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Silver(I)-Catalyzed Denitrative Trifluoromethylation of β -Nitrostyrenes with CF₃SO₂Na

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ABSTRACT

Article history: Received Received in revised form Accepted Available online A novel and convenient approach to the synthesis of substituted β -trifluoromethyl styrenes *via* a silver(I)-catalyzed denitrative trifluoromethylation with CF₃SO₂Na under relatively mild conditions has been developed. This protocol delivered excellent stereoselectivity and showed wide substrate tolerance.

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1. Introduction

The introduction of fluorinated moieties into the organic molecules often results in dramatic changes in the physical, chemical, pharmacological and biological properties of these compounds.¹ Especially, the incorporation of CF_3 groups into aromatics generally enhances their chemical and metabolic stability, lipophilicity and binding selectivity.² Therefore, many chemists have been focusing their attention on the discovery and development of the new trifluoromethylation reaction recently.³

In the past decade, various synthetic strategies for trifluoromethylations of arenes have been developed.⁴ Particularly, protocols concerning the construction of C_{vinyl} -CF₃ bonds have been gotten so much attention. As shown in Scheme 1, there are two routes which are mainly used to synthesize trifluoromethylating olefins. One route is decarboxylative trifluoromethylation, which often requires prefunctionalized alkenes as substrates and suffers from expensive Togni's reagents.⁵ The process developed by Hu^[5a] mainly relies on utilizing a costly and electrophilic trifluoromethyl reagent (Scheme 1a). To overcome these limitations, our group^{5e} reported a kind of mild copper/silver-mediated decarboxylative trifluoromethylation of α,β -unsaturated carboxylic acids with cheap CF₃SO₂Na (Scheme 1a). Another route is direct C-H trifluoromethylation of alkenes.⁶ However, it requires either costly catalysts or trifluoromethyl reagents.

Nitro olefins are regarded as the significant and valuable reagents in the synthesis of complex target compounds for their easy availability.⁷ The Henry reaction, condensing aldehydes with nitroalkanes, is one of the general methods to access conjugated nitro olefins.⁸ Other useful methods for synthesizing nitro olefins are nitration of alkenes⁹ and decarboxylative

nitration.¹⁰ Yao¹¹ reported a series of approaches that β -nitrostyrenes reacted with carbon-centre radicals to construct new C-C bonds accompanied by releasing of the NO₂ radical. Recently, denitrative reaction of β -nitrostyrenes has attracted

Scheme 1. Formation of C_{vinyl} -R moieties (R= CF₃, PO₃Et₂, SO₂Ar).

Previous work

a. trifluoromethylation of functionalized alkenes







Togni's reagent b. the denitratation of nitrostyrenes



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much attention as a useful method for the construction of C_{vinyl} -R moieties. Pan^{12a} and Yadav^{12c} discovered the formation of C_{vinyl} -P and C_{vinyl} -S bonds by denitrative reaction respectively (Scheme 1b). In addition, Yi^{12b} reported a Fe(III)-catalyzed trifluoromethylation of β -nitrostyrenes using Togni reagent as CF₃ source (Scheme 1b). Herein, we report the silver(I)-catalyzed denitrative trifluoromethylation of β -nitrostyrenes with electrophilic trifluoromethyl radical derived from inexpensive Langlois reagent CF₃SO₂Na.

2. Results and discussion

Initially, denitrative trifluoromethylation of β -nitrostyrene (1) with CF₃SO₂Na was selected as a model reaction (Table 1). When this reaction was carried out with 1.0 equivalent AgNO₃ as catalyst, di-t-butyl peroxide (DTBP) as oxidant, tetra-(n-butyl) ammonium iodide (TBAI) as PTC at 70°C for 24 h, β trifluoromethylstyrene (1a) was obtained only in 22% yield (entry 1). Fortunately, addition of acids could improve the yield of the target product (1a) (entries 2-5). Among those screened acids, TsOH is the best one. Moreover, testing different catalysts showed that AgNO₃ is superior to the other silver salts, such as Ag₂O, AgOAc and Ag₂CO₃ (entries 5-7). When the amount of AgNO₃ catalyst was decreased to 15 mol%, the yield of **1a** was increased to 83% (entries 8-9). Maybe excess AgNO₃ catalyst led to the generation of trifluoromethyl radical fastly, so that other side reaction took place rather than the slow denitrative trifluoromethylation of β -nitrostyrene. Without AgNO₃ catalyst, the yield of 1a was only 23% (entry 10). Screening various oxidants, such as di-t-butyl peroxide (DTBP), t-butyl hydroperoxide (TBHP), Bz₂O₂, H₂O₂, K₂S₂O₈, we found that DTBP showed the best result (entries 9, 11-14). Finally, without addition of TBAI caused a lower yield (entry15). Notably, no detectable amount of Z-isomers of target products was found in these reactions.

Table 1.	Optimization	of reaction	conditions
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	$\sim NO_2 + NaSC$		3, IBAI/DIBF	- []]	•		
	TsOH, DMSO/DCM = 2:5						
1			70 °C	1a			
Entry	Catalysis	oxidant	Addictiv	Acid	Yield ^b		
1	AgNO ₃ (100)	DTBP	TBAI	-	22		
2	AgNO ₃ (100)	DTBP	TBAI	TFA	28		
3	AgNO ₃ (100)	DTBP	TBAI	AlCl ₃	34		
4	AgNO ₃ (100)	DTBP	TBAI	TsOH	65		
5	Ag ₂ O(100)	DTBP	TBAI	TsOH	42		
6	AgOAc(100	DTBP	TBAI	TsOH	61		
7	Ag ₂ CO ₃ (100	DTBP	TBAI	TsOH	50		
8	AgNO ₃ (56)	DTBP	TBAI	TsOH	53		
9	AgNO ₃ (15)	DTBP	TBAI	TsOH	83		
10	-	DTBP	TBAI	TsOH	23		
11	$AgNO_3(15)$	TBHP	TBAI	TsOH	70		
12	AgNO ₃ (15)	H_2O_2	TBAI	TsOH	trace		
13	AgNO ₃ (15)	Bz_2O_2	TBAI	TsOH	trace		
14	AgNO ₃ (15)	$K_2S_2O_8$	TBAI	TsOH	trace		
15	AgNO ₃ (15)	DTBP	-	TsOH	60		

^{*a*} Reaction conditions: **1** (0.1 mmol), **2** (3.0 equiv), additive (0.2 equiv), oxidant (5.0 equiv), DMSO/ CH₂Cl₂= 0.4/1 mL, acid (1.0 equiv), 70 °C, 24 h. ^{*b*} Yields were determined by GC analysis, using *n*-dodecane as internal standard.

With the optimized conditions in hand, we next investigated the substrate scope of silver(I)-catalyzed denitrative

trifluoromethylation of β -nitrostyrenes with CF₃SO₂Na (Table 2). The denitrative trifluoromethylation reactions of β -nitrostyrenes with electron-donating groups at o-, m- or p-position, such as Me-, t-Bu-, AcO-, and MeO-, afforded corresponding trifluoromethyl styrenes in moderate to good yields (Table 2, 1b-**1g**). Moreover, dimethoxyl substituted β -nitrostyrene gave desired product in good yield (Table 2, 1h). It is pleased to find that the trifluoromethylation of o-, p-bromo and p-chloro substituted β -nitrostyrenes worked relatively well (Table 2, 1i, 1j, **1k**). Interestingly, the dichloro substituted β -nitrostyrenes also gave the trifluoromethylated product in moderate yield (Table 2, **11**). *p*-Phenyl substituted β -nitrostyrenes only gave the target product in 48% yield owing to its big conjugate system (Table 2, **1m**). Similarly, β -nitrovinyl-naphthalene was also a poor substrate only obtaining 38% yield of trifluoromethylated product (Table 2, 1n). The substrates with electron-withdrawing groups gave trifluoromethylated products in poor yields because of their lower electron density (Table 2, 10, 1p). Notably, the reactions were found to be highly stereoselective, and only the Eisomer of the desired product was observed in each process through J value of 1 H-NMR(see datas in Experimental Section).

Table 2. Silver(I)-catalyzed denitrative trifluoromethylation of β nitrostyrenes with CF₃SO₂Na^{*a*}



 a Reaction conditions: 1(0.4 mmol), CF₃SO₂Na (3.0 equiv), AgNO₃ (15 mol%), TBAI (0.2 equiv), DTBP (5.0 equiv), DMSO/ CH₂Cl₂= 0.8/2 mL, TsOH (1.0 equiv), 70 °C, 24 h. b Isolated yields.

To gain mechanistic insights into the current denitrative trifluoromethylation, a set of comparative experiments were designed (Scheme 2). We chose 1,1-diphenyl-ethylene (2 equiv) as a radical scavenger to capture the trifluoromethyl radical. The reaction of CF₃SO₂Na with 1,1-diphenyl-ethylene was tested under the standard conditions. The desired trifluoromethyl 1,1-diphenyl-ethylene product **4a** was detected by GC-MS, and the yield of **4a** was determined by ¹⁹F-NMR (Eq.(1) of Scheme 2). Notably, when 1,1-diphenyl-ethylene was added to take the competition reaction with β -nitrostyrene and CF₃SO₂Na, the trifluoromethyl 1,1-diphenyl-ethylenen**4a** was obtained in 20 % in ¹⁹F-NMR yield (Eq.(2) of Scheme 2). The controlled experiments showed that the reaction proceeded through a radical process.

Based on the experimental results and earlier studies^{12, 14}, a plausible silver(I)-catalyzed denitrative trifluoromethylation mechanism was proposed as follows (Scheme 3). Initially, silver(I) was oxidized to silver(II) by DTBP due to its strong oxidation. In the presence of silver(II) ions, $CF_3SO_2^-$ was oxidized to CF_3SO_2 , which subsequently released one molecule of SO_2 to generate a trifluoromethyl radical. The addition of the *in situ* generated trifluoromethyl radical to the double bond of **1** led to the formation of intermediate **5** which subsequently underwent the elimination of NO₂ radical to give the desired product **1a**.

Scheme 2 Radical trapping experiments of toluylene as radical scavenger



Scheme 3 Proposed mechanism for β -nitrostyrenes trifloromethylation



3. Conclusions

In summary, we have developed an efficient protocol for the construction of C_{vinyl} -CF₃ bonds through a silver(I)-catalyzed denitrative trifluoromethylation of β -nitrostyrenes with CF₃SO₂Na. This method tolerates a variety of functional groups and provides a useful and practical strategy for stereospecific synthesis of CF₃-substituted *E*-alkenes with operational simplicity under relatively mild conditions. Since both β -nitrostyrenes and CF₃SO₂Na are easily available, this denitrative trifluoromethylation method will have great advantages for academic and industrial application.

Acknowledgments

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Supplementary Material

Supplementary data (experimental section and copies of ¹ H , ¹³C, ¹⁹F NMR, MS spectral data) associated with this article can be found, in the online version, at http://dx.doi.org/xx.xxx/j.tetlet.2016.xx.xxx.

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Highlights

► A novel silver(I)-

catalyzed denitrative trifluoromethylation was developed.

► The cheap and economical trifluoromethyl reagent was used.

trifluoromethyl styrenes delivered stereoselectivity.

Accepted substrate tolerance.

Graphical Abstract

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