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The efficient one-step chlorination of methylsulfanyl group on pyrimidine ring system with sulfuryl chloride

Young Jin Ham [a,b], Duck-Hyung Lee [b], Hwan Geun Choi [a,b], Jung-Mi Hah [a], Taebo Sim [a,*]

[a] Life/Health Division, Korea Institute of Science and Technology, PO Box 131, Cheongryang, Seoul 130-650, Republic of Korea
[b] Department of Chemistry, Sogang University, Seoul 121-742, Republic of Korea

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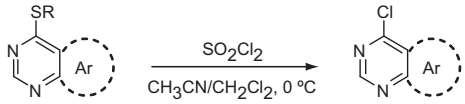
ABSTRACT

A facile one-step transformation of methylsulfanyl and arylsulfanyl groups on pyrimidine ring system into the corresponding chloride group was achieved using sulfuryl chloride in acetonitrile/dichloromethane.

Taking into account that heteroaromatic rings have widely been adopted as one of the most privileged core structures of drugs in the market, their efficient chemical transformations have received a great deal of attention in the field of organic and medicinal chemistry.[1] In particular, extensive efforts have been devoted to handle effectively pyrimidine and purine analogs in the area of medicinal chemistry.[2] An alkylsulfanyl group such as methylsulfanyl group, widely been installed on pyrimidine derivatives as methylsulfanyl group adjacent to the nitrogen atom of the pyrimidine ring system is readily oxidized to the corresponding sulfoxide or sulfone groups that could be further substituted with reasonably nucleophilic amines. In addition, introduction of the methylsulfanyl group at the C-4 position of 2,4-dichloropyrimidine system allows for sequential and orthogonal functionalization on this pyrimidine system.[3] On account of the fact that these sulfoxide or sulfone groups are in some cases displaced with amines in very poor yields[4] and moreover since this alkylsulfanyl group could not be an effective coupling partner for metal-assisted reactions including Suzuki cross-coupling reaction, it is necessary to convert these alkyl or arylsulfanyl groups into the corresponding halides such as chloride. Tremendous significance of the metal-catalyzed cross-coupling reactions is obvious in the field of medicinal chemistry.[5] Halides on heteroaromatic system have been utilized as effective substrates for metal-catalyzed coupling reactions in the vast majority of cases[6–8] while it has rarely been reported that sulfone[9] and sulfanyl[10] groups at highly reactive positions on pyrimidine-containing heteroaromatic ring system could participate in metal-promoted cross-coupling reactions. An alkylsulfanyl group at nitrogen α-positions of pyrimidine derivatives could be normally transformed to the corresponding chloride by performing strong acid hydrolysis followed by $POCl_3$ chlorination.[4] A drawback of this conversion strategy is that the strong acid condition is not compatible with acid-sensitive functional groups. To the best of our knowledge, one-step reaction methodology for this transformation has never been reported with the exception of Robinson's method.[11–13] Based on his description, 6-methylthio group of purine was directly converted into the corresponding chloride using chlorine gas in anhydrous methanol whereas a prolonged reaction time required for a larger scale of this transformation resulted in a substantial amount of the by-product, 6-methoxypurine. Taking into consideration this side reaction, methoxy group incorporation as well as severe toxicity and inconvenient manipulation of chlorine gas, it is worthwhile to identify a more safe, effective, and amenable method rather than chlorine gas in anhydrous methanol. We would now like to describe an efficient and affordable single-step reaction methodology using sulfuryl chloride to meet these purposes. Sulfuryl chloride (SO_2Cl_2) is widely known as a chlorine source and used to convert methylthiomethyl (MTM) group to the corresponding chloromethyl group. This fact prompted us to find that sulfuryl chloride (SO_2Cl_2), a readily commercially available and inexpensive reagent is capable of converting directly alkyl and phenylsulfanyl groups at nitrogen α-positions of pyrimidine-bearing heteroaryl rings into the corresponding chloride in good yields (Scheme 1).

Sulfuryl chloride in dichloromethane rapidly transformed 4-methylsulfanyl group on pyrimidine into the corresponding chloride group at 0 °C in acetonitrile solvent.[14] It is worth noting that enough volume (pH >7) of saturated sodium bicarbonate solution was used in the work-up process to avoid formation of acid-promoted hydrolyzed by-products. Methylsulfanyl and phenylsulfanyl groups at the C-4 or C-6 position of pyrimidine-fused heteroaromatic ring system were also converted into the corresponding



Scheme 1. One-step chlorination reaction.

* Corresponding author. Tel.: +82 2 958 6437; fax: + 82 2 958 5189.
E-mail address: tbsim@kist.re.kr (T. Sim).

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Table 1
Chlorination of methylsulfanyl, phenylsulfanyl, and benzylsulfanyl groups on pyrimidine or pyrimidine-fused heteroaromatic rings

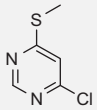
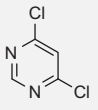
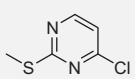
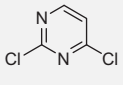
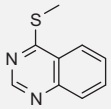
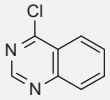
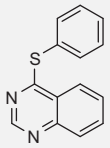
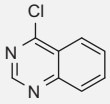
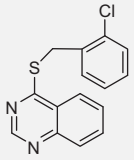
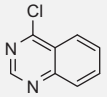
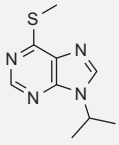
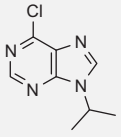
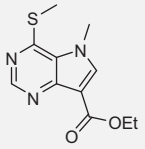
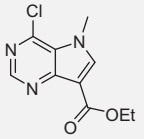
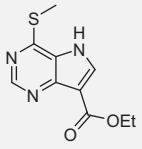
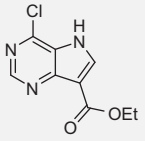
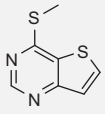
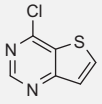
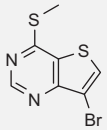
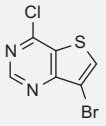
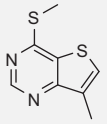
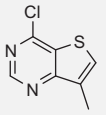
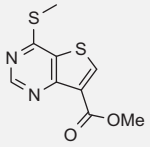
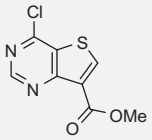
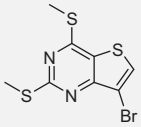
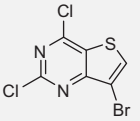
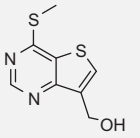
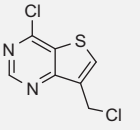
Entry	Substrate	Product	Yield[a] (%)
1			76
2			60[b]
3			99
4			79
5			66
6			87
7			99
8			99
9			99
10			99
11			99
12			74

Table 1 (*continued*)

Entry	Substrate	Product	Yield[a] (%)
13			10[b,c]
14			76

[a] Isolated yield.
[b] Reaction time is 24 h.
[c] Yield is estimated based on analysis of liquid chromatography–mass spectrometry (LC–MS) chromatogram.

chloride groups under the same reaction conditions. Purine, 5*H*-pyrrolo[3,2-*d*]pyrimidine, thieno[3,2-*d*]pyrimidine, and quinazoline as representative pyrimidine-fused heteroaromatic core structures were employed to demonstrate this efficient transformation methodology.

The reactivity of sulfuryl chloride toward 2-, 4- or 6-methylsufanyl and 4-phenylsulfanyl groups on pyrimidine or pyrimidine-fused heteroaromatic rings was investigated as described in Table 1. The methylsufanyl group of 4-chloro-6-(methylthio)pyrimidine was readily converted into the corresponding chloride group in 76% yield (entry **1**) in 30 min. In contrast, a significantly prolonged reaction time (24 h) was required for the substitution of 2-methylsufanyl group in pyrimidine with a chloride group even though the starting material was rapidly consumed within 10 min (entry **2**). On the basis of liquid chromatography–mass spectrometry (LC–MS) analysis, a major by-product of entry **2** would be 4-chloro-2-(chloromethylthio)pyrimidine. The methylsulfanyl and arylsulfanyl groups at C-4 position of quinazoline were readily transformed to the corresponding chloride group in moderate to excellent yields (entry **3**–**5**) as expected. It is noteworthy that conversion time (6 h) of phenylsulfanyl and benzylsulfanyl groups (entry **4** and **5**) was more prolonged than that (30 min) of methylsulfanyl group (entry **3**). As expected, 6-methylthiopurine derivative turned out to be one of the most suitable substrates for this methodology (entry **6**). 4-(Methylthio)-5*H*-pyrrolo[3,2-*d*]pyrimidine derivatives were treated with sulfuryl chloride to furnish the corresponding chlorinated products in 99% yields (entries **7** and **8**). Almost quantitative yields were also obtained with 4-(methylthio)thieno[3,2-*d*]pyrimidine substrate (entry **9**) and its analogs (entries **10**–**12**). Meanwhile, the action of sulfuryl chloride on a pyrimidine derivative bearing two methylsulfanyl groups, 7-bromo-2,4-bis(methylthio)thieno[3,2-*d*]pyrimidine resulted in a rapid disappearance of the starting material owing to the fast conversion of 4-methylsulfanyl group but with very poor yield (10%) of the desired product presumably due to the sluggish transformation of the 2-methylsulfanyl group (entry **13**). This low yield was not enhanced even with prolonged reaction time, elevated reaction temperature and/or additional 5 equiv of sulfuryl chloride. As is the case with entry **2**, a major by-product of entry **13** would contain 2-chloromethylthio group as the peak corresponding to 7-bromo-4-chloro-2-(chloromethylthio)thieno[3,2-*d*]pyrimidine was detected on LC–MS chromatogram (detected mass : 328.69, 330.68, 332.67). Not surprisingly, the alcohol group of entry **14** substrate was concomitantly transformed into the corresponding chloride group to afford the expected product in a yield of 76%.

This one-step chlorination methodology using sulfuryl chloride should be superior to a precedent one using chlorine gas. It is therefore believed that this report may offer the most facile and

efficient one-step transformation methodology to convert alkyl-aryl sulfanyl groups on pyrimidine ring systems to the corresponding chloride group.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.056.

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14. *General procedure*: To a cooled solution of substrate (1 equiv) in acetonitrile (0.05 M) was added 0.2 M sulfuryl chloride solution (5 equiv) in dichloromethane at 0 °C. After stirring at 0 °C for 0.5 h, saturated sodium bicarbonate solution was added and the reaction mixture was extracted with dichloromethane three times. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography to afford the desired product.