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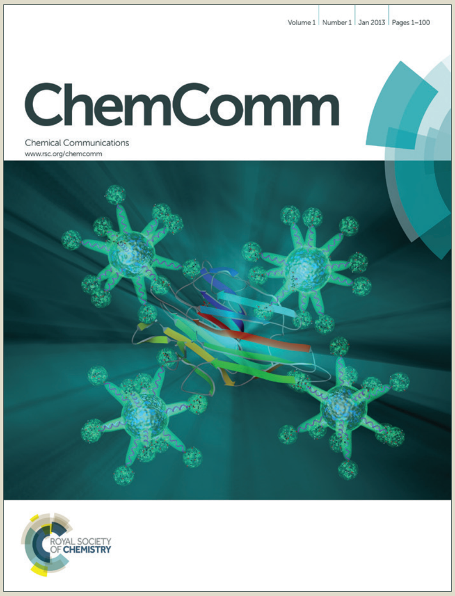

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Synthesis of Multi-Substituted Pyrroles Using Enamides and Alkynes Catalyzed by Pd(OAc)$_2$ with Molecular Oxygen as Oxidant†

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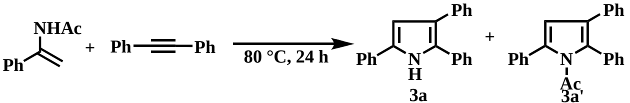
A cyclization reaction between enamides and alkynes catalyzed by palladium(II) acetate is described. In this method, the molecular oxygen serves as efficient oxidant for the Pd(II)/Pd(0) catalytic cycle. The simple reaction conditions permit this methodology to be a general tool for the preparation of multi-substituted pyrroles.

Pyrrole ring is a core structure featured in a wide variety of natural products, organic materials and pharmaceuticals.[1] They are also important industrial synthetic building blocks.[2] Consequently, the synthesis of the multi-substituted pyrroles has attracted much attention among organic chemists.[3] Among the methods developed, metal-mediated or -catalyzed reaction using enamides as the starting materialsis is one of the best methods to acccess the pyrrole products.[4] In 2006, Crawley and co-workers adapted the "Larock Indole Synthesis" approach and developed an efficient palladium-catalyzed pyrrole synthesis by the reaction of 2-amino-3-iodoacrylates with alkynes.[5] Following this finding, Stuart and Fagnou reported a rhodium(III)-catalyzed cyclization of enamides and alkynes to afford the pyrroles.[6] Simultaneously, Glorius found that the multi-substituted pyrroles could be achieved from the coupling of enamines with alkynes using [Cp*RhCl$_2$]$_2$ as catalyst via allylic sp^3 C–H activation of enamines.[7] Recently, Wang's and Ackermann's research groups respectively developed a ruthenium-catalyzed pyrrole synthesis reaction using enamides and alkynes as the starting materials.[8] Inspired by these pioneering work, and following our continuing interest in palladium-catalyzed enamide's β C–H bond direct functionalization,[9] we would like to report a new method to synthesize the multi-substituted pyrroles via coupling of enamides with alkynes catalyzed by palladium catalyst by using molecular oxygen as oxidant.[10] In this method, the need to use the performed halogenated substrates and excess amount of metal salt as oxidant are avoided.

The feasibility of the coupling reaction was initially examined using enamide **1a** and diphenylacetylene (Table 1). A careful examination of the solvents in the presence of 10 mol % Pd(OAc)$_2$ and 2 equivalents of NaOAc as additive revealed that DMSO is a better choice for this reaction (Table 1, entries 1-5). Different palladium catalysts were tested and only Pd(OAc)$_2$ could afford only the deacylation product **3a**. Other Pd(II) catalysts afforded the product in poor yield and/or chemoselectivity (Table 1, entries 7-10). When different bases were added as additive to promote the reaction, NaHCO$_3$ was found to efficiently afford a mixture of products (**3a**:**3a'** > 95:5)

Table 1. Optimization of the Reaction Conditions.[a]



entry	catalyst (mol%)	base	solvent	3a/3a'	yield (%)[b]
1	Pd(OAc)$_2$ (10)	NaOAc	toluene	--	--
2	Pd(OAc)$_2$ (10)	NaOAc	dioxane	--	--
3	Pd(OAc)$_2$ (10)	NaOAc	*t*-Am-OH	--	--
4	Pd(OAc)$_2$ (10)	NaOAc	DMF	--	--
5	Pd(OAc)$_2$ (10)	NaOAc	DMSO	> 99:1	53
6	Pd(OAc)$_2$ (10)	NaOAc	DMSO	> 99:1	17[c]
7	Pd(PhCN)$_2$Cl$_2$ (10)	NaOAc	DMSO	58:42	36
8	Pd(OTFA)$_2$ (10)	NaOAc	DMSO	98:2	32
9	Pd(acac)$_2$ (10)	NaOAc	DMSO	60:40	30
10	[Pd(CH$_3$CN)$_4$](BF$_4$)$_2$ (10)	NaOAc	DMSO	10:90	51
11	Pd(OAc)$_2$ (10)	NaHCO$_3$	DMSO	> 95:5	67
12	Pd(OAc)$_2$ (10)	K$_2$CO$_3$	DMSO	> 95:5	31
13	Pd(OAc)$_2$ (10)	Cs$_2$CO$_3$	DMSO	> 95:5	< 5
14	Pd(OAc)$_2$ (10)	Et$_3$N	DMSO	> 95:5	21
15	Pd(OAc)$_2$ (10)	KOAc	DMSO	> 99:1	67
16	Pd(OAc)$_2$ (5)	KOAc	DMSO	> 99:1	56
17	Pd(OAc)$_2$ (10)	CsOAc	DMSO	> 99:1	72

[a] Unless noted otherwise, the reaction was carried out on enamide 1a (0.4 mmol), diphenylacetylene 2a (0.44 mmol), base (2 equiv) with palladium catalyst (10 mol %) under oxygen (1 atm) in solvent (4.0 mL). TFA = trifluoroacetyl. [b] Isolated yield. [c] Under 1atm N$_2$ atmosphere.

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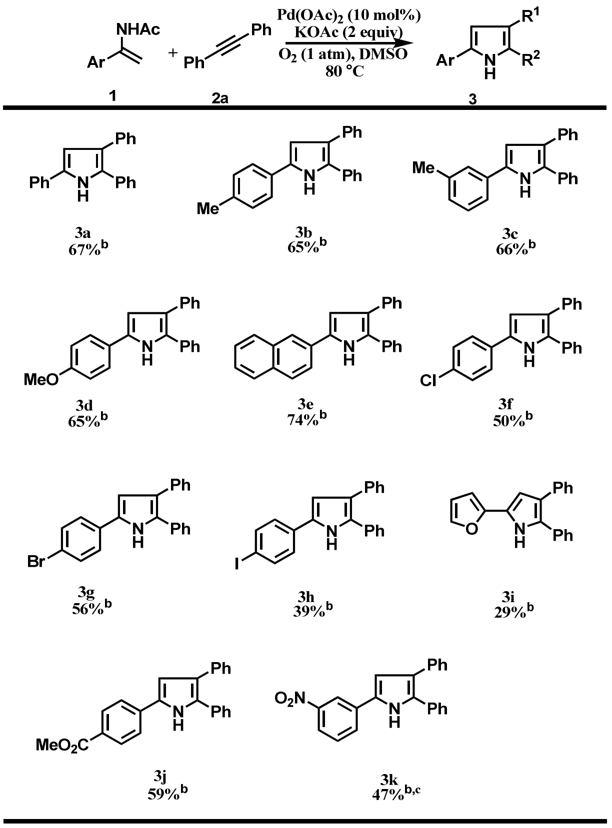
Table 1, entry 11). Other bases such as K_2CO_3, Cs_2CO_3 or Et_3N gave the product in poor yield (Table 1, entries 12-14). But it was observed that KOAc and CsOAc both could generate only **3a** in good yield (Table 1, entries 15 and 17). When the catalyst loading was reduced, a slightly lower yield of the **3a** was found (Table 1, entry 16). Due to the moisture sensitive nature of CsOAc in air, we decided to use KOAc as the additive.

Table 2. Cyclization of Various Enamides with Diphenylacetylene.[a]

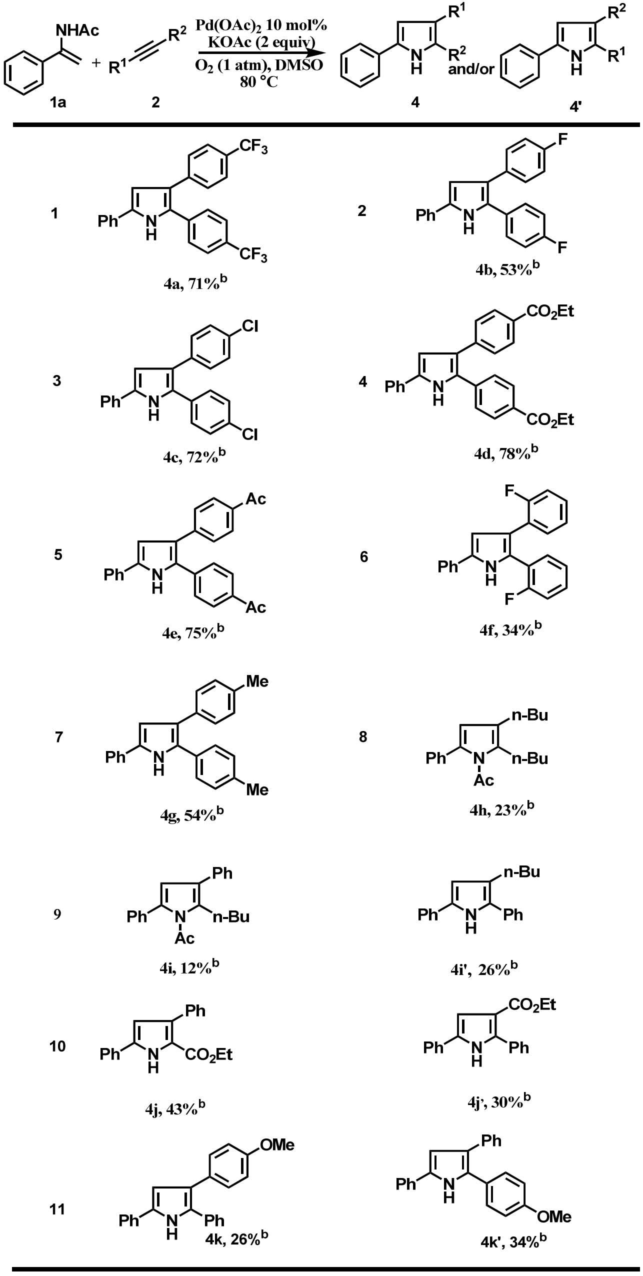


[a] Reaction conditions: enamide 1 (0.4 mmol), diphenylacetylene 2a (0.44 mmol), KOAc (2.0 equiv) and $Pd(OAc)_2$ (10 mol %) in DMSO (4.0 mL) under oxygen (1 atm) was heated for 24 h at 80 °C. [b] Isolated yields of the products. [c] The reaction time is 36 h.

With the optimized reaction conditions in hand, we next examined the scope of the enamide in this reaction (Table 2). It was noticed that the substituent on the phenyl ring of the compound **1** affected the product's yield significantly. The substrates with electron-donating group favored this cyclization reaction (Table 2, entries **3b**, **3c** and **3d**). The naphthalene substituted substrate could also afford the product in good yield (Table 2, entry **3e**). When the halogens were introduced at the *para*-position of the phenyl ring, the desired cyclization products were still prefered (Table 2, entries **3f**, **3g** and **3h**). The tolerance of halogen substituents will permit the product to be able for further functionalized at the next step. However, a low yield of the product was obtained when N-(1-(furan-2-yl)vinyl)acetamide was applied in this reaction (Table 2, **3i**).

Next, we turned our attention to test the scope of the acetylene derivatives. We applied the N-(1-phenylvinyl)acetamide (**1a**) to react with different acetylene derivatives under the standard reaction conditions. As outlined in Table 3, all the symmetrical diarylsubstituted ethyne could afford the corresponding cyclization products in good yields (Table 3, entries 1-5). Only 34% yield of the product **4f** was obtained when the 1, 2-bis(2-fluorophenyl)ethyne was used as the coupling partner. The alphatic-substituted ethyne does not favor this cyclization reaction (Table 3, entry 8). Furthermore, the non-symmetrical disubstituted ethynes could be successfully employed in this palladium-catalyzed cyclization reaction. The products **4** and **4'** could be obtained in reasonable to good yields but with poor regioselectivities (Table 3, entries 9, 10 and 11).

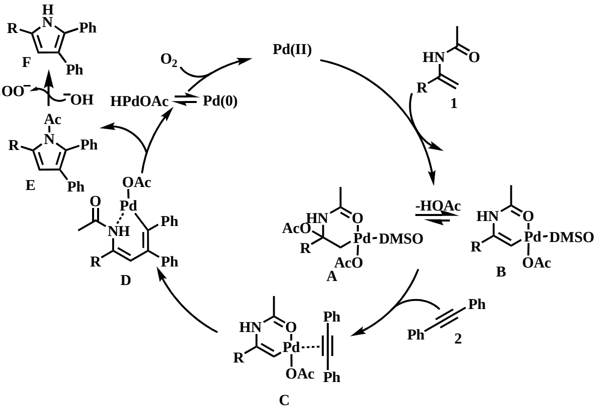
Table 3. Cyclization of Enamide **1a** with Different Disubstituted Alkynes.[a]



[a] Reaction conditions: unless otherwise noted, enamide 1a (0.40 mmol), alkyne (0.44 mmol), KOAc (2.0 equiv) and $Pd(OAc)_2$ (10 mol %) in DMSO (4.0 mL) under oxygen (1 atm) was heated for 24 h at 80 °C. [b] Isolated yields of the products.

Based on the observed results, a possible catalytic cycle was proposed as shown in Scheme 1. Firstly, a vinylpalladium species **B** was formed via the addition of palladium(II) acetate to the enamide (**A**) or via direct vinyl C–H bond activation.[9b] Next the alkyne replaces the DMSO and coordinates with palladium center followed by migratory insertion to give intermediate **D**. The *cis*-configuration of two phenyl groups favors the new C–N bond formation. After palladium reductive elimination, the final product was formed under basic hydrolysis.[11] The Pd(0) generated was oxidized back to Pd(II) and involved in the next catalytic cycle.

Scheme 1. Possible Mechanism for this Cyclization Reaction Catalyzed by Palladium(II) Acetate.



Conclusions

In conclusion, we have developed a palladium-catalyzed cyclization reaction of enamides and internal alkynes to prepare multi-substituted pyrroles in reasonable yields. The scope of tolerated substrates in this work is rather broad. Moreover, the reaction conditions of this method are quite mild in which only molecular oxygen was used as the oxidant to recycle the palladium catalyst.

Author Contributions

T. H. and Q. Z contributed equally to this work.

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Notes and references

1 (a) X. Sui, R. Zhu, G. Li, X. Ma, Z. Gu, *J. Am. Chem. Soc.* 2013, **135**, 9318; (b) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885; (c) Z. Gu, A. Zakarian, *Org. Lett.* 2010, **12**, 4224; (d) I. S. Young, P. D. Thornton, A. Thompson, *Nat. Prod. Rep.* 2010, **27**, 1801; (e) E. M. Beck, R. Hatley, M. J. Gaunt, *Angew. Chem., Int. Ed.* 2008, **47**, 3004; (f) C. T. Walsh, S. Garneau-Tsodikova, A. R. Howard – Jones, *Nat. Prod. Rep.* 2006, **23**, 517; (g) P. M. Jordan, *in Biosynthesis of Tetrapyrroles*, ed. P. M. Jordan, Elsevier, Amsterdam, 1991, **19**, 1–66; (h) *The Chemistry of Pyrroles*, ed. A. R. Jones and G. P. Bean. Academic Press, London, 1977.

2 A. L. Harreus, *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, 2000.

3 (a) G, Mass, *Science of Synthesis*. Thieme. New York. 2001; (b) V. Ferriera, *Org. Prep. Proceed. Int.* 2001, **33**, 411; (c) *Handbook of Heterocyclic Chemistry*, 2nd ed. Pergamon. San Diego: 2000. Part of recently reported examples of transition-metal catalyzed or mediated synthesis of pyrroles; (d) Z. Chen, B. Lu, Z. Ding, K. Gao, N. Yoshikai, *Org. Lett.* 2013, **15**, 1966; (e) W. Yang, L. Huang, H, Liu, W. Wang, H. Li, *Chem. Commun.* 2013, **49**, 4667; (f) L. Ran, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, *Green Chem.* 2014, **16**, 112; (g) M. Gao, C. He, H. Chen, R. Bai, B. Cheng, A. Lei, *Angew. Chem., Int. Ed.* 2013, **52**, 6958; (h) X. Tang, L. Huang, C. Qi, W. Wu, H. Jiang, *Chem. Commun.* 2013, **49**, 9597; (i) M. Zhang, H. Neumann, M. Beller, *Angew. Chem., Int. Ed.* 2013, **52**, 597; (j) J. Schranck, A. Tlili, M. Beller, *Angew. Chem., Int. Ed.* 2013, **52**, 7642. and references therein; (k) A. Abdukader, Q. Xue, A. Lin, M. Zhang, Y. Cheng, C. Zhu, *Tetrahedron Lett.* 2013, **54**, 5898; (l) X. Wang, X.-P. Xu, S.-Y. Wang, W. Zhou, S.-J. Ji, *Org. Lett.*2013, **15**, 4246; (m) D. G. Dunford, D. W. Knight, R. C. Wheeler, *Arkivoc.* 2012, 253; (n) M. Zhao, F. Wang, X. Li, *Org. Lett.* 2012, **14**, 1412; (o) Q. Li, A. Fan, Z. Lu, Y. Cui, W. Lin, Y. Jia, *Org. Lett.* 2010, **12**, 4066; (p) J.-X. Chen, M.-C. Liu, X.-L. Yang, J.-C. Ding, H.-Y. Wu, *J. Braz. Chem. Soc.* 2008, **19**, 877; (q) R. Martín, C. H. Larsen, A. Cuenca, S. L. Buchwald, *Org. Lett.* 2007, **9**, 3379.

4 Part of recently reported works of using enamides as starting materials in organic synthesis, see: (a) M. Chen, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, *Angew. Chem., Int. Ed.* 2013, **52**, 14196; (b) M.-N. Zhao, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, *Chem. Commun.* 2012, **48**, 8105; (c) Z.-H. Guan, K. Huang, S. Yu, X. Zhang, *Org. Lett.* 2009, **11**, 481; (d) D. R. Carbery, *Org. Biomol. Chem.* 2008, **6**, 3455. and references therein; (e) H. Huang, Z. Zheng, H. Luo, C. Bai, X. Hu, H. Chen, *J. Org. Chem.* 2004, **69**, 2355. and references therein; (f) W. Tang, X. Zhang, *Chem. Rev.*, 2003, **103**, 3029. and references therein; (g) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, *Adv. Synth. Catal.* 2003, **345**, 103; (h) A.-G. Hu, Y. Fu, J.-H. Xie, H. Zhou, L.-X. Wang, Q.-L. Zhou, *Angew. Chem., Int. Ed.* 2002, **41**, 2348; (i) I. D. Gridnev, M. Yasutake, N. Higashi, T. Imamoto, *J. Am. Chem. Soc.* 2001, **123**, 5268; (j) M. J. Burk, J. R. Lee, Y. M. Wang, *J. Am. Chem. Soc.* 1996, **118**, 5142.

5 M. L. Crawley, I. Goljer, D. J. Jenkins, J. F. Mehlmann, L. Nogle, R. Dooley, P. E. Mahaney, *Org. Lett.* 2006, **8**, 5837.

6 D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* 2010, **132**, 18326.

7 S. Rakshit, F. W. Patureau, F. Glorious, *J. Am. Chem. Soc.* 2010, **132**, 9585.

8 (a) B. Li, N. Wang, Y. Liang, S. Xu, B. Wang, *Org. Lett.* 2013, **15**, 136; (b) L. Wang, L. Ackermann, *Org. Lett.* 2013, **15**, 176.

9 (a) H. Zhou, Y. H. Xu, W. J. Chang, T. P. Loh, *Angew. Chem., Int. Ed.* 2009, **48**, 5355; (b) Y. H. Xu, Y. K. Chok, T. P. Loh, *Chem. Sci.* 2011, **2**, 1822; (c) C. Feng, T. P. Loh, *Chem. Sci.* 2012, **3**, 3458; (d) S. Pankajakshan, Y. H. Xu, J. K. Cheng, M. T. Low, T. P. Loh, *Angew. Chem., Int. Ed.* 2012, **51**, 5701.

10 For another example on palladium-catalyzed coupling reaction between enamides and alkynes for the synthesis of pyrroles appearing after submission of this work, see: M. N. Zhao, Z. H. Ren, Y. Y. Wang, Z. H. Guan, *Org. Lett.* 2014, **16**, 608.

11 (a) P. Linda, A. Stener, A. Cipiciani, G. Savelli, *J. Het. Chem.* 1983, **20**, 247; (b) A. Cipiciani, P. Linda, G. Savelli, *J. Phys. Chem.* 1983, **87**, 5262.