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Dual Brønsted Acid/Nucleophilic Activation of Carbonylimidazole Derivatives

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ABSTRACT

Carbonylimidazole derivatives have been found to be highly active acylation reagents for esterification and amidation in the presence of pyridinium salts. These reactions are thought to involve both Brønsted acid and nucleophilic catalysis. This mode of activation has been applied to the synthesis of difficult to access oxazolidinones, as well as esters and amides. Finally, the use of pyridinium salts has been shown to accelerate the esterification of carboxylic acids with imidazole carbamates.

Carbonylimidazole derivatives constitute an important and versatile class of acylation reagents, particularly in the preparation of esters and amides.[1] Recently we, as well as Batey, have explored the chemistry of imidazole carbamate and carbamylimidazole derivatives as acylating reagents that obviate the need to preform an acylimidazole.[2] Like their parent compound, 1,1′-carbonylimidazole (CDI), carbonylimidazole derivatives are attractive reagents because of their enhanced stability relative to acid halides.[3] This property has led to their rapid adoption in industrial chemistry for a variety of applications.[4]

However, because of their reduced reactivity relative to carbonyl halides, carbonylimidazole derivatives are often used in conjunction with an activating reagent. For instance, Staab observed that most alcohols do not react with acylimidazoles at room temperature but rapidly yield esters in the presence of catalytic amounts of alkoxide.[5] The carbonylimidazole group can also be activated by engaging with electrophiles such as NBS[6] or by alkylating at the distal nitrogen of the imidazole nucleus.[7] Alternatively, displacement of the imidazole by coupling reagents such as HOBt has been explored in the context of amidation.[8] Finally, we and others have investigated activation of these species through nitrogen protonation.[9] However, the weak basicity of most carbonylimidazoles makes Brønsted acid activation challenging. Keeping each of the aforementioned activation strategies and their attendant limitations in mind, we sought to develop alternative methods for the activation of carbonylimidazole derivatives that would be mild, selective, and general.

As an entry into new activation paradigms, we chose to study the synthesis of sterically encumbered oxazolidinones that are inaccessible through simple treatment of

(1) (a) Staab, K. M.; Bauer, H.; Schneider, K. M. *Azolides in Organic Synthesis and Biochemistry*; Wiley-VCH: Weinheim, 1998. (b) Armstrong, A. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, UK, 1995; Vol. 2, p 1006.

(2) (a) For synthesis of esters from imidazole carbamates, see: Heller, S. T.; Sarpong, R. *Org. Lett.* **2010**, *12*, 4572. (b) For the synthesis of amides from carbamylimidazoles, see: Grzyb, J. A.; Shen, M.; Yoshina-Ishii, C.; Chi, W.; Brown, R. S.; Batey, R. A. *Tetrahedron* **2005**, *61*, 7153and references therein.

(3) Larrivée-Aboussafy, C.; Jones, B. P.; Price, K. E.; Hardink, M. A.; McLaughlin, R. W.; Lillie, B. M.; Hawkins, J. L.; Vaidyanathan, R. *Org. Lett.* **2010**, *12*, 324.

(4) (a) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2004**, *4*, 2337. (b) Dunn, P. J.; Hoffmann, W.; Kang, Y.; Mitchell, J. C.; Snowden, M. J. *Org. Process Res. Dev.* **2005**, *9*, 956. (c) Dale, D. J.; Dunn, P. J.; Golighty, C.; Hughes, M. L.; Levett, P. C.; Pearce, A. K.; Searle, P. M.; Ward, G.; Wood, A. S. *Org. Process Res. Dev.* **2000**, *4*, 17.

(5) Staab, H. A.; Mannschreck, A. *Chem. Ber* **1962**, *95*, 1284.

(6) Katsuki, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2019.

(7) (a) Esters from 1-acyl-3-alkylimidazolium salts: Kamijo, T.; Harada, H.; Iizuka, K. *Chem. Pharm. Bull.* **1984**, *32*, 5044. (b) Ureas and carbamates from carbamylimidazolium salts: Grzyb, J. A.; Batey, R. A. *Tetrahedron Lett.* **2008**, *52*, 5279. (c) Carbamates from imidazolium carboxylates: Ballatore, C.; Aspland, S. E.; Castillo, R.; Desharnais, J.; Eustaquio, T.; Sun, C.; Castellino, A. J.; Smith, A. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2477. (d) CDI can be activated using MeOTf: Saha, A. K.; Rapoport, H.; Schultz, P. *J. Am. Chem. Soc.* **1989**, *111*, 4856.

(8) Dunn, P. J.; Hughes, M. L.; Searle, P. M.; Wood, A. S. *Org. Process Res. Dev.* **2003**, *7*, 244.

(9) (a) See ref 2a. (b) Heller, S. T.; Sarpong, R. *Tetrahedron* **2011**, *67*, 8851. (c) Oakenfull, D. G.; Salvesen, K.; Jencks, W. P. *J. Am. Chem. Soc.* **1971**, *93*, 188. (d) Wolfenden, R.; Jencks, W. P. *J. Am. Chem. Soc.* **1961**, *83*, 4390. (e) Woodman, E. K.; Chaffey, J. G. K.; Hopes, P. A.; Hose, D. R. J.; Gilday, J. P. *Org. Process Res. Dev.* **2009**, *13*, 106.

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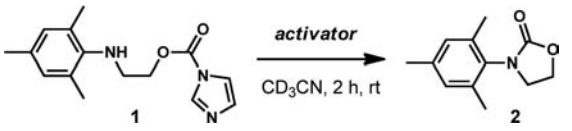
an amino alcohol with CDI. Instead, imidazole carbamates such as **1** (Table 1) are produced. Treatment of **1** with bases or nucleophilic additives did not effect ring closure to **2** (Table 1, entries 1–4), whereas acids promoted the formation of the desired oxazolidinone (**2**, entries 5–16). In these cases, a strong correlation between conversion and the pK_a of the acid activator was noted.[10,11]

Table 1. Initial Investigation of Imidazole Carbamate Activation



entry	activator	pK_a[a]	equiv	% conversion[b]
1	[c]			0
2	TEA		1	0
3	imidazole		1	0
4	DMAP		1	0
5	AcOH	12.3	1	0
7	AcOH-d_4	12.3	~85[e]	49
6	imidazole·HCl[d]	7.0	2	trace
8	TFA	3.5	1	48[f]
9	*N*,*N*-dimethylaniline·HOTs	2.5	2	33
10	(+)-CSA	1.6	1	53
11	pyridine·HCl	3.4	1	20
12	pyridine·HCl	3.4	2	36
13	pyridine·HOTs	3.4	1	38
14	pyridine·HOTs	3.4	2	63
15	pyridine·HOTf	3.4	2	76
16	pyridine·HCl	3.4	2	>95[g]

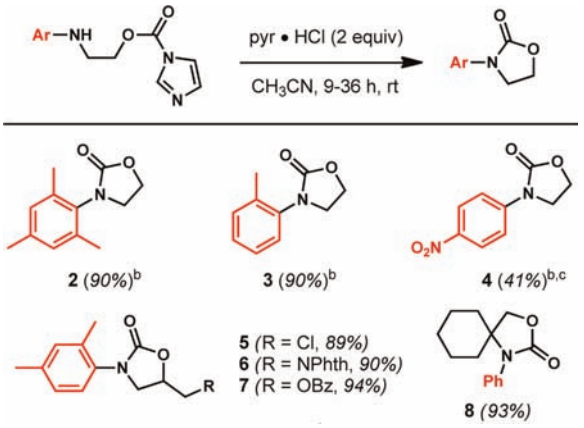
[a] In DMSO, see ref 10. [b] Conversions determined by integration of resonances in ^{1}H NMR. [c] Compound **1** was heated to 130 °C in DMF-d_7. [d] The reaction was run in DMSO-d_6. [e] AcOH-d_4 was used as solvent. [f] 2.5:1 ratio of **2** to trifluoroacetylation products obtained. [g] The reaction was run at 40 °C for 24 h.

Surprisingly, PPTS (entries 13 and 14), which is less acidic than *N*,*N*-dimethylanilinium tosylate (entry 9), was a superior acid source for the activation of **1**. This result suggested that pyridinium salts may be unique activators for carbonylimidazole derivatives. Accordingly, we were drawn to these mild acid sources, as they would allow for greater functional group compatibility than could be achieved using strong acids such as TFA or CSA (entries 8 and 10).

Our initial results with pyridinium salts demonstrated that less coordinating counteranions were beneficial for the reaction (entries 12, 14, and 15), but we elected to use pyridinium chloride (entries 11 and 12) because of its low cost and availability as an industrial waste product.[12] Further optimization revealed conditions that led to complete conversion of **1** to **2** using 2 equiv of pyridinium chloride at 40 °C (entry 16).[13] In cases where the chloride salt was ineffective, we generally found success by employing pyridinium triflate (see Schemes 3 and 4).

Following the identification of optimal conditions for oxazolidinone formation (Table 1, entry 16), we investigated the substrate scope of the oxazolidinone synthesis (Scheme 1). Both sterically encumbered (see the corresponding products, i.e., **2** and **3**) and electronically deactivated aniline derivatives (see **4**) can be acylated to provide the corresponding oxazolidinones in good to excellent yields. We also investigated the use of polyfunctional substrates, finding that oxazolidinone formation occurred in preference to displacement of a primary chloride (see **5**) or benzoyl group migration (see **7**). Similarly, α-tertiary anilines can be transformed to the corresponding spirocyclic oxazolidinones (**8**).

Scheme 1. Scope of Oxazolidinone Synthesis[a]



[a] Yields are for isolated compounds. [b] Reaction performed at 40 °C. [c] >90% conversion to **4** observed by ^{1}H NMR.

The observation that the facility of oxazolidinone formation was not strictly dependent on the pK_a of the activating agent (Table 1, compare entries 9 and 14) led us to further investigate the seemingly special role of pyridinium salts. Specifically, we wondered whether pyridine generated from an acid–base reaction of a carbonylimidazole derivative with pyridinium chloride could be acting as a nucleophilic catalyst.[14]

(10) (a) pK_as in DMSO: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (b) pK_a of imidazolium = 7.0 in DMSO: Kozak, A.; Czaja, M.; Chmurzynski, L. *J. Chem. Thermodyn.* **2006**, *38*, 599.

(11) The reaction of **1** with trifluoroacetic acid likely proceeds through the generation of a mixed anhydride intermediate, which gives rise to esterification products as well as **2** (see ref 9b).

(12) (a) For instance, in the synthesis of Tamiflu: Rohloff, J. C.; Kent, K. M.; Postich, M. J.; Becker, M. W.; Chapman, H. H.; Kelly, D. E.; Lew, W.; Louie, M. S.; McGee, L. R.; Prisbe, E. J.; Schultze, L. M.; Yu, R. H.; Zhang, L. *J. Org. Chem.* **1998**, *63*, 4545. (b) On Feb 9, 2012, pyridine hydrochloride could be purchased from Sigma-Aldrich (SKU: 243086) for 0.26 $/g, or 30.1 $/mol.

(13) See the Supporting Information for reaction optimization details. Reactions performed with dried pyridinium chloride were generally slightly higher yielding as no product arising from carbonylimidazole hydrolysis was observed. This side product was typically obtained as a 3–5% impurity in reactions run with commercial pyridinium chloride.

(14) (a) Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed.* **1969**, *8*, 981. (b) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed.* **1978**, *17*, 569. (c) Litvinenko, L. M.; Kirichenko, A. I. *Dokl. Akad. Nauk SSSR Ser. Khim.* **1967**, *176*, 97. (d) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560 and references cited therein.

Initial studies into this possibility were conducted by using sterically encumbered pyridinium salts as activating agents. In the event, comparison of two pyridinium salts of nearly equal acidity[15] but differing steric profiles (Figure 1, **10** and **11**) demonstrated that reduction of the nucleophilicity of pyridine led to dramatically decreased reactivity. This same effect can be observed by comparing **10** and **12**, where the latter is nearly 10 times less acidic but still outperforms the less nucleophilic **10**. The fact that PPTS (**9**) is a superior promoter relative to **12**, which is much less acidic but provides a more nucleophilic conjugate base, suggests that a balance between acidity and nucleophilicity must be achieved in order to obtain efficient carbonylimidazole activation.

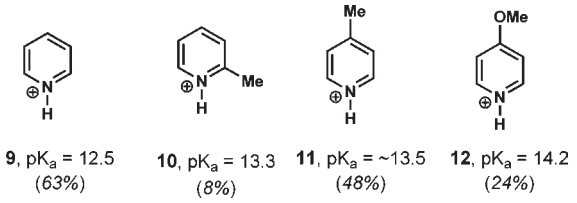


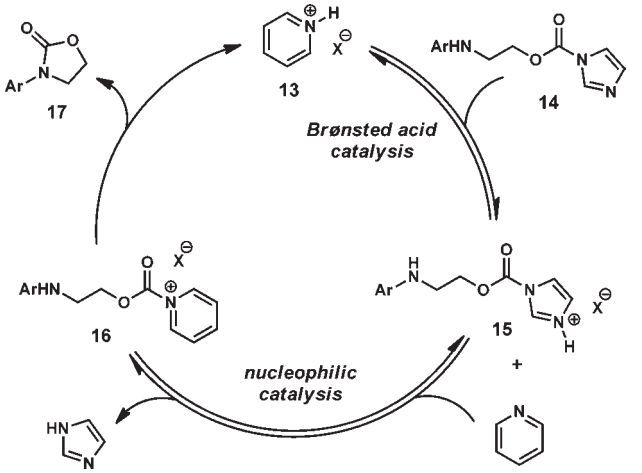
Figure 1. Pyridinium derivatives as mechanistic probes.

Compound **1** was treated with 2 equiv of the pyridinium salt in CD_3CN for 2 h. Values in parentheses represent conversions determined by integration of resonances in ^1H NMR. pK_a values refer to measurements performed in pure MeCN (see ref 15). All compounds are tosylate salts (anion omitted for clarity).

These observations are consistent with pyridinium salts (**13**, Scheme 2) acting as both Brønsted acid and nucleophilic catalysts in the acylation reactions of carbonylimidazole derivatives (e.g., **14**). Initially, an acid−base equilibrium develops to generate a carbonylimidazolium salt (**15**). This intermediate could then undergo an exchange reaction with pyridine (generated in the acid−base equilibrium) to form a strongly electrophilic acylpyridinium salt (**16**). Finally, this activated ester species is engaged by the amine (or alcohol) nucleophile to generate the desired amide (or ester) linkage (e.g., **17**). Even though we propose that this reaction is formally catalytic in pyridinium salt, free imidazole formed during the reaction acts as a terminal base, thereby requiring the use of stoichiometric amounts of pyridinium salts.

With a mechanistic hypothesis in hand, we reasoned that this mode of activation should be applicable to any transformation where a carbonylimidazole derivative acts as an electrophilic acylating reagent. Therefore, we sought to extend this mode of carbonylimidazole activation to intermolecular reactions, the most basic of which is the coupling of acylimidazoles with heteroatomic

Scheme 2. Proposed Mechanism of Pyridinium Dual Catalysis



nucleophiles. To this end, we first investigated the effect of pyridinium salts on the reaction of acylimidazoles with alcohols.

Treatment of benzoylimidazole with a range of alcohols at room temperature in the presence of pyridinium chloride typically led to clean production of esters (Scheme 3). More sterically congested primary alcohols such as neopentyl alcohol were efficiently esterified at room temperature using pyridinium triflate (see **18** and **19**). Similarly, secondary esters such as isopropyl 3-phenylpropanoate (**26**) could be prepared in good yield but generally required mild heating.[16]

The mild conditions required for acylimidazole esterification allowed for a high degree of functional group tolerance. PMB, TBS, and Boc protecting groups were all unaffected (see **21**, **22**, and **24**), and even reactive primary bromides (see **23**)[17] survived the esterification conditions. We did not observe isomerization when *Z*-alkenes were used (see **20**) or racemization when enantioenriched 1-phenylethanol was benzoylated (see **25**).[18]

Although the reaction of acylimidazoles with most amine nucleophiles need not be catalyzed, anilines can sometimes be challenging as substrates for amide synthesis. However, the generation of benzamides is greatly accelerated using pyridinium salt activation of the acylimidazole electrophile. For example, **27** formed nearly instantaneously using pyridinium chloride as a promoter. Additionally, **28** (Scheme 3) could be prepared in 8 h at 40 °C. In comparison, the use of imidazole hydrochloride as an activating agent for this purpose was reported to require heating to 100 °C for 10 h.[9e]

The esterification of carboxylic acids with imidazole carbamates, a reaction we reported recently,[2a] is also accelerated by pyridinium salts (Scheme 4) but most

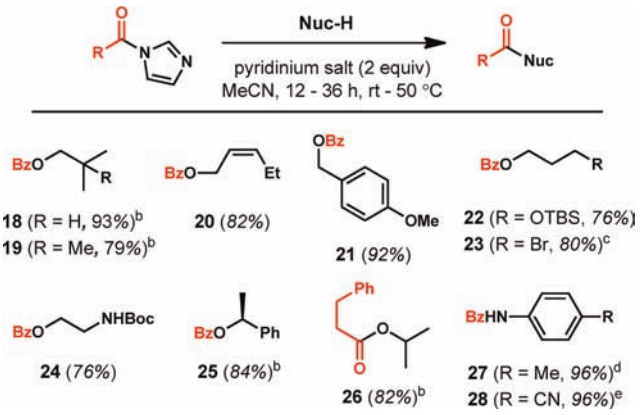
(15) pK_a of pyridinium salts in MeCN: Kaljurand, I.; Kütt, A.; Sooväli, L.; Rodima, T.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019. The pK_a of **11** is apparently unknown in MeCN using the scale reported in the above reference. However, it is known that 4-picoline is slightly more basic than 2-picoline in organic solvents: Hallé, J.-C.; Lelievre, J.; Terrier, F. *Can. J. Chem.* **1996**, *74*, 613.

(16) See the Supporting Information for full details on reaction temperatures and times.

(17) Esterification occurs at room temperature with pyridinium chloride; however, some alkyl chloride is produced as well. The use of pyridinium tosylate ameliorates this problem.

(18) As expected, this ester was produced with retention of stereochemistry.

Scheme 3. Esterification and Amidation of Acylimidazoles[a]



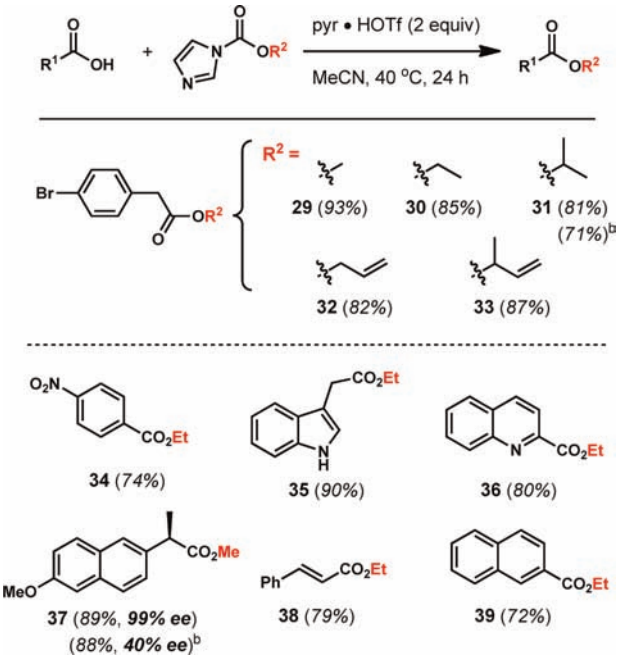
[a] Yields in parentheses are for isolated compounds. [b]Pyridinium triflate was used. [c]Pyridinium tosylate was used. [d]10 min, rt. [e]8 h, 40 °C.

efficiently by pyridinium triflate. Reactions that proceeded at 80 °C without a promoter can now be effectively performed at 40 °C with comparable results (**29**–**33**). Notably, secondary imidazole carbamates can now be used as esterification reagents at 40 °C (see **31**), whereas this transformation required 48 h at 80 °C under our previously reported conditions.[2a]

The scope of this new esterification protocol appears to be similar to that previously reported. Aryl and heteroaryl carboxylic acids were well-tolerated (**34**, **36**, and **39**), and acid-sensitive ring systems such as indoles were chemoselectively esterified (**35**). Notably, this method of carbonylimidazole activation also allowed for sequestration of imidazole through protonation, which makes possible the esterification of α-chiral carboxylic acids without racemization (see **37**). This was previously a serious limitation to the use of imidazole carbamates as esterification reagents.[9a] Finally, enoates such as **38** could be prepared in good yield, though we observed small quantities of a side product arising from the conjugate addition of imidazole when the esterification of cinnamic acid is monitored by ^{1}H NMR.

In conclusion, we have developed a mild and selective method for the activation of carbonylimidazole derivatives using pyridinium salts that is applicable to both intermolecular and intramolecular reactions. This activation mode was applied to the synthesis of oxazolidinones from amino alcohols that would be difficult to prepare without the use of phosgene, thereby providing an alternative to this

Scheme 4. Imidazole Carbamate Mediated Esterification Under Pyridinium Salt Catalysis[a]



[a] Yields in parentheses are for isolated compounds. [b]Results obtained by preparation of esters by heating imidazole carbamates with carboxylic acids at 80 °C for 24–48 h (refs 2a and 9a).

less-desirable reagent. Furthermore, this method enables the preparation of esters from acylimidazoles at room temperature. Similarly, pyridinium salt additives accelerated the reaction of imidazole carbamates with carboxylic acids to yield esters. Additional studies on the mechanism by which these salts activate carbonylimidazole derivatives and application to new acylation protocols are ongoing.

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Supporting Information Available. Experimental details and copies of ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.