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Photoinduced Cascade Reaction of Tertiary Amines with Sulfonyl Azides: Synthesis of Amidine Derivatives

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Abstract. A metal-free cascade reaction of tertiary amines with sulfonyl azides promoted by acridinium salts under blue light irradiation was developed and provided amidine derivatives in moderate to good yields. Enamine was generated from tertiary amine *via* single-electron transfer promoted by acridinium salts, and the following [3+2] cyclization with sulfonyl azide and CH_2N_2 release afforded the desired products.

Keywords: photocatalysis; enamination; [3+2] cyclization; cascade reaction; amidine derivatives

Given their wide existence in natural products and drugs, the functionalization of tertiary amines has always been of great interest. Enamine is an important intermediate to achieve the direct functionalization of tertiary amines.^[1] However, the formation of enamine is difficult because of the strong competition of iminium ion and amino radical in the process. In traditional methods, enamines are promoted by transition metals, such as Ru,^[2] Pt,^[3] Pd,^[4] and Co,^[5] and undergo subsequent reactions with different electrophilic reagents. In the above methods, expensive catalysts are needed, and the following reactions are very limited, which mainly focus on nucleophilic addition with nitrostyrenes and aldehydes. In recent years, visible-light photoredox catalysis has attracted considerable attention as a green technology.^[6] Tertiary amines can be functionalized rapidly through photocatalysis. Most reported reactions involve iminium ion or α aminoalkyl radical pathway.^[7] However, reports about the photoinduced formation of enamines from tertiary amines are very few. Rueping and co-workers achieved the β -sulforylation of pyrrolidines via a dehydrogenative enamine pathway promoted by the

Previous work:



(b) Synthesis of amidines via the coupling of tertiary amines and sulfonaimdes promoted by NBS

$$\begin{array}{c} & \bigwedge_{R^2}^{R^1} & \bigoplus_{H_2N}^{O} & \stackrel{\text{NBS (2.5 equiv)}}{\longrightarrow} & \underset{R^3}{\overset{O}{\xrightarrow}} & \bigwedge_{R^3}^{O} & \bigwedge_{R^2}^{O} & \stackrel{O}{\longrightarrow} & \underset{R^3}{\overset{O}{\longrightarrow}} & \underset{R^3}{\overset{C}{\overset{O}{\overset{O}{\longrightarrow}} & \underset{R^3}{\overset{C}{\overset{C}{\overset{O}{\overset{O}{\overset{O}{\overset{O}{\overset{R$$

(c) Synthesis of amidines via the cascade reaction of tertiary amines with sulfonyl azides



Scheme 1. The reported synthesis of amidine derivatives.

iridium photocatalyst.^[8] Xu reported the [2+2] cycloaddition of propiolic acid ester with enamine from tertiary amine promoted by visible-light photocatalysis.^[9] Zeng reported the cross coupling of sulfonyl azides with tertiary amines to synthesize amidines in good yields, and the enamine generated from the photoinduced dehydrogenation of tertiary amines played an important role in this reaction.^[10] Therefore, studying the reaction of photoinduced enamines is important.

Amidine is a fundamental unit in medicinal and synthetic chemistry that is widely applied in pharmaceutical science^[11] and metal complexation ligands.^[12] In the past years, great efforts have been focused on developing a new method to prepare amidines. Wan and co-workers found that the direct condensation of amides and sulfonamides gave amidines in good yields under the condition of NaI/TBHP^[13] or Zn(OTf)₂/EDA (Scheme 1a).^[14] The coupling of tertiary amines with sulfonamides offered amidines on the basis of the in situ generation of TsNBr₂ (Scheme 1b).^[15] Recently, excellent strategies were applied to prepare amidines through the cascade reaction of tertiary amines with sulfonyl azides promoted by CuCl/CCl₄,^[16] electrocatalysis,^[17] diethyl azodicarboxylation,^[18] and FeCl₃,^[19] and the enamine generated from oxidative dehydrogenation as a key intermediate in these reactions (Scheme 1c). Excess oxidants and dehydrogenating agents, which are harmful to the environment, are needed in the above reactions.

Acridinium salts are a class of organic photocatalysts that are applied to initiate olefins and electric-rich aromatics into radical cations.^[20] Previously, we reported the formation of thioamide radicals promoted by acridinium salt under visiblelight irradiation, and the following intramolecular cyclization with p-quinone methides provided 1,2,4-

Table 1. Optimization of the photoinduced cascade reaction. a)

∕_N 1a	+ , S N ₃	photocatalyst solvent blue LEDs	
Entry	Photocatalyst	Solvent	Yield(%) ^{b)}
1	Ru(bpy) ₃ Cl ₂	CH ₃ CN	71
2	Ir(ppy) ₃	CH ₃ CN	45
3	Ir(bpy)(ppy) ₂ PF ₆	CH ₃ CN	59
4	Mes-Acr-Ph ⁺ BF ₄	DCE	76
5	TPT	DCE	26
6	Eosin Y	CH ₃ CN	trace
7 ^{c)}	Mes-Acr-Ph ⁺ BF ₄	DCE	64
8 ^{d)}	Mes-Acr-Ph ⁺ BF ₄	DCE	53
9 ^{e)}	Mes-Acr-Ph ⁺ BF ₄	DCE	55
10 ^{f)}	Mes-Acr-Ph ⁺ BF ₄	DCE	60
11 ^{g)}	Mes-Acr-Ph ⁺ BF ₄	DCE	0
	N+ BF4]

^{a)} Conditions: **1a** (0.3 mmol). **2a** (0.9 mmol), photocatalyst (5 mol %), and solvent (2 mL) were stirred in air atmosphere under the irradiation of 12 W blue LEDs for 10 h at rt. ^{b)} Isolated yields. ^{c)} K₂CO₃ (0.3 mmol). ^{d)} Na₂CO₃ (0.3 mmol). e) 2a (0.6 mmol) was used. f) Photocatalyst (2.5 mol %) was used. ^{g)} The reaction was carried out in dark.

R ¹	, ^ _{R² 0,}	O Mes-Acr-Ph ⁺ B	F ₄ (5 mol %) 0 0	
l	R ³ R ⁴	N ₃ blue LEDs	R ⁴ N N	N R ²
	1	DCE 2	3	'R ³
Entry	Amine 1	Azide 2	Product 3 (%)	_
1	<u></u>	0,,,0		_
	1a	N ₃		
2	$\sim \sim_{\rm N} \sim$	2a 2a	3aa, 76% 0、_0	
Z	5	2a	S'NNN	
	16		3ba, 85%	
3	Ph~_N~Ph	2a	S N N Ph	
] 1c ^{Ph}			
4	a L	2a	30a,88% Ph	
•	×_N <		∫ S ^S N ^N N [−]	
_	1d		3da, 40%	
5	()	2a		
			3ea. 35%	
6		2a	0,0	
0	└_ _N	24	S'N N	()
	1f		3fa , 34%	
7	$\left\langle \right\rangle$	2a	O S N N	
	Ph 1g		3ga, 35% Ph	
8	1a	0,,0	0,00	
-		U UN3		
0		~ 2b	3ab , 70%	
9	la	S [×] N ₃	S ^S N ^N N	
		F 2c	F 3ac, 67%	
10	1a	O, O		
		Br 2d	Br 3ad 64%	
11	1a	0,,,0	0,0	
		2e	3ae, 85%	
12	1a	O S N3		
		t-Bu 2f	t-Bu 3af, 57%	
13	1a	O S		D
		MeO 27	MeO 3ag, 68%	
14	1a	/-Pr O	(Pr O	
		↓ Store		\bigcirc
1 c b)		² -Pr ² h	3ah, 65%	
15%	la	S N3		Ð
			HN 3ai, 59%	
16	19		$\bigcap $	\cup
10	1	S'N3		()
17	1.	[∞] 2j	3aj, 80%	
1/	1a	S ^S N ₃	Š ^Š N ^N N	
		Ph 2k	Ph 3ak, 62%	
18	1a	O S No	^N ^N ^N ^N ^N ^N	
		N 2I	N 3al, trace	
19	1a	0,0 S_ >S	S_S_N_N	
		2m	3am 52%	
20	1я	1 20	- 22.0	
20	14	0 K-S-N3	of K-s. N N	
		2n	3an, 73%	_

dithiazoles.^[21] We speculated that this organic photocatalyst could also promote amines to form radical cations and underwent subsequent reaction. As a source of amide, the application of acyl azides in the photoinduced amidations also received great attention in recent years.^[22] Herein, we would report a photoinduced cascade reaction of tertiary amines and sulfonyl azides to synthesize amidines.

First, we examined the cascade reaction of triethylamine and sulfonyl azide in the catalysis of 5 mol % Ru(bpy)₃Cl₂ under blue light irradiation; **3aa** was obtained in 71% yield (entry 1, Table 1). Then the reaction conditions were further explored, and results are shown in Table 1. Other metal photocatalysts such as Ir(ppy)₃ and Ir(bpy)(ppy)₂PF₆ were unsuitable in this reaction as they reduced the yield of **3aa** to 45% and 59%, respectively (entries 2 and 3, Table 1). Then, organic photocatalysts such as TPT, Eosin Y, and Acr-Mes-Ph⁺BF₄ were examined, and Acr-Mes-Ph⁺BF₄ was found to be the best catalyst, which gave 3aa in 76% yield (entries 4-6, Table 1). Bases were used as additive, which decreased the yield (entries 7 and 8, Table 1). Decreasing the amount of Acr-Mes-Ph+BF4 and sulfonyl azide resulted in lower product yields (entries 9 and 10, Table 1). When the reaction was carried out in dark, 3aa was not obtained (entry 11, Table 1). Finally, the optimized reaction conditions were 5 mol % Acr-Mes-Ph⁺BF₄ in DCE under blue light irradiation for 10 h.

Under the optimum conditions, the substrate scope of amines and sulfonyl azides were investigated, as shown in Table 2. Tripropylamine and triphenethylamine reacted smoothly and gave 3ba and 3ca in 85% and 68% yields, respectively. When N-ethyl-N-isopropylpropan-2-amine was used, 3da was obtained in 40% yield, indicating that the large steric hindrance reduced the product yield. Cyclic tertiary amines were also studied, and Nmethylpiperidine, *N*-methylpyrrolidine, and 1phenylpyrrolidine were used as substrates. 3ea, 3fa, and 3ga were obtained via the hydrogen abstraction of cyclic α -carbon. In the sulforyl azide moiety, when benzenesulfonyl azide was used, 3ab was obtained in 70% vield. Other substituents such as halogen, tertbutyl, and methoxy in benzene ring offered the corresponding products in good yields (3ac-3ag). Considering the effect of steric hindrance, 2,4,6triisopropyl-benzenesulfonyl azide was used, and **3ah** was obtained in 65% yield, indicating that the steric hindrance did not exert considerable influence on the reaction. Acetamido was tolerant and offered 3ai in 59% yield. 1-Naphthyl and 1,1'-biphenyl provided 3aj and 3ak in 80% and 62% yields, respectively. Unfortunately, when pyridyl was introduced, only a



1a, 4 mmol2a, 12 mmol3aa, 0.61 g, 60%Scheme 2. Investigation of other substrates and a larger-
scale reaction.

trace amount of **3al** was observed. 2-Thienyl was suitable and generated **3am** in 52% yield. To our delight, when camphorsulfonyl azide was used, **3an** was obtained in a good yield (73%).

We also studied the coupling of triethylamine with benzoyl azide, azidobenzene, and diphenyl phosphorazidate (Scheme 2). Unfortunately, only a trace amount of **3ao** was detected, and **3ap** and **3aq** were not produced. We found that almost all 20 converted into isocvanatobenzene 4ao. When 1h was introduced, 3ha and 3ha' were obtained in 26% and 20% vields, respectively. The different chemoselectivities were attributed to the two of generating pathways enamine. We also investigated the large-scale reaction of 1a with 2a (4 mmol), and **3aa** was obtained in 60% yield.

To study the mechanism, several control experiments were performed as shown in Scheme 3. Firstly, the reaction of **1i** and **2a** gave **3ia** in 55% yield under the catalysis of acridinium salt (eq 1, Scheme 3). Without the addition of photocatalyst, **3ia** was also obtained in 60% yield, indicating that the photoinduced enamine could be the key intermediate in the cascade reaction of tertiary amine with sulfonyl



Scheme 3. Mechanism studies.

azide (eq 2, Scheme 3). Furthermore, benzaldehyde and benzyl alcohol were detected by GC-MS in the reaction of 1c and 2a (see Supporting Information for details). We speculated that benzaldehyde and benzyl alcohol were obtained from the reaction of (diazomethyl)benzene with oxygen^[23] and water,^[24] respectively. According to the above experiment results and the reported literatures, ^[8, 9, 18] a possible mechanism was proposed (Scheme 4). Firstly, the photocatalyst was induced to an excited state under blue light irradiation. Then, single-electron transfer to the excited-state photocatalyst resulted in a tertiary amine radical cation A, and the photocatalyst was reduced. The reduced photocatalyst transferred an electron to the oxygen, generating oxygen radical anion and completing the photocatalyst recycle. The oxygen radical anion abstracted a hydrogen radical from the intermediate A and gave an ammonium cation B, which underwent double bond shift and resulted in the generation of enamine C. Finally, the enamine C underwent 1,3-dipolar addition with 2a, and the following open-ring reaction and CH₂N₂ release provided the product 3aa. When the cyclic tertiary amine 1f was used as the substrate, the intermediate F was formed through the above pathway. Then, the following open-ring reaction, N₂ release, and 1,2-*H* shift gave the product **3fa**.^[25]



Scheme 4. Proposed mechanism.

In summary, a photoinduced cascade reaction of tertiary amines and sulfonyl azides that provided a series of amidines in moderate to good yields was developed. In this reaction, the enamine from tertiary amine promoted by photocatalysis was a key intermediate, and the subsequent [3+2] cyclization with sulfonyl azide and CH_2N_2 release gave the final product. Compared with previous work, this method

does not require special substrates, and the green oxidant oxygen was used.

Experimental Section

Typical experimental procedure for the synthesis of 3.

A solution of **1a** (0.3 mmol, 30 mg), **2a** (0.9 mmol, 180 mg), and Mes-Acr-Ph⁺BF₄ (0.015 mmol, 7 mg) in DCE (2 mL) was stirred under the irradiation of blue LEDs at rt for 10 h. The mixture was diluted with DCM (10 mL), extracted with NaOH aqueous solution (0.5 mol/L, 10 mL), and dried with Na₂SO₄. Then, the organic layer was concentrated under reduced pressure, and the residue was purified by flash column chromatography to provide **3aa** in 76% yield.

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