Organic LETTERS

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Synthesis of Pyrrolo-/Indolo[1,2-*a*]quinolines and Naphtho[2,1-*b*]thiophenes from *gem*-Dibromovinyls and Sulphonamides

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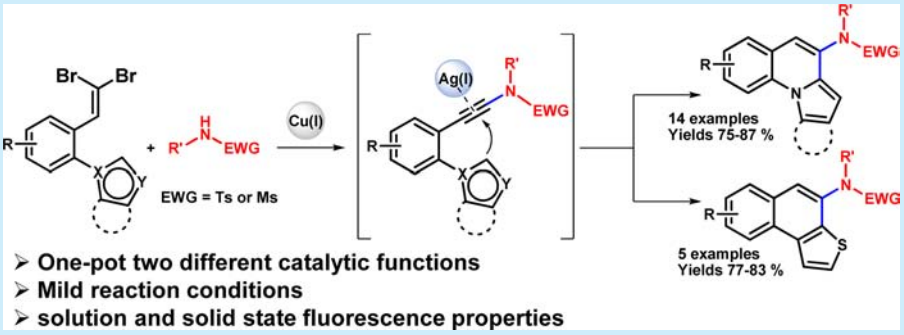
Supporting Information



ABSTRACT: A highly efficient and simple route for the synthesis of pyrrolo-/indolo[1,2-*a*]quinolines and naphtho[2,1-*b*]thiophenes from *gem*-dibromovinyls and sulphonamides is reported. The noteworthy feature of this report is that the methodology involves a two-step protocol to synthesize tri- and tetracyclic heterocycles in a one-pot fashion through the Cu(I)-catalyzed formation of ynamide followed by a Ag(I)-assisted intramolecular hydroarylation. The photophysical properties of representative examples of pyrrolo- and indolo[1,2-*a*]quinolines in solid and solution states have also been studied.

Over the past few decades, heteroatom substituted alkynes are growing as an important class of substrates since they have contributed significantly toward the construction of various heterocycles. Remarkable advancements, both in synthesis and in the study of synthetic utilities of alkynes possessing N, O, P, or S atoms, are being constantly reported.[1−4] Among the several classes of nitrogen-containing alkynes available, ynamides have attracted the special attention of organic chemists which is undoubtedly evident from the notable progress reported in recently.[5] The emergence of ynamides can be attributed to the exceptional stability and versatile reactivity resulting in their profound use for the insertion of nitrogen-based functionalities in organic molecules.[6] The distinct feature of ynamide reactivity is that it allows regioselective addition of electrophiles or nucleophiles onto the ynamide which may be due to the polarization of the nitrogen triple bond or the possible chelation of the reagent with the electron-withdrawing group (EWG).[5a,e] Hence the addition at the α-position of the ynamides (position adjacent to the nitrogen) is extensively being developed.[7]

Fused nitrogen heterocycles, in particular pyrrolo-/indolo-[1,2-*a*]quinolines, occur in numerous natural products;[9] display a wide range of applications in pharmaceuticals,[8] host−guest chemistry,[10] organic semiconductors,[11] and liquid crystal chemistry;[12] and have also been found to exhibit electron transport properties.[13] Therefore, there is a growing demand to devise versatile methodologies for the construction of fused quinolines.[14]

Our preceding report pertained to the synthesis of 2-amidoindoles from *gem*-vinyldihalides and sulphonamides through an intramolecular hydroamidation reaction of 2-amido substituted ynamides (Scheme 1a).[15] In our continuing effort to exploit the reactivity of ynamide at the α-position, we herein wish to report the synthesis and photophysical study of pyrrolo-/indolo[1,2-*a*]quinolines from 1-(2-(2,2-dibromovinyl)phenyl)-1*H*-pyrrole/-indole and sulphonamides via intramolecular hydroarylation of ynamides possessing heterocyclic nucleophiles within proximity (Scheme 1b).

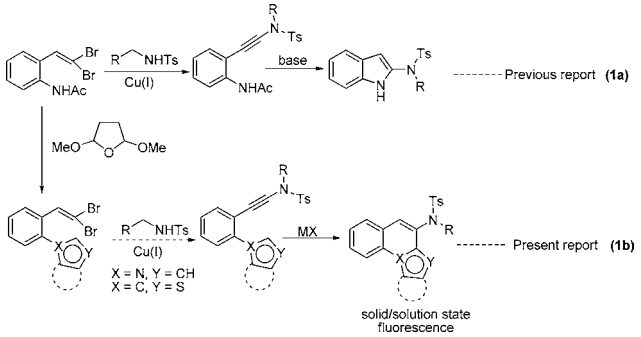
In a preliminary experiment we investigated the feasibility of forming ynamide **4a** by the Cu(I)-catalyzed reaction of *gem*-dibromovinyl phenyl-1*H*-pyrrole **2a** and *N*-benzyl-4-methylbenzenesulfonamide **3a**.[16] The reaction afforded a maximum yield of 89% in the presence of 3 mol % CuI, 5 mol % 1, 10-phenanthroline, and 3 equiv of Cs_2CO_3 in THF at rt (Scheme 2).

Upon the isolation of the ynamide **4a**, we attempted the intramolecular hydroarylation to achieve the target pyrrolo[1,2-*a*]quinoline **5a** (Table 1). Initially the screening was done with Au/Ag catalysts. Among the Au/Ag salts screened, AgOTf showed a promising catalytic tendency to afford pyrrolo[1,2-

Received: July 3, 2014
Published: August 11, 2014

dx.doi.org/10.1021/ol5019085 | *Org. Lett.* 2014, 16, 4424−4427

Scheme 1. Synthesis of Heterocycles from *gem*-Dibromovinyls and Sulfonamides



Scheme 2. Synthesis of Ynamide 4a

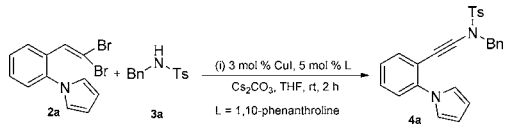
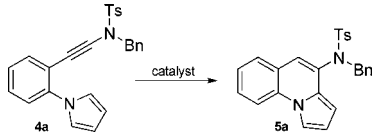


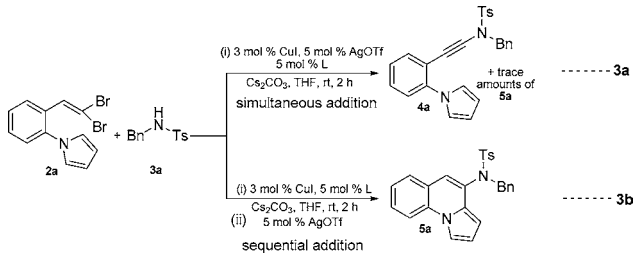
Table 1. Screening of Catalysts for the Intramolecular Hydroarylation of Ynamide 4a[a]



entry	catalyst	solvent	time (h)	yield[b] (%)
1	$AuCl_3$	THF	24	–
2	AgOTf	THF	0.5	90
3	$AgCO_2CH_3$	THF	24	–
4	$Zn(OTf)_2$	THF	5	50
5	$In(OTf)_3$	THF	8	63
6	$Yb(OTf)_3$	THF	20	25
7	$FeCl_3$	THF	24	–
8	I_2	THF	24	–
9	Tf_2NH	THF	8	65
10	PNBSA	THF	24	40
11	AgOTf	DMF	1	80
12	AgOTf	CH_3CN	0.75	77

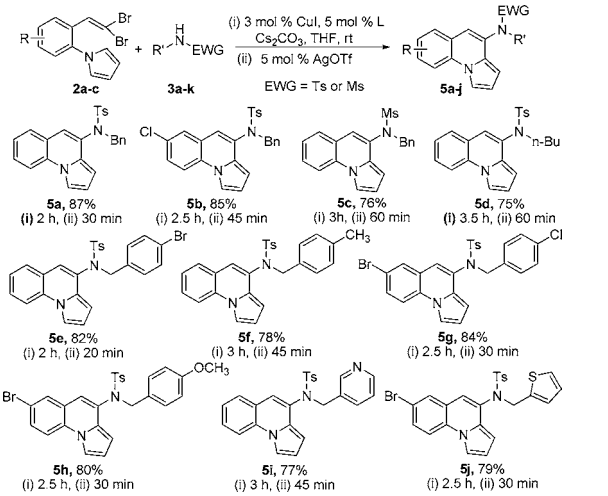
[a]All the reactions were performed using 5 mol % of the catalyst, at room temperature. [b]Isolated yields after column chromatography.

Scheme 3. Simultaneous/Sequential Synthesis of Pyrrolo[1,2-*a*]quinoline 5



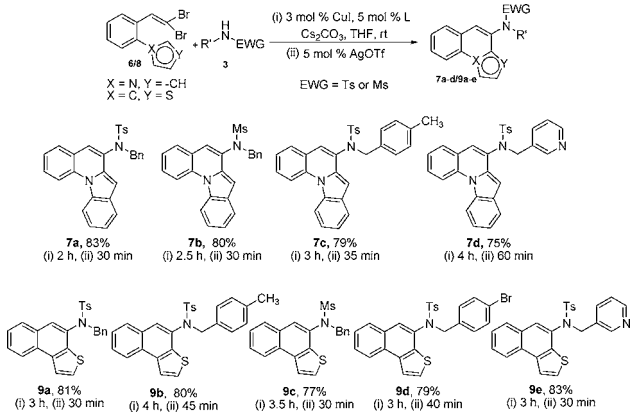
a]quinoline **5a** (Table 1, entry 2) whereas $AuCl_3$ (Table 1, entry 1) and $AgOCOCH_3$ (Table 1, entry 3) did not provide the expected product. With the above results, the reaction was attempted using other metal triflates (Table 1, entries 4–6). The reaction was found to proceed with $Yb(OTf)_3$ and

Scheme 4. Synthesis of Pyrrolo[1,2-*a*]quinolines 5a–j[a]



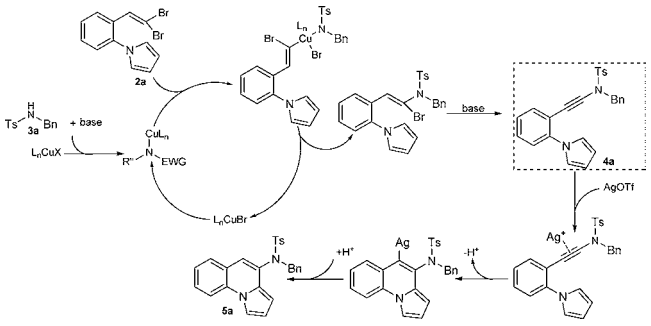
[a]Isolated yields after flash column chromatography.

Scheme 5. Synthesis of Indolo[1,2-*a*]quinolines 7a–d and Naphtho[2,1-*b*]thiophenes 9a–e[a]



[a]Isolated yields after flash column chromatography.

Scheme 6. Mechanism for the Synthesis of Pyrrolo[1,2-*a*]quinolines 5a



$Zn(OTf)_2$ which provided the pyrrolo[1,2-*a*]quinoline **5a** in yields as low as 25% and 50% respectively. $In(OTf)_3$ showed reasonable catalytic activity, affording **5a** in 63% yield. Other catalysts such as $FeCl_3$ and I_2 (Table 1, entries 7 and 8) were tried, but the reaction did not proceed to provide **5a**. Bronsted acids namely Tf_2NH and *p*-nitrobenzenesulfonic acid (PNBSA) were also used as catalysts (Table 1, entries 9 and 10). However, AgOTf was found to be the optimum catalyst in

dx.doi.org/10.1021/ol5019085 | *Org. Lett.* 2014, 16, 4424–4427

Table 2. Optical Properties of Compounds 5a−b, 5g, 5j, and 7a−b

	$\lambda_{max,ab}$ (nm)		$\lambda_{max,em}$ (nm)			Stokes shift (cm^{-1})	
compd	solution (ε M^{-1} cm^{-1})[a]	aggregation[b]	solution[a] (Φ)[c]	aggregation[b]	solid	solution[a]	aggregation[b]
5a	362 (5631)	370	427 (0.039)	474	438, 468	4205	5930
5b	371 (4890)	378	444 (0.132)	450	455	4432	4233
5g	371 (6408)	377	447 (0.101)	455	468	4583	4547
5j	370 (5434)	378	447 (0.099)	483	496	4655	5751
7a	405 (3966)	413	481 (0.215)	508	514, 557	3901	4528
7b	386 (5784)	410	480 (0.356)	496	515, 553	5073	4229

[a]Recorded at 20 μM concentration in CH_3CN. [b]In CH_3CN/H_2O (1:99) mixture at 10 μM concentration. [c]Quininine sulfate in 1 N H_2SO_4 was used as a reference.

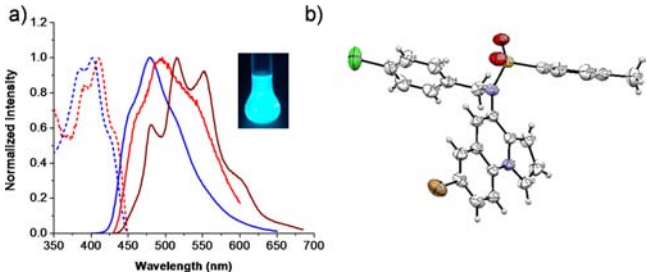


Figure 1. (a) Normalized absorption (dotted line) and PL (solid line) spectra of compound **7b** in solution state (blue) and aggregated solution (CH_3CN/H_2O (1:99) mixture) state (red), solid (brown). The inset in panel a: photo of **7b** in CH_3CN solution. (b) Ortep of **5g**.

terms of both rate and yield (Table 1, entry 2). This might be due to the possibility of chelation with the EWG of the ynamide. We also found that the reaction proceeded only at rt. The reaction was also attempted by increasing the temperature to 80 °C; the pyrrolo[1,2-*a*]quinoline was not isolated, and the reaction resulted in the formation of an undesirable mixture.

The accomplishment of the expected intramolecular hydroarylation prompted us to explore the one-pot synthesis of pyrrolo[1,2-*a*]quinolines. The one-pot reaction was monitored by the simultaneous addition of both Cu(I) and Ag(I) catalysts. Unfortunately this reaction afforded the ynamide **4a** in major quantities and only a trace amount of the pyrrolo[1,2-*a*]quinoline **5a** was isolated (Scheme 3a). The reaction was then tried with the initial addition of the copper catalyst and addition of silver triflate upon the formation of ynamide **4a**. In contrast, the reaction readily afforded the pyrrolo[1,2-*a*]-quinoline **5a** in an 87% yield (Scheme 3b).

To examine the scope of the present methodology we extended the reaction conditions to synthesize various derivatives of pyrrolo[1,2-*a*]quinolines **5** (Scheme 4). The reaction was explored by varying the substituents on both substrates **2** and **3**. The reaction proceeded well for almost all substrates bearing electron-rich, halogen, or heterocyclic substituents. The reaction also performed well when the electron-withdrawing counterpart on **2** was altered from -Ts to -Ms. The structure of the compounds **5** was confirmed by X-ray single crystal analysis (Figure 1b).[17] We also found that the reaction outcome was dependent on the nature of the EWG on the amide **3**. The sulphonamides were found to be the best coupling partners for the intramolecular hydroarylation reaction.[15] The reaction could not proceed to give the desired pyrrolo[1,2-*a*]quinoline by varying the nature of the EWG on the amide (−Boc, $-COCF_3$, $-COCH_3$), even when the temperature and catalyst loading were increased.

In studying the reaction scope, we next devoted our efforts to synthesize fused tetracyclic nitrogen analogues by varying the heterocyclic nucleophiles attached on the *gem*-dibromovinyl. A reaction was carried out between *gem*-dibromovinyl phenyl-1*H*-indole **6** with *N*-benzyl-4-methylbenzenesulfonamide **3a** under our standard conditions. To our delight the reaction afforded the expected indolo[1,2-*a*]quinoline **7a** in 83% yield. This result was extended to synthesize other analogues of indolo-[1,2-*a*]quinolines **7a−d** by varying substituents on sulphonamides. Upon the successful synthesis of tricyclic and tetracyclic quinolines, we wanted to probe the applicability when a thiophene ring is introduced at the ortho position to the *gem*-vinyldihalide. As we expected, the reaction proceeded under the Cu(I)/Ag(I) conditions to yield the naphtho[2,1-*b*]thiophenes **9a−e** in excellent yields (Scheme 5).

A mechanistic proposal for the formation of representative fused nitrogen heterocycle **5a** is described in Scheme 6. The mechanism is based on the higher reactivity of the trans C−Br bond of *gem*-dibromovinyl **2a** toward oxidative addition with Cu(I). Stereoselective coupling with **3a**, followed by dehydrobromination, affords ynamide **4a**. Then, activation of the C−N triple bond by coordination to Ag^+ allows intramolecular hydroarylation, affording the resultant pyrrolo[1,2-*a*]quinoline **5a**.

After accomplishing the synthesis of various fused quinolines and naphthothiophenes, we found that the synthesized compounds exhibited interesting photo luminescence properties in solid and solution states. Among the compounds synthesized, unfortunately the naphtho[2,1-*b*]thiophenes did not show any distinct photophysical properties. Hence we attempted to study the photophysical properties of representative examples. Compounds **5a−b**, **5g**, **5j**, and **7a−b** were used to study the photophysical properties in solid and solution states (Table 2). The absorption maxima of the compounds in CH_3CN solution showed absorption maxima in the range of 362−405 and 370−413 nm for the solution and aggregation states, respectively. The results also indicated that the compounds displayed shifts in PL spectra in the solution, solid, and aggregation states. The emission results showed a red shift for indolo[1,2-*a*]quinolines (Table 2, Figure 1) compared to pyrrolo[1,2-*a*]quinolines which was a common observation in the solid, solution, and aggregation states. The quantum efficiencies (Φ) ranged from 0.039 to 0.356 in the solution state, and moreover the indolo[1,2-*a*]quinolines displayed higher quantum efficiencies than the pyrrolo[1,2-*a*]quinolines. The Stokes shifts for the representatives in the solution and aggregation states have also been calculated (Table 2).

In conclusion this letter brings forth a simple and convenient route for the synthesis of fused heterocycles from *gem*-vinyldihalides and sulfonamides involving Cu(I) and Ag(I) as

dx.doi.org/10.1021/ol5019085 | *Org. Lett.* 2014, 16, 4424−4427

catalysts. Thus, this method is economical, practical, and reliable and more advantageous as it involves milder reaction conditions, a shorter reaction time, and high yields. The compounds were found to exhibit photophysical properties, and some of the representative examples of the pyrrolo- and indolo[1,2-*a*]quinolines under study have exhibited distinct fluorescence in the solid, solution, and aggregation states.

■ ASSOCIATED CONTENT

Supporting Information

Experimental section; ^{1}H and ^{13}C NMR spectra; mass, UV−visible, and PL spectra of representative compounds. 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.

■ ACKNOWLEDGMENTS

The authors S.E.K. and A.N. thank the Council of Scientific and Industrial Research (CSIR), New Delhi, India for the research fellowship. The authors thank Dr. Luxmi Varma, NIIST for HRMS analysis and Dr. D. Gayathri, Department of Biophysics, University of Madras for single crystal X-ray analysis.

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(16) See Supporting Information for detailed optimization for the synthesis of ynamide **4a**.

(17) Crystallographic data for compound **5g** in this paper have been deposited with the Cambridge crystallographic data centre as supplemental publication no. CCDC 1010852.