Synthesis of Unsymmetric Cyclic Urea Diols, a Novel Class of HIV Protease Inhibitors.

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Abstract:

Unsymmetric cyclic urea diols of general structure 1 can be prepared either *via* an isourea derived from the symmetric diamine 2 or by the selective removal of a benzyl group from certain symmetric cyclic ureas 8, employing dissolving metal reduction. © 1998 The DuPont Merck Pharmaceutical Company. Published by Elsevier Science Ltd. All rights reserved.

As part of ongoing efforts to discover new HIV protease inhibitors, unsymmetric cyclic urea diols of general structure 1 are being investigated[1]. Our commercial route to symmetric cyclic urea diols such as DMP 450 uses the diamine 2 as a key intermediate[2]. Although the synthesis of 2 from dimethyl L-tartrate is facile and proceeds in high overall yield, using 2 as an intermediate for the synthesis of unsymmetric cyclic ureas is problematic because of its C_2 symmetry. Two synthetic methods, the monoalkylation of an isourea derived from 2 and a selective mono-debenzylation of a bis benzylated urea 8, which effectively 'desymmetrize' 2, are described herein.


1   DMP 450   2
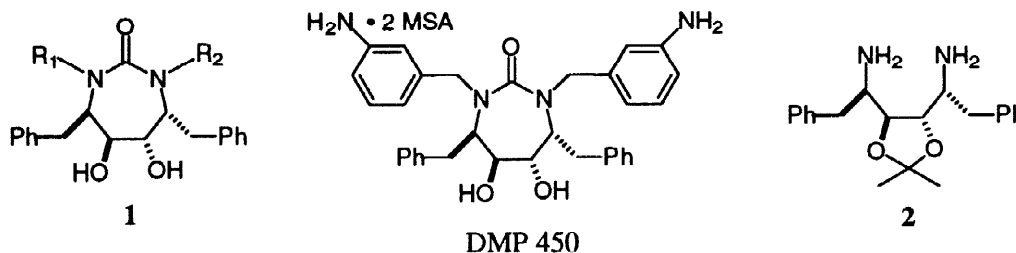
Isoureas

Molecular modeling indicates that the side chains bearing the primary amines in 2 have a *trans* relationship in the lower energy configurations relative to the acetonide ring. Since the amines are separated by a distance of approximately 4 Å, one would not expect any significant chemical differentiation of the amines arising from either intramolecular steric or

acid/base interactions. Indeed, titration of **2** with hydrochloric acid exhibits a single inflection point after two equivalents of acid have been added, indicating that selective reaction of one primary amine over the other using pH control is unlikely.

However, a cyclic isourea derived from **2** forces differentiation of the two amines while at the same time constructs a cyclized system that may subsequently be converted to the desired unsymmetrically substituted urea. Methyl isoureas can be prepared directly from ureas[3]. Using these conditions, the methyl isourea **3** was prepared from **5**. Although methyl isoureas have been prepared directly[4] from diamines, we were unable to transform **2** into the desired isourea **3**, using the published conditions (tetramethylorthocarbonate, acetic acid, reflux).

**3** R=Me
4 R=Et

5
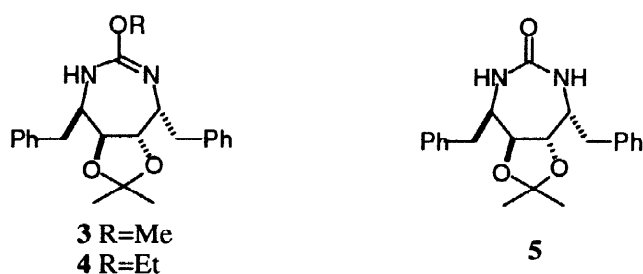
Instead, the ethyl isourea **4** was produced by the reaction of **2** with tetraethylorthocarbonate in refluxing toluene in the presence of an appropriate carboxylic acid while removing the ethanol that is produced as a byproduct by co-distillation with toluene. Hexanoic acid was selected because, unlike acetic and propionic acid, it does not co-distill with toluene. Removal of the alcohol produced in the reaction is required in order to drive the reaction to completion. Under these same conditions formation of the methyl isourea **3**, utilizing tetramethylorthocarbonate, gave a lower yield (40%) because tetramethylorthocarbonate boils below toluene and co-distills during the course of the reaction.

Using solvents that have a lower boiling point than toluene results in a significantly lower yield of isourea, presumably because of the high energy required to bring the *trans* side chains in **2** into closer proximity, which is required for the intramolecular cyclization reaction to occur.

The ethyl isourea **4** is isolated in 65% yield as a white solid that recrystallizes from isopropanol. The main impurity (5%) generated during the reaction is the urea **5**, presumably formed by "trans esterification" of hexanoic acid by **4**, a process known in the literature[5]. Acids other than carboxylic acids, for example *para*-toluene sulphonic acid and mineral acids, failed to promote this reaction. Only carboxylic acids have the appropriate pKa to act as a catalyst in the direct conversion of diamines such as **2** to their corresponding isoureas. Under these conditions, cyclization to the isourea is rapid, and the reaction is complete within 30 minutes.
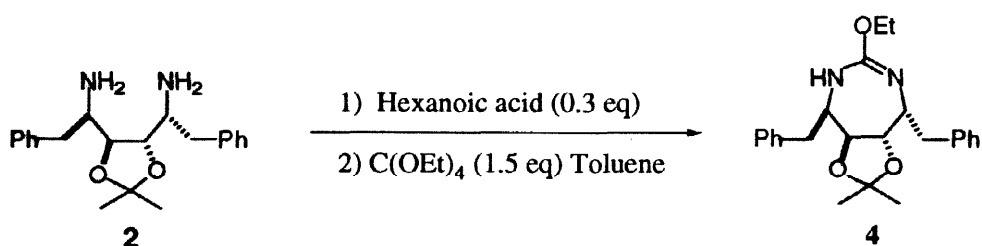
With the isourea now in hand we were able to synthesise unsymmetric cyclic ureas by sequential, selective alkylations. For example, 4 was treated with n-butyl lithium in THF at 0° C followed by benzyl bromide or iodobutane to give the alkylated isoureas 6a and 6b, which were used without further purification. The isoureas were converted to the ureas 7a and 7b with propionic acid in refluxing toluene, then purified either by recrystallization from cyclohexane (7a, 83% yield from 4) or by silica gel chromatography (7b, 60% yield from 4). A subsequent alkylation of the mono-substituted ureas can be carried out using potassium tertiary butoxide in THF in the presence of a suitable alkylating agent, affording selective N vs O alkylation of these substrates.
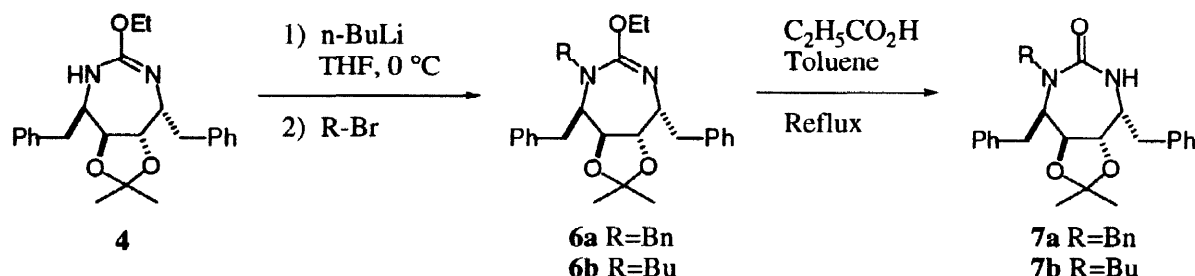

Selective de-benzylation

Alternatively, selective mono-debenzylation of certain diarylmethyl ureas 8a-c to give 7a and 7c-7d affords unsymmetric ureas with at least one arylmethyl substituent. An examination of the literature[6] indicates that selective debenzylation of such a dibenzyl urea moiety should not be facile. However, treatment of 8a, prepared by bis-alkylation of 5 with an excess of benzyl bromide using potassium tertiary butoxide in THF, with three equivalents of sodium in liquid ammonia gives 7a in 75% yield. The symmetric ureas 8b and 8c are also readily debenzylated under these conditions to give 7c and 7d in 86% and 76% yields respectively.
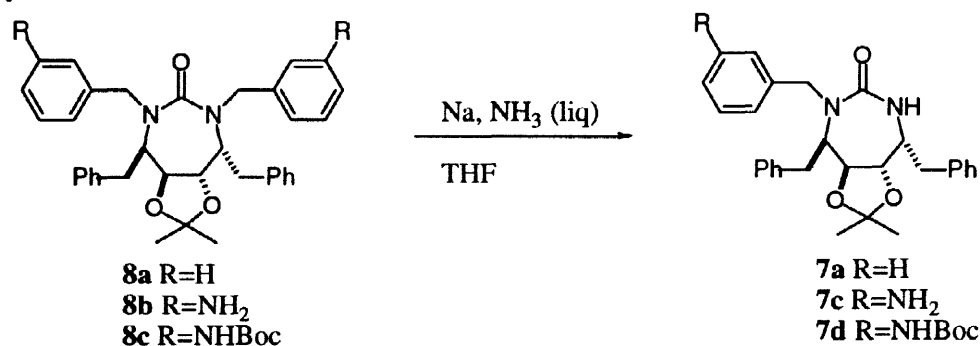
The mono-benzyl ureas, such as **7a**, are readily alkylated with a variety of alkylating agents, including allyl bromide, cyclopropylmethyl bromide and 5-bromomethyl-2-fluorobenzonitrile using potassium tertiary butoxide in THF to give the ureas **9** in yields of 70 - 80%. Removal of the acetonide protecting group with hydrochloric acid in methanol gives the desired urea diols **10** in 90 - 95% yields.
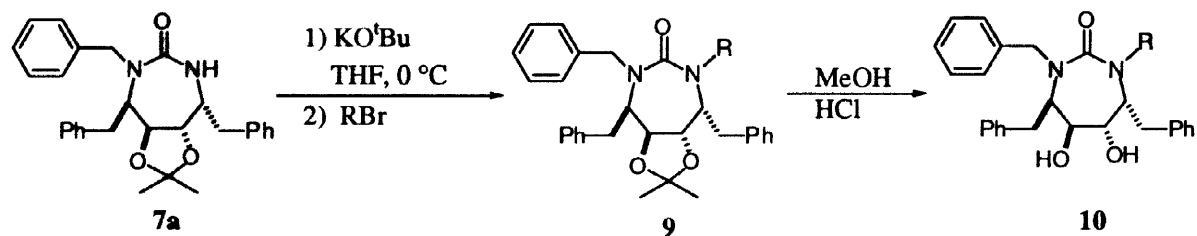
9, 10 R=allyl; cyclopropylmethyl; 3-cyano-4-fluorobenzyl

In summary, we have demonstrated that isoureas such as **4** can be effectively synthesized from symmetric diamines and used to generate a broad range of unsymmetric cyclic ureas. In addition, entry into monobenzyl unsymmetric ureas may also be achieved by the selective debenzylation of a symmetric dibenzyl urea followed by mono N-alkylation.

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