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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

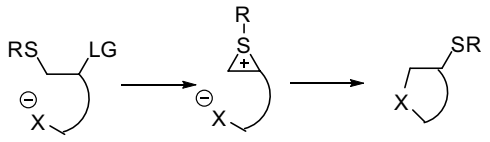
A facile and efficient method for the synthesis of 2,4-dihalo-3-thio-furans via the electrophilic cyclization and 1,2-migration of the thio group of 4-thio-but-2-yn-1-ols was developed. As a result of the ready availability of starting materials and the simple and convenient operation, this synthetic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

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

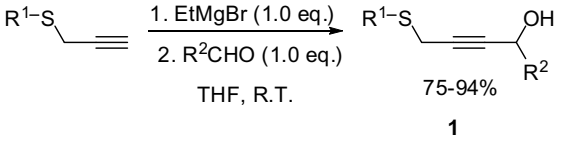
In the last decades, the electrophilic cyclization of heteroatomic nucleophiles with tethered alkynes has been proven to be one of most effective methods for preparing heterocyclic compounds, particularly for poly-substituted furans.[1–3] However, before conducting electrophilic cyclization, organic chemists have to build suitable alkynes, which generally becomes the main challenge for developing more facile and efficient synthetic methods.[3] Thus, the development of simple and convenient routes using readily available substrates for producing hetereocyclic 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.[4,5] 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).[4]

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_2CO_3 in acetonitrile at

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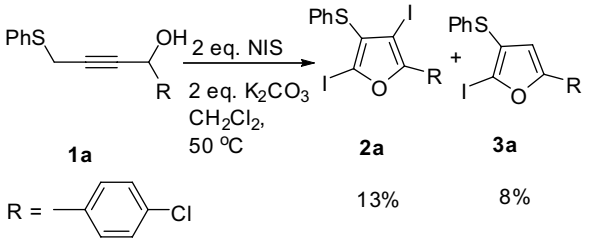
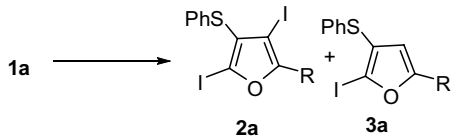


Scheme 3. First attempt of 1-(4-chlorophenyl)-4-(phenylthio) but-2-yn-1-ol treated with *N*-iodosuccinimide.

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



Solvent	E^+	Base[b]	Temperature (°C)	Time (h)	Yield[a] (%)	
					2a	**3a**
CH_2Cl_2	NIS (2 equiv)	K_2CO_3	rt	24	13	8
CH_2Cl_2	NIS (1.5 equiv)	K_2CO_3	rt	24	10	4
CH_2Cl_2	NIS (3 equiv)	K_2CO_3	rt	24	20	6
CH_2Cl_2	NIS (4 equiv)	K_2CO_3	rt	24	24	3
MeOH	NIS (4 equiv)	K_2CO_3	50	12	32	—
DMF	I_2 (4 equiv)	K_2CO_3	50	12	—	—
CH_3CN	I_2 (4 equiv)	Et_3N	50	8	—	—
CH_3CN	NIS (4 equiv)	K_2CO_3	50	6	**58**	—
CH_3CN	NIS (4 equiv)	Et_3N	50	6	15	4
CH_3CN	NIS (4 equiv)	K_2CO_3	80	4	45	—
CH_3CN	NIS (3.5 equiv)	K_2CO_3	50	6	**61**[c]	—

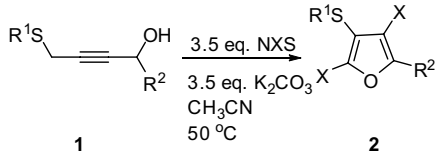
[a] The ratio of **2a** and **3a** was determined by ^1H NMR.
[b] The equivalent of base was same as the electrophile.
[c] 0.5 equiv of NIS was added 3 h later than the other 3 equiv.

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^2 carbon atom and proposed a thiiranium zwitterion intermediate.[6] 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**.[7] In the presence of base, the hydrogen transfer in thiiranium **B** occurs to produce thiiranium zwitterion intermediate **C**,[6] in which the cyclization

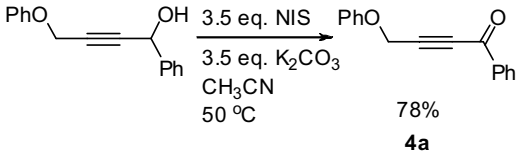
Table 2
Synthesis of 2,4-dihalo-3-thio-furans via electrophilic cyclization of 4-thio-but-2-yn-1-ols[8]



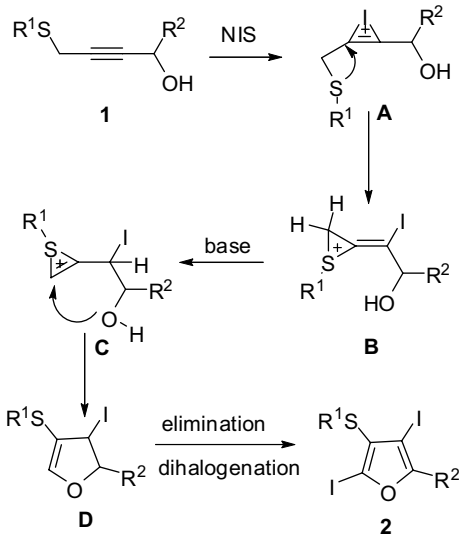
Entry	R^1	R^2	NXS[a]	Time (h)	Yield[b] (%)
1	Ph	4-Cl-Ph-	NIS	6	61 (**2a**)
2	Ph	*n*-Pr	NIS	6	65 (**2b**)
3	Ph	Ph	NIS	6	56 (**2c**)
4	*n*-Bu	*n*-Pr	NIS	6	58 (**2d**)
5	Ph	Ph	NBS	5	66 (**2e**)
6	*n*-Bu	*n*-Pr	NBS	5	57 (**2f**)
7	Ph	4-Cl-Ph-	NBS	5	68 (**2g**)
8	Ph	*n*-Pr	NCS	5	71 (**2h**)
9	Ph	Ph	NCS	5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

[a] 0.5 equiv of NIS was added 3 h later than the other 3 equiv.
[b] Isolated yields.
[c] Monoiodo-substituted furan was observed.

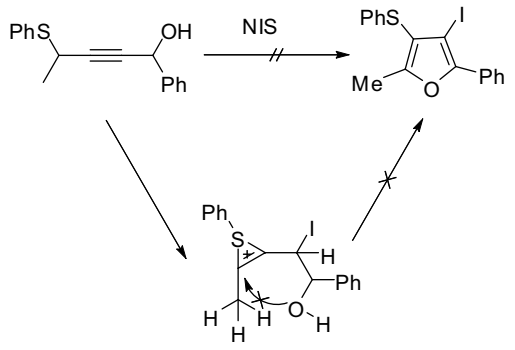
via the intramolecular nucleophilic attack of hydroxyl group affords intermediate **D**. Intermediate **D** gives product **2** via elimination and dihalogenation (Scheme 5).



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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8. *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_4Cl, extracted with dichloromethane, and dried over anhydrous Na_2SO_4. 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_2CO_3 and 3 mmol of *N*-halosuccinimide (NXS) in 10 mL of CH_3CN 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_2SO_4. 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**). ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR ($CDCl_3$, 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^+−127, 5.9), 139 (100); IR (neat, cm^{-1}) 1775, 1583. Anal. Calcd for $C_{16}H_9ClI_2OS$: C, 35.68; H, 1.68; found: C, 36.02; H, 1.99.