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Hydro-amination/-amidation of 1,3-diynes with indoles/azoles/amides under modified Ullmann conditions: stereo- and regio-selective synthesis of *N*-alkenynes via N–H bond activation ☆

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ABSTRACT

An efficient strategy for the stereo- and regio-selective synthesis of *N*-alkenynes has been described. The salient feature of the reaction involves hydro-amination/amidation of 1,3-diynes with indoles/azoles/amides via transition-metal catalyzed activation of N–H bond. The resulting *N*-alkenynes derived from *N*-heterocycles and cyclic amides were obtained as a mixture of *Z*/*E* isomers with *Z*-stereoselectivity ranging from 60% to 95%. In contrast, acyclic amides afforded *N*-alkenynes with exclusive *E*-stereoselectivity, albeit in reduced yield ranging from ~10% to 41%.

In recent years transition-metal catalyzed functionalization reactions of unreactive N–H or C–H bonds especially in *N*-heterocycles have received significant attention in modern organic chemistry. Among *N*-heterocycles, indoles scaffolds are ubiquitous subunits of a variety of biologically active substances and have been grouped under privileged structures.[1] The N–H center in the indole has a pK_a of 21 in DMSO[2] thereby requiring very strong bases under anhydrous conditions for complete deprotonation. In recent years although there are several reports dealing with the transition-metal catalyzed intermolecular direct regioselective functionalization of either NH or C2/C3–H in indole,[3] reports dealing with the hydroamination of diynes with indoles has not yet been investigated. This is in contrast to several reports dealing with the metal-catalyzed addition of heterocyclic-, primary- and secondary-amines onto terminal and internal alkynes.[4]

During the course of our reaction involving indole **1a** with terminal alkynes under modified Ullmann conditions,[5] we came across an interesting observation wherein the formation of 1,3-diyne **2a** and regioselective formation of 1-(1,4-diphenyl-but-1-en-3-ynyl)-1*H*-indole **3a** occurred in 27% and 18% yield, respectively. The century old Cu-catalyzed Ullmann condensations,[6] have been widely used for the arylation of aryl/alkyl amines, amides, imides, carbamates, *N*-heterocycles, alkynes, synthesis of enamides/ynamides/allenamides, and for the yne–yne bond formation.[7] We hypothesized that under the modified Ullmann conditions, the terminal alkynes initially underwent dimerization to form symmetrical 1,3-diyne **2a** followed by hydroamination preferably (in the presence of activated *C*-2 and *C*-3 nucleophile in **1a**) with the *N*-1 of the indole ring to form *N*-alkenyne **3a**. The poor yields of **2a** and **3a** can be attributed to the unfavorable reaction condition for the formation of 1,3-diynes **2a** from terminal alkynes. A careful survey of the literature did not reveal any report dealing either with the hydroamination of 1,3-diynes with indoles or with the synthesis of *N*-alkenynes per se except for a recent report dealing with the synthesis of *S*-alkenynes.[8] This prompted us to optimize the conditions for the formation of **3** from 1,3-diynes **2** in quantitative yields. The studies are in continuation of our effort to synthesize indole-based derivatives[9] for our ongoing antimalarial program.[10] In our initial experiments, we examined the ability of phenylacetylene alone to form 1,3-diyne **2a** under the modified Ullmann condition (CuI/Ligand/Cs_2CO_3). As expected, the formation of **2a** occurred in poor (30%) yield, which then prompted us to choose the Cu-catalyzed literature procedure for the formation of **2** in quantitative yields. Out of the numerous protocols reported for the synthesis of 1,3-diynes from terminal alkynes, the use of CuI/Na_2CO_3/I_2[11] was found to be the most favorable, furnishing **2a–d** in excellent yields (Table 1). Next, we treated **2a** (1.0 mmol) with indole **1a** (1.0 mmol) and Cs_2CO_3 (1.5 mmol) in DMSO at 100 °C for 5 h. This resulted in the formation of **3a** (entry 1; 83% yield) as a mixture of *Z* and *E* isomers in the ratio of 6:4 as observed

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Table 1
Synthesis of 1,3-diynes **2** from respective alkynes

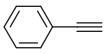
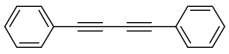
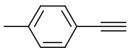
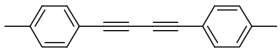
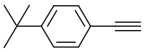
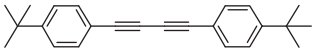
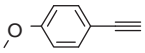
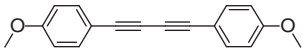
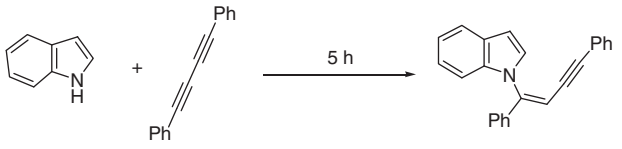
Compound no.	Alkyne	1,3-Diyne	Yield (%)
2a			95
2b			90
2c			91
2d			90

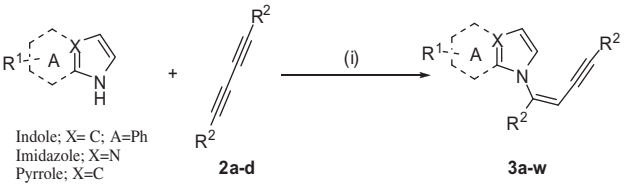
Table 2
Optimization of the reaction conditions for conversion of substrate **1a** and **2a** to **3a**



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

S. No.	Reagent	Solvent	**3a**
1	CuI/Cs_2CO_3; 100 °C	DMSO	83%
2	CuI/1,10-phenanthroline/Cs_2CO_3; 100 °C	DMSO	90%
3	CuI/L-proline/Cs_2CO_3; 100 °C	DMSO	N.R
4	CuI/L-4-hydroxyproline/Cs_2CO_3; 100 °C	DMSO	N.R
5	CuI/1,10-phenanthroline/Pot. *t*-butoxide; 100 °C	DMSO	41%
6	CuI/1,10-phenanthroline/DABCO; 100 °C	DMSO	N.R
7	CuI/1,10-phenanthroline/Na_2CO_3; 100 °C	DMSO	N.R
8	CuI/1,10-phenanthroline/Cs_2CO_3; 80 °C	ACN	N.R
9	CuI/1,10-phenanthroline/Cs_2CO_3; 80 °C	THF	N. R
10	CuI/1,10-phenanthroline/Cs_2CO_3; 100 °C	DMF	85%
11	CuI/1,10-phenanthroline/Cs_2CO_3; 80 °C	DMSO	22%

by both HPLC and NMR. Attempts to improve the stereoselectivity/yields during hydroamination with **3a** as a probe (Table 2) using various ligands such as 1,10 phenanthroline, L-proline, and *trans*-4- hydroxy-L-proline, led to marginal increase in the yield of **3a** from 83% to 90% when 1,10-phenanthroline was used in combination with CuI and Cs_2CO_3 in DMSO at 100 °C (entry 2). The remaining two ligands were inactive (entries 3 and 4). Replacing Cs_2CO_3 with bases such as DABCO, Na_2CO_3, and potassium *t*-butoxide were ineffective except for potassium *t*-butoxide furnishing **3a** in 41% yield (entry 5).



Indole; X= C; A=Ph
Imidazole; X=N
Pyrrole; X=C

2a-d **3a-w**

1a = Indole
1b = 5-methoxyindole
1c = 5-bromoindole
1d = 5-benzyloxyindole
1e = 2-methylimidazole
1f = 2-isopropylimidazole
1g = 2-phenylimidazole
1h= 2-methyl-4-ethylimidazole
1i = 3,5-dimethyl-1*H*-pyrazole
1j = Pyrrole

2a R^2 = Ph
2b R^2 = 4-CH_3Ph
2c R^2= 4-$(CH_3)_3$CPh
2d R^2 = 4-OMe-Ph

Scheme 1. Reagents and conditions: (i) CuI (0.1 mmol), 1,10-phenanthroline (0.05 mmol), Cs_2CO_3 (1.5 mmol) in DMSO, 100 °C, 5–16 h.

Replacing DMSO with solvents like acetonitrile (entry 8) and THF (entry 9) were found to have detrimental effect, however, use of DMF as solvent furnished product **3a** in 85% yield (entry 10). It is interesting to note that although use of ligand led to a marginal improvement in the yield, the *Z*/*E* stereoselctivity ratio of **3a** obtained for entry 2 as well as for entries 5 and 10 with reduced yield remained unchanged (6:4). Besides, the role of solvent and base, the reaction temperature was also found to be an important factor in the hydroamination process. At 100 °C, the reaction went to completion within 5 h and afforded the product in higher yield, however, at reduced temperature of 80 °C, the reaction was incomplete after 5 h and furnished **3a** in reduced yield (22%; entry 11). Thus, the optimal condition for hydroamination involved CuI/1,10-phenanthroline/Cs_2CO_3 in DMSO at 100 °C.

The role of copper in the hydroamination of 1,3-diyne appears to be crucial since it could be activating either of the two reactants. Based on literature precedence,[12] the two plausible mechanistic pathways for hydroamination could be either activation of the alkyne or N–H activation. However, based on our observation that *N*-protected indole failed to furnish either *C*-3 or *C*-2 linked alkenynes, the activation of N–H appears to be the most probable route for hydroamination. The amine activation mechanism may proceed via oxidative addition of the amine N–H bond to the coordinatively unsaturated metal center to form an amido–hydrido complex, followed by one of the acetylenic coordination from 1,3-diyne **2a**, insertion of the alkyne into the metal–nitrogen bond, and finally C–H reductive elimination, liberating the product and closing the catalytic cycle. Although, there is no experimental evidence for this reaction, a recent work by Ribas et al.,[13] demonstrated direct evidence for the role of Cu^{I}/Cu^{III} redox steps in Ullmann-type coupling reactions.

Once the reaction conditions for the formation of **3a** under the modified Ullmann conditions were optimized,[14] we then proceeded with the characterization of isomers. Initial attempts to separate the isomers by column chromatography were not successful which prompted us to separate them by crystallization. Pleasingly, we were able to separate the isomers of **3a** by subjecting the crude mixture to crystallization using DCM/EtOH as solvents. The stereochemistry of the pure isomer so obtained was established as *Z*-isomer using ^{1}H, 2D NMR, and NOE studies. Further it is interesting to note that under the modified Ullman conditions, we observed regioselective formation of *N*-alkenynes with no formation of *C2* or *C3* alkenynes. We next examined the scope and limitation of our strategy for the preparation of *N*-alkenynes **3** by extending the methodology to a series of *N*-heterocycles. Accordingly, several indole derivatives with the substitution on the phenyl ring, imidazole derivatives, and pyrazole were treated with symmetrical 1,3-diynes **2a**–**d** (Scheme 1) and the results have been summarized in Table 3. As is evident, addition of 1,3-diynes to indoles (**1a**–**d**), imidazoles ((**1e**–**h**), and pyraozle (**1i**) derived substrates furnished *N*-alkenynes **3a**–**w** as a mixture of *Z*/*E* in excellent yields. Indeed, the time required for the completion of