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Carbamoylimidazolium salts as diversification reagents: an application to the synthesis of tertiary amides from carboxylic acids

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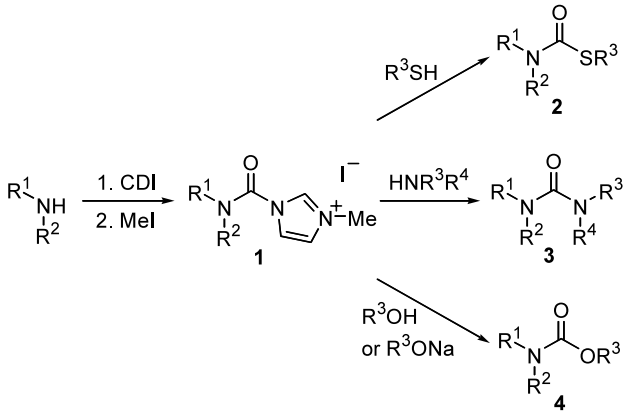
Abstract—An efficient method for the preparation of tertiary amides from carbamoylimidazolium salts and carboxylic acids is described. The transformation occurs at room temperature and under relatively mild conditions. The carbamoylimidazolium salts are obtained from the reaction of secondary amines with *N*,*N*′-carbonyldiimidazole, followed by methylation with methyl iodide. The utility of this reaction was demonstrated in the formation of Weinreb amides and in a short synthesis of fused bicyclic amides. The introduction of this reaction now permits carbamoylimidazolium salts to be utilized in the formation of tertiary amides, ureas, carbamates and thiocarbamates under a single set of conditions.

Carbamoylimidazolium salts **1** are versatile electrophiles in organic synthesis, reacting with a variety of nucleophiles (Scheme 1).[1,2] Treatment of the salts **1** with thiols results in the formation of thiocarbamates **2**,[2] whereas reaction with secondary or primary amines generates tetra- or trisubstituted ureas **3**.[1] Reaction of **1** with phenols or the alkoxides of aliphatic alcohols generates carbamates **4**.[2] In each of these reactions the carbamoylimidazolium salt acts as a disubstituted carbamoyl cation equivalent. A further advantage of this protocol, is that carbamoylimidazolium salts are readily prepared by the sequential treatment of secondary amines with the commercially available crystalline solid *N*,*N*′-carbonyldiimidazole (CDI)[3] and iodomethane. The reactivity of **1** is significantly enhanced over that of the corresponding carbamoyl imidazoles, as a result of the methylation of the imidazole ring.[4] This method avoids the direct use of phosgene or triphosgene that is required for the synthesis of carbamoyl chlorides (the most commonly employed disubstituted carbamoyl cation equivalent). The salts **1** are more readily handled than carbamoyl chlorides, and in most cases are stable crystalline solids that can be stored in sealed vessels for extended periods. By contrast, carbamoyl chlorides often display poor stability and are difficult to obtain as high purity samples, a feature that has limited their use and, in all but the simplest cases, their commercial availability.



Scheme 1. Synthesis and reactivity of carbamoylimidazolium salts **1** with various nucleophiles.

As part of a study into the reactivity patterns of carbamoylimidazolium salts, we now report their reaction with carboxylic acids for the generation of tertiary amides. The experimental protocol is quite straightforward, with treatment of **1** with carboxylic acids in the

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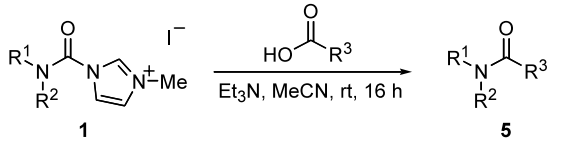
presence of 1 equivalent of triethylamine in acetonitrile at room temperature for 16 h resulting in the formation of amides **5** in excellent yields (Table 1).[5] Stronger bases, such as potassium carbonate also give high yields of the product. However, with weaker bases such as pyridine or resin-supported bases like poly(4-vinylpyridine) and Amberlyst® A-21 the yields are very low. In the absence of base, the product yields are negligible. Amide **5a** was isolated with yields of 71 and 85% when the reaction was worked up after 1 and 5 h, respectively. Other solvents such as chloroform may be used as a suitable substitute for acetonitrile. The methylimidazole byproduct is easily removed by washing the organic layer with dilute acid. The tertiary amide products are generally of high enough purity after aqueous work-up that chromatographic purification is not required. Reaction with simple carboxylic acids resulted in good to excellent yields of amides **5a**–**h**. Reaction with Cbz-protected α-amino acids also worked well, as illustrated by the examples of *N*-CBz-glycine and *N*-CBz-phenylalanine (Table 1, **5i**–**k**). In the latter case, racemization was not detected to have occurred under the reaction conditions by HPLC analysis, and the purity of the product **5k** was 97% without column chromatography.

This approach also provides a very convenient way of generating *N*-methoxy-*N*-methyl amides (**5l**–**p**, Table 1), otherwise known as Weinreb amides, which are widely used in the synthesis of ketones from Grignard and organolithium reagents.[6,7] The *N*-methoxy-*N*-methyl carbamoylimidazolium salt reacts with one equivalent of carboxylic acid and triethylamine to afford the Weinreb amides in excellent yields without the need for further purification. Although the precursor imidazolium salt is less stable than most other salts that we have studied, it can be stored for several months at −20°C without noticeable decomposition. The *N*-methoxy-*N*-methyl carbamoylimidazolium salt is also more reactive towards carboxylic acids, and generates the amides in good yields, even when weaker bases such as pyridine are used.

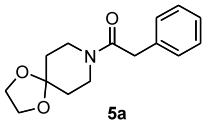
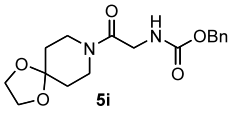
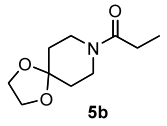
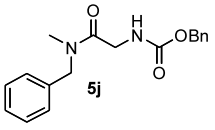
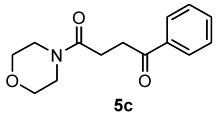
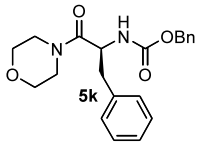
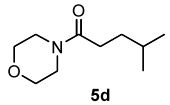
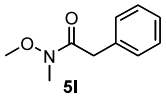
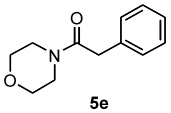
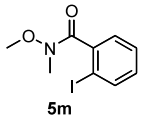
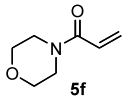
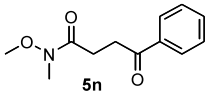
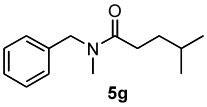
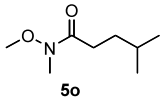
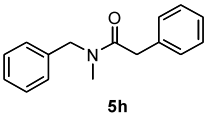
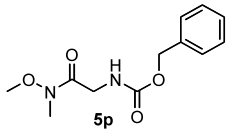
The formation of the tertiary amides, presumably proceeds by reaction of the carboxylate anion with the carbamoylimidazolium salt to generate the corresponding mixed anhydride, with concomitant release of *N*-methylimidazole. Subsequent attack of the *N*-methylimidazole then generates an acylimidazolium species with release of carbon dioxide and the free amine. The amine then reacts with the acylimidazolium species to form the final product. Thus, the carbamoylimidazolium salt serves as both the source of the amine donor *and* as the activation reagent for the carboxylic acid acceptor. The activation step is similar to the use of both CDI[8] and *N*,*N*′-carbonylbis(3-methylimidazolium) triflate[9] for carboxyl activation of carboxylic acids and α-amino acids. The overall transformation is analogous, and complementary, to the conversion of isocyanates with carboxylic acids into *secondary* amides,[10] a process that is known to proceed via a mixed acid anhydride, which subsequently undergoes decarboxylation to give the product at elevated temperatures. A modification of this process utilizes imidazole as an additive, which initially attacks the isocyanate to form a corresponding azolide intermediate, which is then transformed into the secondary amide.[11]

While numerous methods are known for the direct or indirect transformation of carboxylic acids into amides, this operationally straightforward method provides potentially useful opportunities in organic synthesis.

Table 1. Synthesis of tertiary amides **5** from carbamoylimidazolium salts **1**[a]



1 **5**

Amide	% Yield	Amide	% Yield
 **5a**	92	 **5i**	87
 **5b**	99	 **5j**	80[b]
 **5c**	94	 **5k**	96
 **5d**	97	 **5l**	93
 **5e**	92	 **5m**	86
 **5f**	75	 **5n**	95
 **5g**	94[b]	 **5o**	92
 **5h**	90[b]	 **5p**	93

[a]Carbamoylimidazolium salt **1** was stirred overnight at room temperature with carboxylic acid (1 equiv) and Et_3N (1 equiv) in acetonitrile.
[b]Isolated yield following column chromatography.

In particular, a single reagent is now available for the formation of tertiary amides, ureas, carbamates and thiocarbamates. These divergent transformations occur under a unified set of conditions, a feature that should allow for their use in parallel synthesis or combinatorial chemistry applications. Indeed, carbamoylimidazolium salts have already been applied to the synthesis of urea libraries, using both parallel solution-phase synthesis and solid-phase synthesis techniques.[12]

The multifarious reactivity of carbamoylimidazolium salts presents potential chemoselectivity problems for those substrates containing multiple functional groups capable of reacting with these salts. A competition study of the reaction of **1a** with carboxylic acids, amines, anilines, thiols, phenols and alcohols was undertaken to establish an approximate guide to their reactivity. NMR analysis of the crude product ratios from the reaction of **1a** with an excess of pairs of nucleophiles (5 equivalents) and triethylamine (10 equivalents) in acetonitrile at room temperature, provided a reactivity profile as indicated in Figure 1. Thiophenol was found to be the most reactive substrate, and was about 50-fold more reactive than cyclohexanethiol, which was the next most reactive nucleophile examined. Aliphatic alcohols or anilines were unreactive under these conditions, and require much stronger bases for reaction to occur. The reactivity differences between primary and secondary aliphatic amines (e.g. *n*-butylamine, tetrahydroisoquinoline), carboxylic acids and phenols were moderate, and useful selectivity levels cannot be assured in substrates bearing these competing functionalities.

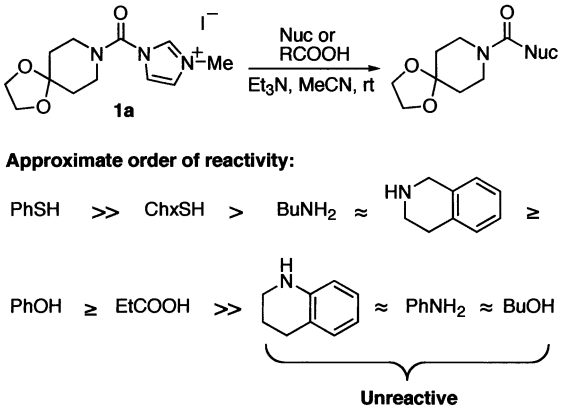
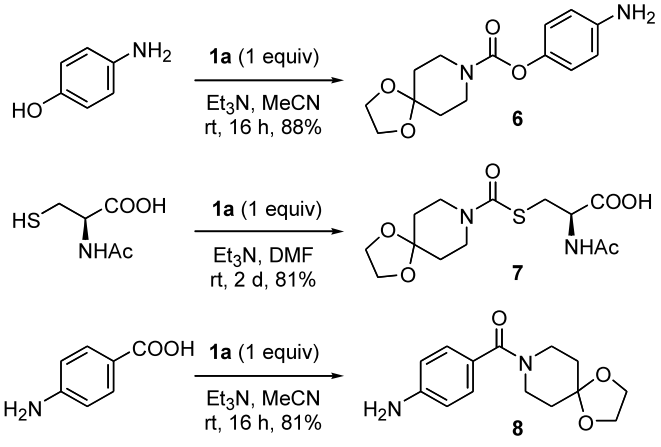


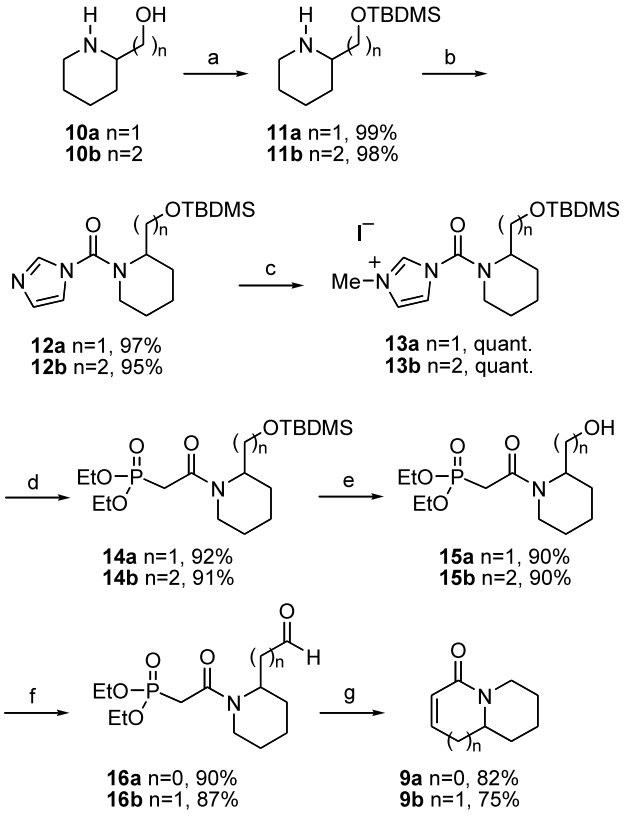
Figure 1. Relative reactivities of various nucleophiles and carboxylic acids towards carbamoylimidazolium salt **1a**.



Scheme 2. Examples of chemoselective transformations of **1a** with bifunctional substrates.

The reactivity profile allows the rational planning of chemoselective transformations of bifunctional substrates (Scheme 2). Thus, using **1a** as a model substrate, *p*-cresol was converted into carbamate **6** in 88% yield, without any evidence of reaction of the aniline functionality. The reaction of *N*-acetyl-L-cysteine with **1a** resulted in the clean reaction of the thiol group over the carboxylic acid, and an isolated 81% yield of thiocarbamate **7**. Finally, reaction with *p*-aminobenzoic acid led to the corresponding amide **8** in 81% yield.

To demonstrate the synthetic utility of the tertiary amide formation, the reaction was applied to the synthesis of fused bicyclic lactams **9a** and **9b** (Scheme 3). The key reactions in these approaches are the forma-



Scheme 3. *Reagents and conditions*: (a) TBDMSCl, pyr, CH_2Cl_2, rt, 4 h. (b) CDI, CH_2Cl_2, rt, 1 day. (c) MeI, MeCN, rt, 1 day. (d) Diethyl phosphonoacetic acid, NEt_3, MeCN, 50°C, 1 day. (e) TBAF, THF, rt, 30 min. (f) $C_6H_4COOI(OAc)_3$ (i.e. Dess–Martin periodinane reagent), CH_2Cl_2, rt, overnight. (g) NaH, THF, 0°C, 40 min.

tion and intramolecular Wadsworth–Horner–Emmons of a phosphonate amide substrate using the carbamoylimidazolium salt protocol. Bicyclic lactam **9a** is an intermediate in the synthesis of indolizidines such as 2-epilentiginosine and lentiginosine,[13] while **9b** can be used in the synthesis of quinolizidine ring systems and is an intermediate in the synthesis of leontiformine and leontiformidine.[14] The synthesis began with the protection of 2-piperidinemethanol **10a** or 2-piperidineethanol **10b** with TBDMSCl in essentially quantitative yields. The resultant amines **11a** and **11b**, used without purification, were reacted with CDI in CH_2Cl_2 at room temperature to generate the carbamoyl imidazoles in greater then 95% yield after column chromatography. Activation of **12a** and **12b** through methylation with methyl iodide, according to the standard procedure, generated the carbamoylimidazolium salts **13a** and **13b** in quantitative yields. The phosphonate moiety necessary for the Wadsworth–Horner–Emmons reaction was accomplished through the amide bond forming reaction between **13a** and **13b** and commercially available diethyl phosphonoacetic acid at 50°C to give **14a** and **14b** in 92 and 91% yield, respectively. Deprotection with TBAF occurred in 90% yield for the formation of both **15a** and **15b**, and was followed by oxidation with the Dess–Martin reagent to give **16a** and **16b** in 90 and 87% yields, respectively. Aldehydes **16a** and **16b** had to be chromatographed through a very short silica column to minimize decomposition, with impurities at this stage leading to poor yields in the next step. The final intramolecular Wadsworth–Horner–Emmons cyclization was carried out with sodium hydride in THF at 0°C to give the products **9a** and **9b** in 82 and 75% yield, respectively.

In conclusion, the reaction of carbamoylimidazolium salts with carboxylic acids is demonstrated for the formation of tertiary amides. The experimental protocol is straightforward and utilizes mild conditions. The product amides are generated in high yields, and show excellent purity after aqueous work-up. The utility of the salts was further demonstrated in the synthesis of Weinreb amides, phosphonate amides, as well as in the chemoselective transformation of bifunctional substrates. Stable carbamoylimidazolium salts can thus be used for the formation of tertiary amides, ureas, carbamates and thiocarbamates under a single set of conditions. Further explorations of these reagents in small molecule library synthesis will be reported in due course.

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5. Representative procedure: To a suspension of **1a** (379 mg, 1.00 mmol) in acetonitrile (6 mL) were added phenylacetic acid (136 mg, 1.00 mmol) and triethylamine (101 mg, 1.00 mmol). The reaction was stirred at room temperature overnight. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (15 mL) and washed with 0.2N HCl (15 mL). The aqueous layer was extracted with three 15 mL portions of dichloromethane. The combined organic layers were washed sequentially with 0.2N HCl (15 mL), 0.5 M potassium carbonate (25 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under vacuum to give **5a** as a yellowish oil (240 mg, 92%). IR (thin film) ν 2962, 2878, 1630, 1440, 1360, 1250, 1097, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.16 (m, 5H), 3.85 (d, $J=2.0$ Hz, 4H), 3.68 (s, 2H), 3.65 (t, $J=6.0$ Hz, 2H), 3.43 (t, $J=6.0$ Hz, 2H), 1.58 (t, $J=6.0$ Hz, 2H), 1.37 (t, $J=6.0$ Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.5, 135.3, 128.9, 128.7, 127.0, 107.0, 64.6, 44.4, 41.3, 40.1, 35.4, 34.8; MS m/z (relative intensity) 170 (100), 142 (80), 91 (70), 261 (73); HRMS (EI) m/e calcd (M^+) 261.1365, found 261.1368.
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