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Direct *N*-Acylation of Lactams, Oxazolidinones, and Imidazolidinones with Aldehydes by Shvo's Catalyst

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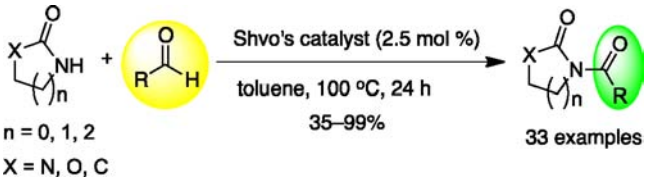
ABSTRACT



Direct *N*-acylation of lactams, oxazolidinones, and imidazolidinones was achieved with aldehydes by Shvo's catalyst without using any other stoichiometric reagent. The *N*-acylations with α,β-unsaturated aldehydes were achieved with excellent yields.

N-Acylated lactams, oxazolidinones, and imidazolidinones are important organic molecules with a wide range of biological activity. They are associated with certain natural products and drugs, such as variotin,[1] aniracetam,[2] piperlotine G,[3] and imidapril.[4] Functionalized chiral oxazolidinones are widely used as chiral auxiliaries and ligands in asymmetric synthesis.[5] A typical method for the *N*-acylation of lactams, oxazolidinones, and imidazolidinones is the usage of acyl chlorides or anhydrides in the presence of a strong base such as *n*BuLi.[6] Recent representative approaches are the *N*-acylation of oxazolidinones with acid fluorides[7] and mild bases, and the copper-catalyzed coupling of aldehydes with free amides using 1.5 equiv of *N*-bromosuccinimide (NBS).[8] These synthetic methods are not environmentally friendly and atom economical, as the reactions require more than stoichiometric amounts of bases and generate halide and/or other wastes.

To develop a more versatile, operatively simple, and environmentally friendly synthetic route to the *N*-acylation of cyclic amides from a readily available source, we envisioned that the acylation could be carried out directly with aldehydes generating hydrogen as the sole byproduct, through generation of a hemiaminal intermediate and dehydrogenation of the hemiaminal by a transition-metal catalyst. Although there have been many reports on amide

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(1) (a) Takeuchi, S.; Yonehara, H.; Umezawa, H. *J. Antibiot*. **1959**, *12*, 195. (b) Sakakiba., M; Matsui, M. *Agric. Biol. Chem*. **1973**, *37*, 911. (c) Ishida, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **1978**, *51*, 2077.

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(9) For representative examples: (a) Yoo, W. J.; Li, C. J. *J. Am. Chem. Soc*. **2006**, *128*, 13064. (b) Seo, S.; Marks, T. J. *Org. Lett*. **2008**, *10*, 317. (c) Muthaiah, S.; Ghosh, S. C.; Jee, J. E.; Chen, C.; Zhang, J.; Hong, S. H. *J. Org. Chem*. **2010**, *75*, 3002. (d) Naota, T.; Murahashi, S. I. *Synlett* **1991**, 693.

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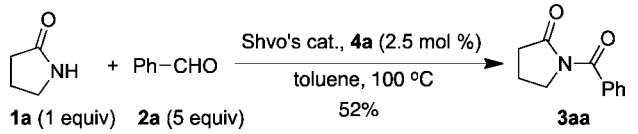
synthesis from amines and aldehydes,[9] the acylation of amides, which have a less nucleophilic N-atom, with aldehydes has not been well studied.

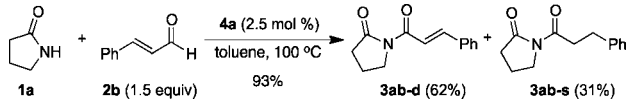
To achieve this goal, several transition-metal complexes known to be active for alcohol dehydrogenation were screened to afford *N*-benzoylpyrrolidone (**3aa**) from a reaction of 2-pyrrolidinone (**1a**) and benzaldehyde (**2a**) (Scheme 1). Among them, Ru-based Shvo's catalyst (**4a**) exhibited activity with a 21% yield of **3aa** when 2.5 mol % of **4a** were used. Other Ru, Ir, or Rh complexes did not exhibit any significant activity (please see the Supporting Information, Table S1). Further optimization attempts to improve the reaction by adding ligands and additives, such as phosphines, bases, and Lewis acids, or by using a different solvent were unsuccessful (Table S1). As we observed benzyl benzoate and benzyl alcohol to be major byproducts, we tried to increase the equivalence of aldehyde. The reaction was improved further to afford 52% of **3aa** when the equivalence of **2a** was increased to 5 equiv (Scheme 1).

Scheme 1. Direct *N*-Acylation of 2-Pyrrolidinone with Benzaldehyde



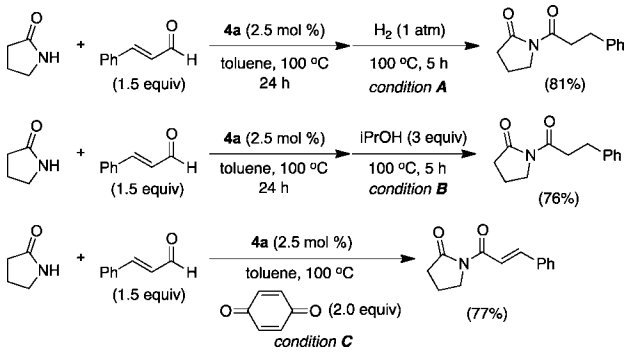
Encouraged by the results, we searched for more activated aldehydes for the direct acylation of **1a**. When cinnamaldehyde (**2b**) was reacted with **1a**, excellent yields for the acylation products (93%, overall yields, Scheme 2) were obtained with 1.5 equiv of **2b**. As hydrogen transfer is involved in the process, concurrent reduction of double bond was observed with the acylation, generating two products, **3ab-d** and **3ab-s**.

Scheme 2. Improved Reactivity of Cinnamaldehyde for *N*-Acylation of 2-Pyrrolidinone



To selectively obtain either **3ab-d** or **3ab-s** as the product, we devised a few conditions (Scheme 3). First, atmospheric pressure of hydrogen gas was applied to the reaction mixture after the acylation reaction (condition **A**). Hydrogenation catalyzed by a ruthenium species proceeded well producing **3ab-s** with a good yield of 81%. Even transfer hydrogenation by adding isopropyl alcohol after the acylation reaction was successful yielding 76% of **3ab-s** (condition **B**). These hydrogenations were carried out in one pot without isolation of **3ab-d**. Next, to obtain **3ab-d** selectively, 1,4-benzoquinone was added as a hydrogen acceptor. With 2 equiv of 1,4-benzoquinone, transfer hydrogenation of the double bond did not occur and only **3ab-d** was formed in 77% yield (condition **C**).

Scheme 3. Selectivity Control by Sequential Hydrogenation or a Hydrogen Acceptor



Due to the success in achieving a facile acylation of 2-pyrrolidinone directly with cinnamaldehyde, the scope of the reaction was investigated (Table 1). Various functional groups including thiophene and furan were tolerated in the reaction. Aliphatic aldehydes and aromatic aldehydes showed lower reactivity than α,β-unsaturated aldehydes. (2*E*,4*E*)-2,4-Hexadienal (**2d**) having a conjugated diene group was a good acylating reagent, and there was no observation of a product with a reduced double bond, in contrast to the cases using **2b** (entries 5, 17, 20, and 23). When α-methyl-*trans*-cinnamaldehyde (**2e**) was used, a significantly lowered yield (20%) of **3ae** was obtained indicating the sensitivity to the steric hindrance of aldehydes. In the case of **3ae** formation, no double bond reduction was observed. From the results in Table 1 (entries 1, 2, 4, 6, 10, and 11), we speculate that the higher reactivity of cinnamaldehyde, compared to aromatic or aliphatic aldehydes, may be due to less steric hindrance. Another reason could be the bis-coordination of olefin and the carbonyl group as proposed in the Yi's report,[10] which would facilitate the coordination of ruthenium to the carbonyl group. In addition, α,β-unsaturated aldehydes such as **2b** and the acylation products such as **2ab-d** could work as hydrogen acceptors to facilitate the reactions. A nootropic ampakine drug, aniracetam (**3ag**),[2] could be synthesized directly from **1a** and **2g** with a moderate yield of 40% (entry 8).

While 2-pyrrolidinone only showed moderate reactivity to both alkyl aldehydes and aromatic aldehydes, 2-azetidinone (**1b**), which has a more nucleophilic N-atom, performed much better (entries 12−18). Good to excellent yields were obtained with aliphatic, aromatic, and α-enals. 2-Azetidinone (β-lactam) derivatives have been widely used as antibiotics.[11] Here, a series of *N*-acylated β-lactam

(10) Kwon, K. H.; Lee, D. W.; Yi, C. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 1692.

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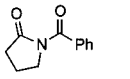
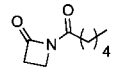
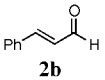
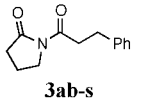
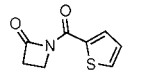
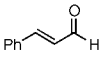
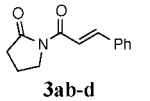
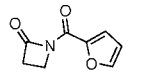
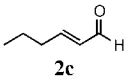
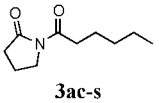
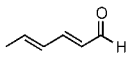
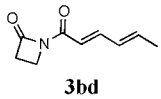
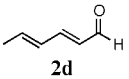
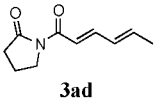
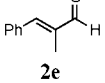
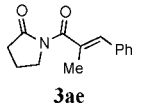
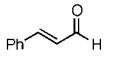
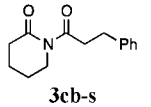
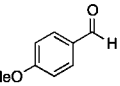
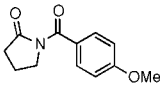
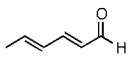
derivatives were successfully synthesized from aldehydes. Even *N*-formylation of **1b** was successful using paraformaldehyde (entry 18).

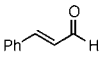
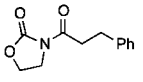
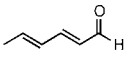
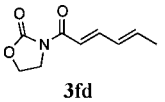
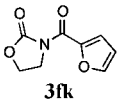
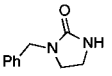
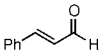
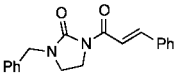
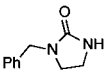
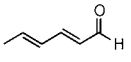
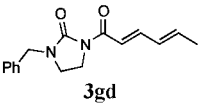
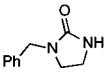
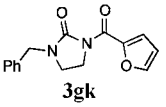
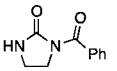
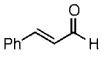
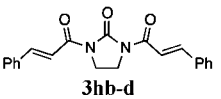
Acylation of six-membered 2-piperidone (**1c**) with **2b** went smoothly (entry 19). A reduced yield of 47% was observed with **2d** (entry 20). With a seven-membered lactam (**1d**), the product yield dropped significantly demonstrating the reaction efficiency was affected by the nucleophilicity of the N-atom of lactams (entry 21). Dihydro-isoindol-1-one (**1e**) also showed comparable reactivity with **1a** (entries 22−25).

Table 1. Direct *N*-Acylation of Lactams with Aldehydes[a]

entry	lactam	aldehyde	product	yield % (cond.)[b]	entry	lactam	aldehyde	product	yield % (cond.)[b]
1	 **1a**	 **2a**	 **3aa**	51[c]	14			 **3bj**	93[c]
2	 **1b**	 **2b**	 **3ab-s**	81[d] (**A**) 76[d] (**B**)	15			 **3bf**	99[c] 69[d]
3	 **1c**	 **2d**	 **3ab-d**	77 (**C**)	16		 **2k**	 **3bk**	96[c] 60[d]
4	 **1d**	 **2c**	 **3ac-s**	92 (**A**)	17			 **3bd**	85
5	 **1e**	 **2e**	 **3ad**	75	18		$HO(CH_2O)_nH$ (**2l**)	 **3bl**	53[e]
6	 **2f**	 **3ae**		20	19	 **1c**		 **3cb-s**	98 (**A**)
7	 **2g**	 **3af**		65[c]	20			**3cd**	47
8	**2h**	**3ag**		40[c]	21	**1d**		**3db-s**	36 (**A**)
9	**2i**	**3ah**		39[c]	22	**1e**		**3eb-d**	80 (**C**)
10	**2j**	**3ai**		55[c]	23			**3ed**	75
11	**1b**	**2b**	**3aj**	49[c]	24			**3ek**	61[c]
12	**2k**	**3ba**		62[d]	25			**3ej**	49[c]
13	**1e**	**2l**	**3bi**	55[d]					

[a] Reaction conditions: Lactam (0.25 mmol, 1.0 equiv), aldehyde (3.0 equiv, unless otherwise noted), **4a** (2.5 mol %), toluene (0.5 mL), 100 °C, 24 h. [b] Yields are of the isolated product, and hydrogenation or hydrogen acceptor conditions applied after the reaction were noted in parentheses. [c] 5.0 equiv of aldehyde were used. [d] 1.5 equiv of aldehyde were used. [e] Reaction was carried out in a sealed tube with 10 equiv of **2l** at 120 °C for 24 h.

Table 2. Direct *N*-Acylation of Oxazolidinones and Imidazolidinones with Aldehydes[a]

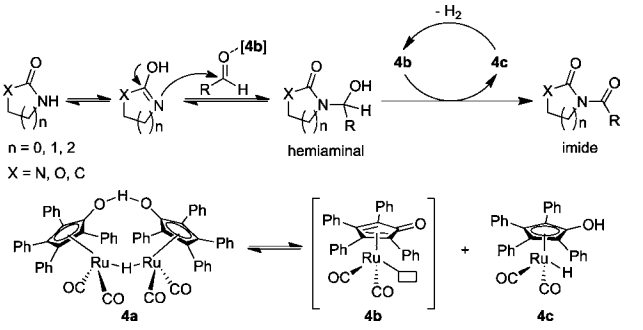
entry	lactam	aldehyde	product	yield % (cond.)[b]
1	 **1f**		 **3fb-s**	77[d] (**A**)
2			 **3fd**	86
3			 **3fk**	51[c]
4	 **1g**		 **3gb-d**	86 (**C**)
5			 **3gd**	61
6			 **3gk**	63[c]
7	 **1h**		 **3ha**	35
8			 **3hb-d**	46[c] (**C**)

[a] Reaction conditions: Heterocycle (0.25 mmol, 1.0 equiv), aldehyde (3.0 equiv, unless otherwise noted), **4a** (2.5 mol %), toluene (0.5 mL), 100 °C, 24 h. [b] Yields are of the isolated product, and hydrogenation or hydrogen acceptor conditions applied after the reaction were noted in parentheses. [c] 5.0 equiv of aldehyde were used. [d] 1.5 equiv of aldehyde was used.

Next, we investigated the *N*-acylation of oxazolidinones and imidazolidinones, which have a wide range of applications in biological and synthetic organic chemistry (Table 2). Recently, Carreira and co-workers reported the *N*-acylation of oxazolidinone derivatives using acid fluorides.[7] Here, *N*-acyl oxazolidinones were successfully synthesized directly from oxazolidinone and aldehydes with moderate to good yields. Interestingly, monosubstituted *N*-benzoyl imidazolidin-2-one (**3ha**) was obtained if imidazolidin-2-one (**1h**) reacted with **2a**, while bis-substituted product **3hb-d** was isolated if **2b** was employed. We attributed this to a solubility difference among the products as well as the reactivity difference between **2a** and **2b**. Compound **3ha** was precipitated out of the toluene solution as the reaction proceeded.

Based on the results and the reported studies on the working mechanism of Shvo's catalyst,[12] a possible mechanism was proposed (Scheme 4). Nucleophilic attack of lactam to the carbonyl functional group of aldehyde, activated by **4b**, could form a hemiaminal, which could be further oxidized by a β-hydride elimination and proton transfer to produce the acylation product and ruthenium species **4c**.[12]

Scheme 4. Proposed Mechanism



In summary, we have demonstrated that operatively simple *N*-acylations of lactams, oxazolidinones, and imidazolidinones could proceed directly with aldehydes by Shvo's catalyst without using any stoichiometric reagent. The *N*-acylations with α,β-unsaturated aldehydes were achieved with excellent yields. This current development is a step forward to realizing the environmentally benign and atom-economical *N*-acylation of amides directly with aldehydes, which has wide applications in organic synthesis.

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Supporting Information Available. Details of experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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