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From Heteroaromatic acids and Imines to Azaspirocycles: 
Stereoselective Synthesis and 3D Shape Analysis

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Abstract: Heteroaromatic carboxylic acids have been directly coupled with imines using T3P and NEt(4-iPr)2 to form azaspirocycles via intermediate N-acyliminium ions. Spirocyclic indolines (3H-indoles),azaizidolines,2H-pyrroles and 2H-pyrroles were all accessed using this metal-free approach. The reactions typically proceed with high diastereoselectivity and 3D shape analysis confirms that the products formed occupy areas of chemical space that are under-represented in existing drugs and high throughput screening libraries.

In recent years, the biological evaluation of under-explored regions of chemical space has attracted significant attention in the search for new pharmaceutical lead compounds. In particular, rigid, three-dimensional scaffolds have been targeted, as they are generally poorly represented in current drugs and screening libraries. With this in mind, functionalised spirocycles are of much current interest and efficient methods to generate such compounds are of high value.1,2

In this paper, the formation and 3D shape analysis of spirocyclic indolines and related azaspirocycles are described. Spirocyclic indolines (also known as 3H-indoles)3 are important scaffolds in their own right, being present in a number of bioactive natural products, and also since they serve as precursors to other privileged heterocycles including β-carbolines,4 oxaizidolines5 and indolines.6 The most common synthetic strategies currently used to generate spirocyclic indolines are shown in Figure 1A. Interrupted Fisher-indole reactions (1 → 4)7 and intramolecular imine condensation routes (2 → 4)8 have each been well used over the years, while dearomatising spirocyclisation reactions (3 → 4)9 are of particular current interest10 and underpin the approach described herein.

Our new, connective method is based on the coupling of aromatic carboxylic acids 5 with imines 6 to form reactive N-acyliminium ions 7[1,12] in situ, that can then be intercepted by intramolecular nucleophilic attack, exemplified in Figure 1B by the formation of spirocyclic indolines 8.13 The high electrophility of the N-acyliminium ion intermediate is a key design feature, as it means sufficiently mild conditions can be used to allow the products to be isolated, without competing 1,2-migration and dimerisation/trimersisation reactions taking place.3 Herein we report the successful implementation of this strategy, which allows indoles and other simple, electron-rich aromatics to be converted into complex azaspirocycles, in a one-pot, metal-free, stereoselective process. Furthermore, 3D shape analysis,14 using the principal moments of inertia (PMI) method,15 shows that most of the products formed occupy interesting and under-exploited regions of ‘3D chemical space’.

Figure 1. Previous and new strategies for spirocyclic indoline synthesis.

To explore the viability of this new approach, the reaction between 2-methyl-3-indole acetic acid 5a and imine 6a was first examined (Scheme 1), by stirring these compounds in the presence of NEt(4-iPr)2 and propylphosphonic anhydride (T3P) in THF at RT. Pleasingly, this led to the formation of the expected spirocycle as a mixture of diastereoisomers (8a:9a, 11:1), via a process that is conceptually similar to an interrupted Pictet–Spenger reaction.16 The diastereomeric products were partially separable by column chromatography, and isolated in 92% overall yield (Scheme 1). The stereocchemistry of the major diastereoisomer 8a was confirmed by X-ray crystallography (Figure 2, see later).17 Following a temperature and solvent screen (see Supporting Information), a range of other 2-methyl indole acetic acid derivatives (5b–5f)18 were also coupled with imine 2 under the optimised conditions; substitution on all positions of the indole ring was examined and the desired spirocyclic indolines were formed in good to excellent overall yield (8f:9f, 78–96%). The diastereoselectivity was universally high (d.r. 6:1–13:1) with the same major diastereoisomer being formed in all cases.19
Scheme 1. Spirocyclisation with 2-methyl 3-indole acetic acid derivatives. 

For full experimental details see Supporting Information; Major diastereoisomer shown, d.r. values based ¹H NMR analysis before chromatography; Yields following column chromatography.

Indole acetic acid itself (5g) was also compatible with the standard procedure, furnishing spirocycles 8g/9g in good yield (Scheme 2), demonstrating that substitution on the indole 2-position is not a requirement, which is pleasing given the propensity for related compounds to undergo 1,2-migration reactions.²⁰ Phenyl substitution at the 2-position (acid 5h) was also well tolerated, with spirocycles 8h/9h being formed in good yield, and interestingly the major product in this case was 9h (confirmed by X-ray crystallography, Figure 2), which shows opposite diastereoselectivity to the previous examples.¹⁷ Finally, 6-membered ring spirocyclic lactams 8i/9i were formed in good overall yield, using higher homologue 5i.

Scheme 2. Additional acid substrates in the spirocyclisation with imine 6a; for full experimental details see Supporting Information.

A plausible explanation for the observed diastereoselectivities is depicted in Figure 3, using the reaction of indole 5a and imine 6a as an example. The reaction is thought to proceed via activation of the carboxylic acid with T3P, followed by N-acylation to generate a reactive N-acyliminium ion 7a. Assuming that this is correct, the stereoselectivity is then determined by the facial selectivity of the nucleophilic attack onto the N-acyliminium ion (7a → 8a/9a). In A, the benzenoid rings of the imine and indole components appear to be relatively close together in space and look well-suited to experience a stabilising π-stacking interaction, whereas in B, this interaction is absent, and replaced by a potentially destabilising steric clash between the imine and the indole 2-methyl group. These transition state models also offer a plausible explanation for the switch in stereoselectivity in products 8h/9h; in this case, as the indole 2-position is substituted with a phenyl group rather than a methyl, a stabilising π-stacking interaction now appears to be viable in model B. The reactions are believed to be under kinetic control, based on the fact that re-subjecting a purified sample of spirocycle 8a to the optimised reaction conditions led to no change in the dr, indicating that the spirocyclisation is not reversible in this case.

Figure 3. Stereochemical model for the spirocyclisation of indole acetic acid derivatives with imine 6a.
The scope of the reaction with respect to the imine coupling partner was examined next, with the imines used (6b–6g) shown in Figure 4 and spirocyclisation results in Scheme 3. Dimethoxy-substituted imine 6b successfully gave the expected products 8j and 9j in moderate diastereoselectivity. Tetrasubstitution around the aromatic ring of the imine did not hinder the reaction as 2,5-dibromo-3,4-dimethoxy-substituted substrate 6c gave products 8k and 9k in good yield and diastereoselectivity. Thiophene- and pyrrole-fused imines 6d and 6e were also suitable substrates, as was benzylated imine 6f, all forming the expected spirocycles 8l–8n with generally good diastereoselectivity and in good yield. Acyclic imines, which are often avoided in related methods based on N-acyliminium ion chemistry due to their tendency to hydrolyse,22 are also well tolerated, with spiroproducts 8o/9o and 8p/9p each isolated in good overall yields. The major diastereoisomer formed in each case was assigned based on 1H NMR spectroscopy,19 and in the case of spirocycles 8n and 8o, confirmed by X-ray crystallography (Scheme 3).17

Preliminary work also confirms that this method can be extended to other heterocyclic systems. Aza-indoles are important structures in medicinal chemistry23 and pleasingly we found that aza-indoleacetic acid 10 reacted with imine 6a under the usual conditions to give the spirocyclic product 11 in excellent yield as a single diastereoisomer (Scheme 4), with the stereoselectivity seemingly being consistent with the analogous indole examples. Dearomatising via the 2-position of pyroles 12 and 1321 is also possible;25 on these systems, only a small amount of the desired product was formed when the standard conditions were used, but by switching the reaction solvent to CHCl₃ and increasing the temperature to 70°C, spirocycles 14 and 15 were each formed in good yield, with good to excellent diastereoselectivity. In the phenyl-substituted case, the major diastereoisomer 15 was separable by chromatography and X-ray crystallography was used to assign the configuration depicted.17,27 Finally, this same modified set of conditions were used to form spirocycle 17 via the reaction of pyrrole 16 with imine 6a; this example is noteworthy, given that 3H-pyrroles are known to be unstable and their synthesis is a considerable challenge using existing methods.20

The dearomatisation reactions described allow access to a diverse array of spirocyclic scaffolds, and the products formed are well primed to undergo further transformations, allowing additional structural diversity to be introduced or the properties of the compounds to be tuned. This is exemplified using spirocycles 8a and 8g (Scheme 5), and it is likely that similar processes (and many more) will be broadly applicable across the other spirocyclic products described in this paper. For example, indolenines 8a and 8g were both reduced to indolines 18 and 19 respectively by sodium borohydride in refluxing...
methanol. In the case of product 18, the reduction was completely diastereoselective, with the hydride source approaching the indolenine from the less sterically hindered side (i.e. away from the two benzenoid rings, verified by X-ray crystallography). Indolenines 18 and 19 could also be reduced further, forming products 20 and 21, upon reaction with lithium aluminium hydride in refluxing THF. Products with complementary relative stereochemistry to indoline 18 could also be obtained through the addition of carbon-based nucleophiles; products 22 and 23 were formed, again with complete diastereoselectivity, via the addition of pyrrole and methyl magnesium bromide respectively to indolenine 8g.

Finally, the principal moments of inertia (PMI) method was used in order to characterise the 3D shape of the azaspirocycles produced. The PMI method utilises the molecular mechanics-generated lowest energy conformation and the normalized principal moments of inertia ratios, NPR1 and NPR2, are displayed on a triangular plot, with the three vertices corresponding to rod, disc, and spherical-shaped molecules. A PMI plot containing the major diastereoisomeric forms of all of the azaspirocyclic products synthesised during the course of our study is shown in Figure 5. As this plot highlights, 88% (22 out of 25, compounds 8a–g, 8i–p, 9h, 14, 15, 17–21, 23) of the new azaspirocycles occupy the highlighted ‘3D region’ (blue triangle) and have values of (NPR1 + NPR2) >1.2. These 3D shape properties are in stark contrast to the majority of current drugs, most of which lie close to the rod-disc axis. For example, PMI analysis of 1439 FDA-approved small molecule drugs shows that just 23% are found within the (NPR1 + NPR2) >1.2 area (see Supporting Information), and most drug screening libraries have a similar shape distribution. Hence, these results are significant, in view of the current interest in the synthesis of compounds that populate under-explored regions of chemical space, especially spherical areas, in pharmaceutical lead-identification programs.

In conclusion, a new, metal-free, connective method for the synthesis of a range of 3D spirocyclic scaffolds has been reported, starting from far simpler 2D building blocks. The reactions proceeded in moderate to excellent yields and are diastereoselective, with the major diastereoisomers isolated in good overall yield in the majority of cases. This study focused predominantly on the synthesis of spirocyclic indolenines, but the successful results obtained using azaindoleacetic acid, as well as 2- and 3-substituted pyrrole acetic acids, indicate that the process is much more general. 3D shape analysis indicates that a high percentage of the compounds generated in this study occupy under-explored regions of chemical space, and the ability to modify the scaffolds further has also been demonstrated, meaning that their desirable spatial and physicochemical properties can be further tuned. Future applications in the generation of medicinally relevant scaffolds/lead compounds and natural products are anticipated, and the development of asymmetric variants of these reactions will also be explored.

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Keywords: Spirocycles • Dearomatisation • N-acyliminium ions • 3D space • Lead identification


[17] The relative stereochemistry in products contain an aromatic proton signal between 6.54–6.32 ppm and/or a methyl signal between 2.65–2.54 ppm. The corresponding signals in the minor diastereoisomers appear in different ppm ranges: 5.99–5.81 ppm for the aromatic signal and 1.97–1.66 ppm for the methyl.


[26] For representative examples see: (a) Overman, L. E.; Robertson, G. M.; Wu, Q.-F.; Zheng, C.; You, S.-L.


[33] Taylor and Jacobsen have previously reported a related asymmetric acyl Pictet-Spengler protocol for the synthesis of tetrahydrocarboline using a range of thiourea organocatalysts. Preliminary efforts to employ such catalysts in cyclisation reactions using our in situ T3P activation conditions were unsuccessful, resulting in no enantiomeric enrichment of the product. M. S. Taylor, E. N. Jacobsen, J. Am. Chem. Soc. 2004, 126, 10588.
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