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Thioether-functionalized trifluoromethyl-alkynes, 1,3-dienes and allenes: divergent synthesis from reaction of 2-trifluoromethyl-1,3-conjugated enynes with sulfur nucleophiles†

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A divergent synthesis of thioether-functionalized trifluoromethyl-alkynes, 1,3-dienes and allenes *via* regioselective nucleophilic addition of sulfur nucleophiles to 2-trifluoromethyl-1,3-conjugated enynes was developed. The addition patterns depend on the type of enyne, sulfur nucleophile and reaction conditions used. 1,4-Addition leading to thioether-functionalized trifluoromethyl-allenes was realized when enynes possessing electron-withdrawing aryl groups on the alkyne moiety were used as reaction partners and alkanethiols were used as nucleophiles, whereas solvent-controlled construction of thioether-functionalized 1,3-dienes and alkynes was realized, respectively, *via* a 3,4-addition pattern or 1,2-addition pattern if thiophenols were applied as nucleophiles. The three types of compounds containing both sulfur and fluorine elements are valuable building blocks for synthesis of multifunctional fluorinated vinyl sulfides and thiophene derivatives.

Introduction

Owing to their unique structural properties and reactivity, allene chemistry,[1] alkyne chemistry,[2] as well as 1,3-diene chemistry,[3] have attracted particular attention by chemists in the past few decades. They have proven themselves to be important and valuable building blocks toward complex molecular targets in organic synthesis. As a consequence, substantial efforts have been made over the years by synthetic organic chemists in order to design and develop methods allowing efficient access to a variety of functionalized allenes,[4] alkynes[5] and 1,3-dienes.[6] Meanwhile, the widespread use of fluorinated, especially trifluoromethylated, compounds in pharmaceutical chemistry, agrochemistry[7] and materials science[8] has attracted considerable interest in development of various synthetic methodologies for synthesis of these trifluoromethylated species.[9] In this context, special attention has naturally been brought to trifluoromethyl-allene,[10] alkyne[11] and 1,3-diene[12] building blocks and how to access them.

During the last few years, our research group and others have demonstrated that 2-trifluoromethyl-1,3-conjugated enynes are readily available fluorinated building blocks for the synthesis of fluorinated heterocycles and carboncycles. They could act as four- or two- carbon components in palladium catalyzed intermolecular formal [4 + 2] or [3 + 2] cycloaddition reactions for trifluoromethyl benzenes or exomethylene cyclopentane derivatives synthesis (Scheme 1a).[13] They also could serve as novel electrophiles to react with bisnucleophiles such as hydroxylamine, primary amine, aminomalonate and 1,3-dicarbonyl compounds for various fluorinated heterocycles synthesis such as pyrrole, *N*-hydroxypyrrole, isoxazole, cyclic nitrone, pyrroline, pyrrolidine and fluorinated carboncycles synthesis such as cyclopentene derivatives, *etc.* in transition metal catalysed or simple base mediated cascade reactions (Scheme 1b).[14]

Sulfur-containing compounds (SCCs) have important applications in pharmaceuticals,[15] materials,[16] and foods.[17] Within this context, we became interested in the regioselective nucleophilic addition of sulfur nucleophiles to 2-trifluoromethyl-1,3-conjugated enynes to construct useful building blocks containing both sulfur and fluorine elements, which are both leading constituents of the pharmaceuticals that comprise our medicinal history.[15a] We herein report our investigation toward this aim and found that 1,4-addition leading to thioether-functionalized trifluoromethyl-allenes was realized when enynes possessing electron-withdrawing aryl groups on the

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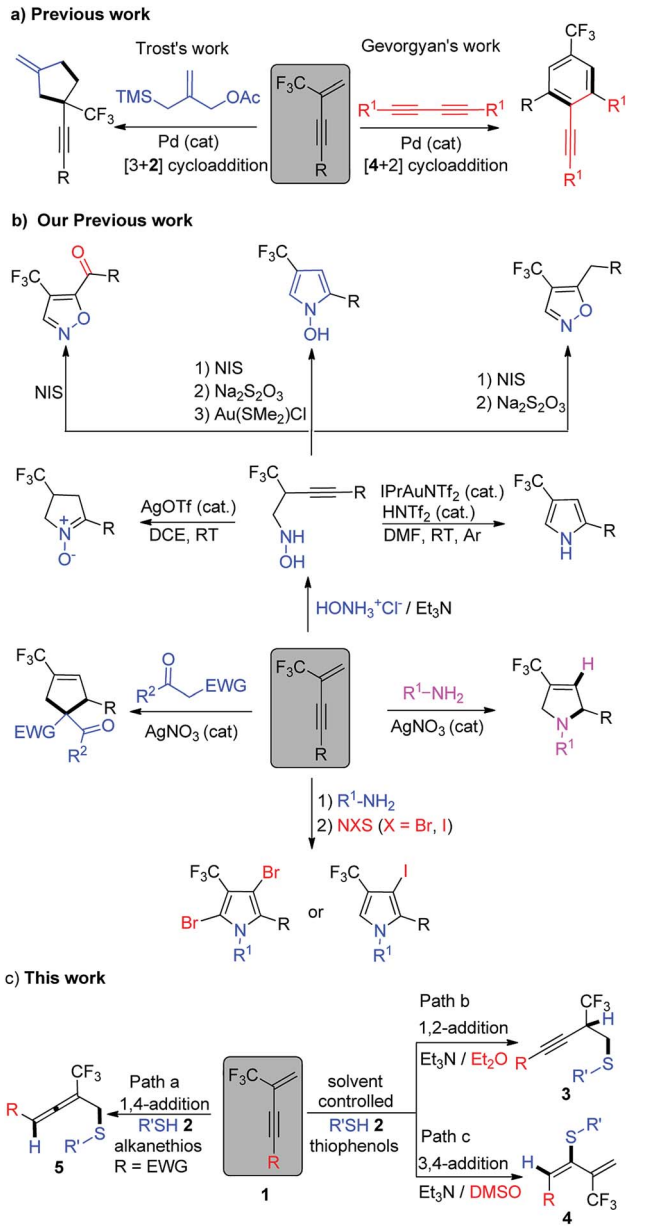

Scheme 1 Divergent synthesis from 2-trifluoromethyl-1,3-conjugated enynes.

alkyne moiety were used as reaction partner and alkanethiols were used as nucleophiles, whereas solvent-controlled construction of functionalized 1,3-dienes and alkynes were realized, respectively, *via* 3,4-addition pattern or 1,2-addition pattern if thiophenols were applied as nucleophiles (Scheme 1c).

Results and discussion

We initiated this project using enyne **1a** and 4-methylthiophenol **2a** as model substrates for screening reaction conditions. Under base free conditions, no reaction occurred, the result prompted us to test base as additives. Considering that the replacement of the alkaline metal ion with ammonium cation formed by deprotonation of hydrosulfuryl of thiophenol will weaken the metalfluorine interaction, thus suppress the defluorination process,[18,19] we choose organic base such as tertiary amine for reaction screening (for detailed reaction conditions screening, please see ESI Table 1†). During our initial screens, we found that two main regioselective nucleophilic adducts, that is, functionalized alkyne **3aa** *via* 1,2-addition pattern and functionalized 1,3-diene **4aa** *via* 3,4-addition pattern were formed, which relied heavily on the solvent and base used. In order to control regioselectivity and to have the optimized reaction conditions for the formation of **3aa** and **4aa**, respectively, extensive optimizations were performed. After many attempts, we were pleased to find that the combination of Et_3N as base and ether as solvent was found to be the optimal reaction conditions for 1,2-nucleophilic addition pattern, and functionalized alkyne **3aa** could be obtained in 77% isolated yield. Interestingly, simply use DMSO instead of ether as solvent invert the regioselectivity to 3,4-nucleophilic addition pattern, and functionalized 1,3-diene **4aa** could be obtained in 80% isolated yield. We hypothesize that thiophenol has a relatively high acidity and is easily ionized with increasing nucleophilicity in a polar solvent with relatively high dielectric constant such as DMSO compared with Et_2O under basic reaction conditions,[20] which facilitate both allene intermediate formation and subsequent stereospecific nucleophilic addition to allene and β-heteroatom elimination tandem process, leading to functionalized 1,3-diene formation.[21]

With the optimal reaction conditions established, the enyne substrate scope as well as thiophenol substrate scope were then examined and demonstrated with sixteen examples for these two regioselective nucleophilic addition patterns, respectively, as shown in Scheme 2. There are several points that are noteworthy: (1) in most cases, the reactions are solvent-controlled regioselectivity, functionalized alkynes **3** and 1,3-dienes **4** are two predominate adducts while the amount of the allene **5** is negligible, which accounts for the mass balance; (2) in one case for synthesis of functionalized alkynes **3ha**, enyne **1h** bearing strong electron-withdrawing group such as nitro group in *para*-position of the benzene ring on the alkyne moiety exhibits substrate-controlled regioselectivity and allene **5ha** is formed predominately (61% isolated yield); (3) enynes **1e**, **1f** bearing relatively weakly electron-withdrawing group such as acyl, nitrile group afford functionalized alkynes **3ea**, **3fa** in 22%, 33% isolated yield along with the formation of 1,3-butadiene **4ea** and **4fa** in 60%, 52% isolated yield, respectively; (4) in most cases, both enyne and thiophenol show good functional groups tolerance for 3,4-nucleophilic addition pattern, and good to excellent yields of the 1,3-butadiene products could be obtained with high stereoselectivity, most of addition products were observed as single double bond *E*-isomers (**4aa–4da**, **4ia–4ja**, **4ab–4ag**), and (5) the structure of compound **4ag** was further confirmed by means of single-crystal X-ray crystallography (Fig. 1);[22] (6) owing to its insolubility in ether, 4-nitrobenzenethiol **2g** failed to afford corresponding alkyne **3ag** in ether, however, it reacts well with enyne **1a** in DMSO to afford corresponding 1,3-diene **4ag** in 84% isolated yield.

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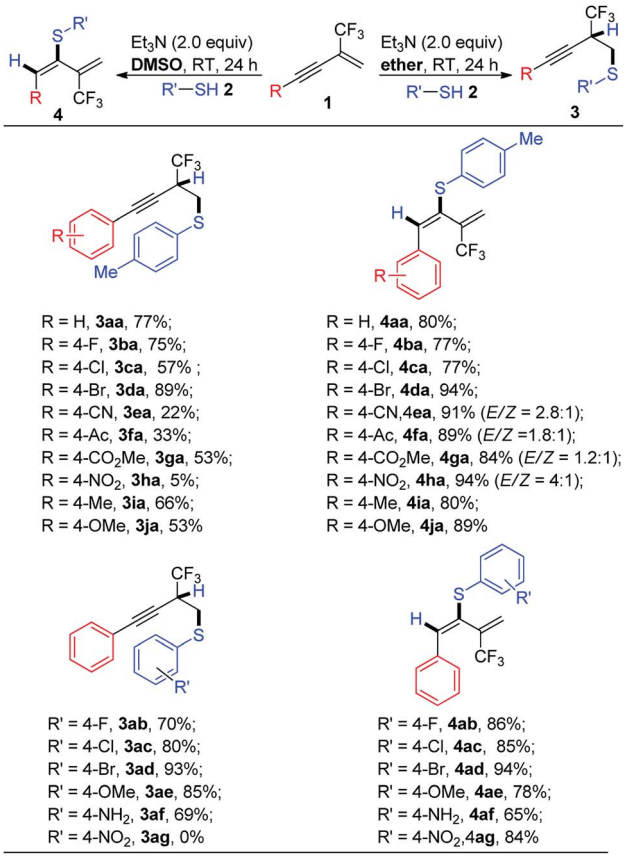


Scheme 2 Scope of 2-trifluoromethyl-1,3-enynes **1** and thiophenols **2** for synthesis of thioether-functionalized trifluoromethyl-alkynes **3** and 1,3-dienes **4**.

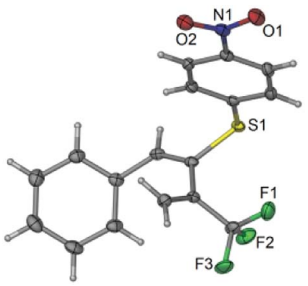
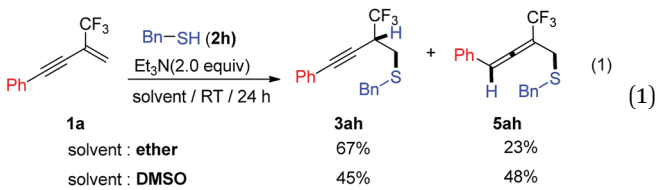
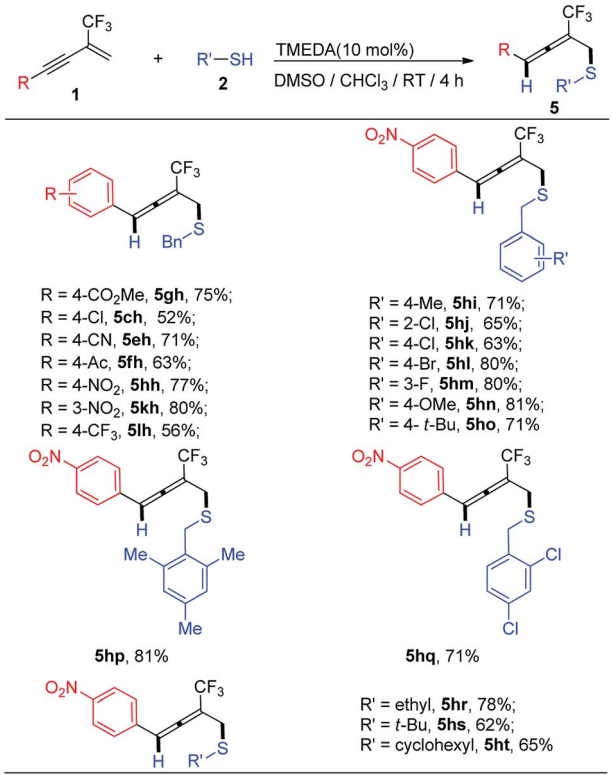


Fig. 1 ORTEP depiction of compound **4ag**.



Next, we evaluated the use of alkanethiol instead of thiophenol as nucleophile. Initially, benzyl mercaptan **2h** was selected as a representative alkanethiol reagent to react with enyne **1a** under above two optimal reaction conditions. It is interesting to note that regioselective nucleophilic addition pattern varied from 1,2-/3,4-addition pattern to 1,2-/1,4-addition pattern and functionalized alkynes **3ah** and allene **5ah** were two predominately formed adducts according to crude ^{1}H NMR analysis, while the amount of the 1,3-diene **4ah** was negligible [eqn (1)]. The interesting results prompted us to further explore optimal reaction conditions for allene synthesis. Based on the formation of allene **5ha** and our previously published paper for cyclopentene synthesis,[14f] concerning the significant role of electronic effects in allene formation, enyne **1g** with an ester substituent was selected as model substrate to react with benzyl mercaptan **2h** for optimal reaction conditions screening. After numerous attempts, we were pleased to find that allene **5gh** could be obtained in 75% isolated yield when reaction was performed in the co-solvent of DMSO and $CHCl_3$ (v/v = 1 : 1) at room temperature by using 10% TMEDA as catalytic base (TMEDA = *N*,*N*,*N*′,*N*′-tetramethyl-ethane-1,2-diamine) (see ESI Table 2†).



Scheme 3 Scope of 2-trifluoromethyl-1,3-enynes **1** and aliphatic thios **2** for synthesis of thioether-functionalized trifluoromethyl-allenes **5**.

With these results in hand, the enyne substrate scope as well as alkanethiol scope were then carried out (Scheme 3). Points to note: (1) in general, enynes possessing electron-withdrawing aryl group on the alkyne moiety are general good candidates for allene formation and the desired thioether-functionalized-allenes could be obtained in moderate to good yield (**5gh**–**5ht**); (2) although 1,4-addition pattern proceeded well with alkanethiols and enyne bearing electron-withdrawing groups, product mixture were generally observed and functionalized alkynes were predominated by-products; (3) a variety of

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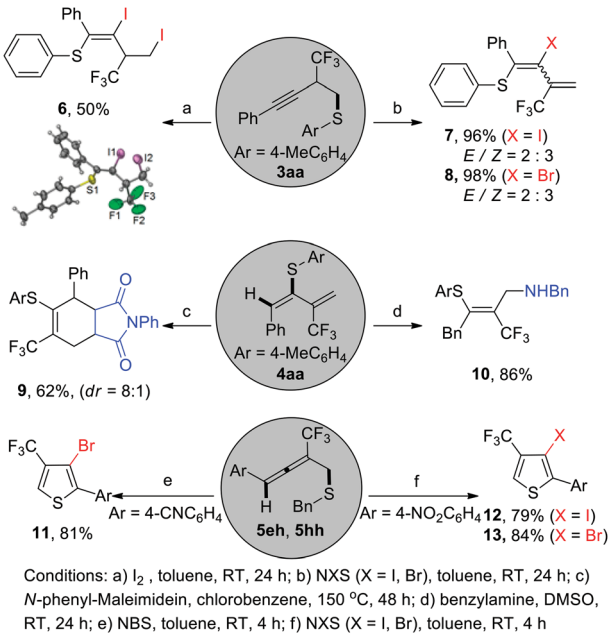

Scheme 4 Synthetic transformation of alkyne **3aa**, 1,3-diene **4aa** and allenes **5eh**, **5hh**.

substituted benzyl thiols, including hindered substrate underwent 1,4-addition smoothly and corresponding functionalized allenes could be obtained in moderate to good yield (**5hi–5hp**); (4) both primary and secondary alkanethiol (**5ht**) as well as tertiary alkanethiol (**5hs**) are suitable nucleophiles. Using alkanethiols as nucleophiles, 3,4-nucleophilic addition pattern leading to functionalized 1,3-diene was suppressed. We hypothesize that this may be due to its relatively low acidity and hardly ionization in DMSO compared with thiophenols,[20] which reduces its ability to nucleophilic attack to allene intermediate to form functionalized 1,3-diene.[21]

To highlight the synthetic utilities of present transformation, several selective transformations of the representative functionalized alkyne **3aa**, 1,3-diene **4aa** as well as functionalized allenes **5eh** and **5hh** are shown in Scheme 4. The results show that they are versatile organic building blocks in organic synthesis. For example, upon treatment of **3aa** with molecule iodine, a I^+ induced electrophilic cyclization and subsequent I^- induced ring-opening reaction occurred and diiodic compound **6** featured with alkenyl and alkyl iodide was obtained in 50% isolated yield, which was further confirmed by an X-ray crystallography analysis.[22] Interestingly, synthetically valuable β-halo alkenyl sulfides **7** or **8** could be delivered in quantitative yield but with poor stereoselectivity by the treatment of **3aa** with *N*-halosuccinimides (NXS). As we know, vinyl sulfides have wide applications in organic synthesis, material science and pharmaceutics, thus, novel and efficient methods for constructing them are still of contemporary importance to the synthetic community and have received continuous attention.[23] Notably, functionalized 1,3-diene can also serve as novel electrophiles for the nucleophilic addition. 1,3-Diene **4aa** can react readily with benzylamine to afford multifunctional tetrasubstituted alkenes **10** in 86% isolated yield *via* a consecutive regioselective nucleophilic addition followed by double bond isomerization. Furthermore, 1,3-diene **4aa** could undergo Diels–Alder reaction with *N*-phenyl-maleimidein in chlorobenzene at 150 °C, yielding the corresponding cycloaddition product **9** in 62% isolated yield with moderate diastereoselectivity. It is also important to highlight that halogenated trifluoromethylated thiophenes **11–13** could be delivered in good isolated yield upon treatment of allene **5eh**, **5hh** with three equivalents of *N*-halosuccinimide (NXS) in toluene at room temperature *via* sequential electrophilic cyclization/oxidation/debenzylation cascade process.[24]

Conclusions

In summary, we have discovered the divergent synthesis of thioether-functionalized trifluoromethyl-alkynes, 1,3-dienes and allenes from the regioselective nucleophilic addition reactions of 2-trifluoromethyl-1,3-conjugated enynes with sulfur nucleophiles. The addition patterns depend on the type of enynes, sulphur nucleophiles and reaction conditions used. The three types of compounds containing both sulfur and fluorine elements are valuable building blocks for synthesis of multifunctional fluorinated vinyl sulfides and thiophenes derivatives.

Experimental

General procedure for the synthesis of thioether-functionalized trifluoromethyl-alkynes 3

To the solution of 2-trifluoromethyl 1,3-conjugated enynes **1** (1.0 mmol), thiophenol **2** (1.5 mmol) in toluene (5.0 mL) under nitrogen at room temperature was added Et_3N (2.0 mmol), the reaction was stirred at room temperature for 24 h. After **1** was completely consumed, which was determined by TLC analysis, the solvent was removed under reduced pressure and the crude reaction mixture was purified by flash column chromatography on silica gel (petroleum ether : ethyl acetate = 1 : 0–5 : 1) to give the desired **3**.

General procedure for the synthesis of thioether-functionalized trifluoromethyl-1,3-dienes 4

To the solution of 2-trifluoromethyl 1,3-conjugated enynes **1** (1.0 mmol), thiophenol **2** (1.1 mmol) in DMSO (5.0 mL) under nitrogen at room temperature was added Et_3N (2.0 mmol), the reaction was stirred at room temperature for 24 h. After **1** was completely consumed, which was determined by TLC analysis, water (15 mL) was added to reaction mixture and extracted with ethyl acetate (3 × 5 mL). Organic layers were combined, washed with brine (4.0 mL) and dried over $MgSO_4$, after filtration and evaporation, the residue was purified through flash column chromatography on silica gel (petroleum ether : ethyl acetate = 1 : 0–5 : 1) to give the desired **4**.

General procedure for the synthesis of thioether-functionalized trifluoromethyl-allenes 5

To the solution of benzyl mercaptan **2** (1.0 mmol) in DMSO/$CHCl_3$ (v/v = 1 : 1, 5.0 mL) under nitrogen at room temperature

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was added TMEDA (0.1 mmol), then added 2-trifluoromethyl 1,3-conjugated enynes **1** (1.6 mmol), the reaction was stirred at room temperature for 4 h. After **2** was completely consumed, which was determined by TLC analysis, water (2.0 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 4.0 mL). The combined organic extracts were washed with brine (4.0 mL) and dried over $MgSO_4$. After filtration and evaporation, the residue was purified by flash column chromatography on silica gel (petroleum ether : ethyl acetate = 100 : 0–50 : 1) to give the desired **5**.

Conflicts of interest

There are no conflicts to declare.

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