Published in final edited form as:

Org Lett. 2013 July 19; 15(14): 3614–3617. doi:10.1021/ol401465y.

Synthesis of Spirocyclic Indolines by Interruption of the Bischler–Napieralski Reaction

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Abstract

The development of a versatile method for the synthesis of spirocyclic pyrrolidinoindolines is discussed. Treatment of *N*-acyltryptamines with trifluoromethanesulfonic anhydride–2-chloropyridine reagent combination affords highly persistent spiroindoleninium ions which are subject to intra- and intermolecular addition at C2 by nucleophiles.

Spirocyclic pyrrolidinoindolines represent a ubiquitous substructure in nature, representing the core of the *aspidosperma*, *strychnos*, and *kopsia* alkaloid families, and are prevalent also in pharmaceutically active compounds and other fine chemicals (Figure 1).¹ The importance of this structural motif has motivated the development of a number of elegant synthetic strategies in the context of complex alkaloid synthesis.² A direct route to the spiropyrrolidinoindoline substructure would involve intramolecular electrophilic trapping of an appropriate tryptamine derivative at C3; however, the inherent tendency of 2*H*-indole systems to undergo rapid Wagner–Meerwein rearrangement (Scheme 1) makes such an approach difficult. Previously reported methods^{2c,2g,3} for such transformations overcome this problem by employing strongly nucleophilic intramolecular traps or electron-withdrawing groups on the indole and aliphatic nitrogen to minimize such rearrangements, which can still occur. We have recently reported the use of an interrupted Bischler–Napieralski reaction as a highly stereoselective and general strategy for the synthesis and arylative dimerization of *aspidosperma* alkaloids.⁴ Herein, we report a method for the efficient synthesis of spiropyrrolidinoindolines by interruption of the Bischler–Napieralski reaction of 2*H*-*N*-acyltryptamines via persistent spiroindoleninium intermediates with high resilience to Wagner–Meerwein rearrangements.

Earlier, we reported the use of the reagent combination trifluoromethanesulfonic anhydride (Tf₂O)–2-chloropyridine (2-ClPyr)⁵ to induce the Bischler–Napieralski reaction of secondary amides.⁶ Interestingly, exposure of amide **1a** to Tf₂O (1.1 equiv) in the presence of 2-ClPyr (1.2 equiv) followed by warming and addition of excess triethylamine⁷ provided the expected Bischler–Napieralski product **2a** (76%) along with the unexpected spirocyclic side product (±)-**3a** in low yield (~5%, Scheme 1). The sulfonylation of the amide nitrogen

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of spirocycle ($\pm$)-**3a** was rationalized by interception of a putative spirocyclic indoleninium intermediate ($\pm$)-**4a** with the slight excess of Ti_2O to afford spiroindoleninium ($\pm$)-**5a**. Consistent with this hypothesis, the use of excess Ti_2O (2.1 equiv) and 2-ClPyr (3.2 equiv) increased the yield of ($\pm$)-**3a** to 30% together with a complex mixture of side products and none of the Bischler–Napieralski product **2a**. Given the propensity of spiropyrrolidinoindoleninium intermediates to undergo Wagner–Meerwein rearrangement unless a strongly nucleophilic trap is present during spirocyclization,^{2c,g,3a–f,h–k} we hypothesized that the reduction at C2 may have been the result of a rapid hydride transfer reaction between two intermediates along the reaction pathway (Scheme 1).⁸

However, such a disproportionation reaction was ruled out with a concise set of deuterium labeling studies. When hexadeuterated amide **1a-d₆** was subjected to the reaction conditions, the spirocycle ($\pm$)-**3a-d₆** was isolated in 29% yield with complete deuterium retention on the alkenyl methyl groups and no deuterium enrichment at C2 (Equation 1). Furthermore, when amide **1a** was exposed to the reaction conditions with lithium aluminum deuteride used in place of triethylamine (after warming to 23 °C for 1 h), monodeuterated spirocycle ($\pm$)-**3a-d₁** was isolated in 60% yield with incorporation of exactly one deuterium atom at C2 (Equation 2, 6:1 dr at C2).⁹ This showed unequivocally that ($\pm$)-**5a** persists until an exogenous hydride source is introduced to afford reduction at C2. We posited that triethylamine might be acting as a hydride source,^{10,11} and conjectured that the modest mass balance might be the result of spiroindoleninium ($\pm$)-**5a** undergoing competitive decomposition upon warming. Importantly, when lithium aluminum hydride (Equation 1) or lithium aluminum deuteride (Equation 2, without warming to 23 °C) were introduced 5 min after warming the respective reactions to 0 °C, products ($\pm$)-**3a-d₆** and ($\pm$)-**3a-d₁** were isolated in 95% and 96% yields, respectively.

(1)

(2)

These results suggested that spirocyclic *N*-trifluoromethanesulfonyl indoleninium ($\pm$)-**5a** was electrophilic at C2 but recalcitrant to undergo a Wagner–Meerwein rearrangement due to deactivation of the trifluoromethanesulfonamide nitrogen lone pair. Electrophilic activation of **1a** followed by reduction with lithium aluminum hydride afforded spirocycle ($\pm$)-**3a** in excellent yield (Table 1, entry 1, 98% yield). When a less potent hydride source, triethylsilane, was introduced after activation and the resulting mixture warmed to ambient temperature, spirocycle ($\pm$)-**3a** was afforded in just 55% yield (Table 1, entry 2). On the other hand, 1-methyl-*N*-acetyltryptamine (**1b**), which bears no β -hydrogens, underwent highly efficient spirocyclization and reduction to afford spirocycle ($\pm$)-**3b** using either

triethylsilane (Table 1, entry 3, 97% yield), lithium aluminum hydride (Table 1, entry 4, 92% yield), or triethylamine (Table 1, entry 5, 72% yield) as reducing agent. Spirocyclization followed by reduction with triethylsilane proceeded smoothly with 1-benzyl-*N*-acetyltryptamine (**1c**) and even with electron-deficient 1-*p*-toluenesulfonyl-*N*-acetyltryptamine (**1d**), providing the corresponding spirocycles ($\pm$)-**3c** (Table 1, entry 6, 100% yield) and ($\pm$)-**3d** (Table 1, entry 7, 94% yield), respectively.

Furthermore, trapping the spiroindoleninium of amide **1b** at C2 with a carbon nucleophile, 1-methylindole, afforded the spirocyclic indole adduct ($\pm$)-**6b** in excellent isolated yield (Equation 3, 76%) as a single diastereomer.⁹ The stereochemical outcome of the reaction is consistent with approach of the 1-methylindole nucleophile opposite the bulky and highly electronegative¹² trifluoromethanesulfonamide moiety.

Additionally, we hypothesized that a rapid, reversible nucleophilic trap at C2 with an oxygen nucleophile might give a persistent intermediate that could be further derivatized. Thus, treatment of tryptamine–oxazolidinone urea **1e** with Tf₂O (1.1 equiv) and 2-ClPyr (2.2 equiv) followed by sequential addition of 1-methyltryptamine, titanium tetrachloride, and heating to 45 °C afforded 1-methyltryptamine adduct ($\pm$)-**6e** in 83% yield as a single diastereomer⁹ (Equation 4) that was consistent with nucleophile approach from the same face of the spiroindoleninium as seen with amide **1b** (Equation 3). The use of titanium tetrachloride was found to be essential to achieve C–C bond formation, consistent with competitive nucleophilic inhibition at C2 by the oxazolidinone oxygen atom.

(3)

(4)

Motivated by a desire to extend the range of diastereoselective trappings of spiroindoleninium intermediates and based on our prior synthetic work,⁴ we hypothesized that non-enolizable tertiary amides would, upon activation with Tf₂O–2-ClPyr, undergo rapid spirocyclization to afford a putative persistent diiminium dication resilient to Wagner–Meerwein rearrangement. To our delight, treatment of tertiary pivalamide **1f** with Tf₂O–2-ClPyr at 0 °C in acetonitrile¹³ and warming to 23 °C, followed by sequential trapping with triethylsilane and lithium aluminum hydride, afforded spirocyclic indoline ($\pm$)-**7f** as a single diastereomer⁹ in 91% yield (Equation 5), suggesting the in situ formation of a persistent diiminium ion intermediate. The diastereoselectivity is likely a result of the steric bulk of the arene, which blocks approach of lithium aluminum hydride. Use of lithium aluminum deuteride in place of lithium aluminum hydride afforded monodeuterated spirocyclic

indoline ($\pm$)-**7f**-*d*₁, demonstrating the regioselective trapping at C2 with triethylsilane.⁹ Similarly, activation of lactam **1g** followed by tandem reduction with triethylsilane–lithium aluminum hydride afforded tetracyclic indoline ($\pm$)-**7g** in quantitative yield as a single diastereomer⁹ (Equation 6).

(5)

(6)

Encouraged by the efficiency of the spirocyclization/intermolecular nucleophilic trapping protocol, we envisaged a double-cyclization cascade making use of enolizable secondary amides with pendant nucleophiles. To explore and optimize this transformation, tryptamine–phenylacetamide **1h** was selected as substrate. Activation with Tf₂O (2.1 equiv) in the presence of 2-ClPyr (3.2 equiv) in CH₂Cl₂ followed by warming to 23 °C provided pentacycle ($\pm$)-**8h** in 40% yield (Scheme 2) accompanied with monocyclized side products and no recovered starting material or Bischler–Napieralski derived products. Heating the reaction to 45 °C in an oil bath afforded ($\pm$)-**8h** in excellent yield¹⁴ (Scheme 2, 91% yield), while brief heating in a microwave¹⁵ to 130 °C provided ($\pm$)-**8h** in quantitative yield. While similar cascades have been reported previously, the lack of any requirement of large excesses of activating agents^{3a,c,d} and the ability to completely avoid Wagner–Meerwein rearrangement^{3d} are specific advantages to the chemistry described here, and highlight the importance of nitrogen lone pair deactivation by the highly electronegative trifluoromethanesulfonyl group. Not surprisingly, electron-rich 3,4-dimethoxyphenylacetamide **1i** provided pentacycle ($\pm$)-**8i** in 98% yield as a single regio- and diastereomer⁹ under 45 °C conditions on half-gram scale (Scheme 2). Even highly electron-deficient 4-nitrophenylacetamide **1j** afforded pentacycle ($\pm$)-**8j** in moderate yield (53%) under microwave heating conditions (130 °C, 10 min), and vinylacetamide **1k** afforded tetracyclic spiroindoline ($\pm$)-**8k** in 56% yield after heating at 45 °C. The trifluoromethanesulfonyl group present in the spirocyclic indolines derived from secondary amides is removed under reductive or eliminative conditions: desulfonylation of pentacycle ($\pm$)-**8i** with sodium and ammonia in the presence of methanol provided pentacyclic diamine ($\pm$)-**9i** in excellent yield (95%) as a single diastereomer (Equation 7), while dehydrosulfinylation of tricycle ($\pm$)-**3a** is affected upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile under microwave heating conditions (Equation 8) to afford the unsaturated imine ($\pm$)-**10a** in 71% yield.

(7)

(8)

We have presented a method for the efficient generation of distinctively persistent spiroindoleninium intermediates from secondary and tertiary *N*-acyl tryptamines. The exceptional resilience of the intermediates, accessed under the described reaction conditions, to Wagner–Meerwein rearrangement allows for efficient intra- and intermolecular trapping with nucleophiles, including weak nucleophiles such as deactivated arenes, even after activation and spirocyclization. The use of urea and tertiary amides under our conditions allows for the direct and highly diastereoselective synthesis of spiropyrrolidinoindolines without competitive rearrangement^{2c,3a,c–e,h,k} or the need for an electron-withdrawing group^{2c,3a,c,d,g,j} on the aliphatic or indole nitrogen atoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful for financial support by NIH–NIGMS (GM074825). M. M. is a Camille–Dreyfus Teacher–Scholar. J. W. M. acknowledges a National Defense Science and Engineering Graduate Fellowship.

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7. The addition of triethylamine at the end of the reaction was carried out with the intention of neutralizing the trifluoromethanesulfonate salts prior to work-up.
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10. Product ($\pm$)-**3a** was not detected when potassium carbonate or 1,4-diazabicyclo[2.2.2]octane was used for neutralization prior to workup.
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14. 2-Chloropyridine was found to be the optimal base additive for this reaction; the use of 2-fluoropyridine or 2,6-lutidine gave yields of 90% and 66%, respectively, of ($\pm$)-**8h** under 45 °C conditions.
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Figure 1.
Representative spirocyclic pyrrolidinoindolines.

Scheme 1.

A plausible mechanism for spirocycle formation

Scheme 2. Double-cyclization cascades^a

^aIsolated yields of single diastereomers. ^b Tf_2O (2.1 equiv), 2-ClPyr (3.2 equiv), 130 °C (microwave), 5 min. ^c45 °C, 3 h. ^d23 °C, 3 h. ^e Tf_2O (2.1 equiv), 2-ClPyr (3.2 equiv), 45 °C, 3 h. ^f Tf_2O (3.1 equiv), 2-ClPyr (4.2 equiv), 130 °C (microwave), 10 min. ^g Tf_2O (3.1 equiv), 2-ClPyr (4.2 equiv), 45 °C, 3 h.

Table 1

Spirocyclization and reduction

entry	amide	R ¹	R ²	temp	time	yield ^a
1	1a	Me	Me	0 °C	5 min	98% ^b
2	1a	Me	Me	23 °C	30 min	55%
3	1b	Me	H	0 °C	30 min	97%
4	1b	Me	H	0 °C	5 min	92% ^b
5	1b	Me	H	23 °C	60 min	72% ^c
6	1c	Bn	H	0 °C	30 min	100%
7	1d	Ts	H	23 °C	30 min	94%

^a Isolated yield.

^b LiAlH_4 (3.0 equiv) used as reducing agent at 0 °C.

^c Et_3N (5.0 equiv) used as reducing agent.