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A simple and efficient synthesis of new cyclic ureas

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Abstract—A facile access to a wide range of original saturated N-heterocyclic ureas is described using, as a key step, a Michael-type reaction involving isocyanates or amines on a piperidine framework possessing an α,β-unsaturated ester functionality.

Amino heterocycles are widespread in nature and have great biological importance.[1] Thus, a great deal of work has been devoted to the synthesis of cyclic ureas, due mainly to their applications as intermediates for biologically active compounds. In this context, piperidine derivatives **A** (Fig. 1) were proved to be a novel class of selective δ opioid agonists[2] with several potential applications in pain relief, urinary incontinence, depression, drug addiction, and cardiac ischemia. Polyhydroxylated cyclic ureas **B** have been recently studied as glycosidase inhibitors and showed potential activities against viral infections, cancer or metabolic disorders.[3]

During the past few years, we have been engaged in the development of efficient routes to enantiopure polysubstituted piperidines from readily available precursors.[4]

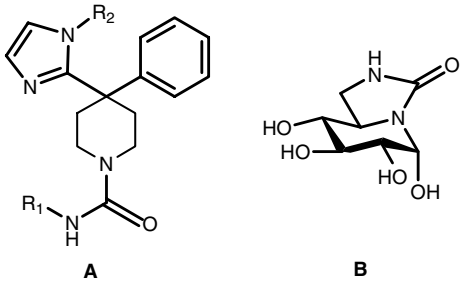
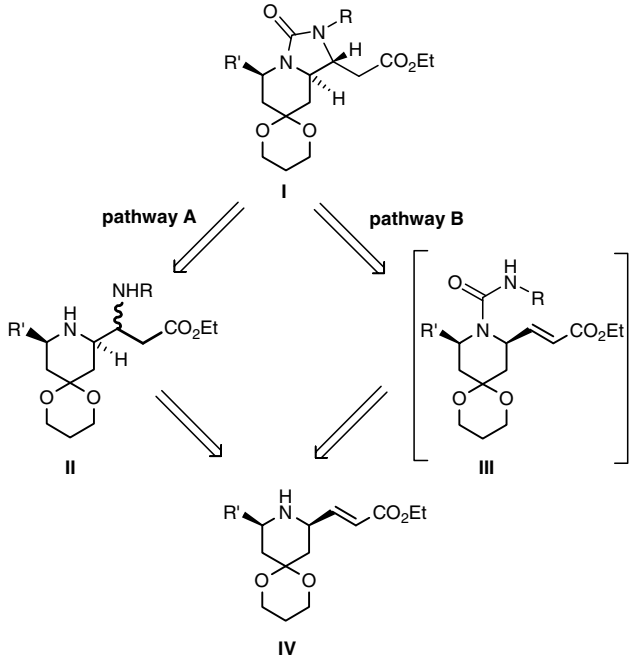


Figure 1.

Our approach, based on an intramolecular Mannich type reaction between an α-chiral 1,3-aminoketal and an aldehyde, was validated through the enantioselective synthesis of various piperidine alkaloids.[4,5] We now envisaged to carry out the synthesis of a new class of cyclic ureas of type **I** using the methodology developed in our group (Scheme 1).



Scheme 1.

Keywords: Cyclic ureas; Michael reaction; Piperidines; Cyclization.
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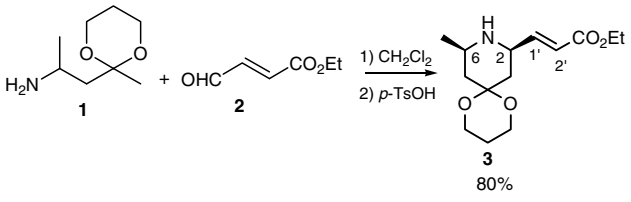
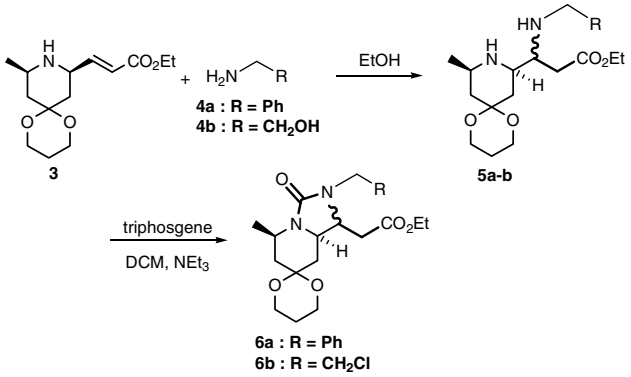
At the inception of this work, we planned two different strategies (pathway A and B) starting from the common synthon **IV**. Route A consisted first in a Michael addition of an amino derivative on the α,β-unsaturated ester function of **IV**, leading to intermediate **II**, which should further be cyclized to give the corresponding cyclic ureas **I**. Alternatively, in route B, the treatment of piperidine **IV** with substituted isocyanates should furnish intermediate **III** precursor of ureas **I** by an intramolecular Michael addition process (Scheme 1). In this Letter, we describe our work on the synthesis of cyclic ureas **I** together with the evaluation of the efficiency of the two synthetic pathways proposed. The condensation of aminoketal **1**[6] with commercially available ethyl-*trans*-4-oxo-buten-2-oate **2** under our standard acidic cyclization conditions,[4b] cleanly afforded the expected 2,6-*cis*-disubstituted piperidine **3**[7] in high yield (80%) and high diastereoselectivity (up to 95%) (Scheme 2). The relative configuration of piperidine **3** was unambiguously established from the ^{1}H NMR data,[7] notably with the signals relative to axial H-3 and axial H-5 showing typical coupling constants for a 2,6-diequatorial disubstitution in a chair conformation.[4]

Having now in hands the key piperidine **3**, we tested the efficiency of route A towards the elaboration of ureas **I**. For this, compound **3** was first treated with primary amine derivatives **4a**,**b** (Scheme 3) at room temperature in ethanol, and furnished a diastereoisomeric mixture (1:1 ratio) of Michael adducts **5a**,**b** in moderate yields (respectively 60% and 43%). Subsequent treatment of **5a** with triphosgene (1.1 equiv) in dichloromethane gave the corresponding diastereoisomeric mixture of urea **6a** in a 60% yield. In the case of compound **5b**, and for the same conditions, unexpected in situ chlorination[8] of the alcohol moiety was also observed and 2-chloroethyl urea **6b** was obtained in a 70% yield. Spectral data obtained for **6b** were in total agreement with the proposed structure.



Scheme 2.

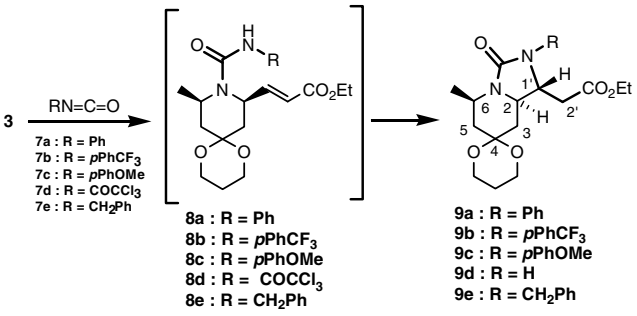


Scheme 3.

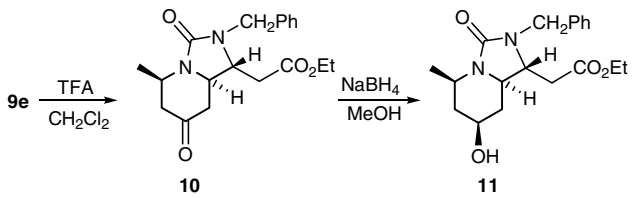
These results, which were unsatisfactory in terms of yield and diastereoselectivity, prompted us to explore the other strategy (route B). So, the condensation of piperidine **3** with various commercially available isocyanates **7a**–**e** led to intermediates **8a**–**e** which spontaneously, without isolation, cyclized smoothly to the corresponding ureas **9a**–**e**[7] in good yields (Scheme 4).[9] The use of trichloroacetyl isocyanate **7d** led as expected, to N-deprotection[10] of the urea, furnishing **9d** in a 78% yield. In the case of **7e** more basic conditions (DBU instead of NEt_3) were required to efficiently obtain the corresponding urea **9e**. Thus, this strategy allowed the preparation of a wide range of polysubstituted cyclic ureas, which were in this case obtained as a single diastereoisomer due to the intramolecular Michael process.[11]

As some active ureas present hydroxyl groups in their skeleton,[2,3] we considered to take advantage of the ketone moiety to introduce this functionality on the piperidine framework. Thus, the deacetalation of urea **9e** was cleanly and rapidly carried out by treatment with trifluoroacetic acid in dichloromethane leading to ketone **10** in high yield (Scheme 5). Stereoselective reduction was then performed with sodium borohydride known to promote a predominantly axial attack.[12] As expected, 2,4,6-*cis*-trisubstituted piperidine **11** was obtained in a 90% yield, as the major epimer (de >95%). Relative configuration of the hydroxyl group was established from ^{1}H NMR data.[13]

To summarize, we have developed a simple and efficient method to prepare a novel class of cyclic ureas. We first synthesized the key intermediate **3** using the method developed in our group to prepare polysubstituted piperidines in high yield and high stereoselectivity.



Scheme 4.



Scheme 5.

Compound **3** was transformed into various substituted cyclic ureas **9a**–**e** with yields ranged from 60% to 90% by taking advantage of the ability of urea functionality to undergo nucleophilic attack on the α,β-ethylenic ester moiety. The evaluation of their specific biological activities is in progress in our laboratory and will be reported in due course.

Acknowledgment

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