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Direct Photoassisted α-Trifluoromethylation of Aromatic Ketones with Trifluoroacetic Anhydride (TFAA)

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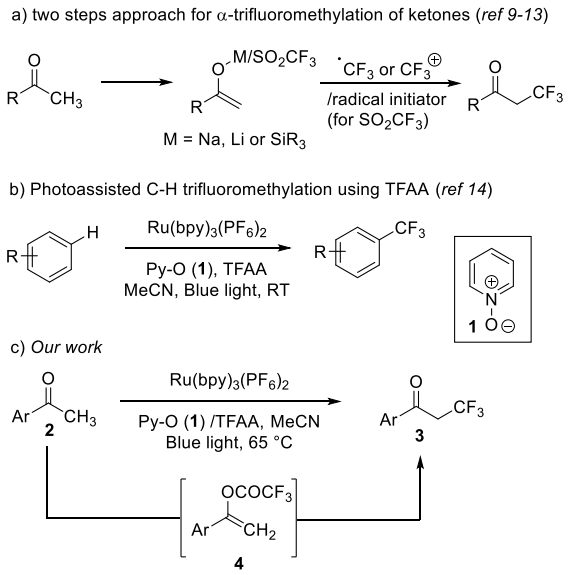
Abstract. Direct α-Trifluoromethylation of acetophenone derivatives was achieved by using trifluoroacetic anhydride (TFAA) as the trifluoromethyl source and pyridine-*N*-oxide (Py-O) as activator and oxidant under visible light irradiation and tris-(2,2´-bipyridine)ruthenium(II) hexafluorophosphate ($Ru(bpy)_3(PF_6)_2$) as the photocatalyst. Different acetophenone derivatives could be converted to the corresponding α-CF_3 derivatives with high selectivity. Extensive mechanistic investigation revealed the formation of vinyl trifluoroacetate as the key intermediate for this transformation.

Keywords: Trifluoromethylation; Fluorinated organic compounds; Photoredox catalysis; Aromatic ketone; Trifluoroacetic anhydride.

Fluorinated organic compounds are particularly important molecules because of their widespread application in pharmaceuticals and agrochemicals. In fact, 20-30% of modern pharmaceuticals and agrochemicals contain at least one fluorine atom.[1] One approach of incorporating fluorine atom in organic molecules is *via* the installation of trifluoromethyl (CF_3) group which can have a profound influence on the pharamacokinetic properties of the molecules.[2] Many elegant approaches for the trifluoromethylation of organic molecules[3] using electrophilic,[4] nucleophilic[5] and radical[6] sources are now available. Despite this, most of the reagents available for this purpose are expensive and a large-scale application would be limited due to availability and costs. Thus, the development of new trifluoromethylation methods applying cheap and abundant CF_3 sources will be very useful in synthetic chemistry.[7]

α-CF_3 carbonyl compounds are valuable building blocks for the synthesis of various complex CF_3 containing molecules.[8] Different approaches for the synthesis of such molecules have been reported, either directly from the ketones or from other starting materials.[9] The most common strategies for the synthesis of α-trifluoromethylated carbonyl compounds from carbonyl molecules usually are based on the two steps shown in **Scheme 1a**. Enolates derived from the ketones are reacted with either a radical CF_3 or an electrophilic CF_3 source to provide the α-CF_3 products.[10][11]



Scheme 1. a) Trifluoromethylation of ketones using radical or electrophilic CF_3 sources as reported in the literature; b) photoredox C-H trifluoromethylation of aromatics using TFAA as CF_3 source as reported by Stephenson's group; c) our work on the direct α-trifluoromethylation of acetophenones *via* the *in situ* formation of vinyl trifluoroacetate.

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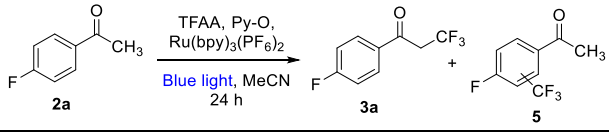
Several reports on the α-C-H trifluoromethylation of carbonyl compounds appeared in the last years. Macmillan *et al* achieved an α-trifluoromethylation of ketones *via* the reaction of silyl enol ether and CF_3I as the CF_3 source under photoassisted conditions.[12] Recently, Kamimura *et al*. have shown another interesting protocol for the synthesis of α-CF_3 ketones.[13] Vinyl triflates derived from a ketone can be rearranged to α-CF_3 carbonyl compounds in the presence of a radical initiator, *e.g.* triethyl borane (BEt_3). The same rearrangement can also be performed by photocatalysis as shown by Liu *et al*.[14] Despite these advancements, most of the reported procedures use CF_3-sources which are expensive and all these procedures are based on a two-step approach for the trifluoromethylation of ketones.

Recently, Stephenson's group reported a photoredox trifluoromethylation protocol using trifluoroacetic anhydride (TFAA) as CF_3 source and pyridine N-oxide **1** (Py-O) as the activator for TFAA as well as the oxidant.[15] Using $Ru(bpy)_3(Cl)_2$ as the photocatalyst, they achieved trifluoromethylation of a series of electron-rich aromatics and heteroaromatics under mild conditions (**Scheme 1b**). TFAA is a cheap and easily available CF_3 source, thus expansion of this protocol could be valuable for the synthesis of other CF_3-containing molecules. Inspired by their report, we were wondering if this trifluoromethylation approach could be extended for the synthesis of other CF_3-containing building blocks. In particular, the target was the α-trifluoromethylation of acetophenone derivatives. We envisioned that in the presence of TFAA and Py-O, the trifluoroacetate **4** can be generated *in situ*, which can react with the CF_3 radical under photochemical condition to provide the α-CF_3 product **3**. Herein, we report this direct trifluoromethylation of acetophenone derivatives using the TFAA/Py-O system under photoassisted condition.

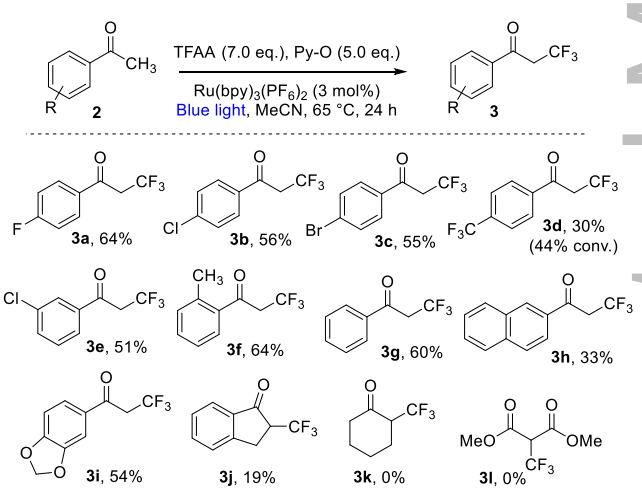
Table 1. Initial screening results for the α-trifluoromethylation of 4-fluoroacetophenone.



Entry[a]	TFAA/Py-O (eq.)	Temp.	Conversion[b]	**3a**/**5**
1	2.2/2.0	RT	-	-
2	4.4/4.0	RT	30%	1/3
3	4.4/4.0	50 °C	34 %	3.5/1
4	4.4/4.0	65 °C	57%	9/1
5[c]	4.4/4.0	65 °C	52%	12/1
6	5.5/5.0	65 °C	85%	100/-
7[d]	4.4/4.0	65 °C	0%	-
8[e]	4.4/4.0	65 °C	0%	-

[a] 0.25 mmol of substrate was used in 1.5 mL MeCN. [b] Conversion refers to the total conversion of **2a** to products (**3a** + **5**) and was determined from GC after work up with an aq. $NaHCO_3$ solution. [c] $Ru(bpy)_3(Cl)_2.6H_2O$ was used as the catalyst. [d] The reaction was carried out in the dark. [e] No photocatalyst.

To start these investigations, 4-fluoroacetophenone **2a** was used as the model substrate and $Ru(bpy)_3(PF_6)_2$ as the photocatalyst. The use of 2 eq. of Py-O and TFAA at room temperature did not provide any significant conversion of the substrate **2a** after 24 h. Twice the amount of TFAA/Py-O provided 30% conversion. Unfortunately, we obtained a mixture of both the α-CF_3 product **3a** as well as the trifluoromethylation product **5** (Table 1, entries 1-2). Interestingly, increasing the temperature from RT to 50 °C increased the conversion and the selectivity towards the α-CF_3 product **3a** (entry 3). Increasing the temperature further to 65 °C, provided reasonable conversion and good selectivity to the α-CF_3 product **3a** (entry 4). Changing the photocatalyst from $Ru(bpy)_3(PF_6)_2$ to $Ru(bpy)_3(Cl)_2$ under otherwise similar condition, gave a slightly lower yield (entry 5). The conversion could be further increased by using 5.5 eq. of TFAA and 5.0 eq. of Py-O (entry 6). Under these conditions, no aromatic trifluoromethylation product **5** was observed. Addition of external bases *e.g.* K_3PO_4 or Na_2CO_3 did not improve the conversion (see SI **Table S1**, page 3 for full optimisation and screening). Control experiments showed no conversion to the product in the absence of light or catalyst (entries 7-8).



Scheme 2. Substrate scope for the α-trifluoromethylation of acetophenones under photoassisted conditions using TFAA as CF_3 source and $Ru(bpy)_3(PF_6)_2$ as the photocatalyst. Isolated yields after the chromatographic purification.

With the optimised reaction conditions for the α-trifluoromethylation of **2a** in hand, we next examined the substrate scope for this method. Different acetophenone derivatives were screened under the optimised reaction conditions. Similar isolated yields were obtained for the different 4-halo-substituted acetophenones to their corresponding CF_3 products.

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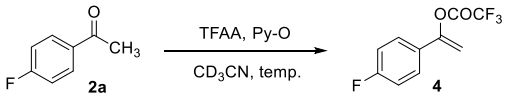
For *p*-CF_3 acetophenone, the conversion was only 44% (from ^{1}H NMR) and the isolated yield of the product **3d** was 30%. Other acetophenone derivatives gave similar yields of the products as shown in **Scheme 2**; *e.g.* for 3-chloro and 2-Me acetophenones, the yield obtained for the corresponding α-CF_3 products **3e** and **3f** were 51% and 64% respectively. While acetophenone as substrate gave the corresponding product **3g** in 60% yield, 2-acetopnaphthone provided only 33% of the corresponding product **3h**. Also, in the case of indanone, the product **3j** was obtained in very low yield. When cyclohexanone or dimethyl malonate were used as substrates, no corresponding α-CF_3 products were obtained under these conditions.

Table 2. Optimisation study for the vinyl trifluoroacetate **4** formation in the presence of TFAA and Py-O.



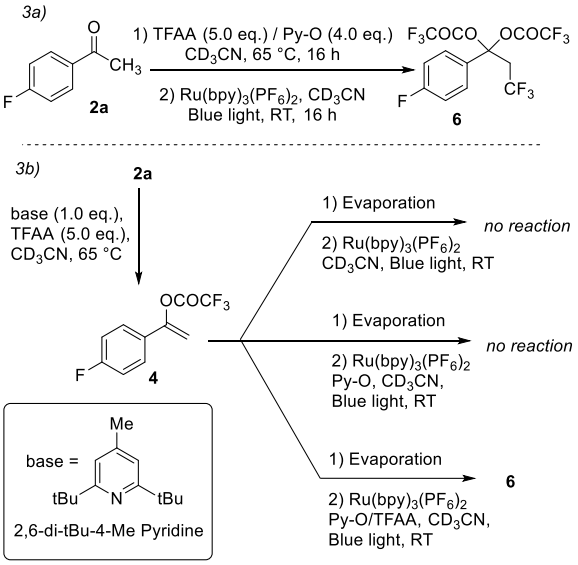
Entry[a]	TFAA (eq.)	Py-O (eq.)	Temp.	Conversion[b]
1	4	1	RT	2%
2	2	1	65 °C	34%
3	5	1	65 °C	60%
4	5	0	65 °C	0%
5	5	2	65 °C	89%
6	5	3	65 °C	97%
7	5	4	65 °C	*quant.*

[a] All reactions were carried out in 0.25 mmol scale in 1.5 mL of CD_3CN. [b] Conversions are given relative to the product and were measured from ^{1}H NMR of the crude reaction mixture.

To investigate the role of TFAA and Py-O for this transformation, the initial step of the reaction in the dark which involves the formation of vinyl trifluoroacetate **4** was examined. As shown in Table **2**, no vinyl trifluoroacetate **4** is formed at room temperature, which explained the low conversion under ambient conditions. Higher temperatures accelerate the formation of **4** and the formation of **4** was completely stopped in the absence of pyridine N-oxide. Almost 5.0 eq. of TFAA and 4.0 eq. of Py-O are required for the quantitative conversion of the substrate **2a** to the vinyl trifluoroacetate **4**. This can explain the necessity of the demand for the excess of TFAA and Py-O to obtain reasonable conversions and yields.

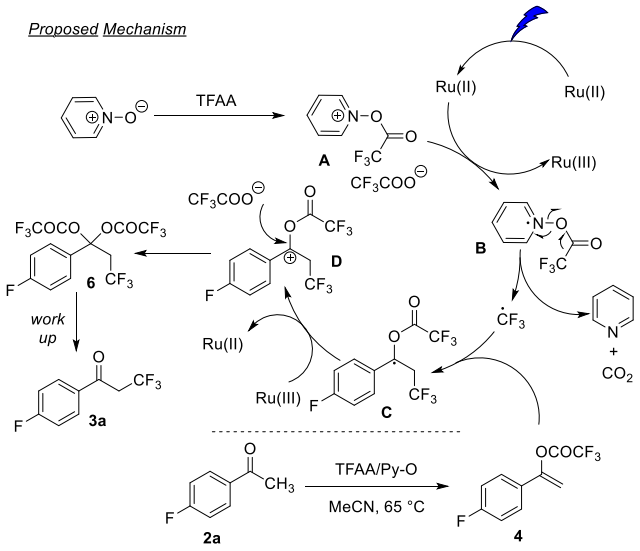
Interestingly, this vinyl trifluoroacetate **4** reacted smoothly under photoassisted condition to provide the α-CF_3 product **6** at room temperature (**Scheme 3a**, also see SI **Figure S1,** page 10 for more details). As from the first step there was already Py-O and TFAA present in the crude reaction mixture, this experiment could not provide any details about the role of Py-O and TFAA for the second step of the reaction.

To examine the role of TFAA/Py-O for the formation of the product **3a** from the vinyl trifluoroacetate **4,** the vinyl trifluoroacetate **4** was prepared *in situ* using 2,6-di-*t*Bu-4-Me pyridine as the base[16] (**Scheme 3)**. When **4** was treated under photoassisted conditions in the absence of TFAA, in contrast to the vinyl triflates as shown by Lie *et al*,[14]no rearrangement to **3a** could be observed. Also, no product was formed when **4** was treated under photoassisted conditions in the presence of Py-O. The product formation only occurred when both reagents TFAA and Py-O were present in the reaction mixture. This observation could explain the requirement for an excess of both the reagents TFAA and Py-O for achieving good yields of the α-CF_3 product.



Scheme 3. Synthesis of vinyl trifluoroacetate **4** and subsequent control reactions.

Based on the observations described above and following literature reports, the mechanism as shown in **Scheme 4** can be proposed, exemplified by 4-fluoro acetophenone **2a** as the substrate. First, vinyl trifluoroacetate **4** is formed from the acetophenone **2a**. This step requires both reagents TFAA and Py-O as well as higher temperature. This step is a light independent reaction. The second step is the photoassisted cycle, where the formed vinyl trifluoroacetate **4** will trap the CF_3 radical formed from the pyridinium intermediate **A** as proposed by Stephenson's group.[15] Oxidation of this radical by Ru(III) will form the carbocation **D**. This will be captured by the trifluoroacetate anion to form the trifluoroacetyl-protected acetal **6**. This compound upon work up will give the product **3a**.



Scheme 4. Mechanistic proposal for the photoassisted α-trifluoromethylation of acetophenones with TFAA exemplified by 4-fluoroacetophenone as the substrate.

In summary, we achieved the direct α-trifluoromethylation of aromatic ketones under photoassisted conditions. This method utilizes TFAA as CF_3 source and pyridine-*N*-oxide as oxidant. Because of the low cost and the availability of these materials, we expect that this method will find numerous applications for the synthesis of α-CF_3 ketones.

Experimental Section

In a 4 mL screw-capped vial with a rubber septum, 4-fluoroacetophenone (60 µl, 0.5 mmol), pyridine-*N*-oxide (240 mg, 2.5 mmol), $Ru(bpy)_3(PF_6)_2$ (13.0 mg, 0.015 mmol) were dissolved in 2 mL dry MeCN. The vial was closed and degassed by bubbling argon for 30 sec. Trifluoroacetic anhydride (480 µl, 3.5 mmol) was added to the reaction mixture and stirred for 16 h at 65 °C under blue light irradiation (435-445 nm, 500 mA, 5-6 watts). After this time, the reaction mixture was quenched by adding 10 mL sat. aq. $NaHCO_3$ solution and extracted with EtOAc (3 X 15 mL). The organic layer was dried using anhydrous $MgSO_4$ and concentrated *in vacuo*. The pure product was obtained after the chromatographic purification as colorless oil. Yield: 64%; 66 mg. R_f = 0.22 (5% EtOAc in pet ether); ^{1}H NMR (301 MHz, $CDCl_3$) δ 8.00 – 7.92 (m, 1H), 7.21 – 7.13 (m, 1H), 3.76 (q, J = 9.9 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 188.11 (q, *J* = 2.5 Hz), 166.37 (d, *J* = 257.1 Hz), 132.30 (dq, *J* = 3.2, 1.7 Hz), 131.17 (d, *J* = 9.6 Hz), 123.86 (q, *J* = 277.0 Hz), 116.20 (d, *J* = 22.2 Hz), 42.14 (q, *J* = 28.4 Hz); ^{19}F NMR (283 MHz, $CDCl_3$) δ -62.00 (s), -102.87 (s).

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COMMUNICATION

Direct Photoassisted α-Trifluoromethylation of Aromatic Ketones with Trifluoroacetic Anhydride (TFAA)

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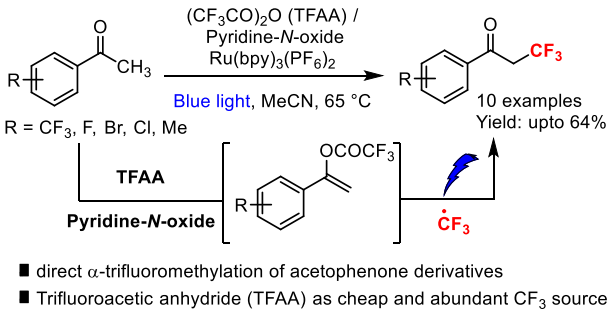

- direct α-trifluoromethylation of acetophenone derivatives
- Trifluoroacetic anhydride (TFAA) as cheap and abundant CF_3 source