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Communication

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Chemoselective Acylation of Primary Amines and Amides with Potassium Acyltrifluoroborates under Acidic Conditions

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Supporting Information

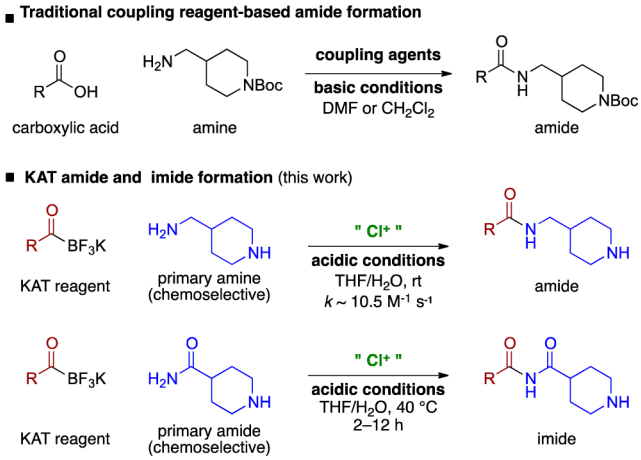
ABSTRACT: Current methods for constructing amide bonds join amines and carboxylic acids by dehydrative couplings—processes that usually require organic solvents, expensive and often dangerous coupling reagents, and masking other functional groups. Here we describe an amide formation using primary amines and potassium acyltrifluoroborates promoted by simple chlorinating agents that proceeds rapidly in water. The reaction is fast at acidic pH and tolerates alcohols, carboxylic acids, and even secondary amines in the substrates. It is applicable to the functionalization of primary amides, sulfonamides, and other N-functional groups that typically resist classical acylations and can be applied to late-stage functionalizations.

Amide bond formation is one of the most widely practiced transformations of organic molecules.[1] Nearly all amides are produced by the condensation of an activated carboxylic acid, or occasionally the acid itself, with an amine—processes that typically require an excess of organic solvent or high reaction temperatures (Scheme 1). In the context of pharmaceutical production, expensive, and often dangerous, coupling reagents are typically used in excess. These factors contribute to the widely recognized desire for new amide-forming processes that operate cleanly under more sustainable conditions.[2,3] Likewise, there is enormous interest in chemoselective amide-forming ligations under aqueous conditions,[4,5] although the use of specialized starting materials and conditions renders them appropriate only for high-value products such as peptides or proteins.

In 2012, we disclosed the reaction of potassium acyltrifluoroborates (KATs) and *O*-acylhydroxylamines.[6] It proceeds with fast kinetics and absolute chemoselectivity in water, which makes it attractive for the bioconjugation of proteins and peptides.[7] The key starting materials are robust salts[8] that are already becoming available—at the time of this submission, 19 KATs were commercially available—and can be readily prepared from aldehydes, enol ethers, organohalides, or acyl chlorides.[9] The *O*-acylhydroxylamines, however, require several steps to prepare and are sometimes unstable compounds, especially in the case of α-amino acid derivatives. We postulated that simple amines could be employed by in situ activation of the nitrogen atom. *N*-Chlorination of amines is a fast and well-studied process that proceeds in water,[10] the preferred solvent for the KAT ligation. The reagent could also oxidize the acylboronate, as similar reactions are known for organoborons.[11]

In this Communication we document the coupling of primary amines and KATs under aqueous conditions, using inexpensive chlorinating agents to activate the amine (Scheme 1). It operates chemoselectively at room temperature in the presence of other functional groups, including carboxylic acids, alcohols, alkenes, and secondary amines. With slight modification of the reaction conditions, it can also be applied to the acylation of primary amides, ureas, sulfonamides, and carbamates, which are typically resistant to acylation under mild conditions.[12]

Scheme 1. Chemoselective Amide Formation with KATs



We chose potassium 4-fluorobenzoyltrifluoroborate **1a** and 2-phenethylamine **2a** in a mixture of aqueous buffer and organic co-solvents as a model reaction for screening conditions and halogenating agents. We identified *N*-chlorosuccinimide (NCS) and related reagents, particularly 1,3-dichloro-5,5-dimethylhydantoin (DCH), as the most effective choice.

These were superior to brominating or iodinating agents, a fact that we attributed to the poor stability of these reagents.[13] No amide formation was observed in the absence of halogenating source. The reaction was tolerant to a broad variety of solvents in combination with acidic aqueous buffers,[14] and we selected 1:1 THF/pH 3 citrate buffer for further studies. Experimentally, the reaction performed well between pH 2 and 6, and we selected pH 3 as optimal in terms of both

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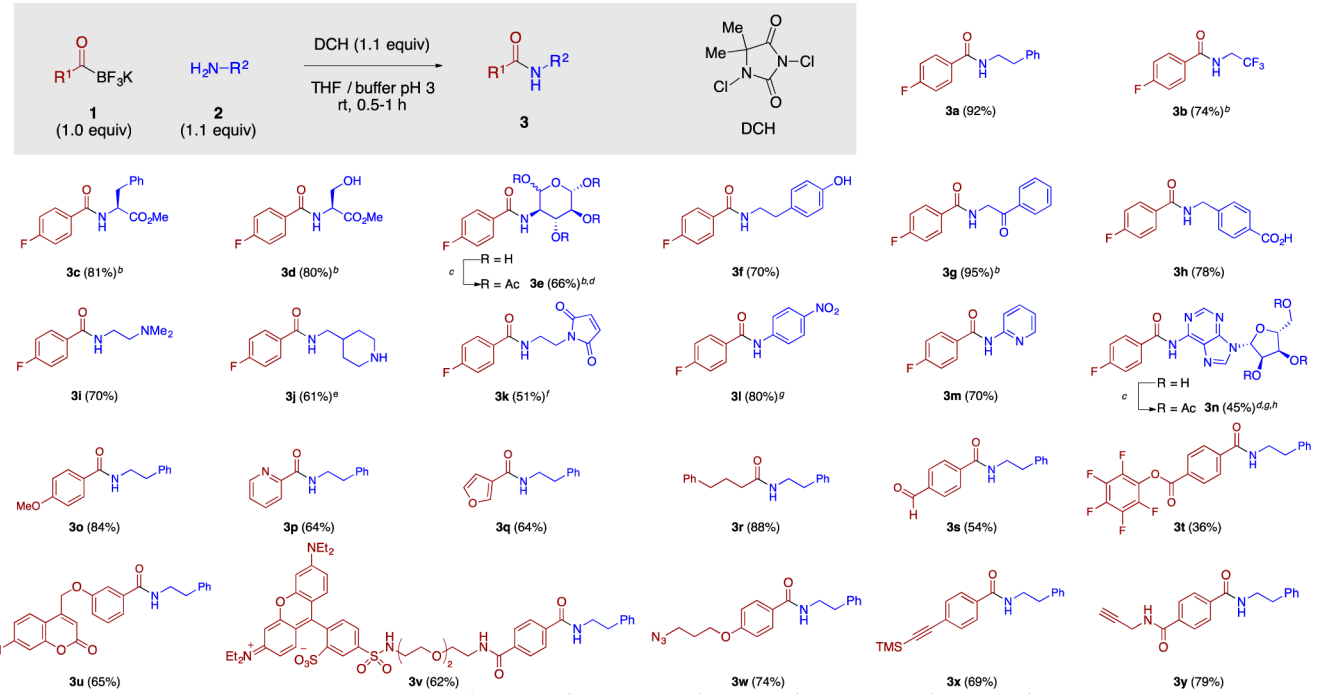
Table 1. Substrate Scope for the Amide-Forming Reaction[a]



[a]Performed on a 0.10 mmol scale with KATs **1** (1.1 equiv), amines **2** (1.0 equiv), and DCH (1.1 equiv) in 1:1 THF/pH 3 citrate buffer (final concentration, 0.10 M). Values in parentheses are isolated yields of the corresponding products **3a**–**3y**. [b]Amines used as HCl salts. [c]For purification, the reaction mixture was treated with Ac_2O and pyridine in acetone. [d]Isolated yield over two steps. [e]NCS (2.0 equiv) was used instead of DCH. [f]Amine was used as CF_3CO_2H salt. [g]Performed with TCCA instead of DCH. [h]Isolated as a CF_3CO_2H salt.

rate and functional group compatibility. This optimal value may be due to the pK_a of *N*-chloroamines—in the range of 0–2—which are not likely to be protonated under these conditions.[15] Free amines or their salts can be used directly in the reaction. After completion of the reaction, any excess chloramine is quenched by the addition of aqueous sodium bisulfite.[16]

With the optimized conditions in hand, we explored the scope of the reaction. A wide variety of primary amines underwent smooth amide formation using DCH as the chlorinating agent (Table 1). We did not observe epimerization of the α-carbon when optically active L-phenylalanine methyl ester was used as substrate (product **3c**, see the Supporting Information for details), although this more sterically hindered amine required longer reaction times than amines on primary carbons. The reaction is chemoselective; it tolerates unprotected alcohols (**3d**, **3e**), phenols (**3f**), ketones (**3g**), and carboxylic acids (**3h**). Acylation of primary amines occurs selectively in the presence of tertiary (**3i**) and unprotected secondary amine groups (**3j**). Substrates having double bonds, which may be sensitive to chlorinating agents, were also good substrates (**3k**), although small amounts of halogenated byproducts were observed. Electron-rich anilines often gave complex mixtures derived from ring chlorination or oxidation, but electron-poor aryl and heteroarylamines could be smoothly acylated using 1,3,5-trichloroisocyanuric acid (TCCA) as the chlorinating agent (**3l**–**3n**). This is a notable contrast to classical amide formations with coupling reagents, which often fail with electron-deficient amines.[17] The reaction conditions, including the chlorination step, also tolerated a variety of KATs having different aryl, heteroaryl, and alkyl residues (**3o**–**3r**), as well as KATs with reactive groups such as an aldehyde (**3s**) or an activated ester (**3t**). Coumarin and sulforhodamine KATs (**3u**, **3v**) afforded the corresponding amide in good yields. KATs bearing azide and alkyne groups (**3w**–**3y**) were suitable substrates as well.

Although it is well known that primary amides can be chlorinated, we did not expect the resulting *N*-chloroamides to react with KATs. However, by warming the reactions to 40 °C and replacing DCH with TCCA,[18] we identified general conditions for acylation of primary amides under aqueous, acidic conditions (Table 2). Aromatic (**5a**), aliphatic (**5b**), and α,β-unsaturated amides (**5h**) were effectively converted to the corresponding imides. Carbamates (**5c**), ureas (**5d**, **5e**), sulfonamides (**5f**), and guanidines (**5g**) were also suitable partners for the reaction. Remarkably, primary amides could be acylated even in the presence of secondary amines (**5i**). KATs having triple bonds (**5l**), activated esters (**5m**), azide groups (**5n**), and coumarin-bearing KATs (**5o**) afforded the corresponding imide in moderate to good yields. There are relatively few methods known for preparation of their mixed acyclic imides and related compounds, which are interesting components of bioactive natural products, pharmaceuticals, and catalysts.[12,19]

At the current stage of development, the amide and imide formation is limited to primary amines and amides. Morpholine did not react under the standard conditions. This appears to be a steric effect, rather than a mechanistic limitation, as an excess of the preformed *N*-chloromorpholine undergoes acylation with KATs under neat conditions (see the Supporting Information for details).

We also applied this method to the late-stage functionalization of more complex molecules (Scheme 2). Streptomycin bears two guanidino groups in addition to one aldehyde and one secondary amine, yet acylation occurred chemoselectively on the guanidino groups. Alkyne KAT **1l** was coupled to gentamicin C_1 to give a mixture of adducts, exclusively on the

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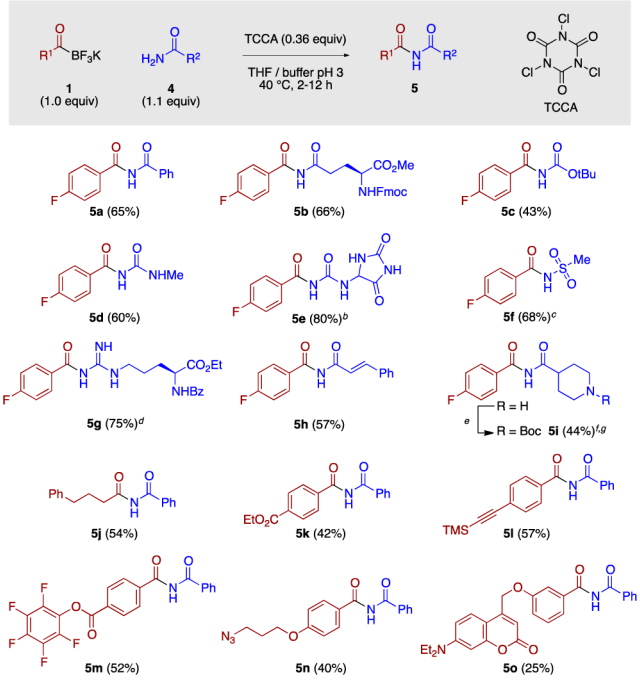
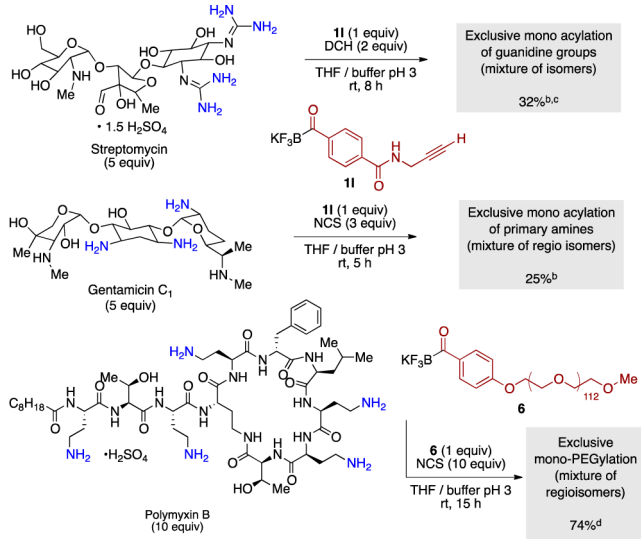
Table 2. Substrate Scope for the Imide-Forming Reaction[a]



[a]Performed on a 0.10 mmol scale with KATs **1** (1.1 equiv), amides **4** (1.0 equiv), and TCCA (0.36 equiv) in 1:1 THF/pH 3 citrate buffer (final concentration, 0.10 M) at 40 °C. [b]Performed with DCH (1.1 equiv) instead of TCCA. [c]Performed at 60 °C in 1:1 MeCN, pH 3 citrate buffer (final concentration, 0.10 M). [d]Guanidine used as HCl salt. [e]For purification, the reaction mixture was treated with Boc_2O (1.5 mmol) and $NaHCO_3$ (pH 7–8). [f]Yield over two steps. [g]TCCA (0.66 equiv) was employed.

Scheme 2. Late-Stage Functionalization of Natural Products[a]



[a]Performed on up to 0.10 mmol scale with KATs **6** or **1l** (1.0 equiv), natural products (5–10 equiv), and DCH or NCS (3–10 equiv) in THF/pH 3 citrate buffer ([KAT] = 10–25 mM) at room temperature. Products were isolated as a mixture of isomers acylated on any of the nitrogen atoms marked in blue. [b]Isolated yield (CF_3CO_2H salt) after preparative HPLC. [c]Mixture of C_1/C_3 acylated hemiaminal tautomers (1:1). [d]Yield after isolation by spin filtration.

primary amines. By using a 5 kDa PEG-KAT **6** as the limiting reagent, we obtained a mixture of mono-PEGylated derivatives of polymyxin B—which has five primary amines—in good yield.[20]

This reaction is related to amide formation from α-ketoacids and hydroxylamines[21] or *N*-iodoamines[22] and, more generally, to the oxidative amidation of aldehydes with amines.[23] These reactions typically require the use of strong oxidizing agents[24] and/or transition metal catalysts,[25] although the direct coupling of aldehydes and amines with NBS has been documented.[26] Under our reaction conditions, no amide product could be detected when 4-fluorobenzaldehyde was used in place of KAT **1a**; α-ketoacids also failed to give amides under these conditions. The oxidative chlorination of the KAT to form an acyl chloride was ruled out by control experiments.

Mechanistically, we favor direct interaction of the *N*-chloroamine and the KAT carbonyl group—as in the case of *O*-benzoylhydroxylamines[6]—over an interaction of the nucleophile with the boron and subsequent acyl migration. As a control experiment, *N*-chlorobutylamine was freshly prepared from *n*-butylamine and NCS in $CDCl_3$; its purity and concentration were determined by NMR. This reacted rapidly with KAT **1a**, yielding quantitatively the corresponding amide (see the Supporting Information for details). Although this experiment does not completely rule out the involvement of other pathways, it favors our mechanistic hypothesis. This protocol was used to determine the reaction rate for amide formation at pH 3 to be ~10 M^{-1} s^{-1},[27] which is several orders of magnitude faster than amidation using activated esters at room temperature.[28]

In summary, we have developed a mild, rapid, and chemoselective acylation of in situ generated *N*-chlorinated amines or amides using KAT reagents. As the key starting materials—potassium acyltrifluoroborates—are becoming widely available, we believe this method will emerge as an attractive alternative to classical acylation chemistry by being completely tolerant to the presence of water, being fast at acidic pH, and offering unique chemoselectivity over many different functional groups, including secondary amines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b00059.

Experimental procedures, supplementary results, and spectroscopic data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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