

Mechanistic Pathways in Amide Activation: Flexible Synthesis of Oxazoles and Imidazoles

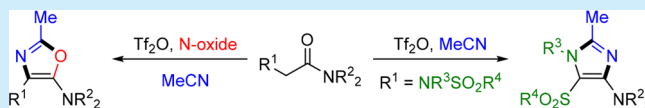
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S Supporting Information

ABSTRACT: The preparation of substituted aminooxazoles and aminoimidazoles from α -arylamides and α -aminoamides through triflic anhydride-mediated amide activation is reported. These reactions proceed via the intermediacy of nitrilium adducts and feature N-oxide-promoted umpolung of the α -position of amides as well as a mechanistically intriguing sequence that results in sulfonyl migration from nitrogen to carbon. Quantum-chemical mechanistic analysis sheds light on the intricacies of the process.



Nitrogen-containing heterocycles are a nearly ubiquitous feature in nature. In particular, both oxazoles and imidazoles are core structural motifs of several pharmaceuticals and bioactive compounds (Figure 1).¹ Oxazoles are known for

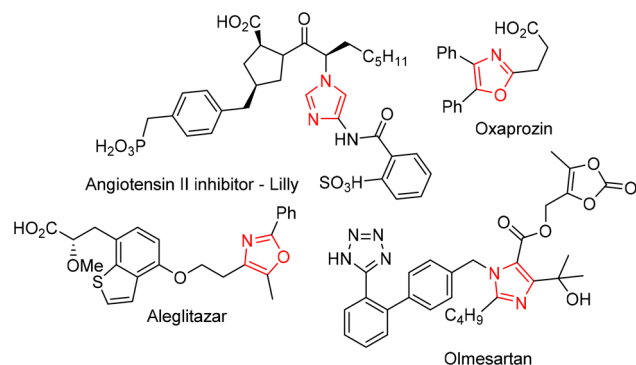


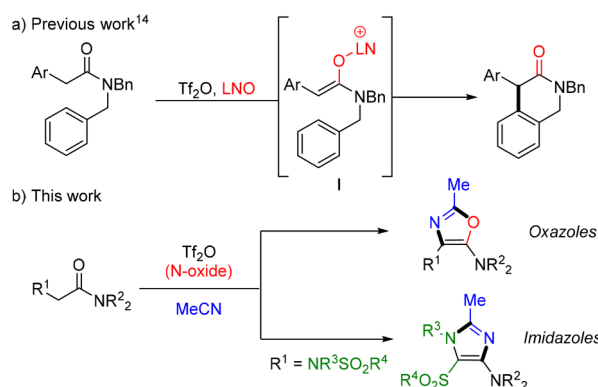
Figure 1. Pharmaceuticals and bioactive compounds containing oxazole and imidazole motifs.

their use as nonsteroidal anti-inflammatory drugs, PPAR modulators, hypoglycemics, and antibacterial agents,² while imidazoles play important therapeutic roles, for example as antifungals, proton pump inhibitors, angiotensin inhibitors, and kinase inhibitors.³ As a result of this central role, a vast number of approaches and synthetic routes for the formation of both oxazoles and imidazoles have been reported.^{4–6}

Amide activation using triflic anhydride has shown considerable synthetic versatility and utility in organic synthesis.⁷ Since the pioneering work of Ghosez,⁸ a plethora of synthetic methods for the functionalization of amides have been developed.⁹ In particular, the preparation of heterocycles has received a great deal of attention in recent years, with the syntheses of pyrimidines,¹⁰ pyridines,¹¹ lactones,¹² and tetrazoles¹³ at the forefront of these developments.

Recently, our group disclosed the lutidine N-oxide (LNO)-mediated oxidative C–C coupling of arenes and alkenes with amides (Scheme 1a).¹⁴ Therein, the formation of a latent

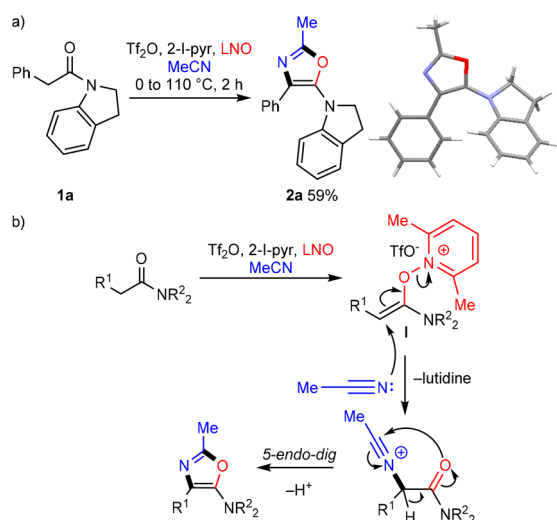
Scheme 1. (a) Oxidative C–C Coupling at the α -Position of Amides; (b) Formation of Imidazoles and Oxazoles by Alternative Pathways



electrophilic enolonium species (I) enabled intramolecular nucleophilic attack on the α -position of a selectively activated amide, generating tetrahydroisoquinolinones.

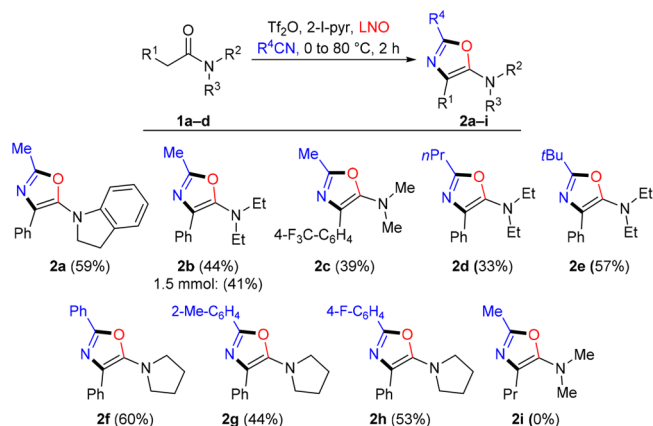
During the exploration of this transformation, we were intrigued by the side products obtained from premature interception of putative reactive intermediates with nucleophiles other than the aromatic rings (or olefins) employed in the bulk of the work (Scheme 1b). In the case of an α -arylamide with lowered capability of intramolecular cyclization (1a; Scheme 2a), we were surprised to isolate oxazole 2a as the exclusive reaction product, as confirmed by X-ray crystallog-

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Scheme 2. (a) Unexpected Oxazole Formation; (b) Putative Reaction Mechanism

raphy (CCDC 1537944; see the [Supporting Information](#) (SI) for further details). Mechanistically, this reaction outcome can be explained by the addition of LNO to the activated amide, forming α -electrophilic intermediate **I**,¹⁴ followed by intermolecular addition of acetonitrile ([Scheme 2b](#)). Oxazole formation is finalized via 5-endo-dig cyclization of the amide onto the transiently formed nitrilium ion.¹⁵

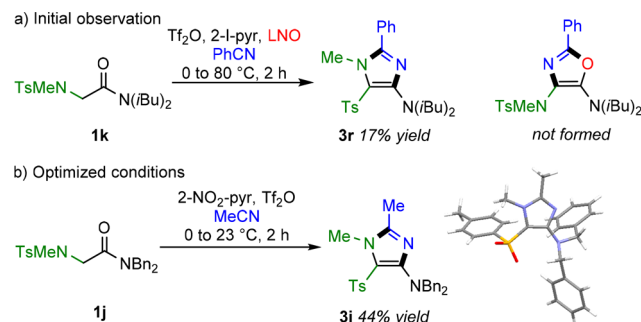
Brief optimization (see the [SI](#)) identified milder conditions that, for simple substrates, reliably afforded the desired substituted oxazoles in moderate to good yields ([Scheme 3](#)).

Scheme 3. Formation of Oxazoles from Simple Amides^a

^aReaction conditions: To amide **1** (0.2 mmol) and 2-I-pyr (0.4 mmol) in R⁴CN (2 mL) at 0 °C was added Tf₂O (0.2 mmol). After 15 min, LNO (0.21 mmol) was added, followed by heating to 80 °C for 2 h. Isolated yields are shown.

Varying substitution on nitrogen was tolerated, and the use of different nitriles similarly afforded the desired compounds (**2a–h**). We were additionally able to scale up the synthesis of **2b** to 1.5 mmol with comparable isolated yield. It quickly became evident, however, that the possible substituent R¹ was limited to aromatics (cf. **2i**, for which R¹ = Pr). We attributed this observation to increased LUMO stabilization of intermediate **I** by virtue of the aryl moiety.¹⁴

We thus logically attempted to widen the scope of R¹ to heteroatoms, such as protected nitrogens (**1k**). To our surprise, however, reaction of **1k** with benzonitrile under the standard conditions did not lead to the expected oxazole; in the event, a 1,2,4,5-substituted imidazole (**3r**) was observed as the only product ([Scheme 4a](#)). Particularly striking is the observation

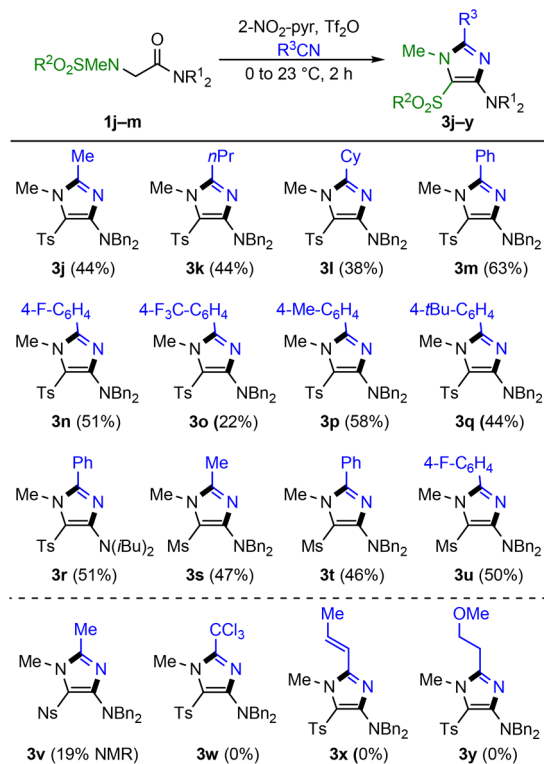
Scheme 4. Unexpected Imidazole Formation

that in the course of the reaction, the tosyl substituent of substrate **1k** appears to have migrated from nitrogen to carbon. Additionally, intermediate **I**—formed by attack of LNO (see [Scheme 2b](#))—does not appear to be involved in this transformation. Indeed, optimization of the reaction conditions using **1j** confirmed that LNO plays no role in the formation of the imidazole and also showed that the reaction could be run at room temperature ([Scheme 4b](#); see the [SI](#) for details). Further optimization showed an added beneficial effect of using 2-nitropyridine (2-NO₂-pyr), presumably due to decreased nucleophilicity (in comparison to 2-I-pyr) and therefore an increased fraction of keteniminium in solution (vide infra for a mechanistic discussion). Additionally, X-ray crystallographic analysis unambiguously confirmed the assigned structure of **3j** as well as the tosyl migration ([Scheme 4b](#), CCDC 1553624; see the [SI](#) for further details).

With the optimized conditions in hand, the scope of the reaction was explored ([Scheme 5](#)). While alkyl nitriles gave low to moderate conversions throughout (**3j–l**), benzonitrile led to imidazole formation in good yield (**3m**). Other aryl nitriles were also tolerated (**3n–q**), showcasing a trend where less nucleophilic (i.e., electron-poor) nitriles afforded lower yields (compare **3m** and **3o**). Simple alkyl substituents on the amide nitrogen, as in the case of diisobutylamide **1k**, also allowed the formation of the corresponding 2-aminoimidazole (**3r**). Besides the tosyl protecting group, mesyl sulfonamides were also viable substrates (**3s–u**). The nosyl protecting group, however, led to a marked decrease in product yield (**3v**), presumably due to the much diminished O-nucleophilicity of the sulfonamide (vide infra). Nitriles containing electron-withdrawing groups or functionality that could interfere with triflic anhydride were not viable coupling partners in this reaction (**3w–y**).

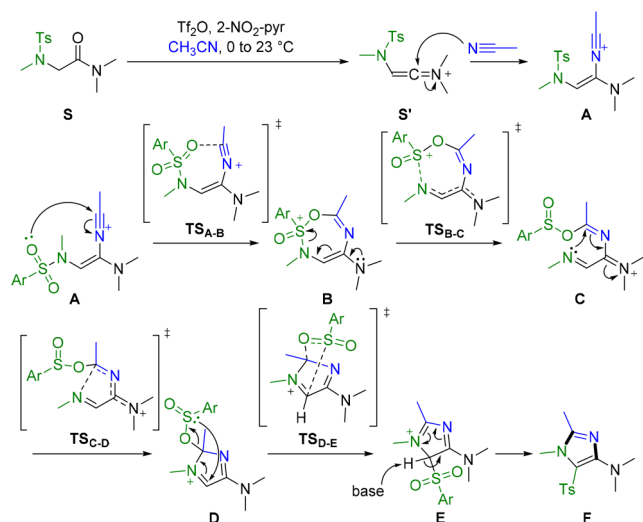
The imidazoles presented in [Scheme 5](#) are products of a mechanistically interesting net N-to-C sulfonyl migration. In order to further elucidate the mechanism of this reaction, quantum-chemical calculations were performed. [Scheme 6](#) depicts the mechanism of this transformation, as calculated for the simplified substrate **S** (see the [SI](#) for the computational details). The first two steps are the activation of the starting material **S** by virtue of triflic anhydride and the subsequent reaction of the keteniminium ion **S'** with acetonitrile leading to intermediate **A**. Although similar steps are well-known,^{10,16}

Scheme 5. Scope and Limitations of Imidazole Formation with Various Nitriles^a



^aReaction conditions: To amide **1** (0.2 mmol) and 2-NO₂-pyr (0.4 mmol) in R³CN (2 mL) at 0 °C was added Tf₂O (0.4 mmol). After 15 min, the reaction mixture was warmed to 23 °C for 2 h. Isolated yields are shown.

Scheme 6. Mechanism of the Formation of Tetrasubstituted Imidazoles



initially it was not clear how **A** could be converted into the final product, imidazole **F**. Scheme 6 and Figure 2 present the structures of the computed intermediates (**A**–**F**) and the corresponding transition states as well as the reaction profile.

Intermediate **A** forms the seven-membered intermediate **B** via O-nucleophilic attack of the sulfonamide on the nitrilium (7-*endo-dig*), forming a new C–O bond. Although this step is endergonic ($\Delta G(\text{A–B}) = +14$ kcal mol^{−1}), it predetermines a

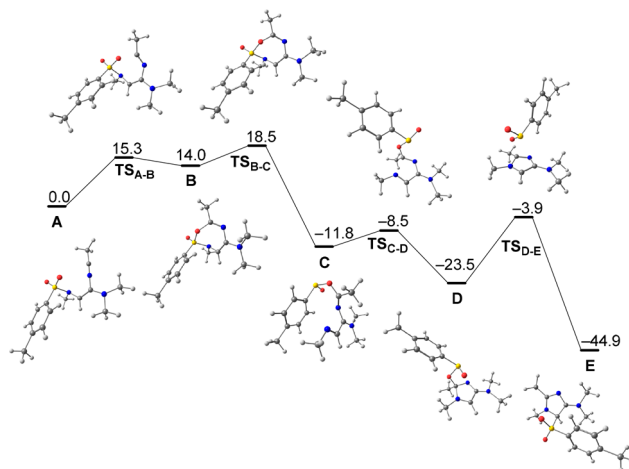


Figure 2. Computed reaction pathway ($\Delta G_{298, \text{MeCN}}$, kcal mol^{−1}) for the conversion of **A** to **E** (see Scheme 6) and the optimized structures.

substantial energetic stabilization in the next step, where the S–N bond breaks, forming intermediate **C** ($\Delta G(\text{B–C}) = -25.8$ kcal mol^{−1}). Additional thermodynamic stabilization is achieved via the second annulation step and TS_{C–D}. The five-membered-ring intermediate **D** undergoes a strongly exergonic [2,3]-sigmatropic rearrangement ($\Delta G(\text{D–E}) = -21.4$ kcal mol^{−1}), affording intermediate **E** with the concerted formation of the C–S bond and breaking of the C–O bond. Finally, intermediate **E** is deprotonated by the base, generating the final product **F** through aromatization.

While the formation of intermediate **A** was to be expected, informed by similar attacks of nitriles on activated amides,^{10,15} the subsequent 7-*endo-dig* cyclization was initially less obvious. The experimental observation that electron-poor sulfonamides do not allow the transformation to take place, however, is in good agreement with the O-nucleophilicity necessary for going from **A** to **B**.

Following the cleavage of **B** to give sulfinate **C** and subsequent cyclization to form **D**, a [2,3]-sigmatropic rearrangement—reminiscent of a retro-Mislow–Evans-type reaction—constitutes the final peculiarity of this mechanism, driven to completion by final aromatization from **E** to **F**. This last step is evident and does not require a theoretical explanation; accordingly, it was excluded from the computational study. Although a mechanism involving addition of the sulfonamide nitrogen to nitrilium ion **A** might seem plausible at first glance, our computations argue against it, as the necessary intermediates could not be found using two different quantum-chemical approaches: density functional theory (DFT) and an even higher level, second-order Møller–Plesset perturbation theory (MP2).

In summary, we have herein reported the facile syntheses of fully substituted 5-aminoxazoles and 4-aminoimidazoles. The title products are formed upon electrophilic activation of simple amides with triflic anhydride in the presence of nitriles. Computational studies shed light on the unusual mechanistic pathway of imidazole formation, showcasing an intriguing N-to-C sulfonyl migration via a [2,3]-sigmatropic rearrangement of a sulfinate intermediate.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01678.

Crystallographic data for **3j** (CIF)

Crystallographic data for **2a** (CIF)

Experimental procedures, characterization data for all new compounds, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

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