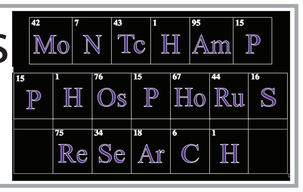
Preparation of Clickable Monomers Compatible with Automated PNA Synthesis

Grace Newell, Axel Sabourin, and Jean-Luc Montchamp*
Department of Chemistry and Biochemistry, TCU Box 268860, Texas Christian University, Fort Wort, Texas, 76129, USA. Email: j.montchamp@tcu.edu

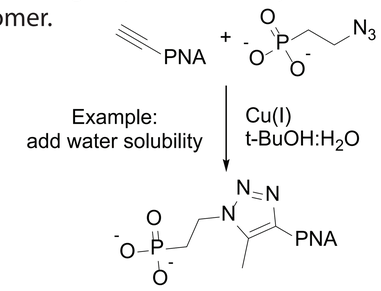


Abstract

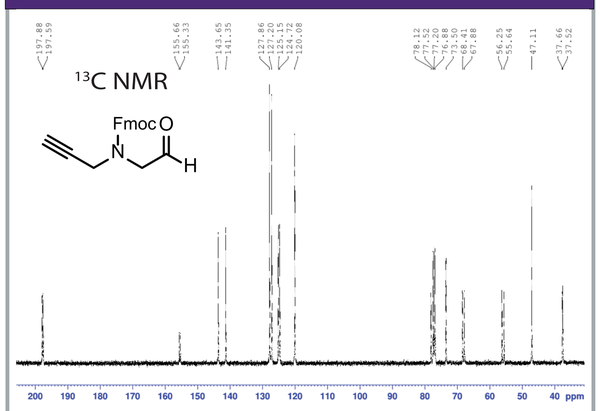
Peptide nucleic acids (PNA) are artificially synthesized monomers or polymers that mimic DNA or RNA sequences[1]. Due to their stability in biological conditions and their ability to bind complementary to DNA or RNA, PNAs have potential medicinal value since they can be used to block processes like replication, transcription, and protein synthesis[2]. Though most PNAs are commercially synthesized, the goal of this project was to introduce a propargyl moiety. This enables the final PNA monomer to have an alkyne which allows functional groups (like a polyamine tail, fluorescent tag, or an alkylating group) to be added at the end or any time throughout the synthesis. The PNA monomer will be made with all four DNA bases (thymine, cytosine, adenine, and guanine). Another importance of this PNA monomer is its ability to undergo click reactions to add functional groups or a charge[3]. Click chemistry is a chemical reaction that uses copper-catalyzed coupling to combine an azide with an alkyne. The ability to use click chemistry is beneficial since it can be done in biological conditions, has a near quantitative yield with few byproducts, and is relatively quick to perform. In conclusion, this project is useful since these PNA sequences can be used to modulate processes and treat a variety of diseases while having the ability to add groups that will give the PNA various functionalities.

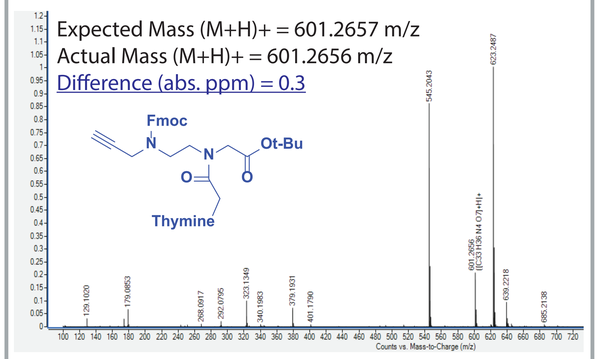
Click Chemistry

Click chemistry is beneficial since it is quick, has a quantitative yield, and can be done in biological conditions. Click chemistry can be used to add a charge (as seen below) or attach functional groups to the synthesized PNA monomer.



Spectra

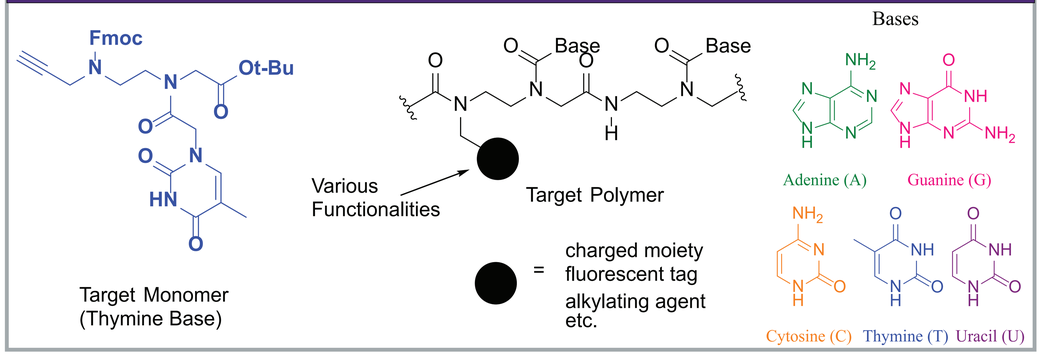




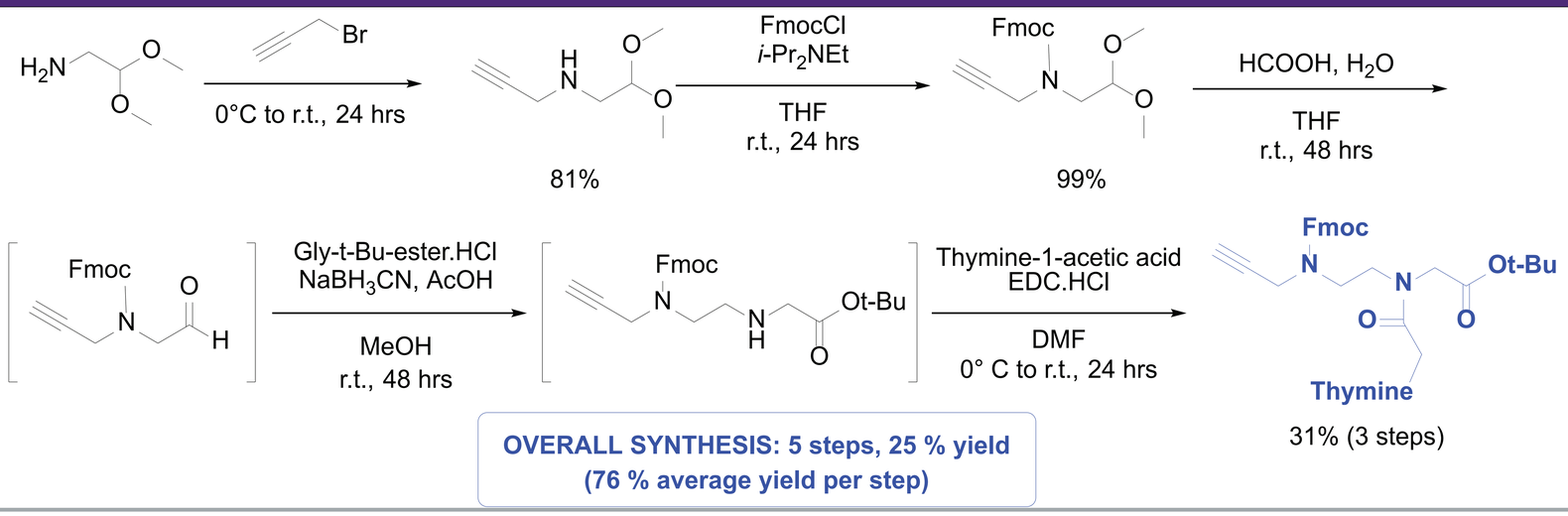
Background

PNAs have been found to be successful at binding to DNA and RNA sequences in order to regulate cellular processes like replication, transcription or translation[1,2]. Much research has shown PNAs ability to target and inhibit certain enzymes involved in viral infections or cancer progression indirectly via DNA or RNA. This project differs from other research in that the PNA is able to be functionalized via an alkyne group using click chemistry[3]. For example, a fluorescent tag could be added in order to track the progress of the PNA in the cell and help with diagnostics, or a charge may be added to help with solubility in water.

Target Compounds



Synthesis of the Monomer



OVERALL SYNTHESIS: 5 steps, 25 % yield
(76 % average yield per step)

Conclusion

The synthesis of the proargyl-containing thymine PNA monomer was completed over 5 steps and resulted in a 25% yield.

References

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2. a) "Recent highlights in modified oligonucleotide chemistry", Cobb, A. J. A. Org. Biomol. Chem. 2007, 5, 3260-3275. b) Crooke, S. T. Antisense Drug Technology (2nd Edition) CRC Press, Boca Raton, 2008.

3. a) "Click Chemistry: Diverse Chemical Function from a Few Good Reactions", Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Angew. Chem. Int. Ed. 2001, 40, 2004-2021. b) "The growing applications of click chemistry", Moses, J. E.; Moorhouse, A. D. Chem. Soc. Rev. 2007, 36, 1249-1262.

Acknowledgments

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