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Convenient synthesis of 2-(methylsulfonyl)pyrimidine derivatives

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ABSTRACT

An efficient and convenient approach for the preparation of functionalized 2-(methylsulfonyl)pyrimidine derivatives has been developed through cyclic condensation of malonate derivatives with *S*-methylisothiouronium sulfate followed by derivation and oxidation in water–acetone mixture using oxone as the oxidant. This synthetic strategy provides an efficient and environmentally friendly approach for easy access to 2-(methylsulfonyl)pyrimidine derivatives with considerable yields.

GRAPHICAL ABSTRACT

ARTICLE HISTORY
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KEYWORDS
2-(Methylsulfonyl) pyrimidine; 2-(methylthio) pyrimidine; Cyclization; oxidation

Introduction

Drugs containing pyrimidine moieties have received much attention for their pharmacological and biological effects.[1] Ambrisentan and darusentan, for example, are highly selective endothelin receptor antagonists for the treatment of pulmonary hypertension.[2] Avanafil is phosphodiesterase type 5 inhibitor used to treat erectile dysfunction.[3] Etravirine and rilpivirine are non-nucleoside reverse transcriptase inhibitors used for the treatment of HIV infection.[4] Pazopanib is a multitargeted receptor tyrosine kinase inhibitor that has been approved for the treatment of renal cell carcinoma and soft tissue sarcoma.[5] A number of pyrimidine derivatives were recently reported to be antimalarial agents,[6] adenosine receptors (ARs) antagonists,[7] CRF1 receptor antagonists,[8] and anti-HIV agents[9] in a range of therapeutic areas. Overall, many of the pyrimidine derivatives are synthesized by using 2-(methylsulfonyl)pyrimidines as key intermediates.

The literature survey identified one principal method for the preparation of such compounds. The synthesis were accomplished through cyclic condensation of 1,3-dicarbonyl derivatives with thiourea, followed by the *S*-methylation and subsequent oxidation of 2-methylthio group to form a 2-methysulfonyl group, which can then undergo a substitution reaction at C2.[10,11] However, this approach usually suffers from multistep

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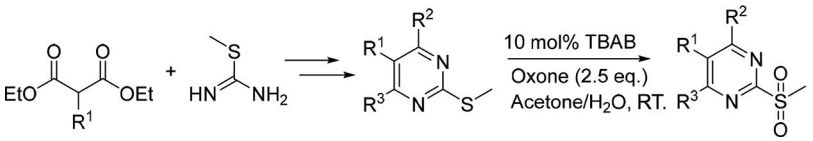
reactions, harsh reaction conditions, and/or unsatisfactory yields in the actual operation. For example, the use of dimethyl sulfate[11,12] or methyl iodide[13,14] in the *S*-methylation reaction suffers from the drawback of toxicity. The identified oxidants for the 2-methylthio group oxidation include *meta*-chloroperoxybenzoic acid,[15,16] peracetic acid,[17] sodium periodate,[18] hydrogen peroxide,[11] and chlorine gas.[10] While these oxidation conditions are still less than ideal, particularly for scale-up, due to their safety profile and/or difficulty in product isolation. As shown in Scheme 1, we report herein an efficient and convenient approach for the preparation of highly functionalized 2-(methylsulfonyl)pyrimidine derivatives. Alternative to the reported approaches, we performed the synthesis through cyclic condensation of malonate derivatives with *S*-methylisothiouronium sulfate, derivation and oxidation using oxone as the oxidant to give the corresponding 2-(methylsulfonyl)pyrimidine derivatives. This synthetic route provides the advantage of less synthetic steps, avoids hazardous reaction conditions and proceeds with considerable yields.

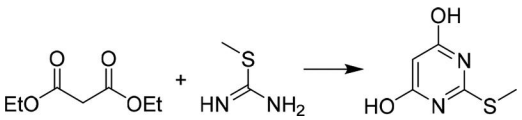
Results and discussion

The reaction of ethyl acetoacetate with 2-methyl-2-thiopseudourea sulfate in the presence of potassium carbonate was reported to give 6-methyl-2-(methylthio)pyrimidin-4-ol.[19] However, when the approach is adopted to the synthesis of 2-(methylthio)pyrimidine-4,6-diol according to the reported procedure, the low yields appeared in our attempt even heated at 80 °C in a lengthened reaction time (48 h, Table 1, entry 1). Hence, we performed the model reaction experiment with diethyl malonate and 2-methyl-2-thiopseudourea sulfate in different reaction media. A preliminary screening of catalysts for the reaction revealed that the use of sodium hydroxide is crucial for this cyclic condensation. Among the solvents screened, polar solvent such as ethanol gave the best reaction profiles (Table 1, entries 6 and 7). The use of water as solvent retarded the reaction, presumably in part due



Scheme 1. General scheme for synthesis of 2-(methylsulfonyl)pyrimidine derivatives.

Table 1. Optimization of reaction conditions and yields.



Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	K_2CO_3	H_2O	80	48	Trace
2	NaOH	H_2O	80	24	Trace
3	H_2SO_4	H_2O	80	24	–
4	K_2CO_3	EtOH	Reflux	24	Trace
5	H_2SO_4	EtOH	RT	24	–
6	NaOH	EtOH	RT	24	60
7	NaOH	EtOH	reflux	4	82

[a]Isolated yields after simple filtration.

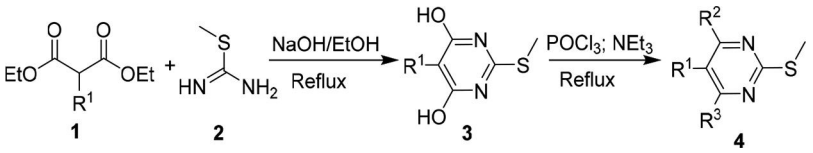
to the low solubility of the substrate (Table 1, entries 2). The following optimal conditions were used in the subsequent investigation: malonate derivatives (1 equiv), 2-methyl-2-thiopseudourea sulfate (1.2 equiv), sodium hydroxide (2.5 equiv), ethanol (2 mL/mmol), reflux 2–4 h. After completion of the reaction, the product was obtained after a simple filtration, and the results are summarized in Table 1.

Having established the optimal conditions for the cyclization, we intended to determine the substrate scope. Various substituted malonate derivatives were reacted with 2-methyl-2-thiopseudourea sulfate smoothly. After cyclization, the intermediate **3** was not purified and submitted to chlorination and/or derivation yielding the corresponding 2-(methylthio)pyrimidine derivatives according to the reported procedure.[19] As shown in Table 2, most of the reactions gave considerable yields (Table 2, entries 1, 2, 3, 7, and 8), and relatively low yields were observed in the cases of **4d, 4e**, and **4f** (Table 2, entries 4, 5, and 6). Hence, we speculate that the presence of electron-withdrawing and steric hindrance group at the 2 position of 1,3-dicarbonyl derivatives may obstruct the cyclization.

As mentioned above, 2-(methylsulfonyl)pyrimidine derivatives can be viewed as the precursors of multifunctionalized pyrimidines through the oxidation of the 2-sulfane pyrimidines. Thomann et al.[20] recently described a practical procedure for the oxidation of 2-sulfane pyrimidines using Oxone as oxidant in MeOH. We also attempted the Thomann's method, while the conversion to 4,6-dichloro-2-(methylsulfonyl)-5-phenylpyrimidine **5d** was quite unsatisfying (Table 3, entries 2), as indicated by TLC and crude NMR monitoring (less than 50% by NMR). There were no increases in yield and conversion in different solvents and lengthened reaction time (Table 3, entries 1, 3, and 4). We postulated that the oxidation process should mainly occur in organic phase, whereas the low conversion may be attributed to low solubility of Oxone in reaction solvent.

The phase transfer catalyst would be helpful to promote the oxidation. Thus, tetrabutylammonium bromide (TBAB) in catalytic amount (10 mol%) was attempted to raise the concentration of Oxone in solvent and accelerate the reaction, and good yields in shortened reaction times were obtained (Table 3, entries 5). Meanwhile, different phase transfer catalysts, TBAB and triethylbenzylammonium bromide (TEBAB) have no obvious effect on the yields (Table 3, entries 5, 6). Thus, all reactions proceeded well in acetone–water solution in the presence of Oxone (5 equiv), and TBAB (10 mol%). As shown in Table 4,

Table 2. Preparation of 2-(methylthio)pyrimidines.

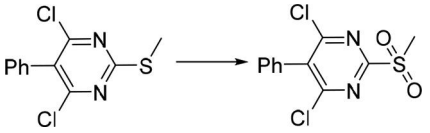


1 2 3 4

Entry	Compound no.	R^1	R^2	R^3	Yield[a] (%)
1	**4a**	H	Cl	Cl	72
2	**4b**	Et	Cl	Cl	81
3	**4c**	Bu	Cl	Cl	75
4	**4d**	Ph	Cl	Cl	52
5	**4e**	Bz	Cl	Cl	55
6	**4f**	NO_2	Cl	Cl	35
7	**4g**	H	OMe	Cl	70
8	**4h**	H	NMe_2	NMe_2	75

[a]Isolated yields.

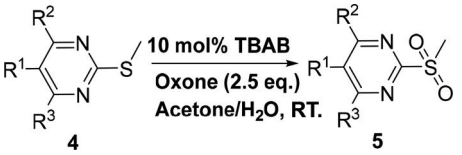
Table 3. The oxidation of 2-(methylsulfonyl)pyrimidine **5d** at different conditions.



Entry	Oxidant	Additive	Solvent	Temp (°C)	Time (h)	Conversion[a] (%)
1	Oxone	–	H_2O	Reflux	48	NT[b]
2	Oxone	–	MeOH	Reflux	48	<50
3	Oxone	–	MeOH/H_2O	Reflux	48	<10
4	Oxone	–	Acetone	RT	48	<10
5	Oxone	TBAB	Acetone/H_2O	RT	4	>95 (81)[c]
6	Oxone	TEBAB	Acetone/H_2O	RT	4	>95 (80)[c]

[a]The conversions of starting material were estimated based on crude NMR spectra; [b]not detected; [c]isolated yields.

Table 4. Preparation of 2-methylsulfonyl)pyrimidines.



4 **5**

Compound no.	R^1	R^2	R^3	Yield[a] (%)
5a	H	Cl	Cl	85
5b	Et	Cl	Cl	90
5c	Bu	Cl	Cl	86
5d	Ph	Cl	Cl	81
5e	Bz	Cl	Cl	75
5f	NO_2	Cl	Cl	70
5g	H	OMe	Cl	78
5h	H	NMe_2	NMe_2	72

[a]Isolated yields.

all reactions were completed within 4–6 h and respective 2-(methylsulfonyl)pyrimidines were obtained in considerable yields. The products precipitated during the reactions and were separated from the reaction mixtures through simple filtration or extraction.

Conclusion

In conclusion, an efficient and versatile synthesis of 2-(methylsulfonyl)pyrimidine derivatives through the cyclic condensation, derivation, and subsequent oxidation has been developed. The present synthetic route provided an alternative approach for the synthesis of 2-(methylsulfonyl)pyrimidine derivatives. The key feature of this route possesses the advantages of less synthetic steps, considerable yields and the aversion of hazardous reaction conditions that other methods can't easily access.

Experimental

General

All reagents and solvents used in the reaction were obtained from commercial sources and used without any further purification. Melting points were determined on a Buchi B-545 melting point apparatus and uncorrected. NMR were recorded in $CDCl_3$ on a Jeol

GX-400 spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS). Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Mass spectra were measured on a LC-MS-2010A spectrometer with ESI. Elementary analyses were taken on a Vario EL III elementary analysis instrument.

General procedure for the synthesis of 2-(methylthio)pyrimidines (4a–4f)

To a stirred solution of 2-methyl-2-thiopseudourea sulfate (8.35 g, 60 mmol) in ethanol 120 mL was added 1,3-dicarbonyl derivatives (50 mmol) and sodium hydroxide (2.4 g, 60 mmol) at room temperature, and then heated at refluxed for 4 h. After this time, the reaction mixture was cooled to room temperature, the residue was precipitated and filtered, yielding compounds **3** as white solid. The solid was dried in vacuum and used directly to react with $POCl_3$ (40 mL) in the presence of NEt_3 (5.05 g, 50 mmol) heated at reflux for 3 h. The solvent was evaporated under reduced pressure, the residue was dissolved in 100 mL ethyl acetate and washed with saturated sodium bicarbonate, saturated sodium chloride, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The desired products 4-chloro-2-(methylthio)pyrimidines **4a**–**4f** were obtained by recrystallization from the mixed solvent of EtOAc-petroleum ether. Yields, melting points and spectroscopic data for selected 2-(methylsulfonyl)pyrimidines are listed as follows.

4,6-Dichloro-2-(methylthio)-5-phenylpyrimidine (4d)

White solid, yield 52%, mp 104–105 °C; IR (KBr, cm^{-1}): 3453, 2925, 1550, 1474, 1361, 1231, 812; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 3H, SCH_3), 7.28 (d, $J = 6.0$ Hz, 2H, Ar-H), 7.45–7.49 (m, 3H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.57, 127.98, 128.72, 129.17, 129.43, 129.66, 133.07; LC–MS (*m*/*z*): 269.9. Anal. Calcd for $C_{11}H_8Cl_2N_2S$: C, 48.72; H, 2.97; N, 10.33; Found: C, 48.76; H, 2.92; N, 10.28.

General procedure for the synthesis of 4-chloro-6-methoxy-2-(methylthio) pyrimidine (4g)

To a solution of sodium (0.28 g, 12 mmol) in ethanol 20 mL was added in 4,6-dichloro-2-(methylthio)pyrimidine **4a** (1.95 g, 10 mmol) and the resulting mixture was stirred at room temperature until disappearance of the starting material **4a** as judged by TLC. The mixture was evaporated under reduced pressure, water was added, and after workup (CH_2Cl_2 extraction, water washing, Na_2SO_4 drying of the organic phase), the residue was evaporated under reduced pressure, and the residue was recrystallized from ethylether yielded the desired product **4 g**. White solid, yield 70%, mp 39–40 °C; IR (KBr, cm^{-1}): 3003, 2939, 1544, 1328, 1274, 1505, 1030, 820; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.55 (s, 3H, SCH_3), 3.97 (s, 3H, OCH_3), 6.41 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.29,54.52, 102.43, 160.34, 169.90, 172.92; LC–MS (*m*/*z*): 190.0. Anal. Calcd for $C_6H_7ClN_2OS$: C, 37.80; H, 3.70; N, 14.69. Found: C, 37.72; H, 3.75; N, 14.78.

General procedure for the synthesis of N^4,N^4,N^6,N^6-tetramethyl-2-(methylthio) pyrimidine-4,6-diamine (4h)

A mixture of **4a** (2 mmol) and dimethylamine (0.54 g, 12 mmol) in butyl alcohol (40 mL) in the presence of NEt_3 (1.21 g, 12 mmol) was stirred for 3 h at 80 °C and subsequently cooled

to room temperature. The mixture was evaporated under reduced pressure, and the residue was crystallized from ethylether yielded the desired product **4h**. White solid, yield 75%, mp 95–96 °C; IR (KBr, cm^{-1}): 2916, 2868, 1575, 1508, 1410, 976, 784; ^1H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3H, SCH_3), 3.02 (s, 12H, NCH_3), 5.04 (s, 1H, pyrimidine-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.01, 37.27, 75.82, 162.90, 169.13; LC–MS (*m*/*z*): 212.1. Anal. Calcd for $C_9H_{16}N_4S$: C, 50.91; H, 7.60; N, 26.39. Found: C, 50.82; H, 7.52; N, 26.45.

General procedure for the synthesis of 2-(methylsulfonyl)pyrimidines (5a–5h)

A mixture of 2-(methylthio)pyrimidines (5 mmol), tetrabutylammonium bromide (0.16 g, 0.5 mmol, 10 mol%) and acetone (20 mL) was stirred at room temperature. The Oxone (12.5 mmol, 2.5 equiv) in water (20 mL) was added slowly to the vigorously stirred solution. After 4–6 h, TLC indicated the consumption of the starting material. The products **5** were isolated by filtering through a Buechner funnel and washed with water, and then dried to give the solid product.

4,6-Dichloro-2-(methylsulfonyl)-5-phenylpyrimidine (5d)

White solid, yield 81%, mp 151–152 °C; IR (KBr, cm^{-1}): 3009, 2923, 1320, 1136, 965, 760; ^1H NMR (400 MHz, $CDCl_3$): δ 3.42 (s, 3H, SO_2CH_3), 7.31 (d, $J = 3.6$ Hz, 2H, Ar-H), 7.53–7.55 (m, 3H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.34, 128.85, 129.17, 130.17, 131.63, 136.96, 163.25, 163.72; LC–MS (*m*/*z*): 301.9. Anal. Calcd for $C_{11}H_8Cl_2N_2O_2S$: C, 43.58; H, 2.66; N, 9.24. Found: C, 43.45; H, 2.72; N, 9.36.

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References

[1] Roopan, S. M.; Sompalle, R. *Synth. Commun.* **2016**, *46*, 645–672.
[2] Lepist, E.; Gillies, H.; Smith, W.; Hao, J.; Hubert, C.; Claire, R.; Brouwer, K.; Ray, A. *PLoS One* **2014**, *9*, e87548.
[3] Sakamoto, T.; Koga, Y.; Hikota, M.; Matsuki, K.; Murakami, M.; Kikkawa, K.; Fujishige, K.; Kotera, J.; Omori, K.; Morimoto, H.; *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5460–5465.
[4] Huang, B. S.; Liang, X.; Li, C. C.; Chen, W. M.; Liu, T.; Li, X.; Sun, Y. Y.; Fu, L.; Liu, H. Q.; De Clercq, E.; *Eur. J. Med. Chem.* **2015**, *93*, 330–337.
[5] Motzer, R. J.; Hutson, T. E.; Cella, D.; Reeves, J.; Hawkins, R.; Guo, J.; Nathan, P.; Staehler, M.; Souza, P. D.; Merchan, J. R.; *N. Engl. J. Med.* **2013**, *369*, 722–731.
[6] Desai, N. C.; Kotadiya, G. M.; Trivedi, A. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3126–3130.
[7] Federico, S.; Ciancetta, A.; Porta, N.; Redenti, S.; Pastorin, G.; Cacciari, B.; Klotz, K. N.; Moro, S.; Spalluto G. *J. Med. Chem.* **2014**, *57*, 6210–6225.
[8] Saito, T.; Obitsu, T.; Minamoto, C.; Sugiura, T.; Matsumura, N.; Ueno, S.; Kishi, A.; Katsumata, S.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2011**, *19*, 5955–5966.
[9] Okazaki, S.; Mizuhara, T.; Shimura, K.; Murayama, H.; Ohno, H.; Oishi, S.; Matsuoka, M.; Fuji, N. *Bioorg. Med. Chem.* **2015**, *23*, 1447–1452.
[10] Xu, D. F.; Zhu, Z. L.; Wang, Z. Q. *J. Chem. Res.* **2013**, *37*, 720–721.
[11] Huang, T. H.; Tu, H. Y.; Aibibu, Z.; Hou, C. J.; Zhang, A. D. *ARKIVOC* **2010**, *2*, 1–17.
[12] Babaev, E. V.; Ermolat, D. S. *Russ. J. Gen. Chem.* **2010**, *80*, 2572–2589.

[13] Rioz-Martinez, A.; de Gonzalo, G.; Pazmino, D. E. T.; Fraaije, M. W.; Gotor, V. *Eur. J. Org. Chem.* **2010**, *33*, 6409–6416.
[14] Cho, H.; Nishimura, Y.; Yasui, Y.; Kobayashi, S.; Yoshida, S. I.; Kwon, E.; Yamaguchi, M. *Tetrahedron* **2011**, *67*, 2661–2669.
[15] Kamijo, S.; Kamijo, K.; Murafuji, T. *J. Org. Chem.* **2017**, *82*, 2664–2671.
[16] Angiolini, M.; Bassini, D. F.; Gude, M.; Menichincheri, M. *Tetrahedron Lett.* **2005**, *46*, 8749–8752.
[17] Tumula, V. R.; Bondwal, S.; Bisht, P.; Pendem, C.; Kumar, J. *React. Kinet. Mech. Cat.* **2012**, *107*, 449–466.
[18] Rong, J.; Deng, L.; Tan, P.; Ni, C.; Gu, Y.; Hu, J. *Angew. Chem.* **2016**, *55*, 2743–2747.
[19] Devarasetty, K.; Tharikoppula, G.; Sridhar, T.; Eppakayala, L.; Kyasani, M.; Arumugam, P.; Pusuluri, S. *Synth. Commun.* **2016**, *46*, 263–274.
[20] Thomann, A.; Brengel, C.; Borger, C.; Kail, D.; Steinbach, A.; Empting, M.; Hartmann, R. W. *Chem. Med. Chem.* **2016**, *11*, 2522–2533.