Iodospirocyclization of tryptamine-derived isocyanides : formal total synthesis of aspidofractinine

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

Jordy M. Saya, Thomas R. Roose, Jarryt J. Peek, Bram Weijers, Thomas J.S. de Waal, Christophe M. L. Vande Velde, Romano V. A. Orru and Eelco Ruijter*[a]

Dedicated to Prof. Dr. Henk Hiemstra on the occasion of his retirement

Abstract: The *N*-iodosuccinimide-mediated spirocyclization of tryptamine-derived isocyanides to generate spiroindolinenes 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 (Fig. 1) have garnered much attention, as demonstrated by the high number of approaches to construct the spirocyclic unit.[3] Next to 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]

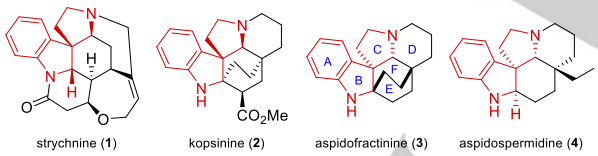
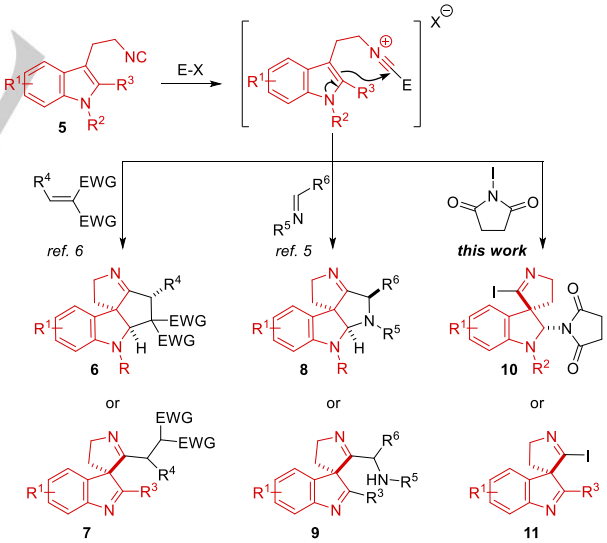


Figure 1. Selected naturally occurring indole alkaloids.

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. Although the compatibility of isocyanides and electrophilic halogenating agents is well-established,[8] we were delighted to see quantitative formation of spiroindolenine **11a-b** within 5 min after treatment of **5a** ($R^1 = R^2 = R^3 = H$) 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.



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

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

[a] J. M. Saya, T. R. Roose, J. J. Peek, B. Weijers, T. de Waal, Prof. Dr. Romano V. A. Orru, Dr. E. Ruijter
Department of Chemistry & Pharmaceutical Sciences
Amsterdam Institute for Molecules, Medicines & Systems
Vrije Universiteit Amsterdam
De Boelelaan 1108, 1081 HZ Amsterdam, the Netherlands
E-mail: e.ruijter@vu.nl
[b] Dr. C. M. L. Vande Velde
Faculty of Applied Engineering
Advanced Reactor Technology
University of Antwerp
Groenenborgerlaan 171, 2020 Antwerpen, Belgium
E-mail: christophe.vandevelde@uantwerpen.be

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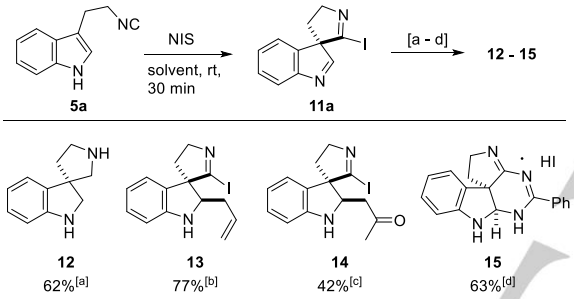
our delight, the reaction proceeded quantitatively in most attempted aprotic organic solvents. Even methanol was compatible with this reaction as the imidoyl iodide was formed in 85% yield, without observation of the imidate.

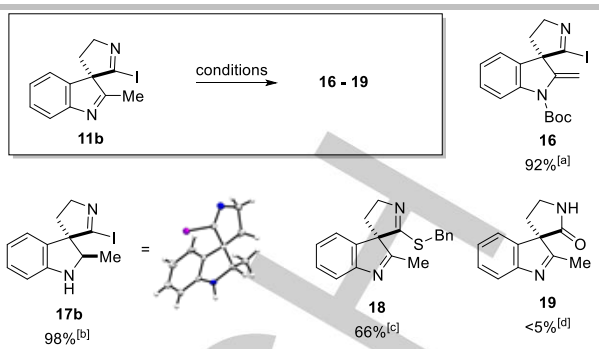
We then preliminarily probed the reactivity of the two potential electrophilic sites of **11a**, *i.e.* the imine and the imidoyl iodide (Scheme 2). After *in situ* formation of **11a**, treatment with NH_3•BH_3 (3 eq.) led to complete reduction of both functionalities to give the saturated spiro product **12**, which is the scaffold structure of known Sky kinase inhibitors.[9] 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.



Scheme 2. One-pot iodospirocyclization/post-modification strategies to evaluate the reactivity of imidoyl iodide **11a**. [a] NH_3•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.

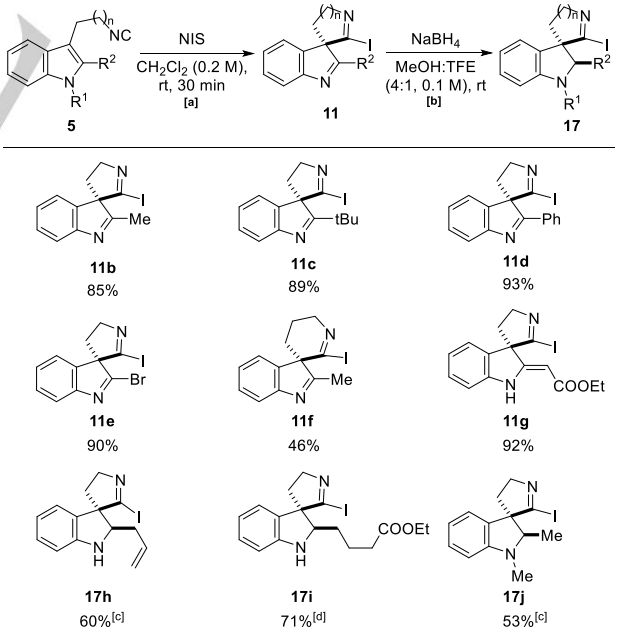
Since imidoyl iodide **11b** was found to be stable upon isolation, we also performed several experiments with this substrate (Scheme 3). First, we showed that **11b** can be efficiently converted to the Boc-protected enamine after deprotonation with LiHMDS. Surprisingly, sodium borohydride reduction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



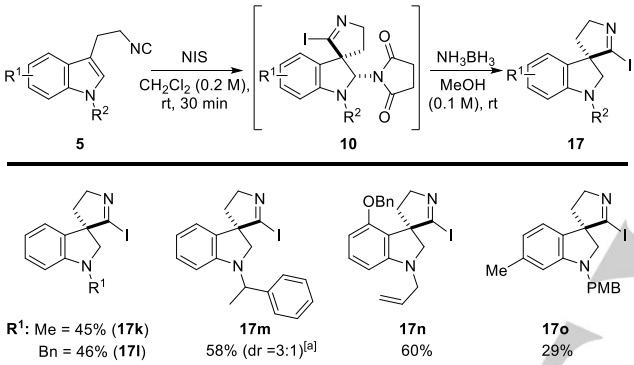
Scheme 3. Evaluation of the reactivity of imidoyl iodide **11b**. [a] LiHMDS, THF (0.15 M), −78 °C, 1 h; then Boc_2O, −78 °C, 3 h. [b] $NaBH_4$, MeOH:TFE (4:1, 0.2M), 0 °C to rt, 1 h. [c] Cs_2CO_3, BnSH, 0 °C, 30 min. [d] 1 M HCl (aq), THF (0.1 M), 0 °C. Boc = *tert*-butyloxycarbonyl, Bn = benzyl.

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 as the C2 substituent gave the corresponding spirocyclic product **11g** as the enamine tautomer in excellent yield. As significant decomposition occurred of the spiroindolenines derived from isocyanides **5h-j**, we decided to reduce them *in situ* to the more stable spiroindolines **17h-j**.[10] Even N1,C2-disubstituted isocyanide **5i** was selectively converted to spiroindoline **17j**, indicating the compatibility of N1-substituents with our method.



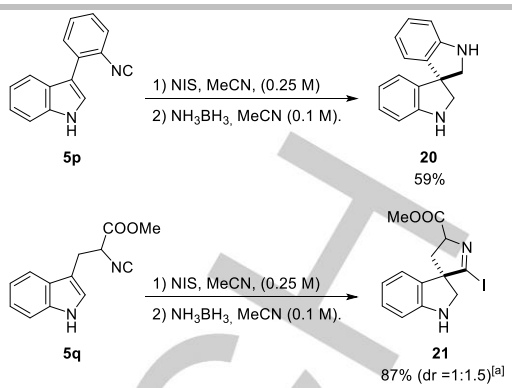
Scheme 4. Scope of the C2 substituted tryptamine isocyanides. [a] Reaction conditions: isocyanide **5** (1 mmol), NIS (1.05 mmol), CH_2Cl_2 (0.25M). [b] Reaction conditions: isocyanide **5** (1 mmol), NIS (1.05 mmol), CH_2Cl_2 (0.25M); then $NaBH_4$ (5.0 mmol) in MeOH:TFE (4:1, 0.1 M). [c] Both iodospirocyclization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

Next, we shifted our attention to C2-unsubstituted isocyanides, starting with N1-substituted isocyanides (Scheme 5).[11] 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.[12] However, treatment of the N1-methyl substituted isocyanide **5k** with NIS instead led 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•BH_3 (5 eq.) 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.



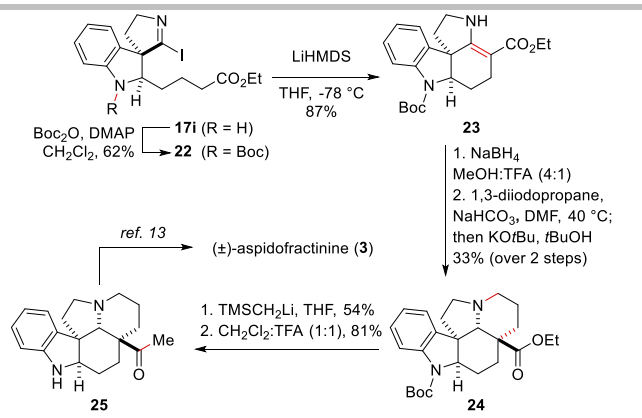
Scheme 5. Scope of the N1 substituted tryptamine isocyanides. Reaction conditions: isocyanide **5** (1 mmol), NIS (1.05 mmol), CH_2Cl_2 (0.2 M); then NH_3•BH_3 (5.0 mmol) in MeOH (0.1 M). [a] Diastereomeric ratio based on ^{1}H NMR analysis. PMB = *p*-methoxybenzyl.

Finally we evaluated substitution on the bridging ethylene linker (Scheme 6). With phenyl-bridged isocyanide **5p** we were reluctant to believe that this rigid system would still produce the spirocyclic framework. Pleasingly, 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, tryptophane-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•BH_3, the spirocyclization/ reduction sequence of isocyanide **5q** instead afforded spiroindoline **21**, leaving the imidoyl iodide unaffected. In addition, we again observed some chirality transfer, however, in modest selectivity (dr = 1.5:1).



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•BH_3 (5.0 mmol) in MeOH (0.1 M). [a] diastereomeric ratio based on ^{1}H NMR analysis.

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**),[13] 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 in synthetic strategies toward related indoline alkaloids.[4b,c,13b,c,14] 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 mixture of MeOH:TFA (4:1), the more acidic solvent mixture facilitated the reduction, resulting in full conversion within 5.5 hours.[15] We then used the conditions reported by Dufour *et al.* to form the pentacyclic framework in a two-step alkylation procedure.[13c] 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 Dufour *et al.*,[13c] we suspect our selectivity to be derived from the instability of the undesired diastereomer. To complete the 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 ^{1}H NMR and ^{13}C NMR spectra of our synthetic sample fully matched the data reported by Dufour *et al.*[13c]



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

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 **17h** 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.

Experimental Section

General procedure for the synthesis of spiroindolenines **11**: To a solution of a tryptamine-derived isocyanide **5** (1 equiv) in CH_2Cl_2 (0.25 M) was added NIS (1.05 equiv). After stirring for 30 min, the mixture was concentrated and purified by flash chromatography.

General procedure for the synthesis of spiroindolines **17h-j**: To a solution of a tryptamine-derived isocyanide **5** (1 equiv) in CH_2Cl_2 (0.25 M) was added NIS (1.05 equiv). After stirring for 30 min, the mixture was cooled to 0 °C and diluted with MeOH:TFE (4:1, final concentration 0.075 M). Subsequently, $NaBH_4$ (5 equiv) was added and the reaction was stirred for 1 hour. After full conversion as monitored by TLC, water was added and the reaction was stirred for an additional 30 min. The product was extracted with CH_2Cl_2, and the combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography.

General procedure for the synthesis of spiroindolines **17k-o**: To a solution of a tryptamine-derived isocyanide **5** (1 equiv) in CH_2Cl_2 (0.25 M) was added NIS (1.05 equiv). After stirring for 30 min, the mixture was diluted with MeOH (0.1 M). Subsequently, $NH_3{\bullet}BH_3$ (5 equiv) was added and the reaction was stirred for 1 hour. After full conversion as monitored by TLC, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and stirred for 30 min. The aqueous layer was extracted with CH_2Cl_2 and the collected organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography.

Acknowledgements

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

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[11] *N*-Boc substituted **5** was completely consumed under the reaction conditions, however, merely decomposition was observed.

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[15] Although a large amount of TFA was used, Boc cleavage was not observed.

Entry for the Table of Contents

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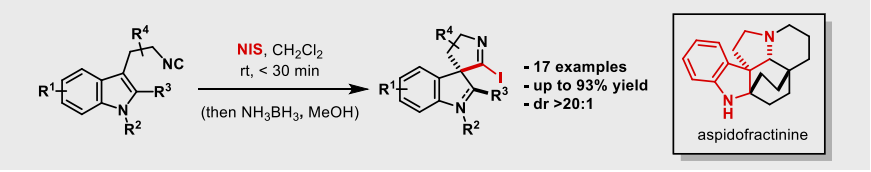

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Page No. – Page No.

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

I make(s) spirocycles: Iodospirocyclization of tryptamine-derived isocyanides affords highly substituted spiroindolenine imidoyl iodides. The imine functionality can undergo a variety of diastereoselective addition reactions, including *in situ* reduction, while the imidoyl iodide functionality is remarkable stable. The utility of the method was demonstrated by the formal total synthesis of (±)-aspidofractinine.