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An I_2O_5-promoted decarboxylative trifluoromethylation of cinnamic acids

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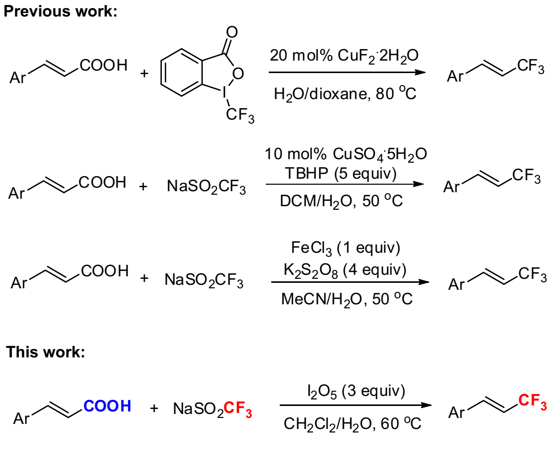
ABSTRACT

An I_2O_5-promoted decarboxylative trifluoromethylation of a series of cinnamic acids and their derivatives by using sodium trifluoromethanesulfinate in aqueous media was demonstrated. This strategy provides a safe and convenient access to various trifluoromethylated (*E*)-alkenes in a very high selectivity.

Numerous highly valuable pharmaceuticals, agrochemicals, and materials contain the trifluoromethyl (CF_3) group, which provides a driving force for exploring more efficient strategies for incorporation of CF_3 into organic molecules.[1] Among them, free-radical-initiated trifluoromethylation has drawn much attention and considerable developments have been made in the past decades.[2,3] The Langlois reagent, sodium trifluoromethanesulfinate, first synthesized by Langlois et al., is one of the most commonly used trifluoromethyl sources in atom transfer trifluoromethylation processes.[4] For example, a series of efficient trifluoromethylation of heterocycles using $NaSO_2CF_3$ via direct C—H bond functionalization was achieved by Baran and co-workers in 2011.[5] Later, several other groups such as Sanford,[6] Maiti,[7] Qing,[8] and ours[9] successively reported free-radical trifluoromethylation using Langlois reagent. However, most of the systems require large excess of potentially explosive peroxides and/or transition metal salts. Very recently, we have developed a series of safe and transition-metal free strategies for radical trifluoromethylation.[10] In these novel systems, a low-cost and stable inorganic compound, iodine pentoxide (I_2O_5, IP) was used as the single electron oxidant, which oxidizes sodium trifluoromethanesulfinate to the corresponding trifluoromethyl radical resulting in a variety of C—CF_3 bond formations.

In 2012, we successfully realized a very efficient decarboxylative C—C bond construction through coupling reaction of various α, β-unsaturated carboxylic acids with a wide range of molecules containing sp^3C—H bond such as alcohols, alkanes, ethers, and amines.[11] Subsequently, a copper-catalyzed decarboxylative trifluoromethylation and iron-catalyzed difluoromethylation of cinnamic acids using $NaSO_2CF_3$ and zinc difluoromethanesulfinate, respectively via a free-radical addition/elimination process was



Scheme 1. Decarboxylative trifluoromethylation of cinnamic acid.

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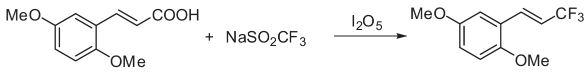
Table 1
Optimization of the typical reaction conditions[a]

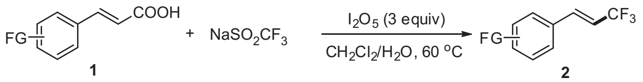


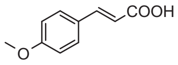
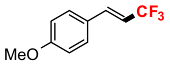
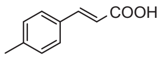
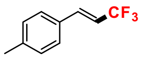
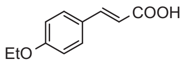
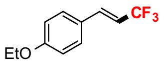
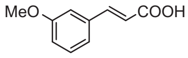
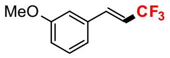
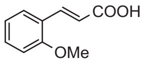
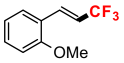
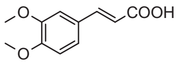
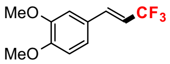
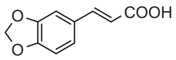
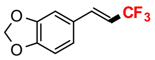
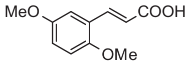
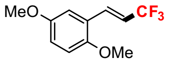
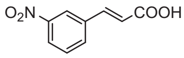
Entry	$NaSO_2CF_3$ (equiv)	I_2O_5 (equiv)	Solvent (V/V, mL)	*T* (°C)[b]	Yield[c] (%)
1	2	3	DCM/H_2O(2.5/1)	60	20
2	**3**	**3**	**DCM/H_2O(2.5/1)**	**60**	**80**
3	5	3	DCM/H_2O(2.5/1)	60	76
4	3	1	DCM/H_2O(2.5/1)	60	Trace
5	3	5	DCM/H_2O(2.5/1)	60	72
6	3	3	DCM/H_2O(2.5/1)	25	Trace
7	3	3	DCM/H_2O(2.5/1)	90	56
8	3	3	CH_3CN/H_2O(2.5/1)	60	Trace

[a] Reaction conditions: (*E*)-3-(2,5-dimethoxyphenyl)acrylic acid (1 equiv, 0.2 mmol), sealed tube, 22 h.
[b] Measured temperature of the oil bath.
[c] Relative yield based on the conversion of the starting material.

developed by us.[9] Inspired by these previous studies, we began to reason whether a decarboxylative trifluoromethylation of α,β-unsaturated carboxylic acids by using $NaSO_2CF_3$ and I_2O_5 through free radical addition–elimination process could be realized. If it does work, it would be attractive to organic synthetic chemistry because this method would hold the advantages of metal-free, low-cost, and safe over the previous protocols (Scheme 1).[12]

Table 2
Trifluoromethylation of cinnamic acids by using $NaSO_2CF_3$ and I_2O_5[a]



Entry	Substrate	Product	*E*/*Z*[b]	Yield[c] (%)
1		 **2a**	32/1	80
2		 **2b**	32/1	90
3		 **2c**	32/1	75
4		 **2d**	13/1	83
5		 **2e**	49/1	85
6		 **2f**	19/1	82
7		 **2g**	19/1	85
8		 **2h**	19/1	80
9		—	—	—

[a] Reaction conditions: cinnamic acid (1 equiv, 0.2 mmol), $NaSO_2CF_3$ (3 equiv, 0.6 mmol), I_2O_5 (3 equiv, 0.6 mmol), CH_2Cl_2/H_2O (2.5/1, 3.5 mL), 60 °C (Measured temperature of the oil bath), sealed tube, 22 h.
[b] Ratio of the *E*/*Z* isomers determined by ^{19}F NMR spectroscopy.
[c] Relative yield of the *E*/*Z* isomers based on the conversion of the starting material (see also the Supporting information).

In order to test our hypothesis of the free radical trifluoromethylation of α,β-unsaturated carboxylic acids by using $NaSO_2CF_3$ and I_2O_5, a series of experiments were carried out to optimize the typical reaction conditions. It can be seen from Table 1 that the amount of $NaSO_2CF_3$ and I_2O_5, solvent as well as temperature are very important to this transformation. Finally, the desired product was obtained in 80% yield under the following conditions: 1 equiv of cinnamic acid, 3 equiv of $NaSO_2CF_3$, 3 equiv of I_2O_5, CH_2Cl_2/H_2O (2.5/1, 3.5 mL), 60 °C (Measured temperature of the oil bath), in a sealed tube, and 22 h.

We next investigate the substrate scope with the modified conditions in hand. As depicted in Table 2, various electron-rich aryl substituted α,β-unsaturated carboxylic acids gave the desired CF_3-substituted (*E*)-styrenes in high yields and selectivities. The substrates with *para*-, *meta*-, and *ortho*-substituent on the aromatic core led to the corresponding products in 75–90% yields, and the ratio of *E*/*Z* range from 13/1 to 49/1 (entries 1–8). However, no desired product was observed by using cinnamic acids with electron-withdrawing groups such as NO_2 and CN substituted on the aryl (entry 9). Although only electron-rich aryl-substituted α,β-unsaturated carboxylic acids are effective substrates in this system, it is believed to be attractive to organic synthetic chemistry with the features of easy operation and no requirement of transition-metal salts.

The mechanistic studies through combination of electron-spin resonance (ESR) with spin trapping technology are designed to gain insight into the details of this process. Since free radical intermediates would be involved in this system, a radical spin trap

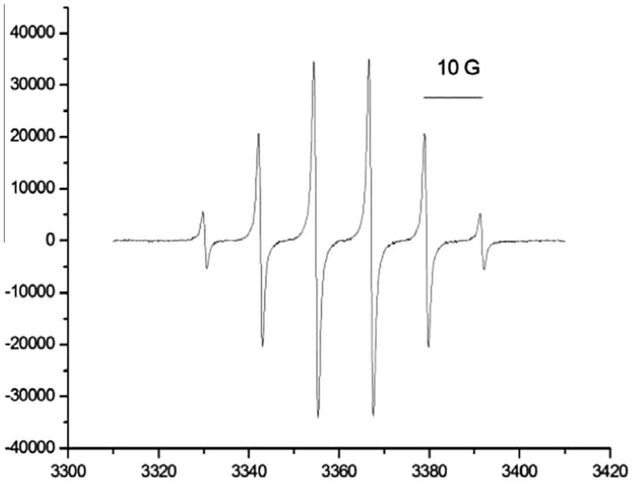
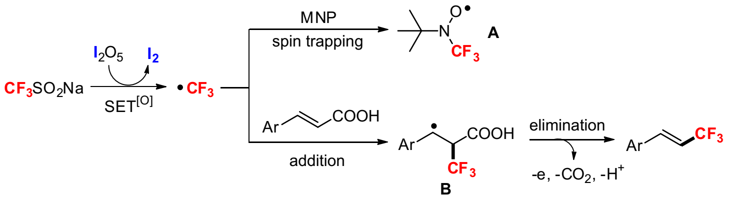


Figure 1. ESR spectra of radical intermediate trifluoromethyl *tert*-butyl nitroxide.



Scheme 2. Possible mechanism.

reagent 2-methyl-2-nitrosopropane (MNP) was added into the reaction. As a result, a sextet signal was recorded by ESR with $g = 2.0060$ and $a = 12.25$ G, which should be the radical adduct trifluoromethyl *tert*-butyl nitroxide (Fig. 1).[10,13] It indicates that the trifluoromethyl radical would be formed in this system.

A free-radical addition/elimination mechanism for this process was proposed in Scheme 2. Single-electron oxidation of Langlois reagent by IP would generate the trifluoromethyl radical, which adds to acrylic acid leading to radical **B**. Single-electron-transfer (SET) followed by elimination of CO_2 and deprotonation would give the final product.

In conclusion, we have developed an I_2O_5-promoted decarboxylative trifluoromethylation of cinnamic acids and its derivatives by using Langlois reagent in aqueous media. A series of trifluoromethylated (*E*)-styrenes could be prepared through this method. Mechanistic investigations suggest it might undergo a free-radical addition/elimination process.

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Supplementary data

Supplementary data (experimental procedures and spectral data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.076.

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