the oligomers formed are monofunctional to nucleophilic attack by 4-(*p*-nitrobenzyl)pyridine (Scheme III). The observed kinetics are then consistent with eq 1 and 2 for a simple pseudo-first-order reaction. Evidence for oligomer formation under acid conditions is evident in the FAB spectrum of 2,3-dihydro-1*H*-pyrrolizin-1-ol (**3**), which shows peaks for oligomer ions up to a heptamer (M_7, Figure 2). This compound (**3**) seems to undergo oligomerization much more readily than does dehydroretronecine (**2**). Each oligomer displays a series of ion peaks at $(M - H)^+$, $M^{\bullet+}$, MH^+, $[MH - H_2O]^+$, and MK^+ (when a potassium salt is added to the FAB matrix). Similar aromatic nitrogen compounds from fossil fuels have been shown to give characteristic $(M - H)^+$, $M^{\bullet+}$, and MH^+ clusters under FAB conditions.[25] The facile loss of water from the allylic hydroxyl of each oligomer MH^+ gives rise to the abundant $[MH - H_2O]^+$ ions. It is this facile loss of water under acid-catalyzed conditions, whether under FAB experimental conditions or in solution such as the conditions of kinetic experiments that lead to a resonance stabilized allylic carbonium ion (**21**, Scheme III) which can readily undergo nucleophilic attack by a neutral pyrrole molecule, monomer **3**, or oligomer **22** or **23**. Because the allylic hydroxyl group of the oligomers **22** and **23** is also acid labile, polymerization most likely occurs on each end of the forming oligomer chain **23**. It is expected that dehydrosupinidine (**4**) polymerizes in similar fashion.

Dehydroretronecine (**2**) and the macrocyclic pyrrolizidine alkaloid pyrroles **5**–**10** have the potential for being bifunctional alkylating agents. Both in vitro and in vivo evidence has been published showing that monocrotaline pyrrole may induce DNA cross-linking, presumably by bialkylation,[26] and recently direct spectroscopic evidence has been obtained for cross-linking of strands in the duplex by mitomycin C, a compound with structural similarities to dehydroretronecine, and its derivatives.[27] Our results indicate that these bifunctional monomeric pyrrolizidine derived pyrroles, in fact, can undergo polymerization to produce multifunctional oligomers. This may be significant when one considers alkylation and repair mechanisms of DNA. Oligomers of dehydroretronecine (Scheme II) are polyhydroxylic compounds that would exhibit adsorption properties toward other polar molecules because of the multiple hydrogen bond adsorption sites. Molecular orientations in solution due to such interactions could place these pyrrole polymers in a more facile possition to alkylate DNA chains. The polyhydroxylic nature of these oligomers may also help explain the relatively rapid demise of enzymes used to digest DNA that has been reacted with dehydroretronecine (**2**) and the inability to completely hydrolyze such DNA adducts.[9]

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Total Synthesis of Linear Polyprenoids. 2.[1] Improved Preparation of the Aromatic Nucleus of Ubiquinone

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Highly efficient copper-catalyzed polymethoxylation of tribromocresol is the key process in a three-step, practical approach to obtain ubiquinone 0 from *p*-cresol. Short syntheses of several ubiquinones were achieved via direct, copper-mediated coupling of 2-lithio-3,4,5,6-tetramethoxytoluene to the appropriate polyprenyl bromide.

Introduction

Quinones and hydroquinones with polyprenyl side chains, such as ubiquinones, plastoquinones, phylloquinone (vitamin K_1), and menaquinones (vitamin K_2), are widely distributed in plant and animal tissues.[2] In addition to vital roles in promoting electron transfer in respiratory chains and photosynthesis, these compounds also exhibit various pharmacological activities.[3] Of special interest is ubiquinone 10 (coenzyme Q_{10}), **1**, which is used clinically as a cardiovascular agent and has attracted significant synthetic activity over the past two decades.[4] However, because construction of linear polyprenoid chains still represents a major synthetic challenge, the practical total

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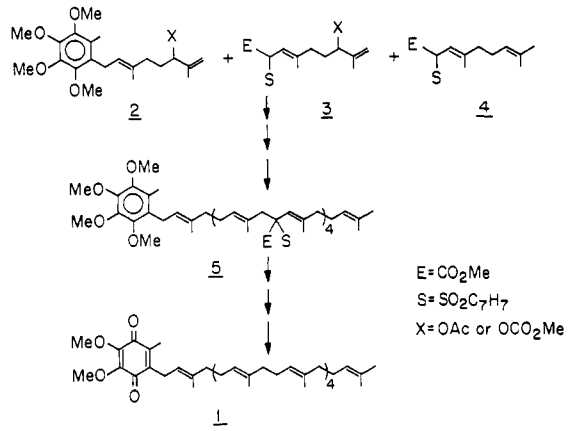
Scheme I



synthesis of ubiquinone 10 is still an unresolved problem.

In an attempt to develop a convenient approach for the total synthesis of ubiquinone 10 (1) and other naturally occurring linear polyprenoids, we have recently designed a general methodology for highly regio- and stereoselective Pd(0)-catalyzed stepwise allylic coupling of bifunctional monoterpene monomers.[5] Synthesis of 1 (Scheme I) can be carried out from either 2 or 4 by adding sequentially monomer 3 three times, followed by termination via coupling of the growing polyprenyl chain to the appropriate monfunctional monomer, 4 or 2, yielding the desired decaprenyl carbon skeleton 5. The final product could thus be obtained by removing the activating groups, methoxycarbonyls and tolyl sulfones, and oxidizing the aromatic ring to the quinone.

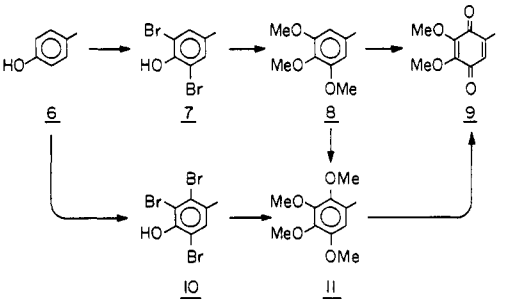
Monomers 3 and 4 are relatively easy to produce from geraniol. For 2, however, we required its precursor, 2-geranyl-3,4,5,6-tetramethoxytoluene (**12a**). In this paper we report on a short synthesis of **12a**, involving efficient preparation of the aromatic ubiquinone nucleus and its coupling to the appropriate prenylic side chain. Preparation of the other monomers, as well as detailed total synthesis of 1 are to be reported in a following paper of this series.[5]

Results and Discussion

The synthesis of **12a** involves the solution of two basic problems: polyoxygenation of an aromatic ring, leading to ubiquinone 0 (**9**) or one of its derivatives and subsequent coupling of that ring to a geranyl side chain.

Most of the reported synthetic approaches to **9** employ highly functionalized aromatic starting materials, such as vanilline,[6] gallic acid,[7] pyrogallol,[7,8] etc. We decided to employ a more readily available precursor, having a lower level of substitution, and yet carry out the required aromatic substitution in a minimal number of steps. Such an approach would be advantageous for the practical large-scale production of ubiquinone 0.

Scheme II



Polyalkoxy aromatic compounds are readily available via copper(I)-catalyzed nucleophilic aromatic substitution of halide by alkoxide.[9] For example, dibromination of *p*-cresol (**6**) gave **7**, which upon reaction with sodium methoxide and copper(I) catalyst[9c] followed by methylation with dimethyl sulfate, yielded trimethoxytoluene **8** in 84% yield (Scheme II). Unfortunately, oxidation of **8** with various reagents, including ceric ammonium nitrate (CAN),[10] Fremy's salt,[6b] *m*-chloroperbenzoic acid[7] or H_2O_2 in AcOH, and H_2SO_4,[11] gave **9** in only low yields. Oxidation of **8** with H_2O_2 and catalytic amounts of $K_3Fe(CN)_6$[12] was reported to be more efficient but still with moderate yields (<50%). Obviously, this oxidant is incompatible with olefinic side chains and would not be suitable for oxidation of the aromatic rings already bearing a polyprenyl side chain.

We therefore considered the use of tetramethoxytoluene (**11**), whose oxidation proceeds under milder conditions and in higher yields.[10] Conversion of **8** to **11** was easily achieved by monobromination followed by copper-catalyzed methoxylation. Finally, we found that **11** can be prepared directly from **6** in a two-step procedure. Tribromination of *p*-cresol provided 2,3,6-tribromo-4-methylphenol (**10**).[13] Copper-catalyzed methoxylation of **10**, followed by methylation with dimethyl sulfate (both carried out in the same pot) yielded 2,3,4,5-tetramethoxytoluene (**11**) in 94% yield. Oxidation of **11** with CAN[10] to ubiquinone 0 (**9**) proceeded in good yield. Furthermore, **11** itself may be used directly as a protected form of **9** when further manipulations are needed, an additional advantage of this approach.

Having the appropriately functionalized aromatic ring **11** at our disposal, we turned our attention to its geranylation. The most common approach for direct prenylation of electron-rich aromatic compounds involves Friedel–Crafts allylation under acidic conditions.[7,8,14,15a] Despite a number of modifications, this approach is limited by the inherent instability of an allylic alcohol under the acidic

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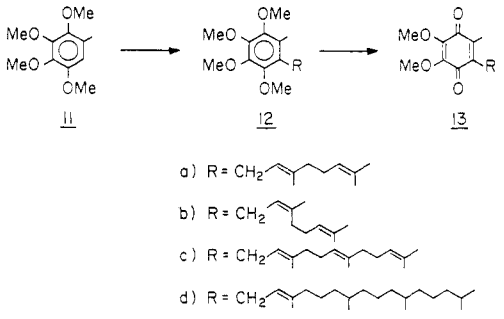
Scheme III



conditions employed[14e] and by troublesome side reactions. For example, one of our attempts to employ geraniol and Amberlyst-15[14h] produced **12a** with disappointingly low yields.

Another known approach to this coupling is a two-step sequence involving bromination of the available ring carbon, followed by conversion to the corresponding Grignard reagent and coupling to geranyl bromide in the presence of cuprous halide.[8,16] We attempted to modify this organometallic approach by directly metalating the ring carbon of **11**, thereby bypassing the bromination step. When employing *n*-butyllithium in THF for this purpose, no lithiation could be observed (monitored by quenching with methyl iodide). However, the reaction was carried out quantitatively with hexane and tetramethylethylenediamine (TMEDA).[17]

As with the Grignard approach,[16b] the lithiated derivative of **11** failed to couple with geranyl bromide in the absence of copper(I) salts. But even the diaryl cuprate of **11** (formed with 0.5 equiv of CuI) gave rather poor yields of **12a**. However, the mixed cuprate approach (involving 1 equiv of either CuI or CuBr and 1 equiv of methyllithium added to lithiated **11**) was more successful, resulting in yields of 41%, with even better results being obtained by using 1 equiv of cuprous cyanide, yielding 66% of isolated **12a**. Direct coupling of **11** to other prenyl bromides (neryl, farnesyl, and phytyl) under similar conditions proceeded smoothly with comparable yields (Scheme III). Subsequent oxidative demethylation with CAN provides an easy entry to variety of short-chain ubiquinones (**13a–d**).[18,19]

Conclusion

The above three-step procedure for preparation of ubiquinone 0 represents the shortest total synthesis of this compound described to date. Direct aromatic lithiation of tetramethoxytoluene followed by copper-mediated coupling to the appropriate polyprenyl bromide provides a short approach to all members of the ubiquinone family. Protected ubiquinone 2 (**12a**) serves as a key building block in our total synthesis of long-chain ubiquinones.[5]

Experimental Section

General Methods. Elemental analyses were carried out at the microanalytical laboratory of the Hebrew University, Jerusalem. ^{1}H NMR spectra were measured in deuteriochloroform on a Bruker WH-270 NMR spectrometer. All chemical shifts are reported in δ units downfield from Me_4Si, and the J values are given in hertz. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60, F254, Art. 5549). Column chromatographic separations were carried out on silica gel (Merck, Kieselgel 60, 230-400 mesh, Art. 9385) under pressure of 0.5 atm (flash chromatography). Preparative TLC was performed on glass plates precoated with silica gel (Merck, Kieselgel 60 F-254 Art. 5717). Distillations were usually carried out with a Buchi Kugelrohr apparatus (the temperatures reported here are pot temperatures). Tetrahydrofuran (THF), dimethoxyethane (DME), and diethyl ether was distilled over sodium benzophenone ketyl. All polyprenyl bromides were prepared from the corresponding alcohols (geraniol, nerol, farnesol, and phytol) and phosphorous tribromide in diethyl ether.[15]

Oxidation of Trimethoxytoluene to Ubiquinone 0 (9). Trimethoxytoluene[9c] (2.4 g, 13.2 mmol) was added to glacial acetic acid (50 mL) containing 0.5 mL of concentrated H_2SO_4. Hydrogen peroxide (0.5 mL of a 50% aqueous solution) was then added over 12 h at room temperature. The mixture was stirred for 12 h and then poured into water (150 mL) and extracted with chloroform. The organic extract was washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue chromatographed over silica gel (hexane/ethyl acetate, 20:1) to give **9** in the form of red crystals (0.6 g, 25% yield): mp 59 °C (lit. mp 59 °C[20]).

2,3,6-Tribromo-4-methylphenol (10). Following an early method,[13] *p*-cresol (108 g, 1 mol) was dissolved in $CHCl_3$ (120 mL) containing iron powder (4 g, 0.071 mol). Bromine (500 g, 3.12 mol) was then added dropwise over 5 h at room temperature. The solution was stirred for additional 48 h and then filtered, washed with dilute aqueous $NaHSO_3$, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was recrystallized from hexane to yield **10** (262 g, 76%, lit.[13] 80%).

2,3,4,5-Tetramethoxytoluene (11). Sodium (2.3 g, 100 mmol) was dissolved in methanol (40 mL), DME (30 mL) and dimethyl carbonate (5 mL) were added, and most of the methanol (30 mL) was removed by distillation. CuCN (1.5 g, 16.7 mmol) was introduced into the mixture, and a solution of **10** (3.44 g, 10.3 mmol) in 10 mL of DME was added dropwise over 3 h while the temperature was kept at 80 °C. The mixture was stirred for 5 h more at this temperature, followed by addition of water (80 mL), cooling to 50 °C, and dropwise introduction of dimethyl sulfate (10 mL). The mixture was stirred at room temperature for an additional 2 h and concentrated aqueous NH_4OH (25 mL) was added. The mixture was extracted with CH_2Cl_2, and the organic extract was washed with dilute aqueous HCl and water and dried over $MgSO_4$. The solvent was removed under reduced pressure, giving tetramethoxytoluene **11** (1.98 g, 94%), which was found to be essentially pure by TLC, NMR, and GC–MS: bp 110 °C (0.1 mm) [lit. bp 108 °C/(3 mm)[8]].

Ubiquinone 0 (9). Oxidation was carried out as described earlier.[10] Pyridine-2,6-dicarboxylate (3.34 g, Fluka) was added to a cold (0 °C) solution of **11** (1.70 g, 8.0 mmol) in 40 mL of 7:3 acetonitrile/water. A cold (0 °C) solution of ceric ammonium nitrate (CAN) (10.96 g, 20 mmol) in 40 mL of 1:1 acetonitrile/water was slowly added over 20 min, and the mixture was stirred for 20 min at 0 °C and for 10 min at room temperature. The reaction mixture was poured into 40 mL of water and extracted with CH_2Cl_2. The organic solution was dried over $MgSO_4$, followed by solvent removal under reduced pressure and column chromatography (silica gel; hexane/ethyl acetate, 20:1), giving **9** (1.22 g, 84%) in the form of red crystals: mp 59 °C[20]; NMR (270 MHz) 6.44 (s, 1 H), 4.06 (s, 3 H), 4.01 (s, 3 H), 2.03 (s, 3 H). Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.14; H, 5.59.

(2′*E*)-1-(3,7-Dimethylocta-2,6-dienyl)-6-methyl-2,3,4,5-tetramethoxybenzene (12a). *n*-Butyllithium (30 mL of a 1.1 M solution in hexane) was added over 30 min under argon to a solution of **11** (4.9 g, 23.1 mmol) in 50 mL of hexane containing TMEDA (5 g) at 0 °C. The mixture was stirred for additional 30 min, followed by addition of THF (250 mL) and CuCN (3 g, 33 mmol). After the mixture was stirred for 30 min, a solution of geranyl bromide (5 g, 23 mmol) in THF (50 mL) was added

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slowly over 60 min, and the mixture was stirred for additional 60 min. The reaction was then quenched with saturated aqueous NH_4Cl, ether (250 mL) was added, and the organic phase was separated, washed with aqueous NH_4OH, water, and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue chromatographed over silica gel (hexane/ethyl acetate, 25:1) to give **12a**[21] as a colorless oil (5.3 g, 66 %): NMR (270 MHz) 5.06-5.02 (m, 2 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.78 (s, 6 H), 3.32 (d, J = 4 Hz, 2 H), 2.14 (s, 3 H), 2.05 (t, J = 6 Hz, 2 H), 2.01 (t, J = 6 Hz, 2 H), 1.76 (s, 3 H), 1.64 (s, 3 H), 1.57 (s, 3 H).

(2′*Z*)-1-(3,7-Dimethylocta-2,6-dienyl)-6-methyl-2,3,4,5-tetramethoxybenzene (12b). Coupling neryl bromide to **11** according to the procedure described above gave compound **12b**[21] (68% yield): NMR (270 MHz) 5.19 (t, J = 7 Hz, 1 H), 5.04 (t, J = 6 Hz, 1 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.80 (s, 6 H), 3.32 (d, J = 7 Hz, 2 H), 2.27-2.05 (m, 4 H), 2.14 (s, 3 H), 1.69 (s, 3 H), 1.65 (s, 3 H), 1.57 (s, 3 H).

(2′*E*,6′*E*)-1-(3,7,11-Trimethyldodeca-2,6,10-trienyl)-6-methyl-2,3,4,5-tetramethoxybenzene (12c). Coupling farnesyl bromide to **11** according to the procedure described above gave 5.3 g of **12c**[21] (73% yield): NMR (270 MHz) 5.11-5.01 (m, 3 H), 3.90 (s, 6 H), 3.78 (s, 6 H), 3.31 (d, J = 6.3 Hz, 2 H), 2.14 (s, 3 H), 2.08-1.91 (m, 8 H), 1.77 (s, 3 H), 1.66 (s, 3 H), 1.61 (s, 3 H), 1.57 (s, 3 H).

(2′*E*)-1-(3,7,11,15-Tetramethylhexadec-2-enyl)-6-methyl-2,3,4,5-tetramethoxybenzene (12d). Coupling phytyl bromide to **11** according to the procedure described above gave **12d**[21] (52% yield): NMR (270 MHz) 5.02 (t, J = 6 Hz, 1 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.78 (s, 6 H), 3.32 (d, J = 6 Hz, 2 H), 2.14 (s, 3 H), 1.94 (t, J = 7.6 Hz, 2 H), 1.75 (s, 3 H), 1.59-1.43 (m, 2 H), 1.41-0.96 (m, 17 H), 0.86 (br d, J = 7 Hz, 6 H), 0.83 (br d, J = 7 Hz, 3 H), 0.82 (br d, J = 6 Hz, 3 H).

Ubiquinone 2 (13a). Oxidation of **12a** with CAN according to the procedure described above for preparation of ubiquinone 0 (**9**) gave ubiquinone 2 (**13a**)[18] in 87% yield (2.21 g): NMR (270 MHz) 5.03 (t, J = 8 Hz, 1 H), 4.93 (t, J = 7 Hz, 1 H) 4.00 (s, 3 H), 3.99 (s, 3 H), 3.19 (d, J = 8 Hz, 2 H), 2.07-1.93 (m, 4 H), 2.01 (s, 3 H), 1.74 (s, 3 H), 1.65 (s, 3 H), 1.57 (s, 3 H). Anal. Calcd or $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 70.25; H, 8.26.

(2′*Z*)-2-(3,7-Dimethylocta-2,6-dienyl)-3-methyl-5,6-dimethoxy-1,4-benzoquinone (13b). Oxidation of **12b** according to the procedure described above gave **13b**[18] in 73% yield: NMR (270 MHz) 5.15 (t, J = 6.6 Hz, 1 H), 4.93 (t, J = 6.9 Hz, 1 H), 3.99 (s, 3 H), 3.98 (s, 3 H), 3.19 (d, J = 6.9 Hz, 2 H), 2.21-2.04 (m, 4 H), 2.02 (s, 3 H), 1.70 (s, 3 H), 1.68 (s, 3 H), 1.63 (s, 3 H). Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 70.50; H, 8.23.

(2′*E*,6′*E*)-2-(3,7,11-Trimethyldodeca-2,6,10-trienyl)-3-methyl-5,6-dimethoxy-1,4-benzoquinone (Ubiquinone 3) (13c). Oxidation of **12c** according to the procedure described above gave **13c**[18] in 48% yield: NMR (270 MHz) 5.07 (t, J = 6.0 Hz, 1 H), 5.05 (t, J = 6.0 Hz, 1 H), 4.93 (t, J = 6.9 Hz, 1 H), 3.99 (s, 3 H), 3.98 (s, 3 H), 3.18 (d, J = 6.0 Hz, 2 H), 2.08-1.91 (m, 8 H), 2.01 (s, 3 H), 1.74 (s, 3 H), 1.67 (s, 3 H), 1.59 (s, 3 H), 1.57 (s, 3 H). Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.58; H, 8.86. Found: C, 73.59; H, 8.94.

(2′*E*)-2-(3,7,11,15-Tetramethylhexadec-2-enyl)-3-methyl-5,6-dimethoxy-1,4-benzoquinone (13d). Oxidation of **12d** according to the procedure described above gave **13d**[19] in 55% yield: NMR (270 MHz) 4.92 (t, J = 7 Hz, 1 H), 3.99 (s, 3 H), 3.98 (s, 3 H), 3.18 (d, J = 7 Hz, 2 H), 2.01 (s, 3 H), 1.92 (t, J = 7.2 Hz, 2 H), 1.72 (s, 3 H), 1.56-1.42 (m, 2 H), 1.45-0.92 (m, 17 H), 0.87-0.81 (m, 12 H). Anal. Calcd for $C_{29}H_{48}O_4$: C, 75.61; H, 10.50. Found: C, 75.09; H, 10.63.

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$Ba(OH)_2$ as Catalyst in Organic Reactions. 17. Interfacial Solid-Liquid Wittig-Horner Reaction under Sonochemical Conditions

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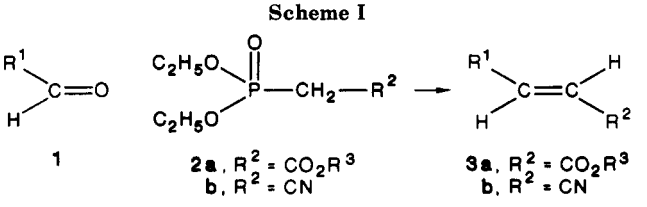
The sonochemical Wittig-Horner reaction, catalyzed by an activated barium hydroxide catalyst, is carried out in interfacial solid-liquid conditions. The sonochemical process takes place at room temperature and with a lower catalyst weight and reaction time than the thermal process. In these conditions, similar yields to those of the thermal process are obtained. The influence on the yield of the sonication time, catalyst weight, and the solvent is analyzed. Small amounts of water must be added in order for the reaction to take place. The nature of the active site of the catalyst acting in the process is analyzed. An ETC mechanism is proposed for the sonochemical process.

The Wittig-Horner reaction is a versatile method for the synthesis of functionalized olefins such as acrylates **3a** or acrylonitriles **3b** from aldehydes **1** under mild conditions with good yields (Scheme I).

Therefore, many works have been done to improve the yield of the process.[1] Recently, the Wittig-Horner reaction has been carried out by using polymer-supported phosphonates[2] and two-phase liquid-liquid[3] or solid-liquid

Scheme I



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