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Solid Phase Synthesis of Alkenes Using The Horner-Wadsworth-Emmons Reaction and Monitoring by Gel Phase ^{31}P NMR

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Abstract: Phosphonoacetamide esters bound to solid supported peptides or peptide synthesis supports are active as Horner-Wadsworth-Emmons (HWE) reagents with a variety of aldehydes. HWE reagents can be attached to the solid support via the amide or phosphono ester. Mild basic conditions, triethylamine and Li salts, with excess aldehyde give high conversions to alkenes.

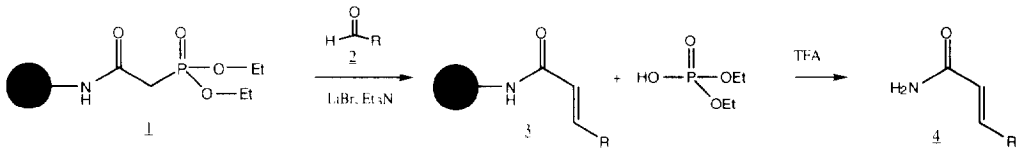
Recent interest in small molecule combinatorial libraries has led to a rebirth in solid supported organic synthesis. The production of structurally diverse libraries on solid supports requires that a large number of solution synthetic transformations be adapted for reliable use on solid phase. At the present time, only a few carbon-carbon bond forming reactions have been applied to solid phase synthesis.[1] Generality and selectivity make the modified Wittig olefinations especially attractive candidates for solid phase carbon carbon bond construction.[2] Attachment to solid phase allows easy isolation of the olefinic product from the phosphorus containing by-products. For combinatorial library generation, Wittig-style olefination reagents will react with many commercially available, structurally diverse aldehydes and ketones. In principle, these phosphorus containing reagents present the opportunity to follow the reaction progress by gel phase ^{31}P NMR.

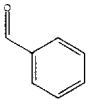
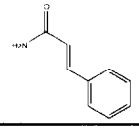
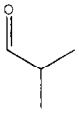
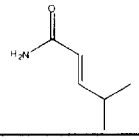
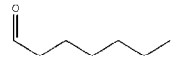
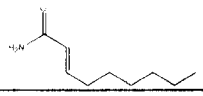
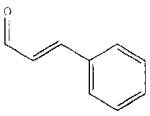
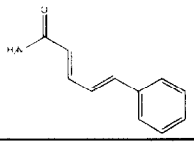
Interestingly, supported Wittig reagents were first examined in 1971.[3] However, the methods were not compatible with solid phase peptide or DNA synthesis. Chiefly, for this reason, the solid phase mediated Wittig reaction was not widely utilized. Recently, very mild conditions for the Horner-Wadsworth-Emmons (HWE) variant of the Wittig reaction have been developed.[4] The use of amine bases and lithum salts is compatible with peptide synthesis as well as many of the desirable functional groups utilized in non-peptide combinatorial library synthesis. Since these recently reported reaction conditions are so mild, we attempted to apply them to the development of a solid phase olefination protocol. Fortunately this approach has provided ready access to alkenes in both high yield and high purity. In addition, we report the use of ^{31}P gel phase NMR as a highly sensitive means to monitor reactions on a solid phase.

Initially, diethylphosphonoacetic acid was coupled to the N-terminus of a solid phase peptide support with PYBOP and N-methylmorpholine in DMF. Solid supported 1 was treated with excess aldehyde, LiBr and triethylamine. The reaction was stopped by rinsing away excess reagents from resin bound alkene 3. The α, β unsaturated amide 4 was cleaved from the solid support with trifluoroacetic acid. Shown in Table 1 are the conversions, after 24 hours, of diethylphosphonoacetamide linked to PEG-PAL resin in the reaction with various aldehydes in ten fold excess. Conversion was calculated by comparing the ratio of phosphonoacetamide to alkene from integration of the ^{1}H NMR after TFA cleavage.[5] Only the E alkene was observed, as judged by the coupling constants of the alkene protons.

The reaction progress was monitored by gel phase phosphorus-31 NMR of the solid support suspended in acetonitrile.[6] ^{31}P gel phase NMR shows the resonance of the starting resin bound diethylphosphonoacetamide as a narrow multiplet at δ 22.[7] After the reaction is complete the δ 22 peaks have disappeared and a new broad resonance for diethylphosphate has appeared near δ 0.

Table 1: Conversion of solid supported diethylphosphonoacetamide to α,β unsaturated amides

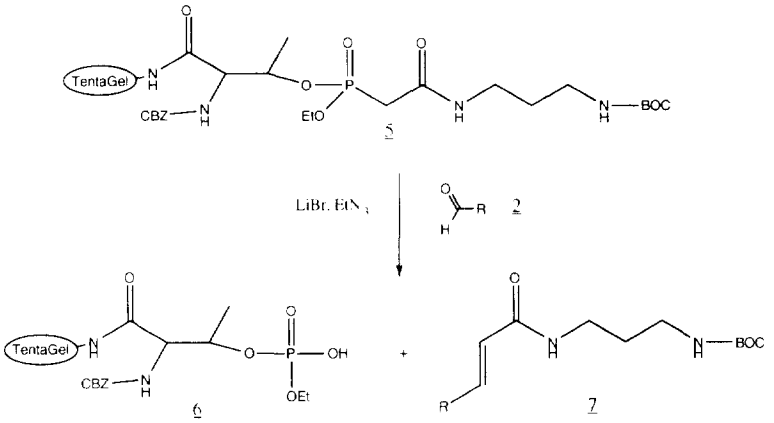


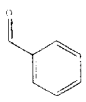
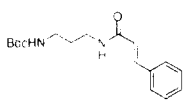
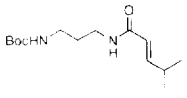
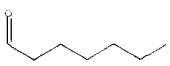
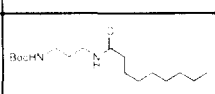
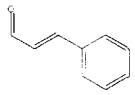
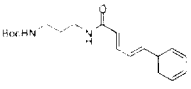
Entry	aldehyde	% conversion	product	alkene δ,J
1		>95		δ6.64 (d, 1H, J= 15.6) 7.74 (d, 1H, J = 15.6)
2		>95		5.79 (dd, 1H, J = 15.4, 1.4) 6.97 (dd, 1H, J = 15.4, 6.6)
3		85		5.83 (dt, 1H, J = 15.3, 1.5) 7.00 (dt, 1H, J = 15.3, 7.0
4		75		6.02 (d,1H, J = 14.9) 6.80 (m, 2H)

An alternative approach to solid phase HWE reactions would release the product upon successful reaction. This approach requires the synthesis of a phosphono ester as the attachment to the solid phase. Therefore, phosphonoacetamide monoesters were coupled to solid supported alcohols, in pyridine with 2,4,6-triisopropylbenzenesulfonyl chloride.[8] Treatment with aldehyde, LiBr, and triethylamine lead to HWE reaction and release from the solid support. Shown in Table 2 are the conversions of 5, phosphonoacetamide linked to Tentagel Cbz threonine via a phosphoester bond, in reaction with 10 fold excess of various aldehydes for 24 hours. Conversion was determined by integration of the gel phase ^{31}P NMR spectrum of the resin after reaction.[9] The phosphate resonance near δ -1 representating the HWE reaction was compared to the total of all other phosphonate resonances. After 24 hours of reaction, none of the starting phosphonate 5 remained.[10] The alkene product was isolated from the salts and excess aldehyde by extraction from aqueous bisulfite. In the ^{1}H NMR of the products, only the E alkenes are observed as evidenced by the coupling constants. In a library

context, react and release procedures leave unreacted material still attached to the resin effecting separation from the desired product.

Table 2. React and Release Approach to the HWE Preparation of Alkenes.



Entry	aldehyde R	% conversion	product	δ , J
1		76%		6.46 (d, 1H, J = 15.6) 6.76 (d, 1H, J = 15.6)
2		72%		5.73 (d, 1H, J = 15.3) 6.81 (dd, 1H J = 15.3, 6.7)
3		45%		5.73 (d, 1H J = 15.4) 6.83 (dt, 1H, J = 15.4, 6.7)
4		50%		6.00 (d, 1H J = 14.8) 7.05 (m, 2H)

In summary, amine base and lithium salt HWE reaction conditions have been shown to be effective with aldehydes and solid supported phosphonoacetamides. A procedure for the HWE synthesis of solid supported α,β unsaturated amides has been developed and shown to be useful with a variety of aldehydes. This protocol is well suited for the production of combinatorial libraries. A react and release HWE reaction sequence has been demonstrated. In addition, solid supported HWE reactions can be conveniently followed by gel phase phosphorus NMR.

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5. Fmoc PEG PAL resin (Millipore) 0.1 g (0.20 meq/g) in a fritted plastic syringe (Gilson) was treated with 20% piperidine in DMF. After 20 min., the resin was washed 6X DMF, 6X CH_2Cl_2, 2X DMF. A 0.3 M solution (0.8 ml) of diethylphosphonoacetic acid (Aldrich), PyBOP (Novabiochem), HOBt, and N-methylmorpholine was added to the resin and shaken for 2h. The resin was washed and dried under vacuum. A negative Kaiser test indicated that acylation was complete. In an NMR tube, the resin was suspended in 0.6 ml of d_3-acetonitrile. ^{31}P NMR shows a resonance at δ 22 ppm. The solution was treated with 20ul isobutyraldehyde, 20 mg LiBr, 30 ul triethylamine. After 24 h, ^{31}P NMR shows only a resonance at δ 0 ppm. The resin was washed with water, DMF, methanol and dried. Cleavage from the resin was with 2 ml of TFA / water (95/5) for 1 h. The solution was conc. and dried under vacuum. ^1H NMR shows only the alkene and no resonances for the phosphorus coupled methylene of the starting phosphonate at δ 2.91, J = 21.5 Hz.

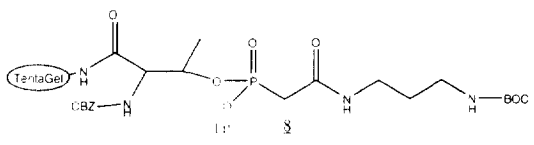
6. Spectra were acquired on a General Electric QE plus 300. Shifts are relative to neat H_3PO_4. A sample of about 50 mg of resin in a regular 5mm NMR tube was used. Addition of about 25% deuterated solvent was adequate for a lock signal. The spectra were acquired at 122 MHz and a recycle time of 1.3 seconds. Spectra with adequate signal to noise ratios required a few hundred acquisitions, but less than 10 minutes of spectrometer time.

7. The literature value for the ^{31}P resonance of diethylphosphono-N,N-dimethylacetamide is δ18.7 in chloroform. *CRC Handbook of Phosphorus-31 Nuclear Magnetic Resonance Data*, Ed. John C. Tebby, **1991**.

8. In a separate experiment, starting with the same 0.23 meq/g TentaGel S-NH_2 resin a loading of 0.05 meq/g was measured using the Fmoc containing version of 5. Lohrmann, R.; Khorana, H.G. *J. Am.Chem. Soc.* **1966**, *88*, 829. For a different method of attachment of phosphorus esters to solid supports see Campbell, D.A.; Bermak, J.C. *J. Org. Chem.* **1994**, *59*, 658-660.

9. Integration of gel phase ^{13}C NMR for quantitation has been validated on TentaGel resin. Look, G.C.; Holmes, C.P.; Chinn, J.P.; Gallop, M.A. *J. Org. Chem.* **1994**, *59*, 7588-7590. Bayer, E.; Albert, K.; Willisch, H.; Rapp, W.; Hemmasi, B. *Macromolecules* **1990**, *23*, 1937-1940.

10. ^{31}P gel phase NMR shows the starting P-ester linked phosphonate resonances near δ 24. Treatment with aldehyde and base causes the conversion of the HWE reagent 5 to two new P containing materials. The HWE reaction is represented by the resin bound diesterphosphate 6 with resonances near δ -1. The other resin bound product has resonances around δ 17.6. We believe this resonance is from the monoester monoanion phosphonate 8 resulting from hydrolysis of the ethyl ester. For example, the precursor to 5, 3-sodium ethylphosphonoacetamido-1-BOC-aminopropane, shows a ^{31}P resonance at δ 16.6 in D_2O solution. Addition of TEA and lithium bromide to the resin 5 in acetonitrile without aldehyde results in complete conversion to the material with the P resonace at δ 17.6. However, neither the amide linked phosphonate 1 nor triethylphosphonoacetate show rapid ester cleavage under the same conditions. The difference in reactivity is probably due to participation of the threonine linker. Low conversion of heptaldehyde and cinnamaldehyde are due to inactivation of the resin bound HWE reagent by this rapid competing reaction. After 24 hours of reaction, none of the starting phosphonate 5 remained. In this case, the use of ^{31}P NMR rapidly identified a competing side reaction which would have been difficult to show by other analytical techniques.



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