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# 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.



## Introduction

Substituted derivatives of pyridoxine (vitamin $B_6$) 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 $CH_2Cl_2$ 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 $Et_3N$ 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, $Et_3N$ was successfully used in the reaction of various aldehydes with a mono-phosphonium salt of pyridoxine.[5]

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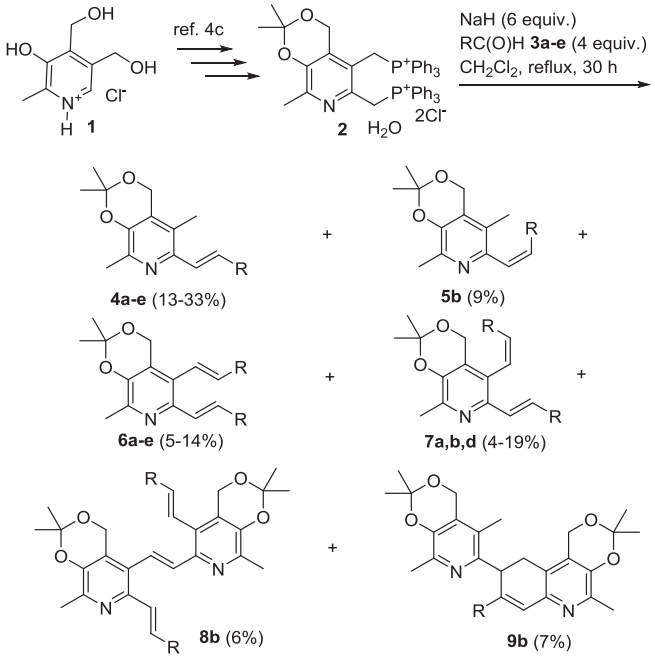
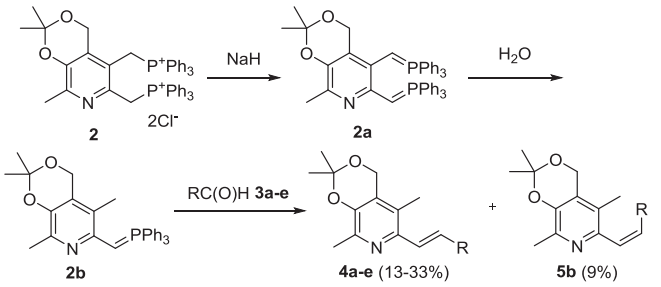



R = $C_6H_5$ (**a**); 3,4-$(CH_3O)_2C_6H_3$ (**b**); $C_6H_5CH$=CH (**c**); $C_2H_5$ (**d**); $C_5H_{11}$ (**e**)

**Scheme 1.** Wittig reaction products obtained in this work.




**Scheme 2.** Possible mechanism of **4a–e** and **5b** formation.

All reactions led to a number of different products which were isolated by silica gel column chromatography (Scheme 1). The isolated yields of products **4**–**9** are indicated in Table 1.

Unexpectedly, the major products in the studied reactions were 5-methyl-6-alkenyl substituted derivatives **4a–e** with a *trans*-configuration of the alkene fragment, rather than 5,6-bis-alkenyl substituted structures which would be considered "normal" products of the Wittig reaction of aldehydes with the two ylide moieties. One exception was the reaction of **2** with **3d** (Entry 4), which yielded an inseparable mixture of 4,5-bis-alkenyl substituted compounds **6d** and **7d** as the major isolated product. Compounds **4a-e** could be separated from other products by silica gel column chromatography, and were obtained in low to moderate isolated yields (13–33%) as white and yellow crystalline substances. Characteristic features of these compounds were the signals of *trans*-alkene protons at 6.50–7.70 ppm (AB-pattern, $^3J_{HH}$ = 15.6 Hz). The structure of **4b** was also confirmed by single crystal X-ray analysis (Fig. 1). In one case (Entry 2) we observed the formation of *cis*-alkene **5b**, which was isolated in 9% yield. This product had characteristic $^1$H NMR signals at 6.53 and 6.65 ppm (AB-pattern, $^3J_{HH}$ = 12.2 Hz).

The possible mechanism for the formation of **4a–e** and **5b** (Scheme 2) involves, as a first step, reaction of the initial bis-phosphonium salt **2** with NaH leading to the corresponding bis-ylide **2a**. Next, bis-ylide **2a** is hydrolyzed by residual water to yield the mono-ylide intermediate **2b**. The latter then reacts with aldehydes **3a–e** to give the corresponding olefins **4** and **5**. An interesting feature of the described mechanism is the regioselective reaction of water with the ylide moiety at position 5 of the pyridoxine ring.

In all reactions the expected products of the Wittig reaction, bis-alkenes **6a–e** with *trans*-configuration of both alkene fragments were also obtained. Compounds **6a**, **6c** and **6e** could be separated as individual *trans*,*trans*-isomers, while **6b** and **6d** were obtained as inseparable mixtures with *cis*,*trans*-isomers **7b** and **7d**. In one case we were able to isolate the individual *cis*,*trans*-isomer **7a** in a relatively good yield (19%). The reasons for the observed *cis*/*trans* regioselectivity remain unclear.

In most cases, the studied reactions also gave complex mixtures of by-products which could not be separated or identified. However, the reaction of **2** with 3,4-dimethoxybenzaldehyde **3b** (Entry 2) led to a mixture of products which were isolated and characterized. According to analytical studies, including 1D and 2D NMR

**Table 1**
Isolated yields of compounds **4**–**9**.

| Entry | R | Yield **4**–**9** (%)[a] | | | | | |
|---|---|---|---|---|---|---|---|
| | | **4** | **5** | **6** | **7** | **8** | **9** |
| 1 | $C_6H_5$ (**a**) | 30 | – | 14 | 19 | – | – |
| 2 | 3,4-$(CH_3O)_2C_6H_3$ (**b**) | 21 | 9 | 9[b] (**6b**:**7b** ~ 4:3) | 6 | 7 | |
| 3 | $C_6H_5CH$ = CH (**c**) | 13 | – | 9 | – | – | – |
| 4 | $C_2H_5$ (**d**) | 19 | – | 30[b] (**6d**:**7d** ~ 5:1) | – | – | |
| 5 | $C_5H_{11}$ (**e**) | 33 | – | 5 | – | – | – |

[a] Isolated yield.
[b] Yield for inseparable mixtures of *trans*,*trans*-isomers **6** and *cis*,*trans*-isomers **7**.

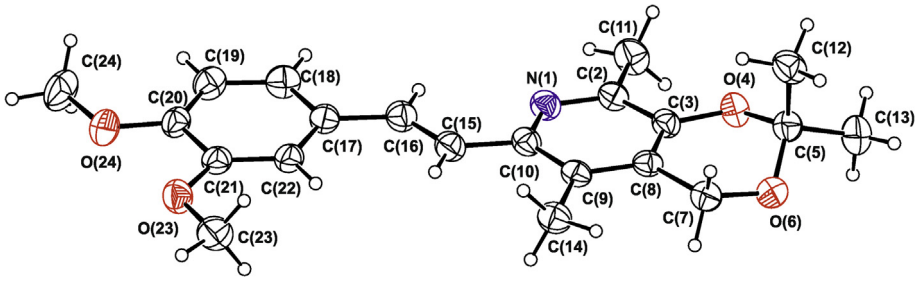


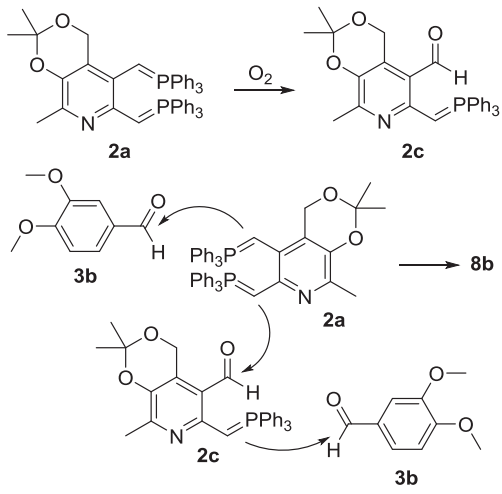

**Figure 1.** Single-crystal X-ray structure of **4b**.

spectroscopy ($^{1}$H, $^{13}$C, COSY, HSQC, NOESY), high-resolution mass-spectrometry, and single-crystal X-ray diffractometry, in addition to compounds **4b–7b**, the reaction led to interesting and unexpected products **8b** and **9b**.

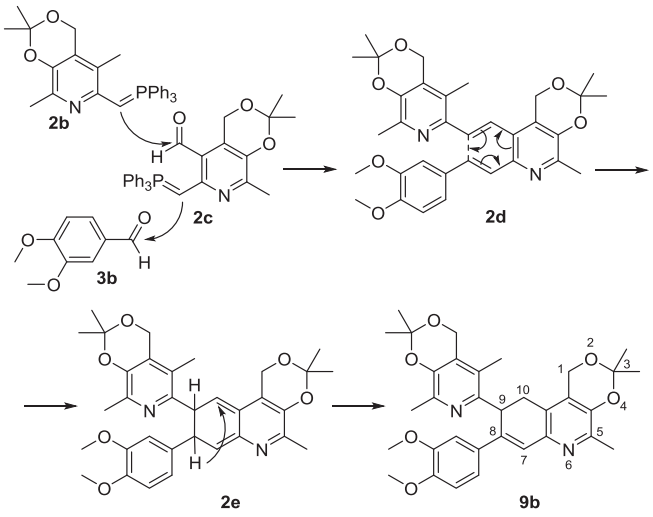
A retrospective analysis allowed us to identify the following hypothetical reaction sequence leading to compound **8b** (Scheme 3). The key stage is the oxidation of bis-ylide intermediate **2a** with the air oxygen leading to carbonyl ylide **2c**. In a similar manner to the above-described hydrolytic cleavage (Scheme 2), the oxygen molecule selectively reacts with the ylide moiety at position 5. A series of concerted intermolecular Wittig reactions with the participation of **2a**, **2c** and two molecules of **3b** then lead to the formation of compound **8b** (6%) containing a rare *Z*-shaped conjugated structure with *trans*-configuration for all three alkene fragments. The structure of **8b** was characterized by spectroscopic methods. Thus its $^{1}$H NMR spectrum showed two characteristic ABX patterns corresponding to the aromatic protons in the terminal 3,4-dimethoxyphenyl fragments between 6.70 and 7.09 ppm, and three AB patterns corresponding to *trans*-alkene protons between 6.50 and 7.53 ppm. Moreover, the structure of **8b** was confirmed by a single-crystal X-ray analysis (Fig. 2).

An important theoretical and practical question is the relative chemical reactivity of the ylide moieties at positions 5 and 6 of the pyridoxine system. The exact reasons for such regioselectivity remain unclear and, apparently, are based on a fine balance between steric and electronic factors. One possible explanation is the electron-deficient nature of the *ortho*- and *para*-positions of the pyridine ring. Therefore, the ylide moiety at position 6 of the pyridoxine system is less reactive than that at position 5, resulting in higher reactivity of the 5-ylide group in intermediate **2a** towards small reactive species, such as oxygen and water.

Scheme 4 shows an alternative reaction route which results in the formation of compound **9b**. The carbonyl ylide intermediate **2c** (Scheme 3) reacts with the complementary ylide and carbonyl moieties of compounds **2b** (Scheme 2) and **3b**, respectively. The concerted intermolecular Wittig reactions of these three reactants lead to the formation of bis-alkenyl derivative **2d**. The *trans*,*trans*-divinyl intermediate **2d** then undergoes a relatively rare type of




**Scheme 3.** Possible mechanism leading to **8b**.




**Scheme 4.** Possible mechanism leading to **9b**.

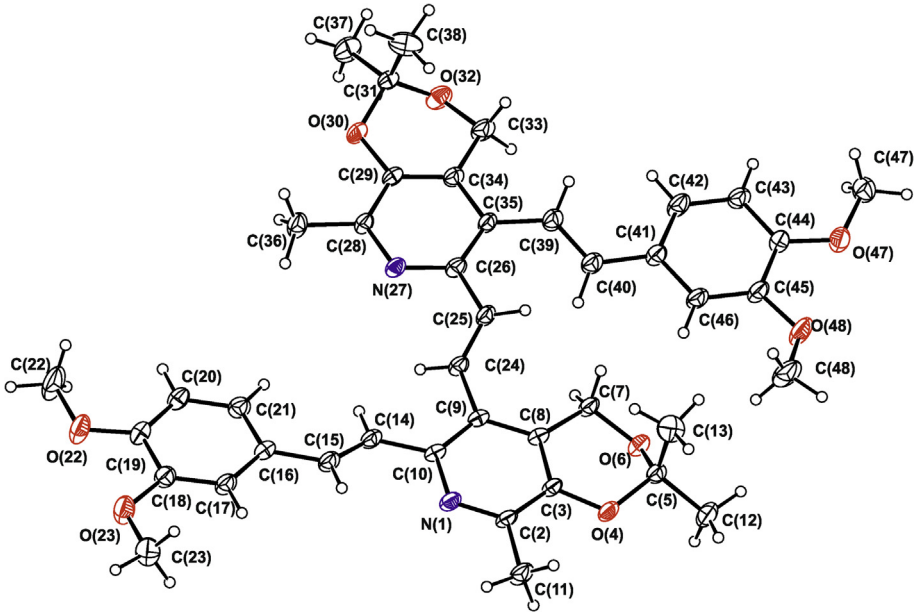



**Figure 2.** Single-crystal X-ray structure of **8b**.

thermal intramolecular electrocyclization with the formation of unstable intermediate **2e** which undergoes a 1,5-H shift to give the final stable dihydroquinoline derivative **9b**. A similar process of photochemical transformations of β,β′-dithienyl substituted *o*-divinylbenzenes leading to 1,2-dihydronaphthalenes was observed by Vuk and co-workers.[6] The $^1$H NMR spectrum of **9b** showed a characteristic ABXY pattern between 2.69 and 7.37 ppm corresponding to a three-proton system with one asymmetric center at position 9 and two non-equivalent protons at position 10 of the 9,10-dihydro-1*H*-[1,3]dioxino[4,5-*c*]quinoline scaffold.

The described results suggest that the key bis-ylide intermediate **2a** is quite unstable and prone to rapid oxidation by air oxygen or base-catalyzed hydrolysis. This observation prompted us to investigate the same Wittig reaction under an argon atmosphere. The modified reaction conditions gave an increased yield of the major product **4b** (21% *vs.* 32% for air and argon atmospheres, respectively). In agreement with the suggested conversion routes (Schemes 2–4), the reaction of bis-phosphonium salt **2** with 3,4-dimethoxybenzaldehyde under the inert atmosphere did not lead to detectable amounts of **8b** and **9b**, but still resulted in an inseparable mixture of side-products which could not be isolated and identified. Similar results were obtained with other studied aldehydes **3a**, **3c–e**; specifically, their reaction with **2** under an inert atmosphere gave an increased yield of the corresponding 6-alkenyl substituted products **4**, but did not lead to detectable amounts of 5,6-bis-alkenyl substituted structures **8** and **9**. The important role of oxygen and water in the described synthetic routes suggests the possibility for their controlled use as reactants in the synthesis of complex structures, such as **8b** and **9b**, from bis-phosphonium salts such as **2**.

Compounds **4**–**7** represent novel derivatives of pyridoxine with potential biological properties. The pyridoxine moiety is responsible for effective penetration through biomembranes, while the alkene fragments can act as efficient scavengers of reactive oxygen species (ROS) in the intracellular space. Such molecules also possess promising potential as anticancer, geroprotective and antibacterial agents. Preliminary studies indicate that several compounds possess moderate to high cytotoxic activity against a panel of tumor cells; experimental results will be reported soon.

Structures **8b** and **9b** belong to novel heterocyclic scaffolds with unique properties which are currently under active investigation within our group. Thus, compound **8b** has interesting drug-like motifs and possesses moderate cytotoxic activity against a number of tumor cells (data not shown). The hyperconjugated structure of **8b** with a rare *Z*-shaped geometry also has remarkable optical properties. For example, this compound possesses an intense green fluorescence in visible light (emission maximum at 550 nm). Preliminary data indicate that the fluorescence is sensitive to the microenvironment (e.g. solvent, ionic strength, pH) and to the nature of substituents on the terminal phenyl rings. The acetonide protective group can be easily hydrolyzed, and the free hydroxyl groups used as convenient reactive functional groups for labeling biomolecules and the design of interaction- or microenvironment-sensitive fluorescent probes. The fluorescent properties of this compound and possible applications will be reported and discussed in a complementary paper.

## Conclusions

In conclusion, we have studied the Wittig reactions of a previously reported bis-triphenylphosphonium pyridoxine derivative **2** with several aromatic and aliphatic aldehydes **3a–e**. The reaction led to a series of mono- and bis-alkenyl substituted products **4**–**7** as well as to unexpected structures, such as a *Z*-shaped hyperconjugated structure **8b**, and tricyclic 9,10-dihydro-1*H*-[1,3]dioxino[4,5-*c*]quinoline **9b** formed as the result of a non-symmetric Wittig olefination followed by a rare type of intramolecular cyclization. The key intermediate in the developed approach is a sterically highly constrained bis-ylide **2a**, which readily reacts, in a regioselective manner, with small reactive species such as oxygen and water, even when they are present in trace amounts. The exact reasons for such regioselectivity generally remain unclear and, apparently, are based on a fine balance of the steric and electronic factors. Hypothetically, the regioselectivity can be explained by the electron-deficient nature of the *ortho*-position of the pyridine ring which results in decreased reactivity of the ylide moiety at position 6 compared to position 5. The observed reactivity patterns are directed by highly concerted inter- and intramolecular interactions of a number of reactants, both initial and generated *in situ*, thus leading to complex and often inseparable mixtures of products. The reactions are highly sensitive to the steric and electronic parameters of the aldehyde reagents and their substituents.

The products and yields of the reactions are strongly affected by the reaction time, solvents, temperature, amounts and nature of aldehydes, the presence of oxygen, water and organic peroxides, and the nature of the base. The influence of these experimental conditions is currently under systematic investigation within our group and will be reported elsewhere.

Despite inherent complications, the developed synthetic approach can be recommended as a method of choice for the preparation of 5-deoxy-6-alkenyl pyridoxines (exemplified by compounds **4a–e** and **5b**) and 5,6-bis-alkenyl pyridoxines (**6a–e**, **7a,b,d**). These compounds, which can be isolated as major products, represent promising biologically active agents, while the minor products, such as hyperconjugated **8b**, have a rich potential as microenvironment- and interaction-sensitive molecular probes.

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## A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.01.031.

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