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A Facile Route to Polysubstituted Indoles via Three-Component Reaction of 2-Ethynylaniline, Sulfonyl Azide, and Nitroolefin

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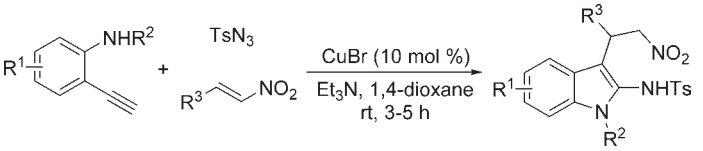
ABSTRACT



A copper-catalyzed three-component reaction of 2-ethynylaniline, sulfonyl azide, and nitroolefin is reported. This reaction generates functionalized indoles in good yields and proceeds smoothly under mild conditions. Some hits as an HCT-116 inhibitor are found from the preliminary biological screening.

The indole core is recognized as a "privileged motif" because of its presence in many biologically active natural products and pharmaceuticals.[1] Much effort has been paid toward the synthesis and functionalization of indoles, and methods for the preparation of indole derivatives have been well developed.[2−5] Classical routes for indole formation include Fischer synthesis[3] (from arylhydrazone), Batcho−Leimgruber synthesis (from *o*-nitrotoluenes and dimethylformamide acetals), Gassman synthesis (from *N*-haloanilines), Madelung cyclization of *N*-acyl-*o*-toluidines, and the reductive cyclization of *o*-nitrobenzyl ketones.[4] Recently, transition-metal-catalyzed transformations and multicomponent reactions have also been widely applied in indole synthesis.[5] While these methods have contributed greatly to this area, the development of efficient catalytic methods for the preparation of functionalized indoles using a diversity-oriented synthesis strategy remains an active research field.

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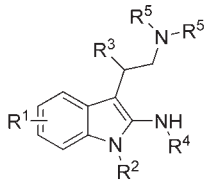
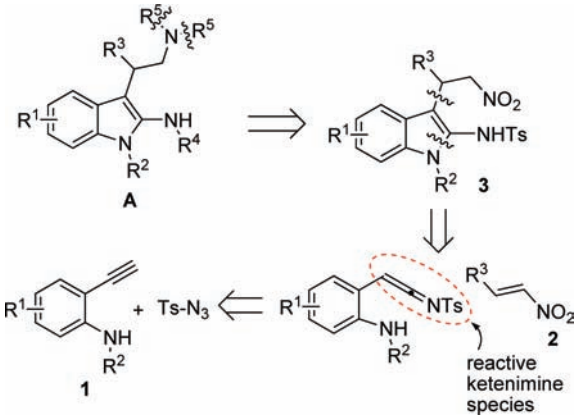


Figure 1. Structure of 3-(2-aminoethyl)-1*H*-indol-2-amine.

Among the family of indoles, compounds containing 3-(2-aminoethyl)-1*H*-indol-2-amine (Figure 1) have attracted much attention recently. For example, Celogentin C is a bicyclic octapeptide isolated from the seeds of *Celosia argentea*,[6a] which inhibits the polymerization of tubulin.[6b] As part of our program for combinatorial construction of privileged scaffolds used in different biological assays,[7] we are interested in the generation of 3-(2-aminoethyl)-1*H*-indol-2-amine derivatives. Recently, a Cu-catalyzed multicomponet reaction of sulfonyl azide, a terminal alkyne, and a nucleophile has been well developed.[8−11] The reaction involves a Cu-catalyzed azide−alkyne cycloaddition which generates a ketenimine intermediate. In this field, most of the effort is contributed by Chang and Wang.[8−10] As described, the developed procedures are characterized by high selectivity, mild reaction conditions, a wide substrate scope, and excellent functional group tolerance. Prompted by the advancement mentioned above, we conceive that 3-(2-aminoethyl)-1*H*-indol-2-amine derivatives could be synthesized as well from a reaction of sulfonyl azide, a terminal alkyne, and a nucleophile. The proposed synthetic route is described in Scheme 1. We envisioned that the target compound **A** could be traced back to indole **3**, which might be generated from the three-component reaction of 2-ethynylaniline **1**, sulfonyl azide, and nitroolefin **2**. Herein, we wish to disclose our recent efforts for this transformation.

Scheme 1. Proposed Synthetic Route for 3-(2-Aminoethyl)-1*H*-indol-2-amine Formation



Initial studies were performed for the reaction of *N*-acetyl-2-ethynylaniline **1a**, *p*-toluenesulfonic azide, and (*E*)-(2-nitrovinyl)benzene **2a** in the presence of copper salt as a catalyst. At the beginning, CuI was used as the catalyst and triethylamine (TEA) was employed as the base. To our delight, the desired product **3a** was obtained in 73% yield after 6 h when the reaction occurred in anhydrous CH_3CN under a N_2 atmosphere (Table 1, entry 1). The structure of **3a** was confirmed by X-ray

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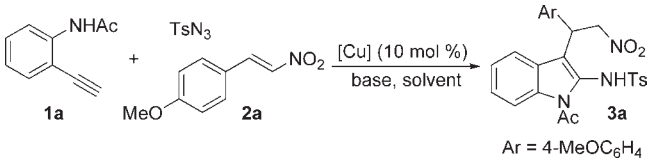
Table 1. Initial Studies for the Three-Component Reaction of 2-Ethynylaniline, Sulfonyl Azide, and Nitroolefin



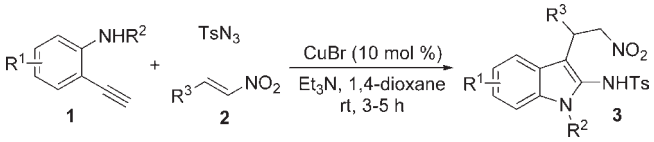
entry	Lewis acid	base	solvent	time (h)	yield (%)[a]
1	CuI	TEA	CH_3CN	6	73
2	CuBr	TEA	CH_3CN	6	81
3	CuCl	TEA	CH_3CN	24	32
4	$Cu(OTf)_2$	TEA	CH_3CN	24	25
5	IPr/CuI	TEA	CH_3CN	24	24
6	IPr/CuCl	TEA	CH_3CN	24	52
7	CuBr	DIPEA	CH_3CN	12	21
8	CuBr	Py	CH_3CN	24	trace
9	CuBr	n-Bu_3N	CH_3CN	8	61
10	CuBr	TEA	THF	8	32
11	CuBr	TEA	DMSO	4	54
12	CuBr	TEA	1,4-dioxane	6	91
13	CuBr	TEA	Toluene	6	45
14	CuBr	TEA	$CHCl_3$	10	54
15	CuBr	TEA	DCE	12	48
16	CuBr	TEA	DMF	6	24
17	CuBr[b]	TEA	1,4-dioxane	8	83
18	CuBr[c]	TEA	1,4-dioxane	20	60

[a] Isolated yield based on *N*-acetyl-2-ethynylaniline **1a**. [b] In the presence of 8 mol % of CuBr. [c] In the presence of 5 mol % of CuBr.

diffraction analysis as well. However, it seems that there is still a chance of spreading the double bond character over the ring and "tosylamido" moiety by analyzing the related bond lengths (see Supporting Information). Other copper catalysts were screened subsequently (Table 1, entries 2−6). The results showed that CuBr was the best one for the transformation (81% yield), compared with CuCl (32%), $Cu(OTf)_2$ (25%), IPr/CuI (24%), and IPr/CuCl (52%). Further screening of bases including diisopropylethylamine (DIPEA), pyridine (Py), and n-Bu_3N revealed that no obvious improvement was achieved (Table 1, entries 7−9). The reaction was tested in various solvents as well, which showed that the best result (91% yield) was generated in 1,4-dioxane (Table 1, entry 12). Inferior yields were isolated when the catalyst loading was reduced (Table 1, entries 17−18).

Having defined an efficient catalytic system [CuBr (10 mol %), Et_3N, 1,4-dioxane, room temperature], the scope of this three-component reaction of 2-ethynylaniline **1**, sulfonyl azide, and nitroolefin **2** was explored. The results are summarized in Table 2. To assess the impact of the structural and functional motifs on the reaction, we tested a range of 2-ethynylanilines and nitroolefins. For all cases, *N*-acetyl-2-ethynylaniline **1** reacted with sulfonyl azide and nitroolefin **2** leading to the corresponding polysubstituted indoles **3** in good to excellent yields.

Table 2. Generation of Polysubstituted Indoles via Three-Component Reaction of 2-Ethynylaniline, Sulfonyl Azide, and Nitroolefin



entry	R^1, R^2	R^3	yield (%)[a]
1	H, Ac (**1a**)	4-$MeOC_6H_4$ (**2a**)	91 (**3a**)
2	H, Ac (**1a**)	C_6H_5 (**2b**)	83 (**3b**)
3	H, Ac (**1a**)	1-naphthalene (**2c**)	95 (**3c**)
4	H, Ac (**1a**)	4-FC_6H_4 (**2d**)	60 (**3d**)
5	H, Ac (**1a**)	4-BrC_6H_4 (**2e**)	88 (**3e**)
6	H, Ac (**1a**)	2-BrC_6H_4 (**2f**)	86 (**3f**)
7	H, Ac (**1a**)	n-pentyl (**2g**)	40 (**3g**)
8	H, Ac (**1a**)	furan-2-yl (**2h**)	70 (**3h**)
9	H, Ac (**1a**)	thiophen-2-yl (**2i**)	60 (**3i**)
10	4-Me, Ac (**1b**)	4-$MeOC_6H_4$ (**2a**)	61 (**3j**)
11	4-^{n}Bu, Ac (**1c**)	4-$MeOC_6H_4$ (**2a**)	92 (**3k**)
12	4-^{n}Bu, Ac (**1c**)	4-BrC_6H_4 (**2e**)	91 (**3l**)
13	4-^{n}Bu, Ac (**1c**)	furan-2-yl (**2h**)	92 (**3m**)
14	4-F, Ac (**1d**)	4-$MeOC_6H_4$ (**2a**)	55 (**3n**)
15	4-F, Ac (**1d**)	4-BrC_6H_4 (**2e**)	71 (**3o**)
16	4-F, Ac (**1d**)	furan-2-yl (**2h**)	50 (**3p**)
17	4-CF_3, Ac (**1e**)	C_6H_5 (**2b**)	65 (**3q**)
18	4-CF_3, Ac (**1e**)	2-BrC_6H_4 (**2f**)	52 (**3r**)
19	4-CF_3, Ac (**1e**)	thiophen-2-yl (**2i**)	60 (**3s**)
20	H, H (**1f**)	4-$MeOC_6H_4$ (**2a**)	messy
21	H, Boc (**1g**)	1-naphthalene (**2c**)	85 (**3t**)
22	H, Boc (**1g**)	4-BrC_6H_4 (**2e**)	81 (**3u**)

[a] Isolated yield based on *N*-acetyl-2-ethynylaniline **1**.

For instance, reaction of *N*-(2-ethynylphenyl)acetamide **1a**, sulfonyl azide, and nitrostyrene **2b** gave rise to the desired product **3b** in 83% yield (Table 2, entry 2). When (*E*)-1-(2-nitrovinyl)naphthalene **2c** was employed in the above reaction, the desired product **3c** was isolated in 95% yield (Table 2, entry 3). A lower yield was obtained when (*E*)-1-fluoro-4-(2-nitrovinyl)benzene **2d** was used as a replacement (60% yield, Table 2, entry 4). Good results were generated when (*E*)-1-bromo-4-(2-nitrovinyl) benzene **2e** was utilized as a partner in the reaction (Table 2, entries 5 and 6). However, an inferior yield was displayed when aliphatic-substituted nitroolefin **2g** was employed in the reaction (40% yield, Table 2, entry 7). This result is reasonable due to the less reactive alkyl nitroolefin.[12a,b] Additionally, other factors, such as polymerization of alkyl nitroolefin, may also affect the efficiency of the transformation.[12c] An electrophile containing a heterocycle, such as furanyl or thiophenyl, was also tolerated, leading to the desired products in good

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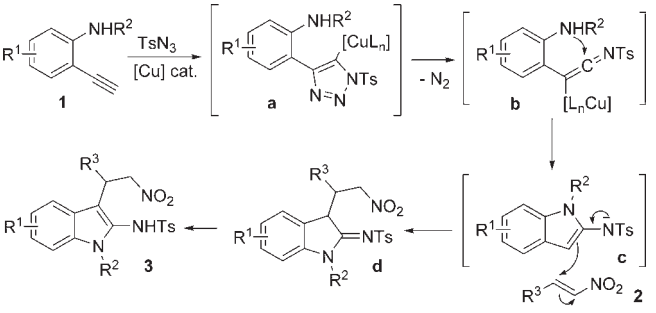
yield (Table 2, entries 8 and 9). We next examined the reaction of *N*-acetyl-2-ethynylaniline **1** with substituents on the aromatic ring (**1b**−**1e**) (Table 2, entries 10−19). As expected, the corresponding products were obtained in good yields, whether the nitroolefin was attached with an electron-donating or -withdrawing group. As for the protecting group of amine in 2-ethynylaniline **1**, it was found that a one-pot reaction of 2-ethynylaniline **1f**, sulfonyl azide, and nitroolefin **2a** was not workable under the standard conditions (Table 2, entry 20). In the case of *N*-Boc-2-ethynylaniline **1g**, the reaction worked well in furnishing the expected products in good yields (Table 2, entries 21 and 22). However, when *N*-tosyl-2-ethynylaniline was used as the substrate in the transformation, only a copper-catalyzed azide−alkyne [3 + 2] cycloaddition product was observed.[13] The reaction was complex when *N*-alkyl-2-ethynylaniline was employed (data were not shown in Table 2).

Scheme 2. Possible Mechanism for the Three-Component Reaction of 2-Ethynylaniline, Sulfonyl Azide, and Nitroolefin



The possible mechanism for this three-component reaction is described in Scheme 2. As reported by Chang and Wang,[8−10] the reactive ketenimine **b** would be generated by the ring-opening rearrangement of triazole intermediate **a**, which was formed from alkyne **1** and sulfonyl azide in the presence of CuBr and triethylamine. Subsequently intramolecular nucleophilic addition occurred, leading to the intermediate **c**. Afterwards intermolecular Michael addition and tautomerization afforded the desired product **3**.

The subsequent biological screening as an HCT-116 inhibitor revealed that the results were promising. The data for active compounds are presented in Table 3.

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Table 3. Biological Screening Result as HCT-116 Inhibitor

compd	concn	result type	result	error
3b	20 μg/mL	%Activity	8.045	5.258
		IC_{50} (μg/mL)	4.305	0.378
3c	20 μg/mL	%Activity	8.053	3.578
		IC_{50} (μg/mL)	7.842	0.716
3e	20 μg/mL	%Activity	15.491	3.197
		IC_{50} (μg/mL)	11.588	1.024
3f	20 μg/mL	%Activity	13.515	13.415
		IC_{50} (μg/mL)	7.784	0.734
3h	20 μg/mL	%Activity	13.937	3.128
		IC_{50} (μg/mL)	9.279	1.056
3i	20 μg/mL	%Activity	19.139	3.057
		IC_{50} (μg/mL)	7.766	0.631
3j	20 μg/mL	%Activity	4.312	0.701
		IC_{50} (μg/mL)	3.495	0.384
3k	20 μg/mL	%Activity	17.706	1.629
		IC_{50} (μg/mL)	11.272	1.229
3n	20 μg/mL	%Activity	4.588	0.604
		IC_{50} (μg/mL)	6.262	0.546
3o	20 μg/mL	%Activity	17.583	6.207
		IC_{50} (μg/mL)	8.89	0.915
3q	20 μg/mL	%Activity	6.952	2.444
		IC_{50} (μg/mL)	7.199	0.796
3r	20 μg/mL	%Activity	5.855	1.956
		IC_{50} (μg/mL)	4.989	0.449
3s	20 μg/mL	%Activity	48.453	1.206
		IC_{50} (μg/mL)	17.061	2.003

Compound **3j** was discovered as being the best (IC_{50} 3.495 μg/mL). These results are encouraging for the further construction of the library of indole **3**.

In conclusion, we have developed an efficient copper (I)-catalyzed three-component reaction of 2-ethynylaniline **1**, sulfonyl azide, and nitroolefin **2**. A variety of polysubstituted indole derivatives were obtained in moderate to good yields. In this transformation, a broad substrate scope has been demonstrated. Additionally, the reaction conditions are extremely mild. Some hits as an HCT-116 inhibitor are found from the preliminary biological screening. We believe that this method is attractive for further library construction.

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Supporting Information Available. Experimental procedure, characterization data, ^1H and ^{13}C NMR spectra of compounds **3**, and X-ray crystal data of compound **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.