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An Efficient Combination of Microwave Dielectric Heating and the Use of Solid-Supported Triphenylphosphine for Wittig Reactions

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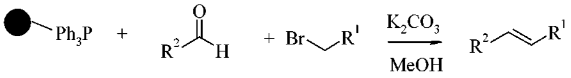
ABSTRACT



Reaction condition: 150° C, 5 min.

Olefins could be formed in an efficient way by the use of stable ylides in just a few minutes using microwave dielectric heating. The drawback with the Wittig reaction in solution phase is the formation of 1 equiv of triphenylphosphine oxide. To avoid this, the corresponding protocol using the efficient combination of solid-supported triphenylphosphine and microwave dielectric heating was developed. An even more efficient one-pot three-step Wittig reaction was also developed.

For a number of different reactions such as 1,3-dipolar cycloadditions, Diels−Alder reactions, pyrrol synthesis and Michael additions, olefins are used as important and useful starting materials and have therefore a large value in the drug development process. Olefins could be formed under a number of various conditions such as Wittig,[1] Heck,[2] condensation reactions,[3] by dehydration of aldols[4] or by the use of benzotriazole as a good leaving group for the formation of olefins.[5] Wittig reactions have been known for a long time and used successfully in solution. The reaction has also been described a number of times since the early 1970s with the use of solid-supported reagents.[6] The major benefit with the solid-supported approach is the possibility to separate the byproduct triphenylphosphine oxide by a simple filtration. Obtaining products free from organophosphorus contamination is known to be quite problematic.[7]

In recent years there has been a great deal of interest in polymer-supported reactions.[8] The major benefits associated with the use of solid-supported reagents are the ease of workup and the fact that combinations of supported reagents can be added without interaction between them. Unfortunately there are also some limitations, e.g., reactions are often slower than their homogeneous analogues; the support needs to be compatible with the reaction conditions; solvent and reagents can be expensive to prepare and the loading can be low, which might limit the scale of an experiment.[9] There is therefore a need to speed up the reaction and find good methods for preparing the reagent, preferably in situ. The conventional Wittig reaction is often very tedious, and the long reaction times could be the reason the use of solid-supported triphenylphosphine has not been used extensively. This limitation could however be overcome with the use of microwave dielectric heating.

Microwave heating has been used in organic synthesis since 1986[10] and is today accepted as a method for reducing the reaction times by several orders of magnitude for a large

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variety of reactions. The yields of the reactions are often increased as compared to conventional methods, probably as a result of the possibility to optimize the reaction in a very short time. Wittig reactions from stable ylides by the use of microwave heating have been published several times both in solution and under solvent-free conditions.[11] The Wittig reaction could also be performed from the corresponding phosphonium salt, which under basic conditions forms the ylide in situ.[12] To verify the Wittig reaction using microwave heating, pyridine 3-carboxaldehyde was treated either with commercially available carbomethoxymethyl triphenylphosphorane (**1**) in DMF 180 °C for 3 min or with carbomethoxymethyl triphenylphosphonium bromide (**2**) and 1 M sodium methoxide in MeOH at 160 °C for 5 min to give the product **3**, (Figure 1) in both cases in almost quantitative yield. Kiddle has presented the synthesis of phosphonium salts, the first step in the formation of Wittig reagents using microwave heating.[13] The protocol gave high yields in just a few minutes. Since the Wittig reaction is very rapid under microwave conditions, the efficiency of the reaction should be many times higher if all steps to form the reagent could be synthesized with the same speed or preferably be synthesized in situ.

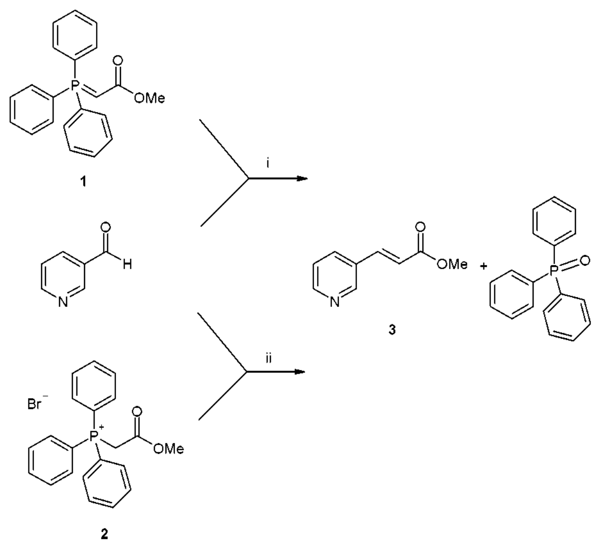

Figure 1. (i) DMF, 180 °C, 3 min. (ii) MeO$^-$/MeOH, 160 °C, 5 min.

This inspired us to try to form the salt and also the following reaction step to a Wittig reagent on solid-supported triphenylphosphine by the use of microwave heating, which has not been disclosed earlier. Polymer-supported triphenylphosphine was treated with methyl bromoacetate in toluene at 150 °C for 3 min. The resin was then washed several times with methylene chloride and methanol and dried in a vacuum. The yield was determined by the increased weight, which indicated a yield of the polymer-bounded carbomethoxymethyl triphenylphosphonium bromide (**4**) between 70% and 85%. The resin was treated with aqueous potassium carbonate at 125 °C for 5 min in order to form the corresponding ylide (**5**). After washing the resin was treated with pyridine 3-carboxaldehyde in DMF at 180 °C for 5 min, giving the product **3** in quantitative yield based on LC/MS analysis (Figures 2 and 4). It should be noted

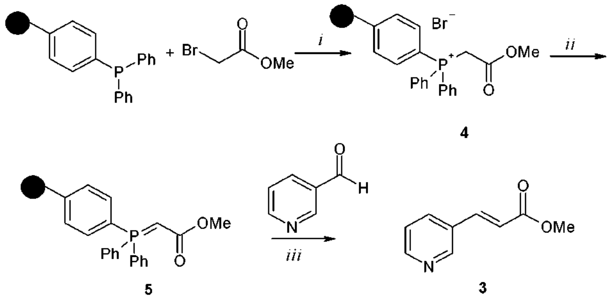

Figure 2. (i) Toluene, 150 °C, 3 min. (ii) K_2CO_3 (aq), 125 °C, 5 min. (iii) DMF, 180 °C, 5 min.

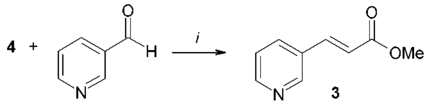

Figure 3. (i) 1 M MeO$^-$/MeOH, 150 °C, 3 min.

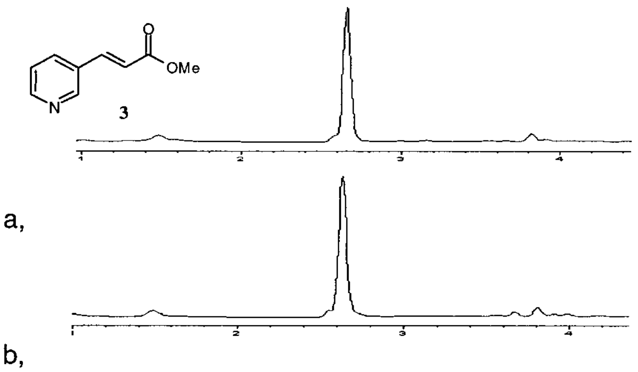

Figure 4. The picture shows the LC/MS chromatogram for the synthesis of **3**: (a) the "two-step procedure" and (b) the "one-pot procedure".

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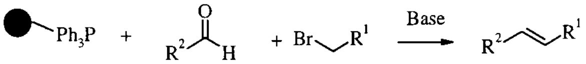

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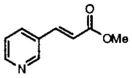
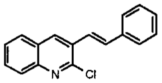
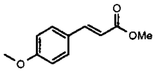
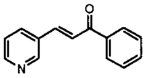
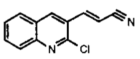
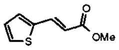
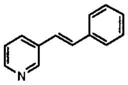
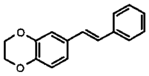
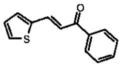
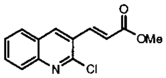
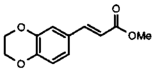
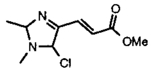
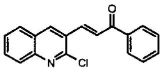
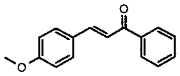
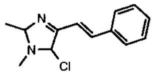
	81%		35%		25%
	48%		92%		95%
	n.d[a]		53%		35%
	46%		42%		38%
	44%		11%		50%

Figure 5. The table shows some synthesized compounds and the isolated yield after RF-HPLC; the purity is better than 98%. [a]n.d. = yield not determined as a result of partially volatile products.

that the reaction conditions are not optimized. As a comparison, Castells et al. reported the formation of carbomethoxymethyl triphenylphosphonium bromide on solid support in 75% yield after 7 days at room temperature[14] using benzene as solvent. They found that the methyl bromoacetate was thermally instable under reflux conditions for many hours. Our approach took approximately 40 min in total.

To find a faster and more convenient way of producing olefins, a two-step procedure was adopted. The resin **4** was treated in the same way as above under basic conditions to form product **3** with excellent yield (Figures 3 and 4) based on LC/MS analysis.

The next obvious step was to develop a one-pot reaction protocol. To the best of our knowledge this has only been presented once by Castell et al. using conventional methods (reaction time, 3 days at rt). Different bases and solvent were used in order to find the most general procedure both with respect to yield and, more importantly, convenience. For the formation of compound **3**, a number of different conditions worked well on the basis of LC/MS analysis (Figure 4), but when testing different aldehydes and alkylhalides we found that the most general protocol was the use of K_2CO_3 and MeOH at 150 °C for 5 min.[15] It should be noted that MeOH is not the common solvent of choice when using solid-phase chemistry because of the fact that the resin does not swell in the solvent. However, it is known that the solvent changes its properties at high temperatures and becomes less polar.[16] It is therefore possible that the polarity of MeOH decreases enough to swell the resin and make the reaction feasible. Figure 5 gives some examples of olefins synthesized by this method. The conversion of the aldehydes were always >80% and in most cases >95% based on LC/MS analysis. The purification of the products were done in a fully automated manner, including filtration of the reaction mixture through a silica plug, evaporation of the solvent, dissolution and RF-HPLC purification and finally evaporation of the solvent to give the isolated products in a varying yield (Figure 5), from poor to very good but always with a high purity, in all cases >98%.[17] When poor yield or no yield had been determined, this was attributed to the products being partially volatile in some cases, or it may have been a consequence of the automated purification strategy.

In conclusion, we have described an easy and fast one-pot method for the production of olefins using the Wittig reaction conditions. A variety of organic halides and aldehydes were used, and by in situ formation of the ylide using the combination of solid-supported reagent and microwave dielectric heating, the products were formed in high purity.

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Supporting Information Available: Experimental procedures, crude LC/MS data, and ^1H NMR data of the purified products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) **General Procedure for Formation of Olefins.** One equivalent of the aldehyde was mixed with 3 equiv of solid-supported triphenylphosphine oxide, 4 equiv of alkylhalide, and 4 equiv K_2CO_3 in 2 mL of MeOH. The mixture was heated in a Smith synthesizer (available from Personal Chemistry) in 5 min at 150 °C. The residue was then filtered through a short plug of silica gel and washed. The solution was concentrated and purified by RF-HPLC to give the compound with purity higher than 98% based on NMR analysis.

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(17) Purity of the compounds after preparative HPLC was determined by LC/MS-ELSD analysis.