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Conformationally Constrained Serotonin Analogues: Stereoselective Synthesis of *trans* -3-(2-aminocycloalkyl)Indoles by Aziridine Ring Opening

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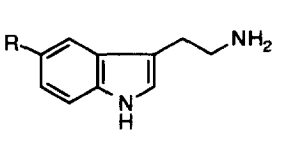
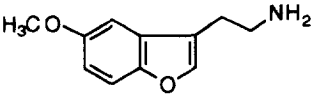
Abstract: *Trans*-3-(2-aminocyclopentyl)indoles **9a,c** and *trans*-3-(2-aminocyclohexyl)indoles **9b,d** have been stereoselectively prepared by nucleophilic ring opening reaction of *N*-Boc cycloalkylaziridines **6a,b** and the "lower order" magnesium cuprate **II**, generated from the corresponding indolilmagnesium bromides derived from **7a,b**.

The tryptamine nucleus is prevalent in many natural occurring products.[1] Serotonin (**1**, 5-HT) (Figure 1) is one of the most interesting due to its many physiological functions. The molecular manipulation of the serotonin aromatic ring has enabled the development of selective serotoninergic drugs such as *Sumatriptan* **2**[2] or benzofuran bioisosteres of tryptamines like **3**[3] among many others.[4] The synthesis of restricted analogues of the tryptamines[5] has provided a useful insight into the ligand recognition requirements for the receptor subtypes.



1 R= OH
2 R= $CH_2SO_2NH_2$



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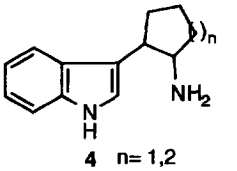


4 n= 1,2

Figure 1

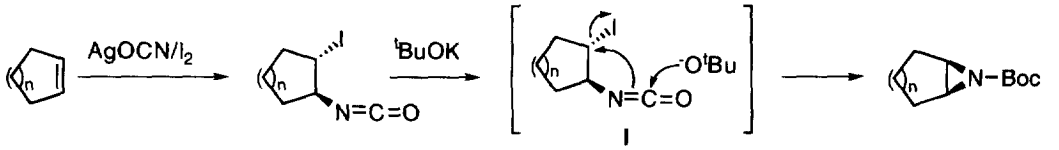
The synthesis of tryptamines **4** (n=1,2)[6] has been accomplished by the reaction of indolylmagnesium bromide with the corresponding cycloalkene epoxide to yield the 3-(2-hydroxycycloalkyl)indole. Subsequent oxidation of the alcohol to the ketone and then reductive amination, using the Danheiser conditions,[7] gave the *trans* isomers of **4** (n=2) as the major product in the reaction mixture (8:1 ratio). On the other hand, the

conversion of the ketone to the enamine under $TiCl_4$ catalysis, followed by reduction with $NaCNBH_3$ yielded the *cis* tryptamine.[6b]

Aziridines are very useful synthetic intermediates[8] and react with nucleophiles to form 2-substituted ethylamines. Aziridines require activation by an electronwithdrawing protecting group on the ring nitrogen atom. The most used protecting group has been the *p*-toluenesulphonyl[9] (Ts) and others, like diphenylphosphinyl[10] (Dpp), which avoides the problems associated with the cleavage of the sulphonamide bond.[11] Less attention has been paid to *N*-urethane aziridinines[12] due to the problems associated with their preparation[13] and lack of reactivity with hard nucleophiles.[9a]

In this communication we would like to report a new stereoselective syntheis of 3-(2-aminocycloalkyl)indoles by means of nucleophilic *N*-Boc aziridine ring opening.

The activated aziridines **6a,b** (Scheme 1) were prepared by addition of iodine isocyanate to either cyclopentene or cyclohexene. Subsequent treatment with potassium *tert*-butoxide in DMF of the corresponding *trans* 2-iodo-1-isocyanates **5a** (95% yield) and **5b** (90% yield) gave rise to the *N*-Boc aziridines **6a** (75% yield) and **6b** (85% yield).



5a n=1
5b n=2

6a n=1
6b n=2

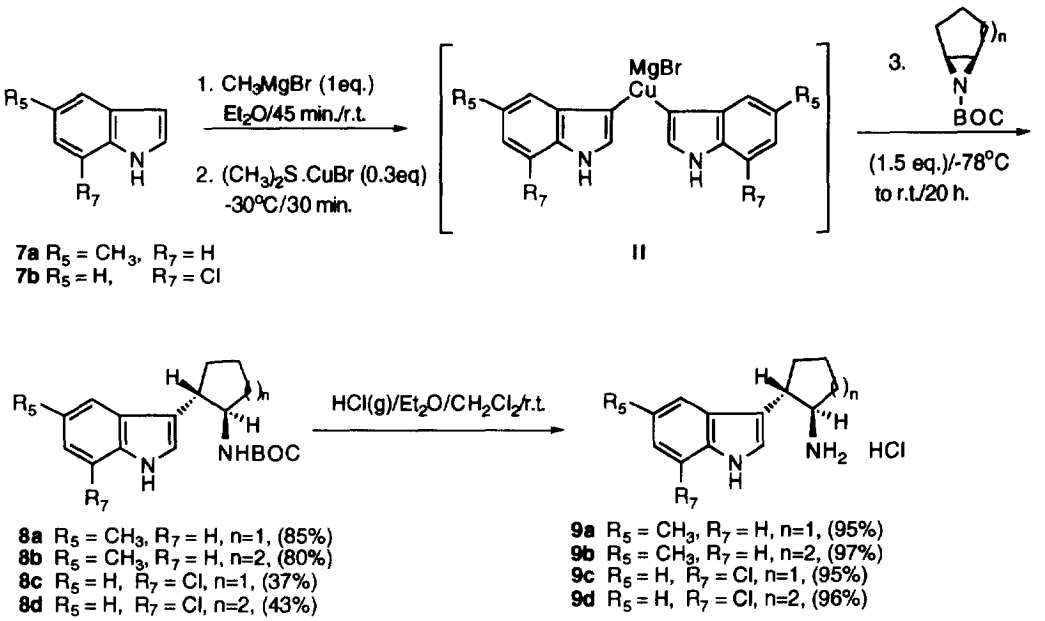
Scheme 1

This procedure represents a modification of the previously reported one by Hassner[14] where **5b** was treated first with an alcohol, yielding the *trans* 2-iodo-1-carbamate which was further transformed into the *N*-urethane aziridine when treated with base (NaH).

The exemplification of this nucleophilic ring opening reaction (Scheme 2) has been carried out using commercially available 5-methylindole (**7a**) and 7-chloroindole (**7b**), prepared using Bartoli's methodology.[15]

Indolylmagnesium bromides derived from **7a** and **7b** were prepared from the corresponding indoles and CH_3MgBr following literature procedures.[6c] Addition of 0.3 equivalents of $(CH_3)_2S{\bullet}CuBr$ resulted in the formation of a "lower order" magnesium cuprate[16] **II** which upon reaction with the *N*-Boc aziridines **6a,b** gave the *trans* cycloalkylamines **8a-d**. Yields are dependent on the substituent present in the reacting indole. Thus, electron donating substituents gave better yields [**8a** (85%); **8b** (80%)] while indoles having electron withdrawing substituents gave lower yields in this nucleophilic ring opening reaction [**8c** (37%); **8d** (43%)]. This reactivity has been observed previously by Kozikowski[12a] in the synthesis of tryptophanes from aziridine-2-carboxylates and various substituted indoles in the presence of zinc triflate as Lewis acid.

Finally, the *N*-Boc protected cycloalkylamines **8a-d** were deprotected to give the amines hydrochlorides **9a-d** with HCl (g) in a 1:1 mixture of CH_2Cl_2/Et_2O in almost quantitative yields.



Scheme 2

The *trans* stereochemistry of compounds **9** was ascertain by ^{1}H NMR (Figure 2) by measuring the diaxial coupling constant[17] (J H_{1ax},H_{2ax} = 11 Hz) for **9b** and by nOe experiments on the *cis* isomer **10**[18] which displayed an 7% enhancement of H_1 when H_2 was irradiated. When the same experiment was performed on the parent compound **9b** no substantial nOe was observed.

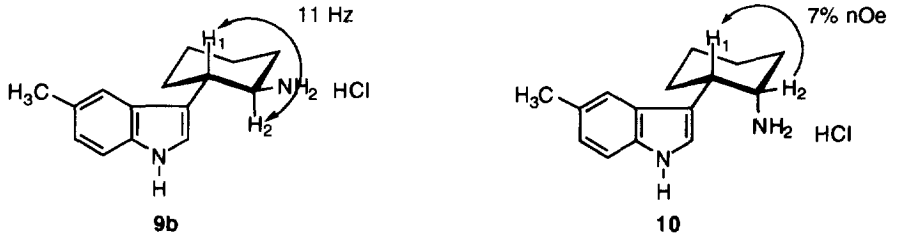


Figure 2

In conclusion, the presented method represents a novel approach to obtain conformationally constrained tryptamines in a stereoselective fashion by the nucleophilic ring opening of non-polarised *N*-urethane activated aziridines.[19] The easy removal of the aziridine activating group (Boc) makes this procedure superior to the more classical *N*-sulfonyl aziridines, where the final cleavage of the sulphonamide bond is sometimes difficult. Further applications of this methodology to other non-cyclic derived aziridines is in progress in these laboratories and will be reported in due course.

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18. This compound was prepared by reductive amination as described in *ref.* 5a
19. Satisfactory spectroscopic data (^1H NMR, ^{13}C NMR, IR and HRMS) have been obtained for all compounds reported in this communication.

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