The Wittig Reaction with Pyridylphosphoranes

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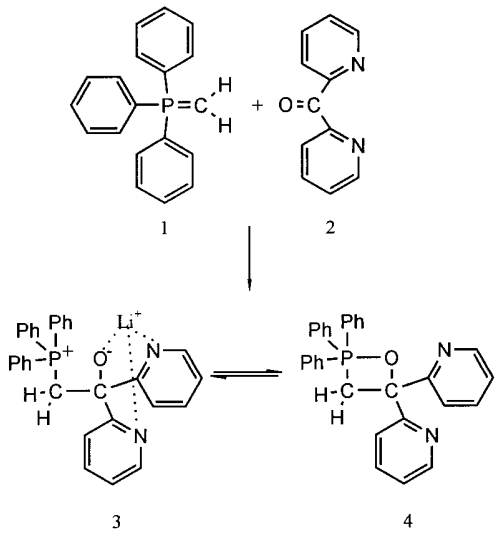
The Wittig reaction was studied by replacing one, two, or three phenyl rings in the triphenylethylidenephosphorane **(8)** with pyridyl rings, which were attached in the *alpha* position. It is shown that when using *n*-butyllithium as the base, the yield of the Wittig reaction is severely affected and it is proposed that the formation of a betaine salt adduct as intermediate suppresses the formation of oxaphosphetanes. In contrast, with sodium bis(trimethylsilyl)amide as the base, the yields are similar to the reaction with **8**, although the Z-selectivity reaches values of over 18:1. The reactions have been monitored by ^{31}P NMR spectroscopy and the position of the pyridyl ring in the oxaphosphetane **4a** elucidated by ROESY NMR spectroscopy at low temperatures.

Introduction

The Wittig reaction[1] is one of the fundamental transformations in organic chemistry[2] and is constantly used in natural product synthesis to form an olefinic C=C linkage. The reaction is carried out either in the presence or absence of lithium salts, resulting in different stereochemistries.[3,4] In addition, one can distinguish between stabilized, half stabilized and unstabilized (or "reactive") ylides.

The oxaphosphetanes **4** are generally accepted as being the only intermediates so far observed (by ^{31}P NMR spectroscopy)[5] in the reaction, and the occurrence of the earlier proposed betaines is difficult to ascertain. Computational chemistry favors a cycloaddition-like reaction to yield oxaphosphetanes.[6] In our previous work on the mechanism of the Wittig reaction we have shown NMR-detectable dynamic equilibria of oxaphosphetanes which are complexed by the lithium ions in solution.[7] In the special case[8] of a Wittig reaction between triphenylmethylenephosphorane **(1)** and dipyridylketone **2**, however, we have demonstrated[9] the occurrence of a betaine salt adduct **3**, since, in the presence of lithium salts the corresponding oxaphosphetane **4** is destabilized by complexation of the lithium ion to the two pyridyl rings (Scheme 1).

Although this is of theoretical interest, in practice the use of dipyridyl ketone as one of the reactants is of no general importance. However, it occurred to us that the use of the pyridyl rings could be of significant use in this reaction if the pyridyl moiety were not placed in the ketone part, where it ends up in the formed olefin, but rather in the ylide part, where it ends up in the phosphane oxide after work up of the reaction. Much to our surprise, and despite the huge volume of variations investigated for the conditions of the Wittig reaction (e.g. the recent replacement of one phenyl group by an alkyl group)[10] this idea has apparently not been used or, to the best of our knowledge, not looked at



Scheme 1

systematically. This is even more surprising, since phosphanes with *ortho* substituents were used to direct the stereochemistry of the reaction,[11] with the idea of complexing the metal ion in order to obtain the extremely high *Z*/*E* selectivities very recently reported by Schlosser.[12] We have therefore initiated a study to replace one, two, or all three phenyl groups of the usual triphenylphosphane with *alpha*-attached pyridyl rings.

This investigation had the following objectives: (i) Since, during the Wittig reaction of **2** a betaine salt adduct can be isolated, it was of interest to see whether the same effect can be observed by placing the pyridyl rings in the phosphorane part. (ii) Since *ortho*-substituted phosphoranes direct significantly the *Z*/*E* ratio, it was expected that an *alpha*-attached pyridyl ring would also influence the stereochemistry.

Results and Discussion

Synthesis of Starting Products

For the synthesis of the pyridylphosphanes **5a–c** the method of Keene et al.[13] was chosen, although the trans-

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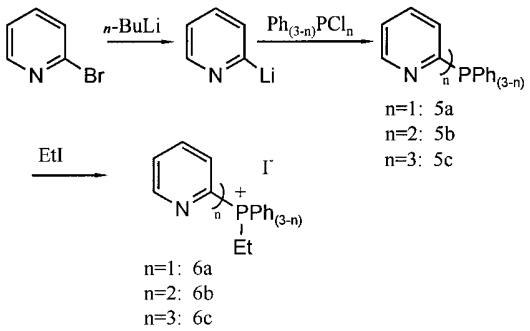
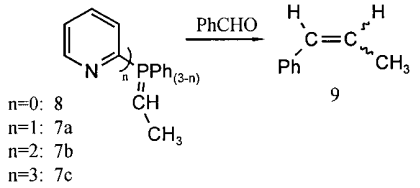
formation from 2-bromopyridine to the three pyridylphosphanes is, with a yield of typically 35%, quite unsatisfactory. Since the preparation of **5a−c** is currently the limiting step of this reaction, the subsequently formed phosphane oxides may have to be reduced and reused in order to avoid the somewhat cumbersome first step. The quaternisation[14] of **5a−c** with ethyl iodide to form the phosphonium salts **6a−c** (Scheme 2) is unproblematic and the corresponding yields are typically 90%.



Scheme 2

The deprotonation of compounds **6a−c** was always done twice in parallel, using *n*-butyllithium or sodium bis(trimethylsilyl)amide (NaHMDS) as a base under otherwise identical conditions at −75 °C in dry THF under nitrogen. As the aldehyde component, freshly distilled benzaldehyde was used throughout this work. Therefore, the alkylidene part of the ylide and the aldehyde component remained constant throughout the study, whereas the bases for the generation of the ylide, and the number of pyridyl rings in the phosphorane were varied (Scheme 3).



Scheme 3

Yield and Stereochemistry of the Wittig Reaction

The three pyridylphosphoranes **7a−c** and the standard triphenylethylidenephosphorane **8** were subjected to the Wittig reaction with benzaldehyde to form a mixture of *E*/*Z* 1-phenylpropene **9**, the composition of which was analyzed by ^{1}H NMR spectroscopy after chromatographic workup. As can be seen from the results given in Table 1, the ylide **8** in our hands gives, with both bases, yields of about 80% and a *Z*/*E* ratio of about 2:1 in agreement with the literature data.[15] Replacing the phenyl rings with *ortho*-attached pyridyl rings and using *n*-butyllithium as base has a drastic effect on the yield and, with more than one pyridyl ring, 1-phenylpropene is formed only in traces. The yields using NaHMDS are comparable with **8**; however, the *Z*/*E* ratio is increased enormously. From a practical point of view, one pyridyl ring is sufficient to improve the stereochemical outcome significantly compared to the result obtained by use of **8**, with insignificant loss in yield. Thus, this small modification of the Wittig protocol might be a quite useful alternative in practice.

NMR Spectroscopy of the Intermediates

In order to clarify the dramatic loss of yield in case of the use of *n*-butyllithium as a base in the presence of the pyridyl rings, the reaction was monitored by temperature-dependant ^{1}H and ^{31}P NMR spectroscopy between −100 and +10 °C. Generally, in comparison with the spectra observed with **8**,[7] it must be stated that the spectra obtained with the pyridyl-substituted systems are much more complicated due to a variety of complexation equilibria with the metal ions. Even before their reaction with benzaldehyde the ylides formed show dynamic NMR spectra between −70 and −100 °C, depending on the number of pyridyl rings attached and the metal ion in use. In Table 2 the ^{31}P NMR chemical shifts of the observed species are listed. With *n*-butyllithium at −70 °C, compound **6a** forms a broad ylide signal at $\delta_P = -2$, which splits at −90 °C into two sharpened signals at $\delta_P = -4$ and $\delta_P = -0.6$ in an integral ratio of 4:1. Under these conditions compound **6b** yields only one sharp resonance at $\delta_P = 6.7$, whereas **6c** forms the ylide **7c** ($\delta_P = 7.2$) only partly. In addition to several other minor signals, one observes another main component at $\delta_P = -16$. The relative intensity of this signals increases when an excess of butyllithium is used. The ylide signals of **7a−c** disappear instantly after addition of the aldehyde; however, an oxaphosphetane signal can only be detected in the case of **7a**, and the Wittig reaction does not occur in the case of **7b** and **7c**. As in our previous study[9] with **2**, after addition of the aldehyde we observed a very broad signal at $\delta_P = -10$, which we ascribe to a betaine salt adduct. Addition of hexamethylphosphorous acid triamide (HMPT) or the crown ether 12-crown-4 to these solutions yields the observation of an oxaphosphetane signal. Apparently, these reagents can complex the lithium ions, and therefore the Wittig pathway can be initiated.

Table 1. Yield and stereochemical outcome of the Wittig reaction between pyridylphosphoranes and benzaldehyde using *n*-butyllithium and NaHDMS as deprotonating base

Compound	1-Phenylpropene yield with *n*BuLi	*Z*/*E* ratio with *n*BuLi	1-Phenylpropene yield with NaHMDS	*Z*/*E* ratio with NaHMDS
Ph_3PEtI **8**	76%	1.7:1	81%	2:1
$Ph_2PyPEtI$ **6a**	66%	4:1	79%	11:1
$PhPy_2PEtI$ **6b**	traces	not determined	85%	18.5:1
Py_3PEtI **6c**	traces	not determined	65%	12.5:1

Table 2. ^{31}P NMR observations at −70 °C during the course of the Wittig reaction of the pyridylphosphoranes **7a−c**

System and base used		Ylides **7**	Oxaphosphetanes or betaine salt adducts	Phosphane oxides at +10 °C
$Ph_2PyPEtI$ **6a**	*n*-butyllithium	−2.0, exchanging	very broad signal at −12	18.3
	NaHMDS	11.0	−59.5, −60.7	17.7
$PhPy_2PEtI$ **6b**	*n*-butyllithium	6.7	very broad signal at −10	
	NaHMDS	8.7	−60.7, −62.3. At −100 °C two exchanging signals at −58/−63	15.2
Py_3PEtI **6c**	*n*-butyllithium	7.2	very broad signal at −10	
	NaHMDS	1.0, exchanging	−61.6, −63.4. At −100 °C two exchanging signals at −60/−64	10.0

The situation is quite different with NaHDMS as a base. Compound **7a** shows only a single ylide signal at $\delta_P = 11$, and, after addition of benzaldehyde, two sharp signals of *Z*/*E* oxaphosphetanes at $\delta_P = -59.5$ and −60.7 are observed instantaneously with an integration ratio of 15:1. Compound **7b** behaves very similarly to **7a** with an initially observed *Z*/*E* oxaphosphetane ratio of more than 30:1. Compound **7c** displays a dynamic ylide spectrum with a very broad signal at −70 °C which splits at −90 °C into two signals at $\delta_P = -5$ and 7.3 with an integral ratio of 3:1. Thus the tripyridyl ylide has a similar behavior with sodium ions as the monopyridyl ylide with lithium ions. The addition of benzaldehyde generates two oxaphosphetane signals in a *Z*/*E* ratio of 12:1. In the di- and tripyridyl case, on lowering the temperature after the oxaphosphetane formation yet another dynamic equilibrium is observed. The oxaphosphetane signals broaden and a new broad oxaphosphetane signal at $\delta_P = -57$ appears, which increases in intensity towards −100 °C, where the ratio of the two oxaphosphetane signals is about 1:1. We ascribe these signals to the sodium-complexed and -uncomplexed oxaphosphetanes as found earlier for the oxaphosphetanes **4** formed from dipyridylketone. On warming the solutions above −10 °C, the formed oxaphosphetane signals disappear and the corresponding signals of the phosphane oxides appear.

We have attempted to shed some light on the *alpha* effect and to explain why even one *alpha* pyridyl unit changes the *Z*/*E* ratio from 2:1 to 11:1. For this purpose, we have prepared an oxaphosphetane **4a** starting from **7a** (Scheme 4) with one *alpha* pyridyl ring but using a perdeuterated benzaldehyde[16] in order to simplify the aromatic proton region and therefore to enable safe proton assignments in this region. The aim was to determine by ROESY[17] spectra at −70 °C how the pyridyl ring is situated with respect to the oxaphosphetane protons. An expansion of this spectrum is given in Figure 1 showing ROE contacts between the methyl group at the oxaphosphetane ring and the *ortho* protons of one phenyl ring at $\delta_H = 7.63$. Both protons of the oxaphosphetane ring show contacts to the *ortho* protons at the other phenyl ring at $\delta_H = 7.76$. Very weak ROE contacts can also be found between the methyl group and the pyridyl protons H-1 ($\delta_H = 8.56$) and H-4 ($\delta_H = 6.74$), and the oxaphosphetane proton H_a (at the same carbon atom as the methyl group) also shows a very weak contact to the pyridine proton H-1. These data are consistent with the pyridyl ring being placed in an equatorial position with both phenyl rings placed in axial positions opposing each other. These findings lead to the following interpretation of the stereochemical outcome. In the ylide the metal ion chelates the electron pair of the pyridine nitrogen and that at C_α in such a manner that a planar five-membered ring ($M-C_\alpha-P-C_q-N$) is formed. The aldehyde can only approach from the bottom,[18] and, by an inspection of simple molecular models, it can be easily demonstrated, that the *Z* oxaphosphetane is favored by lower steric interaction with the approaching aldehyde. The phenyl rings move in the bisaxial position, whereas the pyridyl ring remains equatorial. As found in the case of the Wittig reaction for dipyridylke-

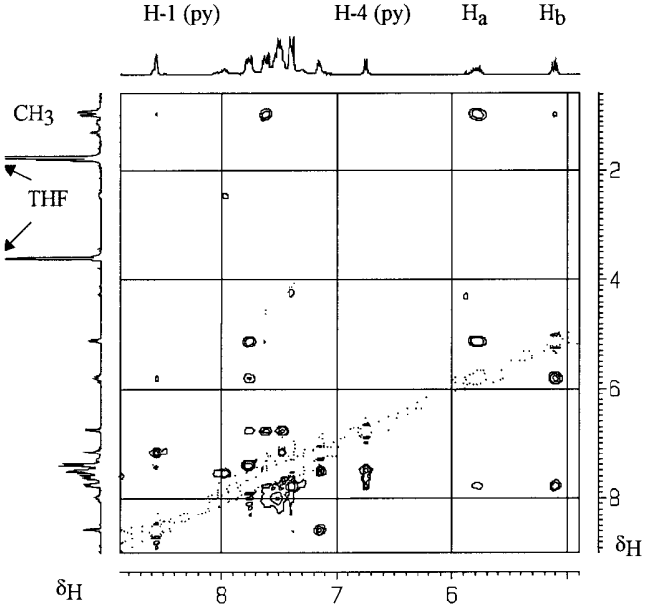
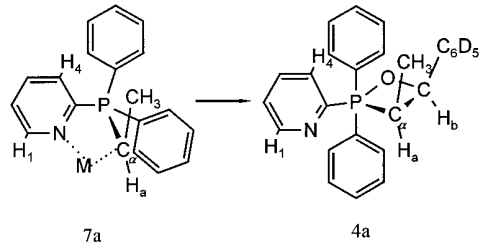


Figure 1. 2D-ROESY NMR spectrum of oxaphosphetane **4a** at −70 °C, mixing time (duration of spin-lock pulse) 300 ms



Scheme 4

tone **2**, the oxaphosphetane can be reopened by chelation of the lithium ion between the pyridine nitrogen and the oxygen atom of the aldehyde to form a betaine lithium salt complex, which gives rise to very broad signals at $\delta_P = -10$.

Conclusion

We have shown in this work that replacement of the phenyl rings in triphenylphosphane with pyridyl rings leads to a significant increase in *Z*-selectivity during a Wittig reaction, without affecting the yields, as long as no lithium base is used to generate the ylide. Even one pyridyl ring is sufficient to create this effect. By ROESY NMR spectroscopy at low temperatures, we could determine the structure of an oxaphosphetane intermediate and deduce a stereochemical model to explain the *Z*-selectivity. Further structural studies to confirm this stereochemical model are currently being undertaken.

Experimental Section

General Remarks. − Dynamic NMR Measurements: Low temperature ^{31}P NMR measurements were performed in THF with a Bruker DRX-600 NMR spectrometer using a 10 mm multinuclear probe head under standard measurement conditions and proton decoupling. The shift values are referenced with respect to external H_3PO_4 at room temperature, The ROESY spectra[17] were recorded on a Bruker DRX-400 spectrometer at −70 °C using a spin-lock mixing time of 300 ms.

Synthesis: The 2-pyridyl-/phenylphosphanes **5a−c**[19] were prepared using the method described for tris(2-pyridyl)phosphane **5c** by Keene et al.[13] The 2-pyridyl-/phenyl-ethylphosphonium iodides **6a−c** were obtained according to Schmidbaur et al.[14] by refluxing the phosphanes **5a−c** with a 10-fold molar amount of ethyl iodide and recrystallizing the product from methanol/diethyl ether.

6a: $C_{19}H_{19}INP$ (M = 419.22); yield 92%; m.p. 136−137.5 °C; ^{31}P NMR ($CDCl_3$): δ = 23.9.

6b: $C_{18}H_{18}IN_2P$ (M = 420.21); yield 93%; m.p. 161−163 °C; ^{31}P NMR ($CDCl_3$): δ = 20.2.

6c: $C_{17}H_{17}IN_3P$ (M = 421.20); yield 88%; m.p. 164−166 °C; ^{31}P NMR ($CDCl_3$): δ = 16.1.

General Procedure for the Wittig Reactions: Under nitrogen, 6 mmol of the 2-pyridyl-/phenyl-ethylphosphonium iodide **6a−c** was suspended in 50 mL dry THF. To this suspension, an equimolar amount of the base solution (*n*-butyllithium, 1.6 M in *n*-hexane; NaHMDS, 1.0 M in THF; Aldrich) was added at −75 °C and the mixture was stirred for 30 min, after which time an equimolar amount of benzaldehyde was added. The solution was left stirring to reach room temperature during 12 hours. The THF was evaporated and the residue poured into 50 mL of water, followed by extraction three times with diethyl ether (50 mL). The ether phase was dried with Na_2SO_4. After filtration, the solvent was removed and the mixture was worked up by column chromatography (silica gel, petroleum ether as eluent). For the dynamic NMR measurements, the ylide solution was transferred at −70 °C to an NMR tube with exclusion of moisture and air before the addition of benzaldehyde. One equivalent of benzaldehyde was added directly to the NMR tube at −70 °C through a septum. In the case of using the deuterated benzaldehyde C_6D_6CHO[16] dry perdeuterated THF was used as solvent for the Wittig reaction as well as for the base NaHMDS.

Acknowledgments

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