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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 stereospecific 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 α 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.

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 aminoamide **5** (Table 1, entries 1 and 2).^[11] Since *sec*-BuLi also gave alkylated 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.^[10f, 12] 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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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]

Scheme 3. Ring expansion products with quaternary centres and fused rings. [a] e.r. determined by HPLC on chiral stationary phase. [b] Starting material (S)-8 (99:1 e.r.), (S)-9 (99:1 e.r.).

Scheme 4. Migratory ring expansion to 10-12 membered rings.

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]

Scheme 5. Diastereoselective ring expansions. [a] dr was determined by ^1H NMR of the crude reaction mixture. [b] The relative chemistry of ($\pm$)-**17b** was assigned in analogy to ($\pm$)-**17a**. [c] dr of purified product. [d] Reaction run without DMPU. [e] Reaction conditions: Triphosgene (1.2 mmol) treated with pyridine (2.6 mmol) in anhydrous CH_2Cl_2 (0.7 M) at -78°C . 2-Phenylindoline (2.6 mmol) added and reaction warmed to RT. 2-Phenylindolinecarbamoyl chloride (0.78 mmol) treated with 2-phenylindoline (1.0 mmol) and triethylamine (1.24 mmol) in anhydrous MeCN (0.4 M) at RT.

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Chiral starting materials with substituents in the expanding ring underwent migratory ring expansion with complete diastereoselectivity (Scheme 5). 2-Substituted indolines, 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).^[18]

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 benzodiazonine **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. Telescoped 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.

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

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- [18] X-ray structures and NMR data for **16d** and **17d** show that this reaction is stereosepecific and retentive. By analogy, and from ref 10a and 13, we assume this is also the case for ring expansion of **8** and **9**.

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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.

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