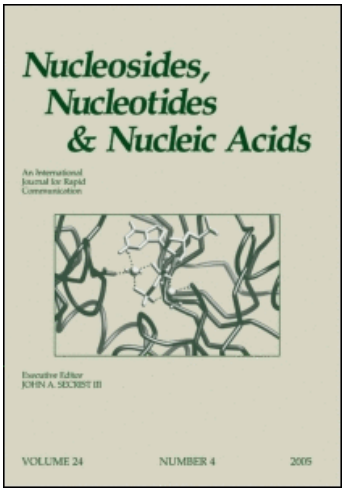

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of Peptide Nucleic Acid Monomers

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To cite this Article Kovács, L. , Timár, Z. and Penke, B.(1999) 'Synthesis of Peptide Nucleic Acid Monomers', Nucleosides, Nucleotides and Nucleic Acids, 18: 4, 727 — 729
To link to this Article: DOI: 10.1080/15257779908041555
URL: http://dx.doi.org/10.1080/15257779908041555

NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 727–729 (1999)

SYNTHESIS OF PEPTIDE NUCLEIC ACID MONOMERS

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ABSTRACT: The chemical synthesis of peptide nucleic acid (PNA) monomers is described using Fmoc (backbone), anisoyl (cytosine, adenine), 4-*tert*-butylbenzoyl (cytosine) and isobutyryl/diphenylcarbamoyl (guanine) protecting group combinations. For the guanine monomer the alkylation was realized both in a Mitsunobu [DIAD, triphenylphosphine or (4-dimethylaminophenyl)diphenylphosphine, *tert*-butyl glycolate] and in a low-temperature, sodium-hydride mediated alkylation (*tert*-butyl bromoacetate) to give the N^9-substituted derivative.

Peptide nucleic acids (PNA) are oligonucleotide analogues in which the sugar-phosphodiester backbone is replaced by a nucleobase-derivatized *N*-(2--aminoethyl)glycine chain. PNA oligomers have a number of properties (*e.g.* DNA and RNA recognizing ability) which make them very useful in antisense therapeutics and as diagnostics tools.

Until recently the assembly of PNA oligomers was based on a Merrifield solid--phase synthesis of Boc/Z-protected monomers[1]. Relatively few experience is available with other combination of protecting groups (*e. g.* Fmoc/Z[2], monomethoxytrityl/anisoyl[3]) and there is a continuous need for deprotection conditions compatible with different protocols.

We would like to report herein on our results concerning the synthesis of PNA monomers (**1-5**, FIG) using Fmoc group for the backbone and various other groups for the heterobase *N*-protection in order to enable the oligomer synthesis to be performed on a peptide synthesizer using Fmoc strategy. Nucleobase-substituted acetic acids were

prepared as follows. Thymin-1-ylacetic acid was prepared according to a published procedure[1]. Cytosine was anisoylated and subsequently alkylated to give the corresponding acid. As this compound was very poorly soluble in most organic solvents the more lipophilic 4-*tert*-butylbenzoylated derivative was alkylated and the acid was obtained using the procedure by Will *et al.*[3]. The anisoylated adenine derivative was similarly prepared[3]. However, we have found more convenient to peranisoylate and then hydrolyze N^9-ethoxycarbonyladenine to afford the same acid.

For the guanine monomer N^2-isobutyryl-O^6-diphenylcarbamoylguanine was chosen following the methodology by Zou and Robins[4,5] in order to avoid the formation of regioisomers. The persilylated derivative of the above compound can effectively be glycosylated or alkylated with alkoxymethyl halides[5] at N^9 but it does not undergo reaction with *tert*-butyl bromoacetate neither in the absence nor in the presence of mercury(II) cyanide[6,7]. We then investigated the Mitsunobu reaction[8] of N^2-isobutyryl-O^6--diphenylcarbamoylguanine with *tert*-butyl glycolate[9]. The resulting ester was obtained along with a negligible amount of the N^7 regioisomer. It was difficult to remove completely the triphenylphosphine oxide byproduct therefore (4-dimethylaminophenyl)-diphenylphosphine[10] was used which gave an acid-removable phosphine oxide[11]. Alternatively, low-temperature, sodium hydride-mediated alkylation with *tert*-butyl bromoacetate gave the product with excellent N^9/N^7 selectivity. When the alkylation was performed near room temperature significant amounts of N^7 isomer was formed. The free acid was then obtained in an acidic hydrolysis of the *tert*-butyl group.

The coupling of the appropriate nucleobase-substituted acetic acids with the common backbone *tert*-butyl *N*-[2-(*N*-9-fluorenylmethoxycarbonyl)aminoethyl]glycinate hydrochloride[2] was performed using standard methods of peptide synthesis.

The synthesis of some new PNA oligomers from our monomers is under way.

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