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Copper-Catalyzed Multicomponent Coupling/Cycloisomerization Reaction between Substituted 1-Formyl-9*H*-β-carbolines, Secondary Amines, and Substituted Alkynes for the Synthesis of Substituted 3-Aminoindolizino[8,7-*b*]indoles

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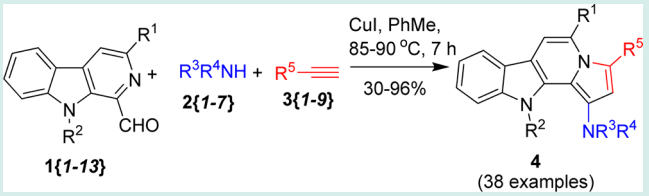
Supporting Information

ABSTRACT: A copper-catalyzed efficient one step three component strategy for preparing a library of aminoindolizino-[8,7-*b*]indoles from *N*-substituted 1-formyl-9*H*-β-carbolines, secondary amines, and substituted alkynes with high atom economy has been developed.



KEYWORDS: *multicomponent reaction, copper, β-carbolines, aminoindolizino[8,7-b]indole*

INTRODUCTION

Indolizino[8,7-*b*]indole is an interesting core represented in alkaloids such as harmicine, fascaplysin, and bromofascaplysin (Figure 1).[1] This structural unit has been of significant interest

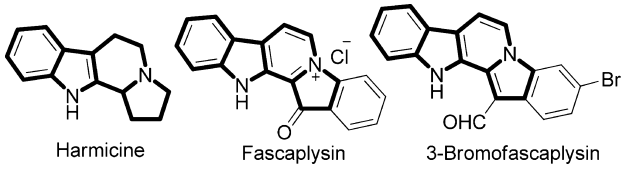


Figure 1. Natural products with an indolizino[8,7-*b*]indole core.

to the pharmaceutical industry also.[2] Besides, the property of the quaternized pyridine to undergo rapid nucleophilic attack has been utilized to derive more complex structures from this scaffold.[3] There have been several elegant strategies which successfully afford this scaffold, though some of them are multistep or involve use of expensive reagents.[4] Very recently, we reported the synthesis of substituted indolizino[8,7-*b*]indoles from *N*-substituted 1-formyl-9*H*-β-carbolines employing the Morita−Baylis−Hillman adducts (MBH).[5] However, the diversity of this protocol is limited, which is an impediment for building a chemical library based on this scaffold. Therefore, we considered an alternative strategy for developing a diversity-oriented library of compounds containing this core from the same starting substrates. Structural analysis of indolizino[8,7-*b*]indole indicates it contains the indole and the indolizine unit. It is widely reported that the indolizine unit, which in itself is represented in several naturally occurring alkaloids and compounds displaying a variety of biological activities[6] and electronic properties,[7] can be rapidly and directly synthesized through transition-metal based multicomponent reaction between 2-pyrdinecarbaldehyde, secondary amine, and alkyne.[8] Yan and Liu reported the synthesis of aminoindolizines from 2-pyridinealdehyde, secondary amines, and alkynes under solvent free conditions or in water in the presence of gold catalyst.[8a] Later Liu and co-workers reported the synthesis of a library of aminoindolizines from similar substrates by employing silver catalyst instead of gold.[8b] Conceptually, both these protocols proceeded via Grignard-type direct addition of alkyne to imine involving C−H activation to initially afford the NR^1R^2-propargylic amine, which undergoes a metal-catalyzed cycloisomerization. Although the literature revealed that formation of propargylic amines via analogous coupling reaction has been reported to be successful by a variety of metal catalysts,[9] these reports[8] showed the success of their protocols essentially with either gold or silver catalysts (Figure 2). More recently, however, Bobade and co-workers succeeded in synthesizing similar 3-aminoindolizines by the use of iron catalyst in the presence of tetrabutylammonium hydroxide.[8c]

Since we had efficient access to 1-formyl-9*H*-β-carbolines, it was anticipated that a multicomponent reaction (MCR) between this substrate, secondary amines, and substituted alkynes would lead to the synthesis of diverse 3-aminoindolizino[8,7-*b*]indoles via a similar reaction pathway. To the best of our knowledge, the MCR route to 3-aminoindolizino[8,7-*b*]indole remains unreported in the literature. Working on the envisaged strategy, we discovered that we could successfully accomplish the synthesis of desired aminoindolizino[8,7-*b*]indoles via a one-pot copper-catalyzed tandem process[10] involving coupling/cycloisomerization reaction without any elaborate reaction conditions. We found that

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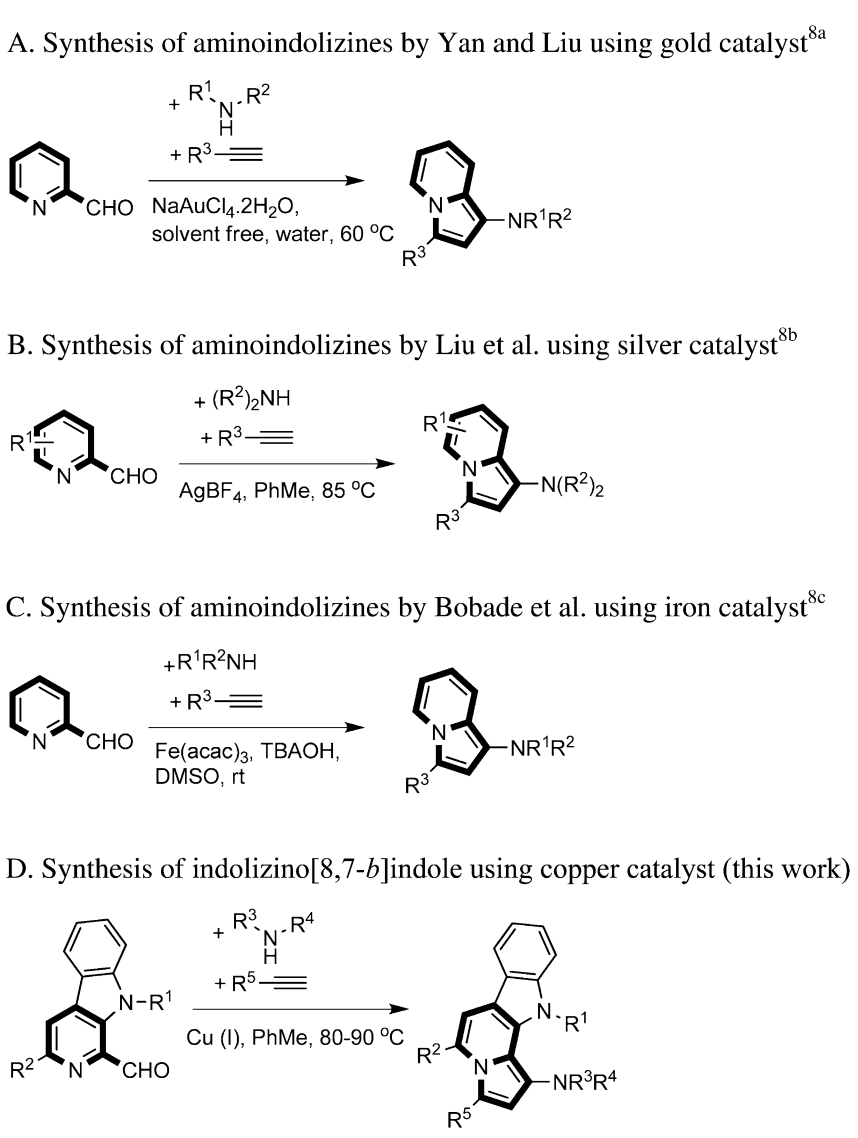

Figure 2. Approaches to aminoindolizine core.

the presence of a slight excess of the amine facilitates the formation of product and that copper salt in the Cu(I) oxidation state is better suited for the reaction. Moreover, the duration of the reaction was significantly reduced by performing the reaction under microwave heating. Results of our study in this regard are presented herein.

RESULTS

To test the success of our strategy, we first screened various metal catalysts for the coupling reaction of methyl *N*-allyl-1-formyl-9*H*-*β*-carboline-3-carboxylate **1**{*1*}, morpholine **2**{*1*}, and phenyl acetylene **3**{*1*} under different reaction conditions, and the results are summarized in Table 1. Interestingly, during the optimization we observed that, as compared to gold and silver catalysts, the three components coupling/cycloisomerization proceeded more efficiently in the presence of copper(I) salts in toluene as medium to afford the desired methyl 11-allyl-1-morpholino-3-phenyl-11*H*-indolizino[8,7-*b*]indole-5-carboxylate **4**{*1,1,1*} after 12 h at 90 °C in 68% yields (entries 1−6, Table 1). Lowering the catalyst load to less than 5 mol % resulted in lowering of the yields of **4**{*1,1,1*} (entry 7−8, Table 1). However, increasing the catalyst load to 10 mol % of CuI yielded **4**{*1,1,1*} in 96% yield (entry 9, Table 1). Further titrating the amount of reagents, we discovered that increasing the amount of phenyl acetylene from 1.1 to 1.5 equiv (*ca.* for the synthesis of indolizines[8]) had no bearing on the outcome but using 1.5 equiv of morpholine instead of 1.1 equiv reduced the reaction time from 12 to 7 h without affecting the yields of the product formed (entry 10, Table 1). It was realized that the toluene was the best solvent for the reaction to furnish **4**{*1,1,1*}. Inferior results were obtained when polar solvents such as dioxane, DMSO, DMF, or MeCN were used as the medium (compare entry 10 with entries 11−14, Table 1). As indicated in Table 1, different Cu(I) and Cu(II) salts were also examined and it was observed that the yields were better with Cu(I) salts and the CuI was the most suited for the reaction (compare entries 10 with 15−19, Table 1). Therefore, the standardized conditions which worked best for us were aldehyde (1.0 equiv), phenyl acetylene (1.1 equiv), and morpholine (1.5 equiv) in the presence of 10 mol % of CuI in toluene at 85 °C for 7 h.

With the optimized conditions, we investigated the scope of this multicomponent strategy for the construction of a library of 3-amino indolizino[8,7-*b*]indoles. It may be noted that in our

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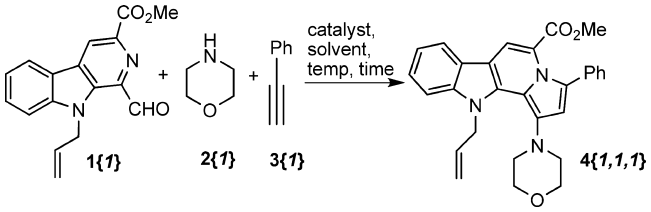
Table 1. Results of the Study for Optimization[a] of the Catalyst and Reaction Conditions for the MCR



entry	mol %	catalyst	solvent	temp	time (h)[b]	yield (%)
1	5	$AuCl_3$	toluene	85	12	21
2	5	Ag_2O	toluene	85	12	34
3	5	$AgBF_4$	toluene	85	12	64
4	5	CuI	toluene	85	12	68
5	5	CuBr	toluene	85	12	65
6	5	CuCl	toluene	85	12	54
7	4	CuI	toluene	85	12	60
8	3	CuI	toluene	85	12	55
9	10	CuI	toluene	85	12	96
10	10	CuI	toluene	85	7	96
11	10	CuI	dioxane	85	7	47
12	10	CuI	DMSO	85	7	58
13	10	CuI	MeCN	85	7	36
14	10	CuI	DMF	85	7	42
15	10	CuBr	toluene	85	7	90
16	10	CuCl	toluene	85	7	53
17	10	Cu_2O	toluene	85	7	15
18	10	$CuBr_2$	toluene	85	7	79
19	10	$Cu(OAc)_2$	toluene	85	7	22

[a]All reactions were performed with 0.13 mmol of aldehyde. [b]Entries 1−9: 1.1 equiv of sec amine was employed. Entries 10−17: 1.5 equiv of sec amine was employed.

hands the reaction of unsubstituted 1-formyl-9*H*-*β*-carboline with phenyl acetylene and morpholine resulted in a complex mixture of products; therefore, it was out of the scope. In all 13 N-substituted 1-formyl-9*H*-*β*-carbolines (**1**), seven secondary amines (**2**) and 9 alkynes (**3**) (Figure 3) were employed for preparing the library, and different products synthesized during the present study are illustrated in Table 2. It is worthwhile to mention that all products were obtained by initially passing the reaction mixture (without any workup) through a small band of silica gel using hexane as eluent to remove the excess alkyne, followed by elution with hexane/EtOAc (97:3, v/v). In general, different aldehydes whose reactions were performed in toluene furnished the products in excellent yields. But as a few aldehydes **1**{*3* & *4*} were insoluble in toluene, their reactions were carried out in DMSO as the medium, which led to the formation of the respective products **4**{*3,1,1*} and **4**{*4,1,1*} in low yields. It was interesting to note that different substitutions present on the indole nitrogen do not have any influence on the outcome of the reaction. In the case of substrates having the benzyl substitution **1**{*6*−*11, 13*}, the electronic character of the substitution (donating or withdrawing) on the phenyl ring of the benzyl group also does not affect the formation of product. It was observed that, among all the secondary amines examined during the study, the diphenylamine **2**{*7*} failed to produce the required product **4**{*1,7,1*}. On the other hand since diethyl amine **2**{*6*} was able to afford the respective aminoindolizino-[8,7-*b*]indole **4**{*6,6,1*}, we speculate that the presence of diphenyl rings attached to the amino group induces steric hindrance unsuited for the reaction. Of the nine alkynes investigated for the protocol, we found trimethylsilyl acetylene **3**{*9*} did not produced the required aminoindolizino[8,7-*b*]indole **4**{*1,1,9*}. On the basis of the work of Liu and co-workers,[8b] it is likely that the TMS group is removed in the presence of copper salt, leading to in situ generation of acetylene which did not participate in the reaction. Moreover, the aldehydes originating from tryptophan and tryptamine reacted with similar efficiency, but the products generated from the tryptamine have to be stored at lower temperature to prevent them from decomposing.

The plausible mechanism for the formation of the 3-aminoindolizino[8,7-*b*]indole is delineated in Figure 4. This mechanism is analogous to Cu-catalyzed cycloisomerization of alkynylimines to afford pyroles and Cu-catalyzed cycloisomerisation of propargylic pyridines.[11,9d] It is assumed that initially morpholine reacts with the aldehyde II, leading to the formation of iminium ion III with the loss of a water molecule. Subsequently, Cu-coordinated alkyne I formed in situ reacts with III, wherein a nucleophilic attack of pyridyl nitrogen on the Cu-coordinated allenyl double bond occurs, resulting in formation of cationic intermediate IV. The morpholine captures a proton from IV to furnish the intermediate V, which upon protonolysis yields the product VI.

Since the intermediate species were ionic, we were prompted to test the reaction under microwave conditions to potentially decrease the reaction time. An optimization study under microwave (MW) conditions was performed via coupling reaction of methyl *N*-allyl-1-formyl-9*H*-*β*-carboline-3-carboxylate **1**{*1*}, morpholine **2**{*1*}, and phenylacetylene **3**{*1*}. We were delighted to note that at 90 °C under MW the reaction was complete in 45 min to afford the product **4**{*1,1,1*} in 94% yields. Hence, a few more reactions were investigated under MW conditions, and the results are presented in Table 3. As evident, all reactions successfully gave the products but the yields were relatively less as compared to the conventional route.

Since we were unable to include the N-unsubstituted 1-formyl-9*H*-*β*-carboline for the study, we decided to unmask the N-allyl or N-benzyl groups in representative products using literature strategies. Initially, in order to remove the allyl group, compound **4**{*1,1,1*} was treated with $RhCl(PPh_3)_3$ in a MeCN/H_2O mixture under reflux, as reported earlier.[12] However, the reaction resulted in a complex mixture of products which could not be purified. On the other hand, debenzylation in **4**{*6,1,1*}, which was attempted either by hydrogenation[13] or via different chemical methods,[14] also failed to give the desired results.

The successful use of copper salts for the coupling/cycloisomerization reaction in *β*-carboline inspired us to reinvestigate the three component reaction between of pyridine-2-carbaldehyde, secondary amine, and alkyne under the optimized conditions of our study. Accordingly, pyridine-2-carbaldehyde was treated with phenyl acetylene (1.1 equiv) and morpholine or piperidine (1.5 equiv) in toluene at 85 °C (Scheme 1). It was gratifying to note that both reactions were successful and gave the respective products in 82 and 74% yields.

In summary, we have developed a Cu-mediated multicomponent route involving coupling/cycloisomerization for the synthesis of 3-aminoindolizino[8,7-*b*]indoles. As illustrated, the methodology is efficient and amenable to library development. The protocol is amenable to microwave conditions, thereby reducing the reaction time significantly. Further work is

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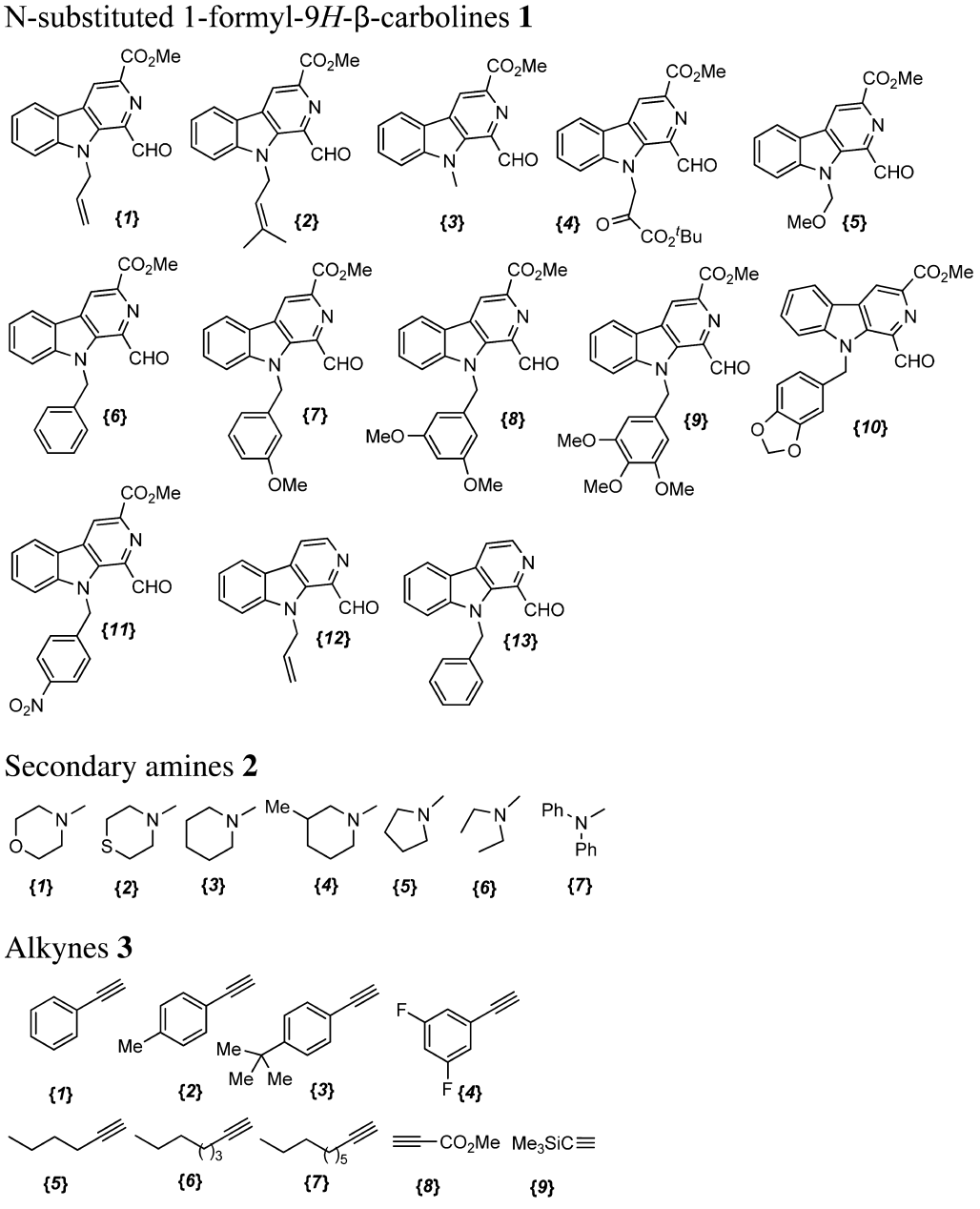

Figure 3. Diversity of reagents.

underway to develop the chemistry of these 3-aminoindolizino-[8,7-*b*]indoles for obtaining new fused *β*-carbolines.

EXPERIMENTAL PROCEDURES

Melting points are uncorrected and were determined in capillary tubes on a Precision melting point apparatus containing silicon oil. IR spectra were recorded using a Perkin-Elmer's RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker DPX-200 or Bruker Avance DRX-300 spectrometer, using TMS as an internal standard (chemical shifts in δ). The ESMS were recorded on a Thermo Finnigan LCQ Advantage, Ion Trap Mass spectrometer. The HRMS spectra were recorded as EI-HRMS on an Agilent 6520 Q-TOF, LC-MS/MS mass spectrometer. The reactions under microwave heating were carried out in a Biotage initiator 2.5 microwave system. All aldehydes were prepared following the method reported earlier.[5]

General Procedure for the multicomponent reaction as exemplified for the synthesis of methyl 11-allyl-1-morpholino-3-phenyl-11*H*-indolizino[8,7-*b*]indole-5-carboxylate 4{*1,1,1*}. . To a reaction vessel in 10 mL of toluene were added **1**{*1*} (150 mg, 0.51 mmol), morpholine (67.0 μL, 0.76 mmol), phenylacetylene (61.0 μL, 0.56 mmol), and CuI (10 mg, 0.05 mmol) and then nitrogen was bubbled for 10 min to deoxygenate the reaction mixture. Thereafter, the resulting solution was stirred at 85 °C for 7 h. On completion, the reaction mixture was cooled to room temperature and was purified by silica gel column chromatography (hexanes/EtOAc, 97:3, v/v) to obtain pure **4**{*1,1,1*} as a yellow solid (228 mg, 96%). Mp: 116−118 °C; R_f = 0.54 (hexanes/EtOAc, 80:20); IR (KBr) ν: 1500, 1629, 1715 2384, 2855 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.02−3.16 (m, 4H), 3.24 (s, 3H),

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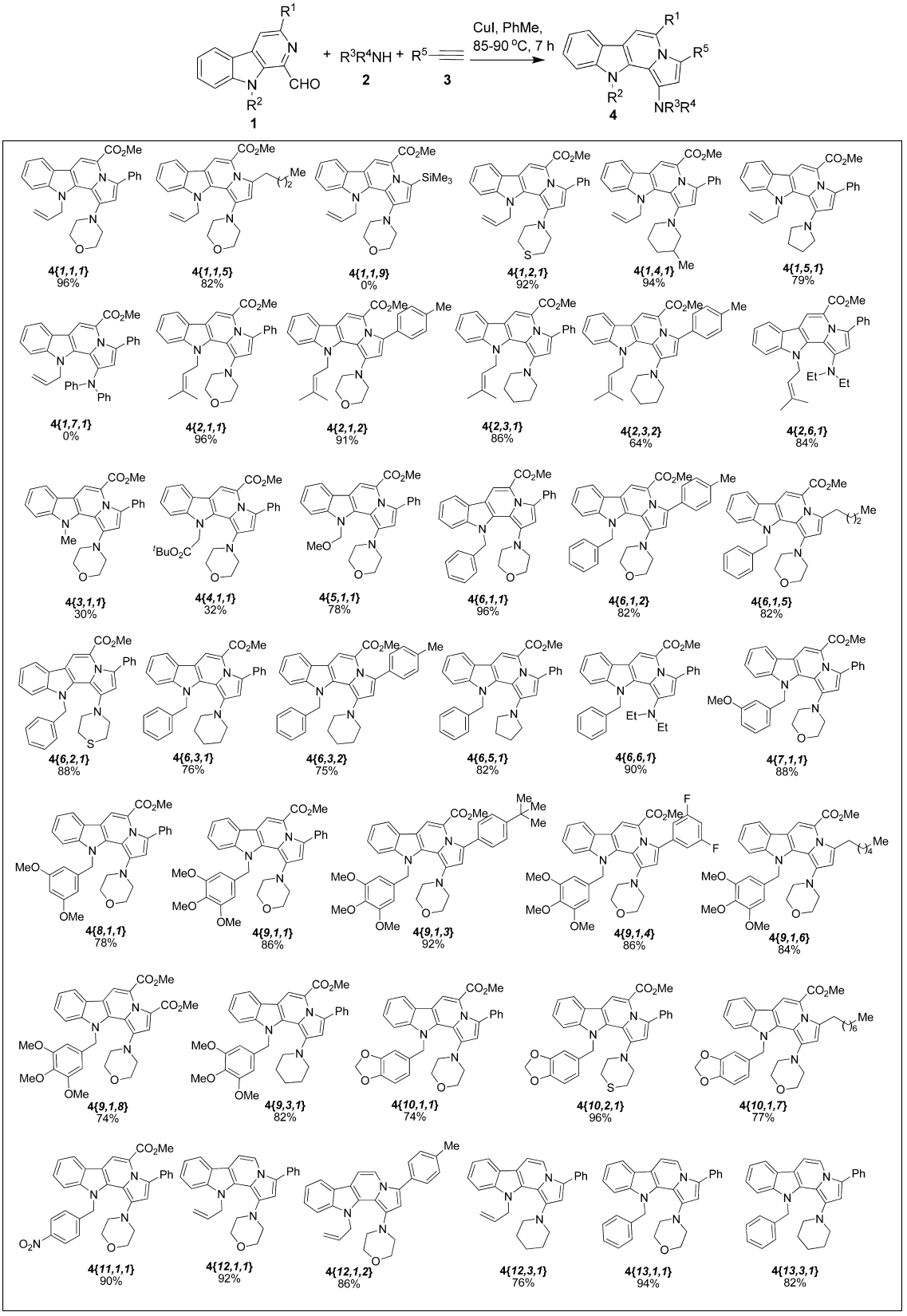
Table 2. Copper-Catalyzed Three-Component Reactions[a] To Synthesize a Library of Aminoindolizino[8,7-*b*]indoles



[a]All reactions were performed by using 1.0 equiv of aldehyde, 1.5 equiv of *sec* amine, and 1.1 equiv of alkyne, 10 mol % of CuI in toluene at 85 °C; the yields included in the table are the isolated yields of compounds.

3.83−3.98 (m, 4H,), 4.92 (d, 1H, J = 17.2 Hz), 5.10 (d, 1H, J = 10.1 Hz), 5.95−6.04 (m, 1H), 6.25 (s, 2H), 6.88 (s, 1H), 7.26−7.49 (m, 8H), 7.81 (s, 1H), 7.88 (d, 1H, J = 7.4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 49.5, 51.6, 55.6, 67.3, 109.5,

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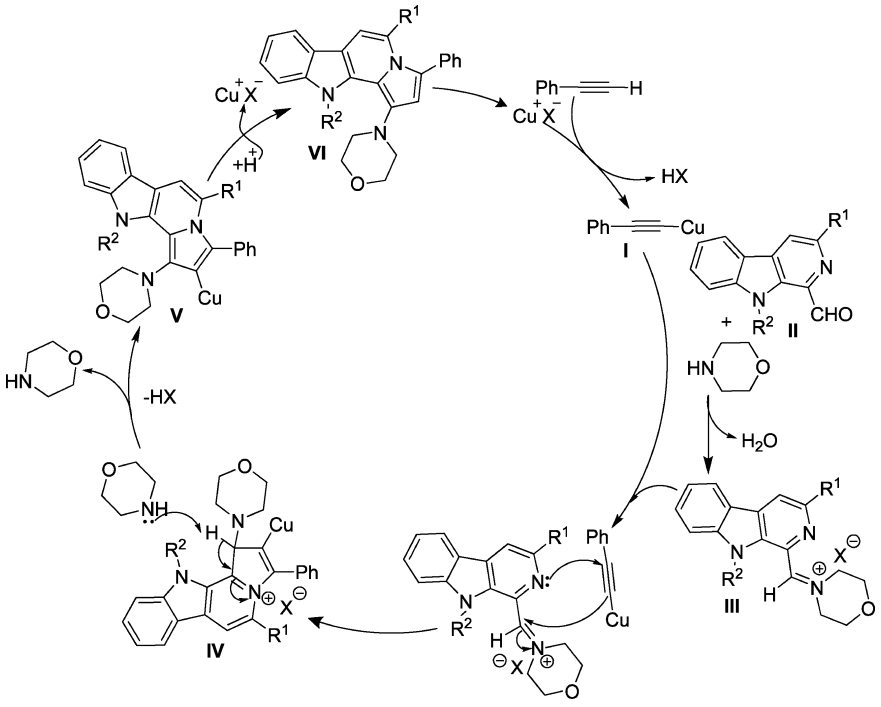
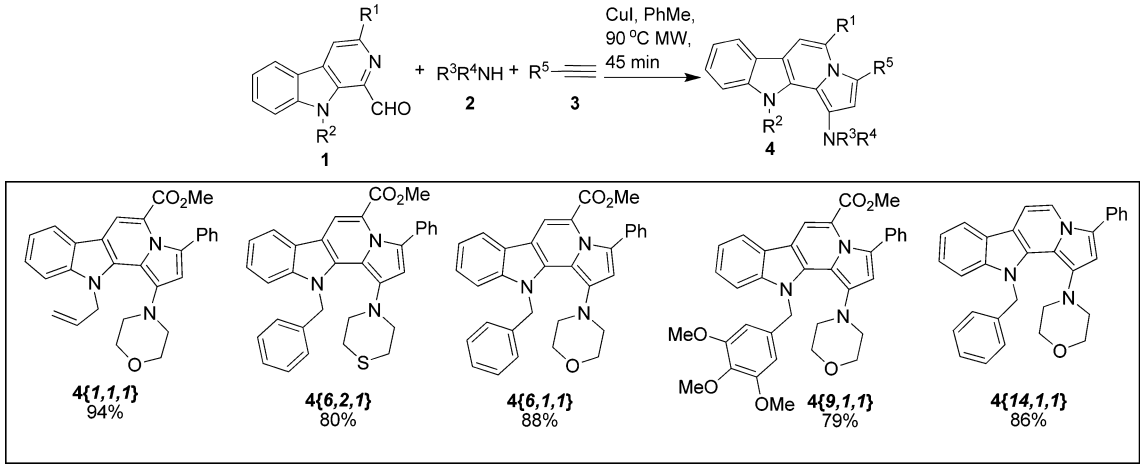


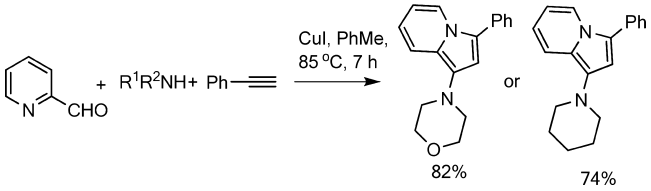
Figure 4. Plausible mechanism for the formation of the aminoindolizino[8,7-*b*]indole.

Table 3. Copper-Catalyzed Three-Component Reactions[a] To Synthesize Aminoindolizino[8,7-*b*]indoles under Microwave Conditions



[a]All reactions were performed by using 1.0 equiv of aldehyde, 1.5 equiv of *sec* amine, and 1.1 equiv of alkyne, 10 mol % of CuI in toluene at 85 °C; the yields included in the table are the isolated yields of compounds.

Scheme 1. Copper Catalyzed Three-Component Reactions To Synthesize Aminoindolizines



111.1, 114.3, 116.0, 118.7, 121.2, 123.9, 124.6, 125.2, 127.2, 129.2, 132.0, 134.6, 139.9, 164.7. MS (ESI+) *m*/*z*: = 466.2 (M + H)$^+$. ESI-HR-MS calculated for $C_{29}H_{28}N_3O_3$ [MH]$^+$: 466.2131, found: 466.2121.

Methyl 11-Benzyl-1-morpholino-3-phenyl-11*H*-indolizino[8,7-*b*]indole-5-carboxylate 4{*6,1,1*}. The compound was prepared following a similar procedure as described above. Yield: 96% (0.197 g from 0.15 g); yellow solid; mp: 166−168 °C; R_f = 0.52 (hexanes/EtOAc, 80:20); IR (KBr) ν: 1220, 1630, 1713 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.86 (d, 2H, J = 11.2 Hz), 3.00 (dd, 2H, J_1 = 9.5 Hz, J_2 = 11.4 Hz), 3.26−3.31 (m, 5H), 3.71 (d, 2H, J = 10.2 Hz), 6.84 (s, 2H), 6.88 (s, 1H), 7.09 (d, 2H, J = 6.7 Hz), 7.19−7.31 (m, 7H), 7.40−7.50 (m, 4H), 7.86−7.89 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 51.1, 51.6, 55.9, 66.8, 109.8, 111.2, 114.3, 118.6, 119.8, 121.2, 124.1, 124.7, 125.2, 126.1, 127.2, 128.8, 129.2, 130.5, 132.0, 135.7, 138.9, 139.7, 164.7. MS (ESI +) *m*/*z*: = 516.2 (M + H)$^+$. ESI-HR-MS calculated for $C_{33}H_{30}N_3O_3$ [MH]$^+$: 516.2287, found: 516.2281.

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■ ASSOCIATED CONTENT

Supporting Information

Spectral and analytical data along with copies of ^{1}H- and ^{13}C-NMR for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

SD, SH and SB conceived and designed the experiments, SD and SH performed the experiments, SD and SB co-wrote the manuscript.

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Notes

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