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UV Light-Mediated Difunctionalization of Alkenes with CF₃SO₂Na: Synthesis of Trifluoromethyl Phenanthrene and Antrone Derivatives

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A metal-free and cost-effective protocol of UV light-mediated difunctionalization of alkenes with CF_3SO_2Na was developed. This strategy realized the direct formation of Csp^3 - CF_3 and C-C bonds through a proposed tandem radical cyclization process, which produced a variety of phenanthrene and anthrone derivatives in moderate yields.

Introduction

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The trilfluoromethyl group plays a significant role in pharmaceuticals and agrochemicals because its introduction into drug candidates could strengthen chemical and metabolic stability, electronegativity, ameliorate lipophilicity, bioavailability, and enhance binding selectivity.^{1,2} In recent years, a number of synthetic methods for C-CF₃ bond formation have been constantly developed.³ These strategies can be classified into Csp-CF₃,⁴ Csp²-CF₃⁵ and Csp³-CF₃⁶ bond construction according to trifluoromethylation reaction of hydrocarbons. As the formation of Csp³-CF₃ bonds was relatively limited, the difunctionalization of alkenes has arose as a highly attractive strategy.7 However, most of these reactions go through by transition-metal-mediates, such as palladium- and copper-catalyzed trifluoromethylation, which tend to require expensive catalysts and trifluoromethyl reagents, as well as high temperatures.⁸⁻¹⁰ Therefore, development of an environmental friendly process is appealing for the trifluoromethylation area.

In the realm of organic synthesis, synthetic methodologies, and radical chemistry,¹¹ organic photochemical research is one of most important branch. Based on our previous work on the photochemical behaviour of radicals¹² and the studies on radical trifluoromethylation,¹³ we tried to realize the trifluoromethylation of alkenes under photochemical condition. Successfully, we found that the inexpensive and stable solid CF₃SO₂Na (Langlois' reagent) could generate CF₃' via UV-light in the presence of sensitizer and smoothly carry out difunctionalization of alkenes followed by C–C bond formation.¹⁴ Herein we report our recent advances on trifluoromethylation of aromatic unsaturated ketones (Scheme 1).

Results and discussion

Originally, we chose the aromatic α,β -unsaturated ketone **1a**



(Table 1) as the model substrate, separately irradiated with the CF₃ reagents of CF₃SO₂Na, CF₃SO₂Cl, CF₃I and Tognis' reagent in dried MeCN by a 500W medium pressure lamp through a Pyrex filter, but no reaction occurred. Then we added benzophenone (BP) as a sensitizer, to our delight the product 3a was obtained in 54% yield by detection on GC-MS (Table 1, entry 1) in the system of CF₃SO₂Na. Such a result promoted us to further study of this reaction. Then we tried other sensitizers, such as anthracene-9,10dione (AQ), benzoquinone (BQ), terephalonitrile (DCB), benzene-1,2,4,5-teracarbonitrile (TCB), naphthalene-1,4-dicabonitrile (DCN), and andanthracene-9,10-dicarbonitrle (DCA), which led to lower yields (Table 1, entries 2-7). A solvent screening revealed that other solvents did not or only sluggishly promote this reaction (Table 1, entries 8-12). Other wavelength, such as 300 nm or 350 nm gave the desired product in 21% and 25% yields, respectively (Table 1, entries 13 and 14). When the reaction proceeded in dried solvent in air, the complicated products were obtained. In addition, the reaction conducted in undried MeCN under N2 atmosphere led to 21% yield (Table 1, entry 15). Finally, the reaction condition was optimized to use a 500 W medium mercury lamp as the light source, 2 equiv of CF₃SO₂Na, 0.2 equiv of BP as the sensitizer, and dried MeCN as the solvent.

We therefore prepared a series of aromatic α,β -unsaturated

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⁺ Electronic Supplementary Information (ESI) available: Experimental procedures and ¹H and ¹³C NMR spectra for all new compounds. See DOI: 10.1039/x0xx00000x

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Table 1 Screening for optimal reaction condition ^a				
\bigcirc	+	CF ₃ SO ₂ Na -	h_{V} , Sens. solvent	CF ₃
1a		2	3а	
entry	Sens.	hv	Solvent	Yield $[\%]^b$
1	BP	280 nm	MeCN	54
2	AQ	280 nm	MeCN	13
3	BQ	280 nm	MeCN	32
4	DCB	280 nm	MeCN	trace
5	TCB	280 nm	MeCN	37
6	DCN	280 nm	MeCN	26
7	DCA	280 nm	MeCN	10
8	BP	280 nm	DMF	trace
9	BP	280 nm	DMSO	trace
10	BP	280 nm	toluene	trace
11	BP	280 nm	DCM	trace
12	BP	280 nm	THF	trace
13	BP	350 nm	MeCN	25
14	BP	300 nm	MeCN	21
15 ^c	BP	280 nm	MeCN	21
^a Reaction	n conditions:	1a (0.2 mmol), 2	(0.4mmol), Sen	s. (0.04 mmol), hv,
solvent (a	anhydrous, 10) mL) under N ₂ a	tmosphere. ^b Yie	lds were detected by
GC-MS. Undried MeCN				

ketones to investigate the scope of the reaction. As shown in Table 2, the reactions were completed within 4-10 hrs to form the desired products in 30-70% yield. The substrates bearing electron-withdrawing or -donating groups at the *meta*- and *para*-positions of \mathbb{R}^1 were tolerant of the reaction conditions to provide the desired products (**3a-3d**, **3j-3o**). The electron-withdrawing groups of \mathbb{R}^2 led to better yield within shorter reaction time, e.g. 70% yield for $\mathbb{R}^2 = \mathbb{F}$ (**3h**). Otherwise, when the *meta*-position of \mathbb{R}^2 was methoxyl, the product of **3q** afforded the isomers with a ratio of 2:1. In addition, a thiophene group was also tolerated under the optimal conditions to furnish the corresponding product in acceptable yield (**3p**). However, no desired product was observed when the hydrogen at terminal position of C-C double bond of the alkene was replaced by a phenyl group, only the *cis*-isomer was isolated.

To further investigate the applicability of this protocol, aromatic γ , δ -unsaturated ketone **4a** (Table 3) was therefore prepared and subjected to the reaction conditions. We envisioned that, the addition of generated CF₃ radical to the double bond of **4a** followed by a subsequential intramolecular radical cyclization might lead to the formation of anthrone derivatives. It was nice to see that the desired product **5a** was obtained in 23% yield after 70 minutes. When the sensitizer was replaced by anthracene-9,10-dione (AQ), the yield was improved to 55%. Then a variety of substituted aromatic γ , δ -unsaturated ketones were prepared and submitted to the standard reaction conditions using AQ as the sensitizer, and the results were summarized in Table 3. The reactions were completed at room temperature within 70 minutes to form the desired products in 35-55% yield. The electronic effect on the pendent aryl group has no



^{*a*}Reaction condition: **1** (0.2 mmol), **2** (0.4 mmol), BP (0.04 mmol), hv (280 nm), MeCN (anhydrous 10 mL) under N₂ atmosphere. ^{*b*}Isolated yield.

significant influence on the results of the reactions, such as the aryl group substituted with electron-withdrawing or -donating groups. including methyl, F, Cl, Br, t-Bu, and methoxy were smoothly converted to the corresponding products in moderate yields. Moreover, although two ortho-positions of the Ar group were available for reaction, only one isomer was obtained possibly due to the influence of election cloud density (5g-5k). When a hydrogen atom at the end of double bond was replaced by a methyl group, the desired product 5m could be isolated in 51% yield. However, when the methyl group connected to the C-C double bond of the trisubstituted alkene was replaced by a hydrogen atom, no main product was obtained. Importantly, the desired product could also be prepared when Ar was naphthalene (51), pyridine (5n) or thiophene (50). It should be noted that it was indispensable for the substrates furnished with two aryl or conjugated groups, for example, when Ar was replaced by an iso-butyl group, no trifluoromethylation occurred. In addition, low conversion and yield were obtained when the substrate was furnished without a carbonyl group even if longer time was involved (5r).

Before a reaction mechanism was proposed, a control experiment of **1a** in the presence of 2.2 equiv of TEMPO¹⁵ was carried out under the standard conditions for 4 h, TEMPOCF₃ (M = 225 g/mol) and only trace amount of product **3b** was detected based upon GC-MS analysis. Such a result suggested that the reaction involves a radical pathway. Accordingly, a plausible mechanism of this reaction is depicted in scheme 2.^{16,9c} The CF₃ radical, which was generated from CF₃SO₂Na was added to the C-C double bond of **1** to form C-

ectronic effect on the pendent

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^{*a*}Reaction condition: **3** (0.1 mmol), **2** (0.2 mmol), AQ (0.02mmol), hv (280 nm), MeCN (anhydrous, 5 mL) under N_2 atmosphere, 70 mins. ^{*b*}Isolated yield.

centered radical **A** (blue). Subsequently, the radical attacked the *ortho*-position of benzene to produce the intermediate **B**. Then enolization of ketone to afford the intermediate **C**. The final product **3** was formed after loss of a hydrogen radical. Similarly, the CF_3 radical was added to the C-C double bond of **4** to form the intermediate **D** (black). Subsequently, a radical addition the aromatic ring occurred to perform the intermediate **E**, which donated a hydrogen radical rapidly to give the final product **5**.

Conclusions

In summary, we have developed an efficient, cost-effective, and metal-free protocol for the direct trifluoromethylation of alkenes through UV light synthetic strategy using CF_3SO_2Na as the CF_3 source. This approach provided a highly atom-economic access to



various CF_3 -containing phenanthrene and anthrone derivatives *via* cascade trifluoromethyl radical addition. The reaction was highlighted by operational simplicity, excellent functional group tolerance, and a wide range of compatible substrates.

Experimental

General Procedure

General procedure for the photo-induced trifluotomethylation of 1: In a Pyrex filter, the magnetic stir bar was added. Then it was charged with substrate 1 (0.2 mmol), CF_3SO_2Na (0.4 mmol), dried MeCN (10 mL) and sensitizer BP (0.04 mmol). The mixture was charged with N₂ for 30 minutes under room temperature and then irradiated by UV lamp (280 nm). After the substrate was consumed (monitored by TLC), the mixture was filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ ethyl acetate) to afford the desired product **3**.

10-(2,2,2-trifluoroethyl) phenanthren-9-ol (**3a**): White solid. ¹H NMR (400 MHz, CDCl₃): δ 8.71 (d, *J* = 8.4 Hz, 1H), 8.68 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.74-7.63 (m, 3H), 7.57 (t, *J* = 7.6 Hz, 1H), 5.47 (s, 1H), 4.02 (q, *J* = 10.8 Hz, 2H); ¹³C NMR (151 MHz, CDCl₃): δ 148.8, 131.8, 131.4, 127.7, 127.5, 127.1, 126.9, 126.7 (q. *J* = 278.7 Hz), 125.2, 124.7, 123.6, 123.1, 123.0, 121.4, 106.7, 30.4 (q, *J* = 30.2 Hz); ¹⁹F NMR (376 MHz, DMSO): δ -62.2 (s, decoupled, 3F); GC-MS (EI): 276, 256, 236, 207, 179, 152, 118, 89, HRMS (ESI): [M+H]⁺ calcd. for C₁₆H₁₂F₃O⁺: 277.0835, found: 277.0835.

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