OL Organic Letters

Cite This: *Org. Lett.* XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

Silver-Mediated [3 + 2] Cycloaddition of Alkynes and *N*-Isocyanoiminotriphenylphosphorane: Access to Monosubstituted Pyrazoles

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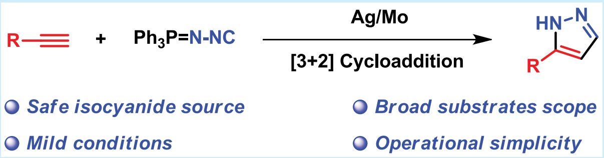
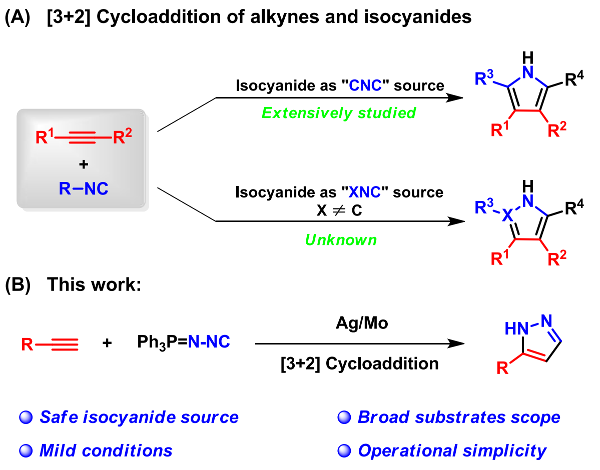
Supporting Information

ABSTRACT: A silver-mediated [3 + 2] cycloaddition of “CNN” and “$C\equiv C$” for constructing pyrazoles has been described. The “CNN” building block used is *N*-isocyanoiminotriphenylphosphorane, which is a stable, safe, easy-to-handle, and odorless solid isocyanide. The reaction is characterized by its mild conditions, broad substrate scope, and excellent functional group tolerance.



Alkynes[1] and isocyanides[2] are two classes of commercially available and versatile starting materials. The reactions of alkynes and isocyanides are the most powerful and representative route for the construction of nitrogen-containing compounds.[3] Among these reported protocols, [3 + 2] cycloadditions of alkynes and isocyanides have attracted much attention due to their high efficiency and atom-economy. In the past, substantial advances have been achieved in the use of this strategy for the synthesis of pyrroles and their derivatives (Figure 1A).[4] However, these processes often rely on isocyanides with an α-acidic hydrogen, as these species efficiently provide the “CNC” building block. To the best of our knowledge, there are no examples of [3 + 2] cycloadditions of alkynes and isocyanides lacking an α-acidic hydrogen. Herein, we wish to report a novel silver-mediated [3 + 2] cycloaddition of alkynes and NIITP for the assembly of monosubstituted pyrazoles; such molecules show broad biological activities, such as analgesic, antipyretic, antibacterial, antihyperglycemic, and anti-inflammatory.[5]


(A) [3+2] Cycloaddition of alkynes and isocyanides

(B) This work:

Figure 1. [3 + 2] cycloaddition of alkynes and isocyanides.

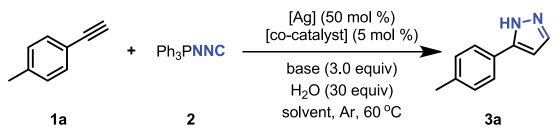
NIITP, a functionalized isocyanide, is synthetically attractive as a stable, safe, easy-to-handle, and odorless solid isocyanide.[6] It is a versatile synthetic intermediate with a variety of applications, serving as a key intermediate in multicomponent reactions,[7] as “NNC” sources in cyclization reactions,[8] and as one-carbon units in insertion reactions.[9] Recently, our group has reported the application of NIITP as a novel and safe “cyano” source in the cyanation of alkynes.[10] In a continuation of our program, we sought to further explore and expand the synthetic utility of NIITP. While taking advantage of NIITP as a “CNN” source, we envisaged that NIITP could be utilized in the [3 + 2] cycloaddition of alkynes and isocyanides.

To probe the feasibility of our hypothesis, we started our investigation by reacting 1-ethynyl-4-methylbenzene (**1a**) and NIITP (**2**) in the presence of Ag_2CO_3 and $Mo(CO)_6$ (Table 1, entry 1). Gratifyingly, after 12 h, pyrazole **3a** was obtained in 54% yield. We then tested a variety of silver salts (entries 1−4). Ag_2CO_3 was found to be the most suitable promoter for this process, giving **3a** in 54% yield (entry 1). A control experiment confirmed the necessity of the silver catalyst in the reaction (entry 5). In the absence of $Mo(CO)_6$, the yield of **3a** sharply decreased to 18%, which suggests that $Mo(CO)_6$ plays a critical role in activating the isocyanide and promoting the cycloaddition of the isocyanide and the alkyne (entry 6).[11] A range of other additives, including $Cr(CO)_6$, $W(CO)_6$, $Sc(OTf)_3$, and CuI were also evaluated instead of $Mo(CO)_6$, and all of them resulted in inferior yields (entries 7−10). Among the tested solvents, THF provided the best yield (entries 11−15). Additionally, a survey of various bases

Received: March 9, 2019

DOI: 10.1021/acs.orglett.9b00860
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of the Reaction Conditions[a]



entry	[Ag]	additive	solvent	base	**3a**, yield[b] (%)
1	Ag_2CO_3	$Mo(CO)_6$	THF		54
2	Ag_3PO_4	$Mo(CO)_6$	THF		33
3	$AgNO_3$	$Mo(CO)_6$	THF		<5
4	AgOTf	$Mo(CO)_6$	THF		<5
5		$Mo(CO)_6$	THF		0
6	Ag_2CO_3		THF		18
7	Ag_2CO_3	$Cr(CO)_6$	THF		10
8	Ag_2CO_3	$W(CO)_6$	THF		23
9	Ag_2CO_3	$Sc(OTf)_3$	THF		<5
10	Ag_2CO_3	CuI	THF		<5
11	Ag_2CO_3	$Mo(CO)_6$	CH_3CN		<5
12	Ag_2CO_3	$Mo(CO)_6$	dioxane		42
13	Ag_2CO_3	$Mo(CO)_6$	DMF		22
14	Ag_2CO_3	$Mo(CO)_6$	PhCl		8
15	Ag_2CO_3	$Mo(CO)_6$	DME		30
16	Ag_2CO_3	$Mo(CO)_6$	THF	LiOH	55
17	Ag_2CO_3	$Mo(CO)_6$	THF	*t*-BuONa	51
18	**Ag_2CO_3**	**$Mo(CO)_6$**	**THF**	**MeOLi**	**76 (76[c])**
19	Ag_2CO_3	$Mo(CO)_6$	THF	K_2CO_3	39

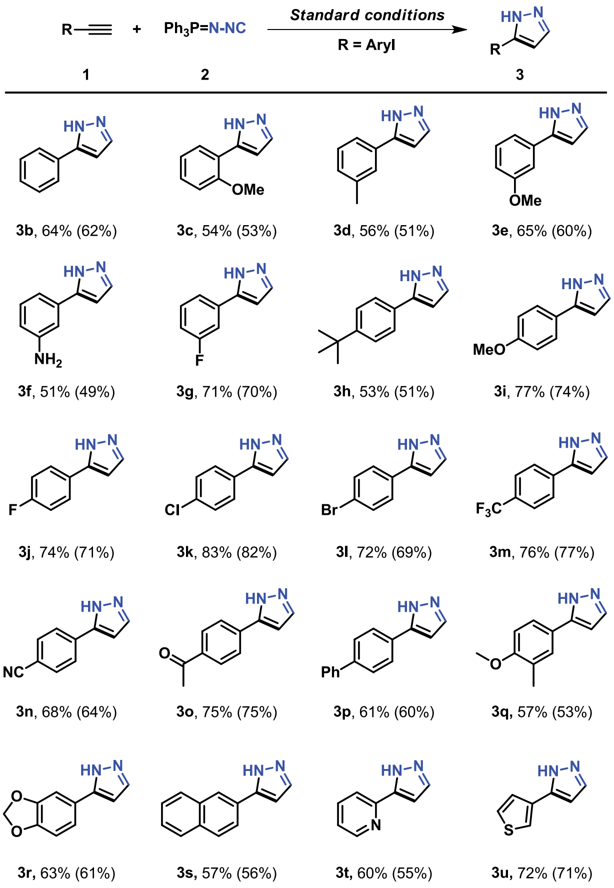
[a]Reaction conditions: **1a** (0.5 mmol), **2** (1 mmol), [Ag] (0.5 equiv), $Mo(CO)_6$ (5 mol %), base (2 equiv) in THF (2.5 mL) at 60 °C for 12 h under Ar. [b]Determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. [c]Isolated yield.

revealed that the nature of the counterion has a significant impact on the reaction, and the utilization of MeOLi substantially improved the yield of the pyrazole (entries 16–19). We thus selected the conditions illustrated in entry 18 as the optimal conditions for further evaluation of the substrate scope.

With the optimal conditions in hand, we then explored the scope of this cycloaddition reaction first with respect to arylalkynes (**1**), and the results are shown in Scheme 1. The results revealed that the electronic effect of the substituent on the aryl acetylene had little effect on the reaction. However, the position of the substituents and the associated steric hindrance had a significant impact on the yield of the desired product. The *ortho*-substituted arylalkyne (**1c**) gave the corresponding products in a lower yield than the *meta*- (**1d–g**) or *para*-substituted arylalkynes (**1h–p**). In addition, arylalkynes with less steric hindrance would readily undergo the cycloaddition. Disubstituted aryl- (**1q** and **1r**) and naphthylalkynes (**1s**) were also smoothly converted to the corresponding products in good yields. Notably, alkynes bearing heterocycles, including pyridyl (**1t**) and thienyl (**1u**) moieties, gave the desired products in good yields. Several pyridyl pyrazoles have been used in pharmaceutical chemistry; for example: LY-364947[12] is an ATP-competitive and tight-binding inhibitor, 4-(1*H*-pyrazol-3-yl)pyridine[13] is a kinase inhibitor, and morpholino-(3-(pyridin-3-yl)-1*H*-pyrazol-1-yl)methanone[14] is an FAAH inhibitor.

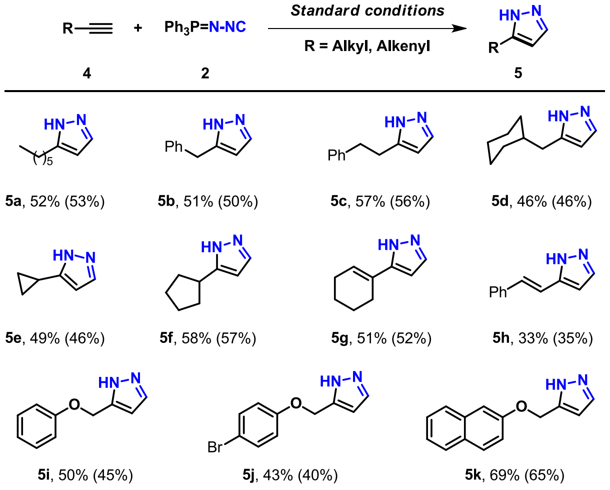
Next, we examined a variety of alkyl- and alkenylalkynes (**4**) with NIITP under the optimal conditions (Scheme 2). A series of alkynes bearing alkyl (**4a**), benzyl (**4b**), phenylethyl (**4c**), and cycloalkyl (**4d–f**) substituents exhibited good reactivities

Scheme 1. Substrate Scope of Arylalkynes[a–c]



[a]Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), [Ag] (0.5 equiv), $Mo(CO)_6$ (5 mol %), base (2 equiv) in THF (2.5 mL) at 60 °C for 12 h under Ar. [b]The yields were determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. [c]The yields in parentheses are isolated yields.

Scheme 2. Substrate Scope of Alkyl- and Alkynylalkynes[a–c]

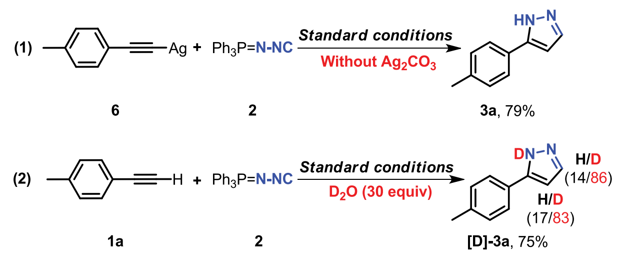


[a]Reaction conditions: **4** (0.5 mmol), **2** (1 mmol), [Ag] (0.5 equiv), $Mo(CO)_6$ (5 mol %), base (2 equiv) in THF (2.5 mL) at 60 °C for 12 h under Ar. [b]The yields were determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. [c]The yields in parentheses are isolated yields.

but afforded the corresponding alkylpyrazoles in lower yields than those obtained from aryl-substituted substrates. Interestingly, eneynes, including a cycloeneyne (**4g**) and linear eneyne (**4h**), were also acceptable substrates for this cycloaddition reaction. Moreover, functionalized pyrazoles (**5j**, **k**) could also be prepared by this protocol.

To elucidate the reaction mechanism, two control experiments were carried out (Scheme 3). First, the reaction of silver acetylide (**6**) and NIITP (**2**) was performed under the standard conditions, but in the absence of Ag_2CO_3. As expected, pyrazole **3a** was obtained in 79% yield (eq 1). Next, substrate **1a** and NIITP (**2**) were subjected to the standard reaction conditions, except H_2O was replaced by D_2O. Deuterium labeling at both C3 (86%) and C4 (83%) was observed by ^1H NMR spectroscopy (eq 2). Both results demonstrated that the activation of the alkyne by the silver is vital in this cycloaddition, and silver acetylide was the key intermediate.

Scheme 3. Mechanistic Investigations



On the basis of previous studies[15] and the above-described experimental results, we developed a plausible mechanism for the [3 + 2] cycloaddition of alkynes and NIITP (Figure 2).

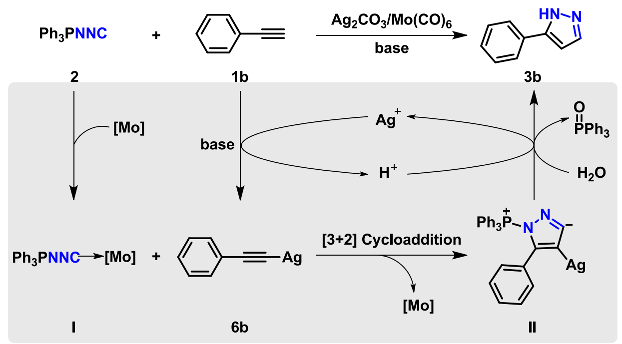


Figure 2. Proposed Mechanism.

First, NIITP (**2**) was activated by $Mo(CO)_6$, and a molybdenum isocyanide complex (**I**) was generated. Meanwhile, in the presence of Ag_2CO_3 and a base, σ-activation of alkyne **1b** occurred to form a silver acetylide intermediate (**6b**). Then the [3 + 2] cycloaddition of intermediate **I** and silver acetylide **6b** occurred to give intermediate **II**. Finally, intermediate **II** underwent facile hydrolysis in the presence of H_2O to provide the desired product **3a**. Furthermore, triphenylphosphine oxide, which is formed as a side product, has been isolated and characterized by ^1H and ^{13}C NMR spectroscopy.

In summary, we have developed a [3 + 2] cycloaddition of “C≡C” and “NNC”. The novel cycloaddition protocol provides synthetically useful pyrazoles. In this reaction, the “C≡C” sources are alkynes which are commercially available and versatile staring materials, and the “NNC” source is NIITP, which is a safe, easy-to-handle, and odorless solid isocyanide. Mechanistic investigations revealed that the silver acetylide derived from ion exchange between the alkyne and Ag_2CO_3 was the key intermediate for the cycloaddition. Further studies on the utilization of NIITP are ongoing in our group.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00860.

> Experimental procedures along with characterization data and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (21871043, 21522202, 21502017, 21604082) and the Department of Science and Technology of Jilin Province (20180101185JC, 20190701012GH) is acknowledged.

■ REFERENCES

(1) *Acetylene Chemistry*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, 2005.

(2) (a) Ugi, I. *Isonitrile Chemistry*; Academic Press: New York, 1971. (b) *Isocyanide Chemistry*; Nenajdenko, V. G., Ed.; Wiley-VCH: Weinheim, 2012.

(3) For selected reviews on the reaction of alkynes and isocyanides, see: (a) Qiu, G.; Ding, Q.; Wu, J. *Chem. Soc. Rev.* **2013**, *42*, 5257–5269. (b) Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. *Chem. Rev.* **2015**, *115*, 2698–2779. (c) Fang, G.; Bi, X. *Chem. Soc. Rev.* **2015**, *44*, 8124–8173. (d) Wang, Y.; Kumar, R. K.; Bi, X. *Tetrahedron Lett.* **2016**, *57*, 5730–5741. (e) Song, B.; Xu, B. *Chem. Soc. Rev.* **2017**, *46*, 1103–1123.

(4) For selected examples on the [3 + 2] cycloaddition of alkynes and isocyanides, see: (a) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260–9266. (b) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664–5667. (c) Cai, Q.; Zhou, F.; Xu, T.; Fu, L.; Ding, K. *Org. Lett.* **2011**, *13*, 340–343. (d) Gao, M.; He, C.; Chen, H.; Bai, R.; Cheng, B.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 6958–6961. (e) Liu, J.; Fang, Z.; Zhang, Q.; Liu, Q.; Bi, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6953–6957. (f) Liu, J.; Liu, Z.; Liao, P.; Bi, X. *Org. Lett.* **2014**, *16*, 6204–6207. (g) Meng, X.; Liao, P.; Liu, J.; Bi, X. *Chem. Commun.* **2014**, *50*, 11837–11839. (h) Liu, J.; Chen, X.; Shen, X.; Wang, Y.; Wang, X.; Bi, X. *Adv. Synth. Catal.* **2019**, *361*, 1543–1548.

(5) (a) Parameswaran, P. S.; Naik, C. G.; Hegde, V. R. *J. Nat. Prod.* **1997**, *60*, 802−803. (b) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*, 2nd ed.; Wiley & Sons: New York, 2004; pp 179−184. (c) Bildirici, İ.; Şener, A.; Tozlu, İ. *Med. Chem. Res.* **2007**, *16*, 418−426. (d) Dadiboyena, S.; Nefzi, A. *Eur. J. Med. Chem.* **2011**, *46*, 5258−5275. (e) Yoon, J.; Lee, S.; Shin, H. *Curr. Org. Chem.* **2011**, *15*, 657−674. (f) Schmidt, A.; Dreger, A. *Curr. Org. Chem.* **2011**, *15*, 1423−1463.

(6) Giustiniano, M.; Basso, A.; Mercalli, V.; Massarotti, A.; Novellino, E.; Tron, G. C.; Zhu, J. *Chem. Soc. Rev.* **2017**, *46*, 1295−1357.

(7) (a) Souldozi, A.; Ramazani, A.; Bouslimani, N.; Welter, R. *Tetrahedron Lett.* **2007**, *48*, 2617−2620. (b) Adib, M.; Kesheh, M. R.; Ansari, S.; Bijanzadeh, H. R. *Synlett* **2009**, *2009*, 1575−1578. (c) Adib, M.; Ansari, S.; Fatemi, S.; Bijanzadeh, H. R.; Zhu, L. *Tetrahedron* **2010**, *66*, 2723−2727. (d) Adib, M.; Sheikhi, E.; Kavoosi, A.; Bijanzadeh, H. R. *Synthesis* **2010**, *2010*, 4082−4086. (e) Adib, M.; Ansari, S.; Feizi, S.; Bijanzadeh, H. R. *Synlett* **2010**, *2010*, 921−923. (f) Ramazani, A.; Rezaei, A. *Org. Lett.* **2010**, *12*, 2852−2855. (g) Nasrabadi, F. Z.; Ramazani, A.; Ahmadi, Y. *Mol. Diversity* **2011**, *15*, 791−798. (h) Adib, M.; Ansari, S.; Bijanzadeh, H. R. *Synlett* **2011**, *2011*, 619−622. (i) Adib, M.; Ansari, S.; Zhu, L.; Bijanzadeh, H. R. *Helv. Chim. Acta* **2013**, *96*, 675−681. (j) Brockmeyer, F.; van Gerven, D.; Saak, W.; Martens, J. *Synthesis* **2014**, *46*, 1603−1612. (k) Frost, J. R.; Scully, C. C. G.; Yudin, A. K. *Nat. Chem.* **2016**, *8*, 1105−1111.

(8) (a) Souldozi, A.; Ramazani, A. *Tetrahedron Lett.* **2007**, *48*, 1549−1551. (b) Rouhani, M.; Ramazani, A.; Joo, S. W. *Ultrason. Sonochem.* **2014**, *21*, 262−267.

(9) (a) Aller, E.; Molina, P.; Lorenzo, Á. *Synlett* **2000**, *2000*, 526−528. (b) Cui, L.; Liu, Q.; Yu, J.; Ni, C.; Yu, H. *Tetrahedron Lett.* **2011**, *52*, 5530−5533.

(10) Wang, H.; Mi, P.; Zhao, W.; Kumar, R.; Bi, X. *Org. Lett.* **2017**, *19*, 5613−5616.

(11) Adams, C. J.; Anderson, K. M.; Bartlett, I. M.; Connelly, N. G.; Orpen, A. G.; Paget, T. J.; Phetmung, H.; Smith, D. W. *J. Chem. Soc., Dalton Trans.* **2001**, 1284−1292.

(12) Bouquet, F.; Pal, A.; Pilones, K. A.; Demaria, S.; Hann, B.; Akhurst, R. J.; Babb, J. S.; Lonninq, S. M.; DeWynqaert, J. K.; Formenti, S. C.; Barcellos-Hoff, M. H. *Clin. Cancer Res.* **2011**, *17*, 6754−6765.

(13) Medina, J. R.; Blackledge, C. W.; Heerding, D. A.; Campobasso, N.; Ward, P.; Briand, J.; Wright, L.; Axten, J. M. *ACS Med. Chem. Lett.* **2010**, *1*, 439−442.

(14) Kiss, L. E.; Learmonth, D. A.; Rosa, C. P. C. P.; Gusmão de Noronha, R.; Palma, P. N. L.; Soares da Silva, P. M. V. A.; Beliaev, A. (to Bial-Portela and C^a S. A.) International Patent WO2010074588, 2010.

(15) (a) Liu, J.; Liu, Z.; Wu, N.; Liao, P.; Bi, X. *Chem. - Eur. J.* **2014**, *20*, 2154−2158. (b) Xiao, P.; Yuan, H.; Liu, J.; Zheng, Y.; Bi, X.; Zhang, J. *ACS Catal.* **2015**, *5*, 6177−6184. (c) Bounar, H.; Liu, Z.; Zhang, L.; Guan, X.; Yang, Z.; Liao, P.; Bi, X.; Li, X. *Org. Biomol. Chem.* **2015**, *13*, 8723−8728. (d) Kumar, R. K.; Bi, X. *Chem. Commun.* **2016**, *52*, 853−868.

DOI: 10.1021/acs.orglett.9b00860
Org. Lett. XXXX, XXX, XXX−XXX