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Beyond Amide Bond Formation: TCFH as a Reagent for Esterification

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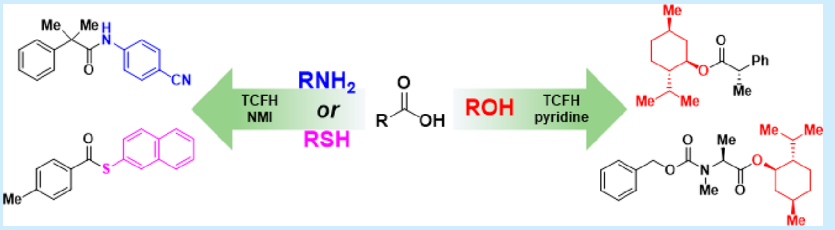


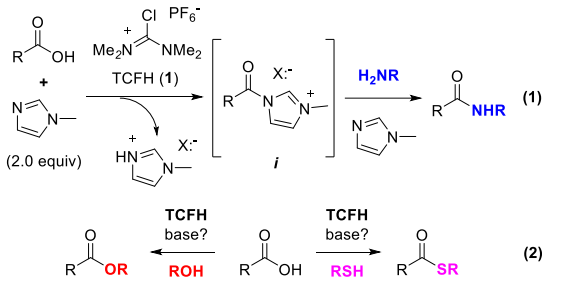
ABSTRACT: In this Communication, an investigation of the combination of *N*,*N*,*N*′,*N*′-tetramethylchloroformamidinium hexafluorophosphate (TCFH) and *N*-methylimidazole (NMI) for the synthesis of esters and thioesters is described. This work revealed the unique challenges of the reactions of less nucleophilic alcohols and more reactive thiols with the *N*-acyl imidazolium intermediate and led to the identification of general enabling conditions that provide high yields and selectivity for a range of alcohols and thiols.

Acylation reactions make up a broad class of chemical transformations for accessing carbonyl compounds. Combining an electrophilic carbonyl with a nucleophile leads to amides, esters, thioesters, and ketones. Each of these bond formations presents unique challenges for the development of efficient methods. However, the shared intermediacy of an electrophilic carbonyl group, often called an "activated ester", reminds chemists of the opportunity to apply developments across all these bond formations in an effort to identify more robust acylation conditions.

The most common carbonyl electrophile used in acylation reactions is an acid chloride. Acid chlorides are competent electrophiles in amidation, esterification, thioesterification, and Friedel−Crafts acylations. These reactive electrophiles can be prepared from readily available stable carboxylic acids using well-established procedures with chlorinating reagents such as oxalyl chloride, thionyl chloride, or phosphoryl chloride. However, these highly corrosive chlorinating reagents present a range of safety issues that extend even into reaction workup and product isolation.[1] Chemists continue to develop new methods for the activation of carboxylic acids. The goal is to find activated esters with similar reactivity profiles to acid chlorides *without* the concerns tied to those methods.

Although countless reagents for the activation of carboxylic acids in amide bond formation have been identified, it is important to ask what the generality of these reagents is across all types of acylation reactions if they are to be considered alternatives to acid chloride formation.[2] The combination of *N*,*N*,*N*′,*N*′-tetramethylchloroformamidinium hexafluorophosphate (TCFH, **1**) and *N*-methylimidazole (NMI) has been demonstrated as a mild method for the generation of reactive *N*-acylimidazolium ions ***i*** (Scheme 1, eq 1).[3] These carbonyl electrophiles exhibit high reactivity that enables the reaction

Scheme 1. TCFH−NMI as a General Acylation Method



with hindered or weakly nucleophilic amines under mildly basic conditions, reducing concerns about the epimerization of labile stereogenic centers. Although this method was developed specifically in the context of amide bond formation and is beginning to see application even at scale,[4] some reports have demonstrated isolated examples of its use in esterification[5] and thioesterification[6] as well. In an effort to expand the use of this noncorrosive, simple, and robust reagent[7] we sought

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to conduct a systematic exploration of the scope of esterification and thioesterification reactions with TCFH (Scheme 1, eq 2). With an understanding of the scope and limitations of the method, we can assess if TCFH is a more desirable alternative for acylations compared to acid chloride formation.

The first question that needed to be addressed to evaluate esterification with TCFH was the choice of substrate for optimization of the reaction conditions. For the carboxylic acid component, (*S*)-2-phenyl propionic acid **2a** was chosen due to α-branching, which presents a degree of steric hindrance, as well as the risk of Brønsted base-promoted epimerization adjacent to the phenyl group. The benzyloxycarbamate of *N*-methylalanine **3a** (CbzNMeAlaOH) was also selected, since it can epimerize via a distinct dihydrooxazolone intermediate. Considering these two substrates for the acid component would provide generality with respect to both reactivity and epimerization concerns. For the alcohol nucleophile, a review of the literature revealed a complex situation. Numerous alcohols have been proposed as stringent test substrates in esterifications due to their low reactivity (Figure 1). This

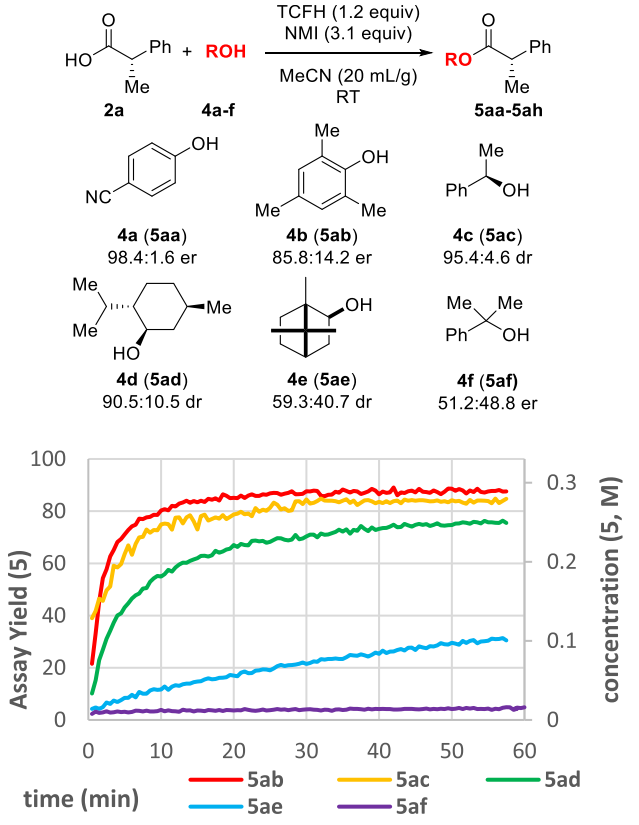

Figure 1. Rate comparison of alcohols in esterification with **2a**.

includes a range of phenols such as electron-deficient phenol **4a** or hindered phenol **4b**. Aliphatic alcohols like 1-phenylethanol **4c**,[8] menthol **4d**,[9] isoborneol **4e**,[10] or 2-phenyl isopropanol **4f**[11] represent hindered unreactive substrates. To ensure an informed selection of the test alcohol, we investigated the kinetic reaction profiles of alcohols **4a**−**4f** in reaction with **2a** under the optimal conditions for TCFH-NMI amidations using *in situ* IR. The results illustrate a dramatic range of reactivity for these alcohol substrates. The electron-deficient phenol **4a** and hindered phenol **4b** reacted rapidly with **2a**, with the reaction of **4a** reaching full conversion in <30 s. Comparing the ester products **5aa** and **5ab** shows variable levels of retention of the α-stereogenic center despite the rapid reaction rates. Aliphatic secondary alcohols such as **4c**, **4d**, and **4e** show a wider range of reactivity and lower levels of stereochemical purity in the ester products **5ac**−**5ae**, respectively. The tertiary alcohol 2-phenyl-2-propanol **4f** is the least reactive substrate and only gives low yields and nearly racemic product **5af** after extended reaction times.

Based on this analysis, the parallel optimization of the esterification of menthol **4d** with **2a** and **3a** was conducted to identify general enabling conditions (Table 1).[12] Since epimerization of the α-stereogenic center was observed using 3.1 equiv of NMI in acetonitrile (MeCN), we examined the effect of the NMI stoichiometry, which had resolved this epimerization in the case of amide bond formation (entries 1−3). Due to the lower nucleophilicity of alcohols compared to amines (N = 5−7 vs 10−18, respectively),[13] this system required the more strongly basic conditions provided by using NMI in excess of the 2 equiv required for formation of the *N*-acylimidazolum intermediate ***i*** (see Scheme 1, eq 1). Although lower levels of epimerization were observed, buildup of unreactive anhydrides was now observed (*vide infra*), and high yields of the ester product **5ad** or **6ad** could not be achieved despite the observation of high conversion based on consumption of the carboxylic acids **2a** and **3a**. To identify alternative conditions, an evaluation of solvent, base choice, and base stoichiometry was undertaken.[12] Base choice was most impactful, with the change from NMI to pyridine giving a significant improvement in selectivity (entries 3 and 4). Focused optimization of the solvent and stoichiometry led to an additional upgrade in yield and selectivity using 4.1 equiv of pyridine in dichloromethane (DCM, entries 5−8). The trends observed with both **2a** and **3a** were similar despite the unique mechanisms for epimerization in each substrate. In light of the improvement in yield on going from MeCN/pyridine to DCM/pyridine for **6ad** (entry 4 vs entry 8), the conditions using DCM/pyridine were chosen to maximize yield, selectivity, and generality in the exploration of a range of substrates.

The substrate scope was investigated under both the original TCFH-NMI conditions as well as the newly identified reaction conditions with 4.0 equiv of pyridine in DCM (Scheme 2). Across a range of substrates, good-to-excellent yields with preservation of the α-stereogenic center were observed. Looking across the range of alcohols originally surveyed in Figure 1, good-to-excellent yields can be achieved with little to no epimerization of the α-stereogenic center derived from acid **2a** under the pyridine/DCM conditions and, in some cases, the original NMI/MeCN conditions. Consistent yield and selectivity were observed for preparation of **5ad** using pyridine in both DCM and MeCN. The most hindered alcohols **4f** and **4h** demonstrate the limits of this method. Low conversion and significant loss of enantiopurity were observed, even after extended reaction times at room temperature. Consistent with a literature report,[5e] heating to 40 °C can drive these reactions to full conversion in 16 h, albeit with high levels of epimerization. In the case of **4f**, these forcing conditions led to near racemization of the α-stereogenic center in product **5af**. Regardless, with tertiary alcohol **4f**, using pyridine in DCM at 40 °C led to the optimal results. Alcohols like the base-sensitive dioxinone-containing alcohol **4g**[14] or the acid-sensitive tertiary allylic alcohol linalool **4h**[15] were explored due

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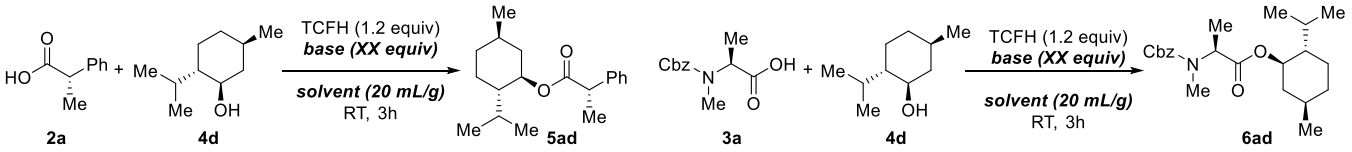
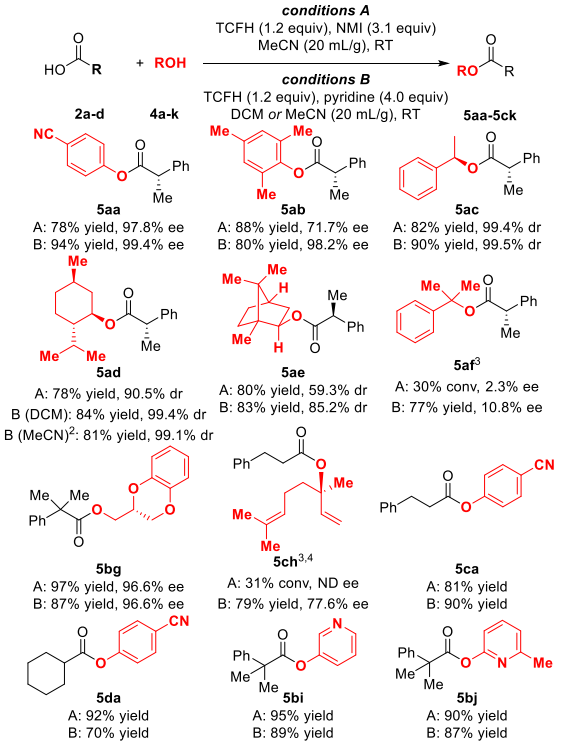
Table 1. Optimization of Esterification with 2a and 3a



entry	solvent	base (equiv)	AY (**5ad**, %)[1]	conv (%)[2]	dr	entry	solvent	base (equiv)	AY (**6ad**, %)[1]	conv (%)[2]	dr
1	MeCN	NMI (1.1)	19	35	99.4	1	MeCN	NMI (1.1)	19	89	97.6
2	MeCN	NMI (2.1)	21	67	97.3	2	MeCN	NMI (2.1)	61	93	97.5
3	MeCN	NMI (3.1)	70	97	87.7	3	MeCN	NMI (3.1)	92	97	92.5
4	MeCN	pyridine (3.1)	68	98	99.2	4	MeCN	pyridine (3.1)	65	96	98.9
5	DCM	pyridine (1.1)	13	38	99.6	5	DCM	pyridine (1.1)	24	83	98.5
6	DCM	pyridine (2.1)	58	93	99.6	6	DCM	pyridine (2.1)	64	93	99.3
7	DCM	pyridine (3.1)	71	99	99.8	7	DCM	pyridine (3.1)	83	94	99.5
8	DCM	pyridine (4.1)	90	97	99.0	8	DCM	pyridine (4.1)	86	94	98.6

[1]Assay yield (%) was determined by LC analysis of the reaction mixture, see the Supporting Information for the detailed procedure. [2]Conversion based on LC area counts (AC) using conv = 100 × (AC(**5ad**)/(AC(**2a**) + AC(**5ad**)), for example. Conversion values were not adjusted for the response factor.

Scheme 2. Scope of Aliphatic and Aromatic Alcohols[1]

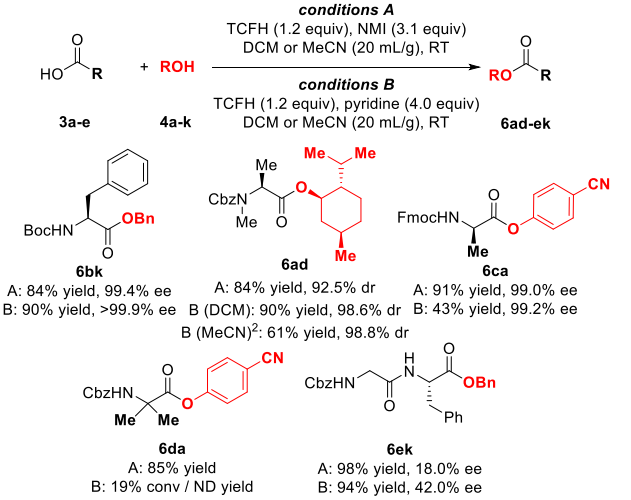


[1]All ee and dr values were obtained from end-of-reaction mixtures by chiral HPLC analysis prior to workup and isolation unless otherwise noted. [2]The reaction was run with 3.1 equiv of pyridine. [3]The reaction was run at 40 °C. [4]The ee was determined on material isolated after column chromatography.

to their reported instability under strongly acidic or basic conditions. In the case of **4h**, side products derived from rearrangement and epimerization of the stereogenic center in the alcohol were observed, leading to a reduced yield of the desired product **5ch**. In contrast, dioxanone-containing alcohol **4g** provided high yields and full retention of the stereogenic center in product **5bg** under both conditions. Less-challenging linear and branched carboxylic acids **4c** and **4d** performed comparably with the NMI and pyridine conditions. Looking beyond simple alcohol substrates, heterocyclic alcohols **4i** and **4j** provided high yields of esters **5bi** and **5bj** in couplings with tertiary carboxylic acid **2b** using either NMI or pyridine as the base.

Esterification of amino acid-derived substrates **3a**–**3e** demonstrate the compatibility of the common *tert*-butoxy (Boc), benzyloxy (Cbz), and fluorenylmethyloxy (Fmoc) carbamate protecting groups (Scheme 3). A lower yield but

Scheme 3. Scope of Amino Acid Substrates[1]



[1]All ee and dr values were obtained from end-of-reaction mixtures by a chiral HPLC analysis prior to workup and isolation unless otherwise noted. [2]The reaction was run with 3.1 equiv of pyridine.

comparable selectivity was observed for preparation of **6ad** using pyridine in MeCN versus DCM. Low levels of epimerization are observed, and in the case of compound **6bk** these results were identical to those reported under well-established conditions for epimerization-prone substrates with EDAC.[16] However, some limitations became evident with the well-known Anteunis peptide,[17] which is used as a challenging test for epimerization in peptide-derived substrates. The pendant amide contained in the glycine residue of **3e** leads to significant levels of epimerization in product **6ek**, presumably via a dihydrooxazolone intermediate, even when the pyridine/DCM conditions are employed, suggesting

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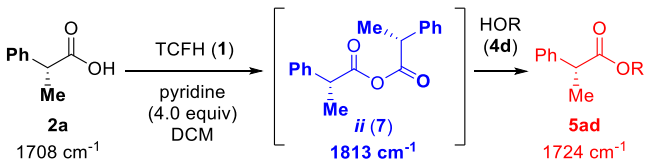
limitations for this esterification method in the context of peptide-derived substrates.

Although we believe the *N*-acylimidazolium ion ***i*** is still the active intermediate in the esterification using NMI, additional IR and NMR studies were conducted to provide some clarity regarding the mechanism using pyridine (Scheme 4).[12] *In situ*

Scheme 4. Mechanism of TCFH/Pyridine Esterification



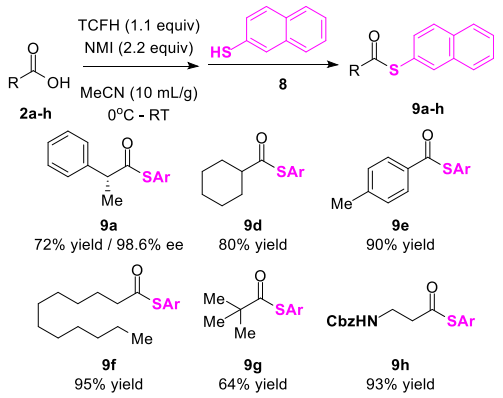
IR spectroscopy revealed that, upon the addition of TCFH to a mixture of carboxylic acid **2a**, alcohol **4d**, and pyridine in DCM, the complete disappearance of the acid and the formation of a new intermediate ***ii*** with a strong signal at 1813 cm^{-1} were observed in <30 s. This intermediate then slowly converted to the desired ester product **5ad** at 1724 cm^{-1}.

Comparison to an authentic standard demonstrated that intermediate ***ii*** was not the acid chloride (1778 cm^{-1}). By combining acid **2a** with only 0.55 equiv of TCFH, this intermediate ***ii*** could be formed and persisted for further analysis by IR and NMR. Initial results seemed inconsistent with an *N*-acylpyridinium ion but supported an anhydride.[18] After the isolation of this material, it was confirmed to be anhydride **7**.[19] As observed in the study of amide bond formation with TCFH–NMI, anhydrides are a common product of carboxylic acid activation with TCFH and appear to be the observed reaction intermediates in TCFH esterifications using pyridine as base. The intermediacy of the anhydride is consistent with the decreased level of epimerization of α-stereogenic centers observed under the pyridine conditions. The pK_a of the anhydride is expected to be significantly higher than that of the cationic *N*-acylimidazolium intermediate. The fact that the pK_a of the conjugate acid of pyridine is significantly lower than that of NMI (5.2 vs 6.2 in DMSO, respectively)[20] helps rationalize the observed dr and ee trends.

The synthesis of thioesters compared to esters presents a different challenge due to the high reactivity of thiol nucleophiles. TCFH reacts quickly and preferentially with thiols compared with carboxylic acids. Therefore, preactivation of the carboxylic acid with TCFH–NMI in MeCN is required for the formation of thioesters. Adding the thiol last to a mixture of carboxylic acid, TCFH and NMI can provide good yields of thioesters **9a–9h** (Scheme 5). A high yield is obtained in the case of aromatic acid **2e**, as well as aliphatic acids. The reaction gives high yields in the case of the linear and α-branched acids **2f** and **2d** as well as the β-amino acid-derived substrate **2h**. A slightly lower yield is obtained with hindered tertiary carboxylic acid **2g**. Using these conditions, the reaction of acid **2a** also gives a high yield and enantiopurity of the product **9a**.

In conclusion, we hope these studies will expand the use of TCFH as a noncorrosive[7] and broadly applicable reagent for acylations. To achieve this goal, improved conditions were identified using pyridine for the preparation of challenging esters. The intermediacy of anhydrides with pyridine as a base was established and may help explain the reactivity and

Scheme 5. Scope of Thioester Synthesis



selectivity differences compared to NMI. High-yielding thioesterifications could be achieved when preactivation of the carboxylic acid component was performed to avoid unproductive reactions of TCFH with the thiol. We hope these studies will encourage the adoption of TCFH as the preferred choice for activation of carboxylic acids for acylation reactions.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c01611.

Detailed experimental procedures, characterization, and copies of ^{1}H, ^{13}C NMR spectra of new compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds **5aa–5ck**, **6ad–6ek**, **7**, and **9a–9h** (ZIP)

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Notes

The authors declare no competing financial interest.

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