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Syntheses of 4-, 5-, 6- and 7-Substituted Tryptamine Derivatives and the Use of a Bromine Atom as a Protecting Group

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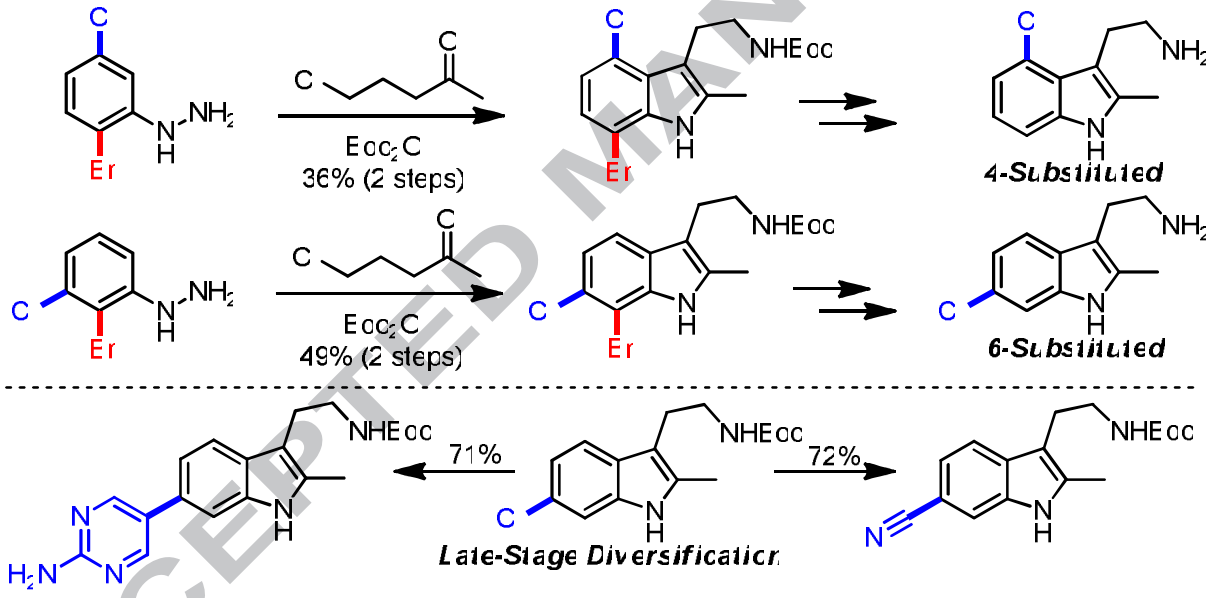
Graphical Abstract.



Abstract. Orthogonal syntheses of 4-, 5-, 6- and 7-chloro substituted tryptamine derivatives were performed under the Grandberg-Zuyanova-modified Fisher indole-synthesis conditions. In the 4- and 6-substituted tryptamine cases, a bromine atom was utilized as an easily cleavable protecting group, which allowed complete regiocontrol. In addition, a chlorine substituent was preserved in the

debromination step and could be utilized as a synthetic handle for late-stage diversification under modern Pd(0) catalysis conditions.

keywords: tryptamine; Fisher indole synthesis; bromine; protecting group; late-stage functionalization

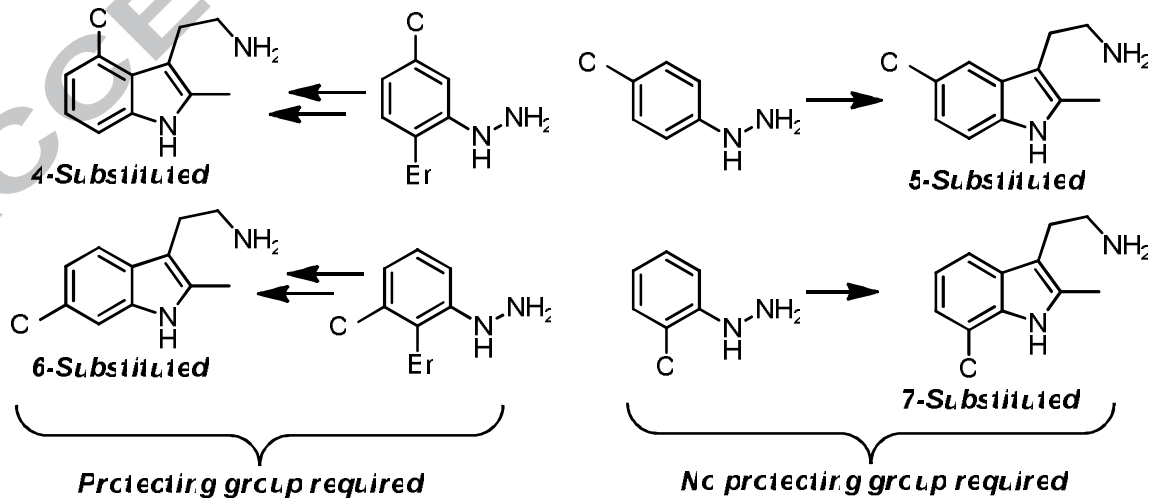
Tryptamines are of pharmaceutical significance due to their presence in multiple biologically-active natural products as well as several marketed drugs.[1] In addition, 4,6-dichloro-2-methyl-3-aminoethylindole (DCAI), a dichlorinated tryptamine derivative, was recently identified through an NMR-based fragment screen as a small-molecule ligand binding to a distinct pocket in oncogenic K-ras (G12D) and inhibited SOS-mediated nucleotide exchange activity.[2] Further exploration of the tryptamine scaffold and synthesis of a diversified variety of 4-, 5-, 6- and 7-substituted analogs is therefore of interest.

Following the initial report of the tryptamine synthesis by Ewins,[3] other classical syntheses include the Abramovitch-Shapiro tryptamine synthesis,[4] and tryptophan decarboxylation.[5] More generally, tryptamine derivatives may be synthesized from a pre-formed indole scaffold, followed by C-3 functionalization under electrophilic aromatic substitution conditions using oxalyl chloride,[6] nitroethylene[7] or *N*-acetylaminoacetaldehyde dimethyl acetal[8] as electrophiles. Alternatively, the Grandberg-Zuyanova modification of the Fisher indole synthesis[9] is an efficient one-step process wherein the indole ring and the C-3 aminoethyl substituent are installed in a single step. However, the above-mentioned tryptamine synthesis reports do not describe concise and orthogonal syntheses of 4-, 5-, 6- and 7-substituted tryptamine derivatives that would allow for late-stage diversification at all four isomeric benzo- positions. Furthermore, substitution at the 4- and 6-positions cannot be installed on an

arylhydrazine precursor prior to a Fisher indolization[10] due to the limited regioselectivity typically observed at the cyclization step.[11]

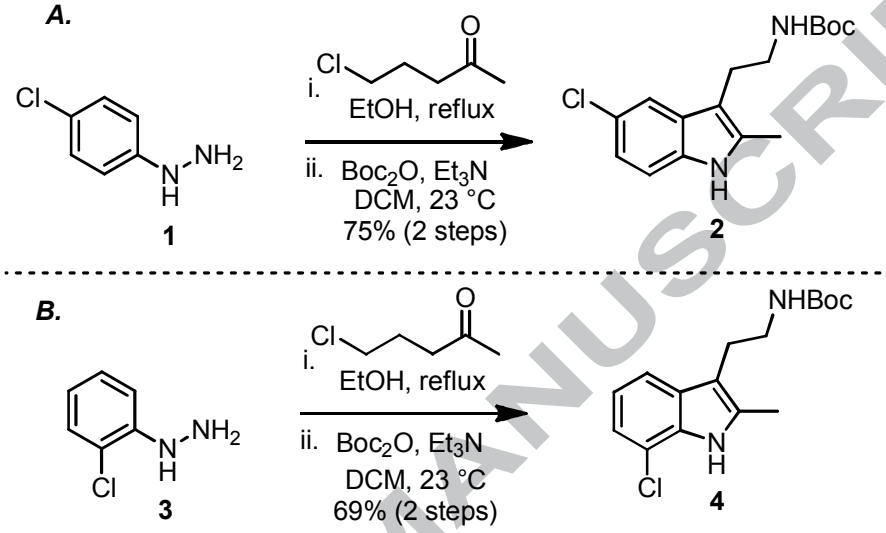
Consequently, we decided to harness the intrinsic lability of the carbon-bromine bond under reductive conditions[12] and utilize it as a protecting group[13] in the Grandberg-Zuyanova modification of the Fisher indole synthesis. Positioned appropriately, a bromine atom would enable the indolization step to occur with the desired regiochemistry, followed by a debromination step, giving access to 4- and 6-substituted tryptamines as single isomers with complete regiocontrol. Additionally, due to its lower reactivity, a chloro substituent could be used in addition to the bromine as a synthetic handle for further diversification of the tryptamine scaffold upon removal of the bromine. 5- And 7-substituted tryptamine derivatives would not require such a protecting group, as in each case, cyclization could only afford a single product (Scheme 1).

Scheme 1. The traditional syntheses of 4- and 6-chloro-2-methyl-3-aminoethylindole syntheses via Fisher indolization are poorly regioselective. Using bromine as a protecting group to block reactivity on the aromatic ring, followed by debromination, can overcome this limitation.



Hence, for the cases in which no protecting group was required, 5-Chlorotryptamine derivative **2** was synthesized from commercially available (4-chlorophenyl)hydrazine **1** and 5-chloropentan-2-one under refluxing ethanol conditions. A one-pot *t*-butylcarbamate formation on the aminoethyl chain was subsequently performed in order to facilitate the purification and further functionalization, and gave product **2** in 75% yield over 2 steps (Scheme 2A). Similarly, the 7-chloro substituted analog **4** was obtained from commercially available (2-chlorophenyl)hydrazine **3**, followed by a Boc-group installation on the primary amine substituent, and afforded tryptamine derivative **4** in 69% yield over 2 steps (Scheme 2B).

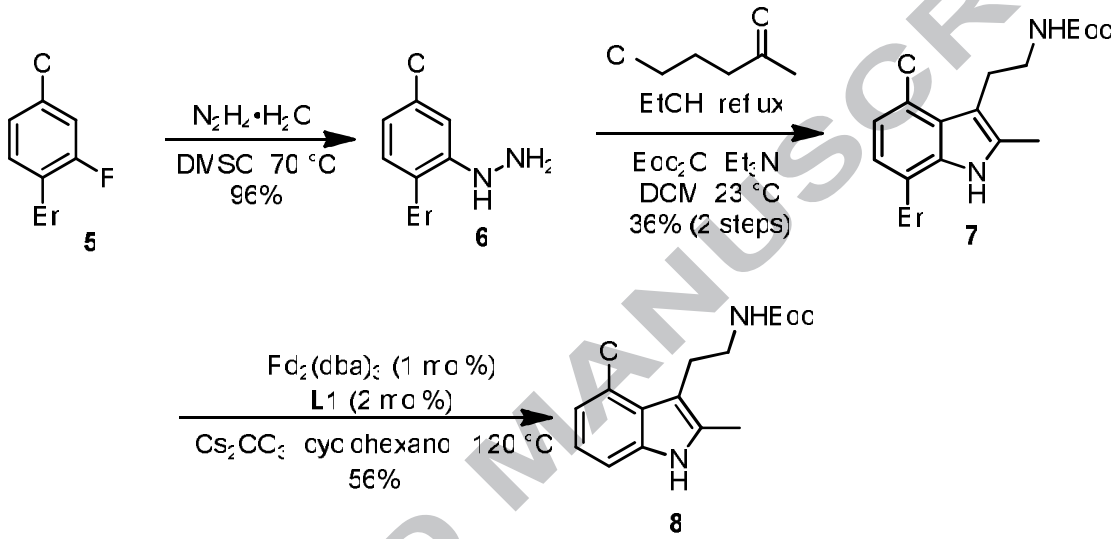
Scheme 2. Syntheses of Boc-Protected 5-chloro-2-methyl-3-aminoethylindole **2** (A) and 7-chloro-2-methyl-3-aminoethylindole **4** (B).



As discussed previously, the syntheses of 4-chloro-2-methyl-3-aminoethylindole **8** and 6-chloro-2-methyl-3-aminoethylindole **12** required the use of the bromine atom as a protecting group to ensure proper regiochemistry at the cyclization step (Scheme 3). Hence, the synthesis of **8** began with 1-bromo-4-chloro-2-fluorobenzene **5**, which underwent a nucleophilic aromatic substitution of the fluorine atom with hydrazine monohydrate, and gave arylhydrazine intermediate **6** in excellent yield. Cyclization of the arylhydrazine intermediate under the typical indole cyclization conditions with 5-chloropentan-2-one, followed by *tert*-butylcarbamate formation on the aminoethyl substituent, gave the desired 7-bromo-4-chlorotryptamine derivative **7** in 36% yield over 2 steps. An effective de-bromination protocol in the presence of a chloride had been reported, using tris(2,4-di-*t*-butylphenyl)phosphite **L1** as the ligand.[14] Subjection of intermediate **7** to these catalytic reductive conditions successfully provided the 4-

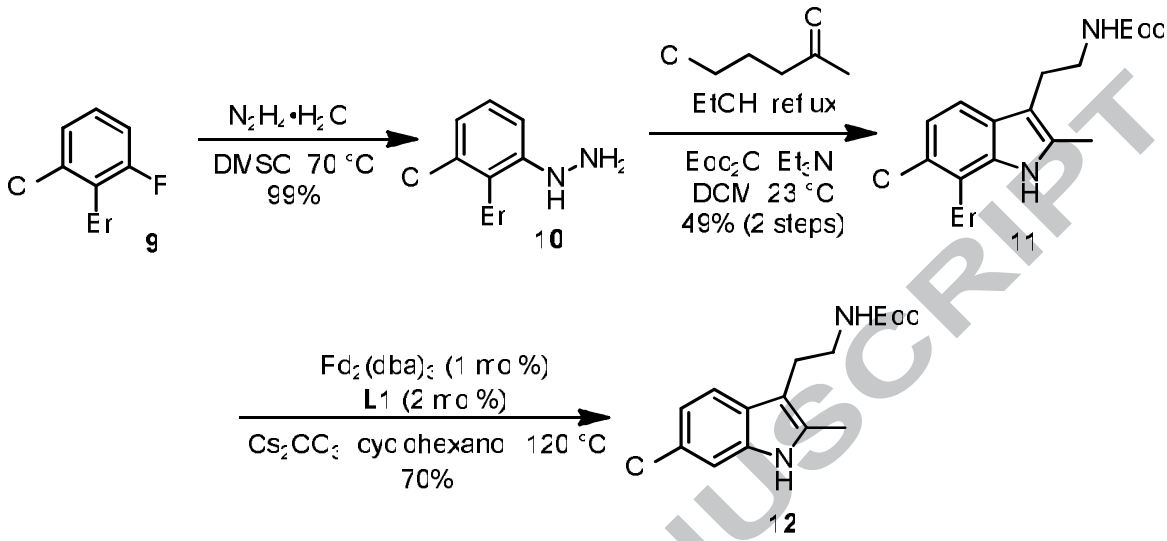
chlorotryptamine product **8** in 56% yield. Of note, standard catalytic hydrogenation conditions were also attempted to remove the bromine selectively, but led to unsatisfactory conversions or poor selectivity.[15]

Scheme 3. Synthesis of Boc-protecting 4-chloro-2-methyl-3-aminoethylindole **8**.



Analogously, the synthesis of 6-chloro-2-methyl-3-aminoethylindole **12** also necessitated the use of the bromine atom as a protecting group (Scheme 4). (2-Bromo-3-chlorophenyl)hydrazine **10** was first obtained from 2-bromo-1-chloro-3-fluorobenzene **9** under nucleophilic aromatic substitution conditions with hydrazine monohydrate in 99% yield. In the next step, the hydrazine intermediate **10** underwent Fisher-indole cyclization, followed by aminoethyl Boc-protection, to afford the desired 7-bromo-6-chloro intermediate **11** in 49% yield over 2 steps. Finally, treatment of compound **11** with cyclohexanol under established Pd(0)-catalysis de-bromination conditions led to the desired 6-chlorotryptamine derivative **12** in 70% yield.

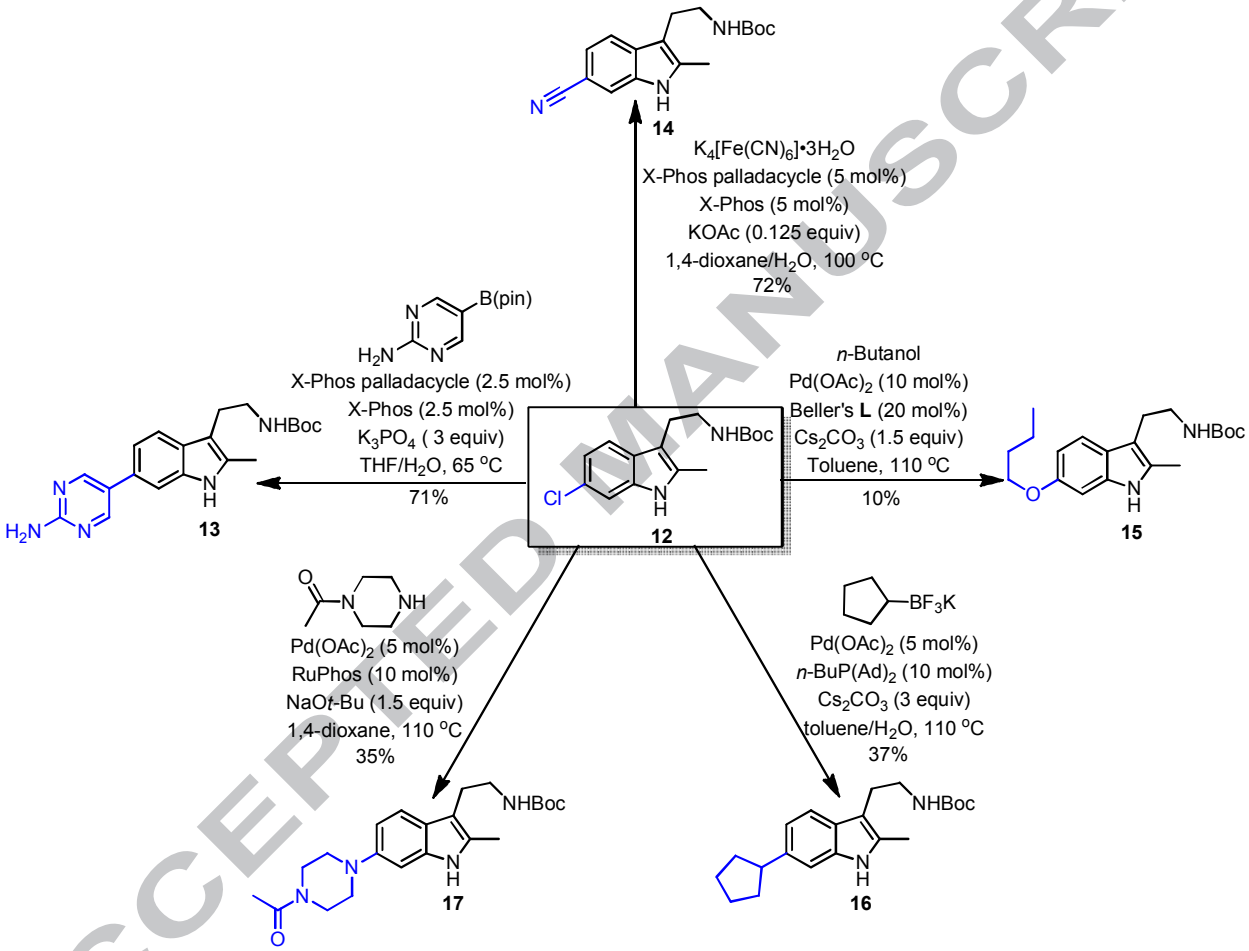
Scheme 4. Synthesis of Boc-protected 6-chloro-2-methyl-3-aminoethylindole **12**.



Having completed the orthogonal syntheses of Boc-protected 4-, 5-, 6- and 7-chloro-2-methyl-3-aminoethylindole (compounds **8**, **2**, **12** and **4**, respectively), we had set the stage for a divergent derivatization to transform the chlorine atom to other functional groups.[16] Under Pd(0)-catalyzed conditions,[17] the chloride successfully underwent arylation, cyanation, etherification, alkylation and amination reactions (Scheme 5). For example, aminopyrimidine **13** was uneventfully obtained *via* a Suzuki-Miyaura coupling[18] in 71% yield. The reaction proceeded smoothly and efficiently in the presence of four unprotected hydrogen-bond donors and two heterocyclic rings. Also, the carbon-chlorine bond could undergo a facile cyanation with potassium ferrocyanide trihydrate[19] under Pd(0) catalysis conditions to afford 4-cyanotryptamine compound **14** in 72% yield. Additionally, we demonstrated the possibility of performing etherification chemistry[20] with *n*-butanol, giving rise to ether product **15**, albeit in low yield (10% yield) under un-optimized conditions.[21] Moreover, the use of potassium cyclopentyltetrafluoroborate[22] under Pd(0) catalysis successfully gave cyclopentyl-tryptamine product

16 in a synthetically useful yield of 37%. Finally, a Buchwald-Hartwig coupling[23] was also performed with *N*-acetylpiperazine and afforded the desired amine product **17** in 35% yield.

Scheme 5. Late-stage diversification of 6-chloro-2-methyl-3-aminoethylindole



In conclusion, we have shown that a bromine atom can be used as an easily cleavable protecting group in the presence of a chlorine substituent, allowing for the orthogonal syntheses of 4-, 5-, 6- and 7-chloro substituted tryptamine derivatives under the Grandberg-Zuyanova-modified Fisher indole-

synthesis conditions. In addition, the chlorine atom can be utilized as a versatile synthetic handle for late-stage diversification under Pd(0) catalysis conditions.

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