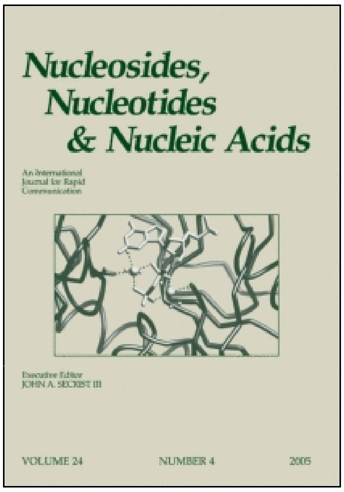

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Chemoselectivity in Oxidative Coupling of Bifunctional Nucleophiles with Dinucleoside H-Phosphonate and Dinucleoside H-Phosphonothioate Diesters

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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

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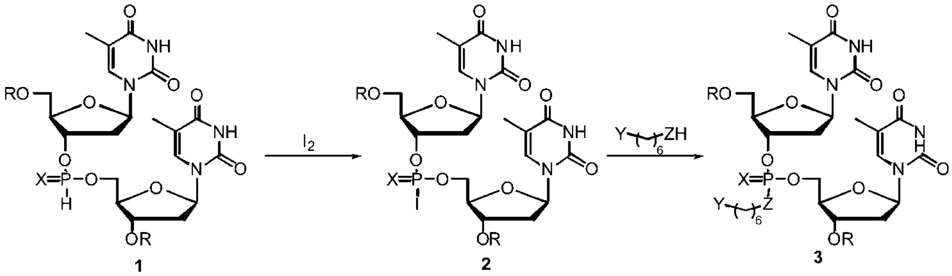
with *N*-nucleophiles (inversion of configuration) to produce in high yields phosphoramidate derivatives **3**. *O*-Nucleophiles were much less reactive towards **2** and required the presence of nucleophilic catalysts (e.g. pyridine) to form the corresponding phosphotriester derivatives **3**. Due to 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 = O,S) instead of phosphoramidate **3a** (X = O,S) were formed.



R= 4,4'-dimethoxytrityl; X= O or S; 3a; Y=OH, Z=NH; 3b; Y=OTBDMS, Z=O; 3c; Y=NH_3Cl, Z=O; 3d; Y=NH_2, 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.

Table 1. ^{31}P-NMR chemical shifts and yields of the products.

	X = O			X = S		
Compound	$\delta_P(CDCl_3)$		Yield	$\delta_P(CDCl_3)$		Yield
3a. Z = NH Y = OH	9.21[de]	8.85[cf]	93%	73.13[cf]	72.27[de]	87%
3b. Z = O Y = OTBDMS	−2.10[bf]	−2.18[be]	81%	67.92[bf]	67.69[be]	83%
3c. Z = O Y = NH_3Cl	−0.88[abg]	−1.00[abg]	90%	68.75[abg]	68.51[abg]	88%
3d. Z = NH Y = NH_3Cl	11.01[acg]	10.80[adg]	89%	74.57[acg]	74.23[adg]	87%
3e[h]. Z = O Y = OH	−2.08[be]	−2.19[bf]	80%	67.81[be]	67.65[bf]	91%

[a] $\delta_P(d_6\text{-DMSO})$.
[b] Epimerized in pyridine.
[c] From the fast diastereomer (R_p) of the H-phosphonate/thioate.
[d] From the slow diastereomer (S_p) of the H-phosphonate/thioate.
[e] Fast diastereomer of the product.
[f] Slow diastereomer of the product.
[g] Unseparable diastereomers.
[h] Obtained 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.

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