

Iron-Catalyzed Azidoalkylthiation of Alkenes with Trimethylsilyl Azide and 1-(Alkylthio)pyrrolidine-2,5-diones

Jipan Yu,^a Min Jiang,^a Zhixuan Song,^a Tiancheng He,^a Haijun Yang,^a and Hua Fu^{a,*}

Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, People's Republic of China Fax: (+ 86)-10-6278-1695; e-mail: fuhua@mail.tsinghua.edu.cn

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Abstract: A simple, efficient and practical iron-catalyzed azidoarylthiation of alkenes has been developed at room temperature, and the corresponding products containing ortho-sited sulfide and azide units were obtained in moderate to good yields with good tolerance of functional groups. The protocol uses readily available 1-(alkylthio)pyrrolidine-2,5-diones and trimethylsilyl azide as the alkylthiation and azidation reagents, respectively, inexpensive and environmentally friendly iron chloride as the catalyst without addition of any ligand and additive.

Keywords: alkylthiation; azidation; difunctionalization; iron-catalyzed reaction; synthetic methods

Transition metal-catalyzed difunctionalizations of alkenes have attracted much attention,^[1] and some interesting reactions such as dioxygenation,^[2] aminooxygenation,^[3] diamination,^[4] aminohalogenation,^[5] and fluoroamination^[6] have been developed. Meanwhile, we also have developed some useful difunctionalizations of alkenes.^[7] The energy-rich and flexible organic azides are widely used in chemistry, biology, medicine and materials.^[8] For example, the Staudinger reaction^[9] as a ligation method for the conjugation of biomolecules has been popular among bioorganic chemists.^[10] The 1,3-dipolar cycloaddition of alkynes with azides, an application of the Huisgen reaction in the field of "click chemistry", was widely investigated.^[11] Reactions of thioacids or thioesters with organic azides have been actively studied as a chemical ligation method.^[12] On the other hand, sulfides are important building blocks in organic synthesis, materials science and the pharmaceutical industry.^[13] To the best of our knowledge, azidoalkylthiation of alkenes has been not reported. 1-(Alkylthio)pyrrolidine-2,5diones are interesting alkylthiation reagents, and they were used in various organic reactions by us and other groups.^[14] Very recently, we have developed a catalyst-free isothiocyanatoalkylthiation of styrenes with (alkylthio)pyrrolidine-2,5-diones and trimethylsilyl isothiocyanate.^[15] Inspired by the excellent results, we here report an azidoalkylthiation of alkenes.

As shown in Table 1, the three-component coupling of styrene (1a), 1-(phenylthio)pyrrolidine-2,5-dione (2a) and trimethylsilyl azide was selected as the model to optimize the conditions. At first, the reaction was performed under the same conditions (DMF as the solvent at 90 °C under argon) as for the isothiocyanatoalkylthiation of styrenes.^[15] Unfortunately, only a trace amount of the target product (3a) was observed. One possible reason is that the azido group has weaker nucleophilicity than the isothiocyano. Next, various catalysts were screened in 1,2-dichloroethane (DCE) at room temperature under argon (entries 2-13), and FeCl₃ provided the highest yield (entry 2). Other azido sources were tested, and they gave poor results (entries 14 and 15). The effect of solvents was investigated (compare entries 2, 16-20), and the result showed that DCE was a suitable solvent. Reaction in air led to a lower yield (entry 21). Therefore, the optimized conditions are as follows: using 10 mol% FeCl₃ as the catalyst, TMSN₃ as the azido source, and DCE as the solvent at room temperature under argon.

With the optimized reaction conditions in hand, we investigated the scope of alkenes and 1-(alkylthio)pyrrolidine-2,5-diones. As shown in Table 2, both aromatic and aliphatic alkenes were suitable substrates. For styrenes with different substituents on the phenyl rings, their electronic effect was not evident, but the steric hindrance greatly affected their reactivity, and the substrates with substituents at ortho-sites provided lower yields (see 3d, 3i and 3l). Several styrenes with disubstituents on the C=C bonds were screened, and they provided satisfactory yields (see **3n-r**). Interest-

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Table 1. Optimization of reaction conditions for the threecomponent coupling of styrene (**1a**), 1-(phenylthio)pyrrolidine-2,5-dione (**2a**) and trimethylsilyl azide.^[a]



Entry	Catalyst	Azido source	Solvent	Time [h]	Yield [%] ^[b]
1	-	TMSN ₃	DMF	12	trace ^[c]
2	FeCl ₃	TMSN ₃	DCE	12	84
3	$Cu(OAc)_2$	TMSN ₃	DCE	12	trace
4	CuI	TMSN ₃	DCE	12	trace
5	$Pd(OAc)_2$	TMSN ₃	DCE	12	trace
6	$BF_3 \cdot Et_2O$	TMSN ₃	DCE	12	trace
7	AgOAc	TMSN ₃	DCE	12	trace
8	Fe_2O_3	TMSN ₃	DCE	12	trace
9	FeS·7H ₂ O	TMSN ₃	DCE	12	35
10	FeS	TMSN ₃	DCE	12	22
11	$Fe_2(SO_4)_3 \cdot H_2O$	TMSN ₃	DCE	12	45
12	FeSO ₄	TMSN ₃	DCE	12	37
13	$Fe(acac)_3$	TMSN ₃	DCE	12	13
14	FeCl ₃	NaN ₃	DCE	24	trace
15	FeCl ₃	TsN ₃	DCE	24	trace
16	FeCl ₃	TMSN ₃	$CHCl_3$	12	80
17	FeCl ₃	TMSN ₃	MeCN	12	77
18	FeCl ₃	TMSN ₃	THF	12	46
19	FeCl ₃	TMSN ₃	EtOAc	12	70
20	FeCl ₃	TMSN ₃	toluene	12	17
21	FeCl ₃	TMSN ₃	DCM	12	63 ^[d]

[a] Reaction conditions: under argon atmosphere, 1a (0.2 mmol), 2a (0.3 mmol), catalyst (0.02 mmol), azido source (0.4 mmol), solvent (2.0 mL), temperature (room temperature, ca. 25 °C), time (12 h). DCE=1,2-dichloro-ethane.

^[b] Isolated yields.

^[c] Temperature (90 °C).

^[d] Under air.

ingly, only anti-diastereomers were observed in the ¹H NMR spectra for 1,2-disubstituted alkenes (see **30**, **3p**, **3r** and **3ae**), and norbornene gave two diastereomers (dr=2:1) (see **3af**). The results indicated that a three-membered cyclic thiiranium intermediate (V) could occur during azidoalkylthiation of alkenes (see reaction mechanism in Scheme 2). Next, various 1-(arylthio)pyrrolidine-2,5-diones (2) were attempted (see 3s-aa), and the substrates (2) containing electron-donating groups on the phenyl rings exhibited higher reactivity than those containing electron-withdrawing groups. For aliphatic alkenes, they also afforded reasonable yields (see **3ab-aj**). We used 1-(alkylthio)pyrrolidine-2,5-diones as the sulfur source, and they also gave satisfactory results (see 3ak-am). The present method exhibited tolerance of some functional groups



Scheme 1. Synthesis of 3a on a gram scale under the standard conditions.

including C-F bond (**3f** and **3w**), C-Cl bond (**3g**i and **3x-z**), C-Br bond (**3j-l**), CF₃ (**3m** and **3aa**) and ethers (**3v**, **3ab**, **3ac** and **3ah**).

A scale-up experiment was investigated using azidoarylthiation of **1a** as the example (Scheme 1). Reaction of **1a** (10 mmol, 1.04 g), **2a** (15 mmol, 3.11 g) and trimethylsilyl azide (20 mmol, 2.3 g) under the standard conditions provided **3a** in 68% yield (1.74 g). Therefore, the present method is effective for the scaled-up synthesis of β -alkyl sulfide azides.

We explored the three-component reaction mechanism. When a radical scavenger, 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO), was added to system of styrene (1a), 1-(phenylthio)pyrrolidine-2,5-dione (2a) and trimethylsilyl azide, and the reaction did not work, which indicated that the reaction could involve in a free radical intermediate process. Electron spin resonance (ESR) was applied to track the iron-catalyzed reaction of 1a, 2a and TMS-N₃ with 5,5-dimethyl-1-pyrroline N-oxide (DMPO) as a radical trapping agent, and the results showed that an N-centered radical was observed (see the Supporting Information for details). Therefore, a plausible mechanism for the azidoalkylthiation of alkenes is proposed in Scheme 2. One single electron transfer (SET) from sulfur in 1 to Fe^{3+} gives radical cation I and Fe^{2+} , and cleavage of N-S bond in I provides cation II and radical III (the N-centered radical was observed by ESR). Treatment of III with Fe^{2+} regenerates the Fe^{3+} catalyst leaving IV. Meanwhile, electrophilic addition of II to alkene



Scheme 2. Possible mechanism for the iron-catalyzed azidoalkylthiation of alkenes.

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Table 2. Substrate scope for the iron-catalyzed azidoalkylthiation.^[a,b]

[a] Reaction conditions: under argon atmosphere, 1 (0.2 mmol), 2 (0.3 mmol), FeCl₃ (0.02 mmol), TMSN₃ (0.4 mmol), DCE (2.0 mL), temperature (room temperature, ca. 25 °C), time (12 h) in a sealed Schlenk tube.

^[b] Isolated yields.

(1) gives three-membered cyclic thiiranium intermediate V, and reaction of TMSN₃ with VI in the presence of IV provides the target product (3) freeing IV-TMS. A similar process was reported in the previous studies.^[16]

It is noteworthy that azido compounds are very useful synthetic intermediates and they are often applied in the synthesis of other molecules. For instance, β -amino sulfide **4a** was easily prepared *via* reduction of (2-azido-2-phenylethyl)(phenyl)sulfane (**3a**) with PPh₃ and water^[17] at room temperature. Copper-catalyzed coupling of **3a** with phenylacetylene afforded the corresponding triazole (**5a**) in 68% yield (Scheme 3).

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Scheme 3. Applications of synthesized compound 3a.

In summary, we have developed a simple, efficient and practical iron-catalyzed azidoalkylthiation of alkenes with the readily available 1-(alkylthio)pyrrolidine-2,5-diones and TMSN₃ as the azidoalkylthiation reagents. The mild method provides diverse molecules with sulfide and azide units in moderate to good yields with tolerance of some functional groups, and the synthesized compounds are important and useful building blocks in organic synthesis.

Experimental Section

General Procedure for Synthesis of Compounds 3aam

A 25-mL oven-dried Schlenk tube was charged with FeCl₃ (0.02 mmol, 3.3 mg), and 1-(alkylthio)pyrrolidine-2,5-dione (2) (0.3 mmol), dry 1,2-dichloroethane (2.0 mL), alkene (0.2 mmol) and TMSN₃ (0.4 mmol, 46 mg, 53 μ L) were added to the tube under an argon atmosphere. The tube was sealed and the mixture was stirred at room temperature for 12 h. The resulting mixture was filtered through Celite, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate as the eluent to provide the desired target product (**3a-am**). Three representative examples are shown as follows:

(2-Azido-2-phenylethyl)(phenyl)sulfane (3a): Eluent: petroleum ether/ethyl acetate (25:1); isolated yield: 43 mg (84%); colorless film; ¹H NMR (600 MHz, CDCl₃): $\delta =$ 7.39–7.37 (m, 4H), 7.34 (t, *J*=7.3 Hz, 1H), 7.32–7.28 (m, 4H), 7.24 (t, *J*=7.3 Hz, 1H), 4.58 (t, *J*=7.1 Hz, 1H), 3.25 (d, *J*=7.1 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): $\delta =$ 138.4, 135.2, 130.4, 129.2, 129.0, 128.8, 127.0, 126.9, 66.3, 41.0; ESI-MS: m/z = 256.2 [M+H]⁺.

(2-Azido-2-phenylethyl)(4-chlorophenyl)sulfane (3x): Eluent: petroleum ether/ethyl acetate (25:1); isolated yield: 25 mg (43%); colorless film; ¹H NMR (400 MHz, CDCl₃): δ =7.40–7.34 (m, 3H), 7.33–7.25 (m, 6H), 4.56 (t, *J*=7.1 Hz, 1H), 3.22–3.20 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 138.1, 133.7, 133.0, 131.8, 129.4, 129.1, 128.9, 126.9, 65.3, 41.3; ESI-MS: *m*/*z*=290.3 [M+H]⁺.

(2-Azido-2-phenylethyl)(phenethyl)sulfane (3al): Eluent: petroleum ether/ethyl acetate (100:1); isolated yield: 42 mg (74%); colorless film; ¹H NMR (400 MHz, CDCl₃): $\delta =$

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7.41–7.34 (m, 3H), 7.33–7.27 (m, 4H), 7.23–7.19 (m, 1H), 7.17–7.15 (m, 2H), 4.57 (dd, J=8.0 Hz, J=6.0 Hz, 1H), 3.91(s, 2H), 2.90–2.80 (m, 4H), 2.78–2.73 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ =140.3, 138.6, 129.0, 128.8, 128.6, 127.0, 126.6, 66.6, 38.9, 36.4, 34.6; ESI-MS: m/z=284.3 [M + H]⁺.

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UPDATES

6 Iron-Catalyzed Azidoalkylthiation of Alkenes with Trimethylsilyl Azide and 1-(Alkylthio)pyrrolidine-2,5-diones

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Jipan Yu, Min Jiang, Zhixuan Song, Tiancheng He, Haijun Yang, Hua Fu*





