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Real-Time 100 MHz Benchtop NMR Monitoring of the Wittig Reaction: Influence of Aldehyde Activity on Rate and Stereoselectivity

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INTRODUCTION

The Wittig Reaction was first reported in 1954 by Georg Wittig who received the Nobel Prize in Chemistry in 1979 together with Herbert C. Brown "*for their development of the use of boron- and phosphorus-containing compounds, respectively, into important reagents in organic synthesis*".[1] The reaction is a widely utilized method in organic synthesis for the stereoselective formation of alkenes via reaction of the Wittig reagent with carbonyl compounds, typically aldehydes or ketones.

The Wittig reagent is a phosphonium ylide which is generated from the reaction of triphenylphosphine with a primary or secondary alkyl halide in the presence of a strong base (**Figure 1a**). The proposed reaction mechanism proceeds via [2+2] cycloaddition, forming an oxaphosphetane intermediate, which then undergoes elimination of triphenylphosphine oxide (driving force) to yield the alkene product (**Figure 1b**).

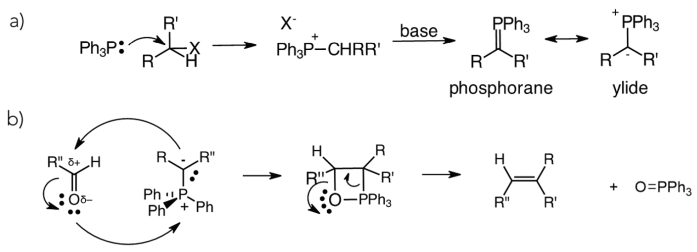


Figure 1. *a) Formation of the phosphonium ylide (Wittig reagent); b) proposed mechanism of the Wittig reaction.*

Unlike other sp^2-bond forming reactions, the Wittig reaction provides convenient access to both (*E*) and (*Z*)-alkenes. The *E/Z* selectivity depends on the stability of the ylide as well

as the electronic nature of the carbonyl component. While the mechanism is not yet fully understood, it is known that stabilized ylides predominantly afford (*E*)-alkenes. Conversely, unstabilized ylides often result in (*Z*)-selective products (**Figure 2**).

Stabilized ylides have conjugating or anion-stabilizing substituents (like carboxylic acids, esters, and aldehydes). Non-stabilized ylides have alkyl substituents which don't stabilize the negative charge at the ylide carbon. Semi-stabilized ylides with aryl-substituent like benzylidene phosphoranes show intermediate behavior, often displaying moderate *E*-selectivity.

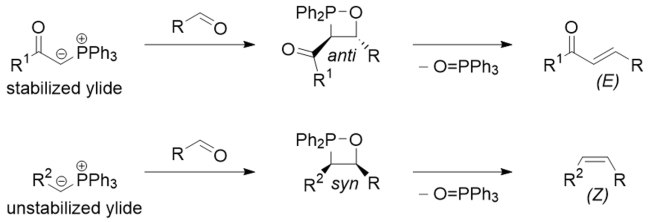


Figure 2. *The E/Z selectivity in the Wittig reaction. Stabilized ylides favor the formation of an anti oxaphosphetane with an aldehyde leading to (E)-alkene products (top). Non-stabilized ylides favor (Z)-alkenes via the respective syn intermediate (bottom).*[2]

Further, the carbonyl reactivity plays an important role in the selectivity. Electron withdrawing groups (EWG) on the carbonyl lead to higher electrophilicity and faster reaction, promoting the *Z*-selectivity. Electron donating groups (EDG) reduce carbonyl reactivity and slow down the reaction, favoring the formation of *E*-alkenes.

Realtime monitoring of the Wittig reaction provides insights into the kinetics and selectivity, allowing to optimize the reaction time and conditions to screen for highest yields. Unlike conventional approaches that require calibration for quantification (*e.g.*, FTIR and UV-Vis), NMR spectroscopy stands out as uniquely suited for reaction monitoring because it requires no calibration and delivers data quickly and frequently. The flow cell kit allows easy inter-conversion of any Nanalysis-60 or Nanalysis-100 benchtop NMR spectrometers into an NMR online detector either as a stand-alone tool or in conjunction with other analytical techniques. Furthermore, the Nanalysis-100 provides the best signal dispersion at the highest available field strength in benchtop NMR spectrometers, allowing to integrate baseline separated signals.

Here we are using a Nanalysis-100 with a flow cell to monitor the effect of electron withdrawing and donating groups in benzaldehyde derivatives in the Wittig reaction. We will examine the influence of the less frequently discussed carbonyl reactivity using the same ylide on the *E/Z*-selectivity and reaction rate. These examples will highlight the advantage of benchtop NMR reaction monitoring in research and academic teaching.

Procedure

Materials

Benzaldehyde (99%), *para*-methoxybenzaldehyde (98%), *para*-nitrobenzaldehyde (98%), (carbethoxymethylene) triphenylphosphorane (95%) and chloroform (anhydrous, 99%) were purchased from Sigma Aldrich. All reagents were used without further purification.

Instrumentation

All NMR data were collected using a Nanalysis-100 benchtop NMR in flow setup. The ^{1}H NMR (99.6 MHz) data was acquired with the following experiment parameters: spectral width: 30 ppm; spectral center: 10 ppm; number of points: 16384; number of scans: 8; dummy scans: 0; interscan delay: 1 s; pulse angle: 30°; and receiver gain: auto. All the spectra presented were processed and manually corrected for phase and baseline distortions using MestReNova software (v15.1.0).

Experimental setup and general procedure for monitoring the three Wittig Reactions

A continuous flow setup was used, where a peristaltic pump (Cole Palmer Masterflex L/S 7551-00) with an adapter kit from the peristaltic pump tubing to 1/16" PTFE tubing was used to transport the reaction mixture from a vial placed in the fume hood through the Nanalysis-100 (flow direction: bottom to top) and back to the flask at a flow rate of 1.0 mL/min at room temperature.

For each reaction 522 mg (1.5 mmol, 1 equiv.) of (carbethoxymethylene)triphenylphosphorane was dissolved in 200 µL of $CHCl_3$ and 1.6 mmol (1.1 equiv.) of the respective aldehyde was added to initiate the reaction and monitoring was started.

Results and Discussion

*First Case: Benzaldehyde (***1***)*

The reaction of benzaldehyde (**1**) with the stabilized ylide **2** showed smooth conversion to ethyl cinnamate (**3**) with an overall yield of 61% after 80 minutes at room temperature (with remaining ylide in the product mixture). From the stacked plot (**Figure 3**) the decreasing signals **a** at 10.00 ppm (s) for the aldehyde, **b** at 3.96 ppm (q, J = 7.07 Hz) and **c** at 1.03 ppm (t, J = 7.07 Hz) corresponding to the CH_2 and CH_3 groups of the ethyl fragment of the ylide starting material, respectively, as well as the increasing signals **d** at 4.25 ppm (q, J = 7.13 Hz) and **e** at 1.30 ppm (t, J = 7.13 Hz) of the CH_2 and CH_3 groups of the alkene product **3** are clearly resolved and allow fully baseline separated signal integration at 100 MHz for monitoring the reaction progress.

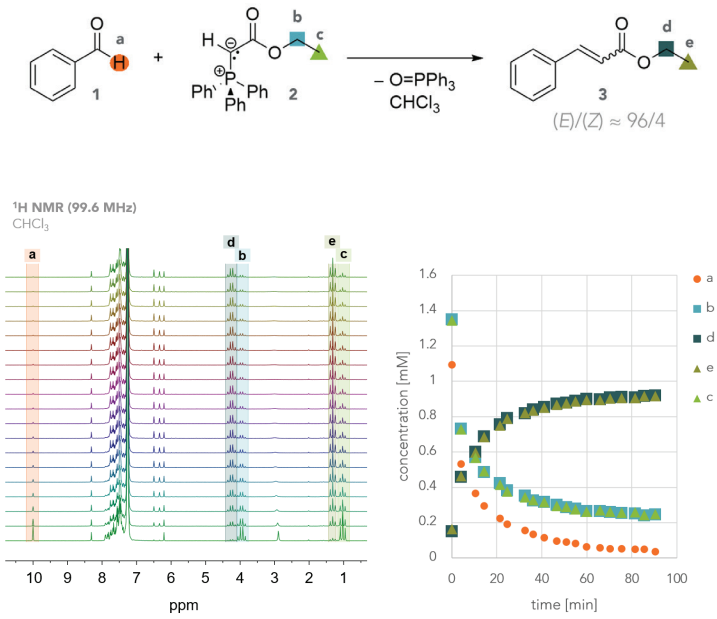


Figure 3. *Stacked plot (left) and conversion vs. time graph (right) of the Wittig Reaction yielding ethyl cinnamate (**3**) starting from benzaldehyde (**1**) and ylide **2**.*

The carbonyl in benzaldehyde (**1**) is moderately electrophilic and the reaction with the stabilized phosphonium ylide **2** yielded the (*E*)-ethyl cinnamate as the major isomer with a great selectivity of (*E*)/(*Z*) = 96.1/3.9 (**Figure 4**).

The two stereoisomers can clearly be differentiated by the vicinal *J* coupling constants of their doublet signals $^3J_{HH}$ = 16.0 Hz ($^3J_{HH}$ = 12-24 Hz range is typical for (*E*)-alkenes) and $^3J_{HH}$ = 12.8 Hz ($^3J_{HH}$ = 6-12 Hz range is typical for (*Z*)-alkenes), respectively.[3] In terms of reaction kinetics it is to note, that the half-conversion time of ylide **2** with benzaldehyde **1** was observed to be relatively quick with only 10 minutes.

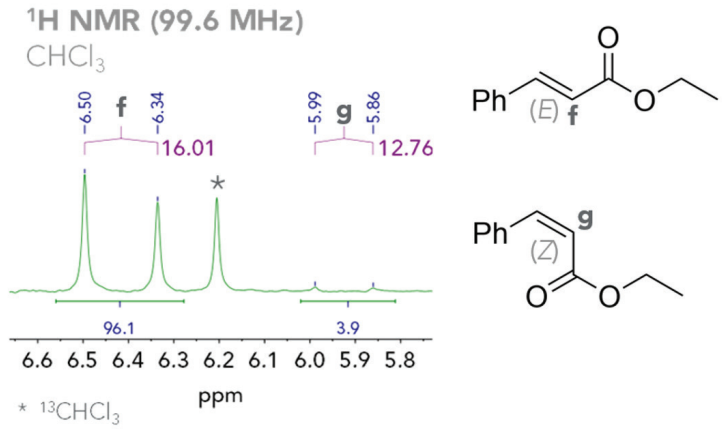


Figure 4. *Zoomed view of doublet signals of the vinylic protons **f** and **g** of ethyl cinnamate (**3**) in (E)- and (Z)- configuration, respectively.*

*Second case, p-methoxybenzaldehyde (**4**)*

With the presence of the *para*-methoxy substituent as an electron-donating group in aldehyde **4**, we would expect a lower electropositivity of the carbonyl center which should be leading to a slower conversion with an even higher (*E*)-selectivity as compared to the unsubstituted benzaldehyde. Indeed, here the half-conversion time of the ylide **2** takes 60 minutes, six times longer than the unsubstituted benzaldehyde. As the substrate (3.85 ppm) and product (3.80 ppm) methoxy group singlet signals overlap with the ylide CH_2 signal **l** at 3.95 ppm (q, $^3J_{HH}$ = 7.10 Hz), in this case the reaction was monitored by the methyl triplet signals **m** at 1.30 ppm and **n** at 1.02 ppm of the alkene product **5** and of the ylide substrate **2**, respectively, as well as the aldehyde consumption. The overall yield of alkene **5** was observed as 85% after 3 hours.

Interestingly, the (*E*)-selectivity was not further increased, and the exact same (*E*)/(*Z*) = 96.1/3.9 ratio as with benzaldehyde was observed. For determining the ratio of the two isomers, due to signal overlap of alkene signal **i** of the (*E*)-isomer with the carbon satellite signal of chloroform at 6.21 ppm, the integration area of the non-overlapping carbon satellite signal at 8.31 ppm needs to be subtracted from the overlapping signals integration area (**Figure 5**). Again, the coupling constants of the vinylic proton signals **i** of the (*E*)-isomer, $^3J_{HH}$ = 15.9 Hz, and **j** of the (*Z*)-isomer, $^3J_{HH}$ = 12.8 Hz, allow for the unambiguous assignment.

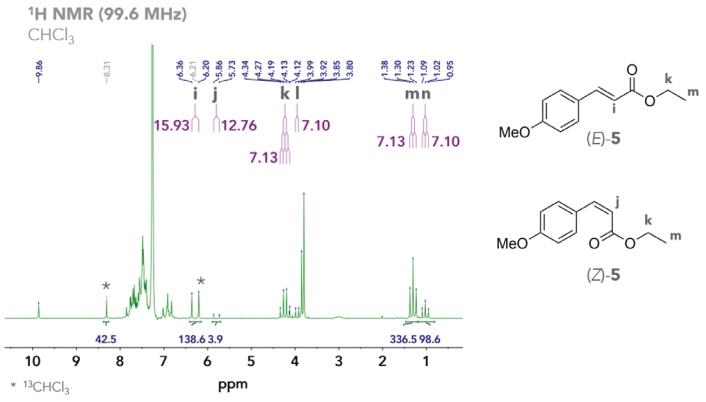


Figure 5. *Product mixture overview spectrum and stereoselectivity of the Wittig Reaction starting from p-methoxybenzaldehyde (**4**) providing (E)- and (Z)-alkene **5**.*

*Third case, p-nitrobenzaldehyde (**6**)*

With the strongly electron-withdrawing nitro substituent in *para*-position, aldehyde **6** has an increased reactivity at the electrophilic carbonyl center which should be leading to a higher reaction rate and favored formation of the kinetic (*Z*)-alkene product **7**. By keeping the stabilized ylide **2** which conversely favors the formation of (*E*)-alkenes, the reaction of aldehyde **6** and ylide **2** is expected to yield a product mixture of the (*E*) and (*Z*)-alkene 7.

As expected, the reaction proceeded much faster than with the other aldehydes **4** and **1**. Full conversion was obtained within only 9 minutes and the half-conversion time of ylide **2** was observed to be as short as 61 seconds. The stereoselectivity resulted in an isomer ratio of (*E*)/(*Z*) = 92.9/7.1, a small increase of the (*Z*)-alkene formation as compared to the other two systems (**Figure 6**).

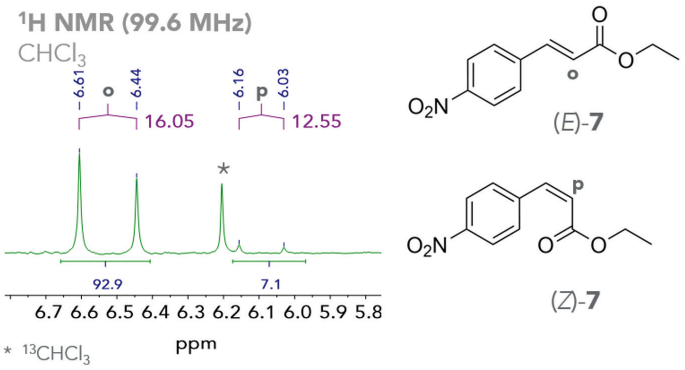


Figure 6. *Stereoselectivity of the Wittig Reaction starting from p-nitrobenzaldehyde (**6**) leading to (E)- and (Z)-alkene **7**.*

Conclusion

The Wittig reaction can be effectively monitored in real time with a Nanalysis-100 equipped with a flow cell. The methylene and/or methyl signals of the ethyl fragment in the ylide substrate and the alkene product provide reliable handles for following the reaction. A systematic study was conducted by varying the aldehyde substrate while keeping the ylide identity, its stability, and all other reaction conditions constant. This allowed investigations on the influence of the carbonyl activity on the reaction rate and (*E*)/(*Z*)-selectivity of the alkene products.

While the reaction rate showed a clear correlation with the altered carbonyl activity, the effect on the (*E*)/(*Z*)-selectivity was small, and the following conclusions can be made:

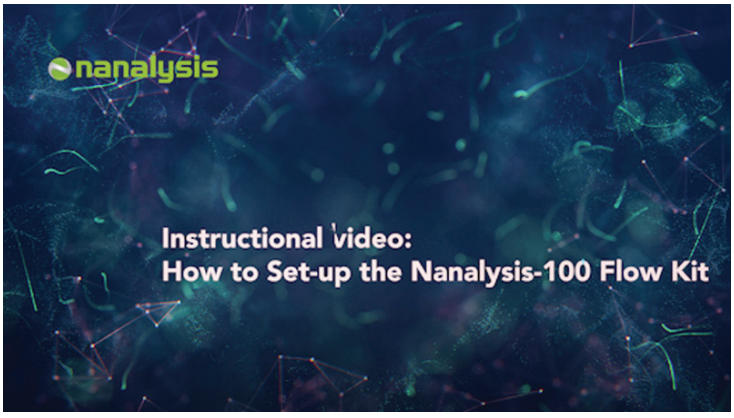
- EDG substituents on the aldehyde decreased the reaction rate but did not further increase the (*E*)-alkene formation, resulting in the same stereoselectivity as compared to the unsubstituted benzaldehyde with the stabilized ylide.

-EWG substituents significantly increased the reaction rate and slightly reduced (*E*)-selectivity, shifting the (*E*)/(*Z*) ratio towards more (*Z*)-isomer formation as compared with benzaldehyde.

Possible explanations for these observations might be steric effects of the aldehyde playing a more significant role in the stereoselectivity, or the reactivity of unsubstituted benzaldehyde already being high and the substituents in the phenyl ring being of less importance. Also, the ylide stability might be predominantly determining the selectivity in the herein tested reactions where the differences in the carbonyl activity of the chosen aldehydes might be too small to result in a significant change of the product (*E*)/(*Z*) ratios. Further reaction monitoring experiments involving ylides with different stability and aldehydes with more drastically varying carbonyl activity will help to learn more about their interplay and influence on the selectivity and reaction rate.

These experiments highlight the value of benchtop NMR spectroscopy for real-time reaction monitoring, especially in evaluating reaction kinetics and optimizing conditions. The high magnetic field strength of the Nanalysis-100 enhances signal dispersion, enabling precise differentiation between substrate and product signals and supporting accurate monitoring through signal integration. The unparalleled richness of structural information provided by NMR spectroscopy facilitates mechanistic understanding of complex transformations like the Wittig reaction.

Watch the Nanalysis100 Flow setup video:



References

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Bay 1, 4600 – 5 Street NE
Calgary, Alberta, Canada
T2E 7C3

Tel: +1.403.769.9499

nanalysis.com

sales@nanalysis.com