The dual role of thiourea in the thiotrifluoromethylation of alkenes

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Alkenes substituted with a thiourea undergo C–CF₃ followed by intramolecular C–S bond formation with the Togni reagent and trifluoroacetic acid (TFA) at room temperature; thiols and thioamides are not suitable S-sources for this reaction. This anti-addition process involves a CF₃ radical, and affords CF₃-substituted thiazolines and thiazines for medicinal applications. A metal or photoredox catalyst is not required as the thiourea acts as a reductant, as well as serving as an S-source capable of adding to a C-centered radical. Mechanistic work comparing the reactivity of thiourea, urea, thioamide and thiol in the context of alkene thiotrifluoromethylation demonstrates that in this series, the thiourea is unique for its ability to release CF₃ radical from the Togni reagent, and to orchestrate trifluoromethylation followed by S-cyclization with both activated and unactivated alkenes.

Introduction

A large number of pharmaceuticals contain a trifluoromethyl group because this structural motif affects the properties of organic molecules.¹ The installation of trifluoromethyl groups onto sp³ hybridized carbon has progressed significantly with numerous addition reactions of CF₃ across alkenes. Alkene vicinal functionalizations featuring C–CF₃ combined with C–H, C–C or C–heteroatom bond formation have been disclosed, most requiring a transition metal or photoredox catalyst to activate the CF₃ reagent (Scheme 1a).² Vicinal difunctionalizations involving sulfur heteroatom are notoriously rare; this process is much more challenging as, in contrast to amines and alcohols, thiols undergo facile S-trifluoromethylation with the Togni or Umemoto reagents in the absence of catalyst.³ A case of alkene thiotrifluoromethylation was reported by Langlois in 2000.⁴ In this process, photolysis of CF₃SO₂SPh generates a CF₃ radical (CF₃·) that adds to the alkene; this step affords a weakly nucleophilic radical that reacts with CF₃SO₂SPh to provide the thioether product and the chain propagating trifluoromethylsulfonyl radical. The reagent in this reaction serves both as CF₃ and S-source, thereby minimizing S–CF₃ bond formation. In a related approach, Zard reported the net addition of S-trifluoromethyl xanthates reagents onto alkenes, a process initiated with lauroyl peroxide.⁵ The abundance of sulfur containing heterocycles in medicinal chemistry⁶ prompted us to study alkene difunctionalization via C–CF₃ and C–S bond formation where the CF₃ and SR groups would not stem from a single reagent. In 2015, Liu and co-workers reported a case of intermolecular difunctionalization with the copper-catalyzed

![Scheme 1](image)

**Scheme 1** Trifluoromethylation/thiocyclization of alkenes (M = metal, Pc = photoredox catalyst).
trifluoromethylthiocyanation of alkenes; this process requires trimethylsilylsoconate, a silicon-based S-source that acts as Lewis acid to activate the Togni reagent.\(^7\)

In our design plan, we opted to examine the reactivity of olefins with pending thioureas, a decision driven by synthetic and mechanistic considerations. Trifluoromethylation followed by C–S bond formation would afford novel trifluoromethylated 2-aminothiazolines and 2-aminothiazines for applications in medicinal chemistry.\(^8\) Selected 2-aminothiazines and -thiazines are important scaffolds in the development of aspartate beta-secretase enzyme (BACE-1) inhibitors, a therapeutic target for Alzheimer’s disease,\(^9\) and are common motifs in several bioactive compounds (Scheme 1b). Mechanically, the ability of thioureas to act as reducing agent\(^10\) and radical scavenger\(^11\) suggests that this group may induce the release of CF\(_3\) from the Togni reagent,\(^12\) and serve as an S-source capable of adding on a C-centered radical. Here we report that thiourea-substituted alkenes undergo C–CF\(_3\) followed by C–S bond formation with the Togni reagent and TFA. This operationally simple reaction does not require a metal catalyst, and affords diverse CF\(_3\)-substituted 2-aminothiazolines and thiazines resulting from overall anti-addition across the C=C π bond (Scheme 1c).

### Results and discussion

To identify suitable reaction conditions, we selected the unactivated alkene 1aa, and the Togni I, II\(^13\) and Umemoto III\(^14\) reagents as CF\(_3\) source (Table 1).\(^15\) The desired 2-amine-thiazoline 2aa resulting from trifluoromethylation followed by S-cyclization was formed in low yield when the reaction was carried out at room temperature in CHCl\(_3\) with I, II or III in the absence of catalyst or additive (Table 1, entries 1–3). No side-products resulting from oxidative dimerization or S-CF\(_3\) bond formation were detected. The conversion of 1aa into 2aa decreased at 60 °C (Table 1, entries 2 and 3).

Activation of the Togni reagents by protonation with Brønsted acid is well documented,\(^16\) but not typically considered for CF\(_3\) addition onto alkenes. We envisioned that upon protonation of II with trifluoroacetic acid (TFA), the resulting highly electrophilic iodine centre could undergo S–I(III) coordination with the thiourea functionality followed by single electron transfer (SET) with more effective release of CF\(_3\) radical. Gratifyingly, 62% of 2aa was observed after 1 h when the reaction was conducted in the presence of 2 equiv. of TFA, and the yield reached 76% after 24 h (Table 1, entry 4). The reaction was less effective using 1 equiv. of TFA (Table 1, entry 5). The presence of the acid did not induce protocyclization, and its benefit was not significant with Umemoto III (Table 1, entry 6).

With the conditions described in entry 4 of Table 1, the scope of the thiotrifluoromethylation was investigated (Scheme 2). Allyl and metallyl thioureas afforded 2-aminothiazines 2aa and 2ba in 80% and 96%, respectively. A range of para-substituted styrenes underwent thiotrifluoromethylation with yields up to 92%. The reaction was extended to 1,2-dihydronaphthalenes, 2H-chromene, 2H-thiochromene and indene; in this series, all thiazolines were formed as a single stereoisomer resulting from anti-addition (d.r. > 20 : 1).\(^17\) The 1,2-dihydronaphthalene scaffold was selected to investigate the tolerance of the reaction to variation of the thiourea N-substituent. The resulting products anti-2ga–2gl were isolated in yields ranging from 53% to 83%. No reaction occurred with 1gm, a substrate possessing the free NH\(_2\) sub-motif. The corresponding 2-aminothiazoline 2gm was obtained by a detour pathway involving \textit{in situ} deprotection of the N-tBu group of 2gi under acidic conditions. The thiotrifluoromethylation of the chiral substrate 1-(3,4-dihydronaphthalen-1-yl)propyl)-3-phenylthiourea provided adduct 2gm in moderate yield as a mixture of diastereomers (ratio = 3.5 : 1).\(^17\) Thiazines are also within reach applying this methodology. The spirocyclic product 2ka was obtained in 53% yield and an eroded d.r. = 6 : 1 favoring the anti-isomer. Styrenes, with different points of attachment for the thiourea, delivered additional trifluoromethylated scaffolds. The 2,2,2-trifluoroethyl-substituted 4H-benzo[d][1,3]-thiazin-2-amines 2la and 2ma were obtained in moderate yields. Products possessing the CF\(_3\) group on the thiazine ring itself were accessible from 3-substituted 1-cinnamyl-thioureas; for example, 2na was isolated in 40% yield with a d.r. > 20 : 1. In this series, substrates on the ary rings are well tolerated. The reaction with the internal alkyl-substituted alkene, \(E\)-1-(hex-2-en-1-yl)-3-phenylthiourea delivered a mixture of 5-exo- and 6-endocycloisomers in a ~1 : 1 ratio (isolated yields were 22% and 20%, respectively).\(^17\) The spirocyclic thiazine anti-2ra, a CF\(_3\)-substituted analogue of a neuroprotector,\(^18\) was prepared in 60% yield (d.r. > 20 : 1, after purification). A larger scale reaction on 2.3 mmol provided consistent yield of 2ra (61%), an indicator of the robustness of the process. Thiazine 2rc is a trifluoromethylated analogue of...
Mechanistic experiments

We probed the mechanism of this reaction with a series of experiments (Scheme 3). The presence of 1 equiv. of TEMPO significantly inhibited the thiotrifluoromethylation of 1aa, yielding 23% of TEMPO-CF3 and 6% of 2aa. Complete inhibition for the formation of 2aa was observed in the presence of benzoquinone. The cyclopentane 5 was isolated in 20% yield when diethyl 2,2-diallylmalonate was submitted to the reaction conditions in the presence of 1 equiv. of N,N-diphenylthiourea (DPTU); in the absence of thiourea, no reaction occurred (eqn (1)). Both E-1na and Z-1na gave anti-2na with d.r. > 20 : 1 (eqn (2)). Collectively, these data indicate that a CF3 radical is involved in the reaction.

Next, we investigated the uniqueness of the thiourea functionality for its ability to induce CF3 formation. We compared the reactivity of the thiourea 1ga with the corresponding urea 6.
and amide 8 (eqn (3)). We found that 6 and 8 did not react under the standard reaction conditions. Notably, the cyclized products 7 and 9 were isolated in 13% and 22% yield respectively, when the trifluoromethylation was performed in the presence of 1 equiv. of DPTU. In a similar vein, 1-allyl-3-phenylurea 10 did not react under the standard reaction conditions, but was consumed in the presence of DPTU with evidence that CF₃ radical addition to the alkene took place, but cyclization to 11 did not occur (eqn (4)).¹⁵ The thiourea therefore acts as an activator leading to CF₃⁺ formation, and subsequent addition of this radical on the C=C π bond. The contrasting reactivity of thiourea and urea is consistent with their oxidation potentials (+1.19 V vs. SCE in CH₃CN for thiourea 1aa and +1.36 V vs. SCE in CH₃CN for urea 10); similar values were found for cyclic voltammetry measurements performed in CH₃CN in the presence of TFA.¹⁵ Moreover, thioureas are superior to ureas for thiourea is the only product observed in the crude reaction mixture (eqn (2)).¹⁵ We propose that activation of the Togni reagent II with TFA affords the highly electrophilic iodine(III) species [III.H⁺]⁷ that can associate with 1aa via iodine–sulphur coordination leading to A. Coordination of thiourea to the highly electrophilic I(III) in [III.H⁺]³ is unprecedented, but S-I(III) coordination has been evoked in the S-CF₃ bond formation for thiols reacting with the Togni reagent.²⁴ Homolytic dissociation releases B, iodobenzoic acid and the electrophilic radical CF₃⁺, which is suited to add regioselectively to the alkene substrate 1aa. The alternative dissociative electron transfer pathway towards CF₃ radical formation is also plausible. The resultant carbon radical C undergoes ring closure with C=S bond formation to provide adduct D, which should be easier to oxidize than C; SET to the Togni reagent II, [III.H⁺]³ and/or A affords after proton transfer 2aa, and CF₃⁺ that starts a new reaction cycle.²⁵ For radicals arising from CF₃⁺ addition to aryl-substituted alkenes, oxidation prior to S-cyclization is viable (Scheme 4).

**Conclusions**

In summary, we developed the first trifluoromethylation followed by S-cyclization across C=C π bonds using thiourea as the S-source. The substrate itself, through its thiourea functionality, acts as an initiator, thereby avoiding metal species or light/photoredox catalysts to induce facile formation of the CF₃ radical that adds to the alkene. Thiourea can react with C-centered radical, so a range of alkenes including unactivated systems underwent facile thiophosphoromethylation. This reaction is an attractive method for medicinal and other applications, because of its broad substrate scope, anti-selectivity and operational simplicity. The discovery that NH₂-diphenylthiourea is an effective additive to induce the trifluoromethylation-cyclization of ureas and benzamides opens the possibility to investigate the value of this category of activators for the development of novel metal-free trifluoromethylation across double bonds.

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