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Synthesis of 4-, 5-, 6-, and 7-azidotryptamines

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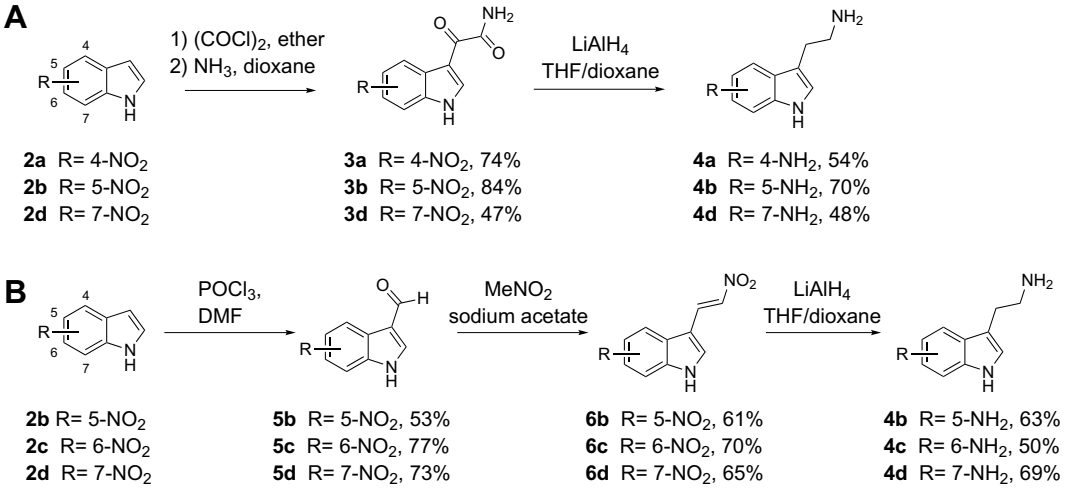
ABSTRACT

Synthesis of azidotryptamines from commercially available nitroindoles via the corresponding amino tryptamines in good overall yields (15–38%) is presented.

Photoaffinity-derivatized ligands have been used to covalently label and to identify numerous classes of enzymes. Aryl azides, diazirines, and benzophenones have all been used as photolabels.[1] The use of azidoindoles for photocrosslinking is precedented; for example, 6-azidotryptophan has been used to label the tryptophan $\alpha_2\beta_2$ synthase complex,[2] and 5-azidoindole-3 acetic acid has been shown to efficiently cross-link to auxin receptors in plant cell extracts.[3] Despite the utility of the indole azide labeling group, and the participation of tryptamine in metabolic pathways, no synthetic route had been previously reported for the azidotryptamines **1**. Herein, we report an efficient synthesis of 4-, 5-, 6-, and 7-azidotryptamines **1a**–**d** starting from commercially available nitroindoles.

Adapting a previously reported protocol for tryptamine synthesis, nitroindoles **2a,b,d** were reacted with oxalylchloride in ether (Scheme 1A).[4] The resulting indole oxalylchlorides were treated with ammonia in 1,4-dioxane to give the corresponding oxalylamides **3a,b,d** in good yields. Simultaneous reduction of the nitro group and amide side chain with lithium aluminum hydride in refluxing THF/1,4-dioxane led to the aminoindoles **4a,b,d** (Scheme 1A). Surprisingly, 6-nitroindole **2c** failed to react with oxalylchloride to form the desired product under a variety of temperatures and reagent concentrations. Therefore, an alternative strategy for the synthesis of the 6-aminoindole **4c** was employed (Scheme 1B). Nitroindole-3-carboxaldehyde **5c** was prepared by utilizing the *Vilsmeier–Haack* reaction, followed by addition of nitromethane



Scheme 1. (A) Synthesis of 4-, 5-, and 7-aminotryptamine **4a**,**b**,**d** from nitroindoles **2a**,**b**,**d** via the indole oxalylamides **3a**,**b**,**d**. (B) Synthesis of 4-, 5-, and 7-aminotryptamine **4b**,**c**,**d** from nitroindoles **2b**,**c**,**d** via the nitro vinyl indoles **6b**,**c**,**d**.

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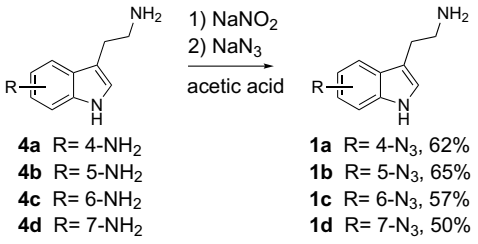
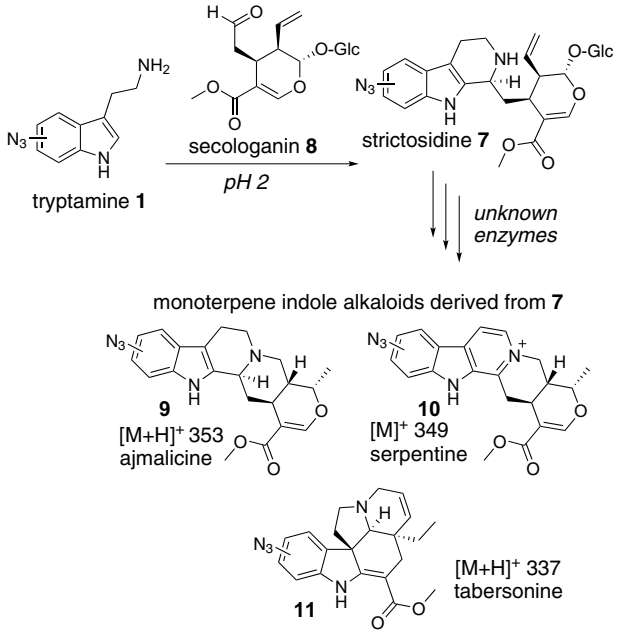


Scheme 2. Diazotation of aminotryptamines **4a–d** to form azidotryptamines **1a–d**.



Scheme 3. Chemical reaction of tryptamine **1a–d** and secologanin **8** to yield strictosidine **7a–d**, which appears to be incorporated into several terpene indole alkaloids including **9**, **10**, and **11**.

and elimination (*Henry* reaction) to give nitro vinyl indole **6c**. Reduction with lithium aluminum hydride in refluxing THF gave 6-amino-tryptamine **4c**. This method could also be used to generate 5-aminotryptamine **2b** and 7-aminotryptamine **2d**, though addition/elimination and reduction of **2a** to **4a** did not proceed in good yields through this route (Scheme 1B).[5]

With aminotryptamines **4a–d** in hand, the azide group could be introduced by diazotation of the corresponding amines. Following a protocol from Melhardo et al., sodium nitrite and sodium azide in glacial acetic acid were used to convert the aminotryptamines **4a–d** into the azidotryptamines **1a–d**.[6] The primary alkyl amine did not react under these conditions, and all four azidotryptamines **1a–d** could be obtained in good yields in one step from **4a–d** (Scheme 2). From the nitroindoles **2a–d**, the corresponding azidotryptamines **1a–d** could be obtained in overall yields ranging from 15% to 38%.

A concern when using photoaffinity-derivatized substrates to identify proteins is that the azide group could disrupt binding to highly substrate-specific enzymes. To examine this issue, we chemically synthesized the metabolic biosynthetic intermediate strictosidine **7a–d** from **1a–d** (Scheme 3). Photolabeled azidostrictosidines **7a–d** were incubated with *Catharanthus roseus* plant cell culture that produces monoterpene indole alkaloids ajmalicine (*m/z* 353) **9**, serpentine (*m/z* 349) **10**, and tabersonine (*m/z* 337) **11** that are derived from strictosidine **7**.[7] Mass spectrometry analysis of these *C. roseus* extracts revealed the formation of new compounds displaying masses consistent with azido analogs of alkaloids with *m/z* 353.[8] Furthermore, in cultures supplemented with azidostrictosidines **7c** and **7d**, compounds with molecular formulae consistent with azido analogs of alkaloids having *m/z* 349[9] and *m/z* 337[10] were also observed. These compounds were not observed in control cultures lacking azidostrictosidine.

Although MS analysis cannot allow us to predict the structure of these unknown analogs, these studies nevertheless strongly suggest that the biosynthetic enzymes of an alkaloid metabolic pathway can bind to and turn over azide-labeled precursors. Biosynthetic intermediates derived from **1a–d** and **7a–d** may therefore potentially be used for photoaffinity labeling of enzymes in this metabolic pathway. In combination with a chemoselective handle (such as an alkyne installed at the ester of **7**)[11] that allows for identification in a crude mixture, these photolabeled compounds could be used to identify desired metabolic enzymes in cell lysates.

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Supplementary data

Supplementary data (experimental protocols and spectroscopic characterization of compounds **1**–**5a–d**, **7a–d**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.091.

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5. An older report of the synthesis of aminotryptamines is described in: Hiremath, S. P.; Siddappa, S. *J. Med. Chem.* **1965**, *8*, 142–143. However, no yields or spectroscopic characterization were provided in this study.
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8. Azido analog of $[M+H]^+$ 353 (e.g., **9**). Expected $[M+H]^+$ 394.1879. Observed $[M+H]^+$ after co-culture with: *no substrate* not observed; **7a** 394.1886; **7b** 394.1884; **7c** 394.1873; **7d** 394.1893.
9. Azido analog of $[M]^+$ 349 (e.g., **10**). Expected $[M]^+$ 390.1566. Observed $[M+H]^+$ after co-culture with: *no substrate* not observed; **7a** not observed; **7b** not observed; **7c** 390.1581; **7d** 390.1581.
10. Azido analog of $[M+H]^+$ 337 (e.g. **11**). Expected $[M+H]^+$ 378.1930. Observed $[M+H]^+$ after co-culture with: *no substrate* not observed; **7a** not observed; **7b** not observed; **7c** 378.1933; **7d** 378.1943.
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