Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

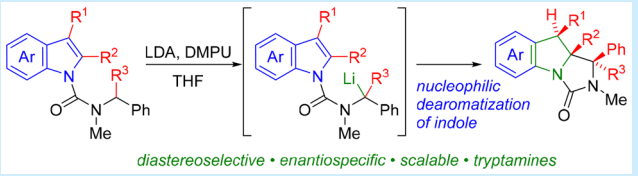
Polycyclic Indoline Derivatives by Dearomatizing Anionic Cyclization of Indole and Tryptamine-Derived Ureas

Jessica E. Hill,[‡] Quentin Lefebvre,[‡] Laura A. Fraser, and Jonathan Clayden*

School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, U.K.

Supporting Information

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.

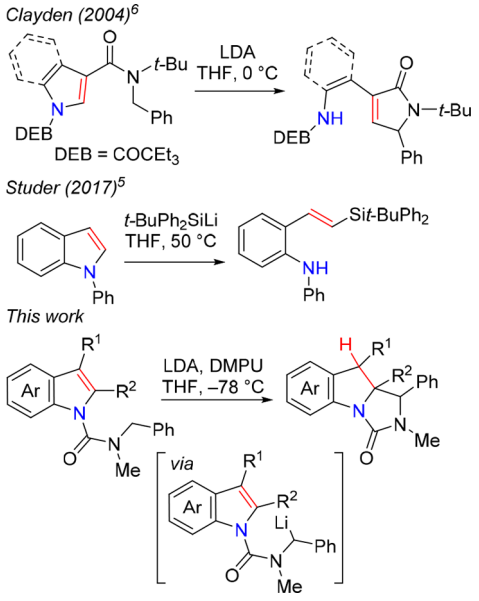


The amino acid tryptophan provides the starting material for the biosynthesis of a broad array of indole-derived secondary metabolites, many of them with valuable biological activity.[1] Not all contain the aromatic indole structure: a significant proportion of indole-derived alkaloids retain the indole 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 iminum 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 iminum 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 Studer[5] and ourselves[6] 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 benzothiophenes[7] 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 metalation of indole-derived *N*-benzyl ureas. Treating *N*-benzyl-*N*-methyl-*1H*-indole-1-carboxamide **1a** with 2 equiv of LDA in THF at −78 °C led to rapid decomposition to indole

Scheme 1. Nucleophilic Dearomatization of Indoles

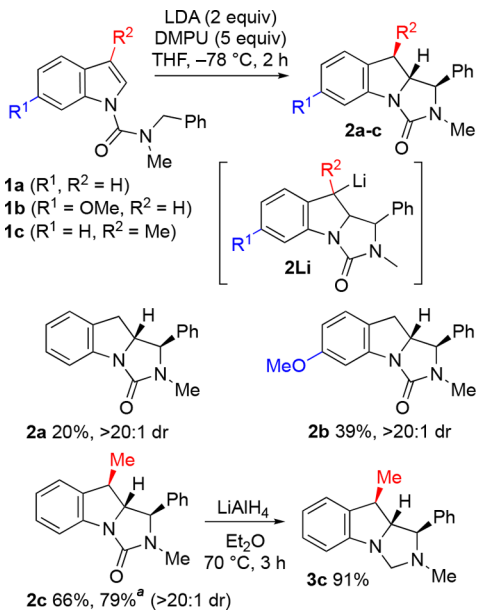


and other unidentified side products. However, in the presence of 5 equiv of the lithium-coordinating cosolvent DMPU, full conversion was attained after 2 h and the tricyclic indoline **2a** was obtained in 20% yield as a single diastereomer (Scheme 2). A similar reaction with the 6-methoxy indole **1b** provided a 39% yield of **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 $LiAlH_4$

Received: August 2, 2018

DOI: 10.1021/acs.orglett.8b02468
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Dearomatizing Cyclization of Indoles: Initial Results



[a]Yield on 1 g scale.

transformed it to the imidazolidine **3c**, indicating possible applications of this dearomatizing cyclization to the synthesis of polycyclic amines with alkaloid-like structures.

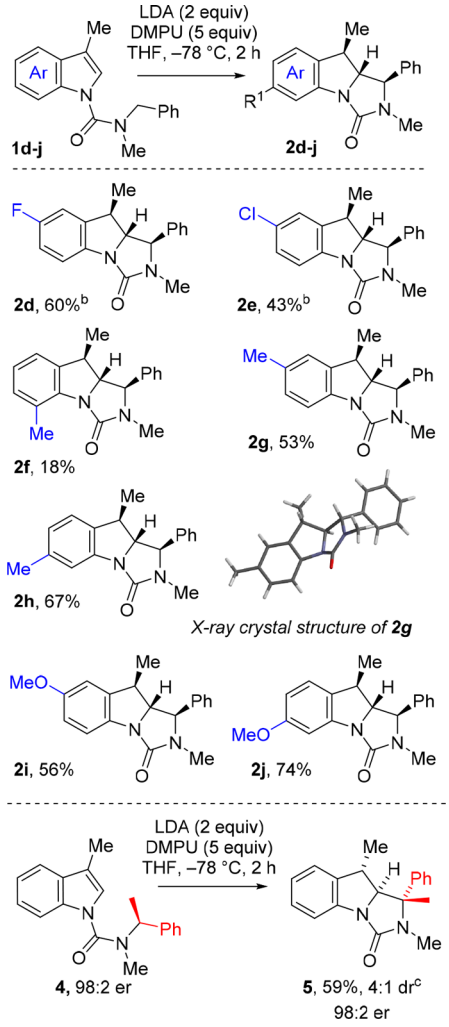
The success of these cyclizations suggested that the increased basicity of the organolithium intermediate **2Li** presumably generated by anionic cyclization may promote a cleaner reaction by favoring proton transfer from *i*-Pr_2NH (see mechanistic discussion below). We thus proceeded to develop further reactions of 3-substituted indoles.

A further range of starting materials **1d–j** were made from their parent indoles by a Vilsmeier–Haack reaction followed by reduction with $LiAlH_4$ and N-acylation[9] (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-position 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 essentially single diastereomers[11] with the X-ray crystal structure of **2g** (CCDC 1859678), 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.

A reaction performed on the related substrate **4** bearing an enantioenriched 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,[12] 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

Scheme 3. Cyclizations of 3-Methylindole Derivatives[a]



[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.

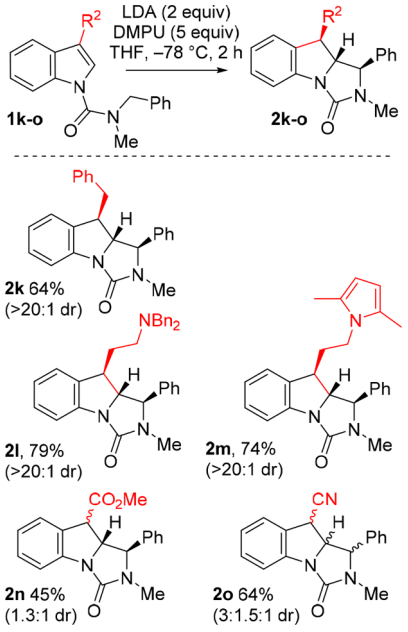
yield of **2k** as a single diastereoisomer. The particular success of these dearomatizing cyclizations of 3-alkylindoles suggested that tryptophan-derived ureas might also be suitable substrates, allowing the formation of alternatively connected tricyclic products.[13] Pleasingly, tryptamine derivatives **1l** and **1m** reacted cleanly to give the products **2l** and **2m** with dibenzyl and 2,6-dimethylpyrrole protecting groups.

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).

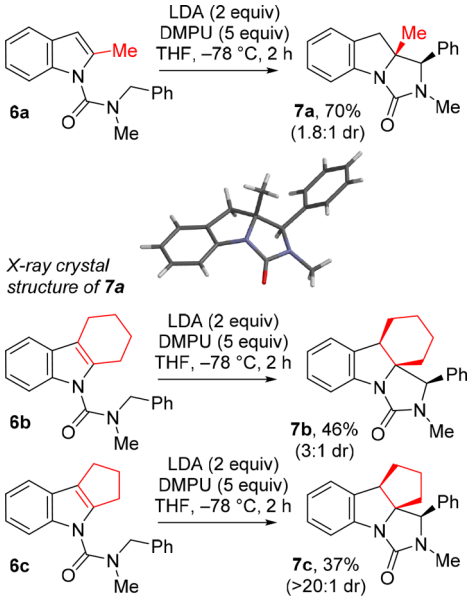
A final set of starting materials was made in which the 2-position of the indole was substituted. The first of these, the 2-methylindole derivative **6a**, cyclized in good yield under the standard conditions, although a mixture of diastereoisomers was obtained (Scheme 5; X-ray crystallography revealed the relative stereochemistry of the major diastereoisomer (**7a**, CCDC 1541914)).[14] 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

DOI: 10.1021/acs.orglett.8b02468
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 4. Cyclizations of Other 3-Substituted Indoles



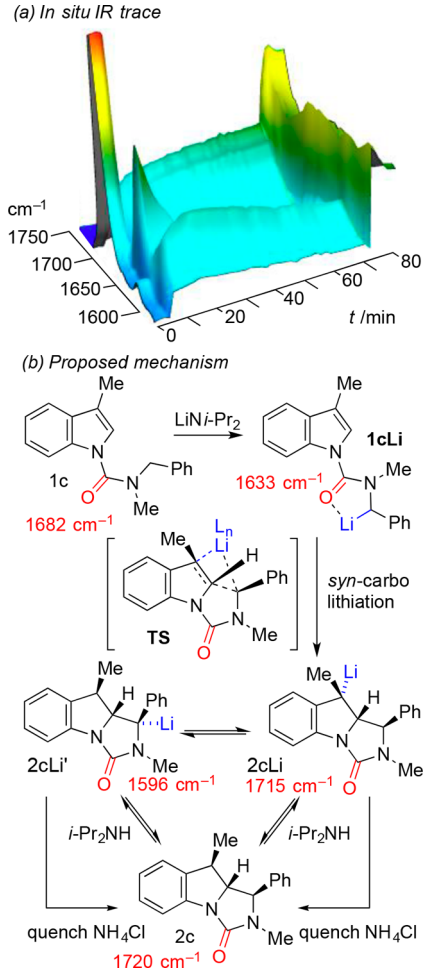
Scheme 5. 2-Substituted and Tricyclic Indole Derivatives



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.

Some details of the mechanism of the cyclization of **1c** were revealed by in situ infrared spectroscopy (Scheme 6).[15] To eliminate the obscuring effect of its urea carbonyl absorption, we performed the reaction in the absence of DMPU. A solution of **1c** in THF showed a strong carbonyl absorption at 1682 cm^{-1}. Upon addition of 2 equiv of LDA at −78 °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.[15b] Over a period of a few minutes this transient signal was replaced by

Scheme 6. In Situ IR Investigation and Postulated Mechanism[a]



[a]Solvation or aggregation of the organolithium species is not shown but may be assumed.

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 workup 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.[16] 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

DOI: 10.1021/acs.orglett.8b02468
Org. Lett. XXXX, XXX, XXX−XXX

led to less predictable yields and selectivities. Substrates derived from tryptamine, as well as other biorelevant structures such as tricyclic indoles **6**, underwent the reaction. The reaction proved to be diastereoselective and (with enantioenriched α-chiral organolithiums) enantiospecific, and the method has potential for the modular synthesis of modified indole alkaloid derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02468.

Full experimental data and NMR spectra of all new compounds (PDF)

Accession Codes

CCDC 1541914 and 1859678 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: j.clayden@bristol.ac.uk.

ORCID

Jonathan Clayden: 0000-0001-5080-9535

Author Contributions

‡J.E.H. and Q.L. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the EPSRC, the Bristol Centre for Doctoral Training in Chemical Synthesis, AstraZeneca through a CASE award and the Deutsche Forschungsgemeinschaft (research fellowship LE 3853/1-1). We thank Dr. Hazel Sparkes and Dr. Natalie Pridmore (School of Chemistry, University of Bristol) for determining the X-ray crystal structures of **2g** and **7a**.

■ REFERENCES

(1) (a) Seigler, D. S. *Plant secondary metabolism*; Springer: Boston, MA, 1998; p 628. (b) Xu, W.; Gavia, D. J.; Tang, Y. *Nat. Prod. Rep.* **2014**, *31*, 1474. (c) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Nat. Prod. Rep.* **2015**, *32*, 1389.

(2) Examples of such alkaloids are found in *Aspidosperma* and *Strychnos spp.*, as well as among pyrroloindoles, cyclotryptamines, communesines, and spiroindolines.

(3) (a) Dearomatizing reactions using organolithiums: Lemière, G.; Clayden, J. *Sci. Synth.*, **2011**, *4*, 139. (b) Clayden, J.; Kenworthy, M. N.; Helliwell, M. *Org. Lett.* **2003**, *5*, 831. (c) Clayden, J.; Purewal, S.; Helliwell, M.; Mantell, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1049. (d) Bragg, R. A.; Clayden, J.; Bladon, M.; Ichihara, I. *Tetrahedron Lett.* **2001**, *42*, 3411. (e) Clayden, J.; Menet, C. J. *Tetrahedron Lett.* **2003**, *44*, 3059. (f) Clayden, J.; Hamilton, S. D.; Mohammed, R. T. *Org. Lett.* **2005**, *7*, 3673.

(4) (a) Nandi, R. K.; Ratsch, F.; Beaud, R.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Chem. Commun.* **2016**, *52*, 5328. (b) Morimoto, N.; Morioku, K.; Suzuki, H.; Takeuchi, Y.; Nishina, Y. *Org. Lett.* **2016**, *18*, 2020.

(5) Xu, P.; Würthwein, E.-U.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2017**, *95*, 1527.

(6) Clayden, J.; Turnbull, R.; Pinto, I. *Org. Lett.* **2004**, *6*, 609.

(7) Clayden, J.; Turnbull, R.; Helliwell, M.; Pinto, I. *Chem. Commun.* **2004**, *21*, 2430.

(8) (a) Hill, J. E.; Matlock, J. V.; Lefebvre, Q.; Cooper, K. G.; Clayden, J. *Angew. Chem., Int. Ed.* **2018**, *57*, 5788. (b) Hall, J. E.; Matlock, J. V.; Ward, J. W.; Gray, K. V.; Clayden, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 11153. (c) Corbet, B. P.; Matlock, J. V.; Mas Roselló, J.; Clayden, J. *C. R. Chim.* **2017**, *20*, 634. (d) Tait, M. B.; Butterworth, S.; Clayden, J. *Org. Lett.* **2015**, *17*, 1236. (e) Maury, J.; Clayden, J. *J. Org. Chem.* **2015**, *80*, 10757. (f) Clayden, J.; Dufour, J.; Grainger, D. M.; Helliwell, M. *J. Am. Chem. Soc.* **2007**, *129*, 7488. (g) Tetlow, D. J.; Hennecke, U.; Raftery, J.; Waring, M. J.; Clarke, D. S.; Clayden, J. *Org. Lett.* **2010**, *12*, 5442. (h) Clayden, J.; Donnard, M.; Lefranc, J.; Minassi, A.; Tetlow, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 6624. (i) Clayden, J.; Farnaby, W.; Grainger, D. M.; Hennecke, U.; Mancinelli, M.; Tetlow, D. J.; Hillier, I. H.; Vincent, M. A. *J. Am. Chem. Soc.* **2009**, *131*, 3410.

(9) Cheng, H.-G.; Lu, L.-Q.; Wang, T.; Yang, Q.-Q.; Liu, X.-P.; Li, Y.; Deng, Q.-H.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 3250.

(10) A similar substrate containing a bromine atom completely decomposed under the reaction conditions, presumably due to competitive aryne generation.

(11) For **2d** and **2e**, 10% of a minor diastereoisomer was obtained.

(12) Vincent, M. A.; Maury, J.; Hillier, I. H.; Clayden, J. *Eur. J. Org. Chem.* **2015**, *2015*, 953.

(13) This method provides an unusual 6−5−5 tricyclic system, comparable to the ubiquitous 6−5−6 tricyclic system of tryptolines. For examples and relevance of such tricycles in medicinal chemistry, see: (a) Alagille, D.; Pfeiffer, B.; Scalbert, E.; Ferry, G.; Boutin, J. A.; Renard, P.; Viaud-Massuard, M.-C. *J. Enzyme Inhib. Med. Chem.* **2004**, *19*, 137. (b) Chaulet, C.; Croix, C.; Alagille, D.; Normand, S.; Delwail, A.; Favot, L.; Lecron, J.-C.; Viaud-Massuard, M.-C. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1019. (c) Kong, W.-J.; Chen, X.; Wang, M.; Dai, H.-X.; Yu, J.-Q. *Org. Lett.* **2018**, *20*, 284.

(14) Replacing the methyl by a phenyl group almost completely diverted the reaction to decomposition, giving the product in less than 10% yield.

(15) (a) Atkinson, R. C.; Leonard, D. J.; Maury, J.; Castagnolo, D.; Volz, N.; Clayden, J. *Chem. Commun.* **2013**, *49*, 9734. (b) Fournier, A. M.; Nichols, C. J.; Vincent, M. A.; Hillier, I. H.; Clayden, J. *Chem. - Eur. J.* **2012**, *18*, 16478.

(16) Deuterolysis of the reaction mixture did not give deuterated products, maybe because of rapid H/D exchange with *i*-Pr_2NH.

DOI: 10.1021/acs.orglett.8b02468
Org. Lett. XXXX, XXX, XXX−XXX