Ring expansion and re-contraction for the synthesis of 1-aryl tetrahydroisoquinolines and tetrahydrobenzazepines from readily available heterocyclic precursors

Jessica E. Hill, Johnathan V. Matlock, Quentin Lefebvre, Katie G. Cooper and Jonathan Clayden*

Abstract: Tetrahydroisoquinolines and tetrahydrobenzazepines are prepared by acid-promoted ring contraction of cyclic ureas, themselves formed by ring expansion of indolines and tetrahydroquinolines. The consequent overall one-carbon insertion reaction gives these 6- and 7-membered heterocyclic scaffolds in three steps from readily available precursors. Other ring sizes may be formed by an alternative elimination reaction of bicyclic structures. Scalability of the method was demonstrated by operating it in a flow system.

Tetrahydroisoquinolines, benzazepines and related benzo-fused nitrogen heterocycles are privileged scaffolds in medicinal chemistry for library design and drug discovery.[1,2] The many isoquinoline alkaloids also exhibit diverse pharmacological and biological properties.[3] The benzazepine scaffold forms the key motif for a number of pharmaceutical agents which target the central nervous system.[4] A few examples are shown in Figure 1.[1]

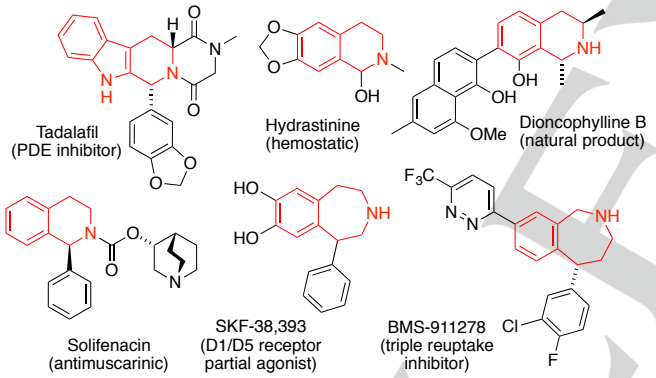
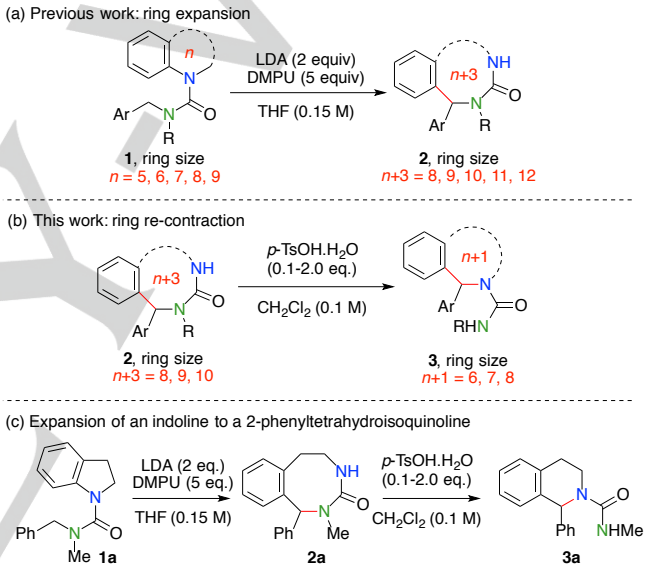


Figure 1. Tetrahydroisoquinolines, benzazepines, and related motifs in molecules with biological activity.

The most practical methods for the synthesis of tetrahydroisoquinolines and tetrahydroisoquinolones are the Pictet–Spengler[5] and the Bischler-Napieralski reactions.[6] Despite modern advances in the field,[7] the scope of these reactions is generally limited by the need for electron-donating groups on the aromatic ring, and typical reaction conditions are strongly acidic or electrophilic. Neither reaction works well for the formation of ring sizes other than 6.

We recently discovered that treatment of benzo-fused N-carboxamido heterocycles with base leads to insertion of the urea substituent into the Ar-N bond, resulting in the migratory ring expansion of an *n*-membered heterocycle to an *n*+3-membered cyclic urea.[8-10] These medium-ring (8- to 12-membered) heterocycles have structures that themselves provide interesting scaffolds for drug discovery, but in this paper we show that they also possess further valuable reactivity. Treatment with acid results in an *n* to *n*–2 ring contraction (scheme 1b), the products of which are the desirable 1-aryltetrahydroisoquinoline and 1-aryltetrahydrobenzazepine targets.



Scheme 1. (a) Migratory ring expansion of metallated ureas gives medium-sized rings. (b) Acid–mediated ring contraction of medium sized rings. (c) One-carbon ring expansion of an indoline.

The tendency of cyclic ureas **2** to undergo rearrangement was discovered when **2a**, which is readily formed by migratory ring expansion of the indoline-derived urea **1a** (Scheme 1c), was treated with mild acid. Tetrahydroisoquinoline **3a** was formed by a ring contraction in which the more heavily substituted benzylic carbon atom migrates from one urea nitrogen atom to the other. *p*-Toluenesulfonic acid monohydrate (p-TsOH), trifluoroacetic acid and hydrochloric acid all promoted this ring contraction, with *p*-TsOH giving the highest yields. Good yields were obtained even with 0.1 equivalents of *p*-TsOH, constituting much milder conditions thans those required for Pictet–Spengler and Bischler-Napieralski chemistry.[5,6]

With the aim of exploring this ring-expansion-contraction strategy as a general way of making tetrahydroisoquinolines and related compounds, these conditions were then applied to a series of substrates **2a-l**, each made by ring expansion of the appropriate urea **1a-l**.[8] The results are summarised in Scheme 2.

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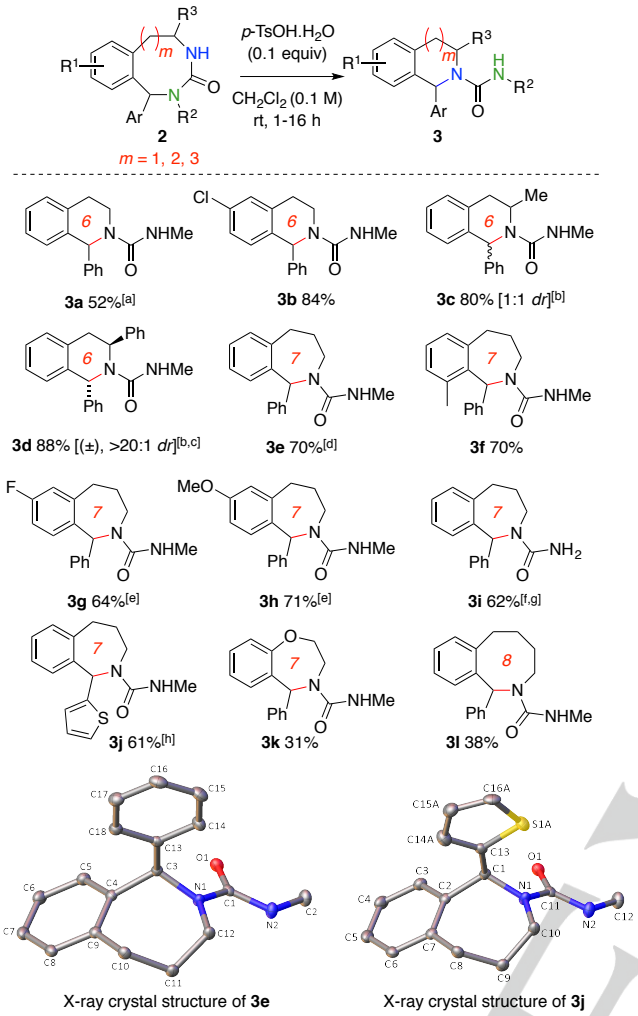
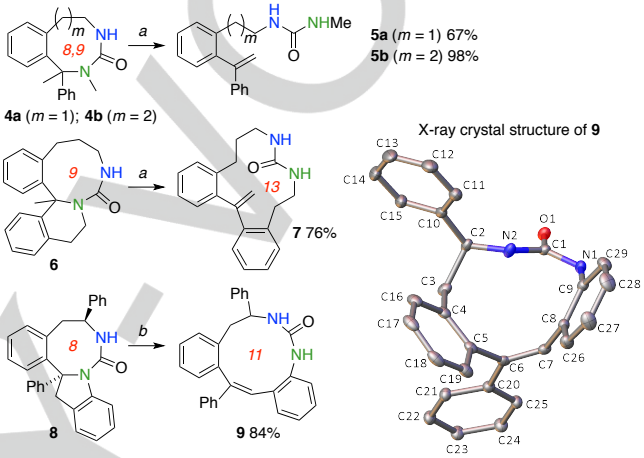


Scheme 2. Ring contraction substrate scope. [a] Using 2.0 equiv *p*-TsOH.H_2O [b] From a single diastereoisomer of **2c** or **2d**. [c] Stereochemistry assumed from the established *trans* selectivity of related acid-catalysed isomerisations of Pictet-Spengler products.[11] [d] Comparison of different acids (yields by internal standard): TsOH.H_2O (98%), HCl in Et_2O (81%), TFA in $CDCl_3$ (91%). [e] Product formed from **1** by a one pot ring expansion–recontraction, using 10 equiv *p*-TsOH.H_2O [f] Using 2.5 equiv methanesulfonic acid at 0 °C. [g] From **2i**, in which R^2 = *t*-Bu: the *t*-Bu group is lost in the reaction. [h] Product formed directly from **1j** by ring-contraction in the absence of TsOH.H_2O.

The reaction was successful using alternatively substituted 8-membered starting materials (*n* = 1) **2a-d** giving the tetrahydroisoquinolines **3a-d** in good yield. Single diastereoisomers of ring-substituted starting materials **2c** and **2d** produced a diastereoisomeric mixture of products **3c**, but a single diastereoisomer of phenyl-substituted **3d**. These 1-aryl tetrahydroisoquinolines have important pharmacological activity, and **3a** is a precursor to the drug solifenacin.[12] The structures of **3e** and **3j** were confirmed by X-ray crystallography.[13]

Nine-membered starting materials (*n* = 2) **2e-k**, which are available[8] from tetrahydroquinolines **1e-j** or morpholine **1k** likewise underwent the ring contraction, giving the otherwise difficult to obtain 1-substituted 2,3,4,5-tetrahydro-1H-benzo[*c*]azepines **3e-j** and their oxa-analogue **3k**. **3i** was formed from a precursor **2i** in which the *N*-substituent R^2 is *t*-Bu, which is deprotected under the conditions of the reaction, allowing access to alternatively substituted urea products.

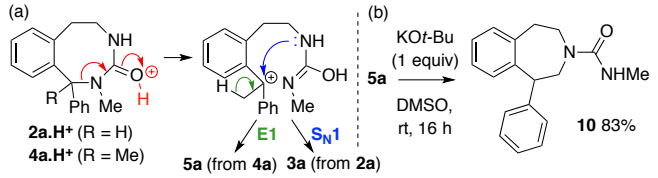
The ring contraction reaction was tolerant of variously substituted rings, with electronically diverse **3b**, **3g**, **3h** and sterically hindered **3f** all being formed successfully. With a powerfully electron-donating substituent at the migrating carbon, in other words the thiophene substituent of **3j**, we found that the ring contraction proceeded unavoidably, even in the absence of acid, on attempted isolation of the eight-membered precursor **2j** (formed by ring expansion of **1j**: see supporting information).



Scheme 3. Acid-mediated elimination reactions can generate medium rings. Conditions: *a* *p*-TsOH.H_2O (2.0 equiv), CH_2Cl_2 (0.1 M), rt, 16 h; *b* *p*-TsOH.H_2O (2.0 equiv), CH_2Cl_2 (0.1 M), μw, 15 min.

Medium-ring substrates in which an alternative E1 elimination pathway is available did not generally undergo ring contraction. Instead, treatment with acid promoted elimination, giving alkene products. **4**, **6** and **8** are all available by published migratory ring expansion reactions,[8] and each undergoes elimination on treatment with acid, rather than a possible alternative ring re-contraction. The monocyclic compounds **4** gives the simple 1,1-diarylethylenes **5**, while bicyclic **6** and **8** generate 13- and 11- membered cyclic alkenes **7** and **9** from the nine- and eight-membered precursors (scheme 3). X-ray crystallography confirmed the *Z*-alkene geometry of the 11-membered **9**.[13]

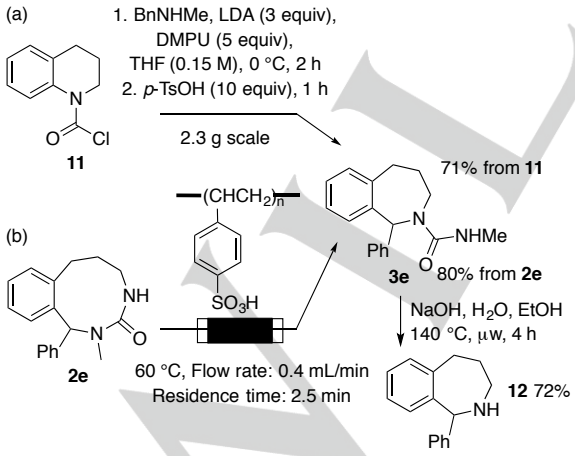
In combination, these results point to a common mechanism in which protonation of the electron-rich oxygen atom of the urea initiates the formation of a carbocation that either provides the intermediate for E1 elimination when a β-proton may be lost, or alternatively is trapped by the remote urea nitrogen in an intramolecular S_N1 substitution that leads to ring contraction (Scheme 4a).[14]



Scheme 4. (a) Mechanisms for elimination or ring contraction; (b) Formation of a benzazepine by intramolecular base-promoted hydroamination

The formation of alkene **5a** makes possible an alternative pathway for ring contraction using base, rather than acid. The diarylalkene is electrophilic towards attack by a nitrogen nucleophile, and treatment of **5a** with potassium *tert*-butoxide promotes intramolecular hydroamination to form the benzazepine **10** in excellent yield (Scheme 4b).[15] Similar reactions to form eight-membered rings turned out to be unsuccessful, but the formation of **10** from **5a** and hence from the indoline precursor to **4** represents an alternative "*n*+3–1" ring expansion-recontraction strategy for the synthesis of this alternatively substituted class of 1-aryl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepines.

These ring expansion and contraction reactions of ureas are in principle scalable, and to demonstrate the practical utility of the method, a 'one-pot' urea formation, ring expansion and ring contraction was performed using a tetrahydroisoquinoline-derived starting material **11** on a 2.4 gram scale (Scheme 5a). Carbamoyl chloride **11**, accessible in one step from commercially available tetrahydroquinoline, was converted into a urea, then ring-expanded with lithium diisopropylamide and N,N'-dimethylpropylideneurea, and finally re-contracted to product **3e** with an excess of *p*-TsOH. The yield of this telescoped sequence was comparable to that when the ring contraction was performed as a separate transformation (Scheme 2). Hydrolysis of the urea by heating under microwave conditions with sodium hydroxide in aqueous ethanol gave the parent tetrahydrobenzazepine.



Scheme 5. Practical formation of a benzazepine by (a) one-pot urea formation, ring expansion and ring contraction or (b) ring contraction using a solid-supported acidic resin in a flow apparatus.

The acid-promoted ring contraction was also achievable in a flow apparatus, with acidic resin Amberlyst-15 instead of *p*-TsOH (Scheme 5b), avoiding work-up and purification. 4 g of **3e** were formed in near-quantitative yield.

In summary, acid-mediated *n* to *n*-2 ring contraction of medium-ring cyclic ureas, coupled in tandem to a practical starting material synthesis using readily available heterocycles, allows the rapid and scalable synthesis of potentially bioactive tetrahydroisoquinoline and tetrahydrobenzazepine derivatives.

Experimental Section

'One-pot' synthesis of (±)-N-methyl-1-phenyl-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxamide ***3e****.* DMPU (7.0 mL, 57 mmol, 5 eq.) and *N*-benzylmethylamine (1.6 mL, 13 mmol, 1.1 eq.) were added to a solution of 3,4-dihydroquinoline-1(2*H*)-carbonyl chloride **11** (2.3 g, 11.5 mmol, 1 eq.) in anhydrous THF (76 mL, 0.15 M) at room temperature under nitrogen. A thick white suspension formed, which was cooled to 0 °C and stirred vigorously. LDA (17 mL, 35 mmol, 3 eq.) was added dropwise. The reaction mixture became homogeneous after the first few drops of LDA were added. The reaction was stirred for 2 h at 0 °C or until consumption of carbamoyl chloride **11** by TLC. *p*-Toluenesulfonic acid (21 g, 115 mmol, 10 equiv.) was added and the reaction was allowed to stir at room temperature for 1 h. Aqueous $NaHCO_3$ was added and the mixture extracted three times with CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (20 to 100 % EtOAc/petrol) gave **3e** as a white solid (2.3 g, 71%).

Acknowledgements

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Keywords: heterocycle, urea, ring contraction, benzazepine, tetrahydroisoquinoline.

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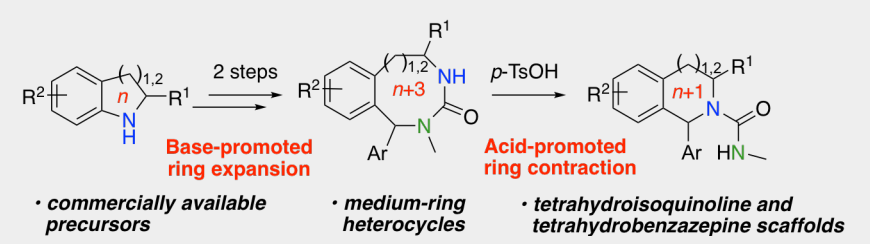

Acid-induced ring contraction of medium-ring ureas provides access to valuable bioactive scaffolds such as tetrahydroisoquinolines and tetrahydrobenzazepines in three steps from commercially available heterocyclic precursors.

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