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C(sp^2)–H Trifluoromethylation of enamides using TMSCF$_3$: access to trifluoromethylated isoindolinones, isoquinolinones, 2-pyridinones and other heterocycles†

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A method for the direct C(sp^2)–H trifluoromethylation of enamides, including biologically relevant isoindolinones, isoquinolinones and 2-pyridinones using TMSCF$_3$ under oxidative conditions is presented. The protocol is convenient, operationally simple and exhibits high tolerance across a multitude of relevant handles and functional groups.

Trifluoromethylation as a means to impart enhanced biological activity has received significant interest since the 1950s.[1] The sustained interest in organofluorine compounds for medicinal applications[2] has led to the development of a plethora[3] of trifluoromethylation procedures targeting pharmacologically important scaffolds, utilizing electrophilic,[4] radical[5] or nucleophilic[6] trifluoromethyl sources. Recently, the use of *S*-trifluoromethylsulfonium salts[7] and trifluoromethyl-λ^3-iodanes[8] as electrophilic trifluoromethyl sources has enabled trifluoromethylation of a variety of nucleophilic substrates. However, practical application of these reagents remains limited due to their high cost, and in some cases, their shock sensitivity.[9] To overcome these limitations, the use of readily available nucleophilic CF$_3$-transfer reagents such as the Ruppert–Prakash reagent, under oxidative conditions has been reported. Thus, in recent years, more efficient, safe and cost-effective protocols have become available.[10]

Enamides are found in many naturally-occurring substances and designed pharmaceuticals, as core structural and functional components, and are quintessential synthetic intermediates in the preparation of heterocycles, chiral amines and amides.[11] In this context, 3-methylene-isoindolin-1-ones,[12] isoquinolinones[13] and 2-pyridinones[14] represent an important class of heterocycles, all of which possess the enamide functionality (Fig. 1).

Still, despite their biological importance, methods for the synthesis of their trifluoromethyl analogues are scarce (*vide infra*). The direct trifluoromethylation of enamides, affording β-trifluoromethyl enamides,[15] has been achieved using Togni's reagent (**I**) and Umemoto's reagent (**II**), using Cu,[16a] Fe[16b] catalysis or light irradiation.[17] However, application of these protocols in the preparation of trifluoromethylated isoindolinones or isoquinolinones has hitherto not been reported. In the case of 2-pyridinones, methods to access these CF$_3$-substituted heterocycles through C–H trifluoromethylation employ CF$_3$COOH,[18] (CF$_3$CO)$_2$O,[19] CF$_3$SO$_2$Na,[20] CF$_3$SO$_2$Cl[21a] and CF$_3$I,[22] however, these transformations require expensive additives such as Rh, Ru or Ir photoredox catalysts, or oxidants such as XeF$_2$ (Scheme 1). Cu-Mediated cross-coupling approaches[23] using iodopyridinones as substrates have been established, however, the requirement to preinstall the iodo- motif and the need for stoichiometric amounts of Cu(I) salts pose significant drawbacks.

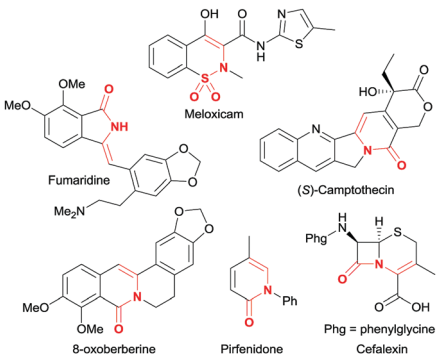

Fig. 1 Biologically relevant isoindolinones, isoquinolinones, 2-pyridinones and other enamides.

Recently, we disclosed a streamlined process to perform a difluorination-hydroxylation, C(sp^2)–H fluorination and trifluorination of enamide isoindolinones.[24] Surprisingly, despite numerous reports on oxidative trifluoromethylation using TMSCF$_3$,[10] there are no reports on the analogous C(sp^2)–H trifluoromethylation of this kind of scaffold (Scheme 2).

Thus, stemming from our interest in organofluorine and heterocyclic chemistry,[25] we set out to develop a practical, safe

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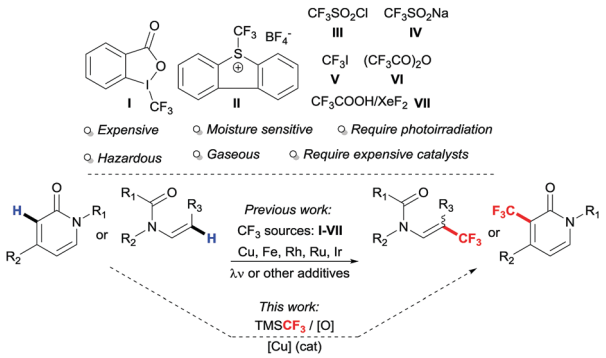
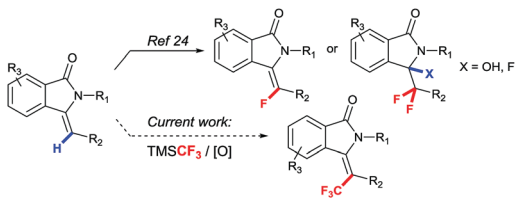
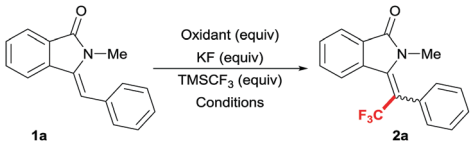


Scheme 1 Current methods for C–H trifluoromethylation of enamides and 2-pyridinones.



Scheme 2 Fluorofunctionalization of 3-methylene-isoindolinones.

Table 1 Optimization of the reaction conditions[a]



Entry	Solvent	Oxidant (equiv.)	$TMSCF_3$ (equiv.)	KF (equiv.)	Additive	Yield[b] (%)
1	CH_3CN	PIDA (2)	4	4	—	22
2	CH_3CN	PIFA (2)	4	4	—	42
3	CH_3CN	PIFA (2)	2	2	—	52
4	CH_3CN	PIFA (1.5)	1.5	1.5	—	52
5	CH_3CN	PIFA (1.5)	1.5	1.5	CuCl	59
6	CH_3CN	PIFA (1.5)	1.5	1.5	$Cu(OTf)_2$	56
7	CH_3CN	PIFA (1.5)	1.5	1.5	$Fe(OAc)_2$	7
8	CH_3CN	PIFA (1.5)	1.5	1.5	$ZnCl_2$	30
9	CH_3CN	PIFA (1.5)	1.5	1.5	$Cu(OAc)_2$	62
10[c]	**CH_3CN**	**PIFA (1.5)**	**2.0**	**1.5**	**$Cu(OAc)_2$**	**73**
11[d]	CH_3CN	PIFA (1.5)	1.5	1.5	$Cu(OAc)_2$	39

[a] Conditions: **1a** (0.25 mmol), solvent (2.5 mL), 0.1 equiv. of additive unless otherwise specified, room temperature for 1 h. [b] Yield determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard. [c] 0.3 equiv. of additive. [d] 1 equiv. of additive. PIFA = bis(trifluoroacetoxy)iodobenzene; PIDA = diacetoxyiodobenzene; **2a** was obtained as a (3 : 1) mixture of *E* : *Z* isomers in all cases.

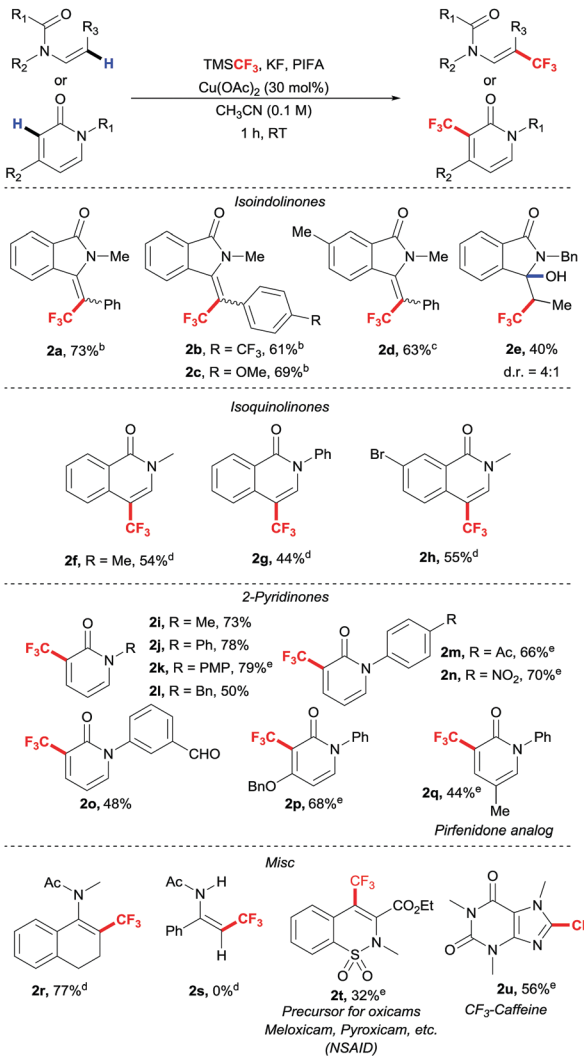
and operationally simple protocol for the C(sp^2)–H trifluoromethylation of enamide isoindolinones, isoquinolinones, 2-pyridinones and other heterocycles under oxidative conditions, employing $TMSCF_3$ as an inexpensive and readily available source of the $-CF_3$ functionality. Toward this end, isoindolinone **1a** was selected as our model substrate, and the results of our optimization are summarized in Table 1.[28]

Initial investigations employing (diacetoxyiodo)benzene (PIDA) as oxidant and KF, in combination with $TMSCF_3$, conditions similar to those previously reported,[26] afforded low yield (22%) of the expected trifluoromethylated isoindolinone **2a** (entry 1). Between the two oxidants screened, [bis(trifluoroacetoxy)iodo]benzene (PIFA) was found to be better suited for this reaction in acetonitrile, affording **2a** in 42% yield (entry 2). These results contrast with previous reports in which PIFA was inferior[26a] to PIDA or completely unsuitable[26b,c] to promote C–H trifluoromethylations of other substrates. The stoichiometry of the reaction played a decisive role in affording **2a** in high yield. Thus, decreasing the amount of PIFA and KF to 1.5 equiv. was beneficial for the reaction, providing the target product in 52% yield (entry 4). At this point, our assumption was that the reaction proceeded through an *in situ* generated I^{III}–CF_3 reagent. In this context, previous studies with Togni's reagent demonstrated the beneficial effect of redox-active and/or Lewis acid additives in trifluoromethylation reactions.[16,27] Thus, the effect of such additives was studied (entries 5–11). The addition of CuCl (10 mol%) increased the yield of **2a** to 59%. Equal loadings of $Cu(OTf)_2$, $Fe(OAc)_2$ or $ZnCl_2$ gave diminished yields (entries 5–8). In contrast, $Cu(OAc)_2$ provided the highest yield of 62% (entry 9). Subsequent optimization revealed that 2 equiv. of $TMSCF_3$ and 0.3 equiv. of $Cu(OAc)_2$ afforded **2a** in 73% yield, while conducting the reaction in the presence of 1 equiv. $Cu(OAc)_2$ significantly inhibited the formation of **2a** (entries 10 and 11, respectively).

Having found the optimal conditions for this transformation (Table 1, entry 10), we explored the generality of the C(sp^2)–H trifluoromethylation, and the conditions were applied to a series of enamide-containing scaffolds (Table 2). Aryl-substituted isoindolinones responded well, affording trifluoromethylated products **2a–2d** in good isolated yields (63–73%) as mixtures of *E* : *Z* geometrical isomers in a 4 : 1 to 3 : 1 ratio. A slightly decreased yield was observed in the substrate possessing electron-withdrawing CF_3-group (**1c**). Isoindolinone bearing an alkyl group on the alkene functionality (**1e**), afforded the hydroxytrifluoromethylation product **2e** in 40% yield. Given the lower reactivity of endocyclic double bonds, Isoquinolinones **1f–1h** were less responsive to the optimized reaction conditions. Nevertheless, the target molecules could be obtained, provided that a slight excess of reagents is employed. In this fashion, utilizing $TMSCF_3$ (4.5 equiv.), KF (3 equiv.) and PIFA (3 equiv.), the hitherto unknown CF_3-substituted isoquinolinones (**2f–h**) were successfully prepared in 44–55% isolated yields. The bromo substituent was found amenable to the reaction conditions, allowing for downstream chemical elaborations (Table 2, **2h**). Next, given their tremendous biological importance,[14] we shifted our attention to 2-pyridinones. Under the optimized reaction conditions, *N*-methyl- and *N*-phenyl-2-pyridinone (**1i** and **1j**, respectively) provided high yields of the corresponding 3-trifluoromethylated products (73% and 78%, respectively). Though heterocycles or substrates such as **1s** bearing a free N–H functionality did not afford the expected products, acid stable, easily removable protecting groups, including –Bn and –PMP are well tolerated, successfully providing the desired trifluoromethylated products (**2e**, **2k**, **2l**).

Subsequently, several *N*-arylated 2-pyridinones were subjected to the optimized reaction conditions. In the case of Ac-, NO_2-, and

Table 2 Substrate scope of C(sp^2)–H trifluoromethylation[a]

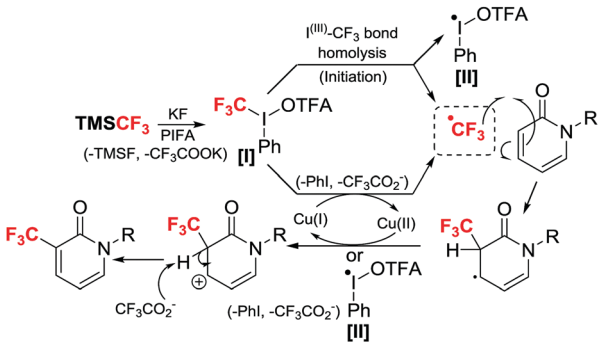


[a] Reaction conditions: Unless otherwise stated, substrate **1** (0.25 mmol), PIFA (1.5 equiv.), KF (1.5 equiv.), $TMSCF_3$ (2 equiv.) and $Cu(OAc)_2$ (0.3 equiv.) in MeCN (2.5 mL) at room temperature for 1 h. Isolated yields (average of two trials) are shown. [b] 3 : 1 ratio of *E* : Z isomers. [c] 4 : 1 ratio of *E* : *Z* isomers. [d] KF (3 equiv.), PIFA (3 equiv.) and $TMSCF_3$ (4.5 equiv.) was used. [e] A second portion of KF (1.5 equiv.), PIFA (1.5 equiv.) and $TMSCF_3$ (2 equiv.) was added after 1 h. See ESI for complete experimental details. Bn = benzyl; PMP = *p*-methoxyphenyl.

CHO-substituted 2-pyridinones, the corresponding 3-CF_3-substituted products **2m–2o** could only be obtained in modest yields (48–58%). These results could be attributed to the strong electron-withdrawing effect of these groups. However, the yields could be successfully increased by adding a second portion of reagents. In this manner, **2m** and **2n** could be accessed in 66% and 70% isolated yields, respectively. Similarly, benzyloxy-substituted 2-pyridinone **1p** afforded the corresponding product in 68% yield. Noticeably, a trifluoromethylated analogue of pirfenidone, a drug used for the treatment of idiopathic pulmonary fibrosis, could be accessed in 44% yield using this protocol (**2q**). In the case of 2-pyridinones, selectivity toward the 3-position was always observed, in agreement with previous findings.[18–20,21b] Reaction with tetralone-derived enamide afforded **2r** in a good isolated yield (77%) and over-oxidation or aromatization did not occur. Importantly, as evidenced by the successful preparation of **2m** and **2o**, the present protocol shows great compatibility with carbonyl functionality (ketone and aldehyde), and no trifluoromethyl addition products were detected.[6a,b] These results are notable, as they allow for further product functionalization.

In pursuit of medicinally active trifluoromethylated heterocycles, we explored the possibility of utilizing our method to perform a C–H trifluoromethylation of benzosultams. Benzothiazine-1,1-dioxide derivatives are of particular interest, as their frameworks are widespread in a variety of pharmaceutical compounds such as the oxicams: a family of non-steroidal anti-inflammatory drugs (NSAID), including Meloxicam (Fig. 1), Piroxicam, Ampiroxicam, *etc.* Gratifyingly, benzothiazine dioxide **1t** afforded the expected CF_3-substituted product **2t** in practical yield. Though these results could be certainly improved, the successful preparation of **2t** without affecting the ester functionality,[29] should be highlighted, as it enables a subsequent amidation step, required in the preparation of piroxicam and meloxicam trifluoromethyl analogues.[30] Finally, trifluoromethyl-caffeine **2u** was obtained in 56% isolated yield, constituting a significant improvement over previous synthesis using $TMSCF_3$.[31]

To gain insight into the mechanism of this reaction, a series of control experiments were conducted.[28] The reaction of **1a** under optimized conditions in the presence of radical scavengers like BHT and TEMPO, completely inhibited the formation of **2a** (<1%). TEMPO-CF_3 adduct was formed in high yields both in the presence and in the absence of substrate. The reaction of **1i** with $TMSCF_3$, KF and $Cu(OAc)_2$ (1 equiv.) in the absence of PIFA (rt, 1 h), did not afford **2i** and large amounts of [$CuCF_3$] species, along with CF_3H were observed by ^{19}F NMR spectroscopy. Addition of PIFA to this mixture led to the formation of **2i** in only 3% yield after 1 h. These results demonstrate that PIFA is essential for the process, and that Cu(II) is not a competent oxidant for [CF_3^-] under these conditions. Similarly, reaction of **1i** with well-defined (phen)$CuCF_3$,[32] in the presence of PIFA, afforded **2i** in only 9% yield, showing that *in situ* formed [$CuCF_3$] species can play only a minor role.[33] While further studies are necessary to gain a complete mechanistic understanding, taken together, these results lend support that a CF_3 radical derived from $TMSCF_3$ is the active trifluoromethylating species, rather



Scheme 3 Plausible mechanistic pathways.

than a trifluoromethyl iodonium species $[Ph–I–CF_3]^+$ as postulated in previous reports.[26a] A plausible mechanism is shown in Scheme 3 and discussed in detail in the ESI.†

In conclusion, we have developed an efficient method for the direct C–H trifluoromethylation of enamides using $TMSCF_3$ as a convenient, inexpensive and readily available CF_3 source. Under oxidative conditions, a series of hitherto unknown CF_3-containing isoindolinones, isoquinolinones and 2-pyridinones were efficiently prepared. Application of this protocol for the preparation of trifluoromethyl analogues of active pharmaceutical ingredients such as pirfenidone, caffeine and benzothiazine dioxide derivatives was also established.

Conflicts of interest

There are no conflicts to declare.

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