

# Electrophilic cyclization of 4-thio-but-2-yn-1-ols via 1,2-migration of the thio group: efficient synthesis of 2,4-dihalo-3-thio-substituted furans

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## Abstract

A facile and efficient method for the synthesis of 2,4-dihalo-3-thio-furans via the electrophilic cyclization and 1,2-migration of the thio group of 4-thio-but-2-yn-1-ols was developed. As a result of the ready availability of starting materials and the simple and convenient operation, this synthetic route would have potential utility in organic synthesis.

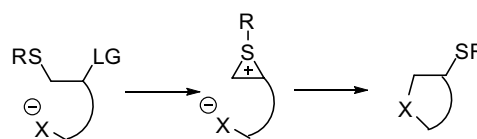
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**Keywords:** Electrophilic cyclization; 1,2-Migration of thio group; 2,4-Dihalo-3-thio-furan; 4-Thio-but-2-yn-1-ol

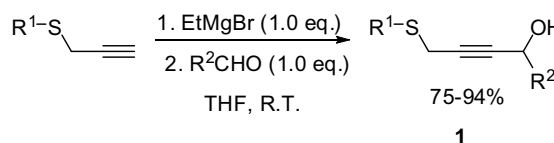
In the last decades, the electrophilic cyclization of heteroatomic nucleophiles with tethered alkynes has been proven to be one of most effective methods for preparing heterocyclic compounds, particularly for poly-substituted furans.<sup>1–3</sup> However, before conducting electrophilic cyclization, organic chemists have to build suitable alkynes, which generally becomes the main challenge for developing more facile and efficient synthetic methods.<sup>3</sup> Thus, the development of simple and convenient routes using readily available substrates for producing heterocyclic structures has become an important area of research in organic chemistry.

The 1,2-migration of the thio group is an important chemical transformation extensively used in the synthesis of heterocyclic compounds.<sup>4,5</sup> Especially, 1,2-migration of thio group with substitution of tethered nucleophiles to thiiranium intermediate provides a valuable synthetic tool for building expected heterocycles (Scheme 1).<sup>4</sup>

These facts stimulated us to investigate the possibility of the electrophilic cyclization of 4-thio-but-2-yn-1-ols, which could be easily prepared via Grignard reaction of magnesium acetylides with aldehydes (Scheme 2).



Scheme 1. Cyclization via 1,2-migration of thio group with substitution of tethered nucleophiles to thiiranium intermediate.



Scheme 2. Synthesis of 4-thio-but-2-yn-1-ols via Grignard reaction.

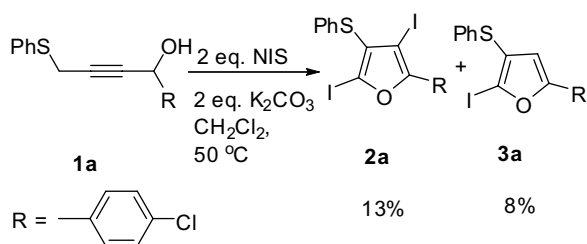
Using 1-(4-chlorophenyl)-4-(phenylthio) but-2-yn-1-ol (**1a**) as the starting material and *N*-iodosuccinimide (NIS) as the electrophile, we started the first attempt (Scheme 3).

The monoiodo-substituted compound **3a** was not isolated as a major product, indicating that **3a** is very active to halogenating reagent. For obtaining the single product in acceptable yield, we optimized the reaction conditions (Table 1).

As shown in Table 1, when compound **1a** was treated with NIS in the presence of K<sub>2</sub>CO<sub>3</sub> in acetonitrile at

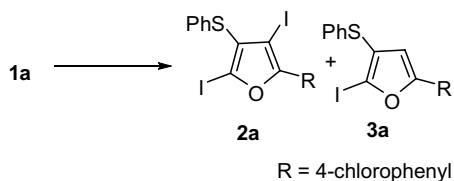
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Scheme 3. First attempt of 1-(4-chlorophenyl)-4-(phenylthio)but-2-yn-1-ol treated with *N*-iodosuccinimide.

Table 1  
Optimization of electrophilic cyclization of **1a**



Solvent	E <sup>+</sup>	Base <sup>b</sup>	Temperature (°C)	Time (h)	Yield <sup>a</sup> (%)	
					<b>2a</b>	<b>3a</b>
CH <sub>2</sub> Cl <sub>2</sub>	NIS (2 equiv)	K <sub>2</sub> CO <sub>3</sub>	rt	24	13	8
CH <sub>2</sub> Cl <sub>2</sub>	NIS (1.5 equiv)	K <sub>2</sub> CO <sub>3</sub>	rt	24	10	4
CH <sub>2</sub> Cl <sub>2</sub>	NIS (3 equiv)	K <sub>2</sub> CO <sub>3</sub>	rt	24	20	6
CH <sub>2</sub> Cl <sub>2</sub>	NIS (4 equiv)	K <sub>2</sub> CO <sub>3</sub>	rt	24	24	3
MeOH	NIS (4 equiv)	K <sub>2</sub> CO <sub>3</sub>	50	12	32	—
DMF	I <sub>2</sub> (4 equiv)	K <sub>2</sub> CO <sub>3</sub>	50	12	—	—
CH <sub>3</sub> CN	I <sub>2</sub> (4 equiv)	Et <sub>3</sub> N	50	8	—	—
CH <sub>3</sub> CN	NIS (4 equiv)	K <sub>2</sub> CO <sub>3</sub>	50	6	<b>58</b>	—
CH <sub>3</sub> CN	NIS (4 equiv)	Et <sub>3</sub> N	50	6	15	4
CH <sub>3</sub> CN	NIS (4 equiv)	K <sub>2</sub> CO <sub>3</sub>	80	4	45	—
CH <sub>3</sub> CN	NIS (3.5 equiv)	K <sub>2</sub> CO <sub>3</sub>	50	6	<b>61<sup>c</sup></b>	—

<sup>a</sup> The ratio of **2a** and **3a** was determined by <sup>1</sup>H NMR.

<sup>b</sup> The equivalent of base was same as the electrophile.

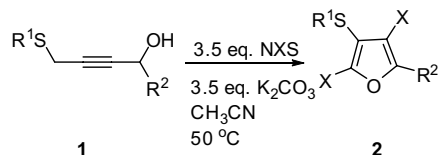
<sup>c</sup> 0.5 equiv of NIS was added 3 h later than the other 3 equiv.

50 °C, the reaction gave the best result as the diiodo-substituted product **2a** was obtained in 61% yield. With this result in hand, we examined a series of 4-thio-but-2-yn-1-ols, using NIS, NBS or NCS as the halogenating reagent, respectively, and the 2,4-dihalo-3-thio-substituted furans were obtained in moderate yields (Table 2).

It is notable that 4-oxy-but-2-yn-1-ol did not give the similar product but 4-phenoxy-1-phenylbut-2-yn-1-one (**4a**) under the same conditions, demonstrating that the thio group plays a role in the electrophilic cyclization (Scheme 4).

Gevorgyan reported an unprecedented 1,2-migration of the thio group from an sp<sup>2</sup> carbon atom and proposed a thiiranium zwitterion intermediate.<sup>6</sup> This thiiranium zwitterion could be the key intermediate in our reaction. At first, an iodine ion attacks the carbon–carbon triple bond of **1** to give an ethidium ion **A**, in which an intramolecular nucleophilic attack of the lone pair of electrons of the sulfur atom offers thiiranium **B**.<sup>7</sup> In the presence of base, the hydrogen transfer in thiiranium **B** occurs to produce thiiranium zwitterion intermediate **C**,<sup>6</sup> in which the cyclization

Table 2  
Synthesis of 2,4-dihalo-3-thio-furans via electrophilic cyclization of 4-thio-but-2-yn-1-ols<sup>8</sup>



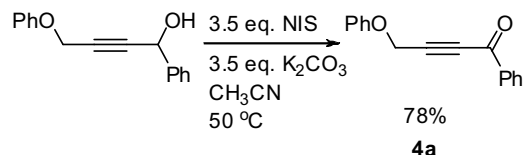
Entry	R <sup>1</sup>	R <sup>2</sup>	NXS <sup>a</sup>	Time (h)	Yield <sup>b</sup> (%)
1	Ph	4-Cl-Ph-	NIS	6	61 ( <b>2a</b> )
2	Ph	<i>n</i> -Pr	NIS	6	65 ( <b>2b</b> )
3	Ph	Ph	NIS	6	56 ( <b>2c</b> )
4	<i>n</i> -Bu	<i>n</i> -Pr	NIS	6	58 ( <b>2d</b> )
5	Ph	Ph	NBS	5	66 ( <b>2e</b> )
6	<i>n</i> -Bu	<i>n</i> -Pr	NBS	5	57 ( <b>2f</b> )
7	Ph	4-Cl-Ph-	NBS	5	68 ( <b>2g</b> )
8	Ph	<i>n</i> -Pr	NCS	5	71 ( <b>2h</b> )
9	Ph	Ph	NCS	5	55 ( <b>2i</b> )
10	<i>n</i> -Bu	<i>n</i> -Pr	NCS	5	70 ( <b>2j</b> )
11	Et	Bn	NIS	6	62 ( <b>2k</b> )
12	Et	Bn	NBS	5	60 ( <b>2l</b> )
13	Et	Bn	NCS	5	66 ( <b>2m</b> )
14	Naphthalene-1-yl	Et	NIS	5	42 ( <b>2n</b> ) <sup>c</sup>
15	Et	Et	NIS	6	58 ( <b>2o</b> )

<sup>a</sup> 0.5 equiv of NIS was added 3 h later than the other 3 equiv.

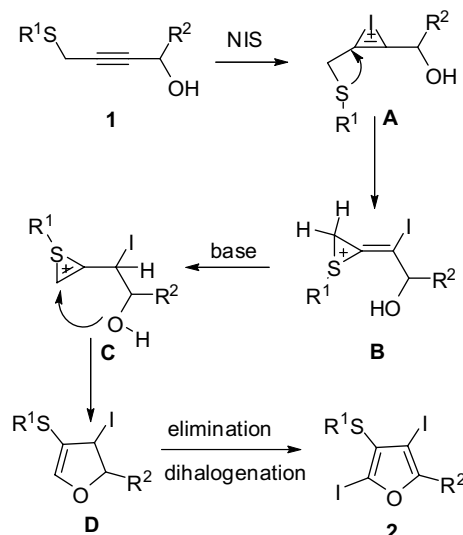
<sup>b</sup> Isolated yields.

<sup>c</sup> Monoiodo-substituted furan was observed.

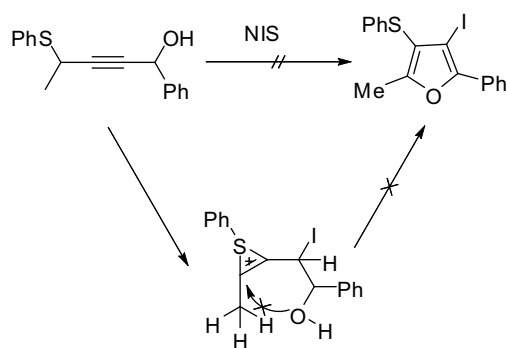
via the intramolecular nucleophilic attack of hydroxyl group affords intermediate **D**. Intermediate **D** gives product **2** via elimination and dihalogenation (Scheme 5).



Scheme 4. Oxidation of 4-oxy-but-2-yn-1-ol under similar conditions.



Scheme 5. Proposed mechanism.



Scheme 6. Hindrance of the group on 4-position.

For intermediate **C**, the intramolecular nucleophilic attack of hydroxyl group indicates that a group on 4-position might prevent this process, which was confirmed by the fact that the treatment of 1-phenyl-4-(phenylthio)pent-2-yn-1-ol with NIS in acetonitrile gave an unidentified mixture instead of 3-iodo-5-methyl-2-phenyl-4-(phenylthio)furan (Scheme 6).

In summary, we developed a facile and efficient method for the synthesis of 2,4-dihalo-3-thio-furans. As a result of the ready availability of starting materials and the simple and convenient operation, this type of reaction presented here has potential utility in organic synthesis.

## Acknowledgments

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## References and notes

- For a review, please see: Sromek, A. W.; Gevorgyan, V. *Top. Curr. Chem.* **2007**, *274*, 77.
- (a) Peng, L.; Zhang, X.; Ma, M.; Wang, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1905; (b) Peng, L.; Zhang, X.; Ma, J.; Zhong, Z.; Wang, J. *Org. Lett.* **2007**, *9*, 1445; (c) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037; (d) Sniady, A.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2005**, *7*, 1769; (e) Peng, A.; Ding, Y. *Org. Lett.* **2004**, *6*, 1119; (f) Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432; (g) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905; (h) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2003**, *5*, 4377; (i) Yao, T.; Campo, M. A.; Larock, R. C. *Org. Lett.* **2004**, *6*, 2677; (j) Yue, D.; Della, Ca. N.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581; (k) Barluenga, J.; Trincado, M.; Marco-Arias, M.; Ballesteros, A.; Rubio, E.; Gonzalez, J. M. *Chem. Commun.* **2005**, 2008; (l) Liu, Y.; Song, F.; Cong, L. *J. Org. Chem.* **2005**, *70*, 6999.
- (a) Nie, J.; Zhu, H.; Cui, H.; Hua, M.; Ma, J. A. J. *Org. Lett.* **2007**, *9*, 3053; (b) Worlikar, S. A.; Kesharwani, T.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 1347; (c) Pedrosa, R.; Andres, C.; Mendiguchia, P.; Nieto, J. *J. Org. Chem.* **2006**, *71*, 8854; (d) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 62; (e) Zhang, X.; Sarkar, S.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 236; (f) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292; (g) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *7*, 5203.
- (a) Peng, L.; Zhang, X.; Zhang, S.; Wang, J. *J. Org. Chem.* **2007**, *72*, 1192; (b) Xu, F.; Shi, W.; Wang, J. *J. Org. Chem.* **2005**, *70*, 4191; (c) Fox, D. J.; House, D.; Warren, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2462; (d) House, D.; Warren, S. *Phosphorus Sulfur Silicon Relat. Elem.* **1999**, *153*; (e) Baldwin, I. C.; Briner, P.; Eastgate, M. D.; Fox, D. G.; Warren, S. *Org. Lett.* **2002**, *4*, 4381.
- (a) Caggiano, L.; Davies, J.; Fox, D. J.; Moody, D. C.; Warren, S. *Chem. Commun.* **2003**, 1648; (b) Caggiano, L.; Fox, D. J.; Warren, S. *Chem. Commun.* **2002**, 2528.
- Gevorgyan, V.; Kel'in, A. V.; Kim, J. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 98.
- Hamel, P. *Tetrahedron Lett.* **1997**, *38*, 8473.
- General procedure for the synthesis of 4-thio-but-2-yn-1-ol*: To a solution of EtMgBr (100 mmol in 200 mL of THF) was added 100 mmol of 3-thioprop-1-yne dropwise under a nitrogen atmosphere at room temperature for 3 h, which was followed by addition of 100 mmol of aldehyde in ice-water bath. The mixture was stirred for 5 h and quenched with saturated NH<sub>4</sub>Cl, extracted with dichloromethane, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After evaporation, chromatography on silica gel (eluent: EtOAc/petroleum ether = 1:10) of the crude product afforded 4-thio-but-2-yn-1-ol, generally in yield higher than 80%. *General procedure for the synthesis of 2,4-dihalo-3-thio-furans*: To a mixture of 3.5 mmol of K<sub>2</sub>CO<sub>3</sub> and 3 mmol of *N*-halosuccinimide (NXS) in 10 mL of CH<sub>3</sub>CN was added 1 mmol of 4-thio-but-2-yn-1-ol (**1**), followed by heating at 50 °C and stirring for 3 h. Then 0.5 mmol of NXS was added. After 3 h, the reaction mixture was quenched with 30 mL of water, extracted with dichloromethane, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After evaporation, chromatography on silica gel (eluent: petroleum ether) of the crude product afforded 2,4-dihalo-3-thio-furan (**2**).  
*2-(4-Chlorophenyl)-3,5-diiodo-4-(phenylthio)furan (2a)*. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.95–7.92 (m, 2H), 7.43–7.41 (m, 2H), 7.33–7.30 (m, 3H), 7.30–7.27 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 155.8, 147.4, 135.1, 133.7, 129.3, 128.9, 128.7, 127.9, 127.6, 127.3, 95.6, 76.4. MS (*m/z*) 411 (M<sup>+</sup>–127, 5.9), 139 (100); IR (neat, cm<sup>-1</sup>) 1775, 1583. Anal. Calcd for C<sub>16</sub>H<sub>9</sub>ClI<sub>2</sub>OS: C, 35.68; H, 1.68; found: C, 36.02; H, 1.99.