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Polycyclic indoline derivatives by dearomatizing anionic cyclization of indole and tryptamine-derived ureas

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Supporting Information Placeholder

ABSTRACT: The base-promoted dearomatizing cyclization of anionic indole-containing urea derivatives provided tri- or tetracyclic indoline-containing scaffolds from lithiated urea intermediates. 3-Substituted indoles, including tryptamine derivatives, generally underwent the reaction in high yield and with excellent diastereoselectivity. In-situ IR spectroscopy suggests a deprotonation-carbolithiation-reprotonation mechanism.

The amino acid tryptophan provides the starting material for the biosynthesis of a broad array of indole-derived secondary metabolites, many of them with valuable biological activity.¹ Not all contain the aromatic indole structure: a significant proportion of indole-derived alkaloids retain the indole connectivity, but are saturated in the five membered ring.² Synthetic approaches to these indoline-containing products commonly entail dearomatization of an indole precursor by electrophilic attack at the C-3 position, followed by nucleophilic addition into C-2 of the resulting iminium intermediate. Dearomatization is a powerful strategy for the synthesis of partially saturated heterocycles,³ and recent work building upon this reactivity showed that the combination of a strong Lewis acid and a proton source could generate the iminium intermediate without C3-functionalization, resulting in dearomatizing C2-functionalization upon addition of an aryl nucleophile.⁴

By contrast, dearomatization reactions initiated by nucleophilic attack on the electron-rich indole ring are virtually unknown.^{3a} Both Studer⁵ and ourselves⁶ have shown that attack on the C-2 position by a silyllithium or organolithium reagent results in ring opening to give products that no longer contain the indoline scaffold (Scheme 1). Indoles, pyrroles,⁶ thiophenes and benzothiophenes⁷ undergo comparable reactions, but for indoles the structural requirements for successful reactions are rather stringent: the bulky DEB protecting group was essential, for example. Likewise, Studer's silylation is limited to *N*-aryl indoles, and carbolithiation was unsuccessful with *n*-BuLi or *t*-BuLi. A general method for the nucleophilic dearomatization of *N*-protected indoles to provide polycyclic indoline-containing alkaloid-like structures is still lacking.

Recent work has shown that the carbonyl-directed lithiation of heterocyclic ureas provides fertile ground for the generation of new reactivity.⁸ As part of this work, we explored the metallation of indole-derived *N*-benzyl ureas. Treating *N*-benzyl-*N*-methyl-1*H*-indole-1-carboxamide **1a** with 2 equiv of LDA in THF at -78°C led to rapid decomposition to indole and other unidentified side-products. However, in the presence of 5 equiv of the lithium-coordinating co-solvent DMPU, full conversion was attained after 2 hours and the tricyclic indoline **2a** was obtained in 20% yield as a single diastereomer (Scheme 2). A similar reaction with the 6-methoxy indole **1b** provided a yield of 39% **2b**. Substitution of the 3-position of the indole starting material had an even more beneficial effect on the reaction. 3-Methylindole derivative **1c** reacted cleanly under the same conditions to give **2c** as a single diastereomer in 66% yield. Repeating the reaction on a 1 g scale further increased this yield to 79%, and treatment of the product with LiAlH_4 transformed it to the imidazolidine **3c**, indicating possible applications of this dearomatizing cyclization to the synthesis of polycyclic amines with alkaloid-like structures.

The success of these cyclizations suggested that the increased basicity of the organolithium intermediate **2Li** presumably generated by anionic cyclization may promote a cleaner reaction by favoring proton transfer from *i*-Pr₂NH (see mechanistic discussion below). We thus proceeded to develop further reactions of 3-substituted indoles.

Scheme 1. Nucleophilic dearomatization of indoles.

Scheme 2. Dearomatizing cyclization of indoles: initial results.

Footnotes: ^aYield on 1 g scale

A further range of starting materials **1d-j** were made from their parent indoles by a Vilsmeier-Haack reaction followed by reduction with LiAlH₄ and N-acylation⁹ (see Supporting Information). These new starting materials were subjected to the conditions (LDA, DMPU) used for **1a-c** (Scheme 3). 5-Fluoro and 5-chloro-substituted indoles cyclized successfully to give products **2d** and **2e**.¹⁰ Similarly, substrates with methyl or methoxy groups at the 5 or 6 positions gave the dearomatized products in good yields (**2g-j**). In contrast, substitution at the 7-position was detrimental to the reaction, and the product **2f** (from 3,7-dimethylindole) was obtained in only 18% yield. All the products were obtained as essen-

tially single diastereomers¹¹ with the X-ray crystal structure of **2g**,¹² supported by NOESY of **2c**, confirming relative stereochemistry in which the phenyl and methyl substituents occupy the *exo* face of the 5,5-fused bicyclic system.

Scheme 3. Cyclizations of 3-methylindole derivatives.^a

Footnotes: ^a > 20:1 dr unless otherwise stated. ^b 10:1 dr. ^c Minor diastereoisomer has the opposite configuration at the two centers of the indoline ring.

A reaction performed on the related substrate **4** bearing an enantiomer-enriched α -methylbenzyl substituent (98:2 er) also led to cyclization of the intermediate organolithium to a product **5** in 59% yield as a separable 4:1 mixture of diastereomers. The major diastereoisomer was formed without erosion of enantiomeric ratio, and presumably with retention of configuration,¹³ indicating that the cyclization is faster than the racemization of the intermediate organolithium under the conditions of the reaction.^{8f}

Alternative substituents at the 3-position were tolerated well (Scheme 4). The 3-benzyl-substituted indole **1k** gave a good yield of **2k** as a single diastereoisomer. The particular success of these

dearomatizing cyclizations of 3-alkylindoles suggested that tryptophan-derived ureas might also be suitable substrates, allowing the formation of alternatively connected tricyclic products.¹⁴ Pleasingly, tryptamine derivatives **1l** and **1m** reacted cleanly to give the products **2l** and **2m** with dibenzyl and 2,6-dimethylpyrrole protecting groups.

Scheme 4. Cyclizations of other 3-substituted indoles.

Similar cyclizations of **1n** and **1o** bearing electron-withdrawing groups at the 3-position also gave the products **2n** and **2o** in good yield. However, these reactions were much less diastereoselective, perhaps because the delocalized, planar product anion is protonated less diastereoselectively (see Scheme 6).

A final set of starting materials was made in which the 2-position of the indole was substituted. The first of these, the 2-methylindole derivative **6a**, cyclized in good yield under the standard conditions, although a mixture of diastereoisomers was obtained (Scheme 5; X-ray crystallography revealed the relative stereochemistry of the major diastereoisomer).^{12,15} The fact that cyclization onto a substituted position was successful made possible the synthesis of a series of more elaborate tetracyclic products from ring-fused starting materials. Thus, tetrahydrocarbazole **6b** gave the tetracycle **7b** in 46% yield with a 3:1 diastereomeric ratio, while its 5-ring congener **6c** gave *cis*-**7c** in moderate yield with small amounts of the other diastereoisomer. The stereochemistry of the major isomers of **7b** and **7c** was confirmed by NOESY NMR analysis.

Scheme 5. 2-Substituted and tricyclic indole derivatives.

Some details of the mechanism of the cyclization of **1c** were revealed by in-situ infrared spectroscopy (Scheme 6).¹⁶ To eliminate the obscuring effect of its urea carbonyl absorption, we performed the reaction in absence of DMPU. A solution of **1c** in THF showed a strong carbonyl absorption at 1682 cm^{-1} . Upon addition of 2 equiv LDA at $-78\text{ }^{\circ}\text{C}$, this absorption was rapidly replaced by another carbonyl absorption at 1633 cm^{-1} corresponding to a transient species that we assume to be the lithiated starting material **1cLi**, possibly in a more complex solvated/aggregated state.^{16b} Over a period of a few minutes this transient signal was replaced by three new absorptions at 1596, 1715 and 1720 cm^{-1} whose relative intensities changed over the remaining 70 min of the reaction, with the 1596 cm^{-1} signal decreasing while the other two increased. Quenching with aqueous ammonium chloride led to the disappearance of signals at 1596 and 1715 cm^{-1} and simultaneously intensified the signal at 1720 cm^{-1} . This signal was assigned to the product **2c** by comparison with the spectrum of the authentic sample, obtained in 52% yield after work-up and purification. We tentatively assign the structures **2cLi** and **2cLi'** to the absorptions at 1715 and 1596 cm^{-1} , respectively.^{8b} These results point toward a mechanism that entails rapid benzylic lithiation followed by *syn*-carbolithiation of the indole ring. Slower equilibration then occurs by proton transfer between the diisopropylamine generated in the deprotonation step and the two alternative weakly acidic sites of the product.¹⁷ Control over this equilibrium may be the reason why 3-substituents enhance the dearomatization reaction.

In summary, this intramolecular hydroalkylation reaction of lithiated indole-containing urea derivatives leads to heterocyclic indoline-containing polycyclic ring systems in a rare nucleophilic indole dearomatization reaction. The reactions proceed with high yields and excellent selectivity for 3-alkylated indole substrates, while other substitution patterns led to less predictable yields and selectivities. Substrates derived from tryptamine, as well as other bio-relevant structures such as tricyclic indoles **6**, underwent the reaction. The reaction proved to be diastereoselective and (with enan-

tioenriched α -chiral organolithiums) enantiospecific, and the method has potential for the modular synthesis of modified indole alkaloid derivatives.

Scheme 6. *In-situ* IR investigation and postulated mechanism.^a

Footnote: ^aSolvation or aggregation of the organolithium species is not shown but may be assumed.

Supporting Information

Full experimental data and NMR spectra of all new compounds.

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17. Deuterolysis of the reaction mixture did not give deuterated products, maybe because of rapid H/D exchange with *i*-Pr₂NH.