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Cyclization of Bis-Urethanes as a New Method for the Synthesis of Cyclic Ureas

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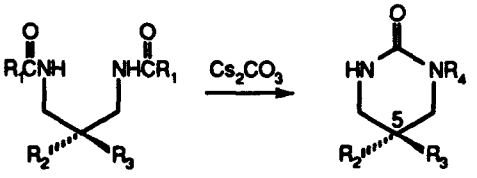
A new method of synthesis of 5-substituted, 6-membered cyclic ureas was found in which urethane derivatives of 1,3-diaminopropane were cyclized using Cs_2CO_3.



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Cyclization of Bis-Urethanes as a New Method for the Synthesis of 5-Substituted, 6-Membered Cyclic Ureas

by

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Manuscript submitted to *Tetrahedron Letters*

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Cyclization of Bis-Urethanes as a New Method for the Synthesis of 5-Substituted, 6-Membered Cyclic Ureas

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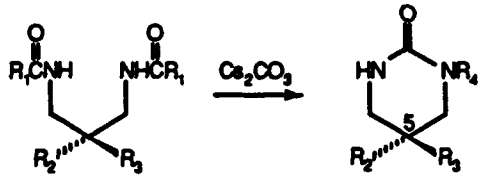
Abstract: A convenient synthesis of 5-substituted 6-membered cyclic ureas is described. The key step involves intramolecular cyclization of 1,3-diaminopropane derivatives with urethane protecting groups on the nitrogen atoms.

The ability of compounds containing two amino groups, in which at least one is protected as a urethane, to cyclize has been recognized by those in the field of peptide synthesis for over sixty years.[1] For example, formation of hydantoin derivatives has been shown to occur when glycine is the second amino acid in a peptide chain and the terminal amine is protected by a benzyloxycarbonyl group.[2] Treatment of such a peptide with alkali may result in the elimination of benzyl alcohol and formation of a hydantoin. This reaction is a problem for those synthesizing peptides and possibly for this reason has not received much attention outside this field.

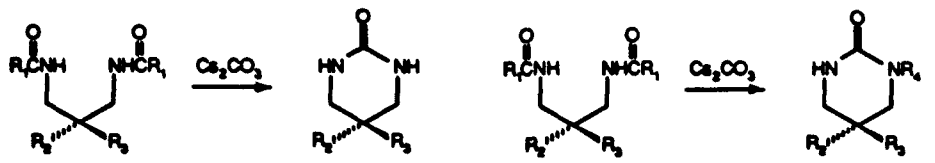
The published procedure for formation of 6-membered cyclic ureas involves simply heating 1,3-diaminopropane and urea.[3] While this procedure produces tetrahydro-2(1H)-pyrimidinone in high yield, the conditions are quite harsh, and consequently this procedure is not applicable to compounds containing substituents that are not very thermally stable. Also substitution on the propylene chain may significantly lower the yield or possibly prevent ring formation.

We report here a new method for synthesizing 5-substituted 6-membered cyclic ureas based on ring closure of bis-urethanes derived from 1,3-diaminopropanes in conjunction with the elimination of the corresponding alcohol. This procedure involves mild conditions and has potential for allowing a wide variety of substituents on C-5.



An example is the preparation of 5-azido-1,3-diazacyclohex-2-one.[4] Reaction of 1,3-diamino-2-hydroxypropane with benzylchloroformate produced 2-hydroxy-N,N'-bis(benzyloxycarbonyl)-1,3-diaminopropane. The hydroxy group was then transformed to an azide via the mesylate under standard conditions.[5] The bis-urethane was stirred with 5 equiv. anhydrous Cs_2CO_3 in CH_3CN at reflux under N_2 for two days. The resulting solution was filtered and chromatographed on silica gel ($CHCl_3$/MeOH gradient). The cyclization step was found to occur in 96% isolated yield in this case. Byproducts of the reaction were dibenzyl carbonate and benzyl alcohol which were easily separated from the desired urea. Several examples of 5-substituted cyclic ureas that were prepared are given in Table I.

Table 1



entries 1 & 2 entries 3 & 4

ENTRY	R_1	R_2	R_3	R_4	TEMP	SOLVENT	TIME	YIELD
1	OCH_2Ph	H	N_3	H	70°C	CH_3CN	48 h	96%
2	OCH_2Ph	CH_2NH-CO_2CH_2Ph	CH_3	H	70°C	CH_3CN	24 h	61%
3	$OC(CH_3)_3$	H	OBn	$OC(CH_3)_3$	50°C	DMF	15 h	35%
4	OCH_2Ph	H	OBn	OCH_2Ph	70°C	DMF	20 h	43%

The success of the reaction depends upon the urethane and the reaction conditions. For example, a tert-butyloxycarbonyl-substituted diamine cyclized in one case (entry 3) whereas the tBoc analog of entry 1 did not. Cyclizations occurred in either acetonitrile or DMF, but not necessarily in both solvents. Depending upon the exact reaction conditions and starting materials, one or both of the urethane protecting groups may be removed in the cyclization step. The requirement for a base being present indicates that Cs_2CO_3 may deprotonate one of the nitrogen atoms which then attacks the carbonyl carbon on the other urethane eliminating benzyl alcohol. Dibenzyl carbonate and benzyl alcohol were isolated in the first reaction described in Table 1, thus indicating that in this case a small amount of benzyl alcohol is deprotonated and the alkoxide ion nucleophilically attacks the remaining urethane.

In conclusion, the methodology presented herein provides a simple and direct route to 5-substituted cyclic ureas. Routine hydrogenation of the azido group in the case where there is an azide on the 5-C, or utilizing another substituent in this position, would enable access to a variety of functionalized ureas. However, hydroxyl groups in the 5-position must be protected during cyclization since use of a free hydroxyl results in an alternative cyclization to a 5-membered cyclic urethane rather than a 6-membered cyclic urea.

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2. MacLaren, J. A. *Aust J. Chem.*, 1958, 11, 360-365.
3. Michels, J. G. *J. Org. Chem.* 1960, *25*, 2246-2247.
4. ^1H NMR (CH_3OH): δ 3.99 (m, 1H,), 3.48 (ABX, 2H, J_{AB}=11.9Hz, J_{AX}=2.6Hz), 3.31 (ABX, 2H, J_{AB}=11.9Hz, J_{BX}=3.7Hz); ^{13}C (CH_3OH): 158.8, 52.4, 44.5; IR (KBr) 2105 cm^{-1} (N_3).
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