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1,2-Migration of the Thio Group in Allenyl Sulfides: Efficient Synthesis of 3-Thio-Substituted Furans and Pyrroles**

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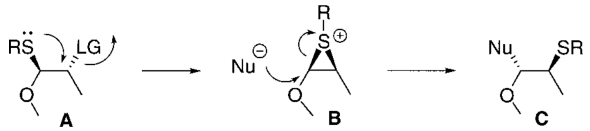
The 1,2-migration of the thio group is an important chemical transformation that is extensively used in carbohydrate chemistry for stereoselective Mitsunobu-type substitution at the anomeric center [Eq. (1)].[1] There are also reports on employment of a 1,2-shift of the thio group in the synthesis of heterocycles [Eq. (2)][1a,b] Known 1,2-migrations of the thio group can be classified as one of two types: 1) An S_N2-type attack of the lone pair of electrons of the sulfur atom at the adjacent sp^3 center in **A** produces the thiiranium intermediate **B**, which after subsequent nucleophile-assisted ring opening affords **C**, a product of 1,2-migration of the thio group [Eq. (1)].[1] 2) The migration is triggered by attack of the sulfur atom at the sp^2 carbon atom of the iminium[2a,b] or imine[2c] moiety of **D** to form the thiiranium species **E**. The latter either produces sulfide **F** through nucleophilic attack[2c] or gives the thioenamine **G** as a result of a deprotonation/ring-opening process [R^1 = H, Eq. (2)].[2a,b] In all cases the migrations of the thio group proceeded from an sp^3 center to either another sp^3 [Eq. (1)][1] or to an sp^2 [Eq. (2)][2] carbon center. To the best of our knowledge, there are no reports of 1,2-migration of the thio group from an olefinic carbon atom.

Herein we wish to report a novel 1,2-migration of the thio group from an sp^2 carbon atom in allenyl sulfides. This unprecedented migration allowed the development of an



(1)

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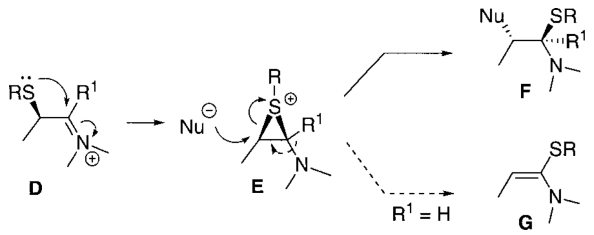
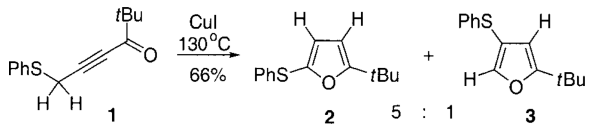


(2)

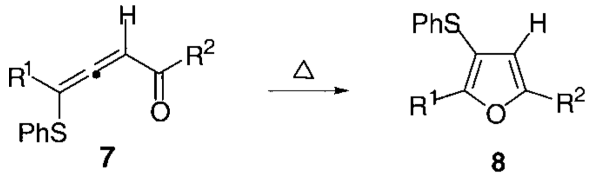
efficient method for the synthesis of 3-thio-substituted furans and pyrroles.

During the investigation of the scope of the recently found Cu-catalyzed transformation of alkynyl ketones and alkynyl imines into 2,5-disubstituted furans[3] and pyrroles,[4] we discovered that heating ketopropargyl sulfide **1** in *N*,*N*-dimethylacetamide (DMA) in the presence of CuI (10 mol%) not only gave the targeted 2,5-disubstituted furan **2**, but also a small amount of the unexpected 2,4-disubstituted furan **3** [Eq. (3)]. It was hypothesized that first, propargyl–allenyl isomerization[5] produces an allenic intermediate **4** (Scheme 1).



(3)

Next, the allenyl sulfide **4**, according to the "standard" cycloisomerization scenario (Scheme 1, path a)[3] produces the major reaction product, furan **2**.[3] It was proposed that alternatively, an intramolecular nucleophilic attack of the lone pair of electrons of the sulfur atom at the central carbon atom of the allene can transform it into the aromatic thiirenium zwitterion **5**.[6] The latter, either via Ad_N-E (**5**→**6**) or through a direct S_N2-Vin-type[7] process, affords the minor isomeric furan **3** (Scheme 1, path b). Although the role of the copper catalyst in this reaction is not completely understood, there are some indications that it facilitates propargyl–allenyl isomerization,[3, 4,8] and in some cases it is also required for further transformations [Eq. (4)], probably as a result of the stabilization of carbanionic intermediates.[8] It occurred to us that if the above mechanistic proposal is correct, then replacement of H^b in allene **4** with any other nonmigrating group should enforce selective migration of the thio group to produce 2,4-disubstituted furan **3** exclusively (path b). To examine this proposal, thioallenes **7a,b** were prepared by independent methods and subjected to the cycloisomerization conditions described above [Eq. (4)]. Remarkably, it was found that thioallenyl phenyl ketone **7a**, even in the absence of CuI, underwent *quantitative* thermal transformation to **8a**. In contrast, attempts to perform analogous thermal cycloisomerization of thioallenyl alkyl ketone **7b** resulted in total decomposition of the starting material, whereas 82% of **8b** was isolated when the reaction was performed at room temperature in the presence of CuI (5 mol%) [Eq. (4)].



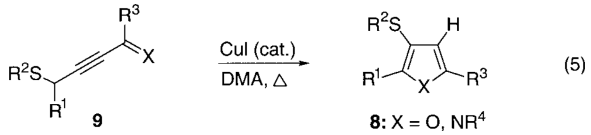
8a: $R^1 = n$Bu, R^2 = Ph
(130°C, 2h, 100%)
8b: $R^1 = n$Bu, $R^2 = (CH_2)_3OMOM$
(CuI, (5 mol%), RT, 36h, 82%)

(4)

Naturally, we next attempted a selective migrative cycloisomerization of substituted propargyl sulfides, undoubtedly superior precursors when compared with allenyl sulfides from a synthetic point of view. Accordingly, a series of alkyl-substituted propargyl sulfides **9** were synthesized and subjected to the cycloisomerization reaction [Eq. (5)].

We were very pleased to find that thiopropargyl aldehyde **9c** underwent smooth and selective cycloisomerization, producing 2-butyl-3-phenylsulfanyl-furan (**8c**) in 71% yield as a *single* reaction product (Table 1, entry 1). Cycloisomerization of thiopropargyl ketones **9a,d,e** proceeded provided the trisubstituted furans **8a,d,e** in very good yields (Table 1, entries 2–4).[9] Cycloisomerization of phenylsulfanyl propargyl ketones possessing alkenyl (**9 f**), ester (**9g**), and protected alcohol (**9h**) functionalities in the side chain proceeded readily to afford the corresponding trisubstituted furans **8 f–h** in good to very high yields (Table 1, entries 5–7). The alkyl sulfanyl group migrated with an efficiency comparable to that of its phenylsulfanyl analogue to give the corresponding furan **8i** in 72% yield (Table 1, entry 8).

Inspired by the successful synthesis of trisubstituted furans, the cycloisomerization of thiopropargyl imines was then investigated. It was found that thiopropargyl imines **9j–o** in the presence of



(5)

(5)

CuI underwent a similar transformation to give the corresponding 3-thio-substituted pyrroles **8j–o** in very good yields (Table 1, entries 9–14).[10] Again, the dodecyl sulfanyl group (Table 1, entry 10) migrated comparably to the phenyl sulfanyl analogue (Table 1, entry 9) and the THP-protected alcohol functionality was tolerated (Table 1, entry 14). It is worth mentioning that all synthesized pyrroles have removable groups at the nitrogen atom, for example, the *tert*-butyl (**8j,k**, Table 1, entries 9, 10),[11] trityl (**8 l**, Table 1, entry 11),[12] and 3-ethylbutyryl[4, 13] (**8m–o**, Table 1, entries 12–14) groups, and thus can be easily functionalized further at the nitrogen site.[14]

In conclusion, a novel 1,2-migration of the thio group in thioallenyl ketones and thioallenyl imines was discovered. An efficient method for the synthesis of di- and trisubstituted furans and trisubstituted pyrroles that possess an aryl sulfanyl or alkyl sulfanyl substituent at C3 has been developed.

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5. For an example of propargyl–allenyl isomerization, see: Garratt PJ, Neoh SB. J. Am. Chem. Soc. 1975; 97:3255.
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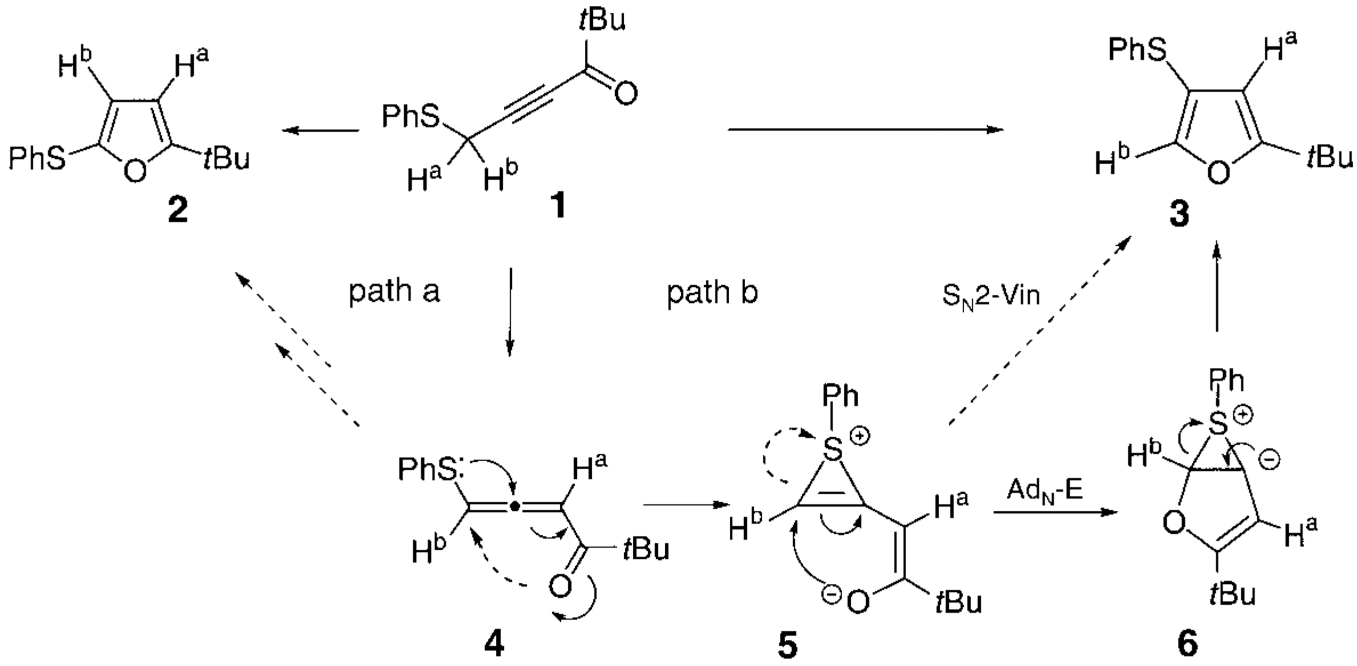
8. For the cuprate-assisted transformation of propargylic thioacetals into allenyl copper species, see: Tseng H-R, Lee C-F, Yang L-M, Luh T-Y. J. Am. Chem. Soc. 2000; 122:4992. Tseng H-R, Lee C-F, Yang L-M, Luh T-Y. J. Org. Chem. 1999; 64:8582.
9. Typical procedure (**9d**): A mixture of propargyl ketone **9d** (246 mg, 1.0 mmol), CuI (12 mg, 0.05 mmol), and anhydrous DMA (2.0 mL) was stirred in a Wheaton microreactor (3 mL) under an Ar atmosphere at 130 °C. The reaction was monitored by TLC and GC/MS until completion. After 12 h, the mixture was cooled to room temperature and poured into saturated aqueous NH_4Cl (20 mL). The phases were separated, and the aqueous phase was extracted (hexanes, 2 × 10 mL). The combined organic extracts were washed (brine, 10 mL), dried (Na_2SO_4, 2 g), and concentrated under reduced pressure. The residue was purified by means of silica-gel chromatography with hexanes to give furan **8d** (187 mg, 76%).
10. Cycloisomerization of **9j–o** to form pyrroles **8a–i** proceeded under slightly different reaction conditions to those in the synthesis of furans **8a–i**. See Supporting Information for details.
11. For deprotection of *N*-*t*Bu group in pyrroles, see: Leroy J, Wakselman C. Tetrahedron Lett. 1994; 35:8605. La Porta P, Capuzzi L, Bettarini F. Synthesis. 1994; 3:287.
12. For deprotection of *N*-Tr group in pyrroles, see: Chadwick DJ, Hodgson ST. J. Chem. Soc. Perkin Trans. 1. 1983:93.
13. For deprotection of analogous group in pyrroles, see: Roder E, Wiedenfeld H, Bourauel T. Liebigs Ann. Chem. 1985:1708.
14. It was found that EB protecting group can very easily be removed from the pyrroles. Thus, thio-substituted pyrrole **8m** underwent a facile retro-Michael reaction in the presence of KO*t*Bu to give the corresponding pyrrole **8p** quantitatively.

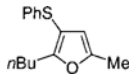
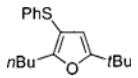
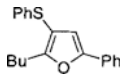
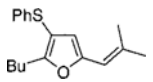
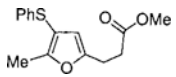
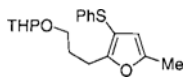
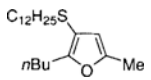
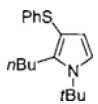


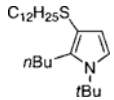
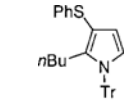
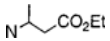
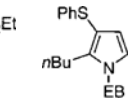
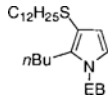
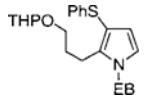
Scheme 1.

Different routes for the cyclization of the ketopropargyl sulfide **1** to give either furan **2** or **3**. Based on this mechanistic proposal, the reaction of ketopropargyl sulfides in which H^b of **4** is replaced with any other nonmigrating group should exclusively follow path b.

Table 1

Cu-catalyzed synthesis of 3-substituted furans and pyrroles.

Entry			Substrate			Product	Yield [%][a]
	9	R^1	R^2	R^3	X	8	
1	**c**	*n*Bu	Ph	H	O		71
2	**d**	*n*Bu	Ph	Me	O		76
3	**e**	*n*Bu	Ph	*t*Bu	O		89
4	**a**	*n*Bu	Ph	Ph	O		91
5	**f**	*n*Bu	Ph		O		95
6	**g**	Me	Ph	$(CH_2)_2CO_2Me$	O		71
7	**h**	$(CH_2)_3OTHP$	Ph	Me	O		93
8	**i**	*n*Bu	$(CH_2)_{11}CH_3$	Me	O		72
9	**j**	*n*Bu	Ph	H	N-*t*Bu		78

Entry		Substrate				Product	Yield [%][a]
	9	R^1	R^2	R^3	X	8	
10	**k**	*n*Bu	$(CH_2)_{11}CH_3$	H	N-*t*Bu		86
11	**l**	*n*Bu	Ph	H	N-Tr		85
12	**m**	*n*Bu	Ph	H			74
13	**n**	*n*Bu	$(CH_2)_{11}CH_3$	H	N-EB		67
14	**o**	$(CH_2)_3OTHP$	Ph	H	N-EB		78

[a]Yield of isolated product. THP = tetrahydropyran, Tr = trityl = triphenylmethyl, EB = ethyl butyryl.

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