J|A|C|S COMMUNICATIONS

Published on Web 06/28/2010

Pyrrole Synthesis via Allylic sp^3 C−H Activation of Enamines Followed by Intermolecular Coupling with Unactivated Alkynes

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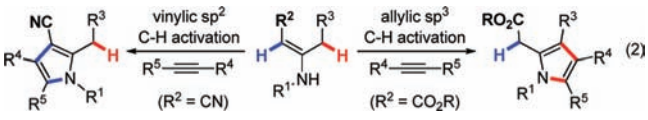
Abstract: A conceptually novel pyrrole synthesis is reported, efficiently merging enamines and (unactivated) alkynes under oxidative conditions. In an intermolecular Rh catalyzed process, the challenging allylic sp^3 C−H activation of the enamine substrates is followed by the cyclization with the alkyne (R^3 = CO_2R). Alternatively, in some cases (R^3 = CN), the enamine can be utilized for a vinylic sp^2 C−H activation. A total of 17 examples with yields above 60% is presented, together with the results of an initial mechanistic investigation.

Arguably, pyrroles represent one of the most important classes of heterocycles found in biologically active compounds.[1,2] Consequently, a plethora of methods for their synthesis has been developed over the years,[3] with metal-catalyzed ones becoming increasingly popular.[4] Recently, the groups of Jones, Miura, and Fagnou have independently reported Rh(III)-catalyzed oxidative couplings using a directing group for aryl C−H bond activation followed by insertion of an internal alkyne leading to various annulated heterocycles,[5] e.g. indoles.[5g] Along the same lines, the selective synthesis of multisubstituted pyrroles by oxidative combination of enamines and (unactivated) alkynes would constitute a powerful method (eq 1).

(1)

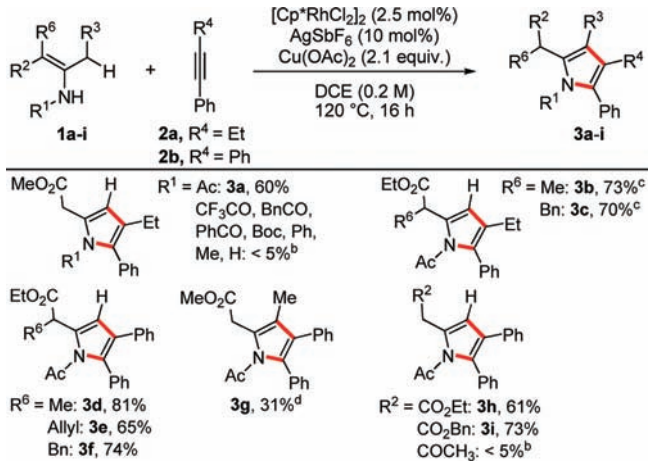
Enamines are of great importance in organic chemistry and play a prominent role in organocatalysis.[6] Recently, the utility of enamines in transition metal catalysis for the oxidative formation of valuable indoles has been shown.[7] Inspired by this work, we investigated the Rh catalyzed reaction of enamines with unactivated alkynes, finding surprising results. Herein, we report the challenging allylic sp^3 C−H activation[8] and also an alternative vinylic sp^2 C−H activation[9] of enamines and the subsequent coupling with unactivated alkynes yielding pyrroles (eq 2).



(2)

We commenced our investigation with the coupling of *N*-acetyl enamine **1a** (R^1 = Ac; R^3, R^6 = H; R^2 = CO_2Me) and 1-phenyl-1-butyne **2a**. The use of a combination of $[Cp^*RhCl_2]_2$ and $AgSbF_6$ as the catalyst together with $Cu(OAc)_2$ as the oxidant in DCE resulted in the formation of pyrrole **3a** as the single regioisomer[10] (Table 1). A less coordinating counterion in the Ag salt, a noncoordinating but solubilizing solvent, and the choice of oxidant (several Cu salts fail) were found to be important.[11] Whereas the presence of chloride anions shuts down the reaction completely, $AgSbF_6$ is essential.[5g] In addition, a Rh(I) catalyst precursor ($[RhCl(cod)]_2$) also provided product, but only in low yield.[11]

Table 1. Enamine Scope in the Rhodium Catalyzed Oxidative Pyrrole Synthesis[a]



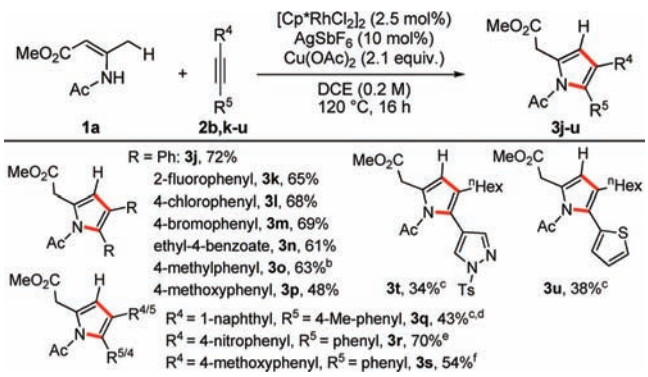
[a] Conditions: **1** (1.3 mmol), **2** (1.0 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10.0 mol %), $Cu(OAc)_2$ (2.1 equiv), DCE (0.2 M), 120 °C, 16 h; isolated yield is given. [b] Determined by ^{1}H NMR. [c] Only one regioisomer was observed by ^{1}H NMR and GC-MS analysis of crude product mixture. [d] $[Cp^*RhCl_2]_2$ (5.0 mol %), $AgSbF_6$ (20.0 mol %), at 140 °C for 24 h.

With these optimized conditions in hand, we embarked on an investigation of the enamine scope of this interesting transformation (Table 1). First, several different N-substituents were compared and the acetyl group was found to be critical for success, with other common groups providing only trace amounts of product. Furthermore, using β-substituted enamines **1b** and **1c** together with the unsymmetrical alkyne **2a** resulted in the smooth cyclization to **3b** and **3c**, intriguingly, as single regioisomers.

Good results were also obtained with diphenyl acetylene, providing the products **3d**−**f** in up to 81% yield. Even the formation of pentasubstituted pyrroles was achieved (**3g**), although under more forcing conditions (5 mol % catalyst and 140 °C) and in quite low yield. Whereas the ester could be varied, replacement with a ketone failed (Table 1, **3h**,**i**).

In view of these results, we turned our attention to investigate several differently substituted alkynes. A variety of internal alkynes with aromatic substituents were successfully coupled (Table 2). Electron-neutral, electron-deficient, and electron-rich aromatic groups on the alkyne gave moderate to good yields (**3j**−**u**). Gratifyingly, functional

Table 2. Alkyne Scope in the Rhodium Catalyzed Oxidative Pyrrole Synthesis[a]



[a] Conditions: **1a** (1.3 mmol), **2** (1.0 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10.0 mol %, $Cu(OAc)_2$ (2.1 equiv), DCE (0.2 M), 120 °C, 16 h; isolated yields are given; regioisomeric ratios for **3q**−**s** were determined by ^{1}H NMR analysis of crude product mixture. [b] Reaction was carried out on a 0.75 mmol scale. [c] Reaction was carried out at 140 °C for 24 h. [d] Regioisom. ratio 61:39. [e] Regioisom. ratio 75:25. [f] Regioisom. ratio 56:44.

groups like bromide, chloride, and carboxylic ester were well tolerated. These functional groups provide ample opportunity for further functional group manipulations, for example, by modern cross-coupling reactions. More sterically demanding alkynes like 1-naphthyl (**2q**) can also be employed. When two electronically unsymmetrical aromatic groups were present as in alkynes **2r** and **2s**, moderate regioselectivities of 75:25 to 56:44 were observed for the formation of **3r** and **3s**, respectively. Heterocyclic substituents, such as pyrazoles and thiophenes may transform into the pyrrole products (**3t**,**u**). However, activated alkynes bearing esters ($R^4 = CO_2Et$) or propargylic alcohol derivatives ($PhCCCH_2OR$; R = H, Me, or TBS) did not yield the corresponding pyrrole, maybe due to poisoning of the catalyst by chelation.[12] Competition experiments showed a slight preference for electron-poor alkynes [electron-poor **2k** > **2b** > electron-rich **2p**].[11]

In addition, to probe the nature of the reaction mechanism, two reactions between **1a** and **2a** were performed in the absence of $Cu(OAc)_2$ at 120 °C:

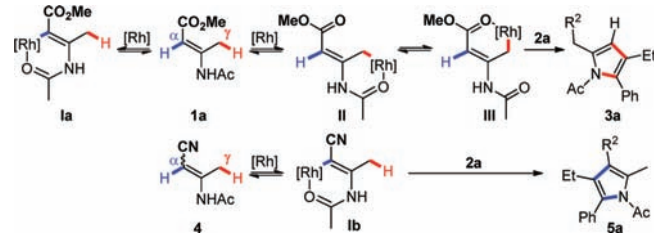
(i) 20 mol % $[Cp^*RhCl_2]_2$ with 80 mol % $AgSbF_6$ and

(ii) 2.5 mol % $[Cp^*RhCl_2]_2$ with 10 mol % $AgSbF_6$.

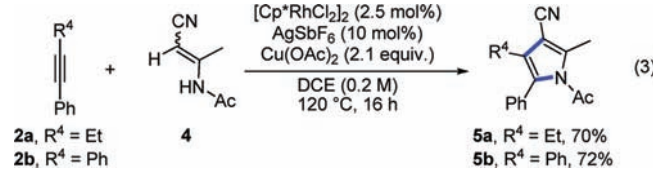
After 16 h, **3a** was formed in 18% and 2% yield (^{1}H NMR), respectively. After this time, addition of 2.1 equiv of $Cu(OAc)_2$ to these mixtures and prolonged heating for 24 h at 120 °C resulted in continued turnover and 54% and 48% yield (^{1}H NMR), respectively. These results indicate that Cu(II) is not essential for product formation.[11]

Interestingly, deuteration experiments support the presence of intermediate **I**: whereas only N−H deuteration was observed in the absence of Rh, an additional rapid C−H deuteration in the α-position of **1a** was obtained in the presence of the Rh catalyst.[11] However, the corresponding pyrrole product, resulting from the C−H functionalization in the α-position, was not observed.[10] Considering the observed sp^3 C−H activation at the γ-position leading to pyrrole **3a**, the rhodacycle **III** should be involved. The importance of this ester chelate **III** is supported by the outcome of the cyclization of substrate **4** (Scheme 1). Intriguingly, the change from ester **1a** to a nitrile **4** resulted in the α-functionalization of the enamine and, consequently, the formation of a regioisomeric pyrrole **5a** (eq 3). This important observation indicates the crucial role of the ester group to activate the allylic sp^3 C−H bond.

Scheme 1. Proposed Modes of Activation



Furthermore, deprotection of the ester and acetyl moieties of **3l** proceeds under mild conditions (4 N aq NaOH in MeOH at 45 °C) to provide the free CO_2H and free N−H pyrrole in a single step in 96% yield.[11] These pyrrole products are valuable building blocks for medicinal chemistry and natural product synthesis.[13]



In conclusion, we have successfully formed pyrroles by a novel Rh catalyzed sp^3 C−H bond activation of enamines and successive coupling with unactivated alkynes. Studies are ongoing to understand the reaction mechanism and apply this C−C/C−N bond formation cascade to the synthesis of other heterocycles.

Acknowledgment. We thank the NRW Graduate School of Chemistry (S.R.), the Alexander von Humboldt Foundation (F.W.P.), and AstraZeneca for generous support. The research of F.G. was supported by the Alfried Krupp Prize for Young University Teachers of the Alfried Krupp von Bohlen und Halbach Foundation.

Supporting Information Available: Experimental and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Remarkably, of the four possible regioisomers (R4/R^5; α/γ) only **3a** was detectable in the crude reaction mixture (^{1}H NMR, GC-MS).

(11) See Supporting Information for further details.

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JA104305S