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Intramolecular nucleophilic substitution at an sp^2 carbon: synthesis of substituted thiazoles and imidazole-2-thiones

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ABSTRACT

The nucleophilic substitution reactions of vinylic bromides with intramolecular thioamide or thiourea moieties proceed to give a series of substituted thiazoles and imidazole-2-thiones.

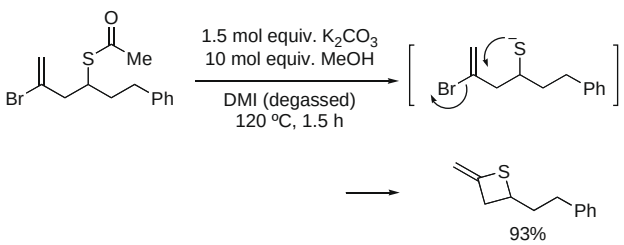
Concerted nucleophilic substitution reactions at sp^3 atoms are commonly encountered in mechanistic and synthetic organic chemistry. Although such a substitution reaction at a vinylic sp^2 carbon of unactivated vinyl halides rarely occurs, some examples were reported recently. For examples, 2-bromoallylamines were cyclized to aziridines by base treatment, and the stereospecificity of the cyclization reaction suggested that amino group approached from the backside of the C–Br bond.[1] Ochiai et al. published the intermolecular vinylic substitution reactions of vinyl iodonium salts,[2] in which the products were formed with inversion of the stereochemistry.

We have also reported nucleophilic substitution reactions of unactivated vinylic halides.[3] That is, various haloalkenes bearing intramolecular alcohol, sulfonamide, active methine, and thiol moieties at the suitable position gave the corresponding five-membered ring compounds by treatment with base.[3a] We were particularly interested in the substitution with a thiol moiety, and it was recently found that unique four-membered ring compounds, 2-alkylidenethietanes could be prepared by the cyclization of *S*-acetyl 3-bromo-3-alkenethiols (Scheme 1).[3b]

These findings had prompted us to examine the synthesis of 2,5-disubstituted thiazoles by the cyclization of *N*-2-bromoalk-2-enylthioamides. There have been some synthetic approaches[4] of 2,5-disubstitued thiazoles, mainly by condensation reactions, such as *Hantzsch* synthesis[5] via the cyclocondensation of α-halocarbonyl compounds with thioamide and the *Gabriel* synthesis,[6] in which the α-(acylamino)ketones react with P_4S_{10} or Lawesson's reagent. It was supposed that this intramolecular nucleophilic substitution reaction would provide another unique method to prepare 2,5-disubstituted thiazoles by an intramolecular cyclization of *N*-2-bromoalk-2-enylthioamides (Scheme 2).

When *N*-(2-bromo-prop-2-enyl)benzothioamide (**1a**) was treated with potassium carbonate in *N*,*N*-dimethylformamide (DMF) at 80 °C, 5-methyl-2-phenylthiazole (**2a**) was obtained in 79% yield (Scheme 3), which suggested that five-membered ring closure (*S*-attack) was preferred over three-membered ring formation (*N*-attack).

As the above substitution reaction proceeded smoothly, generality of the cyclization of various *N*-(2-bromoprop-2-enyl)thioamides **1** was investigated under the same reaction conditions, and the results are summarized in Table 1.[7] The cyclization was found



Scheme 1.

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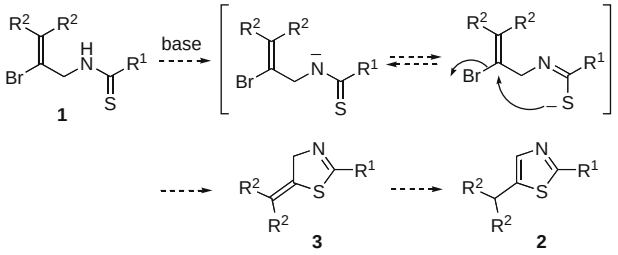
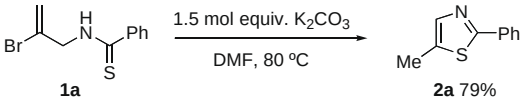


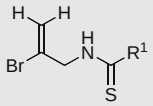
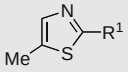
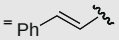
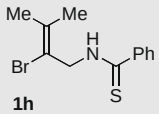
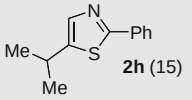
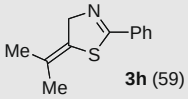
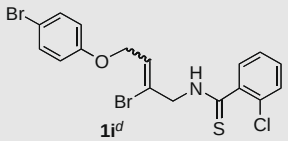
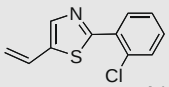
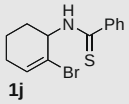
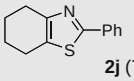
Scheme 2.



Scheme 3.

to proceed smoothly in most cases, affording the corresponding 2,5-disubstituted thiazoles in good yields (entries 1–5). Notably, acetylenic thioamide **1f** (entry 6, 23% yield) and dithiocarbamate **1g** (entry 7, 35% yield) gave the products in low yields due to the instability of the starting materials even though CsF was utilized as a base instead of K_2CO_3. Take entry 7, for example, 1,2-diphenyldisulfide that was isolated as a by-product, which suggested the elimination of benzenethiol from **1g**. Generally, the initially formed 4,5-dihydrothiazoles **3** were isomerized to five-substituted thiazole. Only in the reaction of a thioamide having a terminal disubstituted vinyl moiety, *N*-(2-bromo-3-methylbut-2-enyl)benzothioamide (**1h**) (entry 8), dihydrothiazole **3h** (59% yield) was obtained as a major product with 15% yield of thiazole **2h**. When *N*-4-aryloxy-2-bromobutenylthioamide **1i** was treated with K_2CO_3 (entry 9), 5-vinylthiazole **2j** was obtained with the elimination of 4-bromophenol. Bicyclic thiazole **2j** was successfully prepared from **1j** in 75% yield (entry 10).

Table 1
Synthesis of substituted thiazoles 2[a]

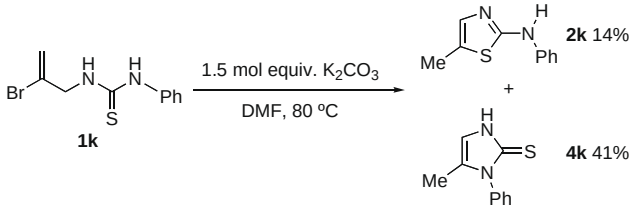
Entry	Thioamides **1**	Thiazoles **2** (yield%)[b]
		
1	**1a**: R^1 = Ph	**2a** (79)
2	**1b**: R^1 = 	**2b** (83)
3	**1c**: R^1 = *n*-$C_{10}H_{21}$	**2c** (68)
4	**1d**: R^1 = 	**2d** (76)
5	**1e**: R^1 = 	**2e** (74)
6	**1f**: R^1 = Ph–≡–	**2f** (23)
7	**1g**: R^1 = SPh	**2g** (35)[c]
8	 **1h**	 **2h** (15)  **3h** (59)
9	 **1i**[d]	 **2i** (70)[e]
10	 **1j**	 **2j** (75)[f]

[a] Reaction conditions unless otherwise noted: treatment of **1** with K_2CO_3 (1.5 mol equiv) in DMF at 80 °C.
[b] Isolated yield.
[c] CsF (1.5 mol equiv) was used instead if K_2CO_3.
[d] A single stereoisomer was used. Stereochemistry (*E* or *Z*) was not determined.
[e] 4-Bromophenol was detected from the crude mixtures.
[f] K_2CO_3 (3.0 mol equiv) was used.

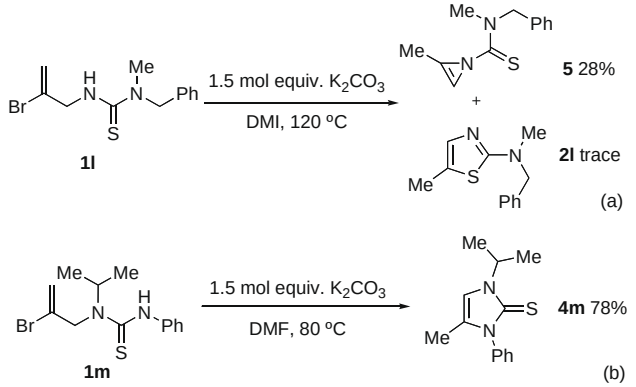
Thus, thiazoles bearing a variety of substituents such as aliphatic, aromatic, heterocyclic, or alkenyl groups were prepared from *N*-2-bromoalk-2-enylthioamides. We then turned our attention to the cyclization of *N*-2-bromoalk-2-enylthioureas. When *N*-2-bromoalk-2-enyl-*N*′-phenylthiourea **1k** was treated with K_2CO_3, 2-aminothiazole **2k** and 1,5-disubstituted imidazole-2-thione **4k** were isolated in 14% and 41% yields, respectively (Scheme 4). This result demonstrated the competition reactions between *S*- and *N*-nucleophiles.

Imidazole-2-thiones and its derivatives have received attentions because of their bioactivities and application for pharmaceutical synthesis. The Marckward method[8] has long been known as a general synthetic tool, which has been modified into a one-pot fashion[9] in 1997. They could be also prepared by the condensation[10] between thioureas and 3-hydroxy-2-butanones in boiling 1-hexanol. Although many synthetic methods[11] have been reported on the formation, here, we described the first intramolecular vinylic substitution to approach them.

To control the chemoselectivity of the cyclization of thiourea derivatives, we prepared two types of *N*,*N*′-trisubstituted thioureas **1l** and **1m**. As shown in Scheme 5, when the terminal nitrogen has two substituents such as **1l**, azirine **5** was obtained although the yield was not good (Scheme 5a). It was noted that 1,3,4-trisubsti-

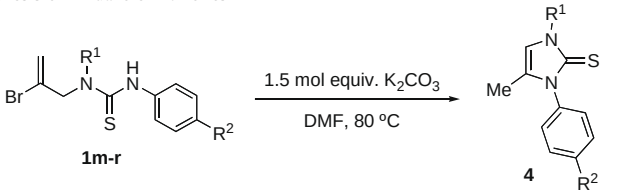


Scheme 4.



Scheme 5.

Table 2
Synthesis of imidazole-2-thiones **4**



Entry	Thioureas	R^1	R^2	Imidazole-2-thiones **4** (yield%)[a]
1	**1m**	*i*-C_3H_7	H	**4m** (78)
2	**1n**	*i*-C_3H_7	NO_2	**4n** (77)
3	**1o**	*i*-C_3H_7	MeO	**4o** (81)
4	**1p**	Ph	H	**4p** (87)
5	**1q**	Ph	MeO	**4q** (91)
6	**1r**	$PhCH_2$	H	**4r** (65)

[a] Isolated yield.

tuted imidazole-2-thione **4m** could be prepared selectively in good yield from *N,N′*-trisubstituted thiourea **1m** whose inner nitrogen has two substituents (Scheme 5b).[12,13]

Several 1-(2-bromoprop-2-enyl)thioureas **1m–r** have been evaluated under the same reaction conditions as shown in Table 2. Various 1,3,4-trisubstituted imidazole-2-thiones **4** were prepared in good yields.

In summary, by the nucleophilic substitution reaction of vinyl bromide with intramolecular thioamide moieties, substituted thiazoles and imidazole-2-thiones could be successfully synthesized. This vinylic substitution method would provide unique synthetic routes for a variety of heterocycles.

Acknowledgment

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7. *Typical procedure for 2-(furan-2-yl)-5-methylthiazole* (**2e**): To a solution of *N*-(2-bromoprop-2-enyl)furan-2-carbothioamide (**1e**) (100 mg, 0.41 mmol) in DMF (20 mL) was added K_2CO_3 (84 mg, 0.61 mmol), and the mixture was stirred at 80 °C for 17 h. After the completion of the reaction, the mixture was quenched with a pH 9 ammonium buffer solution, and extracted with diethyl ether (10 mL × 3), the combined extracts were washed by brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the resulting crude was purified by PTLC (silica gel; ethyl acetate/hexane = 1/4) to afford the pure product 2-(furan-2-yl)-5-methylthiazole (**2e**) in 74% yield. Yellow solid; mp 65–66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.46 (2H, m, overlapped), 6.90 (1H, d, J = 3.4 Hz), 6.50 (1H, dd, J = 1.8, 3.4 Hz), 2.49 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 149.1, 143.2, 141.2, 133.2, 112.1, 108.0, 11.9; IR (NaCl) ν 3117, 2922, 1526, 1499, 1437, 1225, 1134, 1022, 883, 737 cm^{-1}; HRMS (ESI) calcd for C_8H_7NOS (M+H$^+$) 166.0327, found: 166.0326.
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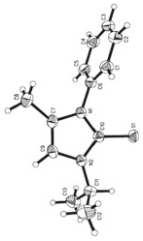
12. *Typical procedure for 1-isopropyl-4-methyl-3-phenyl-1H-imidazole-2(3H)-thione* (**4m**): To a solution of 1-(2-bromoprop-2-enyl)-1-isopropyl-3-phenylthiourea (**1m**) (100 mg, 0.31 mmol) in DMF (20 mL), was added K_2CO_3 (66 mg, 0.48 mmol), and the mixture was stirred at 80 °C for 2 h. After the completion of the reaction, the mixture was quenched with a pH 9 ammonium buffer solution, and extracted with ethyl acetate (10 mL × 3), the combined extracts were washed by brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the resulting crude was purified by PTLC (silica gel; ethyl acetate/hexane = 1/2) to afford the pure product **4m** in 78% yield. Faint yellow crystals; mp 185–186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.50 (3H, m), 7.28–7.32 (2H, m), 6.59 (1H, s), 5.17 (1H, septet, J = 6.8 Hz), 1.93 (3H, s), 1.38 (6H, d, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 136.5, 129.4(2), 129.0, 128.5(2), 126.5, 110.1, 48.5, 21.8(2), 11.0; IR (NaCl) ν 2976, 1518, 1499, 1408, 1344 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{16}N_2S$ (M+H$^+$): 233.1112, found: 233.1112.
13. The structure of **4m** was secured by X-ray crystallographic analysis as shown below

X-ray of **4m**



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CCDC-706193 contains the supplementary crystallographic data for compound **4m**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB21 EZ, UK; fax: (+44)1223-336-033; or deposit@cdc.cam.ac.uk).