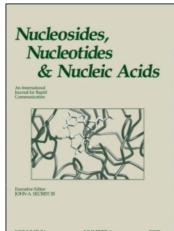
This article was downloaded by:

On: 26 January 2011

Access details: Access Details: Free Access

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides, Nucleotides and Nucleic Acids

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

Chemoselectivity in Oxidative Coupling of Bifunctional Nucleophiles with Dinucleoside H-Phosphonate and Dinucleoside H-Phosphonothioate

Johan Nilsson^a; Adam Kraszewski^b; Jacek Stawinski^{ab}

- ^a Department of Organic Chemsitry, Arrhenius Laboratory, Stockholm University, Stockholm, Sweden
- ^b Institute of Bioorganic Chemistry, Polish Academy of Science, Poznan, Poland

Online publication date: 09 August 2003

To cite this Article Nilsson, Johan , Kraszewski, Adam and Stawinski, Jacek (2003) 'Chemoselectivity in Oxidative Coupling of Bifunctional Nucleophiles with Dinucleoside H-Phosphonate and Dinucleoside H-Phosphonothioate Diesters', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 1467 - 1469

To link to this Article: DOI: 10.1081/NCN-120023012 URL: http://dx.doi.org/10.1081/NCN-120023012

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS Vol. 22, Nos. 5–8, pp. 1467–1469, 2003

Chemoselectivity in Oxidative Coupling of Bifunctional Nucleophiles with Dinucleoside H-Phosphonate and Dinucleoside H-Phosphonothioate Diesters

Johan Nilsson, Adam Kraszewski, and Jacek Stawinski 1,2,*

¹Department of Organic Chemsitry, Arrhenius Laboratory, Stockholm University, Stockholm, Sweden ²Institute of Bioorganic Chemistry, Polish Academy of Science, Poznan, Poland

ABSTRACT

Chemoselectivity and stereospecificity of iodine mediated oxidative couplings using separate diastereomers of dinucleoside H-phosphonate and H-phosphonothioate with various N- and O-binucleophiles were investigated.

Key Words: H-Phosphonates; H-Phosphonothioates; Oxidative coupling; Binucleophiles.

As a model reaction an oxidative condensation of dinucleoside H-phosphonate 1 (X = O) and H-phosphonothioate 1 (X = S) with 6-aminohexanol, 1,6-diaminohexane, and 1,6-hexanediol was used. In non-nucleophilic solvents (e.g. acetonitrile) phosphoroiodidates 2 (X = O or S), generated in situ from the corresponding H-phosphonate (1, X = O) or H-phosphonothioate (1, X = S) reacted stereospecifically

1467

DOI: 10.1081/NCN-120023012 Copyright © 2003 by Marcel Dekker, Inc.

1525-7770 (Print); 1532-2335 (Online)

www.dekker.com



^{*}Correspondence: Jacek Stawinski, Department of Organic Chemsitry, Arrhenius Laboratory, Stockholm University, S-10691 Stockholm, Sweden; Fax: +46 8 154 908; E-mail: js@organ. su.se.

Downloaded At: 11:19 26 January 2011

with N-nucleophiles (inversion of configuration) to produce in high yields phosphoramidate derivatives 3. O-Nucleophiles were much less reactive towards 2 and required the presence of nucleophilic catalysts (e.g. pyridine) to form the corresponding phosphotriester derivatives 3. Due to the formation of reactive pyridinium adduct as intermediates, [2] the latter reaction was not stereospecific. The use of ammonium salt of 6-aminohexanol inverted the chemoselectivity^[1] of the reaction and phosphotriesters 3c (X = 0,S) instead of phosphoramidate 3a (X = 0,S) were formed.

R= 4,4'-dimethoxytrityl; X= O or S; 3a; Y=OH, Z=NH; 3b; Y=OTBDMS, Z=O; 3c; Y=NH₃CI, Z=O; 3d; Y=NH₂, Z=NH

In contradistinction to 1,6-diaminohexane and 6-aminohexanol, which reacted fast and cleanly to the corresponding phosphoramidates 3 (Z = N), 1,6-hexanediol gave phosphorotriester 3 (X = O or S; Z = O), usually contaminated with pyrophosphates and other side products. Since hydrolysis by adventitious water seemed to be a major problem in the reactions with O-nucleophiles, we used t-butyldiphenylsilyl chloride (TBDPSCl) as water scavenger. [3] Also, to avoid the formation of doubly phosphorylated derivatives, 1-O-TBDMS-hexanediol-6 was used for the oxidative coupling.

³¹P-NMR chemical shifts and yields of the products.

	X = O			X = S		
Compound	δ _P (CDCl ₃)		Yield	δ _P (CDCl ₃)		Yield
3a. Z = NH Y = OH 3b. Z = O Y = OTBDMS 3c. Z = O Y = NH ₃ Cl 3d. Z = NH Y = NH ₃ Cl 3e ^h . Z = O Y = OH	9.21 ^{de} -2.10 ^{bf} -0.88 ^{abg} 11.01 ^{acg} -2.08 ^{be}	8.85 ^{cf} -2.18 ^{be} -1.00 ^{abg} 10.80 ^{adg} -2.19 ^{bf}	93% 81% 90% 89% 80%	73.13 ^{cf} 67.92 ^{bf} 68.75 ^{abg} 74.57 ^{acg} 67.81 ^{be}	72.27 ^{de} 67.69 ^{be} 68.51 ^{abg} 74.23 ^{adg} 67.65 ^{bf}	87% 83% 88% 87% 91%

 $^{^{}a}\delta_{P}(d_{6}\text{-DMSO}).$

^bEpimerized in pyridine.

^cFrom the fast diastereomer (R_p) of the H-phosphonate/thioate.

^dFrom the slow diastereomer (S_p) of the H-phosphonate/thioate.

^eFast diastereomer of the product.

Slow diastereomer of the product.

^gUnseparable diastereomers.

^hObtained from **3d**.

All the reactions were complete within a few minutes, affording the desired products in high yields. The phosphoramidates of type 3 (X=O or S; Z=N) could be prepared stereospecifically, in contradistinction to the phosphotriesters 3 (X=O or S; Z=O) that required presence of pyridine and thus, afforded mixture of P-diastereomers during oxidative coupling. The products were purified by silica gel chromatography and characterized by ^{31}P - and ^{1}H NMR spectroscopy.

ACKNOWLEDGEMENTS

The financial support from the Swedish Research Council and the State Committee for Scientific Research, Republic of Poland, is gratefully acknowledged.

REFERENCES

- Sobkowski, M.; Stawinski, J.; Kraszewski, A. Studies on nucleoside H-phosphonate diesters with bifunctional reagents. Part 4. Chemoselectivity during oxidative coupling of nucleoside H-phosphonate diesters with amino alcohols controlled by protonation of the amino function. Tetrahedron Lett. 1995, 36, 2295–2298.
- 2. Nilsson, J.; Kraszewski, A.; Stawinski, J. Reinvestigation of the 31P NMR evidence for the formation of diorganyl phosphoropyridinium intermediates. J. Chem. Soc., Perkin Trans. 2, 2001, 2263–2266.
- 3. Nilsson, J.; Stawinski, J. Oxidative coupling of H-phosphonate and H-phosphonothioate diesters. Iodine as a reagent and catalyst. Coll. Czech. Chem. Comm. **2002**, *5*, 87–92.