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Chemoselective Esterification and Amidation of Carboxylic Acids with Imidazole Carbamates and Ureas

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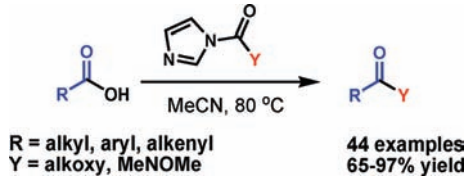
ABSTRACT



Imidazole carbamates and ureas were found to be chemoselective esterification and amidation reagents. A wide variety of carboxylic acids were converted to their ester or amide analogues by a simple synthetic procedure in high yields.

The chemoselective esterification of carboxylic acids is a ubiquitous synthetic operation. In addition to the venerable Fischer esterification,[1] numerous other methods have been developed toward this end. Transformations that involve activation of the carboxylic acid group have become a mainstay of ester synthesis, and though substantial progress has been made in this area,[2] acid activation often adds an additional step and can be challenging in the presence of other reactive functional groups.

Perhaps the most reliable and powerful selective esterification method is the methylation of acids with diazomethane, which activates the carboxylic acid *in situ*.[3] However, this reagent poses serious health and safety risks. Furthermore, diazoalkane analogues have found only limited use as chemoselective esterification reagents due to the difficulty associated with their handling and preparation, limiting this approach to the preparation of methyl esters.[4]

An alternative strategy for esterification involves deprotonation of the carboxylic acid to form a more nucleophilic carboxylate salt, which can be alkylated in a subsequent step.[5,6] This paradigm has been met with considerable success in methylation, allylation, and benzylation reactions. However, acidic or nucleophilic functional groups elsewhere in the substrate are often incompatible with this approach, and many of the alkylating agents employed are highly toxic.

(1) Fischer, E.; Speier, A. *Chem. Ber.* **1895**, *28*, 3252–3258.

(2) Methods include: (a) DCC/DMAP: Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, *19*, 4475–4478. (b) "Mixed anhydride method": Kim, S.; Kim, Y. C.; Lee, J. I. *Tetrahedron Lett.* **1983**, *24*, 3365–3369. (c) Mitsunobu (and references therein): Mitsunobu, O. *Synthesis* **1981**, 1–27. (d) BOPCl: Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernández-Lizarbe, J. R.; Zugaza-Bilbao, A. *Synthesis* **1980**, *54*, 7–551. (e) DMFDMA: Brechbühler, H.; Büchi, H.; Hatz, E.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1965**, *48*, 1746–1771. (f) Yamaguchi: Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993. (g) EEDQ: Zacharie, B.; Connolly, T. P.; Penny, C. L. *J. Org. Chem.* **1995**, *60*, 7072–7074.

(3) Pizey, J. S. *Synthetic Reagents*; Horwood: New York, 1974; Vol. 2, p 65.

(4) (a) Diazoethane: Fenton, S. W.; DeWald, A. E.; Arnold, R. T. *J. Am. Chem. Soc.* **1955**, *77*, 979–984. (b) Phenyldiazomethane: Overberger, C. G.; Anselme, J.-P. *J. Org. Chem.* **1963**, *28*, 592–593.

(5) Methods include: (a) MeI/Cs_2CO_3: Pfeffer, P. E.; Silbert, L. S. *J. Org. Chem.* **1976**, *41*, 1373–1379. (b) Me_2CO_3/K_2CO_3: Jiang, X.; Tiwari, A.; Thompson, M.; Chen, Z.; Cleary, T. P.; Lee, T. B. K. *Org. Process Res. Dev.* **2001**, *5*, 604–608. (c) Me_2SO_4/LiOH: Chakraborti, A. K.; Basak (née Nandi), A.; Grover, V. *J. Org. Chem.* **1999**, *64*, 8014–8017. (d) Me_3OBF_4/DIPEA: Raber, D. J.; Gariano, P.; Brod, A. O.; Gariano, A.; Guida, W. C.; Guida, A. R.; Herbst, M. D. *J. Org. Chem.* **1979**, *44*, 1149–1154.

(6) Alkylisoureas have been used as *in situ* alkylating reagents: (a) Mathias, L. J. *Synthesis* **1979**, *8*, 561–576, and references therein. (b) Crosignani, S.; White, P. D.; Steinauer, R.; Linclau, B. *Org. Lett.* **2003**, *5*, 853–856.

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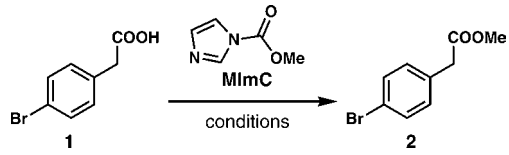
Herein, we wish to report that alkyl imidazole carbamates and ureas efficiently mediate the chemoselective esterification and amidation of carboxylic acids. These inexpensive reagents are easily prepared, can be stored on scale, and do not appear to pose a safety risk.[7] Despite operating in a manifold seemingly similar to 1,1′-carbonyldiimidazole-mediated esterification or amidation,[8] these reagents obviate the need for multi-operation synthetic procedures as well as monitoring of the acid activation step.

During the course of a synthesis of a complex molecule, we observed that the alkoxy group of imidazole carbamates was rapidly acetylated when dissolved in acetic acid. Intrigued by this previously unreported reactivity, we treated **1** (Table 1) with methyl imidazole carbamate (MImC)[9] at room temperature for 18 h but observed only starting materials. However, heating the mixture to 60 °C resulted in clean but partial conversion to **2**.

Table 1. Optimization of Methylation of **1** with MImC[a]



entry	solvent	temp (°C)	MImC (equiv)	[**1**] (M)	% yield
1	$CDCl_3$	25	1.5	0.2	0
2	$CDCl_3$	60	1.5	0.2	33
3	DCE	80	1.2	0.2	63
4	toluene	80	1.2	0.2	58
5	EtOAc	80	1.2	0.2	66
6	MeCN	80	1.2	0.2	72
7	MeCN	60	1.2	0.2	47
8	MeCN	60	1.2	0.5	70
9	MeCN	60	1.2	1.0	74
10	MeCN	60	1.2	2.0	69
11	MeCN	60	2.0	0.5	72
12	MeCN	60	3.0	0.5	80
13	MeCN	60	4.0	0.5	83
14	MeCN	80	1.2	0.5	85
15	MeCN	80	2.0	0.5	93

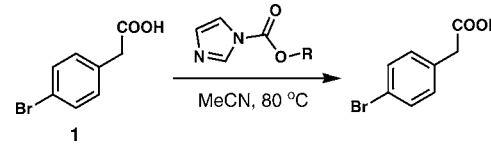
[a] All reactions were performed in sealed vials under a nitrogen atmosphere and run for 18 h.

Using more polar solvents had a dramatic positive effect on the reaction (entries 3−6), as did raising the reaction temperature (entries 6 and 7). Increasing the amount of the MImC reagent (entries 11−13) led to improved conversion but also to substantially higher levels of *N*-methylimidazole as a byproduct.[10] Because the esterification reaction produces imidazole, significant amounts of *N*-methylimidazole begin to form once the majority of the carboxylic acid substrate has been consumed. Higher reaction concentrations also accelerated imidazole alkylation. Thus, a balance between these two pathways was negotiated by reducing the concentration, using 2 equiv of MImC and running the reaction at relatively high temperature (entry 15).

Importantly, the typical reaction products of a MImC esterification are imidazole, *N*-methylimidazole, and the desired ester. As such, a simple aqueous workup provides pure ester products.[11]

A variety of esters could be prepared by treatment of a carboxylic acid substrate (e.g., **1**) with the appropriate imidazole carbamate (Table 2).[12,13] The preparation of secondary esters from simple aliphatic alkoxy groups was somewhat less efficient (entry 3). However, secondary allyl esters were synthesized without event (entry 8). No loss of regiochemical information was observed when substituted allyl imidazole carbamates were employed (entries 7 and 8).

Table 2. Alkyl Group Scope[a]

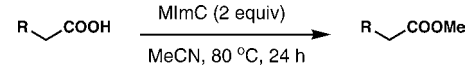


entry	R	% yield
1	methyl	93
2	ethyl	89
3	isopropyl	70[b]
4	allyl	91
5	benzyl	81[c]
6	propargyl	87
7	*trans*-crotyl	84
8	3-butenyl	85

[a] All reactions were run for 24 h, except entries 3 and 8, which were run for 48 h. [b] The reaction did not reach completion. [c] Chromatography was required to remove benzyl carbonate.

Investigation of several glycine and glycolic acid derivatives demonstrated the high degree of chemoselectivity provided by esterification with MImC (Table 3). Relatively acidic protected amines were well-tolerated (entries 1 and 2), though very acidic functional groups such as tosylamides

Table 3. Chemoselectivity of MImC-Mediated Esterification



entry	R	% yield
1	NHCbz	93
2	NHBoc	93
3	NHFmoc	ND[a]
4	NHTs	83[b]
5	NHAc	92
6	NPth	92
7	OBz	90
8	OPMP	94

[a] The Fmoc group was cleaved. [b] A 7% yield of the *N*-acylated methyl ester was obtained.

(7) A full safety evaluation has yet to be performed. MImC was stable for weeks at −20 °C and could be stored for prolonged periods at 4 °C. All other prepared imidazole carbamates could be stored at room temperature without observable decomposition.

(8) Staab, H. A. *Angew. Chem., Int. Ed.* **1962**, *1*, 351–367.

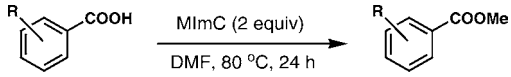
(9) (a) Crumbie, R. L.; Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1982**, *47*, 4040–4045. (b) Trost, B. M.; Zhang, Y.; Zhang, T. *J. Org. Chem.* **2009**, *74*, 5115–5117.

(10) Subjecting MImC to 2 equiv of imidazole in MeCN at 60 °C for 16 h led to nearly quantitative conversion to 1-methylimidazole.

were partially acylated by MImC, presumably via initial deprotonation by imidazole.

MImC also efficiently mediates the esterification of benzoic acids under the standard conditions using DMF as solvent (Table 4).[14] With this modification, excellent yields

Table 4. Methylation of Benzoic Acids



entry	R	% yield
1	4-Br	94
2	4-OMe	94
3	4-NO_2	91[a]
4	4-Ac	82
5	4-NHAc	83
6	2-Me	90
7	2-I	84

[a] 5% conversion to the corresponding *N*,*N*-dimethylbenzamide was observed.

were obtained for most benzoic acid substrates. Carboxylic acids of varied acidity reacted comparably (entries 1−3). However, steric hindrance of the carboxylic acid group led to slightly lower yields (entries 6 and 7).

As shown in Figure 1, the esterification proved to be general for a range of substrates. For example, branching at the α-position is tolerated, as are a variety of functional group arrays and heterocyclic scaffolds. Notably, mildly basic functionality such as a quinoline did not have a negative impact on the esterification. *N*-Protected amino acids such as Boc-Phe-OH or Boc-Cys(Trt)-OH were also esterified in good yield but were partially racemized. Therefore, the use of MImC with carboxylic acids bearing epimerizable stereocenters is not recommended at the present time.[15]

We propose that esterification with imidazole carbamates proceeds by a mechanism similar to that postulated by Staab for the formation of acylimidazoles from carboxylic acids and CDI (Scheme 1).[16] Specifically, an imidazolium carboxylate ion pair (**3**) decomposes to an acylcarbonate (**4**) that can be intercepted at either carbonyl by imidazole. In the productive pathway, an acylimidazole intermediate (**5**) forms along with a carbonic ester, which presumably undergoes decarboxylation. The liberated alcohol then scavenges the acylimidazole (**5**), providing the ester product. This proposal is supported by the isolation of an acylimidazole intermediate (such as **5**) when the MImC-mediated esterification was conducted in an open vessel so that methanol vapor was released as the reaction proceeded.

At this stage, other mechanistic hypotheses cannot be discarded since initial results suggest that the mechanism of esterification may depend on the type of carbamate used.[17]

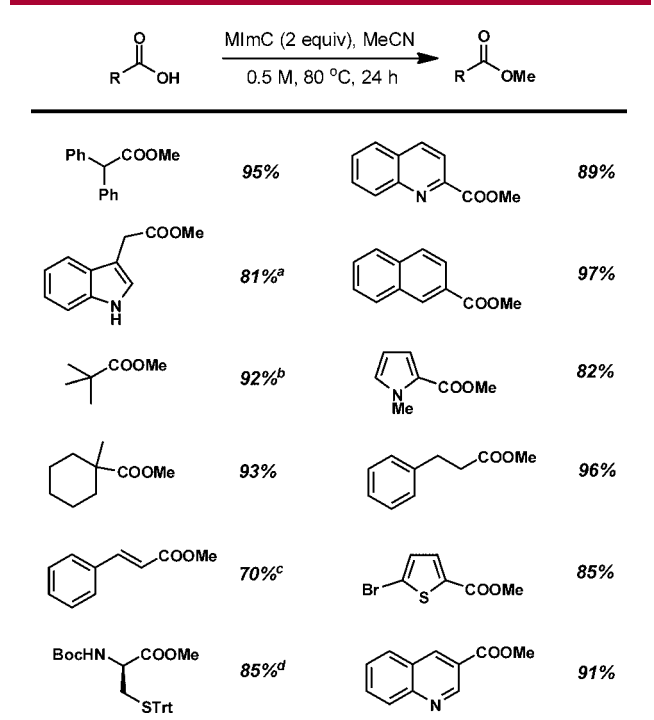
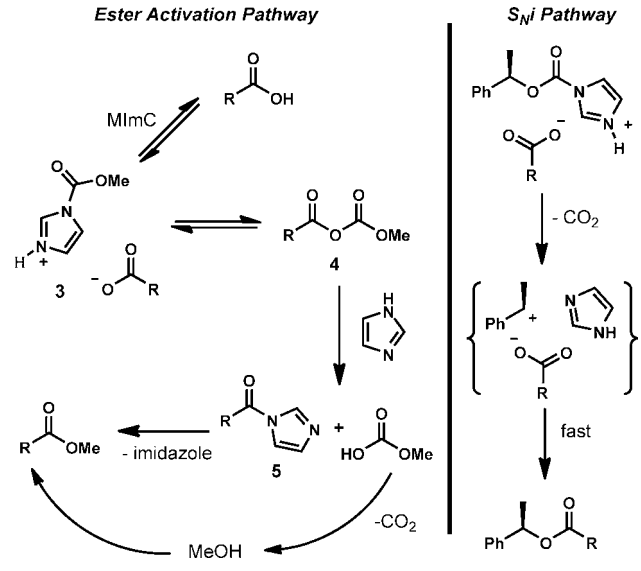


Figure 1. Substrate scope of methylation with MimC. [a]A 12% yield of the *N*-acylated product was obtained. [b]NMR yield using piperonylonitrile as an internal standard. [c]The remainder of the crude material was the product of conjugate addition by imidazole. [d]Extensive racemization was observed.

Scheme 1. Proposed Mechanism of Esterification by Imidazole Carbamate Reagents



(11) Unless a minor product is reported, all yields reported herein are for reactions purified only by aqueous workup to give analytically pure products.

(12) Imidazole carbamates were prepared either by treating imidazole (2 equiv) with the appropriate alkyl chloroformate (1 equiv) or by treating 1,1′-carbonyldiimidazole (1.05 equiv) with the appropriate alcohol (1 equiv). See the Supporting Information for details.

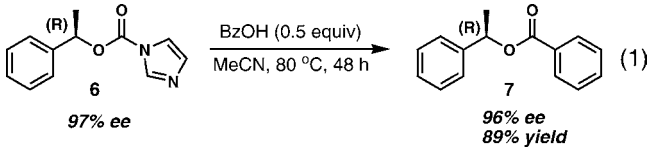
(13) All esterification reactions were run for 24 h. No attempt was made to optimize reaction time for individual substrates.

(14) In some cases, small amounts of *N*,*N*-dimethylbenzamide byproducts were observed. Using freshly distilled DMF usually suppressed this side reaction except in the case of very electron-poor benzoic acids such as 4-nitrobenzoic acid.

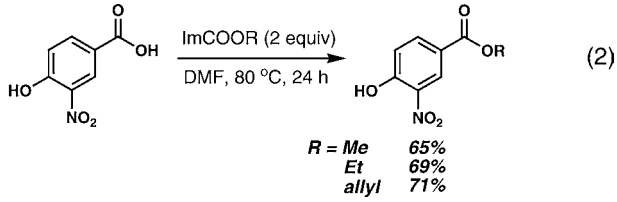
(15) Efforts to mitigate amino acid racemization are underway.

(16) For a discussion see, ref 8.

We can, however, discount an S_N1 process (via decarboxylation of ion pair intermediates such as **3**) because of the regiospecificity observed with substituted allyl carbamates (Table 2, entries 7 and 8). Rather, this result lends some support to a potential S_Ni mechanism (see Scheme 1) in the case of allylic carbamates because of the qualitative observation that but-3-en-2-yl imidazole carbamate mediates esterification much faster than isopropyl imidazole carbamate (Table 2, entry 3).[18] In addition, esterification of benzoic acid with enantioenriched imidazole carbamate **6** (eq 1) was found to proceed through a retentive process to afford **7**.[19,20]



Given the proposed mechanistic hypotheses (Scheme 1), it is perhaps unsurprising that MImC reacts sluggishly with phenols.[21] Intriguingly, more acidic phenols were methylated less efficiently, and the use of either ethyl or allyl imidazole carbamate led to only trace *O*-alkylation.[22] As a representative example, 4-hydroxy-3-nitrobenzoic acid was treated with a variety of imidazole carbamates (eq 2) under standard conditions to demonstrate the chemoselectivity of these reagents toward phenolic acids.[23] Analysis of the reaction mixture revealed that no phenol methylation had taken place. However, the presence of the highly acidic phenol group impeded esterification.[24] Presumably, the additional acidic functionality sequestered some amount of the MImC in an unproductive equilibrium.



Finally, Weinreb amides can also be prepared directly from carboxylic acids using imidazole urea **8**[25] (WImC).[26] Treating 4-bromophenylacetic acid with 2 equiv of WImC led to quantitative conversion to the desired amide. Functionalized carboxylic acids could also be transformed into their corresponding Weinreb amide analogues in excellent yield (Figure 2). Amidation proceeded with a high degree of chemoselectivity

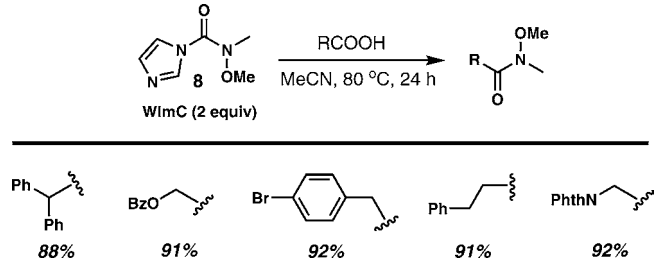


Figure 2. Substrate scope of amidation with WImC.

in cases where multiple electrophilic carbonyls were present and appears to be tolerant of sterically congested carboxylic acids as well.[27]

In conclusion, we have developed practical and highly chemoselective esterification and amidation reactions using imidazole carbamates and ureas. In particular, we have demonstrated the utility of imidazole carbamates as powerful and chemoselective esterification reagents. We believe these reagents will be a useful alternative to diazoalkanes for the synthesis of esters. In addition, we have demonstrated the utility of an imidazole urea reagent for direct Weinreb amide formation. Efforts to elucidate the mechanisms by which these transformations occur, suppress racemization, and expand the utility of this methodology are underway.

Acknowledgment. The authors are grateful to the NSF for financial support (CAREER: CHE-0643264 and predoctoral fellowship for STH).

Supporting Information Available: Experimental details and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) In many regards, MImC is unique among the imidazole carbamates investigated. It is easily hydrolyzed by water and seems to be a competent electrophile in the methylation of imidazole, whereas ethyl imidazole carbamate (EImC) can be purified by aqueous extraction and does not act as an ethylating agent toward imidazole. As such, a simple S_N2 displacement mechanism cannot be excluded.

(18) Cowdrey, W. A.; Hughes, E. D.; Ingold, C. K.; Masterman, S.; Scott, A. D. *J. Chem. Soc.* **1937**, 1271–1277.

(19) The product ester was assigned as the R enantiomer by comparison of its optical rotation with literature values: Chênevert, R.; Pelchat, N.; Morin, P. *Tetrahedron: Asymmetry* **2009**, *20*, 1191–1196.

(20) Retentive and regiospecific esterification can also be explained by a mechanism involving an acylimidazole intermediate. Further experimentation to delineate these mechanisms is underway.

(21) 11% conversion to 4-methoxytoluene anisole was observed when MImC was mixed with *p*-cresol under the standard esterification conditions.

(22) Mixing ethyl and allyl imidazole carbamates (EImC and AllImC) with *p*-cresol led to <1% and 6% conversion to *p*-ethoxytoluene and *p*-allyloxytoluene, respectively.

(23) When 4-hydroxy-3-nitrobenzoic acid was treated with 1 equiv of $TMSCHN_2$ in CH_2Cl_2/MeOH for 4 h at room temperature, only the methyl ester was observed.

(24) 4-Hydroxy-3-nitrobenzoic acid was obtained in 31% isolated yield when using MImC (eq 2, top entry).

(25) Grzyb, J. A.; Shen, M.; Yoshina-Ishii, C.; Chi, W.; Brown, R. S.; Batey, R. A. *Tetrahedron* **2005**, *61*, 7153–7175.

(26) Other methods for the direct conversion of carboxylic acids to Weinreb amides include: (a) Niu, T.; Zhang, W.; Huang, D.; Xu, C.; Wang, H.; Hu, Y. *Org. Lett.* **2009**, *11*, 4474–4477. (b) Tunoori, A. R.; White, J. M.; Georg, G. I. *Org. Lett.* **2000**, *2*, 4091–4093.

(27) The transformation of hindered acids can be problematic when standard conditions are used. See: Woo, J. C. S.; Fenster, E.; Dake, G. R. *J. Org. Chem.* **2004**, *69*, 8984–8986.