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Medium Ring Nitrogen Heterocycles by Migratory Ring Expansion of Metallated Ureas

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Abstract: Simple benzo-fused nitrogen heterocycles (indolines, tetrahydroquinolines and their homologues) undergo migratory ring expansion by deprotonation of their benzylic urea derivatives with LDA in the presence of DMPU. The products of the reactions are benzodiazepines, benzodiazocines and their homologues, with ring sizes of 8-12. The reactions tolerate a range of substituent patterns and types, and may exhibit enantiospecificity or diastereoselectivity. Considerable complexity is rapidly generated in an efficient synthesis of these otherwise difficult to obtain medium-ring nitrogen heterocycles.

Medium-ring (8 to 12-membered) heterocycles are a class of challenging synthetic targets.[1] Natural products containing medium ring N and O heterocycles and exhibit a broad range of biological activities,[2] so the scarcity of 8 to 12-membered rings among approved pharmaceutically active agents[3] is surprising, and indicative of the acknowledged difficulties associated with their synthesis.[4] Over 80% of drugs contain nitrogen heterocycles of four to seven members,[3] with benzodiazepines constituting a particularly privileged structure.[5] Larger heterocyclic rings are likewise prevalent in biologically active macrolides[6] and cyclic peptides.[7] Recent exploration of drug candidates containing medium ring nitrogen heterocycles,[8] has highlighted the importance of conformational constraints in these structures.[9] Methodology allowing the straightforward synthesis of classes of nitrogen heterocycles with ring sizes of eight or more would prove particularly valuable for exploring this less charted area of chemical space.

In this paper we report a method for the synthesis of medium ring (8 to 12-membered) benzo-fused nitrogen-containing heterocycles by \( n \rightarrow n+3 \) ring expansion of readily available heterocyclic precursors. The method is summarised in Scheme 1, and builds on our studies of sterosepecific N to C migration of aryl rings within metallated ureas.[10] By analogy with this previous work, we expect selective deprotonation of the highlighted position \( \alpha \) to nitrogen in ureas 1 to give the anion shown (or its organolithium equivalent). Such anions, in the absence of a "tether", undergo nucleophilic attack on the N-aryl substituent shown in blue, and with a cyclic substrate we would expect consequent migratory ring expansion of the \( n \)-membered ring of 1 to the \( n+3 \) membered product 2. The ready availability of 5-7 membered heterocyclic precursors makes this a particularly appealing route for the synthesis of the 8-10 membered products.

![Scheme 1. Migratory ring expansion of metallated ureas.](image)

Preliminary investigations (Table 1) employed as a model substrate the urea 3a, available in two steps from commercially available indoline. Deprotonation of 3a with either freshly prepared lithium diisopropylamide (LDA) or sec-butyllithium did not lead to ring expansion. Instead, a 1,2-acyl shift, resulting from attack of the benzylic anion onto the urea carbonyl group generated the aminoindole 5 (Table 1, entries 1 and 2).[11] Since sec-BuLi also gave alkylation by-products[10d] as a consequence of nucleophilic attack on the urea, LDA was used as the base in all subsequent reactions.

**N,N-Dimethylpropylideneurea (DMPU) can dramatically alter reaction pathways of organolithium species in solution when used as a ligand or co-solvent.[10e]**[10f] Significantly, treatment of 3a with LDA in the presence of DMPU suppressed completely the acyl shift leading to 5 and gave instead the ring expanded benzodiazocine 4a in good yield (Table 1, entry 4). An even higher yield of benzodiazocine 4b was obtained with the 5-chloroindoline-derived urea 3b (entry 5).

**Table 1. Optimisation of the ring expansion.**

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Optimisation carried out on 0.38 mmol scale. [b] LDA freshly prepared by treatment of anhydrous disopropylamine with n-BuLi at -78 °C in THF. [c] 1H NMR showed side-products resulting from the addition of sec-BuLi to both 3a and 4a. [d] DMPU was added to a solution of 3a in THF at RT prior to cooling to -78 °C to ensure effective mixing. [e] Commercially sourced LDA purchased from Sigma Aldrich as a 2.0 M solution in THF/heptane/ethylbenzene. LDA = lithium diisopropylamide; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone.

These conditions (LDA, 2 equiv.; DMPU, 5 equiv.; THF, -78 °C, 1-16 h) were applied successfully to a series of ureas 6a-i derived from commercially available 6-membered heterocycles, and allowed the synthesis of a range of substituted 9-membered benzodiazonines 7a-j in good to excellent yield (Scheme 2). Ring-expansion of 6a generated 7a in good yield on a scale of both 0.4 mmol and 3 mmol, with X-ray crystallography confirming the benzodiazonine structure of 7a. The ring-expansion reaction is insensitive to both electronic or steric demands, giving the ring expansion products with electronically diverse (7b, 7c) and ortho-substituted hindered (7d) migrating substituents in good to excellent yields.

Heteroaromatic (2-pyridyl and 2-thiophenyl) rings may be incorporated into the migrating aryl ring (7e) or α to the benzylic anions (7f, 7g). Higher temperatures are required for the reactions of pyridyl-containing substrates to reach completion. By contrast, the 2-thiophenyl-stabilised anion derived from 6g rearranged successfully to 7g even in the absence of DMPU. Incorporation of a heteroatom into the tether by expansion of a urea 6h derived from commercially available benzomorpholine gave the benzoxadiazonine 7h. Replacing the N-methyl substituent with a tert-butyl group substantially decreased the rate of the reaction of 6i, which required an elevated temperature to obtain a good yield of the ring expansion product 7i.

<table>
<thead>
<tr>
<th>Entry</th>
<th>S.M.</th>
<th>Base</th>
<th>Additive</th>
<th>Time (h)</th>
<th>Product, Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>LDA</td>
<td>-</td>
<td>4</td>
<td>5 66</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>sec-BuLi</td>
<td>-</td>
<td>2</td>
<td>5 62</td>
</tr>
<tr>
<td>3</td>
<td>3a</td>
<td>sec-BuLi</td>
<td>-</td>
<td>4</td>
<td>5 12</td>
</tr>
<tr>
<td>4</td>
<td>3a</td>
<td>LDA</td>
<td>DMPU (5 equiv.)</td>
<td>4</td>
<td>4a 68, 70</td>
</tr>
<tr>
<td>5</td>
<td>3b</td>
<td>LDA</td>
<td>DMPU (5 equiv.)</td>
<td>4</td>
<td>4b 88</td>
</tr>
</tbody>
</table>

[a] Optimisation carried out on 0.38 mmol scale. [b] LDA freshly prepared by treatment of anhydrous disopropylamine with n-BuLi at -78 °C in THF. [c] 1H NMR showed side-products resulting from the addition of sec-BuLi to both 3a and 4a. [d] DMPU was added to a solution of 3a in THF at RT prior to cooling to -78 °C to ensure effective mixing. [e] Commercially sourced LDA purchased from Sigma Aldrich as a 2.0 M solution in THF/heptane/ethylbenzene. LDA = lithium diisopropylamide; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone.

Scheme 2. Ring expansions to yield 9-membered nitrogen heterocycles. [a] Yield in parenthesis: reaction conducted on 0.4 mmol scale. [b] Yield in parenthesis: reaction conducted on 3 mmol scale. [c] Reaction run at -60 °C. [d] Reaction run at -30 °C. [e] Reaction run at -40 °C without DMPU. [f] Reaction run at -10 °C.

Chiral substrates 8 and 9 were made from enantiopure (S)-α-methylbenzylamine and were ring-expanded under the same conditions (Scheme 3). Each gave a product, 10 and 11, with a new quaternary centre within the expanded 8- or 9-membered ring. Both rearrangements were stereospecific, with only slight erosion of e.r. in the case of 11, and must proceed through a configurationally stable organolithium intermediate.13
The methodology was also amenable to the synthesis of bicyclic structures by migratory ring fusion (Scheme 3). The unsymmetrical ureas 12, formed by coupling two isomeric 6-membered nitrogen heterocycles, underwent ring expansion by insertion of the tetrahydroisoquinoline ring into the tetrahydroquinoline. The diazabicyclo[7.4.0]tetradecane products 13a and 13b were formed at −40 °C in excellent yield, highlighting the way that structural complexity is rapidly generated from the simple urea precursor.

Having made 8- and 9-membered heterocycles in just two or three steps from commercially available 5- and 6-membered precursors, we extended the ring expansion method to larger ring sizes (Scheme 4). The requisite 7-, 8- and 9-membered ureas 14 were made either from a commercially available precursor (14a, two steps from benzazepine) or by using literature procedures (14b and 14c[14]). All three ureas underwent ring expansion to give 10-, 11- and 12-membered heterocycles in good yields.[15]
Chiral starting materials with substituents in the expanding ring underwent migratory ring expansion with complete diastereoselectivity (Scheme 5). 2-Substituted indoles, prepared from the corresponding 2-substituted indoles,[16] were converted into the starting ureas 16. Ring-expansion of methyl-substituted 16a gave 17a in good yields and as a single diastereoisomer. X-ray crystallography showed an 1.5-anti relationship between the two ring substituents, and indicated that both occupied pseudoequatorial positions on the chair-chair conformer of the eight-membered ring.[17] The related substrates 16b–c also underwent ring expansion to single diastereoisomers of the eight-membered products.

A fourth indoline-derived substrate 16d was formed by coupling of racemic 2-phenylindoline with its own carbamoyl chloride derivative. Remarkably, a single diastereoisomer of the symmetrical urea was formed, which X-ray crystallography showed to be the meso diastereoisomer. Migratory ring-fusion of this urea allowed one indoline ring to insert into the other, and gave diazabicyclo[6.3.0]undecane 17d as a single diastereoisomer, with the anti relationship of the two phenyl rings determined by X-ray crystallography (Scheme 5).[16]

A particularly appealing feature of this migratory ring expansion is the ready availability of the starting materials, most of which are formed in two or three steps from commercial products. However, the practicality of the method can be increased even further by carrying out the urea formation and ring expansion as part of a single transformation (Scheme 6). Tetrahydroquinoline 18 can be ring expanded to the benzodiazepine 7a in a single step by treatment with 19 and LDA (3 equiv.) in THF (0.15 M)/DMPU (5 equiv.) in moderate yield. An improved yield could be obtained by treatment of 18 with triphosgene/pyridine followed by in situ urea formation with N-benzylmethylamine and LDA (3 equiv.) to give 7a in 84% yield on a gram scale.

Scheme 6. Telescopred ring expansion.

In conclusion, this new method provides synthetic tools to form, rapidly and efficiently, medium ring nitrogen-containing heterocycles with a range of benzo-fused cyclic urea structures. The compounds formed by the method exhibit substantial structural diversity, and occupy a skeletally novel and hitherto unexplored region of chemical space.

Acknowledgements

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Keywords: Medium Rings • Heterocycles • Migration • Ring Expansion • Organolithium •


We assume this is the result of epimerisation of the newly formed stereocenter after ring expansion.


[13] We assume from precedent [see ref 10a and M. A. Vincent, J. Maury, I. H. Hillier, J. Clayden, Eur. J. Org. Chem. 2015, 953-959.] that the rearrangement is configurationally retentive. This assumption is supported by the diastereosepecific rearrangement of 16d to 17d [see ref 18.]


[15] In common with other medium ring nitrogen heterocycles (K. Tomooka, N. Komine, D. Fujki, T. Nakai, S. Yanagitsu, J. Am. Chem. Soc. 2005, 127, 12182-12183) some of these compounds (7b, 7d, 7h, 7i, 11, 15b, 15c, 17c showed exchange-broadened signals in their NMR spectra.


We assume this is also the case for ring expansion of 8 and 9.
Ringing in ureas: Simple benzo-fused nitrogen heterocycles (indolines, tetrahydroquinolines and their homologues) undergo migratory ring expansion under basic conditions to generate a range of medium ring nitrogen heterocycles with ring sizes of 8-12. Considerable complexity is rapidly generated in an efficient synthesis of these otherwise difficult to obtain rings.