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MACROPOROUS POLYMERIC SUPPORTS FOR ORGANIC SYNTHESIS
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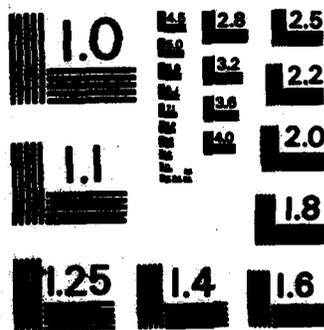
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REPORT DOCUMENTATION PAGE

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1. REPORT NUMBER		2. GOVT ACCESSION NO. AL20901	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Macroporous Polymeric Supports for Organic Synthesis		5. TYPE OF REPORT & PERIOD COVERED Final, 9-01-79 to 8-31-82	
7. AUTHOR(s) Warren T. Ford		8. CONTRACT OR GRANT NUMBER(s) DAAG29-79-C-0195	
9. PERFORMING ORGANIZATION NAME AND ADDRESS Department of Chemistry Oklahoma State University Stillwater, Oklahoma 74078		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS	
11. CONTROLLING OFFICE NAME AND ADDRESS U.S. Army Research Office P.O. Box 12211 Research Triangle Park, NC 27709		12. REPORT DATE 10-25-82	
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		13. NUMBER OF PAGES	
		15. SECURITY CLASS. (of this report) unclassified	
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE	

16. DISTRIBUTION STATEMENT (of this Report)
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17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)
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18. SUPPLEMENTARY NOTES
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19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

→ **Chemical reactions on insoluble polymer supports require transport of reagents from solution into the cross-linked polymer matrix. Most previous polymeric reagents have employed 1-2% cross-linked polystyrene, which swells greatly in organic solvents. Such polystyrene gels, however, are weak**

mechanically, preventing their large scale application, and are unable to retard reactions between two polymer-bound species sufficiently to allow many site-isolation^g syntheses. Our research has been directed toward the use of more highly cross-linked polystyrene supports for organic synthesis. Examples include the generation and trapping of ester enolates by acylation and alkylation at room temperature (rather than the usual -78°C) in high yield with no self-condensation of the ester, and effective Wittig olefin syntheses with macroporous supports having up to 20% cross-linking. Molecules as large as a 3-ketosteroid and a C₁₉ aliphatic ketone are able to penetrate the 20% cross-linked polystyrene in Wittig syntheses. Transport of large organic molecules into reactive sites of the polymer succeeds in the presence of a good solvent when the polymer has been functionalized initially by a transport-sensitive chemical reaction.



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MACROPOROUS POLYMERIC SUPPORTS FOR ORGANIC SYNTHESIS

FINAL TECHNICAL REPORT

WARREN T. FORD

OCTOBER 25, 1982

U.S. ARMY RESEARCH OFFICE

DAAG29-79-C-0195

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MACROPOROUS POLYMERIC SUPPORTS FOR ORGANIC SYNTHESIS

Final Technical Report

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INTRODUCTION

Transport of organic molecules in polymeric matrices takes place whenever polymers and organic liquids or vapors contact one another. In some cases transport is desired, such as the use of polystyrene supports for organic syntheses in this investigation. In some cases transport of organic material should be restricted, such as the use of polymeric membranes for water purification. In still other cases it may be worthwhile either to promote or to restrict organic transport. If a fabric or filler in a garment employed for protection against chemical agents contains reactive sites designed to detoxify the agents, transport to those sites is essential. On the other hand a garment might be designed as a protective barrier.

Chemical reactions on insoluble polymer supports require transport of reagents from solution into the cross-linked polymer matrix. Most previous polymeric reagents have employed 1-2% cross-linked polystyrene, which swells greatly in organic solvents. Such polystyrene gels, however, are weak mechanically, preventing their large scale application, and are unable to retard reactions between two polymer-bound species sufficiently to allow many "site-isolation" syntheses. This investigation has been directed toward the use of more highly cross-linked polystyrene supports for organic synthesis. Examples include the generation and trapping of ester enolates by acylation and alkylation at room temperature (rather than the usual -78°C) in high yield with no self-condensation of the ester, and effective Wittig olefin syntheses with macroporous supports having up to 20% cross-linking. Even molecules as

large as a 3-ketosteroid and a C₁₉ aliphatic ketone are able to penetrate the 20% cross-linked polystyrene in Wittig syntheses.

Results

Site Isolation of Ester Enolates

The enolate of polystyrene-bound 3-phenylpropanoic ester has been prepared with triphenylmethyl lithium in tetrahydrofuran at room temperature and trapped with carboxylic acid chlorides and alkyl bromides.¹ (See Scheme 1). Gas chromatographic yields exceeded 90%, and isolated yields were 73-87% using a partially esterified 10% divinylbenzene-cross-linked gel copolymer containing 0.67 mmol ester/g. Yields of *p*-nitrobenzoylation and self-condensation depend upon degree of cross-linking of the polystyrene support, gel or macroporous morphology of the polymer, degree of functionalization of the polymer, % conversion of the chloromethylpolystyrene to ester, structure of the base used to form the enolate, time between enolate generation and trapping with *p*-nitrobenzoyl chloride, and temperature. Yields of acylation product increase and yields of self-condensation product decrease as the % cross-linking increases from 2% to 20% and as the concentration of ester in fully esterified polymers decreases from 1.08 and 0.18 mmol/g. When the original esterification of the polymer is carried to only partial conversion, the subsequent enolate acylation yields increase, self-condensation yields decrease, and unreacted ester yields decrease. Macroporous 20% cross-linked polymers gave better site isolation than 10% cross-linked gel polymers but lacked physical stability necessary for recycling. One sample of 10% cross-linked polymer gel in three esterification/enolate acylation/hydrolysis cycles showed no decrease in acylation yield but a decrease in degree of functionalization. The higher

degrees of cross-linking and functionalization of the polystyrene permit ester enolate acylation in 77% yield at room temperature on a 0.1 mol scale in only 1400 mL of reaction mixture.

Prior to these results site isolation in syntheses via ester enolates had been demonstrated by Kraus and Patchornik,² but the yields of acylation products never exceeded 40%, and the level of functionalization of the polystyrene in their highest yield experiments was <0.15 mequiv ester/g using a highly swellable 2% cross-linked polystyrene support. Overall comparison of their experiments with ours shows that with more highly cross-linked polystyrene by our method the same amount of product can be prepared in one-twentieth the volume of reaction mixture.

Chain Mobility in Cross-linked Polystyrene Gels

Study of the line widths, spin-lattice relaxation times, and signal areas in high resolution ¹³C NMR spectra of cross-linked polystyrene gels swollen in CDCl₃ was undertaken to determine how cross-linking affects the mobility of polymer chains in solvent-swollen condition.³ Presumably the relative rates of rotational diffusion measured by dipolar relaxation in ¹³C NMR correlate with rates of translational diffusion of the polymer chains (over the short distances allowed by the network structure) and of small molecules in the liquid phase. (Both rotational diffusion and translational diffusion depend upon the microviscosity of the solvent according to the Stokes-Einstein equation). As the degree of cross-linking of the gel increases from 0.5% to 10%, the spectral line widths increase markedly, the T₁ values are almost invariant, and the NOE ratios decrease significantly. These results can be explained only by distributions of correlation times for polymer motions that increase as the cross-linking of the gel increases. The most unusual result is that the signal areas of the aliphatic and aromatic carbon resonances decrease

relative to a low molecular weight internal standard as the degree of cross-linking increases. Increased cross-linking puts more of the carbon nuclei in environments in which their motion is so slow that they are dipolar coupled to protons, as in the solid state.

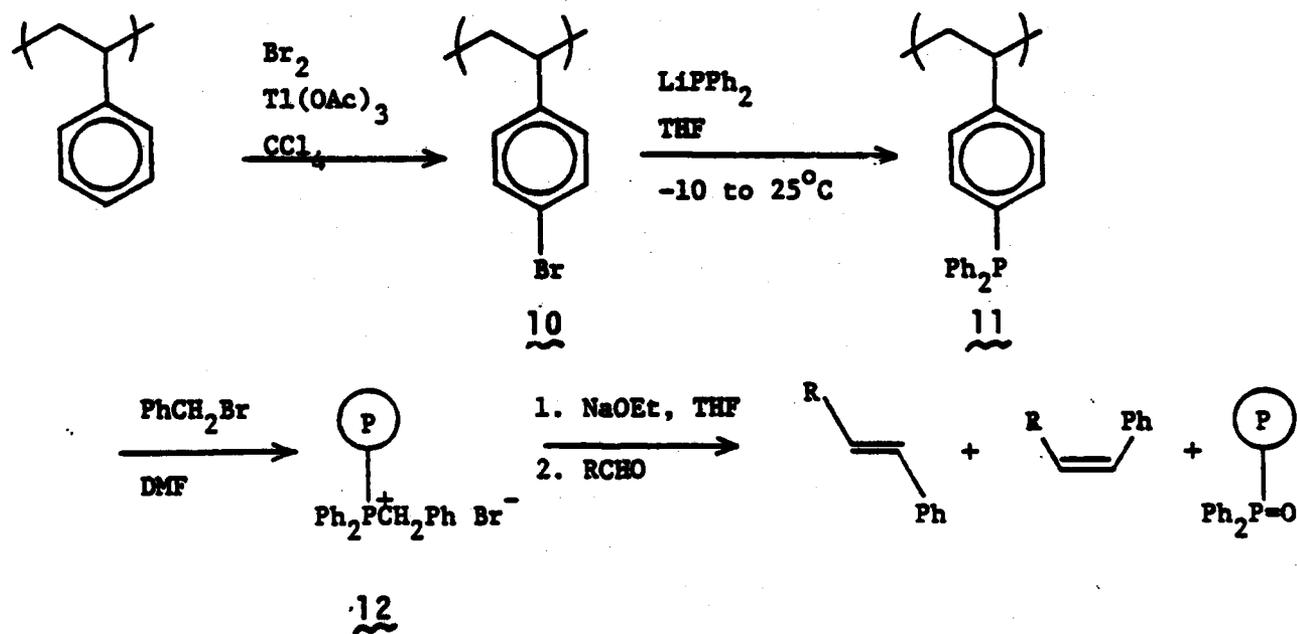
Polymer-supported Wittig Reagents

Previous investigations of polymer-supported Wittig reagents have shown that in most cases yields of alkenes using 2% cross-linked polystyrene are about the same as yields from Wittig reactions in solution.⁴ Heitz and Michels⁵ found that some increases in yields could be attained by use of 0.5% cross-linked polystyrene supports. If polymer-supported Wittig reagents are to be useful on a large scale, neither 2% nor 0.5% cross-linked polystyrenes will be satisfactory, because both are too gelatinous in solvent-swollen condition for large scale filtration. Of all the reactions that have been carried out in the past with polymer-supported reagents, the Wittig reaction is probably the most widely used in organic synthesis, and because of the difficulty of separating triphenylphosphine oxide (by-product) on a large scale in solution experiments, it is a prime candidate for industrial scale use of a polymer-supported reagent.

We have investigated polymer-supported Wittig reagents using more highly cross-linked gel and macroporous polystyrene supports.⁶ Experiments using 2% and 8% cross-linked gel supports and a 20% cross-linked macroporous support have been carried out with a benzylidenephosphorane as shown in Scheme 2. The bromination of polystyrene proceeds quantitatively and rapidly with all of the polymers. Replacement of the bromine with lithium diphenylphosphide proceeds to >90%, 83% and 35% conversion with 2%, 8% and 20% cross-linked polymers respectively. Apparently lithium diphenylphosphide is not transported to the most hindered sites of the bromopolystyrenes. All of the phosphine polymers 11 were converted to phosphonium salts 12 in 86-96% yield. Generation of the

phosphoranes with sodium ethoxide in THF and treatment with benzaldehyde, cinnamaldehyde, α -methylcinnamaldehyde and dodecanal gave the expected alkenes in 72-99% yields as mixtures of E and Z isomers regardless of the degree of cross-linking of the polymeric support. The rates of phosphorane generation and alkene formation do depend on the polymer, decreasing in the order 2% > 20% macroporous > 8%. The fraction of E double bond product is greater with the 20% cross-linked macroporous polymer than with the 2% cross-linked polymer. Successful Wittig reactions with the 8% and 20% cross-linked supports contradict the conclusion in the earlier work of Heitz and Michels⁵ that only lightly cross-linked polymers would be satisfactory.

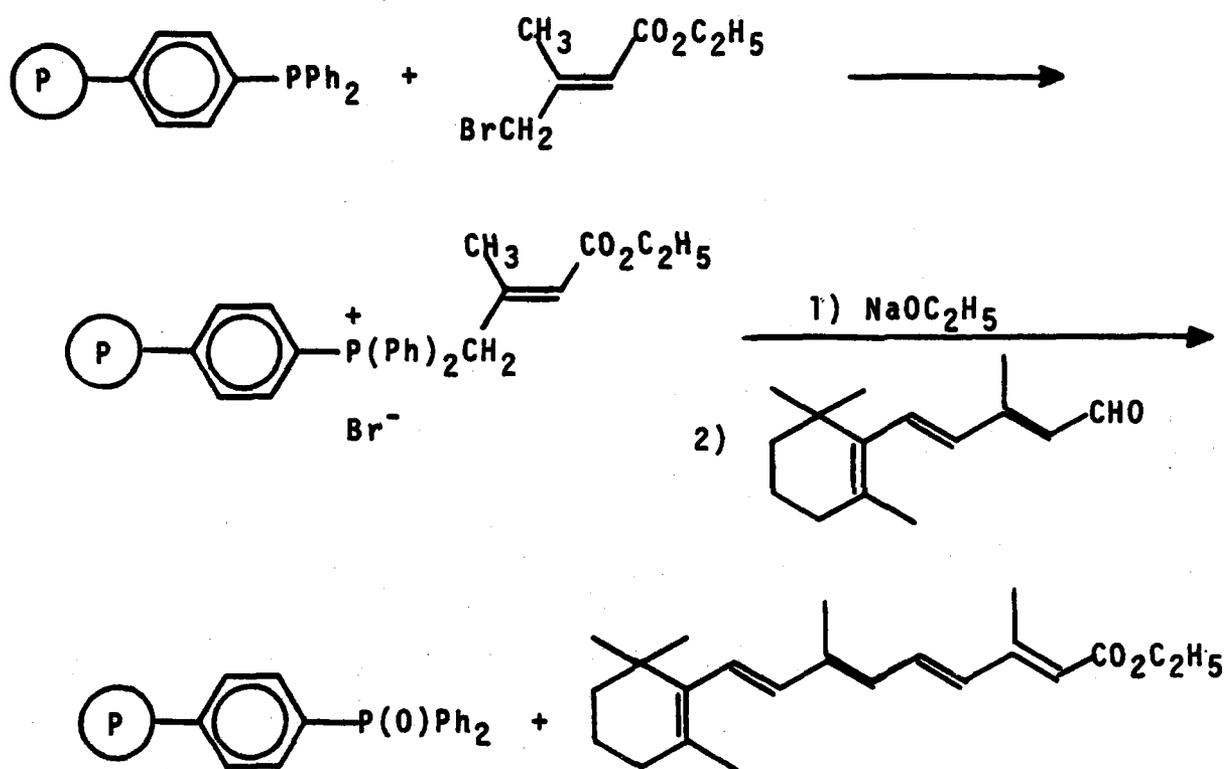
Scheme 2



The study reported investigated the reaction of polymer-bound
functional groups with the 20% 25, 25 and macroporous 20% cross-
linked polymers. Using the above set of reagents it was found that the
macroporous, rigid of silica from methanol, trimethylolpropane, benzophenone,
2,2,2-trifluoroethanol and acetone (1:1:1:1:1) (by GLC analysis) with the
25 cross-linked polymer and 20% with the 20% cross-linked macroporous
polymer. Even large molecules were able to reach the reactive sites in the 20%
cross-linked polymer and to act as a swelling solvent.

Further studies of the macroporous polymer reaction chemistry aimed at
the synthesis of various polymers are in progress at the completion of
this work. The macroporous polymer was used for synthesis of
polymers with various functional groups. The lower distribution
coefficient of the macroporous polymer giving more
uniformly distributed light, heat,
and other physical properties. The macroporous polymer
has a potential utility of
synthesis of complex organic
molecules.

Scheme 3



Conclusions

Polystyrenes cross-linked with as much as 20% divinylbenzene are suitable as supports for organic synthesis. Good solvents enable even large organic molecules to be transported to reactive sites in the polymer networks. The use of 10-20% cross-linked supports has also succeeded in the prevention of polymer-polymer reactions between highly reactive ester enolates and the parent esters. Moreover, these more highly cross-linked supports offer greater mechanical strength and ease of filtration compared with the 1-2% cross-linked polystyrenes most commonly used in polymer-supported synthesis.

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Warren T. Ford, Principal Investigator, 7/1/80 to 8/31/80 (at 50% time) and 7/1/82 to 8/31/82.

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