ORGANIC LETTERS

2010
Vol. 12, No. 2
356−359

Sulfur-Assisted Five-Cascade Sequential Reactions for the Convenient and Efficient Synthesis of Allyl Thiophen-2-yl Acetates, Propionates, and Ketones

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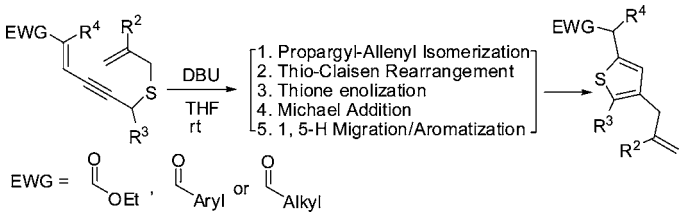
Received November 22, 2009

ABSTRACT



A sulfur-assisted five-cascade sequential reaction, wherein the in situ-generated allenyl allyl sulfides undergo thio-Claisen rearrangement, intramolecular Michael addition, and 1, 5-proton migration/aromatization to obtain allyl thiophen-2-yl acetates, propionates, and ketones as the final products, was reported. As a result of the ready availability of starting materials and the extremely simple and convenient operation, this type of reaction presented here has potential utility in organic synthesis. Application of this efficient method for the synthesis of potentially pharmaceutical compounds also might be useful for the pharmacists.

The preparation of polyfunctionalized heterocyclic compounds has been of interest for the organic community over the past half century. In this regard, thiophene-based compounds are considered an important class due to their intrinsic properties such as drug activity, wide range of photobiological activity, luminescence, redox activity, and electron transport.[1,2] 2-(Thiophen-2-yl)acetic acids and propanoic acids, as members of aryl acetic acids and propanoic acids, play a role in the nonsteroidal anti-inflammatory drug class. A famous example is Tiaprofenic acid, which is used to treat pain, especially arthritic pain (Figure 1).

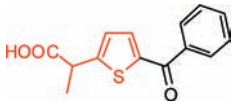


Figure 1. The structure of tiaprofenic acid.

Thio-Claisen rearrangement (TCR), classically a [3,3] sigmatropic rearrangement in the allyl vinyl sulfides leading to a homoallyl thiocarbonyl unit, has received considerable attention since its first appearance in the literature.[3,4]

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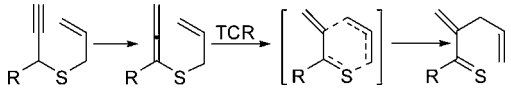
10.1021/ol902690h
Published on Web 12/10/2009

However, due to the instability of thials and thiones, most of the reports about TCR focused on the access to thioamides and dithioesters.[5] Although less attention was paid, the thials and thiones having an α-proton could be used as useful "Michael attackers" via the thermodynamically stable enethiols. Thus, the appropriate substrate design may allow the thione as an intermediate, which is trapped in situ by an intramolecular electrophile.

Sulfur-assisted propargyl-allenyl isomerization has been a useful and efficient method to thio-allenes.[6,7] The allene moiety could be thought of as an "activated olefin", which generally enhances the diversity of the reaction possibility compared with that of a normal olefin. Thus, it is hypothesized that the allenyl allyl sulfides should undergo TCR more smoothly than allyl vinyl sulfides, giving allyl-enethiones as the intermediates (Scheme 1).

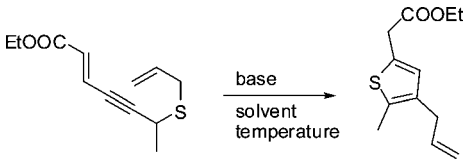
Scheme 1



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.[8,9] However, the complexity and diversity of the sequential reaction increases with the number of cascades, which offers a more challenging and exquisite task for organic chemists bent on reaction design. Herein we wish to report a sulfur-assisted five-cascade sequential reaction, wherein the in situ-generated allenyl allyl sulfides undergo thio-Claisen rearrangement, leading to 2-allyl-2-ene-thiones. That rearrangement is followed by a thione enolization, an intramolecular Michael addition, and 1,5-proton migration/aromatization to give allyl thiophenes as the final products.

As a first attempt, we chose ethyl 6-(allylthio)hept-2-en-4-ynoate (**1a**)[10] as the starting material and initiated our study by testing the reaction of **1a** in the presence of various bases and examining the solvent effect. Weak bases such as triethylamine or K_2CO_3 could not trigger the reaction whereas strong bases such as *t*-BuOK or EtONa gave an unidentified mixture. DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and DBN (1,5-diazabicyclo[4.3.0]non-5-ene.) were suitable options and gave ethyl 2-(4-allyl-5-methylthiophen-2-yl)acetate (**2a**) as the product in acceptable yields at room temperature. Further study showed that there were only slight solvent and temperature effects (Table 1).

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



1a **2a**

entry	base	solvent	temp (°C)	yield of **2a** (%)[b]
1	Et_3N	THF	reflux	NR
2	Et_3N	toluene	reflux	NR
3	K_2CO_3	THF	reflux	NR
4	K_2CO_3	toluene	reflux	NR
5	*t*-BuOK	THF	rt	unidentified mixture
6	EtONa	THF	rt	unidentified mixture
7	DBN	toluene	rt	36
8	DBN	THF	rt	48
9	DBU	toluene	rt	42
10	DBU	THF	rt	63
11	DBU	1,4-dioxane	rt	55
12	DBU	Et_2O	rt	46
13	DBU	THF	50	52

[a] Conditions: substrate **1a** (0.5 mmol) and base (0.6 mmol) in solvent (2 mL) under a N_2 atmosphere. [b] Isolated yields.

Inspired by this result, we examined the scope of the reaction and obtained allyl thiophenes in moderate to good yields under mild conditions (Table 2).

As shown in Table 2, the substituent group R^3 must have an α-proton, which allows the enolization of the intermediate enethione to enethiol. Thus, starting materials with no substituent, or *tert*-butyl and phenyl group on R^3 cannot reach the expected products (entries 22−24).

It is notable that a substituent at C3 of the allyl group prevents the reaction, probably because the transition state of the key step (TCR) is sensitive to steric hindrance (Scheme 2).

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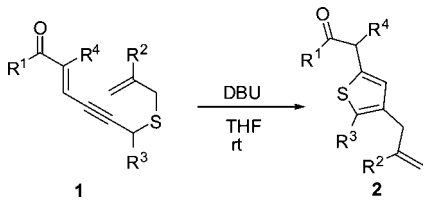
(10) The substrates (**1a**−**u**) could be easily prepared via a Sonogashira reaction with iodoethenes (**3**) and allyl propargyl sulfanes (**4**) as the materials: to a solution of **3** (2.0 mmol) and **4** (2.4 mmol) in 10 mL of THF were added CuI (10 mg. 0.05 mmol) and $PdCl_2(PPh_3)_2$ (35mg, 0.05mmol), then 1 mL of diisopropylamine under N_2 atmosphere was added at room temperature for 1 h. The reaction mixture was quenched with water, extracted with Et_2O, and dried over anhydrous Na_2SO_4. After evaporation of the Et_2O, chromatography on silica gel (eluent: EtOAc/petroleum ether = 1:20) of the crude product afforded **1**, generally in a yield higher than 80%.

Table 2. Synthesis of Allyl Thiophenes[a]



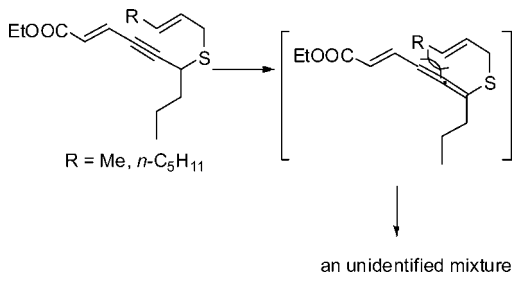
1 2

entry	R^1	R^2	R^3	R^4	yield of **2**[b]
1	OEt	H	Me	H	**2a** (63%)
2	Ph	H	Me	H	**2b** (68%)
3	Ph	H	*n*-Pr	H	**2c** (65%)
4	*n*-Pr	H	Me	H	**2d** (60%)
5	*n*-Pr	H	*n*-Pr	H	**2e** (70%)
6	OEt	Me	Me	H	**2f** (73%)
7	Ph	Me	Me	H	**2g** (62%)
8	*n*-Pr	Me	Me	H	**2h** (71%)
9	OEt	Me	*n*-Pr	H	**2i** (80%)
10	Ph	H	Me	Me	**2j** (62%)
11	OEt	Me	Me	Me	**2k** (65%)
12	4-Cl-C_6H_4	Me	*n*-Pr	H	**2*l*** (63%)
13	4-Me-C_6H_4	Me	*n*-Pr	H	**2m** (78%)
14	OEt	Ph	Me	H	**2n** (68%)
15	4-Me-C_6H_4	Ph	Me	H	**2o** (66%)
16	4-Me-C_6H_4	Me	Me	H	**2p** (62%)
17	Ph	Me	*n*-Pr	Me	**2q** (80%)
18	4-Cl-C_6H_4	Ph	Me	H	**2r** (60%)
19	Ph	Ph	Me	Me	**2s** (66%)
20	*t*-Bu	Ph	Me	H	**2t** (63%)
21	OEt	Ph	Me	Me	**2u** (62%)
22	OEt	Me	H	H	0
23	OEt	Me	*t*-Bu	H	0
24	Oet	Me	Ph	H	0

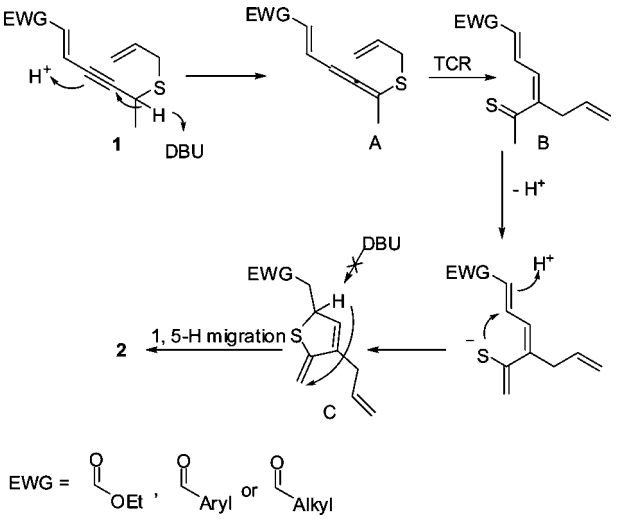
[a] Standard conditions: **1** (0.5 mmol) and DBU (0.6 mmol) in THF (2 mL) at room temperature for 1 h under a N_2 atmosphere. [b] Isolated yields.

We propose a plausible pathway as shown in Scheme 3. At first **1**, via a propargyl-allenyl isomerization in the presence of DBU, gives intermediate **A**,[7c] which undergoes a TCR to afford enethione **B**. Then the enethiol anion via deprotonation of the α-proton of the enethione (**B**) undergoes an intramolecular Michael addition, giving the intermediate 5-methylene-2,5-dihydrothiophene (**C**). In the intermediate (**C**), a 1,5-proton migration occurs to finish the last step: aromatization to afford **2**.

Scheme 2. The Influence of Substituent at C3 of the Allyl Group

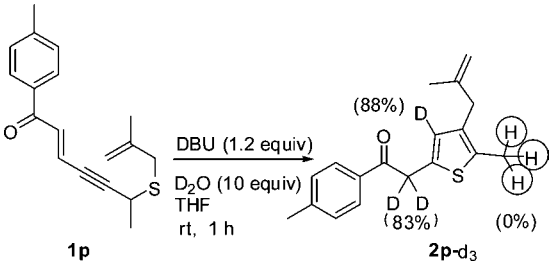


Scheme 3. Proposed Mechanism



Further control experiments conducted might be helpful for supporting this pathway. We treated **1p** with 1.2 equiv of DBU and 10 equiv of D_2O in 2 mL of THF at room temperature for 1 h (compared with entry 16) and obtained deuterated **2p**. However, only the protons of the thiophene ring and the α-carbon of the carbonyl group were deuterated and the protons on the methyl group adjacent to the thiophene ring were not exchanged, demonstrating that the intermediate (**C**) experiences a 1,5-proton migration, instead of the deprotonation−aromatization on C2 in the presence of DBU (Scheme 4).

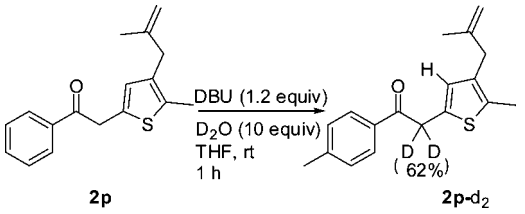
Scheme 4. Control Experiment



Unlike the α-protons of the carbonyl group, the thiophene proton of **2p**, due to the very weak acidity, could not undergo H−D exchange after the completion of the reaction. Treatment of **2p** under the same conditions as shown in Scheme 4 gave a product undeuterated on the thiophene ring, showing that the deuteration on the thiophene ring occurs in the step of propargyl-allenyl isomerization through the deprotonation by DBU (Scheme 5).

In summary, we developed a sulfur-assisted five-cascade sequential reaction for the synthesis of allyl thiophen-2-yl acetates, propionates, and ketones. As a result of the ready availability of starting materials and the extremely simple

Scheme 5. Control Experiment



and convenient operation, this type of reaction presented here has potential utility in organic synthesis. Application of this efficient method for the synthesis of potentially pharmaceutical compounds also might be useful for pharmacists.

Acknowledgment. This paper is dedicated to Prof. John Warkentin on the occasion of his 80th birthday. Financial support was received from the Natural Science Foundation of China (Nos. 20702046 and 20972134) and the Natural Science Foundation of Zhejiang Province (R405066).

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

OL902690H