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PII: S0040-4039(16)31333-8
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.10.030
Reference: TETL 48200

To appear in: *Tetrahedron Letters*

Received Date: 1 September 2016
Revised Date: 1 October 2016
Accepted Date: 8 October 2016

Please cite this article as: Yang, Z-W., Wang, J-F., Peng, L-J., You, X-L., Cui, H-L., Thermal 1,3-Dipolar Cycloaddition of Azomethine Imines with Alkynes Affording *N,N*-bicyclic Pyrazolidinones Under Microwave Irradiation, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.10.030

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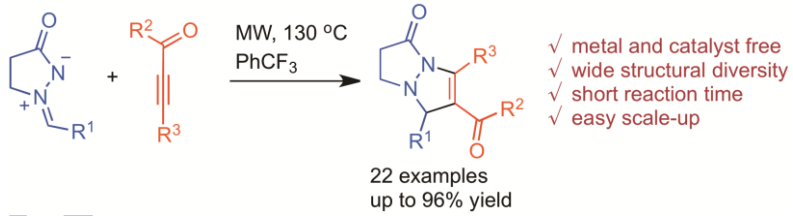
Abstract A metal and catalyst free 1,3-dipolar cycloaddition reaction of azomethine imines with internal alkynes have been developed. Various *N,N*-bicyclic pyrazolidinones could be prepared quickly under microwave irradiation in moderate to excellent yields (up to 96%). A wide range of azomethine imines and electron-deficient internal alkynes were applicable to this reaction. In addition, gram-scale reaction could be achieved and fully substituted pyrazole can be obtained by easy transformation of *N,N*-bicyclic pyrazolidinone. This environment friendly dipolar cycloaddition is remarkable for its simplicity in conditions and wide structural diversity.



Keywords: 1,3-Dipolar Cycloaddition, Microwave, Internal Alkynes, Azomethine Imines, *N,N*-Bicyclic Pyrazolidinones

Pyrazolidinone heterocycles can be found in plenty of bioactive compounds possessing a wide range of activities.[1] For example, tetrahydropyrazolo[1,2-*a*]pyrazolones have been studied as analogues of penicillin and cephalosporin antibiotics (Figure 1).[2] Given the significant importance of pyrazolidinones and their derivatives in drug discovery, the development of efficient synthesis of pyrazolidinone derivatives, especially *N,N*-bicyclic pyrazolidinones, has attracted considerable attention and thus great efforts have been paid to this field.

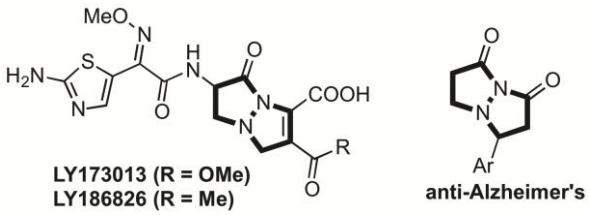


Figure 1. Examples of bioactive compounds bearing *N,N*-bicyclic pyrazolidinone framework.

Among a variety of reported approaches, 1,3-dipolar cycloaddition of azomethine imines with alkynes is one of the most useful and straightforward tool for the assembly of *N,N*-bicyclic pyrazolidinone derivatives (Figure 2).[3-9] Dorn and Otto firstly reported their synthesis of *N,N*-bicyclic pyrazolidinones as early as 1968, albeit mixtures of regioisomers were always obtained in their work.[4] Since then, many elegant approaches using Copper as catalyst have been achieved by Fu, Pale, Sommer, Maruoka, Mizuno, Kobayashi, Arai, and others, even in asymmetric version with excellent enantioseletive control (eq a).[5] However, besides the employment of metal catalyst, all the methods are limited to the use of terminal alkynes. Later, Ishihara group reported a convenient 1,3-dipolar cycloaddition of azomethine imines with internal alkynes using copper as Lewis acid catalyst (eq b).[6] Although good yields and enantiocontrol have been reached, this protocol suffered the use of special internal alkynes which required the incorporation of electron-withdrawing groups at γ-positions for activation and amide moieties for coordination with copper. From the point of view of green chemistry, thermal 1,3-dipolar cycloaddition is a good choice in order to avoid the use of metal or catalyst. Back group disclosed an example of thermal 1,3-dipolar cycloaddition of azomethine imine with electron-deficient acetylenic sulfone, but in poor yield (32%, eq c).[7] Yu and co-workers developed an efficient [3+2] cycloaddition of azomethine imines with alkynyl Fischer carbene complexes. However, a further oxidative demetalation was required to deliver *N,N*-bicyclic pyrazolidinones (eq d).[8] Practical and direct methods for the construction of these molecules are extremely desirable. To the best of our knowledge, there is no method available for the direct catalyst-free 1,3-dipolar cycloaddition of azomethine imines with simple internal electron-deficient alkynes.[10,11] Here, we report our development of a thermal 1,3-dipolar cycloaddition of azomethine imines with internal alkynes under microwave irradiation affording *N,N*-bicyclic pyrazolidinones.

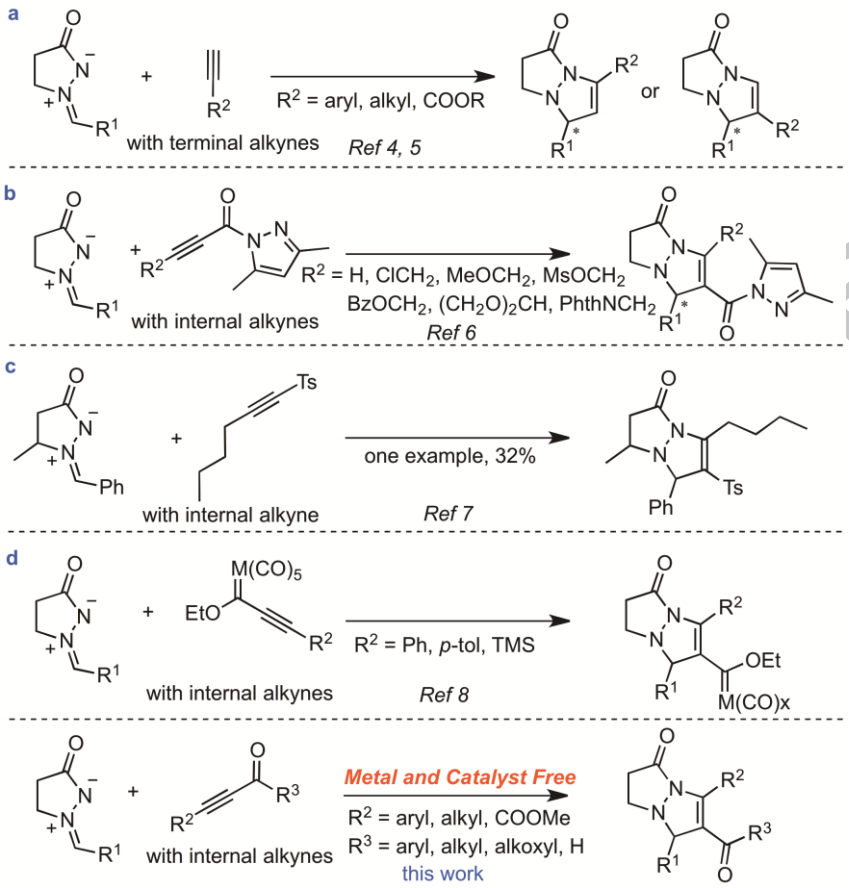


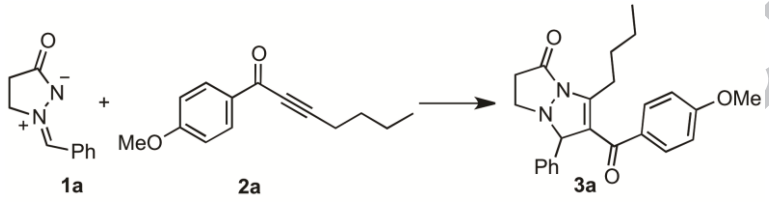
Figure 2. Synthesis strategies through dipolar cycloaddition of azomethine imines with alkynes.

As part of our continuous efforts on phosphine-catalyzed construction of heterocycles with ynones through *in situ* generation of α-nucleophile, our group intended to develop a phosphine-catalyzed [3+3] annulation of azomethine imine with ynone.[12,13] We conducted the reaction of azomethine imine **1a** and ynone **2a** in the presence of tributylphosphine in $PhCF_3$ at 130 ^oC for 30 minutes under microwave irradiation. To our surprise, what we obtained is not the desired [3+3] cycloaddition product but [3+2] annulation product **3a** (Table 1, entry 1). Furthermore, blank experiment without catalyst gave similar yield in comparison with the reaction under the catalysis of tributylphosphine (entry 2). We reasoned that a thermal 1,3-dipolar cyclization reaction occurred. Single-crystal X-ray diffraction analysis confirmed the structure of annulation product **3a**.[14] To our delight, $PhCF_3$ as solvent led to significant increase on yield (86%, entry 3). Higher concentration also gave better result in terms of yield (91%, entry 4). However, either lower reaction temperature or decreased amount of ynone resulted in dramatically reduced yields

(entries 5, 6). In the absence of microwave irradiation, only 9% yield could be obtained by conventional heating (entry 7). Prolonged reaction time failed to give significant improvement on yield (entry 8). This indicates microwave irradiation is essential to this transformation.[15]

Table 1

Optimization Studies[a,b]



1a 2a 3a

Entry	Solvent	T (^{o}C)	Yield [%]
1[c]	toluene	130, MW	26
2	toluene	130, MW	28
3[c]	$PhCF_3$	130, MW	86
4[d]	**$PhCF_3$**	**130, MW**	**91(86)[e]**
5[d]	$PhCF_3$	100, MW	10
6[d,f]	$PhCF_3$	130, MW	51
7[d,g]	$PhCF_3$	130, conventional heating	9
8[d,h]	$PhCF_3$	130, conventional heating	13

[a] Unless otherwise noted, reaction was performed with 0.1 mmol of **1a** and 0.2 mmol of **2a** in 1.0 mL of solvent irradiated by microwave for 30 minutes.

[b] Yield determined by ^{1}H NMR with CH_2Br_2 as internal standard.

[c] In the presence of 30 mol% of PBu_3.

[d] Performed with 0.2 mmol of **1a** and 0.4 mmol of **2a** in 1.0 mL of solvent.

[e] Isolated yield.

[f] Performed with 0.2 mmol of **1a** and 0.22 mmol of **2a** in 1.0 mL of solvent.

[g] Heated at 130 ^{o}C for 30 minutes by conventional heating.

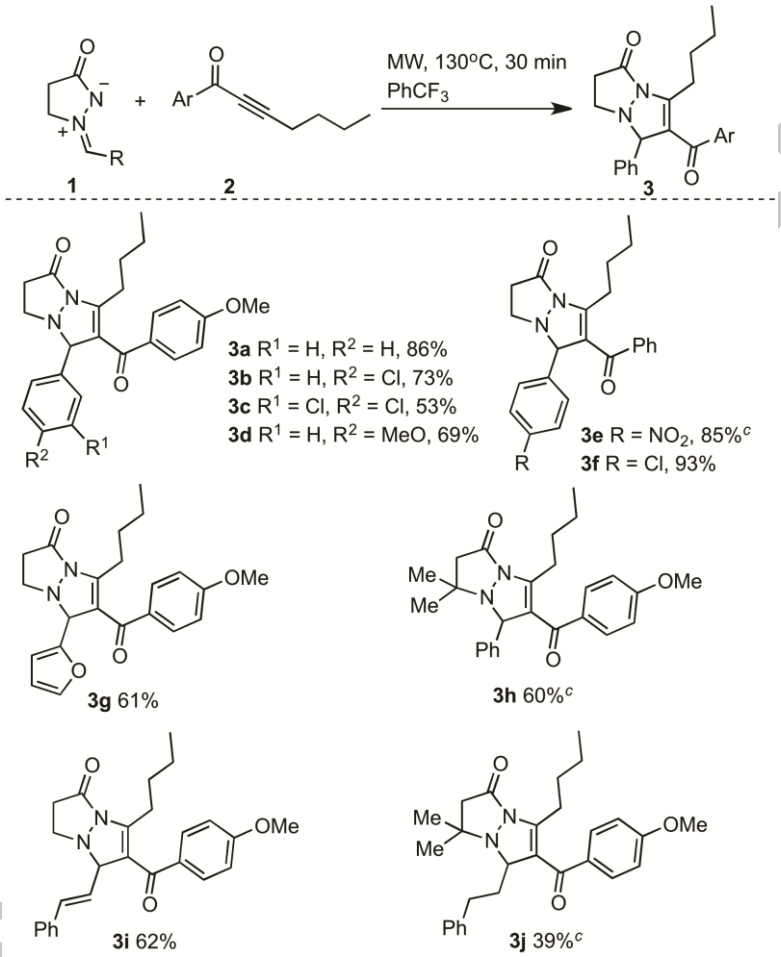
[h] Heated at 130 ^{o}C for 5 hours by conventional heating.

As we have identified the optimal reaction conditions for the dipolar cycloaddition, we then examined generality of substrates. As shown in Table 2, azomethine imines derived from aromatic and heteroaromatic aldehydes can provide corresponding products in moderate to excellent yields ranging from 53% to 93%. With respect to substituted pyrazolidinone ring of the dipole, the reaction gave compound **3h** in slightly decreased yield (60%) even at higher reaction temperature, probably due to steric reason. Product **3i** bearing alkenyl group could be successfully obtained under the current conditions (62%). Aliphatic aldehyde derived azomethine imine was then submitted to this procedure affording compound **3j** in relatively

low yield (39%) because of the poor reactivity.

Table 2

Examination of Substrate Scope[a,b]



[a] Unless otherwise noted, reaction was performed with 0.2 mmol of **1** and 0.4 mmol of **2** in 1.0 mL of $PhCF_3$ irradiated by microwave for 30 minutes.

[b] Isolated yield.

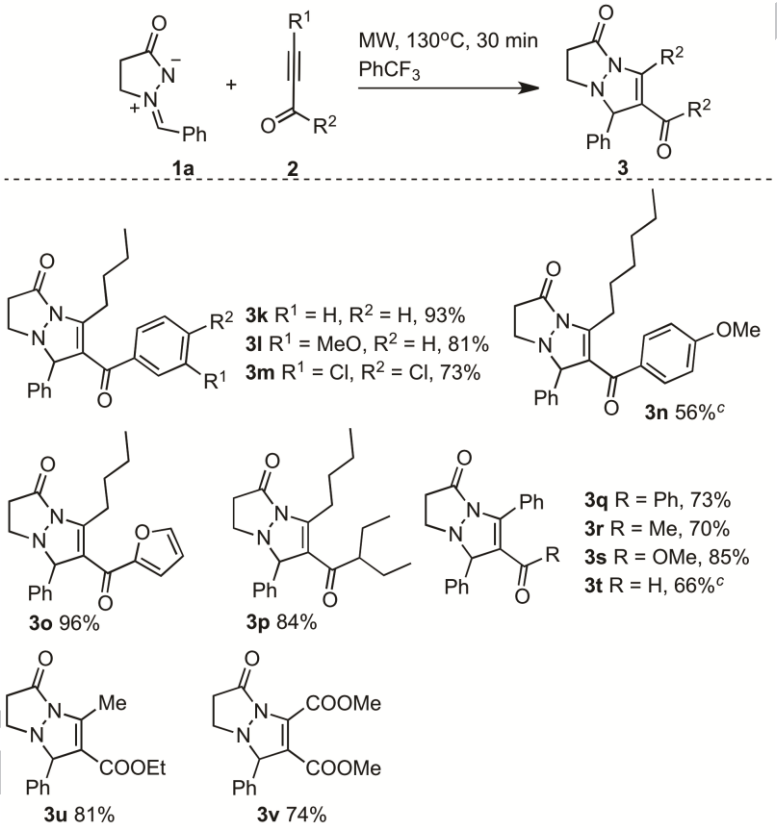
[c] Irradiated by microwave at 140 °C for 30 minutes.

Next, we examined the substrate scope of electron-deficient alkynes. As shown in Table 3, all the tested alkynes provided moderate to excellent yields of *N,N*-bicyclic pyrazolidinones. Aromatic ynones bearing electron-donating or electron-withdrawing groups as well as ynone bearing longer chain can react with azomethine imine smoothly affording desired *N,N*-bicyclic pyrazolidinones in moderate to good yields (56-93% yields). 2-Furyl-substituted ynone was a good candidate for this dipolar cycloaddition giving excellent yield (96%). Ynone bearing aliphatic substitution on both terminals gave compound **3p** in good yield (84%). Products **3r** and **3s** could be obtained when 4-phenylbut-3-yn-2-one and

1,3-diphenylprop-2-yn-1-one were submitted to this system.[16] Methyl phenylpropargylate and phenylpropiolaldehyde are both successful substrates affording corresponding products in 85% and 66% yields respectively. Ethyl 2-butynoate and dimethyl acetylenedicarboxylate can also be tolerated in this process.

Table 3

Examination of Substrate Scope[a,b]

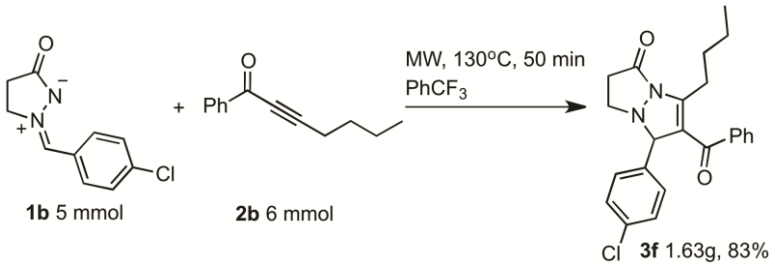


[a] Unless otherwise noted, reaction was performed with 0.2 mmol of **1** and 0.4 mmol of **2** in 1.0 mL of $PhCF_3$ irradiated by microwave for 30 minutes.

[b] Isolated yield.

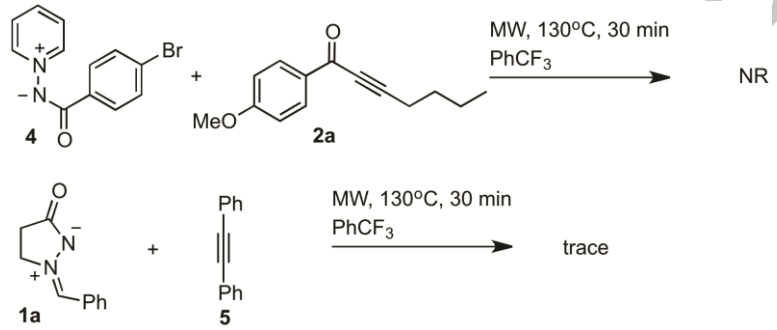
[c] Irradiated by microwave at 140 °C for 30 minutes.

This procedure could be easily scaled up for further biomedical research. As shown in scheme 1, treatment of **1b** and **2b** at 130 °C for 50 min under Microwave irradiation provided 1.63 g of *N,N*-bicyclic pyrazolidinone **3f.**



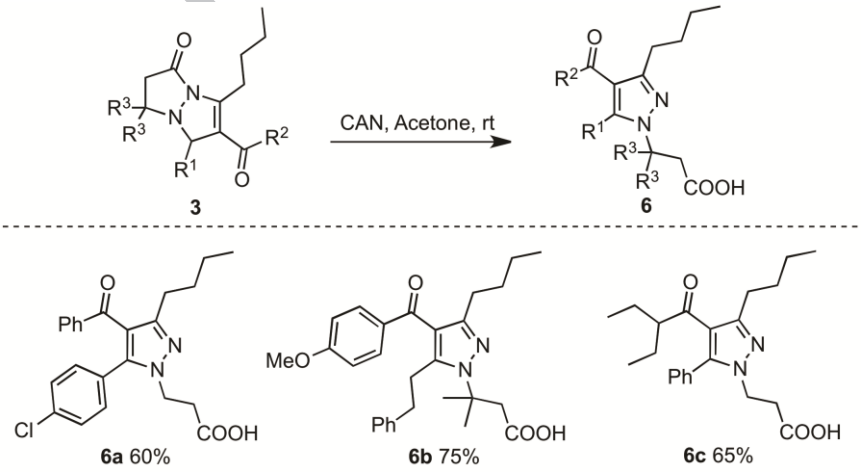
Scheme 1. Gram-scale reaction

As we have shown the generality of this methodology for various *N,N*-cyclic azomethine imines, we tried to expand to *C,N*-cyclic azomethine imines (Scheme 2). However, no reaction occurred when pyridine derived *C,N*-cyclic azomethine imine **4** and ynone **2a** were treated under the current conditions. We also tested unactivated alkyne **5** in order to further extend the substrate scope, but low conversion was observed even at higher temperature. Since we failed to afford desired products from *C,N*-cyclic azomethine imine or unactivated alkyne, we can see the limitations of this process.



Scheme 2. Limitations of substrate scope

To further demonstrate the utility of this process, we tested the aromatization reaction by oxidized with CAN. The desired fully substituted pyrazole **6** could be obtained through oxidative aromatization along with ring opening.



Scheme 3. Transformation of *N,N*-bicyclic pyrazolidinone

In conclusion, we have developed a catalyst-free 1,3-dipolar cycloaddition of azomethine imines with internal alkynes. Various *N,N*-bicyclic pyrazolidinones could be prepared under microwave irradiation in moderate to excellent yields (up to 96%). This

process has shown significant potential for inexpensive, rapid and easy access to pharmacologically relevant molecules and could be easily scaled up for further biomedical research. Fully substituted pyrazole can be obtained by easy transformation of *N,N*-bicyclic pyrazolidinone.

Acknowledgments

We are grateful for the support provided for this study by the National Science Foundation of China (21502013), the Scientific and Technological Research Program of the Chongqing Municipal Education Commission (KJ1501111), and Chongqing University of Arts and Sciences (R2015BX01).

Supplementary data

Supplementary data (experimental procedures, characterization data, copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds and crystallographic information on compound **3e**) associated with this article can be found.

References and notes

1. (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles,* 2nd ed.; Wiley-VCH: Weinheim, 2003; (b) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron*, **1997,** *53,* 12789; (c) Davis, L. O. *Org. Prep. Proced. Int.*, **2013,** *45,* 437.

2. Jungheim, L. N.; Sigmund, S. K. *J. Org. Chem.* **1987,** *52,* 4007.

3. For reviews on 1,3-dipolar cycloaddition, see: (a) Hashimoto, T.; Maruoka, K. *Chem. Rev.*, **2015,** *115,* 5366; (b) Coldham, I.; Hufton, R. *Chem. Rev.*, **2005,** *105,* 2765; (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.*, **1998,** *98,* 863; (d) Stanley, L. M.; Sibi, M. P. *Chem. Rev.*, **2008,** *108,* 2887; (e) Nájera, C.; Sansano, J. M.; Yus, M. *Org. Biomol. Chem.*, **2015,** *13,* 8596.

4. (a) Dorn, H.; Otto, A. *Ber.* **1968,** *101,* 3287; (b) Dorn, H.; Otto, A. *Angew. Chem. Int. Ed. Engl.* **1968,** *7,* 214.

5. For recent examples on 1,3-dipolar cycloaddition of azomethine imines with terminal alkynes, see: (a) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.*, **2003,** *125,* 10778; (b) Hashimoto, T.; Takiguchi, Y.; Maruoka, K. *J. Am. Chem. Soc.*, **2013,** *135,* 11473; (c) Arai, T.; Ogino, Y.; Sato, T. *Chem. Commun.*, **2013,** *49,* 7776; (d) Keller, M.; Sido, A. S. S.; Pale, P.; Sommer, J. *Chem.-Eur. J.* **2009,** *15,* 2810;

(e) Yoshimura, K.; Oishi, T.; Yamaguchi, K.; Mizuno, N. *Chem.-Eur. J.* **2011,** *17,* 3827; (f) Imaizumi, T.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc*., **2012,** *134,* 20049.

6. Hori, M.; Sakakura, A.; Ishihara, K. *J. Am. Chem. Soc.*, **2014,** *136,* 13198.

7. Gao, D.; Zhai, H.; Parvez, M.; Back, T. G. *J. Org. Chem.*, **2008,** *73,* 8057.

8. Luo, N.; Zheng, Z.; Yu, Z. *Org. Lett.*, **2011,** *13,* 3384.

9. For an example on 1,3-dipolar cycloaddition of azomethine imines with ynolates, see: Winterton, S. E.; Ready, J. M. *Org. Lett.*, **2016,** *18,* 2608.

10. Based on the hypothesis that allenes exhibit similar reaction mode as alkynes and alkenes, allenes have been used instead of alkynes, see: Na, R.; Liu, H.; Li, Z.; Wang, B.; Liu, J.; Wang, M.-A.; Wang, M.; Zhong, J.; Guo, H. *Tetrahedron*, **2012,** *68,* 2349.

11. For selected examples on catalyst free cycloaddition involving the use of azomethine imines, see: (a) Hu, X.-Q.; Chen, J.-R.; Gao, S.; Feng, B.; Lu, L.-Q.; Xiao, W.-J. *Chem. Commun.*, **2013,** *49,* 7905; (*b*) Turk, C.; Svete, J.; Stanovnik, B.; Golič, L.; Golič-Grdadolnik, S.; Golobič, A.; Selič, L. *Helv. Chim. Acta.*, **2001,** *84,* 146; (*c*) Soeta, T.; Tamura, K.; Ukaji, Y. *Org. Lett.*, **2012,** *14,* 1226; (d) Jungheim, L.N.; Sigmund, S.K.; Jones, N.D.; Swartzendruber, J.K. *Tetrahedron Lett.*, **1987,** *28,* 285; (e) Pezdirc, L.; Groselj, U.; Meden, A.; Stanovnik, B.; Svete, J. *J. Heterocyclic. Chem.*, **2008,** *45,* 181.

12. For selected examples on [3+2], [3+3] and [4+3] annulations of azomethine imines with alkynes under nucleophilic catalysis, see: (a) Liu, J.; Liu, H.; Na, R.; Wang, G.; Li, Z.; Yu, H.; Wang, M.; Zhong, J.; Guo, H. *Chem. Lett.*, **2012,** *41,* 218; (*b*) Liang, L.; Huang, Y. *Org. Lett.*, **2016,** *18,* 2604; (c) Li, Z.; Yu, H.; Feng, Y.; Hou, Z.; Zhang, L.; Yang, W.; Wu, Y.; Xiao, Y.; Guo, H. *RSC Adv.*, **2015,** *5,* 34481.

13. For selected examples on annulations of azomethine imines with allenes, see: (a) Zhou, W.; Li, X.-X.; Li, G.-H.; Wu, Y.; Chen, Z. *Chem. Commun.*, **2013,** *49,* 3552; (*b*) Wang, D.; Lei, Y.; Wei, Y.; Shi, M. *Chem.-Eur. J.* **2014,** *20,* 15325; (c) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard ш, W. A.; Guo, H.; Kwon, O. *J. Am. Chem. Soc.*, **2011,** *133,* 13337.

14. CCDC 1491045 for compound **3e**. See supporting information for details.

15. For reviews on microwave assisted organic synthesis, see: (a) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.*, **2002,** *35*, 717; (b) Roberts, B.; Strauss, C. R. *Acc. Chem. Res.*, **2005,** *38*, 653; (c) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95; (d) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001,** *57*, 9225; (e) Perreux, L.; Loupy, A. *Tetrahedron* **2001,** *57*, 9199.

16. In Huang group's work, [3+3] cycloaddition product was formed instead of compound **3r** when azomethine imines reacted with 4-phenylbut-3-yn-2-one in the presence of phosphine catalyst, see: Ref 12b.

17. (a) Shintani R.; Hayashi, T. *Org. Lett.*, **2005,** *7*, 2071; (b) Li, W.; Wu, X.-F. *Org. Biomol. Chem.*, **2015,** *13*, 5090.

Highlights

- A metal and catalyst free 1,3-dipolar cycloaddition has been developed.
- Gram-scale reaction could be achieved.
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