# Esterification Using a Polymer-Supported Phosphine Reagent

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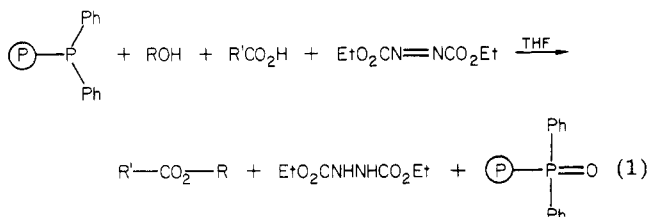*Ohio Wesleyan University, Delaware, Ohio 43015*

Pursuant to our interest in developing macrolide cyclization techniques which avoid high-dilution requirements, we have investigated the use of a polymer-supported reagent for the preparation of a wide variety of esters. The use of triphenylphosphine and diethyl azodicarboxylate (DEAD) has become well established as a means of formation of esters from alcohols and acids[1] and of macrolides from precursor ω-hydroxy acids.[2] The use of polystyryldiphenylphosphine[3] as a reagent in this reaction would afford convenience in terms of preparation and purification of esters and could provide site isolation in the case of macrolide formation.[4] Careful selection of polymer cross-linking and phosphine substitution could control formation of dilide and higher order lactones and polymers, without the need for large solvent volumes.

Prior to investigation of the lactonization process, we felt it was essential to demonstrate the viability of the method for bimolecular esterification. In addition to investigating reaction yields, it was essential to demonstrate that the reaction is kinetically rapid since site isolation requires that the macrolide be formed more rapidly than the polymer chain can undergo conformational change.[5]

We report that the esterification process is fast, convenient, and generally high yielding and constitutes a valuable synthetic method for the preparation of a wide variety of esters. The procedure consists of the addition of the carboxylic acid and alcohol to a solvent- (THF) swollen polymer, followed by the addition of the DEAD reagent. The reaction is generally complete in minutes at room temperature, although longer reaction times (3-4 h) do not degrade product and can be employed to ensure maximum yields, particularly with more hindered secondary alcohols. The major advantage of the polymer-based reaction is the convenient use of excess phosphine and DEAD to maximize ester yields without the difficulties in their removal during workup that are inherent in the solution-phase reaction. The excess reactants and the triphenylphosphine oxide byproduct remain attached to the polymer backbone and are removed by simple filtration. The only other product of the reaction, the highly polar *sym*-dicarbethoxyhydrazine, is easily removed by a short-path silica gel column (reaction 1).

**Table I**

| entry | compd | % yield[a] |
|---|---|---|
| 1 | PhCO$_2$CH$_2$Ph | 86 |
| 2 | Ph–CH=CH–CO$_2$–CH$_2$Ph | 86 |
| 3 | Ph–CH=CH–CO$_2$–CH(CH$_3$)C$_2$H$_5$ | 64 |
| 4 | CH$_3$O–C$_6$H$_4$–CO$_2$-cyclopentyl | 75 |
| 5 | 2-CH$_3$-C$_6$H$_4$–CO$_2$(CH$_2$)$_6$CH$_3$ | 90 |
| 6 | 2,4-Cl$_2$C$_6$H$_3$–CO$_2$(CH$_2$)$_6$CH$_3$ | 89 |
| 7 | O$_2$N–C$_6$H$_4$–CO$_2$(CH$_2$)$_6$CH$_3$ | 84 |
| 8 | (CH$_3$)$_3$CCO$_2$CH$_2$Ph | 99 |
| 9 | EtO$_2$C(CH$_2$)$_4$CO$_2$Et | 79 |
| 10 | CH$_2$=CH(CH$_2$)...CO$_2$(CH$_2$)$_6$CH$_3$ | 92 |
| 11 | (+)-PhCO$_2$CH(CH$_3$)(CH$_2$)$_5$CH$_3$ | 65 |
| 12 | (CH$_2$)$_{11}$ lactone C=O | 10[b] |

[a] All yields are isolated except as noted. [b] GC yield.

The method works equally well with aromatic and aliphatic acids and is compatible with a variety of functional groups as indicated in Table I. No apparent effect on yield was noted in a series of benzoate esters substituted with a variety of electron-donating and withdrawing substituents (entries 1, 4-7). As expected, primary alcohols (entries 1, 2, 5-10) gave the highest yields, with secondary alcohols (entries 3, 4, 11) being consistently lower. *tert*-Butyl alcohol failed to give any significant amount of product upon attempted esterification with benzoic acid. These observations are in accord with the accepted mechanism of the solution-phase version of this reaction: the nucleophilic attack by the carboxylate anion on the alcohol carbon in an S$_N$2 process (reaction 2).[1] Secondary alcohols would
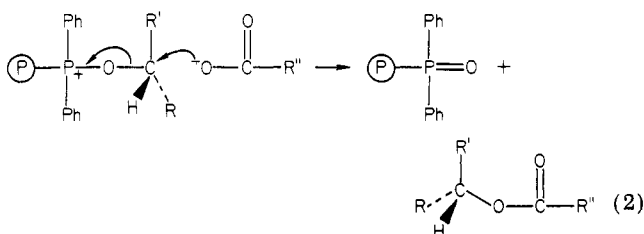
be expected to undergo this inversion with more difficulty, and the steric demands of a bulky polymer chain might be expected to further retard the process. Tertiary alcohols are too hindered to react.

The occurrence of chiral secondary hydroxyl carbons in a wide variety of macrolides[6] makes it imperative that the stereochemistry of the ring forming reaction be clearly defined. It is well recognized that the Ph$_3$P, DEAD reagent combination leads to inversion of the hydroxyl center as shown in reaction 2.[1,2] However, there was some concern that the steric bulk of the polymer might cause some deviation from this expected course. To test the stereochemical integrity of the method, we esterified 2-(-)-octanol[7] with benzoic acid in a 65% yield, affording an ester

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(2) For representative examples see: Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, 2455. Seebach, D.; Seuring, B.; Kalinowski, H.-O.; Lubosch, W.; Renger, B. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 264. Seebach, D.; Pohmakotr, M. *Helv. Chim. Acta* **1979**, *62*, 843. Still, W. C.; Ohmizu, H. *J. Org. Chem.* **1981**, *46*, 5242. Meyers, A. I.; Amos, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 870.
(3) Relles, H. M.; Schluenz, R. W. *J. Am. Chem. Soc.* **1974**, *96*, 6469.
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(5) Fréchet, J. M. J. *Tetrahedron* **1981**, *37*, 663 and references cited therein.

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whose $[\alpha]^{22}_D$ (*c* 107 mg/mL, CHCl$_3$) was +34.4°. The same alcohol, when esterified by a route which does not involve inversion of the hydroxyl center (PhCOCl, Et$_3$N, CH$_2$Cl$_2$), gave an ester whose $[\alpha]^{22}_D$ (*c* 64 mg/mL, CHCl$_3$) was −35.0°. Thus, within experimental error, the polymer-based esterification does give the expected inversion of the hydroxyl carbon.

One distinct advantage that polymeric reagents possess, in addition to ease of workup, is the possibility of recycling reagents. In this case, the polystyrene containing the phosphine oxide was reduced by using trichlorosilane and triethylamine.[8] The use of this recycled reagent in the esterification reaction led to reduced yields, typically 15–20% lower, with the same quantities of reagents. The use of a larger excess of recycled phosphine reagent restored the ester yields to their former levels. Other methods of recycling the polymer are being investigated in order to improve the conversion.

The use of polymeric reagents to control macrocyclization reactions is a very recent development, with only two reports of successful reactions in the literature. One generates macrolides by carboxylate anion displacement of a mesylate using triphase catalysis;[9] the other uses polymer-bound palladium to catalyze an isomerization of a vinyl epoxide to an allylic alcohol, followed by nucleophilic attack with a stabilized anion to give a carbocyclic system.[10] Both methods utilize site isolation on the polymer chain to control intermolecular reactions. A similar potential for site isolation exists in our system utilizing the dipolar intermediate 1 attached to the polymer
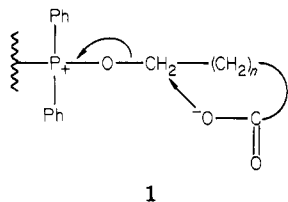


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backbone. Intramolecular nucleophilic attack by the carboxylate anion results in formation of the phosphine oxide and subsequent release of the lactone from the polymer. We report that in some preliminary studies, 12-hydroxydodecanoic acid (40 mM in THF) undergoes lactonization to give the 13-membered ring, but in a disappointing yield of 10%. The reaction has not been optimized, and we are currently investigating the effects on yield of changes in polymer cross-linking and extent of phosphine substitution. The polymer used for this lactonization was one prepared for the esterification reaction where high phosphine loadings are desirable. The lactonization process will probably require much lower loadings for optimum yields.

In summary, the use of polystyryldiphenylphosphine and DEAD constitutes a valuable and convenient method for the esterification of a variety of acids and holds promise for the formation of macrolides under very mild conditions and without the need for large solvent volumes.

## Experimental Section

**General Procedures.** IR spectra were obtained on a Beckman Acculab instrument by using thin films on NaCl plates. NMR spectra were obtained on a Varian T-60 instrument with either CCl$_4$ or CDCl$_3$ as the solvent and with tetramethylsilane as an internal standard. Gas chromatographic data was obtained on a Varian 3700 instrument with FID detectors. All reagents were used as received except for the chlorodiphenylphosphine (Aldrich), which was vacuum distilled prior to use. The THF used as the solvent was dried by distillation from sodium–benzophenone ketyl. All reactions were run under a dry N$_2$ atmosphere. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

**Washing of Polystyrene Beads.** The polystyrene beads (Eastman, 2% divinylbenzene, 200–400 mesh) were washed by using the following sequence: 1 N NaOH, 60 °C; 1 N HCl, 60 °C; 1 N NaOH, 60 °C; 1 N HCl, 60 °C; H$_2$O, 25 °C; DMF, 40 °C; 1 N HCl, 60 °C; H$_2$O, 60 °C; CH$_3$OH; 2:3 CH$_2$Cl$_2$–CH$_3$OH (v/v); 3:1 CH$_2$Cl$_2$–CH$_3$OH; 9:1 CH$_2$Cl$_2$–CH$_3$OH; pure CH$_2$Cl$_2$ (the latter washings all at 25 °C).[3] The beads were dried at 100 °C for 24 h at 1.0 mmHg. This extensive washing procedure is necessary to remove surface residues remaining from the polymerization process. Failure to do so can result in reduced yields in reactions with organometallic reagents.[3]

**Bromination of Cross-Linked Polystyrene.** Polystyrene beads (41.8 g, 0.40 mol) were brominated by the method of Relles.[3] Drying of the product at 100 °C (0.5 mmHg) for 18 h gave 68.0 g of a pale yellow product. Elemental analysis gave 40.90% Br, equivalent to 5.12 mmol of Br/g of resin. Bromination using Tl(OAc)$_3$ as a catalyst in a CCl$_4$ solvent is an alternative procedure which appears to give more consistent results.[11]

**Preparation of Polystyryldiphenylphosphine.** Freshly cut lithium metal (6.68 g, 0.963 mol) was added to 250 mL of dry THF in a three-necked 500-mL flask. Freshly distilled chlorodiphenylphosphine (69.1 mL, 0.385 mol) was added by syringe. The reaction became moderately exothermic and was cooled occasionally with an ice bath. A white insoluble salt appeared rapidly, and the solution turned a deep reddish brown within 1.5 h. After the mixture was stirred for 18 h, the lithium diphenylphosphide was transferred via a stainless steel cannula under N$_2$ pressure to a flask containing 40.0 g of the brominated polystyrene (0.205 mol contained bromine). The resin was preswollen in 150 mL of dry THF. The pale yellow polymer beads immediately turned very dark, and the mixture warmed slightly. After the mixture was stirred for 24 h at room temperature, the product was hydrolyzed with 50 mL of 3:1 acetone/water. The polystyryldiphenylphosphine was filtered off and washed thoroughly with water, acetone, chloroform, toluene, and finally ether. The polymer beads were dried 12 h at 100 °C (0.5 mmHg) to give 52.4 g of a pale yellow solid. Elemental analysis gave 9.15% P and 2.07% Br, corresponding to 2.95 mmol of P/g of resin.

**Typical Procedure for Esterification.** The carboxylic acid (2.5 mmol) and the polymer (1.5 g, 4.4 mmol contained P) were weighed into an oven-dried 50-mL flask. Dry THF (10 mL) was then added under a N$_2$ atmosphere, followed by 2.5 mmol of the alcohol diluted with 5 mL of THF. The flask was cooled on a 25 °C water bath while 3.5 mmol of DEAD was added by syringe over a 2–3-min period. The polymer darkened in appearance, but little yellow color from the DEAD reagent remained in solution. TLC indicated rapid reaction, usually with very little change after 5–10 min. After being stirred under a N$_2$ atmosphere for up to 4 h, the mixture was filtered, washing the polymer thoroughly with ether. Evaporation of the solvent afforded an oily white solid containing the ester and the *sym*-dicarbethoxyhydrazine. This mixture was transferred to and eluted from a short-path silica gel column by using 5–10% ether/hexane (the majority of the hydrazine product is insoluble in this solvent). Removal of solvent from the chromatographed material gave clear oils, whose NMR and IR spectra were compatible with the expected structures.

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$C_6H_4CO_2(CH_2)_6CH_3$, 5462-02-2; 2,4-$Cl_2C_6H_3CO_2(CH_2)_6CH_3$, 86954-32-7; $O_2N$-$p$-$C_6H_4CO_2(CH_2)_6CH_3$, 14309-44-5; $(CH_3)_3CCO_2CH_2Ph$, 2094-69-1; $EtO_2C(CH_2)_4CO_2Et$, 141-28-6; $H_3CCH{=}CO_2(CH_2)_6CH_3$, 16930-99-7; (+)-$PhCO_2CH(CH_3)$-$(CH_2)_5CH_3$, 34881-29-3; DEAD, 1972-28-7; cyclopentyl $p$-methoxybenzoate, 5421-01-2; 1-oxa-2-cyclotridecanone, 947-05-7; cyclopentanol, 96-41-3; (−)-2-octanol, 6169-06-8.

## Temperature Dependence of the Kinetic Isotope Effect in the Homolytic Abstraction of Benzylic Hydrogen by Bromine

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The competitive bromination of hydrocarbons with bromine, as well as with *N*-bromosuccinimide, has been widely studied.[2-5] The intramolecular kinetic isotope effects of bromination of deuterium-substituted toluene has been reported at two temperatures.[6] In view of the importance of the temperature dependence of the primary kinetic hydrogen isotope effect as a mechanistic criterion, recently summarized by Kwart,[7] it is surprising that no such complete study has been reported for bromination. We present such a study at this time.

### Results and Discussion

Reactivities of bromine to toluene and to deuteriotoluene each relative to 4-chlorotoluene in benzene solution were determined at 0, 10, 25, 40, and 60 °C. Values of the isotope effect were obtained from these reactivities. Results are reported in Table I.

The reacted toluenes accounted for at least 80% of the bromine added. This loss of bromine is explained by the entrainment of bromine with the nitrogen flow used to remove HBr as it is formed. No attempt was made to return unreacted bromine to the reaction flask nor was any attempt made to analyze for the amount lost. The relative rate of deuteriotoluene to 4-chlorotoluene reported in Table I for 40 °C includes three values determined with use of toluene-$\alpha,\alpha,\alpha$-$d_3$. These three runs afforded $k_D/k_c$ = 0.215 ± 0.004, while four determinations using toluene-$d_8$ gave $k_D/k_c$ = 0.208 ± 0.066. As these values were indistinguishable, they were combined and all other reported values were determined with use toluene-$d_8$.

The kinetic isotope effects, $k_H/k_D$, were determined from the selectivities and are reported in Table I and are in satisfactory agreement with the bromine value of 4.6 at 77 °C reported by Wiberg and Slaugh and of 3.6 at 110 °C for *N*-bromosuccinimide bromination.[6] This data gives a good fit to the Arrhenius relation (eq 1, $S$ = 0.059, $r^2$ = 0.969) which affords the activation parameters $E_D{}^* - E_H{}^*$ = 2.5 ($S$ = 0.22) kcal/mol and $A_H{}^*/A_D{}^*$ = 0.188 (ln $A_H{}^*/A_D{}^*$ = −1.669, $S$ = 0.374). The interpretation of these

$$\ln (k_H/k_D) = \ln (A_H{}^*/A_D{}^*) + (E_D - E_H)/RT \quad (1)$$

values may be based upon the criteria given by Bell[9] and

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**Table I. Relative Rates of and Isotope Effect for Bromine Atom Abstraction from Toluene**

| $T,$ °C | no. expts | $K_H/k_c{}^a$ | no. expts | $k_D/k_c$ | $k_H/k_D$ |
|---|---|---|---|---|---|
| 0 | 3 | 1.01 ± 0.01 [b] | 3 | 0.109 ± 0.012 | 9.27 |
| 10 | 3 | 1.04 ± 0.03 | 4 | 0.117 ± 0.012 | 8.89 |
| 25 | 3 | 1.20 ± 0.04 | 4 | 0.161 ± 0.010 | 7.19 |
| 40 | 3 | 1.31 ± 0.04 | 7 | 0.211 ± 0.043 | 6.21 |
| 60 | 6 | 1.59 ± 0.10 | 5 | 0.348 ± 0.072 | 4.57 |

$^a$ $k_H$ is rate constant for toluene, $k_c$ for 4-chlorotoluene, and $k_D$ for deuterated toluene. $^b$ Experimental error represents average deviation of the number of experiments shown. Each experiment represents at least triplicate analysis.

more recently by Kwart.[7] The $k_H/k_D$ value, 7.2, at 25 °C is in the range of Kwart's criteria for a linear H-transfer transition state, while the values of $E_D{}^* - E_H{}^*$ and $A_H{}^*/A_D{}^*$ are both in the ranges anticipated for a linear H-transfer transition state that involves quantum mechanical tunneling and are well outside the criteria for a nonlinear transition state. Indeed it appears that the observation reported earlier of a linear transition state with tunneling for benzylic H abstraction with *tert*-butoxy radical[10] is reproduced for benzylic bromination. Kwart has reported a nonlinear transition state for the *tert*-butoxy abstraction of allylic hydrogen.[11]

The "polar effect" in homolytic benzylic hydrogen abstraction reactions as observed by good Hammett-type $\rho$–$\sigma$ plots for the relative reactivities of meta- and para-substituted toluenes has generally been interpreted in two ways. Zavitsas[12] has suggested that the order of reactivity of toluenes with a number of abstracting radicals simply parallels their benzylic C–H bond strengths without the need of postulating charge separation in the transition state. This arguement requires that all $\rho$ values be negative for abstraction from toluenes. The finding of positive $\rho$ values obtained with use of alkyl radicals as the abstracting species, summarized by Henderson,[13] casts doubt on the Zavitsas' interpretation although the validity of the results have been questioned[14] due to the apparent incursion of side reactions. The second interpretation has been summarized by Pryor[15] and employs polar resonance structures to stabilize the transition state. This interpretation suggests that the sign of $\rho$ is determined by the electronegativity of the abstracting radical. The results reported in Table I for the reactivity of toluene relative to that of 4-chlorotoluene call both of these interpretations into question. Certainly the observation that 4-chlorotoluene is less reactive than toluene is consistent with the reported[5] negative value of $\rho$ for bromination. The data in Table I give an Arrhenius relationship (eq 2, $S$ = 0.036, $r^2$ = 0.972) with the Arrhenius parameter $E_{Tol}{}^* - E_{4-ClTol}{}^*$ = 1.38 kcal/mol ($S$ = 0.13). This result corresponds to a "two-

$$\ln (k_{Tol}/k_{4-ClTol}) =$$
$$[2.51(S = 0.23) - 692.4(S = 67.7)]/T \quad (2)$$

point isokinetic relationship"[16] and an isokinetic temper-

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