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SYNTHESIS OF [1,4]OXATHIINO[2,3-*d*]PYRIMIDINES STARTING WITH 4,6-DICHLORO-2-(METHYLSULFANYL)PYRIMIDINE

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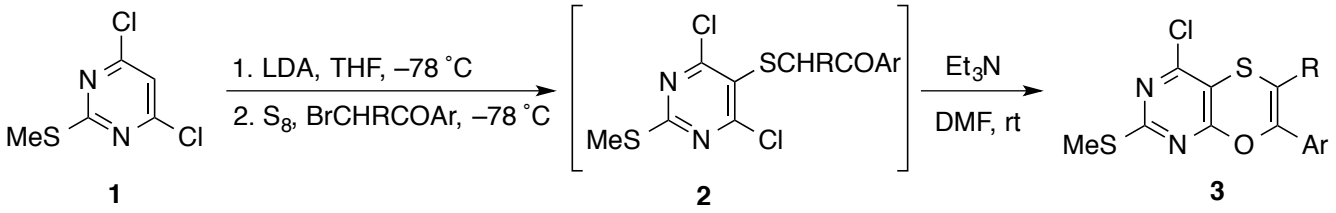
Abstract – A convenient method for the preparation of 7-(het)aryl[1,4]oxathiino[2,3-*d*]pyrimidine derivatives using an easily operated two-step sequence starting from 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) have been developed. Thus, the starting material is treated with LDA to generate the 5-lithio derivative, which is allowed to react with sulfur and then phenacyl bromide and its derivatives to give 1-(het)aryl-2-{[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]sulfanyl}ethanones. These pyrimidinyl ketones undergo ring closure upon treatment with triethylamine to provide the corresponding desired products in reasonable overall yields from DCSMP.

We have been investigating the utility of 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) (**1**) in the preparation of pyrimidine-fused heterocycles.[1] We recently demonstrated that 5-lithiated DCSMP reacted successively with sulfur and 2-bromoacetonitrile to give 2-{[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]sulfanyl}acetonitrile, which could be transformed into 7-(alkylsulfanyl)[1,4]dithiino[2,3-*d*]pyrimidine-6-carbonitrile derivatives on treatment with carbon disulfide in the presence of two equivalents of sodium hydride followed by addition of alkyl halides.[1e] We became interested in utilizing phenacyl bromide and its derivatives in place of 2-bromoacetonitrile and envisaged that the resulting 1-(het)aryl-2-

{[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]sulfanyl}ethanones (**2**) could provide 7-(het)aryl[1,4]oxathiino[2,3-*d*]pyrimidines (**3**) on treatment with an appropriate base. In the present paper, we wish to demonstrate results of our investigation, which provide a very simple and experimentally convenient method for the preparation of this new heterocyclic system.[2] It may offer the possibility to access compounds of potential biological interest.



1 **2** **3**

Scheme 1

Table 1. Preparation of [1,4]oxathiino[2,3-*d*]pyrimidines (**3**)

Entry	**3**	R	Ar	Yield/%[a]
1	**3a**	H	Ph	66
2	**3b**	H	*p*-Tol	63
3	**3c**	H	4-ClC_6H_4	63
4	**3d**	H	4-BrC_6H_4	46
5	**3e**	H	4-$MeOC_6H_4$	47
6	**3f**	H	3-$(NO_2)C_6H_4$	53
7	**3g**	H	naphthalen-2-yl	58
8	**3h**	H	thiophen-2-yl	74
9	**3i**	Me	Ph	47
10	**3j**	Ph	Ph	65

[a] Yields of isolated products based on **1**.

The synthesis of **3** from **1** was conducted according to the sequence illustrated in Scheme 1. As the first step of our sequence, 4,6-dichloro-5-lithio-2-(methylsulfanyl)pyrimidine was generated by the treatment of **1** with LDA in THF at –78 °C[1a] and allowed to react successively with sulfur and phenacyl bromide and its derivatives, which were all commercially available. The reactions performed well to result in the formation of the corresponding 1-aryl-2-{[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]sulfanyl}ethanones (**2**). These compounds were then transformed into the desired products (**3**) without any purification after aqueous workup. This transformation was easily carried out by treating the crude (**2**) with an equivalent of triethylamine in DMF at room temperature. The results of the reactions are summarized in Table 1 and allowed us to conclude that a variety of phenacyl bromide derivatives and 2-(2-bromoacetyl)thiophene could be used in the present transformation, and the desired products (**3**) were obtained in reasonable overall yields from **1**. The reactions forming products (**3i**) and (**3j**) took much longer reaction times for completion of the ring closure compared to those forming the others (see

Experimental), though the yields were comparable (Entries 9 and 10). This may be rationalized by the crowdedness due to the 6- and 7-substituents of the products.

It should be mentioned that compound (**1**) were initially treated with two equivalents of LDA and allowed to react with sulfur and phenacyl bromide in order to develop a one-pot method. Unfortunately, however, the reaction gave an intractable mixture of products, from which a considerably low yield (14%) of the desired product (**3a**) was isolated.

In conclusion, an efficient method for the preparation of a new heterocyclic system, [1,4]oxathiino[2,3-*d*]pyrimidine, from 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) has been developed. The method commences with the reaction of 5-lithiated DCSMP with sulfur and then phenacyl bromide and its derivatives giving the corresponding 1-aryl-2-{[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]sulfanyl}ethanones and these are converted into the desired products on treatment with triethylamine under very mild conditions. The present method may be of use in organic synthesis because of the ease of operations as well as the ready availability of the starting materials and reagents.

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). 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. *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of [1,4]Oxathiino[2,3-*d*]pyrimidines (3). 4-Chloro-2-(methylsulfanyl)-7-phenyl[1,4]oxathiino[2,3-*d*]pyrimidine (3a). To a stirred solution of LDA (2.0 mmol), generated by the standard method from *i*-Pr_2NH (0.30 g, 2.0 mmol) and *n*-BuLi (1.6 M in hexane; 2.0 mmol), in THF (6 mL) at –78 ˚C was added a solution of **1** (0.39 g, 2.0 mmol) in THF (1.5 mL) dropwise. After 15 min, a solution of S_8 (64 mg, 0.25 mmol) in THF (6.5 mL) and a solution of $BrCH_2Bz$ (0.40 g, 2.0 mmol) in THF (1.5 mL) were successively added and stirring was continued at the same temperature for an additional 5 min before addition of saturated aqueous NH_4Cl (20 mL). The mixture was warmed to rt and extracted with AcOEt (3 × 15 mL). The combined extracts were washed with brine

(15 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was dissolved in DMF (10 mL) and Et_3N (0.20 g, 2.0 mmol) was added and the solution was stirred for 2 h at rt. The resulting mixture was diluted with AcOEt (30 mL), washed with H_2O (3 × 15 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was recrystallized to afford **3a** (0.41 g, 66%); a yellow solid; mp 132–134 °C (hexane/CH_2Cl_2); IR 1555, 1497 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H), 5.71 (s, 1H), 7.35–7.38 (m, 3H), 7.54 (dd, *J* = 7.4, 1.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.3, 93.0, 106.6, 124.1, 128.5, 129.3, 131.5, 148.2, 155.2, 163.5, 170.8. HR-MS (positive). Calcd for $C_{13}H_{10}ClN_2OS_2$ (M+H): 308.9923. Found: *m/z* 308.9916. Anal. Calcd for $C_{13}H_9ClN_2OS_2$: C, 50.56; H, 2.94; N, 9.07; S, 20.76. Found: C, 50.32; H, 2.88; N, 9.16; S, 21.09.

4-Chloro-7-(4-methylphenyl)-2-(methylsulfanyl)[1,4]oxathiino[2,3-*d*]pyrimidine (3b): a yellow solid; mp 123–125 °C (hexane/CH_2Cl_2); IR 1550, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.45 (s, 3H), 5.57 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 21.3, 91.8, 106.8, 124.0, 128.8, 129.2, 139.5, 148.4, 155.2, 163.6, 170.6. HR-MS (positive). Calcd for $C_{14}H_{12}ClN_2OS_2$ (M+H): 323.0079. Found: *m/z* 323.0074. Anal. Calcd for $C_{14}H_{11}ClN_2OS_2$: C, 52.09; H, 3.43; N, 8.68. Found: C, 51.95; H, 3.53; N, 8.80.

4-Chloro-7-(4-chlorophenyl)-2-(methylsulfanyl)[1,4]oxathiino[2,3-*d*]pyrimidine (3c): a yellow solid; mp 129–131 °C (hexane/CH_2Cl_2); IR 1553, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (s, 3H), 5.72 (s, 1H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 93.7, 106.4, 125.4, 128.8, 130.0, 135.2, 147.2, 155.4, 163.3, 171.0. HR-MS (positive). Calcd for $C_{13}H_9Cl_2N_2OS_2$ (M+H): 342.9533. Found: *m/z* 342.9531. Anal. Calcd for $C_{13}H_8Cl_2N_2OS_2$: C, 45.49; H, 2.35; N, 8.16; S, 18.68. Found: C, 45.45; H, 2.29; N, 8.21; S, 19.05.

7-(4-Bromophenyl)-4-chloro-2-(methylsulfanyl)[1,4]oxathiino[2,3-*d*]pyrimidine (3d): a yellow solid; mp 143–145 °C (hexane/CH_2Cl_2); IR 1550, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (s, 3H), 5.73 (s, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 93.8, 106.3, 112.5, 125.6, 130.4, 131.8, 147.2, 155.4, 163.3, 171.0. HR-MS (positive). Calcd for $C_{13}H_9BrClN_2OS_2$ (M+H): 386.9028. Found: *m/z* 386.9023. Anal. Calcd for $C_{13}H_8BrClN_2OS_2$: C, 40.27; H, 2.08; N, 7.23. Found: C, 40.34; H, 1.96; N, 7.08.

4-Chloro-7-(4-methoxyphenyl)-2-(methylsulfanyl)[1,4]oxathiino[2,3-*d*]pyrimidine (3e): a yellow solid; mp 153–155 °C (hexane/CH_2Cl_2); IR 1609, 1548, 1501 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H), 3.83 (s, 3H), 5.55 (s, 1H), 6.88 (d, *J* = 9.2 Hz, 2H), 7.48 (d, *J* = 9.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 55.3, 90.5, 107.0, 113.9, 124.3, 125.7, 148.3, 155.2, 160.5, 163.6, 170.6. HR-MS (positive). Calcd for $C_{14}H_{12}ClN_2O_2S_2$ (M+H): 339.0028. Found: *m/z* 339.0022. Anal. Calcd for $C_{14}H_{11}ClN_2O_2S_2$: C, 49.63; H, 3.27; N, 8.27; S, 18.92. Found: C, 49.48; H, 3.27; N, 8.36; S, 19.27.

4-Chloro-2-(methylsulfanyl)-7-(3-nitrophenyl)[1,4]oxathiino[2,3-*d*]pyrimidine (3f): a yellow solid; mp 188–190 °C (hexane/CH_2Cl_2); IR 1554, 1528, 1500, 1356 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.49 (s, 3H), 6.83 (s, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 8.29 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.8, 97.6, 106.1, 117.8, 123.5, 129.6, 130.3, 132.5, 144.0, 148.0, 154.3, 162.7, 170.0. HR-MS (negative). Calcd for $C_{13}H_7ClN_3O_3S_2$ (M–H): 351.9618. Found: *m*/*z* 351.9616. Anal. Calcd for $C_{13}H_8ClN_3O_3S_2$: C, 44.13; H, 2.28; N, 11.88; S, 18.12. Found: C, 43.98; H, 2.07; N, 11.80; S, 18.34.

4-Chloro-2-(methylsulfanyl)-7-(naphthalen-2-yl)[1,4]oxathiino[2,3-*d*]pyrimidine (3g): a yellow solid; mp 174–176 °C (hexane/CH_2Cl_2); IR 1634, 1557, 1497 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.56 (s, 3H), 5.86 (s, 1H), 7.50–7.54 (m, 3H), 7.81 (d, *J* = 8.6 Hz, 2H), 7.89 (d, *J* = 9.2 Hz, 1H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 93.5, 106.7, 121.3, 123.5, 126.8, 126.9, 127.2, 128.4, 128.5, 128.7, 133.0, 133.5, 148.2, 155.3, 163.5, 170.9. HR-MS (positive). Calcd for $C_{17}H_{12}ClN_2OS_2$ (M+H): 359.0079. Found: *m*/*z* 359.0075. Anal. Calcd for $C_{17}H_{11}ClN_2OS_2$: C, 56.90; H, 3.09; N, 7.81; S, 17.87. Found: C, 56.85; H, 3.05; N, 7.72; S, 17.82.

4-Chloro-2-(methylsulfanyl)-7-(thiophen-2-yl)[1,4]oxathiino[2,3-*d*]pyrimidine (3h): a yellow solid; mp 149–151 °C (hexane/CH_2Cl_2); IR 1640, 1553, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H), 5.61 (s, 1H), 7.01 (dd, *J* = 5.2, 4.0 Hz, 1H), 7.27 (d, *J* = 5.2 Hz, 1H), 7.28 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 91.7, 106.5, 124.5, 125.9, 127.6, 135.0, 143.9, 155.4, 163.1, 170.8. HR-MS (positive). Calcd for $C_{11}H_8ClN_2OS_3$ (M+H): 314.9487. Found: *m*/*z* 314.9481. Anal. Calcd for $C_{11}H_7ClN_2OS_3$: C, 41.97; H, 2.24; N, 8.90. Found: C, 41.80; H, 1.97; N, 9.12.

4-Chloro-6-methyl-2-(methylsulfanyl)-7-phenyl[1,4]oxathiino[2,3-*d*]pyrimidine (3i). The treatment with Et_3N was continued for 2 days. A pale-yellow solid; mp 127–129 °C (hexane/CH_2Cl_2); IR 1664, 1551, 1508 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92 (s, 3H), 2.50 (s, 3H), 7.36–7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.3, 18.4, 105.4, 107.8, 128.3, 128.6, 129.2, 132.3, 143.8, 154.6, 164.0, 170.5. HR-MS (DART). Calcd for $C_{14}H_{12}ClN_2OS_2$ (M+H): 323.0079. Found: *m*/*z* 323.0073. Anal. Calcd for $C_{14}H_{11}ClN_2OS_2$: C, 52.09; H, 3.43; N, 8.68; S, 19.87. Found: C, 51.90; H, 3.34; N, 8.55; S, 20.21.

4-Chloro-2-(methylsulfanyl)-6,7-diphenyl[1,4]oxathiino[2,3-*d*]pyrimidine (3j). The treatment with Et_3N was continued for a day. A yellow solid; mp 144–146 °C (hexane/CH_2Cl_2); IR 1637, 1551, 1498 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H), 7.15–7.28 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.4, 108.3, 111.0, 127.9, 128.7, 128.9 (2 overlapped Cs), 129.0, 129.4, 132.3, 134.5, 144.4, 154.7, 164.1, 170.7. HR-MS (positive). Calcd for $C_{19}H_{14}ClN_2OS_2$ (M+H): 385.0236. Found: *m*/*z* 385.0231.

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