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Synthesis of Pyrrolidine-2,4-diones from Urethane N-carboxyanhydrides (UNCAs)

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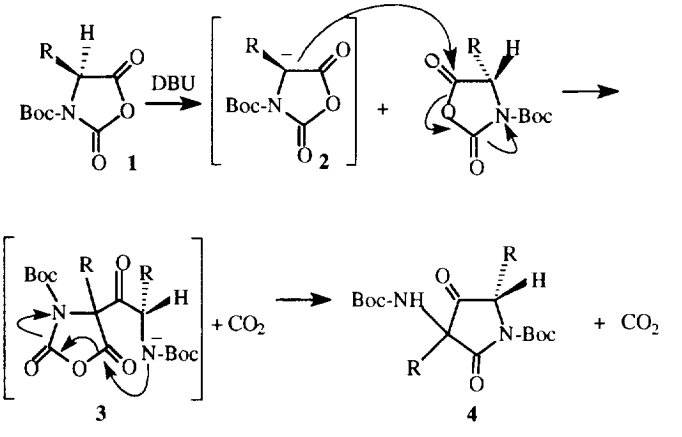
Abstract : In the presence of a base in aprotic medium, UNCAs lead to N-urethane protected-3,5-dialkyl-3-amino pyrrolidine-2,4-diones as racemic cis/trans mixtures. Consequently the choice of the base should be carefully considered to optimize yields and avoid side products when UNCAs are used in peptide synthesis.

Our laboratory is investigating the use of urethane N-protected carboxyanhydrides (UNCAs)[1] in peptide synthesis and in several reactions leading to aminoacid derivatives. UNCAs are very reactive aminoacid derivatives. They have been used with success in solid phase peptide synthesis (SPPS)[1] and we have shown their usefulness in the synthesis of peptides in solution.[2] We have also shown that UNCAs can be considered as starting material for the synthesis of various aminoacid derivatives such as β-amino alcohols[3], statine derivatives[4], α-amino-aldehydes[5] and vicinal tricarbonyl compounds[6] in good yields.



Scheme 1. Proposed mechanism of formation for pyrrolidine-diones from UNCAs.

Recently we demonstrated that UNCAs are reactive enough to yield to the corresponding tert-butyl esters when tert-butanol is used as solvent, in the presence of potassium bicarbonate at 45°C[7]. Simplicity, efficiency and mild conditions characterize all these reactions. We describe here the synthesis of pyrrolidine-2,4-dione derivatives **4** by reaction of UNCAs in the presence of a base[8]. The reaction mechanism and the configuration of the resulting pyrrolidine-2,4-diones are discussed.

We have found that UNCAs **1** produced the corresponding pyrrolidine-2,4-diones **4** almost instantaneously, at room temperature in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Mass and ^{1}H NMR spectroscopy of the obtained compounds confirmed their structures. When Boc-Ala-NCA reacted with DBU, the resulting product exhibited a molecular peak at MH^+ 343, with two fragments at MH^+ 243 (343 minus Boc) and MH^+ 143 (343 minus 2 Boc groups). Furthermore the ^{1}H NMR spectrum showed the presence of: (i) two different Boc groups; (ii) two different methyl groups (one is coupled with an α proton and one is a singlet); (iii) one signal corresponding to the α proton; (iv) one amide proton. All these data confirmed the pyrrolidine-2,4-dione structure **4** (Scheme 1). Furthemore, the ketone function of the pyrrolidine-2,4-diones **4** could be quantitatively reduced by sodium borohydride in dichloromethane. The two Boc groups could be removed by TFA treatment and further coupling with a N-protected aminoacid residue in the presence of an activating reagent produced the corresponding mono-acylated product, supporting the presence of one reactive amine function.

A hypothetic mechanistic route leading to these dimers is presented in Scheme 1. This possible mechanism is supported by the fact that the reaction occurs even in the presence of catalytic amounts of DBU. Some pyrrolidine-2,4-diones derived from aminoacids have already been described in the literature as side products from the base-catalyzed polymerization of 5-oxazolones.[9]

Different bases were used to find a suitable one that did not produce the pyrrolidine-2,4-diones **4** and that could be used in peptide synthesis without side reactions. Experiments using Boc-Phe-NCA and Boc-Ala-NCA were run at room temperature with various bases and in different solvents (Table 1). The formation of pyrrolidine-2,4-diones **4** occurred in the presence of even catalytic amounts of N-diisopropylethylamine (DIEA) and triethylamine (NEt_3) in DMF or DCM as solvents. No reaction occurred in THF. When N-methylmorpholine (NMM) or 4-dimethylaminopyridin (DMAP) was used, no reaction was observed whatever the solvent used (DCM, DMF, THF). It is then recommended to use NMM as base when UNCAs are used for the acylation of an amine function like in peptide synthesis.

base	solvent	formation of **4**
NEt_3	DMF	yes
NEt_3	DCM	yes
NEt_3	THF	no reaction
DIEA	DMF	yes
DIEA	DCM	yes
DIEA	THF	no reaction
DBU	DCM, THF, DMF	yes
NMM	DCM, THF, DMF	no reaction
DMAP	DCM, THF, DMF	no reaction

Table 1. Formation of pyrrolidine-2,4-diones **4** with various bases in different solvents.

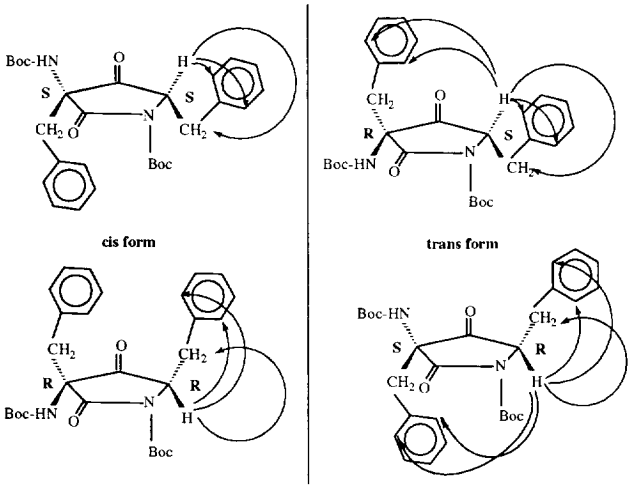
According to our proposed mechanism (Scheme 1) two different species can be obtained (Scheme 2). One species with the two aminoacid side chains on the same side of the pyrrolidine cycle (cis form) and the other species with aminoacid side chains on different sides of the cycle (trans form).

HPLC analysis of the crude reaction mixture of Boc-Ala-NCA in the presence of DBU[10] showed two peaks almost equivalent in various conditions (0.3 or 1 equivalent of base at room temperature or at -10°C).^{1}H NMR studies of these crudes revealed the presence of two different species of pyrrolidine-2,4-diones (50% cis, 50% trans, the trans form eluting first). However, the two peaks observed by analytical HPLC could be separated by preparative chromatography and studied by ^{1}H NMR spectroscopy. In the case of Boc-Phe-NCA, reaction in the presence of DBU produced a major peak (90% identified as the trans form) and a minor peak (10%, identified as the cis form) as shown by ^{1}H NMR spectroscopy. When the reaction was performed in the presence of DIEA, ^{1}H NMR spectra revealed the presence of the two species in a 60/40 ratio (cis/trans).

We will particularly present our results concerning the pyrrolidine-2,4-diones isolated from Boc-Phe-NCA. The α-proton (H_5) and the chemical shifts of the two methylene groups were very different for the two species (see Table 2). The large chemical shift differences observed for H_5 proton are probably due to a ring current effect of the aromatic cycle beared by the quaternary carbon (C_3) for one of the two forms. Such a ring current effect could be expected for the trans species. According to this hypothesis the NOE between H_5 and C2-H, C6-H of the Phe ring located in position 3 (Scheme 2) allowed us to unambiguously assign the trans conformation for this compound. This type of NOE was not observed for the other compound referred as cis.

Boc-Ala	H_5	CH_3-C5	CH_3-C3	**Boc-Phe**	H_5	CH_2-C5	CH_2-C3
cis form	4.63	1.45	1.27	cis form	4.4	2.3 and 1.8	2.9 and 2.6
trans form	4.34	1.46	1.23	trans form	3.25	3.1 and 2.9	3.0 and 2.9

Table 2. Typical ^{1}H NMR chemical shifts (δ, ppm) observed with pyrrolidine-2,4-diones obtained from Boc-Phe-NCA and Boc-Ala-NCA.



Scheme 2. Schematic representation of the cis and trans forms of pyrrolidine-2,4-diones **4** and observed NOEs from α proton.

The optical rotation of the pyrrolidine-2-4-diones obtained from Boc-Phe-NCA and Boc-Ala-NCA in different reaction conditions and purified by HPLC showed values close to zero, suggesting that they could have epimerized. Indeed, both the cis and trans forms could contain two different diastereoisomers: (3S,5S), (3R,5R) and (3S,5R), (3R,5S) respectively (Scheme 2). In the experiments that were performed, these diastereoisomers of the cis and trans form could not be distinguished by ^1H NMR spectroscopy.

The formation of pyrrolidine-2,4-diones **4** was not limited to Boc-Phe-NCA and Boc-Ala-NCA. Several other UNCAs led to the corresponding pyrrolidine-2,4-diones (Table 3). Even aminoacids bearing bulky side-chain (i.e.: Val, Ile) produced the corresponding pyrrolidine-2,4-diones in the presence of DBU or DIEA, but with lower yields. Z-UNCAs also produced these dimers, but the reaction was less clean. Fmoc-UNCAs could not be used in this reaction.

UNCAs	Yield (%)	mp (°C)	MH^+
Boc-Ala	75	125	343
Boc-Phe	90	230	495
Boc-Leu	75	105	427
Boc-Val	30	135-140	399
Boc-Ile	30	132	427
Boc-Tyr(OBzl)	55	121	707
Boc-Asp(OChx)	35	oil	595
Boc-Met	60	110-115	463
Boc-Asp(OBzl)	40	60	611
Boc-Glu(OBzl)	40	oil	639
Z-Phe	40	154-155	563

Table 3. Synthesis of different pyrrolidine-diones **4** (mixture of cis/trans) from various UNCAs.

The use of UNCAs allows easy synthesis of pyrrolidine-2,4-diones **4** that can be considered as new aminoacid derivatives and can be useful as bioactive entities or for the introduction of biologically active moieties into pseudo-peptides or peptoïds. They can also be used as heterocyclic building blocks for combinatorial chemistry. The reaction described in this paper also pointed out that in couplings involving UNCAs as activated aminoacid derivatives the base that is used should be carefully selected to avoid side reactions.

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10. Typical experimental procedure for the synthesis of pyrrolidine-2,4-diones: To a stirred solution of a N-protected N-Carboxyanhydride (10 mmol) in anhydrous tetrahydrofuran (THF, 10ml) was added DBU (10 mmol, 1.49 ml). After 15 min the solvent was removed *in vacuo* and the residue dissolved in ethyl acetate, washed with potassium hydrogen sulfate solution (5% in water), saturated sodium hydrogen carbonate solution and brine. The organic layer was dried over sodium sulfate and the solvent concentrated *in vacuo*. The residue can be purified by flash column chromatography. Cis and trans products were separated by HPLC on a Waters Prep 4000 apparatus using C18 15µm Deltaprep column (40 x 100 mm) with a gradient mode.

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