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ARTICLE TYPE

Iron-Mediated Markovnikov-Selective Hydro-trifluoromethylthiolation of Unactivated Alkenes

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An iron-mediated hydro-trifluoromethylthiolation of unactivated olefins under mild conditions was described, for the first time. The reaction occurred to full conversion within 30 min at 0 °C and tolerates a variety of functional groups. 10 Preliminary mechanistic studies suggested that the reaction proceeds via a free-radical pathway.

It is well-known that incorporation of the trifluoromethylthio (CF₃S-) group into drug molecules will significantly enhance the drug's transmembrane permeation ability and consequently ¹⁵ improve the drug's pharmacological properties and efficiency.¹ One main reason that leads to these favourable properties of the trifluoromethylthiolated drugs is due to the trifluoromethylthio group's high lipophilicity. With a Hansch value of 1.44, the trifluoromethylthio group is considered as one of the most ²⁰ lipophilic groups.² As a result, the development of new methods for the efficient incorporation of the trifluoromethylthio group into small molecules under mild conditions has become an intense focus of recent research.³ In the last few years, several elegant methods have emerged for the trifluoromethylthiolation

- ²⁵ of aromatic compounds by either employing transition metal catalysts⁴ or using electrophilic trifluoromethylthiolating regents.⁵ Likewise, methods for selective introduction of the trifluoromethylthio group into the α-position of the carbonyl compounds have been well-established.⁶ However, few methods
 ³⁰ for the formation of unactivated secondary alkyl trifluoremethylthiotemethyl
- trifluoromethylthioethers from unactivated alkenes have been reported.⁷ One straightforward method for the formation of unactivated

secondary alkyl trifluoromethylthioethers is the Markovnikov-³⁵ selective hydro-trifluoromethylthiolation⁸ of unactivated olefins since olefins are inexpensive and readily available starting materials.⁹ Interestingly, anti-Markovnikov additions of thiols across alkenes, namely thio-ene reaction, have been well studied,¹⁰ while the Markovnikov-selective hydrothiolation ⁴⁰ remains much less studied.¹¹ In addition, to the best of our knowledge, hydro-trifluoromethylthiolation of olefins has not been reported previously. Because of the ubiquity of the trifluoromethylthio group in pharmaceuticals and agrochemicals, such a process would be highly desirable. Herein, we report an ⁴⁵ iron-mediated Markovnikov-selective hydro-trifluoromethyl-

thiolation of unactivated olefins. The reactions were extremely facile and typically completed within 30 min at 0 °C. In addition, a variety of functional groups such as fluoride, chloride, iodide, ester, hydroxy and electron-rich arenes were compatible with the ⁵⁰ reaction conditions.

The development of an iron-mediated Markovnikov-selective hydro-trifluoromethylthiolation of unactivated olefins was inspired by Boger and co-workers' recent work on Fe(III)/NaBH₄ mediated free radical hydro-functionalization of alkenes.¹² The 55 reaction was proposed to be initiated by the addition of a hydrogen atom to the alkene to form an alkyl free radical which was then trapped to give the final products. In the meantime, we developed a silver-catalyzed decarboxylative recently trifluoromethyl-thiolation of aliphatic acids.¹³ Mechanistic studies 60 showed that the reaction proceeded by decarboxylation from Ag(II) alkylcarboxylate to form an alkyl radical, which was then trapped by the trifluoromethylthiolating reagent. We envisioned that if the alkyl radical that was generated from Boger's conditions could be trapped by the trifluoromethylthiolating 65 reagent. а general Markovnikov-selective hydrotrifluoromethylthiolation could be developed.

$$R \xrightarrow{Fe(III)/BH_3} \left[R \xrightarrow{H} \right] \xrightarrow{[SCF_3]} R \xrightarrow{SCF_3} H$$

Figure 1. Iron-mediated hydro-trifluoromethylthiolation.

⁷⁰ With this idea in mind, we initially choose the reaction of 4allylanisol and the trifluoromethylthiolating reagent **2** as the model reaction to optimize the reaction conditions. A quick screening of the Fe(III) salts showed that Fe(NO₃)₃ was the better iron salt than other salts such as Fe₂(SO₄)₃, Fe(claac)₃, FeCl₃ and

⁷⁵ Fe₂(ox)₃ for the hydro-trifluoromethylthiolation reaction when solid NaBH₄ was used as hydrogen source (Table 1, entries 1-5). Interestingly, when a solution of NaBH₄ in ethanol was added dropwise within 5 min, the yield of the product improved to 57% (Table entry 6). Furthermore, when BH₃•THF was used as the hydrogen source, the yield was further increased to 77%, while the reactions using PhSiH₃ or Et₃SiH as the hydrogen source were not effective (Table 1, entries 11-12). The reaction was sensitive to the concentration of the reaction mixture. When the reaction was conducted at 0.08 N instead of 0.02 N, the yield of the section was hampered by the higher reaction temperature (Table 1, entry 13). It is likely that at room temperature, the trifluoromethylthiolated reagent partially reacted with BH₃ to give undesired side products.

Table	1.	Optimization	of	conditions	for	iron-mediated	hydro-				
trifluoromethylthiolation of unactivated olefins. ^a											

MeO´	la	← Me + Ph+O- Me 2	Fe(I H sc CH ₃ CN temp, 3	II) salt ource I/H ₂ O(1:1) 30 min	MeO	3	→ SCF ₃
	entry	Fe(III) salt	H source	temp	conc	yield (%) ^c	_
	1	Fe(NO ₃) ₃ ·9H ₂ O	NaBH₄	0°C	0.02	30	
	2	Fe ₂ (SO ₄) ₃	NaBH ₄	0°C	0.02	11	
	3	Fe(acac) ₃	NaBH₄	0°C	0.02	0	
	4	FeCl3	NaBH₄	0°C	0.02	5	
	5	Fe ₂ (ox) ₃	NaBH₄	0°C	0.02	0	
	6 ^b	Fe(NO ₃) ₃ .9H ₂ O	NaBH₄	0°C	0.02	57	
	7 ^b	Fe ₂ (SO ₄) ₃	NaBH₄	0°C	0.02	16	
	8 ^b	FeCl ₃	NaBH₄	0°C	0.02	15	
	9	Fe(NO ₃) ₃ 9H ₂ O	BH ₃ .THF	0°C	0.02	77	
	10	Fe ₂ (ox) ₃	BH ₃ .THF	0°C	0.02	18	
	11	Fe(NO ₃) ₃ .9H ₂ O	PhSiH ₃	0°C	0.02	0	
	12	Fe(NO ₃) ₃ ,9H ₂ O	Et ₃ SiH	0°C	0.02	0	
	13	Fe(NO ₃) ₃ ,9H ₂ O	BH ₃ .THF	rt	0.02	57	
	14	Fe(NO ₃) ₃ .9H ₂ O	BH ₃ .THF	0°C	0.01	74	
	15	Fe(NO ₃) ₃ .9H ₂ O	BH ₃ .THF	0 °C	0.08	54	

^{*a*}Reaction condition: **1a** (0.2 mmol), reagent **2** (0.3 mmol), Fe(III) salt (0.4 5 mmol), H source (1.0 mmol), solvent (10.0 mL) at 0 °C for 30 min; ^{*b*}NaBH₄ was dissolved in EtOH (0.5 mL); 'Yield was determined by ¹⁹F NMR spectroscopy in the presence of 1-fluoronaphthenlene as an internal standard.

With a reliable procedure in hand, we proceed to examine the 10 scope of the hydro-trifluoromethylthiolation reaction, and the results are summarized in Table 2. A wide range of substrates and functional groups including unprotected and protected alcohols, esters, halides, heterocyclic and sulfonates were compatible with the reaction conditions. All the terminal olefins tested showed 15 excellent Markovnikov selectivity, while the internal olefin provided the addition product with a ratio of 1:1. Notably, reactions of sterically hindered trisubstituted alkenes with trifluoromethylthiolating reagent 2 generated only trace amount of the desired product. To tackle this problem, we try to use other 20 trifluoromethylthiolating reagent such as trifluoromethylthiolated phthalimide 4 as the radical trap. To our delight, the hydrotrifluoromethylthiolation products were obtained at 30-54% yields for tri-substituted alkenes when Fe₂(SO₄)₃ was used as the catalyst (see the Supporting Information for details). The new 25 conditions also worked well for the terminal olefins with slightly lower yields than those using $Fe(NO_3)_3$ as the catalyst and reagent

2 as the radical trap. To gain insights into the reaction, we carried out some preliminary mechanistic investigations of the process. To probe if

- ³⁰ a radical was involved in the iron-mediated hydrotrifluoromethylthiolation reaction, we prepared compound **5** and subjected it to the standard reaction conditions by using **2** or **4** as the radical trap reagent.¹⁴ In both cases, the ring-closed products **6** were obtained in 70% and 50% yields, respectively. We
- ³⁵ reasoned that the alkyl radical generated from the addition of a hydrogen atom to the alkene undergoes irreversible intramolecular 5-exo-cyclization at a much faster rate than those of the bimolecular radical quenching process. This experiment strongly suggests the involvement of a free-radical mechanism in 40 the iron-mediated hydro-trifluoromethylthiolation reaction.

In a second experiment, we evaluated a cyclopropyl-substituted olefin 7 as a radical clock to probe if the radical is indeed

Table 2. Scope of Iron-mediated hydro-trifluoromethylthiolation.^a



⁴⁵ "Reaction conditions: olefin **1** (0.4 mmol), reagent **2** (0.6 mmol), Fe(NO₃)₃ • 9H₂O (0.6 mmol), BH₃ • THF (2.0 mL), solvent (20 mL) at 0 °C for 30 min; ^bIsolated yield (Yields in parentheses were obtained using Fe₂(SO₄)₃ as the catalyst and reagent **4** as the trifluoromethylthiolating reagent); ^cNaBD₄ was used.

50 involved under the standard reaction conditions. Interestingly, two unexpected products 8a and 8b were observed in both cases in similar yields and ratios. It is likely that hydrogen radical initially reacts with the alkene moiety of compound 7 to form radical species 7a, which undergoes faster ring opening to form 55 intermediate 7b or 7c. Intermediate 7b or 7c is then protonated to 7d. which generate compound undergoes hvdrotrifluoromethylthiolation to give final compounds 8a and 8b. These observations also supported our assertion that the ironmediated hydro-trifluoromethylthiolation proceeded via a free 60 radical pathway.

In summary, we have developed a facile iron-mediated hydrotrifluoromethylthiolation of unactivated olefins process for the preparation of secondary alkyl trifluoromethylthioethers. The reaction was typically completed within 30 min at 0 °C. In 65 addition, a variety of functional groups such as fluoride, chloride,

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iodide, ester, hydroxy and electron-rich arenes were compatible with the reaction conditions. Radical cyclization and radical clock experiments suggested that the reaction proceeds through a free 5 radical process. Our ongoing efforts focus on its application in organic synthesis and the results will be reported in due course.

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