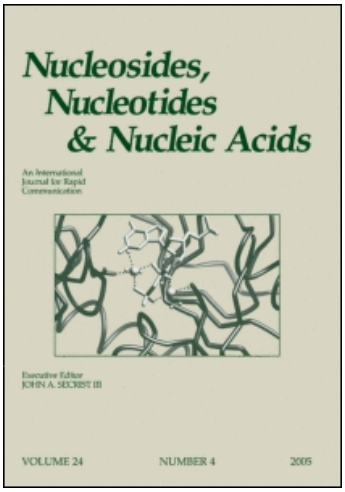

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Convenient Method for the Synthesis of DNA Conjugate

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CONVENIENT METHOD FOR THE SYNTHESIS OF DNA CONJUGATE

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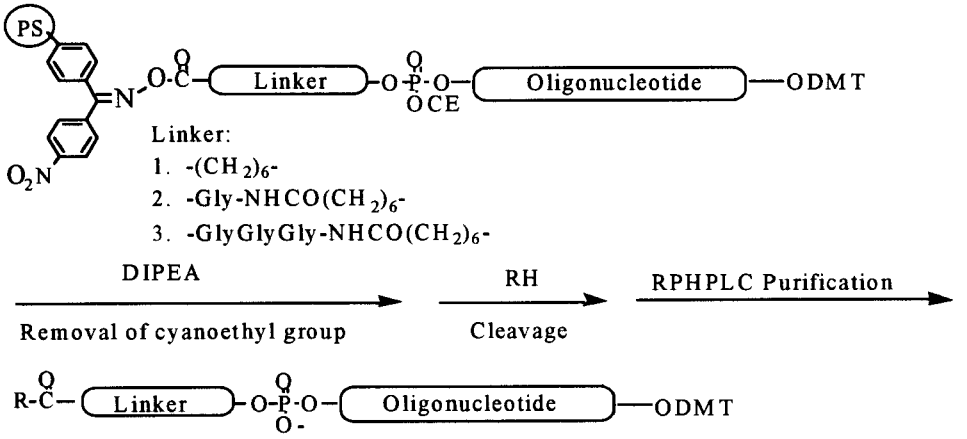
ABSTRACT

It is found that application of oxime resin to an automated DNA synthesis and succeeding cleavage of DNA fragment bound to oxime resin by various nucleophiles, such as amines, alkoxides and protected peptides, give DNA conjugate molecules conventionallyin moderate to good yields.

The present study describes a novel and conventional preparation of DNA conjugate molecules using oxime resin.[1] The strategy of this study involves that oligonucleotide and peptide are covalently linked by cleaving DNA fragment automatically synthesized on modified oxime resin with separately prepared α-amino free peptide bearing protected side chain residues. (Scheme 1)



Scheme 1. DNA Synthesis on Oxime Resin

Decamer of thymidine was prepared on the modified oxime resin and the coupling efficiencies were monitored by measuring U.V. absorbance at 495 nm of removed DMT cation. The results are summarized in Table 1.

TABLE 1. DNA Synthesis on Oxime Resin

	Linker	DNA	Yield[a] /%
1a	$-(CH_2)_6-$	T_{10}	84[b] (21)[c]
2a	$-Gly-NHCO(CH_2)_6-$	T_{10}	88 (32)
3a	$-GlyGlyGly-NHCO(CH_2)_6-$	T_{10}	94 (57)

a. Based on trityl assay. b. Average coupling yield. c. Overall yield.

After removal of cyanoethyl group by the treatment with diisopropylethylamine in DMF, cleavage of thus obtained oxime resin bound DNA by various nucleophiles gave protected oligonucleotide conjugates. Removal of protective groups on peptide side chains and oligonucleotide bases was performed by treatment with 35 % ammonia at 50°C for 20h, and purification was carried out by RPHPLC with linear gradient of acetonitrile and triethylammonium acetate buffer. Isolated yields were determined by quantification of nucleobase concentration by UV measurement at 260 nm.

TABLE 2. Cleavage Oxime Resin Bound DNA by Nucleophiles (RH)

RH	Resin bound DNA	Yield[a] /%
$H_2NGlyOEt$	1a	58
	2a	83
	3a	86
$H_2NGlyGlyGly-NEt_2$	2a	56
	3a	72
$H_2NLAK(tfa)L-NEt_2$	2a	61
	2b	74

a. Isolated yield by RPHPLC based on UV absorbance at 260 nm.

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