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A Versatile Linkage Strategy for Solid-Phase Synthesis of *N*,*N*-Dimethyltryptamines and β-Carbolines

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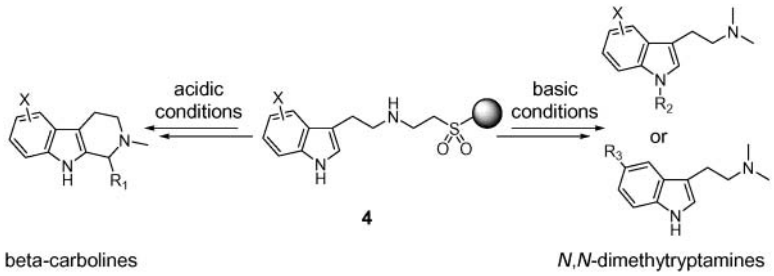
ABSTRACT



Various tryptamines are captured by a vinylsulfonylmethyl polystyrene resin, generating a safety-catch linkage. β-Carbolines can be formed from 4 by a Pictet–Spengler reaction with the introduction of R_1. Tryptamine 4 can also be derivatized by acylation or copper-mediated coupling to introduce R_2. If X = Br, Suzuki coupling can be used to introduce R_3. After derivatization, the indole derivatives are activated with methyl iodide and released under mild basic condition.

The tryptamine and β-carboline scaffolds are present in many naturally and synthetically derived molecules with interesting biological activities.[1] Consequently, many solid-phase synthetic approaches have been developed to generate small molecules containing these core structures.[2−4] However, these approaches still have limitations with regards to functionalization of the indole scaffolds. For example, current solid-phase methodologies for synthesizing β-carbolines derivatives use linkers that leave a polar functional group (e.g., COOH, $CONH_2$) after cleavage; the solid-phase synthesis of tryptamine analogues involves attaching the molecule onto resin either through a linkage at the indole nitrogen or an ester/amide linkage on the benzo ring. Herein we report a novel and versatile safety-catch linkage strategy that can be used to generate libraries of functionalized *N*,*N*-dimethyltryptamines and β-carbolines in a simple and straightforward manner.

Our approach starts with the synthesis of different tryptamine scaffolds (Scheme 1) in three facile steps using previously reported protocols.[5] Commercially available indoles **1** were reacted with oxalyl chloride in refluxing ether. The resulting indole oxalyl chlorides were filtered and treated

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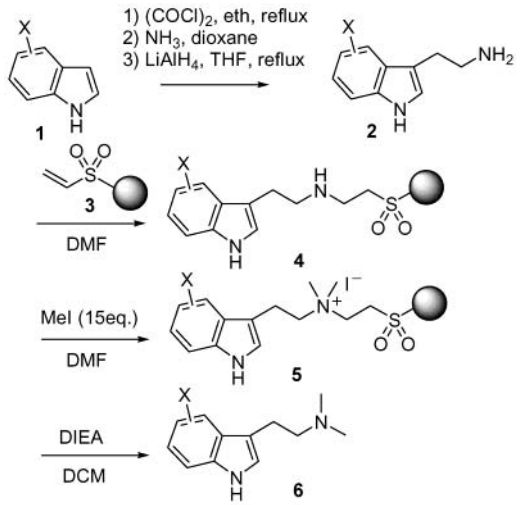
Scheme 1



with ammonia in dioxane to give the corresponding indole oxalyl amides. These were again filtered and reduced to the corresponding tryptamines **2** using lithium aluminum hydride in refluxing THF. After aqueous workup, the crude tryptamines were directly mixed with vinylsulfonylmethyl polystyrene resin **3** (Novabiochem).[6] This also served as a purification step, as only the fully reduced tryptamines were captured onto the resin, affording **4**. Activation of the safety catch linker can be achieved by treatment with excess methyl iodide to form the quaternary ammonium salt **5**, though other alkylating agents have been used in the past.[6] A Hoffman elimination using *N*,*N*-diisopropylethylamine releases tryptamine **6** from the resin. The yield of the cleaved products ranged from 10% to 20% overall, based on the resin-loading level of **4**. A variety of commercially available indoles with either electron-donating or electron-withdrawing functional groups on the benzo ring as well as alkyl and aryl groups at the C-2 position are compatible with this scheme (Figure 1). Purity of the resin-bound indoles is determined by cleaving a small amount of resin and subjecting the product to LCMS.

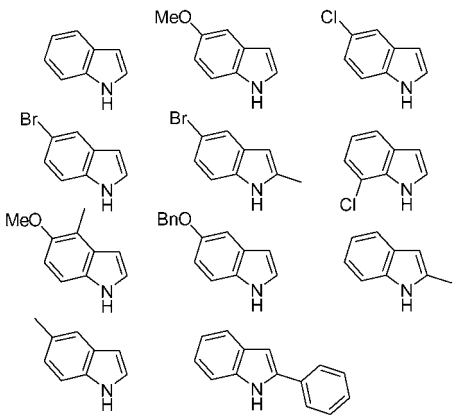
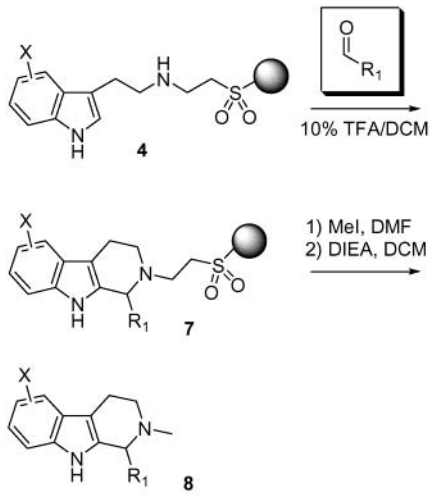


Figure 1. Indoles used as precursors for the tryptamine scaffolds.

All scaffolds in Figure 1 were tested to give >90% purity as analogues of tryptamine **6**.

The safety-catch linkage described here is stable to acidic conditions. Treatment of **4** with aldehydes in 1−10% trifluoroacetic acid (TFA) in dichloromethane (DCM) at room temperature for 12 h affords the β-carboline scaffold **7** through a Pictet−Spengler reaction[7] without premature cleavage of the molecule from the solid support (Scheme 2). Activation of the resin followed by Hoffman elimination

Scheme 2



yielded β-carboline **8**. Indoles with electron-rich substituents (e.g., alkoxy groups) tend to react with 1% TFA/DCM; other indoles with relatively electron-neutral substituents (e.g., alkyl, aryl) or electron-poor substituents (e.g., halides) require 5−10% TFA/DCM. Several alkyl and aryl aldehydes were validated to give products with purity over 80% and 10−20% purified yield when tested with unsubstituted tryptamine derivatized resin **4** (Figure 2).

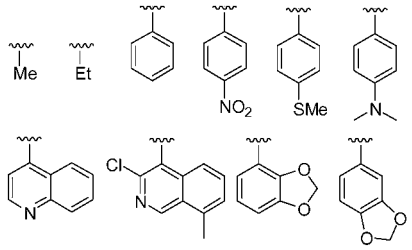
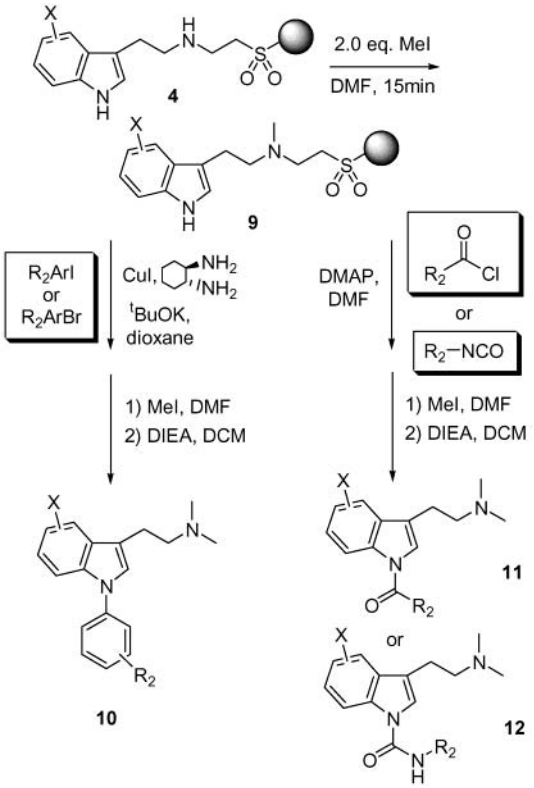


Figure 2. R_1 introduced through aldehydes.

Resin-bound tryptamine **4** can be monomethylated by treatment with 2.0 equiv of methyl iodide in DMF for 15 min at room temperature. The resulting product (**9**) was derivatized at the indole nitrogen by two different methods (Scheme 3). A copper-mediated coupling with aryl bromides

Scheme 3



or aryl iodides (depending on commercial availability) introduced an R_2 aryl substituent.[8] The reaction involved heating the resin and the aryl bromide/iodide in the presence of copper(I) iodide, *trans*-1,2-diaminocyclohexane, and potassium *tert*-butoxide in anhydrous dioxane at 80 °C for 1 day. Alternatively, the indole nitrogen can be acylated with acid chlorides and isocyanates using 10 equiv of *N*,*N*-(dimethylamino)pyridine as the base in DMF at 80 °C for 12 h. Both the *N*-aryl bond and the *N*-acyl bond are stable in subsequent activation and cleavage steps. Both reactions are compatible with a variety of building blocks, generating products with over 80% purity and 10−20% purified yield when tested with unsubstituted tryptamine resin **9** (Figure 3).

When X is a bromine, resin-bound monomethylated tryptamine **9** can undergo derivatization through Suzuki coupling using tris(dibenzylideneacetone) dipalladium(0) as the catalyst and 2-(dicyclohexylphosphino)biphenyl as the ligand (Scheme 4).[9] The resin, boronic acid, catalyst, and ligand were reacted in anhydrous dioxane in the presence of dry K_3PO_4 at 80 °C for 1 day. Eight boronic acids were tested for this reaction, and all of them afforded the expected products with purity over 80% and yielded between 10% and 20% after purification when tested with 5-bromotryptamine derivatized resin **9**.

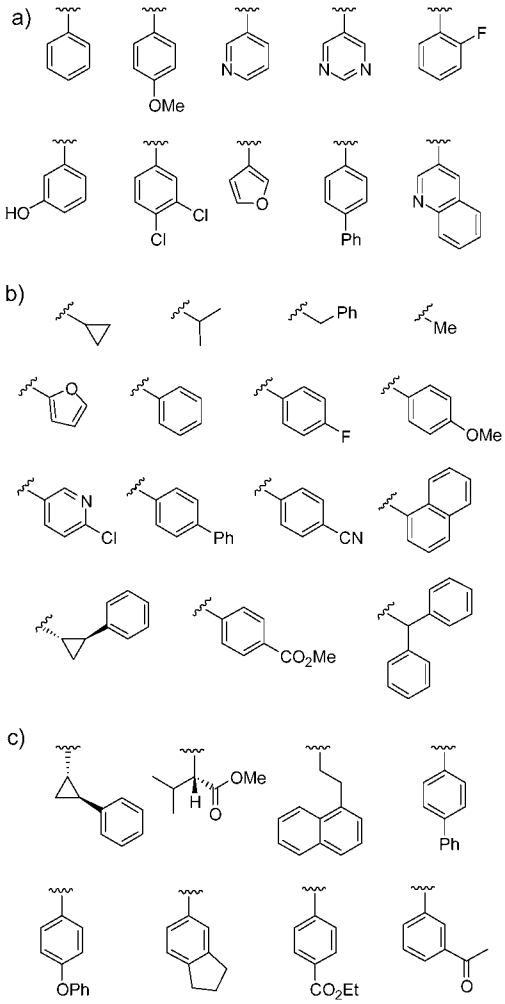
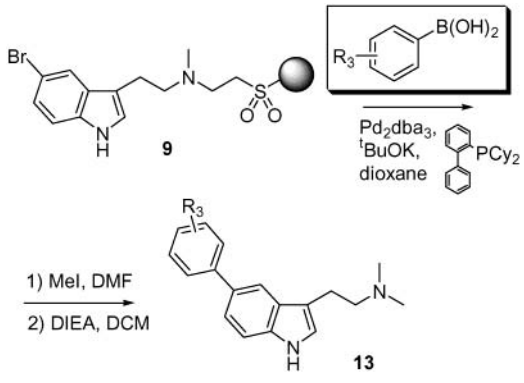


Figure 3. (a) R_2Ar introduced through aryl bromides and aryl iodides. (b) Representative R_2 introduced through acid chlorides. (c) Representative R_2 introduced through isocyanates.

Scheme 4



In conclusion, we have described a novel linkage strategy for making *N*,*N*-dimethyltrypatmines and β-carbolines. The

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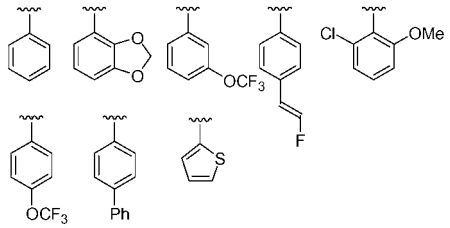

Figure 4. R_3 introduced through boronic acids.

linkage utilizes a safety-catch vinylsulfonylmethyl resin that is stable under acidic, basic, and heating conditions. Several solid-phase organic transformations were used to derivatize the indole scaffold. Further work involving library synthesis and biological testing is in progress.

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Supporting Information Available: LCMS and ^{1}H NMR of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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