

Chemoselective Conversion of α -Unbranched Aldehyde to Amide, Ester, and Carboxylic Acid by NHC-Catalysis

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Received (in XXX, XXX) Xth XXXXXXXXXX 200X, Accepted Xth XXXXXXXXXX 200X

First published on the web Xth XXXXXXXXXX 200X

DOI: 10.1039/b000000x

Depending on the N-heterocyclic carbene catalyst utilized, α -unbranched aldehyde selectively provided amide, ester, or carboxylic acid through oxidation by NCS. The α -unbranched aldehyde underwent these reactions chemoselectively in the presence of an aromatic or α -branched aldehyde.

N-Heterocyclic carbenes (NHCs) are used as organocatalysts for various transformations.¹ NHC-catalyzed esterification and amidation of α -oxidized aldehydes were demonstrated² using α,β -epoxyaldehyde,^{2a,f} α -haloaldehyde,^{2b,f,g} alkenal,^{2c,f,g} and α -acyloxyaldehydes^{2k} as substrates. Direct conversion of aldehydes to esters or amides was also achieved by NHC-catalysis,³ but only aromatic and unsaturated aldehydes were suitable for the reported direct amidation. Herein, we report a new method for direct conversion of α -unbranched aldehydes to amides, as well as ester and carboxylic acid, with NHC-catalysis. The first report of an NHC-dependent selectivity switch of nucleophiles is also described.

We unexpectedly found that diethylamide **3a** was produced in 18% yield when hydrocinnamaldehyde (**1a**) and triethylamine were heated in refluxing toluene in the presence of benzoyl peroxide (BPO), *N*-hydroxyphthalimide (NHPI), and chiral NHC precursor **2a**⁴ (Figure 1 and Table 1, entry 1). Although benzaldehyde failed to undergo amide formation, the reaction proceeded even at room temperature, and produced **3a** in 20% yield when triethylamine was replaced with diethylamine (entry 2). Without NHPI, the yield of **3a** decreased to 7% (entry 3).

These results led us to speculate that the pathway to amide **3a** was as follows (Scheme 1). First, aldehyde **1a** and diethylamine formed enamine, which was then oxidized by BPO to give α -benzoyloxy aldehyde **4**.⁵ Diethylamine may have been produced by the reaction of triethylamine with BPO in entry 1.⁶ The NHC underwent addition to **4** to form Breslow intermediate **5**. Liberation of benzoate followed by tautomerization gave acyltriazolium **6**,^{2k} which was then converted into activated

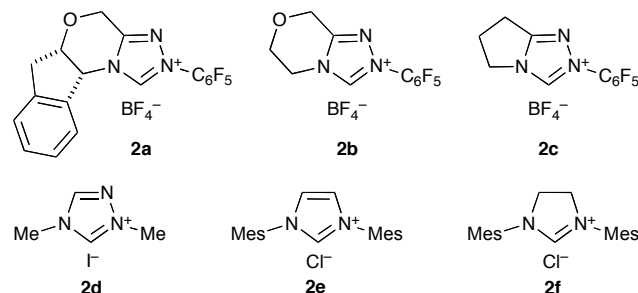


Figure 1. NHC Precursors **2a–f**

Table 1. Survey of Oxidant, Additive, and Catalyst Loading^a

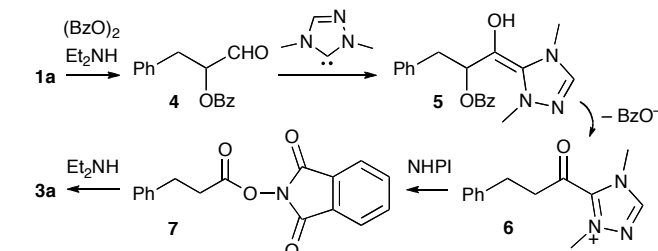
entry	oxidant/equiv	additive	2a mol %	time h	3a % yield
1 ^b	(BzO) ₂ /0.6	NHPI	20	19	18
2	(BzO) ₂ /0.6	NHPI	20	20	20
3	(BzO) ₂ /0.6	-	20	17	7
4	(BzO) ₂ /1	NHPI	20	19	29
5	(BzO) ₂ /1	HOBt	20	18	45
6	(BzO) ₂ /2	HOBt	20	20	55
7	(3-ClC ₆ H ₄ CO ₂) ₂ /2	HOBt	20	20	44
8	NIS/1.3	HOBt	20	10	20
9	NBS/1.3	HOBt	20	7	69
10	NCS/1.3	HOBt	20	6	76
11 ^c	NCS/1.3	HOBt	20	6	96
12 ^c	NCS/1.3	HOBt	10	12.5	92
13 ^c	NCS/1.3	HOBt	5	12.5	88
14 ^c	NCS/1.3	HOBt	2	12.5	79

^a The solvent was toluene in entries 1–7 and CH₂Cl₂ in entries 8–14.

^b Under reflux with Et₃N instead of Et₂NH. ^c With 1.2 equiv Et₃N.

ed ester **7** by NHPI, and the diethylamine underwent acylation to produce amide **3a**. The failed reaction with non-enolizable benzaldehyde is also explained by this enamine-pathway.

Based on this hypothesized pathway, the reaction conditions were optimized. First, the reaction was performed with a stoichiometric amount of BPO, and **3a** was obtained in 29% yield after 19 h (entry 4). The use of 1-hydroxybenzotriazole (HOBt) instead of NHPI made the reaction cleaner, and gave **3a** in 45% yield (entry 5). Although other NHC precursors **2b–f** were tested, less satisfactory results were obtained. Then, the reaction was performed with an increased amount of BPO (2 equiv), and the yield of **3a** slightly improved to 55% (entry 6). No improvement was observed when *m*-chlorobenzoyl peroxide was used in place of BPO, and **3a** was in 44% yield (entry 7). Then, NCS was tested as the oxidant, replacing BPOs. The reaction of **1a** with NCS (1.3 equiv) in dichloromethane produced **3a** in 76% yield (entry 10), though



Scheme 1. Working Hypothesis

NIS and NBS gave less satisfactory results (entries 8 and 9). Finally, when the reaction was conducted with triethylamine (1.2 equiv) to neutralize the hydrogen chloride liberated during the reaction, **3a** was obtained in excellent yield after 6 h (entry 11). When the reaction was quenched after 30 min, **3a** was produced in 32% yield and α -chlorohydrocinnamaldehyde was mainly obtained in 60% yield. The chloroaldehyde and diethylamine were then converted into **3a** in 94% yield after 6 h in the presence of **2a** and triethylamine in dichloromethane at room temperature. These results indicate that the reaction proceed mainly through the α -chlorination of aldehyde followed by NHC-catalyzed acylation of nucleophiles, and not through oxidation of a Breslow intermediate. Thus, the reaction was best performed by pre-mixing **1a** and NCS in the presence of diethylamine before the addition of **2a**, triethylamine, and HOBt, and catalyst loading of **2a** was reducible (2–10 mol %) with only a slight decrease in the product yield (entries 12–14).

Other aldehydes and amines were applied to the reaction (Table 2). Linear aliphatic aldehyde **1b** was a good substrate, and amide **3b** was obtained in 91% yield (entry 2). A siloxy group was compatible with this transformation, and the reaction with aldehyde **1c** provided **3c** in 87% yield using 10 mol % **2a** (entry 3), though the yield was decreased to 56% with 5 mol % **2a**. α -Branched aldehyde was not suitable; the reaction of cyclohexanecarbaldehyde gave the corresponding diethylamide in only 25% yield. The reaction of **1a** and dibenzylamine gave *N,N*-dibenzyl amide **3d** in 49% yield along with *N*-benzyl amide **3e** in 11% yield. The production of **3e** indicates that dibenzylamine was debenzylated by the action of NCS. To avoid the reaction of the amine and NCS, an α -chlorination step was performed using L-proline as a catalyst; a solution of **2a**, triethylamine, HOBt, and dibenzylamine was added to a solution of **1a**, NCS, and L-proline (5 mol %) in dichloromethane pre-mixed for 9 h, and **3d** was obtained in 71% yield (entry 4). The use of L-proline was effective for the reactions of other amines. In the reaction of benzylamine, however, slow addition of the amine over 3 h was important to obtain **3e** in 72% yield (entry 5), and adding

Table 2. NHC-Catalyzed Amidation of Aldehydes with Amines^a

$\text{R}^1\text{CHO} + \text{R}^2\text{R}^3\text{NH} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt}]{\text{NCS 1 equiv, (L-proline 5 mol \%); 2a 5 mol \%, Et}_3\text{N 1.2 equiv, HOBt 0.2 equiv}}$				
entry	1/R ¹	amine ^b R ² , R ³	time/h	3 % yield
1 ^c	1a /Ph(CH ₂) ₂	Et, Et	12.5	3a /88
2	1b /Me(CH ₂) ₅	Et, Et	12	3b /91
3 ^d	1c /TBSO(CH ₂) ₃	Et, Et	9	3c /87
4	1a /Ph(CH ₂) ₂	Bn, Bn	20	3d /71
5 ^e	1a /Ph(CH ₂) ₂	H, Bn	23	3e /72
6 ^f	1a /Ph(CH ₂) ₂	H, OMe	23	3f /81
7 ^f	1a /Ph(CH ₂) ₂	H, $\text{CH}(\text{CO}_2\text{tBu})\text{Bn}$	19	3g /76 ^g

^a Entries 1–3 were conducted without L-proline, while entries 4–7 were conducted with L-proline. ^b Used 2 equiv in entries 1–3 and 1.5 equiv in entries 4–7. ^c From Table 1, entry 13 for comparison. ^d With 10 mol % **2a**. ^e BnNH₂ was added over 3 h. ^f HCl salt of R²R³NH was added instead of free amine. ^g Without racemization.

Table 3. NHC-Dependent Selectivity between Formation of **3a** and **8a**.

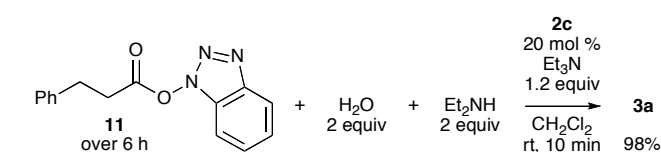
$\text{1a} + \text{Et}_2\text{NH} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt}]{\text{2 20 mol \%, Et}_3\text{N 1.2 equiv, NCS 1.3 equiv, HOBt 0.2 equiv}}$				
entry	2	time/h	3a /% yield	8a /% yield
1 ^a	2a	6	96	0
2	2b	6	67	14
3	2c	6	23–37 ^b	31–38 ^b
4 ^c	2a	7	90	6
5 ^c	2c	6	10	83

^a From Table 1, entry 11 for comparison. ^b Range of three reactions. ^c In the presence of 2 equiv H₂O.

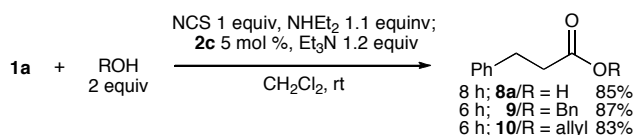
the amine in one portion decreased the yield to 39%. Formation of Weinreb amide efficiently proceeded, and the reaction of **1a** with methoxyamine hydrochloride salt provided **3f** in 81% yield (entry 6). An amino acid was also a good reaction partner; the reaction of **1a** and phenylalanine *tert*-butyl ester hydrochloride salt produced *N*-acyl amino acid **3g** without racemization (entry 7). The reaction rates of the amino acid enantiomers, however, were not significantly different, suggesting that amidation proceeded via an achiral intermediate such as **11** in Scheme 2.

Studies to investigate the best NHC catalyst under the conditions using NCS revealed that **2a** was the best among **2a–f**, and also led to an interesting NHC-dependent selectivity switching of the nucleophilic partner. When the reaction was conducted in the presence of triazolium **2b**, instead of **2a**, along with amide **3a** in 67% yield, carboxylic acid **8a** was obtained in 14% yield (Table 3, entry 2). With triazolium **2c**, **8a** and **3a** were obtained in similar amounts (31–38% and 23–37%, respectively) (entry 3), while complex mixtures were produced using **2d–f**. The varying yields of **3a** and **8a** in the reaction with **2c** indicate that the formation of the carboxylic acid is due to a reaction of intermediate **6** or **7** with exogenous water. Indeed, additional water (2 equiv) increased the yield of the carboxylic acid, and we obtained **8a** in 83% yield and **3a** in 10% yield (entry 5). In contrast, the reaction with NHC derived from **2a** preferentially produced amide **3a** even in the presence of water (entry 4).

In this reaction, amides were likely formed via activated esters **11**, because acylazoliums, such as **6**, react predominantly with water and alcohols over amines,⁷ and indeed, the yield of amide **3a** was poor without NHPI and HOBt (Table 1, entry 3). Recently, activation of O-nucleophiles by hydrogen bonding with NHC was proposed to explain the O-preference of acylazoliums;^{3e,8} thus, a competitive reaction of water and diethylamine with benzotriazolyl ester **11** was conducted in the presence of 20 mol % **2c** (Scheme 2). Although **11** was slowly added over 6 h, no activation of water over amine was observed, and amide **3a** was quantitatively produced. This



Scheme 2. Reaction of Benzotriazolyl Ester **11** with Diethylamine in the Presence of Water and **2c**-derived NHC.



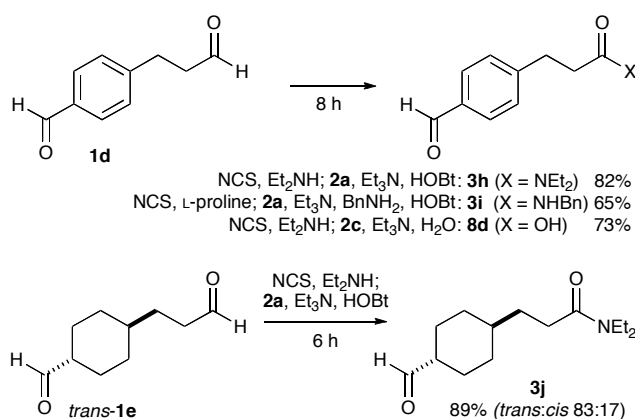
Scheme 3. Reaction of **1a** with O-Nucleophiles.

result also indicates that carboxylic acid **8a** was directly produced by the reaction of acyltriazolium **6** with water.

As expected from the pKa values (HOBt 4.6,⁹ water 15.7), DFT calculations suggested higher stability of an NHC–HOBt hydrogen-bond complex, in which the O–H bond of HOBt was more elongated and thus activated, than an NHC–water complex.¹⁰ The reaction of HOBt was, however, faster than that of water with more bulky **2a**-derived NHC (entry 4), and became slower with less bulky **2c**-derived NHC (entry 5). In contrast to entry 5, using 5 mol % **2c**, **3a** was produced in 43% yield with **8a** in 53% yield. These results are contradictory to the hydrogen-bond activation model, and seem to suggest that a hydrogen bond with NHC is not an important factor of the chemoselectivity of acylazoliums, at least in this reaction, although the choice of the NHC catalyst controls whether acyltriazolium **6** reacts with HOBt or water.

Thus, the reaction of O-nucleophiles was best performed with 1.1 equiv of diethylamine in the absence of HOBt. In the presence of 5 mol % **2c**, carboxylic acid **8a** was obtained in 85% yield without production of amide **3a** (Scheme 3). Alcohols such as benzyl and allyl alcohols were also good nucleophiles, and aldehyde **1a** was converted into the corresponding esters **9** and **10**, respectively, in good yields.

Taking advantage of this reaction, chemoselective conversion of dialdehyde **1d** and **1e** was demonstrated (Scheme 4). With **1d** having both aliphatic and aromatic formyl groups, the reaction with diethylamine and water gave amide **3h** in 82% yield and carboxylic acid **8d** in 73% yield. The reaction of benzylamine also proceeded in a chemoselective manner using proline as a co-catalyst to give α -unbranched amide **3i** in 65% yield and no amidation of the aromatic aldehyde moiety was observed. The reaction of diethylamine and **1e** having both α -branched and α -unbranched aldehyde moieties proceeded selectively at the α -unbranched moiety to provide mono-amide **3j** in 89% yield. Partial isomerization (*trans* only to *trans:cis* 83:17) was observed at the α -position of the



Scheme 4. Chemoselective Conversion of α -Unbranched Aldehyde to Amide and Carboxylic Acid

branched aldehyde moiety in the reaction of **1e**, suggesting reversible enamine formation of the α -branched aldehyde moiety. Therefore, the selectivity is likely due to the slower chlorination of the more hindered enamine.

In summary, we developed a new one-pot transformation of α -unbranched aldehydes to amide, ester, and carboxylic acid with NHC-catalysis. It is advantageous that selective conversion of α -unbranched aldehydes is possible and isolation of unstable α -chloroaldehyde intermediates is unnecessary. The observed NHC-dependent nucleophile-selectivity shows that chemoselectivity can be controlled by the selection of the NHC-catalyst.

We thank financial support by a Grant-in-Aid for Young Scientist (B) from JSPS, Targeted Protein Research Program from JST, and Uehara Memorial Foundation.

Notes and references

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