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[5 + 1] Cycloaddition of *C,N*-Cyclic *N′*-Acyl Azomethine Imines with Isocyanides

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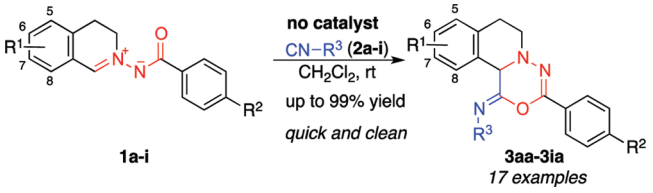
ABSTRACT



A catalyst-free [5 + 1] cycloaddition reaction between isocyanides and *C,N*-cyclic *N′*-acyl azomethine imines as the "isocyanophile" leading to novel heterocycles has been developed. These reactions proceeded quickly and cleanly to afford the corresponding imin-1,3,4-oxadiazin-6-one derivatives in high to excellent yields. A wide range of *C,N*-cyclic *N′*-acyl azomethine imines and isocyanides were applicable to this reaction.

Isocyanides are powerful for constructing polyfunctional molecules with increased molecular diversity for drug discovery and natural product synthesis.[1] Historically, an isocyanide was synthesized by Lieke in 1859 as an allyl isocyanide by alkylation of silver cyanide.[2] These compounds remained laboratory curiosities for decades, as their strong repulsive smell prevented most chemists from working with them. In 1921, a breakthrough with isocyanides was achieved by Passerini to synthesize α-hydroxyamides using aldehydes and carboxylic acids.[3] Forty years later, Ugi developed multicomponent reactions using aldehydes, amines, carboxylic acids, and isocyanides to afford α-amino amides.[4] The Passerini and Ugi reactions are the most important multicomponent reactions in organic and medicinal chemistry.[5] In addition, isocyanides are used as two-electron donating ligands in organometallic chemistry,[6] as well as in oligo- and polymerizations.[7] Furthermore, the most important application of isocyanides is the synthesis of versatile heterocycles,[8] such as in the Barton–Zard and the Leusen pyrrole syntheses,[9a,b] as well as the Fukuyama and Saegusa–Itoh indole syntheses.[9c,d] Zhu and others reported that the reaction of α-isocyanoacetamides with aldehydes or imines led to the corresponding oxazoles, including asymmetric versions.[10] Recently, Chatani and co-workers reported the $GaCl_3$-catalyzed [4 + 1] cycloaddition of α,β-unsaturated carbonyl compounds with isocyanides to afford the corresponding five-membered heterocycles in good to high yields.[11] As far as we know, there are no examples of [5 + 1] cycloadditions of isocyanides to afford the six-membered heterocycles. Herein, we describe the first example of novel six-membered heterocycle construction based on the nucleophilic addition of an isocyanide.

The Passerini and Ugi reactions generally require a carboxylic acid, which activates an aldehyde or imine

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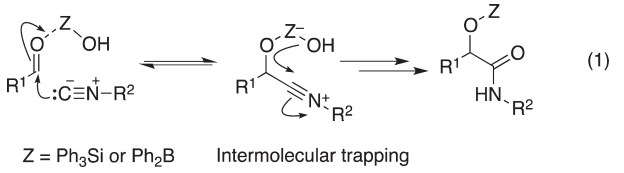
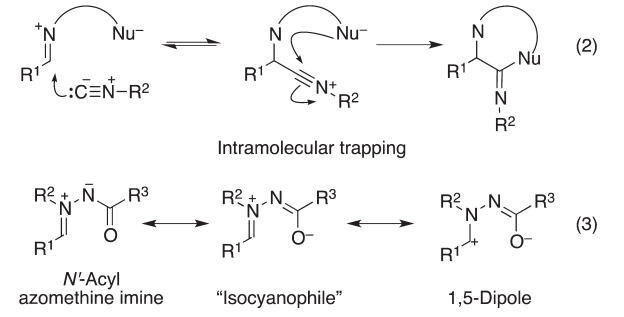
and traps a nitrilium ion to form an acyloxylated intermediate. Subsequent acyl transfer leads to the corresponding α-acyloxy amides or α-amino amides. In our previous studies, silanol or borinic acid acted as a carboxylic acid in the Passerini-type reaction (eq 1).[12]



(1)

In these reactions, a nitrilium intermediate formed from the aldehyde and isocyanide was intermolecularly trapped by the hydroxyl group on the silicon or boron atom to afford the corresponding products. We sought to expand this concept to the intramolecular trapping of the nitrilium intermediate in the Ugi-type reaction. Thus, if a molecule contains both an electrophile (C═N) and a potential nucleophilic group (Nu^-), intramolecular trapping of the nitrilium intermediate could be readily realized relative to the intermolecular version (eq 2).[13] Based on this hypothesis, we chose *N*′-acyl azomethine imine as an "isocyanophile",[14] which is an extended conjugated 1,3-dipole and could function as a "1,5-dipole"[15] to afford the corresponding heterocycles (eq 3).

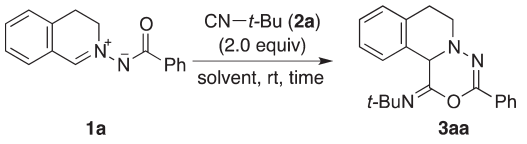


(2)

(3)

At first, we examined whether the *N*′-acyl azomethine imine could act as a 1,5-dipolar equivalent, which can trap an isocyanide as a C1 source to afford the corresponding imin-1,3,4-oxadiazin-6-one derivatives (Table 1).

Table 1. Reaction Conditions for [5 + 1] Cycloaddition Reaction



entry	solvent	time/m	yield / %
1	CH_2Cl_2	10	95
2[a]	CH_2Cl_2	10	85
3[b]	CH_2Cl_2	30	62
4[c]	CH_2Cl_2	180	83
5	$CHCl_3$	15	80
6	AcOEt	30	82
7	THF	30	82
8	MeCN	30	83
9	MeOH	30	85
10	toluene	40	75
11[d]	CH_2Cl_2	10	96
12[e]	CH_2Cl_2	30	70

[a] 30 mol % of $Mg(OTf)_2$ was used. [b] 30 mol % of $Zn(OTf)_2$ was used. [c] Reaction was conducted at −20 °C. [d] Isocyanide **2a** (1.2 equiv) was used. [e] Isocyanide **2a** (1.0 equiv) was used.

Our initial study began using the well-known *C,N*-cyclic *N*′-acyl azomethine imine **1a**[16,17] as a 1,5-dipolar compound as shown in Table 1. To our delight, 2.0 equiv of *tert*-butyl isocyanide (**2a**) cleanly reacted with the *N*′-acyl azomethine imine **1a** in dichloromethane at room temperature to afford the corresponding iminoxadiazinone derivative **3aa** in 95% yield (entry 1). Surprisingly, we found that the reaction proceeded very quickly, and **1a** was consumed within 10 min at room temperature. In this reaction, activation by some Lewis acids did not appear to be significant, i.e., the reaction of the azomethine imine **1a** and the isocyanide **2a** in the presence of $Mg(OTf)_2$ or $Zn(OTf)_2$ gave the product in 85% or 62% yield, respectively (entries 2 and 3). When the reaction was conducted at −20 °C, it was complete within 180 min to afford **3aa** in 83% yield (entry 4). This reaction proceeded smoothly in

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(14) "Isocyanophile" is herein defined as a substrate which is subject to nucleophilic attack of an isocyanide.

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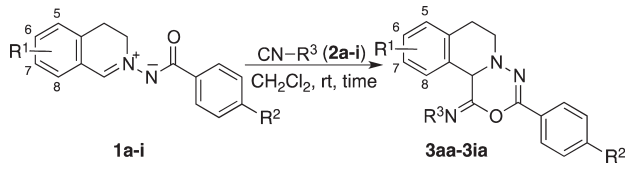
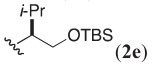
(16) (a) Hashimoto, T.; Omote, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 8952–8955. (b) Hashimoto, T.; Omote, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3489–3492. (c) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 4076–4077.

(17) We have already revealed that **1a** functions as an electrophile toward cyanide ion in the Strecker-type reaction. Sakai, T.; Soeta, T.; Inomata, K.; Ukaji, Y. *Bull. Chem. Soc. Jpn.* **2012**, *85*, 231–235.

Table 2. Scope of Isocyanides and Azomethine Imines



entry[a,b]	R^1	R^3	time	yield / %
1	H (**1a**)	*t*-Bu (**2a**)	10 m	96 (**3aa**)
2	H (**1a**)	*t*-Oct (**2b**)	16 h	95 (**3ab**)
3	H (**1a**)	*c*-Hex (**2c**)	30 m	99 (**3ac**)
4	H (**1a**)	Bn (**2d**)	25 m	99 (**3ad**)
5	H (**1a**)	 (**2e**)	30 m	85 (**3ae**)
6	H (**1a**)	Ph (**2f**)	22 h	69 (**3af**)
7	H (**1a**)	4-$MeOC_6H_4$ (**2g**)	50 m	87 (**3ag**)
8	H (**1a**)	4-BrC_6H_4 (**2h**)	50 m	89 (**3ah**)
9	H (**1a**)	4-$O_2NC_6H_4$ (**2i**)	77 h	79 (**3ai**)
10	5-Me (**1b**)	*t*-Bu (**2a**)	30 m	85 (**3ba**)
11	6-Me (**1c**)	*t*-Bu (**2a**)	40 m	56 (**3ca**)
12	7-Me (**1d**)	*t*-Bu (**2a**)	30 m	92 (**3da**)
13	8-Me (**1e**)	*t*-Bu (**2a**)	180 m	34 (**3ea**)
14	6-MeO (**1f**)	*t*-Bu (**2a**)	70 m	87 (**3fa**)
15	7-Cl (**1g**)	*t*-Bu (**2a**)	210 m	96 (**3ga**)
16[c]	H (**1h**)	*t*-Bu (**2a**)	10 m	94 (**3ha**)
17[d]	H (**1i**)	*t*-Bu (**2a**)	10 m	64 (**3ia**)

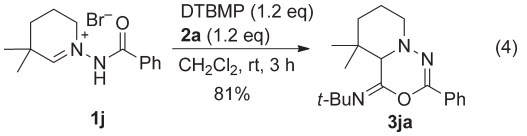
[a] 1.5 equiv of **1a** and 1.0 equiv of **2b**−**i** were used (entries 2−9) and 1.0 equiv of **1a**−**i** and 1.2 equiv of **2a** were used (entries 1, 10−17). [b] R^2 = H otherwise mentioned. [c] R^2 = Me. [d] R^2 = Cl.

polar, cyclic ether and protic solvents to afford **3aa** in high yields (entries 1, 5−9). The reactivity was slightly less when toluene was used as a solvent likely due to the solubility of the substrate **1a** (entry 10). We have found that 1.2 equiv of isocyanide was enough to afford the product in high yield (entry 11), although fewer equivalents of isocyanide (1.0 equiv) were also applicable to this reaction (entry 12).

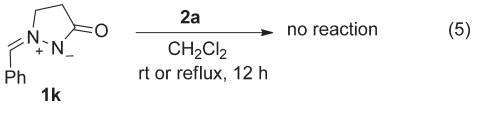
We then examined the scope of isocyanides and azomethine imines applicable to the present [5 + 1] cyclization reaction as shown in Table 2. For the scope of isocyanides, the optimal amounts of the azomethine imine **1a** (1.5 equiv) and isocyanides **2a**−**i** (1.0 equiv) were used in dichloromethane because it was difficult to separate the products and unreacted isocyanides (entries 2−9). From these results, we found that the conditions were applicable to a wide variety of isocyanides. Most of the reactions were complete within 1 h. The reaction of the aliphatic isocyanides (R^3 = *t*-Bu, *t*-Oct, *c*-Hex, and Bn) with **1a** gave the iminoxadiazinone derivatives in high yields (entries 1−4). The azomethine imine **1a** was consumed in 16 h when *tert*-octyl isocyanide (**2b**) was used, giving **3ab** in 95% yield (entry 2). In the case of cyclohexyl isocyanide (**2c**) and benzyl isocyanide (**2d**), reactivities were higher to afford the products in 99% yields (entries 3 and 4). The chiral isocyanide **2e**, which was prepared from the corresponding amino acid, gave the product in 85% yield; however, no chiral induction was observed (entry 5). Phenyl isocyanide (**2f**) and aromatic isocyanides bearing electron-withdrawing or -donating groups at the *para* position also afforded the corresponding heterocycles in high yields, although the reactivities were lower than for the aliphatic isocyanides (entries 6−9).

The reactivity toward various azomethine imines using *tert*-butyl isocyanide (**2a**) was next examined by treatment of 1.0 equiv of azomethine imines **1a**−**i** and 1.2 equiv of **2a**. Regarding the substitution pattern of the *C,N*-cyclic *N*′-acyl azomethine imines, the 5-, 6-, and 7-methyl substituents were all tolerated, furnishing the corresponding heterocycles (entries 10−12). The only exception was the incorporation of the 8-methyl substituent wherein the reaction was very sluggish (entry 13). The *C,N*-cyclic azomethine imine **1f** having an electron-donating group was utilized as well (entry 14). In addition, the *C,N*-cyclic azomethine imine **1g** with an electron-withdrawing group on the aromatic ring reacted slowly to afford the product **3ga** in 96% yield (entry 15). The influence of the substituent of the benzoyl group on the nitrogen was also examined. We found that a methyl group on the aromatic moiety was more effective than a chloride to afford the products in 94% and 64% yields, respectively (entries 16 and 17). From these results, it was determined that the electron density of the *N*′-acyl moiety played an important role in trapping the nitrilium intermediate for the cyclization.

This study prompted us to examine structurally distinct azomethine imines. The reaction of a *C,N*-cyclic azomethine imine not fused to the aromatic ring, which was generated in situ from **1j** in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as a base,[16c] was conducted with *tert*-butyl isocyanide (**2a**) to afford the product **3ja** in 81% yield (eq 4). On the other hand, a *N,N*′-cyclized azomethine imine **1k**, which geometrically could not afford the iminoxadiazinone derivatives, did not react with *tert*-butyl isocyanide (**2a**) even under dichloromethane reflux conditions (eq 5). These results suggested that the direction of the amidocarbonyl oxygen was crucial to promote the nucleophilic addition of isocyanide.



(4)



(5)

In conclusion, we have developed the catalyst-free [5 + 1] cycloaddition reaction of isocyanides and *C,N*-cyclic *N*′-acyl azomethine imines as an "isocyanophile". These reactions proceeded quickly and cleanly to afford the imin-1,3,4-oxadiazin-6-one derivatives in high yields. A wide range of *C,N*-cyclic *N*′-acyl azomethine imines and isocyanides were applicable to this reaction.

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Supporting Information Available. 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.