



COMMUNICATION

WILEY-VCH

Silver-Induced [3+2] Cycloaddition of Isocyanides with Acyl Chlorides: Regioselective Synthesis of 2,5-Disubstituted Oxazoles

Jian-Quan Liu,^[a,b] Xuanyu Shen,^[a] Andrey Shatskiy,^[b] Enlong Zhou,^[c]* Markus D. Kärkäs,^[b]* Xiang-Shan Wang^[a]*

Abstract: A silver-mediated cycloaddition of isocyanides with acyl chlorides has been developed. This transition metal-catalyzed strategy provides an effective and scalable approach for the formation of 2,5-disubstituted oxazoles in good to high yields. The employed silver-based MOF catalyst can be efficiently recycled without compromising the yield.

Isocyanides are versatile starting materials and have been widely applied in the synthesis of nitrogen-containing motifs.^[1,2] Among the reported manifolds, the [3+2] dipolar cycloaddition reactions constitute an appealing route for construction of *N*-heterocyclic skeletons.^[3] However, most of these protocols are associated with poor regioselectivity (Figure 1a).^[4] Thus, altering the reaction conditions to selectively favor formation of one regioisomer is an ongoing challenge in isocyanide chemistry.

The cycloaddition reaction of isocyanides with acyl chlorides is well established and has been widely investigated to generate 4,5-disubstituted oxazoles (Figure 1b).^[5,6] In 2009, El Kaïm and coworkers reported the regioselective cycloaddition to furnish 2,5-disubstituted oxazoles. The reaction was presumed to proceed via the corresponding imidoyl chloride,^[7] which in the presence of 2,6-lutidine could cyclize to give the corresponding cycloaddition adduct (Figure 1c).^[8] In terms of the scope, the protocol is generally limited to benzyl isocyanides, and a catalytic protocol remains elusive. Herein, we disclose a practical silver-mediated cycloaddition between a wide array of isocyanides and acyl chlorides (Figure 1d).

Metal-organic frameworks (MOFs) are assembled from metal ions or clusters coordinated with multidentate organic ligands.^[9] Owing to their high surface area, tunable porosity, and versatile architecture, MOFs can act as templates or hosts to

[a]	Dr. JQ. Liu, X. Shen, Prof. XS. Wang
	School of Chemistry and Chemical Engineering, Jiangsu Key
	Laboratory of Green Synthesis for Functional Materials, Jiangsu
	Normal University
	Xuzhou Jiangsu 221116, P. R China
	E-mail: xswang1974@yahoo.com
[b]	Dr. JQ. Liu, Dr. A. Shatskiy, Dr. M. D. Kärkäs
	Department of Chemistry, Organic Chemistry, KTH Royal Institute of
	Technology, SE-100 44 Stockholm, Sweden
	E-mail: karkas@kth.se
[c]	Prof. E. Zhou
	College of Chemistry and Material Science, Shandong Agricultural
	University
	Taian, Shandong 271000, P. R. China
	E-mail: iamelzhou@njtech.edu.cn
	Supporting information for this article is given via a link at the end of the document.



Figure 1. Cycloaddition reactions of isocyanides with acyl chlorides.

Scalable

Reusable catalvst

Broad substrate scope

direct the formation of surfactant-free metal nanoparticles with tuneable size and uniform shape, which may lead to unexpected synergistic catalysis with improved efficiency and selectivity.^[10] On the basis of these precedents and our continued efforts in metal-catalyzed cyclization manifolds, we wondered if silver-containing MOFs could mediate the cycloaddition of isocyanides and acyl chlorides. To our delight, treatment of benzoyl chloride (**1a**) and ethyl isocyanoacetate (**2a**) in the presence of AgMOF-1 (for details see the Supporting Information), afforded 2,5-disubstituted oxazole **3a** in 37% isolated yield along with a significant amount of **4a** (29%; Table 1, Entry 1).

Encouraged by these findings further examination of the reaction conditions was pursued. First, several AgMOFs with different Ag loadings were screened (Table 1, Entries 2–4; for details see the Supporting Information). AgMOF-3 displayed the highest catalytic activity towards the 2,5-disubstituted oxazole **3a**,

COMMUNICATION

while the other screened AgMOF catalysts inferior activity. Next, the solvent effect was evaluated, demonstrating that the use of 1,4-dioxane greatly increased the yield of 3a to 83% while nearly completely suppressing the formation of 4a (Table 1, Entry 5). In contrast, aprotic polar solvents, such as DCE and CH₃CN, had a negative effect and delivered 3a in only 62% and 53% yields, respectively (Table 1, Entries 6 and 7). Furthermore, the protic solvent EtOH only offered trace amounts of 3a (Table 1, Entry 8). In the absence of a silver catalyst the cycloaddition was entirely suppressed (Table 1, Entry 9). In contrast, several commercially available silver catalysts, including Ag₂CO₃, AgNO₃ and AgOAc, only afforded the Nef and Schollkopf products (Table 1, Entries 10-12). A control experiment between 1a and 2a under El Kaïm's reaction conditions^[8] failed to produce the desired product 3a (Table 1, Entry 13). Thus, AgMOF-3 (100 mg) in 1,4dioxane (2.0 mL) and a temperature of 80 °C was selected as the optimal reaction conditions.

Table	1.	Optimization	of	reaction	conditions.1ª	IJ
-------	----	--------------	----	----------	---------------	----

O Ph 1a	CN + CI 2a	[Ag] solvent, Ar 80 °C, 2 h	N CO ₂ Et +	EtO ₂ C Ph 4a
Entry	[Ag] (mg)	Solvent	Yie	ld (%) ^[b]
1 ^[c]	AgMOF-1	DMF	37	29
2 ^[c]	AgMOF-2	DMF	45	16
3 ^[c]	AgMOF-3	DMF	79	trace
4 ^[c]	AgMOF-4	DMF	68	11
5 ^[c]	AgMOF-3	1,4-dioxane	83	trace
6 ^[c]	AgMOF-3	DCE	62	trace
7 ^[c]	AgMOF-3	CH₃CN	53	trace
8 ^[c]	AgMOF-3	EtOH	trace	trace
9	-	1,4-dioxane	0	0
10 ^[d]	Ag ₂ CO ₃	1,4-dioxane		94
11 ^[d]	AgNO₃	1,4-dioxane	0	0
12 ^[d]	AgOAc	1,4-dioxane	0	97
13 ^[e]	-	toluene	0 ^[f]	O ^[f]

[a] Reactions were performed on a 0.5 mmol scale, at 0.25 M (with respect to **1a**). [b] Isolated yields. [c] Reactions were performed with 100 mg catalyst (3.7 mol% Ag). [d] Reactions were performed with 10 mol% catalyst. [e] Reaction performed in the presence of 2,6-lutidine. [f] Yields determined by ¹H NMR.

Having established the optimal reaction conditions, the scope with respect to the acyl chloride component was initially examined. As summarized in Scheme 1, all the reactions proceeded smoothly and afforded the desired 2,5-disubstituted oxazoles in moderate to high yields within 2–5 h under an Ar atmosphere. Aromatic acyl chlorides bearing electron-donating groups, such as Me and MeO, electron-withdrawing groups, such as CO_2Et and NO_2 , as well as halogens (e.g. Br, Cl) on the arene were shown to be competent reaction partners in this transformation. In addition, *ortho-*, *meta-*, *para-* and

polysubstituted acyl chlorides were well-tolerated, showing no deleterious steric effects. Analogously, the fused aryl product 3k (R = 2-naphthyl) could also be produced in 67% yield. Next, heteroaryl acyl chlorides containing furyl (10) and pyridyl (1n) motifs were subjected to the cyclization, leading to moderate yields of the corresponding products 30 and 3n, respectively. Subsequently, several aliphatic acyl chlorides (1p-1s) including benzyl, "Bu, iBu, and 'Bu were investigated, and were efficiently converted to the corresponding 2,5-disubstituted oxazoles 3p-3s in good to high yields. Besides ethyl isocyanoacetate (2a), other isocyanides, such as methyl isocyanoacetate (2b), tertbutyl isocyanoacetate (2c), TosMIC (2d) and benzyl isocyanide (2e), were also treated with benzoyl chloride (1a) under the optimal reaction conditions. To our delight, the corresponding products were obtained in 52-83% yields. Finally, the structure of compound 3 was also confirmed through single-crystal X-ray diffraction analysis for compound 3b (CCDC 1831231, see the Supporting Information).



Scheme 1. Scope of silver-induced cycloaddition of isocyanides with acyl chlorides.

As a heterogeneous catalyst, AgMOF-3 could also easily be recycled from the reaction mixture by centrifugation. To further evaluate the catalytic activity and practicability of the developed protocol, recycling tests with catalyst AgMOF-3 for the

COMMUNICATION

WILEY-VCH

cycloaddition between **1a** and **2a** were carried out. As shown in Figure 2, catalyst AgMOF-3 could be recovered and reused at least four times without significant decrease in the catalytic activity. These results highlight the practicality and the stability of the AgMOF-3 catalyst under the employed reaction conditions.^[10b]



Figure 2. Recycling tests with AgMOF-3 for cycloaddition of 1a and 2a.

The feasibility of the process was further demonstrated through a gram-scale application (Scheme 2). For this purpose, the reaction between **1a** and **2a** was carried out on a 20 mmol scale under the optimal reaction conditions. Delightedly, the corresponding oxazole **3a** was isolated in 70% yield, even in the presence of merely 1.85 mol% Ag (100 mg AgMOF-3 per 1 mmol **1a**). Then, treatment of **3a** with 100 equivalents of morpholine led to the synthesis of amide **5a**, a potentially biologically active compound.^[11]



Scheme 2. Gram-scale cycloaddition between 1a and 2a.

Subsequently, the reaction mechanism was explored (Scheme 3). Initially, the commonly used radical-trapping reagents 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and butylhydroxytoluene (BHT) were added to the reaction system.^[12] In both systems, the desired product **3a** was formed in good yields, which strongly indicate that the silver-induced reactions do not involve a free radical pathway. Next, a deuterium labeling experiment in which 2.0 equivalents of D₂O were added to the reaction between **1a** and **2a** under the standard conditions. This experiment revealed that the deuterium incorporation in **3a** was 41%. Collectively, these results differ from the simple alkali-promoted approaches.^[6–8]

Based on the experimental observations and related literature precedents,^[13,14] a plausible reaction mechanism was conceived (Scheme 4). First, exposure of isonitrile **2** to acyl chloride **1** furnishes the α -keto imidoyl halide intermediate **6**.



Then, the AgMOF catalyst interacts with **6** to form a nitrilium intermediate **7**. A subsequent 1,3-H shift occurs to give intermediate **8**,^[13e] which can be transformed to the desired product **3** through two possible pathways. One pathway is similar to El Kaïm's work (Pathway B) in which species **8** undergoes a deprotonation sequence to form nitrilium adduct **10** that subsequently cyclizes to form the desired product **3**.^[8] The other pathway (Pathway A) involves intramolecular nucleophilic addition from **8** to generate the cyclized cationic intermediate **9**.^[13d] Finally, the target product **3** is produced via a proton shift process along with regeneration of the AgMOF catalyst.^[15] These two reaction pathways are all reasonable and account for the outcome in the abovementioned deuterium-labeling experiment (Scheme 3).





Scheme 4. Proposed mechanistic pathways.

In summary, we have developed a silver-induced cycloaddition of acyl chlorides with isocyanides, providing a practical and scalable method for the construction of synthetically useful 2,5-disubstituted oxazoles. For the first time,

ChemCatChem

an improved and regioselective cyclization of isocyanides with acyl chlorides has been realized using a silver-based MOF catalyst. The strategy features a broad substrate scope, good functional group compatibility, and allows catalyst recycling. Considering the practicality and scalability of the process, the methodology described herein undoubtedly will find wide applications in future synthetic endeavors.

Experimental Section

Preparation of AgMOFs: MIL-101 was synthesized according to a reported procedure.^[16] Subsequently, the activated MIL-101 powder (100 mg) was immersed in acetonitrile (8 mL) containing various amounts of silver nitrate (20 mg, 40 mg, 60 mg and 80 mg for preparation of AgMOF-1, AgMOF-2, AgMOF-3, and AgMOF-4, respectively). The mixture was stirred for 24 hours at room temperature. After the impregnation, the suspension was centrifuged to separate the solid and washed with CH₃CN. The as-synthesized sample was further dried at 150 °C for 8 h, followed by treatment with a H₂/Ar stream (50 ml·min⁻¹/50 ml·min⁻¹) at 200 °C for 3 h to yield the desired AgMOF. Finally, the sample was kept under an Ar atmosphere for further use.

Typical procedure for synthesis of 3 (with **3a** as an example): To a mixture of **1a** (58 μL, 0.5 mmol) and **2a** (67 μL, 0.6 mmol) in 1,4-dioxane (2.0 mL) was added AgMOF-3 (100 mg, 3.7 mol% Ag). The reaction mixture was stirred at 80 °C under an Ar atmosphere until substrate **1a** was consumed as indicated by TLC (about 3 h). The resulting mixture was concentrated under reduced pressure and the residue was taken up in CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification of the crude product by column chromatography (silica gel; petroleum ether/ethyl acetate 5:1) afforded compound **3a** in 83% yield as a yellow solid. m.p. 54–55 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.76 (t, *J* = 5.2 Hz, 2H), 7.53 (s, 1H), 7.45–7.39 (m, 3H), 4.50 (q, *J* = 7.2 Hz, 2H), 1.46 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 101 MHz): δ 155.7, 154.3, 151.6, 129.8, 129.0, 126.6, 125.1, 123.8, 62.6, 14.2; HRMS (ESI-TOF) *m/z* calculated for C₁₂H₁₂NO₃ [M+H]⁺: 218.0817, found: 218.0816.

Acknowledgements

This work was supported by NSFC of China (No. 21702078), NSF of Jiangsu Province (No. BK20170231, BK20170968), Natural Science Foundation of Jiangsu Higher Education Institution (17KJA150003), the open project of Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis (130028830) and KTH Royal Institute of Technology. The Wenner-Gren Foundations and the Olle Engkvist Byggmästare Foundation are kindly acknowledged for postdoctoral fellowships to J.L. and A.S., respectively.

Keywords: acyl chlorides • cycloaddition • isocyanides • oxazoles • silver

a) S. Lang, *Chem. Soc. Rev.* 2013, *42*, 4867; b) G. Qiu, Q. Ding and J.
 Wu, *Chem. Soc. Rev.* 2013, *42*, 5257; c) U. K. Sharma, N. Sharma, D.
 D. Vachhani and E. V. Van der Eycken, *Chem. Soc. Rev.* 2015, *44*,

1836; d) V. P. Boyarskiy, N. A. Bokach, K. V. Luzyanin and V. Y. Kukushkin, *Chem. Rev.* **2015**, *115*, 2698; e) B. Zhang and A. Studer, *Chem. Soc. Rev.* **2015**, *44*, 3505; f) B. Song and B. Xu, *Chem. Soc. Rev.* **2017**, *46*, 1103.

- [2] Isocyanide Chemistry (Eds: V. G. Nenajdenko), Wiley-VCH, Weinheim, 2012.
- [3] S. Chakrabarty, S. Choudhary, A. Doshi, F.-Q. Liu, R. Mohan, M. P. Ravindra, D. Shah, X. Yang, F. F. Fleming, *Adv. Synth. Catal.* 2014, 356, 2135.
- [4] Y. Wang, R. K. Kumar, X. Bi, Tetrahedron Lett. 2016, 57, 5730.
- [5] a) M. Suzuki, T. Iwasaki, M. Miyoshi, K. Okumura, K. Matsumoto, J. Org. Chem. 1973, 38, 3571; b) S. Maeda, M. Suzuki, T. Iwasaki, K. Matsumoto, Y. Iwasawa, Chem. Pharm. Bull. 1984, 32, 2536; c) W. L. F. Armarego, H. Taguchi, R. G. H. Cotton, S. Battiston, L. Leong, Eur. J. Med. Chem. 1987, 22, 283; d) J. Tang, J. G. Verkade, J. Org. Chem. 1994, 59, 7793; e) M. Baumann, I. R. Baxendale, S. V. Ley, C. D. Smith, G. K. Tranmer, Org. Lett. 2006, 8, 5231; f) W.-S. Huang, Y.-X. Zhang, C.-Y. Yuan, Syn. Commun. 1996, 26, 1149; g) W.-S. Tian, T. Livinghouse, J. Chem. Soc., Chem. Commun. 1989, 13, 819.
- a) U. Schöllkopf, R. Schröder, Angew. Chem. 1971, 83, 358; Angew. Chem., Int. Ed. 1971, 10, 333; b) U. Schöllkopf, P.-H. Porsch, Chem. Ber. 1973, 106, 3382; c) R. Schröder, U. Schöllkopf, E. Blume, I. Hoppe, Justus Liebigs Ann. Chem. 1975, 533; d) J. Rachoń, U. Schöllkopf, Justus Liebigs Ann. Chem. 1981, 1186.
- [7] J. U. Nef, Justus Liebigs Ann. Chem. 1892, 270, 267.
- [8] A. Dos Santos, L. El Kaïm, L. Grimaud, C. Ronsseray, Chem. Commun. 2009, 3907.
- [9] a) R. V. Jagadeesh, K. Murugesan, A. S. Alshammari, H. Neumann, M.-M. Pohl, J. Radnik, M. Beller, *Science*. 2017, *358*, 326; b) K. Natte, H. Neumann, R. V. Jagadeesh, M. Beller, *Nature Commun*. 2017, *8*, 1344; c) R. V. Jagadeesh, H. Junge, M. Beller, *Nature Commun*. 2014, *5*, 4123; d) H. Furukawa, K. E. Cordova, M. O'Keeffe, O. M. Yaghi, *Science* 2013, *341*, 1230444.
- a) R. V. Jagadeesh, A.-E. Surkus, H. Junge, M.-M. Pohl, J. Radnik, J. Rabeah, H. Huan, V. Schünemann, A. Brückner, M. Beller, *Science*. **2013**, *342*, 1073; b) X.-H. Liu, J.-G. Ma, Z. Niu, G.-M. Yang, P. Cheng, *Angew. Chem.* **2015**, *127*, 1002; *Angew. Chem. Int. Ed.* **2015**, *54*, 988.
- [11] M. Krasavin, M. Korsakov, M. Dorogov, T. Tuccinardi, N. Dedeoglu and C. T. Supuran, *Eur. J. Med. Chem.* 2015, 101, 334.
- [12] T. J. Montavon, J. Li, J. R. Cabrera-Pardo, M. Mrksich, S. A. Kozmin, Nat. Chem. 2012, 4, 45.
- [13] a) M. Westling, R. Smith, T. Livinghouse, J. Org. Chem. 1986, 51, 1159;
 b) S. Tong, Q. Wang, M.-X. Wang, J. Zhu, Angew. Chem. 2015, 127, 1309; Angew. Chem. Int. Ed. 2015, 54, 1293; c) J. Liu, Z. Liu, P. Liao, L. Zhang, T. Tu, X. Bi, Angew. Chem. 2015, 127, 10764; Angew. Chem. Int. Ed. 2015, 54, 10618; d) Z. Hu, J. Dong, X. Xu, Adv. Synth. Catal. 2017, 359, 3585; e) J.-Q. Liu, X. Shen, Y. Wang, X.-S. Wang, X. Bi, Org. Lett. 2018, 20, 6930; f) J.-Q. Liu, X. Chen, X. Shen, Y. Wang, X.-S. Wang, X. Bi, Adv. Synth. Catal. 2019, 361, 1543; g) J.-Q. Liu, X. Chen, A. Shatskiy, M. D. Kärkäs, X.-S. Wang, J. Org. Chem. DOI: 10.1021/acs.joc.9b00528.
- [14] a) J. Daru, Z. Benda, Á. Póti, Z. Novák and A. Stirling, *Chem. Eur. J.* **2014**, 20, 15395; b) Z. Hu, J. Dong, Y. Men, Z. Lin, J. Cai, X. Xu, *Angew. Chem.* **2016**, *128*, 7193; *Angew. Chem., Int. Ed.* **2016**, *55*,
 7077; c) Z. Hu, J. Dong, Y. Men, Z. Lin, J. Cai, X. Xu, *Angew. Chem.* **2017**, *129*, 1381; *Angew. Chem. Int. Ed.* **2017**, *56*, 1805.
- [15] The presence of HCl can prevent the isocyanide to react completely with the acyl chloride. However, the presence of HCl α -keto imidoyl halides presumably proceed to form nitrilium intermediates.
- [16] G. Férey, C. Mellot-Draznieks, C. Serre, F. Millange, J. Dutour, S. Surblé, I. Margiolaki, *Science* 2005, 309, 2040.

WILEY-VCH

Entry for the Table of Contents

COMMUNICATION



A practical and efficient approach for the formation of 2,5-disubstituted oxazoles has been achieved using a heterogeneous AgMOF catalyst, thereby addressing the limitations of current methods. The developed strategy features a broad substrate scope, good functional group compatibility, and is also amenable to catalyst recycling.

Jian-Quan Liu, Xuanyu Shen, Andrey Shatskiy, Enlong Zhou,* Markus D. Kärkäs,* Xiang-Shan Wang*

Page No. – Page No.

Silver-Induced [3+2] Cycloaddition of Isocyanides with Acyl Chlorides: Regioselective Synthesis of 2,5-Disubstituted Oxazoles