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Ga(OTf)$_3$-Promoted Sequential Reactions via Sulfur-Assisted Propargyl-Allenyl Isomerizations and Intramolecular [4 + 2] Cycloaddition for the Synthesis of 1,3-Dihydrobenzo[*c*]thiophenes[§]

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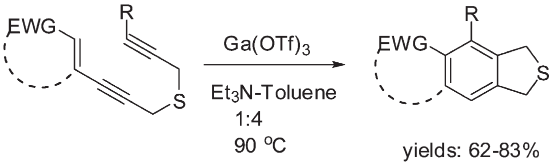

A Ga(OTf)$_3$-promoted sequential reactions via sulfur-assisted propargyl-allenyl isomerizations and intramolecular [4 + 2] cycloaddition for the synthesis of 1,3-dihydrobenzo[*c*]thiophenes. As a result of the ready availability of materials and the simple and convenient operation, the type of reaction presented here has potential utility in organic synthesis.

The preparation of polyfunctionalized heterocyclic compounds has been of interest to the organic community over the past half century. Because of the importance of thiophene-based compounds in many areas including medicinal and synthetic chemistry, benzo[*c*]thiophenes are also considered an important class.[1,2]

Combining two or more reactions into one sequential reaction, which usually involves a series of inter- or intramolecular processes wherein the product of one reaction is programmed to be the substrate for the next, represents an elegant and efficient way to access novel and complex molecules from simple, readily available starting materials.[3,4] In the past decades, sequential reactions have been routinely employed to construct core skeletons of many important compounds.[5]

Sulfur-assisted propargyl-allenyl isomerization has been a useful and efficient method to thio-allenes.[6] The allene moiety could be thought as an "activated olefin", which generally enhances the diversity of reaction possibility compared with a normal olefin. Thus, it is hypothesized that the intramolecular [4 + 2] cycloaddition of yne-allenes should provide a more convenient route than traditional intramolecular Diels–Alder reaction for the construction of complex ring systems. It may be reasonably envisioned that the vinylallene serves as diene to undergo cycloaddition with triple bonds to give cyclic compounds (Figure 1).

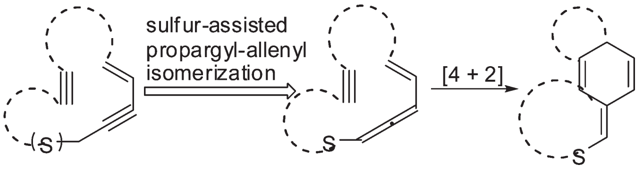

FIGURE 1. Propargyl-allenyl isomerization and [4 + 2] cycloaddition.

Herein we wish to report a sulfur-assisted sequential reaction wherein vinylallenes generated *in situ* undergo an intramolecular [4 + 2] cycloaddition of yne-allenes in the presence of Ga(OTf)$_3$, followed by an aromatization to give 1,3-dihydrobenzo[*c*]thiophenes as the final products.

As a first attempt, we chose (*E*)-ethyl 6-(3-*p*-tolylprop-2-ynylthio) hex-2-en-4-ynoate (**1a**)[7] qtgciial and initiated our study by testing the reaction of **1a** in the presence of various bases and examining the solvent effect. Weak inorganic bases such as Na$_2$CO$_3$ or K$_2$CO$_3$ could not trigger the reaction, whereas strong bases such as *t*-BuOK or EtONa gave an unidentified mixture. Triethylamine, DBU (1, 8-diazabicyclo[5.4.0]undec-7-ene), and DBN (1,5-diazabicyclo[4,3,0] non-5-ene) gave ethyl 4-*p*-tolyl-1,3-dihydrobenzo[*c*]thiophene-5-carboxylate (**2a**) as the product in a low yield (Table 1).

[§] Dedicated to the memory of Prof. Xian Huang.

(1) (a) *Handbook of Oligo- and Polythiophenes*; Fichou, D., Ed.; Wiley-VCH: Weinheim, 1999. (b) *Polythiophenes - Electrically Conductive Polymers*; Schopf, G., Kossmehl, G., Eds.; Springer: Berlin, 1997.

(2) (a) Ortiz, R. P.; Casado, J.; Hernande, V.; Navarrete, J. T. L.; Letizia, J. A.; Ratner, M. A.; Facchetti, A.; Marks, T. J. *Chem.—Eur. J.* **2009**, *15*, 5023. (b) Cosimelli, B.; Neri, D.; Roncucci., G. *Tetrahedron* **1996**, *52*, 11281. (c) Hom, D. H. S.; Lamberton., J. A. *Aust. J. Chem.* **1963**, *16*, 475.

(3) (a) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reaction in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Ho, T. L. *Tandem Organic Reactions*; John Wiley & Sons: New York, 1992.

(4) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Parsons, P. J.; Penkett, C. S.; Shell, A. *J. Chem. Rev.* **1996**, *96*, 195. (c) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (d) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831.

(5) (a) Arns, S.; Barriault, L. *Chem. Commun.* **2007**, 2211. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (c) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304.

(6) (a) Zhou, H.; Xie, Y.; Ren, L.; Su, R. *Org. Lett.* **2010**, *12*, 356. (b) Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel'in, A. V; Gevorgyan., V. *J. Am. Chem. Soc.* **2008**, *130*, 1440. (c) Sromek, A. W.; Gevorgyan., V. *Top. Curr. Chem.* **2007**, *274*, 77. (d) Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 98. (e) Zafrani, Y.; Gottlieb, H. E.; Sprecher, M.; Braverman, S. *J. Org. Chem.* **2005**, *70*, 10166. (f) Zafrani, Y.; Cherkinsky, M.; Gottlieb, H. E.; Braverman, S. *Tetrahedron* **2003**, *59*, 2641. (g) Braverman, S.; Cherkinsky, M.; Birsa, M. L.; Zafrani, Y. *Eur. J. Org. Chem.* **2002**, *18*, 3198. (h) Braverman, S.; Zafrani, Y.; Gottlieb, H. E. *Tetrahedron* **2001**, *57*, 9177. (i) Garratt, P. J.; Neoh, S. B. *J. Am. Chem. Soc.* **1975**, *97*, 3255. (j) Iwai, I.; Ide, J. *Chem. Pharm. Bull.* **1964**, *12*, 1094.

(7) The substrate **1a** could be easily prepared via a Sonogashira reaction using (*E*)-ethyl-3-iodoacrylate (**4**) and prop-2-ynyl(3-*p*-tolylprop-2-ynyl)-sulfane (**5**) as the starting materials. To a solution of **4** (2.0 mmol) and **5** (2.4 mmol) in 10 mL of THF were added CuI (10 mg. 0.05 mmol) and PdCl$_2$(PPh$_3$)$_2$ (35 mg, 0.05mmol), and 1 mL of diisopropylamine was added under a N$_2$ atmosphere at room temperature for 1 h. The reaction mixture was quenched with water, extracted with Et$_2$O, and dried over anhydrous Na$_2$SO$_4$. After evaporation of the Et$_2$O, chromatography on silica gel (eluent, EtOAc/petroleum ether = 1:20) of the crude product afforded **1a** in a yield of 88%. The other substrates **1b**–**1p** could be synthesized via similar process generally in a yield higher than 80%. For the detailed processes, please see Supporting Information.

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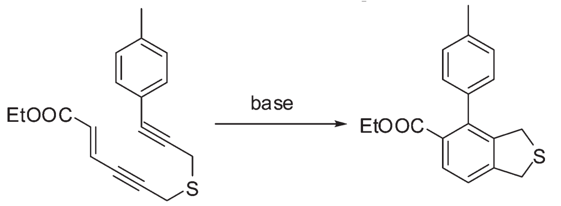
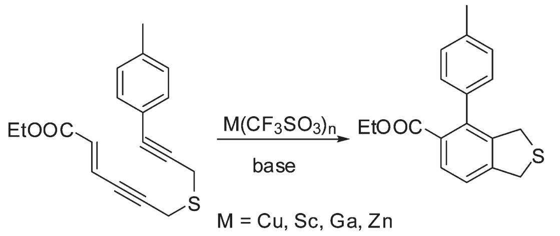
TABLE 1. Base and Solvent Effects on the Sequential Reaction[a]



entry	base	solvent	time	temp (°C)	yield of **2a** (%)
1	Na_2CO_3	THF	24 h	reflux	NR
2	Na_2CO_3	toluene	24 h	reflux	NR
3	K_2CO_3	THF	24 h	reflux	NR
4	K_2CO_3	toluene	24 h	reflux	NR
5	*t*-BuOK	THF	3 min	rt	unidentified mixture
6	EtONa	THF	5 min	rt	unidentified mixture
7	Et_3N	toluene	48 h	reflux	12[b]
8	Et_3N	THF	72 h	reflux	8[c]
9	Et_3N	benzene	72 h	reflux	15[d]
10	DBN	toluene	24 h	90	27
11	DBN	THF	24 h	reflux	30
12	DBU	toluene	24 h	90	18
13	DBU	THF	24 h	reflux	20
14	DBU	DMSO	1 h	90	0
15	DBU	CH_3CN	1 h	50	7

[a] Substrate **1a** (0.5 mmol) and base (2 mmol) in solvent (5 mL) under a N_2 atmosphere. [b] 60% of **1a** was recovered. [c] 70% of **1a** was recovered. [d] 65% of **1a** was recovered.

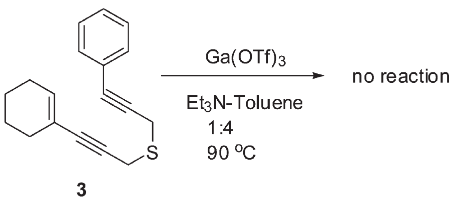
TABLE 2. Lewis Acid Effects in the Presence of Lewis Base[a]



entry	base	M(OTf)$_n$	solvent	time (h)	temp (°C)	yield of **2a** (%)
1	Et_3N	Cu(OTf)$_2$	toluene	24	reflux	16
2	Et_3N	Cu(OTf)$_2$	toluene	24	90	20
3	Et_3N	Sc(OTf)$_3$	toluene	24	reflux	46
4	Et_3N	Sc(OTf)$_3$	toluene	24	90	42
5	Et_3N	Ga(OTf)$_3$	toluene	16	reflux	56
6	Et_3N	Ga(OTf)$_3$	toluene	24	90	**63**
7	Et_3N	Ga(OTf)$_3$	benzene	48	reflux	45
8	Et_3N	Zn(OTf)$_2$	toluene	24	reflux	18
9	Et_3N	Zn(OTf)$_2$	toluene	24	90	16
10	DBN	Ga(OTf)$_3$	toluene	24	reflux	28
11	DBN	Ga(OTf)$_3$	toluene	24	90	32
12	DBU	Ga(OTf)$_3$	toluene	24	reflux	22
13	DBU	Ga(OTf)$_3$	toluene	24	90	19
14	Et_3N	Ga(OTf)$_3$	toluene	24	90	**68**[b]

[a] All reactions were run under the following conditions, unless otherwise specified: substrate **1a** (0.5 mmol), base (2 mmol), and M(OTf)$_n$ (0.025 mmol) in solvent (5 mL) under a N_2 atmosphere. [b] A mixture of 1 mL of Et_3N and 4 mL of toluene was used as the solvent.

SCHEME 1



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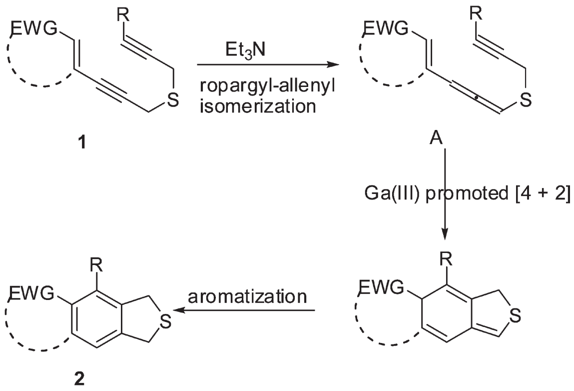
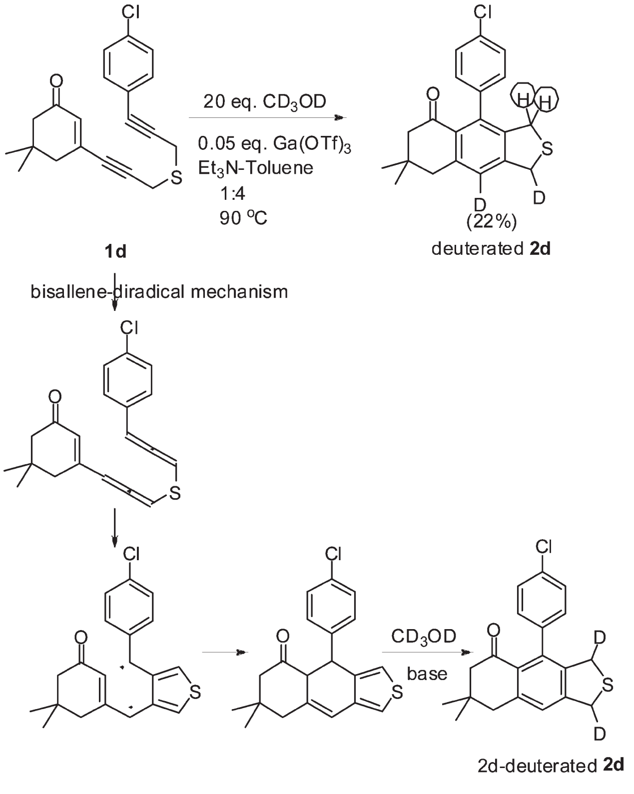


SCHEME 3



For further optimization, we expected use of Lewis acid to promote the [4 + 2] cycloaddition. Although it is well-known that Lewis acids can accelerate pericyclic reactions, finding the right Lewis acid and reaction conditions remains a challenging task for organic chemists because the Lewis acid may react with the Lewis base before activating the pericyclic reactions.[8] We chose metal triflates to examine this reaction because of their stability to Lewis bases (Table 2).

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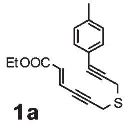
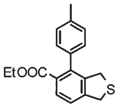
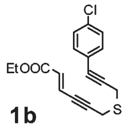
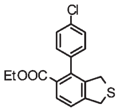
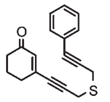
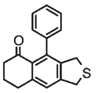
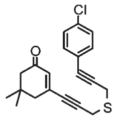
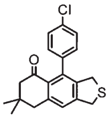
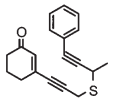
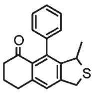
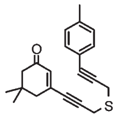
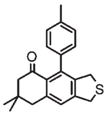
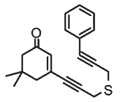
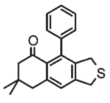
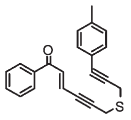
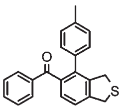
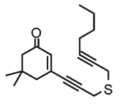
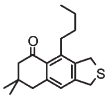
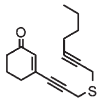
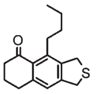
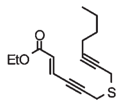
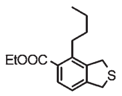
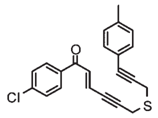
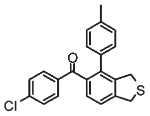
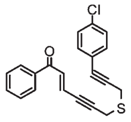
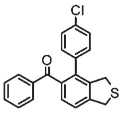
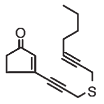
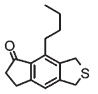
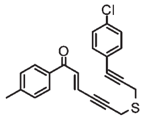
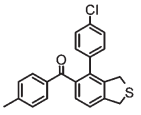
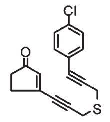
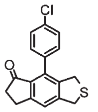
(8) For reviews of bifunctional catalysis of cooperative Lewis acid/base systems, please see: (a) Paull, D. H.; Abraham, C. J.; Scerba, M. T.; Alden-Danforth, E.; Lectka, T. *Acc. Chem. Res.* **2008**, *41*, 655. (b) Murahashi, S. C.; Takaya, H. *Acc. Chem. Res.* **2000**, *33*, 225.

TABLE 3. Synthesis of 1,3-Dihydrobenzo[c]thiophenes[a]

$$\mathbf{1} \xrightarrow[\substack{\text{Et}_3\text{N-Toluene} \\ 1:4 \\ 90\ ^{\circ}\text{C}}]{\text{Ga(OTf)}_3} \mathbf{2}$$

Entry[b]	Substrate 1	Products 2	Yield of 2 (%)
1	 **1a**	 **2a**	68
2	 **1b**	 **2b**	65
3	 **1c**	 **2c**	66
4	 **1d**	 **2d**	62
5	 **1e**	 **2e**	72
6	 **1f**	 **2f**	70
7	 **1g**	 **2g**	68
8	 **1h**	 **2h**	66
9	 **1i**	 **2i**	83
10	 **1j**	 **2j**	77
11	 **1k**	 **2k**	75
12	 **1l**	 **2l**	65
13	 **1m**	 **2m**	62
14	 **1n**	 **2n**	79
15	 **1o**	 **2o**	62
16	 **1p**	 **2p**	68

[a] All reactions were run under the following conditions, unless otherwise specified: substrate **1a** (0.5 mmol) and Ga(OTf)_3 (0.025 mmol) in solvent (5 mL) under a N_2 atmosphere. [b] A mixture of 1 mL of Et_3N and 4 mL of toluene was used as the solvent.

With this result in hand, we examined the scope of the reaction and obtained 1,3-dihydrobenzo[*c*]thiophenes in moderate to good yields under mild conditions (Table 3).

We examined the reaction of (3-cyclohexenylprop-2-ynyl)-(3-phenylprop-2-ynyl)sulfane (**3**)[9] under the same conditions (compared with entry 3) but recovered only the starting material in 92% yield, demonstrating that the electron-withdrawing group, such as an ester group or carbonyl group, is essential to trigger the propargyl-allenyl isomerization in the presence of a mild base (Scheme 1).

We propose a plausible pathway as shown in Scheme 2. At first **1**, via a propargyl-allenyl isomerization in the presence of Et_3N, gives intermediate A,[6b] which undergoes an intramolecular [4 + 2] cycloaddition of yne-allenes in the presence

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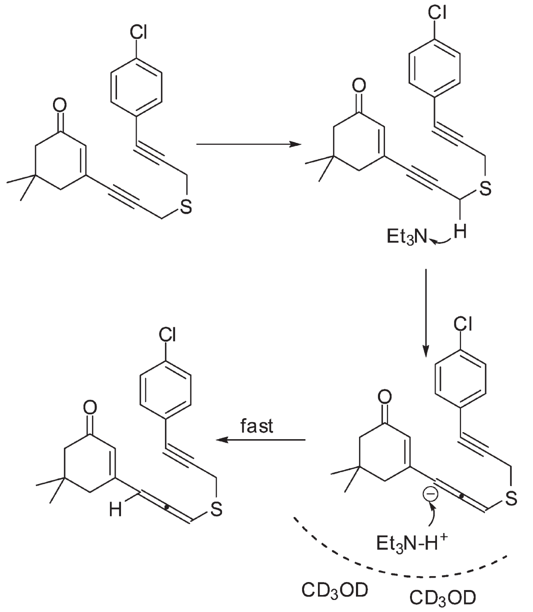
[9] Braverman, S.; Zafrani, Y.; Gottlieb, H. E. *J. Org. Chem.* **2002**, *67*, 3277.

SCHEME 4



of Ga(OTf)$_3$, followed by an aromatization to give 1,3-dihydrobenzo[*c*]thiophenes as the final products **2** (Scheme 2).

Garrant reported a bisallene-diradical mechanism,[6i] and Braverman demonstrated the presence of a diradical intermediate,[6e−h] in contrast with the [4 + 2] cycloaddition mechanism suggested by Iwai.[6j] To examine the possible pathway for our reaction, we treated **1d** with 20 equiv of methanol-d_4 in 5 mL of Et$_3$N-toluene (1:4) in the presence of 0.05 equiv of Ga(OTf)$_3$ at 90 °C and obtained deuterated **2d**. However, only one proton of the two methylene groups adjacent to the sulfur atom was deuterated, showing that the monoallene intermediate and [4 + 2] cycloaddition mechanism are more plausible in the case of our reaction because the bisallene-diradical pathway should influence both methylene groups (Scheme 3).

Interestingly, we just observed 22% deuterium on the new benzene ring, probably because the propargyl-allene isomerization is so fast that the protonated triethylamine does not have enough time to leave (Scheme 4).

In summary, we developed a Ga(OTf)$_3$-promoted sequential reactions via sulfur-assisted propargyl-allenyl isomerizations and intramolecular [4 + 2] cycloaddition for the synthesis of 1,3-dihydrobenzo[*c*]thiophenes. As a result of the ready availability of materials and the simple and convenient operation, this type of reaction presented here has potential utility in organic synthesis.

Experimental Section

Typical Procedure for Synthesis of 1,3-Dihydrobenzo[*c*]thiophenes (2). To a solution of (*E*)-ethyl-6-(3-*p*-tolylprop-2-ynylthio) hex-2-en-4-ynoate (**1a**, 0.5 mmol) in 5 mL of solvent (toluene/Et$_3$N = 4:1) was added 0.025 mmol of Ga(OTf)$_3$ under a nitrogen atmosphere at 90 °C for 24 h. The reaction mixture was quenched with 20 mL of water, extracted with ethyl ether, and dried over anhydrous Na$_2$SO$_4$. After evaporation of the ethyl ether, chromatography on silica gel (eluent, petroleum ether/EtOAc = 25:1) of the crude product afforded the desired product **2a**: yield 68%, 101 mg; oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79−7.77 (m, 1H), 7.29−7.26 (m, 1H), 7.21−7.19 (m, 2H), 7.09−7.07 (m, 2H), 4.35 (s, 2H), 4.07−4.01 (q, J = 7.1 Hz, 2H), 3.97 (s, 2H), 2.40 (s, 3H), 1.00−0.97 (t, J = 7.0 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 167.7, 144.0, 140.7, 139.6, 136.8, 136.8, 130.0, 128.9, 128.8, 127.8, 123.3, 60.7, 38.3, 37.8, 21.2, 13.6; MS (*m*/*z*) 298 (M, 60), 297 (M − 1, 30); IR (neat, cm^{-1}) 1709.2, 1285.1, 1124.2. HRMS calcd for C$_{18}$H$_{18}$O$_2$S: 298.1208. Found: 298.1206[§]Dedicated to the memory of Prof. Xian Huang.

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Supporting Information Available: Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.