



Wittig reactions of a bis-triphenylphosphonium pyridoxine derivative



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ABSTRACT

Wittig reactions of a bis-triphenylphosphonium pyridoxine derivative with five aromatic and aliphatic aldehydes led to a series of mono- and bis-alkenyl substituted products. The reactions also demonstrated unusual reactivity patterns leading to unexpected products, including a Z-shaped hyperconjugated structure with *trans*-configuration for all three alkene fragments, and a tricyclic 9,10-dihydro-1*H*-[1,3]dioxino [4,5-*c*]quinoline formed as a result of non-symmetric Wittig olefination followed by a rare type of intramolecular cyclization. The obtained products represent prospective biologically active agents, while one compound is a potential microenvironment- and interaction-sensitive molecular probe.

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Introduction

Substituted derivatives of pyridoxine (vitamin B₆) carrying alkenyl substituents at various positions of the pyridine ring represent interesting molecular structures with rich bioactivity potential. In particular, pyridoxine molecules carrying a 5-ethenyl substituent possess anti-inflammatory properties,¹ 6-phenylethenyl substituted pyridoxines have been described as purine receptor antagonists,² and 2-ethenyl derivatives possess antitumor activity.³ In our group, we have systematically studied the chemistry and biological activity of pyridoxine derivatives.⁴ Recently, we synthesized a series of *cis*- and *trans*-5-alkenyl substituted pyridoxines, which demonstrated promising antitumor activity.⁵

Despite promising bioactivity potential, synthetic approaches to such compounds with various substituents remain difficult. In continuation of previous experimental and theoretical work, we have directed our effort towards the search for convenient and versatile synthetic routes to structures bearing alkenyl substituents at positions 5 and 6 of the pyridoxine ring based on the Wittig reaction.

Results and discussion

Herein, the Wittig reactions of bis-phosphonium pyridoxine derivative **2** with a series of aromatic and aliphatic aldehydes were

studied (Scheme 1). The key reagent **2** was obtained from pyridoxine hydrochloride **1** according to our previously reported approach.^{4c} According to single-crystal X-ray diffractometry (ESI), the crystal structure of compound **2** consists of the bis-phosphonium cationic motif, two chloride ions, one water molecule and one disordered acetone molecule. The chloride ions form a hydrogen bond with the water molecule and also participate in a nonclassical hydrogen bonding with the α -proton of the methylenephosphonium cation. Interestingly, the residual acetone and water molecules in the crystalline structure of compound **2** cannot be removed by conventional laboratory methods, such as vacuum thermal drying. The presence of water is an important feature of this reagent which plays a key role in the studied reaction.

The Wittig reactions of **2** monohydrate with five aliphatic and aromatic aldehydes **3a–e** were performed in CH₂Cl₂ in the presence of NaH (6 equiv.) at reflux for 30 h. These conditions were found to be optimal, and all attempts to increase conversion of the initial reagents by varying the nature of the base, solvent, temperature and reaction time led to decreased yields of compounds **4–9** and more complex mixtures of unidentified products. Thus, the use of Et₃N as a base did not lead to the desired olefin products, probably, due to steric hindrance and/or low acidity of the methylene protons at the phosphorus atom. Of note, in our recent work, Et₃N was successfully used in the reaction of various aldehydes with a mono-phosphonium salt of pyridoxine.⁵

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