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Continuous Flow α-Trifluoromethylation of Ketones by Metal-Free Visible Light Photoredox Catalysis

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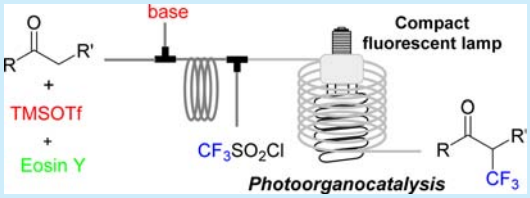
Supporting Information

ABSTRACT: A continuous-flow, two-step procedure for the preparation of α-CF_3-substituted carbonyl compounds has been developed. The carbonyl substrates were converted *in situ* into the corresponding silyl enol ethers, mixed with the CF_3 radical source, and then irradiated with visible light using a flow reactor based on transparent tubing and a household compact fluorescent lamp. The continuous protocol uses Eosin Y as an inexpensive photoredox catalyst and requires only 20 min to complete the two reaction steps.



Organic compounds with polyfluoroalkyl moieties such as CF_3 groups are very important in the production of agrochemicals and pharmaceuticals, as these molecules typically exhibit enhanced biological properties.[1] Thus, in the past few years significant efforts have been made to develop effective methods of trifluoromethylation for a wide range of interesting scaffolds.[2] One of the motifs that has drawn particular attention is the preparation α-CF_3-substituted carbonyl compounds. Introduction of a CF_3 group at the α-position of carbonyl compounds is considered to be a difficult task[3] and, in recent years, has been the subject of intense research.[3−9] In this context, several electrophilic and radical trifluoromethylation protocols involving enolate,[4] silyl enol ether,[5] and enamine[6] intermediates have been described, which today are the most commonly employed methods. Recently, the synthesis of α-CF_3-substituted ketones by trifluoromethylation of α-haloketones[7] and oxidative trifluoromethylation of olefins[8] has also been reported.

In 2011 MacMillan and co-workers described a convenient procedure for the preparation of α-trifluoromethyl carbonyl compounds from silyl enol ethers by means of photoredox catalysis, using CF_3I to generate the electrophilic trifluoromethyl radical and $Ru(bpy)_3Cl_2$ as the catalyst.[9] In this work, an elegant one-pot procedure for the direct α-trifluoromethylation of carbonyl compounds was also introduced. Although good yields were obtained for the desired trifluoromethylated products, the method required 10 equiv of CF_3I gas and approximately 24 h of visible light exposure for completion. These drawbacks and the problems typically associated with scaling UV or visible light photochemistry[10] somewhat limits the applicability of this method for large scale preparations. Based on these factors, we envisaged a continuous-flow protocol for the direct two-step α-trifluoromethylation of carbonyl compounds, where the substrate is initially converted into the corresponding silyl enol ether and *in situ* subjected to a visible light induced trifluoromethylation in a flow regime. It has been well documented that microreactor/continuous flow technology can overcome the problems associated with larger scale photochemical transformations.[11,12] The relatively low reactor volume and in particular the high surface to volume ratio of capillary flow reactors assure intense and uniform irradiation of the reaction mixture for a specific time period very precisely controlled by the pump flow rate, thus avoiding overirradiation of the solution. Moreover, the optimized reaction conditions can be readily scaled by a simple scale-out or numbering up of the reactor.[11]

Herein we present a continuous-flow procedure for the two-step α-trifluoromethylation of ketones. Initially, the ketones were transformed into the corresponding silyl enol ethers in flow and *in situ* subjected to visible light induced radical trifluoromethylation using Eosin Y and triflyl chloride (CF_3SO_2Cl) as a novel and highly efficient combination system for photoredox-catalyzed trifluoromethylations.

Our flow setup consisted of two connected parts designed to accomplish each of the reaction steps (Figure 1). In the first part of the reactor the formation of the silyl enol ether from the corresponding ketone takes place. For this purpose trimethylsilyl triflate (TMSOTf) was selected as a silylating agent, and diisopropylethylamine (iPr_2EtN), as a base. Preliminary batch experiments revealed that by using these reagents, the silyl enol ethers of acetophenone and of the less reactive 4-fluoroacetophenone were formed after only 2 min at room temperature (see Supporting Information for details).[13] Thus, using two separated feeds, the substrate, TMSOTf, and the photoredox catalyst (Feed A) (Figure 1), and the base (Feed B), dissolved in THF were introduced into the reactor. For this purpose, sample loops of 2 mL and standard HPLC pumps were employed. The two streams were pumped with flow rates of 0.5 mL min^{-1}, mixed using a standard T-mixer, and reacted in a

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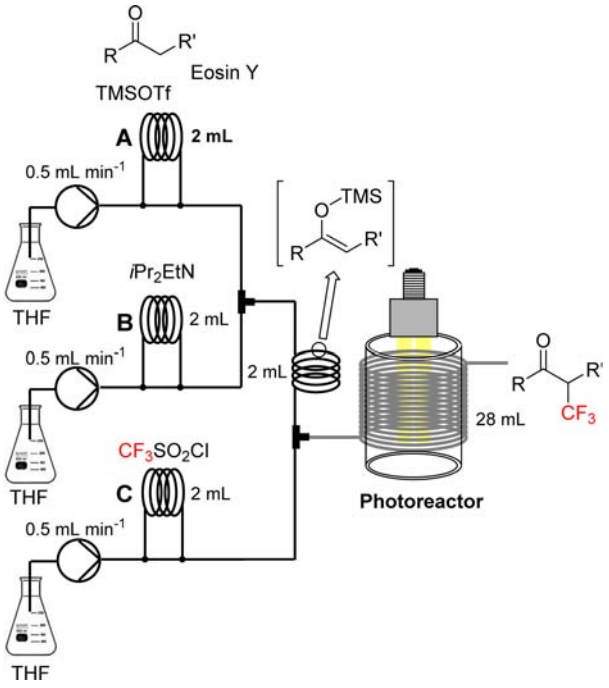


Figure 1. Continuous flow setup for the two-step visible light induced α-trifluoromethylation of ketones. Feed A: ketone (0.75 M), TMSOTf (1.5 equiv), and Eosin Y (0.5 mol %) in THF. Feed B: iPr$_2$EtN (1.5 equiv) in THF. Feed C: CF_3SO_2Cl (1.5 equiv) in THF. For a detailed description of the flow reactor, see Supporting Information.

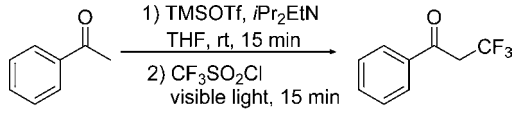
residence time unit of 2 mL (2 min residence time). It should be pointed out that the use of the comparatively inexpensive TMSOTf as the silylating agent significantly reduces the cost of this procedure with respect to the more costly triisopropylsilyl and *tert*-butyldimethylsilyl triflates utilized by MacMillan and co-workers.[9] After the formation of the silyl enol ether intermediate, the solution was mixed with a third stream (Feed C) (Figure 1) containing the trifluoromethylation reagent dissolved in THF. The combined streams then entered the photoreactor, which consisted of transparent fluorinated ethylene propylene (FEP) tubing (ø 1/8") coiled around a glass cylinder.[14] Inside the glass cylinder a commercial cool-white household compact fluorescent lamp was placed.

One of the main aims of this work was to substitute the expensive and rare metal based $Ru(bpy)_3Cl_2$ catalyst typically employed in this type of photoredox catalysis reactions[15] with a cheaper and readily available alternative. Several organic dyes[16] including Eosin Y[17] and Rose Bengal[18] have been reported as useful photosensitizers in light mediated organic transformations. Eosin in particular attracted our attention owing to its low price, low toxicity, and analogous redox properties with respect to those reported for $Ru(bpy)_3Cl_2$.[16,19]

Thus, a set of preliminary batch reactions were carried out to test the performance of Eosin B and Y toward the visible light mediated trifluoromethylation of *in situ* generated silyl enol ethers, using acetophenone as the model substrate and triflyl chloride (CF_3SO_2Cl) as the source of trifluoromethyl radicals. The batch reactions were performed in 2 mL Pyrex vials of ca. 15 mm diameter and exposed to the light generated by a cool-white 30 W compact fluorescent lamp for 15 min (see Supporting Information for details). It should be noted that when the silylating agent was added to a dispersion containing Eosin Y in THF the catalyst rapidly solubilized. This possibly points to a reversible silylation of Eosin Y in the presence of TMSOTf.

In all batch experiments (Table 1) variable amounts of phenacyl chloride were observed as a side product, probably

Table 1. Preliminary Batch Experiments for the One-Pot, Two-Step α-Trifluoromethylation of Acetophenone[a]



entry	catalyst	conv (%)[b]	selectivity (%)[b]
1	none	30	50
2	$Ru(bpy)_3Cl_2$	20	<10
3	Eosin B	60	75
4	Eosin Y	85	95
5	Eosin Y[c]	<10	<10

[a]Reaction conditions: (1) 1 mmol of acetophenone, 1.2 equiv of TMSOTf, 1.2 equiv of iPr$_2$EtN, 1 mol % catalyst, 1.5 mL of THF, 15 min of stirring at rt. (2) 2 equiv of CF_3SO_2Cl, 30 W of white CFL irradiation, 15 min. [b]HPLC (254 nm). [c]No light irradiation.

resulting from the electrophilic addition of the CF_3SO_2Cl chlorine atom to the silyl enol ether intermediate. Unfortunately, other triflyl halides (CF_3SO_2X) are not commercialy available, and when triflic anhydride $(CF_3SO_2)_2O$ was used as a reagent no conversion was observed. As expected, poor conversion and selectivities were observed not only in the absence of a photoredox catalyst (entry 1) but also when $Ru(bpy)_3Cl_2$ was used as additive (entry 2). Better performance was observed for Eosin B, and 60% conversion with moderate selectivity was obtained after 15 min (entry 3). Gratifyingly, Eosin Y showed excellent results for the α-trifluoromethylation of acetophenone (Table 1, entry 5). After only 15 min of light exposure high conversion with excellent selectivity was obtained. It should be pointed out that the $Ru(bpy)_3/CF_3I$ system required 10 equiv of reagent and 24 h of light exposure.[9] Therefore, the Eosin Y/CF_3SO_2Cl combination appears to be an extremely efficient system for these trifluoromethylation reactions. Importantly, no degassed solvents or inert atmosphere was required for these reaction, and all solutions were prepared in a standard fume hood.[20]

After the catalytic system was established we moved forward and translated the above-described batch reaction conditions to our continuous flow setup. Thus, a solution containing CF_3SO_2Cl in THF was loaded into Feed C of our flow reactor (Figure 1). Eosin Y was introduced through Feed A, together with the substrate and TMSOTf, in order to avoid early interaction with the trifluoromethylation reagent and premature decomposition. A series of flow reactions were then carried out using acetophenone as the model substrate to establish the optimal flow conditions (see Table S2 in the Supporting Information). Gratifyingly, under continuous flow conditions the selectivity was improved compared to the batch reaction, and only trace amounts of the phenacyl chloride side product were detected. The catalyst loading could be reduced to 0.5 mol %, which corresponds to the $Ru(bpy)_3Cl_2$ concentration utilized by MacMillan and co-workers.[9] Using 1.5 equiv of TMSOTf and base[21] and 3 equiv of CF_3SO_2Cl, the two reaction steps were completed (93% overall conversion) after only 20 min, which corresponds to a flow rate of 0.5 mL min^{-1}

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for each of the three feeds of the reactor (total 1.5 mL min^{-1}). The crude reaction mixture was collected at the reactor output and quenched with methanol. Evaporation of the solvent under reduced pressure and purification of the residue by column chromatography yielded the desired 2-trifluoromethylacetophenone (86%).

Using the optimized reaction conditions a diverse set of ketones was transformed into the corresponding α-trifluoromethyl derivatives using the continuous-flow regime (Figure 2). Thus, several *para*- (**1b–d**) and *ortho*- (**1e**) substituted

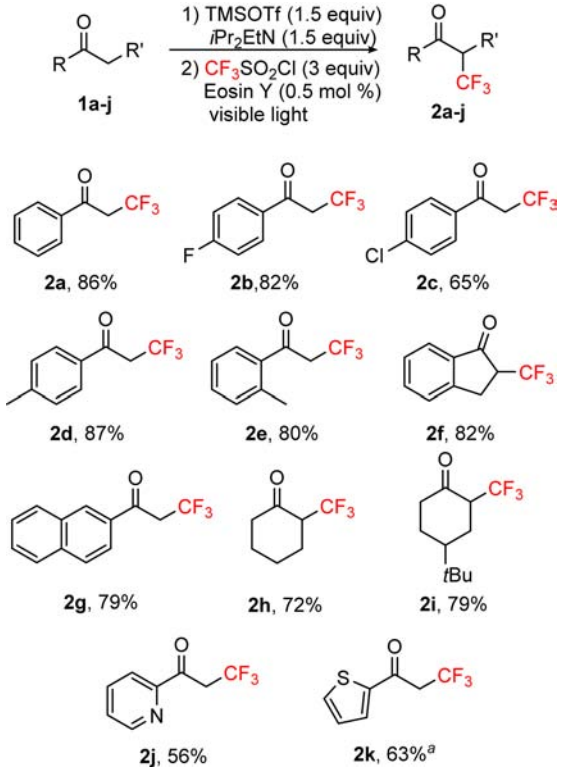

Figure 2. Continuous-flow visible light induced preparation of α-trifluoromethyl ketones catalyzed by Eosin Y. For experimental details, see Supporting Information. [a] 2 mol % Eosin Y.

acetophenones were successfully trifluoromethylated. The cyclic indanone as well as the polycyclic 2-acetonaphthone also gave excellent results (**1f,g**). Aliphatic ketones (**1h,i**) were also successfully transformed to the corresponding trifluoromethyl derivatives. Notably, heteroaromatic ketones such as 2-acetylpyridine and 2-acetylthiophene could also be α-trifluoromethylated using this novel protocol (**1j,k**). It should be noted that the preparation of α-trifluoromethylated pyridine-ketones had only been reported using the corresponding haloketones as starting materials.[7] In the case of the electron-rich 2-acetylthiophene (**1k**), significant amounts of the chlorinated side product were observed. Gratifyingly, the side reaction could be minimized by increasing the catalyst loading to 2 mol %. To the best of our knowledge, this is the first application of microreactor/continuous flow technology merged with photoredox catalysis for the trifluoromethylation of organic compounds.[22]

In conclusion, we have developed a continuous-flow procedure for the two-step preparation of α-trifluoromethyl ketones. During the first step the ketones were converted in flow into their silyl enol ethers by reaction with TMSOTf and diisopropylethylamine (iPr_2EtN) as the base. The *in situ* generated silyl enol ethers were then subjected to a visible light induced trifluoromethylation process in a simple to construct photochemical reactor based on transparent FEP tubing and a household compact fluorescent lamp. In this context, a novel system has been introduced for the α-trifluoromethylation of carbonyl compounds, which combines CF_3SO_2Cl as a source of CF_3 radicals and Eosin Y as an inexpensive, nontoxic, and readily available photoredox catalyst. The two-step process requires only 20 min for completion and has been successfully tested for a variety of substrates. In principle, application of this protocol for the trifluoromethylation of aldehydes should be straightforward, while amides and esters would require the use of stronger bases. In future work the full scope of this continuous flow trifluoromethylation chemistry will be explored.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, optimization of reactions, and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) $Ru(bpy)_3Cl_2$: ∼100 €/g; Eosin Y (disodium salt): ∼2 €/g (Aldrich Chem. Co.).
(20) This is in stark contrast to the original McMillaan protocol (ref 9) where degassed solvents and an inert atmosphere were utilized. Analogous results were obtained when the reactions were carried out using anhydrous THF or using THF containing butylated hydroxytoluene (BHT) as a stabilizer. However, large amounts of water (>1%) in the solvent will inhibit the reaction by hydrolyzing the silyl enol ether and/or destroying the CF_3SO_2Cl reagent.
(21) Notably, the ratio of TMSOTf and *i*PrEtN introduced into the reactor was critical and played an important role in the reaction outcome. When the base was used in excess over the silylating agent low conversions were obtained, while formation of gels was observed if an excess of TMSOTf was employed.
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