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Efficient trifluoromethylation of C(sp^2)–H functionalized α-oxoketene dithioacetals: a route to the regioselective synthesis of functionalized trifluoromethylated pyrazoles†

N. Sharma,[a] N. Kumari,[b] T. S. Chundawat,[c] S. Kumar[d] and S. Bhagat*[a]

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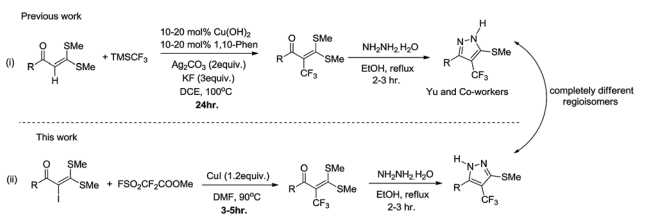
An operationally simple approach for the regioselective construction of diversely substituted trifluoromethylated pyrazoles *via* nucleophilic trifluoromethylation of iodo-substituted α-oxoketene dithioacetals is described. X-ray crystallographic studies confirmed the trifluoromethylation as well as formation of a regioselective cyclized product. Furthermore, trifluoromethylated pyrazoles bearing thiomethyl groups may allow further functionalization and are of considerable interest in medicinal chemistry.

Organofluorine compounds, particularly trifluoromethylated molecules have generated considerable attention in the field of organic chemistry due to their wide range of applications in material sciences as well as in pharmaceutical & agrochemical industries.[1,2] The interesting medicinal properties that the trifluoromethyl group imparts are anticipated due to an increase in lipophilicity and metabolic stability.[3,4] As naturally occurring trifluoromethylated compounds are not reported in the literature, tremendous research efforts from synthetic organic chemists are focused on the development of an efficient route for selective introduction of the trifluoromethyl group onto aromatic and heteroaromatic ring systems under mild and selective reaction conditions.[5–7]

Functionalized α-oxoketene dithioacetals have emerged as versatile intermediates for the synthesis of various heterocyclic compounds in the field of organic synthesis.[8] Among them, α-halogenated oxoketene dithioacetals are of special interest due to their diverse applications as synthons in metal catalysed reactions.[9] Despite their wide scope, synthetic utility of α-halogenated oxoketene dithioacetals has not been well documented. α-Iodinated ketene dithioacetals, to our knowledge, have been reported to be synthesized by iododecarboxylation which suffers from low efficiency and undesired side reactions.[10] Furthermore, there are no reports on the utilization of these iodofunctionalized oxoketene dithioacetals in organic transformation reactions. In view of these reported limitations and our ongoing efforts to explore oxoketene dithioacetals for construction of N-heterocycles,[11] we envisioned that the development of efficient iodination strategy as well as trifluoromethylation protocol of these α-iodo substituted dithioacetals would allow for a new access to multisubstituted trifluoromethylated oxoketene dithioacetals under mild reaction conditions. Moreover, elaborations on these trifluoromethylated synthons in cyclization reactions resulted in regioselective construction of biologically important functionalized trifluoromethylated pyrazoles.[12,13] Here it should be noted that there are only few reports of trifluoromethylations of C(sp^2)–H bond of oxoketene dithioacetals[14] which are suffering from drawbacks such as use of oxidant, ligands and additives as well as longer reaction hours. Adding to this, using similar reaction conditions trifluoromethylated pyrazoles of completely different regioselectivity were obtained as compared to compounds reported by Yu *et al.*[14a] (Scheme 1).



Scheme 1 Functionalization of α-iodinated oxoketene dithioacetals.

[a]*Organic Synthesis Research Laboratory, Department of Chemistry, A. R. S. D. College, University of Delhi, New Delhi-110021, India. E-mail: sunitabhagat28@gmail.com*

[b]*Institute of Nuclear Medicine & Allied Sciences, Defence Research & Development Organization, Brig. SK Mazumdar Marg, Delhi-110054, India*

[c]*Department of Applied Sciences, The Northcap University (formerly ITM University), Gurgaon-122001, Haryana, India*

[d]*Physical Chemistry Division, CSIR-National Chemical Laboratory, Dr Homi Bhabha Road, Pune-411008, India*

† Electronic supplementary information (ESI) available: Copies of ^{1}H, ^{13}C NMR & HRMS data for target compounds. X-ray crystallographic data of compounds **3l** with CCDC no. 1051488 and **4i** with CCDC no. 1051460. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ra01130j

To probe the viability of the designed strategy, α-oxoketene dithioacetals[15] were subjected to first direct C(sp^2)–H iodination using *N*-iodosuccinimide as environmental friendly iodine source to get the desired compounds **2a–l** in excellent yields. Formation of products was confirmed on the basis of ^{1}H NMR and ^{13}C NMR data. Disappearance of peak of vinylic proton at δ 6.4–6.8 due to substitution by iodine with co-presence of peak at δ 94–100 due to vinylic C–I confirmed the presence of iodine atom at α position.

Encouraged by the versatility of α-oxoketene dithioacetals to rapidly undergo substitution reactions,[8e] α-iodo substituted oxoketene dithioacetals were subjected to undergo trifluoromethylation reactions using relatively inexpensive, convenient but underutilized methyl fluorosulfonyl difluoroacetate (FSO_2CF_2COOMe)[16] as reagent through transition metal catalysed cross coupling reaction in the presence of CuI.

To identify the optimal conditions for the reaction, α-iodo oxoketene dithioacetal **2f** was subjected to transition metal catalysed trifluoromethylation using methyl fluorosulfonyl difluoroacetate (FSO_2CF_2COOMe) and different reagents by varying solvents to yield **3f**. When 1.5 eq. of FSO_2CF_2COOMe and 1.2 eq. of CuI were used in DMF as solvent at 60 °C, 40% yield of product **3f** was observed (Table 1, entry 1). An increase of temperature to 80 °C resulted in the increase of yield to 60% (Table 1, entry 2). From the Table 1 it is clear that yield of desired compound **3f** was maximum *i.e.* 86% when the reaction was heated at 90 °C (Table 1, entry 3). However no change in yield was observed when reaction temperature was increased from 90 °C to 110 °C (Table 1, entry 4). It should be noted that increase in equivalents of FSO_2CF_2COOMe and CuI to 2 eq. did not had any effect on yield of **3f** (Table 1, entry 5). An examination of other copper source such as $Cu(OAc)_2$ was not effective for this transformation and deiodination of **2f** was observed (Table 1, entry 6). CuI was essential to the reaction because when KI was used in place of CuI or in absence of CuI desired product was not formed (Table 1, entries 7 & 8). By screening with polar organic solvents, such as *n*-BuOH, *t*-BuOH and PEG-400 there was no formation of desired product **3f** (Table 1, entries 9–11).

Table 1 Optimization of reaction conditions[a]

Entry	Source of CF_3	Reagent	Solvent	Temp (°C)	Yield[b] (%)
1	FSO_2CF_2COOMe	CuI	DMF	60	40
2	FSO_2CF_2COOMe	CuI	DMF	80	60
3	**FSO_2CF_2COOMe**	**CuI**	**DMF**	**90**	**86**
4	FSO_2CF_2COOMe	CuI	DMF	110	86
5	FSO_2CF_2COOMe	CuI	DMF	90	86[c]
6	FSO_2CF_2COOMe	$Cu(OAc)_2$	DMF	90	—
7	FSO_2CF_2COOMe	KI	DMF	90	—
8	FSO_2CF_2COOMe	—	DMF	90	—
9	FSO_2CF_2COOMe	CuI	*n*-BuOH	90	—
10	FSO_2CF_2COOMe	CuI	*t*-BuOH	90	—
11	FSO_2CF_2COOMe	CuI	PEG-400	90	—

[a] Reactions were performed using **2f** (1 mmol), 1.5 equiv. of FSO_2CF_2COOMe, 1.2 equiv. of reagent 3 h unless otherwise stated. [b] Isolated yield. [c] Reaction were performed using FSO_2CF_2COOMe (2eq.), catalyst (2eq.).

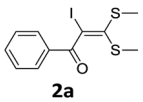
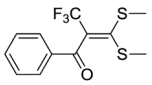
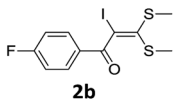
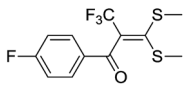
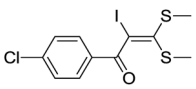
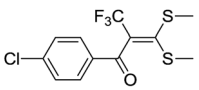
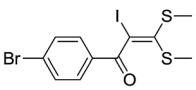
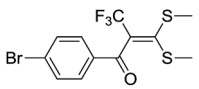
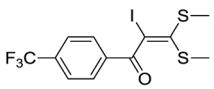
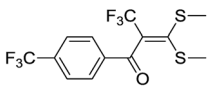
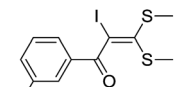
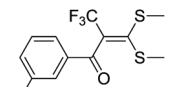
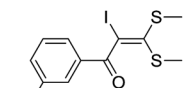
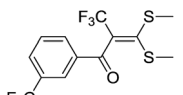
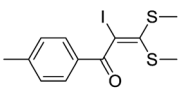
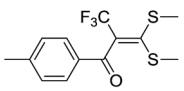
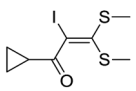
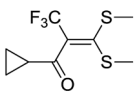
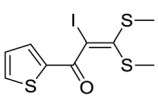
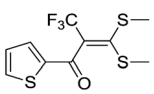
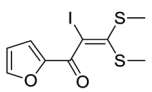
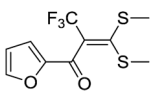
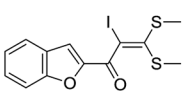
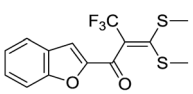
With the optimized conditions in hand (Table 1, entry 3), the scope of the reaction was explored considering both the yield and variety of substituents at α-iodo oxoketene dithioacetals (Table 2). The results shown in Table 2 suggested that the reaction of α-iodo oxoketene dithioacetals **2b–g** bearing electron withdrawing substituents at both *-m* and *-p* positions could afford α-trifluoromethylated oxoketene dithioacetals **3a–g** in good yields (entry 2–7).

For substrates with electron releasing group on aromatic ring, effective conversion was observed only with $-pCH_3$ as substituent (entry 8).

However, α-iodo oxoketene dithioacetals substituted with $-OCH_3$ at *-o* or *-p* positions were proven ineffective. This may be anticipated due to inability of nucleophilic substitution reaction to take place due to increased electron density at vinylic position through conjugation. Cyclopropyl substituted α-trifluoromethylated oxoketene dithioacetals were obtained in 86% yield (entry 9). Furthermore, when a heteroaromatic nucleus was introduced in substrates **2j–l**, the reaction provided the desired products **3j–l** in good to excellent yields (entries 10–12). Structural assignments have been made on the basis of ^{1}H NMR, ^{13}C NMR and HRMS data. In ^{13}C NMR data of compounds **3a–l**, disappearance of peak at δ 94–100 with simultaneous appearance of peaks at δ 122 and δ 119 which corresponds to vinylic carbon as well as carbon atom of $-CF_3$ group was observed. HRMS data of each compound showed M+1 peak. The structure of the product **3l** was determined by single crystal X-ray diffraction (Fig. 1). The structures of the other products were concluded by analogy.

Finally, we demonstrated the further applicability of α-trifluoromethylated oxoketene dithioacetals **3a–l** in cyclization reactions, regioselective construction of aromatic/heteroaromatic multisubstituted 1*H*-pyrazoles **4a–l** was achieved in 72–83% yield by cyclization with hydrazine hydrate (Table 3). Formation of the regioselective cyclized product was confirmed on the basis of ^{1}H NMR and X-ray crystallographic studies of **4i** (Fig. 2). Structural assignments of **4a–l** have been made on the basis of IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS data. IR spectra of the products revealed absorption peaks for secondary amino groups (in the region 3170–3460 cm^1) while no peak for ketocarbonyl group around 1670–1690 was observed which confirmed that –C=O was utilized in cyclization reaction. In the ^{1}H NMR spectra, disappearance of one of the characteristic peak of –SMe group with appearance of upfield shift of –NH protons as broad singlet at δ 7.8–9.3 ppm as compared to –NH protons of literature reported compound **5** (ref. 14*a*) which appeared at δ 11.9–12.2 ppm supported the formation of cyclized pyrazole ring of **4(a–l)** regioselectively instead of compound **5**. Disappearance of peaks in ^{13}C NMR for carbonyl carbon at δ 175.5–195.5 ppm and $-SCH_3$ carbon at 14.2–14.9 ppm confirms that the cyclized product was formed. Appearance of a singlet at δ −53.0–55.0 in ^{19}F NMR data

Table 2 Synthesis of trifluoromethylated α-oxoketene dithioacetals[a]

Entry	Substrate 2	Product 3	Yield[b] (%)
1	 2a	 3a	80%
2	 2b	 3b	85%
3	 2c	 3c	84%
4	 2d	 3d	86%
5	 2e	 3e	86%
6	 2f	 3f	85%
7	 2g	 3g	83%
8	 2h	 3h	82%
9	 2i	 3i	86%
10	 2j	 3j	85%
11	 2k	 3k	84%
12	 2l	 3l	93%

[a] Reactions were performed using **2a–l** (1 mmol), 1.5 equiv. of FSO_2CF_2COOMe, 1.2 equiv. of CuI 2–3 h. [b] Isolated yield.

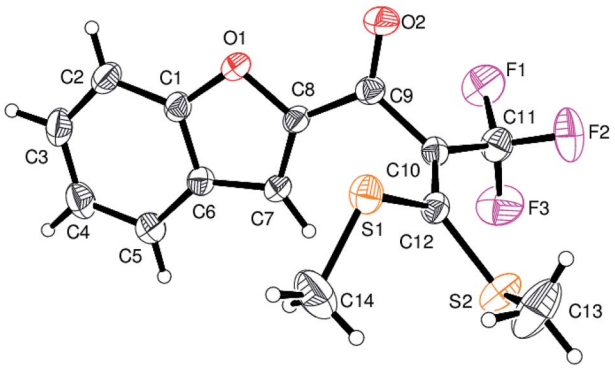
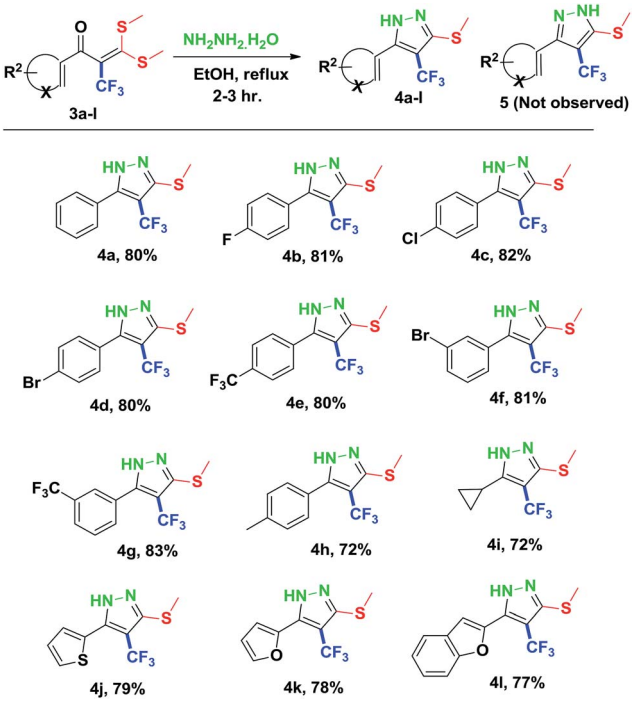


Fig. 1 ORTEP drawings of compound **3l**.

Table 3 Regioselective synthesis of aromatic/heteroaromatic trifluoromethylated 1*H*-pyrazoles[a]



[a] Unless otherwise specified, reactions were performed using 1 equiv. of **3**, 1.2 equiv. of $\mathbf{NH_2NH_2 \cdot H_2O}$ in EtOH.

confirmed the presence of $-CF_3$ group in the desired cyclized compound.

In conclusion, we have developed a mild, ligand free approach for the trifluoromethylation of readily synthesized α-iodo oxoketene dithioacetals in excellent yields. The reaction was well tolerant towards a wide variety of substituents. The simplicity and generality of this method makes it attractive for the introduction of CF_3 group into functionally diverse α-iodo substituted oxoketene dithioacetals. The resultant trifluoromethylated synthons were further utilized as bifunctional building blocks in cyclocondensation reaction for the exclusive regioselective synthesis of valuable trifluoromethylated

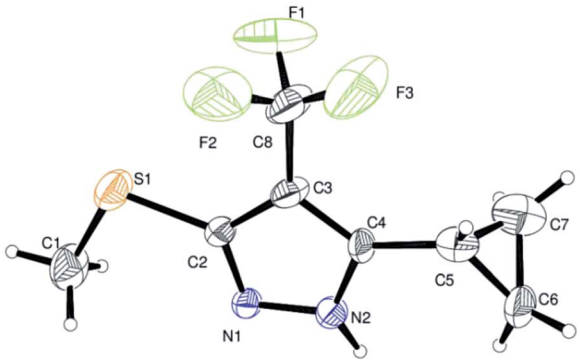


Fig. 2 ORTEP drawings of compound 4i.

pyrazoles. These five membered heterocycles also has the flexibility to offer further diversification of the thiomethyl moiety by employing arylboronic acids in the substitution reactions.[17]

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