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Synthesis of 5-Azaindoles via a Cycloaddition Reaction between Nitriles and Donor−Acceptor Cyclopropanes

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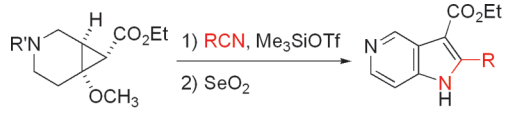
ABSTRACT



A new method for the synthesis of 5-azaindole derivatives is reported. A [3+2] dipolar cycloaddition between nitriles and a 3,4-cyclopropanopiperidine followed by SeO_2 oxidation affords the target compounds in moderate to excellent yields. The divergent nature and cost effectiveness of this method makes it very suitable for combinatorial applications in the pharmaceutical industry.

Considerable attention has been directed to the development of azaindole based pharmaceuticals as indole isosteres due to their role in patent evasion, often enhanced solubility, and perhaps superior bioavailability.[1] These efforts have resulted in the discovery of many active drug candidates (see Figure 1 for representative examples).[2] Despite the promising potential of these heterocycles, they remain largely under-explored, in part due to the limited synthetic methods to prepare and functionalize the azaindole nucleus.

While there are many synthetic methods available for the preparation of substituted indoles,[3] only a few have been developed for the preparation of azaindoles. Some of the classic methods either do not work or are inefficient.[1] The alternative methods generally rely on highly functionalized pyridine substrates, which are expensive or require multistep syntheses to prepare.[4] Additionally, C2 and C3 substituted 5-azaindoles are notoriously difficult to access as they often

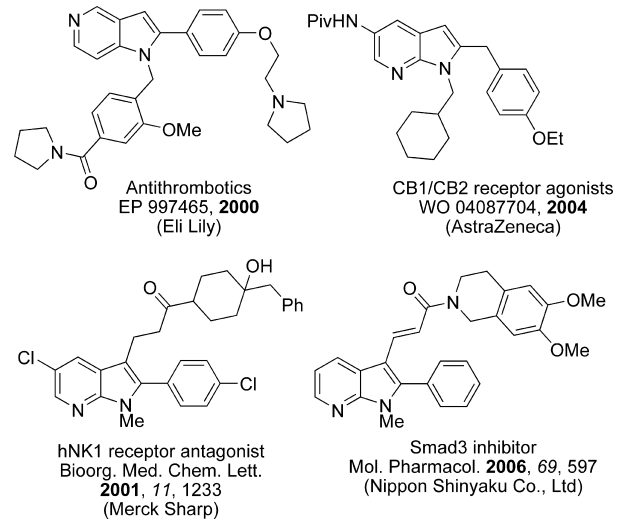


Figure 1. Examples of pharmacologically active azaindoles.

(1) For recent reviews and references cited therein see: (a) Popowyez, F.; Mérour, J.-Y.; Joseph, B. J. *Tetrahedron* **2007**, *63*, 8689–8707. (b) Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120–1132. (c) Popowycz, F.; Routier, S.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2007**, *63*, 1031–1064.

(2) (a) Bastian, J. A.; Fisher, M. J.; Harper, R. W.; Lin, H.-S.; Mccowan, J. R.; Sall, D. J.; Smith, G. F.; Takeuchi, K.; Wiley, M. R.; Zhang, M. Eur. Pat. Appl. EP 997465, 2000. *Chem. Abstr.* **2000**, *132*, 293756. (b) Wei, Z.; Dolaine, R.; Walpole, C.; Yang, H. Appl. Int. WO 2004087704, 2004. *Chem. Abstr.* **2004**, *141*, 332183. (c) Cooper, L. C.; Chicchi, G. G.; Dinnell, K.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Locker, K. L.; Morrison, D.; Shaw, D. E.; Tsao, K.-L.; Watt, A. P.; Williams, A. R.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1233–1036. (d) Jinnin, M.; Ihn, H.; Tamaki, K. *Mol. Pharmacol.* **2006**, *69*, 597–607.

(3) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, *7*, 1045–1075.

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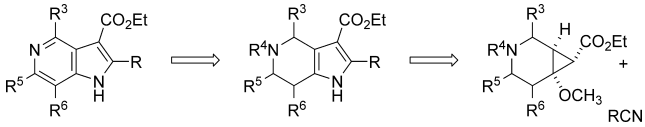
depend on multistep approaches involving highly functionalized pyridines, or strong bases to lithiate the 5-azaindole itself followed by electrophile trapping.[5] The formal dipolar cycloaddition reaction developed by our group[6] has been shown to be useful for the preparation of pyrroles,[7] bipyrroles,[8] indolizines,[9] and indole alkaloid natural products.[10] Herein, we report a two-step sequence for the synthesis of 5-azaindoles by oxidation of a tetrahydro-1*H*-pyrrolo[3,2-*c*]-pyridine intermediate obtained through a cycloaddition reaction between nitriles and a 3,4-cyclopropanopiperidine (Scheme 1).[11]

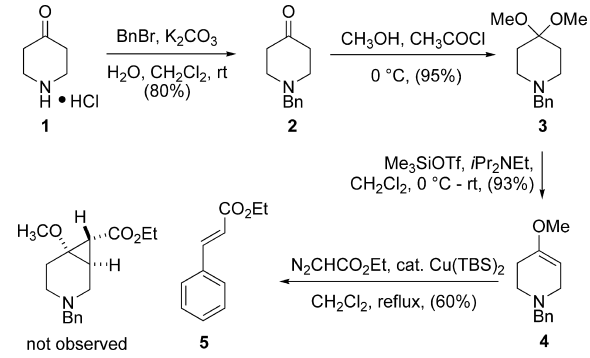
Scheme 1. Retrosynthetic Analysis



This strategy allows access to a wide variety of C2 functionalized azaindoles simply by varying the starting nitrile.

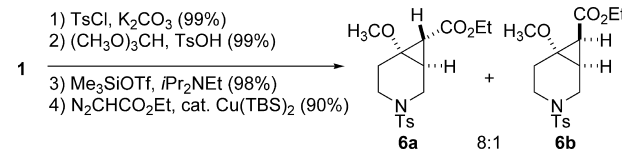
The synthesis of the cyclopropanopiperidine began with benzyl protection of 4-piperidone **1** followed by acetalization in acidic methanol (Scheme 2).[12] Then the resulting acetal **3** was converted to enol ether **4** under standard conditions;[13] however, when **4** was subjected to cyclopropanation with

Scheme 2. Attempted Synthesis of the Cyclopropanopiperidine



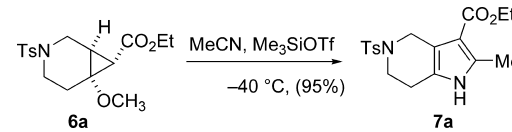
ethyl diazoacetate in the presence of $Cu(TBS)_2$,[14] the ethyl cinnamate **5** was obtained in 60% yield and none of the desired cyclopropane was observed. The cinnamate is likely formed by carbene insertion at the benzylic position followed by elimination. To avoid this undesired reaction a tosyl protecting group was employed (Scheme 3),[15] and cyclopropanation under the same conditions afforded the desired cyclopropane **6** in 90% yield as an inconsequential 8:1 mixture of *trans* to *cis* diastereomers.[16]

Scheme 3. Access to Cyclopropanopiperidines



With cyclopropane **6** in hand it was allowed to react with acetonitrile under the standard annulation conditions (1.0 equiv of Me_3SiOTf, −40 °C) to give the tetrahydropyrrolopyridine **7a** in 95% isolated yield (Scheme 4).[7] This material was easily and economically prepared on gram scale, and was selected as a model substrate for screening oxidation conditions to provide the desired azaindole nucleus (Table

Scheme 4. Nitrile Annulation



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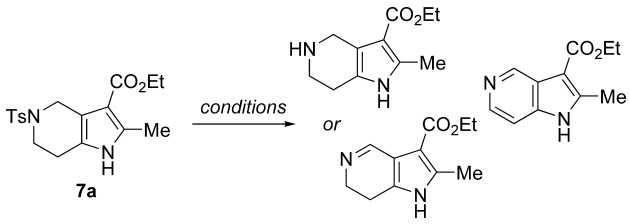
(15) Engler, T. A.; Wanner, J. *J. Org. Chem.* **2000**, *65*, 2444–2457.

(16) (a) Benzyl protecting group was first selected to allow for an easy deprotection in the subsequent oxidation step. (b) Both diastereomers work equally well in the subsequent cyclization.

1). It was thought that either a two-step sequence involving elimination or deprotection of the tosylate followed by

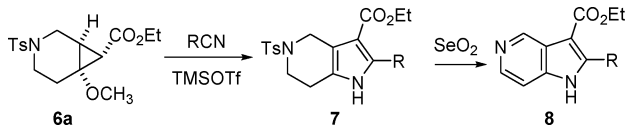
Table 1. Deprotection and Oxidation

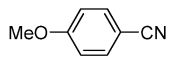
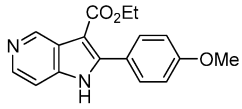
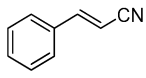
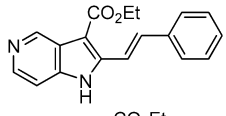
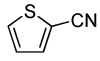
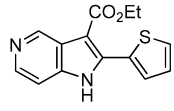


entry	conditions	yield (%)
1	MeONa/MeOH	decomposition
2	*t*-BuOK/*t*-BuOH	decomposition
3	Na-naphthalenide/THF	decomposition
4	DDQ/toluene	decomposition
5	5% Pd/C, mesitylene	no reaction
6	MnO_2,CH_2Cl_2	no reaction
7	SeO_2, dioxane	92% (azaindole)

oxidation would be acceptable, as well as a one-step process to give the azaindole directly. Various strategies were explored, including strong bases,[17] Na-naphthalenide,[18] DDQ,[19] Pd/C,[10] and MnO_2.[20] In each case, either decomposition or no reaction was observed (Table 2, entries 1−6). Ultimately it was found that SeO_2 executed the desired oxidation extraordinarily well and afforded the azaindole in 92% isolated yield.[21]

Table 2. Scope of Azaindole Synthesis[a]



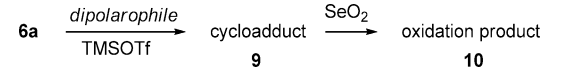
entry	nitrile	azaindole	ann. yield	ox. yield
a	MeCN	R = Me	95%	92%
b	EtCN	R = Et	62%	94%
c	PhCN	R = Ph	92%	97%
d			86%	81%
e			69%	61%
f			87%	61%

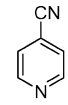
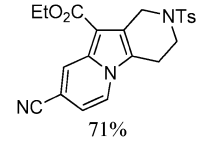
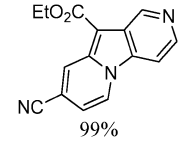
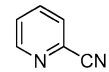
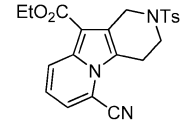
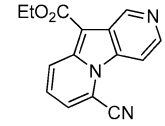
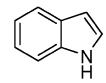
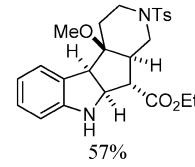
[a] Cycloaddition reactions were run at −40 °C, using 1.0 equiv of cyclopropane, 2.0 equiv of nitrile, and 1.0 equiv of Me_3SiOTf in nitromethane solvent. In the case of acetonitrile (entry a), excess nitrile was used as solvent. Oxidation conditions: 5 equiv of SeO_2 in refluxing dioxane.

With reaction conditions established for both the nitrile annulation and subsequent oxidation the reaction scope was explored, and the results are summarized in Table 2. The reaction works well with other aliphatic nitriles (entry b) as well as benzylic and electron rich benzylic nitriles (entries c and d). Unsaturated nitriles are effective (entry e) as are those containing heteroatoms, such as 2-thiophenecarbonitrile (entry f). The annulation reaction is conveniently run with a large excess of nitrile as solvent, but where this is impractical, nitromethane was employed. Sterically hindered (e.g., pivalonitrile and isobutyronitrile) or electron deficient nitriles (e.g., 4-bromobenzonitrile) did not engage in the reaction.

We have shown previously that other functional groups can react in formal dipolar cycloadditions with DA cyclopropanes, including electron deficient pyridines[9] and indoles.[22] While not intended to be exhaustive, Table 3 shows

Table 3. [3+2] Cycloannulation between Pyridines and Indole with Cyclopropane **6a**



entry	dipolarophile	cycloadduct (**9**)/yield	oxidation product (**10**)/yield
a		 71%	 99%
b		 53%	 64%
c[a]		 57%	decomposition

[a] Relative stereochemistry was not determined but was assigned by analogy only. For a relevant discussion with similar systems, see ref 22.

that the 3,4-cyclopropanopiperidine reacts analogously to afford fused azaindoles very efficiently. The reactions with both 4-cyanopyridine and 2-cyanopyridine gave their respective tetrahydropyridoindolizines (Table 3, entries a and b), and both underwent oxidation with SeO_2 to the pyridoindolizine. The single crystal X-ray structure of **10b** was solved and the ORTEP is presented in Figure 2. The cycloaddition

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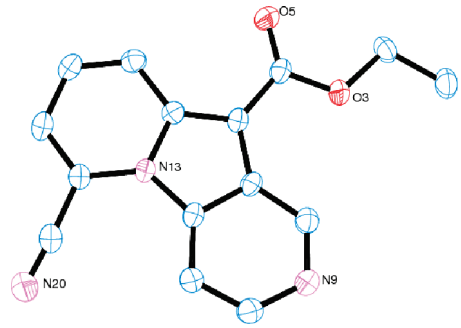

Figure 2. X-ray structure of **10b**.

with indole provided the cycloadduct **9c** in 57% yield, but the standard SeO_2 oxidation conditions were ineffective in this case.

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(22) Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631–9634.

In summary, we have reported a novel and practical two-step sequence for the preparation of C2 substituted 5-aza-indoles and fused azaindoles, in 34−87% overall yield. The synthetic sequence starts with an easily prepared and inexpensive piperidine based DA cyclopropane, which is then allowed to react with nitriles, pyridines, and indoles. A subsequent SeO_2 mediated oxidation cleaves the tosyl protecting group and oxidizes the substrates to provide the aromatic azaindoles.

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Supporting Information Available: General experimental procedures and characterization of all new compounds, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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