Visible-Light-Mediated Sulfonylimination of Tertiary Amines with Sulfonylazides Involving $C_{sp^3}-C_{sp^3}$ Bond Cleavage

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ArSO₂N₂

(5) Supporting Information

ABSTRACT: Visible-light-induced cross-coupling of arylsulfonyl azides with tertiaryamines in the presence of Eosin Y at room temperature has been achieved. This transformation features alkyl C–C bond cleavage and provides a green approach to *N*-sulfonylamidines under mild conditions.

A midines are often encountered in many natural products and bioactive small molecules, and also serve as useful synthons to assemble complex molecules.¹ In recent decades, different synthetic methodologies have been developed to construct versatile amidines. Among them, the direct condensation reaction between formamides and sulfonamides could produce *N*-sulfonyl amidines in the presence of a stoichiometric amount of acyl chlorides or oxidants (Scheme 1a).² To avoid the use of these hazardous reagents and harsh conditions, Wang,³ Stahl,⁴ Odell,⁵ and others⁶ developed transition-metal-catalyzed and electrochemical systems for assembling these compounds (Scheme 1b and 1c). Meanwhile, Wang also reported an easily available tertiary amine-based cross-coupling for making amidine derevatives using FeCl₃ as a

Scheme 1. Synthetic Strategies of N-Sulfonylamidines



promoter (Scheme 1d).⁷ However, considering that a trace amount of transition-metal ions will limit their application in biological pharmaceutical industry,⁸ the development of metalfree catalyzed strategies for green synthesis of amidines is therefore highly desired.

Eosin Y (5 mol %) Na₂CO₃ (1.0 equiv)

30 W blue LEDs

On the other hand, photoredox catalysis has attracted much attention because this synthetic strategy provides a low-carbon platform for chemical transformation at ambient temperatures and pressures.⁹ In this regards, double bond (C=C, C=O, and C=N)-containing substrates could be activated by photosensitizers to generate radical species, which could be further captured by other coupling partners.¹⁰ In contrast, inert $C_{sp}^{3}-C_{sp}^{3}$ bond activation by visible light or transition-metal catalysts is more difficulty due to its high bond-dissociation energy and low polarity.¹¹ Recently, Xu reported that tertiary amines could be transferred into enamines via a single electron transfer (SET) process under visible-light conditions, and then the corresponding enamine species reacted with alkynes to form highly strained bicycles (Scheme 1e).¹² This is in combination with the fact that the 1,3-diopolar addition between enamines and sulfonazides could easily occur, sometimes followed by degradation of triazolines.¹³ Xu's work encouraged us to expect that tertiary amines could possibly couple with sulfonazides for assembling amidines via C_{sp^3} - C_{sp^3} cleavage of alkanes under a photocatalytical system (Scheme 1f).

To verify this hypothesis, the mixture of TsN_3 (1a), *N*-ethyl-*N*-isopropylpropan-2-amine (2a), Eosin Y (2.0 mol %), and Na_2CO_3 (1.0 equiv) in CH₃CN (2.0 mL) was irradiated with blue LEDs (446 nm, 30 W) for 3 h under an air atmosphere at room temperature. *N*,*N*-Diisopropyl-*N'*-tosylformimidamide (3-1a) was obtained in 91% yield after chromatogaphic isolation (Table 1, entry 1). In comparison, the use of organoor noble-metal photocatalysts including TPT, [Mes-Acr]ClO₄, [Ir(dtbbpy)(ppy)₂][PF₆], and Ru(bpy)₃Cl₂ gave considerably

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Table 1. Optimization of the Reaction Parameters^a

Me 1a (2.0 equiv)	+ _N_ 2a	Eosin Y (5 mol %) Na_2CO_3 (1.0 equiv) CH_3CN (0.2 M), air 30 W blue LEDs room temp., 3 h	Me 3-1a
entry	changes to standard conditions		3-1a yield (%) ^b
1	none		91/88 ^c
2	TPT (2 mol %)		39
3	[Mes-Acr]ClO ₄ (2 mol %)		46
4	[Ir(dtbbpy)(ppy) ₂][PF ₆]		63
5	Ru(bpy) ₃ Cl ₂ (2 mol %)		51
6	Cs ₂ CO ₃		50
7	K ₂ CO ₃		80
8	NaOMe		75
9	no base		40
10	no light		0
11	THF		47
12	DMF		51
13	toluene		41

^{*a*}Reaction conditions: 0.2 mmol of TsN_3 **1a**, 0.1 mmol of tertiary amine **2a**, photocatalysts eosin Y (5 mol %), and Na_2CO_3 (1.0 equiv) in CH₃CN (0.2 M) under an air atmosphere at room temperature for 3 h, blue LED light. ^{*b*}Isolated yield. ^{*c*}1.0 mmol of **2a** was employed.

lower yields (entries 2-5, 39-51%). The coupling reaction between **1a** and **2a** in the presence of Cs_2CO_3 , K_2CO_3 , or NaOMe also proceeded with inferior conversions under our optimized conditions (entries 6-8). It should be noted that the transformation only produced 40% yield of **3-1a** in the absence of bases (entry 9), and no desired product **3-1a** was observed when the mixture was subjected to the standard reaction conditions without the photoirradiation (entry 10). Finally, the change of solvent to THF, DMF, and toluene did not show any promising results (entries 11–13).

We next examined the scope of sulfonylazides and tertiaryamines (Scheme 2 and Scheme 3). In general, kinds of arylsulfonylazides including phenylsulfonyl azides and heteroarylsulfonyl azides could smoothly couple with Nethyl-N-isopropylpropan-2-amine (2a) to produce the target *N*-sulfonylamidines 3-1, in which ethyl $C_{sp}^{3}-C_{sp}^{3}$ bond of 2a was cleavaged (Scheme 2). Among them, 4- or 3-alkyl or halogen-substituted phenylsulfonyl azides could give moderate to excellent yields of 3-1a, 3-1b, 3-1h, 3-1i, 3-1j, and 3-1l, repectively. In contrast, ortho-substituted phenylsulfonyl azides including 2,4,5-trimethylphenylsulfonyl azide led to inferior conversions due to the adjacent steric hindrance (63% for 3-1c, 43% for 3-1d, and 21% for 3-1k). Compared with phenylsulfonyl azide (81% for 3-1g), stronger electrondonating-group-substituted 4-methoxyphenylsulfonyl azide only afforded a moderare yield of 3-1e (64%), and 4acetylaminophenylsulfonyl azide could not be transformed into 3-1f at all. Meanwhile, the electron-deficient phenylsulfonyl azides such as 4-nitro, 4-acetyl, or 4-trifluorophenylsulfonyl azides also produced poorer yields of the desired amidines 3-1m (41%), 3-1n (20%), 3-10 (39%), and 3-1p (19%). Apart from the phenylsulfonyl azides, other arylsulfonyl azides such as biphenylsulfonyl azide, naphthylsulfonyl azide, 3-pyridylsulfonyl azide, and 2-thienylsulfonyl azide were well tolerated in this reaction, giving the target products 3-1q, 3-1r, 3-1s, and 3-1t in moderate to good yields (52-75%). Unfortunately, the cross-coupling between ethylsulfonyl azide¹⁴ and tertiaryamine 2a did not lead to the formation of amidine 3-1u.

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^{*a*}All the reactions were performed using sulfonylazides 1 (0.20 mmol), tertiaryamine **2a** (0.1 mmol), and Na₂CO₃ (0.1 mmol) with photocatalyst Eosin Y (5 mol %) in CH₃CN (1.0 mL) at room temperature for 3 h under air atmosphere irradiation using 30 W blue LEDs in a sealed reaction tube. Followed by flash chromatography on SiO₂. ^{*b*}Isolated yield.

Subsequently, we evaluated the coupling reaction of TsN₃ (1a) with different tertiaryamines and found different lengths of linear trialkylamines proceeded smoothly to furnish the desired products (3-2a-3-2d) in acceptable yields. Compared with tri-*n*-propylamine and triethylamine (76% for 3-2b, 80% for 3-2c), longer or shorter linear tri-n-butyl- and trimethylsubstituted tertiaryamines made the transformation a little sluggish, providing lower yields of 3-2a (23%) and 3-2d (27%), respectively. Although diverse linear alkyl chainsubstituted tertiaryamines (2f, 2g, 2h, 2i, and 2j) could efficiently react with 1a with excelent overall yields (81-86%), the carbon-carbon activation occurred mainly at the ethyl moiety, and different regioselectivity was still observed (entries 4-6). Interestingly, except N-methyl morpholine (20) which only produced N-Tos-N-morpholinoamidine 3-20 (41%), when other cyclic tertiaryamines such as N-methylpiperidine (2k), *N*-methylpyrrolidine (2l), *N*-benzylpiperidine (2m), and N-allylpyrrolidine (2n) were subjected to the standard conditions, the *N*-methylene C_{sp}^{3} -H bond could also directly couple with 1a to furnish complex amidines (3-2i, 3-2k, 3-2l, and 3-2m), which are possibly derived from 1,2-H migration accompanied by releasing N₂ after 1,3-dipolar addition.¹¹ Disappointingly, N-ethylindoline did not afford the desired amidine $3-2o_1^{16}$ and the starting material 2p was almost completely recovered.

Scheme 3. Tertiary Amine $\text{Scope}^{a,b}$



^{*a*}All the reactions were performed using sulfonylazide 1a (0.20 mmol), tertiaryamine 2 (0.1 mmol), and Na_2CO_3 (0.1 mmol) with photocatalyst Eosin Y (5 mol %) in CH₃CN (1.0 mL) at room temperature for 3 h under air atmosphere irradiation using 30 W blue LEDs in a sealed reaction tube. Followed by flash chromatography on SiO₂. ^{*b*}Isolated yield.

Several control experiments were performed to further explore the reaction mechanism (Scheme 4). At first, the crosscoupling between TsN_3 (1a) and tertiaryamine (2a) was carried out under our standard catalytic system in an oxygen atmosphere, giving 90% yield of 3-1a (eq 4a). In comparison, this transformation in an Ar atmosphere led to the formation of 3-1a only in 27% yield (eq 4b), which indicated that molecular oxygen was possibly involed in a single-electrontransfer (SET) process. Subsequently, the use of TEMPO (3.0 equiv) in the cross-coupling between 1a and 2a inhibited the reaction conversion to some degree (eq 4c), further demonstrating that radical intermediates were possibly produced in this transformation. Finally, when *N*-isopropyl-*N*-vinylpropan-2-amine (2q)¹⁷ was subjected to our standard

Scheme 4. Preliminary Mechanism Studies



reaction system to react with 1a, a 57% yield of 3-1a could be obtained (eq 4d). This result implied that tertiaryamines could be possibly transferred into vinyl amines under the O_2 mediated photocatalysis system. It should be noted that the cross-coupling reaction between 1a and 2q still gave a 40% yield of 3-1a in the absence of Eosin Y (Scheme 4e). In contrast, no desired product 3-1a could be observed in the absence of visible light (Scheme 4f), demonstrating that visible light enhanced the coupling reaction of TsN₃ and enamine 2q.

Based on the above-mentioned investigations and recent reports,¹⁸ a possible reaction mechanism for this reaction was proposed in Scheme 5. The reaction starts with the

Scheme 5. Proposed Mechanism



photoexcitation of EosinY (EY) to produce the excited state EY*, which is reductively quenched by *N*-ethyl-*N*-isopropylpropan-2-amine to generate the key cation radical intermediate **A** and the anion radical EY^{•-}. Meanwhile, molecular oxygen abstracts one electron from the anion radical EY⁻ to regenerate the photocatalysts EY and superoxide anion radical $O_2^{\bullet-}$. Subsequently, the intermediate **A** is deprotonated by $O_2^{\bullet-}$ to produce radical **B** and further oxidized to the iminium ion **D**. The intermediate **D** can be further deprotoned to form vinylamine **E**. Finally, the visible-light-enhanced 1,3-dipolar cycloaddition of vinylamine **E** with TsN₃ followed by the release of CH₂N₂¹⁹ gives the desired amidine **3a**.¹⁵

In conclusion, a room-temperature cross-coupling reaction between sulfonylazides and tertiaryamines for assembly of amidines was developed via a productive merger of visible-light photoredox catalysis and 1,3-dipolar cycloaddition. This transformation features a photocatalyzed C–C d-bond cleavage using molecular oxygen as the terminal oxidant, and provides a green approach to amidine compounds. Further investigations of photocatalyzed cross-coupling of *N*-methylene C-C d-bonds with different coupling partners are currently being carried out in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b00786.

Detailed experimental procedures, characterization data, copies of ¹H NMR and ¹³ C NMR spectra for all isolated compounds (PDF)

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Notes

The authors declare no competing financial interest.

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