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Tuning the Annulation Reactivity of Vinyl Azides and Carbazates: A Divergent Synthesis of Aza-pyrimidinones and Imidazoles

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Supporting Information

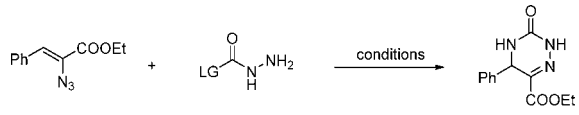
ABSTRACT: A divergent cascade annulation has been developed using readily available vinyl azides and carbazates with a wide range of substituents. Vinyl azides were successfully applied as bifunctional partners to prepare aza-pyrimidinones via 6-ring closure with carbazates as well as to construct polyfunctionalized imidazoles via 5-ring closure with *N*-substituted carbazates. The aza-heterocycles were obtained with high levels of chemoselectivity and excellent yields.

Aza-heterocycles are present as core scaffolds in many natural products with a wide spectrum of biological activity. Consequently, the efficient and selective construction of these heterocycles is of importance.[1] The divergent synthesis strategy appears to be popular and useful in the construction of aza-heterocycles, requiring an understanding of the reactivity and chemoselectivity of intermediates and substrates.[2,3] Vinyl azides possess unique chemical reactivity and serve as versatile synthons for the synthesis of various aza-heterocycles.[4,5] Recently, our group has been interested in exploring the potential reactivity of vinyl azides with a range of reactive partners.[6]

Carbazates, namely as "blocked" hydrazines, bear unique functionalities.[7] Carbazates could *in situ* generate amino isocyanates via thermolysis, which possess the electrophilic nature of isocyanates and the nucleophilicity of the only nitrogen atom.[7b] In the above-mentioned case, the reactivity of carbazates has shifted from ambident molecules[8] to amphoteric reagents. While pioneering work showed that vinyl azides and carbazates favorably undergo a thermal reaction to form the reactive intermediates 2*H*-aziridines and amino isocyanates respectively, the efficiency of their cascade reactions remained speculative.

Our efforts toward this putative reactivity initiated using vinyl azides **1a** and various carbazates **2**. Gratifyingly, we observed the formation of aza-pyrimidinone **3a** with an acceptable yield (85%) in dioxane at 130 °C (Table 1, entry 1). The aza-pyrimidinone derivatives are reported to have valuable pharmacological properties, such as being Gpr119 agonists[9a] and a modulator of the Edg-2 receptor.[9b] Further studies found that the solvent and temperature of the reaction have a significant impact on the efficiency for the formation of **3a**. When the reaction was carried out at 130 °C in MeCN, the yield of **3a** slightly improved to 89% (Table 1, entry 2). While the reaction yield (Table 1, entry 3, 20%) significantly decreased in toluene under the identical reaction conditions.

Table 1. Optimization of the Reaction Conditions



1a **2** **3a**

entry	conditions[a]	LG	yield [%][b]
1	Dioxane, 130 °C, 6 h	O*t*-Bu	85
2	MeCN, 130 °C, 6 h	O*t*-Bu	89
3	Toluene, 130 °C, 6 h	O*t*-Bu	20
4	MeCN, 120 °C, 6 h	O*t*-Bu	86
5	MeCN, 80 °C, 6 h	O*t*-Bu	40
6	MeCN, 80 °C, 24 h	O*t*-Bu	45
7	MeCN, 130 °C, 6 h	OEt	<10
8	MeCN, 130 °C, 6 h	OPh	92

[a]Unless otherwise noted, the reactions were carried out with vinyl azides **1a** (0.3 mmol) and carbazates **2** (0.33 mmol) heating in solvents (0.5 M, sealed tubes). [b]Isolated yields.

Lowering the temperature to 80 °C for 6 or 24 h reduced the yields below 50% (Table 1, entries 5−6). Screening of the leaving groups (LG) revealed that the *tert*-butoxy (O*t*-Bu) and phenoxyl (OPh) groups worked efficiently, thus leading to **3a** in 86% and 92% yields, respectively (entries 4 and 8). In contrast, the ethoxy (EtO) group in **2** suppressed the formation of **3a** (Table 1, entry 7).

With the optimal reactivity defined at 130 °C in MeCN, the generality of this aza-pyrimidinone synthesis was next explored using a series of vinyl azides **1** and carbazates **2** (Scheme 1). *β*-Aryl substituted vinyl azides reacted smoothly with carbazates **2** in excellent yields (80%−95%), allowing the introduction of electron-rich and -deficient benzene rings as the substituent R_1

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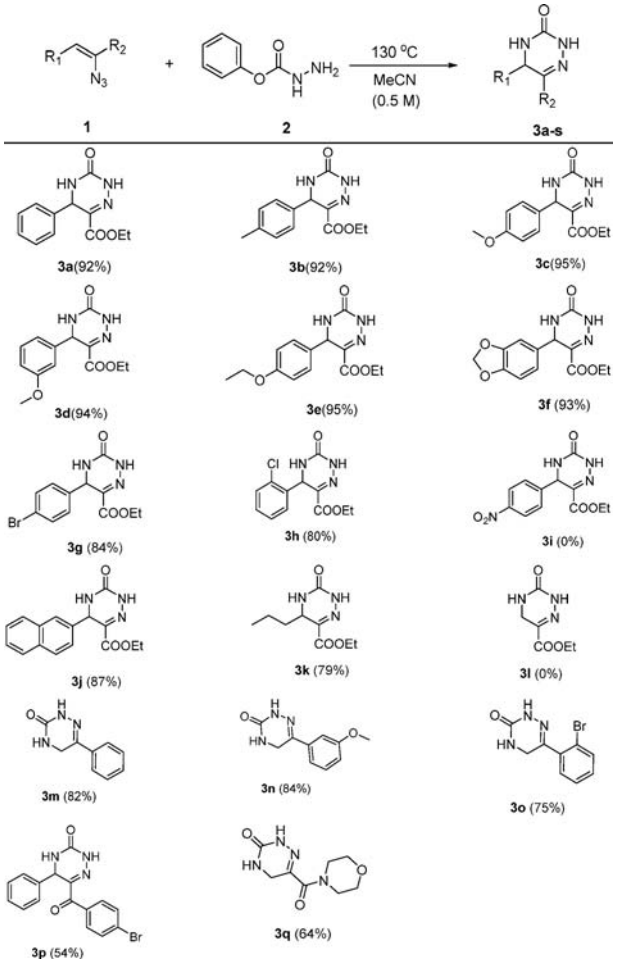
Scheme 1. Scope of Aza-pyrimidinone from Vinyl Azides 1 and Carbazates 2[a]



[a]Reaction conditions: vinyl azides **1** (1.0 mmol), carbazates **2** (1.1 mmol) in MeCN (0.5 M) heated in a sealed tube (130 °C, 6 h). Yields shown are those of the isolated products.

(for **3b**−**3g**), as well as the sterically hindered 2-chlorophenyl group (for **3h**). However, the reaction with a strongly electron-deficient vinyl azide having a 4-nitrobenzene ring as R_1 resulted in no formation of the desired product **3i**. A *β*-alkyl substituted vinyl azide was also capable of coupling with carbazate **2** to yield the product **3k** in 79%, while a *β*-hydrogen substituted vinyl azide failed to obtain the product **3l**. This may be due to the instability of 2*H*-azirdine generated. We next examined the compatibility of various *α*-substituted vinyl azides **1** in this synthesis. Installation of aryl groups as the substituent R_2 favored the reactions to deliver aza-pyrimidone **3m**−**3o** in excellent yields (75%−84%). Likewise, replacement of substituents R_2 with the aryl carbonyl or 6-morpholinyl carbonyl group could also be realized in this reaction, albeit in moderate yields (for **3p**, 54%; for **3q**, 64%).

Products **3a**−**3q** were characterized by ^{1}H and ^{13}C NMR spectra as well as HRMS analysis. The structure of one representative product **3e** was further confirmed by X-ray analysis (Figure 1).

The so-obtained aza-dihydropyrimidinones could be further elaborated to oxidative dehydrogenation (Scheme 2). For example, a solution of **3a** in the presence of a catalytic amount of $Cu(OAc)_2$, K_2CO_3, and 2.0 equiv of TBHP[10] afforded ethyl

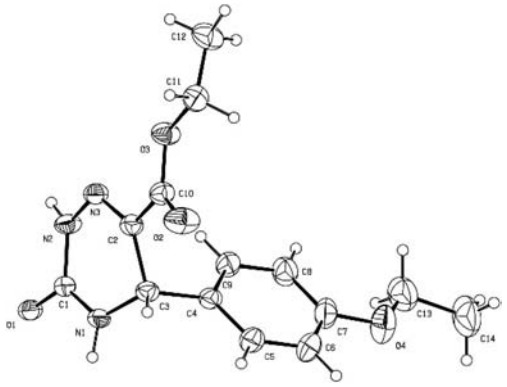
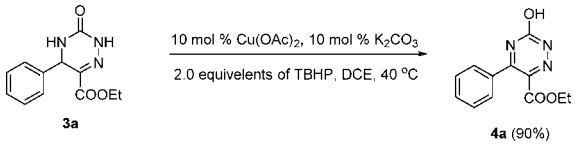


Figure 1. X-ray Crystal Structure of Product **3e** (CCDC 1406472).

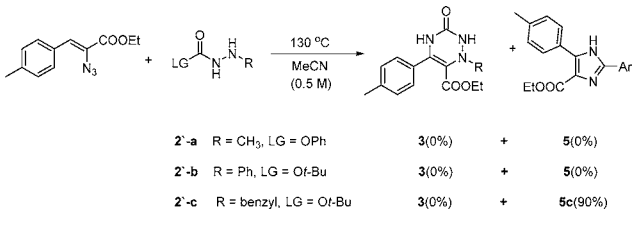
Scheme 2. Further Structural Elaboration of Aza-pyrimidinones 3



3-hydroxy-5-phenyl-1,2,4-triazine-6-carboxylate **4a** in 90% yield. And this extension would significantly broaden the applicability of this approach.

We next investigated the scope of *N*-substituted carbazates **2′** instead of carbazates **2**. The results turned out to be rather challenging (Scheme 3). In the case of *N*-methyl carbazate **2′-a**

Scheme 3. Cascade Reactions with *N*-Substituted Carbazates 2′



and *N*-phenyl carbazate **2′-b**, the reactions resulted in a complex mixture without the formation of desired aza-pyrimidinone product **3** under the reaction conditions stated above (Scheme 3). In the case of *N*-benzyl carbazate **2′-c**, the cyclization led to the selective formation of a five-membered imidazole **5c** over the six-membered aza-pyrimidinone **3** (Scheme 3).

The structure of product **5c** has been conclusively confirmed by single crystal X-ray analysis (Figure 2). The results unambiguously showed the special chemical reactivity of *N*-substituted carbazates **2′** in this present transformation, rather than via putative amino isocyanate intermediates reported in Scheme 1.

Based on the observed reactivity feature in this reaction, we further explored the generality of this cascade reactions. *β*-Aryl substituted vinyl azides reacted efficiently with *N*-substituted carbazates **2′** in excellent yields (75%−90%), allowing the introduction of electron-rich and -deficient benzene rings as the substituent R_1 (for **5a**−**5d** and **5f**−**5g**), as well as a heterocyclic substituent at the R_1 position (for **5e**). However, a *β*-hydrogen substituted vinyl azide failed to result in the desired product

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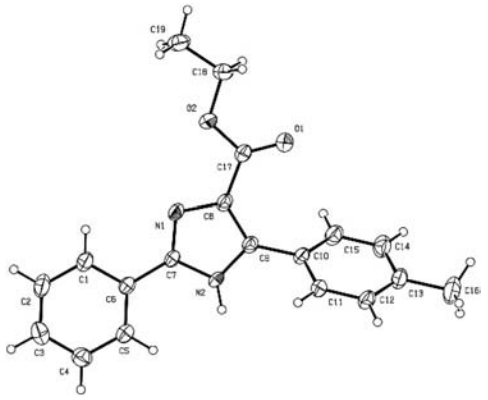
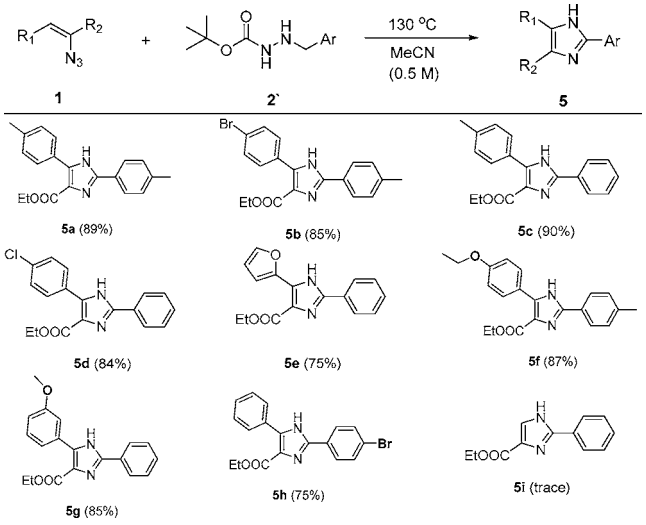


Figure 2. X-ray crystal structure of product **5c** (CCDC 1406473).

(for **5i**). When varying the groups on the Ar substituent of *N*-substituted carbazates **2′**, both electron-rich and -deficient benzene rings were tolerated by the present method and proceed efficiently with *N*-benzyl substituted carbazates **2′** in good to excellent yields (for **5a**, **5c**, and **5h**) (Scheme 4).

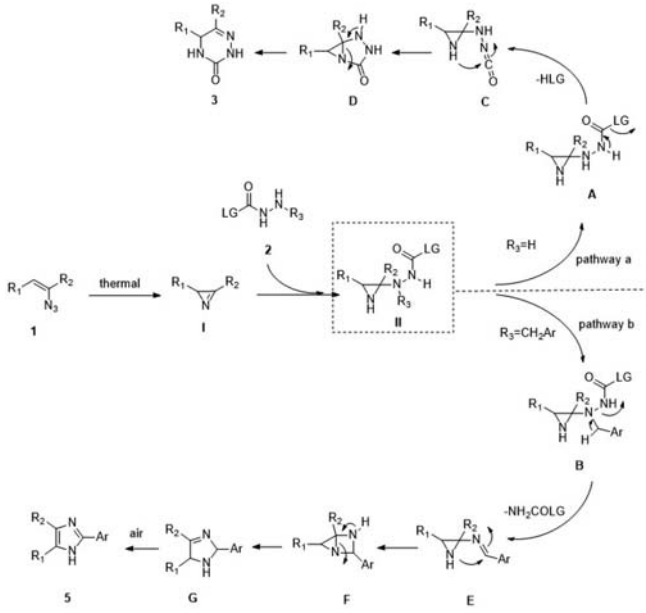
Scheme 4. Scope of Polyfunctionalized Imidazoles from Vinyl Azides 1 and *N*-substituted Carbazates 2′[a]



[a]Reaction conditions: vinyl azides **1** (1.0 mmol), *N*-substituted carbazates **2′** (1.1 mmol) in MeCN (0.5 M) heated in a sealed tube (130 °C, 6 h). Yields shown are those of the isolated products.

On the basis of the above results, a plausible mechanism is outlined in Scheme 5. In the stated reaction conditions, vinyl azide **1** is converted to 2*H*-aziridine **I** by thermal decomposition. Subsequently, nucleophilic attack takes place between **I** and carbazates **2** leading to the adduct product **II**. In the case of H as substituent R_3 (pathway a), the resulting adduct **A** undergoes subsequent removal of HLG leading to amino-isocyanate intermediate **C**. Then, the intramolecular nucleophilic attack of the nitrogen of the aziridine to isocyanate gives the adduct **D**. Ring opening of the strained three-membered ring in adduct **D** affords aza-pyrimidinone **3**. An alternative 5-ring closure pathway leading to polyfunctionalized imidazoles was observed in the case of the benzyl group as substituent R_3 (pathway b). Nucleophilic attack similarly takes place between **I** and the benzyl substituted nitrogen atom of carbazates. Concomitant loss of a carbamate residue by cleavage of the

Scheme 5. Proposed Reaction Pathways Leading to Aza-pyrimidinone and Imidazoles



N−N bond of adduct **B** affords imine intermediate **E**.[11] Then, intermediate **E** undergoes a facile ring expansion to **G**. Finally, the product **5** is achieved through aromatization of **G**.

In summary, we have developed an efficient divergent approach for the controlled construction of aza-pyrimidinones or imidazoles from readily available vinyl azides and carbazates. The products were obtained with high levels of chemoselectivity and excellent yields. The broad applicability of the reaction sequence is remarkable for the rapid synthesis of a number of pharmaceutical agents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02180.

Crystallographic data for **3e** (CCDC 1406472) (CIF)
Crystallographic data for **5c** (CCDC 1406473) (CIF)
Experimental procedures, characterization, and spectral data of the final products (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Trost, B. M. *Science* **1983**, *219*, 245.
(2) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Kuruvilla, F. G.; Shamji, A. F.; Sternson, S. M.; Hergenrother, P. J.; Schreiber, S. L. *Nature* **2002**, *416*, 653.
(3) (a) Dixon, D. D.; Lockner, J. W.; Zhou, Q.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 8432. (b) Dai, H.-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222.
(4) Selected reactions with vinyl azides: (a) Xiang, L.; Niu, Y.; Pang, X.; Yan, R. *Chem. Commun.* **2015**, *51*, 6598. (b) Hu, B.; DiMagno, S. G. *Org. Biomol. Chem.* **2015**, *13*, 3844. (c) Wang, Y.-F.; Lonca, G. H.; Chiba, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 1067. (d) Zhu, X.; Wang, Y.-F.; Zhang, F.-L.; Chiba, S. *Chem. - Asian J.* **2014**, *9*, 2458. (e) Donthiri, R. R.; Pappula, V.; Reddy, N. N.; Bairagi, D.; Adimurthy, S. *J. Org. Chem.* **2014**, *79*, 11277. (f) Jung, N.; Bräse, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 12169. (g) Sajna, K. V.; Kumara Swamy, K. C. *J. Org. Chem.* **2012**, *77*, 8712. (h) Wang, Y. F.; Toh, K. K.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 6411. (i) Wang, Y.-F.; Toh, K. K.; Lee, J.-Y.; Chiba, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 5927.
(5) (a) Timén, Å. S.; Risberg, E.; Somfai, P. *Tetrahedron Lett.* **2003**, *44*, 5339. (b) Chiba, S.; Wang, Y.-F.; Lapointe, G.; Narasaka, K. *Org. Lett.* **2008**, *10*, 313.
(6) Selected reactions with vinyl azides: (a) Zhang, G.; Chen, B.; Guo, X.; Guo, S.; Yu, Y. *Adv. Synth. Catal.* **2015**, *357*, 1065. (b) Liu, S.; Chen, W.; Luo, J.; Yu, Y. *Chem. Commun.* **2014**, *50*, 8539. (c) Zhang, G.; Ni, H.; Chen, W.; Shao, J.; Liu, H.; Chen, B.; Yu, Y. *Org. Lett.* **2013**, *15*, 5967. (d) Shao, J.; Yu, W.; Shao, Z.; Yu, Y. *Chem. Commun.* **2012**, *48*, 2785. (e) Chen, W.; Hu, M.; Wu, J.; Zou, H.; Yu, Y. *Org. Lett.* **2010**, *12*, 3863.
(7) (a) Vincent Rocan, J.-F.; Clavette, C.; Leckett, K.; Beauchemin, A. M. *Chem. - Eur. J.* **2015**, *21*, 3886. (b) Clavette, C.; Vincent Rocan, J.-F.; Beauchemin, A. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12705. (c) Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A. B.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16111. (d) Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C. J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740.
(8) Nigst, T. A.; Ammer, J.; Mayr, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1353.
(9) (a) Grauert, M.; Barker, R.; Breitfelder, S.; Buettner, F.; Eickelmann, P.; Fox, T.; Grundl, M.; Lehmann-Lintz, T. WO2011138427. (b) Shankar, G.; Solow-Cordero, D.; Spencer, J. V.; Gluchowski, C. WO2003062392.
(10) Yamamoto, K.; Chen, Y. G.; Buono, F. G. *Org. Lett.* **2005**, *7*, 4673.
(11) Attanasi, O. A.; Davoli, P.; Favi, G.; Filippone, P.; Forni, A.; Moscatelli, G.; Prati, F. *Org. Lett.* **2007**, *9*, 3461.

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