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Advanced Synthesis & Catalysis

Chemoselective, Isomerization-Free Synthesis of *N*-Acylketimines from N–H Imines

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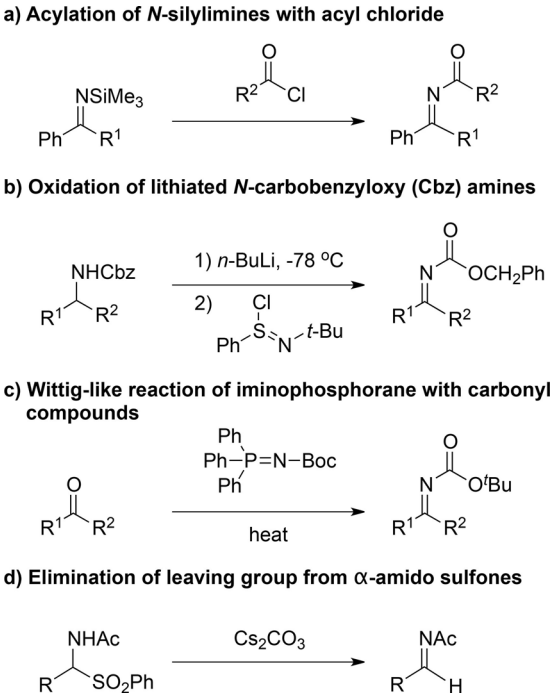
Abstract: *N*-Acylketimines were synthesized through a ruthenium-catalyzed generation of N–H ketimines from secondary azides and subsequent acylation with mixed anhydrides under mild conditions. The synthetic scope was broad to give *N*-acylimines having various functional groups, including those with aliphatic groups that are prone to tautomerization to the corresponding enamides. In addition, various acyl moieties were accommodated. The synthetic utility of this chemoselective imine generation was illustrated by a highly diastereoselective nucleophilic addition of a Grignard reagent to a cyclic *N*-acylimine.

Keywords: acyl alkyl carbonates; acylimines; carbamates; N–H imines; ruthenium

N-Acylimines are pivotal intermediates in organic synthesis, which have electron-withdrawing acyl substituents to overcome the low electrophilicity and limited utility of *N*-alkylamines and *N*-arylamines. *N*-Acylimines have been employed in numerous C–C and C–heteroatom bond forming reactions, including asymmetric arylation,[1] allylation,[2] allenylation,[3] Mannich,[4] and heteroatom addition reactions.[5,6]

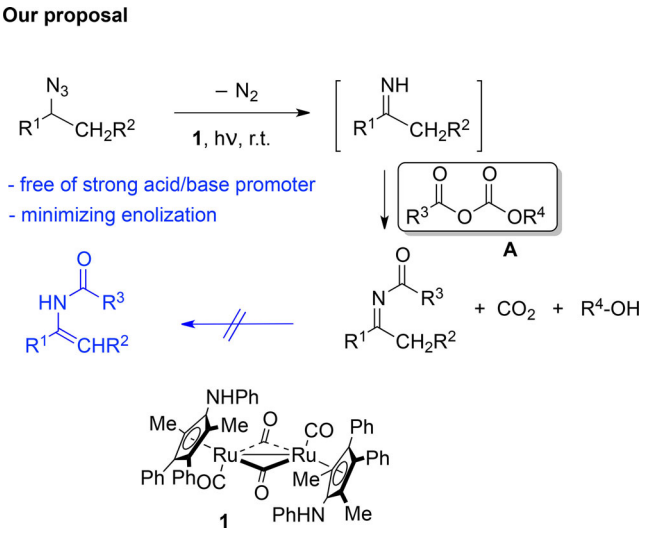
Conventionally, *N*-Acylimines can be formed by the direct condensation of their carbonyl and amide precursors under reversible conditions. Also, they can be prepared by the reaction of *N*-silylimines with acyl chlorides (Scheme 1a),[7] the oxidation of lithiated *N*-carbobenzyloxy (Cbz) amines (Scheme 1b),[8] and a Wittig-like reaction of iminophosphoranes with carbonyl compounds (Scheme 1c).[9] However, *N*-acylimines are known to be too unstable to be stored under ambient conditions. Thus, they are generally prepared *in situ* for the reaction with nucleophiles. Amido derivatives containing a good leaving group at the α-position are proper precursors of *N*-acylimines. Particularly, α-amido sulfones are frequently employed as the precursors due to their relatively easy preparation and high stability (Scheme 1d).[10]

Because of the issues associated with the stability of *N*-acylimines, most of their synthetic methods are effective only for *N*-acyl aldimines possessing no enolizable hydrogens. Other *N*-acylimines including ketimines are hard to be synthesized as a stable entity. For example, the *N*-Cbz ketimines synthesized from lithiated *N*-Cbz-1-phenylethylamine by oxidation tautomerize even at room temperature when they are dissolved in chloroform.[8] Thus, a general synthetic method that gives access to enolizable *N*-acylimines is still elusive in synthetic organic chemistry.



Scheme 1. Conventional synthetic methods for *N*-acylimines.

Based upon our recent reports on the generation of N–H imines from alkyl azides under ruthenium catalysis,[11] we envisioned that acylation of N–H imines may offer a solution to this challenging problem. Our previous attempts to use anhydrides/acid chlorides failed to generate *N*-acylimines, due to the fast isomerization to the corresponding enamides.[12] We reasoned that the use of a mixed anhydride such as **A** (Scheme 2) is more suitable for *N*-acylimine generation because only CO_2 and alcohol are generated as the by-products during the acylation process. Herein, we report the one-pot synthesis of various *N*-acylketimines including enolizable aliphatic ones from the alkyl azides.

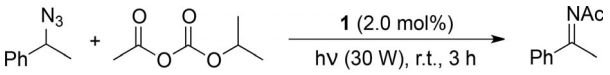


Scheme 2. Synthesis of *N*-acylketimines from secondary azides and acyl alkyl carbonates.

In a preliminary study, the acylation of N–H imine generated from the azide **2a** was examined under various conditions using acetyl isopropyl carbonate **3a** as the mixed anhydride source (Table 1).[13] When an equimolar mixture of **2a** and **3a** was used in THF, the product **4a** was obtained in 72% yield (entry 1). The yield of **4a** was improved substantially by doubling the amount of acetyl isopropyl carbonate (entry 2). Reactions conducted in other solvents afforde significantly reduced yields (entries 3–7). When the amount of the catalyst **1** was halved, the conversion of the reaction was significantly decreased (entry 8).

Then, the substrate scope was investigated under the optimized conditions (Table 2). Aliphatic azides as well as benzylic azides were successfully transformed into the corresponding *N*-acylimines at room temperature by the one-pot procedure. The yield of the substrate having an *ortho*-methyl substituent on the phenyl ring (**4b**) was slightly lower than those of the *meta*- and *para*-derivatives (**4b**–**4d**) probably due

Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent[b]	**3a** (equiv.)[b]	Conv. [%][c]	Yield [%][c]
1	THF	1.0	>99	72
2	THF	1.5	>99	80
3	THF	2.0	>99	96
4	toluene	2.0	>99	88
5	CH_2Cl_2	2.0	>99	87
6	CH_3CN	2.0	63	59
7	acetone	2.0	6	5
8	EtOAc	2.0	30	26
9[d]	THF	2.0	71	64

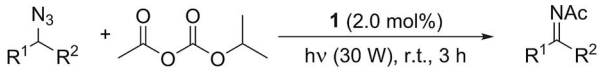
[a] *Typical reaction conditions:* a solution of an azide (0.25 mmol), carbonate (0.50 mmol) and **1** (2.0 mol%) in a solvent (0.50 mL) was illuminated with 30 W fluorescent light. The resulting mixture was stirred for 3 h at room temperature.
[b] THF = tetrahydrofuran.
[c] Estimated by ^{1}H NMR using nitromethane as an internal standard.
[d] 1 mol% of **1** was used.

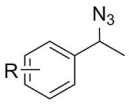
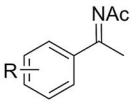
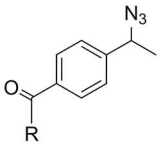
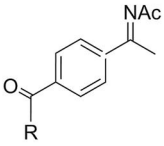
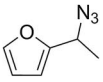
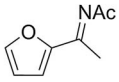
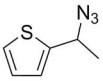
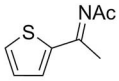
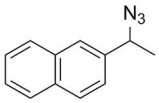
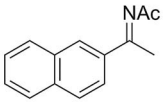
to a steric effect. Various functional groups such as halides (**4e** and **4f**), an ether (**4g**), a thioether (**4h**), esters (**4i**), amides (**4j**), and nitriles (**4k**) were compatible with the reaction conditions. Notably, formyl and acetyl groups (**4l** and **4m**) were compatible with the reaction conditions. Heteroaromatic (**4n** and **4o**) and naphthyl derivatives (**4p**) were also obtained in good yields. The reaction was successfully expanded to the synthesis of imines possessing a longer alkyl group (**4q**) and a benzyl group (**4r**). Our procedure was also effective to prepare benzocyclic derivatives (**4s** and **4t**) as well as aliphatic ones (**4u**–**4w**). 1,2-Azido alcohols were the precursors for the synthesis of α-methoxymethoxy (MOM) *N*-acylimines (**4t**, **4x**–**4z**).

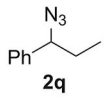
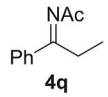
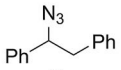
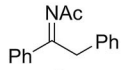
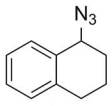
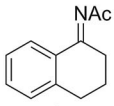
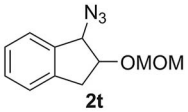
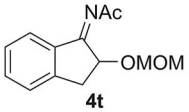
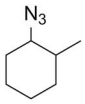
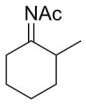
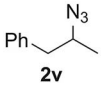
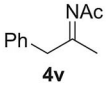
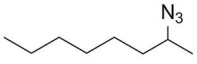
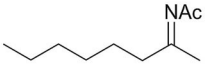
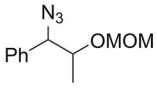
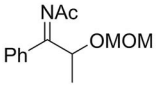
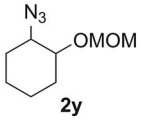
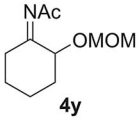
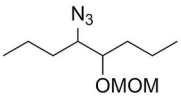
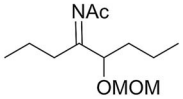
Next, we examined variation of the acyl moiety (Table 3). A methacrylamide (**5a**) and a propiolamide (**5b**) were obtained in high yields in reactions with the corresponding (isopropyl carbonic) anhydrides. Boc-protected keimines (**5c**–**5e**) and Cbz-protected ones (**5f**-**5h**) were formed in reactions with the corresponding dicarbonates. Thus, this reaction was successfully expanded to the synthesis of carbamate derivatives of aliphatic ketimines (**5d**, **5e**, **5g**, and **5h**), which cannot be obtained by the previous condensation methods. Notably, **5d** could be prepared on a gram-scale and purified by silica-gel column chromatography.[14]

Having established the generality of the chemoselective *N*-acylimine synthesis, we investigated the potential utility of this method in the addition reaction. As described in Scheme 3, addition of the anion generated from malonate proceeded nicely to give the corresponding tertiary carbinyl amine **6** in 91% isolat-

Table 2. Synthesis of *N*-acylimines from secondary azides.

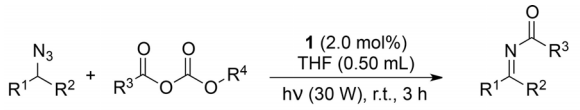


Entry	Azide	Product	Yield [%]
			
1	**2a** (R = H)	**4a**	96
2	**2b** (R = 2-Me)	**4b**	83
3	**2c** (R = 3-Me)	**4c**	93
4	**2d** (R = 4-Me)	**4d**	90
5	**2e** (R = 4-F)	**4e**	91
6	**2f** (R = 4- Br)	**4f**	96
7	**2g** (R = 4-OMe)	**4g**	95
8	**2h** (R = 4-SMe)	**4h**	96
9	**2i** (R = 4-CO_2CH_3)	**4i**	87
10	**2j** (R = 4-NHAc)	**4j**	77
11	**2k** (R = 4-CN)	**4k**	97
			
12	**2l** (R = H)	**4l**	87
13	**2m** (R = Me)	**4m**	84
14	 **2n**	 **4n**	70
15	 **2o**	 **4o**	90
16	 **2p**	 **4p**	> 99

Entry	Azide	Product	Yield [%]
17	 **2q**	 **4q**	92
18	 **2r**	 **4r**	80
19	 **2s**	 **4s**	92
20	 **2t**	 **4t**	98
21	 **2u**	 **4u**	95
22	 **2v**	 **4v**	> 99
23	 **2w**	 **4w**	88
24	 **2x**	 **4x**	91
25	 **2y**	 **4y**	86
26	 **2z**	 **4z**	95

[a] *Typical procedure:* a solution of an azide (0.25 mmol), carbonate (0.50 mmol) and **1** (2.0 mol%) in THF (0.50 mL) was illuminated with 30 W fluorescent light. The resulting mixture was stirred for 3 h at room temperature.
[b] Estimated by ^{1}H NMR using nitromethane as an internal standard.

Table 3. Synthesis of acyl ketimines from various carbonates.



Entry	Azide	Electrophile	Method[a]	Product	Yield [%][b]
1[c]	**2a**	**3b**	A	**5a**	98
2[c]	**2a**	**3c**	B	**5b**	90
3[d,e]	**2a**	**3d**	A	**5c**	95
4[d,e,f]	**2z**	**3d**	B	**5d**	82
5[d,e]	**2u**	**3d**	B	**5e**	83
6[e]	**2a**	**3e**	A	**5f**	90
7[e]	**2z**	**3e**	B	**5g**	90
8[e]	**2u**	**3e**	B	**5h**	99

[a] Method A: a solution of an azide (0.25 mmol), electrophile (0.50 mmol) and **1** (2.0 mol%) in THF (0.50 mL) was illuminated with 30 W fluorescent light. The resulting mixture was stirred for 3 h at room temperature. Method B: a solution of an azide (0.25 mmol) and **1** (2.0 mol%) in THF (0.50 mL) was illuminated with 30 W fluorescent light. After formation of the imine, the electrophile (0.50 mmol) was added. The resulting mixture was stirred for 3 h at room temperature.

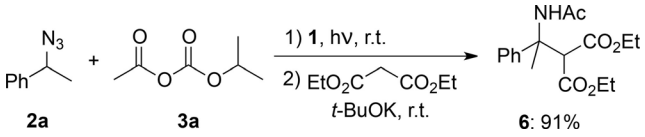
[b] Estimated by ^{1}H NMR using nitromethane as an internal standard.

[c] Reaction was performed in CH_3CN.

[d] Reaction was performed in toluene.

[e] The reaction was carried out at 50 °C.

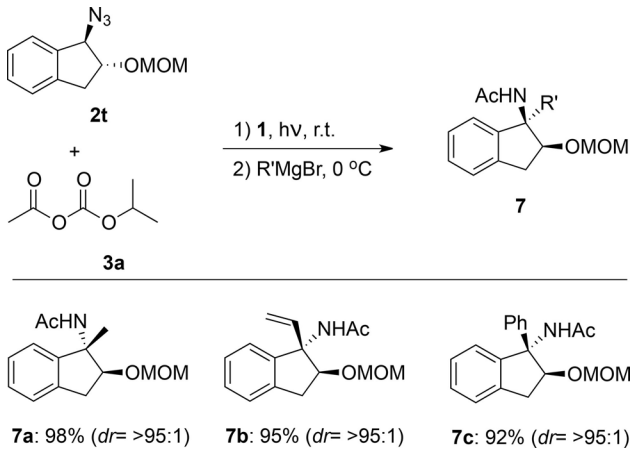
[f] A gram-scale reaction employing 1.0 g (4.7 mmol) of **2z** and 15 mg (1.0 mol%) of **1** in 10 mL of toluene.



Scheme 3. One-pot transformation to a tertiary carbinyl amine.

ed yield.[15] The high yield of this reaction strongly suggests that isomerization under basic conditions is only minimal.

In addition, amides **7a–c** were obtained in high yields with almost perfect diastereoselectivity in the reactions of N–H imine generated from the azide **2t** with MeMgBr, CH_2=CHMgBr, and PhMgBr, respectively (Scheme 4).[16]



Scheme 4. Diastereoselective synthesis of β,β-dibranched amino alcohols.

In conclusion, we have developed a new method for the chemoselective synthesis of *N*-acylketimines which are labile to tautomerization into enamides. The substrate scope was broad, and the variation of the acyl moiety was possible using various electrophiles for N–H ketimines. The utility of the reaction was demonstrated in the nucleophilic addition reactions to give amides containing a stereogenic quaternary carbon center. Currently, we are investigating the asymmetric synthesis of these compounds.

Experimental Section

Representative Procedure for the Synthesis of *N*-Acylimines

In a Schlenk flask, the azide **2z** (0.25 mmol), the ruthenium catalyst **1** (4.9 mg, 2.0 mol%), and dry THF (0.50 mL) were charged under an argon atmosphere. The reaction mixture was stirred at room temperature under 30 W fluorescent

light. The conversion was monitored by TLC. After complete conversion of **2z**, di-*tert*-butyl dicarbonate (0.50 mmol) was added. The reaction mixture was stirred for 3 h at 50 °C, and volatiles were removed under vacuum. The yield of the *N*-acylimine **5d** was 82% according to ^{1}H NMR analysis using nitromethane as an internal standard.

When 1.0 g of **2z** (4.7 mmol) was employed, the crude product was purified by flash column chromatography (hexane:ethyl acetate = 9:1) using deactivated silica gel with 1% triethylamine to afford **5d** as a yellowish oil; isolated yield: 950 mg (71%).

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[14] All our efforts to isolate the *N*-acylimines (by colum chromatography, distillation, recrystalization) failed. However, the *N*-carbamates were more stable. For example, the carbamates could be purified by the column chromatography.

[15] The excess amount of the mixed anhydride **3a** was completely removed under reduced pressure before the addition of the nucleophiles. It should be also noted that the tautomerization of the *N*-acylimines to enamides is very slow, as indicated by the high yield of the reaction.

[16] The other diastereomers were not detected in the ^{1}H NMR spetra of **7a**–**c**. The stereochemistry was assigned on the basis of 2D-NMR analysis: see the Supporting Information.