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TCFH–NMI: Direct Access to *N*-Acyl Imidazoliums for Challenging Amide Bond Formations

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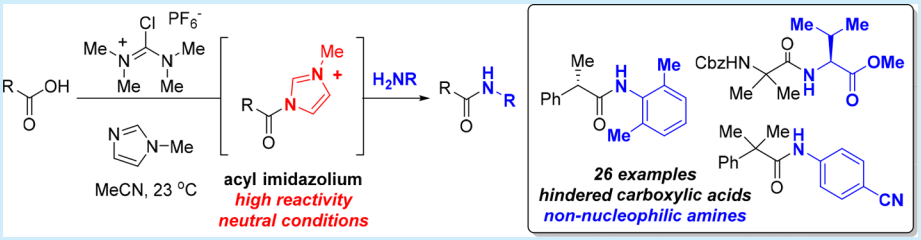
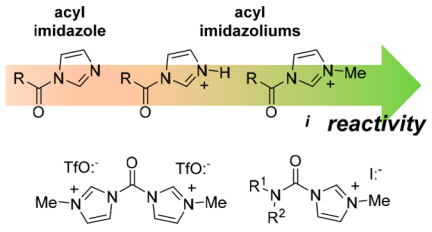
Supporting Information



ABSTRACT: Challenging couplings of hindered carboxylic acids with non-nucleophilic amines to form amide bonds can be accomplished in high yields, and in many cases, with complete retention of the adjacent stereogenic centers using the combination of *N*,*N*,*N*′,*N*′-tetramethylchloroformamidinium hexafluorophosphate (TCFH) and *N*-methylimidazole (NMI). This method allows for *in situ* generation of highly reactive acyl imidazolium ions, which have been demonstrated to be intermediates in the reaction. The reagent delivers high reactivity similar to acid chlorides with the ease of use of modern uronium reagents.

Acyl imidazoliums have been long recognized as highly reactive acyl transfer agents in the context of amide bond formation. Although some attention has been given to the activation of acyl imidazoles with Brønsted acids,[1] these species can be orders of magnitude less reactive than the *N*-alkylated analogues, as was noted by Jencks and Lapshin in their kinetic studies (see Scheme 1).[2] Strategies for the synthesis of *N*-methylimidazoliums ***i*** have relied on activation of preformed acyl imidazoles with strong alkylating agents such as Meerwein's salt (Me_3OBF_4), methyl triflate (MeOTf), or methyl iodide (MeI).[3] Work by Rapoport and Batey identified analogues of carbonyl diimidazole (CDI) for direct access to highly reactive *N*-acyl imidazoliums and use in the preparation of challenging amide bonds (see Scheme 1).[4] The need to isolate these reagents to remove highly reactive alkylating agents such as Meerwein's salt, MeOTf, or MeI has limited their application. A conceptually simpler approach that combines acid chlorides or other active esters with *N*-methylimidazole (NMI) has only found limited use, despite the significant potential of the *N*-acylimidazolium intermediate.[5]

Scheme 1. *N*-Acyl Imidazoles and Imidazoliums



As part of ongoing studies that are focused on the large-scale synthesis of a potential pharmaceutical agent, we discovered the combination of *N*,*N*,*N*′,*N*′-tetramethylchloroformamidinium hexafluorophosphate (TCFH) and NMI is a mild method for *in situ* generation of highly reactive acyl imidazoliums, allowing for the formation of the amide in high yield and with no detectable epimerization. TCFH has found limited application in the literature, as a reagent for the in situ generation of acid chlorides[6] or, more commonly, as a precursor in the synthesis of complex uronium-based amide bond-forming agents.[7] Here, the combination of TCFH and NMI demonstrated advantages in terms of reactivity, but also practical benefits from the perspective of cost, ease of use, and the direct access it provides to *N*-acyl imidazoliums, when compared to the existing literature methods, which require either isolation or preformation of some activated ester.[5] In this report, we describe and explore the scope and limitations of this TCFH-NMI reagent combination for amide bond formation, which is one of the most common transformations in pharmaceutical synthesis (see Scheme 2).[8] This work highlights the unique properties of these *in situ* generated acyl

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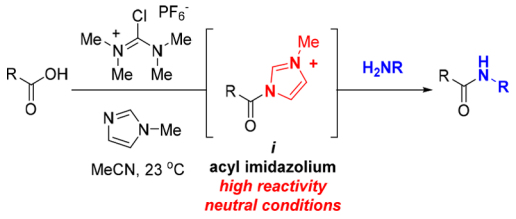
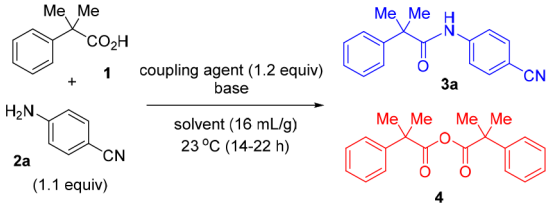
Scheme 2. A General Strategy for TCFH–NMI Couplings



imidazolium reagents, particularly, for coupling of traditionally challenging hindered carboxylic acids and poorly nucleophilic amines.

Our initial studies focused on the coupling between the hindered carboxylic acid **1** and the electron-deficient aniline **2a**. Because of the low nucleophilicity of **2a**, common coupling agents such as HATU, BEP, TFFH, and TCFH with DIPEA as base in DMF, primarily led to the anhydride **4**, along with significant amounts of the corresponding activated esters (see Table 1, entries 1–4).[9] In combination with TCFH, addition of water, allowing for easy removal of reaction byproducts such as NMI salts and tetramethyl urea. Finally, the unique combination of Lewis and Brønsted basicities provided by NMI[11] in this reaction was highlighted by comparison to other strong basic amines. The weakly Lewis basic amine DIPEA gave higher levels of anhydride formation, while the highly Lewis and Brønsted basic amine DBU gave little of the desired product (Table 1, entries 8 and 9). Re-evaluation of the other coupling reagents with the optimal solvent and base highlights the unique properties of TCFH for this transformation, although BEP is comparable (Table 1, entry 7 vs entries 10–12).[12]

Table 1. Screening Amide Bond Formation with 1 and 2a



entry	activator[a]	solvent	base (equiv)	conversion[b] (%)	3a vs 4[b] (%)
1	HATU	DMF	DIPEA (3.0)	2.6	>99:1
2	BEP	DMF	DIPEA (3.0)	>99.9	<1:99
3	TFFH	DMF	DIPEA (3.0)	15.5	<1:99
4	TCFH	DMF	DIPEA (3.0)	96.2	7.6:92.4
5	TCFH	DMF	NMI (3.0)	85.2	72.6:27.4
6	TCFH	MeCN	NMI (3.0)	98.5	>99:1
7	TCFH	MeCN	NMI (3.5)	>99.9	>99:1
8	TCFH	MeCN	DIPEA (3.5)	>99.9	67.8:32.2
9	TCFH	MeCN	DBU (3.5)	24.3	6.7:93.3
10	HATU	MeCN	NMI (3.5)	2.7	>99:1
11	BEP	MeCN	NMI (3.5)	92.5	98.6:1.4
12	TFFH	MeCN	NMI (3.5)	38.0	92.5:7.5

[a]See the Supporting Information for activator/base structures. [b]Conversions are calculated based on HPLC area percentage.

exchanging the strongly Brønsted basic, weakly Lewis basic DIPEA (pK_a = 11.4)[10a] for the less Brønsted basic, but highly Lewis basic amine NMI (pK_a = 7.2)[10b] led to a dramatic change in the reaction, with the desired amide **3a** now being the major reaction product (Table 1, entries 4 and 5). Running the reaction in acetonitrile (Table 1, entry 6) minimized anhydride formation and provided the desired product **3a** in 96 HPLC area percent (AP) after 14 h at room temperature. NMI stoichiometry was examined and it was found that increasing up to 3.5 equiv suppressed the formation of anhydride **4** and significantly improved the reaction purity (Table 1, entries 6 and 7). A wide variety of solvents, including dichloromethane and toluene gave comparable results to MeCN, but TCFH had poor solubility and afforded difficult-to-stir heterogeneous reactions. The homogeneous reaction in MeCN was preferred since it facilitated isolation by the

In order to gain further insight into the high reactivity of this TCFH-NMI system and confirm the intermediacy of an acyl imidazolium, a series of spectroscopic studies was undertaken on the reaction between **1** and **2a**. Monitoring the reaction by *in situ* IR showed that the reaction was fast when TCFH was added last, but several distinct reaction intermediates were visible (see Figure 1). The first short-lived intermediate was a

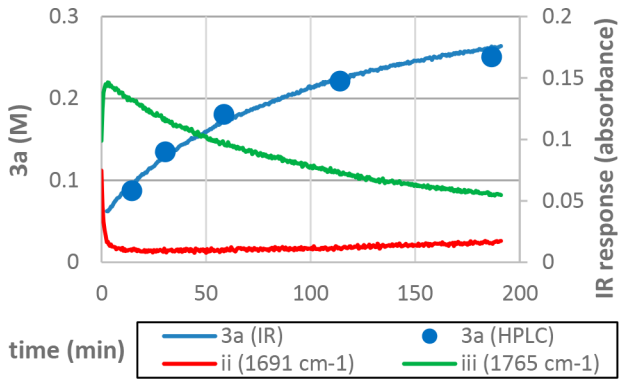


Figure 1. ReactIR analysis of the reaction of **1** and **2a**.

band at 1691 cm^{-1}, which did not correspond to TCFH itself (1653 cm^{-1}) or the starting acid **1** (1737 cm^{-1}). This intermediate was rapidly consumed and replaced by a second intermediate, distinguished by a strong band at 1765 cm^{-1}. Pairwise combination of the reagents revealed that the first intermediate was a complex between TCFH and NMI. NMR characterization of this intermediate suggested the structure ***ii***,[9] which was subsequently crystallized from MeCN/MTBE and the structure was confirmed by X-ray crystallographic analysis. The addition of acid **1** to ***ii*** led to the rapid formation of the second intermediate at 1765 cm^{-1}. Again, NMR and MS characterization of this intermediate was consistent with the proposed acyl imidazolium ***iii***.[13,14]

Based on these data, we propose the following mechanism for the reaction (Figure 2). In the presence of NMI, TCFH is rapidly converted to adduct ***ii***, which reacts with acid **1** to generate ***iii***. This highly reactive acyl imidazolium ***iii*** then reacts with the amine to generate the amide, while simultaneously releasing NMI, which scavenges the proton released in the C–N bond formation. Because of the rapid nature of the reaction, we cannot rule out the intermediacy of an acid chloride.

This clearer understanding of the reaction mechanism gave us confidence in the optimal conditions and we moved on to survey the reaction scope, with respect to the amine, giving particular focus to poorly reactive anilines (see Figure 3). Based on the fact that aniline **2a**, one of the more difficult

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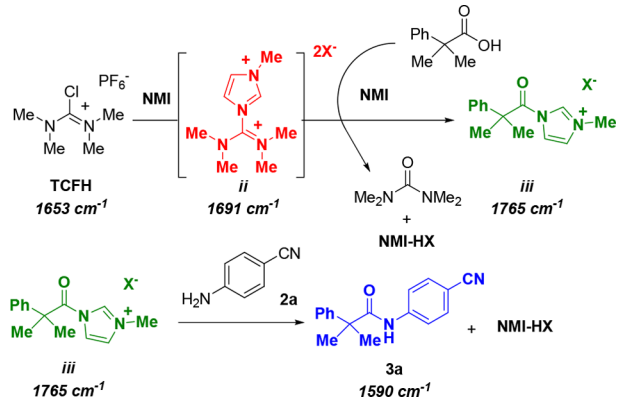


Figure 2. Mechanism of the TCFH–NMI amide formation.

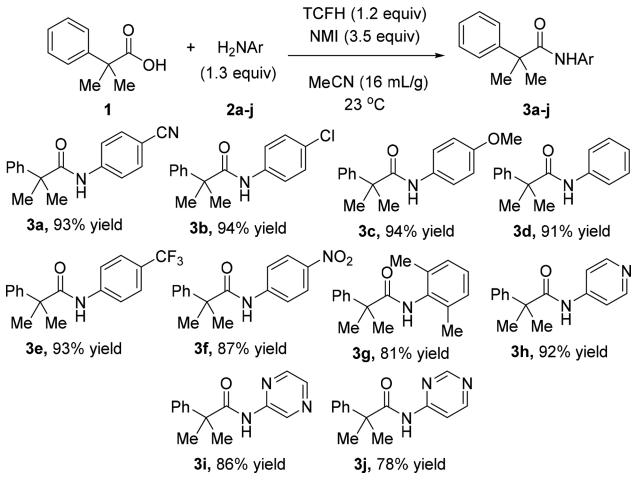
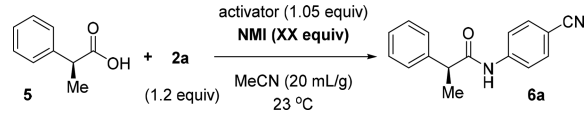


Figure 3. Exploration of substrate scope with acid **1**.

examples in previous work,[15] quickly and smoothly coupled with the sterically hindered acid **1** at room temperature using the TCFH–NMI system (>87 AP product in 2 h), we were hopeful that other challenging amines would also yield acceptable results under mild conditions. A series of sterically and electronically diverse anilines, as well as heteroaryl amines, all coupled in reasonable reaction times and good yields, even when the reactions were run under air, without rigorous anhydrous technique and with no preactivation. As could be expected, the electronic influence of the 4-position substituent on the aniline had a large impact on the reaction rate. Generally, the amide bond formation was complete in less than 24 h at room temperature, and the amides **3a–3g** could be isolated in high yields and >99 AP by the direct addition of water to the reaction mixture.

To further explore the scope of the method and introduce the additional challenge of preserving a stereogenic center adjacent to the carboxylic acid, we investigated the coupling of (*S*)-phenylpropionic acid **5** with **2a** (Table 2).[9] Few examples of couplings with this class of carboxylic acid are known, and little data on the integrity of adjacent stereocenters is available.[16] Under the optimal conditions developed for **1**, the coupling of **5** with **2a** led to high conversion and yield in less than 30 min, but gave only a 86:14 enantiomeric ratio (er) of the isolated amide **6a** (Table 2, entry 1). Lowering the charge of NMI to 2.1 equiv restored the integrity of the α-stereogenic center, allowing for isolation of the desired amide **6a** in 93% yield and >99.9:0.1 er. Because of the rapid rate of

Table 2. Conditions for Amide Bond Formation with (*S*)-5



entry	activator[a]	base (equiv)	conversion[b] (3 h)	enantiomeric ratio, er
1	TCFH	NMI (3.5)	>99	86:14
2	TCFH	NMI (2.1)	>99	>99.9:0.1
3	HBTU	NMI (2.1)	6	57:43
4	HATU	NMI (2.1)	32	57:43
5	HOTU	NMI (2.1)	35	73:27
6	BEP	NMI (2.1)	>99	88:12
7	BOP	NMI (2.1)	11	60:40
8	PyBrOP	NMI (2.1)	74	91:9
9	DMTMM	NMI (2.1)	81	51:49

[a]See the Supporting Information for activator/base structures. [b]Conversions are calculated based on the HPLC area percentage adjusted for UV response factors.

reaction, no difference in yield or enantiopurity of the isolated amide was observed, regardless of whether TCFH was added last or if aniline was added last, attesting to the stability of the acyl imidazolium under these effectively neutral reaction conditions. A comparison to other standard amide coupling reagents demonstrates the advantage of this TCFH–NMI coupling (Table 2, entries 3–9). BEP and PyBrOP, which are often considered optimal reagents for epimerization prone substrates,[17] along with DMTMM, showed high reactivity but exhibited significant scrambling of the stereogenic center. Running the same reactions with DIPEA as base leads to low conversion and numerous side products, even with TCFH. These results further demonstrate the importance of Brønsted base choice in this reaction.

With these improved conditions in hand, a survey of amines in coupling reactions with **5** showed good reactivity with no detectable loss in the purity of the adjacent stereogenic center, even without preactivation, when adding TCFH last (see Figure 4). Additional experiments with more-nucleophilic amines and less-hindered acids also performed well, giving good yields while maintaining the integrity of the stereogenic center (see Figure 5).

The final challenge for this reaction system was the extension to peptide couplings. Peptide couplings, especially

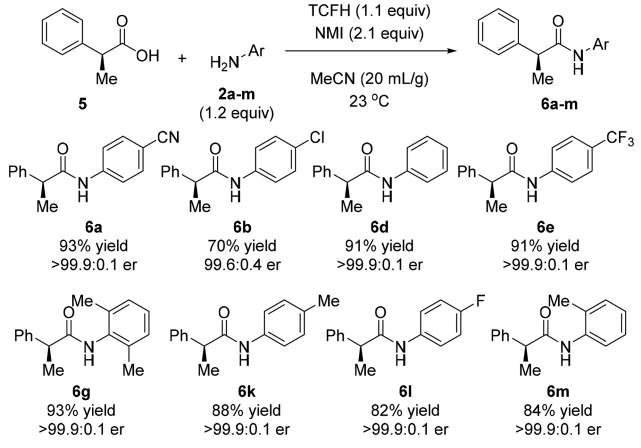


Figure 4. Exploration of substrate scope with acid (*S*)-**5**.

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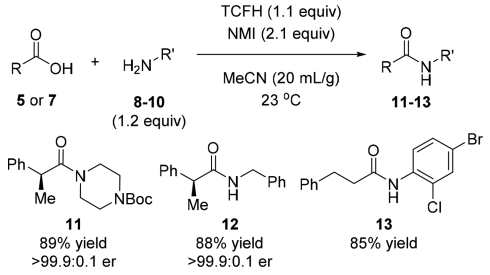

Figure 5. Additional substrate scope with TCFH–NMI.

those involving hindered amino acids or residues that are prone to epimerization, have been a major driver for the development of new amide bond-forming reagents. Initial experiments to form simple dipeptides with hindered residues such as valine, phenylalanine, and protected forms of cysteine proceeded to high yield with nondetectable amounts of epimerization, even without preactivation of the acid (see Figure 6, eqs 1–3). When the reagent was tested in the formation of the Anteunis tripeptide Z-Gly-Phe-Val-OMe **22**,[18] minor amounts of epimerization were observed (Figure 6, eq 4). Despite the neutral reaction conditions, the high reactivity of the acyl imidazolium renders it susceptible to intramolecular attack by a distal amide in a peptide chain, and epimerization is observed. Still, TCFH-NMI may hold some advantages for extremely hindered peptide couplings, such as those involving aminoisobutyric acid (Aib) residues. Under the standard conditions, 92% yield of the desired dipeptide **24** can be obtained within <30 min (Figure 6, eq 5).

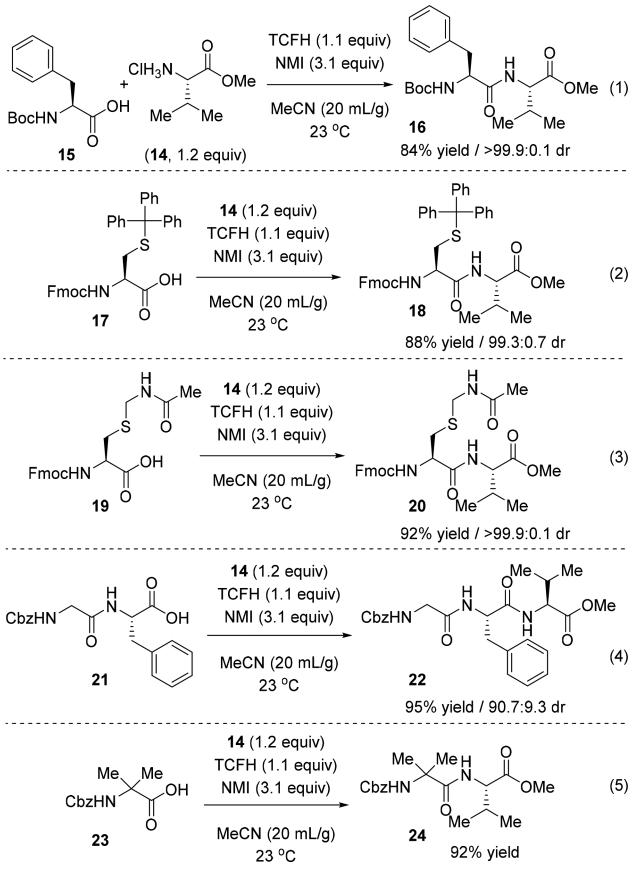

Figure 6. Peptide couplings with TCFH–NMI.

In summary, we have found a simple and robust method to access acyl imidazoliums and leverage their high reactivity for the formation of challenging amide bonds under mild conditions. These conditions also present operational benefits when compared to other reagents for amide bond formation. The fact that the reaction can be run without preactivation, along with the low cost and availability of TCFH makes it a practical choice, even when used at large scale.[19] The avoidance of additives and byproducts, which can be challenging to remove or control, such as phosphoramides or hydroxybenzotriazole derivatives, facilitates handling and improves the safety of the process.[20] Finally, the high water solubility of all reaction byproducts significantly streamlines workup and isolation.

In a more general sense, this work also makes clear how reconsidering our assumptions about Brønsted base choice in a reaction can have dramatic effects. The pK_a of the acidic hydrogen being removed should always be a consideration, but, more importantly, the use of a more Lewis basic amine may lead to unexpected benefits.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01591.

Experimental procedures, characterization data and ^{1}H and ^{13}C NMR data (PDF)

Accession Codes

CCDC 1844135 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(19) Pricing for coupling agents at kilogram scale as of March 2016: TCFH, $56/mol; T3P, $58/mol; EDAC, $93/mol; HATU, $171/mol.

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