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Sulfur-assisted propargyl–allenyl isomerizations and intramolecular cyclization for the synthesis of tricyclic thiophene derivatives

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This Letter is dedicated to the memory of Professor Xian Huang

ABSTRACT

A facile and efficient cyclization for the synthesis of tricyclic thiophene derivatives was developed. As a metal-free process, a result of the ready availability of the starting materials and the simple and convenient operation, the type of reaction presented here has potential utility in organic synthesis.

1. Introduction

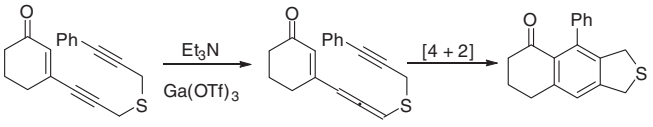
Thiophene-based compounds are of interest to the organic community over the past decades because of their intrinsic properties such as drug activity, wide range of photobiological activity, luminescence, redox activity, and electron transport.[1,2] In this regard, polycyclic *S*-heterocycles could be useful for various applications in organic chemistry.[3]

Sulfur-assisted propargyl–allenyl isomerization has been a useful and efficient method to thio-allenes, which may be used as an 'activated olefin' to achieve cyclization.[4] Recently, we reported a sulfur-assisted propargyl–allenyl isomerizations intramolecular [4+2] cycloaddition promoted by triethylamine and $Ga(OTf)_3$ (Scheme 1).[5]

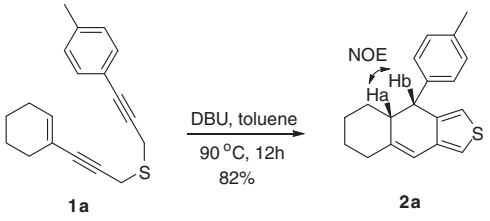
We found that due to the weak basicity of triethylamine, the presence of electron-withdrawing group is essential to trigger the propargyl–allenyl isomerization. It may be reasonably envisioned that (3-cyclohexenylprop-2-ynyl) (3-*p*-tolylprop-2-ynyl)sulfane (**1a**) could undergo cyclization promoted by the stronger bases. Stimulated by this proposal, we initiated our study by treating **1a** with various bases. After careful examination, we isolated 4-*p*-tolyl-4,4a,5,6,7,8-hexahydronaphtho[2,3-*c*]thiophene (**2a**) in 82% yield by treatment of **1a** with DBU in toluene at 90 °C. The stereochemistry of **2a** was established by NOESY experiment which clearly showed an NOE effect between the Ha and Hb (Scheme 2).

This unexpected result and the fact that **2a** could be obtained in good yield without the promotion of Lewis acid attracted us to hypothesize that the possible pathway might be different from the [4+2] cycloaddition shown in Scheme 1. For further confirmation, we conducted a control experiment by treatment of **1a** with DBU and $Ga(OTf)_3$, and no Lewis acid effect was observed (Scheme 3).

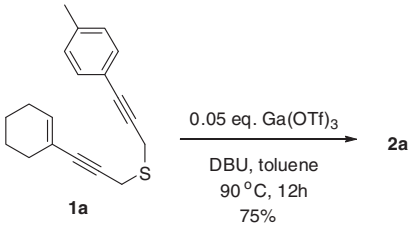
Garratt has reported a bisallene-diradical mechanism[6] which may account for the formation of **2a**. To examine the possible



Scheme 1.



Scheme 2.



Scheme 3.

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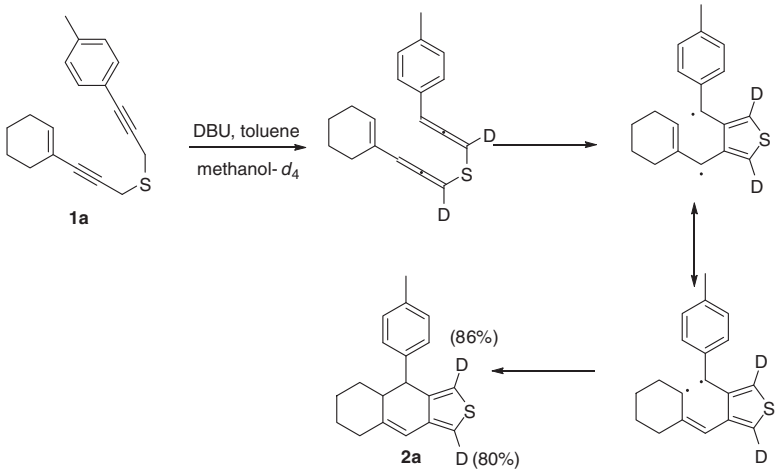


Scheme 4.

Table 1
Synthesis of tricyclic thiophene derivatives[a]

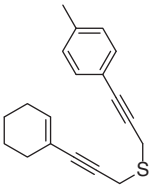
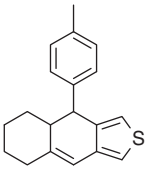
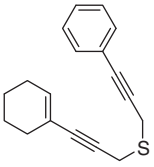
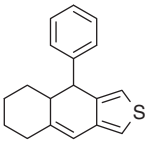
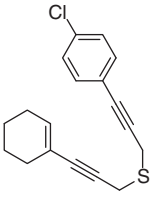
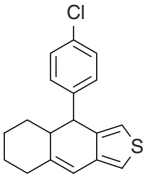
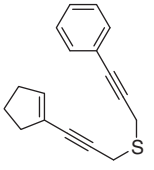
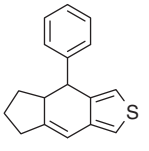
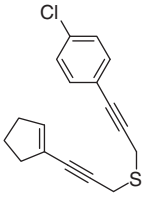
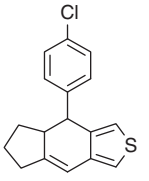
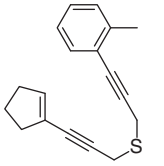
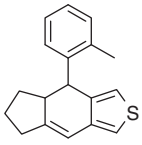
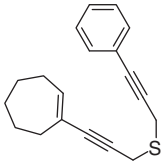
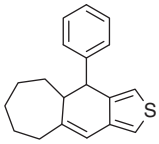
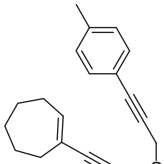
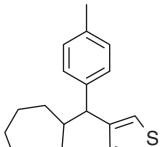
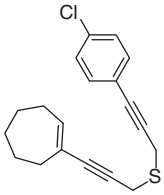
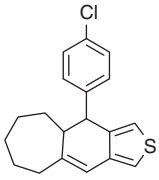
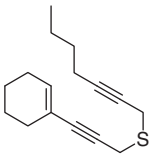
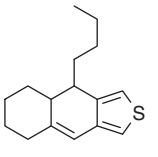
Entry	Substrate	Time (h)	Product	Yield (%)
1	 **1a**	12	 **2a**	82
2	 **1b**	10	 **2b**	75
3	 **1c**	12	 **2c**	68
4	 **1d**	10	 **2d**	73
5	 **1e**	10	 **2e**	71
6		16		64

Table 1 (*continued*)

Entry	Substrate	Time (h)	Product	Yield (%)
7	 **1f**	12	 **2f**	71
8	 **1g**	15	 **2g**	77
9	 **1h**	16	 **2h**	63
10	 **1i**	24	 **2i**	0
	 **1j**		 **2j**	

[a] Substrate **1** (0.5 mmol) and DBU (0.6 mmol) in toluene (2 mL) at 90 °C under a N_2 atmosphere.

pathway for our reaction, we treated **1a** with DBU in the methanol-d_4/toluene (1:10) and observed that both the protons of the thiophene ring were deuterated, demonstrating that the bisallene-diradical mechanism is more plausible because the monoallene intermediate and the [4+2] cycloaddition pathway should influence only one methylene group (Scheme 4).

With this result in hand, we examined the scope of the reaction and obtained tricyclic thiophene derivatives in moderate to good yields (Table 1).

Notably, the (3-cyclohexenylprop-2-ynyl)(hept-2-ynyl)sulfane (**1j**) could not offer the expected product (entry 10, Table 1), probably because the presence of the aryl ring could stabilize the radical intermediate. Compared to the smooth Diels–Alder cyclization of 3-(3-(hept-2-ynylthio)prop-1-ynyl)cyclohex-2-enone,[5] this result may give indirectly further proof for the pathway proposed in Scheme 3.

In summary, we have developed a facile and efficient cyclization for the synthesis of tricyclic thiophene derivatives. As a metal-free process, a result of the ready availability of the starting materials and the simple and convenient operation, the type of reaction presented herein has potential utility in organic synthesis.

2. Experimental section

2.1. General procedure for synthesis of 2

To 0.5 mmol of (3-cyclohexenylprop-2-ynyl) (3-*p*-tolylprop-2-ynyl)sulfane (**1a**) was added 0.6 mmol of DBU in 2 mL of toluene under a N_2 atmosphere, followed by heating to 90 °C for 12 h. After evaporation, chromatography on silica gel (eluent/petroleum ether) of the reaction mixture afforded the desired product **2a** in a yield of 82%.

Compound **2a**: yield: 82%, 115 mg; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.14 (m, 4H), 6.84–6.83 (d, J = 2.4 Hz, 1H), 6.33–6.31 (m, 2H), 3.61–3.58 (d, J = 4.0 Hz, 1H), 2.52–2.45 (m, 1H), 2.48–2.47 (m, 1H), 2.37 (s, 3H), 2.30–2.16 (m, 1H), 1.82–1.78 (m, 2H), 1.38–1.27 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.0, 141.0, 140.8, 137.0, 136.1, 129.1 (double carbon), 128.8 (double carbon), 120.2, 116.8, 116.4, 50.4, 44.1, 34.8, 33.5, 26.7, 25.9, 21.0; MS (m/z) 280 (M, 60), 281 (M+1, 10); HRMS calcd for $C_{19}H_{20}S$: 280.1286. Found: 280.1280.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.063.

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