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Studies Towards Synthesis of Dinucleoside Arylphosphonates with Metal Complexing Properties

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Studies Towards Synthesis of Dinucleoside Arylphosphonates with Metal Complexing Properties

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ABSTRACT

An efficient and stereospecific synthesis of dinucleoside 4'-(2,2':6',2"-terpyridyl)-phosphonate **2** and 5-(2,2'-bipyridyl)phosphonate **3** via a palladium(0) cross coupling strategy has been developed.

Key Words: H-Phosphonates; C-Phosphonates; Arylphosphonates; Terpyridine; Palladium cross coupling.

We have recently developed efficient and general methods for the preparation of dinucleoside 2-pyridyl-,^[1] 3-pyridyl-,^[2] and 4-pyridylphosphonates.^[3] As a continuation of this work, we were aiming towards synthesis of various pyridylphosphonate derivatives with metal complexing properties. Since oligonucleotides appended with

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RO Thy
$$H = \begin{array}{c} Pd(0), Ar-Br, TEA \\ Thy \end{array}$$

$$Thy = \begin{array}{c} Pd(0), Ar-Br, TEA \\ Thy \end{array}$$

$$2: Ar = \begin{array}{c} 3: Ar = \\ N \end{array}$$

$$3: Ar = \begin{array}{c} 3: Ar = \\ N \end{array}$$

Scheme 1.

2,2':6',2"-terpyridine or 2,2'-bipyridine moieties exhibit in the presence of metal ions promising properties as artificial nucleases, [4] we investigated the possibility of attaching these functionalities directly to the phosphorus centre using the recently developed palladium(0) cross coupling strategy^[1] (Sch. 1).

When equimolar amounts of dinucleoside H-phosphonate 1 and 4'-bromo-(2,2':6',2"-terpyridine) in the presence of 1.2 equiv. of triethylamine (TEA) and 0.2 equiv. of Pd(PPh₃)₄ were refluxed in THF for 5 hours, the desired dinucleoside 4'-terpyridylphosphonate 2 was formed as a sole product (³¹P NMR spectroscopy). When the separate diastereomers of H-phosphonate 1 were subjected to the same reaction conditions, a fully stereospecific conversion into 4'-terpyridylphosphonate 2 derivatives was observed and the products were isolated by silica gel chromatography in good yields (2-R_P: 73%, 2-S_P: 66%).

Attempted preparation of dinucleoside 5-(2,2'-bipyridyl) phosphonate 3 in the reaction of equimolar amounts of H-phosphonate 1 and 5-bromo-2,2'-bipyridine, TEA (1.2 equiv.) and Pd(PPh₃)₄ (0.2 equiv.) under reflux in THF (5 h), resulted in only 60% conversion of 1 into 5-bipyridylphosphonate 3 (³¹P NMR spectroscopy). However, by changing the catalytic system to Pd(OAc)₂ and 1,1'-bis(diphenylphosphino)-ferrocene (DPPF), almost quantitative formation of 3 could be achieved. This reaction also, when carried out on separate diastereomers of H-phosphonate 1, proved to be completely stereospecific and the diastereomers of 5-bipyridylphosphonate 3 were isolated in good yields (R_P: 64%, S_P: 61%).

Among other ligands investigated only 2,2'-bis(diphenylphosphino)-1,1'-binaphtyl (BINAP) turned out to be as efficient as DPPF. Neither 1,2-bis(diphenylphosphino)ethane (DPPE) nor 1,3-bis(diphenylphosphino)propane (DPPP) promoted any detectable formation of bipyridylphosphonates 3, probably due to inactivation of the palladium(0) catalyst by a 2,2'-bipyridine moiety (from the substrate or from product 3). The efficacy of rigid and sterically demanding bidentate ligands (DPPF, BINAP) in promoting synthesis of 3 can probably be due to their high complexing affinity that prevents the bipyridine moiety to replace these ligands in active palladium complexes.

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