UC Berkeley College of Chemistry

Chemistry 112B

Organic Chemistry

The Wittig Reaction

Author:

Jonathan Melville

Graduate Student Instructor:

Rebecca Triano

March 13, 2014

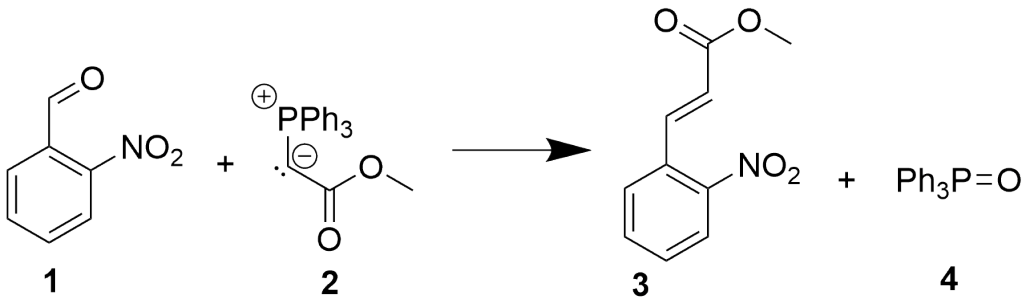
1 Introduction

The Wittig reaction, discovered in 1954 by Georg Wittig, is one of the most common techniques used for the stereoselective preparation of alkenes. Broadly speaking, the reaction allows for the formation of an alkene product and a triphenylphosphine oxide side product from the reaction of an aldehyde or ketone and a "Wittig reagent" (a triphenylphosphonium ylide). In our experiment, we formed methyl (2*E*)-3-(2-nitrophenyl)acrylate and triphenylphosphine oxide from the reaction of 2-nitrobenzaldehyde and methyl (triphenylphosphoranylidene) acetate.

The key step of the mechanism of the ylide reaction is the nucleophilic addition of the ylide to the electrophilic carbonyl group, forming a 4-membered ring that dissociates into the product molecules. The stereoselectivity of the reaction is predicated on the stability of triphenylphosphonium ylide, which determines which of two ring intermediates form: the sterically-unfavored *cis* intermediate that forms via a fast yet reversible process, or the slow, irreversible *trans* intermediate. Because ylides contain (by definition) adjacent positive and negative charges (a positive on the phosphonium, and a negative on the carbon adjacent to the residue), R groups that can better stabilize the adjacent negative charge produce more stable ylides. We can thus classify three distinct levels of stabilization of the ylide by its residue: neutral substituents that do not stabilize negative charge (like alkyl groups or hydrogens) produce an unstabilized ylide that preferentially forms *cis* product, whereas electron-withdrawing residues (like nitro or ester groups) stabilize the charge and preferentially form *trans* product, while "semi-stabilized" substituents (generally aromatic rings) produce a mixture of the two.

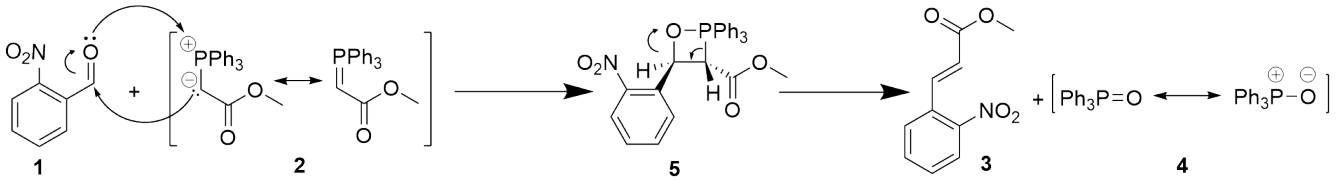
Though the Wittig reaction was published 60 years ago, there has been and continues to be a wealth of research into the subjects, mostly directed toward extending it for the general stereospecific synthesis of arbitrary alkenes. According to a review article by Maercker[1], the Wittig reaction is still a relevant area of study today due to its stereoselective capabilities and ability to be performed in moderate conditions. One major milestone in this regard is the Horner-Wadsworth-Emmons (HWE) reaction, a slightly different approach to the Wittig reaction that is based on a modified Wittig

reaction published by Leopold Horner in 1958. This reaction substitutes phosphonate-stabilized carbanions for the phosphonium ylides used in the standard Wittig reaction. These reagents are more nucleophilic than phosphonium ylides, though of course this means that they are less basic. This variant of the Wittig reaction is valuable because it produces predominately *E*-alkenes, as well as because the side products produced (dialkylphosphate salts) can be easily separated via aqueous extraction, as opposed to the rather tedious column chromatography necessary to separate the triphenylphosphine oxide from our desired product in the standard Wittig reaction. The Wittig reaction is such a central pillar of synthesis chemistry that even its derivatives, like the HWE reaction, see plenty of further research and modification. A paper by Rathke and Nowak[2] details how the use of metals like lithium and magnesium can enable even weaker bases (in their paper, triethylamine) to run the HWE reaction. Similar derivatives of the Wittig reaction have been created over the years, and it is likely that many more will emerge in the future due to its keystone importance in the stereoselective synthesis of alkenes.



Scheme 1: Overall Reaction Scheme of the Wittig Reaction

The Wittig reaction we performed in class involved the reaction of 2-nitrobenzaldehyde **(1)** with methyl (triphenylphosphoranylidene) acetate **(2)** to produce methyl (2*E*)-3-(2-nitrophenyl) acrylate **(3)** with a triphenylphosphine oxide **(4)** side product, and took place in a silica gel matrix to ensure even product dispersion for chromatography. Because the ylide residue in our experiment contains the electron-withdrawing (and thus stabilizing) ester functional group, the *trans* alkene (the *E* product) is preferentially formed over the *cis* alkene (the *Z* product). Because of this selectivity, in this report we focus almost exclusively on the *E* product.



Scheme 2: Primary Reaction Mechanism of the Wittig Reaction

The primary mechanism of the Wittig reaction involves the reaction of the benzaldehyde **(1)** with the methyl (triphenylphosphoranylidene) acetate ylide **(2)** to form a 4-membered ring intermediate **(5)**. This intermediate then undergoes a bond rearrangement which leads directly to the products: an alkene, methyl (2*E*)-3-(2-nitrophenyl) acrylate **(3)**, and triphenylphosphine oxide **(4)**.

2 Results and Discussion

The final product procured was a powdery white crystal, obtained to 94.6% yield. However, our melting-point, TLC, and [most significantly] ^{1}H NMR analyses belie our accurate yield and in fact suggest that our final product was very impure. Our TLC spots, though they show a slight but noticeable trend in the retention factors of our unknowns across multiple fractions, reveal the presence of multiple contaminants, including triphenylphosphine oxide spots (R_f 0.870) in each of our fractions when in theory the product should elute before triphenylphosphine oxide. Our melting point range is a tight band (74.7℃-77.6℃) that unfortunately deviates significantly from the literature[3] value (96.9℃). Most tellingly, our ^{1}H NMR spectrum shows high peaks in the aromatic region (pointing toward the presence of triphenylphosphine oxide adulterant) while simultaneously providing us with a mess of data that largely fails to align with our expected product spectrum. Between our three separate analysis techniques, we can conclude that the most likely source of the significant error in this experiment was a poor choice of eluted fractions for purification from the column chromatograph; though we should expect our product to elute before triphenylphosphine oxide due to decreased interaction with the polar silica gel stationary phase. As a result, the greatest concentration of our products could most likely be found among the earlier fractions collected, whereas our choice to purify the later

fractions, ironically, produced mostly impurities and side products – the exact opposite of the point of the column chromatography.

Besides choosing our fractions for purification more carefully, there are a myriad number of improvements to the experiment that could be made to improve the quality of the process and separation of the final product. A taller column height would certainly increase the separation of the various components, and a reduced sample volume would similarly help improve the sensitivity of the the process. Increasing the number of fractions, decreasing the volume of each fraction, or using a finer stationary phase could all help to improve separation and improve the chances of separate fractions containing only a single product.

2.1 Conclusion

In this lab, we attempted to use the Wittig reaction as a means of creating an alkene product stereoselectively, but were stymied by TLC, melting-point, and NMR analyses that all point toward the impurity of our product, despite what appeared to be a decent yield percentage. This is most likely attributable to an error in our lab procedure where we erroneously selected later fractions of our elution for purification rather than earlier fractions, leading to samples that by the very nature of the chromatographic setup contained small amounts of product and large amounts of impurities. The suggestion that our sample contains mostly impurities due to improper chromatography is corroborated by our chaotic and disordered NMR spectra, as well as our tight melting point band that significantly deviates from the expected value.

3 Experimental

Methyl (2*E*)-3-(2-nitrophenyl)acrylate:

0.084 grams (0.56 mmol) of 2-nitrobenzaldehyde powder were mixed with 0.174 grams (0.522 mmol) of methyl (triphenylphosphoranylidene) acetate, along with 0.108 grams of powdered silica gel in a reaction tube. The vessel was mixed and heated in a microwave

oven at 40% power for 2 minutes, and the resulting gel was easily ground to powder by stirring before cooling to room temperature. Next, a chromatography column with a 50:50 ethyl acetate:hexane mobile phase and a 2-cm-tall (0.656 g) silica gel stationary phase was set up. The reaction mixture was dissolved in 0.50 mL of mobile-phase solvent and transferred onto the bed of the column. The over the course of the separation, seven 1-mL fractions were collected and analyzed via TLC, prompting the collection of the 4th through 7th fractions for precipitation. Evaporation of the solvent via a stream of air produced 0.098 grams (0.473 mmol, 94.6% yield) methyl (2*E*)-3-(2-nitrophenyl)acrylate product as a powdery white crystal, mp 74.7℃-77.6℃(lit[3]96.9℃). TLC: R_f 0.478 (silica gel, 50:50 ethyl acetate:hexane, UV/I_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J=8.2 Hz, 1H), 8.08 (d, J=3.8 Hz, 1H), 7.58 (t, J=7.4 Hz, 1H), 7.50 (t, J=7.4 Hz, 2H), 6.44 (d, J=7.8 Hz, 1H), 3.86 (s, 3H).

References

[1] Maercker, A. The Wittig Reaction. *Org. React.* [Online] **2004**, 2771-2782.

[2] Rathke, M. W.; Nowak, M. The Horner-Wadsworth-Emmons modification of the Wittig reaction using triethylamine and lithium or magnesium salts. *J. Org. Chem.* [Online] **1985**, *50*, 2624-2626.

[3] *Methyl (2*E*)-3-(2-nitrophenyl)acrylate*; Chemspider ID 4510466 [Online]; Royal Society of Chemistry. http://www.chemspider.com/Chemical-Structure.4510466.html (accessed Mar 12, 2014).