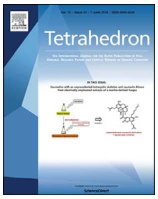
Tetrahedron 74 (2018) 2876–2883

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet



Divergent synthesis of functionalized thioethers via multicomponent reaction of benzynes

Hui Jian, Qiang Wang, Wei-Hua Wang, Zhi-Juan Li, Cheng-Zhi Gu, Bin Dai, Lin He*

Key Laboratory for Green Processing of Chemical Engineering of Xinjiang Bingtuan, School of Chemistry and Chemical Engineering, Shihezi University, Xinjiang Uygur Autonomous Region 832000, People's Republic of China

A R T I C L E I N F O

Article history:
Received 3 February 2018
Received in revised form
18 April 2018
Accepted 21 April 2018
Available online 24 April 2018

Keywords:
Benzyne
Thioether
Multicomponent reaction

A B S T R A C T

Diverse functionalized thioethers were efficiently synthesized through the multicomponent reaction of benzynes, cyclic thioethers and different nucleophiles. Both inorganic salts (KF, KCl, KBr, and KSCN) and silylated reagents (TMSCN, $TMSN_3$, TMSCl) can be utilized as efficient nucleophiles for the reaction.

1. Introduction

Thioethers are privileged motifs found in many natural products, biologically active compounds and pharmaceuticals.[1] Over the past several decades, considerable efforts have been exerted to develop new methodologies for the synthesis of these significant frameworks. Several different strategies,[2] such as transition metal catalyzed cross-coupling reaction and hydrothiolation, organocatalytic sulfa-Michael reaction and sulfenylation reaction, have been well established for the construction of thioethers. Despite remarkable progress made in this research field, the development of efficient protocols for the synthesis of thioethers that bearing some specific functional groups, such as fluorine atom[3] and cyano group,[4] is still lacking.

Benzynes are highly reactive intermediates that are utilized widely in organic synthesis.[5] The electrophilic benzyne can undergo N-, O-, C-insertion with different nucleophiles and trigger a broad variety of transformations.[6] However, reactions initiated by S-insertion of benzyne are very limited. Recently, Studer[7] and coworkers reported that the linear vinyl thioethers can react with benzyne through [3 + 2] cycloaddition to form cyclic sulfonium ylide, and after proton transfer and β-elimination reaction, afford trisubstituted alkenes. Subsequently, through the S-insertion of linear thioethers and benzyne, Xu[8] and co-workers developed a novel method to generate sulfonium ylide, which can be intercepted by isatin to form spiroepoxy oxindoles in high yield. Tan, Xu[9] and co-workers further extended the study to allyl and propargyl thioethers, which can undergo [2,3] sigmatropic rearrangement with benzyne through sulfonium intermediate. Very recently, Tan, Xu[10a], Hoye[10b] and their co-workers reported independently that benzynes can undergo multicomponent reaction with cyclic thioethers and different acidic proton-containing nucleophiles, such as acetic acid, phenol and amide, to give the ring-opening products. As part of our ongoing project,[11] we envisaged that the S-arylation of cyclic ethers can lead to the formation of sulfonium intermediate, which can undergo ring-opening reaction with different nucleophiles to produce various functionalized thioethers. And herein, we wish to report this result.

2. Results and discussion

We initiated our studies with the commercially available Kobayashi's reagent[12] **1a** and tetrahydrothiophene **2a**. To our delight, with 3.0 equiv KF/18-crown-6 and 2.0 equiv H_2O as additives, benzyne reacted with tetrahydrothiophene and fluoride anion smoothly at room temperature in THF to produce the fluorinated thioether **3a** in 59% yield (Table 1, entry 1). However, when H_2O was excluded from the same reaction conditions, only a small amount of product was formed (Table 1, entry 2). Used 2.0 equiv ethanol as the additive, the product can be obtained in 45% yield

---

* Corresponding author.
E-mail address: helin@shzu.edu.cn (L. He).

https://doi.org/10.1016/j.tet.2018.04.072
0040-4020/© 2018 Elsevier Ltd. All rights reserved.

Table 1
Optimization of reaction conditions.[a]

Entry	Additives	Solvent	Time (h)	Yield (%)[b]
1	KF (3 equiv), 18-C-6 (3 equiv), H_2O (2 equiv)	THF	12	59
2	KF (3 equiv), 18-C-6 (3 equiv)	THF	12	<10
3	KF (3 equiv), 18-C-6 (3 equiv), EtOH (2 equiv)	THF	12	45
4	KF (3 equiv), 18-C-6 (3 equiv), H_2O (2 equiv)	CH_3CN	12	58
5	KF (3 equiv), 18-C-6 (3 equiv), H_2O (2 equiv)	DCM	12	76
6	KF (3 equiv), 18-C-6 (3 equiv), H_2O (2 equiv)	DCE	12	64
7	KF (3 equiv), 18-C-6 (3 equiv), H_2O (2 equiv)	toluene	12	<10
8	CsF (3 equiv), 18-C-6 (3 equiv), H_2O (2 equiv)	DCM	12	72
9	TBAF (3 equiv), H_2O (2 equiv)	DCM	12	60
10	TBAT (3 equiv), H_2O (2 equiv)	DCM	12	72
11	CsF (3 equiv), H_2O (2 equiv)	THF	24	<10
12	KF (3 equiv), H_2O (2 equiv)	THF	24	<10
13[c]	KF (3 equiv), 18-C-6 (3 equiv), H_2O (2 equiv)	THF	12	70
14	KF (3 equiv), 18-C-6 (3 equiv), H_2O (1 equiv)	DCM	12	51
15	KF (3 equiv), 18-C-6 (3 equiv), H_2O (3 equiv)	DCM	12	70

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), solvent 1 mL, room temperature.
[b] Isolated yield.
[c] **2a** (0.5 mmol).

(Table 1, entry 3). A brief screening of the reaction media revealed that DCM was the best choice with respect to the reaction yield (Table 1, entries 4–7). Other fluoride sources, such as CsF/18-crown-6, TBAF and TBAT can also promote the reaction in good yield (Table 1, entries 8–10). In the absence of the crown ether, KF or CsF can only promote the reaction in very low efficiency (Table 1, entries 11 and 12). Increasing the amount of tetrahydrothiophene to 5.0 equiv cannot improve the reaction yield (Table 1, entry 13). Neither reducing the amount of water to 1.0 equiv nor increasing to 3.0 equiv can improve the yield (Table 1, entries 14 and 15).

With the optimal reaction conditions in hand (Table 1, entry 5), the generality of the reaction was subsequently studied and the results are summarized in Table 2. Symmetrical benzynes with electron-donating or withdrawing groups efficiently undergo the multicomponent reaction to produce the desired products in moderate to good yields (Table 2, entries 1–4). On the other hand, unsymmetrical benzynes can also react with **2a** and KF smoothly, affording the corresponding products as an inseparable mixture of two regioisomers in good yield (Table 2, entries 5–8). Notably, when unsymmetrical 3-methoxy substituted benzyne precursor **1i** was employed for the reaction, the fluorinated product **3i** was obtained in 78% yield with complete regioselectivity (Table 2, entry 9).[13] Thietane **2b** was proved to be a good candidate for the reaction, providing **3j** in 74% yield (Table 2, entry 10). However, when thiane was used for the reaction, **3k** was only obtained in 28% yield (Table 2, entry 11). Different inorganic salts, such as KCl, KBr and KSCN were also proved to be competent nucleophiles for the reaction, giving chloro-, bromo- and thiocyanate-substituted thioethers in good to high yields (Table 2, entries 12–14).

Surprisingly, under the same reaction conditions, thiirane reacted with benzyne to provide vinyl thioether **4a** in 75% yield, and no fluorinated product was obtained (Scheme 1, eq (1)). We postulated that the high ring strain of the three-membered cyclic sulfonium leads to very fast intramolecular β-elimination and resulted in the formation of the vinyl thioether products.[14] More interestingly, when α-methyl substituted tetrahydrothiophene **2e** was used for the reaction, a similar β-elimination reaction was observed and vinyl thioehters **4b** and **4c** were obtained as an inseparable mixture of 5:1 regioisomers in 72% total yield (Scheme 1, eq (2)).

Silylated reagents such as trimethylsilyl cyanide, Ruppert–Prakash reagent and trimethylsilyl azide are important nucleophiles in organic synthesis. We subsequently explored the multicomponent reaction of benzynes, cyclic thioethers and different silylated nucleophiles. When trimethylsilyl cyanide (**5**a) was used as a nucleophile and the reaction was conducted in THF, the desired thioether **6a** was obtained in 89% yield (Table 3, entry 1). Electron-donating groups substituted benzynes gave higher yield than those bearing electron withdrawing substituents (Table 3, entries 2–5). Unsymmetrical benzynes underwent the reaction efficiently to deliver the corresponding cyanated products as an inseparable mixture of two regioisomers (Table 3, entries 6–9). Once again, **1i** provided the desired product with complete regioselectivity (Table 3, entry 10). Both thietane and thiane reacted very well, giving the corresponding products **6k** and **6l** in 90% and 88% yields, respectively (Table 3, entries 11 and 12). α-Methyl tetrahydrothiophene underwent the reaction smoothly to afford **6m** in 72% yield and no β-elimination product was formed (Table 3, entry 13). Trimethylsilyl azide and trimethylsilyl chloride were also proved to be suitable reactants for the reaction, producing the corresponding functionalized thioethers in high yields (Table 3, entries 14–17). However, other silylated reagents, such as the Ruppert–Prakash reagent and (difluoromethyl)trimethylsilane didn't afford the desired product under the same reaction conditions (Table 3, entries 18 and 19). Interestingly, thiirane underwent a β-elimination reaction to give vinyl thioether **4a** in good 66% yield under the same reaction conditions (Table 3, entry 20).

Based on the pioneering work of Tan, Xu[10a] and Hoye,[10b] a plausible mechanism was proposed and depicted in Scheme 2. Tetrahydrothiophene undergoes nucleophilic addition with benzyne to form zwitterion species **I**, and after 1,4-proton shift, to form the unstable cyclic sulfonium ylide **II**. The intermediate **II** gets a proton from water to give species **III**, and after the following nucleophilic attack of the fluorine anion, to produce the final product.

3. Conclusions

In summary, a multicomponent reaction of benzynes, cyclic thioethers and non-proton containing nucleophiles has been described. The transition-metal free conditions, simple procedure and divergent nucleophiles provide a new methodology for the synthesis of functionalized thioethers.

4. Experimental section

4.1. General experimental methods

Unless otherwise indicated, all reactions were conducted under nitrogen atmosphere in oven-dried glassware with magnetic