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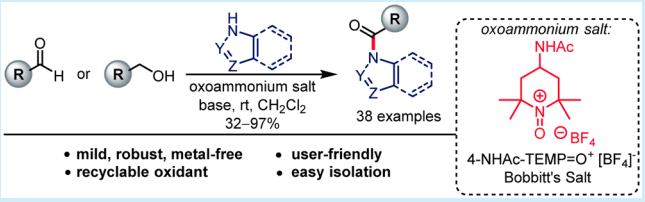
Accessing *N*-Acyl Azoles via Oxoammonium Salt-Mediated Oxidative Amidation

John M. Ovian, Christopher B. Kelly, Vincent A. Pistritto, and Nicholas E. Leadbeater*

Department of Chemistry, University of Connecticut, 55 North Eagleville Road, Storrs, Connecticut 06268, United States

Supporting Information

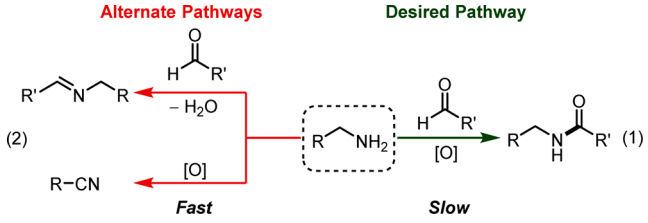
ABSTRACT: An operationally simple, robust, metal-free approach to the synthesis of *N*-acyl azoles from both alcohols and aldehydes is described. Oxidative amidation is facilitated by a commercially available organic oxidant (4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate) and proceeds under very mild conditions for an array of structurally diverse substrates. Tandem reactions of these activated amides, such as transamidation and esterification, enable further elaboration. Also, the spent oxidant can be recovered and used to regenerate the oxoammonium salt.



The unrivaled ubiquity of the amide bond throughout a variety of fields is a testament to its utility.[1] This linkage comprises the backbone of enzymes and the core of some of the most common polymers, in addition to routinely serving as the critical synthetic link between fragments of pharmacons.[1] Indeed, in the context of synthetic chemistry, amide coupling is one of the most important reactions[1b] and, as in nature, the C−N bond is most commonly forged via the condensation of an activated carboxylic acid and an amine. An array of carboxylic acid activators are available, thus enabling practitioners to tailor their synthetic strategy to the appropriate reagent.[2] Divergent from the typical approach is the paradigm of oxidative amidation.[3] Using this model, aldehydes (and alcohols via a separate oxidation event) become the carbonyl-containing progenitor of the amide and are oxidatively functionalized with an amine (Scheme 1, eq 1). Although highly attractive, optimization of such a process is not without its unique challenges. The rapidity with which amines condense with aldehydes as well as the propensity for amines to be oxidized can ultimately render the oxidative amidation pathway inaccessible (Scheme 1, eq 2).[4,5] In spite of these challenges, this approach has been executed elegantly in several reports such as the Ru-catalyzed process described by Milstein and a recent report by Stahl.[6]

N-Acyl azoles are one class of amides whose utility has recently been realized by a number of groups because these amides balance reactivity with stability. In addition to serving as viable amide coupling partners (i.e., *N*-acyl imidazoles), certain *N*-acyl azoles (i.e., *N*-acyl pyrazoles) have been used to great effect for asymmetric transformations.[2,7] The latter capitalizes on the unique ability of *N*-acyl pyrazoles to undergo enolization when coordinated to transition metal catalysts. The resulting functionalized *N*-acyl pyrazole can then be further elaborated through displacement processes. In addition to being a powerful directing group, azole subunits are common structural motifs in medicinally relevant compounds.[8] Current methods to access *N*-acyl azoles via oxidative amidation are restricted to harsh conditions relying on superstoichiometric loadings of peroxides at temperatures exceeding 100 °C.[9] Such methods do not tolerate many functional groups (e.g., electron-rich arenes, olefins, alcohols, etc.) and are not amenable to scale up.

Scheme 1. Potential Outcomes of Oxidative Amidation



Recently, acyl pyridinium species were identified as the key intermediates formed when performing oxidative functionalization using **1a**.[10] Since these are the same intermediates when using acid chlorides and pyridine, we envisioned that *N*-acyl azoles could be accessed via a similar approach (Figure 1). Alternatively, the azole itself could serve as an activator in the same manner as pyridine. Regardless of the mode of activation, both pathways furnish the desired *N*-acyl azole. Given the numerous advantages of this approach such as it being the first instance of direct oxidative amidation using benign, recyclable, metal-free oxidant **1a**,[11] the ability to access *N*-acyl azoles directly from aldehydes at room temperature under mild conditions, and the excellent nucleophilicity of azoles, we explored the viability of this transformation.

Assessment of the feasibility of oxidative amidation began with the examination of the coupling of *p*-tolualdehyde (**2a**) with pyrazole using 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (Bobbitt's salt, **1a**) (Table 1), as the oxidant of choice. Pyrazole, **3a**, was chosen as a representative azole given its low basicity relative to pyridine and that the

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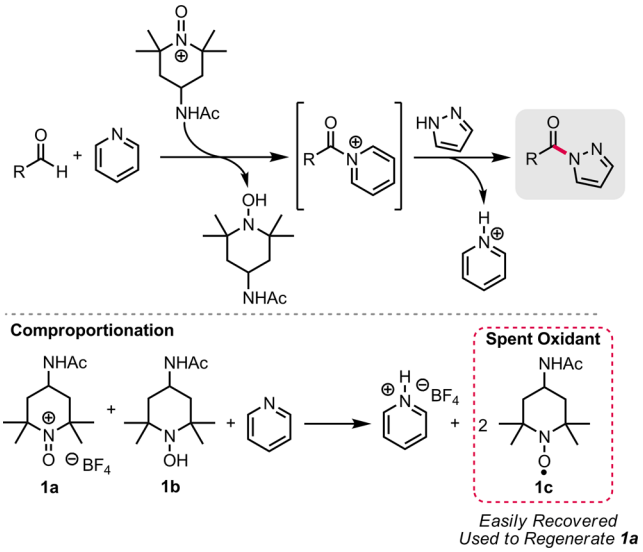
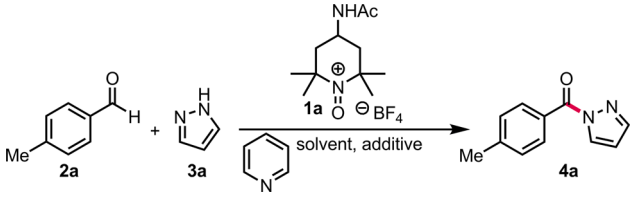


Figure 1. Envisioned mechanistic pathway for oxidative amidation.

Table 1. Optimization of Oxidative Amidation of 2a with 3a[a]



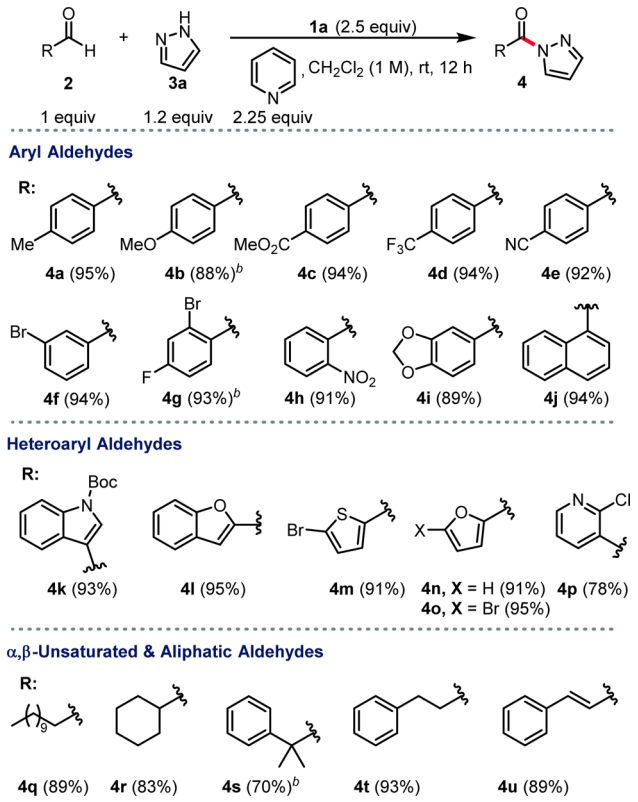
entry	3a (equiv)	pyridine (equiv)	solvent	conv (%)[b]
1[c]	3	12.75	neat	90
2	3	12.75	neat	99
3	3	3	MeCN	100
4	3	0	MeCN	66
5	3	3	DMF	99
6	3	3	EtOAc	100
7	3	3	CH_2Cl_2	100
8	2.5	1.1	CH_2Cl_2	90
9	1.5	2.25	CH_2Cl_2	100
10	1.2	2.25	CH_2Cl_2	100 (95)[d]

[a]Unless otherwise noted, reactions run at 1 M in substrate, using 2.5 equiv of **1a** for 12 h at rt. [b]Conversion determined by ^{1}H NMR. [c]0.1 equiv of HFIP added. [d]Isolated yield in parentheses.

resulting *N*-acyl pyrazole can be readily functionalized. Initially, we elected to employ hexafluoroisopropanol (HFIP) as an additive, thus forming substoichiometric amounts of reactive HFIP esters in the event that pyrazole was too poorly nucleophilic to undergo direct oxidative amidation (Table 1, entry 1).[12] We quickly determined that HFIP was not a necessary additive. Although the reaction could be performed neat, it was somewhat exothermic, and thus we decided to conduct the reaction in a solvent to serve as a thermal sink (Table 1, entries 3−10). Acetonitrile was initially used and served adequately for heat dispersal.[13] We simultaneously reduced the loading of pyridine as well, given that it was no longer serving as the solvent. While the reaction could proceed without pyridine, it was rather sluggish. This indicates that a pyrazole-derived hemiaminal intermediate may form (Table 1, entry 4). This is likely because pyrazole has to serve two roles: as a base in the concomitant comproportionation of **1a** with **1b**, and also as a reactant. Thus, pyridine was necessary for rapid and reliable reactivity. A brief survey of solvents indicated that reaction efficiency was independent of the reaction medium, given a variety of polar solvents could be used with minimal effect on conversion. Ultimately, we elected to utilize dichloromethane as the solvent for two reasons: (1) the low water content of this solvent would deter any possible carboxylic acid formation when screening electronically disparate aldehydes,[14] and (2) this solvent has been used previously with other oxidative functionalization processes facilitated by **1a**. To complete optimization, we varied the loading of pyridine and pyrazole, ultimately finding 1.2 equiv of pyrazole and 2.25 equiv of pyridine to be best.

After establishing optimal conditions, the scope of the transformation was assessed in the context of various aldehydes (Scheme 2). We were very pleased to find that the developed

Scheme 2. Oxidative Amidation of Aldehydes with 3a[a]



[a]Unless otherwise noted, reactions run on 5 mmol at 25 °C; isolated yields after purification. [b]1.5 equiv of pyrazole, 2.5 equiv of pyridine and 3.0 equiv of **1a** were used.

process displayed a broad tolerance across various sterically and electronically distinct aldehydes. Aryl aldehydes were amidated in consistently high yield regardless of substitution pattern or degree of ring electron density. In addition, a number of different heteroaryl aldehydes, such as pyridyl, indolyl, and furyl, could successfully be converted to their corresponding *N*-acyl pyrazoles in good to excellent yields. Conjugated and aliphatic aldehydes (even those with branching at the α-position) underwent amidation without issue and gave similarly good yields. Of note is that, in all cases, no chromatography was required; acyl pyrazoles obtained in this manner were pure upon workup, and the spent oxidant could be recovered following each oxidation (see SI for details).

Not satisfied with using aldehydes as forebears to *N*-acyl pyrazoles, we next investigated whether alcohols were viable

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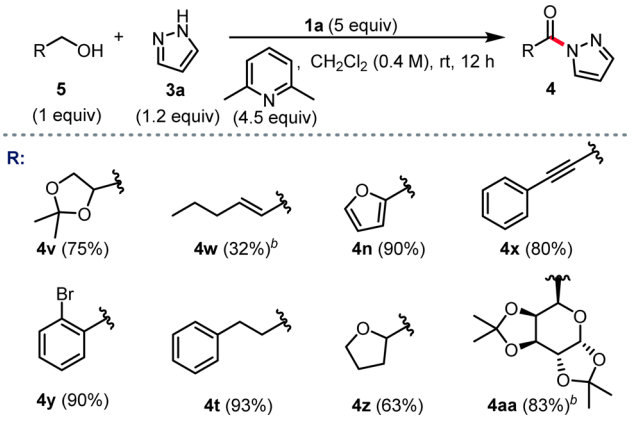
Scheme 3. Oxidative Amidation of Alcohols with 3a[a]

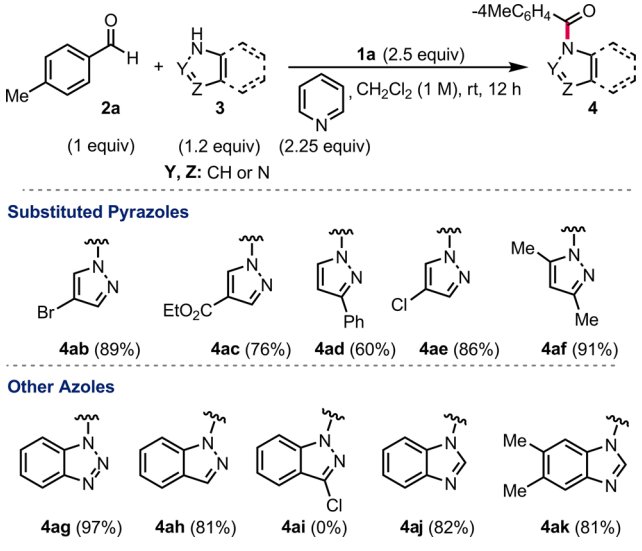


[a]Unless otherwise noted, reactions run on 5 mmol scale at 25 °C; isolated yields after purification. [b]1.5 equiv of pyrazole used.

starting materials for oxidative amidation (Scheme 3). By simply switching to 2,6-lutidine as the base, hence avoiding concomitant oxidative esterification,[10,12] and doubling the loading of the oxidant (adding an additional 2.5 equivalents), we were able to effect this transformation in comparable yield to those obtained when using aldehydes. This is especially noteworthy given these yields represent two distinct chemical steps: alcohol oxidation and oxidative functionalization. A variety of functionally dense alcohols were well-tolerated in this two-step, one-pot process. One exception to this was the allylic substrate **4w** which required more extensive purification resulting in a diminished yield. The greater impurity profile in this case is likely a consequence of various alternate reaction pathways including a Michael-like reaction facilitated by pyrazole.

Finally, the scope of the oxidative amidation process was assessed by varying the azole component (Scheme 4). Both the substitution pattern of pyrazole and other structurally distinct azoles were explored. We were again pleased to find that both electronically and sterically distinct pyrazoles could be coupled in good to excellent yield. Although this reaction tolerates a number

Scheme 4. Oxidative Amidation of 2a with Azoles[a]

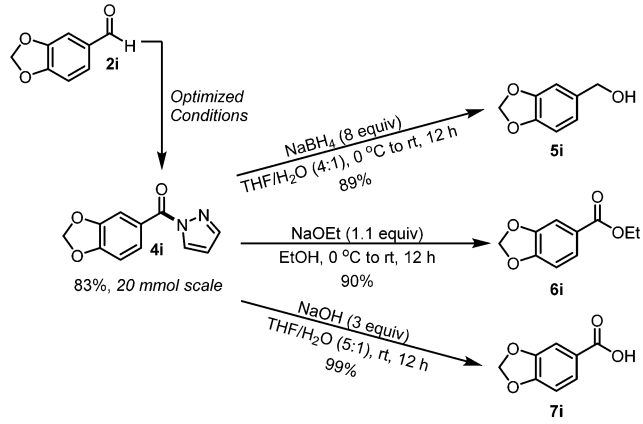


[a]Reactions run on 5 mmol scale at 25 °C; isolated yields after purification.

of azoles, reaction success can be dramatically influenced by the electronic nature of the azole (e.g., **4ah** vs **4ai**). While some acylation was observed when using imidazole (not shown), the low conversion and instability of *N*-acyl imidazoles complicated isolation. Thus, in our view, *N*-acyl imidazoles cannot be prepared using the protocol outlined here, although they could be generated *in situ*.

In addition to the new chemical space accessible using this method, *N*-acyl azoles are ideal partners for further derivatization. *N*-acyl azoles represent a fine balance between long-term stability (most *N*-acyl azoles are bench stable powders that can be stored at room temperature for several months) and reactive acylating agents. *N*-acyl pyrazoles are particularly ideal as compared to the HFIP esters studied previously by our group from both a cost standpoint and lower loading of nucleophile (1.2 equiv vs 3−3.5 equiv), while retaining the same type of reactivity. To demonstrate the utility of these species, a series of tandem reactions were performed. In addition to demonstrating that these systems readily participated in nucleophilic acyl substitution processes in excellent yield (Scheme 5), we also had impetus to

Scheme 5. Functionalization Reactions of 4i



probe the scalability of our process because of the amount of requisite *N*-acyl pyrazole, **4i**, required for these functionalization studies. Pleasingly, the reaction could be scaled easily to 20 mmol, and likely even larger, without significantly compromising the yield. Transamidation was next attempted by forming **4a** and treating the crude *N*-acyl pyrazole (after removal of nitroxide **1c** by precipitation) with several representative amines (Scheme 6). Not only was this highly successful, but this two-step approach effects oxidative amidation without concomitant amine oxidation or imine formation. To further add modularity, we assessed whether alcohols were also compatible with this amidation method. Gratifyingly, **5t** could be converted into amide **6t** in excellent yield, equating to >95% yield per chemical step. To demonstrate further the utility of this net two-step amidation process, we probed whether any loss in stereochemical information occurred over the three chemical steps involved. Starting from (*S*)-(+)-1,2-isopropylideneglycerol, **5v′**, we executed the two-step amidation sequence to prepare the known chiral benzamide **6v′** (Scheme 6).[15] We were pleased to find that no appreciable epimerization occurred thus enabling substrates with chirality at the α-position to be amenable to the both the oxidative amidation process and subsequent functionalization.

In summary, a mild, user-friendly, metal-free oxidative amidation approach to the synthesis of *N*-acyl azoles utilizing

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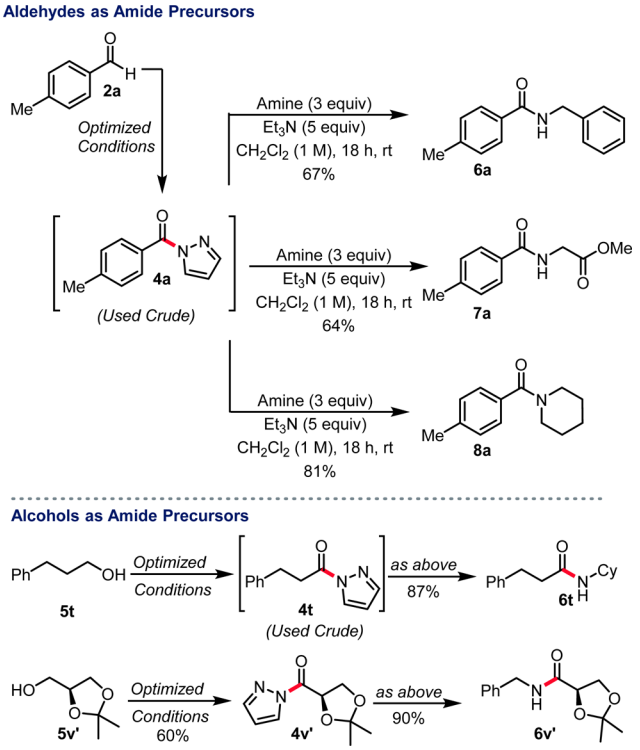
Scheme 6. *N*-Acyl Pyrazoles As Intermediates to Amides



the oxoammonium salt **1a** has been developed. The reaction tolerates an array of aldehydes and alcohols as precursors to the amide carbonyl as well as numerous azoles. The resulting "activated amides", more specifically *N*-acyl pyrazoles, proved suitable for further functionalization. Reduction, esterification, and hydrolysis could be carried out with ease. Using the oxidative amidation strategy outlined here, non-azole amides could be prepared from both alcohols and aldehydes via a multistep, one-pot approach.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00060.

Experimental procedures and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nicholas.leadbeater@uconn.edu.

ORCID

Christopher B. Kelly: 0000-0002-5530-8606

Nicholas E. Leadbeater: 0000-0003-1823-5417

Notes

The authors declare no competing financial interest.

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