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[3 + 3]-Cycloaddition Reactions of α-Acidic Isocyanides with 1,3-Dipolar Azomethine Imines

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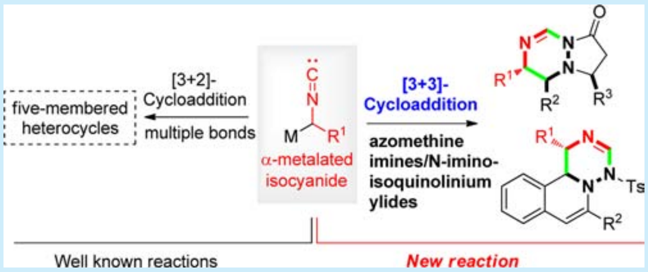
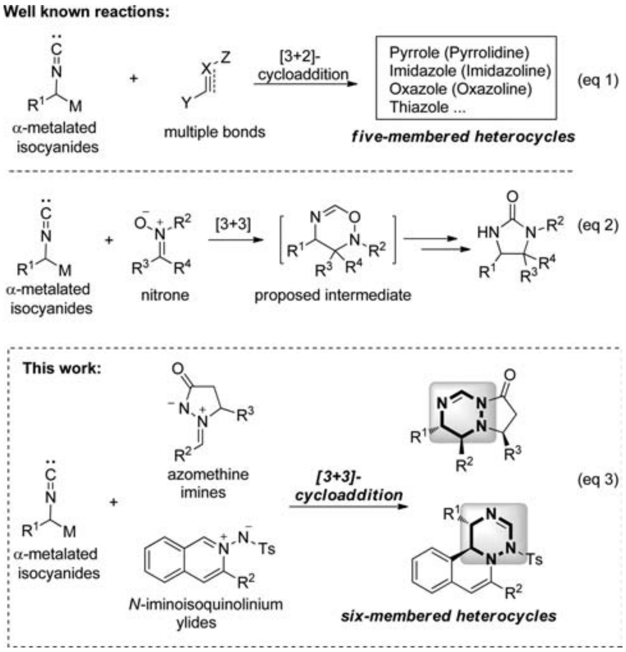
S Supporting Information

ABSTRACT: α-Acidic isocyanides are versatile reagents in organic synthesis, especially for the synthesis of five-membered heterocycles via [3 + 2]-cycloaddition reactions with activated multiple bonds. In this communication, the first [3 + 3]-cross-cycloaddition of α-acidic isocyanides with 1,3-dipolar azomethine imines to generate a series of 1,2,4-triazine derivatives with significant regiochemical control under mild catalytic reaction conditions is described. This new strategy shows that α-acidic isocyanides can also be taken as potent reagents for the synthesis of six-membered heterocycles through [3 + 3]-cross-cycloaddition reactions with 1,3-dipoles.



Synthesis of heterocycles based on α-acidic isocyanides, discovered by Schöllkopf in 1968,[1] has become very popular due to the diverse array of α-metalated isocyanides (a nucleophilic α-carbanion and a divalent isocyanide carbon).[2] Among numerous methods developed, the particularly powerful transformation is the [3 + 2]-cycloaddition reaction of α-metalated isocyanides with activated multiple bonds to produce a wide range of five-membered heterocycles (Scheme 1, eq 1),[2] such as pyrrole,[3] pyrroline,[4] oxazole,[5] oxazoline,[6] imidazole,[7] imidazoline,[8] and thiazole derivatives, etc.[9] For comparison, however, there has been no evidence for the [3 + 3]-cycloaddition reaction on the basis of α-metalated isocyanides,[1−11] although a formal [3 + 3]-cycloaddition intermediate, 3,4-dihydro-2*H*-1,2,5-oxadiazine, has been proposed for the reaction of α-metalated isocyanides with nitrones to produce five-membered 2-imidazolidinones (Scheme 1, eq 2).[2b]

Scheme 1. Cycloaddition Reactions of α-Acidic Isocyanides



In principle, α-metalated isocyanides are ambivalent reagents because both contain nucleophilic and electrophilic centers.[1−11] Consequently, we envisioned that the [3 + 3]-cycloaddition reaction of α-acidic isocyanides with certain 1,3-dipoles should happen to form six-membered heterocycles. As part of our ongoing interest in developing cycloaddition reactions based on α-acidic isocyanides,[12] we present herein the first example of [3 + 3]-cycloaddition reactions based on α-acidic isocyanides, including CuI-catalyzed [3 + 3]-cross-cycloaddition of α-acidic isocyanides with azomethine imines and the AgOTf-catalyzed one-pot [3 + 3]-cycloaddition of ethyl isocyanoacetate with *N*-iminoisoquinolinium ylides, generated in situ from (*E*)-*N*′-(2-alkynylbenzylidene)-4-methylbenzenesulfonohydrazides, to deliver di- and tricyclic 1,2,4-triazine compounds (Scheme 1, eq 3).[13,14] Triazine derivatives have been identified as pharmacologically important heterocycles with diverse biological activities,[13a−d] found in natural products,[13e,f] and applied in organic synthesis.[13g−j]

In the present research, the [3 + 3]-cycloaddition of (*Z*)-2-benzylidene-5-oxopyrazolidin-2-ium-1-ide **1a**[14] and ethyl isocyanoacetate **2a** was employed to screen the reaction conditions. It was found that, catalyzed by CuI (20 mol %) and in the presence of DBU (DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene, 20 mol %) in ethanol at room temperature for 0.5

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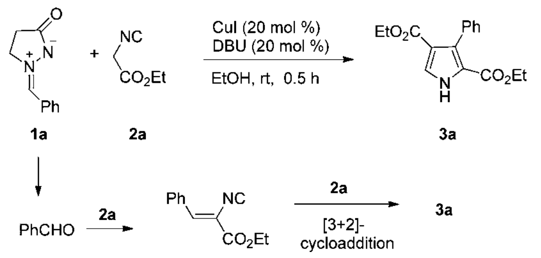
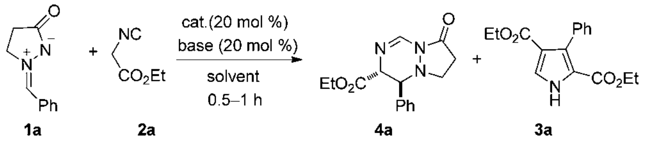
h, only a pyrrole product, diethyl 3-phenyl-1*H*-pyrrole-2,4-dicarboxylate **3a**, instead of the desired [3 + 3]-cycloaddition product, was obtained in 42% yield from the reaction of the azomethine imine **1a** (0.3 mmol) and ethyl isocyanoacetate **2a** (1.2 equiv) (Scheme 2 and Table 1, entry 1). This result indicates that, under basic conditions in protic solvents, solvolysis of **1a** may occur to give benzaldehyde, which condensed with **2a** followed by stepwise [3 + 2]-cycloaddition with **2a** to give **3a**.[15]

Scheme 2. Reaction of 1a with 2a in Ethanol



Under identical conditions as above but using aprotic reaction media, the yields of pyrrole **3a** were substantially reduced. In these cases, the desired [3 + 3]-cross-cycloaddition product, pyrazolo[1,2-*a*][1,2,4]triazine-3-carboxylate **4a**, could be obtained in low to fair yields (Table 1, entries 2–5). Optimization of the reaction conditions could lead to **4a** in 72% isolated yield at room temperature within 1 h when chloroform was selected as the solvent (entry 6). For comparison, CuCl (entry 7), CuBr (entry 8), $Cu(OAc)_2$ (entry 9), $CuBr_2$ (entry 10), Ag_2CO_3 (entry 11), AgOAc (entry 12), and AgOTf (entry 13) were less effective catalysts than CuI. For the bases tested, DBU was the best choice (entry 6 versus entries 14–17) applied in the present research. In addition, it was found that lower product yields of 1,2,4-triazine **4a** were obtained by lowing CuI or DBU loadings (entries 18 and 19). In the absence of CuI (entry 20), no **4a** was detected, showing the importance of CuI for the formation of 1,2,4-triazines **4**.

Table 1. Screening of Reaction Conditions[a]

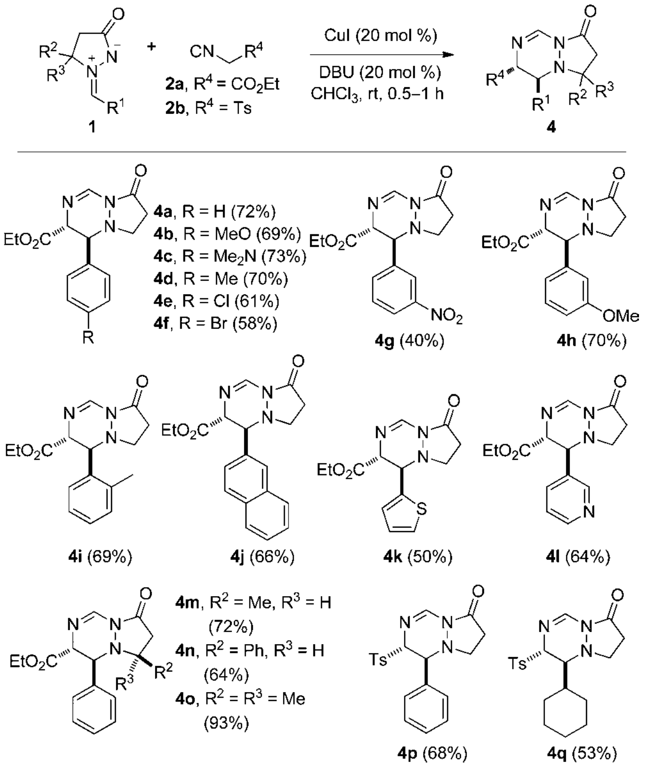


entry	catalyst	base	solvent	yield (%)[b] 4a	3a
1	CuI	DBU	EtOH		42
2	CuI	DBU	CH_2Cl_2	47	12
3	CuI	DBU	DCE	48	14
4	CuI	DBU	CH_3CN	23	10
5	CuI	DBU	THF	45	35
6	***CuI***	***DBU***	***$CHCl_3$***	***72***	***11***
7	CuCl	DBU	$CHCl_3$	41	15
8	CuBr	DBU	$CHCl_3$	64	15
9	$Cu(OAc)_2$	DBU	$CHCl_3$	68	7
10	$CuBr_2$	DBU	$CHCl_3$	38	5
11	Ag_2CO_3	DBU	$CHCl_3$	47	14
12	AgOAc	DBU	$CHCl_3$	49	24
13	AgOTf	DBU	$CHCl_3$	67	
14	CuI	Et_3N	$CHCl_3$		21
15	CuI	Cs_2CO_3	$CHCl_3$	57	12
16	CuI	NaOH	$CHCl_3$	21	11
17	CuI	*t*-BuOK	$CHCl_3$	42	11
18[c]	CuI	DBU	$CHCl_3$	65	12
19[d]	CuI	DBU	$CHCl_3$	64	13
20		DBU	$CHCl_3$		5

[a] Reactions were carried out with **1a** (0.3 mmol) and **2a** (0.36 mmol) in solvent (3 mL) at room temperature. [b] Isolated yields. [c] CuI (10 mol %) was used. [d] DBU (10 mol %) was used.

Under optimal conditions (Table 1, entry 6), a series of experiments were performed, and the results are summarized in Scheme 3. According to the experimental results, a series of pyrazolo[1,2-*a*][1,2,4]triazin-8(4*H*)-ones **4a–o** were obtained in good to high yields under extremely mild conditions within 1 h by the reactions of ethyl isocyanoacetate **2a** with a wide range of azomethine imines **1** bearing various R^1 groups, such as *para*- (**4a–f**), *meta*- (**4g** and **4h**), and *ortho*-substituted aryl groups (**4i**), 2-naphthalenyl (**4j**), and heteroaryl groups (**4k** and **4l**). In addition, 1,2,4-triazine derivatives (**4m–o**) were also prepared in high yields from the reactions of **2a** with azomethine imines **1** bearing varied R^2 and R^3 substituents. Furthermore, it was proved that tosylmethylisocyanide **2b** could also react well with **1** having an aryl or an alkyl group to give the desired [3 + 3] products (**4p** and **4q**) under identical conditions. For comparison, 1-(isocyanomethyl)-4-nitrobenzene **2c** was not reactive for the [3 + 3]-cycloaddition due to, probably, the steric hindrance of the bulky 4-nitrophenyl group.

Scheme 3. Synthesis of Pyrazolo[1,2-*a*][1,2,4]triazin-8(4*H*)-one 4[a,b]

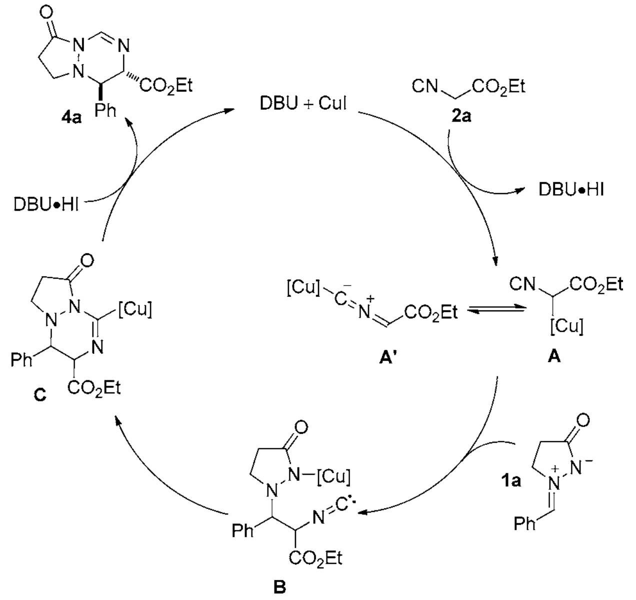


[a] Reactions were carried out with **1a** (0.3 mmol), **2a** (0.36 mmol), CuI (20 mol %), and DBU (20 mol %) in $CHCl_3$ (3 mL) at room temperature. [b] Isolated yields.

The above reactions are stereospecific with two substituents at 3- and 4-positions of **4** being *trans* to each other according to the ^{1}H and ^{13}C NMR spectra of **4a**−**4q**. The structure was further confirmed by the X-ray single-crystal analysis of **4q**,[16] and the relative configurations of **4m** and **4n** were determined by NOE experiments (see Supporting Information).

On the basis of the above experimental results (Table 1 and Scheme 3) and related reports,[2b,3d,e,4,12,13,17] a possible mechanism for the [3 + 3]-cycloaddition of α-metalated isocyanides **2** with azomethine imines **1** is proposed (Scheme 4, with the reaction of isocyanoacetate **2a** with imine **1a** as an example). The reaction starts with the formation of α-cuprioisocyanide **A** or its tautomer **A′** from isocyanoacetate **2a** in the presence of CuI and DBU.[3d,e,4] Then, the nucleophilic addition of α-cuprioisocyanide **A** on the imine **1a** takes place to form intermediate **B**. Insertion of isonitrile into the N−Cu bond generates the imidoyl−copper intermediate **C**[3e,18] followed by protonation to give 1,2,4-triazine **4a** with regeneration of the catalysts, CuI and DBU, for the next catalytic cycle (Scheme 4).

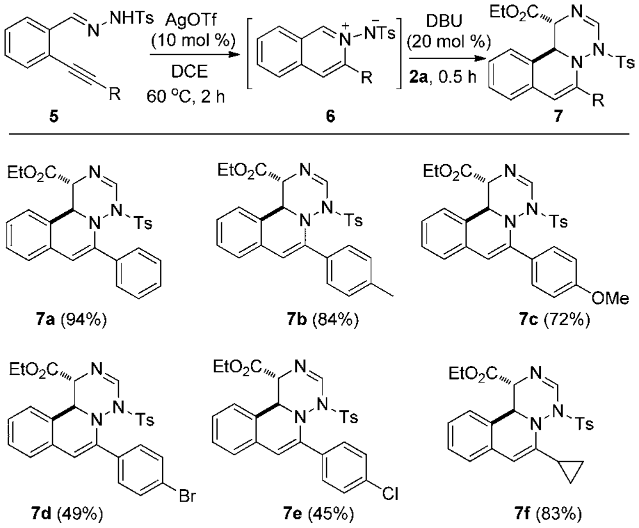
Scheme 4. Proposed Mechanism for Formation of 4



The [3 + 3]-cycloaddition of α-acidic isocyanides with 1,3-dipoles described above represents a simple and efficient protocol for the direct synthesis of the six-membered heterocycles, [1,2,4]triazine derivatives **4**.[13,14] Encouraged by the successful application of α-acidic isocyanides **2** in the [3 + 3]-cross-cycloaddition with azomethine imines **1**, next, we examined the one-pot reaction of ethyl isocyanoacetate **2a** with (*E*)-*N*′-(2-alkynylbenzylidene)-4-methylbenzenesulfonohydrazides **5** as the precursors of *N*-iminoisoquinolinium ylides **6** (Scheme 5).[19] Fortunately, [1,2,4]triazino[6,1-*a*]isoquinoline **7a** was obtained in 94% isolated yield when *N*′-(2-alkynylbenzylidene)hydrazide **5a** was treated with AgOTf (10 mol %) in DCE (DCE = 1,2-dichloroethane) at 60 °C for 2 h followed by the addition of **2a** and DBU (20 mol %). It was found that product **7a** could not be detected for the above reaction if AgOTf was replaced by CuI probably because CuI was not a suitable catalyst for the generation of *N*-iminoisoquinolinium ylides **6** via the 6-*endo* cyclization of **5**.[19c]

The scope of the one-pot intramolecular cyclization/[3 + 3]-cycloaddition reaction was then investigated using selected *N*′-(2-alkynylbenzylidene)hydrazides **5** under the above AgOTf-catalyzed conditions. As a result, the desired products, [1,2,4]triazino[6,1-*a*]isoquinolines **7**, bearing electron-rich (**7b** and **7c**) and electron-poor aryl groups (**7d** and **7e**) and an alkyl group (**7f**), were prepared, respectively, in good to high yields. The reaction of ethyl isocyanoacetate **2a** with *N*′-(2-alkynylbenzylidene)hydrazides **5** proceeds in a highly chemo- and stereoselective manner. In the above reactions, no other diastereomers could be detected by NMR spectra. The structure of product **7a** was confirmed by the X-ray single-crystal analysis.[16]

Scheme 5. One-Pot Synthesis of [1,2,4]Triazino[6,1-*a*]isoquinolines 7[a,b]



[a]Reactions were carried out with **5** (0.3 mmol) and AgOTf (10 mol %) in DCE (3 mL) at 60 °C for 2 h, then **2a** (0.36 mmol) and DBU (20 mol %) were added. [b]Isolated yields.

In summary, we have developed a new transformation of α-acidic isocyanides. In the presence of a catalytic amount of copper salt, the [3 + 3]-cross-cycloaddition reaction of α-acidic isocyanides with 1,3-dipolar azomethine imines proceeded smoothly at ambient conditions within 1 h. This new transformation was further expanded by a silver-catalyzed one-pot *N*-iminoisoquinolinium ylide formation and subsequent [3 + 3]-cycloaddition cascade. The reaction features rapidity, mild reaction conditions, broad substrate scope, and high regio- and diastereoselectivity and provides a straightforward and general method for the synthesis of a variety of 1,2,4-triazine derivatives from readily available starting materials. We expect this isocyanide [3 + 3]-cross-cycloaddition to complement the existing [3 + 2] protocol and to gain broad applications in the preparation of six-membered heterocycles.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all compounds and X-ray data of **4q** and **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) CCDC 993320 (**4q**) and CCDC 997894 (**7a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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