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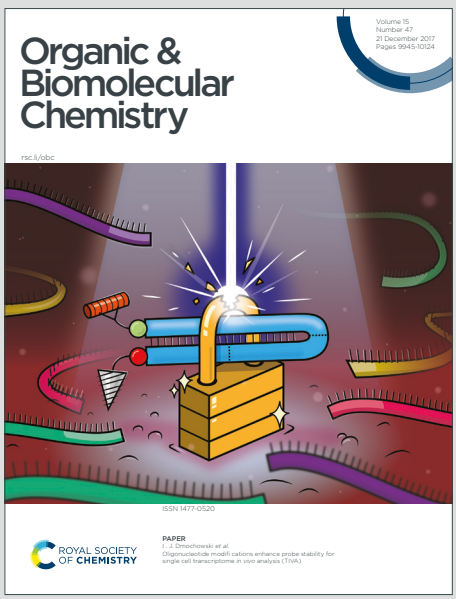

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(*Z*)-Tetrahydrothiophenes and (*Z*)-Tetrahydrothiopyrans Synthesis through Nucleophilic Substitution and Intramolecular Cycloaddition of Alkynyl Halide and $EtOCS_2K$

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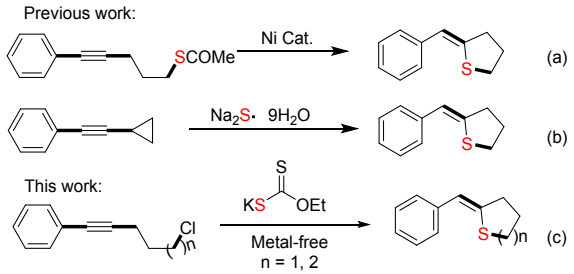
This protocol provides a novel, environmentally friendly and simple method for synthesis of (*Z*)-tetrahydrothiophene derivatives using the nucleophilic thiyl radical intramolecular cycloaddition cascade process to construct C–S bonds under transition-metal-free. This transformation process offers a broad substrate scope, good functional group tolerance, and excellent stereoselectivity (*Z/E* ratios up to 99/1). Moreover, the process uses odourless, stable and cheap $EtOCS_2K$ as the sulfur source.

Sulfur is increasingly occurring in the structures of modern medicines because sulfur compounds exhibit various valence states and rich stereoscopic conformations. Sulfides with the same or similar skeletons and different valence states may exhibit different physiological activities. Tetrahydrothiophenes are versatile structural scaffolds found widely throughout the synthesis of natural products,[1] biological sensors,[2] materials chemistry,[3] organocatalysts[4] and reaction intermediates.[5] Over the past decade, the development of efficient methodologies for the synthesis of tetrahydrothiophene skeletons has attracted considerable interest in synthetic ch emistry. Ozaki and co-workers proposed a straightforward approach which synthesizes cyclic sulfides using the Ni-catalysed electroreduction of unsaturated thioacetates and thiosulphonates (Scheme 1, a).[6] The tetrahydrothiophene derivatives can also be synthesized through conversion to the corresponding alkynyl thiouronium salts by treatment with hydroxide *via* intramolecular *trans* addition to the acetylenic linkage.[7] Recently, Ji and co-workers proposed a simple strategy to construct tetrahydrothiophene derivatives using a [1+3+1] cycloaddition reaction with cyclopropyl alkyne and $Na_2S{\cdot}9H_2O$ (Scheme 1, b).[8] It is worth noting that Scanlan and co-workers developed a novel intramolecular thiol-yne ionic and radical mediated cyclisation strategy for the synthesis of thioglycals.[9a] Photolysis of acetylenic thiols tends to provide thiacycloalkanes with different numbers in the ring and has some problem that acetylenic thiols are unstable and polimerize even at low temperature conditions.[9b] However, some of these methods have the disadvantages of low yields, poor selectivity, multistep reaction sequences and requirements for metal catalysts.

Scheme 1 The major pathways for the synthesis of tetrahydrothiophene derivatives.



Jiang and co-workers use the green reagent to adjust the nature of free radicals by using the "masked strategy" and achieve selective sulfoxide and thioetherification.[10] Despite the existence of numerous techniques for the synthesis and derivatization of sulfur-containing organic skeletons and heterocycles, the development of novel, odourless and efficient strategy is still very important. Xanthates are attractive starting materials in chemistry transformations due to their high reactivity and availability; they are readily prepared from inexpensive alcohols and carbon disulphide.[11] Xanthates and related derivatives are particularly convenient precursors for a variety of radicals that can be captured in both inter- and intramolecular fashions.[12] Xanthates can also be used as a sulfur source for the introduction of sulfur atoms into organic molecules and for formation of sulfur-containing heterocycles.[13] Our group developed a series of methods for synthesis of heterocyclic compounds, in which thiol was formed as reaction intermediate. [14a-c] In addition, xanthate was used for the key mediated synthesis of (*E*)-alkenes through semi-hydrogenation of alkynes.[14d] Recently, we reported an NH_4I-promoted and H_2O-controlled intermolecular bis-sulfenylation and hydroxysulfenylation of alkenes *via* a radical process.[14e] Herein, we developed a transition-metal-free radical mediated cyclisation strategy for the synthesis of (*Z*)-tetrahydrothiophene derivatives in which thiyl radical is produced in situ from xanthates and acts as an active intermediate.

Initially, 1-(5-chloropent-1-ynyl) benzene was selected as a model substrate for the optimization of the reaction conditions

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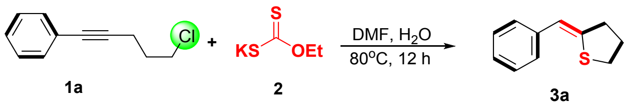
(Table 1). The screening of various sulfur sources revealed that the sources played a very important role in this cyclisation process. Different sulfur sources, including $Na_2S{\cdot}9H_2O$, $C_6H_{12}CuN_2S_4$, S_8, thiourea, $C_5H_{14}N_2S_2$, $C_3H_6NNaS_2{\cdot}2H_2O$ and $EtOCS_2K$, were tested in this reaction (Table 1, entries 1-8). The results indicated that $EtOCS_2K$ was the superior sulfur source, with a product yield of 95% (Table 1, entry 8). The continued screening of various solvents revealed that DMF was the superior solvent (Table 1, entries 8-12). The reaction was most efficient when it was conducted at 80 °C, and higher or lower temperatures resulted in lower yields (Table 1, entry 13). By decreasing the amount of $EtOCS_2K$ (1.5 equiv and 1.0 equiv), the yield was reduced to 71% and 55%, respectively (Table 1, entry 14), and only a trace amount of **3a** was detected when the reaction was carried out in dry DMF (anhydrous conditions) (Table 1, entry 15). The sulfur cyclisation reaction was not affected under oxygen atmosphere condition (Table 1, entry 16). Under N_2 condition, the yield of the sulfur cyclisation reaction is significantly affected (Table 1, entry 17). Therefore, the optimal reaction conditions were **1a** (0.5 mmol) and $EtOCS_2K$ (1.0 mmol) in DMF (2.0 mL) at 80 °C for 12 h (Table 1, entry 8).

Table 1 Optimization of reaction conditions[a]

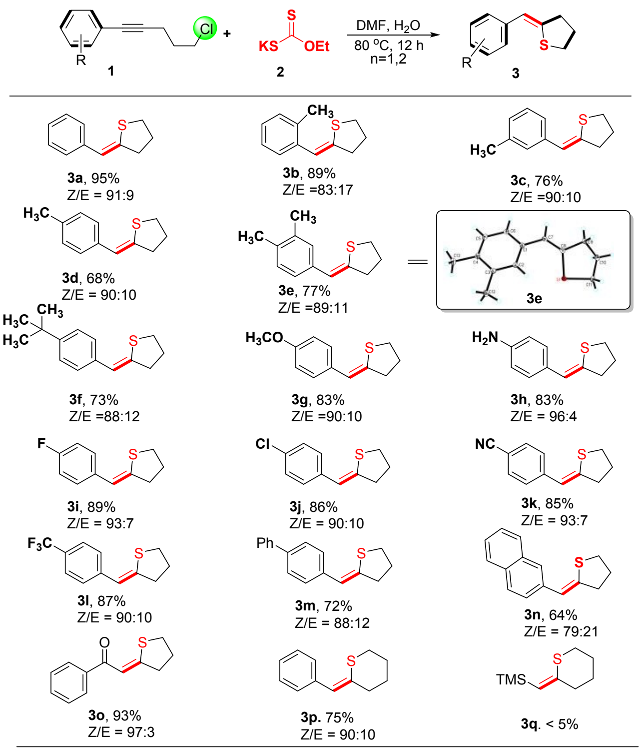


Entry	Sulfur source	Solvent	Yield [b] (%)
1	$Na_2S{\cdot}9H_2O$	DMF	11
2	$C_6H_{12}CuN_2S_4$	DMF	n.r.
3	S_8	DMF	n.r.
4	thiourea	DMF	trace
5	thioacetamide	DMF	trace
6	$C_5H_{14}N_2S_2$	DMF	n.r.
7	$C_3H_6NS_2Na{\cdot}2H_2O$	DMF	n.r.
8	$EtOCS_2K$	DMF	95
9	$EtOCS_2K$	DMSO	8
10	$EtOCS_2K$	DMAc	67
11	$EtOCS_2K$	CH_3CN	16
12	$EtOCS_2K$	H_2O	< 5
13[c]	$EtOCS_2K$	DMF	(8, 62, 75)
14[d]	$EtOCS_2K$	DMF	(71, 55)
15[e]	$EtOCS_2K$	DMF	trace
16[f]	$EtOCS_2K$	DMF	93
17[g]	$EtOCS_2K$	DMF	72

[a] Reaction conditions: alkyne **1** (0.5 mmol), sulfur source (1.0 mmol) in solvent (2.0 mL) and H_2O (5 mmol, normal distilled water) at 80 °C for 12 h; [b] Isolated yields; [c] Yields were with respect to the temperatures at 40 °C, 60 °C and 100 °C, respectively; [d] $EtOCS_2K$ (0.75 mmol, 0.5 mmol) was used; [e] Anhydrous DMF (2 mL); [f] under O_2 (1atm) atmosphere; [g] under N_2 atmosphere. $C_6H_{12}CuN_2S_4$ = Bis(dimethylcarbamodithioato-S,S') copper, $C_3H_6NS_2Na{\cdot}2H_2O$ = *N,N*-Dimethyldithiocarbamate sodium salt.

With the optimized reaction conditions in hand, we turned our attention to the sulfur cyclisation reaction by varying alkynyl halide components (Scheme 2). Both electron-donating and withdrawing substituents on the benzene rings were compatible under the standard conditions and enabled conversion to the corresponding (*Z*)-tetrahydrothiophene products. Electron-donating groups, such as -Me, -*t*Bu, -OMe, also successfully enabled sulfur cyclisation (Scheme 2, **3a–3g**, 68%–95% yield). The structure of **3e** was further investigated using single-crystal XRD analysis (CCDC no. 1881760). Moreover, a number of electrons withdrawing substituents on the aryl rings, including –F, –Cl, –CN, –NO_2 and –CF_3, could be employed to produce the corresponding products in good yields **(3i-3l)**. Next, when 6-chloro-1-phenylhex-2-yn-1-one was employed as the substrate, the expected sulfur cyclisation product **3o** was obtained in 93% yield. It should be noted that (6-chlorohex-1-yn-1-yl)benzene bearing four methylene units was compatible with the reaction protocol (shemee 2,**3p**). Unfortunately, the reaction of terminal alkynes and silyl-substituted alkynes, such as 5-chloropent-1-yne and (5-chloropent-1-yn-1-yl)trimethylsilane, produced a mixture of products (Scheme 2, **3q**).

Scheme 2 Synthesis of (*Z*)-2-benzylidene tetrahydrothiophene derivatives.[a]



[a] Reaction conditions: alkyne **1a** (0.5 mmol), $EtOCS_2K$ (1.0 mmol) in DMF (2.0 mL), H_2O (5 mmol.) at 80 °C for 12 h; [b] Isolated yields; [C] the Z/E ratio was detected by GC-MS.

To continue our investigation of the reaction scope, we explored various pyridine-based substrates for this process under the optimized reaction conditions (Scheme 2). Overall, it was found that most of the substrates could be converted to the corresponding (*Z*)-tetrahydrothiophene products in good to excellent yields with excellent stereoselectivity. Furthermore, when the pyridine ring was substituted at the ortho-, meta-, and para-positions, the yields were not affected (Scheme 2, **3r-3t**). These results show that the sulfur cyclisation reaction is not affected by electron-withdrawing or -donating substituents on the pyridine ring and that the desired product can be successfully obtained. In addition, the bromine-substitution on the ortho- or meta-pyridine was well tolerated, resulting in good yields of 84% and 80%, respectively (Scheme 2, **3w-3x**). It is important to note that the heterocyclic compounds, including quinoline (**3z**), thiophene (**3aa**) and pyrazole (**3ab-3ac**) derivatives, produced good yields. Finally, the six-membered cyclic tetrahydro-2H-thiopyran compounds **3ac** and **3ad** were successfully produced (88% and 87% yield, respectively), by 6-*exo-dig* cyclization in our sulfur cyclisation protocol.

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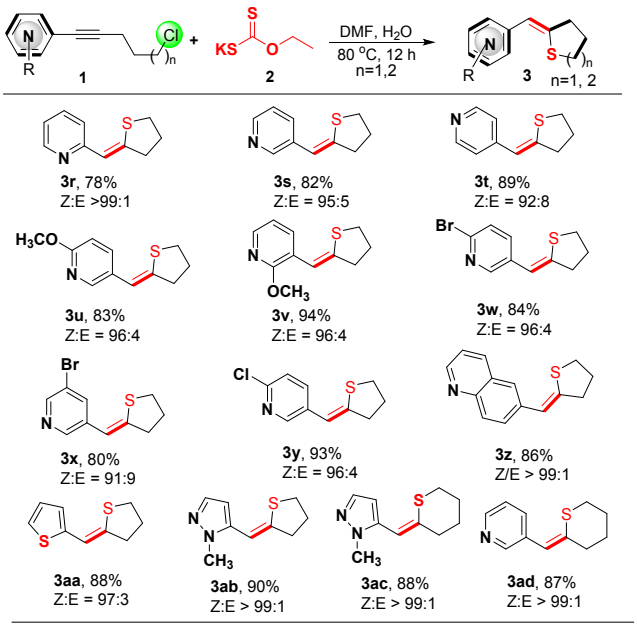
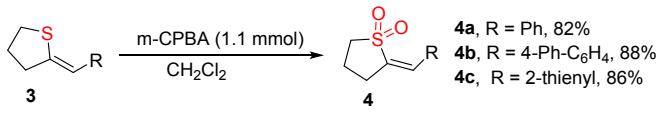
Scheme 3 Substrate scope of alkynyl halides.[a]



[a] Reaction conditions: alkyne **1a** (0.5 mmol), $EtOCS_2K$ (1.0 mmol) in DMF (2.0 mL) and H_2O (5 mmol) at 80 °C for 12 h; [b] Isolated yields; [c] the Z/E ratio was detected by GC-MS.

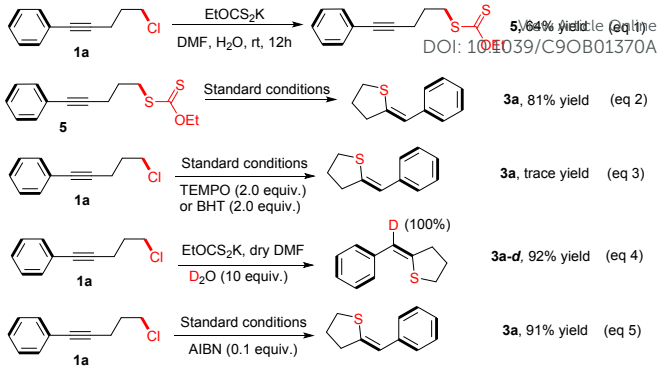
To further develop the methodology, the oxidation of tetrahydrothiophenes was performed to produce sulfone derivatives. Several selected compounds (**3a**, **3m** and **3x**) were treated with *m*-CPBA in CH_2Cl_2 at room temperature for 48 h, producing sulfone derivatives in good yields (Scheme 4).[15] In addition, 2-((dihydrothiophen-2(3*H*)-ylidene)methyl)thiophene (**3x**) contains two sulfur atoms, whereas oxidation occurs selectively on the tetrahydrothiophene ring (**4c**).



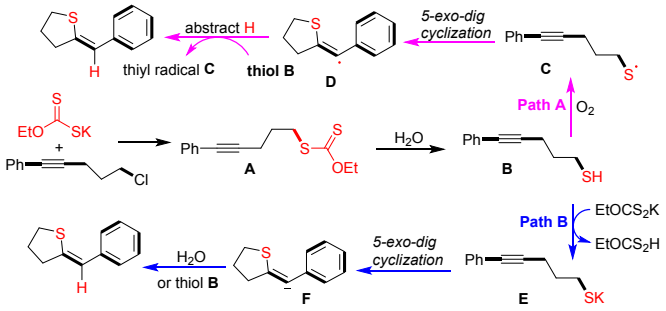
Scheme 4 Oxidation of sulfides to sulphones with m-CPBA.

To gain mechanistic insights into the reaction, several control experiments were conducted (Scheme 5). First, the probable intermediate *O*-ethyl *S*-(5-phenylpent-4-yn-1-yl) carbonodithioate **5** was prepared under mild conditions in moderate yields (Scheme 5, eq 1). Next, the intermediate **5** was successfully converted to the desired product under standard conditions (Scheme 5, eq 2). When the 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylated hydroxytoluene (BHT) were added as radical scavengers, the sulfur cyclisation reaction was cancelled (Scheme 5, eq 3). These results suggest that the present reaction presumably was triggered through a radical pathway. In addition, the reaction of (5-chloropent-1-yn-1-yl)benzene under anhydrous DMF (2 mL) and D_2O (10 equiv.) conditions produced the deuterium products **3a-*d*** in 92% yields, suggesting that water acted as a proton donor in this transformation (Scheme 5, eq 4). The sulfur cyclisation reaction was not affected under radical initiator AIBN condition (Scheme 5, eq 5).

Scheme 5 Control experiments.



The postulated reaction mechanism based on the literature and our control experimental results are depicted in Scheme 6.[8, 16] The sulfur cyclisation reaction is initiated by the nucleophilic substitution of $EtOCS_2K$ to (5-chloropent-1-yn-1-yl)benzene, yielding xanthate **A**, and is followed by the slow hydrolysis of the xanthate **A** to yield thiol **B** with the aid of H_2O and $EtOCS_2K$. Next, the small quantities of thiyl radical **C** were generated by oxidation under oxygen atmosphere. This rapidly cyclizes thiyl radical **C** onto the Csp-Csp triple bonds to produce radical **D**, which abstracts hydrogen (or deuterium) from the thiol to generate the observed product and regenerates thiyl radical **C** to propagate the chain (Scheme 6, Path A). In addition, an ionic chain reaction cannot be excluded, whereby the nucleophilic addition of thiolate **E** (formed by partial deprotonation of the thiol by the xanthate salt) to the Csp-Csp triple bonds yields anion **F**, which is then protonated by water or thiol **B** (Scheme 6, Path B).



Scheme 6 Proposed reaction pathway.

In summary, a simple and efficient method was developed to produce tetrahydrothiophene derivatives using cycloaddition reactions with $EtOCS_2K$ as a thiol precursor under mild reaction conditions. Excellent regioselectivity, excellent functional group compatibility and good to excellent yields were achieved. This intramolecular sulfur cyclisation reaction provides a simple and robust strategy to produce (*Z*)-tetrahydrothiophenes and (*Z*)-tetrahydrothiopyrans for application in pharmaceutical chemistry and organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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