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Cascade Radical Cyclization of *N*-Propargylindoles: Substituents Dictate Stereoselective Formation of *N*-Fused Indolines versus Indoles

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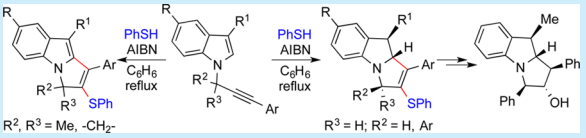
Supporting Information

ABSTRACT: An efficient protocol for the synthesis of pyrrolo[1,2-*a*]indole derivatives having sulfide functionality using cascade radical cyclization on propargylindole is described. The nature of the substituents at the propargylic carbon bearing nitrogen of the indole has a profound effect on the rate, yield, and nature of the product obtained by the cascade radical cyclization. An expeditious one-pot route for cascade radical cyclization−desulfurization is also presented. Products obtained were elaborated to the core of the putative structure of the yuremamine and indoline derivative with five contiguous stereocenters.



Among annelated indoles, pyrrolo[1,2-*a*]indole is a privileged and celebrated scaffold owing to its structural diversity and analogy to antitumor agents mitomycins (**1**), which show the extraordinary ability of cross-linking DNA (Figure 1).[1] Isatisine A (**2**) is a unique fused indolone alkaloid

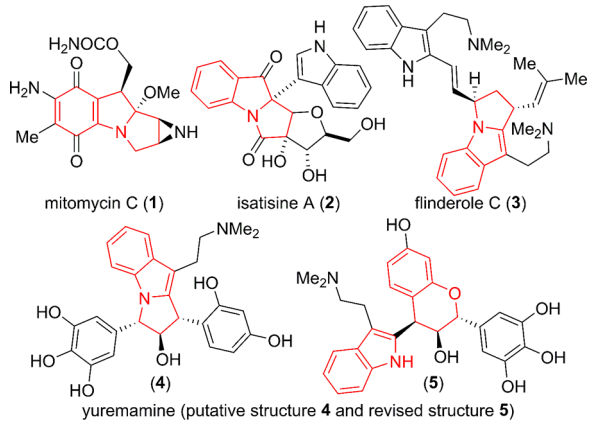


Figure 1. Natural products bearing pyrrolo[1,2-*a*]indole core.

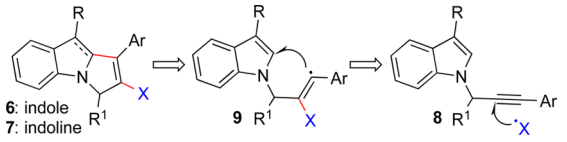
with antiviral activity.[2] Flinderole C (**3**) is a pyrrolo[1,2-*a*]indole that shows antimalarial properties.[3] Callaway and co-workers isolated yuremamine, a phytoindole alkaloid with hallucinogenic and psychoactive properties, from the stem bark of *Mimosa hostilis* and assigned its structure as pyrrolo[1,2-*a*]indole derivative (**4**).[4]

During their biomimetic synthesis of the proposed yuremamine pyrroloindole (**4**), Sperry et al. serendipitously found the true structure of the natural product to be flavonoidal indole (**5**).[5] Interesting biological activity coupled with the structural diversity of the pyrrolo[1,2-*a*]indole scaffold has generated significant interest among synthetic chemists, and efforts toward synthesis of these derivatives have been described.[6]

Organosulfur compounds, such as sulfides and sulfoxides, are valuable building blocks in organic synthesis and commonly found in many natural products and biologically active compounds.[7] In this context, we reasoned that synthesis of *N*-fused indoles bearing sulfide functionality incorporated in the ring would be of interest. In continuation of our interest in the stereoselective synthesis of ring-fused heterocycles in general and pyrrolo[1,2-*a*]indole derivatives in particular, herein we disclose a cascade thiyl radical cyclization of propargyl indoles for the rapid construction of *N*-fused indolines as well as indoles.[8] We also demonstrate that substitution on propargyl indoles has a profound effect on the rate and outcome of these radical cyclizations.

We envisioned that the pyrrolo[1,2-*a*]indole/indolines **6**/**7** could be rapidly assembled using a cascade radical cyclization of *N*-propargylindole **8** initiated by an appropriate radical precursor (X = ArS) via the intermediate **9** (Scheme 1). If the last step of

Scheme 1. Retrosynthetic Analysis for Pyrrolo[1,2-*a*]indole/-indoline (6/7)



the radical cascade proceeds in reductive manner, pyrrolo[1,2-*a*]indolines **7** should be formed in a stereoselective manner. On the other hand, if the radical **9** after 5-*exo*-*trig* cyclization undergoes oxidation, pyrrolo[1,2-*a*]indole **6** would be the product.

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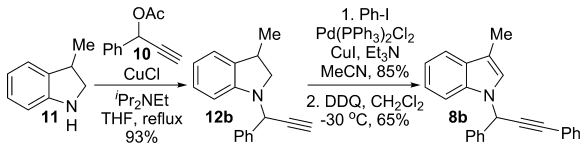
It was also argued that the latter outcome could be potentially used to gain access to the putative core structure of yuremamine (**4**). To test our strategy, synthesis of propargyl indole **8** was initiated. While the primary propargyl indole **8a** is known,[9a] the secondary propargyl indole **8b** was prepared in a three-step protocol (Scheme 2). Thus, copper(I)-catalyzed propargylic

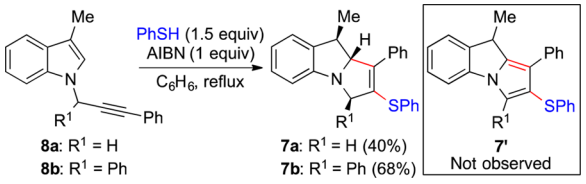
Scheme 2. Synthesis of the Secondary Propargylindole 8b



substitution on acetate **10** using indoline **11** as nucleophile furnished the terminal alkyne **12b** in excellent yield.[10] Sonogashira coupling of terminal alkyne **12b** followed by DDQ mediated aromatization gave the requisite secondary propargylindole **8b** in good yield.

Having the primary and secondary propargylindole **8a,b** in hand, attention was turned toward using them in the proposed cascade radical cyclization for synthesis of *N*-fused indoles. When primary propargylindole **8a** was subjected to reaction with thiophenol and AIBN in refluxing benzene, tandem inter- followed by intramolecular radical cyclization proceeded smoothly to furnish the *N*-fused indoline derivative **7a** in moderate yield and excellent diastereoselectivity (Scheme 3). Interestingly, when the secondary propargylindole **8b** was used as substrate, the pyrroloindoline **7b** was obtained with improved yield.

Scheme 3. Cascade Radical Cyclization for Synthesis of *N*-Fused Indoline Derivatives 7a,b



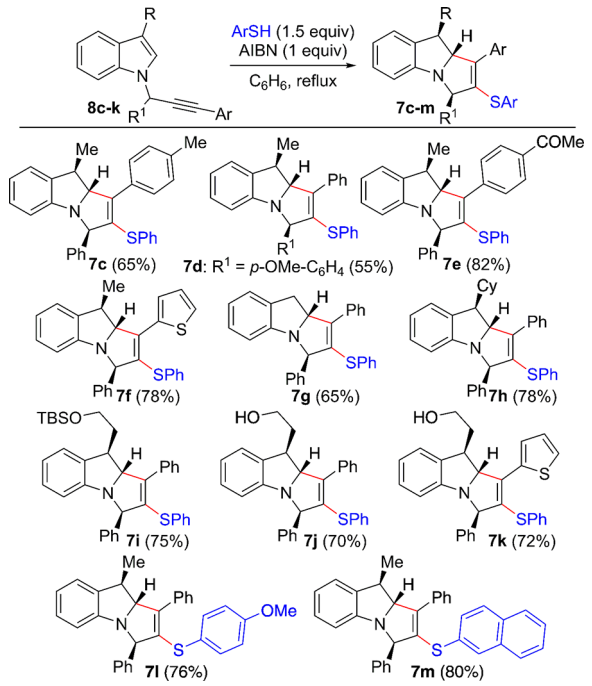
The stereochemistry of the indoline derivatives **7a–b** was assigned on the basis of their spectral data. This was further unambiguously confirmed by single-crystal X-ray diffraction studies on the indoline derivative **7b**.[11]

In all of these reactions, formation of the *N*-fused indolines **7a–b** was observed, and none of the pyrrolo[1,2-*a*]indole derivative 7′ was formed. Interestingly, this reaction outcome is at variance with some of the very recent studies from the groups of Tang, Zhu, and Song who have described silver- and copper-mediated tandem phosphinoylation/cyclization process to construct 2-phosphinoyl-9*H*-pyrrolo[1,2-*a*]indole derivatives.[9] This variation in the outcome can be attributed to neutral conditions employed in the present study instead of acidic ones as in the earlier reports, which led to isomerization of initially formed indole derivatives. While these strategies were useful, they gave only moderate yields of the products. Further, the substituent effect on carbon next to nitrogen has not been studied, which is an important aspect in the context of synthesis of putative structure of yuremamine (**4**). Finally, the choice of thiophenol as radical precursor allows further functionalization of the products, which in turn enhances the utility of this method.

Thus, we started exploring the scope of the radical cascade for the synthesis of *N*-fused indolines **7** using thiophenol derivatives.

The scope of the cascade radical cyclization reaction was studied by changing the substituents on the propargylindole moiety. The cyclization readily took place with propargylindole derivatives **8c–e** having electron rich as well as electron-deficient aryl rings on the alkyne to deliver *N*-fused indoline **7c–e**, with latter giving better yields than former (Scheme 4). The substrate

Scheme 4. Scope of Synthesis of *N*-Fused Indoline Derivatives[a]



[a]In all cases, dr ≥19:1.

8f having a heteroaromatic ring attached to alkyne could be successfully utilized in this transformation, and *N*-fused indoline **7f** is obtained in good yield and excellent diastereoselectivity. In the case of propargylindole **8g** having no substituent at the third position of indole, the reaction proceeded smoothly and furnished the indoline derivative **7g** in moderate yield. *N*-Fused indoline derivatives **7h–k** bearing a cyclohexyl ring and side chain with free alcohol or a TBS protecting group at the third position of indole were also synthesized from the corresponding propargylindoles **8h–k**. *p*-Methoxythiophenol and 2-naphthalenethiol led to indolines **7l,m**, respectively, in excellent yields. The stereochemistry of the three stereocenters in *N*-fused indoline was assigned by single-crystal X-ray diffraction studies on the indoline derivatives **7c** and **7f**.[11]

The scope of tertiary propargylindoles for cascade radical cyclization was investigated next. When propargylindole **13a** was subjected to optimized reaction conditions, cascade radical cyclization took place smoothly but surprisingly resulted in the formation of *N*-fused indole derivative **6a** rather than the indoline derivative (Scheme 5). The reaction was found to be quite general, and alkynes **13b–e** bearing electron-donating as well as electron-withdrawing substituents gave the corresponding pyrrolo[1,2-*a*]indole derivatives **6b–e** in excellent yields. The presence of free alcohol in propargylindole is tolerated under reaction conditions, and pyrrolo[1,2-*a*]indole derivatives

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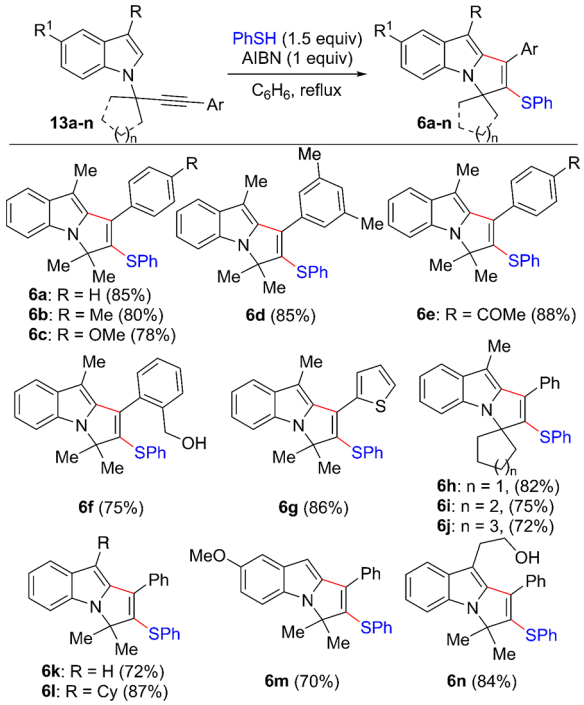
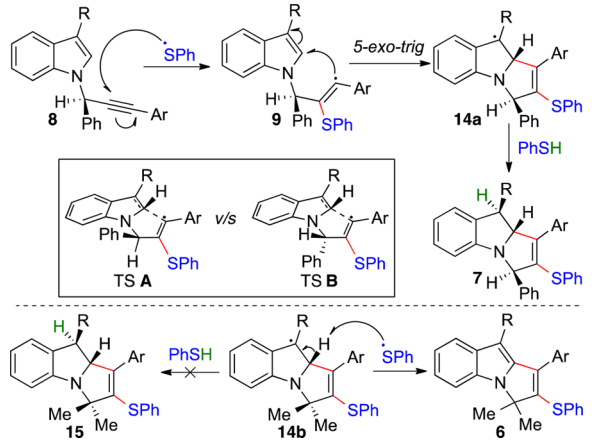
Scheme 5. Scope of Synthesis of Pyrrolo[1,2-*a*]indole Derivatives



6f,n were obtained in excellent yield. Propargylindole derivative **13g** with a heteroaryl ring underwent reaction smoothly to give the corresponding pyrroloindole **6g** in good yield. The spirocyclic pyrrolo[1,2-*a*]indole derivatives **6h−j** were synthesized using tandem radical cyclization on propargylindole precursors **13h−j** in good yields. The absence of a substituent at the third position of the indole or presence of a cyclohexyl ring did not have any impact on the yield of the reaction, and pyrrolo[1,2-*a*]indole derivatives **6k−m** were obtained in good yields. The structure of pyrrolo[1,2-*a*]indole derivatives was assigned on the basis of their spectral data and further unambiguously confirmed by single-crystal X-ray diffraction studies on *N*-fused indole derivatives **6h−j,m**.[11]

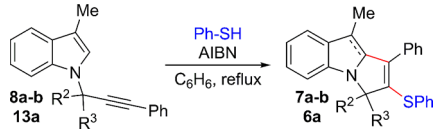
In cascade radical cyclization, primary and secondary propargylindoles **8** gave *N*-fused indoline derivatives **7** in good yield and as a single diastereomer. On the other hand, tertiary propargylindoles **13** gave *N*-fused indoles **6**. This substituent-dependent diverse formation of the products and stereochemical outcomes can be explained on the basis of the mechanism depicted in Scheme 6. Intermolecular thiyl radical addition to alkyne **8** generates the vinyl radical **9**, which undergoes a 5-*exo-trig* radical cyclization on the indole moiety to furnish the intermediate **14a**. During this cyclization, the bulkier aryl ring in vinyl radical **9** prefers to occupy the sterically less crowded convex face (transition state structure **A** vs **B**). The reduction of the radical **14a** proceeds through a late transition state, and hence, the alkyl substituent prefers to be on the sterically less incumbent convex face via delivery of the hydrogen from the concave face to furnish the indoline **7**. In the case of tertiary propargylindole **13**, due to presence of an alkyl group in the concave face in the intermediate **14b**, the delivery of the hydrogen from the PhSH, which would lead to the indoline **15**, is slowed down, and instead, a competing hydrogen abstraction by the PhS leads to the indole derivative **6** with the concomitant aromatization being the driving force.[7f]

Scheme 6. Proposed Mechanism and Rational for Stereochemical Outcome



Further, the thiol radical cyclization leading to the *N*-fused indoline/indole derivative displayed an interesting trend in the rate and yield of the reaction. Thus, while going from primary (**8a**) to secondary (**8b**) to tertiary (**13a**) propargylindole substrates, the reaction time reduced significantly. The yield of the indoline/indole product was also increased (Table 1). This

Table 1. Substrate-Dependent Radical Cyclization Leading to Indoline/Indole: Thorpe−Ingold Effect



entry	substrate	R^2	R^3	time (h)	yield (%)	product
1	**8a**	H	H	10	40	**7a**
2	**8b**	Ph	H	3	68	**7b**
3	**13a**	Me	Me	1	85	**6a**

trend in rate and efficiency could be attributed to the "*gem*-dialkyl effect" also referred to as the "Thorpe−Ingold effect" during the 5-*exo-trig* radical cyclization of the vinyl radical **9** on the indole moiety (cf. Scheme 6).[12] As we increase the size of the substituents at the propargylic position, the angle between alkyne and the indole moiety decreases with a reduction in conformational flexibility, which leads to rate acceleration.

In order to further elaborate these *N*-fused indole derivatives, we attempted Raney nickel mediated desulfurization on the indoline **7b**. Product **16** was obtained in good yield via selective desulfurization, and the olefin reduction was not observed (Scheme 7). Interestingly, addition of excess of thiophenol during cyclization of the alkyne **13a** also resulted in the formation of the product **17a**. The intermediate vinyl sulfide **6a** formed in this reaction underwent desulfurization through the radical path.[13] The method was general for indole derivatives, and propargylindoles **13g**, **13k** also underwent radical cyclization followed by desulfurization smoothly to furnish the corresponding products **17g**, **17k**.

Finally, hydroboration of the indole **17a** followed by oxidation gave the alcohol **18a** in good yield, which constitutes the synthesis of core of the putative structure of yuremamine (**4**) (Scheme 8). Interestingly, hydroboration−oxidation of pyrroloindole **16** gave indoline derivative **19** in a highly regio- and diastereoselective fashion. This sequence is noteworthy as it

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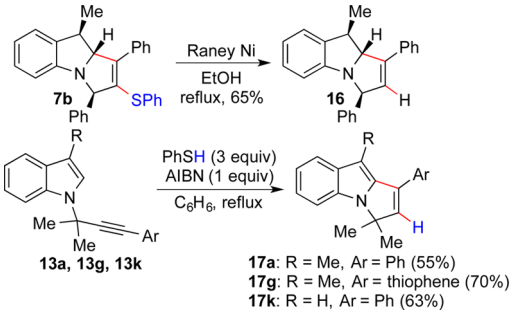
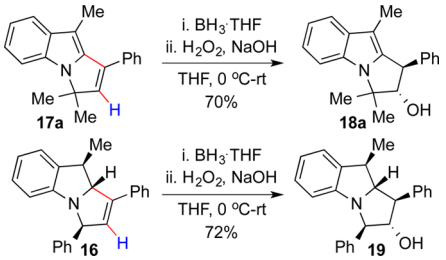
Scheme 7. Desulfurization of *N*-Fused Indolines 7 and Indoles 6



Scheme 8. Synthesis of Core of Putative Structure of Yuremamine (4)



provides an expeditious access to the *N*-fused indoline **19** possessing *five contiguous stereocenters*.

In conclusion, an efficient, cascade thiyl radical cyclization for the synthesis of *N*-fused indole and indoline derivatives has been developed. Primary and secondary propargylindole derivatives furnish *N*-fused indoline in a highly diastereoselective manner, while tertiary propargylindoles gave access to pyrrolo[1,2-*a*]indole derivatives. The reaction is found to be very sensitive with respect to substituents present at carbon next to the nitrogen of indole, and the "Thorpe−Ingold effect" was observed in this cascade radical cyclization. We have also shown that the cascade radical cyclization followed by desulfurization can be carried out in the same pot. The desulfurized products were elaborated to the core of the putative structure of the yuremamine as well as highly stereoselective synthesis of indoline bearing five contiguous stereocenters.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02005.

Synthetic procedures and characterization data of products (PDF)

Crystallographic data for **6h−j,m** and **7b,c,f** (ZIP)

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Notes

The authors declare no competing financial interest.

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(11) CCDC 1555451−1555457 (**7b,c,f, 6h−j,m**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(13) (a) This was confirmed by independently subjecting the sulfide **6a** to reaction conditions, which resulted in the formation of the indole **17a**. No reaction was observed in the absence of radical initiators.. (b) For a review on desulfurization, see: Rentner, J.; Kljajic, M.; Offner, L.; Breinbauer, R. *Tetrahedron* **2014**, *70*, 8983.

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