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Highly regioselective direct halogenation: a simple and efficient method for preparing 4-halomethyl-5-methyl-2-aryl-1,3-thiazoles

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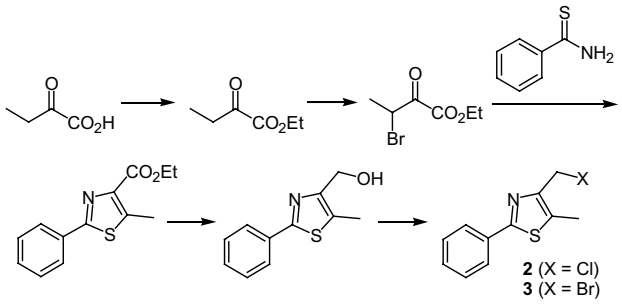
Abstract—An unprecedented C4-methyl regioselective halogenation of 4,5-dimethyl-2-aryl-1,3-thiazoles (**1**) has been accomplished. The reaction of compound **1** with *N*-chlorosuccinimide and *N*-bromosuccinimide under mild conditions provides an efficient and operationally simple method for obtaining 4-chloromethyl-5-methyl-2-aryl-1,3-thiazoles (**2**) and 4-bromomethyl-5-methyl-2-aryl-1,3-thiazoles (**3**), respectively, in good yields without the formation of 4-methyl-5-halomethyl regioisomers.

Substituted 1,3-thiazoles (also known simply as thiazoles) are ubiquitous structural motifs found in compounds of biological interest. As a result, a number of methods have been developed to synthesize these compounds.[1,2] Despite the accessibility of these methods, the ability to approach certain specific synthetic paths is limited and requires the design of novel synthetic strategies. Particular examples of these are 4-chloromethyl- and 4-bromomethyl-5-methyl-2-arylthiazoles, which are able to serve as key intermediates in the synthesis of biologically interesting and pharmaceutically useful molecules as dipeptidyl peptidase IV (DPP-IV) inhibitors, agonists of peroxisome proliferation-activated receptors (PPARs), subtype selective *N*-methyl-D-aspartate antagonists, glucose and lipid lowering agents and antifungal agents.[3]

Previously, these compounds have been prepared via ethyl 5-methyl-2-phenylthiazole-4-carboxylates,[4] which were synthesized by coupling reactions between thiobenzamides and ethyl 3-bromo-4-methyl-2-oxobutanoate (Scheme 1).[5] As a preliminary study, we have tried some synthetic methods including a direct synthesis involving a coupling reaction between thiobenzamide and 1,3-dibromo-2-butanone or a chlorination of 4,5-dimethyl-2-phenylthiazole *N*-oxide via a Pummerer-type rearrangement.[6] However, the former method failed only to give an undesired isomer exclusively and the latter method gave only a minor amount of desired compound in three reaction sequences.



Scheme 1. Conventional method for preparing **2** and **3**.

In our efforts aimed at the development of new methods of synthesizing 4-chloromethyl- and 4-bromomethyl-5-methyl-2-phenylthiazole, we were interested in a direct halogenation of 4,5-dimethyl-2-phenylthiazole, which can be readily prepared from inexpensive thiobenzamide and 2-chlorobutanone,[7] reacted with NCS or NBS as an efficient and useful alternative to a known method (Scheme 2).

Prior to our study, Mohanazadeh reported that a radical halogenation of 4,5-dimethyl-2-phenylthiazole with

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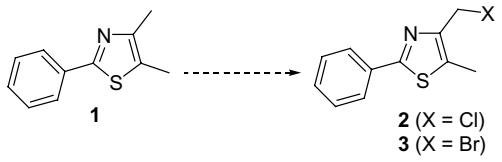
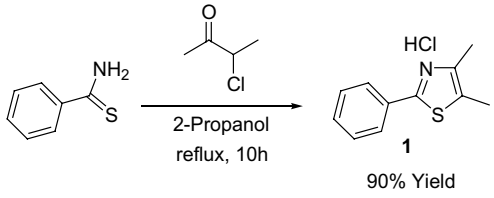


Scheme 2.

NCS using a 200 W light bulb proceeded without selectivity and with NBS occurred C5-methyl site regioselectively.[8] On the other hand, it has been reported that a bromination of 2,3-dimethylbenzofuran derivative with NBS proceeds regioselectively depending on conditions, which allow a selective formation of either 2-chloromethyl derivative (reflux in CCl_4) or 3-chloromethyl derivative (an ambient temperature in CH_2Cl_2).[9] This prompted us to investigate a direct halogenation of 4,5-dimethyl-2-phenylthiazoles (**1**) under mild conditions with NCS or NBS. In general, highly regioselective reactions are required especially in pharmaceutical fields, because even a small amount of regioisomers cannot be removed easily from objective intermediates or drug candidates by any means of purification quite often due to similar physical properties. To the best of our knowledge, there are no reported reactions proceeding at the C4-methyl site with high regioselectivity. Herein we report a highly C4-methyl regioselective synthesis of 4-chloromethyl-5-methyl-2-arylthiazoles (**2**) and 4-bromomethyl-5-methyl-2-arylthiazoles (**3**) from **1**.

Initial attempts were carried out using **1**, NCS (1.2 equiv) and 2,2′-azobis(isobutyronitrile) (AIBN; 0.1 equiv) in acetonitrile at 60 °C. The reaction furnished mono-chlorinated compound, that is 4-chloromethyl-5-methyl-2-phenylthiazole (**2**) or 5-chloromethyl-4-methyl-2-phenylthiazole (the regioisomer of **2**). Surprisingly, the chloride was confirmed as the desired **2** utilizing the conventionally prepared **2** as an authentic sample and 4-methyl-5-chloromethyl-2-phenylthiazole prepared according to a known procedure[10] as a comparison sample by ^{1}H NMR, ^{13}C NMR[11] and HPLC analyses.[12] The reaction also proceeded without AIBN in the absence of light. The result suggests that the chlorination does not proceed via a radical process. It is of note that the regioselectivity of the reaction mixture and isolated compound was considerably high as ascertained by the HPLC analysis (>99% regioselectivity). The results show that the chlorination exclusively proceeds at the C4-methyl site and no 4-methyl-5-chloromethyl regioisomers are obtained even in the reaction mixture.

Conveniently, **1·HCl** could be isolated as a crystal[13] directly from a reaction mixture of thiobenzamide and 2-chlorobutanone in 2-propanol (90% yield) (Scheme 3).

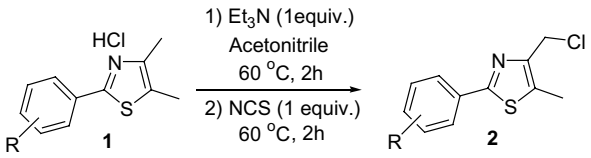


Scheme 3. Preparation of **1**.

With **1·HCl**, the reaction was carried out via the one-pot neutralization (of HCl)—chlorination sequence using 1 equiv of NCS,[14] furnished **2**[15] in a good yield (83%), directly isolated as a crystal by adding water to the reaction mixture (Table 1, entry 1) (>99% purity detected by HPLC analysis as an isolated compound without further purification).[16]

On the basis of this finding, we extended the scope of the chlorination with a variety of different substituted phenyl groups. The reaction worked well with satisfactory yields that ranged from 57% to 89% for each derivative with phenyl groups bearing electron-donating groups

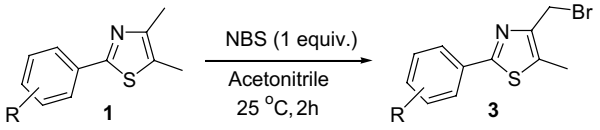
Table 1. Chlorination of 4,5-dimethyl-2-arylthiazoles



Entry	Substrate[a] (R =)	Yield (%)[b]	Regioselectivity (%)[c,d]
1	H	83	>99 (>99)
2	*p*-^{t}Bu	78	>99
3	*p*-Me	89	>99 (>99)
4	*p*-MeO	57	>99 (>99)
5	3,4-Methylenedioxy	85	>99 (>99)
6	*p*-F	75	>99
7	*p*-Cl	73	>99
8	*o*-Cl	87	>99 (>99)

[a] Substrates were used as hydrochlorates.
[b] Yields refer to single runs and are given for isolated products.
[c] Regioselectivity was determined for isolated products by HPLC analysis (YMC Pack-SIL A-002 column with 40:1 *n*-hexane/THF as mobile phase).
[d] Regioselectivity in reaction mixtures determined by HPLC analysis (the same conditions for isolated products) are shown in parentheses.

Table 2. Bromination of 4,5-dimethyl-2-arylthiazoles



Entry	Substrate[a] (R =)	Yield (%)[b]	Regioselectivity (%)[c,d]
1	H	70	>99 (>99)
2	*p*-^{t}Bu	65	>99
3	*p*-Me	78	>99 (>99)
4	*p*-MeO	82	>99
5	3,4-Methylenedioxy	69	>99 (>99)
6	*p*-F	57	>99 (>99)
7	*p*-Cl	57	>99
8[e]	*o*-Cl	53	—

[a] Substrates were used as free form.
[b] Yields refer to single runs and are given for isolated products.
[c] Regioselectivity was determined for isolated products by HPLC analysis (YMC Pack-SIL A-002 column with 40:1 *n*-hexane/THF as mobile phase).
[d] Regioselectivity in reaction mixtures determined by HPLC analysis (the same conditions for isolated products) are shown in parentheses.
[e] Yield was given for the product purified by column chromatography due to a difficulty of crystallization from the reaction mixture. The structure was determined by ^{1}H NMR, ^{13}C NMR and HPLC analyses.

(entries 2–5), as well as electron-withdrawing groups (entries 6–8).

Following the successful demonstration of the regioselective chlorination, we then proceeded to extend the generality of the reaction to bromination with NBS, with the hope that the reaction could proceed at the C4-methyl site regioselectively. The first bromination we carried out between 4,5-dimethyl-2-phenylthiazole (**1**) and NBS (1 equiv) in acetonitrile at 25 °C, and gave a 70% yield of **3** successfully, isolated directly as a crystal by adding water to the reaction mixture (Table 2, entry 1).[17] The regioselectivity of the reaction mixture and the isolated product were determined by HPLC analysis (methods and conditions used were the same as for the chlorination; a >99% regioselectivity were ascertained) and ^{1}H and ^{13}C NMR by an authentic sample of **3** and a comparison sample of the regioisomer, as well.[18]

To examine the generality of this reaction further, we proceeded to study a variety of different substituted phenyl groups. The results are shown in Table 2. Though the reactions proceeded at a lower temperature (25 °C) than the chlorination, almost the same reactivity trends as the chlorination case were observed. The reactions afforded the desired **3** with yields from 53% to 82%. In addition, bromine can also be used instead of NBS, however the yield (30%) is much lower than with NBS, as determined by ^{1}H NMR due to the low conversion and formation of various unknown by-products.

The structures of **2** (Table 1, entry 1) and **3** (Table 2, entry 1) were unambiguously confirmed by X-ray crystallography (Fig. 1).[19]

We have not determined the source of this C4-methyl selectivity and the difference of regioselectivity depending on the reaction conditions. One possibility is that the reaction might proceed with a mechanism via a Pummerer-type rearrangement[20,21] under the mild reaction condition (Scheme 4).

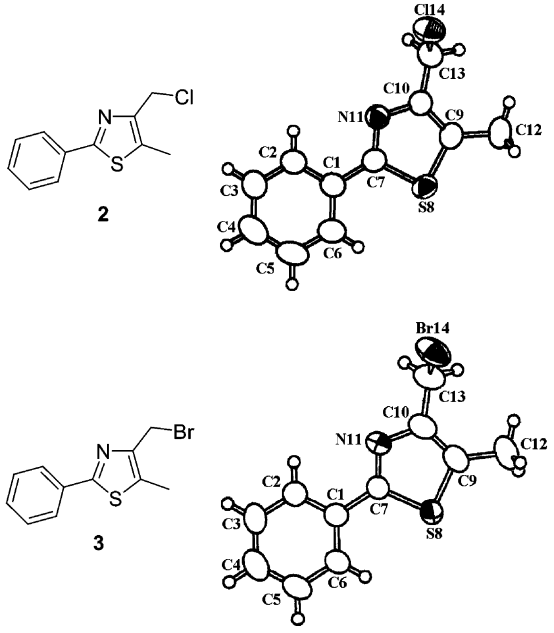
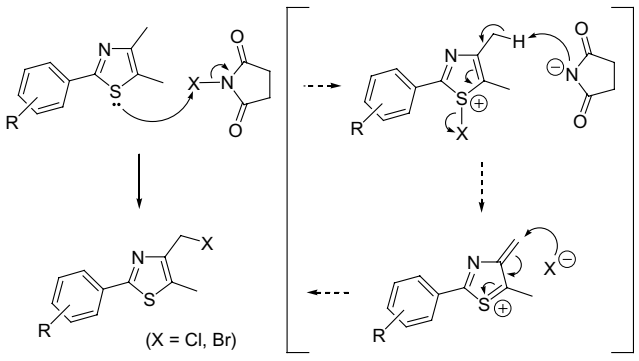


Figure 1. X-ray structures of **2** (Table 1, entry 1) and **3** (Table 2, entry 1).

In summary, we have developed a highly regioselective and efficient method that allows for synthesis of 4-chloromethyl-5-methyl-2-arylthiazoles (**2**) and 4-bromomethyl-5-methyl-2-arylthiazoles (**3**) utilizing the readily prepared 4,5-dimethyl-2-arylthiazoles (**1**) from thiobenzamides and 2-chlorobutanone. This facile process involves no complicated operation. Further



Scheme 4. Proposed reaction mechanism.

application of these methodologies to other substrates such as oxazoles is under investigation in the laboratory.

Acknowledgements

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11. The desired compound and its regioisomer are discriminated apparently by their differences of chemical shifts on ^{1}H and ^{13}C NMR.
12. *HPLC conditions*: YMC Pack-SIL A-002 column with 40:1 *n*-hexane/THF as mobile phase. To investigate regioselectivity, we used HPLC analysis with the normal phase. The 4-methyl-5-halomethyl regioisomers easily decomposed during HPLC analysis with the reverse phase.
13. Compound **1** in a free form is liquid at an ambient temperature.
14. **General procedure for the preparation of compound 2.** To a solution of 4,5-dimethyl-2-phenyl-1,3-thiazole hydrochlorate (**1·HCl**, 13.3 mmol) in acetonitrile (×10 v/w of **1·HCl**), triethylamine (13.3 mmol) was added dropwise at rt, and the reaction mixture was stirred at 60 °C for 2 h, then allowed to cool to rt. To the mixture was added NCS (13.3 mmol) and the reaction mixture was stirred at 60 °C for 2 h, then allowed to cool to rt. Water (×5–10 v/w of **1·HCl**) was added to the reaction mixture dropwise at rt to give colourless to pale yellow precipitation. The mixture was stirred at 0–5 °C for 1 h. The precipitation was filtered and washed with ice-cooled acetonitrile–water (1:1, v/v) (×2 v/w of **1·HCl**) to afford the corresponding chloride **2**.
15. **Data for 4-(chloromethyl)-5-methyl-2-phenyl-1,3-thiazole (Table 1, entry 1).** Colourless crystal: mp 86–88 °C. ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 3H), 4.72 (s, 2H), 7.39–7.44 (m, 3H), 7.87–7.90 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 11.4, 38.9, 126.3, 128.9, 129.9, 132.5, 133.4, 148.6, 164.7. IR (KBr, cm^{-1}): 1468, 1259, 764, 687, 654, 623. LRMS (EI): m/z 223 (M^+). HRMS (EI): Calcd for $C_{11}H_{10}ClNS$ (M): 223.0222. Found: 223.0257. Anal. Calcd for $C_{11}H_{10}NSCl$: C, 59.05; H, 4.51; N, 6.26; S, 14.33; Cl, 15.85. Found: C, 58.95; H, 4.35; N, 6.26; S, 14.39; Cl, 15.81.
16. *HPLC conditions*: YMC Pack-ODS A-302 column with 1:1 0.05 M KH_2PO_4/acetonitrile as mobile phase.
17. **General procedure for the preparation of compound 3.** To a solution of 4,5-dimethyl-2-phenyl-1,3-thiazole (**1**, 22.1 mmol) in acetonitrile (×10 v/w of **1**) was added NBS (22.1 mmol) and the reaction mixture was stirred at 25 °C for 2 h. To the reaction mixture, water (×5–10 v/w of **1**) was added dropwise at rt to give colourless to pale yellow precipitation. The mixture was stirred at 0–5 °C

for 1 h. The precipitation was filtered and washed with water (×3 v/w of **1**) to afford the corresponding bromide **3**.

18. **Data for 4-(bromomethyl)-5-methyl-2-phenyl-1,3-thiazole (Table 2, entry 1).** Pale yellow crystals: mp 90–92 °C. ^{1}H NMR ($CDCl_3$): δ 2.49 (s, 3H), 4.62 (s, 2H), 7.40–7.44 (m, 3H), 7.86–7.89 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 11.6, 25.5, 126.4, 128.9, 130.1, 132.5, 133.1, 148.4, 164.7. IR (KBr, cm^{-1}): 1614, 1485, 1458, 1288, 1252, 1016, 766, 683, 606, 555. LRMS (EI): m/z 267 (M^+). HRMS (EI): Calcd for $C_{11}H_{10}BrNS$ (M): 266.9717. Found: 266.9739.
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21. We do not find evidence of the electrophilic attack on S atom.