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Straightforward Ring Expansion of Pyroglutamates to Perhydro-1,3-diazepine-2,4-diones

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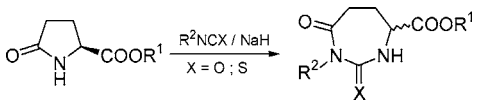
ABSTRACT



Perhydro-1,3-diazepine-2,4-diones are rare and can only be prepared, up to now, by special methods. A new one-step protocol was developed, comprising N-carbamoylation using an isocyanate followed by intramolecular ring expansion. This new methodology provides a straightforward access to this interesting seven-membered skeleton.

Diazepines are a class of compounds exhibiting a wide range of biological activity. Most common are the 1,4-benzodiazepines which have received much attention since the early 1960s because of their value in psychotherapy (e.g., diazepam, the active compound in Valium, which shows strong CNS depressant properties). Since then, they have been reported to have anxiolytic activity,[1] anticonvulsant activity,[2] and antitumor activity,[3] and later on their herbicidal properties were disclosed.[4] Recently 1,4-diazepine-5-ones were synthesized by the intramolecular transamidation of β-lactams with tethered amines using single-mode microwave irradiation.[5]

The 1,3-diazepines have been studied to a lesser extent although they also show some interesting activities. A seven-membered cyclic urea scaffold, for example, was found to be a potent inhibitor of the HIV-1 protease[6] and a ring-expanded nucleoside containing the 1,3-diazepine moiety, a competitive inhibitor of both adenosine deaminase and guanase.[7] 1,3-Diazepine-2,4-diones **2** (Figure 1), however,

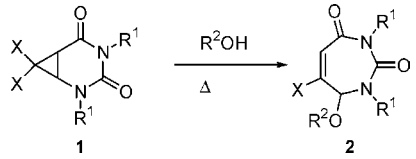


Figure 1. Synthesis of 1,3-diazepine-2,4-diones by ring expansion of halocarbene adducts of uracil derivatives.

are rare[8] and can, up to now, only be prepared by special methods involving photochemical[9] or thermal ring expansion of the halocarbene adducts of 1,3-disubstituted uracil derivatives **1** by heating in the presence of alcohols in a sealed

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tube.[10] Another known method involves the cyclization, in a low yield, of *N*,*N*′-dichloroglutaric diamides (synthesized from glutaric diamides and Cl_2 gas) with triethylamine.[11]

In the past, 1-carbamoyl-2-pyrrolidinones **3** were incorrectly identified as perhydro-1,3-diazepine-2,4-diones **4** (Figure 2).

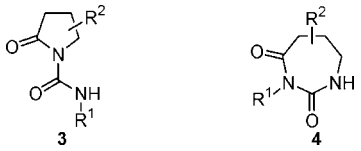
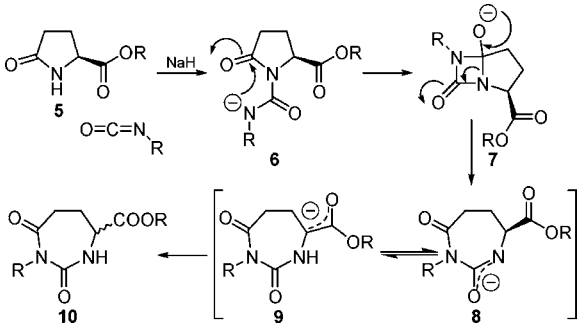


Figure 2. 1-Carbamoyl-2-pyrrolidinones **3** and perhydro-1,3-diazepine-2,4-diones **4**.

For example, the natural product squamolone was originally identified as a seven-membered ring (of type **4**) but later turned out to be a five-membered ring (of type **3**).[12] Also a claim of the preparation of these seven-membered rings by cyclization of 4-ureidobutyric acids with thionyl chloride[13] was later corrected by another research group.[14]

During our research on pyroglutamates for the development of agrochemicals and pharmaceutically interesting azaheterocyclic skeletons,[15] we found that when the sodium salt of an alkylpyroglutamate **5** is treated with 1 equiv of an isocyanate, reaction occurs both on the N-atom and on the C2-atom resulting in a complex mixture of different compounds. However, when a mixture of **5** with an isocyanate is treated with NaH in diethyl ether, a precipitate is formed during the reaction, which after workup proved to be the sodium salt of the expected carbamoyllactam **6** in high purity (Scheme 1). If the reaction is performed in THF on the other

Scheme 1. Synthesis of Perhydro-1,3-diazepine-2,4-diones by Intramolecular Ring Expansion of Pyroglutamates



hand, no precipitate is formed and after workup a compound was isolated which gave a different but very similar ^{1}H NMR

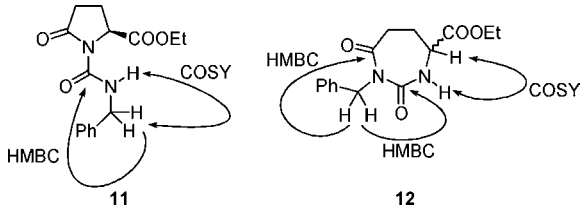
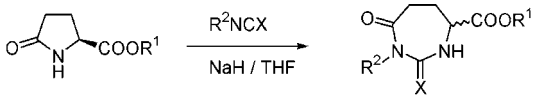
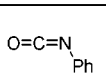
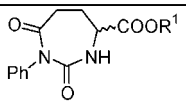
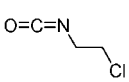
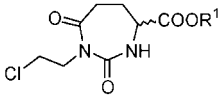
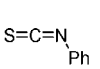
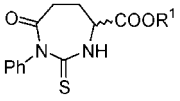
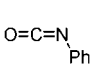
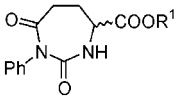
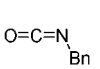
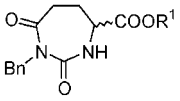
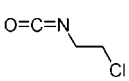
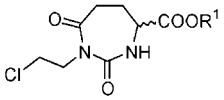
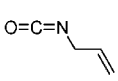
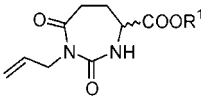
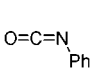
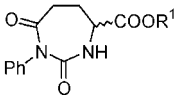


Figure 3. Most important COSY and HMBC couplings of **11** and **12**.

spectrum. It was assumed that intermediate **6**, which is apparently soluble in THF, reacts intramolecularly by a nucleophilic attack on the lactam ring with formation of the unstable intermediate **7**. This intermediate decomposes with loss of ring strain to form the seven-membered ring anions **8** and **9**. These anions are in equilibrium with each other, causing racemization of the chiral center (this was proven

Table 1. Synthesis of Perhydro-1,3-diazepine-2,4-diones by a One-Step Carbamoylation−Ring Expansion Sequence



	R^1	isocyanate	product	yield (%)[a]
1	Bn			56
2	Bn			93
3	Bn			42
4	Et			89
5	Et			87
6	Et			81
7	Et			48
8	Me			81

[a] Isolated yield after flash chromatography or recrystallization.

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by quenching the reaction with D_2O) and upon workup resulted in **10** as a 1:1 mixture of its enantiomers. In contrast, the isolated carbamoyllactams **6** are still optically active.

Since we now had both the five-membered ring **6** and what we believed to be **10** in hands, it was easy to compare all the spectral data. Although both ^1H NMR and ^{13}C-spectra clearly showed they were two different compounds, no conclusions could be made judging these spectra alone. The decisive proof was given by comparing both COSY- and HMBC-coupled spectra (Figure 3).

In the case of **11**, there is a coupling in the COSY spectrum between the proton on the N-atom and the two protons of the benzyl group, the proton on nitrogen appears as an incompletely resolved triplet. In the case of **12**, however, the proton on the N-atom couples with the proton next to the ester function and not with the protons of the benzyl group, proving that the benzyl group is attached to a tertiary nitrogen. Furthermore, in the HMBC spectrum, the protons of the benzyl group of **11** only couple to the urea carbonyl (easily distinguishable from both other carbonyl groups) whereas in the case of **12** they couple to both the urea and the lactam carbonyl.

Since it is was established that the perhydro-1,3-diazepine-2,4-dione was synthesized, the same methodology was performed on other combinations of pyroglutamate esters and isocyanates (Table 1).

We were pleased to find that different esters underwent the reaction, although in some cases, traces of carbamoyllactam could be observed due to the poor solubility of this intermediate in THF. This is probably the reason the benzyl ester formed a perhydro 4-oxo-2-thioxo-1,3-diazepine with phenyl isothiocyanate (entry 3) whereas the ethyl ester only gave the five-membered ring.[16]

In conclusion, a new and very straightforward one-step approach was developed toward these interesting perhydro-1,3-diazepine-2,4-diones. Since the pyroglutamate skeleton can easily be functionalized on different positions with control of the stereochemistry,[17] this new approach offers the possibility of efficiently synthesizing a collection of highly functionalized small molecules which is important for diversity-oriented synthesis, a concept that has recently gained importance.[18] Further research will be reported in due course.

Acknowledgment. Financial support for this research from the Bijzonder Onderzoeksfonds (Research Fund, Ghent University) is gratefully acknowledged.

Supporting Information Available: All carbon spectra of the new compounds synthesized and their complete characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) **Typical Experimental Procedure for Synthesis of Perhydro-1,3-diazepine-2,4-diones.** The pyroglutamate ester (3 mmol) was dissolved into THF (30 mL, freshly distilled from Na metal). To this solution was added the isocyanate (3.3 mmol) followed by NaH (3.3 mmol, washed with hexanes). The reaction was allowed to stir under nitrogen atmosphere at room temperature for 16 h. The reaction was quenched by addition of saturated aqueous NH_4Cl until the pH was neutral. The mixture was extracted with EtOAc, and the organics were dried ($MgSO_4$) and filtered. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica gel; hexane/EtOAc).

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