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Palladium-Catalyzed Multicomponent Coupling of Alkynes, Imines, and Acid Chlorides: A Direct and Modular Approach to Pyrrole Synthesis

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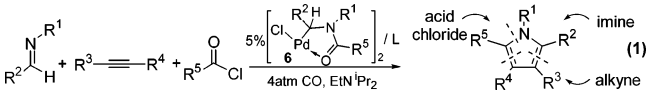
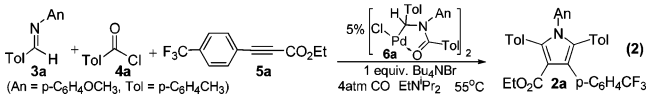
Of the various synthetic and naturally occurring heterocyclic structures, the pyrrole nucleus is among the most prevalent. Pyrroles are found in a tremendous range of natural products[1] and bioactive molecules,[2] including the blockbuster drug Atorvastatin Calcium,[2a] as well as important anti-inflammatants,[2b] antitumor agents,[2c] and immunosuppressants.[2d] Similarly, polypyrroles are of growing relevance in materials science as conjugated polymers.[3] While this broad utility has made pyrroles important synthetic targets, traditional routes to their preparation are multistep reactions, as illustrated by the Paal−Knorr cyclization of amines with pre-formed 1,4-diketones.[4] This has stimulated interest in the design of alternative metal-based routes to pyrroles.[5] Examples include the isomerization of unsaturated imines,[5a] isonitrile/ketone couplings,[5c] and alkyne additions to chromium carbenes,[5e] many of which provide structures not easily generated by classical routes.

Despite these advances, a common feature of most pyrrole syntheses is their requisite use of pre-assembled precursor(s) for cyclization.[1,4,5] This not only imposes further steps on the overall synthesis but also can complicate structural diversification. In principle, a more ideal way to construct complex molecules would involve their preparation in one step, directly from simple, readily available and easily varied substrates, in a fashion similar to the Pauson−Khand reaction for carbocycle synthesis[6] and other multicomponent reactions.[7] We report below our design of such a direct synthesis of pyrroles. This has been done by assembling the pyrrole core via metal catalysis from the basic building blocks shown in eq 1.



(1)

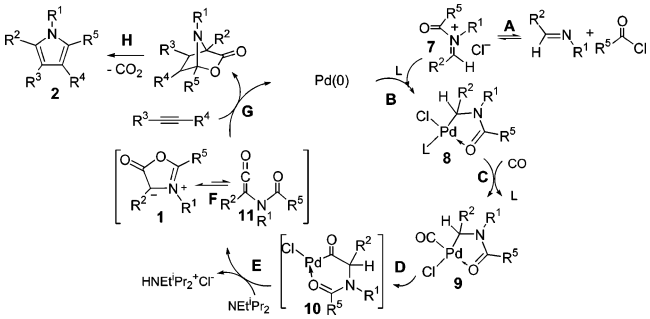
Our approach to this synthesis is based upon the ability of alkynes to undergo 1,3-dipolar addition to 1,3-oxazolium-5-oxides (Münchnones, **1**) to form pyrroles.[8] While Münchnones are typically prepared in situ from amino acid derivatives, we have recently reported their generation by the palladium-catalyzed coupling of imines, acid chlorides, and carbon monoxide.[9] This suggested a potential pathway to construct pyrroles, outlined in Scheme 1. By performing these steps simultaneously, this would provide overall a method to convert imines, alkynes, and acid chlorides directly into a pyrrole. However, examination of this reaction under the conditions reported to generate **1**[9] formed only a trace of pyrrole **2a** (5%, eq 2). Indeed,



(2)

while mechanistically plausible, this process involves four separate reagents, base, and a catalyst, all proceeding selectively through over eight separate steps. Considering the reactivity of the intermediates formed in this cycle (**1**, **7**−**11**), this suggests the potential for numerous other reactions. Thus, we have undertaken a series of

Scheme 1. Potential Mechanism for a Catalytic Pyrrole Synthesis



mechanistic studies on this process, with the goal of designing a metal catalyst that could mediate this synthesis in a selective fashion.

While there are several stages in this cycle wherein the reaction might be inhibited, a useful observation came from mechanistic studies on the Münchnone synthesis itself, which show that the oxidative addition of iminium salt **7** to Pd(0) (step B) is rate determining. This is evidenced by kinetic studies (the formation of **1** is first order in **7**) and consistent with in situ NMR data (the catalyst resting state is not **8**−**10**).[10] Considering that catalyst **6**[11] forms an unligated 14 e$^-$ intermediate **8** (−L) for carbonylation (steps C−E), a slow oxidative addition is not surprising and suggests that the inhibition of pyrrole formation may potentially arise from the alkyne, further slowing this step in the catalytic cycle. Consistent with this postulate, examination of the products of eq 2 reveals significant quantities of **7** after catalysis.

A method to accelerate iminium salt oxidative addition (step B) would be to add donor ligands (L) to stabilize **8**. However, simple phosphines were found to completely inhibit Münchnone formation, even without alkynes (Table 1, entry 2−4), presumably due to tight coordination to **8** blocking subsequent CO binding (step C).[9] A more favorable scenario would be a ligand that could stabilize **8** as well as be sufficiently labile to allow the subsequent catalysis steps. As has been noted in other systems,[12] these features can be obtained by the use of sterically encumbered phosphines. In the case of P(*o*-tolyl)$_3$, this generates a catalyst that is several times more reactive for Münchnone formation (entry 8). More importantly, this catalyst is also capable of mediating these steps in the presence of alkyne (Scheme 1). Thus, the addition of 15 mol % P(*o*-tolyl)$_3$ to the **6a**-catalyzed reaction of imine, acid chloride, alkyne (**3a**−**5a**), 4 atm of CO, and EtN^{i}Pr$_2$ results in the disappearance of these reagents over 16 h and the formation of pyrrole **2a** as essentially the only significant reaction product (81% yield, Table 2).[13] Overall, this optimized protocol provides a straightforward catalytic method to construct a pyrrole in one step from three separate and readily available building blocks.

In addition to its simplicity, a useful feature of this synthesis is the nature of the substrates employed, each of which can be easily varied. As shown in Table 2, catalysis is tolerant to a range of functionalities (e.g., esters, indoles, halides, thioethers). Aryl, heteroaryl, and alkyl substituents can be incorporated into the pyrrole

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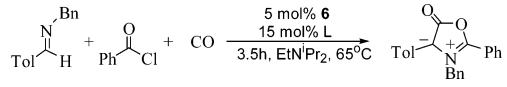
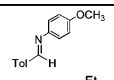
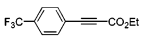
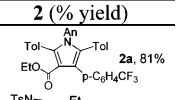
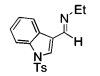
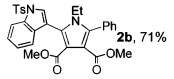
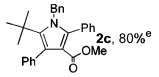
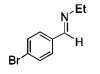
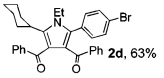
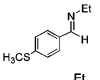
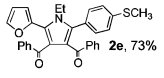
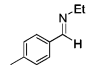
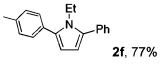
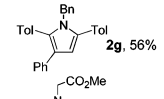
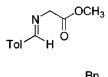
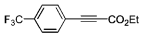
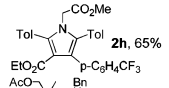
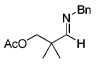
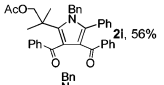
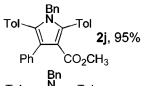
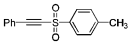
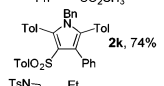
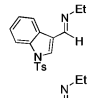
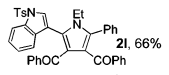
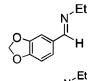
Table 1. Ligand Influence on Münchnone Formation[a]



entry	ligand	yield (%)[b]	entry	ligand	yield (%)[b]
1	*c*	33	5	P^{t}Bu$_3$	29
2	PCy$_3$	0	6	P^{t}Bu$_2$(2-biphenyl)	31
3	PPh$_3$	0	7	P(1-naphthyl)$_3$	51
4	dppe	0	8	P(o-tolyl)$_3$	78

[a] See Supporting Information for details. [b] NMR yield. [c] One equivalent of Bu$_4$NBr.

Table 2. Palladium-Catalyzed Pyrrole Synthesis (Eq 1)[a,b]

cpd	imine	acid chloride	alkyne	**2** (% yield)
a		TolCOCl		 **2a**, 81%
b[c]		PhCOCl		 **2b**, 71%
c[d]		PhCOCl		 **2c**, 80%[e]
d				 **2d**, 63%
e				 **2e**, 73%
f[c]		PhCOCl		 **2f**, 77%
g		TolCOCl		 **2g**, 56%
h		TolCOCl		 **2h**, 65%
i[d]		PhCOCl		 **2i**, 56%
j		TolCOCl		 **2j**, 95%
k		TolCOCl		 **2k**, 74%
l		PhCOCl		 **2l**, 66%
m[c]		PhCOCl		**2m**, 81%
n[c]		PhCOCl		**2n**, 88%

[a] Imine (0.7 equiv), acid chloride, alkyne (1.4 equiv), EtN^{i}Pr$_2$, CO (4 atm), 5% **6**, and 15% P(*o*-tolyl)$_3$ in CH$_3$CN/THF, 16 h, 65 °C. [b] Pd$_2$dba$_3$·CHCl$_3$ or [Pd(allyl)Cl]$_2$ are viable catalysts at ca. 10% lower yield. [c] Alkyne added to preformed **1**. [d] 75 °C, 1 equiv of LiOTf in CH$_3$CN, **6f** catalyst. [e] Major isomer (5:1 ratio).

from the acid chloride or imine nitrogen, as can a variety of bis-, mono-, and unsubstituted alkynes. While unsymmetrical alkynes can lead to mixtures, steric and electronic effects provide a reasonable degree of selectivity (5:1 ratio in **2c**).[8b] Even electron-rich alkynes, typically less potent Münchnone trapping reagents,[8a] form pyrroles in reasonable yield (**2f**,**g**). Considering the nature of the substrates and number of bonds generated in one pot, these all represent effective syntheses of **2a**−**n**.

Interestingly, the phosphine-based catalyst system can also form pyrroles of Münchnones not previously accessible by catalysis, as shown by the synthesis of pyrroles of both C-aromatic and C-alkyl imines (**2c**, **i**). The latter represents a significant expansion in scope of the Münchnone synthesis, which without P(*o*-tolyl)$_3$ is inert toward these imines.[9] In general, while there are some limitations brought on by the complex series of reactions occurring during catalysis,[14] this process provides a method to construct pyrroles wherein each of the five substituents (R^1−R^5) can be independently controlled and varied by modulation of the three substrates. A method to accomplish the latter in a single step reaction is, to our knowledge, previously unknown.

As illustrated in eq 3, this process can also be useful in the incorporation of further levels of product complexity (**12**) into the pyrrole product with minimal steps. The members of this class of multicyclic pyrroles are of utility as potential therapeutics and retinoic acid regulators,[15] in this case generated in three steps from an aldehyde, alkyne, amine, and acid chloride.

In conclusion, these studies have shown that pyrroles can be considered as the product of three basic building blocks coupled via palladium catalysis, providing a modular method to construct these heterocycles with facile diversity and high atom economy. Experiments directed toward understanding of the role of P(*o*-tolyl)$_3$ in this catalysis, as well as the application of this approach to other heterocyclic targets, are underway.

Acknowledgment. We thank NSERC for their financial support. R.D. thanks NSERC for a Postgraduate Fellowship.

Supporting Information Available: Synthesis and characterization of **2** and **12** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) See Supporting Information for full details.
(11) **11** **6** is formed by pre-treating Pd$_2$dba$_3$ with imine and acid chloride (ref 9).
(12) For example: Stambuli, J. P.; Bühl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9346 and references therein.
(13) Pd$_2$dba$_3$ or [Pd(allyl)Cl]$_2$ are also viable catalysts at ca. 10% lower yield.
(14) Enolizable R^2 are not stable, though these units can be incorporated into the 2-pyrrole position via the acid chloride (**2d**). Strong dipolarophiles react with **7** and must be added to a preformed **1** (**2b**,**m**,**n**).
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