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Expanding the Scope and Orthogonality of PNA Synthesis

Srinivasu Pothukanuri,[a] Zbigniew Pianowski,[a] and Nicolas Winssinger*[a]

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Peptide nucleic acids (PNAs) hybridize to natural oligonucleotides according to Watson and Crick base-pairing rules. The robustness of PNA oligomers and ease of synthesis have made them an attractive platform to encode small or macromolecules for microarraying purposes and other applications based on programmable self assembly. A cornerstone of these endeavors is the orthogonality of PNA synthesis with other chemistries. Herein, we present a thorough investigation of six types of protecting groups for the terminal nitrogen atom (Alloc, Teoc, 4-N_3Cbz, Fmoc, 4-OTBSCbz, and Azoc) and five protecting groups on the nucleobases (Cl-Bhoc, F-Bhoc, Teoc, 4-OMeCbz, and Boc).

Introduction

Peptide nucleic acids[1,2] (PNAs) are unnatural oligonucleotide analogues in which the entire sugar–phosphate backbone is replaced by an achiral and uncharged pseudopeptide backbone consisting of *N*-(2-aminoethyl)glycine units to which the nucleobases are attached through methylene carbonyl linkers. PNAs hybridize preferably in the antiparallel alignment to complementary DNA/RNA/PNA in a sequence-specific manner and such a duplex exhibits higher thermal stability than their natural counterparts DNA/DNA and DNA/RNA.[3,4] Additionally, PNAs are remarkably resistant to enzymatic degradation, which makes them an ideal tool for the development of therapeutics, reagents in molecular biology, and diagnostics. From a chemistry standpoint, PNAs do not suffer from facile depurination as ribose-based oligonucleotides do and their oligomerization is based on versatile peptide bond formation, which thus facilitates the parallel synthesis of PNA appended to functional molecules.[5] We have been particularly interested in the use of PNA-encoded small-molecule libraries that can be converted into a microarray format by hybridization to DNA arrays.[6] PNA monomers for both Boc- or Fmoc-based synthesis are commercially available with Cbz or Bhoc-protected nucleobases, respectively. Alternative protecting groups for the terminal nitrogen atom include Mmt,[7] Dts,[8] Dmt,[9] N_3,[10] Alloc,[11] Dde,[12] Nvoc,[13] and Bts.[14] Beyond the commercially available monomers, the most frequently used protecting groups for nucleobases are Cbz, Mmt, and acyl groups.[15] Herein, we report our efforts to extend the orthogonality of PNA chemistry by extending the arsenal of protecting groups (**1**, Figure 1) and report practical procedures for the large-scale preparation of PNA monomers **1** from protected *N*-(2-aminoethyl)glycine backbone **2** and acid **3**.

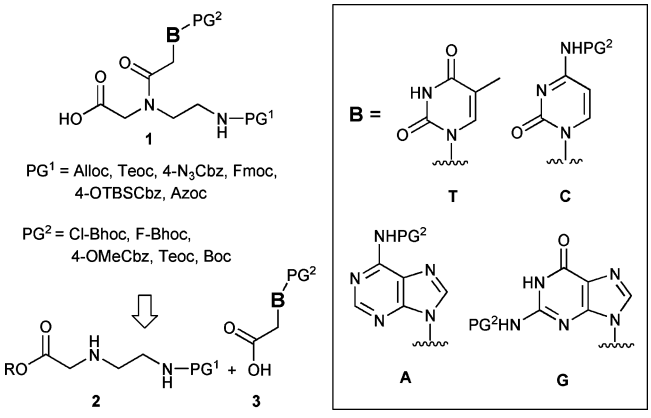

Figure 1. General structure of PNA monomer **1** and its synthetic precursors **2** and **3**. PG = protecting group; B = nucleobases; R = H, Me, or Bn.

Results and Discussion

The nucleobases protected with Bhoc, Cl-Bhoc, F-Bhoc, 4-OMeCbz, Teoc, or Boc groups were obtained in three-to-four steps as shown in Scheme 1. The cytosine (**4**), adenine (**8**), and 6-amino-2-chloropurine (**11**) heterocycles were alkylated with benzyl 2-bromoacetate and the exocyclic nitrogen atoms were converted into an isocyanate, which was then engaged in a reaction with different alcohols **5** to obtain carbamate-protected compounds **6**, **9**, and **12**. The lower reactivity of 6-amino-2-chloropurine necessitated triphosgene for isocyanate formation, whereas the reaction

[a] Organic and Bioorganic Chemistry Laboratory, Institut de Science et Ingénierie Supramoléculaires, Université Louis Pasteur, 8 allée Gaspard Monge 67000 Strasbourg, France
Fax: +33-3-90-24-51-12
E-mail: winssinger@isis.u-strasbg.fr
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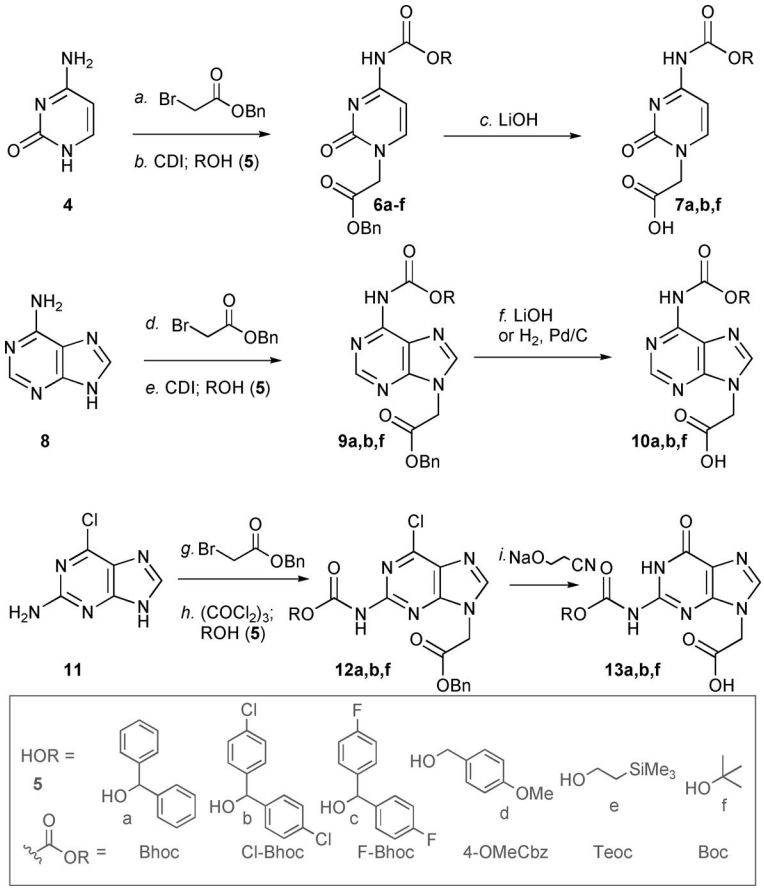
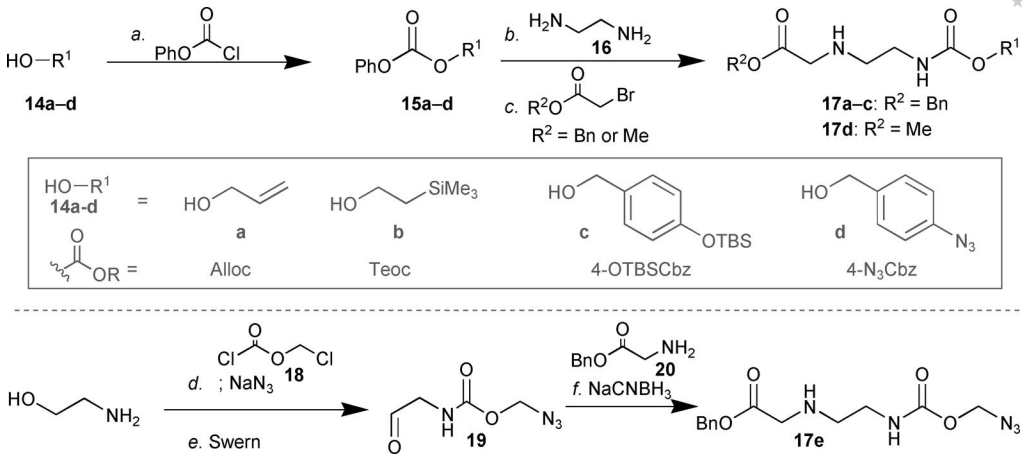


Scheme 1. Synthesis of protected nucleobases **7**, **10**, and **13**. Reagents and conditions: (a) *t*BuOK (1.15 equiv.), DMF, 100 °C for 2 h, then benzyl 2-bromoacetate (1.12 equiv.), 0 °C to 23 °C, 12 h, 92%; (b) CDI (1.6 equiv.), ROH 5 (1.3–5.0 equiv.), DMF, 60–80 °C to 23 °C, 12 h, 72–94%; (c) LiOH (4–10 equiv.), 0 °C or 23 °C, 10 min, 69–94%; (d) NaH (1.2 equiv.), benzyl 2-bromoacetate (1.1 equiv.), DMF 0 °C to 23 °C, 12 h, 84%; (e) CDI (1.5–3 equiv.), ROH (1.5–3 equiv.), DMF, 105 °C→23 °C, 12 h, 51%; (f) LiOH (18 equiv.), MeCN/H_2O/EtOH, 10 °C, 10 min, 73% (R-benzylic); or H_2, Pd/C, EtOH, 23 °C, 91% (R = *t*Bu); (g) K_2CO_3 (1.5 equiv.), DMF, 85 °C for 30 min, then benzyl 2-bromoacetate (1.1 equiv.), 0 °C to 23 °C, 12 h, 89%; (h) triphosgene (0.36 equiv.), Et*i*Pr_2N (2.2 equiv.), ROH (1.2–3.0 equiv.), THF, 0 °C to 23 °C, 12 h, 87%; (i) NaH (5.0 equiv.), 3-hydroxypropionitrile (5.0 equiv.), THF, –78 °C→23 °C, 12 h, 76–86%.

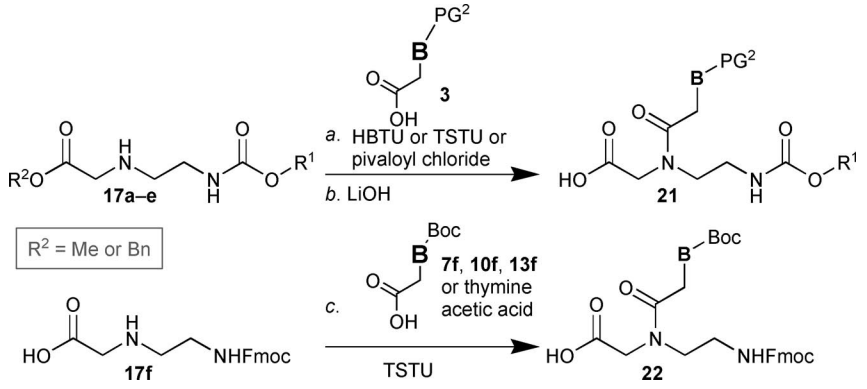
proceeded smoothly with carbonyldiimidazole for the adenine and cytosine heterocycles. The benzyl esters were then hydrolyzed to obtain suitably derivatized nucleobases **7**, **10**, and **13**. Although the benzyl ester of adenine **9f** could be conveniently cleaved under reductive conditions (H_2, Pd/C), hydrogenolysis of cytosine **6f** led to partial reduction of the heterocycle. The hydrolysis of compounds **12** required the concomitant conversion of the 6-chloro functionality into the ketone, which was most conveniently achieved with an excess amount of the alkoxide of 3-hydroxypropionitrile, which undergoes substitution followed by β-elimination.

Suitably protected *N*-(2-aminoethyl)glycine backbones **17a**–**e** were prepared as shown in Scheme 2. Phenyl carbonates **15**, obtained from the reaction of phenyl chloroformate and alcohols **14**, were used for the monoprotection of ethylendiamine[16] followed by alkylation of the remaining primary amine with methyl or benzyl 2-bromoacetate thus affording **17a**–**d**. Azoc[17]-protected backbone **17e** was prepared by reductive amination of glycine benzyl ester **20** and aldehyde **19**, which was in turn obtained in three steps from ethanolamine.

Suitably protected backbones **17** were acylated with nucleobase acetic acids **3** (**7**, **10**, and **13** and thymine acetic acid) as shown in Scheme 3. In general, the acylation with the pyrimidines (thymine acetic acid and cytosine acetic acid **7**) could be carried out by using a variety of activation methods (HBTU, DIC/HOBt, TSTU, or Piv-Cl), whereas the activation of the purines (**10** and **13**) could not be achieved with carbodiimide reagents. Nevertheless, activation in the form of *N*-benzotriazole esters (HBTU), *N*-succinimate esters (TSTU), or mixed anhydrides (pivaloyl chloride) were effective. Hydrolysis of the methyl or benzyl ester afforded acid **21** in good yield except for the compound bearing the 4-OTBSCbz group (**17c**), which was partially hydrolyzed during the reaction. Interestingly, coupling of activated heterocyclic acetic acids **3** with **17a**–**e** proceeded smoothly with the glycine moiety of **17** protected as a methyl or benzyl ester (R^2), whereas the equivalent reaction with **17f** in the form of a benzyl ester (not shown) gave poor results. We found it preferable to carry out the acylation with unprotected **17f** by using a mild activation method such as TSTU, as the use of stronger activation



Scheme 2. Synthesis of protected *N*-(2-aminoethyl)glycine **17**. Reagents and conditions: (a) phenyl chloroformate (1.0 equiv.), pyridine (1.25 equiv.), CH_2Cl_2, 23 °C, 4 h, quantitative; (b) **16** (1.0 equiv.), EtOH, 23 °C, 12 h, 54–68%; (c) benzyl 2-bromoacetate (1.0 equiv.) or methyl 2-bromoacetate (1.0 equiv.), Et_3N (1.0 equiv.), CH_2Cl_2, 0 °C, 4 h, 40–63%; (d) ethanolamine (2.0 equiv.), CH_2Cl_2, **18** (1.0 equiv.), –20 °C, 5 min, then NaN_3 (1.5 equiv.), DMSO, 23 °C, 12 h, 86% for 2 steps; (e) oxalyl chloride (1.5 equiv.), DMSO (3.0 equiv.), CH_2Cl_2, –78 °C; Et_3N (4.0 equiv.) –78→0 °C, 1 h, 86%; (f) **20** (0.8 equiv.), AcOH (1.2 equiv.), $NaCNBH_3$ (0.55 equiv.), MeOH, 0 °C, 2.5 h, 43%.

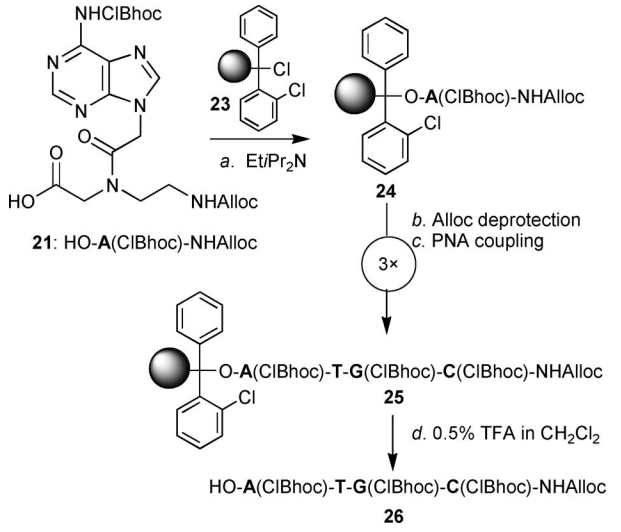


Scheme 3. Synthesis of protected PNA monomers **21** and **22**. Reagents and conditions: (a) HBTU or TSTU (1.1 equiv.), Et*i*Pr_2N (1.3–3.0 equiv.), **7**, **10**, **13**, or thymine-1-acetic acid (1.1 equiv.), DMF, 23 °C, 4–7 h, 55–94%; for coupling to **17e** (Azoc): **10f** or **13f** (1.1 equiv.), pivaloyl chloride (1.15 equiv.), *N*-methylmorpholine (2 × 2.5 equiv.), DMF, 0 °C →23 °C, 4 h; (b) LiOH (3.0–4.0 equiv.), 1,4-dioxane/H_2O or MeOH/H_2O, 23 °C, 2–20 min, 37–98%; (c) TSTU (1.1 equiv.), Et*i*Pr_2N (1.3 equiv.), **7f**, **10f**, **13f**, DMF, 23 °C, 1 h, 62–74%.

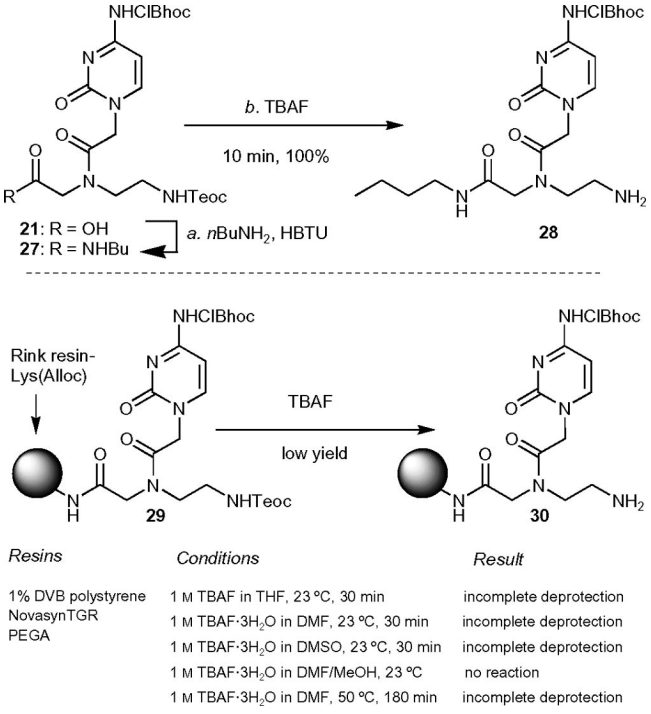
methods led to the formation of a mixed anhydride between **17f** and **3** thus engendering higher-order oligomers in addition to desired product **22**.[18]

Our first objective was to investigate the possibility of preparing PNA oligomers for segment couplings.[19,20] Although we had previously used 2-chlorotrityl resin to load PNA monomers bearing an Fmoc group onto the *N*-terminus and Bhoc groups on the nucleobases,[11] this system suffered from two limitations: first, the basic conditions required for the Fmoc deprotection led to significant cleavage due to cyclization (piperazinone formation), and second, the Bhoc group was not compatible with 1% TFA cleavage of the 2-chlorotrityl resin and required acetic acid cleavage, which was difficult to remove. We thus first investigated the Cl-Bhoc group by reasoning that the electron-withdrawing nature of the chlorine substituents would render this group more acid stable. To our gratification, we found that monomers **21** bearing a Cl-Bhoc group of the nucleobase and an Alloc group of the N-terminus were indeed more stable to TFA. As shown in Scheme 4, we thus prepared tetramer **25** containing all four nucleobases, which was released from the resin by using 0.5% TFA in CH_2Cl_2 to afford fully protected oligomer **26**. The oligomer was then coupled to Rink resin and engaged in two iterative cycles of deprotection/coupling by using DIC/HOBt activation to obtain a dodecamer. The kinetics of the couplings with the use of tetramer **26** were found to be significantly slower than the corresponding reaction with monomers **21** requiring at least 12 h to go to completion. Considering that an excess of monomer is required for the preparation of tetramer **26**, which is in turn used in excess (>4 equiv.) in the subsequent couplings, the synthesis of oligomers by segment coupling was not deemed attractive for our applications.

To explore further protecting groups for the terminal nitrogen atom, we were drawn to the Teoc group for its presumed compatibility to acid-labile groups and the Alloc or

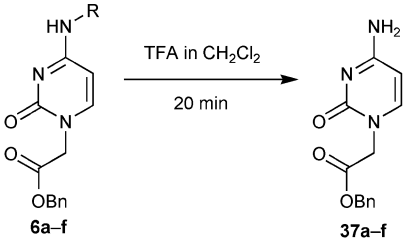


Scheme 4. Synthesis of protected PNA oligomers for segment coupling. Reagents and conditions: (a) **21** (2.0 equiv.), Et*i*Pr$_2$N (2.0 equiv.), DMF, 23 °C, 4 h; (b) Pd(Ph$_3$)$_2$Cl$_2$ (0.1 equiv.), Me$_3$SiN$_3$ (10 equiv.), Bu$_3$SnH (10 equiv.), CH$_2$Cl$_2$, DMF, 23 °C, 1 h; (c) **21** (4.0 equiv.), HBTU (3.5 equiv.), Et*i*Pr$_2$N (8.0 equiv.), NMP, 23 °C, 4 h; (d) TFA (0.5%) in CH$_2$Cl$_2$, 23 °C, 4 × 10 min.



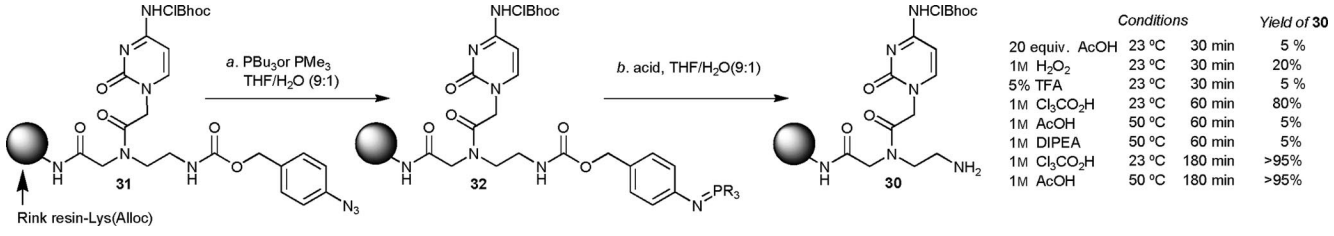
Scheme 5. Deprotection of Teoc-protected PNA monomers **27** and **29**. Reagents and conditions: (a) *n*-butylamine (1.5 equiv.), HBTU (1.5 equiv.), Et*i*Pr$_2$N (3.0 equiv.), DMF, 23 °C, 4 h, 67%; (b) 1 M TBAF in DMSO or DMF, 23 °C, 10 min.

azide-based protecting groups. To evaluate the kinetics of deprotection, monomer **21** (Scheme 5) bearing a Teoc group on the terminal nitrogen atom and a Cl-Bhoc group on the exocyclic nitrogen atom of cytosine was coupled to butylamine thus affording compound **27**. This compound was found to undergo smooth deprotection in 10 min with no evidence of acyl group migration by using 1 M TBAF in DMF or DMSO. Encouraged by this result, the reaction was repeated with the polymer-bound equivalent (**29**); however, the yield of the reaction was disappointingly low (<10% deprotection after 30 min). This result was surprising considering the successful prior use of silyl ethyl linker for carboxylic acid in solid-phase synthesis.[21,22] We ascribed the difference in reactivity between the solution-phase result (**27**→**28**) and the solid-phase result (**29**→**30**) to the hydrophobic environment of the polystyrene resin and investigated the reaction by using different solvents (DMF, DMSO, and DMF/MeOH) and resins (NovasynTGR: a PEG-polystyrene resin and PEGA: a PEG-polyamide resin);[23] however, we were unable to obtain satisfactory results.

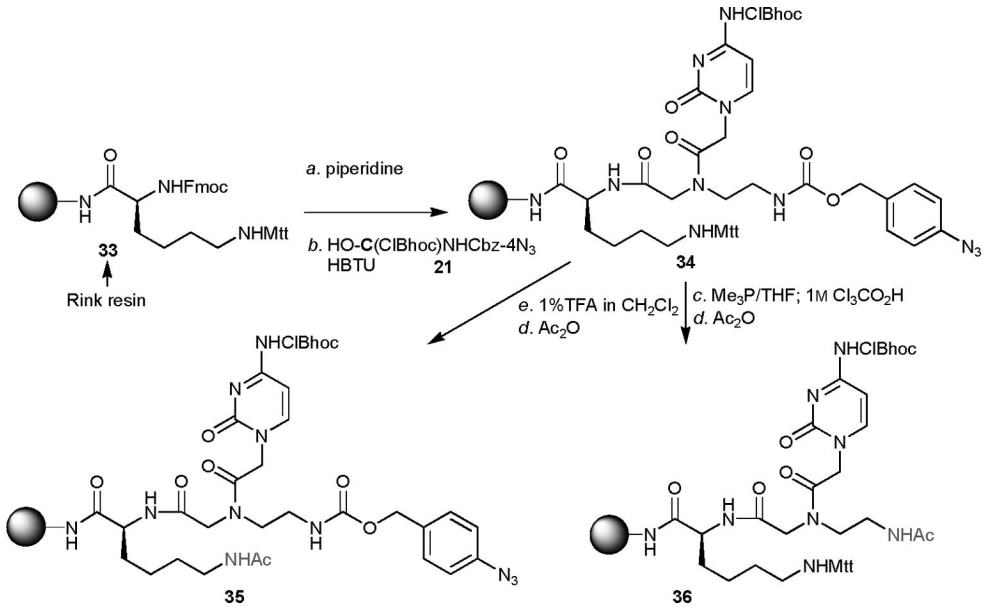


R =	Bhoc	Cl-Bhoc	F-Bhoc	4-OMeCbz	Teoc	Boc
1% TFA	100%	<1%	<1%	<1%	<1%	<1%
5% TFA	100%	100%	100%	100%	<10%	<5%

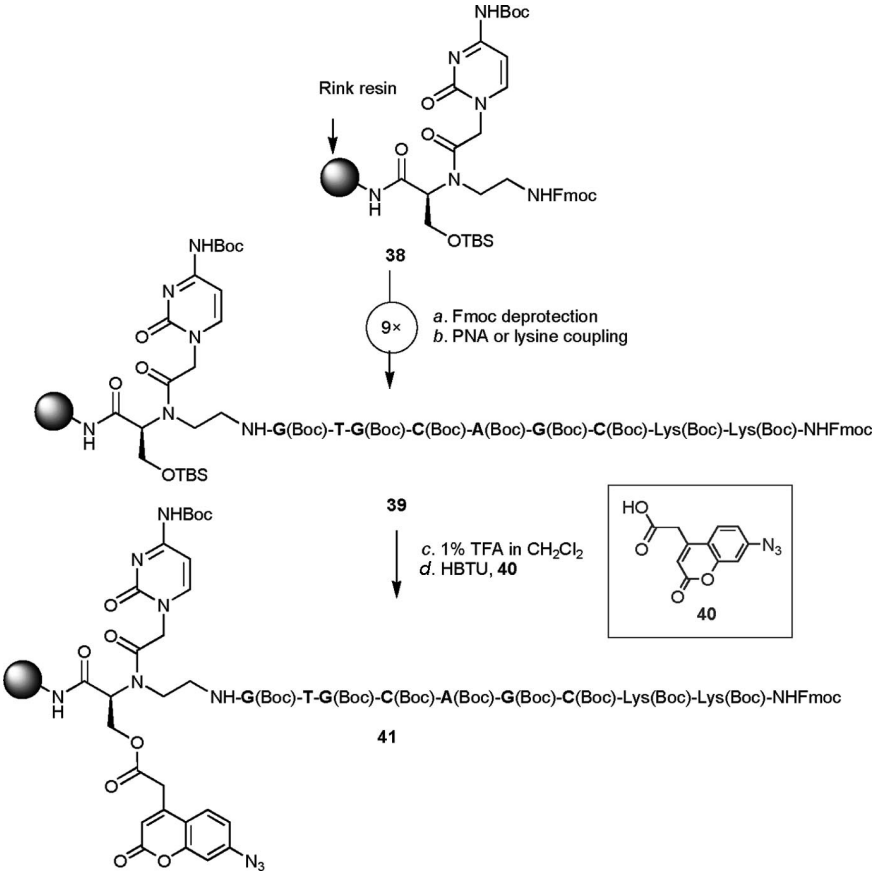
Figure 2. Stability of protected cytosines **6a**–**f** toward TFA in CH$_2$Cl$_2$.



Scheme 6. Deprotection of 4-N$_3$Cbz-protected PNA monomer **31**. Reagents and conditions: (a) 1 M PMe$_3$, THF/H$_2$O (9:1) or 1 M PBu$_3$,THF/H$_2$O (9:1), 23 °C, 15 min; (b) decomposition of the azaylide (see conditions above).



Scheme 7. Orthogonal deprotection of Mtt and 4-N_3Cbz. Reagents and conditions: (a) piperidine/DMF (1:4), 23 °C, 5 min; (b) **21** (4.0 equiv.), HBTU (3.5 equiv.), Et*i*Pr_2N (8.0 equiv.), NMP, 23 °C, 4 h; (c) 1 M PMe_3, THF/H_2O (9:1), 23 °C, 15 min; 1 M Cl_3CO_2H, THF/H_2O (9:1), 23 °C, 4 h; (d) Ac_2O (0.2 M), 2,6-lutidine (0.2 M), DMF, 23 °C, 5 min; (e) TFA (1%), CH_2Cl_2, 23 °C, 30 min; (f) Ac_2O (0.2 M), 2,6-lutidine (0.2 M), DMF, 23 °C, 5 min.



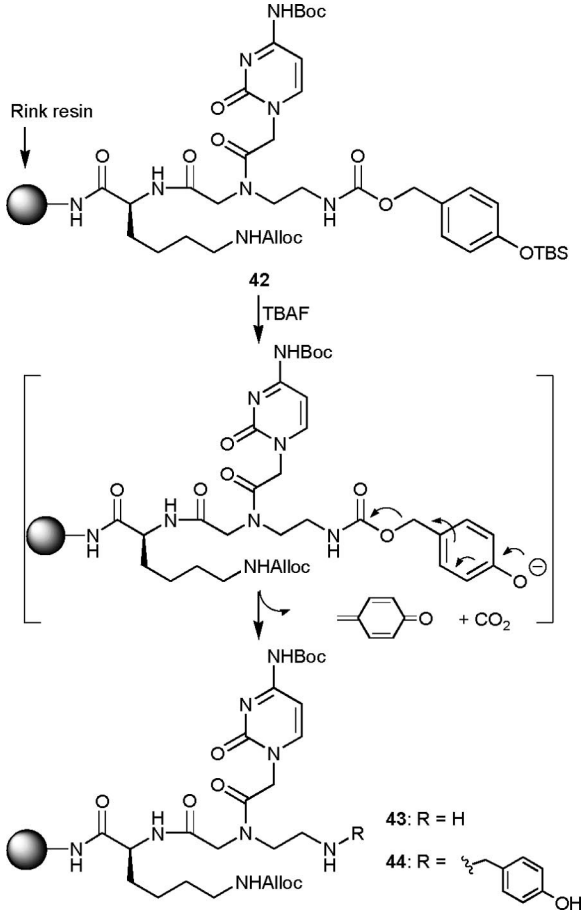
Scheme 8. PNA synthesis by using Boc/Fmoc protected monomers and their orthogonality to silyl ethers (TBS). Reagents and conditions: (a) piperidine/DMF (1:4), 23 °C, 5 min; (b) **22** (4.0 equiv.) or Fmoc-Lys(Boc)-OH (4.0 equiv.), HBTU (3.5 equiv.), Et*i*Pr_2N (4.0 equiv.), 2,6-lutidine (6.0 equiv.), NMP, 23 °C, 30 min; (c) TFA (1%), CH_2Cl_2, 23 °C, 30 min; (d) **40** (4.0 equiv.), HBTU (3.5 equiv.), Et*i*Pr_2N (4.0 equiv.), 2,6-lutidine (6.0 equiv.), NMP, 23 °C, 12 h.

Inspired by the mildness of azide reduction coupled to the benefits of carbamate protecting groups, we investigated the suitability of the 4-N_3Cbz group.[24] Although we previously reported the preparation of azidoPNA monomers[10] (PNA bearing an azide at the N-terminus rather than a carbamate protecting group), rigorous application of the deprotection protocol had to be utilized to avoid chain termination due to cyclization of the iminophosphorane to a dihydroimidazole. This problem was overcome by acylating directly the iminophosphorane product obtained; however, this methodology is not well suited for automated synthesis, which thus limits the applicability of azidoPNA. To evaluate the 4-N_3Cbz group, Rink resin **31** (Scheme 6) bearing a protected PNA monomer (Cl-Bhoc/4-N_3Cbz) was treated either with tributyl phosphane or trimethyl phosphane in THF/H_2O (9:1) thus affording iminophosphorane **32**, which decomposed into amine **30**. In our hands, the decomposition of **32** was sluggish and required an acid to proceed within a reasonable time frame.

The most practical reactions conditions were the use of trichloroacetic acid at room temperature for three hours to obtain complete deprotection. In order to assess the orthogonality of the 4-N_3Cbz group with very acid-labile groups such as amino-protected methyl trityl (Mtt), resin **33** was coupled to 4-N_3Cbz-protected monomer **21** (Scheme 7) and engaged in an orthogonal deprotection of either the Mtt (1% TFA) or 4-N_3Cbz (PMe_3; Cl_3CO_2H) group followed by acylation to obtain **35** and **36**, respectively, thus establishing mutual orthogonality of these two groups. However, caution had to be employed in the deprotection of the Mtt group, as prolonged exposure to 1% TFA led to Cl-Bhoc deprotection. This latter fact incited us to reinvestigate more acid-stable groups for the nucleobases. As shown in Figure 2, the stability of cytosine **6a**–**f** bearing Bhoc, Cl-Bhoc, F-Bhoc, 4-OMeCbz, Teoc, and Boc groups, respectively, were compared when exposed to 1% TFA and 5% TFA for 20 min. Cytosine was used for this experiment, as it is the most susceptible nucleobase to acid-mediated deprotection. Aside from the Bhoc group, all other groups were stable to 1% TFA; the Boc group was the most stable and showed minimal deprotection even with 5% TFA after 20 min. On the basis of the ease of removing the Boc byproduct after deprotection and the fact that adenine **9f** and guanine **12f** were even more resistant to acid, the Boc group was deemed most attractive for our purpose and F-Bhoc-, 4OMeCbz-, and Treoc-protected nucleobases were not further investigated.

Having access to PNA monomers bearing more acid-resistant protecting groups on the nucleobases, we asked whether it would be possible to deprotect a silyl ether under acidic conditions in the presence of an Fmoc-protected PNA oligomer. The basicity of fluoride in TBAF makes the fluoride-based deprotection of silyl ether incompatible with Fmoc groups. Thus, resin **38** bearing an *N*-(2-aminoethyl) serine PNA monomer was engaged in a cycle of nine iterative deprotection/coupling to obtain decamer **39** (Scheme 8). The TBS group was removed quantitatively by using 1% TFA, and the resulting free hydroxy group was coupled to azidocoumarin **40**[25] thus establishing fully orthogonal deprotection conditions. It is instructive to note that the same compound was previously prepared by using commercially available PNA monomers bearing Fmoc/Bhoc protecting groups; however, the Fmoc group had to be exchanged prior to TBAF deprotection of the silyl ether, as that protecting group combination was not orthogonal to silyl ether deprotection.

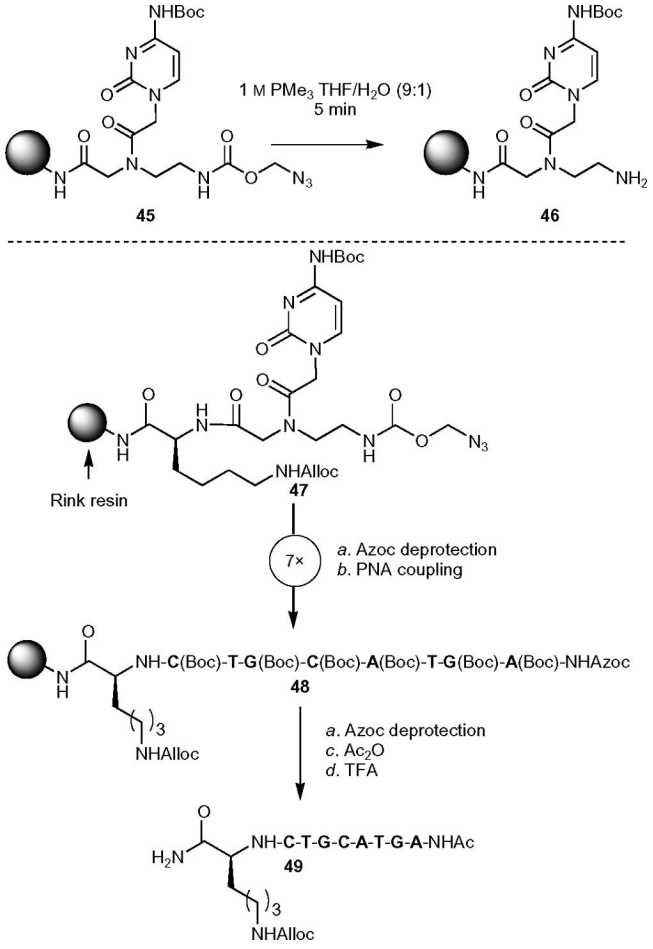
On the basis of the decomposition of iminophosphorane **32** and unsuitability of the Teoc group for our purpose, we speculate that the 4-OTBSCbz group may offer a useful alternative fluoride-labile protecting group. Resin **42** (Scheme 9) loaded with a protected PNA monomer (Boc/4-OTBSCbz) was exposed to TBAF, which thus resulted in complete deprotection within minutes. However, desired product **43** was contaminated with >50% of product **44** presumably stemming from the reaction of **43** with the quinone methide generated under the deprotection conditions. Attempts to suppress this side reaction with the addition of reducing agents or cation scavengers such as Et_3SiH, *m*-cresol, Me_2S, or amines only led to marginal improvements.



Scheme 9. Deprotection of 4-OTBSCbz protected PNA **42**. Reagents and conditions: 1 M TBAF in THF, 23 °C, 5 min.

We recently reported the use of the Azoc group in the context of peptide and carbohydrate chemistry and showed it to be mutually orthogonal to both the Mtt and Fmoc groups thus allowing the parallel synthesis in three dimen-

sions.[17] Encouraged by its fast deprotection under very mild conditions,[26] we investigated its utility for PNA synthesis. As shown in Scheme 10, the deprotection of polymer-bound intermediate **45** was extremely fast and contrarily to the aforementioned 4-N_3Cbz group, did not require an acid for the iminophosphorane decomposition. Azoc-protected monomers were found to perform with equal efficiency in PNA synthesis to Fmoc-protected monomers and are compatible with automated synthesis.



Scheme 10. PNA synthesis by using Boc/Azoc-protected monomers. Reagents and conditions: (a) 1 M PMe_3, THF/H_2O (9:1), 23 °C, 5 min; (b) PNA coupling: **21** (4.0 equiv.), HBTU (3.5 equiv.), Et*i*Pr_2N (8.0 equiv.), NMP, 23 °C, 4 h; (c) acetic anhydride (0.2 M), 2,6-lutidine (0.2 M), DMF, 23 °C, 5 min; (d) TFA (100%), 23 °C, 1 h.

Conclusions

The procedures reported herein provide rapid and scalable access to PNA monomers bearing protecting groups allowing the parallel synthesis of PNA with other molecules. The Alloc, Azoc, and 4-N_3Cbz protecting groups are fully orthogonal to Fmoc chemistry, which thus facilitates the parallel synthesis of PNA with peptides, whereas the orthogonality of Boc-protected nucleobases with Mtt-protected amine or TBS-protected hydroxy groups provide an additional dimension of orthogonality, which may be useful to introduce reporter groups such as fluorophores. The rapid deprotection of the Azoc group and the mildness of the reagents makes it compatible with the fast cycles of automated PNA synthesizers and rivals the efficiency of Fmoc-based synthesis.[27] The most convenient combination of protecting groups was found to be Boc-protected nucleobases with either Azoc or Fmoc protecting groups for the terminal nitrogen atom. The added stability of the Boc group relative to that of the Cl-Bhoc or F-Bhoc group makes reiterative deprotection of Mtt or other acid-labile groups reliable. Although the Alloc group can be removed in the presence of an Azoc or Fmoc group, reiterative deprotection of the Alloc group with tin hydride and palladium tetrakis leads to the precipitation of palladium, which can catalyze the decomposition of Bu_3SnH into H_2 thus leading to partial reduction of the Alloc group to the propyl carbamate or Azoc deprotection. Although this side reaction is marginal, it does decrease the efficiency of a reiterative process.

Experimental Section

Full experimental details and characterization data for compounds outlined in this work are available in the Supporting Information.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data for nucleobases **6**, **7**, **9**, **10**, **12**, and **13** and PNA monomers **21** and **22**; chromatograms and MALDI spectra of oligomers **41** and **49**.

Acknowledgments

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