropyrimidines. Thieno[2,3-*d*]pyrimidines have attracted significant interest from chemical community because of their medicinal and synthetic utilities. A number of compounds having the thieno[2,3-*d*]pyrimidine structure have been reported to show biological activities.[3,4] Thieno[2,3-*d*]pyrimidine derivatives have been utilized for the preparation of structurally more complex and biologically more useful heterocycles.[5] Hitherto many groups have reported efficient methods for the preparation of thieno[2,3-*d*]pyrimidines derivatives.[4,6] However, most of these methods depend on the pyrimidines ring formation starting with appropriately substituted thiophene derivatives.

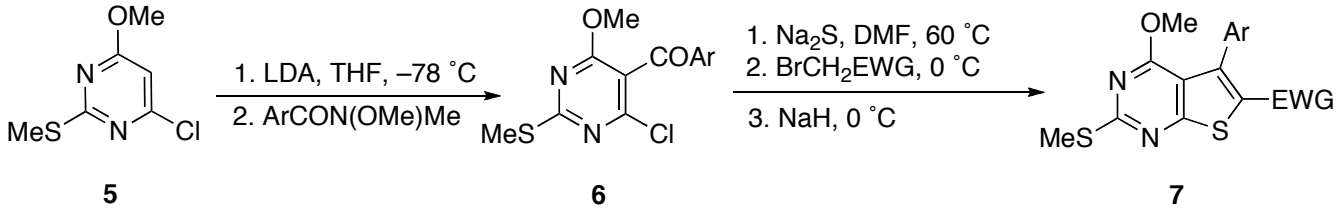
RESULTS AND DISCUSSION

First, we tried direct 5-benzoylation of 4-chloro-6-methoxypyrimidine (**1**) providing (4-chloro-6-methoxypyrimidin-5-yl)phenylmethanone (**3**) in order to prepare 4-methoxy-5-phenylthieno[2,3-*d*]pyrimidines (**4**). Treatment of **1** with LDA in THF at –78 ˚C was followed by the addition of *N*-methoxy-*N*-methylbenzamide. However, this attempt resulted in failure; no benzoylation occurred. Compound **3** proved to be obtainable by the following two-step sequence. After treatment of **1** with LDA under the above conditions, benzaldehyde was added to give upon aqueous workup (4-chloro-6-methoxypyrimidin-5-yl)phenylmethanol (**2**) in good yield. The PCC oxidation of **2** led to rapid and good yield conversion into **3**, as shown in Scheme 1. The previously reported one-pot thiophene ring formation was applied to this chloropyrimidinyl ketone (**3**). Thus, **3** was allowed to react with sodium sulfide in DMF at 60 ˚C to form reddish brown solutions within 1 h, which were successively treated with $BrCH_2EWG$s and sodium hydride at 0 ˚C to afford, after aqueous workup followed by recrystallization, 6-substituted 4-methoxy-5-phenylthieno[2,3-*d*]pyrimidines (**4a**) and (**4b**) in good yields.



Scheme 1

Subsequently, it was found that 4-chloro-6-methoxy-2-(methylsulfanyl)pyrimidine (**5**) performed more capably than **1** to permit direct formation of aryl[4-chloro-6-methoxy-2-(methylsulfanyl)pyrimidin-5-yl]methanones (**6**) as shown in Scheme 2. Thus, treatment of **5** with LDA in THF at –78 ˚C followed by the addition of *N*-methoxy-*N*-methylbenzamides afforded **6** after aqueous workup in fair yields as summarized in Table 1. When the ketones (**6**) thus obtained were treated successfully with sodium sulfide, $BrCH_2EWGs$, and sodium hydride under the same conditions as described for the preparation of **4**, 5,6-disubstituted 4-methoxy-2-(methylsulfanyl)thieno[2,3-*d*]pyrimidines (**7**) were obtained in the yields summarized in Table 2. The yields ranged from moderate to fair depending on the substrates (**6**).



5 **6** **7**

Scheme 2

Table 1. Preparation of aryl(4-chloro-6-methoxy-2-methylsulfanylpyrimidin-5-yl)methanones (**6**)

Entry	Ar	**6**	Yield/%[a]
1	Ph	**6a**	66
2	3-MeC_6H_4	**6b**	66
3	3-ClC_6H_4	**6c**	70
4	4-$MeOC_6H_4$	**6d**	70

[a] Yields of isolated products.

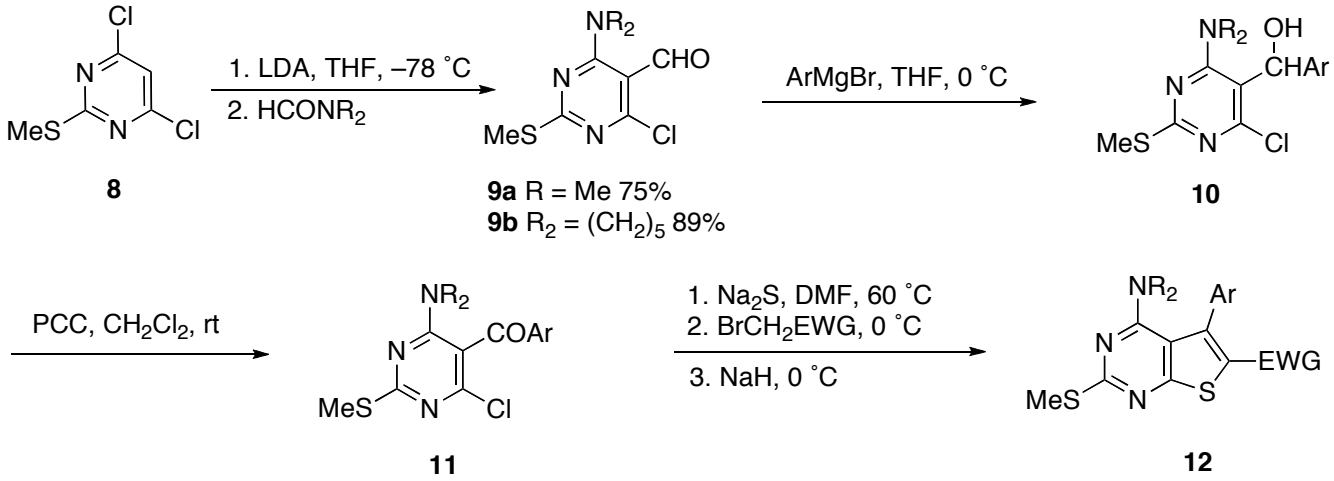
Table 2. Preparation of 4-methoxy-2-methylsulfanylthieno[2,3-*d*]pyrimidines (**7**)

Entry	**6**	EWG	**7**	Yield/%[a]
1	**6a**	CN	**7a**	56
2	**6a**	CO_2t-Bu	**7b**	70
3	**6b**	CO_2t-Bu	**7c**	52
4	**6b**	COPh	**7d**	52
5	**6c**	CN	**7e**	42
6	**6d**	CN	**7f**	61

[a] Yields of isolated products.

In order to extend the present method to the synthesis of 5,6-disubstituted 4-(dialkylamino)thieno[2,3-*d*]pyrimidines (**12**), we initially attempted 5-benzoylation of 4-chloro-6-dimethylamino-2-(methylsulfanyl)pyrimidine under the same conditions as described for the preparation of **6**. Unfortunately, however, this attempt resulted in failure; only a trace amount of the desired product was obtained. Of interest is that when 4,6-dichloro-2-(methylsulfanyl)pyrimidine (**8**) was lithiated with

LDA in THF at –78 ˚C and the resulting lithium product was treated with tertiary formamides, 4-chloro-6-dialkylamino-2-(methylsulfanyl)pyrimidine-5-carboxaldehydes (**9**) were obtained in fair to good yields as shown in Scheme 3. Unfortunately, however, simultaneous 5-benzoylation and 4-dimethylamination could not be accomplished using *N*,*N*-dimethylbenzamide; the reaction gave an intractable mixture of products. The action of arylmagnesium bromide on these aldehydes (**9**)**,** followed by PCC oxidation of the resulting alcohols (**10**), gave aryl(4-chloropyrimidin-5-yl)methanones (**11**) in generally good yields as summarized in Table 3. These ketones (**11**) were subjected to the one-pot sequence under the same reaction conditions described for the preparation of **4** and **7**. It was found that they behaved similarly to give rise to the desired products (**12**) as shown in Scheme 3. The yields of **12** are moderate as summarized in Table 4.



8 **9a** R = Me 75% **9b** $R_2 = (CH_2)_5$ 89% **10** **11** **12**

Scheme 3

Table 3. Preparation of aryl(6-amino-4-chloro-2-methylsulfanylpyrimidin-5-yl)methanones (**11**)

Entry	**9**	Ar	**10**	Yield/%[a]	**11**	Yield/%[a]
1	**9a**	Ph	**10a**	90	**11a**	57
2	**9a**	4-ClC_6H_4	**10b**	92	**11b**	81
3	**9a**	4-$MeOC_6H_4$	**10c**	98	**11c**	79
4	**9b**	Ph	**10d**	94	**11d**	75

[a] Yields of isolated products.

Table 4. Preparation of 4-dialkylamino-2-methylsulfanylthieno[2,3-*d*]pyrimidines (**12**)

Entry	**11**	EWG	**12**	Yield/%[a]
1	**11a**	CN	**12a**	40
2	**11b**	CO_2t-Bu	**12b**	54
3	**11b**	COPh	**12c**	55
4	**11c**	CN	**12d**	39
5	**11c**	CO_2t-Bu	**12e**	46
6	**11d**	CO_2t-Bu	**12f**	58

[a] Yields of isolated products.

In conclusion, we have demonstrated that 5,6-disubstituted 4-methoxy- and 4-(dialkylamino)thieno[2,3-*d*]pyrimidines could be prepared from 4-chloropyrimidines. The method may be of value in organic synthesis because of the ready availability of the starting materials and the easy experimental operations.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Shimadzu FTIR-8300 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or a JEOL LA400FT NMR spectrometer operating at 400 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. 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-methoxypyrimidine (**1**) was prepared according to the reported method.[7] *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

(4-Chloro-6-methoxypyrimidin-5-yl)phenylmethanol (2). To a stirred solution of LDA (1.8 mmol), generated by the standard method from *n*-BuLi and *i*-Pr_2NH, in THF (2 mL) at –78 ˚C was added a solution of **1** (0.25 g, 1.8 mmol) in THF (2 mL) dropwise. After 1.5 h, PhCHO (0.19 mg, 1.8 mmol) was added and stirring was continued for an additional 30 min. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated by evaporation. The residue was purified by column chromatography on silica gel (AcOEt–hexane 1:2) to give **2** (0.33 g, 75%); a white solid; mp 89–91 ˚C (hexane–CH_2Cl_2); IR (KBr) 3310 cm^{-1}; ^{1}H NMR (500 MHz) δ 3.55 (d, *J* = 11.5 Hz, 1H), 4.01 (s, 3H), 6.28 (d, *J* = 11.5 Hz, 1H), 7.28–7.37 (m, 5H), 8.55 (s, 1H). Anal. Calcd for $C_{12}H_{11}ClN_2O_2$: C, 57.49; H, 4.42; N, 11.17. Found: C, 57.19; H, 4.60; N, 11.19.

(4-Chloro-6-methoxypyrimidin-5-yl)phenylmethanone (3). This compounds were prepared by the PCC oxidation of **2** under the conditions reported previously;[2] yield: 87%; a white solid; mp 78–80 ˚C (hexane–CH_2Cl_2); IR (KBr) 1676 cm^{-1}; ^{1}H NMR (500 MHz) δ 3.98 (s, 3H), 7.51 (dd, *J* = 7.8, 7.3 Hz, 2H), 7.66 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.83 (dd, *J* = 7.8, 1.4 Hz, 2H), 8.69 (s, 1H). Anal. Calcd for $C_{12}H_9ClN_2O_2$: C, 57.96; H, 3.65; N, 11.27. Found: C, 57.84; H, 3.49; N, 11.22.

4-Chloro-6-methoxy-2-methylsulfanylpyrimidine (5). This compound was prepared from 4,6-dichloro-2-methylsulfanylpyrimidine under the conditions for the preparation of **1** from

4,6-dichloropyrimidine.[7] **5:** a white solid; mp 36–38 ˚C (hexane); IR (KBr) 1560, 1541 cm^{-1}; ^1H NMR (400 MHz) δ 2.56 (s, 3H), 3.98 (s, 3H), 6.42 (s, 1H). Anal. Calcd for $C_6H_7ClN_2OS$: C, 37.80; H, 3.70; N, 14.69. Found: C, 37.71; H, 3.70; N, 14.68.

Typical Procedure for the Preparation of Aryl(pyrimidin-5-yl)methanones (6). (4-Chloro-6-methoxy-2-methylsulfanylpyrimidin-5-yl)phenylmethanone (6a). To a stirred solution of LDA (0.68 mmol) in THF (3 mL) at –78 ˚C was added a solution of **5** (0.13 g, 0.68 mmol) in THF (1 mL) dropwise. After 1.5 h, *N*-methoxy-*N*-methylbenzamide (0.11 g, 0.68 mmol) was added dropwise and stirring was continued for an additional 30 min at the same temperature. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated by evaporation. The residue was purified by column chromatography on silica gel (AcOEt–hexane 1:15) to give **6a** (0.13 g, 66%); a white solid; mp 143–145 ˚C (hexane–CH_2Cl_2); IR (KBr) 1667 cm^{-1}; ^1H NMR (500 MHz) δ 2.60 (s, 3H), 3.95 (s, 3H), 7.49 (dd, *J* = 8.6, 7.4 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.84 (dd, *J* = 8.6, 1.1 Hz, 2H). Anal. Calcd for $C_{13}H_{11}ClN_2O_2S$: C, 52.97; H, 3.76; N, 9.50. Found: C, 52.85; H, 3.77; N, 9.42.

(4-Chloro-6-methoxy-2-methylsulfanylpyrimidin-5-yl)(3-methylphenyl)methanone (6b): a white solid; mp 119–121 ˚C (hexane–CH_2Cl_2); IR (KBr) 1668 cm^{-1}; ^1H NMR (500 MHz) δ 2.41 (s, 3H), 2.61 (s, 3H), 3.95 (s, 3H), 7.37 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.66 (s, 1H). Anal. Calcd for $C_{14}H_{13}ClN_2O_2S$: C, 54.46; H, 4.24; N, 9.07. Found: C, 54.19; H, 4.19; N, 9.05.

(4-Chloro-6-methoxy-2-methylsulfanylpyrimidin-5-yl)(3-chlorophenyl)methanone (6c): a white solid; mp 89–91 ˚C (hexane–Et_2O); IR (KBr) 1677 cm^{-1}; ^1H NMR (400 MHz) δ 2.61 (s, 3H), 3.96 (s, 3H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.82 (s, 1H). Anal. Calcd for $C_{13}H_{10}Cl_2N_2O_2S$: C, 47.43; H, 3.06; N, 8.51. Found: C, 54.19; H, 4.19; N, 9.05.

(4-Chloro-6-methoxy-2-methylsulfanylpyrimidin-5-yl)(4-methoxyphenyl)methanone (6d): a white solid; mp 127–128 ˚C (hexane–Et_2O); IR (KBr) 1661, 1600 cm^{-1}; ^1H NMR (400 MHz) δ 2.60 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 6.96 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 8.8 Hz, 2H). Anal. Calcd for $C_{14}H_{13}ClN_2O_3S$: C, 51.77; H, 4.03; N, 8.63. Found: C, 51.72; H, 4.01; N, 8.38.

Typical Procedure for the Preparation of 6-(Dialkylamino)pirimidine-5-carboxaldehydes (9). 4-Chloro-6-dimethylamino-2-methylsulfanylpyrimidine-5-carboxaldehyde (9a).[8] To a stirred solution of LDA (1.0 mmol) in THF (2.5 mL) at –78 ˚C was added a solution of **8** (0.20 g, 1.0 mmol) in THF (1.5 mL) dropwise. After 1.5 h, DMF (73 mg, 1.0 mmol) was added dropwise and stirring was continued for an additional 10 min. Water (10 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated by evaporation. The residual solid was recrystallized from hexane–CH_2Cl_2 to give **9a** (0.17 g, 75%); a white solid; mp 122–125 ˚C; IR (KBr) 1664 cm^{-1}; ^1H NMR (400 MHz) δ 2.53 (s, 3H), 3.13 (s, 6H), 10.24 (s, 1H).

4-Chloro-2-methylsulfanyl-6-(piperidin-1-yl)pyrimidine-5-carboxaldehyde (9b): a white solid; mp 126–128 °C (hexane–CH_2Cl_2); IR (KBr) 1664 cm^{-1}; ^1H NMR (400 MHz) δ 1.70 (br s, 6H), 2.51 (s, 3H), 3.60 (br s, 4H), 10.17 (s, 1H). Anal. Calcd for $C_{11}H_{14}ClN_3OS$: C, 48.61; H, 5.19; N, 15.46. Found: C, 48.36; H, 5.26; N, 15.40.

Typical Procedure for the Preparation of Aryl[6-(dialkylamino)pirimidin-5-yl]methanols (10). (4-Chloro-6-dimethylamino-2-methylsulfanylpyrimidin-5-yl)phenylmethanol (10a). To a stirred solution of **9a** (0.23 g, 1.0 mmol) in THF (3 mL) at 0 °C was added dropwise PhMgBr, prepared from PhBr (0.19 g, 1.2 mmol) and Mg (35 mg, 1.4 mmol) in THF (3 mmol). After 10 min, saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated by evaporation. The residual solid was recrystallized from hexane–CH_2Cl_2 to give **10a** (0.28 g, 90%); a pale-yellow solid; mp 152–154 °C (hexane–CH_2Cl_2); IR (KBr) 3262 cm^{-1}; ^1H NMR (400 MHz) δ 2.54 (s, 3H), 2.96 (s, 6H), 3.28 (d, J = 8.8 Hz, 1H), 6.16 (d, J = 8.8 Hz, 1H), 7.26–7.36 (m, 5H). Anal. Calcd for $C_{14}H_{16}ClN_3OS$: C, 54.27; H, 5.21; N, 13.56. Found: C, 54.27; H, 5.45; N, 13.50.

(4-Chloro-6-dimethylamino-2-methylsulfanylpyrimidin-5-yl)(4-chlorophenyl)methanol (10b): a white solid; mp 179–181 °C (hexane–CH_2Cl_2); IR (KBr) 3300 cm^{-1}; ^1H NMR (500 MHz) δ 2.53 (s, 3H), 2.95 (s, 6H), 3.21 (d, J = 9.2 Hz, 1H), 6.11 (d, J = 9.2 Hz, 1H), 7.26 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H). Anal. Calcd for $C_{14}H_{15}Cl_2N_3OS$: C, 48.84; H, 4.39; N, 12.21. Found: C, 48.63; H, 4.48; N, 11.94.

(4-Chloro-6-dimethylamino-2-methylsulfanylpyrimidin-5-yl)(4-methoxyphenyl)methanol (10c): a white solid; mp 161–163 °C (hexane–CH_2Cl_2); IR (KBr) 3272, 1610 cm^{-1}; ^1H NMR (400 MHz) δ 2.54 (s, 3H), 2.95 (s, 6H), 3.27 (d, J = 9.8 Hz, 1H), 3.82 (s, 3H), 6.08 (d, J = 9.8 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H). Anal. Calcd for $C_{15}H_{18}ClN_3O_2S$: C, 53.01; H, 5.34; N, 12.36. Found: C, 52.90; H, 5.47; N, 12.35.

[4-Chloro-2-methylsulfanyl-6-(piperidin-1-yl)pyrimidin-5-yl]phenylmethanol (10d): a white solid; mp 114–116 °C (hexane–Et_2O); IR (KBr) 3313 cm^{-1}; ^1H NMR (400 MHz) δ 1.53–1.56 (m, 6H), 2.54 (s, 3H), 3.04–3.28 (m, 4H), 4.08 (d, J = 9.8 Hz, 1H), 6.07 (d, J = 9.8 Hz, 1H), 7.26–7.35 (m, 5H). Anal. Calcd for $C_{17}H_{20}ClN_3OS$: C, 58.36; H, 5.76; N, 12.01. Found: C, 58.32; H, 5.81; N, 11.82.

Aryl[6-(dialkylamino)pirimidin-5-yl]methanones 11. These compounds were prepared by the PCC oxidation of **10** under the conditions reported previously.[2]

(4-Chloro-6-dimethylamino-2-methylsulfanylpyrimidin-5-yl)phenylmethanone (11a): a white solid; mp 122–124 °C (hexane–Et_2O); IR (KBr) 1663, 1541 cm^{-1}; ^1H NMR (400 MHz) δ 2.55 (s, 3H), 2.98 (s, 6H), 7.50 (dd, J = 8.6, 7.4 Hz, 2H), 7.62 (tt, J = 7.4, 1.1 Hz, 1H), 7.92 (dd, J = 8.6, 1.1 Hz, 2H). Anal. Calcd for $C_{14}H_{14}ClN_3OS$: C, 54.63; H, 4.58; N, 13.65. Found: C, 54.33; H, 4.60; N, 13.57.

(4-Chloro-6-dimethylamino-2-methylsulfanylpyrimidin-5-yl)(4-chlorophenyl)methanone (11b): a white solid; mp 135–137 °C (hexane–CH_2Cl_2); IR (KBr) 1674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.54 (s,

3H), 2.98 (s, 6H), 7.48 (d, J = 8.6 Hz, 2H), 7.86 (d, J = 8.6 Hz, 2H). Anal. Calcd for $C_{14}H_{13}Cl_2N_3OS$: C, 49.13; H, 3.83; N, 12.28. Found: C, 49.09; H, 3.89; N, 12.13.

(4-Chloro-6-dimethylamino-2-methylsulfanylpyrimidin-5-yl)(4-methoxyphenyl)methanone (11c): a white solid; mp 130–132 °C (hexane–Et_2O); IR (KBr) 1657 cm^{-1}; ^1H NMR (500 MHz) δ 2.54 (s, 3H), 3.00 (s, 6H), 3.90 (s, 3H), 6.97 (d, J = 9.8 Hz, 2H), 7.89 (d, J = 9.8 Hz, 2H). Anal. Calcd for $C_{15}H_{16}ClN_3O_2S$: C, 53.33; H, 4.77; N, 12.44. Found: C, 53.07; H, 4.88; N, 12.19.

[4-Chloro-2-methylsulfanyl-6-(piperidin-1-yl)pyrimidin-5-yl]phenylmethanone (11d): a white solid; mp 120–122 °C (hexane–CH_2Cl_2); IR (KBr) 1655, 1544 cm^{-1}; ^1H NMR (400 MHz) δ 1.38–1.44 (m, 4H), 1.53–1.57 (m, 2H), 2.54 (s, 3H), 3.43–3.46 (m, 4H), 7.50 (dd, J = 8.8, 7.4 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.89 (d, J = 8.8 Hz, 2H). Anal. Calcd for $C_{17}H_{18}ClN_3OS$: C, 58.70; H, 5.22; N, 12.08. Found: C, 58.66; H, 5.22; N, 12.05.

Typical Procedure for the Preparation of Thienopyrimidines (4), (7), and (12). 4-Methoxy-5-phenylthieno[2,3-*d*]pyrimidine-6-carbonitrile (4a). A solution of **3** (0.14 g, 0.56 mmol) and Na_2S nonahydrate (0.15 g, 0.62 mmol) in DMF (3 mL) was heated at 60 °C for 1 h. After cooling to 0 °C, $BrCH_2CN$ (74 mg, 0.62 mmol) was added; the mixture was stirred for 15 min. Then NaH (60% in oil; 25 mg, 0.62 mmol) was added and stirring was continued for an additional 10 min before water (20 mL) was added. The precipitate was collected by filtration and recrystallized from hexane–CH_2Cl_2 to give **4a** (0.12 g, 79%); a beige solid; mp 189–190 °C; IR (KBr) 2220 cm^{-1}; ^1H NMR (500 MHz) δ 3.96 (s, 3H), 7.51 (br s, 5H), 8.77 (s, 1H); ^{13}C NMR δ 54.35, 104.88, 113.74, 116.52, 128.07, 129.47, 129.58, 132.19, 146.55, 156.17, 165.36, 168.93; MS m/z 267 (M^+, 100). Anal. Calcd for $C_{14}H_9N_3OS$: C, 62.91; H, 3.39; N, 15.72. Found: C, 62.88; H, 3.29; N, 15.70.

1,1-Dimethylethyl 4-Methoxy-5-phenylthieno[2,3-*d*]pyrimidine-6-carboxylate (4b): a white solid; mp 115–117 °C (hexane); IR (KBr) 1684 cm^{-1}; ^1H NMR (500 MHz) δ 1.31 (s, 9H), 3.80 (s, 3H), 7.27–7.30 (m, 2H), 7.38–7.40 (m, 3H), 8.69 (s, 1H); ^{13}C NMR δ 27.71, 53.89, 82.69, 119.37, 127.21, 127.62, 129.15, 129.70, 135.48, 139.76, 155.01, 161.33, 165.58, 167.64; MS m/z 342 (M^+, 61), 286 (100). Anal. Calcd for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18. Found: C, 63.09; H, 5.47; N, 8.19.

4-Methoxy-2-methylsulfanyl-5-phenylthieno[2,3-*d*]pyrimidine-6-carbonitrile (7a): a pale-yellow solid; mp 200–203 °C (hexane–CH_2Cl_2); IR (KBr) 2222 cm^{-1}; ^1H NMR (500 MHz) δ 2.63 (s, 3H), 3.91 (s, 3H), 7.48–7.50 (m, 5H); ^{13}C NMR δ 14.38, 54.30, 101.88, 112.98, 114.12, 128.02, 129.35, 129.52, 132.35, 146.74, 150.07, 169.80, 171.42; MS m/z 313 (M^+, 100). Anal. Calcd for $C_{15}H_{11}N_3OS_2$: C, 57.49; H, 3.54; N, 13.41. Found: C, 57.49; H, 3.71; N, 13.20.

1,1-Dimethylethyl 4-Methoxy-2-methylsulfanyl-5-phenylthieno[2,3-*d*]pyrimidine-6-carboxylate (7b): a white solid; mp 154–156 °C (hexane–Et_2O); IR (KBr) 1688 cm^{-1}; ^1H NMR (500 MHz) δ 1.29 (s, 9H), 2.62 (s, 3H), 3.77 (s, 3H), 7.26–7.38 (m, 5H); ^{13}C NMR δ 14.33, 27.75, 53.89, 82.37, 115.96, 126.99, 127.15, 127.51, 129.13, 135.64, 140.08, 161.59, 164.44, 168.60, 169.44; MS m/z 388 (M^+, 50), 332 (100).

Anal. Calcd for $C_{19}H_{20}N_2O_3S_2$: C, 58.74; H, 5.19; N, 7.21. Found: C, 58.63; H, 5.27; N, 7.18.

1,1-Dimethylethyl 4-Methoxy-5-(3-methylphenyl)-2-methylsulfanylthieno[2,3-*d*]pyrimidine-6-carboxylate (7c): a white solid; mp 136–138 °C (hexane–CH_2Cl_2); IR (KBr) 1691 cm^{-1}; ^1H NMR (400 MHz) δ 1.23 (s, 9H), 2.39 (s, 3H), 2.62 (s, 3H), 3.79 (s, 3H), 7.05–7.07 (m, 2H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.26 (dd, *J* = 7.8, 7.3 Hz, 1H); ^{13}C NMR δ 14.34, 21.38, 27.75, 53.93, 82.27, 115.94, 126.22, 126.89, 127.03, 128.23, 129.91, 135.41, 136.45, 140.28, 161.68, 164.45, 168.59, 169.33; MS *m/z* 402 (M^+, 69), 346 (100). Anal. Calcd for $C_{20}H_{22}N_2O_3S_2$: C, 59.68; H, 5.51; N, 6.96. Found: C, 59.40; H, 5.81; N, 6.82.

[4-Methoxy-5-(3-methylphenyl)-2-methylsulfanylthieno[2,3-*d*]pyrimidin-6-yl]phenylmethanone (7d): a pale-yellow solid; mp 118–120 °C (hexane–CH_2Cl_2); IR (KBr) 1625 cm^{-1}; ^1H NMR (400 MHz) δ 2.15 (s, 3H), 2.66 (s, 3H), 3.89 (s, 3H), 6.90–6.93 (m, 2H), 6.99–7.05 (m, 2H), 7.13 (dd, *J* = 7.8, 7.3 Hz, 2H), 7.22–7.31 (m, 1H), 7.50 (dd, *J* = 7.8, 2.0 Hz, 2H); ^{13}C NMR δ 14.38, 21.02, 54.00, 114.94, 127.02, 127.61, 127.64, 128.63, 128.72, 129.08, 131.56, 132.13, 133.61, 133.91, 136.62, 137.40, 139.48, 164.64, 169.51, 191.24; MS *m/z* 406 (M^+, 100). Anal. Calcd for $C_{22}H_{18}N_2O_2S_2$: C, 65.00; H, 4.46; N, 6.89. Found: C, 64.90; H, 4.38; N, 6.80.

5-(3-Chlorophenyl)-4-methoxy-2-methylsulfanylthieno[2,3-*d*]pyrimidine-6-carbonitrile (7e): a beige solid; mp 199–200 °C (hexane–CH_2Cl_2); IR (KBr) 2214 cm^{-1}; ^1H NMR (400 MHz) δ 2.70 (s, 3H), 3.57 (s, 3H), 7.35 (d, *J* = 6.8 Hz, 1H), 7.43 (s, 1H), 7.58 (dd, *J* = 8.8, 6.9 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR δ 14.64, 52.28, 107.59, 112.62, 113.98, 127.26, 129.08, 130.98, 131.01, 133.45, 135.72, 143.68, 155.38, 169.91, 172.17; MS *m/z* 347 (M^+, 100). Anal. Calcd for $C_{15}H_{10}ClN_3OS_2$: C, 51.79; H, 2.90; N, 12.08. Found: C, 51.75; H, 2.76; N, 12.02.

4-Methoxy-5-(4-methoxyphenyl)-2-methylsulfanylthieno[2,3-*d*]pyrimidine-6-carbonitrile (7f): a white solid; mp 200–202 °C (hexane–CH_2Cl_2); IR (KBr) 2215, 1609 cm^{-1}; ^1H NMR (400 MHz) δ 2.63 (s, 3H), 3.89 (s, 3H), 3.94 (s, 3H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR δ 14.40, 54.34, 55.32, 101.02, 112.94, 113.45, 114.49, 124.58, 131.02, 146.68, 160.42, 164.02, 169.81, 171.26; MS *m/z* 343 (M^+, 100). Anal. Calcd for $C_{16}H_{13}N_3O_2S_2$: C, 55.96; H, 3.82; N, 12.24. Found: C, 55.74; H, 4.12; N, 12.24.

4-Dimethylamino-2-methylsulfanyl-5-phenylthieno[2,3-*d*]pyrimidine-6-carbonitrile (12a): a beige solid; mp 192–194 °C (hexane–CH_2Cl_2); IR (KBr) 2207 cm^{-1}; ^1H NMR (400 MHz) δ 2.61 (s, 3H), 2.63 (s, 6H), 7.45–7.50 (m, 5H); ^{13}C NMR δ 14.31, 40.49, 99.05, 110.31, 114.93, 128.45, 128.97, 129.35, 134.11, 146.98, 160.43, 168.97, 171.22; MS *m/z* 326 (M^+, 100). Anal. Calcd for $C_{16}H_{14}N_4S_2$: C, 58.87; H, 4.32; N, 17.16. Found: C, 58.60; H, 4.36; N, 17.10.

1,1-Dimethylethyl 5-(4-Chlorophenyl)-4-dimethylamino-2-methylsulfanyl[2,3-*d*]pyrimidine-6-carboxylate (12b): colorless crystals; mp 175–177 °C (hexane–CH_2Cl_2); IR (KBr) 1686 cm^{-1}; ^1H NMR (400 MHz,) δ 1.44 (s, 9H), 2.54 (s, 6H), 2.60 (s, 3H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR δ 14.32, 28.01, 40.61, 82.64, 113.53, 123.82, 127.85, 131.53, 133.87, 134.05, 139.21, 161.20,

161.48, 167.41, 170.03; MS *m/z* 435 (M^+, 69), 379 (100). Anal. Calcd for $C_{20}H_{22}ClN_3O_2S_2$: C, 55.10; H, 5.09; N, 9.64. Found: C, 55.02; H, 5.18; N, 9.39.

[5-(4-Chlorophenyl)-4-dimethylamino-2-methylsulfanyl[2,3-*d*]pyrimidin-6-yl]phenylmethanone (12c): a pale-yellow solid; mp 206–208 ˚C (hexane–CH_2Cl_2); IR (KBr) 1627 cm^{-1}; ^1H NMR (500 MHz) δ 2.59 (s, 6H), 2.63 (s, 3H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 7.20 (dd, *J* = 8.0, 7.4 Hz, 2H), 7.39 (tt, *J* = 7.4, 1.1 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.1 Hz, 2H); ^{13}C NMR δ 14.33, 40.68, 112.52, 127.99, 128.18, 129.48, 130.94, 131.01, 132.64, 133.78, 134.15, 137.34, 137.43, 161.32, 167.52, 170.61, 191.36; MS *m/z* 439 (M^+, 100). Anal. Calcd for $C_{22}H_{18}ClN_3OS_2$: C, 60.06; H, 4.12; N, 9.55. Found: C, 59.94; H, 4.34; N, 9.58.

4-Dimethylamino-5-(4-methoxyphenyl)-2-methylsulfanyl[2,3-*d*]pyrimidine-6-carbonitrile (12d): a white solid; mp 170–173 ˚C (hexane–CH_2Cl_2); IR (KBr) 2202, 1608 cm^{-1}; ^1H NMR (500 MHz) δ 2.60 (s, 3H), 2.66 (s, 6H), 3.89 (s, 3H), 7.01 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR δ 14.34, 40.55, 55.42, 98.31, 110.39, 114.36, 115.26, 126.50, 129.80, 146.92, 160.36, 160.61, 168.85, 171.11; MS *m/z* 356 (M^+, 100). Anal. Calcd for $C_{17}H_{16}N_4OS_2$: C, 57.28; H, 4.52; N, 15.72. Found: C, 57.20; H, 4.60; N, 15.68.

1,1-Dimethylethyl 4-Dimethylamino-5-(4-methoxyphenyl)-2-methylsulfanyl[2,3-*d*]pyrimidine-6-carboxylate (12e): colorless crystals; mp 136–138 ˚C (hexane–CH_2Cl_2); IR (KBr) 1679, 1611 cm^{-1}; ^1H NMR (500 MHz) δ 1.44 (s, 9H), 2.54 (s, 6H), 2.60 (s, 3H), 3.87 (s, 3H), 6.93 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR δ 14.28, 28.04, 40.43, 55.26, 82.22, 113.02, 113.74, 122.87, 127.76, 131.35, 140.65, 159.35, 161.27, 161.75, 167.03, 169.92; MS *m/z* 431 (M^+, 61), 375 (100). Anal. Calcd for $C_{21}H_{25}N_3O_3S_2$: C, 58.44; H, 5.84; N, 9.74. Found: C, 58.31; H, 5.84; N, 9.51.

1,1-Dimethylethyl 2-Methylsulfanyl-5-phenyl-4-(piperidin-1-yl)thieno[2,3-*d*]pyrimidine-6-carboxylate (12f): colorless crystals; mp 155–157 ˚C (hexane–CH_2Cl_2); IR (KBr) 1710 cm^{-1}; ^1H NMR (400 MHz) δ 1.02–1.08 (m, 4H), 1.28–1.34 (m, 2H), 1.38 (s, 9H), 2.60 (s, 3H), 3.04–3.07 (m, 4H), 7.33–7.42 (m, 5H); ^{13}C NMR δ 14.32, 23.92, 24.71, 27.92, 50.44, 82.36, 114.41, 124.66, 127.57, 127.94, 130.17, 135.00, 140.14, 161.66, 161.79, 167.32, 169.98; MS *m/z* 441 (M^+, 52), 385 (100). Anal. Calcd for $C_{23}H_{27}N_3O_2S_2$: C, 62.55; H, 6.16; N, 9.52. Found: C, 62.50; H, 6.20; N, 9.30.

REFERENCES

1. K. Kobayashi, T. Kozuki, and H. Konishi, *Heterocycles,* 2009, **78**, 2993.
2. K. Kobayashi, T. Suzuki, and H. Konishi, *Heterocycles,* 2012, **85**, 403.
3. (a) D. Briel, A. Rybak, C. Kronbach, K. Unverferth, T. C. M. Gonzalez, and M. Guestschow, *J. Heterocycl. Chem.,* 2010, **47**, 634; (b) B. Sirisha, B. Narsaiah, T. Yakaiah, G. Gayatri, G. N. Sastry, and M. R. Prasad, *Eur. J. Med. Chem.*, 2010, **45**, 1739; (c) M. M. El-Kerdawy, E. R. El-Bendary, A. A.-M. Abdel-Aziz, R. R. El-Wasseef, and N. I. A. El-Aziz, *Eur. J. Med. Chem.*, 2010, **45**, 1805; (d)

A. Gopalsamy, M. Shi, Y. Hu, F. Lee, L. Feldberg, E. Frommer, S. Kim, K. Collins, D. Wojciechowicz, and R. Mallon, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2431; (e) T. K. Sasikumar, L. Qiang, D. A. Burnett, W. J. Greenlee, C. Li, M. Grilli, R. Bertorelli, G. Lozza, and A. Reggiani, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2474; (f) J. C. Aponte, A. J. Vaisberg, D. Castillo, G. Gonzalez, Y. Estevez, J. Arevalo, M. Quiliano, M. Zimic, M. Verástegui, E. Máraga, R. H. Gilman, J. M. Bustamante, R. L. Tarleton, Y. Wang, S. G. Franzblau, G. F. Pauli, M. Sauvain, and G. B. Hammond, *Bioorg. Med. Chem.,* 2010, **18**, 2880; (g) A. M. Capelli, L. Castellrtti, C. Salvagno, B. Oliosi, E. D. Lenarda, C. Virginio, A. Lightfoot, J. N. C. Kew, and S. Teague, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 4561; (h) A. E. Rashad, A. H. Shamroukh, R. E. Abdel-Megeid, A. Mostafa, R. El-Shesheny, A. Kandeil, M. A. Ali, and K. Banert, *Eur. J. Med. Chem.*, 2010, **45**, 5251; (i) A. Ts. Mavrova, D. Vuchev, K. Anichina, and N. Vassilev, *Eur. J. Med. Chem.*, 2010, **45**, 5856; (j) J. Deng, L. Peng, G. Zhang, X. Lan. C. Li, F. Chen, Y. Zhou, Z. Lin, L. Chen, R. Dai, H. Xu, L. Yang, X. Zhang, and W. Hu, *Eur. J. Med. Chem.*, 2011, **46**, 71; (k) M.-Y. Jang, Y. Lin, S. De Jonghe, L.-J. Gao, B. Vanderhoydonck, M. Froeyen, J. Rozenski, J. Herman, T. Louat, K. Van Belle, M. Waer, and P. Herdewijn, *J. Med. Chem.*, 2011, **54**, 655; (l) A. Zhao, X. Gao, Y. Wang, J. Ai, Y. Wang, Y. Chen, M. Geng, and A. Zhang, *Bioorg. Med. Chem.,* 2011, **19**, 3906; (m) K. Miwa, T. Hitaka, T. Imada, S. Sasaki, M. Yoshimatsu, M. Kusaka, A. Tanaka, D. Nakata, S. Furuya, S. Endo, K. Hamamura, and T. Kitazaki, *J. Med. Chem.*, 2011, **54**, 4998; (n) W. J. MaClellan, Y. Dai, C. Abad-Zapatero, D. H. Albert, J. J. Bouska, K. B. Glaser, T. J. Magoc, P. A. Marcotte, D. J. Oaterling, K. D. Stewart, and S. K. Davidson, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5620; (o) B. E. Sleebs, G. Nikolakopoulos, I. P. Street, H. Falk, and J. B. Baell, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5992; (p) T. Beckers, A. Sellmer, E. Eichhorn, H. Pongratz, C. Aschächtele, F. Totzke, G. Kelter, R. Krumbach, H.-H. Fiebig, F.-D. Böhmer, and S. Mahboobi, *Bioorg. Med. Chem.*. 2012, **20**, 125; (q) G. K. Packard, P. Papa, J. R. Riggs, P. Erdman, L. Tehrani, D. Robinson, R. Harris, G. Shelvin, S. Perrin-Ninkovic, R. Hilgraf, M. A. McCarrick, T. Tran, Y. Fleming, A. Bai, S. Richardson, J. Katz, Y. Tang, J. Leisten, M. Moghaddam, B. Cathers, D. Zhu, and S. Sakata, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 747.

4. (a) M. Bakavoli, G. Bagherzadeh, M. Vaseghifar, A. Shiri, and P. Pordeli, *J. Chem. Res.,* 2009, 653; (b) C. Shama, S. Yerande, R. Chavan, and A. V. Bhosal, *E-J. Chem.*, 2010, **7**, 655; (c) T. Wang, C.-H. Zheng, S. Liu, and H.-Z. Chen, *Phosphorous Sulfur Silicon Relat. Elem.,* 2010, **185**, 1543; (d) S. Pédeboscq, D. Gravier, F. Casadebaig, G. Hou, A. Gissot, F. De Giorgi, F. Ichas, J. Cambar, and J.-P. Pometan, *Eur. J. Med. Chem.*, 2010, **45**, 2473; (e) K. M. Al-Taisan, H. M. A. Al-Hazimi, and S. S. Al-Shihry, *Molecules,* 2010, **15**, 3932; (f) H. N. Hafez, H. A. R. Hussein, and A-R. El-Gazzar, *Eur. J. Med. Chem.*, 2010, **45**, 4026; (g) S. Tasler, R. Baumgartner, A. Ammendola, J. Schachtner, T. Wieber, M. Blisse, S. Rath, M. Zaja, P. Klahn, U. Quotschalla, and P. Ney, *Bioorg. Med. Chem. Lett.*,

2010, **20**, 6108; (h) X. Deng, B. Okram, Q. Ding, J. Zhang, Y. Choi, F. J. Adrián, A. Wojciechowski, G. Zhang, J. Che, B. Bursulaya, S. W. Cowan-Jacob, and G. Rummel, *J. Med. Chem*., 2010, **53**, 6934; (i) A. G. Golub, V. G. Bdzhola, N. Briukhovetska, A. O. Balanda, O. P. Kukharenko, I. M. Kotey, O. V. Ostrynska, and S. M. Yarmouluk, *Eur. J. Med. Chem*., 2010, **46**, 870; (j) T. Horiuchi, Y. Takeda, N. Haginoya, M. Miyazaki, M. Nagata, M. Kitagawa, and K. Uoto, *Chem. Pharm. Bull*., 2011, **59**, 991.

5. (a) A. E. Rashad, M. I. Hegab, R. E. Abdel-Megeid, M. M. Ali, and F. M. E. Abdel-Megeid, *Phosphorous Sulfur Silicon Relat. Elem.,* 2010, **185**, 74; (b) A. A. Aly, A. B. Brown, M. Ramadan, A. M. Gamel-Eldeen, M. Abdel-Aziz, G. E.-E. A. A. Abuo-Rahma, and M. F. Radwan, *Arch. Pharm. Chem*., 2010, **343**, 301; (c) A. E. Eashed, A. H. Shamroukh, R. E. Abdel-Megeid, and W. A. El-Sayed, *Synth. Commun*., 2010, **40**, 1149; (d) M. A. Ameen, S. Karsten, and J. Liebscher, *Tetrahedron,* 2010, **66**, 2141; (e) H. Y. Son and Y.-H. Song, *Bull. Korean Chem. Soc*., 2010, **31**, 2242; (f) C.-H. Wu, M. S. Coumar, C.-Y. Chu, W.-H. Lin, Y.-R. Chen, C.-T. Chen, H.-Y. Shiao, S. Rafi, S.-Y. Wang, H. Hsu, C.-H. Chen, C.-Y. Chang, T.-Y. Chang, T.-W. Lien, M.-Y. Fang, K.-C. Yeh, C.-P. Chen, T.-K. Yeh, S.-H. Hsieh, J. T.-A. Hsu, C.-C. Liao, Y.-S. Chao, and H.-P. Hsieh, *J. Med. Chem*., 2010, **53**, 7316.
6. (a) A. Davoodnia, M. Bakavoli, M.-R. Asadi, and N. Tavakoli-Hoseini, *Heterocycl. Commun*., 2009, **15**, 429; (b) B. Ochen, E. Perspicace, S. Hesse, and G. Kirsch, *Synthesis,* 2010, 2413; (c) K. S. Kumar, S. Chamakuri, P. Vishweshwar, J. Iqbal, and M. Pal, *Tetrahedron Lett*., 2010, **51**, 3269; (d) A. Fernandez-Mato, C. Peinador, and J. M. Quintela, *Synthesis,* 2011, 3323.
7. B. Zhou, B. Taylor, and K. Kornau, *Tetrahedron Lett.,* 2005, **46**, 3977.
8. A. Kaminskas, M. Dailide, and S. Tumkevicius, *Pol. J. Chem*., 2002, **76**, 725.