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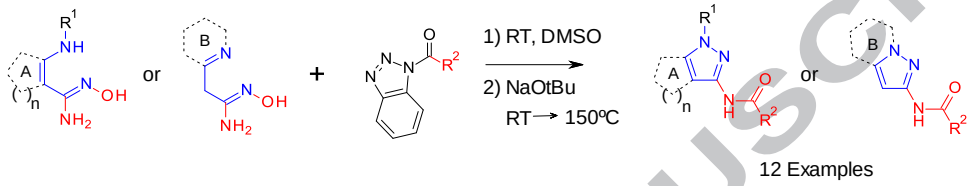

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ABSTRACT

Improved and expanded one-pot, two-component syntheses of bicyclic heterocycles containing a 3-N-acyl-3-amino-1,2-pyrazole motif from N'-hydroxy-carboxyamidines and acylbenzotriazoles have been developed. Importantly, this sequence obviates the need for hydrazine or N-aminating reagents to synthesize the key nitrogen-nitrogen (N-N) bond of these heterocycles, which is formed via Boulton-Katritzky rearrangement. A diverse array of pharmaceutically relevant N-N containing heterocycles has been prepared with this methodology using readily available reagents without the need for special equipment or conditions.

1. Introduction

Bicyclic heterocycles containing carbon and at least one nitrogen are found throughout Nature, notably in the biological macromolecules DNA/RNA (purine bases) and proteins/peptides (indole amino acid tryptophan). In addition, physiologically important biomolecules in this general class include serotonin/melatonin (indole nucleus), kynurenic acid (quinoline), and the natural products caffeine and theobromine (xanthines). In contrast, bicyclic heterocycles containing a nitrogen-nitrogen (N-N) bond are relatively rare in Nature[1] but are pervasive in the pharmaceutical industry. This is likely due to their novelty and properties relative to the naturally occurring congeners, and thusly, this motif is found in many approved drugs (*cf.* ponatinib,[2] olaparib,[3] sildenafil[4]). Methods of installing the key N-N bond of these heterocycles rely mainly on the use of hydrazine[5] or formation via N-amination,[6-10] along with other methods to a lesser extent.[11,12] Limitations for all these methodologies include functional group tolerance, non-convergence, and multiple synthetic manipulations.

In particular, the bicyclic heterocycles shown in Figure 1, all containing a 3-N-acyl-1,2-aminopyrazole motif (highlighted in blue), have been reported for applications in oncology, neurology, and metabolic pathologies (**1**-**3**),[13-15] as adenosine mimics (**4**),[16] as well as for autoimmune/inflammatory diseases (**5**).[17] Methods to synthesize and prepare analogues rapidly around these scaffolds are of specific interest to the medicinal chemistry community.

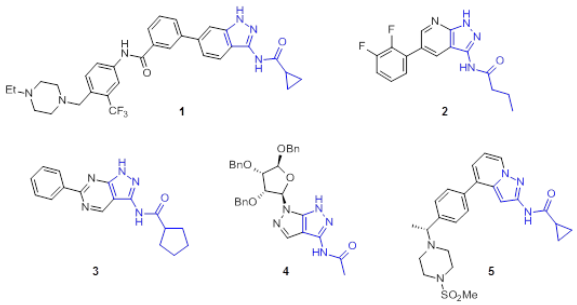

Figure 1. Pharmaceutically relevant heterocycles containing 3-N-acyl-3-amino-1,2-pyrazole motif (blue)

2. Results and Discussion

Previous efforts from our laboratories directed toward the synthesis of 3-N-acyl-aminoindazoles identified new electronic factors in the mononuclear heterocyclic Boulton-Katritzky rearrangement as well as a two-component, one-pot protocol to deliver 3-N-acyl-indazoles from N'-hydroxy-carboxyamidines and esters.[18] Caveats for this one-pot method include the need for microwave irradiation and melt conditions to effect the transformation.

To expand the utility of our convergent, one-pot protocol, we revisited the sequence with an eye toward more diverse substrates. Herein, we report an improved protocol and expanded scope of the one-pot, two-component

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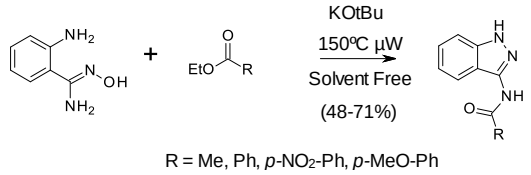
acylation/condensation/Boulton-Katritzky rearrangement for the synthesis of bicyclic heterocycles. The scaffolds synthesized in this manner include those exemplified in Figure 1, namely, indazole, pyrazolo[3,4-*b*]pyridine, pyrazolo[3,4-*d*]pyrimidine, pyrazolo[3,4-*c*]pyrazole, and pyrazolo[1,5-*a*]pyridine. All contain an embedded 3-N-acyl-3-amino-1,2-pyrazole motif. The linchpins of this protocol were the use of acylbenzotriazoles (both aryl and alkyl) as the coupling partners to the N'-hydroxy-carboxyamidines and controlled temperature regulation/base addition. With these reagents and conditions, we were able to efficiently manipulate each phase of the three-step, one-pot transformation which was critical to the success of the overall sequence.

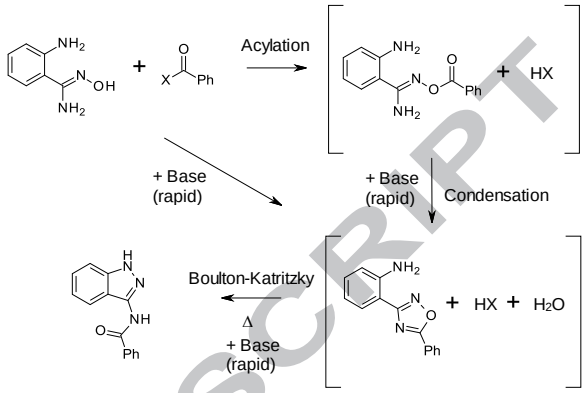
Our initial attempts to expand our protocol to the more diverse set of N'-hydroxy-carboxyamidines proved challenging. Using the original protocol (Scheme 1) of combining all material in the presence of base and microwaving at 150 ºC, the solvent-free conditions proved inconsistent for the new set of substrates, presumably due to solubility or reactivity limitations. Furthermore, when evaluated using added solvent (DMF), product formation was realized, though complex mixtures were observed with unidentified products, potentially due to the extended heating times and/or competing side reactions.



Scheme 1. Originally devised 1-pot protocol

At this juncture, we decided to revisit the protocol and reconfigure to find a general solution for the diverse set of N'-hydroxy-carboxyamidines. We reasoned that the above protocol could result in unwanted side reactions if the initial acylation/condensation did not proceed to completion. For instance, the presence of unreacted ester or retro-addition of hydroxylamine to produce the cyano derivative were of particular concern since these were potentially electrophilic substrates. Towards this end, we focused our attention on the ester component as the point for further optimization. Mechanistically, the ester must first acylate the N'-hydroxy-carboxyamidine to initiate the cascade. Unactivated esters, in general, tend to be poor acylating agents. To gain a full understanding of the sequence of events we repeated the reaction at ambient temperature (Scheme 1, R = Ph) in the presence of 0.3 eq of KOtBu. Interestingly, we did not observe the acylation intermediate (via LC/MS), but rather, rapid formation of the oxadiazole, though the reaction stalled before complete conversion with both unreacted N'-hydroxy-carboxyamidine and ester present, even after 4h. Using the above conditions in the absence of base, no acylation or condensation occurred even at high temperature (>150 ºC) though minor degradation products were evident.

Following the cascade sequence (Scheme 2), we reasoned that improving the acylation-condensation sequence would be paramount to creating a cleaner, higher yielding protocol. Previously, we had examined both acid chlorides as well as acids with coupling reagents, both of which are known for oxadiazole formations.[19] However, they were unsuccessful when used in the one-pot sequence, potentially due to increased reactivity of the acylating agent and of the pendant unsubstituted nitrogen. We decided an acylating reagent with balanced reactivity was needed, one which could undergo direct acylation of the N'-hydroxy-carboxyamidine in the absence of base or heat to suppress over (or under) acylation. A survey of the literature found a report from the Katritzky laboratory that described acylbenzotriazoles as effective coupling components to deliver 1,2,4-oxadiazoles.[20]

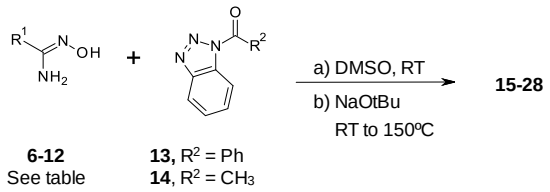


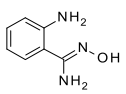
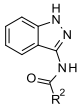
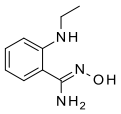
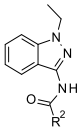
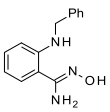
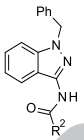
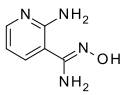
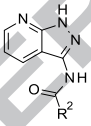
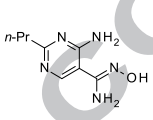
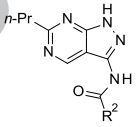
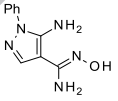
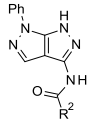
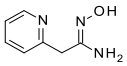
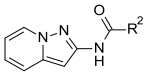
Scheme 2. General Cascade Sequence

The use of acylbenzotriazoles was particularly compelling since these reagents were either commercially available or easily prepared via the acid/benzotriazole/$SOCl_2$[21] and tended to be white, shelf-stable solids. Our initial attempts with the acylbenzotriazole in the one-pot protocol in DMF (150ºC, no added base) were indeed successful with desired product observed. However, multiple side products were evident and long reaction times were needed to drive the reaction to completion. Though DMF proved effective for the rearrangement as demonstrated by our earlier work, we decided to examine a variety of solvents. Katritzky and co-workers used ethanol/triethylamine to obtain the oxadiazole from the acylbenzotriazoles but this was not ideal for the temperatures needed to induce the rearrangement (≥150ºC) and would require a sealed vessel. Thus, we decided to examine other high boiling polar protic/aprotic solvents in place of DMF. In short order, we found that DMSO provided a much cleaner reaction profile. Katritzky and co-workers also showed that the initial acylation with N'-hydroxy-carboxyamidines can be completed at room temperature then heated to reflux to induce cyclocondensation. Likewise in our system, using DMSO as a solvent, we could induce acylation cleanly at room temperature and importantly, induce cyclocondensation using only an increase in temperature (100ºC). A further temperature increase to 150ºC gave the rearrangement to the desired product, though extended reaction times were required. Based upon our earlier observations, to accelerate the cyclocondensation we returned to base-promotion and found addition of a non-nucleophilic base (t-butoxide, sodium or potassium salt, one equivalent) to be effective following the completion of the acylation. Furthermore, addition of another equivalent of base for the final temperature increase also provided a more rapid rearrangement. With addition of 2 equivalents of base at the initiation of the reaction, no intermediate acylation product was observed by HPLC, only rapid conversion to the oxadiazole. However, as observed in earlier iterations, numerous low-level byproducts were observed and incomplete conversion was noted. Timing for base addition following complete acylation proved critical. Two equivalents of base can be added following acylation in a single delivery or stepwise (*i.e.* after acylation and again after cyclocondensation); the reactions proceeded with similar yield and purity profiles. Thus, the single addition of 2 equivalents of base became our optimized protocol.[22]

Shown in Table 1 are the N'-hydroxy-carboxyamidines (**6-12**)[23] that were used in the synthesis of **15-29** using the optimized procedure. For the acylbenzotriazoles, we employed both aryl (**13**, R^2 = Ph) and alkyl (**14**, R^2 = CH_3) derivatives. For the unsubstituted (**15-16**) and the substituted (**17-20**) 2-amino-N'-hydroxy-benzamidine derivatives, reasonable to good yields were obtained (51-85%). The yields were similar for both the pyridine (**21-22**) and the pyrimidine (**23-24**) variants. This protocol could also access 5-5 hetero-bicycles (**25-26**) in reasonable yields. Of particular note, bridgehead nitrogen heterocycle pyrazolo[1,5-*a*]pyridines **27** and **28** were accessible in practical yields using this methodology.[18]

Table 1.
One-pot Syntheses of Bicyclic Nitrogen Heterocycles



	R^1-N'-hydroxy-carboxyamidines	Product	Example (% Isolated Yield)
6			**15,** R^2 = Ph (85%) **16,** R^2 = CH_3 (77%)
7			**17,** R^2 = Ph (57%) **18,** R^2 = CH_3 (51%)
8			**19,** R^2 = Ph (54%) **20,** R^2 = CH_3 (55%)
9			**21,** R^2 = Ph (80%) **22,** R^2 = CH_3 (72%)
10			**23,** R^2 = Ph (65%) **24,** R^2 = CH_3 (85%)
11			**25,** R^2 = Ph (53%) **26,** R^2 = CH_3 (53%)
12			**27,** R^2 = Ph (58%) **28,** R^2 = CH_3 (56%)

3. Conclusions

In summary, we have expanded the scope and improved the one-flask protocol to deliver diverse N-N bond containing heterocycles from N'-hydroxycarboxyamidines and acylbenzotriazoles. The key linchpins of this general strategy were the balanced reactivity of the acylbenzotriazole to acylate the N'-hydroxy-carboxyamidines efficiently in polar aprotic solvent and the ability to induce cyclocondensation to the oxadiazole by base addition and then Boulton-Katritzky rearrangement via temperature increase. This synthetic methodology, forming a nitrogen-nitrogen bond in the rapid, convergent assembly of complex systems from simple starting materials is of utility to both the chemical and pharmaceutical communities.

Acknowledgments

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Supplementary data

Experimental procedures and characterization for compound **26**. Supplementary data associated with this article can be found, in the online version.

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22. General Procedure: The N'-hydroxy-carboxyamidines (1 eq.) and the N-acyl benzotriazole (1 eq.) were added to a scintillation vial and dissolved in DMSO (2 mL/mmol substrate), the cap was replaced, and the mixture stirred at room temperature for 1 hour or until the acylation was complete by HPLC. Sodium t-butoxide (2 eq.) was added and the reaction stirred for 5 min or until oxadiazole formation was complete. The reaction was then heated to 150 ºC for 5 minutes or until the oxadiazole was consumed. The reaction was quenched with aqueous HCl (2 eq). The reaction mixture either worked-up and purified by flash chromatography, directly purified by reverse phase HPLC, or isolated by filtration if a solid precipitate.
23. **6-14** are available commercially or were synthesized using known procedures, see Korbonits, D.; Kanzel-Szoboda, I.; Horvath, K. *J. Chem. Soc., Perkin Trans. 1* **1982**, 759, refs. 18 and 25.
24. **15-25**, **27-28** were characterized by ^{1}H-NMR and high resolution mass spectra and were consistent with published data. For experimental procedure and characterization of compound **26**, see supplementary data.
25. 2-N-acyl-pyrazolo[1,5-*a*]pyridine was reported by heating **12** in acetic anhydride which resulted in a mixture of intermediate oxadiazole, **28**, and over-acylated product, see: Suzue, S.; Hirobe, M.; Okamoto, T. *Chem. Pharm. Bull*. **1973**, *21*, 2146-2160.

Highlights

- Expanded scope of substrates for one-pot, two-component Boulton-Katritzky rearrangement.
- Simplified procedure to build both diversity and complexity in pharmaceutically relevant heterocycles.
- Sequence obviates the need for hydrazine or N-aminating reagents to synthesize the key nitrogen-nitrogen (N-N) bond of these diverse heterocycles.