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Iodospirocyclization of Tryptamine-Derived Isocyanides: Formal Total Synthesis of Aspidofractinine

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Dedicated to Professor Henk Hiemstra

Abstract: *The N-iodosuccinimide-mediated spirocyclization of tryptamine-derived isocyanides to generate spiroindolenines is reported. The products contain both an imine and an imidoyl iodide as flexible handles for follow-up chemistry. Nucleophilic addition typically occurs chemoselectively on the imine moiety with complete diastereoselectivity, providing opportunities for the construction of complex molecular frameworks. The synthetic potential of the method was showcased in the formal total synthesis of (±)-aspidofractinine.*

Indole alkaloids constitute a large and diverse class of natural products.[1] These compounds have attracted tremendous interest from the synthetic community as a result of their diverse biological activities as well as their challenging molecular architectures.[2] In particular spiroindoline alkaloids (Figure 1) have garnered much attention, as demonstrated by the high number of approaches to construct the spirocyclic unit.[3] Besides the interrupted Fischer indole synthesis and aniline condensation cyclizations, the most common strategy is the intramolecular dearomatization of indoles to form spiroindolenines. Noteworthy within this field is the work by MacMillan et al., who have developed an organocatalytic dearomative cascade approach toward a range of indoline alkaloids.[4]

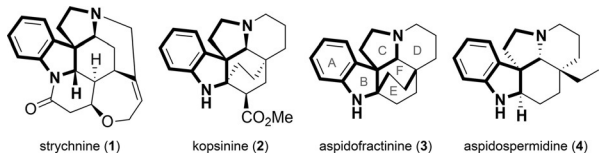
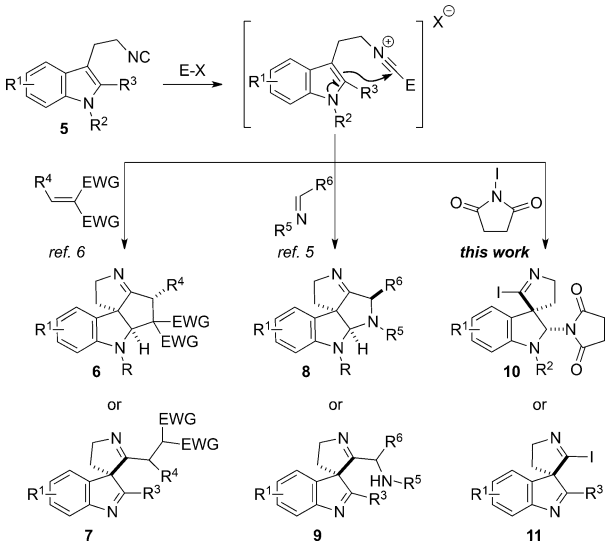


Figure 1. Selected naturally occurring indole alkaloids.

Tryptamine-derived isocyanides **5** have shown great potential in dearomative spirocyclization reactions (Scheme 1). By addition of a suitable electrophile (i.e. imines[5] or Michael acceptors[6]), nucleophilic addition of the isocyanide generates a highly electrophilic nitrilium ion intermediate. Subsequent nucleophilic attack of the indole C3 position triggers the spirocyclization. In the absence of a C2 substituent, the cascade process is completed by a second cyclization reaction to form tetracyclic spiroindolines (**6** and **8**). Considering the robustness of this process and the high potential utility of efficient and selective indole spirocyclizations, we wondered whether other soft electrophiles could give rise to similar cascade cyclizations. Given the diverse reactivity of imidoyl halides in general and imidoyl iodides[7] in particular, we considered electrophilic halogenation as an efficient entry into spiroindolenines **10** and **11** as flexible synthetic intermediates. There is some precedence for reactions of isocyanides and electrophilic halogenating agents,[8] including those involving cyclization to phenanthridines[9] and oxazoles.[10] We were delighted to see quantitative formation of spiroindolenine **11a**,**b** within 5 min after treatment of **5a**



Scheme 1. Tryptamine-derived isocyanides **5** in dearomative couplings with electrophiles.

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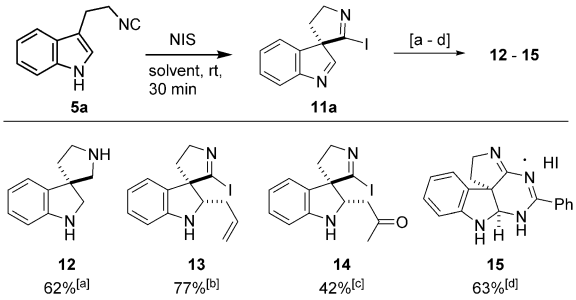
($R^1 = R^2 = R^3 = H$) and **5b** ($R^1 = R^2 = H$, $R^3 = Me$) with *N*-iodosuccinimide (NIS) in $CDCl_3$ as the solvent. This led us to investigate the generality of this reaction and to explore the reactivity of the resulting products.

Our preliminary studies started by determining the scope of the reaction with respect to conditions and halogenating sources. The reaction of **5a** with NBS to give the corresponding imidoyl bromide proceeded less efficiently, while the use of NCS failed to produce the imidoyl chloride altogether. When we encountered stability issues upon concentration of spiroindolenine **11a**, we continued the optimization with **11b**. To our delight, the reaction proceeded quantitatively in most organic solvents. Even methanol was compatible with this reaction as the imidoyl iodide was formed in 85% yield, without observation of the imidate (for details, see the Supporting Information).

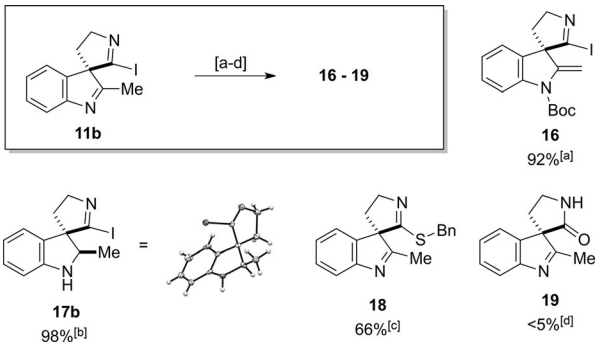
We then preliminarily probed the reactivity of the two potential electrophilic sites of **11a**, that is, the imine and the imidoyl iodide (Scheme 2). After in situ formation of **11a**, treatment with $NH_3{\cdot}BH_3$ (3 equiv.) led to complete reduction



Scheme 2. One-pot iodospirocyclization/post-modification strategies to evaluate the reactivity of imidoyl iodide **11a**. [a] $NH_3{\cdot}BH_3$, MeCN (0.1 M), RT, 2 h. [b] allylBPin, CH_2Cl_2 (0.2 M), RT, 1 h. [c] $(CH_3)_2CO$, KO*t*Bu, THF (0.2 M), −78 °C to RT. [d] benzamidine, 1,4-dioxane (0.1 M), RT, 16 h.

of both functionalities to give the saturated spiro product **12**, which is the scaffold structure of known Sky kinase inhibitors.[11] Reaction of **11a** with allylBpin and acetone afforded **13** and **14**, respectively, with >19:1 dr, indicating that one diastereotopic face of the indolenine is efficiently shielded by the large iodine atom. Finally, we envisioned that bisnucleophiles could undergo double addition, resulting in polycyclic spiroindolines. Indeed, reaction of in situ formed **11a** with benzamidine afforded the poorly soluble polycyclic product **15** in good yield. Interestingly, the stereochemistry at the indoline C2 position suggests attack from the more hindered face. This observation led us to conclude that, while addition of the amidine to the imine may take place reversibly, formation of **15** proceeds via substitution at the imidoyl iodide, followed by aminal formation at the C2 position.

Since imidoyl iodide **11b** was found to be stable upon isolation, we also performed several experiments with this substrate (Scheme 3). First, we showed that **11b** can be efficiently converted to the Boc-protected enamine **16** after deprotonation with LiHMDS. Surprisingly, sodium borohydride reduction resulted in chemoselective conversion of the



Scheme 3. Evaluation of the reactivity of imidoyl iodide **11b**. [a] LiHMDS, THF (0.15 M), −78 °C, 1 h; then Boc_2O, −78 °C, 3 h. [b] $NaBH_4$, MeOH:TFE (4:1, 0.2 M), 0 °C to RT, 1 h. [c] Cs_2CO_3, BnSH, 0 °C, 30 min. [d] 1 M HCl (aq), THF (0.1 M), 0 °C. Boc = *tert*-butyloxycarbonyl, Bn = benzyl.

ketimine without reducing the imidoyl iodide, affording **17b** as a single diastereomer in near quantitative yield. The relative stereochemistry of **17b** was confirmed by X-ray crystallographic analysis. For **11b**, chemoselective reaction of the imidoyl iodide also proved possible,[12] furnishing **18** after reaction with benzyl mercaptan. However, attempts to hydrolyze the imidoyl iodide under acidic conditions mainly led to decomposition, and only trace amounts of lactam **19** were observed.

Having established the optimal conditions of the iodospirocyclization and preliminary reactivity of the resulting imidoyl iodides, we set out to determine the isocyanide scope. Since the reaction proceeded smoothly with **5a** and **5b**, we performed the iodospirocyclization with a wide variety of substituted isocyanides **5**. As we noted the importance of a C2 substituent on the indole for the stability of the resulting spiroindolenine, we first subjected C2-substituted isocyanides to the iodospirocyclization (Scheme 4).

Isocyanides with different indole C2-substituents (*t*Bu, Ph, Br) were all rapidly converted within 30 min to give the corresponding imidoyl iodides **11c–e** in very good yield. The double imidoyl halide **11e** was surprisingly stable toward chromatography. Even the homologous isocyanide **5f** readily reacted to form **11f**, albeit in moderate yield. The presence of an ester functionality in the C2 substituent gave the corresponding spirocyclic product **11g** as the enamine tautomer in excellent yield. As significant decomposition of the spiroindolenines derived from isocyanides **5h–j** was observed during chromatography, we decided to reduce them in situ to the more stable spiroindolines **17h–j**.[13] Even N1,C2-disubstituted isocyanide **5j** was selectively converted to spiroindoline **17j**, indicating the compatibility of N1-substituents with our method.

Next, we shifted our attention to C2-unsubstituted isocyanides, starting with N1-substituted isocyanides **5k–o** (Scheme 5).[14] In this case, iodospirocyclization would lead to the formation of reactive spirocyclic iminium ion intermediate. We wondered whether this intermediate would undergo a 1,2-migration to give the indole, which is a well-known phenomenon in indole chemistry.[15] However, treatment of the N1-methyl substituted isocyanide **5k** with NIS instead led

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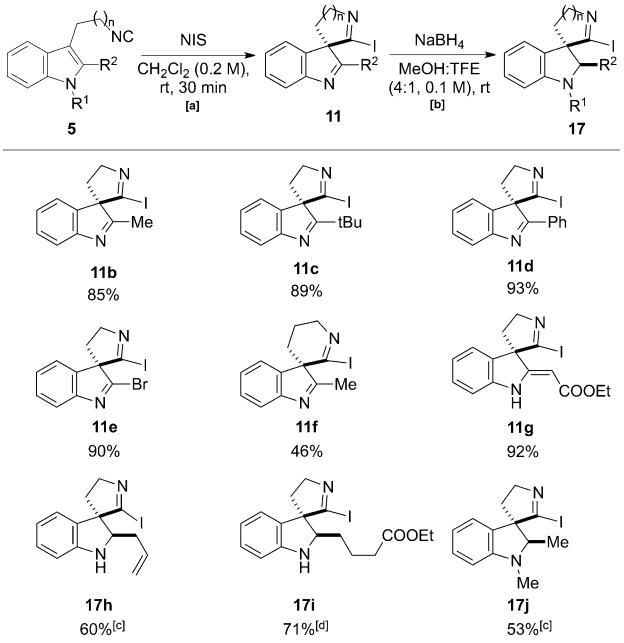
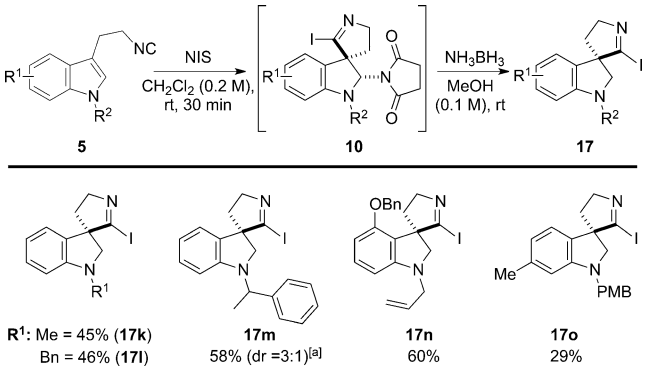


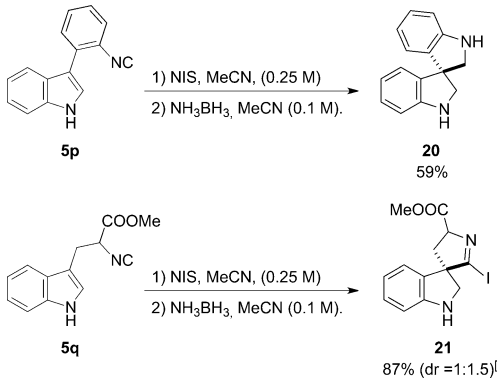
Scheme 4. Scope of the C2 substituted tryptamine isocyanides. [a] Reaction conditions: isocyanide **5** (1 mmol), NIS (1.05 mmol), CH_2Cl_2 (0.25 M). [b] Reaction conditions: isocyanide **5** (1 mmol), NIS (1.05 mmol), CH_2Cl_2 (0.25 M); then $NaBH_4$ (5.0 mmol) in MeOH:TFE (4:1, 0.1 M). [c] Both iodospirocyclization and reduction steps performed at 0 °C. [d] performed at 1.8 mmol scale.



Scheme 5. Scope of the N1 substituted tryptamine isocyanides. Reaction conditions: isocyanide **5** (1 mmol), NIS (1.05 mmol), CH_2Cl_2 (0.2 M); then $NH_3{\cdot}BH_3$ (5.0 mmol) in MeOH (0.1 M). [a] Diastereomeric ratio based on ^{1}H NMR analysis. PMB = *p*-methoxybenzyl.

to succinimide adduct **10k** by interception of the iminium ion intermediate by the succinimide counterion. This product was stable upon concentration, but decomposed slowly during chromatography. We therefore opted to reduce the aminals **10k–o** in situ to afford spiroindolines **17**. This transformation was not trivial, as several competing decomposition pathways were observed. After some optimization, we found that treatment with $NH_3{\cdot}BH_3$ (5 equiv.) in MeOH led to selective reduction of aminals **10** to give spiroindolines **17k–o** in moderate to reasonable yields (29–60%). Interestingly, we observed considerable induction (dr = 3:1) with the N1 α-methylbenzyl-substituted isocyanide **5m**, constituting remarkable transfer of the rather distant chiral information and a promising alternative for asymmetric catalysis.[16]

Finally, we evaluated substitution on the bridging ethylene linker (Scheme 6). Initially, we did not expect the rigid



Scheme 6. Variations on the tryptamine isocyanide linker. Reaction conditions: isocyanide **5** (1 mmol), NIS (1.05 mmol), CH_2Cl_2 (0.2 M); then $NH_3{\cdot}BH_3$ (5.0 mmol) in MeOH (0.1 M). [a] diastereomeric ratio based on ^{1}H NMR analysis.

phenylene-bridged isocyanide **5p** to produce the spirocyclic framework. Pleasingly, however, we observed a clean ^{1}H spectrum after performing the reaction in $CDCl_3$. In a subsequent experiment, the isocyanide was subjected to the one-pot spirocyclization/ reduction procedure to generate C_2-symmetric spirobiindoline **20** in 59% yield. Subsequently, tryptophan-derived isocyanide **5q** was reacted under the same conditions. While the iodospirocyclization products derived from the comparable isocyanides **5a** and **5p** underwent complete reduction after treatment with $NH_3{\cdot}BH_3$, the spirocyclization/ reduction sequence of isocyanide **5q** instead afforded spiroindoline **21**, leaving the imidoyl iodide unaffected. In addition, we again observed some induction of stereochemistry, albeit modest (dr = 1.5:1).

Having demonstrated the compatibility of the iodospirocyclization with a wide variety of tryptamine-derived isocyanides, we sought to apply our method to the synthesis of a relevant natural product. We envisioned that 19-oxoaspidospermidine (**25**), an intermediate in the total synthesis of aspidofractinine (**3**),[17] would be accessible in a few steps from spirocyclization product **17i** (Scheme 7). As nucleophilic substitutions on the imidoyl iodide are possible (see thiol substitution, Scheme 3), we envisioned intramolecular nucleophilic attack of the ester enolate to construct the E ring. Protection of the indoline nitrogen was essential, as addition of LiHMDS immediately resulted in lactamization. This kinetically favored pathway also limited the Boc protection, as the indoline amine is not a strong nucleophile in its neutral form. By using an excess of Boc_2O with DMAP as an activating agent we were able to overcome this problem, obtaining the protected indoline **22** in 62% yield (73% based on recovered starting material). Subsequent treatment of **22** with LiHMDS resulted in clean conversion to tetracycle **23** in 87% yield. Several groups have previously shown the construction of the D ring from similar tetracyclic frameworks

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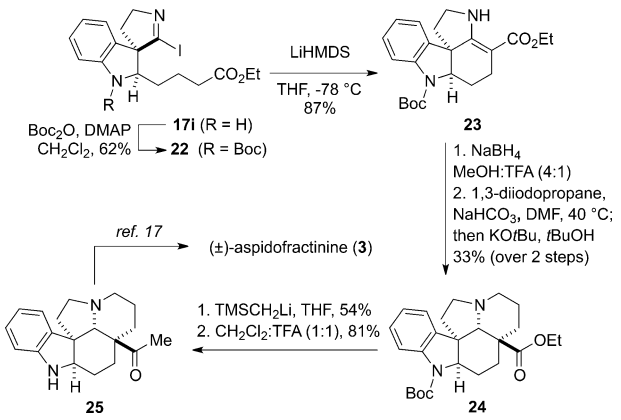

Scheme 7. Formal total synthesis of (±)-aspidofractinine from spiroindoline **17i**.

in synthetic strategies toward related indoline alkaloids.[4b,c,17b,c,18] Based on these precedents, we chose to first reduce the enamine in **23**, followed by dialkylation with 1,3-diiodopropane. Standard reduction procedures initially failed to convert the enamine. Fortunately, when we used $NaBH_4$ as the reducing agent in a MeOH/TFA mixture (4:1), the more acidic solvent mixture facilitated the reduction, resulting in full conversion within 5.5 hours.[19] We then used the conditions reported by Gramain et al. to form the pentacyclic framework in a two-step alkylation procedure.[17c] A single diastereoisomer of **24** was isolated, the relative configuration of which was confirmed by 2D-NOESY experiments. Based on the 33% yield over these two steps and the 1:1 selectivity of the similar enamine reduction reported by Gramain et al.,[17c] we suspect our selectivity to be derived from the instability of the undesired diastereomer. To complete the formal total synthesis, the ethyl ester in **24** was converted to the corresponding methyl ketone by treatment with $TMSCH_2Li$, after which TFA-mediated Boc deprotection afforded 19-oxoaspidospermidine (**25**). The ^1H NMR and ^{13}C NMR spectra of our synthetic sample fully matched the data reported by Gramain et al.[17c]

In conclusion, we have developed the iodospirocyclization of a broad range of tryptamine-derived isocyanides **5**. The reaction is very fast and compatible with most organic solvents. In addition, the reaction tolerates a wide variety of substituents on the isocyanides, creating versatile synthetic intermediates that can undergo various chemical transformations (Schemes 2 and 3). Spiroindoline **17i** was converted in only six steps to 19-oxoaspidospermidine, constituting a formal total synthesis of aspidofractinine (**3**). We believe that the use of this methodology on tailored isocyanides **5** should allow access to a wide variety of other spiroindoline natural products.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Alkaloids · cyclization · isocyanides · natural product synthesis · spiroindolines

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