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CuI-Catalyzed Coupling of *gem*-Dibromovinylanilides and Sulfonamides: An Efficient Method for the Synthesis of 2-Amidoindoles and Indolo[1,2-*a*]quinazolines

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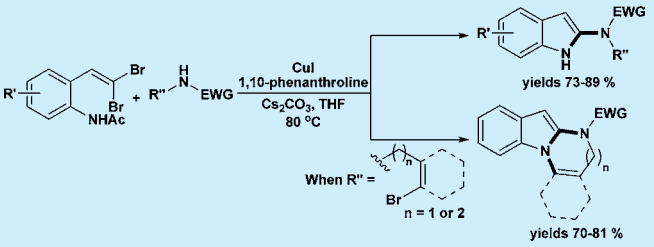
Supporting Information

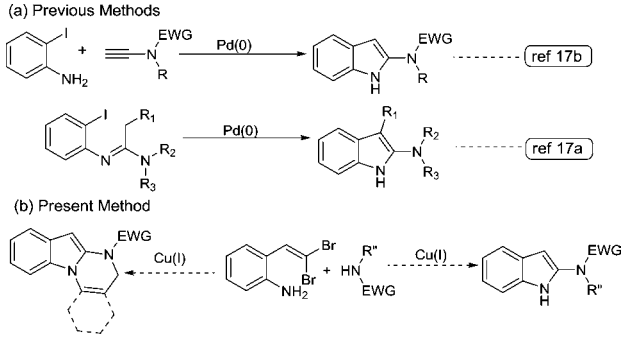
ABSTRACT: A Cu(I)-catalyzed, intermolecular protocol for the synthesis of 2-amidoindoles and tetrahydroindolo[1,2-*a*]quinazolines in shorter time and high yields is reported. The key highlight of this disclosure is the formation of 2-amidoindole and tetrahydroindolo[1,2-*a*]quinazoline moieties directly from *gem*-dibromovinylanilides and sulfonamides in a one-pot fashion through the in situ formation of ynamides followed by a base-promoted intramolecular hydroamidation.



gem-Vinyl dihalides are emerging as intriguing synthetic intermediates[1] and also serve as a key unit in the synthesis of various alkynes,[2] carbocycles,[3] heterocycles,[4] etc. The best coupling partners that are utilized in reactions involving *gem*-vinyl dihalides, especially dibromides, are mostly heteroatoms containing nucleophiles (N, O, P, or S).[5−8] These coupling reactions of *gem*-vinyl dibromides with nucleophiles are generally assisted and catalyzed by transition metals.[1−5] Among the transition metals employed in such reactions, those involving copper as a catalyst are of great significance to synthetic chemists because of their economic advantages and potential application in large-scale reactions.[9] The copper-catalyzed reactions of *gem*-vinyl dibromides with nucleophiles result in the production of heteroatom-containing alkynes which probably display the most versatile and significant class of alkynes.[10] Recent literature reveals that of all the heteroatom-containing alkynes and the nitrogen-containing alkynes, namely ynamines and ynamides, have proven to be promising candidates for numerous elegant transformations.[11−14] Moreover, ynamides have also been tuned as a powerful tool for the construction of various heterocycles in particular indoles which has always been a highly privileged scaffold due to its occurrence in various biologically active compounds.[15,16]

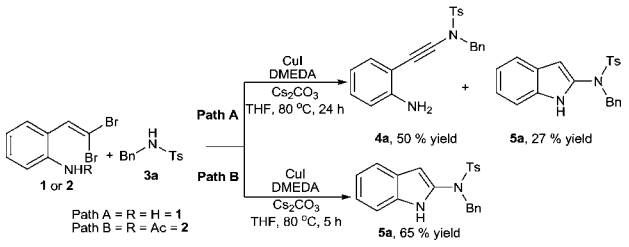
In this context, the strategies employed by Lautens et al.[5a] and Wang et al.[5d] utilizing *gem*-dihalovinylanilides has provided direct access to polycylic indoles through Cu(I)-catalyzed intramolecular domino cyclization. In addition, the Skrydstrup group[17] has previously reported the Pd-catalyzed protocol for the synthesis of 2-amidoindoles involving ynamide methodology (Scheme 1a). In contrast, we envisioned that a Cu(I)-catalyzed coupling of *gem*-dibromovinylanilines with nitrogen nucleophiles could directly generate the ynamides in situ and may undergo a base-promoted intramolecular hydroamination to afford 2-amidoindoles. If successful, our methodology can also be utilized for the straightforward synthesis of polycyclic indoles as a result of *N*-arylation of 2-amidoindole in a single-step fashion from *gem*-dibromovinylanilines and appropriately substituted nitrogen nucleophiles (Scheme 1b).

Scheme 1. Previous and Present Methods for the Synthesis of 2-Amidoindoles



To test the feasibility of such a transformation, we instigated our investigation through a reaction of *gem*-dibromovinylaniline **1** and *N*-tosylbenzylamine **3a** using copper catalysis (Scheme 2, path A). The expected product **5a** was obtained in a yield as

Scheme 2. Synthesis of 2-Amidoindole 5a



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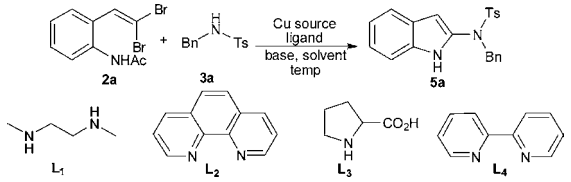
low as 27% with the isolation of ynamide **4a** in 50% yield after 24 h. This low yield prompted us to convert the aniline **1** to its corresponding acetamide **2** which was allowed to react with *N*-tosyl benzylamine **3a** under the same copper-catalyzed conditions. Fortunately, this reaction afforded our anticipated product **5a** in 65% yield in 5 h (Scheme 2, path B).

At the onset of formation of the anticipated product **5a** in moderate yields within shorter time durations, we turned our attention to optimizing reaction parameters such as catalysts, ligands, bases, solvents, and temperature to improve the yield of the reaction (Table 1). The reaction was attempted upon

Table 1. Optimization of Reaction Parameters for the Synthesis of 2-Amidoindole 5a[a]

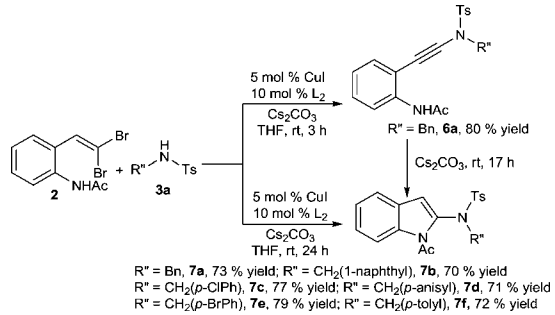


entry	catalyst	ligand	base	solvent	time (h)	yield[b] (%)
1	CuI	L_1	Cs_2CO_3	THF	5	65
2	CuBr	L_1	Cs_2CO_3	THF	6	45
3	CuCl	L_1	Cs_2CO_3	THF	10	40
4	**CuI**	**L_2**	**Cs_2CO_3**	**THF**	**2**	**88**
5	CuI	L_3	Cs_2CO_3	THF	6	51
6	CuI	L_4	Cs_2CO_3	THF	5	67
7	CuI	-	Cs_2CO_3	THF	10	26
8	CuI	L_2	K_2CO_3	THF	5	70
9	CuI	L_2	K_3PO_4	THF	5	66
10	CuI	L_2	Cs_2CO_3	DMF	4	62
11	CuI	L_2	Cs_2CO_3	CH_3CN	2	60
12	CuI	L_2	Cs_2CO_3	toluene	3	72
13	CuI	L_2	Cs_2CO_3	THF	24	*c*

[a]All of the reactions were performed using 5 mol % of the Cu(I) source, 10 mol % of the ligand, and 4 equiv of base at 80 °C. [b]Isolated yields after column chromatography. [c]The reaction was carried out at room temperature.

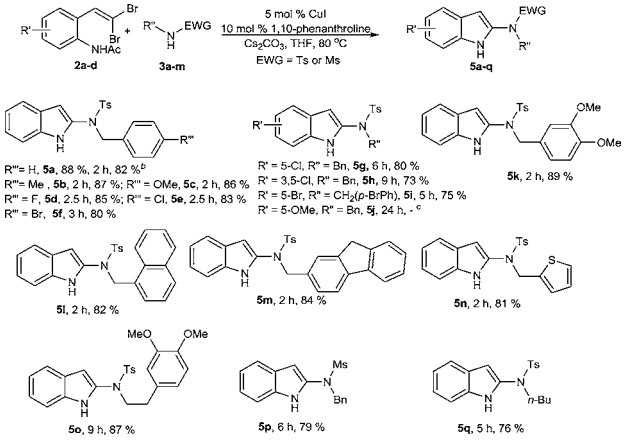
varying the copper sources (CuI, CuBr, CuCl), ligands (DMEDA, 1,10-phenanthroline, L-proline, bipyridine), bases (K_2CO_3, Cs_2CO_3, K_3PO_4), and solvents (THF, DMF, CH_3CN, toluene). The combination of copper source and ligand had a pronounced effect on the yield of the reaction (Table 1, entries 1−6). It was also noticed that the presence of a ligand is necessary for obtaining the best possible yields since a reduced yield of the product **5a** was observed in the absence of the ligand (26%, Table 1, entry 7). The alteration of solvents and bases did not have any dramatic effect on the yield as they resulted in the formation of product **5a** in moderate yields (Table 1, entries 8−12). The best result was obtained when the reaction was carried out in the presence of 5 mol % of CuI, 10 mol % of 1,10-phenanthroline (L_2), and 4 equiv of Cs_2CO_3 in THF at 80 °C (Table 1, entry 4). The reaction under room-temperature conditions (Table 1, entry 13) did not provide the desired product **5a** but proceeded to provide the ynamide **6a** within 3 h and the *N*-acetyl-2-amidoindole **7a** after 24 h. Considering the importance of *N*-protected indoles in the total synthesis of natural products, some examples of *N*-acetyl-2-amidoindoles **7a**−**f** were synthesized in good yields under room-temperature conditions (Scheme 3).

Scheme 3. Stepwise Synthesis of 2-Amidoindole



With the optimized reaction conditions in hand, we explored the substrate scope with various sulfonamides (**3a**−**m**) and *gem*-dibromovinylanilides (**2a**−**d**) (Scheme 4). Gratifyingly,

Scheme 4. Synthesis of Various Derivatives of 2-Amidoindoles 5a−m[a]



[a]Isolated yields after column chromatography. [b]Yield of the product when the reaction was carried out on a 3 g scale. [c]Untractable mixture.

excellent yields were observed generally for substrates containing electron-rich moieties, halogen substituents, or heterocyclic motifs (**5b**−**p**). Moreover, the reaction was found to be compatible with aliphatic substituents such as *n*-butylsulfonamide to afford 2-amidoindole **5q**. The formation of 2-amidoindole is chiefly controlled by the nature of the electron-withdrawing group attached to the nitrogen nucleophile **3**. Sulfonamides (−Ts or −Ms) were found to be the best coupling partners for the formation of ynamides, thereby reflecting the excellent yields of 2-amidoindoles (**5a**−**q**) in shorter time durations. The reaction did not work with acyclic amides or carbamates.[18] The probable reason for the failure could be the lower acidity and steric hindrance of other nitrogen nucleophiles making the formation of the ynamides itself very slow and difficult[5b] prior to which under the same catalytic conditions for prolonged duration occurs the formation of *N*-acetyl-2-bromoindole and 2-bromoindole.[19]

Building on the success of the synthesis of 2-amidoindoles through a copper-catalyzed method and also in an effort to find the utility of the present methodology, we envisaged carrying out an intramolecular *N*-arylation of the 2-amidoindole in the presence of a proximal aryl halide which might lead to the effective construction of tetrahydroindolo[1,2-*a*]quinazoline. With this goal in mind, we carried out a reaction of *gem*-dibromovinyl phenylacetamide **2** with *N*-tosyl-*o*-bromobenza-

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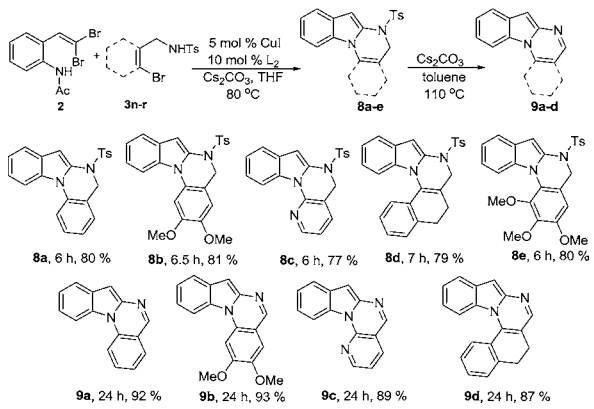
mide **3n** under our standard conditions. To our delight, the reaction afforded the required tetrahydroindolo[1,2-*a*]-quinazoline **8a** in 80% yield within 6 h. The reaction worked well with a variety of *N*-tosyl-*o*-bromobenzamides to yield tetrahydroindolo[1,2-*a*]quinazolines **8a−e** in excellent yields, and the structure was further confirmed from X-ray single-crystal analysis performed on a representative compound **8e**.[20] The synthesized tetrahydroindolo[1,2-*a*]quinazolines were refluxed under basic conditions to afford the indolo[1,2-*a*]quinazolines **9a−d** (Scheme 5).

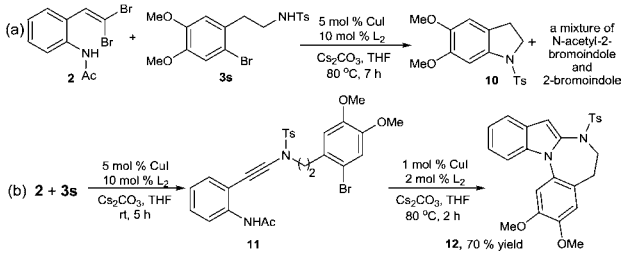
Scheme 5. Synthesis of Tetrahydroindolo[1,2-*a*]quinazolines 8a−e and Indolo[1,2-*a*]quinazolines 9a−d[a]



[a]Isolated yields after column chromatography.

The accomplishment of our targeted synthesis of indolo[1,2-*a*]quinazolines prompted us to attempt the synthesis of a polycyclic indole. Hence, we tried a reaction of 2-(2-bromophenyl)-*N*-tosylethanamine **3s** with *N*-(2-(2,2-dibromovinyl)phenyl)acetamide **2a** using our standard conditions (Scheme 6a). Unfortunately, the reaction led to the

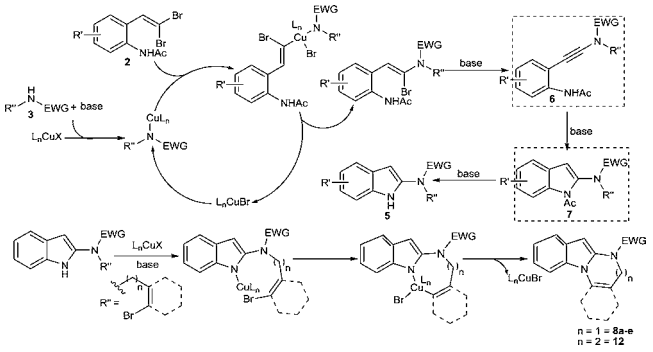
Scheme 6. Synthesis of the Polycyclic Indole



intramolecular cyclization of **3s** resulting in the formation of indoline **10**.[21] We therefore planned to carry out the same reaction under room temperature conditions which afforded the ynamide **11**. The ynamide **11** was isolated and then cyclized under copper catalytic conditions to provide the expected polycyclic indole **12** (Scheme 6b). Thus, this methodology has provided yet another route for the synthesis of polycyclic indole through a copper-catalyzed intermolecular protocol involving ynamide cyclization and intramolecular *N*-arylation, which makes it distinct from the previously reported protocols.[5a,d]

A possible mechanism that could account for the formation of 2-amidoindoles and tetrahydroindolo[1,2-*a*]quinazolines is described in Scheme 7. The mechanism is based on the higher reactivity of the *trans* C−Br bond of *gem*-dibromovinylanilide **2** toward oxidative insertion and may undergo regioselective

Scheme 7. Plausible Mechanism for the Formation of 2-Amidoindoles and Tetrahydroindolo[1,2-*a*]quinazolines



coupling with the sulfonamide **3** followed by concomitant dehydrobromination[5b] to yield the ynamide **6**. Finally, a base-promoted intramolecular hydroamidation[17b] of the ynamide **6** followed by deacetylation of **7** results in the formation of 2-amidoindole **5**. In the presence of a proximal aryl halide, the formation of the 2-amidoindole moiety is accompanied by subsequent intramolecular *N*-arylation[22] to afford the tetrahydroindolo[1,2-*a*]quinazoline **8** or polycyclic indole **12** (Scheme 7).

In conclusion, we have developed a copper-catalyzed intermolecular protocol for the rapid construction of 2-amidoindoles and tetrahydroindolo[1,2-*a*]quinazolines in a one-pot fashion from the readily available *gem*-dibromovinylanilides and sulfonamides. This method is economical, practical, and more reliable in terms of time, yield, and scalability. These noteworthy advantages make the present methodology a very valuable addition to the existing methods available for the synthesis of 2-amidoindole and indolo[1,2-*a*]quinazoline scaffolds. Further studies on extending the use of the methodology to other heterocyclic nucleophiles are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data for all prepared compounds. Crystal data for compound **8e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) The TLC analysis revealed the presence of the carbamate while the *gem*-dibromovinylanilide **2** had completely been consumed. The reaction mixture was passed through Celite and washed with 1−2% EtOAc/hexane to remove the unreacted carbamate. The NMR revealed the presence of *N*-acetyl-2-bromoindole and a minor amount of 2-bromoindole.

(20) Crystallographic data of compound **8e** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplemental publication no. CCDC 978058. See the Supporting Information for details.

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