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Synthesis of Fully Substituted Pyrroles through a Copper-Catalyzed Aza-Michael/Claisen Rearrangement/Cyclization Cascade

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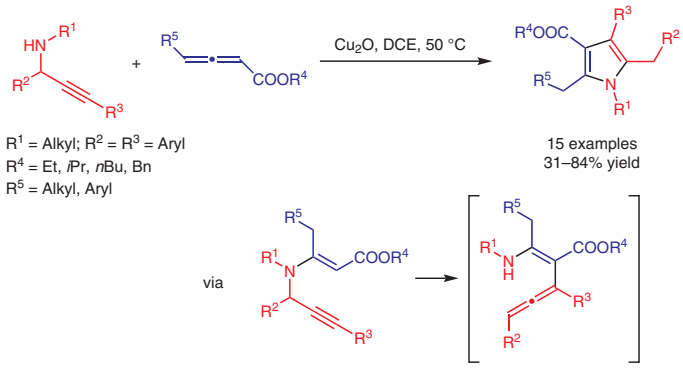

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Abstract We have developed a copper-catalyzed aza-Michael/Claisen rearrangement/cyclization cascade sequence that affords structurally diverse pentasubstituted pyrroles in acceptable to good yields (31–84%).

Key words copper catalysis, Claisen rearrangement, aza-Michael reaction, pyrroles, propargylic amines, allenoates

Fully substituted pyrroles can be found widely as a privileged framework in natural products and pharmaceuticals, as well as being useful in materials science (Figure 1).[1] For example, atorvastatin (Lipitor) is a statin medication used for the prevention of cardiovascular disease and for the treatment of abnormal lipid levels. URB447, as the first mixed CB1 antagonist/CB2 agonist, can be used for reducing food intake and body-mass gain without entering the brain or antagonizing central CB1-dependent responses in mice. Storniamide A is member of a new class of secondary metabolites isolated from a Patagonian sponge that shows antibiotic activity against Gram-positive bacteria. The lamel-

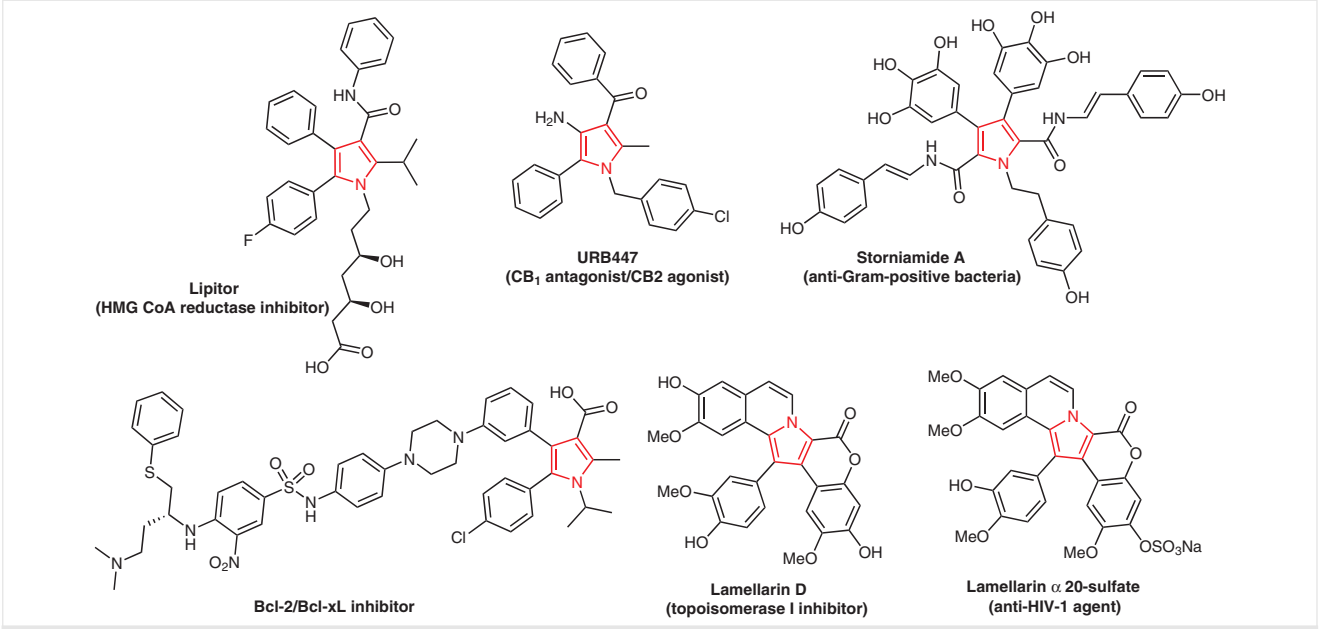

Figure 1 Representative examples

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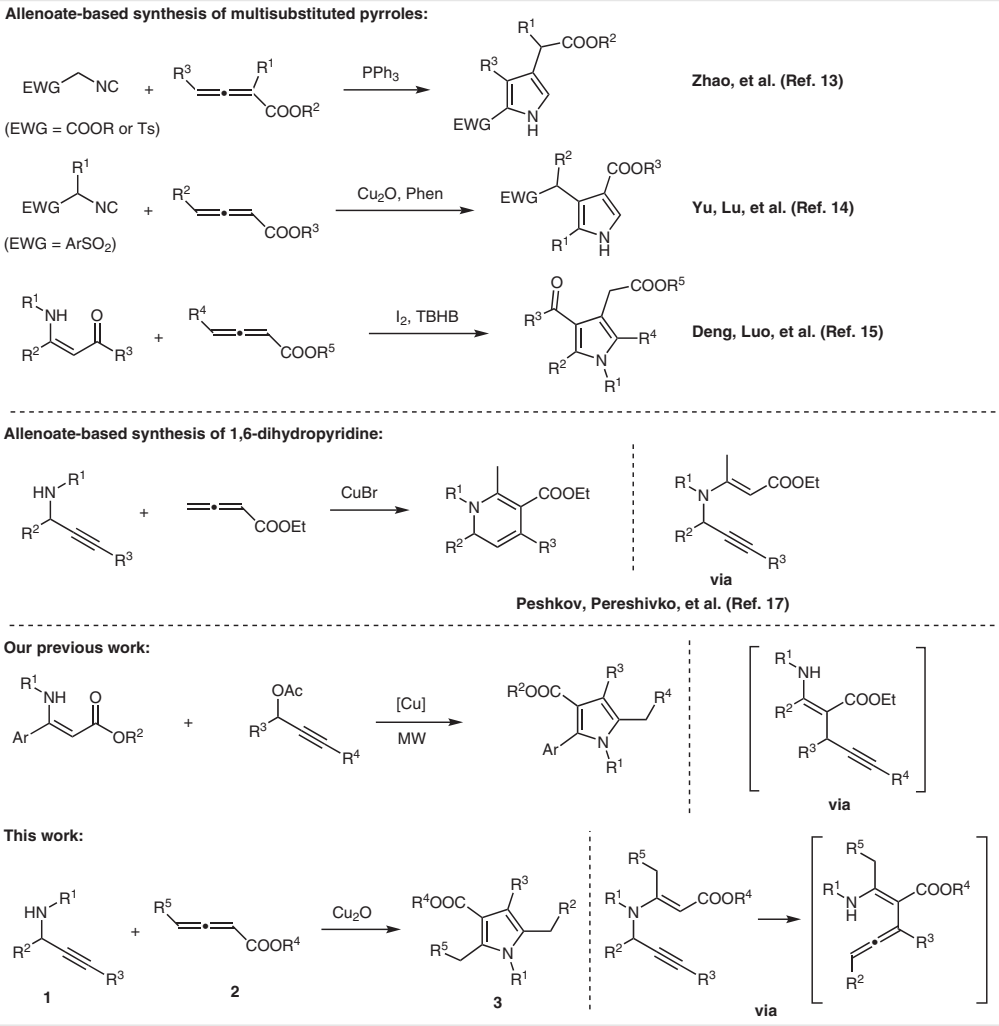
larin family of alkaloids, most of which contain a fully substituted pyrrole moiety, show a diverse range of biological activities, including cytotoxicity, antitumor activity, reversal of multidrug resistance, HIV-1 integrase inhibition, and antibiotic activity. In addition, pentasubstituted pyrroles are important building blocks in the synthesis of natural products and biological molecules. Consequently, the development of simple and efficient approaches for constructing highly functionalized pentasubstituted pyrroles from easily accessible starting material has attracted much attention in the fields of synthetic chemistry and medicinal chemistry.[2]

Many elegant synthetic methods for constructing fully substituted pyrroles have been developed, including multicomponent reactions,[3] 1,3-dipolar reactions,[4] C–H activations,[5] oxidative coupling cyclization reactions,[6] rearrangement-based cascade sequences,[7] and alkyne azacyclization-based [4+1] annulations.[8,9] In these well-documented protocols, enamino carbonyl compounds always play an important role, either as starting materials or as key intermediates formed in situ. These facts suggested that the construction of novel pentasubstituted pyrroles might be realized by rational design of a key enamino carbonyl intermediate generated in situ in a catalytic system.

Previously, we have reported a copper-salt-catalyzed synthesis of α-arylated pentasubstituted pyrroles through a propargylation/carbocyclization/isomerization cascade sequence of enamino esters and propargylic acetates.[10] A C-propargylated enamino ester was proposed as the key intermediate for this transformation. By the same strategy, we have also successfully prepared α-aryl tetrasubstituted pyrroles through the formation of C-propargylated enamino esters from propargylic 1,3-dicarbonyl compounds and amines. Inspired by recent achievements and thinking along this line, we hypothesized that the ready formation of N-propargylated enamino esters from propargylic amines and allenoates might provide multifunctional pentasubstituted pyrroles efficiently through a cyclization/isomerization cascade in the presence of a copper catalyst (Scheme 1).



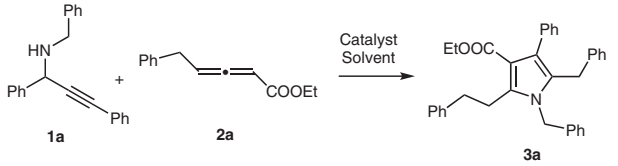
Scheme 1 Allenoate-based synthesis of pyrroles and dihydropyridine

Since the publication of Lu, Zhang, and co-workers' [3+2] pioneering cyclization,[11] allenoate-based transformations have been widely used in the preparation of nitrogen-containing biologically important heterocycles. Although alkynoates and ynones have been employed as effective synthons for the construction of pentasubstituted pyrroles, few examples have been reported of allenoate-based syntheses of highly substituted pyrroles.[12] More recently, the Zhao group reported a convenient organocatalytic synthesis of substituted pyrroles from allenoates and activated isocyanides.[13] Later, Yu, Lu, and co-workers reported a copper-catalyzed synthesis of substituted pyrroles through cyclization of allenoates with activated isocyanides.[14] A novel I_2-catalyzed Michael/oxidative annulation cascade of allenoates and enamines to give polysubstituted pyrroles has also been developed.[15,16] Interestingly, Peshkov, Pereshivko, and co-workers studied a copper-catalyzed protocol for the synthesis of 1,6-dihydropyridines from propargylic amines and ethyl buta-2,3-dienoate.[17] In their study, 6-*endo*-*dig* cyclization of N-propargylated enamino esters generated in situ delivered dihydropyridines. As part of our continuing efforts to develop efficient methods for constructing highly functionalized privileged heterocycles,[18,19] we aimed to develop an allenoate-based method for the ready assembly of polysubstituted pyrroles. Here, we report our development of a synthesis of pentasubstituted pyrroles from propargylic amines and allenoates in the presence of Cu(I).

The reaction of *N*-benzyl-1,3-diphenylprop-2-yn-1-amine (**1a**) with ethyl 5-phenylpenta-2,3-dienoate (**2a**) was selected as a model reaction for optimization of the conditions. In sharp contrast to the report by Peshkov, Pereshivko, and co-workers, when the reaction was performed in the presence of CuI, the fully substituted pyrrole **3a** was isolated as the major product instead of a 1,6-dihydropyridine (Table 1, entry 1). Next, a range of metal catalysts, including copper, nickel, zinc, palladium, iron, scandium, ytterbium, silver, and gold catalysts, were tested (entries 2–21). Among these, the use of Cu_2O as catalyst afforded the best results in terms of the yield (entry 9; 57%). In many cases, the aza-Michael adduct of propargylic amine **1a** with allenoate **2a** was detected in the crude product by NMR spectroscopy, and poor conversions of this intermediate into product **3a**, as well as decomposition of materials and intermediates, resulted in low NMR yields. Unfortunately, further screening of solvents did not give better results (entries 22–27). Performing the reaction at a higher temperature or with a 40 mol% catalyst loading gave similar yields (entries 28–31). Disappointingly, the use of 2,2′-bipyridine had no positive effect on the yield (entry 32).

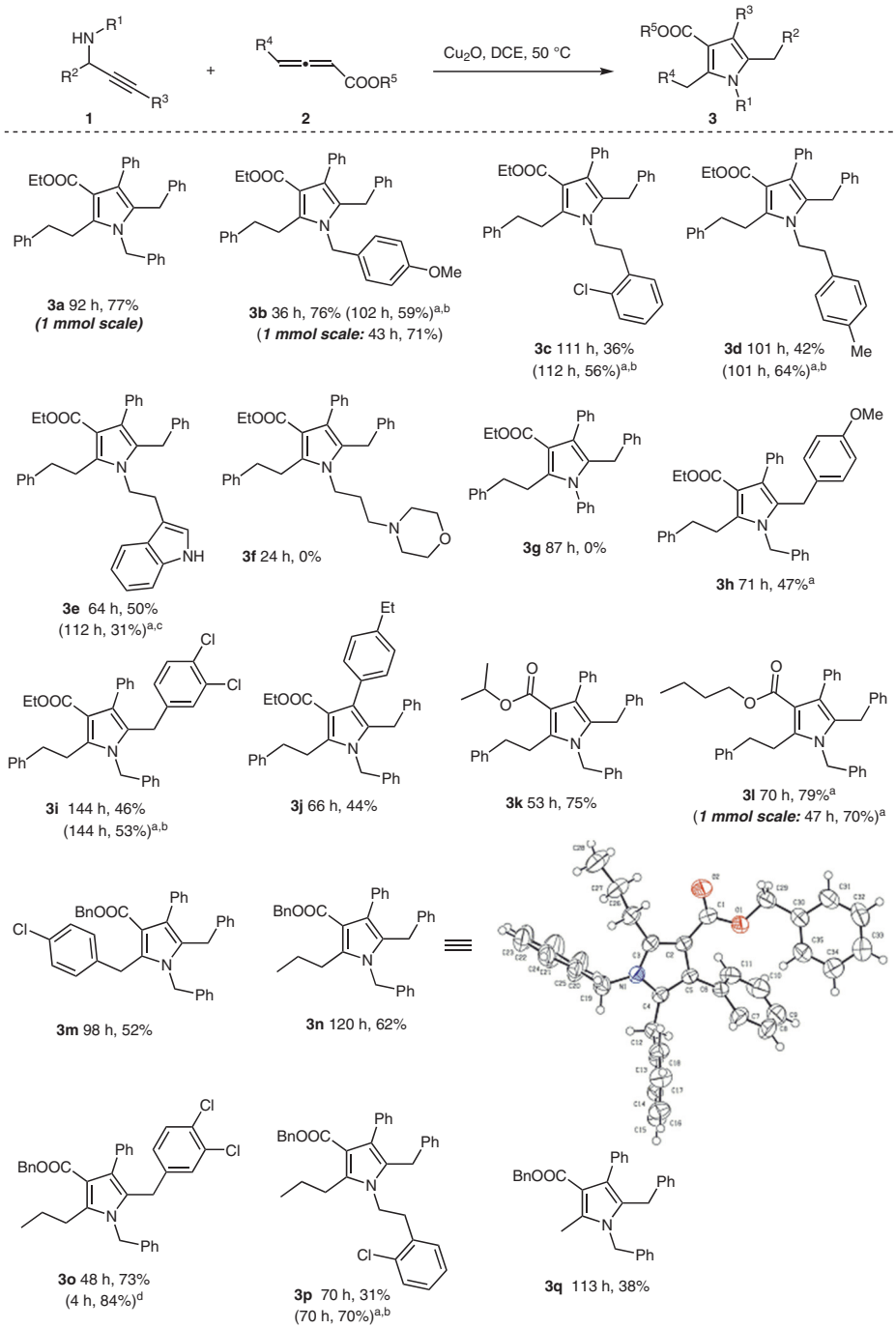
The substrate scope of this method was then examined in the presence of cuprous oxide with DCE as solvent at 50 °C. As shown in Scheme 2, variations of all five positions were successfully accommodated. Substituted benzyl, phenylethyl, and indolylethyl groups were incorporated at the N-1 position to give compounds **3a–e** in yields of 36–77%. It is worthy of note that performing the reaction on a 1 mmol scale gave good yields of **3a**, **3b**, and **3l**. However, a propargylic amine bearing a morpholinyl group failed to deliver the desired pyrrole **3f**; in this case, consumption of

Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	CuI	DCE	50	64	49
2	CuBr	DCE	50	65	27
3	$CuBr_2$	DCE	50	65	27
4	$Cu(OAc)_2$	DCE	50	65	35
5	CuCl	DCE	50	65	<10
6	$CuCl_2$	DCE	50	65	11
7	$Cu(OTf)_2$	DCE	50	65	12
8	$CuNO_3{\cdot}H_2O$	DCE	50	65	34
9	Cu_2O	DCE	50	71	57
10	$Ni(OTf)_2$	DCE	50	39	20
11	$Zn(OTf)_2$	DCE	50	71	30
12	$Pd(OAc)_2$	DCE	50	71	<10
13	$ZnBr_2$	DCE	50	71	13
14	$ZnCl_2$	DCE	50	71	38
15	$Fe_2(SO_4)_3$	DCE	50	71	<10
16	$FePO_4$	DCE	50	71	<10
17	$Sc(OTf)_3$	DCE	50	39	<10
18	$Yb(OTf)_3$	DCE	50	39	24
19	$AgSbF_6$	DCE	50	39	32
20	$AgBF_4$	DCE	50	39	<10
21	$AuPPh_3Cl$	DCE	50	39	<10
22	Cu_2O	*m*-xylene	50	88	36
23	Cu_2O	DMF	50	88	–
24	Cu_2O	DMSO	50	66	<10
25	Cu_2O	1,4-dioxane	50	66	<10
26	Cu_2O	iPrOH	50	67	16
27	Cu_2O	PhCl	50	48	31
28	Cu_2O	PhCl	130	4	52
29c	Cu_2O	PhCl	50	69	60
30c	Cu_2O	DCE–PhCl	50	48	45
31[c]	Cu_2O	DCE	50	70	50
32[d]	Cu_2O	PhCl	130	2	44

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.1 mmol), solvent (0.5 mL).
[b] Determined by ^1H NMR with CH_2Br_2 as internal standard.
[c] with 40 mol% catalyst.
[d] with 40 mol% of 2,2′-bipyridine as a ligand.



Scheme 2 Examination of the substrate scope. *Reagents and conditions*: **1** (0.2 mmol), **2** (0.3 mmol), Cu_2O (20 mol%), DCE (2.0 mL), 50 °C. [a] With 20 mol% of CuI as catalyst. [b] Yield determined by ^1H NMR with CH_2Br_2 as internal standard. [c] Isolated yield. [d] With PhCl as solvent at 130 °C.

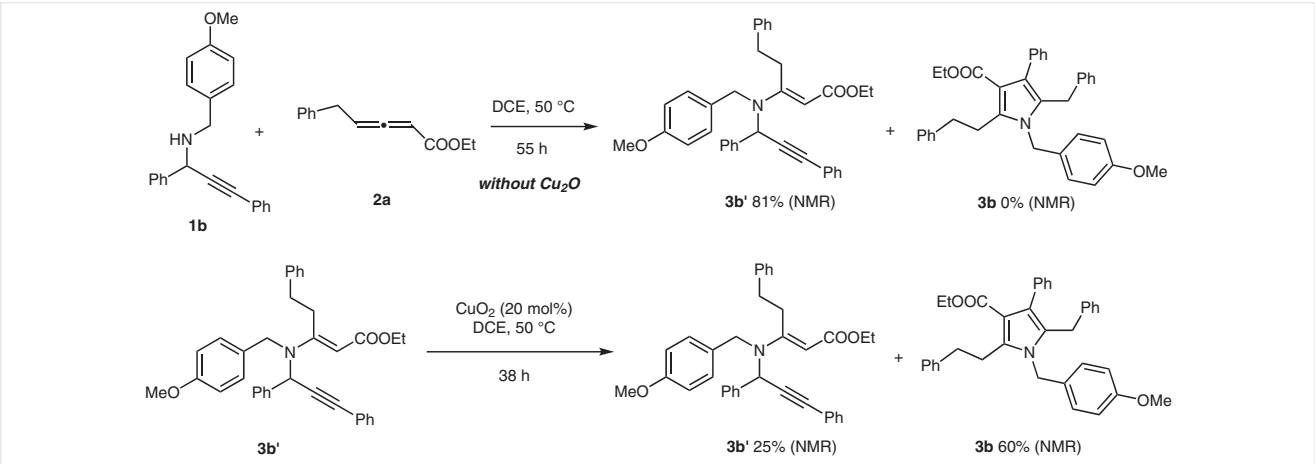
the propargylic amine was completed in a shorter time and a complicated mixture was obtained, probably due to the influence of the tethered tertiary amine moiety. Unfortunately, compound **3g** was not detected, probably due to the low reactivity of the arylamine-derived propargylic amine **1**. Variations in the phenyl group at R^2 (3,4-dichlorophenyl, 4-methoxyphenyl) and R^3 (4-ethylphenyl) of the propargylated amine **1** were accommodated, regardless of their electronic nature, giving compounds **3h**, **3i**, and **3j**.

The reactions of allenoates with isopropyl or butyl groups proceeded smoothly, giving compounds **3k** and **3l** in yields of 75 and 79%, respectively. In the case of benzyl 4-(4-chlorophenyl)buta-2,3-dienoate, the desired pyrrole **3m** was isolated in 52% yield. The use of alkylated allenoates readily gave the corresponding fully substituted pyrroles **3n–q** in yields of 31–73%. Interestingly, in contrast to the report of Peshkov, Pereshivko, and co-workers, the use of benzyl buta-2,3-dienoate afforded the pentasubstituted pyrrole **3q** as the major product under our catalytic conditions; this phenomenon cannot be rationally explained at present. Additionally, some reactions that gave low yields when Cu_2O was used as the catalyst were also conducted by using CuI instead of Cu_2O, because it was found that CuI can also act as an effective catalyst for this transformation. As shown in Scheme 2, the use of CuI as catalyst gave acceptable to good NMR yields (31–70%) of **3b–e**, **3i**, and **3p**. Although only moderate yields were observed in many cases, no significant byproducts were isolated from these reactions. Therefore, the possible decompositions of several intermediates and incomplete conversions of all intermediates into final products probably accounts for the unsatisfactory yields observed in many cases. The structure of **3n** was determined by X-ray single-crystal analysis, and structures of other compounds were assigned by analogy.[20]

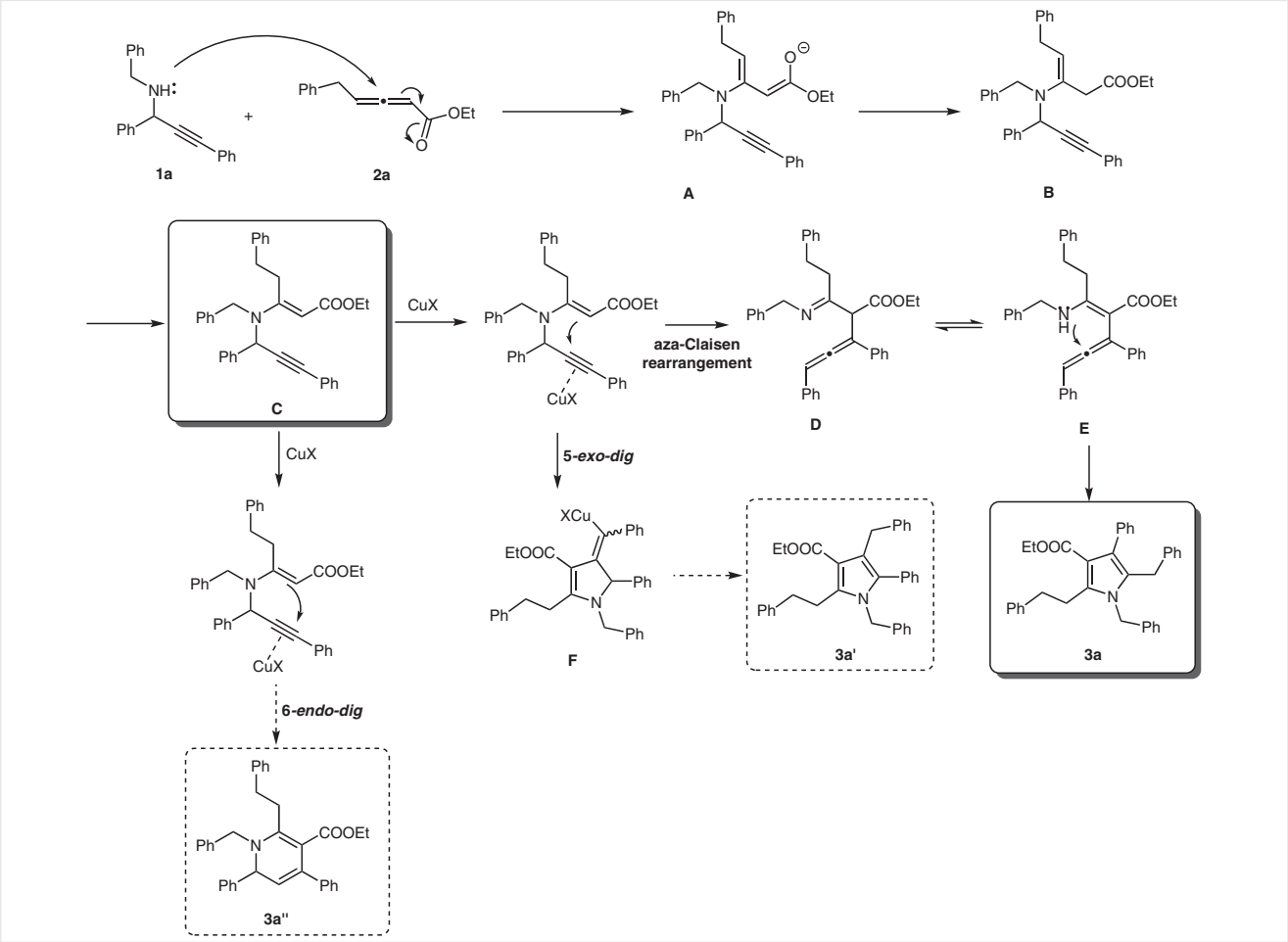
To get more evidence regarding the mechanism, we conducted several control experiments, as shown in Scheme 3. In the absence of copper salts, intermediate **3b′** was detected in 81% yield (NMR), and none of the fully substituted pyrrole **3b** was obtained. In Hanzawa and Saito's work, *N*-propargyl enaminones were used as starting materials for the synthesis of polysubstituted pyrroles through an aza-Claisen rearrangement with catalysis by a cationic N-heterocyclic carbene–gold complex.[7] We wished to know whether intermediate **3b′** isolated in this study might be used as a substrate for the synthesis of polysubstituted pyrroles. As expected, in the presence of a copper catalyst, an aza-Claisen rearrangement/annulation/isomerization cascade sequence occurred, affording pyrrole **3b** in 60% yield (NMR). This showed that the aza-Claisen rearrangement is a key step in the pyrrole synthesis.

A plausible mechanism shown in Scheme 4 is proposed on the basis of our results and previous reports.[7,21–23] The aza-Michael reaction of propargylic amine **1a** and allenoate **2a** gives intermediate **A**. Protonation of intermediate **A** leads to the formation of the N-propargylated enamine **B**, which in turn gives the N-propargylated enamino ester **C** through proton transfer. A copper-catalyzed aza-Claisen rearrangement then affords intermediates **D** and **E**, and a final cyclization delivers pyrrole **3a**. An aza-Claisen rearrangement was also regarded as the key step for the formation of polysubstituted pyrroles in the studies of Hanzawa, Saito, and Jin,[7,21] whereas an oxa-Claisen rearrangement was proposed in Binder and Kirsch's report on the synthesis of pyrrole from propargylic vinyl ethers and aromatic amines in a one-pot process.[22] In comparison with studies using preformed *N*-propargyl enaminones and enamino esters, the current method is distinguished by its in situ formation of N-propargylated enamino esters from easily available propargylic amines and allenoates. Pyrrole **3a′** and dihydropyridine **3a″**, generated from intermediate **C** through 5-*exo*-*dig* and 6-*endo*-*dig* reactions, respectively, were not detected in this study. The selectivity observed in this reaction is not yet fully understood.

In conclusion, we have developed a copper-catalyzed synthesis of fully substituted pyrroles. In the presence of Cu_2O, various pentasubstituted pyrroles were prepared in moderate to good yields (31–84%) through an aza-Michael/Claisen rearrangement/cyclization cascade.[24] Similar yields were obtained by using CuI as the catalyst. By isolation of intermediates and a control experiment, a copper-catalyzed aza-Claisen rearrangement was proposed to be the key step in the pyrrole synthesis.



Scheme 3 Control experiments



Scheme 4 Proposed reaction pathway.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691577.

References and Notes

(1) (a) LoVerme, J.; Duranti, A.; Tontini, A.; Spadoni, G.; Mor, M.; Rivara, S.; Stella, N.; Xu, C.; Tarzia, G.; Piomelli, D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 639. (b) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264; corrigendum: *Chem. Rev.* **2010**, *110*, 3850. (c) Baunbæk, D.; Trinkler, N.; Ferandin, Y.; Lozach, O.; Ploypradith, P.; Rucirawat, S.; Ishibashi, F.; Iwao, M.; Meijer, L. *Mar. Drugs.* **2008**, *6*, 514. (d) Zhou, H.; Aguilar, A.; Chen, J.; Bai, L.; Liu, L.; Meagher, J. L.; Yang, C.-Y.; McEachern, D.; Cong, X.; Stuckey, J. A.; Wang, S. *J. Med. Chem.* **2012**, *55*, 6149. (e) Roth, B. D. US 4681893, **1987**. (f) Roth, B. D. US 5273995, **1993**.

(2) For reviews on the synthesis of polysubstituted pyrroles, see: (a) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084. (b) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402. (c) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2014**, *43*, 4633. (d) Young, I. S.; Thornton, P. D.; Thompson, A. *Nat. Prod. Rep.* **2010**, *27*, 1801.

(3) (a) Liu, X.-t.; Huang, L.; Zheng, F.-j.; Zhan, Z.-p. *Adv. Synth. Catal.* **2008**, *350*, 2778. (b) Cadierno, V.; Gimeno, J.; Nebra, N. *Chem. Eur. J.* **2007**, *13*, 9973. (c) Narboni, N.; El Kaim, L. *Eur. J. Org. Chem.* **2017**, 4242. (d) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468. (e) Kayser, L. V.; Vollmer, M.; Welnhofer, M.; Krikcziokat, H.; Meerholz, K.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2016**, *138*, 10516. (f) Maiti, S.; Biswas, S.; Jana, U. *J. Org. Chem.* **2010**, *75*, 1674. (g) Attanasi, O. A.; Favi, G.; Mantellini, F.; Moscatelli, G.; Santeusanio, S. *J. Org. Chem.* **2011**, *76*, 2860. (h) Dhara, D.; Gayen, K. S.; Khamarui, S.; Pandit, P.; Ghosh, S.; Maiti, D. K. *J. Org. Chem.* **2012**, *77*, 10441. (i) Liu, W.; Jiang, H.;

Huang, L. *Org. Lett.* **2010**, *12*, 312. (j) Wang, X.; Xu, X.-P.; Wang, S.-Y.; Zhou, W.; Ji, S.-J. *Org. Lett.* **2013**, *15*, 4246. (k) Gujarathi, S.; Liu, X.; Song, L.; Hendrickson, H.; Zheng, G. *Tetrahedron* **2014**, *70*, 5267.

(4) (a) Lu, Y.; Arndtsen, B. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 5430. (b) Zou, Y.-Q.; Lu, L.-Q.; Fu, L.; Chang, N.-J.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2011**, *50*, 7171. (c) Huang, L.; Zhao, J. *Chem. Commun.* **2013**, *49*, 3751. (d) Yu, C.; Zhang, Y.; Zhang, S.; Li, H.; Wang, W. *Chem. Commun.* **2011**, *47*, 1036. (e) Li, Y.-J.; Huang, H.-M.; Dong, H.-Q.; Jia, J.-H.; Han, L.; Ye, Q.; Gao, J.-R. *J. Org. Chem.* **2013**, *78*, 9424. (f) Huang, H.-M.; Li, Y.-J.; Ye, Q.; Yu, W.-B.; Han, L.; Jia, J.-H.; Gao, J.-R. *J. Org. Chem.* **2014**, *79*, 1084. (g) Fujiya, A.; Tanaka, M.; Yamaguchi, E.; Tada, N.; Itoh, A. *J. Org. Chem.* **2016**, *81*, 7262.

(5) (a) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (b) Zhang, S.; Ma, Y.; Lan, J.; Song, F.; You, J. *Org. Biomol. Chem.* **2015**, *13*, 5867.

(6) Yan, R.-L.; Luo, J.; Wang, C.-X.; Ma, C.-W.; Huang, G.-S.; Liang, Y.-M. *J. Org. Chem.* **2010**, *75*, 5395.

(7) Saito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2010**, *12*, 372.

(8) (a) Wang, Y.; Bi, X.; Li, D.; Liao, P.; Wang, Y.; Yang, J.; Zhang, Q.; Liu, Q. *Chem. Commun.* **2011**, *47*, 809. (b) Sun, B.; Ma, Q.; Wang, Y.; Zhao, Y.; Liao, P.; Bi, X. *Eur. J. Org. Chem.* **2014**, 7552.

(9) (a) Tan, W. W.; Yoshikai, N. *Chem. Sci.* **2015**, *6*, 6448. (b) Guan, Z.-H.; Li, L.; Ren, Z.-H.; Li, J.; Zhao, M.-N. *Green Chem.* **2011**, *13*, 1664. (c) Bisht, S.; Peddinti, R. K. *J. Org. Chem.* **2017**, *82*, 13617. (d) Yoshida, M.; Sugimura, C. *Tetrahedron Lett.* **2013**, *54*, 2082.

(10) Zhang, X.-Y.; Yang, Z.-W.; Chen, Z.; Wang, J.; Yang, D.-L.; Shen, Z.; Hu, L.-L.; Xie, J.-W.; Zhang, J.; Cui, H.-L. *J. Org. Chem.* **2016**, *81*, 1778.

(11) (a) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906. (b) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836. (c) Lu, X.; Lu, Z.; Zhang, X. *Tetrahedron* **2006**, *62*, 457.

(12) For reviews on the synthesis of heterocycles using allenoates, see: (a) Yu, S.; Ma, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 3074. (b) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (c) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102.

(13) (a) Liao, J.-Y.; Shao, P.-L.; Zhao, Y. *J. Am. Chem. Soc.* **2015**, *137*, 628. (b) Kok, G. P. Y.; Shao, P.-L.; Liao, J.-Y.; Ismail, S. N. F. B. S.; Yao, W.; Lu, Y.; Zhao, Y. *Chem. Eur. J.* **2018**, *24*, 10513.

(14) Lu, K.; Ding, F.; Qin, L.; Jia, X.; Xu, C.; Zhao, X.; Yao, Q.; Yu, P. *Chem. Asian. J.* **2016**, *11*, 2121.

(15) Wang, Y.; Jiang, C.-M.; Li, H.-L.; He, F.-S.; Luo, X.; Deng, W.-P. *J. Org. Chem.* **2016**, *81*, 8653.

(16) For a two-step synthesis of pyrrole using an allenoate as a starting material, see: Grigg, R.; Savic, V. *Chem. Commun.* **2000**, 873.

(17) Liu, C.; Wang, G.; Wang, Y.; Pereshivko, O. P.; Peshkov, V. A. *Eur. J. Org. Chem.* **2019**, 1981.

(18) (a) Cui, H.-L.; Liu, S.; Jiang, L. *Eur. J. Org. Chem.* **2019**, 4941. (b) Yuan, C.; Tan, H.; Jiang, X.-F.; Liu, S.; Jiang, L.; Cao, Q.-Y.; Xu, X.-J.; Deng, X.-Y.; Pan, G.-N.; Chen, J.-Y.; Cui, H.-L. *Asian J. Org. Chem.* **2019**, *8*, 1893.

(19) For our recent efforts on the synthesis of N-containing heterocycles, see: (a) Cui, H.-L.; Jiang, L.; Tan, H.; Liu, S. *Adv. Synth. Catal.* **2019**, *361*, 4772. (b) Cui, H.-L.; Shi, Y.; Deng, H.-Q.; Lei, J.-J.; Xu, X.-J.; Tian, X.; Qiao, J.; Zhou, L. *Synlett* **2019**, *30*, 167. (c) Liu, S.-W.; Gao, Y.-J.; Shi, Y.; Zhou, L.; Tang, X.; Cui, H.-L. *J. Org. Chem.* **2018**, *83*, 13754. (d) Tang, X.; Yang, M.-C.; Ye, C.; Liu, L.; Zhou, H.-L.; Jiang, X.-J.; You, X.-L.; Han, B.; Cui, H.-L. *Org. Chem. Front.* **2017**, *4*, 2128.

(20) CCDC 1954351 contains the supplementary crystallographic data for compound **3n**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(21) Weng, J.; Chen, Y.; Yue, B.; Xu, M.; Jin, H. *Eur. J. Org. Chem.* **2015**, 3164.

(22) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151.

(23) Lambert, T. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 13646.

(24) **Pentasubstituted Pyrroles 3a–p; General Procedure**

Allenoate **2** (0.4 mmol, 2.0 equiv) was added to a mixture of the appropriate propargylic amine **1** (0.2 mmol, 1.0 equiv) and Cu_2O (20 mol%) in DCE (2.0 mL), and the mixture was stirred at 50 °C for the time shown in Scheme 2, without exclusion of air. The mixture was then directly purified by flash chromatography (silica gel, hexane–EtOAc).

Ethyl 1,5-dibenzyl-4-phenyl-2-(2-phenylethyl)-1*H*-pyrrole-3-carboxylate (3a)

Purified by a flash chromatography [silica gel, hexane–EtOAc (50:1)] as a yellow oil; yield: 382.6 mg (77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.11 (m, 14 H), 7.07 (dd, *J* = 6.8, 1.8 Hz, 2 H), 7.01–6.94 (m, 2 H), 6.81 (dd, *J* = 6.7, 1.9 Hz, 2 H), 4.54 (s, 2 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 3.72 (s, 2 H), 3.15 (dd, *J* = 8.7, 6.6 Hz, 2 H), 2.82 (dd, *J* = 8.6, 6.6 Hz, 2 H), 1.05 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 141.5, 139.6, 139.5, 137.5, 136.5, 130.5, 128.8, 128.6, 128.5, 128.4, 128.1, 127.8, 127.4, 127.4, 126.2, 126.1, 126.0, 125.5, 125.2, 110.9, 59.2, 46.9, 36.4, 30.3, 28.2, 13.9. ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{35}H_{34}NO_2$: 500.2584; found: 500.2589.

Ethyl 5-Benzyl-1-(4-methoxybenzyl)-4-phenyl-2-(2-phenylethyl)-1*H*-pyrrole-3-carboxylate (3b)

Purified by a flash chromatography [silica gel, hexane–EtOAc (25:1)] as a pale-yellow foam solid; yield: 373.5 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.05 (m, 11 H), 7.04–6.97 (m, 2 H), 6.95–6.88 (m, 2 H), 6.79–6.72 (m, 2 H), 6.67 (d, J = 8.5 Hz, 2 H), 4.43 (s, 2 H), 4.06 (q, J = 7.1 Hz, 2 H), 3.72 (s, 3 H), 3.66 (s, 2 H), 3.10 (dd, J = 8.8, 6.6 Hz, 2 H), 2.76 (dd, J = 8.7, 6.6 Hz, 2 H), 0.98 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 158.9, 141.5, 139.5, 139.5, 136.5, 130.5, 129.4, 128.5, 128.4, 128.4, 128.0, 127.8, 127.4, 126.7, 126.2, 126.0, 125.2, 114.4, 114.3, 110.8, 59.2, 55.3, 46.4, 36.4, 30.3, 28.2, 14.0. ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{36}H_{36}NO_3$: 530.2690; found: 530.2690.