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Radical trifluoromethylation of ammonium enolates

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Abstract—The easy radical trifluoromethylation of a series of 1,3-dicarbonyl compounds with CF_3I is described. The reaction occurs in the presence of a nitrogen base and sodium dithionite in CH_3CN–H_2O solution. Additionally, we report a new access to ammonium triflinates.

Fluorinated organic compounds are rare in nature whereas man-made fluorinated substances are extremely abundant and span nearly the whole fields of chemistry, including the life sciences and material chemistry.[1] Within organofluorine chemistry, the trifluoromethyl unit is an important structural moiety in diverse classes of organic molecules. Compounds containing the trifluoromethyl group are found in a wide variety of dyes, polymers, agrochemicals and pharmaceuticals. Often, the introduction of a trifluoromethyl unit in target products induced improved properties. In the life science industry, the changes in electronic, steric and physiological properties of fluorinated molecules increase their intrinsic activity, the biodisponibility and the metabolic stability. In the dye industry, it has been demonstrated that trifluoromethylated chromophores exhibit increased light fastness.[2] Most of the liquid crystalline materials currently in use, for example in active matrix LCD, contain fluorine atoms; among them, trifluoromethylated liquid crystals fulfil the reliability requirements for materials used in active matrix LCD.[3] As a consequence, there is a growing demand for trifluoromethylated building blocks that play a pivotal role in the synthesis of new fluorine-containing molecules with improved potency. Numerous synthons incorporating a CF_3 group attached to an aromatic ring are available from many suppliers. In contrast, other types of CF_3 synthons are less frequent; it includes aliphatic trifluoromethylated products, essentially stemming from trifluoroacetic acid, perfluoroalkyl chains, CF_3-sulfoxide and CF_3-sulfonyl groups. These fluorinated building blocks can be used for conversion to more elaborated compounds. On the other hand, the synthetic access of trifluoromethyl-containing compounds is highly challenging by direct trifluoromethylation. The electrophilic trifluoromethylation, including radical processes, is a burgeoning topic that is highly important in organofluorine chemistry.[4] Bromotrifluoromethane, Halon 1301, has been used for generation of trifluoromethyl radicals, but the Montreal protocol has required its complete phase-out. Replacement of freons and halons, in particular for application as fire-fighting agents in aircraft, led to the commercial production of trifluoromethyliodide which has been found to be non-ozone depleting and has an extremely low GWP value.

Trifluoromethyliodide has been used in the sulfinatodehalogenation reaction developed by Huang et al. to transfer the CF_3 radical to a variety of target molecules, which have electron-rich centres such as alkenes, alkynes, arenes.[5] The sulfinatodehalogenation reaction with CF_3I consists in a radical trifluoromethylation promoted by sodium dithionite or related reagent systems. Enol derivatives such as enamines,[6] enol acetates[5a,b] and ketene dithioacetal[7] were also used as substrates, whereas silyl and germyl enol ethers were reacted with CF_3 radical generated by means of triethylborane.[8] Lithium enolates[4b,9] and titanium ate enolates[10] of monocarbonyl compounds reacted with CF_3I in the presence of triethylborane as demonstrated by the groups of Iseki and Mikami. Paradoxically, 1,3-dicarbonyl compounds that are more easily enolisable have received poor attention. Uneyama et al. reported that electrochemically generated CF_3 radical from trifluoroacetic acid can be trapped with enolacetates and enols of 1,3-dicarbonyl

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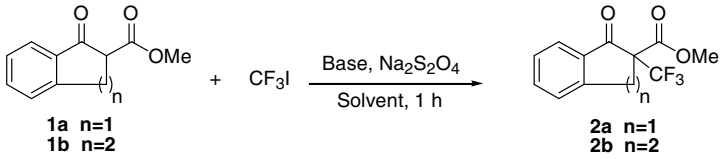


Scheme 1. Radical trifluoromethylation of β-keto esters.

compounds.[11] We herein describe the easy radical trifluoromethylation of ammonium enolates of 1,3-dicarbonyl compounds with CF_3I and sodium dithionite in CH_3CN–H_2O solution.

We initially employed 1-oxo-indan-2-carboxylic acid methyl ester **1a** as a model substrate to set up suitable reaction conditions for radical trifluoromethylation by means of CF_3I in the presence of sodium dithionite as a free radical initiator (Scheme 1). The trifluoromethyl radical, being electron-deficient, is strongly electrophilic. It is generated from monoelectronic reduction of CF_3I with sulfur dioxide radical anion. Different inorganic and organic bases were evaluated in aqueous acetonitrile, dimethylformamide or isopropanol. Representative results are listed in Table 1.

Of the inorganic bases used, cesium carbonate gave the best result in up to 65% yield. However, organic nitrogen bases were found to be superior in the radical trifluoromethylation since the bulky Hünig's base or DBU gave compound **2a** in 81% and 84% yield, respectively.[12] The amount of nitrogen base is also an important factor since 2 equiv are required for high conversion. One equivalent of base is needed to generate the ammonium enolate and the second equivalent probably contributes to the activation of CF_3I by attractive interactions between the carbon-bound iodine in CF_3I and the electronegative nitrogen atom of the base.[13] Optimal conditions were established for a solvent mixture acetonitrile/water (v/v = 3/2) at room temperature. Other polar solvents such as DMF or isopropanol gave lower reaction yields as for changing the volume ratio acetonitrile/water. In the sulfinatodehalogenation reaction, a buffer is usually added in the medium to neutralise the sulfur dioxide and HI formed in the reaction. In our case, we found that addition of sodium hydrogenocarbonate did not improve the yield of the trifluoromethylation. The use of sodium hydroxymethylsulfinate (Rongalite) as an alternative radical source under anhydrous conditions in acetonitrile failed to produce the trifluoromethylated product; interestingly, we observed the hydroxymethylation of the 1,3-dicarbonyl compounds.

Having optimised the reaction conditions, we investigated the radical trifluoromethylation of cyclic and acyclic 1,3-dicarbonyl compounds (β-keto esters and 1,3-diketones) using CF_3I, DBU as the base, $Na_2S_2O_4$ as the radical initiator and CH_3CN/H_2O as the solvent. Cyclic β-keto esters **1a–d** reacted with CF_3 radical generated from $Na_2S_2O_4$ and CF_3I to give the corresponding trifluoromethylated compounds **2a–d** in high isolated yields. No significant diastereoselectivity was observed for product **2d** bearing a chiral menthyl auxiliary. 2-Oxo-cyclopentanecarboxylic acid benzyl ester was used as a cyclic substrate having no aromatic-fused ring, but the trifluoromethylation occurred only in 28% yield. Replacing of the ester moiety with keto group as for 1,3-diketone **1e** gave the trifluoromethylated compound **2e** in 80% yield. In this case, reducing the amount of $Na_2S_2O_4$ to 50 mol % advantageously gave a quantitative reaction with an isolated 86% yield (Table 2).

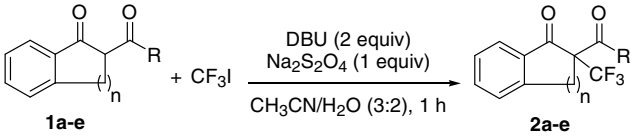
Unfortunately, acyclic 1,3-dicarbonyl compounds provided only very low yields of trifluoromethylated products under the so far optimised reaction conditions for cyclic substrates. For investigation of acyclic 1,3-dicarbonyl compounds, we used 2-methyl-3-oxo-3-phenyl-

Table 1. Set-up of the conditions for radical trifluoromethylation

Substrate	Base	Solvent[a]	Product	Yield[b] (%)
1a	K_2CO_3 (4 equiv)	CH_3CN/H_2O	**2a**	52
1a	Cs_2CO_3 (4 equiv)	CH_3CN/H_2O	**2a**	65
1a	Quinuclidine (1 equiv)	CH_3CN/H_2O	**2a**	41
1a	Et_3N (1 equiv)	CH_3CN/H_2O	**2a**	37
1a	Et_3N (2 equiv)	CH_3CN/H_2O	**2a**	62
1a	Et(*i*-Pr)$_2$N (2 equiv)	CH_3CN/H_2O	**2a**	81
1a	DBU (2 equiv)	CH_3CN/H_2O	**2a**	84
1a	DBU (2 equiv)	DMF/H_2O	**2a**	48
1b	DBU (4 equiv)	*i*-PrOH/H_2O	**2b**	21
1b	DBU (2 equiv)	DMF/H_2O	**2b**	51
1b	DBU (2 equiv)	CH_3CN/H_2O	**2b**	86

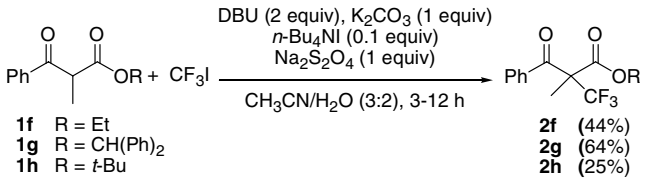
[a] Solvent: v/v = 3/2.
[b] Isolated yields.

Table 2. Radical trifluoromethylation of β-dicarbonyl compounds



Substrate	*n*	R	Product	Conv[a] (%)	Yield[b] (%)
1a	1	OMe	**2a**	95	84
1b	2	OMe	**2b**	92	86
1c	1	OBn	**2c**	93	84
1d	1	OMenthyl	**2d**	98	94
1e	2	Me	**2e**	90 (99)[c]	80 (86)[c]

[a] Conversion were determined by GC.
[b] Isolated yields.
[c] Values in brackets are for reaction run with 50 mol % of $Na_2S_2O_4$.

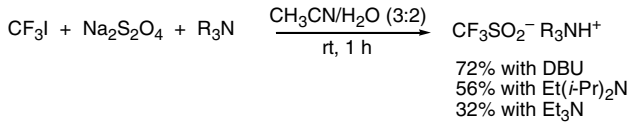


Scheme 2. Radical trifluoromethylation of acyclic 1,3-dicarbonyl compounds.

propanoic acid alkyl esters **1f–h**. The use of DBU alone or K_2CO_3 alone as a base did not allow the reaction to happen, whereas a combination of the two bases in the presence of a phase-transfer catalyst provided the trifluoromethylated products **2f–h** in moderate yields (Scheme 2). Acyclic ammonium enolates generated from **1f–h** are more soluble in water than their cyclic analogs and a phase-transfer catalyst is necessary for the transfer of enolates from water into organic phase. We found that 2 equiv of DBU and 1 equiv of K_2CO_3 with 10 mol % of tetrabutylammonium iodide were effective in the reaction.

A mechanism for the radical trifluoromethylation of 1,3-dicarbonyl compounds was proposed (Fig. 1). The reaction is a free radical process in which sulfinic radical anion $SO_2^{\bullet-}$, existing in equilibrium with dithionite anion $S_2O_4^{2-}$, generate highly electrophilic trifluoromethyl radical from CF_3I by a SET process. The trifluoromethyl radical adds to the enolate (**A**) to give anion-radical intermediate (**B**), which reacts with another molecule of CF_3I to give trifluoromethylated anion (**C**). After elimination of halogen, trifluoromethylated product (**D**) is formed.

Capture of the trifluoromethyl radical with sulfinic anion radical to give the trifluoromethanesulfinate (triflinate) was usually not observed in the trifluoromethylation of 1,3-dicarbonyl compounds. In few reactions, we detected by ^{19}F NMR trace amount of trifluoromethanesulfinate at −88.3 ppm. A control experiment demonstrated that CF_3I does not react with sodium dithionite alone; however, the addition of a nitrogen base (Et_3N, $Et(i\text{-}Pr)_2N$ or DBU) enabled the formation of ammonium trifluoromethanesulfinates (Scheme 3). Here again, the nitrogen base intervenes to activate



Scheme 3. Synthesis of ammonium trifluoromethanesulfinates.

CF_3I. This reaction could be considered as an alternative of choice for the synthesis of organic soluble trifluoromethanesulfinates without use of Halon 1301.[14]

In summary, we have described an unprecedented route to 2-trifluoromethyl-1,3-dicarbonyl compounds by radical trifluoromethylation with CF_3I initiated by sodium dithionite. The use of CF_3I is more atom economical than the use of Umemoto's reagents[15] and the reaction is experimentally very simple. Additionally, we have discovered a new synthesis of ammonium triflinates using CF_3I instead of CF_3Br. The scope and limitations of the radical trifluoromethylation is underway in our laboratory.

Acknowledgment

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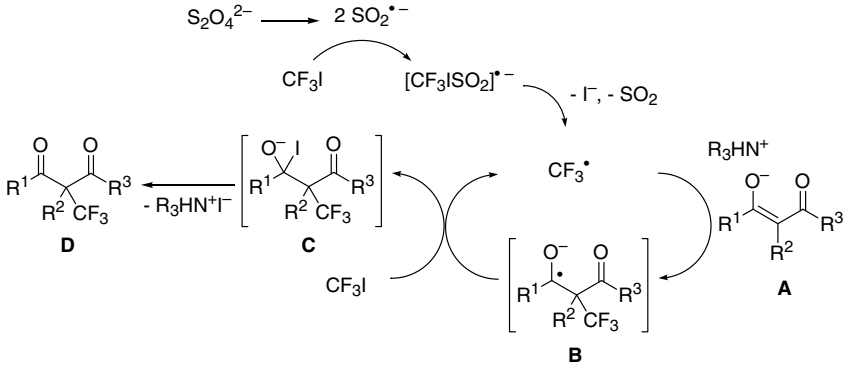

Figure 1. Proposed mechanism for the formation of 2-trifluoromethyl-1,3-dicarbonyl compounds by radical trifluoromethylation.

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12. Representative procedure of trifluoromethylation of β-keto ester **1b**. To a two-neck flask equipped with septum and magnetic stirrer were added **1b** (0.53 mmol, 108.2 mg), DBU (1.06 mmol, 161.4 mg) and CH_3CN (3 mL). The solution was stirred 15 min at room temperature and then was cooled to −30 °C and CF_3I (3 equiv, 588 mg) was added under vacuum via a syringe. A solution of sodium dithionite (0.53 mmol, 92.3 mg) in 2 mL of H_2O was added and the mixture was warmed to room temperature and stirred for 1 h. The end of reaction was monitored by TLC (hexane/ethyl acetate = 8/1). The reaction mixture was diluted with 10 mL water and extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by column chromatography to give compound **2b** in 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35–2.45 (m, 1H), 2.74–2.81 (m, 1H), 2.93–2.97 (m, 2H), 3.70 (s, 3H), 7.17–7.19 (m, 1H), 7.26–7.33 (m, 1H), 7.44–7.53 (m, 1H), 8.05 (d, $J = 7.9$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 28.1, 54.1, 62.4 (q, $J_{C-F} = 24.6$ Hz), 124.2 (q, $J_{C-F} = 282.5$ Hz, CF_3), 127.7, 128.9, 129.1, 131.8, 134.7, 142.5, 166.2, 187.4; ^{19}F NMR (282 MHz, $CDCl_3 + CFCl_3$) δ −67.94 (s, CF_3); MS (EI) *m/z*: 272 (M^+).
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