COMMUNICATION

Formal α-trifluoromethylthiolation of carboxylic acid derivatives via *N*-acyl pyrazoles

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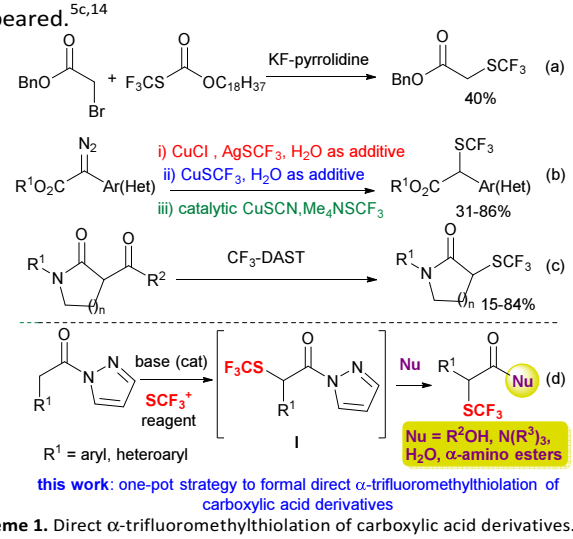
Herein we disclosed a one-pot two-step protocol for the first direct, base-catalyzed α-trifluoromethylthiolation of carboxylic acid derivatives by using readily available *N*-acyl pyrazoles, *N*-(trifluoromethylthio)phthalimide and a nucleophile such as amines, alcohols and water. Straightforward elaboration of the products to alcohols and triflones expands further the synthetic utility of the process.

One of the most exciting and active area of synthetic chemistry is the development of protocols to produce molecules bearing fluorine atoms, which have several applications as drugs, herbicides and in material science.[1] Whereas considerable advances have been achieved in the synthesis of CF_3-containing molecules, comparatively much less has been reported to install the trifluoromethylthio (SCF_3) group.[2] Its electron-withdrawing and lipophilicity character (Hansch π value = 1.44)[3] facilitates tuning of the pharmacokinetics for drug-molecules, thus fostering interest in the pharmaceutical and agrochemical industries. The protocols, useful to install the SCF_3 group, increased significantly in the last decade, affording a respectable toolbox for metal-catalysed C(sp_2)–SCF_3 bond formation.[2] For the construction of C(sp_3)–SCF_3 bonds, important achievements have been disclosed in the α-trifluoromethylthiolation of ketones,[4] aldehydes,[5] silylenol ethers,[6] and 1,3-dicarbonyl compounds[4a,5a,b,7] by using copper- and silver-mediated processes. The organocatalytic approach has been mostly focused on the asymmetric trifluoromethylthiolation of 1,3-dicarbonyl compounds.[8] In contrast, methodologies for the α-trifluoromethylthiolation of carboxylic acid derivatives are scarce, either using nucleophilic or electrophilic SCF_3 sources (Scheme 1). A first example, reported by Zhang and Zard, used an *in situ* generated trifluoromethylthiolated anion from O-octadecyl-S-trifluorothiolcarbonate/KF/pyrrolidine system to afford the ester in 40% yield (Scheme 1a).[9] In 2014, the groups of Hu,[10] Wang[11] and Rueping[12] independently reported diazoesters as reacting compounds with nucleophilic and stoichiometric metal-based trifluoromethylthiolating reagents to provide, under controlled conditions, the corresponding α-trifluorothiomethyl esters in moderate to good yields (Scheme 1b). A catalytic version by using CuSCN was then developed by Goossen.[13] Scattered examples of direct α-trifluoromethylthiolation of esters and amides, working under strongly basic conditions or metal catalysis, have also appeared.[5c,14]



Scheme 1. Direct α-trifluoromethylthiolation of carboxylic acid derivatives.

More recently, Shibata developed a deacylative trifluoromethylthiolation of lactams using CF_3-DAST reagent, leading to α-trifluoromethylthio lactams in generally good yields (Scheme 1c).[15] The paucity of methods illustrated in Scheme 1, prevalently focused on esters and often conducted under stoichiometric metal activation, prompted us to develop a metal-free catalytic and general approach. Being interested in synthetic applications of *N*-acyl pyrazoles,[16] we envisaged they could be used as readily available carboxylic acid

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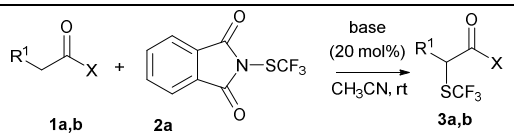
surrogates, amenable of mild conditions for enolate formation.[17] When reacted in the presence of common electrophilic SCF_3 sources, under catalytic basic conditions, an intermediate **I** would be formed, suitable of *in situ* pyrazole replacement with different nucleophiles (Scheme 1d).

Herein, we report a first metal-free, catalytic α-trifluoromethylthiolation of carboxylic acid derivatives. The one-pot process delivered a variety of α-trifluoromethylthio-substituted amides, esters, carboxylic acids in good to high yields. Moreover, one-pot reduction of intermediates **I** to alcohols or oxidation of the carboxylic acid derivatives to triflones showcased the synthetic value of the protocol.

We commenced our study by reacting model compound **1a** with readily available *N*-(trifluoromethylthio)phthalimide **2a** using 20 mol% of common bases in acetonitrile at room temperature (Table 1).

Table 1. Optimization of the reaction conditions [a]



1a,b **2a** **3a,b**

R^1 = 4-ClC_6H_4, X = pyrazole **1a**
R^1 = 4-ClC_6H_4, X = 3-phenylpyrazole **1b**

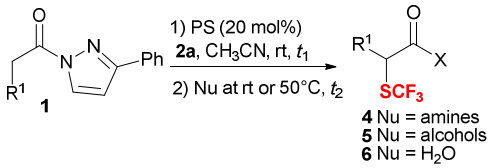
Entry	Base	*t*/h	Conv. **3** %[b]
1	DIPEA	3	41
2	DABCO	4	30
3[c]	*t*BuOK	0.5	60
4	KOH	4	30
5	Proton Sponge (PS)	1.5	78
6	DBU	1.5	55
7[d]	TBD	1.5	65
8[e]	PS	1	84
9	PS	6	77
10[f]	PS	6	91

[a] Reaction conditions: **1** (0.1 mmol,), **2a** (0.12 mmol,), base (0.02 mmol), CH_3CN (0.2 M), under N_2 atmosphere. [b] Determined by ^1H NMR spectroscopy of crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard and by ^{19}F NMR spectroscopy using $CF_3C_6H_5$ as internal standard. [c] 10% of bis-Trifluoromethylthiolated product was detected. [d] 6% of bis-Trifluoromethylthiolated product was detected. [e] 0.1 mmol of PS was used. [f] Reagent **1b** was used.

Tertiary amines, such as diisopropyl ethyl amine (DIPEA) and 1,4-diazabicyclo[2.2.2]octane (DABCO), provided product **3a** in moderate yields (entries 1 and 2). *t*BuOK improved the conversion to the product, but the presence of the bis α-trifluoromethylthiolated compound was detected (entry 3). The inorganic base KOH was poorly effective (entry 4). *N*,*N*,*N*′,*N*′-Tetramethyl-1,8-naphthalenediamine (PS) gave product **3a** in good yield (entry 5). Stronger organic bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) did not improve the conversion and traces of the bis-trifluoromethylthiolated product were detected (entries 6 and 7). When a stoichiometric amount of PS was used, product **3a** was obtained in only slightly better yield (entry 8 *vs* entry 5). Prolonged reaction time, using 20 mol% loading of PS, did not provide a better conversion to **3a** (entry 9). Further reaction conditions optimization,[18] including the nature of leaving group, led to select reagent **1b**, which was converted into compound **3b** in 91% yield (entry 10).[19]

Under the optimized reaction conditions found for the formation of compound **3b**, a one-pot approach was then developed, where the trifluoromethylthiolation step was followed by the addition of nucleophilic species such as amines, anilines, alcohols and water (Table 2). Acyl pyrazoles **1**, bearing *para*-, *meta*- and *ortho*- electron-withdrawing and donating groups in the benzene ring, were efficiently converted into secondary amides (products **4a-f**), after adding at room temperature simple and functionalised primary amines (1.3 equiv) to intermediate **3**. The addition of secondary amines required the temperature to be increased to 50°C to obtain tertiary α-trifluoromethylthiolated amides in very good yields (**4g-j**).

Table 2. Substrate scope for the one-pot synthesis of α-trifluoromethylthiolated amides, esters and acids [a]

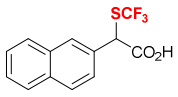


1

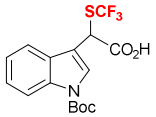
4 Nu = amines
5 Nu = alcohols
6 Nu = H_2O

R^1 = 4-ClC_6H_4, X = -NHBn **4a**: t_1 6h, t_2 2.5 h, rt; 90%
R^1 = 3-ClC_6H_4, X = -NHCH_2(2-MeOC_6H_4) **4b**: t_1 3.5h, t_2 1 h, rt; 72%
R^1 = 4-$CF_3C_6H_4$, X = -NH$(CH_2)_3$Ph **4c**: t_1 1.5 h, t_2 3 h, rt; 98%
R^1 = 4-FC_6H_4, X = -NHCH_2C≡CH **4d**: t_1 5 h, t_2 2 h, rt; 74%
R^1 = 2-FC_6H_4, X = -NH$(CH_2)_3CH_3$ **4e**: t_1 5 h, t_2 3 h, rt; 66%
R^1 = 4-MeOC_6H_4, X = -NH-cC_6H_{11} **4f**: t_1 24 h, t_2 6 h, rt; 75%
R^1 = 4-$NO_2C_6H_4$, X = -N⟨⟩O **4g**: t_1 0.5 h, t_2 3 h, 50°C; 93%
R^1 = 4-$CF_3C_6H_4$, X = -N(CH_3)Ph **4h** t_1 3 h, t_2 6 h, 50°C; 68%
R^1 = 4-BrC_6H_4, X = -N(allyl)$_2$ **4i**: t_1 7 h, t_2 8 h, 50°C; 72%
R^1 = 3,5-$(CF_3)_2C_6H_3$, X = -N(*i*Pr)$_2$ **4j**: t_1 0.3 h, t_2 6 h, 50°C; 73%
R^1 = 3,4-$(Cl)_2C_6H_3$, X = -NHPh **4k**: t_1 3 h, t_2 5.5 h, rt; 83%
R^1 = Ph, X = -NH(2-naphthyl) **4l**: t_1 20 h, t_2 48 h, rt; 79%
R^1 = 2-naphthyl, X = -NHCH_2(4-MeOC_6H_4) **4m**: t_1 5 h, t_2 5 h, rt; 73%
R^1 = 2-thiophene, X = -NHCH_2[3,4-$(MeO)_2C_6H_3$] **4n**: t_1 1 h, t_2 3 h, rt; 72%
R^1 = 4-MeC_6H_4, X = -NH$(CH_2)_2$OH **4o**: t_1 24 h, t_2 3 h, rt; 70%
R^1 = 2-$CF_3C_6H_4$, X = -NH$(CH_2)_2$NHPh **4p**: t_1 4 h, t_2 2 h, rt; 80%

R^1 = 4-$NO_2C_6H_4$, X = OMe **5a**: t_1 0.5 h, t_2 1 h, 50°C; 80%
R^1 = 4-BrC_6H_4, X = OEt **5b**: t_1 14 h, t_2 2 h, 50°C; 78%
R^1 = 4-ClC_6H_4, X = O*i*Pr **5c**: t_1 14 h, t_2 4 h, 50°C; 83%



6a: t_1 7 h, t_2 16 h, rt; 90%



6b: t_1 8 h, t_2 16 h, rt; 70%

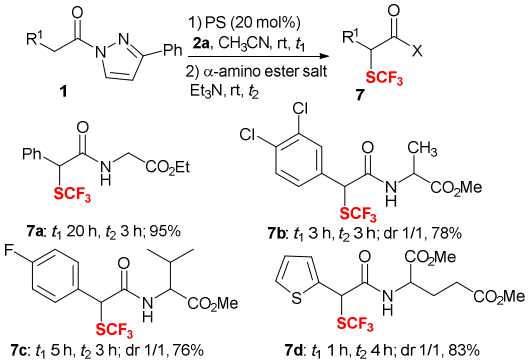
[a] All reactions were carried out using **1** (0.2 mmol,), **2a** (0.24 mmol,), PS (0.04 mmol), CH_3CN (0.2 M), under N_2 atmosphere, at rt for the indicated time; then amine (0.26 mmol) was added, stirring maintained for the required time at the indicated temperature for compounds **4**. In case of compounds **5**, after completion of the first step, acetonitrile was evaporated, DMAP (0.04 mmol) and anhydrous alcohol (2 mL) were added and the mixture stirred at 50°C. In case of compounds **6**, after completion of the first step, acetonitrile was evaporated, LiOH (0.4 mmol) and THF/H_2O in 2:1 ratio, were added and the mixture stirred at rt. In all cases, isolated yields of products are reported.

Anilines and heteroaromatic acyl pyrazoles were also suitable substrates for the one-pot reaction (**4k-n**). A selective formation of products **4o** and **4p** was observed when using an amino alcohol and a diamine as the nucleophiles. Aliphatic *N*-acyl pyrazoles did not give any product when reacted under

usual conditions, likely ascribed to reduced acidity of the α-hydrogen atoms. For the synthesis of α-trifluoromethylthiolated esters **5**, after removing CH_3CN from the crude mixture containing **3**, and the addition of alcohol, the mixture was reacted at 50°C in the presence of 20 mol% of DMAP; final esters **5a-c** were rapidly formed and isolated in good yields. Finally, the crude mixture of compounds **3** was directly hydrolysed with LiOH in THF/H_2O at room temperature to afford the α-trifluoromethylthiolated acids **6a,b** in 90% and 70% yields, respectively.

Interestingly, glycine ethyl ester and racemic α-amino acid ester hydrochloride salts proved to be pertinent nucleophiles to efficiently react, in a one-pot fashion, with intermediates **3** under basic conditions at room temperature (Table 3). This approach represents a first route to prepare highly functionalised α-trifluoromethylthiolated amides.

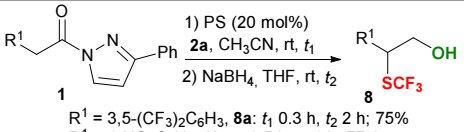
Table 3. One-pot synthesis of functionalised α-trifluoromethylthiolated amides from α-amino acid esters salts [a]



[a] All reactions were carried out using **1** (0.2 mmol,), **2a** (0.24 mmol,), PS (0.04 mmol), CH_3CN (0.2 M), at rt for the indicated time; then α-amino ester hydrochloride (0.26 mmol) and triethylamine (0.26 mmol) were added and the mixture was stirred at rt. Isolated yields of products **7** are reported.

To get better insight into the mechanism, the reaction reported in Table 2 to prepare compound **4a**, was performed in the presence of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 1 equiv).[18] At the end of the process product, **4a** was isolated in 85% yield, thus ruling out the involvement of a radical process. Moreover, monitoring of the model reaction by ^{19}F NMR in CD_3CN (Table 1) showed the amount of compound **3a** to increase over time, whereas a constant decrement of reagent **2a** was observed.[18] All these data are in agreement with a mechanism, where reagent **1** is deprotonated by PS to form the enolate, which would react with electrophilic compound **2a** to produce intermediate **3**.[16b]

To probe further the utility of the methodology, a one-pot, mild elaboration of intermediates **3** to alcohols was developed (Scheme 2).



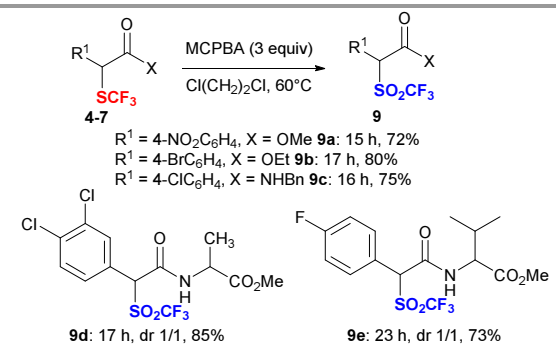
R^1 = 3,5-$(CF_3)_2C_6H_3$, **8a**: t_1 0.3 h, t_2 2 h; 75%
R^1 = 4-$NO_2C_6H_4$, **8b**: t_1 0.5 h, t_2 1 h; 77%
R^1 = 4-MeC_6H_4, **8c**: t_1 24 h, t_2 2 h; 80%
R^1 = 3-$MeOC_6H_4$, **8d**: t_1 22 h, t_2 3 h; 76%

Scheme 2 One-pot synthesis of 2-SCF_3-substituted primary alcohols.

A variety of compounds **1** were α-trifluoromethylthiolated under usual conditions and after removal of the solvent, the crude mixture was smoothly reduced with $NaBH_4$ in THF at room temperature, to give primary alcohols **8** in 75-80% yields. This sequence provides a complementary route to prepare α-trifluoromethylthiolated alcohols.[5e,20]

The introduction of the SO_2CF_3 group at α-position of carbonyl compounds has been rarely reported,[21] although the triflone group is of significant interest in drugs design[22] to modulate properties and bioavailability of compounds, being a highly polar as well as lipophilic residue.[23] An effective approach to prepare α-trifyl amides has been recently disclosed by Shibata, using a trifluoromethanesulfonyl hypervalent iodonium ylide.[24]

An alternative route to prepare triflones would involve a double oxidation of trifluoromethylthioethers. Some examples describing the oxidation of trifluoromethylthioethers to triflones, have been developed by using peracids,[25] hydrogen peroxide,[26] $NaIO_4/RuCl_3$,[27] CrO_3/H_5IO_6,[28] and $KMnO_4$.[29] However, to the best of our knowledge, the oxidation of α-trifluoromethylthiolated carboxylic acid derivatives to the corresponding triflones has not been reported. We found that when using readily available *m*-chloroperbenzoic acid (MCPBA) as the oxidant, working in 1,2-dichloroethane at 60°C, esters and amides **4**, **5**, **7** were smoothly transformed in fairly good yields into the corresponding triflones **9** (Scheme 3).



Scheme 3 Oxidation of compounds **4,5,7** to triflones with MCPBA.

Hence, the one-pot methodology for the α-trifluoromethylthiolation of carboxylic acid derivatives, coupled with oxidation, enables a facile entry to new functionalised triflones which can be of synthetic and pharmaceutical interest.

In summary, we have developed a first, metal-free, general approach for the α-trifluoromethylthiolation[30] of carboxylic acid derivatives, via readily available *N*-acyl pyrazoles.[31] The one-pot sequence proceeded efficiently under mild reaction conditions, using catalytic loadings of a commercial base and the Munavalli's reagent, followed by the addition of alcohols, amine, water and α-aminoacid esters as the nucleophiles. Reductive or oxidative post functionalizations of intermediates **3** and products **4-7**, to primary alcohols and more interestingly to triflones, open the access to other useful classes of fluorine-incorporating compounds.

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Conflicts of interest

There are no conflicts to declare.

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