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Synthesis of Novel Heterocycles by Amide Activation and Umpolung Cyclization

Haoqi Zhang,[§] Margaux Riomet,[§] Alexander Roller, and Nuno Maulide*

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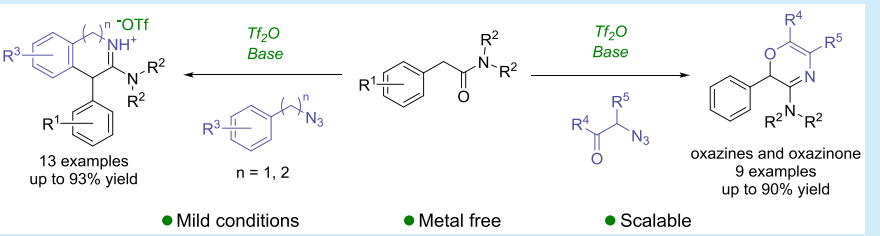


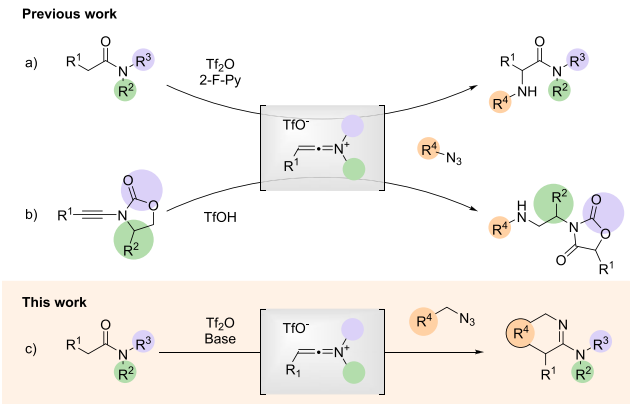
ABSTRACT: Herein, we report a metal-free synthesis of cyclic amidines, oxazines, and an oxazinone under mild conditions by electrophilic amide activation. This strategy features an unusual Umpolung cyclization mode and enables the smooth union of α-aryl amides and diverse alkylazides, effectively rerouting our previously reported α-amination transform.

Since its original report by Ghosez,[1] electrophilic amide activation using trifluoromethanesulfonic anhydride (Tf_2O) has emerged as a particularly versatile synthetic method.[2] The formation of a keteniminium intermediate (in the case of tertiary amides) or a nitrilium species (for secondary amides) and their reaction with diverse cycloaddition partners or nucleophiles have led to a cornucopia of domino-like transformations over the past three decades.[3]

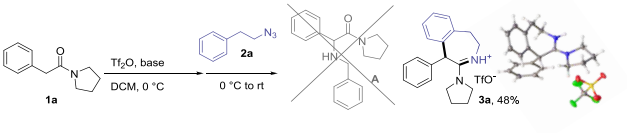
Among the large variety of nucleophiles that can productively interact with a keteniminium intermediate, we were intrigued by the versatility of organic azides. Our group previously reported that the combination of activated amides with azides delivers α-amination products (Scheme 1a).[4] In another study, we opted to generate the reactive keteniminium by protonation of an ynamide.[5] In this case, an entirely different pathway became operative, leading to skeletal rearrangement products (Scheme 1b).[6] Intrigued by these results and other literature precedents,[7] we explored these transformations further and varied the substrate structure and reaction conditions for the α-amination of amide.

Surprisingly, when 2-phenylacetamide **1a** was activated under electrophilic conditions, followed by the addition of homobenzylazide **2a** (Scheme 2), the reaction product was not

Scheme 1. Reactivity of Keteniminiums toward Alkyl Azides



Scheme 2. Unexpected Synthesis of 3a



the expected α-aminoamide **A** as reported previously.[4] Rather, a new product was isolated as a triflate salt whose structure could be confirmed as the seven-membered ring amidinium triflate **3a** by single-crystal X-ray analysis (Scheme 2). This unexpected product appeared to result from reaction of a stabilized intermediate by the pendant arene. We could previously observe such Umpolung reactivity of the α-carbon

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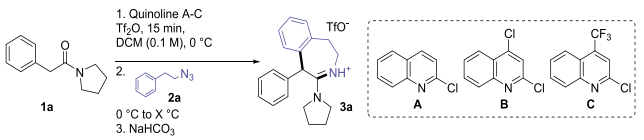
after addition of pyridine *N*-oxide derivatives on activated amides.[7a,8]

In this work, we present the synthesis of cyclic amidinium triflates, oxazines, and an oxazinone by rerouting of our previously reported α-amination transformation, including mechanistic studies of these processes.

At this juncture, we sought to optimize the reaction parameters to enhance the reaction efficiency toward product **3a**. To this end, we screened the stoichiometry of the different reaction partners as well as temperature and several bases (Table 1). An initial study showed that a quinoline base was essential for promoting both amide activation and subsequent elimination as well as interruption by the aromatic ring in this transformation. Further investigation revealed a beneficial impact of the decrease in the number of equivalents of quinoline base (compare entries 1 and 2).

Table 1. Optimization of Conditions for the Formation of Amidinium Triflates[a]



entry	Tf_2O (equiv)	**2a** (equiv)	quinoline (equiv)	*T* (°C)	yield (%)
1	2	2	A (5)	rt	48
2	2	2	A (2)	rt	63
3	2	2	B (2)	rt	75
4	2	2	B (2)	40	63
5	2	2	C (2)	rt	66
6	2	1.1	B (2)	rt	78
7	1.1	1.1	B (2)	rt	53

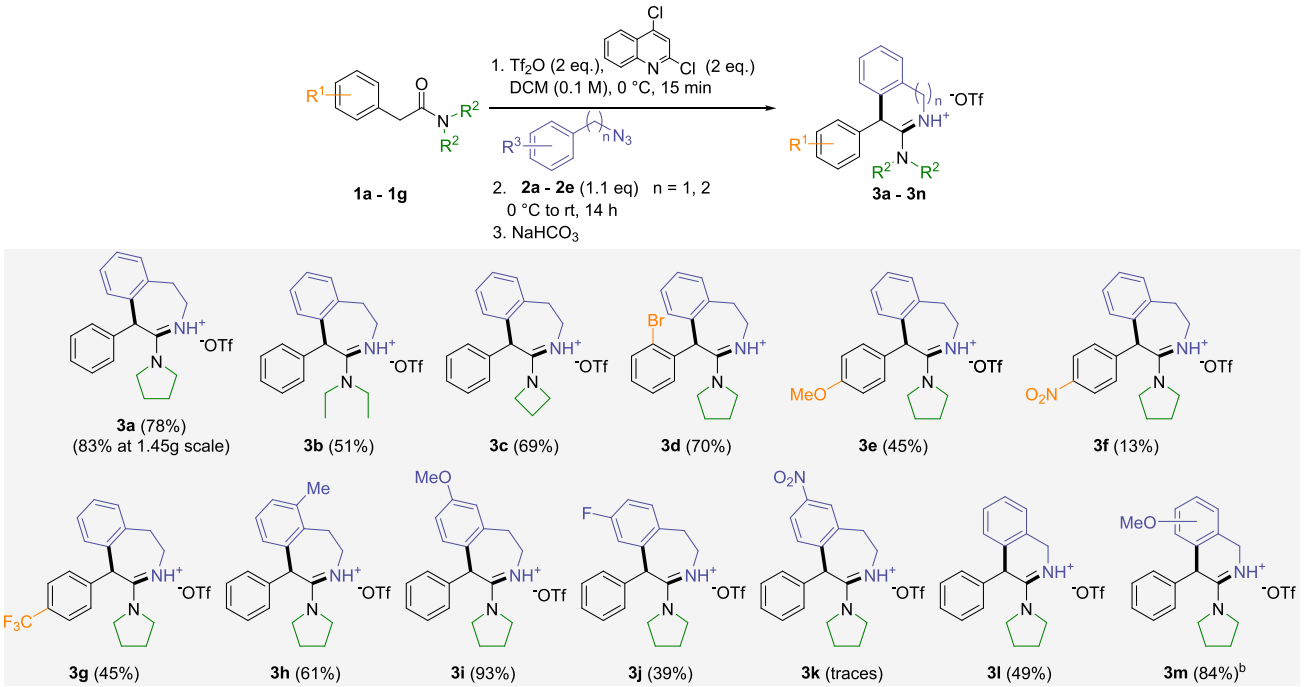
[a]Reactions were carried out on a 0.2 mmol scale. Yields refer to the isolated product.

A first study of the quinoline base motif showed that the 2-chloro substituent was essential in the reaction (see the Supporting Information for details). Electron-deficient quinolines showed better efficiency in the reaction (entries 2, 3, and 5), and 2,4-dichloroquinoline proved to be the best base. We also observed that an increase in temperature (entry 4) as well as a larger excess of azide (compare entries 5 and 6) led to byproducts and decreased the yield of desired product **3a**. Finally, 2 equivalents of triflic anhydride was needed to obtain the desired product in highest yields (compare entries 6 and 7).

With the optimized reaction conditions in hand, we investigated the scope of this cyclization reaction (Scheme 3). First, the tolerance toward the amide partner was investigated (**1a**−**1g**). Different *N*-alkyl substituents were tolerated on the amide partner and did not display a strong impact on the reaction (cf. **3a**−**3c**). On the other hand, substitution on the aromatic moiety was more influential. Strong electron-donating (**3e**) and electron-withdrawing *para*-substitution (**3f** and **3g**) of the phenyl group decreased the yield of the desired product. In the case of a *p*-nitro group (**3f**), the α-aminated amide could be isolated as the major compound (36%). This result supports the necessity of stabilizing a benzylic carbocation to favor the cyclization process. The steric hindrance provided by an *o*-bromo substitution (**3d**) did not affect the reactivity.

We then diversified the azide partner. Changes in its pendant arene moiety particularly affected the reactivity. Electron-donating groups generally gave the desired cyclic amidinium triflates in high yield. On the other hand, electron-

Scheme 3. Scope of Amidinium Triflates with Arylic Azides[a]



[a]Reactions were carried out on a 0.2 mmol scale. Yields refer to the isolated product. [b]Product synthesized with 1-(azidomethyl)-4-methoxybenzene and obtained as a mixture of 6-methoxy and 7-methoxy isomers (0.3:0.7).

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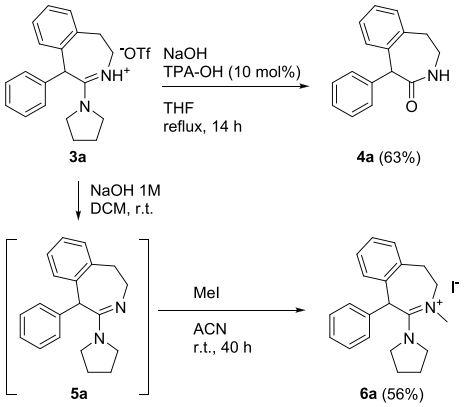
withdrawing substituents showed reduced reactivity. Compound **3j**, bearing a *p*-fluorine substituent, was obtained in 39% yield. A nitro group in the *meta* position completely inhibited the reaction, and only traces of **3k** could be detected. Interestingly, the formation of six-membered ring amidinium salts (**3l** and **3m**) did not proceed as readily as their seven-membered counterparts. Furthermore, unlike the previous reactions, the usage of an azide bearing substituents on the aromatic part led to an unseparable mixture of two regioisomeric six-membered ring amidinium triflates (**3m**). On a 4 mmol scale, **3a** was obtained in 83% yield, i.e., >1 g of material, showing the excellent scalability of the reaction. Unfortunately, this reaction did not permit access to larger cycles (eight- or nine-membered rings).

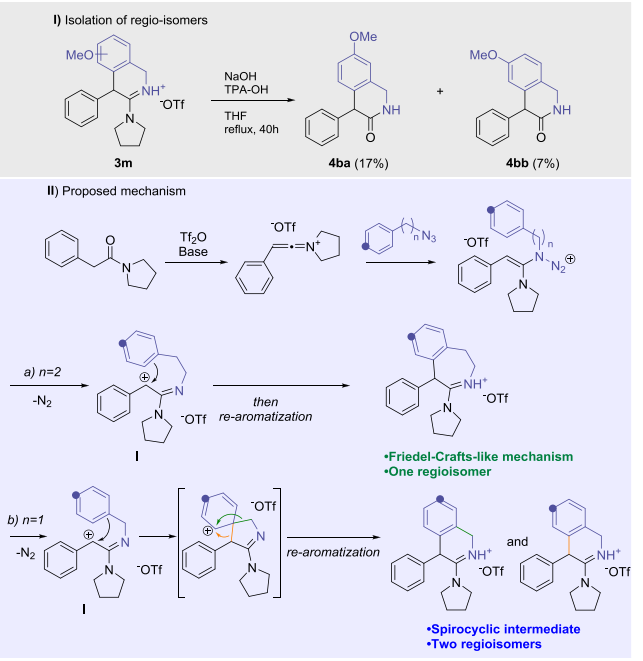
With a general synthetic route to these structures in hand, we investigated further derivatization (Scheme 4). After a short optimization (see the Supporting Information for details), amidinium **3a** could be hydrolyzed using a biphasic system to obtain a phenyl-3-benzazepinone (**4a**) in 63% yield. Benzazepinone derivatives are known for their pharmacological properties, but access to such compounds often requires long synthetic sequences.[9] Additionally, triflate salt **3a** could be easily converted to its deprotonated form (**5a**) by a simple basic extraction. Alkylation then afforded amidinium salt **6a** in 56% yield.

Scheme 4. Further Functionalization of Amidinium Triflates



While the formation of seven-membered rings was completely regioselective, the lack of regioselectivity for their six-membered ring counterparts was puzzling at first. To investigate the mechanism, it was essential to determine which regioisomers were formed. For this purpose, **3m** was hydrolyzed and the resulting **4ba** and **4bb** could be separated and identified giving some insight into their formation (Scheme 5, part I). We propose that, following keteniminium formation, attack by the azide sets the stage for N_2 release, generating stabilized carbocation **I** or a stabilized form thereof. Indeed, nonbenzylic substrates lead to α-amination products under the reaction conditions (see the Supporting Information for more details). For the formation of seven-membered rings, we propose a Friedel−Crafts-like mechanism capturing the carbocation (Scheme 5, part II, step a), which is supported by the observed reactivity difference between electron-withdrawing and -donating substitutions on the azide partner (Scheme 3, **3i**−**3k**). In the case of six-membered rings, the formation of isomers **4ba** and **4bb** suggests that amidine formation proceeds via spiro-cyclic intermediate **II** (Scheme 5, part II, step b), followed by a rearomatizing bond migration event that can take place in two different modes.

Scheme 5. Mechanistic Proposal for the Formation of Amidines[a]

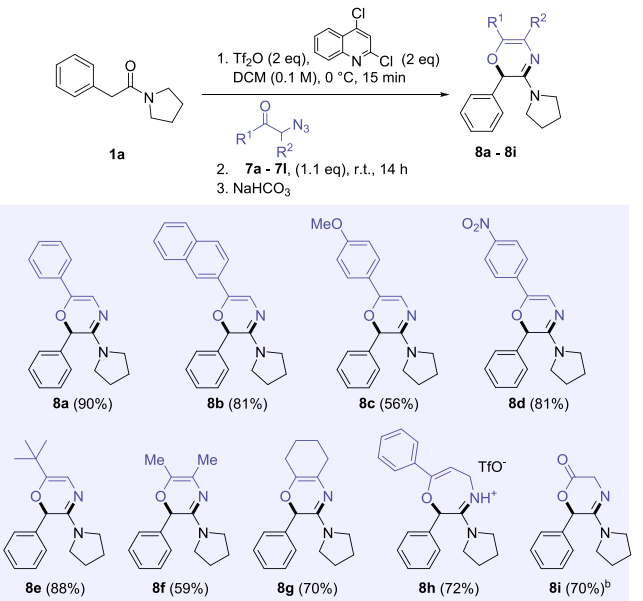


[a]Part I shows the isolation of regioisomers, and part II the proposed mechanism for the formation of seven- and six-membered rings.

Inspired by this novel transformation, we attempted to use different mild nucleophiles for the intramolecular nucleophilic attack by replacing the aromatic portion of the azide partner.

Interestingly, carbonyl groups were highly suitable for this role and led to the formation of pyrrolidinyl-oxazines in great yields (Scheme 6). We could obtain a wide range of new

Scheme 6. Scope of Oxazines with α-Carbonyl-azides[a]



[a]Reactions carried out on a 0.2 mmol scale. Yields refer to the isolated product. [b]Oxazinone was obtained using *tert*-butyl 2-azidoacetate.

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oxazines using this process. The transformation took place with both aromatic and aliphatic azidoketones with good to excellent yields (**8a**−**8h**). The use of a *para*-electron-donating group resulted in a noticeable lower yield (**8c**), unlike its electron-withdrawing counterpart (**8d**). This suggests that the nucleophilic attack of the carbonyl group might not be the kinetically determinant event in this reaction. While bulky substituents at the β-position (**8b**−**8e**) were tolerated, α-substitution decreased the yields (**8f** and **8g**) probably due to increased steric hindrance. In the event, using an azide with a quaternary carbon at the α-position led to a messy reaction mixture, suggesting that either proton elimination is decisive in this oxazine synthesis or tertiary azides are too bulky to be suitable substrates. The formed tetrasubstituted oxazines were also less stable than their trisubstituted counterparts and needed to be handled carefully. The formation of a seven-membered ring oxazine (**8h**) was also possible. It was also possible to generate an oxazinone **8i**, starting from an azido ester instead of a ketone. While both methyl and ethyl esters failed in this transformation, a *tert*-butyl ester was ultimately successful.

In conclusion, we serendipitously discovered and developed a novel approach for the preparation of cyclic amidinium salts and oxazines using domino electrophilic activation of phenylacetamides. We propose that the synthesis of seven-membered ring amidines takes place by Friedel−Crafts-like intramolecular cyclization, whereas their six-membered ring counterparts likely result from an intriguing spirocyclic intermediate, followed by C−C bond migration. Shifting to azidoketone or azidoester substrates led to the formation of oxazines and one oxazinone. The transformations shown here interestingly reroute our previously reported synthesis of α-aminoamides and showcase the wealth of chemical space that can be accessed through electrophilic amide activation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00571.

Expended optimization for the formation of amidinium salts and their hydrolysis, synthetic procedure, and analytical data of all compounds (PDF)

FAIR data including the primary NMR FID files for compounds **1c**−**d**; **3a**−**m**; **4a**; **4ba**; **4bb**; **6a**; **8a**−**i**; **S4**−**6** (ZIP)

Accession Codes

CCDC 1983045−1983046 contain 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.

■ AUTHOR INFORMATION

Corresponding Author

Nuno Maulide − *Institute of Organic Chemistry, Faculty of Chemistry, University of Vienna, 1090 Vienna, Austria*; Email: nuno.maulide@univie.ac.at

Authors

Haoqi Zhang − *Institute of Organic Chemistry, Faculty of Chemistry, University of Vienna, 1090 Vienna, Austria*

Margaux Riomet − *Institute of Organic Chemistry, Faculty of Chemistry, University of Vienna, 1090 Vienna, Austria*

Alexander Roller − *Institute of Inorganic Chemistry, Faculty of Chemistry, University of Vienna, 1090 Vienna, Austria*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00571

Author Contributions

[§]H.Z. and M.R. contributed equally.

Notes

The authors declare no competing financial interest.

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