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Letter

Synthesis of Cyclic Amidines by Iridium-Catalyzed Deoxygenative Reduction of Lactams and Tandem Reaction with Sulfonyl Azides

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03953

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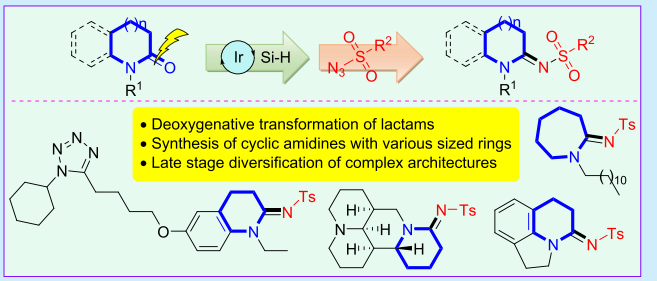
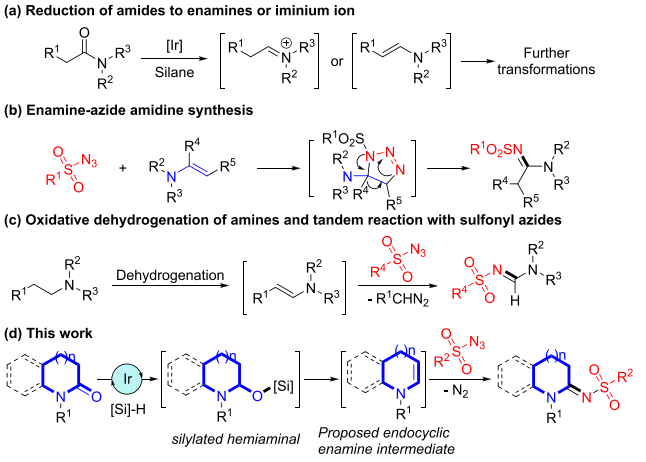
ABSTRACT: An efficient and convenient synthesis of various cyclic amidines has been achieved via iridium-catalyzed deoxygenative reduction of lactams with a silane followed by a one-pot cycloaddition reaction with sulfonyl azides. Using the novel tandem procedure, a large array of cyclic amidines bearing various sized rings were synthesized in good yields from readily available lactams. This methodology has been successfully utilized in the late stage diversification of complex architectures bearing a lactam moiety.



Owing to the wide prevalence of amide/lactam motifs in the structures of fine chemicals, synthetic intermediates, agrochemicals, and pharmaceuticals, reductive transformation of an amido group into other *N*-containing functional moieties is synthetically attractive.[1] However, development of mild, atom-economical, and chemoselective procedures for amide group transformations remains nontrivial due to their inert nature.[2,3] Over the past decade, iridium-catalyzed deoxygenative reduction of an amide and *in situ* trapping of the resultant enamine/iminium ion by another reactant (Scheme 1a) has evolved as a powerful strategy for the transformation of amides/lactams.[4−9] In this context, we envisioned that the [3 + 2] cycloaddition of thus-generated enamines with sulfonyl azides[10,11] might provide a viable route to amidines, which are ubiquitous motifs in natural products,[12] pharmaceuticals,[13] materials, super bases,[14] nucleophilic catalysts, and valuable synthetic precursors (Scheme 1b).[15] To date, several approaches of this strategy for the synthesis of *N*-sulfonylformamidine derivatives have been developed, e.g., based on the dehydrogenation of a tertiary amine to an enamine and the subsequent 1,3-dipolar tandem reaction with a sulfonyl azide (Scheme 1c).[16] However, the chemoselectivity caused by the multi α-H's of tertiary amine during the dehydrogenation step and functional-group tolerance of the procedures can be problematic. Although linear enamine intermediates have been well studied in this enamine-azide amidine synthesis, endocyclic enamine has been less explored for access to important cyclic amidines. Very recently, Joung et al. reported an efficient synthesis of cyclic amidines by a borane-catalyzed hydrosilylation of quinolines to the corresponding dearomatized enamine intermediates as the key step, but the scope of the products is largely limited to benzo-fused six-membered rings.[17] Therefore, the development of efficient synthetic routes to cyclic amidines[18] bearing various ring systems with good functional-group tolerance starting from a readily available molecule under mild conditions is still highly desirable.

Scheme 1. Synthesis of Amidines from Enamine Intermediates



The synthesis of amidines from amides has been developed based on several different methods. For examples, *N*-sulfonylformamidines can be generated by direct condensation of formamides and sulfonamides in the presence of a stoichiometric amount of acyl chlorides or oxidants.[19] To

Received: November 29, 2020

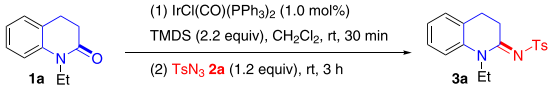
avoid the use of hazardous reagents and harsh conditions, some other strategies for the synthesis of amidines from amides have been developed. In 2013, Chiba, Hatanaka and co-workers reported a coupling reaction of the amide-derived thioamides and sulfonyl azides for the synthesis sulfonyl amidines, including various cyclic amidines.[20] In 2017, Adolfsson and co-workers developed a reductive functionalization of amides into *N*-sulfonylformamidines, using $Mo(CO)_6$-catalyzed reduction of amides to enamines as the key step.[21] However, only linear amides were reported in this protocol to give formamidines. In the same year, Odell and co-workers developed a Pd-catalyzed carbonylation/cycloaddition/decarboxylation cascade synthesis of sulfonyl amidines from sulfonyl azides and amides.[22] However, high loadings of Pd catalyst and $Mo(CO)_6$ were needed. In 2018, Wan and co-workers achieved the synthesis of *N*-sulfonylamidines by a Mn-catalyzed three-component reaction of secondary amide/lactam, diazoacetate, and sulfonamide under relatively high catalyst loadings and high reaction temperature.[23] Given the prime importance of the cyclic amidines, the efficient synthesis of this kind of moiety from widely prevalent lactams by the strategy of enamine-azide amidine synthesis would be highly attractive (Scheme 1d). However, to realize this tandem reaction sequence is synthetically challenging, since the iridium catalyst and silane used in the first step may result in the decomposition of the sulfonyl azide, which might result in byproduct formation and reduce the efficiency.[24]

Herein, we report an efficient protocol for one-pot transformation of stable lactams, giving access to a wide scope of highly functionalized cyclic amidines. The Ir catalyst can be reduced to as low as 0.1 mol % in gram scale synthesis, showing this method is generally applicable. It should be highlighted that various lactams with different ring sizes and functional groups can be smoothly transferred into the products bearing corresponding ring systems. Moreover, modification of complex architectures containing lactam units was also successfully achieved, showing the robustness and utility of the developed transformation.

We started the study by verifying the feasibility of the proposed reaction sequence. Lactam **1a** was selected as a model substrate with 1.0 mol % $IrCl(CO)(PPh_3)_2$ (Vaska's complex) as the catalyst, 2.2 equiv of 1,1,3,3-tetramethyldisiloxane (TMDS) as the reductant, and 1.2 equiv of sulfonyl azide **2a** which was used as the dipole for the cycloaddition step (Table 1). Gratifyingly, *N*-sulfonylamidine **3a** was obtained in 80% isolated yield under ambient temperature in a one-pot procedure, thus confirming that the proposed [3 + 2] cycloaddition of the *in situ* generated enamine with TsN_3 is compatible with the Ir catalyst and silane (Table 1, entry 1). (*E*)-Amidine **3a** was formed exclusively in the reaction, and its solid-state structure was unambiguously established by the X-ray crystallography. A series of control experiments were then conducted to probe into the role of each reacting component. When the amount of TMDS was decreased to 1.0 equiv, the yield of **3a** was reduced to 36%, and a substantial amount (54%) of substrate **1a** was left unchanged (entry 2). Increasing the Ir catalyst loading to 2.0 mol % did not improve the yield (entry 3). The solvent was also found to have a significant effect on the reaction outcome, and dichloromethane turned out to be superior in terms of the yields (entries 4–6 vs 1).

With the optimized conditions in hand, the generality of this protocol was explored in the reactions of lactams **1** and TsN_3 (Scheme 2). To our delight, lactams **1a–1g** bearing either electron-withdrawing or electron-donating substituents at different positions of the phenyl ring reacted smoothly with silane and TsN_3 in this one-pot procedure. Bromo, chloro, and OMe groups were well tolerated, affording the corresponding products in good yields (**3b–3g**, 65%–85% yields), suggesting that the steric hindrance and electronic property of the benzene ring does not have a notable effect on this reaction. It should be noted that the pyridyl ring was also tolerated,

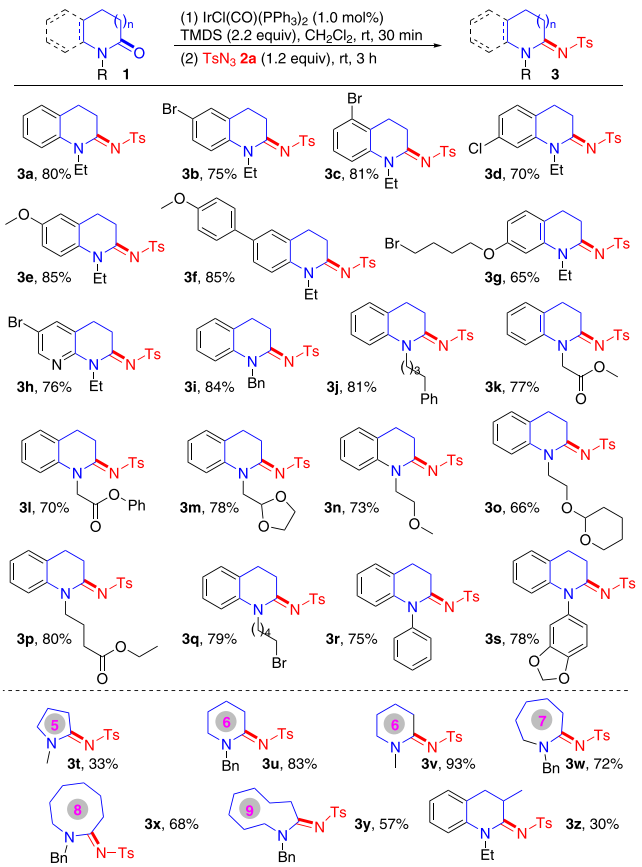
Table 1. Optimization of the Reaction Conditions for 3a[a]



entry	changes to standard conditions	yield (%)[b]
1	none	85 (80)[c]
2	TMDS (1 equiv)	36
3	$IrCl(CO)(PPh_3)_2$ (2.0 mol %)	85
4	THF instead of CH_2Cl_2	59
5	Toluene instead of CH_2Cl_2	48
6	CH_2ClCH_2Cl instead of CH_2Cl_2	47

[a]Reaction conditions: **1a** (0.2 mmol), TMDS (0.44 mmol), and $IrCl(CO)(PPh_3)_2$ (1.0 mol %) in CH_2Cl_2 (1.0 mL) were stirred at rt under an Ar atmosphere for 30 min. Then **2a** (0.24 mmol) was added and stirred at rt for 3 h. [b]NMR yields. [c]Isolated yield.

Scheme 2. Scope of Lactams[a]



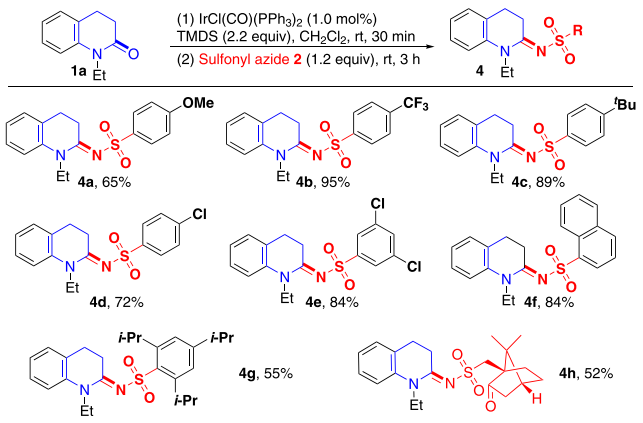
[a]The reaction mixture of the lactam **1** (0.2 mmol), TMDS (0.44 mmol), and $IrCl(CO)(PPh_3)_2$ (1.0 mol %) were stirred in CH_2Cl_2 (1.0 mL) at rt for 30 min under an Ar atmosphere. Then **2a** (0.24 mmol) was added and stirred at rt for further 3 h. Isolated yield.

https://dx.doi.org/10.1021/acs.orglett.0c03953
Org. Lett. XXXX, XXX, XXX–XXX

affording the product **3h** in 76% yield. The substrates with different groups on the nitrogen atom of lactams were next evaluated in this transformation, and the corresponding cyclic amidines were obtained in good yields. Changing the ethyl group on the N atom to benzyl or 4-phenylbutyl group did not affect the reaction outcome, giving the products **3i** and **3j** in 84% and 81% yield, respectively. It is worth noting that the reaction can be applied to the synthesis of amidines containing useful functional groups such as halogens, esters, acetal, and ether, which are potentially reducible under the catalytic conditions (**3k**−**3q**). Likewise, reactions of aryl substituted substrates also resulted in good yields (**3r** and **3s**). Subsequently, we explored the substrate scope for lactams with various ring sizes. The reaction using five-membered amide **1t** as the starting material can still afford the product **3t** in 33% yield. For lactams with larger ring sizes (six- to nine-membered rings), the reactions gave the corresponding compounds **3u**−**3y** in moderate to good yields, proving the robustness and practicability of the protocol in the synthesis of a diversity of cyclic amidines. However, for lactam with a methyl group at the α-position of the carbonyl group, the reaction gave the corresponding product **3z** in low yield (30%).

On the basis of these results, we further investigated the substrate scope with respect to the sulfonyl azides **2** with various substituent patterns, and the results were summarized in Scheme 3. Aromatic sulfonyl azides with either electron-

Scheme 3. Scope of Azides[a]

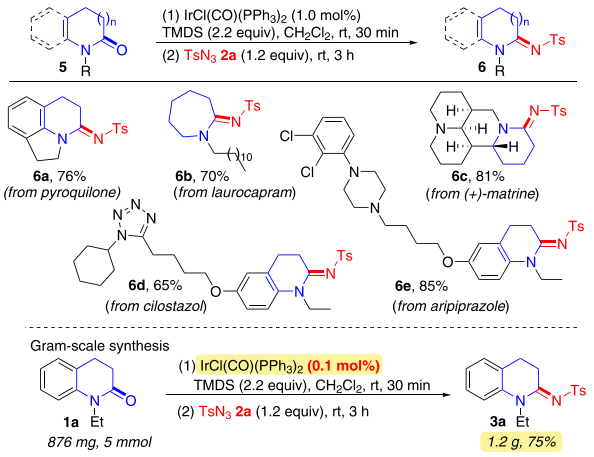


[a]The reaction mixture of the lactam **1a** (0.2 mmol), TMDS (0.44 mmol), and $IrCl(CO)(PPh_3)_2$ (1.0 mol %) was stirred in CH_2Cl_2 (1.0 mL) at rt for 30 min under an Ar atmosphere. Then **2** (0.24 mmol) was added and stirred at rt for a further 3 h. Isolated yield.

withdrawing or electron-donating groups at the phenyl ring worked well as the substrates, and the corresponding products were obtained in good yields (**4a**-**4e**). 2-Naphthalenesulfonyl azide can participate in the coupling substrate as well (84%, **4f**). The reaction of sterically bulkier azide also reacted smoothly to produce the desired product (**4g**) in 55% yield, suggesting the reaction can tolerate bulk steric hindrance of the azides. The reaction of alkyl sulfonyl azide afforded the product **4h** in 52% yield, further showing the wide scope of the sulfonyl azides.

Lactams are ubiquitous structural motifs found in a wide range of natural products and pharmaceuticals. Efficient transfer of lactam units to cyclic amidines represents a unique way to access new pools of functionalized analogues. To demonstrate the synthetic utility of the reaction developed herein, pyroquilone **5a**, laurocapram **5b**, (+)-matrine **5c**, drug-derived ethyl cilostazol **5d**, and ethyl aripiprazole **5e** were applied into the late stage transformation using the present method (Scheme 4). To our delight, all the reactions worked

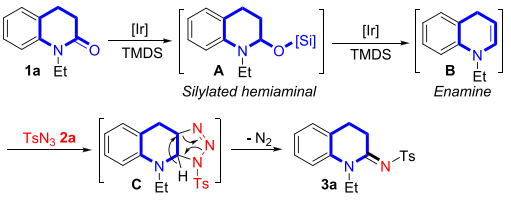
Scheme 4. Modification of Complex Architectures and Gram-Scale Synthesis



smoothly to provide the desired products in good yields (**6a**−**6e**, 65−85%). Furthermore, a 5 mmol scale reaction of **1a** was performed, and **3a** was isolated in good yield using reduced Ir catalyst loading (0.1 mol %), demonstrating the potential practicability of this cyclic amidine synthesis reaction.

Preliminary mechanistic studies were carried out to understand the reaction pathways. In the mixture of **1a**, Ir catalyst (1.0 mol %), and TMDS (2.2 equiv) in CD_2Cl_2, silylated hemiaminal intermediate **A** was witnessed as the major species by ^1H NMR during the first 30 min at rt (see the Supporting Information for details). Enamine intermediate **B** can be formed through this silylhemiaminal intermediate **A** as reported under the reaction conditions.[4b,5a] Furthermore, the addition of styrene together with TsN_3 under the standard conditions had negligible effect on the reaction outcomes and no aziridine was observed, suggesting that an iridium-nitrene intermediate is unlikely involved in this relay process. In accordance with previous studies on Ir-catalyzed reduction of amides[4−9] and enamine-azide chemistry,[16] a mechanistic pathway was proposed in Scheme 5. First the lactam **1a** is

Scheme 5. Proposed Reaction Pathway



partially reduced to silylated hemiaminal intermediate **A** by the action of Vaska's complex and TMDS. Enamine intermediate **B** is formed from **A** under the reaction conditions. Upon the addition of **2a**, enamine **B** reacts with **2a** through a regioselective [3 + 2] cycloaddition and produces intermediate **C**. Subsequently, the product **3a** is formed by a hydrogen

https://dx.doi.org/10.1021/acs.orglett.0c03953
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migration accompanied by one molecule of nitrogen being released.

In conclusion, we have developed an efficient synthesis of cyclic amidines, through a one-pot tandem transformation of Ir-catalyzed reduction of lactams and the *in situ* cycloaddition with sulfonyl azides. The amide reduction is highly chemoselective and allows for a wide variety of functional groups (such as halogen, ester, acetal, and ether) to be tolerated, and the ensuing cycloaddition with the sulfonyl azide also proceeds smoothly under very mild conditions to deliver various cyclic amidines with different ring sizes and functional groups in good to high overall yields. The present methodology also showcases synthetic utilities in the late stage diversification of several complex architectures, and thus will stimulate future work on the transformations of amides/lactams in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03953.

Experimental procedures, complete characterization data, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

Accession Codes

CCDC 2021109 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge financial support from the National Natural Science Foundation of China (21821002). The authors appreciate the valuable discussion of this work with Professor Pei-Qiang Huang at Xiamen University.

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