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A Rapid Three-Component MgI_2-Mediated Synthesis of 3,3-Pyrollidinyl Spirooxindoles

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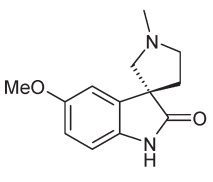
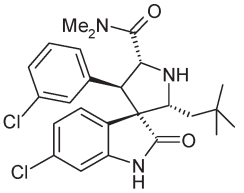
The rapid synthesis of 3,3-pyrollidinyl-spirooxindole cores from readily available cyclopropyl spirooxindoles and commercially available aldehydes, amines, and sulfonamides is reported. This general procedure utilizes microwave heating to access a biologically privileged scaffold in an efficient route amenable to library population.

Recently, there has been growing interest in targets that have been traditionally considered less tractable to small molecules.[1] Low hit rates in relatively new areas of drug discovery, e.g., protein−protein interactions, have raised questions about the composition of chemical libraries.[2] While 35% of drugs approved since 1981 are natural products or their derivatives, compound collections are populated with compounds that have varying degrees of biogenic bias.[3,4] Indeed, it has been suggested that natural product-like scaffolds are under-represented in typical compound collections.[5] It is our assertion that the challenging nature of the chemistry associated with accessing these types of structures has limited their incorporation into compound collections and that innovative synthetic approaches are needed to fill these gaps.



1
(-)-horsfiline



2
MDM2-p53 interaction antagonist

The 3,3′-pyrrolidinyl-spirooxindole core is found in many biologically active natural products, the simplest of which is the alkaloid horsfiline (**1**), which was isolated from the Malaysian medicinal plant *Horsfildea superba*.[6,7] The challenges associated with the synthesis of natural products containing the 3,3′-pyrrolidinyl-spirooxindole core have made them the subject of several elegant synthetic investigations.[8−12] The interesting biological activity associated with this core has also made it the focus of medicinal chemistry investigations. The most notable of these is a structure-based design approach to inhibiting protein−protein interactions,[13,14] in which Wang and co-workers designed 3,3′-pyrrolidinyl-spirooxindoles (e.g., **2**) that inhibited the proliferation of human prostate cancers cells.[15,16]

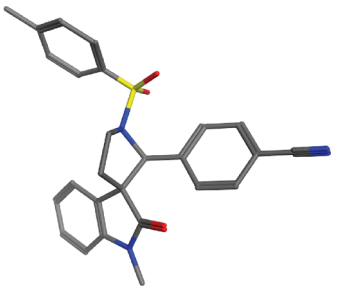


FIGURE 1. Energy-minimized conformation for **4c** (MMFF94 as implemented in MOE).

While each of the reported synthetic approaches has its own advantages, we became most interested in Carreira's MgI_2-catalyzed spirocyclopropyl oxindole ring expansion.[11,17,18] The advantage of this route is that the three major features of the structure can be derived from readily available starting materials. In the final product, the functionality incorporated by this reaction is projected from the compact spirocyclic core

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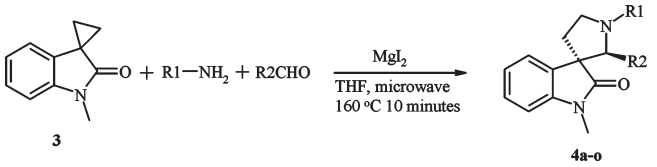
TABLE 1. Three-Component Ring Expansion of *N*-Methyl-3,3-1-methyl-spiro-3,3-cyclopropylindol-2-one (3)



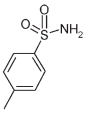
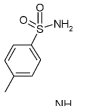
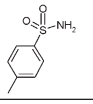
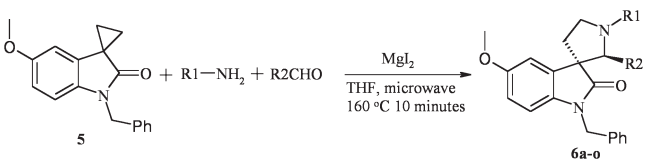
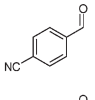
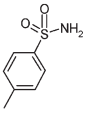
	R2CHO	R1NH$_2$	Yield
a			80 %
b			58 %
c			35 % (3:1)
d			95% (3:1)
e			53%
f			54%
g			37% (1:1)
h			11% (3:1)
i			--
j			94% (3:1)
k			32%
l			25% (3:1)
m			90% (3:1)
n			16%
o			--

TABLE 2. Three-Component Ring Expansion of 1-Benzyl-5-methoxy-spiro-3,3-cyclopropylindol-2-one (5)



	R2CHO	R1NH$_2$	Yield
a			87% (3:1)
b			39%
c			42% (1:1)
d			53% (1:1)
e			33%
f			43% (1:1)
g			6.5%
h			42% (5:1)
i			-
j			77% (1:1)
k			24%
l			68% (1:1)
m			39% (1:1)
n			3%
o			32 (1:1)

into different areas in space. This is in stark contrast to the typical heterocylic-aromatic compounds that predominate in many chemical libraries, in which the appended functionality around the core is often projected into a common plane (Figure 1).

Herein, we report a three-component one-pot variation of Carreira's methodology that makes the synthesis of the 3,3′-pyrrolidinyl-spirooxindole core amenable to library population. We reasoned that *in situ* formation of imines could be undertaken in the presence of spirocyclopropyl oxindole and MgI_2. By generating the imine in situ, a two-step synthesis could be shortened into a one-pot three-component reaction. The primary advantage of this strategy is that diverse sets of

amine and aldehyde building blocks are readily available. Spirocyclopropyl oxindoles can be synthesized at scale from a variety of isatins in two facile steps.[19] We anticipated that even with a moderate number of spirocyclopropyl oxindoles this strategy would allow us to rapidly generate a large and diverse set of pyrollidinyl spirooxindoles. For example, a library synthesized from 10 amines, 10 aldehydes, and 3 cyclopropyl oxindoles would contain 300 compounds.

Initial attempts to perform the three-component reaction using catalytic MgI_2 under conditions similar to those reported by Carreira[19] and co-workers resulted in complex reaction mixtures with only trace amounts of product. Ostensibly, water generated by the in situ formation of the imine degrades the catalyst, necessitating the use of stoichiometric MgI_2. Efforts to overcome this hurdle by the incorporation of molecular sieves, sodium sulfate, or magnesium sulfate with 0.5 equiv of MgI_2 resulted in incomplete consumption of the cyclopropyl spirooxindole. The use of stoichiometric MgI_2 greatly improved conversion of the starting material.

Microwave heating of the reaction mixture to 160 °C successfully decreased the reaction time while having only a minor effect on the diastereomeric ratio of the product.[17] For our purpose, library population, the speed and generality of the reaction was much more important than diastereoselectivity. The diastereomers were separated only in instances when the ratio was greater than 3:1 in the crude reaction mixture; in such cases, the minor diastereomers were typically not isolated. The relative stereochemistry of the major diastereomer was confirmed by NOESY and was consistent with observations of Carreira and co-workers.[18]

This reaction was fairly general and tolerated aliphatic and aromatic aldehydes, although the latter were preferred due to their availability. For the amine component an aniline, an alkyl amine, or a sulfonamide was used. The aniline and alkyl amine typically produced better yields than the sulfonamide. Aryl aldehyde and aniline pairings produced the best yields and most stereoselective reactions.

In summary, a three-component MgI_2-mediated synthesis of compounds containing the 3,3′-pyrrolidinyl-spirooxindole core has been described. This reaction utilized commercially available aldehydes, amines, and magnesium iodide, which were heated by microwave with readily accessible spirocyclopropyl oxindoles to provide rapid access to diverse analogues of a natural product-like core.

Experimental Section

General Procedure for the Synthesis of Series 4 and 6. A microwave vial was charged with the respective spiro-3,3-cyclopropylindol-2-one (**3** or **5**, 0.6 mmol), amine (0.75 mmol), aldehyde (0.75 mmol), and MgI_2 (0.6 mmol) in tetrahydrofuran (2.0 mL) and sealed. The reaction mixture was heated with stirring to 160 °C for 10 min. Upon cooling, the reaction mixture was purified by silica gel chromatography.

Representative Examples: (2′*S)-2′-(4-Cyanophenyl)-1-methyl-1′-[4-(methyloxy)phenyl]spiro[indole-3,3′-pyrrolidin]-2-one (4a).** The crude reaction mixture was purified by column chromatography on silica gel (eluent: 20% AcOEt in hexane). The collected fraction was evaporated to yield the title product as a brown solid (224.4 mg, 0.482 mmol, 80%). LCMS retention time of (2′*S**,3*S**)-diastereoisomer: 0.95 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 8.6 Hz, 1 H), 7.36 (d, J = 8.6 Hz, 2 H), 7.22−7.11 (m, 3 H), 6.86 (t, J = 7.1 Hz, 2 H), 6.76 (dd, J = 3.6, 8.1 Hz, 3 H), 6.68 (d, J = 7.8 Hz, 1 H), 5.03 (s, 1 H), 4.45−4.37 (m, 1 H), 4.24 (m, 1H), 3.94−3.86 (m, 1 H), 3.71 (s, 3 H), 3.20 (s, 3 H), 2.61 (ddd, J = 6.5, 8.3, 12.6 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.7, 143.0, 132.2, 132.1, 129.4, 128.8, 128.0, 122.7, 118.9, 115.1, 114.9, 108.6, 108.3, 59.1, 56.0, 55.9, 34.5, 26.7, 26.2. HMRS (ESI): m/z calcd for $C_{26}H_{23}N_3O_2$ $(M + H)^+$ 410.1870, found 410.1869.

2′-(4-Cyanophenyl)-5-(methyloxy)-1′-[4-(methyloxy) phenyl]-1-(phenylmethyl)spiro[indole-3,3′-pyrrolidin]-2-one (6a). The crude mixture was analyzed by LC-MS and was purified by column chromatography on silica gel (eluent: 20% AcOEt in hexane). The collected fraction was evaporated to yield the title product as a brown solid (288 mg, 0.521 mmol, 87%, 3:1 ratio). LCMS retention time of (2′*S**,3*S**)-diastereoisomer (major): 1.11 min, (2′*R**,3*S**)-diastereoisomer (minor): 1.11 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 8.6 Hz, 2 H), 7.33−7.27 (m, 8 H), 7.23−7.12 (m, J = 10.4 Hz, 10 H), 6.99 (d, J = 2.3 Hz, 1 H), 6.74 (dd, J = 2.0, 9.0 Hz, 6 H), 6.64−6.60 (m, 2 H), 6.59−6.48 (m, 8 H), 6.38 (d, J = 9.0 Hz, 2 H); major diastereoisomer: 5.08 (s, 1 H), 4.98 (d, J = 15.6 Hz, 1 H), 4.75 (d, J = 15.6 Hz, 1 H), 4.53 (q, J = 8.2 Hz, 1 H), 3.88 (td, J = 4.5, 9.3 Hz, 1 H), 3.80 (s, 3 H), 3.71 (s, 3 H), 2.74−2.63 (m, 1 H), 1.93 (quin, J = 7.2 Hz, 1 H); minor diastereoisomer: 4.97 (s, 1 H), 4.93 (d, J = 15.6 Hz, 1 H), 4.25 (t, J = 4.6 Hz, 1H), 4.23 (d, J = 15.6 Hz, 1 H), 3.71 (s, 3 H), 3.64 (s, 3 H), 3.23 (t, J = 6.8 Hz, 1 H), 2.51−2.45 (m, 1 H), 1.72−1.64 (m, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) major diastereoisomer: δ 177.1, 155.7, 152.6, 144.5, 141.9, 136.6, 135.7, 132.0, 130.7, 129.0, 128.0, 127.7, 119.0, 116.4, 114.8, 113.1, 112.3, 111.2, 110.7, 109.9, 71.7, 59.8, 56.0, 55.9, 51.6, 44.2, 34.8; minor diastereoisomer: δ 176.1, 156.5, 152.0, 143.7, 141.3, 135.9, 135.6, 132.2, 131.2, 128.8, 128.0, 127.9, 127.1, 119.2, 115.0, 114.7, 113.0, 111.7, 109.5, 70.2, 60.1, 56.1, 55.9, 51.2, 43.8, 35.0. HMRS (ESI): m/z calcd for $C_{33}H_{29}N_3O_3$ $(M + H)^+$ 516.2288, found 516.2287.

Acknowledgment. We thank the GSK Women in Science Program for support of A.M. and Tim Spitzer for support with NOESY.

Supporting Information Available: Experimental details and characterization of new compounds **4b**−**o** and **6b**−**o** including all ^{1}H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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