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Difunctionalization of the Isocyano Group: Atom-Economic Synthesis of Pyrimidinediones

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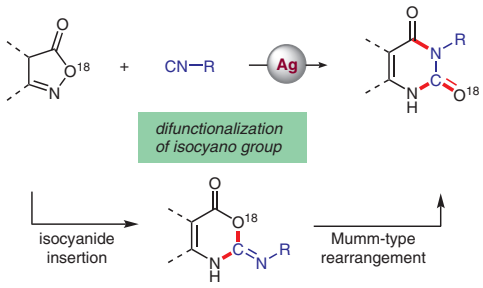
Dedicated to Professor Weiping Su



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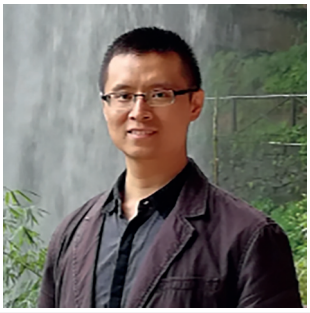
Abstract The exploration of synthetic methods involving the formation of new chemical bonds at both the nitrogen and carbons atoms of the isocyano group would largely enrich the structural diversity of compounds. Herein, we disclosed a silver-catalyzed difunctionalization of the isocyano group with cyclic oximes. This method can generate a great array of structurally novel and interesting pyrimidinediones and features excellent atom economy, good functional group compatibility, and amenability to late-stage modifications.

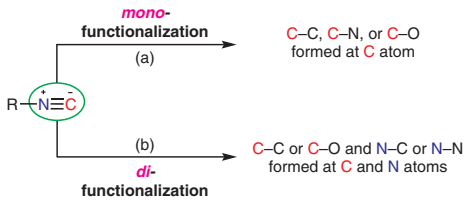
Key words silver, isocyanides, oximes, insertion, N-heterocycles



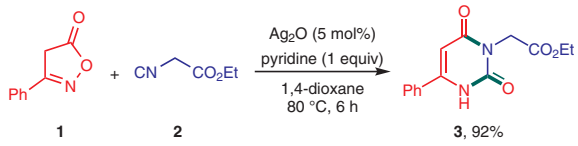
Ye Wei was born in Sichuan province, China, in 1982. He earned his BSc degree in 2005 from Huaqiao University and his PhD degree in 2010 from Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, under the guidance of Prof. Weiping Su. After a two-year postdoctoral appointment with Prof. Naohiko Yoshikai at Nanyang Technological University, he went back to China to join the College of Pharmacy at Third Military Medical University as an Associate Professor. He was promoted to Professor in 2015. Recently, he moved to the School of Chemistry and Chemical Engineering at Southwest University. Wei's research interests are primarily focused on atom- and step-economic synthetic methods, with an emphasis on the transition-metal-mediated novel organic transformations to construct heterocyclic scaffolds.

Isocyanides can participate in numerous organic transformations, such as Ugi and Passerini reactions, for the construction of structurally interesting and useful organic molecules.[1] Therefore, the exploration of the isocyanides as useful building blocks has attracted considerable attention from organic, medicinal, and material chemists. The power of the isocyanides in the generation of chemical diversity would be attributed to the unique reactivity of the isocyano group. Both nitrogen and carbon atoms of the isocyano group are potentially reactive sites toward new chemical-bond formation. However, a vast amount of the known reactions merely involves the functionalization of the terminal carbon atom, and the nitrogen atom remains intact (monofunctionalization of the isocyano group, Scheme 1, a). In order to exploit new reactivity profiles of the isocyanides and enrich the structural diversity of molecules, it is highly desirable to develop new synthetic strategies, utilizing both the nitrogen and carbon atoms as the reactive sites, to simultaneously construct new chemical bonds in one step (difunctionalization of the isocyano group, Scheme 1, b). In this regard, some important work has been reported. For example, three-component reaction of isocyanides, allyl carbonate, and trimethylsilylazide has been utilized to generate allyl cyanamides.[2] In addition, cycloaddition reactions between isocyanides and propargylamines, between isocyanides and enamides, and between two different isocyanides have been realized for the construction of N-heterocycles.[3–5] Despite these significant progress, the reaction type and substrate scope remain limited.

It has been well-established that the isocyanides can take part in various insertion reactions, such as the insertion into heteroatom–hydrogen, carbon–hydrogen, carbon–heteroatom, and carbon–metal bonds.[6] These studies and the carbene-like reactivity of the isocyano group prompted us to expand the realm of the isocyanide insertion chemis-

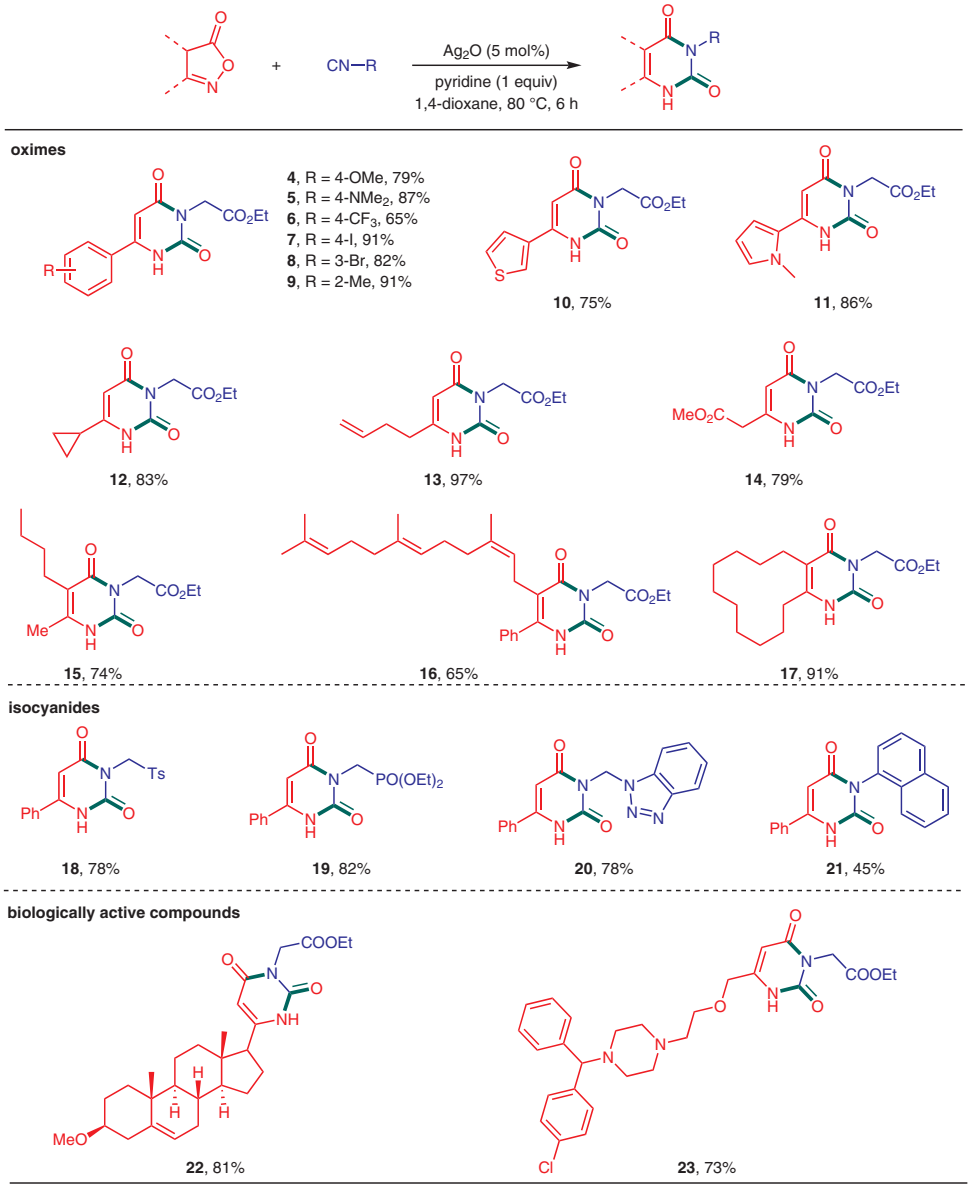


Scheme 1 Functionalization of the isocyano group



Scheme 2 Reaction of 3-phenyl-5-isoxazolone with ethyl isocyanoacetate

try. Our recent work concerning oxime N–O bond transformations (NOT)[7] let us raise a question: Can we realize the isocyanide insertion into the oxime N–O bond and thereby to develop new synthetic methods toward the construction of valuable scaffolds, in particular N-heterocycles (Figure 1)?



Scheme 3 Substrate scope of the reaction

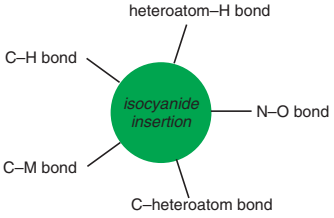
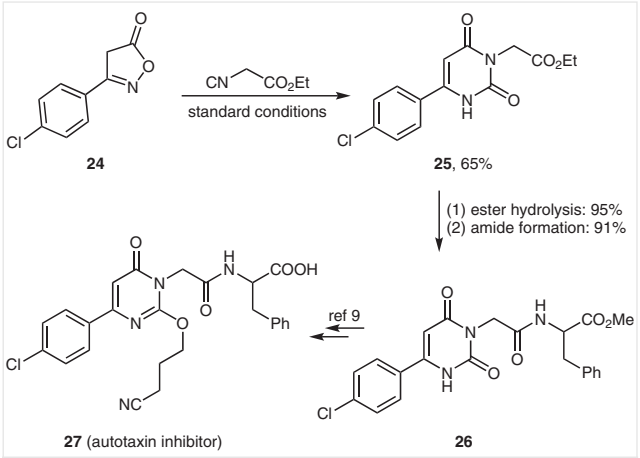


Figure 1 Profiles for isocyanide insertions

With such an idea in mind, we initially investigated the reactions of various acyclic ketoximes or aldoximes with isocyanides. However, the insertion products were not observed. We then turned our attention into isoxazol-5-ones, a class of cyclic oximes. It has been known that the N–O bond of such compounds can be cleaved by low-valent Pd and Ir complexes.[8] Thus, numerous experimentations have been performed to study the reactions between isoxazol-5-ones and isocyanides with Pd or Ir salts as the catalyst. Specifically, 3-phenyl-5-isoxazolone (**1**) and ethyl isocyanoacetate (**2**) were chosen as the substrates. Nonetheless, negative results were obtained. Interestingly, we serendipitously found that the reaction of **1** with **2** gave rise to pyrimidinedione **3** with Ag_2O as a catalyst. In terms of the product structure, the terminal carbon atom of the isocyano group formally inserted into the N–O bond, and two C–N bonds and one C=O bond were newly generated at the isocyano group. The survey of various reaction parameters revealed that the model reaction delivered **3** in 92% yield in the presence of Ag_2O (5 mol%) and pyridine (1 equiv) at 80 °C in 1,4-dioxane within 6 h (Scheme 2).

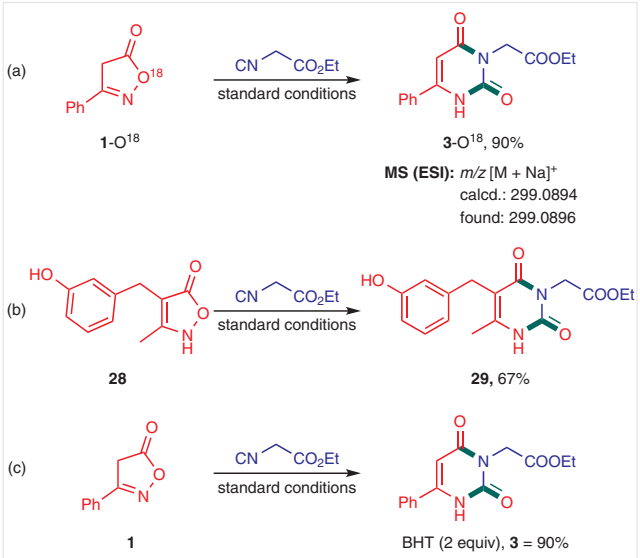
This method exhibited good substrate scope and functional group compatibility, a series of representative examples are shown in Scheme 3. Electron-donating and electron-withdrawing substituents on the aromatic ring did not influence the reaction seriously (**4**–**8**). Oxime bearing an *ortho*-methyl group on the aryl ring also displayed good reactivity (**9**). In addition, thiophene- and pyrrole-derived cyclic oximes were suitable for the transformation (**10** and **11**). Besides (hetero)aromatic functionalities, several other groups including cyclopropyl (**12**), ester (**14**), and polyenic (**16**) groups, can be introduced into the pyrimidinediones. The isocyanides bearing acidic α-C–H bonds generally showed good reactivity, such as *p*-tolylsulfonylmethyl isocyanide (**18**), diethyl isocyanomethylphosphonate (**19**), and benzotriazol-1-ylmethyl isocyanide (**20**). Yet, 1-isocyanonaphthalene displayed moderate reactivity in the reaction (**21**). Unfortunately, *tert*-butyl isocyanide exhibited significantly low reactivity (<10%) and cyclohexyl isocyanide and *n*-butyl isocyanide showed no reactivity in the transformation. More significantly, our method was amenable to the late-stage modification of the biologically active molecules. For instance, the reaction was amenable to pregnenolone- and cetirizine-derived cyclic oximes, and the corresponding products were obtained in good yields (**22** and **23**).

The pyrimidinedione **25** prepared by our method can be easily converted into compound **26**, a precursor of autotaxin inhibitor **27**, through ester hydrolysis and amide-formation steps in 86% total yield (Scheme 4). This synthetic approach shows remarkable superiority over the reported methods. The latter involves six synthetic steps including N-protection/deprotection and Pd-catalyzed Suzuki coupling reaction.[9]



Scheme 4 Synthesis of an autotaxin inhibitor

Several experiments were conducted to gain insight into the reaction mechanism (Scheme 5). O^{18}-labeled substrate **1**-O^{18} reacted with ethyl isocyanoacetate to deliver the target product, and the mass spectrometry result indicated that the O^{18} atom was incorporated into the final product



Scheme 5 Mechanistic investigation

(Scheme 5, a). Thus, all of the atoms in the two substrates entered into the target product **3**-O[18]. In addition, the reaction of isoxazol-5(2*H*)-one derivative **28** with ethyl isocyanoacetate also yielded the pyrimidinedione **29** in 67% yield (Scheme 5, b), which suggested that the isoxazol-5(2*H*)-one might be an intermediate in the reaction. Moreover, the radical mechanism might be ruled out because the addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT) did not inhibit the reaction (Scheme 5, c).

The plausible reaction pathways for the Ag-catalyzed pyrimidinedione synthesis are depicted in Scheme 6. The cyclic oxime **30** might tautomerize to the isoxazol-5(2*H*)-one **30′**[10] that then reacts with Ag(I) salt to generate a silver complex **31** with pyridine as a base. Subsequent isocyanide **32** insertion produces a species **33**, followed by ring opening to deliver a silver-nitrene species **34**.[11] After intramolecular nitrene insertion into the C–Ag bond,[12] a species **35** could be formed, which then occurs protonation to furnish an imidate **36**. Such a compound could undergo ring opening[13] to produce a zwitterion **37**, which is then converted into the final product **38** through intramolecular C–N bond formation. Another role of the pyridine might be to enhance the solubility of the silver salt due to its good coordination ability to the silver salt.[14]

In conclusion, the difunctionalization of the isocyano group has been achieved by means of the isocyanide insertion into the oxime N–O bond, which can generate a great majority of structurally new and interesting pyrimidinediones. It can be envisioned that with the strategy of difunctionalization of the isocyano group, more useful and important N-heterocycles would be generated in the near future.

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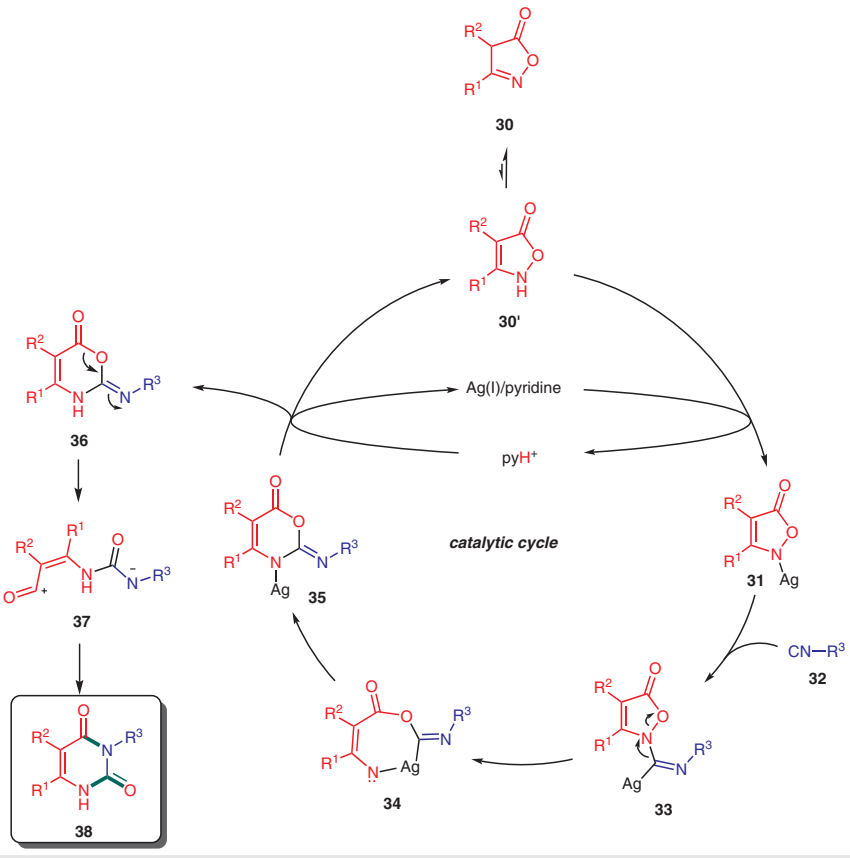
References

(1) (a) Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5253. (b) Lygin, A. V.; de Meijere, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 9094. (c) Lang, S. *Chem. Soc. Rev.* **2013**, *42*, 4867. (d) Giustiniano, M.; Basso, A.; Mercalli, V.; Massarotti, A.; Novellino, E.; Tron, G. C.; Zhu, J. *Chem. Soc. Rev.* **2017**, *46*, 1295.



Scheme 6 Hypothesis for the reaction

(2) Kamijo, S.; Jin, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9453.
(3) Tong, S.; Wang, Q.; Wang, M.-X.; Zhu, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 1293.
(4) Lei, C.-H.; Wang, D.-X.; Zhao, L.; Zhu, J.; Wang, M.-X. *J. Am. Chem. Soc.* **2013**, *135*, 4708.
(5) (a) Kanazawa, C.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 10662. (b) Pooi, B.; Lee, J.; Choi, K.; Hirao, H.; Hong, S. H. *J. Org. Chem.* **2014**, *79*, 9231. (c) Wang, H.; Kumar, R. K.; Yu, Y.; Zhang, L.; Liu, Z.; Liao, P.; Bi, X. *Chem. Asian J.* **2016**, *11*, 2841. (d) Hu, Z.; Yuan, H.; Men, Y.; Liu, Q.; Zhang, J.; Xu, X. *Angew. Chem. Int. Ed.* **2016**, *55*, 6958. (e) Lei, Y.; Hu, Z.; Dong, J.; Liu, J.; Xu, X. *Org. Lett.* **2017**, *19*, 5292.
(6) (a) Qiu, G.; Ding, Q.; Wu, J. *Chem. Soc. Rev.* **2013**, *42*, 5257. (b) Vlaar, T.; Ruijter, E.; Maes, B. U. W.; Orru, R. V. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 7084. (c) Zhang, B.; Studer, A. *Chem. Soc. Rev.* **2015**, *44*, 3505. (d) Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. *Chem. Rev.* **2015**, *115*, 2698. (e) Song, B.; Xu, B. *Chem. Soc. Rev.* **2017**, *46*, 1103.
(7) (a) Zhao, B.; Liang, H.-W.; Yang, J.; Yang, Z.; Wei, Y. *ACS Catal.* **2017**, *7*, 5612. (b) Yang, J.; Zhao, B.; Xi, Y.; Sun, S.; Yang, Z.; Ye, Y.; Jiang, K.; Wei, Y. *Org. Lett.* **2018**, *20*, 1216.
(8) (a) Okamoto, K.; Oda, T.; Kohigashi, S.; Ohe, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 11470. (b) Okamoto, K.; Shimbayashi, T.; Yoshida, M.; Nanya, A.; Ohe, K. *Angew. Chem. Int. Ed.* **2016**, *55*, 7199.
(9) Nagano, T.; Okabe, T.; Kojima, H.; Kawaguchi, M.; Nureki, O.; Ishitani, R.; Nishimasu, H.; Aoki, J.; Tanaka, N.; Kanda, Y.; Kioi, Y.; Takeno, Y.; Kida, S.; Yamane, J. US 20170158704, **2017**.
(10) (a) Krogsgaard-Larsen, P.; Christensen, S. B.; Hjeds, H. *Acta Chem. Scand.* **1973**, *27*, 2802. (b) Zard, S. Z. *Chem. Commun.* **2002**, 1565.
(11) (a) Maestre, L.; Sameera, W. M. C.; Díaz-Requejo, M. M.; Maseras, F.; Pérez, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 1338. (b) Alderson, J. M.; Corbin, J. R.; Schomaker, J. M. *Acc. Chem. Res.* **2017**, *50*, 2147.
(12) Reactions involving nitrene insertion into C–M bonds, see: (a) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (b) Sau, Y.-K.; Yi, X.-Y.; Chan, K.-W.; Lai, C.-S.; Williams, I. D.; Leung, W.-H. *J. Organomet. Chem.* **2010**, *695*, 1399.
(13) (a) Mumm, O. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 886. (b) Schwarz, J. S. P. *J. Org. Chem.* **1972**, *37*, 2906.
(14) Piero, S. D.; Fedele, R.; Melchior, A.; Portanova, R.; Tolazzi, M.; Zangrando, E. *Inorg. Chem.* **2007**, *46*, 4683.