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Regioselective Preferential Nucleophilic Addition of *N*-Heterocycles onto Haloaryl-alkynes over *N*-Arylation of Aryl Halides

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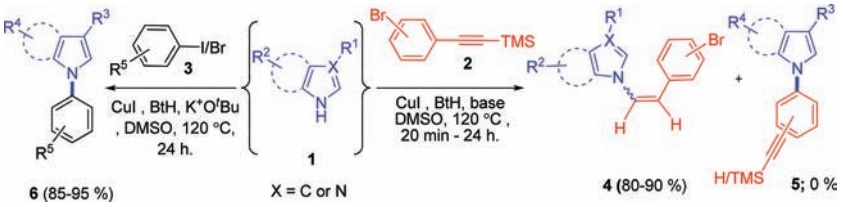
ABSTRACT



The study of preferential addition of heterocyclic amines onto halo-substituted arylalkynes over *N*-arylation under various catalytic conditions is described. The present work supports and confirms the mechanistic pathway of our recent work on the tandem synthesis of indolo- and pyrrolo-[2,1-*a*]isoquinolines via hydroamination followed by oxidative addition and not vice versa.

Heterocyclic nitrogen-containing substrates are common constituents of natural products, agrochemicals, and pharmaceuticals and are also useful intermediates in a number of industrial processes.[1,2] Several synthetic methods have been described for the preparation of enamines, and to our knowledge, hydroamination of alkynes provides an atom-economical route to them.[3−6] Earlier efforts to synthesize both simple and highly complex molecules by *N*-arylation and hydroamination of unsaturated substrates have proved to be very efficient.[2] Synthesis of substituted indoles and analogous heterocyclic substrates using arylation/hydroamination chemistry has been well established in the literature.[6−8]

A remarkable progress has been made in tandem synthesis of substituted indoles from *o*-haloanilines by Sonogashira coupling followed by intramolecular hydroamination.[6]

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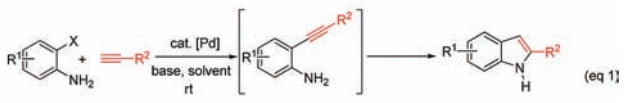
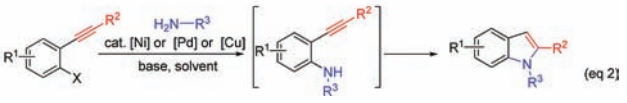
A notable work has been reported by Knochel in 2000 (eq 1).[6b] Recently, Ackermann[7] and Alsabeh[8] (eq 2) showed the synthesis of indoles from *o*-haloarylalkynes and anilines via arylation followed by intramolecular hydroamination.[7,8] Since, the discovery of coupling of aryl/heteroaryl halides with *N*-heterocycles and arylamines using metal and ligands is well documented in the literature and these procedures are known for the tolerance of variety of functional groups,[9] study of the nucleophilic addition or arylation of *N*-heterocycles and halo-substituted arylalkynes remains elusive. In this context, preferential addition of heterocyclic amines to haloalkynes over arylation reactions would be of great interest to synthetic chemists.

Knochel *et al;* (Sonogashira Reaction / Hydroamination)[6b]

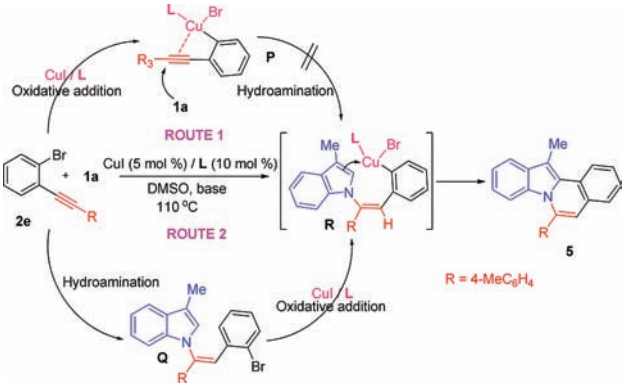


i. Ackermann *et al; ii* Alsabeh *et al;* (Amination / Hydroamination)[7,8]



In continuation of our interest in the coupling reactions[10] and synthesis of fused heterocycles,[11] we recently reported the copper-catalyzed tandem synthesis of indolo- and pyrrolo[2,1-*a*]isoquinolines. In the proposed mechanism, we have shown two possible routes for the generation of the key intermediate **R** (Scheme 1).[11a] Herein, we report that nucleophilic addition of heterocyclic amines onto halo-substituted arylalkynes is preferred over *N*-arylation. This study supports and confirms the previously proposed mechanism via hydroamination followed by oxidative addition (route 2).

Scheme 1. Possible Pathways for the Tandem Synthesis of Indolo[2,1-*a*]isoquinolines via Intermediate **R**



Our initial studies focused on the use of benzotriazole (**L1**) as ligand for the *N*-arylation of heterocycles.[10c] Thus, reaction of 3-methylindole **1a** and ((4-bromophenyl)-ethynyl)trimethylsilane **2a** using 2.0 equiv of K^+O^tBu, 10 mol % of CuI, and 20 mol % of **L1** at 120 °C for 1 h was examined (Table 1, entry 1). Under basic reaction conditions, hydrolysis of the trimethylsilyl group occurred, and a mixture of *E*- and *Z*-addition products **4a** was obtained in 72% yield in 80:20 stereoisomeric ratios along with 5% homocoupling product of alkyne (Table 1, entry 1). Interestingly, the reaction did not show the formation of any *N*-arylated product **5a**. Increase in the reaction time from 1 to 5 h provided the thermodynamically stable *trans*-isomer in 95:5 ratios in 68% yield (Table 1, entry 2). Screening of other bases in the presence of metal and catalyst did not show any formation of aminated products and only mixtures of hydroaminated products were obtained (Table 1, entries 3−6). Weak bases like K_2CO_3 and Cs_2CO_3 provided the *Z*- as the major stereoisomer (Table 1, entries 3 and 4), and strong bases K_3PO_4 and KOH yielded the addition product with *E*- as the major isomer (Table 1, entries 5 and 6). In the absence of copper and **L1**, KOH yielded the *Z*-isomer in 89% yield in 30:70 stereoisomeric ratio (Table 1, entry 7). The reaction also proceeded well in the catalytic amount of the base with the formation of *Z*- isomer as a major product within 20−25 min (Table 1, entry 8). With the recent report on the transition-metal free *N*-arylation of heterocycles using KOH and DMSO by Cano et al.[12] and iron-catalyzed amidation of alkynyl bromides by Yao et al.,[13] when a similar catalytic system was used, only hydroaminated product **4a** was obtained in 82 and 55% yields, respectively (Table 1, entries 9 and 10).

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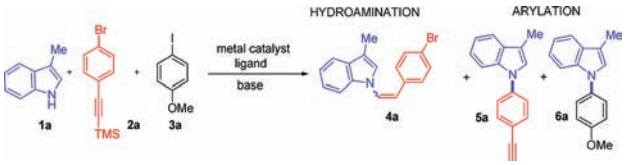
Table 1. Optimization of the Reaction Conditions[a]



				yield (%)[b]	
entry	base	catalyst	ligand	**4** (*E*:*Z*)	**5/6**
1	K^+O^tBu	CuI	BtH	72 (80:20)	
2[c]	K^+O^tBu	CuI	BtH	68 (95:05)	
3	K_2CO_3	CuI	BtH	60 (30:70)	
4	Cs_2CO_3	CuI	BtH	52 (40:60)	
5	K_3PO_4	CuI	BtH	70 (80:20)	
6	KOH	CuI	BtH	80 (60:40)	
7	KOH	–	–	89 (30:70)	
8[d]	KOH	–	–	85 (05:95)	
9[e]	KOH	–	–	82 (90:10)	
10	K_2CO_3	$FeCl_3.H_2O$	DMEDA	55 (60:40)	
11	K_2CO_3	CuI	L-proline	45 (70:30)	
12	K^+O^tBu	CuI	$BtCH_2OH$	70 (80:20)	
13	Cs_2CO_3	$Pd(OAc)_2$	dppf	65 (75:25)	
14	Cs_2CO_3	$Pd(OAc)_2$	Xantphos	56 (80:20)	
15	Cs_2CO_3	$Pd_2(dba)_3$	(±)-BINAP	62 (70:30)	
16	Na^+O^tBu	$Pd_2(dba)_3$	(±)-BINAP	58 (90:10)	
17[f]	K_3PO_4	CuI	BtH	52 (90:10)	10
18[f,g]	K_3PO_4	CuI	BtH		92

[a] Reactions were carried out using **1a** (2.0 equiv), **2** (1.0 equiv), catalyst (10 mol %), ligand (20 mol %),and base (2.0 equiv) in DMSO (1.5 mL) at 120 °C for 1 h. [b] Isolated yield of mixture of *E*/*Z* isomers. [c] Time (5 h). [d] Base (0.2 equiv) and time (20–25 min). [e] Time (72 h) and base (2.5 equiv). [f] **3a** (1.0 equiv), time (24 h). [g] Without **2a**.

Other well established copper- and palladium-catalyzed systems reported in the literature for the arylation of heterocyclic amines[14,15] were also tried, but all of them provided the stereoisomeric mixture of hydroaminated products **4a** along with 5–10% of homocoupling product (Table 1, entries 11–16). Further, addition of 4-iodoanisole (**3a**) to the reaction of **1a** and **2a** in the presence of K_3PO_4 and BtH provided the products **4** in 52% yield along with **6a** in 10%

Scheme 2. Selective Hydroamination

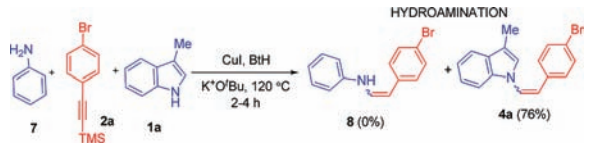


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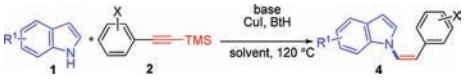
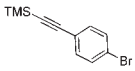
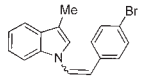
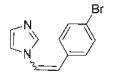
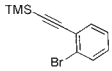
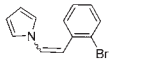
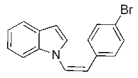
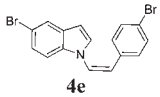
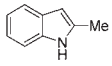
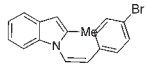
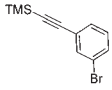
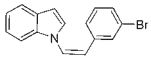
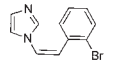
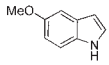
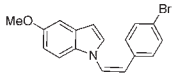
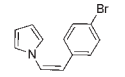
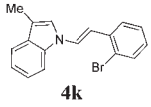
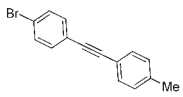
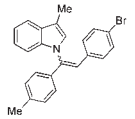
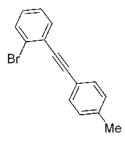
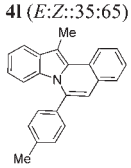
Table 2. Hydroamination of Alkynyl Bromides[a]



entry	*N*-heterocycle **1**	alkyne **2**	product **4**	yield (%)[b]
1[c]	 **1a**	 **2a**	 **4a** (*E*:*Z*:: 89:11)	75
2[c]	 **1b**	**2a**	 **4b** (*E*:*Z*:: 34:66)	58
3[c]	 **1c**	 **2b**	 **4c** (*E*:*Z*:: 50:50)	73
4[d]	 **1d**	**2a**	 **4d**	86
5[d]	 **1e**	**2a**	 **4e**	80
6[d]	 **1f**	**2a**	 **4f**	86
7[d]	**1d**	 **2c**	 **4g**	79
8[d]	**1b**	**2b**	 **4h**	62
9[d]	 **1g**	**2b**	 **4i**	90
10[d]	**1c**	**2a**	 **4j**	85
11[d,e]	**1a**	**2b**	 **4k**	82
12[c,e]	**1a**	 **2d**	 **4l** (*E*:*Z*::35:65)	63
13[c,e]	**1a**	 **2e**	 **4m**	68

[a] Reactions were carried out using **1a** (2.0 equiv) and **2** (1.0 equiv) in DMSO (1.5 mL) at 120 °C for 20–30 min. [b] Isolated yield. [c] CuI (10 mol %), $BtCH_2OH$ (20 mol %), and KOH (2.0 equiv). [d] KOH = 0.2 equiv. [e] Time = 10–12 h.

yield (Table 1, entry 17).[10c] However, in the absence of **2a** only *N*-arylated product **6a** was obtained in 92% yield (Table 1, entry 18).

Further, when reaction of aniline **7** was done with **2a**, in the presence of **1a** using CuI, K^+O^tBu, and BtH, interestingly, no hydroamination product of aniline **8** was observed and only **4a** was isolated (Scheme 2). This observation suggested that hydroamination of heterocyclic aromatic amines is preferred over aryl amines.

To check the scope and limitations of the reaction, further various *N*-heterocycles **1a**–**g** were examined with different bromo-substituted alkynes **2a**–**e** under arylation (Table 2, entries 1–3) and hydroamination conditions (Table 2, entries 4–11). It was observed that the presence of an electron-donating group at the third position of the indole ring in **1a** enhances the conversion of kinetically stable *cis*- to *trans*-isomer, and the reaction was completed within 10–15 min and afforded the hydroaminated product **4a** in 75% yield in 89:11 stereoisomeric ratios (Table 2, entry 1). Electron-deficient heterocycle imidazole **1b** provided the addition product **4b** in 58% yield with the *Z*-isomer as the major product (Table 2, entry 2). It was interesting to see that electron-rich pyrrole **1c** when reacted with ((2- bromophenyl)ethynyl)trimethylsilane **2b** under the catalytic conditions provided the mixture of *E*:*Z* addition products instead of the expected pyrrolo[2,1-*a*]-isoquinoline (Table 2, entry 3). The stereochemistry and isomeric ratio of these products were confirmed and calculated by NMR spectroscopy. Reaction of electron-rich and electron-deficient *N*-heterocycles **1a**–**g** with *ortho*-, *meta*-, and *para*-substituted bromoarylalkynes using 20 mol % of KOH at 120 °C afforded the corresponding hydroaminated products **4d**–**j** stereoselectively in 62–90% yields, respectively, within 15–20 min (Table 2, entries 4–10). Reaction with longer times (10–12 h) using a catalytic amount of KOH afforded the *E*-isomer in 82% yield (Table 2, entry 11).

Internal alkyne 1-bromo-4-(*p*-tolylethynyl)benzene **2d** also provided the mixture of hydroaminated products in 63% yield (Table 2, entry 12). *o*-Bromoarylalkyne **2e** afforded the cyclized product 12-methyl-6-*p*-tolylindolo[2,1-*a*]isoquinoline **4m** in 68% yield (Table 2, entry 13). Further, the X-ray crystallographic data of **4i** also confirmed the stereochemistry and selective formation of hydroaminated product (Figure 1).[16]

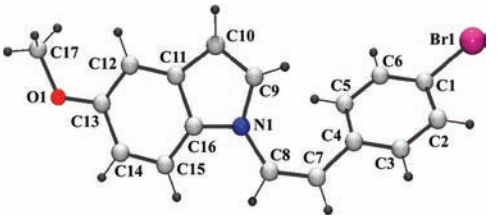


Figure 1. X-ray crystallographic ORTEP drawings of compound **4i** drawn at the 50% probability level.

In summary, for the first time, a reaction of various *N*-heterocycles and halo-substituted arylalkynes was performed, and it was observed that hydroamination is preferred over amination of aryl halide. The results of the present study, preferential addition of *N*-heterocycles onto halo-substituted arylalkynes suggests that the mechanism of the copper-catalyzed tandem synthesis of indolo- and pyrrolo[2,1-*a*]isoquinolines proceeds via generation of intermediate **Q** through hydroamination followed by oxidative addition to the key intermediate **R** and not vice versa (Scheme 2, route 2). Further theoretical investigations in this area are currently underway and will be reported in due course.

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Supporting Information Available. Detailed experimental procedures and copies of HRMS, ^{1}H NMR, and ^{13}C NMR spectra for all new compounds. CIF for compound **4i**. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Crystallographic data have been deposited at the Cambridge Crystallographic data Centre as a CIF deposit with file number 855111. Copies of these data can be obtained free of charge on application to CCDC, email deposit@ccdc.cam.ac.uk. The CIF is also included in the Supporting Information.

The authors declare no competing financial interest.