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Oxidative Amidation and Azidation of Aldehydes by NHC Catalysis

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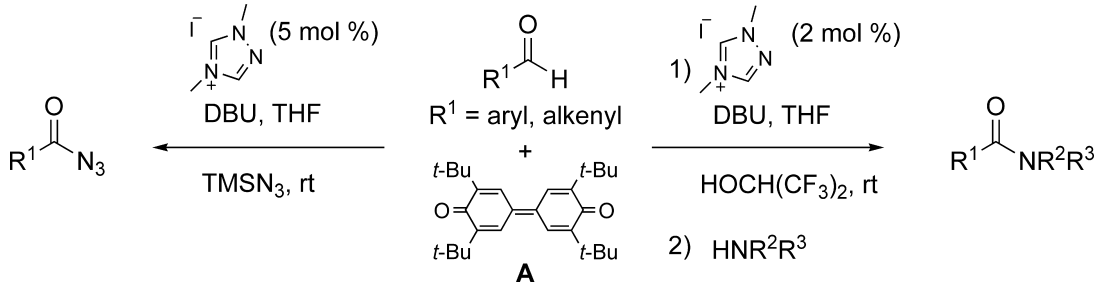
ABSTRACT



N-Heterocyclic carbene catalyzed oxidative amidations of various aldehydes to the corresponding hexafluoroisopropylesters by using the readily available organic oxidant A are described. The hexafluoroisopropylesters prepared in situ are shown to be highly useful active esters for amide bond formation. In addition, oxidative azidation of aldehydes is presented. These mild organocatalytic processes do not use any transition metal.

Amides are generally prepared via activation of carboxylic acids followed by amide bond formation upon treatment with amines in the presence of bases.[1,2] An elegant alternative approach which is often more atom economic is offered by the one-pot oxidative amidation of aldehydes. This alternative process comprises two reaction steps where either an aldehyde is oxidatively transformed to an active ester followed by amidation (C−N bond formation in the second step) or an aldehyde reacts with an amine to form an aminal that is subsequently oxidized to an amide (C−N bond formation prior to oxidation).[3] N-Heterocyclic carbenes (NHCs)[4] have been successfully used as catalysts for oxidative esterifications and amidations of aldehydes.[5−7] In these NHC-catalyzed reactions active esters are generated either by internal redox processes[5,6] or by the use of an external transition metal based oxidant.[7] Application of environmentally benign organic oxidants in NHC-catalyzed oxidative aldehyde transformations has also been reported.[8]

Herein we present oxidative amidations of various aldehydes catalyzed by an NHC with an organic oxidant by using

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(7) For MnO_2-mediated oxidation of the adduct formed by reaction of an NHC with aldehyde, see: (a) Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331. (b) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371. (c) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Tetrahedron* **2009**, *65*, 3102. For Fe^{III} salt as oxidant, see: (d) Jimenez, L.; Diederich, F. *Tetrahedron Lett.* **1989**, *30*, 2759.

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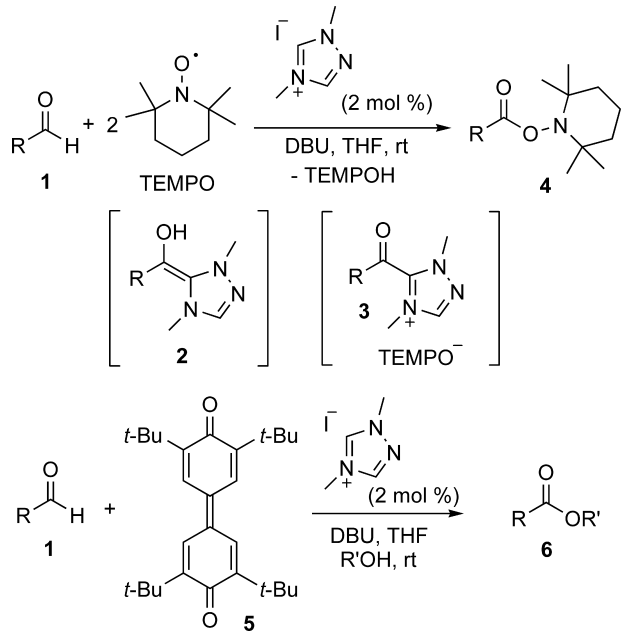
hexafluoroisopropyl esters as efficient active esters for amide bond formation. Moreover, the preparation of acyl azides by oxidative transformation of aldehydes is discussed.

We recently reported on NHC-catalyzed oxidative conversion of various aldehydes **1** to TEMPO-esters **4** by using the 2,2,6,6-tetramethylpiperidine *N*-oxyl radical (TEMPO) as an environmentally benign organic oxidant (Scheme 1).[9,10]

Scheme 1. NHC-Catalyzed Oxidative Esterifications



This transition metal free process comprises a biomimetic single electron transfer (SET) oxidation of Breslow intermediate **2** with subsequent deprotonation and renewed oxidation to give acyl carbenium ion **3**. In cage trapping with the concomitantly formed TEMPO$^-$ eventually affords TEMPO-ester **4**. More recently, we showed that by using 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone **5**[11] instead of TEMPO as organic SET oxidant, the intermediately formed acyl carbenium ion **3** can efficiently be trapped with alcohols to form the corresponding esters **6** in excellent yields.[12] On the basis of these results we decided to apply our method for oxidative aldehyde amidations.

Disappointingly, reaction of cinnamaldehyde with carbene precursor 1,3-dimethyltriazolium iodide (5 mol %), DBU (20 mol %), and **5** (1 equiv) in THF (0.1 molar) in the presence of benzylamine (2.5 equiv) at room temperature for 2 h afforded only 14% of *N*-benzylcinnammic acid amide **7a** (Table 1, entry 1). As a side reaction imine formation was occurring. Surprisingly, the intermediate acyl carbenium ion of type **3** did not react fast enough with benzylamine.[12]

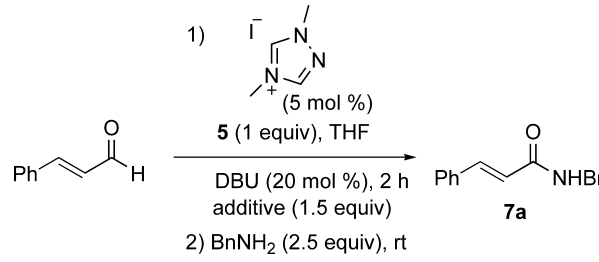
Table 1. Screening of Various Additives

entry	additive	yield [%]
1	none	14
2	HOAt[a]	trace
3	C_6F_5OH	trace
4	DMAP[b]	12
5	imidazole	18
6	$(CF_3)_2CHOH$ (HFIP)	83
7	$(CF_3)_2CHOH$ (HFIP)[c]	83
8	$(CF_3)_2CHOH$ (HFIP)[c,d]	84
9	$(CF_3)_2CHOH$ (HFIP)[e]	trace
10	$(CF_3)_2CHOH$ (HFIP)[f]	trace

[a] HOAt = 1-hydroxy-7-azabenzotriazole. [b] DMAP = 4-dimethylaminopyridine. [c] Amidation for 6 h. [d] With 2 mol % NHC catalyst. [e] $BnNH_2$ present during attempted oxidation. [f] 20 mol % of HFIP used.

We therefore tested various additives in the targeted oxidative amidation. To this end, oxidation was performed in the presence of an additive (1.5 equiv) for 2 h. The reaction mixture was then treated with benzylamine and stirring at room temperature was continued for 12 h (Scheme 2, Table 1). With HOAt formation of amide **7a** was suppressed and only a trace was identified by TLC (entry 2). The same result was observed with pentafluorophenol as an additive (entry 3). Addition of DMAP led to a slightly reduced yield as compared to the additive free process (entry 4) whereas a little improved yield was achieved by using imidazole (entry 5). Pleasingly, a sharp increase in yield was achieved upon adding hexafluoroisopropanol (83%, entry 6).[13] We proved by NMR spectroscopy on the crude product obtained after the first reaction step that oxidation of cinnamaldehyde occurred with >95% conversion (no aldehyde resonances left). Reaction time could be reduced to 6 h without affecting

Scheme 2. Oxidative Amidation of Cinnamaldehyde



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yield (entry 7). Moreover, catalyst loading could be reduced to 2 mol % without diminishing the yield (entry 8). Therefore, all follow-up experiments were performed with 2 mol % catalyst loading. We also tested whether benzylamine can be added at the beginning of this one-pot two-step process; however, reaction did not work (entry 9). Somehow the amine in the presence of HFIP interferes with the oxidation process. It is therefore obvious that attempted use of catalytic amounts of HFIP (20 mol %) in the presence of benzylamine did not deliver the desired amide (entry 10).

We were very surprised to learn that HFIP esters have so far not been used as active esters in intermolecular amide bond formations.[14] It is important to note that for HFIP active esters, the side product formed during amide bond formation is HFIP, which is readily removed by simple evaporation. In particular for industrial scale synthesis this might be a big advantage over other commonly used active esters where the side product formed during amidation must often be removed by more sophisticated separation processes. Moreover, the organic oxidant **5** used is readily available and its reduction product *o*,*o*′-di-*tert*-butyl-*p*-bisphenol can readily be isolated and reoxidized in near quantitative yield to **5** by using dioxygen.[15] Hence O_2 can formally be considered as the terminal oxidant in these reactions. Moreover, **5** is readily prepared by treatment of cheap *o*,*o*′-di-*tert*-butylphenol (Aldrich $29.1 (U.S.)/500 g) with O_2.[11]

To study the scope of our method different amines were tested in the one-pot amidation of different aldehydes under optimized conditions by using 2 mol % catalyst loading (Scheme 3, Table 2). Reactions worked well with propyl and allyl amine to give **7b** and **7e** in 93% and 90% yield, respectively (entries 1 and 4). For the sterically more hindered isopropyl and cyclohexyl amine amidation was slower and reaction time was extended to 12 h (→ **7c**,**d**, entries 2 and 3). The same conditions were optimal for acylation of pyrrolidine (→ **7o**, 92%, Scheme 2). Amino acid esters such as H-Gly-OEt, H-Ala-OMe, and H-Pro-OMe were acylated in good yields (→ **7f**,**g**,**p**, 78−93%, see Scheme 3). In these cases amidation were conducted with 1.5 equiv of amines at higher temperature (entries 5 and 6). Under the optimal amidation conditions no racemization occurred, as for **7g** an er > 99:1 was measured by chiral HPLC. The aldehyde component could also be varied as shown for amidation of benzaldehyde, *p*-nitrobenzaldehyde, 4-$CH_3OC(O)C_6H_4$, and *p*-(trifluoromethyl)benzaldehyde with benzylamine (→ **7h**−**k**, 81−92%, entries 7−10). *m*-Chlorobenzaldehyde and 2-thiophenecarbaldehyde also underwent clean oxidative amidation under the same conditions (→ **7*l***,**m**, 81−91%, entries 11 and 12). For *o*-tolylaldehyde a good yield of the amide was achieved by applying higher temperature for the amidation (→ **7n**, 81%, entry 13).

Scheme 3. Oxidative Amidation of Various Aldehydes Wih Different Amines

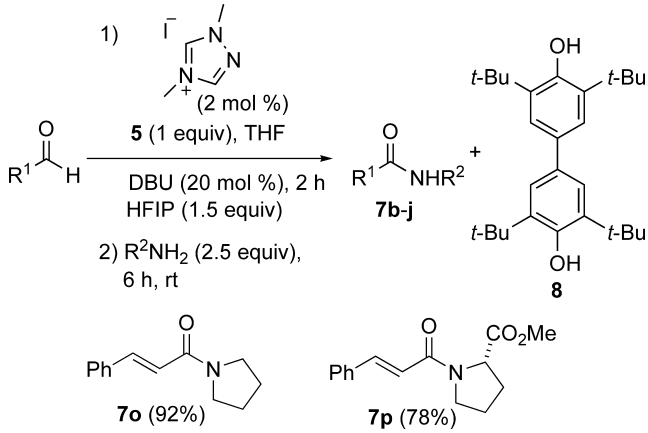

Table 2. Oxidative Amidation: Variation of Aldehyde and Amine Moiety under Optimized Conditions

entry	R^1	R^2	compd no.	yield [%]
1	$C_6H_5CH{=}CH$	$CH_3CH_2CH_2$	**7b**	93
2[a]	$C_6H_5CH{=}CH$	$(CH_3)_2CH$	**7c**	78
3[a]	$C_6H_5CH{=}CH$	C_6H_{11}	**7d**	86
4	$C_6H_5CH{=}CH$	$CH_2{=}CHCH_2$	**7e**	90
5[b,c]	$C_6H_5CH{=}CH$	$C_2H_5OC(O)CH_2$	**7f**	93
6[a,b,c]	$C_6H_5CH{=}CH$	$CH_3OC(O)CH(CH_3)$	**7g**	81
7[d]	C_6H_5	$C_6H_5CH_2$	**7h**	92
8	4-$NO_2C_6H_4$	$C_6H_5CH_2$	**7i**	81
9	4-$MeOC(O)C_6H_4$	$C_6H_5CH_2$	**7j**	92
10	4-$CF_3C_6H_4$	$C_6H_5CH_2$	**7k**	89
11	3-ClC_6H_4	$C_6H_5CH_2$	**7*l***	90
12	2-thienyl	$C_6H_5CH_2$	**7m**	91
13[b,d]	2-$CH_3C_6H_4$	$C_6H_5CH_2$	**7n**	81

[a] Amidation for 12 h. [b] Amidation at 65 °C. [c] 1.5 equiv of amine was used. [d] Oxidation for 8 h.

As another method for oxidative C−N bond formation of the aldehyde carbonyl C atom, we tested azides as nucleophiles to directly convert aldehydes under oxidative conditions to acyl azides[16] which are highly useful intermediates for the preparation of a large number of materials in organic chemistry. Acyl azides undergo thermal Curtius rearrange-

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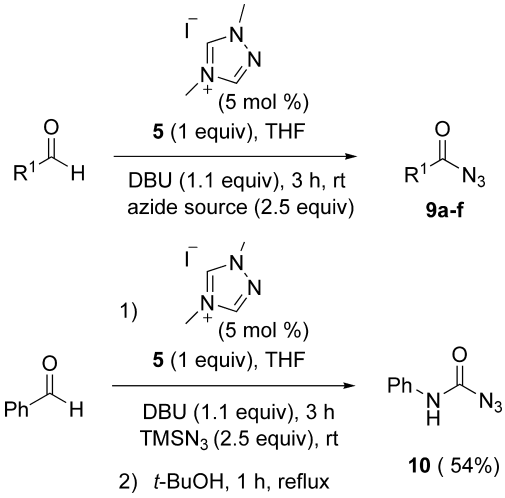
ment to form isocyanates which can be converted to amines, carbodiimides, carbamoylazides, urethanes, ureas, etc.[17]

Three different azide sources were tested by using benzaldehyde as a test substrate in the presence of 1,3-dimethyltriazolium iodide (5 mol %), DBU (1.1 equiv), and **5** (1 equiv, Scheme 4). Reactions with tetrabutylammonium

Scheme 4. Oxidative Azidation of Various Aldehydes with Different Azide Sources



azide and sodium azide lead to <2% of the desired benzoyl azide **9a** (Table 3, entries 1 and 2). Pleasingly, with trimethylsilyl azide as N_3-donor, benzoyl azide was obtained in 74% yield. Electron-rich as well as electron-poor para-substituted benzaldehyde derivatives gave moderate to good yields of the corresponding acyl azides (→ **9b**−**d**, 52−71%, entry 4−6). 2-Pyridinecarbaldehyde (→ **9e**, 73%, entry 7) and *m*-anisaldehyde (→ **9f**, 81%, entry 8) also underwent clean oxidative azidation.

Product azides can readily be converted via thermal Curtius rearrangement to carbamoyl azides[17] as shown for the

Table 3. Oxidative Azidation

entry	R^1	azide source	compd no.	yield [%]
1	C_6H_5	$Bu_4N^+N_3^-$	**9a**	<2
2[a]	C_6H_5	NaN_3	**9a**	<2
3	C_6H_5	$TMSN_3$	**9a**	74[b]
4	4-$NO_2C_6H_4$	$TMSN_3$	**9b**	52
5	4-$MeOC(O)C_6H_4$	$TMSN_3$	**9c**	65
6	4-$OMeC_6H_4$	$TMSN_3$	**9d**	71
7	2-pyridyl	$TMSN_3$	**9e**	73
8	3-$OMeC_6H_4$	$TMSN_3$	**9f**	81[b]

[a] 9:1 THF:H_2O mixture was used. [b] Isolated as a mixture with **5** and **8**.

transformation of benzaldehyde to phenyl carbamoylazide **10** (see Scheme 4). To this end, *t*-BuOH was added to the crude reaction mixture, which was then heated for 1 h to reflux to eventually give **10**.[18]

In summary, we presented a novel method for oxidative amidation of aromatic and α,β-unsaturated aldehydes. The NHC-catalyzed process occurs under mild conditions and does not need any transition metals. Reactions work with a low catalyst loading. Importantly, we showed that hexafluoroisopropyl esters are useful active esters for amide bond formation. Hexafluoroisopropanol generated as side product during amidation is readily removed from the reaction mixture by simple evaporation. Moreover, we developed a mild NHC-catalyzed oxidative azidation of aromatic aldehydes to form the corresponding acyl azides which can be rearranged to carbomoylazides in the same pot.

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

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(17) For direct preparation of carbamoylazides from aldehydes, see: (a) Pedersen, M. C.; Marinescu, L. G.; Bols, M. *Org. Biomol. Chem.* **2005**, *3*, 816. (b) Marinescu, L. G.; Pedersen, M. C.; Bols, M. *Tetrahedron* **2005**, *61*, 123.

(18) Even by replacing *t*-BuOH with MeOH, reaction of the intermediately formed phenylisocyanate with $TMSN_3$ was faster and **10** was formed. Reducing the amount of $TMSN_3$ to 1 equiv led to lower yield of the acyl azide.