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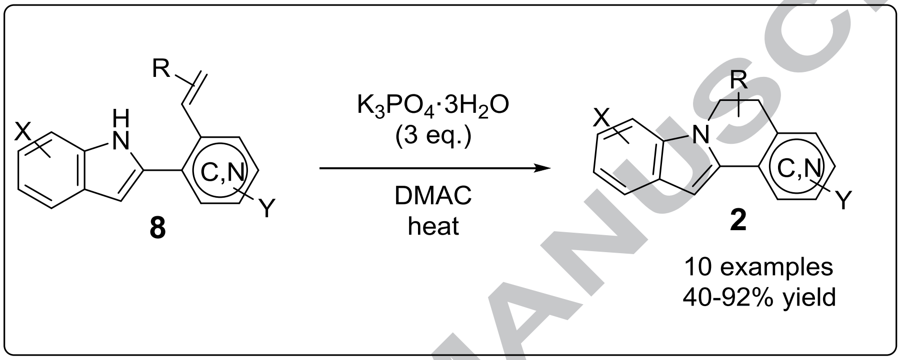

Abstract— We report a general approach for the synthesis of 5,6-dihydroindolo-naphthyridine ring system via an intramolecuar cyclization of the indole NH to an alkene moiety as the key step.

Key words— intramolecular cyclization, 5,6-dihydroindolo-naphthyridine ring system, indole, alkene.

Highlights

- A novel intramolecular cyclization gives access to the title ring system.
- Various precursors containing a six-membered azine are tolerated.
- This method affords 2c with a sterically congested C next to indole N.

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Abstract—We report a general approach for the synthesis of 5,6-dihydroindolo-naphthyridine ring system via an intramolecuar cyclization of the indole NH to an alkene moiety as the key step.

Key words—intramolecular cyclization, 5,6-dihydroindolo-naphthyridine ring system, indole, alkene.

Indole, a ubiquitious pharmacophore, is present in many natural products and pharmaceutical molecules. [1] In Janurary 2016, FDA approved Zepatier to treat patients with chronic hepatitis C virus (HCV) genotypes 1 and 4 infections. Zepatier is a fixed-dose combination product containing elbasvir, a hepatitis C virus (HCV) NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor.[2] As shown in **Figure 1**, elbasvir (MK-8742) has an indole moiety in the central part of the molecule.[3]

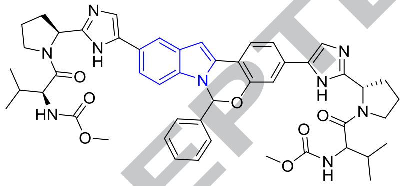


Figure 1 Structure of elbasvir (MK-8742)

Previously, we reported a general approach to access tetracyclic 6*H*-pyrido[2',3':5,6] [1,3]oxazino [3,4-*a*]indole **1** which has a methylene linker to connect the indole nitrogen atom with a hydroxyl group on the pyridyl ring (**Figure 2**). [4] To continue with our SAR effort, we were interested in exploring a related indole containing tetracyclic structure, 5,6-dihydroindolo[1,2-*h*][1,7]naphthyridine **2**, replacing the oxygen atom on the linker with a methylene group. In the literature, there is no report so far describing the synthesis of this class of structures except for a related benzo fused system reported by Baranova group, who described an elegant and practical approach to benzo[b]indolo[1,2-h][1,7]naphthyridine **4** based on the Friedländer condensation of 7,8-dihydropyrido[1,2-a]indol-9(6H)-one with 2-aminobenzaldehyde (**Figure 3**).[5] However, besides the restriction to a benzo fused system, the scope of this method was limited to the product with a pyridyl nitrogen atom at the specific position shown in **4**. In this letter, we will disclose our general approach for the synthesis of 5,6-dihydroindolo[1,2-*h*][1,7]naphthyridine **2** and related compounds with pyridyl nitrogen atoms at various positions.

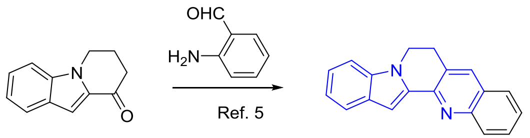
1

6H-pyrido[2',3':5,6]
[1,3]oxazino[3,4-a]indole

2

5,6-dihydroindolo[1,2-*h*]
[1,7]naphthyridine

Figure 2 Indole containing tetracyclic structures.



3

4

Figure 3. Reported route to benzo[b]indolo[1,2-*h*][1,7]naphthyridine

Our strategy focused on a novel intramolecular

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[†] Both authors contributed equally to this Letter.

cyclization of the alkenyl intermediate **8** leading to the target structure **2 (Figure 4)**. This approach was inspired by a patent disclosure reporting the intermolecular version of this reaction: a cyclization of NH of a substituted indole onto a vinyl group of another molecule.[6] Alkenyl intermediate **8** should be available from phenolic intermediate **7**, which was prepared previously from the boronate **5** and iodide **6**. Since each of them could bear a variety of substitutions, this modular approach would allow rapid SAR for our medicinal chemsitry program.

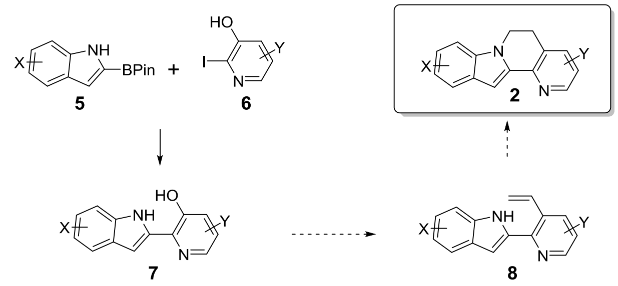
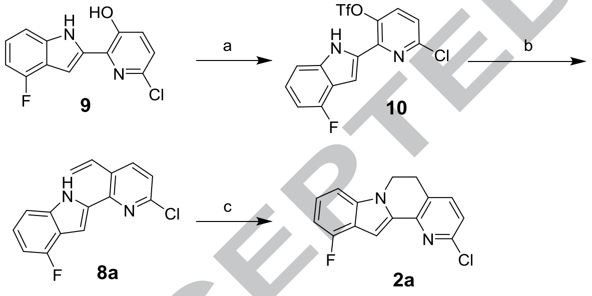


Figure 4 Strategy to access **2** via an intramolecular cyclization from **8**

We successfully demonstrated this strategy during the synthesis of **2a** (**Scheme 1**). The synthesis commenced with known intermediate **9**, which was converted to alkene **8a** via a standard triflation-Stille coupling sequence. Cyclization under slightly modified conditions based on ref. 6 afforded **2a** in a high isolated yield. The chloro group of **2a** would provide a handle to attach an additional fragment for SAR work.



Scheme 1 Preparation of compound **2a**. Reagents and conditions: (a) Tf_2O (2 eq.), CH_2Cl_2, 0ºC to rt, 1 h, 83%; (b) $PdCl_2(PPh_3)_2$ (5 mol%), tributyl(vinyl)stannane, LiCl, DMF, 60ºC, 1 h, 69%; (c) $K_3PO_4{\cdot}3H_2O$ (3 eq.), DMAC, 100ºC, 12 h, 85%.

Starting from the conditions originally reported in ref. 6, we briefly explored alternative bases and solvents. We found that the amount of K_3PO_4 can be reduced to 3 eq. and that K_3PO_4•$3H_2O$ works equally well compared to the anhydrous salt. In contrast to K_3PO_4 or K_3PO_4•$3H_2O$, *t*-BuOK or LiHMDS only produced very messy reactions. Sodium carbonate (Na_2CO_3) or diisopropylethylamine gave low conversions (< 10%). Compared to DMAC (dimethylacetamide), DMF worked equally well. DMSO gave slightly lower product yields. There was no cyclized product observed with THF. Acetonitrile gave poor conversions (<10%). Therefore, in the subsequent work, we used 3.0 eq. of K_3PO_4•$3H_2O$ in DMAC as the standard conditions.

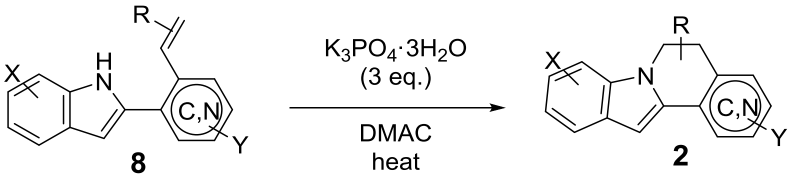
We applied this methodology to the construction of additional cyclic structures from the corresponding alkene precursors (**Table 1**). We prepared alkene precursors with one or two methyl substitutions on the vinyl group (entries 2 and 3, **Table 1**). The cyclization from each precursor completed in about 4 hours with a high isolated yield of the cyclized product. It is remarkable that the cyclization from precursor **8c** produced **2c** with a sterically congested carbon connecting the indole nitrogen atom.

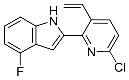
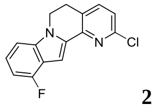
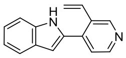
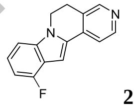
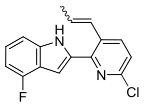
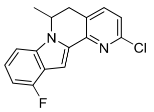
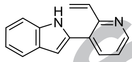
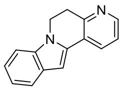
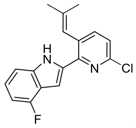
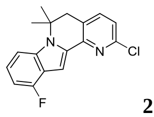
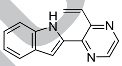
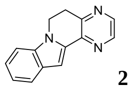
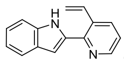
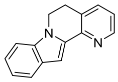
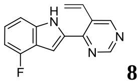
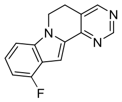
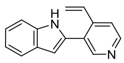
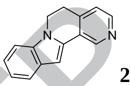
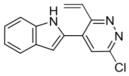
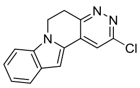
We then examined the impact of the position of nitrogen in the pyridyl ring on the cyclization (entry 4 to 7, **Table 1**). Comparing with **8a**, precursor **8d** also underwent a smooth cyclization to afford **2d** in good yield indicating that F and Cl substitutions in **8a** are not required for the cyclization. The cyclization seemed to be sensitive to the electronic environment since **2d** and **2g** were obtained in good yield while the cyclizations from substrates **8e** and **8f** were sluggish affording **2e** and **2f**, respectively, in somewhat lower yields.

We further extended this chemistry to precursors containing diazines (entry 8-10, **Table 1**). Pyrazinyl, pyrimidyl and pyridazinyl were all tolerated affording the corresponding cyclized products in modest to good yields. The cyclization of precursor **8j** was allowed to react for only 0.5 h and product **2j** was isolated in a modest yield as the starting material and/or the product seemed to be unstable under the reaction conditions.

In summary, we have described a general method for the synthesis of 5,6-dihydroindolo-naphthyridine ring system with a pyridyl nitrogen atom at all possible positions based on a novel intramolecular cyclization of the indole NH to an alkenyl tether. This method can be extended to the diazine precursors as well. The effort applying this method to the SAR for our medicinal chemistry program will be disclosed in due course.

Table 1 Synthesis of **2** from **8** via intramolecular cyclization



Entry	Alkene **8**	Conditions Yield	Cyclized product **2**	Entry	Alkene **8**	Condtions Yield	Cyclized product **2**
1	 **8a**	100°C, 12 h 85%	 **2a**	6	 **8f**	100°C, 12 h 60%	 **2f**
2	 **8b**	100°C, 4 h 85%	 **2b**	7	 **8g**	100°C, 12 h 80%	 **2g**
3	 **8c**	100°C, 4 h 92%	 **2c**	8	 **8h**	100°C, 2.5 h 60%	 **2h**
4	 **8d**	100°C, 7 h 85%	 **2d**	9	 **8i**	100°C, 3 h 80%	 **2i**
5	 **8e**	100°C, 12 h 50%	 **2e**	10	 **8j**	100°C, 0.5 h 44%	 **2j**

Supplementary Material

The supplementary material contains the experimental procedures and characterization data for all new compounds.

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