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A Modified Beckmann Rearrangement for the Facile Synthesis of Amidines and Imidates via Imidoyl Fluoride Intermediates

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Herein, we report a modified Beckman rearrangement using sulfone iminium fluoride (SIF) reagents to rapidly synthesize imidoyl fluoride intermediates. Subsequently, amidine and imidate products can be formed following the introduction of amine and alcohol nucleophiles, respectively. Overall, approximately 50 amidine and imidate products have been isolated in high yields utilizing mild conditions.

Introduction

For nearly a century and a half, the Beckmann rearrangement has been an effective pathway for the formation of amides (Figure 1A).^{1–3} In a traditional Beckmann rearrangement, a ketoxime is activated via strong acid which facilitates the migration of an R group from carbon to nitrogen and leads to the creation of a highly reactive nitrilium ion. Subsequent combination with water and tautomerization yields the desired amide product. The quintessential illustration of this chemistry comes from the conversion of cyclohexanone oxime to caprolactam, a precursor to Nylon 6 synthesized on a 4.5-billion-kilogram scale annually.⁴

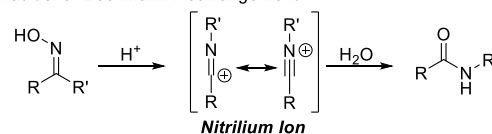
While acidic conditions are often used to activate the ketoxime, other reagent classes are capable of facilitating this rearrangement and generating the necessary nitrilium ion.⁵ A recent effort has been made to utilize sulfur – fluoride reagents which can transform ketoximes to amides under mild conditions.^{6–8} The use of S – F reagents provides an additional transformation that activation via acid does not. With free fluoride now present in solution, combination with the nitrilium electrophile leads to imidoyl fluoride intermediates which are typically ushered on to the amide product either through water present in the reaction or during the work-up procedure.^{6–8}

Under the right conditions, the *in situ*-generated imidoyl fluoride could be a highly valuable synthetic precursor for other desirable products, namely amidines and imidates. The amidine motif not only appears in various natural products, pharmaceuticals and agrochemicals,^{9,10} but they have also been used extensively in organic synthesis.¹¹ Likewise, imidates play a variety of roles, including both electrophile and nucleophile,¹¹ with more recent applications centered on their use as effective

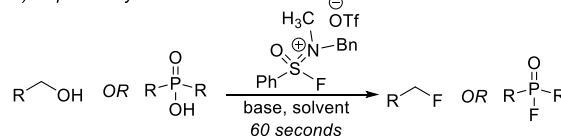
precursors in the synthesis of *N*-heterocycles.¹² A variety of methods exist for the preparation of these important functional groups,^{13–17} but a protocol for the synthesis of both amidines and imidates stemming from a common intermediate would be valuable.

Recently, our group reported the design of sulfone iminium fluorides (SIFs, Figure 1B) and their use in a series of challenging fluorination reactions.^{18, 19} Deoxyfluorination methodologies mediated by SIF reagents are characterized by very short reaction times (60 seconds at room temperature) while still employing a practical set-up. Given the demonstrated affinity of SIFs for hydroxyl-containing functional groups, we aimed to apply these unique reagents to the formation of imidoyl fluorides through a modified Beckmann rearrangement. The rapidly generated intermediates could then be subjected to various nitrogen and oxygen nucleophiles, producing amidines

A) Traditional Beckmann Rearrangement



B) Rapid deoxyfluorination with SIFs



C) This work:

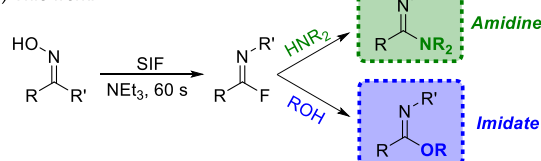


Fig. 1 A) Standard Beckmann rearrangement; B) Previous work using sulfone iminium fluorides (SIFs); C) Application of SIFs towards a modified Beckmann rearrangement.

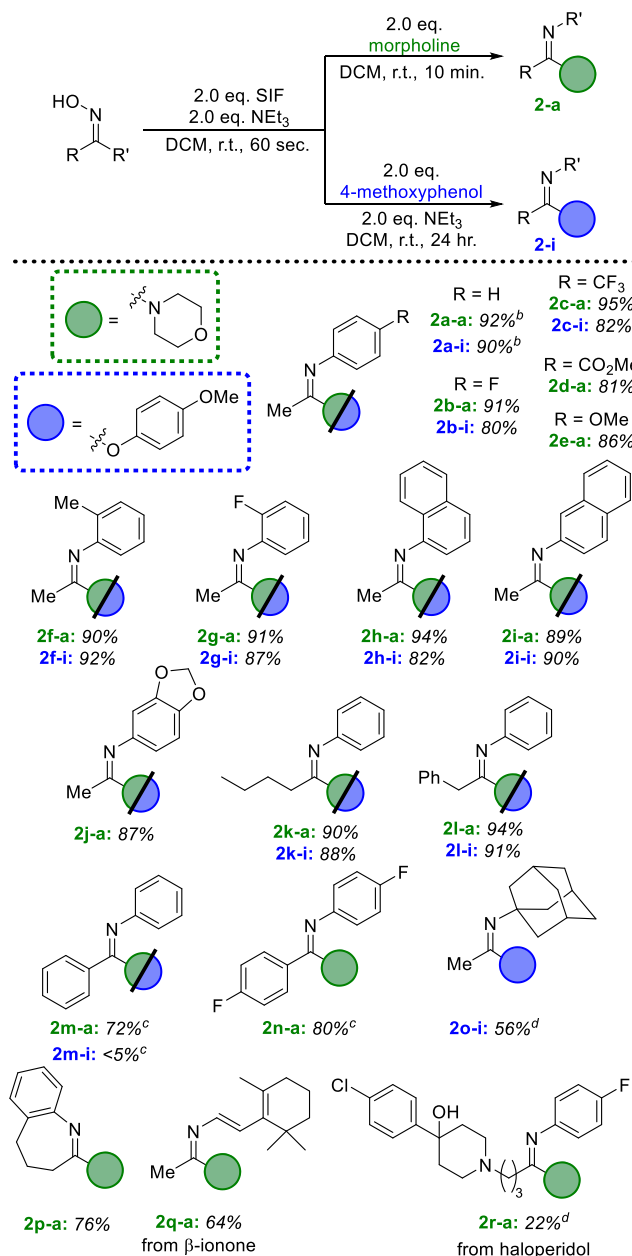
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Results and discussion

$$\text{R}-\text{C}(\text{R}')=\text{N}-\text{OH} \xrightarrow[\text{DCM, r.t., 60 sec.}]{\text{2.0 eq. SIF, 2.0 eq. NEt}_3} \text{R}-\text{C}(\text{R}')=\text{N}-\text{F} \quad (1)$$

R = Me; R' = Ph: 99% (^{19}F NMR)
 R = Ph; R' = Ph: 95% (isolated)

We then looked to expand beyond acetophenone oxime and explore the scope of the ketoxime component of this reaction (Figure 2). Unsurprisingly, several substituted acetophenone oxime derivatives were highly successful at generating the

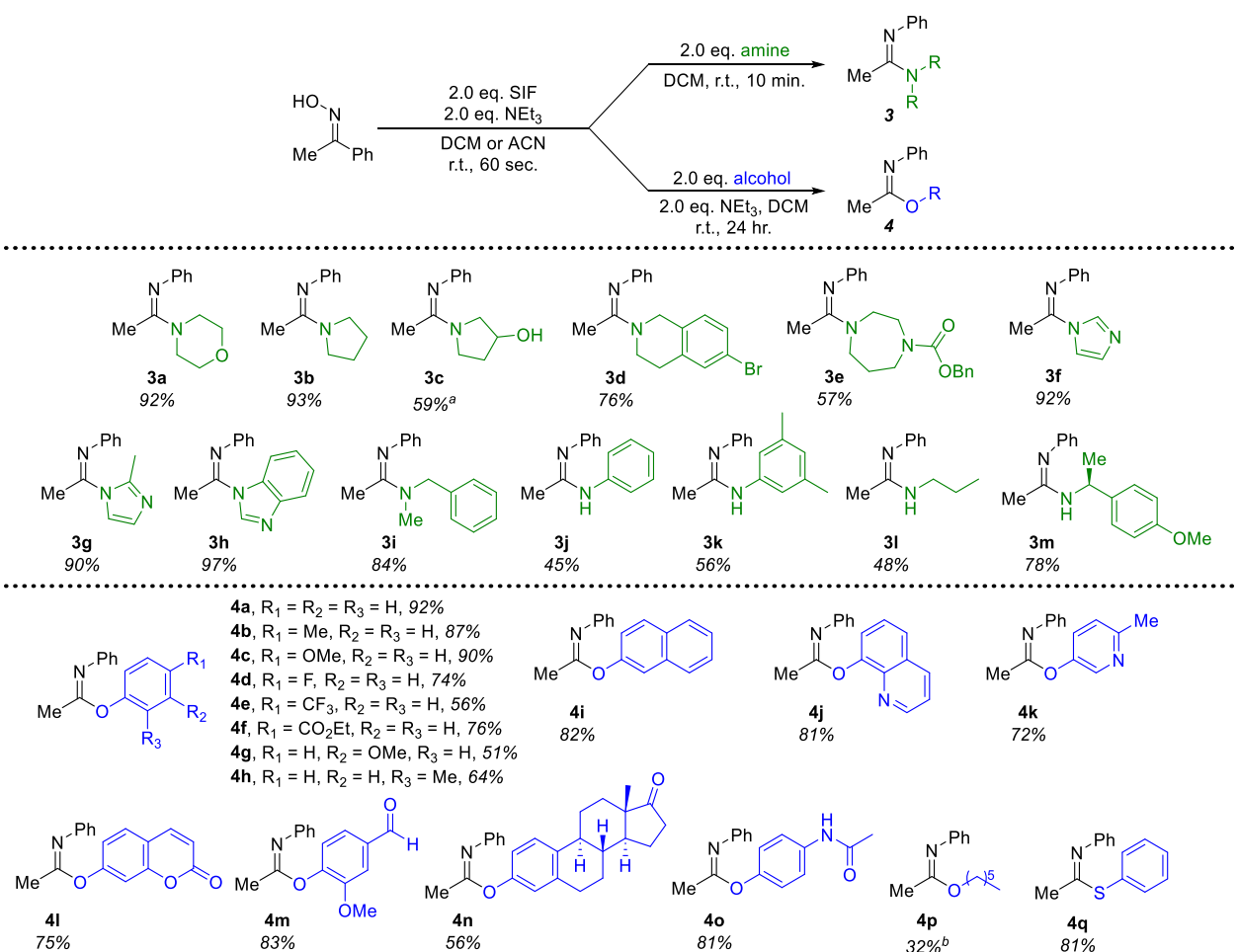


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amidine and imidate products in excellent yields using the standard conditions described above. Both electron withdrawing and donating groups at the *para* position of the phenyl ring were well tolerated (**2b** – **2e**); more importantly, *ortho* substitution did not lead to any significant decrease in the isolated yields (**2f** – **2h**). The methyl substituent of the ketoxime could also be altered to include more sterically hindered groups, such as butyl (**2k**) and benzyl (**2l**). Unfortunately, the use of a larger substituent, such as cyclohexyl or *tert*-butyl, did not lead to any significant conversion to the amidine or imidate products, despite the formation of the corresponding imidoyl fluorides after SIF addition. Next, we investigated benzophenone oxime derivatives; while longer reaction times were needed, good yields of the amidine products were achieved after 24 hours at room temperature (**2m-a**, **2n-a**). The same results were achieved from either the *in situ*-generated imidoyl fluoride or from the isolated compound. The combination of the less reactive benzophenone derived imidoyl fluoride with 4-methoxyphenol did not lead to significant conversion to the imidate product (**2n-i**), even when using elevated temperatures with acetonitrile as the solvent. Ring expansion could also be achieved when using tetralone oxime,

successfully generating a 7-membered ring imidoyl fluorides which efficiently formed the corresponding amidine (**2p-a**).

Moving beyond morpholine, we next investigated other secondary and primary amines for their efficacy in forming amidine products generated from acetophenone oxime (Figure 3). Several cyclic, secondary amines were ideal candidates for this transformation, providing amidines **3a** – **3h** in good to excellent isolated yields. These reactions were once again conducted with only 2 equivalents of the required amine and reached full conversion in just 10 minutes at room temperature. In particular, imidazole, 2-methylimidazole and benzimidazole (**3f** – **3h**) proved to be excellent nucleophiles to pair with the imidoyl fluoride intermediate. An acyclic, secondary amine (**3i**) could also be employed without any significant decrease in the yield. Due to the lessened nucleophilic character, primary anilines produced diminished yields (**3j**, **3k**) of amidines under optimal conditions. A chiral primary amine with steric hindrance proximal to the nitrogen delivered the corresponding amidine with an isolated yield of 78% (**3m**). Overall, this methodology demonstrates that a variety of amidines can be quickly and efficiently synthesized when using SIF reagents to generate the necessary imidoyl fluoride intermediate.



For amidines - oxime (0.2 mmol), SIF (0.4 mmol), NEt₃ (0.4 mmol), morpholine (0.4 mmol) DCM (0.75 mL), 22 °C, 10 minutes. For imidates - oxime (0.2 mmol), SIF (0.4 mmol), NEt₃ (0.8 mmol), 4-methoxyphenol (0.4 mmol), DCM (0.75 mL), 22 °C, 24 hours. Isolated yields reported as the average of two runs. ^a Yield determined by comparison to internal standard in ¹H NMR. ^b 1-hexanol (4.0 mmol, 20 eq.)

Fig. 3 Amine and alcohol substrate scope for the conversion of acetophenone oxime to amidine and imidate products.

Switching to alcohol nucleophiles, a wide selection of imide products stemming from phenols were possible. A variety of electronically-diverse, *para*-substituted phenols were viable candidates for this methodology, including several electron-withdrawing moieties (**4d** – **4f**). Likewise, *meta*- (**4g**, **4i**, **4l**, **4n**) and *ortho*-substituents (**4h**, **4j**, **4m**) were well tolerated. Heterocyclic phenols could also be included, with 8-hydroxyquinoline (**4j**, 81%) 3-hydroxy-6-methylpyridine (**4k**, 72%) and umbelliferone (**4l**, 75%) all providing efficient access to imide products when combined with the SIF-generated imidoyl fluoride. Furthermore, the use of vanillin as the phenol (**4m**) demonstrates that aldehydes are unaffected in this chemistry. Attempts to translate this methodology to aliphatic alcohols were not as successful. Even the use of increased amounts (20 equivalents) of 1-hexanol led to poor conversions to the corresponding imide product (**4p**, 32%). However, when switching to the sulfur derivative, thiophenol, an excellent isolated yield of the thioimide was obtained (**4q**). All told, close to 30 different amidine and imide products could be isolated in good to excellent yields, all stemming from the rapid generation of the imidoyl fluoride of acetophenone oxime.

Finally, ketones are common moieties in many natural products and pharmaceuticals. Therefore, we desired to show how the chemistry described herein could be executed using several of these relevant molecules. To this end, the ketoxime derivatives of β -ionone and haloperidol were synthesized and proved to be excellent candidates for this transformation. Under the ideal conditions described above, morpholine was used in conjunction with both ketoximes (**2q** and **2r**), demonstrating that this methodology could be an effective way to diversify common drug motifs. Likewise, phenols are prevalent functional groups in a variety of important molecules.²⁰ We selected estrone and acetaminophen as two promising candidates to act as the hydroxyl-containing species alongside acetophenone oxime (Figure 3, **4n** and **4o**). Both pharmaceutically relevant phenols were effective partners in this chemistry, providing access to novel imide products in 56% and 81% yield, respectively.

Conclusions

Overall, we have demonstrated that sulfone iminium fluorides are a powerful reagent class for the rapid conversion of ketoximes to imidoyl fluorides. A wide range of ketoximes can be utilized in this methodology, including several with pharmaceutical relevance. Following the 60 seconds required to form imidoyl fluoride intermediates *in situ*, the introduction of amines and phenols leads to excellent yields of amidines and imides, respectively. Using practical, simple conditions, we have represented over 50 different examples of this methodology, demonstrating the diverse power that this transformation holds in the synthesis of amidines and imides. Current work is aimed at expanding this chemistry beyond ketoxime substrates.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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