



# N-Heterocyclic carbene-catalysed amidation of vinyl esters with aromatic amines



Hao Guo, Ying Wang, Guang-Fen Du\*, Bin Dai, Lin He

School of Chemistry and Chemical Engineering, Shihezi University, Xinjiang Uygur Autonomous Region, 832003, PR China

## ARTICLE INFO

### Article history:

Received 13 December 2014  
Received in revised form 16 March 2015  
Accepted 20 March 2015  
Available online 2 April 2015

### Keywords:

N-Heterocyclic carbene  
Amidation  
Vinyl ester  
Amide

## ABSTRACT

A novel amide bond formation reaction was developed via N-heterocyclic carbene (NHC)-catalysed direct amidation of vinyl esters. In the presence of 5.0 mol % NHC catalyst, a variety of aromatic amines undergo acylation reaction with different vinyl esters to produce amides in 51% to quantitative yields.

© 2015 Elsevier Ltd. All rights reserved.

## 1. Introduction

Amides are one of the most important functional groups in natural products, pharmaceutical molecules, and bioactive compounds.<sup>1</sup> Over the past decades, great effort has been devoted for the development of efficient methods for the construction of amide linkages.<sup>2</sup> The direct coupling of carboxylic acids and amines is the most common reaction for amide bond formation.<sup>3</sup> However, the stoichiometric amount of coupling reagents is normally needed to activate carboxylic acids, which leads to the production of stoichiometric waste. Aside from this conventional method, catalytic amidation of esters,<sup>4</sup> dehydrogenation of alcohols and amines,<sup>5</sup> transamidation,<sup>6</sup> and other reactions<sup>7</sup> have also been developed for the synthesis of amides. Despite great progress made in this research, most of the current approaches for the construction of amide bonds still suffer from several disadvantages, such as the usage of transition metals, harsh conditions, and narrow substrate scope. Therefore, the development of environmentally benign and efficient method for the synthesis of amides from readily available substrate is still highly desirable.

Recently, Bode and Rovis independently developed an NHC-catalysed redox-amidation of functional aldehydes, which provides a novel methodology for amide bond formation.<sup>8</sup> However, catalytic to stoichiometric amounts of activating reagents are necessary for the generation of the activated carboxylate. Sarkar and Studer reported<sup>9</sup> an excellent NHC-catalysed oxidative amidation

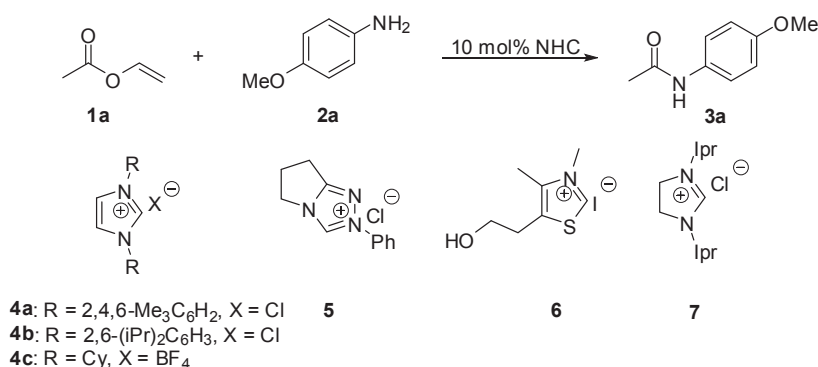
of aldehydes, which provides a facile way of producing amides from simple amines and aldehydes, but stoichiometric amounts of oxidants and co-catalyst are required for those transformations. Surprisingly, compared with NHC-catalysed transesterification reaction,<sup>10</sup> the NHC-promoted amidation of esters is far less examined. To the best of our knowledge, only one example of NHC-catalysed amidation of esters was reported by Movassaghi and Schmidt.<sup>11</sup> Unfortunately, the substrate scope is limited to amino alcohols, and a mechanism study has revealed that the hydroxyl group is necessary for the reaction. General amines are not suitable for these NHC-catalysed amidation reactions. In the course of our study on NHCs catalysis,<sup>12</sup> we decided to explore the NHC-catalysed amidation of esters to construct amide bonds, and herein, we wish to report our preliminary results in this research.

## 2. Results and discussion

Our studies commenced with the amidation reaction of vinyl acetate **1a** and *p*-anisidine **2a** in THF at room temperature. NHC catalysts generated from different precursors and *t*-BuOK favoured the synthesis of the desired amide **3a** but with low efficiency. Fortunately, elevating the temperature to 60 °C efficiently accelerated the transformation (Table 1, entries 1–6). After evaluation of other reaction parameters, including reaction media, base, molar ratio of substrate, and catalyst loading (Table 1, entries 7–17), the optimal reaction conditions were decided as follows: 5.0 mol % IMes and 1.5 equiv aromatic amine at 60 °C in toluene solvent.

With the optimized reaction conditions (Table 1, entry 16), the scope of the reaction was next examined, and the results are

\* Corresponding author. E-mail address: [duguangfen@shzu.edu.cn](mailto:duguangfen@shzu.edu.cn) (G.-F. Du).

**Table 1**  
Optimization of reaction conditions<sup>a</sup>

Entry	NHC	1a:2a	Solvent	T (°C)	t (h)	Yield (%) <sup>b</sup>
1	<b>4a</b> , <sup>t</sup> BuOK	1.5:1	THF	60	40	69 (10) <sup>c</sup>
2	<b>4b</b> , <sup>t</sup> BuOK	1.5:1	THF	60	44	68 (16) <sup>c</sup>
3	<b>4c</b> , <sup>t</sup> BuOK	1.5:1	THF	60	38	67 (17) <sup>c</sup>
4	<b>5</b> , <sup>t</sup> BuOK	1.5:1	THF	60	67	52 (24) <sup>c</sup>
5	<b>6</b> , <sup>t</sup> BuOK	1.5:1	THF	60	83	31 (16) <sup>c</sup>
6	<b>7</b> , <sup>t</sup> BuOK	1.5:1	THF	60	66	53 (39) <sup>c</sup>
7	<b>4a</b> , <sup>t</sup> BuOK	1.5:1	Toluene	60	48	72
8	<b>4a</b> , <sup>t</sup> BuOK	1.5:1	DMF	60	58	29
9	<b>4a</b> , <sup>t</sup> BuOK	1.5:1	CH <sub>3</sub> CN	60	58	53
10	<b>4a</b> , <sup>t</sup> BuOK	1.5:1	DCM	40	58	11
11	<b>4a</b> , <sup>t</sup> BuOK	1.5:1	DCE	60	72	33
12	<b>4a</b> , DBU	1.5:1	Toluene	60	14	54
13	<b>4a</b> , Et <sub>3</sub> N	1.5:1	Toluene	60	14	36
14	<b>4a</b> , K <sub>2</sub> CO <sub>3</sub>	1.5:1	Toluene	60	14	45
15	<b>4a</b> , <sup>t</sup> BuOK	1:1	Toluene	60	14	43
16	<b>4a</b> , <sup>t</sup> BuOK	1:1.5	Toluene	60	14	89
17	<b>4a</b> , <sup>t</sup> BuOK	1:2	Toluene	60	14	88
18 <sup>d</sup>	<b>4a</b> , <sup>t</sup> BuOK	1:1.5	Toluene	60	14	87
19 <sup>e</sup>	<b>4a</b> , <sup>t</sup> BuOK	1:1.5	Toluene	60	14	77
20	5 mol % <b>4a</b>	1:1.5	Toluene	60	14	<10
21	5 mol % <sup>t</sup> BuOK	1:1.5	Toluene	60	14	<10
22	No catalyst	1:1.5	Toluene	60	14	<10

<sup>a</sup> Using 12 mol % NHC precursor and 10 mol % base.<sup>b</sup> Isolated yield.<sup>c</sup> Reaction yield at room temperature.<sup>d</sup> Using 6 mol % NHC precursor and 5 mol % base.<sup>e</sup> Using 1.2 mol % NHC precursor and 1 mol % base.

summarized in Scheme 1. A variety of aromatic amines underwent efficient amidation reaction. Anilines bearing electron-donating groups had higher yields than those with electron-neutral and electron-withdrawing moieties (Scheme 1, 3a–f). In addition, different positions of the substituted groups had limited effect on the reaction yields (Scheme 1, 3g–n). 1-Naphthalenamine and heteroaromatic amine were also acylated smoothly, producing the corresponding amides with 51% and 73% yield, respectively (Scheme 1, 3o and 3p). More interestingly, 4-aminophenol and 2-aminophenol reacted with vinyl acetate to produce the *N*-acylated products with good yields, and no transesterification reaction was observed during these process (Scheme 1, 3q and 3r). However, secondary amines such as *N*-methylaniline and diphenylamine do not undergo the amidation reaction and the substances can be recovered quantitatively (Scheme 1, 3s and 3t). On the other hand, the addition of NHC to alkyl ester is reversible, which restricts the following amidation with amines. Therefore, when methyl or ethyl acetate was used as acetylation reagent for the amidation reaction, no desired amide was obtained under standard conditions (Scheme 1, 3a).

We then examined the scope of vinyl esters. Both aromatic and aliphatic vinyl esters underwent the amidation reaction smoothly to produce the corresponding amides in good to high yields (Scheme 2, 3s–u). Vinyl cinnamate proved to be a good acylation reagent for the amidation of aromatic amines to produce amide 3v

with 84% yield (Scheme 2, 3v). Isopropenyl acetate can also be used as efficient acetylation agent to react with *p*-anisidine 2a, producing amide 1a with 99.6% yield (Scheme 2, 3a). The more active vinyl trifluoroacetate was successfully employed for this process to produce *N*-trifluoroacetylated product 3w and 3x with 98% and 59% yield, respectively (Scheme 2, 3w and 3x).

More interestingly, these NHC-catalysed amidation reactions were scaled up easily while maintaining a high yield (Scheme 3).

Based on the pioneering work<sup>13</sup> of NHC-catalysed transformation of esters,<sup>10,11,14</sup> two possible reaction pathways are outlined in Scheme 4. In path I, NHC functions as a nucleophilic catalyst to undergo irreversible nucleophilic attack with vinyl ester to generate an activated carboxylate A, which might facilitate the subsequent attack of amines and lead to the formation of amide. In the second mechanism (Path II), NHC functions as a Brønsted base to react with amine to form an NHC-amine complex B through hydrogen bond, which might trigger the subsequent nucleophilic attack to produce the desired amide.

We further studied the reaction mechanism by NMR experiments. A 1:1 mixture of vinyl acetate and 3,5-bis(2,6-diisopropylphenyl)imidazol-ylidene (IPr, a stable NHC)<sup>15</sup> was monitored by <sup>1</sup>H NMR and <sup>13</sup>C NMR, respectively, <sup>1</sup>H NMR spectroscopy showed that the characteristic peaks of vinyl acetate (4.56, 4.58, 4.87, 4.90 ppm) disappeared. The <sup>13</sup>C NMR spectroscopy also indicated that the characteristic peaks of vinyl acetate at

Download English Version:

<https://daneshyari.com/en/article/5215006>

Download Persian Version:

<https://daneshyari.com/article/5215006>

[Daneshyari.com](https://daneshyari.com)