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Copper-catalyzed thioketalization of enones featuring trifluoromethyl groups†

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Synthetic methods for the preparation of thioketals featuring CF₃ groups are rare. Here, we have developed a copper-catalyzed thioketalization of enones bearing CF₃ groups and various mercaptans. 24 thioketal molecules have been obtained with moderate to excellent yield. Meanwhile, a preparative scale experiment has been performed giving over 95% yield. This work allows the straightforward formation of thioketals containing CF₃ groups and unsaturated double bonds.

Thioacetals and thioketals are widely used as building blocks for the synthesis of various chemicals including a series of natural products.¹ In most cases, the thioacetal and thioketal were obtained by addition of a thiol, especially 1,3-propanedithiol, to aldehydes and ketones.² Few works on addition of diverse mercaptans to enones to create various thioketals have been reported.

Most methods have adopted Bronsted or Lewis acid catalysis to activate ketone and obtained thioketal.^{3–17} Researchers have discovered catalysts, such as I₂,³ InI₃,⁴ TiCl₄,⁵ InCl₃,^{6,7} InBr₃,⁸ BF₃·OEt₂,⁹ AgOTf,¹⁰ Hf(OTf)₄,¹¹ In(OTf)₃,¹² TMSCl,¹³ NH₂SO₃H,¹⁴ DBSA,¹⁵ Cu(DS)₂,¹⁶ and (COOH)₂ (ref. 17) working well in thioketalization. The Lee group¹⁸ and Xie group¹⁹ later reported two photoredox-catalyzed thioacetalizations respectively (Scheme 1b and c). The Tang group discovered a Fe-catalyzed direct dithioacetalization of aldehydes with 2-chloro-1,3-dithiane (Scheme 1d).²⁰ However, most methods were developed only for aldehyde or ketone. Approaches for more complicated substrates like enone need to be advanced.

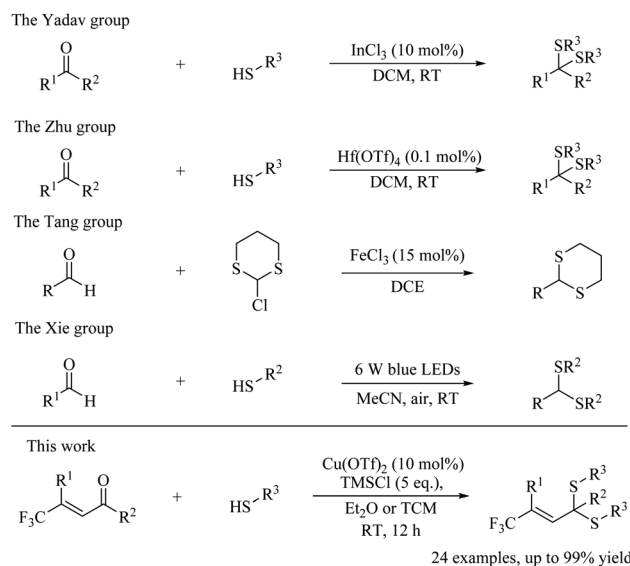
Fluorine have played an important role in chemistry due to the wide applications of fluorinated molecules in pharmaceuticals and materials.^{21,22} The incorporation of fluorine atom into a drug molecule would significantly advance its medicinal properties.²³ Therefore, synthesis of compounds featuring fluorine atoms has been a hot area in organic chemistry.^{24–27}

Among the syntheses of various fluorinated molecules, the installation of trifluoromethyl group is a very important and challenging task, since plenty of drug molecules contain this moiety.^{28–34} Syntheses of compounds featuring both of F and S atoms would be of interest to synthetic chemists.³⁵ Here, we have discovered a copper-catalyzed approach achieving a variety of thioketals featuring CF₃ groups in order to further advance both of

thioketalization and fluorinated molecule synthesis (Scheme 1e). This method is realized by adding abundant thiols to various CF₃ substituted enones³⁶ with good to excellent yields.

We started the exploration from intensive optimizations. We chose substrate (*E*)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-one, **1a** and ethanethiol, **2a** as thioketalization partners (Table 1).

First, we confirmed that this transformation could not proceed spontaneously without catalyst and additive (Table 1, entry 1). With the activation by Lewis acid TMSCl, we collected some product (entry 2). We then remained the additive and screened copper catalysts. No improvement was observed by applying catalyst CuCl, CuBr₂, Cu(OAc)₂ and CuSCN (entries 3–6) until Cu(OTf)₂ (51% yield, entry 7). To further advance the result, we optimized solvents. We tried DCE, MeCN, Et₂O, THF, MTBE, DMF and chloroform (TCM), and finally enhanced the yield to 70% by using TCM (entries 8–14). Further extension of

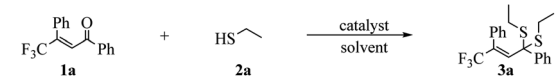


Scheme 1 Previous thioketalization and present work.

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Table 1 Optimization of the reaction condition^a


Entry	Catalyst	Solvent	Time	Yield ^g [%]
1	—	DCM	12 h	0
2 ^b	—	DCM	12 h	14
3 ^b	CuCl	DCM	12 h	6
4 ^b	CuBr ₂	DCM	12 h	7
5 ^b	Cu(OAc) ₂	DCM	12 h	Trace
6 ^b	CuSCN	DCM	12 h	Trace
7 ^b	Cu(OTf) ₂	DCM	12 h	51
8 ^b	Cu(OTf) ₂	DCE	12 h	51
9 ^b	Cu(OTf) ₂	MeCN	12 h	Trace
10 ^b	Cu(OTf) ₂	Et ₂ O	12 h	Trace
11 ^b	Cu(OTf) ₂	THF	12 h	Trace
12 ^b	Cu(OTf) ₂	MTBE	12 h	Trace
13 ^b	Cu(OTf) ₂	DMF	12 h	0
14 ^b	Cu(OTf) ₂	TCM	12 h	70
15 ^b	Cu(OTf) ₂	TCM	20 h	70
16 ^{b,c}	Cu(OTf) ₂	TCM	12 h	58
17 ^{b,d}	Cu(OTf) ₂	TCM	12 h	70
18 ^e	Cu(OTf) ₂	TCM	12 h	16
19 ^f	Cu(OTf) ₂	TCM	12 h	55

^a Reaction conditions: enone 1.0 eq., thiol (2.0 eq.), catalyst (10 mol%).

^b Additive TMSCl (5 eq.) was added. ^c 5 mol% catalyst Cu(OTf)₂ was used. ^d 15 mol% catalyst Cu(OTf)₂ was used. ^e 0.5 eq. TMSCl was used. ^f 3.0 eq. TMSCl was used. ^g Yield of isolated product.

reaction time to 20 hours showed no improvement to the result (entry 15). We also studied the optimal amount of catalyst Cu(OTf)₂ and additive TMSCl. The yield reduced to 58% with 5 mol% catalyst (entry 16), while the yield maintained at 70% using 15 mol% catalyst (entry 17). In terms of TMSCl, we found that decreasing its amount would strongly deteriorate the reaction (entries 18 and 19). Only 16% yield was achieved using TMSCl (0.5 eq.) compared to 70% yield with TMSCl (5.0 eq.). Finally, we obtained our best result using TCM, Cu(OTf)₂ (10 mol%), TMSCl (5.0 eq.) under room temperature after 12 hours.

We next started scope of enone using propane-1,3-dithiol, **2b**, since it is widely used in previous thioetheralization. To our delight, dithiol has shown much better results than monothiol in our thioetheralization. We first studied enone **1a**, and obtained 99% yield with Cu(OTf)₂ (10 mol%) and TMSCl (5 eq.) in TCM (**3b**). We then investigated bromine substituted enone **1b** with **2b**, and received **3c** with 98% yield. We next studied enone substrates with a methyl group instead of benzyl group attached to the carbonyl group (R² is Me instead of Ph). In the reaction of methyl group substituted enones, we replaced solvent TCM with Et₂O, which could afford better results. We found that Et₂O suits methyl group substituted enones, such as **1c**, while TCM performed better in most phenyl group substituted enones, like **1a**. We next investigated the influence of substituent groups in enone. We found that electron donating groups, methyl and methoxyl have no influence on results, giving 99% and 96% yield respectively (**3e** and **3f**). The electron withdrawing groups

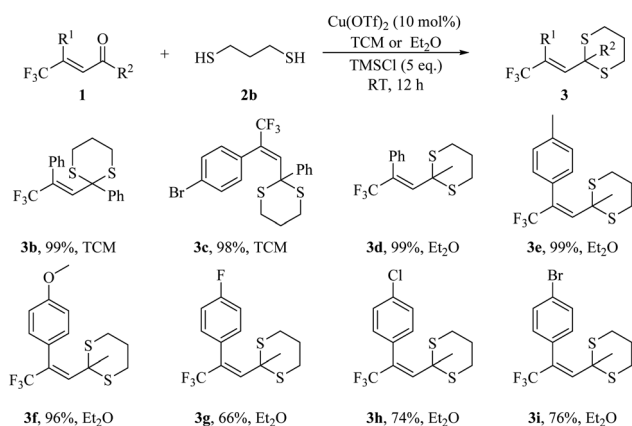
like F, Cl, Br deteriorated the yield, leading to a nearly 20% decrease (**3g**, **3h**, and **3i**, Scheme 2).

We decided to apply both substrate **1a** and (*E*)-5,5,5-trifluoro-4-phenylpent-3-en-2-one **1c** to further explore the scope of thiol in our methodology, since α -phenyl-substituted enone, **1a** and α -methyl-substituted enone, **1c** have different favourable conditions to afford corresponding thioetherals. Using conditions mentioned in entry 14, Table 1, we obtained product **3a** with 70% yield (Scheme 3). We then replaced ethanethiol with more complicated thiols. We introduced hexane-1-thiol, propane-2-thiol, cyclohexanethiol, 2-phenylethane-1-thiol and (4-methoxyphenyl)methanethiol successively into enone **1a** affording different thioetherals (**3j–3n**). We found that the size of thiol would affect the result. With an increasing size of alkyl group on thiol, the yield dropped from 74% to 40% (**3j–3l**). As for aromatic ring substituted thiols, few products were collected in TCM, and moderate results were received (**3m**, 38% and **3n**, 51%) in Et₂O. Adding some electron donating groups, *e.g.* MeO to the aromatic rings would improve the result a bit (**3n**). We also tried other α -phenyl-substituted enone and got medium results (**3o**, 49% and **3p**, 58%).

We next explored more thiol on α -methyl-substituted enone, **1c** in Et₂O. With an increasing carbon chain on thiol, the result enhanced from 79% to 95% (**3q** and **3r**). In terms of bulky thiol, propane-2-thiol, we could also obtain the desired thioether **3s** in 35% yield. We then examined thiols featuring functional groups. We obtained thioetherals bearing unsaturated C–C double bond, phenyl ring, 2-chlorobenzyl, 4-methoxybenzyl, furan ring respectively (**3t** to **3x**). In most cases, excellent yields were achieved, especially for **3v**, 90% yield and **3w**, 87% yield.

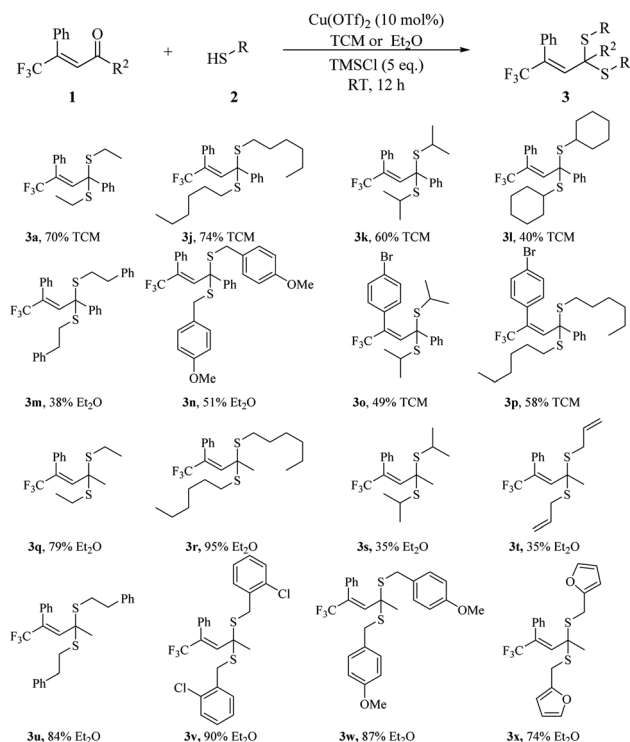
We then attempted the preparative scale reaction to synthesize CF₃-substituted thioether. We got 2.0 g product **3r** with 95% yield using **1b** (4.8 mmol, 1.0 g) and thiol **2b** (9.6 mmol, 1.1 g) catalyzed by Cu(OTf)₂ (10 mol%) and TMSCl (5.0 eq.) in Et₂O after 12 hours reaction under room temperature (Scheme 4).

We also attempted to understand the mechanism of our approach. We did two radical trapping experiments using BHT and hydroquinone as radical scavengers respectively. We excluded free radical reaction mechanism, since no

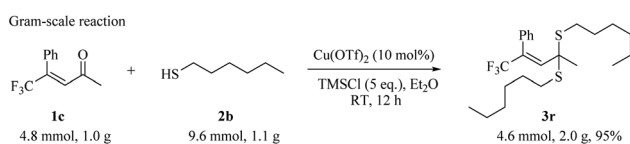


Scheme 2 Scope of enone.





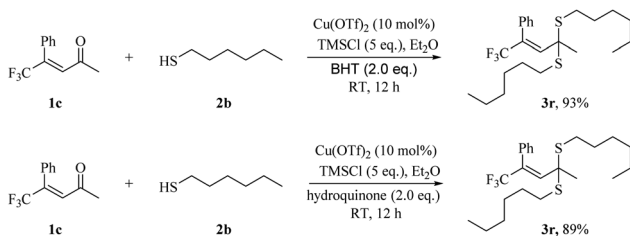
Scheme 3 Scope of thiol to α -phenyl-substituted enone **1a** and α -methyl-substituted enone **1c**.



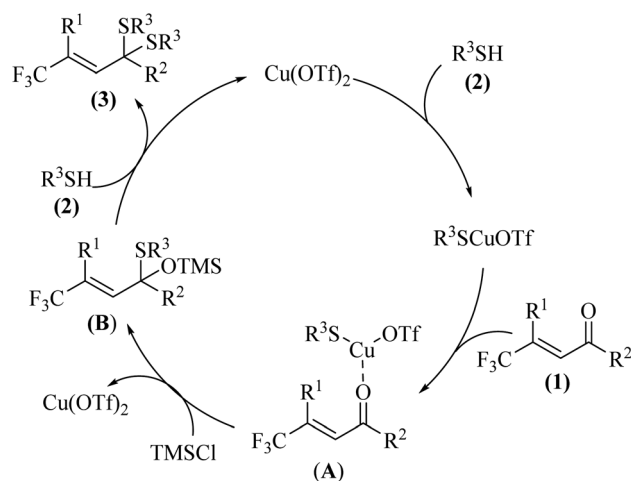
Scheme 4 Preparative scale reaction.

interruption was observed after the addition of these radical trapping reagents (Scheme 5). The product **3r** was obtained in 93% and 89% yield respectively with BHT and hydroquinone, compared to 95% yield without the radical scavenger. The high yield of **3r** for two radical trapping experiments excluded the radical pathway of our approach.

Considering no disulfide by-product was observed in our method, we proposed a plausible mechanism in Scheme 6. We supposed the catalysis started from the combination of $\text{Cu}(\text{OTf})_2$ and thiol giving the copper species. After coordination



Scheme 5 Radical trapping experiments.



Scheme 6 Plausible mechanism of the reaction.

of copper and enone **1**, intermediate **A** was formed. Then the thiol would leave the copper and attack the carbonyl group. With the help of additive TMSCl, intermediate **B** was obtained and $\text{Cu}(\text{OTf})_2$ was recycled. In the final stage, substitution, the OTMS group would leave the intermediate **B** and a second thiol would attack the intermediate to afford the desired product thioketal **3**.

Conclusions

We have reported a new copper-catalyzed method to add various thiols to a series of β - CF_3 -substituted-enones affording plenty of thioketals in moderate to excellent yield. 24 thioketals featuring CF_3 groups and different SR groups were synthesized. We also proved the efficiency of preparative scale reaction and got 2.0 g product **3r**. Thioketals are widely used in organic synthesis, while few CF_3 containing thioketals were reported. Our work opens a new door in this area, and would promote more applications.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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