

Note

Stereoselectivity of the Wittig reaction in two-phase system

Saleh Al Busafi* & Waffa Al Rawahi

Department of Chemistry, College of Science, Sultan Qaboos
University P.O.BOX 36, Al Khod 123, Muscat, Sultanate of
Oman

E-mail: saleh1@squ.edu.om

Received 26 July 2005; accepted(revised) 22 September 2006

The Wittig reaction of benzyltriphenylphosphonium chloride with aliphatic and aromatic aldehydes has been investigated, respectively, in two-phase solvent system (dichloromethane / water) in the presence of sodium hydroxide. Both, the effect of the size of aliphatic aldehydes and the effect of substitution on benzaldehyde to the *cis/trans* ratios have been studied. It has been found that the use of aliphatic aldehydes in Wittig reaction gives higher ratio of *trans* alkene isomer. However, when aromatic aldehyde is used, the ratio of the *cis* alkene isomer is found to be higher than that of the *trans* isomer. In addition, the electronic nature of substituents (electron-donating group versus electron-withdrawing group) causes some changes in the *cis/trans* ratio of the product stilbene.

Keywords: Stereoselectivity, Wittig reaction, benzyltriphenylphosphonium chloride, stilbene

IPC Code: Int. Cl.⁸ C07C

The Wittig reaction is considered to be one of the most effective organic synthetic reactions for the construction of carbon-carbon double bond¹. The usual condition to perform Wittig reaction requires the use of anhydrous, aprotic solvents and an organolithium or amide bases. In anhydrous condition, the base and phosphonium salt are mixed in a dry solvent to generate the phosphonium ylide². The resulted ylide then reacts with the carbonyl compound (aldehyde or ketone) to form the required alkene (**Scheme I**).

An alternative to the use of anhydrous condition is to employ phase transfer catalyst in a mixture of water and organic solvent in which aqueous sodium hydroxide can be used as a base and the phosphonium salt itself can function as the phase transfer catalyst³. The mechanism of the Wittig reaction originally proposed was expressed in term of three steps: (a) reversible nucleophilic addition of the phosphorus ylide to the carbonyl compound to give a betaine

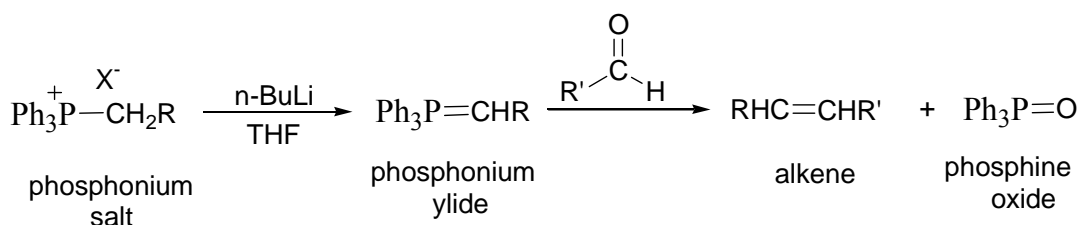
species, (b) formation of the four-membered oxaphosphetane intermediate, and (c) irreversible decomposition of the oxaphosphetane intermediate to give alkene and phosphine oxide (**Scheme II**)⁴.

The stereoselectivity in Wittig reaction to yield *cis* or *trans* alkene depends on the structure of the ylide, the structure of the carbonyl compound, and the reaction conditions. The broadest generalization is that stabilized ylides having conjugating substituents (e.g., COOMe) give mainly the *trans*-alkene whereas unstabilized ylides which lack conjugation give predominantly the *cis*-alkene⁵. Most of the studies of the Wittig reaction were carried out in anhydrous organic solvents. Studies that investigate the effect of the structure of the carbonyl compound on the *cis/trans* ratios of the Wittig reaction in a two-phase system are relatively few. In the study described in this paper, aliphatic aldehydes with different size and aromatic aldehydes with different substituents were added respectively to the same phosphorous ylide namely benzylidenetriphenylphosphorane in water/dichloromethane system at room temperature. The objective of the study is to establish a relationship between the structure of the aldehyde and the *cis/trans* ratio in the produced alkenes. The *cis/trans* ratio in the produced alkenes was determined by proton nuclear magnetic resonance (¹H NMR).

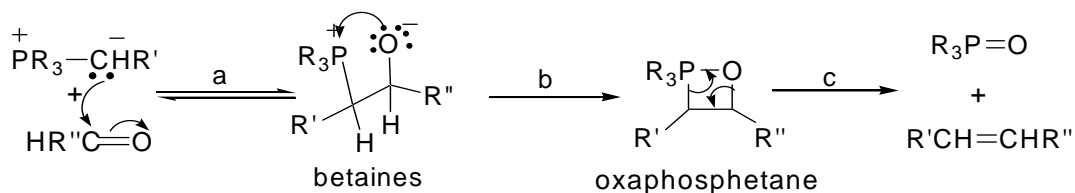
Results and Discussion

Benzyltriphenylphosphonium chloride was reacted with a series of aliphatic and aromatic aldehydes in the presence of sodium hydroxide (**Scheme III**).

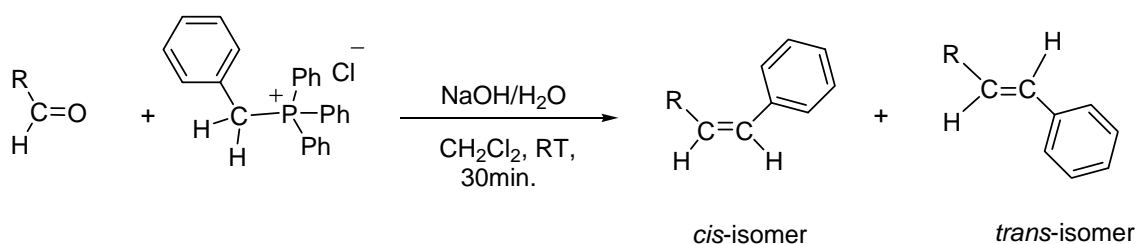
The fact that the *trans* coupling constant (14-16 Hz) is larger than the *cis* coupling constant (9-12 Hz) made it easier to identify the proton's signals of each isomer. The peak intensities were measured for calculating the *cis/trans* ratio. In all cases the ethylene protons showed upfield shift in going from the *trans* to the *cis* isomers (Δ (*trans-cis*) = 0.3-0.8 ppm). Four aliphatic aldehydes ranging from a small size such as ethanal **1** to a large size such as 2-methylpropanal **4** were used. In general, the percentage of the *trans* isomers was found to be higher than those of the *cis* isomers when aliphatic aldehydes were used (**Table I**). The highest *trans* isomer percentage was found when 2-methylpropanal **4** was used (i.e. 70.5%



Scheme I



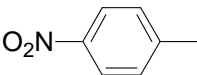
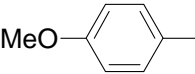
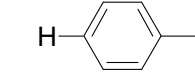
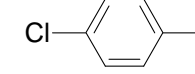
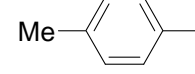
Scheme II



Aliphatic aldehydes

1. R = CH₃2. R = CH₂-CH₃3. R = CH₂-CH₂-CH₃4. R = CH(CH₃)₂

Aromatic aldehydes

5. R = 6. R = 7. R = 8. R = 9. R = 

Scheme III

Table 1 — Wittig reaction of benzyltriphenylphosphonium chloride with aliphatic aldehydes at RT in CH₂Cl₂ / H₂O

No.	Aldehyde	% <i>cis</i>	% <i>trans</i>
1	CH ₃ CHO	44.6	55.4
2	CH ₃ CH ₂ CHO	42.2	57.8
3	CH ₃ CH ₂ CH ₂ CHO	38.2	61.8
4	CH(CH ₃) ₂ CHO	29.5	70.5

compared to 55.4% for ethanal **1**). The high percentage of the *trans* isomer formation can be attributed to the large size of the isopropyl group in 2-methylpropanal compared to the relatively small size of the methyl group in ethanal. In general, it has been observed that the amount of the *trans* isomer increases as the size of the **R** group increases.

The variation of stereochemistry in Wittig reaction is attributed mainly to kinetic control in nearly all

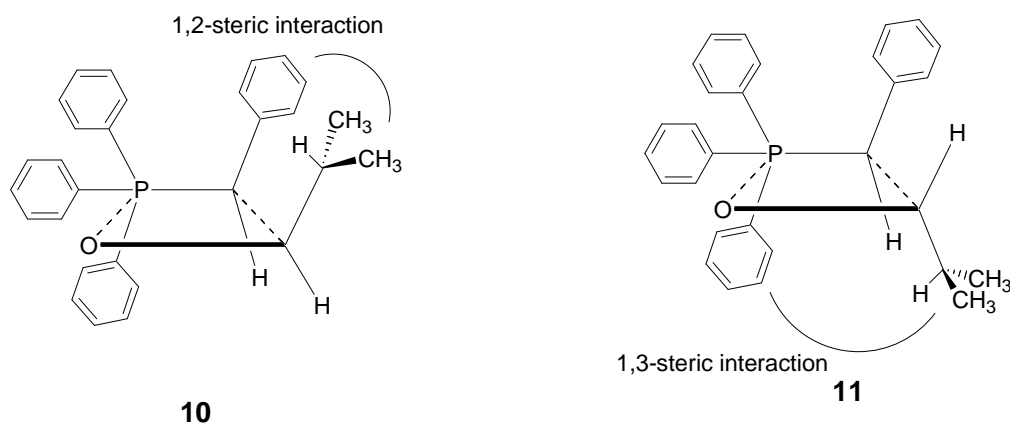


Figure 1 - Proposed *cis* **10** and *trans* **11** transition states

cases⁶. Two limiting geometries for the cyclic transition state: the planar *trans*-selective geometry and the puckered *cis*-selective geometry has been shown to control the stereochemistry of the product⁷. Selectivity of *trans* or *cis* diastereomer is a result of interplay of 1,2 and 1,3 steric interactions between substituents on the four-centered transition state. The 1,2-steric interaction between the isopropyl group and the ylide phenyl group in the *cis* transition state **10** is more severe than 1,3-steric interaction between the isopropyl group and the phosphorus phenyl group in the *trans* transition state **11** (Figure 1). The less harsh 1,3-steric interaction makes the *trans* transition state more favored, which leads to more *trans* product. In the case of ethanal **1**, as the methyl group is small; the 1,2-steric interaction is less severe than isopropyl group, consequently leading to less *trans* product.

Four substituted benzaldehydes were reacted with the benzyltriphenylphosphonium chloride in the presence of sodium hydroxide in $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$ solvent system. Two aromatic aldehydes bear electron-donating groups ($-\text{OCH}_3$ **6** and $-\text{CH}_3$ **9**) and two electron-withdrawing groups ($-\text{NO}_2$ **5** and $-\text{Cl}$ **8**) in the *para* position of the benzene ring. The results of the reactions with these were compared with that of the unsubstituted benzaldehyde **7** (Table II). The aim was to study the effect of substituents with different electronic behaviors on *cis/trans* stilbene ratios. The predominant feature of this study is that when aromatic aldehydes were used, the higher percentages of the *cis* isomers compared to those of the *trans* isomers was formed. This result is exactly opposite to the one found when aliphatic aldehydes were used. In addition, the *cis/trans* ratio also changed considerably on changing the substituents in benzaldehyde.

Table II — Wittig reaction of benzyltriphenylphosphonium chloride with aromatic aldehydes at RT in $\text{CH}_2\text{Cl}_2/\text{H}_2$

No.	Aldehyde	% <i>cis</i>	% <i>trans</i>
5	4- $\text{NO}_2\text{C}_6\text{H}_4\text{CHO}$	81.0	9.0
6	4- $\text{MeOC}_6\text{H}_4\text{CHO}$	74.6	25.4
7	$\text{C}_6\text{H}_5\text{CHO}$	61.0	39.0
8	4- $\text{ClC}_6\text{H}_4\text{CHO}$	59.8	40.2
9	4- $\text{CH}_3\text{C}_6\text{H}_4\text{CHO}$	58.3	41.7

The highest *cis* isomer percentage (81.0%) was recorded for 4-nitrobenzaldehyde **5** compared to only 58.3% of the *cis* isomer when 4-methylbenzaldehyde **9** was used. The puckered transition state **12** depicted in Figure 2 can be used to demonstrate the *cis* stereoselectivity in Wittig reaction when aromatic aldehydes were used. In this puckered *cis*-selective geometry, the 1,2 interactions of the ylide phenyl group with the aldehyde phenyl group and with the adjacent phosphorus substituent are smaller than those in the corresponding *trans* form. In addition, the hydrophobic interaction between the two planar benzene rings (A and B) in the *cis* transition state tends to stabilize the geometry and leads to more *cis* product.

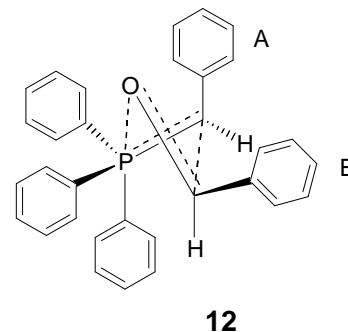


Figure 2 — Proposed puckered *cis* transition state

Experimental Section

General

The reagents and solvent were obtained from Aldrich and used without further purification. ^1H NMR spectra were recorded on a 400 MHz Bruker spectrometer. Chemical shifts (δ_{H}) were recorded in parts per million (ppm) and were referenced to the solvent peak (CDCl_3 at 7.24 ppm). The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

Experimental procedure

Benzyltriphenylphosphonium chloride (7.78 g, 20 mmoles) was suspended in dichloromethane (15 mL) in an Erlenmeyer flask containing a magnetic stirrer bar. Sodium hydroxide (50 g) was dissolved in cold distilled water (75 mL) in a 250 Erlenmeyer flask. The aldehyde (20 mmoles) was added to the reaction mixture followed by the aqueous sodium hydroxide. The neck of the flask was plugged with cotton wool and the yellow mixture stirred for 30 min. Then the mixture was decanted into a separatory funnel through a small funnel. The layers of the mixture were separated and the organic layer was extracted with (2 \times 20 mL) dichloromethane and distilled water (15 mL). The dichloromethane solution was dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was extracted with hot petroleum (25 mL portions) and concentrated *in vacuo* to yield the crude product. ^1H NMR was run for the crude product to measure the *cis/trans* ratio.

***trans*-1-Phenyl-1-propene 13.** ^1H NMR (400 MHz; CDCl_3); δ 1.87 (3H, d, J 6.6 Hz), 6.24 (1H, dq, J = 6.6 and 16.3 Hz), 6.39 (1H, d, J = 16.4 Hz), 7.15-7.69 (5 H, aromatic).

***cis*-1-Phenyl-1-propene 14:** ^1H NMR (400 MHz; CDCl_3); δ 1.89 (3H, d, J = 7.2 Hz), 5.79 (1H, dq, J = 7.2 and 11.6 Hz), 6.43 (1H, d, J = 11.1 Hz), 7.15-7.69 (5 H, aromatic).

***trans*-1-Phenyl-1-butene 15.** ^1H NMR (400 MHz; CDCl_3); δ 1.05 (3H, t, J = 7.5 Hz), 2.22 (2H, m), 6.25 (1H, dt, J = 6.3 and 15.6 Hz), 6.37 (1H, d, J = 15.6 Hz), 7.15-7.69 (5H, aromatic).

***cis*-1-Phenyl-1-butene 16.** ^1H NMR (400 MHz; CDCl_3); δ 1.08 (3H, t, J = 7.4 Hz), 2.34 (2H, m), 5.64 (1H, dt, J = 7.3 and 11.6 Hz), 6.38 (1H, d, J = 11.6 Hz), 7.15-7.69 (5H, aromatic).

***trans*-1-Phenyl-1-pentene 17.** ^1H NMR (400 MHz; CDCl_3); δ 0.92 (3H, t, J = 7.12 Hz), 1.5 (2H, m), 2.18 (2H, q, J = 7.2 Hz), 6.22 (1H, dt, J = 6.8 and 15.8 Hz), 6.34 (1H, d, J = 15.9 Hz), 7.16-7.69 (5H, aromatic).

***cis*-1-Phenyl-1-pentene 18.** ^1H NMR (400 MHz; CDCl_3); δ 0.95 (3H, t, J = 7.23 Hz), 1.5 (2H, m), 2.31 (2H, q, J = 7.4 Hz), 5.66 (1H, dt, J = 7.2 and 11.7 Hz), 6.40 (1H, d, J = 11.7 Hz), 7.16-7.69 (5H, aromatic).

***trans*-3-Methyl-1-phenyl-1-butene 19.** ^1H NMR (400 MHz; CDCl_3); δ 1.08 (6H, d, J = 7.7 Hz), 2.46 (1H, m), 6.19 (1H, dd, J = 6.8 and 15.9 Hz), 6.34 (1H, d, J = 15.9 Hz), 7.16-7.69 (5H, aromatic).

***cis*-3-Methyl-1-phenyl-1-butene 20.** ^1H NMR (400 MHz; CDCl_3); δ 1.04 (6H, d, J = 6.6 Hz), 2.90 (1H, m), 5.47 (1H, dd, J = 10.4 and 11.5 Hz), 6.30 (1H, d, J = 11.5 Hz), 7.16-7.69 (5H, aromatic).

***trans*-4-Nitrostilbene 21.** ^1H NMR (400 MHz; CDCl_3); δ 7.10 (1H, d, J = 16.3 Hz), 7.17-8.06 (9H, aromatic).

***cis*-4-Nitrostilbene 22.** ^1H NMR (400 MHz; CDCl_3); δ 6.57 (1H, d, J = 12.2 Hz), 6.75 (1H, d, J = 12.2 Hz), 7.17-8.06 (9H, aromatic).

***trans*-4-Methoxystilbene 23.** ^1H NMR (400 MHz; CDCl_3); δ 3.8 (3H, s), 6.99 (1H, d, J = 16.6 Hz), 7.05 (1H, d, J = 16.6 Hz), 7.12-7.86 (9H, aromatic).

***cis*-4-Methoxystilbene 24.** ^1H NMR (400 MHz; CDCl_3); δ 3.9 (3H, s), 6.49 (1H, d, J = 12.3 Hz), 6.53 (1H, d, J = 12.3 Hz), 7.12-7.86 (9H, aromatic).

***trans*-Stilbene 25.** ^1H NMR (400 MHz; CDCl_3); δ 7.11 (2H, s), 7.16-7.88 (10 H, aromatic).

***cis*-Stilbene 26.** ^1H NMR (400 MHz; CDCl_3); δ 6.60 (2H, s), 7.16-7.88 (10 H, aromatic).

***trans*-4-Chlorostilbene 27.** ^1H NMR (400 MHz; CDCl_3); δ 7.04 (1H, d, J = 16.4 Hz), 7.09 (1H, d, J = 16.4 Hz), 7.15-7.68 (9H, aromatic).

***cis*-4-Chlorostilbene 28.** ^1H NMR (400 MHz; CDCl_3); δ 6.52 (1H, d, J = 12.2 Hz), 6.62 (1H, d, J = 12.2 Hz), 7.15-7.68 (9H, aromatic).

***trans*-4-Methylstilbene 29.** ^1H NMR (400 MHz; CDCl_3); δ 2.36 (3H, s), 7.04 (1H, d, J = 16.4 Hz), 7.09 (1H, d, J = 16.4 Hz), 7.12-7.55 (9H, aromatic).

***cis*-4-Methylstilbene 30.** ^1H NMR (400 MHz; CDCl_3); δ 2.30 (3H, s), 6.53 (1H, d, J = 12.2 Hz), 6.57 (1H, d, J = 12.2 Hz), 7.12-7.55 (9H, aromatic).

Acknowledgements

The authors are sincerely thankful to the Sultan Qaboos University for the financial support. The authors are grateful to Wafa Al-Shuaily, Department of Chemistry, Sultan Qaboos University for the NMR spectra.

References

- 1 Johnson A W, *Ylide Chemistry*, (Academic Press, New York) **1966**.
- 2 Gosney I & Rowley A G, *Organophosphorus Reagent*, (Academic Press, New York) **1979**.
- 3 Jwo J, Shieh R, Lin R & Hwang J, *Journal of Molecular Catalysis A*, 142, **1999**, 25.
- 4 Maryanoff B, Reitz A, Mutter M, Inners R, Almond H, Whittle R & Olofson R, *J Am Chem Soc*, 108, **1986**, 7664.
- 5 Vedejs E, Marth C F & Ruggeri R, *J Am Chem Soc*, 110, **1988**, 3940.
- 6 Vedejs E, & Marth C F, *J Am Chem Soc*, 112, **1990**, 3905.
- 7 McEwen W E, Lahti P M & Mari F, *J Am Chem Soc*, 114, **1992**, 813.