Organic LETTERS

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Tandem Thien- and Benzannulations of α-Alkenoyl-α-alkynyl Ketene Dithioacetals with Cyanoacetates: Synthesis of Functionalized Benzo[*b*]thiophenes

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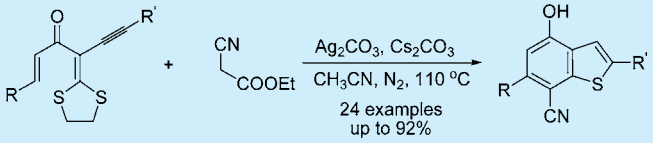
Supporting Information

ABSTRACT: A novel domino annulation strategy for the construction of benzo[*b*]thiophenes has been developed. In the presence of Cs_2CO_3 and Ag_2CO_3, a wide range of α-alkenoyl-α-alkynyl ketene dithioacetals readily react with cyanoacetates in CH_3CN at 110 °C under N_2 to afford multisubstituted benzo[*b*]thiophenes efficiently via tandem thien- and benzannulations. A plausible mechanism is also proposed.



Benzo[*b*]thiophenes represent a class of important heterocyclic compounds which are widely distributed in bioactive natural products.[1] These heterocycles form the core of a number of medicinally important molecules, such as raloxifene,[2a] arzoxifene,[2b] zileuton,[2c] sertaconazole,[2d] and SB-271046[2e] (Figure 1). Furthermore, benzo[*b*]thiophenes are also widespread in catalysis and material chemistry.[3]

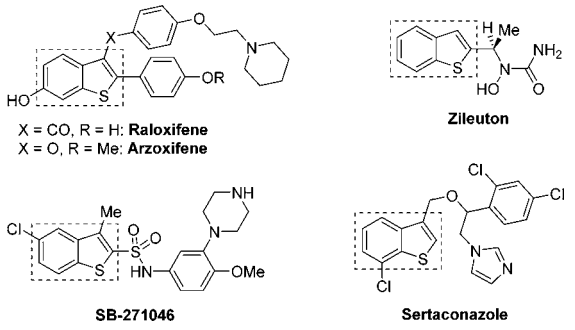
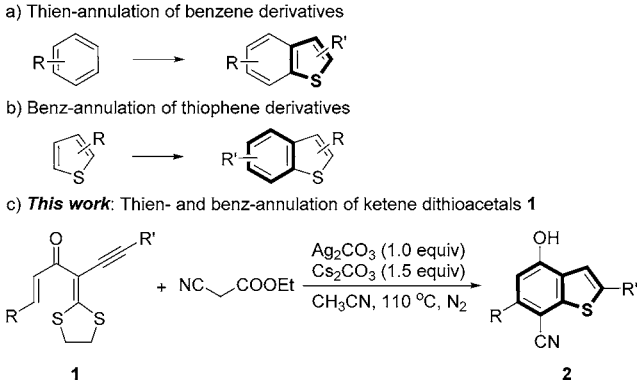


Figure 1. Pharmaceuticals containing the benzo[*b*]thiophene core structure.

Two synthetic strategies for benzo[*b*]thiophenes are commonly used.[4] The first strategy is the thienannulation[5] onto a benzene precursor (Scheme 1a).[6,7] Typical examples include the electrophilic cyclization of *o*-alkynyl thioanisoles, as explored by Larock.[6] Recently, König et al.[7b] reported a photocatalytic reaction of *o*-(methylthio)arenediazonium salts with alkynes for the synthesis of benzo[*b*]thiophene. The second strategy is the benzannulation on a preformed thiophene moiety (Scheme 1b).[8] One elegant example is the gold-catalyzed benzannulation of 2-substituted thiophene, reported by Hashmi and co-workers.[8b] A strategy toward synthesis of benzo[*b*]thiophenes via tandem thien- and benzannulations of simple acyclic precursors is an appealing alternative but has not been developed. To the best of our knowledge, up to now, there has been only one single example reported by Mukai wherein pyrolysis of bicyclic δ-thia-α,β-unsaturated ketone at 520 °C afforded 4-hydroxybenzo[*b*]-thiophene in 28% yield.[9] Although it remains unexploited, this strategy would be highly desirable because it would avoid using prefunctional aromatic ring substrates and the functional groups could be directly introduced onto the benzo[*b*]-thiophene skeletons by choosing appropriate substrates.

Scheme 1. Different Strategies for the Construction of Benzo[*b*]thiophenes



Tandem reactions have attracted considerable attention for simplifying reaction steps, reducing waste, and maximizing atom economy and have been developed as a powerful shortcut for the assembly of ring systems in organic synthesis.[10] Among these processes, the cyclization of enynes is a rapid and powerful approach to prepare cyclic derivatives.[10,11] Herein, we report new tandem cyclization reactions of α-alkenoyl-α-alkynyl ketene dithioacetals **1**[12,13] with ethyl 2-cyanoacetate to synthesize benzo[*b*]thiophene derivatives (Scheme 1c). To

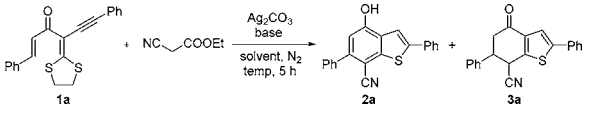
Received: February 19, 2015
Published: March 19, 2015

DOI: 10.1021/acs.orglett.5b00523
Org. Lett. 2015, 17, 1746−1749

the best of our knowledge, this is the first efficient approach for the synthesis of benzo[*b*]thiophenes by the construction of both benzene and thiophene rings in one pot. The readily availability of starting materials enables efficient access to highly functionalized benzo[*b*]thiophenes that might find applications in the pharmaceutical industry and material science.

We commenced our studies by exploring the reaction between (*E*)-4-(1,3-dithiolan-2-ylidene)-1,6-diphenylhex-1-en-5-yn-3-one (**1a**) with ethyl 2-cyanoacetate to optimize the reaction conditions (Table 1). When **1a** was treated with 4.0 equiv of ethyl 2-cyanoacetate, 10 mol % Ag_2CO_3, and 0.5 equiv of DBU in CH_3CN under N_2 at 90 °C, the desired product **2a**[14] was obtained in 15% yield, with **3a** (35%) being the major product (entry 1). As expected, increasing the loading of Ag_2CO_3 to 1.0 equiv improved the yield of **2a** to 50% (entry 2). Changing the oxidants (i.e., AgTFA, O_2, $AgNO_3$) did not afford **2a** or led to reduced yields (see details in the Supporting Information). We then turned our attention to screen different bases (entries 3−6). The results indicated that Cs_2CO_3 could remarkably improve the yield to 62% (entry 6). Among the reaction temperatures examined, it turned out that the reaction at 110 °C gave the best result (entries 6−8). CH_3CN was found to be an optimal solvent in comparison with DMSO and toluene (entries 9 and 10). Control experiments verified the requirement of Cs_2CO_3 and Ag_2CO_3 (entries 11 and 12).

Table 1. Optimization of the Reaction Conditions[a]

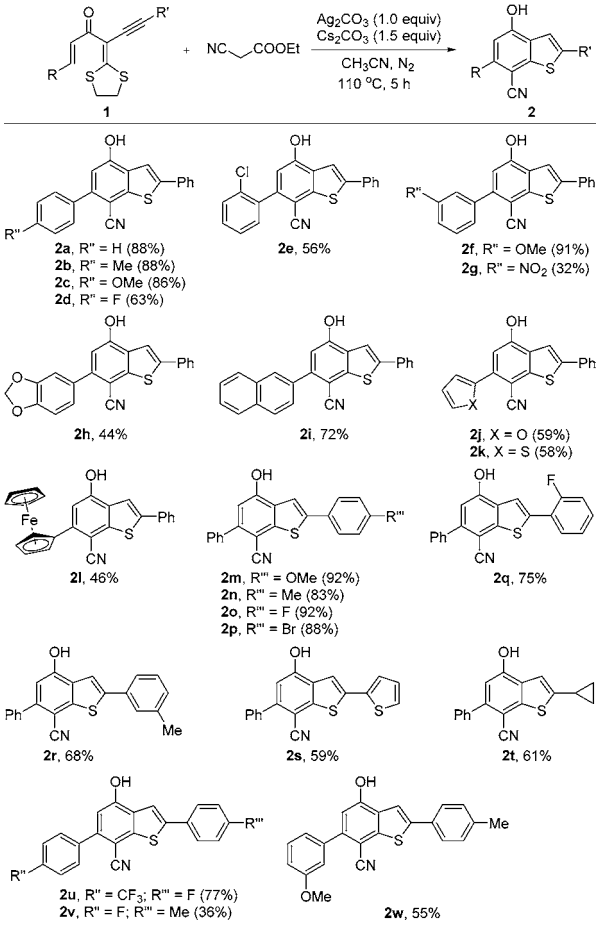


				yield[b] (%)	
entry	base	solvent	temp (°C)	**2a**	**3a**
1[c]	DBU	CH_3CN	90	15	35
2	DBU	CH_3CN	90	50	9
3	K_3PO_4	CH_3CN	90	40	15
4	K_2CO_3	CH_3CN	90	31	12
5	NaOH	CH_3CN	90	37	20
6	Cs_2CO_3	CH_3CN	90	62	10
7	Cs_2CO_3	CH_3CN	110	88	trace
8	Cs_2CO_3	CH_3CN	120	69	trace
9	Cs_2CO_3	DMSO	110	50	10
10	Cs_2CO_3	toluene	110	0	0
11		CH_3CN	110	0	trace
12[d]	Cs_2CO_3	CH_3CN	110	trace	73

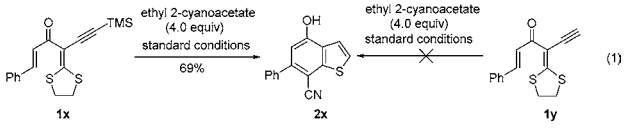
[a]Conditions: **1a** (0.2 mmol), ethyl 2-cyanoacetate (4.0 equiv), Ag_2CO_3 (1.0 equiv), base (1.5 equiv), and solvent (2.0 mL) for 5 h under N_2. [b]Isolated yields. [c]10 mol % Ag_2CO_3 was used. [d]The reaction was run without Ag_2CO_3.

With the optimized conditions in hand, the substrate scope was then investigated. Overall, a number of multisubstituted benzo[*b*]thiophenes were successfully prepared with moderate to excellent yields (Scheme 2). First, substituents on the alkenoyl moiety were investigated (**2a−l**). Arylalkenoyl substrates **1** with electron-donating groups showed better reactivity than those with electron-withdrawing groups. Various kinds of functional groups, such as OMe, NO_2, F, Cl, and Me, were well tolerated. Naphthyl, heteroaryl, and ferrocenyl substrates were also productive, delivering benzo[*b*]thiophenes in moderate yields (**2i−l**). Furthermore, substituents on the terminal alkyne were investigated. A variety of electron-deficient and electron-rich arylalkynyl substrates underwent the annulation to afford benzo[*b*]thiophenes in fair to excellent yields (**2m−t**). Efficiency was not much influenced by electronic variation on the aryl moiety at the terminal alkyne. Moderate yields were found to be achievable from heteroaryl alkyne and aliphatic alkyne substrates (**2s** and **2t**). Notably, substrate **1x** with TMS substituent on the alkyne underwent the annulation reaction to give the de-trimethylsilylation product **2x**. However, substrate **1y** with terminal alkyne could not be transformed into **2x** under the current conditions (eq 1). These results indicate that de-trimethylsilylation proceeded post to the annulation of **1x**.

Scheme 2. Substrate Scope of *α*-Alkenoyl-*α*-alkynyl Ketene Dithioacetals 1[a,b]



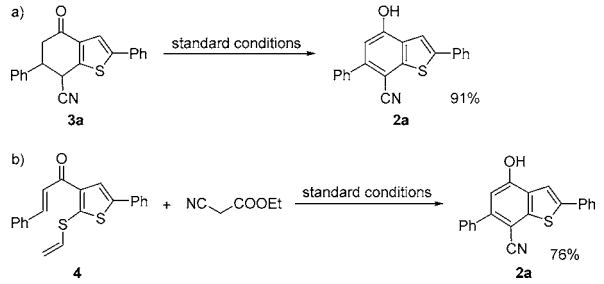
[a]Reaction conditions: **1** (0.2 mmol), ethyl 2-cyanoacetate (4.0 equiv), Ag_2CO_3 (1.0 equiv), and Cs_2CO_3 (1.5 equiv) at 110 °C for 5 h under N_2. [b]Isolated yields.



To gain some preliminary understanding of the reaction mechanism, the following experiments were carried out (Scheme 3). Resubjection of **3a**, which was found during early optimization experiments, to the standard conditions did result in the formation of the benzo[*b*]thiophene **2a** (Scheme 3a), suggesting the intermediacy of **3a** in the reaction. Besides,

DOI: 10.1021/acs.orglett.5b00523
Org. Lett. 2015, 17, 1746−1749

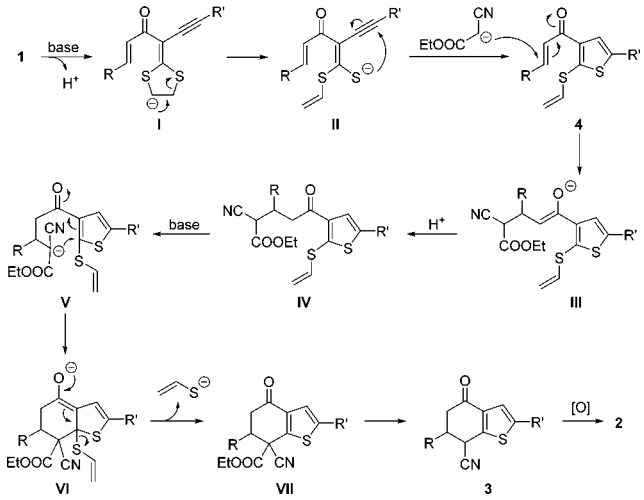
Scheme 3. Preliminary Mechanistic Studies



we investigated the reactivity of thiophene **4**, which might be formed from **1a** under base.[13d] Indeed, upon reaction with ethyl 2-cyanoacetate, **4** was also converted to give benzo[*b*]-thiophene **2a** in 76% yield (Scheme 3b). This result suggested that benzo[*b*]thiophene construction might go through the thienannulation/benzannulation sequence in this reaction.

Although the precise reaction mechanism cannot be definitively established at the current stage, on the basis of the above results and previous reports,[13a,d] a plausible mechanism was proposed in Scheme 4. Initially, deprotonation at one of the

Scheme 4. Putative Reaction Mechanism



methylene groups of the dithiolane moiety[13d,15] triggered the ring-opening reaction to generate the thiolate anion **II**,[13d] which cyclized to form thiophene intermediate **4** through a sequential intramolecular heteroannulation[16] and protonation. Subsequently, Michael addition of the anion of ethyl 2-cyanoacetate to the double bond of **4** followed by protonation formed intermediate **IV**.[13a] Deprotonation of **IV** triggered an intramolecular nucleophilic displacement of the labile thioether furnishing **VII**,[17] which underwent ester elimination[18] followed by oxidative aromatization[19] to produce the desired benzo[*b*]-thiophenes **2**. Existence of intermediates **IV** and **VII** were supported by HRMS analysis.[20]

In summary, a novel tandem annulation of α-alkenoyl-α-alkynyl ketene dithioacetals with ethyl 2-cyanoacetate has been developed, yielding multifunctionalized benzo[*b*]thiophenes in moderate to excellent yields. This work opens up a new approach to realize benzo[*b*]thiophene synthesis by tandem thien- and benzannulations in one pot. Ongoing studies are focused on applying this methodology in the synthesis of functional materials as well as testing bioactivity of some compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data for all compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (No. 21202017) is greatly appreciated.

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DOI: 10.1021/acs.orglett.5b00523
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(14) The benzo[*b*]thiophene **2a** was transformed into a benzenesulfonate **5**, the structure of which was determined by X-ray crystallographic analysis (see the Supporting Information). CCDC 1041997 (**5**) contains the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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(20) Detailed data on the in situ HRMS analysis of the reaction of substrate **1a** and ethyl 2-cyanoacetate is summarized in the Supporting Information.

DOI: 10.1021/acs.orglett.5b00523
Org. Lett. 2015, 17, 1746−1749