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Synthesis of α,α-Dialkylated Amino Acids with Adenine or Thymine Residues A New Mild and Facile Hydrolysis of Hydantoins

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Abstract *The synthesis of α,α-dialkylated amino acids which contain two adenine or thymine residues in their side chains is presented. In this context, a mild method for the cleavage of hydantoins is introduced.*

In nature only nucleic acids are capable of molecular replication. Some time ago,[1] we demonstrated that relatively simple synthetic molecules could also show this behavior. By structurally varying these systems mechanisms of molecular evolution like mutation and selection have been investigated.[2] In contrast to DNA, where information is stored in the sequence of different heterocyclic bases along the chain, our replicators are not informational. We recently proposed a more versatile self-replicating system[3] (Fig. 1), in which nucleic acid bases are attached to a peptide backbone. As in DNA these bases serve both as binding sites and as part of a code.

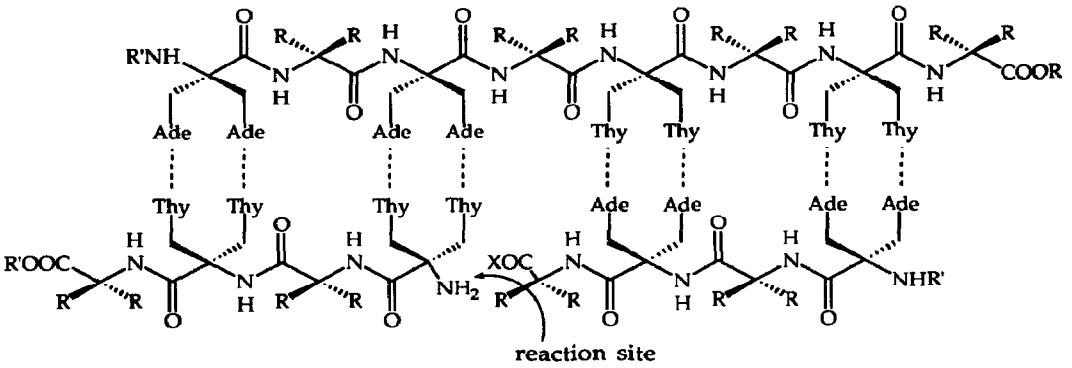
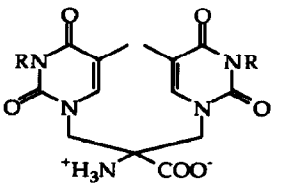
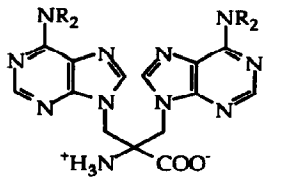


Fig. 1: Schematic representation of a self-replicating peptide (Ade = adenine, Thy = thymine).

Building blocks for these peptides are the amino acids **1a** and **2a**. The α,α-dialkylated amino acids were chosen because they should restrict the conformation of the peptide chain to a β-sheet,[4] and the problems posed by asymmetric centers could be avoided.



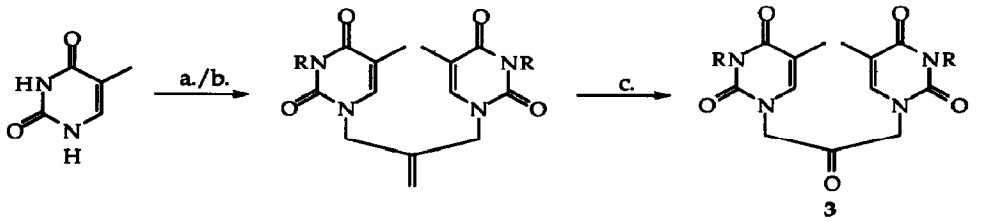
1a R = H
1b R = benzyl



2a R = H
2b R = 4-methoxybenzyl

Amino acids containing only one nucleic acid base are known,[5] but the disubstituted derivatives **1a** and **2a** have not been prepared before. Here we describe their syntheses as protected derivatives and in this context, offer a mild and efficient method for the hydrolysis of hydantoins.

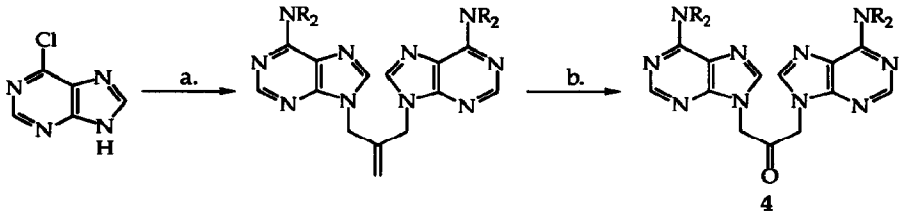
The protected derivatives **1b** and **2b** were obtained from the corresponding ketones (**3**,**4**). These could be synthesized in a straightforward reaction sequence (Schemes 1 and 2).



3

Scheme 1: Synthesis of ketone **3** (R = benzyl; a.: 1. TMSCl/HMDS; 2. 3-chloro-2-(chloromethyl)-1-propene/NaI/DMF[6] (88%); b.: BnBr/Bu_4NF[7] (85%); c.: 1. OsO_4/4-methylmorpholine-N-oxide; 2. $NaIO_4$ (71%)).

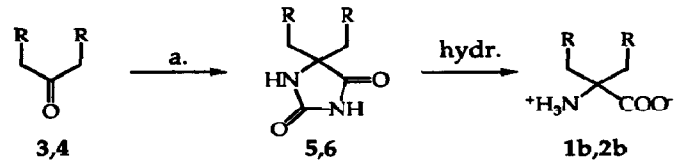
Thymine was alkylated with 3-chloro-2-(chloromethyl)-1-propene under conditions previously reported.[6] The alkene was converted to the ketone **3** by oxidation with OsO_4 followed by cleavage of the resulting diol with $NaIO_4$. The introduction of the benzyl group in the second step was necessary because the thymine ring proved to be unstable to the periodate oxidation. In a similar manner the protected adenine derivative **4** was obtained.



4

Scheme 2: Synthesis of ketone **4** (R = 4-methoxybenzyl; a.: 1. 3-chloro-2-(chloromethyl)-1-propene/K_2CO_3/DMSO[8]; 2. 4,4'-dimethoxydibenzylamine[8] (35%); b.: 1. OsO_4/4-methylmorpholine-N-oxide; 2. $NaIO_4$ (61%)).

Hydantoins are convenient intermediates for amino acid syntheses from aldehydes or ketones. They can be obtained by reaction of the carbonyl compound with $(NH_4)_2CO_3$/NaCN under various conditions and often in very good yields.[9] Hydrolysis under acidic or basic conditions gives the free amino acids. Since this reaction sequence has been used successfully for the syntheses of a variety of cyclic or α,α-dialkylated amino acids it was applied to the syntheses of **1b** and **2b**. Hence, the ketones **3,4** were converted to the corresponding hydantoins **5,6**.

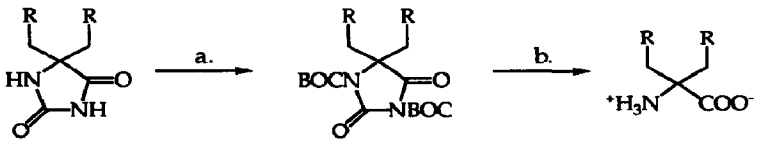


3,4 **5,6** **1b,2b**

Scheme 3: Synthesis of the amino acids (a.: $(NH_4)_2CO_3$/NaCN/NH_3/ethanol/H_2O, 120°C, 4h; **5**: R = 3-benzylthymine (96%); **6**: R = 6-di(4-methoxybenzyl)aminopurine (84%)).

For the hydrolysis of hydantoins drastic conditions are usually required, *e.g.*, concentrated NaOH or $Ba(OH)_2$ at temperatures >100°C or refluxing conc. HBr.[9] Under such conditions the nucleic acid bases proved to be unstable. Under the basic conditions, *e.g.*, the heterocyclic rings proved especially susceptible to degradation. We therefore sought milder methods for the cleavage of hydantoins.

It is reported that 3-N-tosyl derivatives of hydantoins can be cleaved to the corresponding sulfonamides with diluted NaOH or KOH at slightly elevated temperatures.[10] After acidic hydrolysis of the amide the free amino acids have been obtained. However, three steps are involved in this reaction sequence and the overall yield were usually low (<50%). On the other hand, it is possible to hydrolyze, *e.g.*, secondary amides at room temperature with LiOH after replacement of the proton on the nitrogen with a BOC group.[11] The carbonyl group of the BOC-protected amide is more susceptible to nucleophilic attack, and the ease of cleavage may be due to the release of steric strain and the fact that the nitrogen is converted into a better leaving group.



Scheme 4: Cleavage of hydantoins (a.: BOC_2O/DMAP/THF/r.t./1h; b.: LiOH/THF/H_2O/r.t./4h).

Using this methodology we were able to cleave the hydantoins **5,6** effectively without degradation of the adenine or thymine rings. The resulting amino acids **1b,2b** were obtained in yields of ca. 60-70%. We believe that the combination of hydantoin synthesis with this method of hydrolysis may prove generally useful for amino acid syntheses. We will report on peptide synthesis with the new nucleo amino acids in due course.

Typical procedure for the hydrolysis of hydantoins. The hydantoin **5** (560 mg, 1mmol) was treated with di-*tert*-butyl-dicarbonate (660 mg, 3 mmol) in 15 ml of THF at room temperature with a catalytical amount of 4-dimethylamino-pyridine (6 mg, 0.05 mmol). After 1h both the amide and the imide part of the hydantoin were converted to the BOC-protected form almost quantitatively. DMAP was removed by simply filtering the reaction mixture through silica gel and washing the silica gel with 80 ml of THF. The combined filtrates were then treated with 8 ml of aqueous 1n LiOH for 4h at ambient temperature. By this time the hydrolysis of the hydantoin was complete. 250 ml of ethyl acetate was added and the organic layer was extracted with 2% HCl twice and four times with water. Without drying the solvent was evaporated *in vacuo*. The hydrochloride of amino acid **1b** crystallized upon trituration of the residue with ether in high purity (390 mg, 69%).

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