Stereoselectivity of the Wittig reaction in two-phase system

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The Wittig reaction of benzyl triphenylphosphonium 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, benzyltriphenyl phosphonium chloride, stilbene

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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 unstablized 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%...
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
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 product 7. 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 H2O/CH2Cl2 solvent system. Two aromatic aldehydes bear electron-donating groups (-OCH3 6 and -CH3 9) and two electron-withdrawing groups (-NO2 5 and –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.

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.

<table>
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<th>No.</th>
<th>Aldehyde</th>
<th>% cis</th>
<th>% trans</th>
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<tr>
<td>5</td>
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<td>81.0</td>
<td>9.0</td>
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<tr>
<td>6</td>
<td>4-MeOC6H4CHO</td>
<td>74.6</td>
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<td>C6H5CHO</td>
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<tr>
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</tr>
<tr>
<td>9</td>
<td>4-CH3C6H4CHO</td>
<td>58.3</td>
<td>41.7</td>
</tr>
</tbody>
</table>

Table II — Wittig reaction of benzyltriphenylphosphonium chloride with aromatic aldehydes at RT in CH2Cl2 / H2
Experimental Section

General

The reagents and solvent were obtained from Aldrich and used without further purification. \(^1\)H NMR spectra were recorded on a 400 MHz Bruker spectrometer. Chemical shifts (\(\delta_{H}\)) 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 \(<\) vacuo to yield the crude product. \(^1\)H NMR was run for the crude product to measure the cis/trans ratio.

Trans-1-Phenyl-1-propene 13. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 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 (5H, aromatic).

Cis-1-Phenyl-1-propene 14. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 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 (5H, aromatic).

Trans-1-Phenyl-1-butene 15. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 1.05 (3H, t, J = 7.5 Hz), 2.22 (2H, m), 6.25 (1H, d, 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. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 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. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 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. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 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. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 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. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 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. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 7.10 (1H, d, J = 16.3 Hz), 7.17-8.06 (9H, aromatic).

Cis-4-Nitrostilbene 22. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 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. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 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. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 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. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 7.11 (2H, s), 7.16-7.88 (10H, aromatic).

Cis-Stilbene 26. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 6.60 (2H, s), 7.16-7.88 (10H, aromatic).

Trans-Chlorostilbene 27. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 7.04 (1H, d, J = 16.4 Hz), 7.09 (1H, d, J = 16.4 Hz), 7.15-7.68 (9H, aromatic).

Cis-Chlorostilbene 28. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 6.52 (1H, d, J = 12.2 Hz), 6.62 (1H, d, J = 12.2 Hz), 7.15-7.68 (9H, aromatic).

Trans-Methylstilbene 29. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 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-Methylstilbene 30. \(^1\)H NMR (400 MHz; CDCl\(_3\)); \(\delta\) 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).

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References