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Microwave-assisted combined Mitsunobu reaction–Claisen rearrangement and microwave-assisted phenol oxidation: rapid synthesis of 2,6-disubstituted-1,4-benzoquinone natural products

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This paper is dedicated to Professor Steve Ley on the occasion of his 60th birthday

Abstract—Microwave irradiation of a phenol, an allylic alcohol, di-isopropyl azodicarboxylate and triphenylphosphine at 220–240 °C for 30 min results in a combined Mitsunobu reaction and Claisen rearrangement to give the rearranged 2-allylphenol. Following the first detailed study of microwave-assisted phenol oxidation, rapid syntheses of the natural products primin and 2-methoxy-6-pentadecyl-1,4-benzoquinone (four reaction steps, total reaction time 1 h) were achieved using this combined Mitsunobu–Claisen strategy in combination with two further microwave-assisted steps (alkene hydrogenation and phenol oxidation).

Microwave-assisted reactions continue to attract increasing attention from synthetic organic chemists.[1] The advent of dedicated microwave reactors has enabled a wide range of reactions to be carried out rapidly and, critically, reproducibly in the laboratory. As a simple thermal process, the aromatic Claisen rearrangement of allyl aryl ethers is ideally suited to microwave conditions, and reaction times are shortened dramatically.[2–10] We have recently reported the use of the microwave-assisted aromatic Claisen rearrangement as a key step in the synthesis of a range of naturally occurring 1,4-benzoquinones.[11] The substrates for Claisen rearrangement, the allyl ethers **2** were prepared from the corresponding phenols **1** and allylic alcohols using the Mitsunobu reaction,[12] and underwent rapid Claisen rearrangement to the 2-allylphenols **3** upon microwave irradiation in DMF. Although, as far as we are aware, there are only two reports of microwave-assisted Mitsunobu reactions,[13,14] the fact that both the first steps in this reaction sequence are subject to acceleration by microwave irradiation suggested that they could be combined into a single one-pot operation. We now report the realization of this strategy in the first microwave-assisted combined Mitsunobu reaction–Claisen rearrangement protocol. Additionally, we also report the first examples of the microwave-assisted oxidation of phenols to 1,4-benzoquinones, the combination of these strategies enabling rapid syntheses of the natural products primin and 2-methoxy-6-pentadecyl-1,4-benzoquinone (four reaction steps, total reaction time 1 h).

Initially, a small range of phenols **1** and allylic alcohols were reacted under standard Mitsunobu conditions (Ph_3P, DIAD, THF) to give the allyl ethers **2** (64–97%) after ca. 16 h reaction time. The allyl ether **2c** underwent Claisen rearrangement upon heating under reflux in DMF for 72 h or *N*,*N*-dimethylaniline for 4 h to give phenol **3c**. As expected it proved more convenient to carry out the Claisen rearrangement in a microwave reactor, and heating the allyl ethers **2** in DMF for 30 min at 220–290 °C gave the rearrangement products **3** in 43–99% yield. The overall yields of phenols **3** over the two steps were 28–92% with reaction times of over 18 h even when the second step was microwave-assisted.

In order to effect the combined Mitsunobu reaction–Claisen rearrangement, phenol **1**, the allylic alcohol, triphenylphosphine and DIAD were heated in toluene in a sealed tube at 220–240 °C in a microwave reactor. This resulted in the formation of the rearrangement products,

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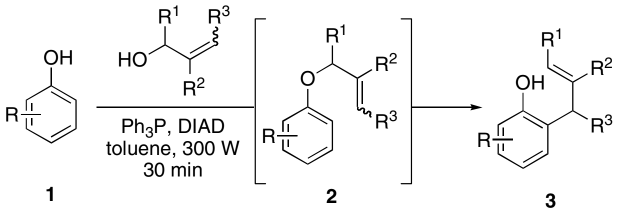
Table 1. The combined Mitsunobu reaction–Claisen rearrangement protocol



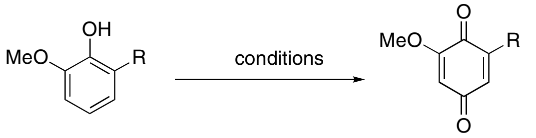
1 **2** **3**

R	R^1	R^3	R^2	**3**	Temperature (°C)	**3** Yield (%)
2-OMe	H	Me	H	**a**	220	60
2-OMe	–$(CH_2)_3$–		H	**b**	220	58
2-OMe	H	H	Me	**c**	220	68
2-NO_2	H	H	Me	**d**	241	36
2-Cl	H	H	Me	**e**	240	84
4-OMe	H	H	Me	**f**	220	95
4-Cl	H	H	Me	**g**	240	95

the 2-allylphenols **3**, in 36–95% yield (Table 1) in reaction times of just 30 min.[15] Hence, although the yields over the two processes are similar, these first examples of a microwave-assisted combined Mitsunobu reaction–Claisen rearrangement protocol result in dramatically reduced reaction times.

Simple 2-methoxy-6-allylphenols, now readily and rapidly available by the above method, were key intermediates in our synthesis of naturally occurring benzoquinones,[11] and therefore we wished to combine the microwave Mitsunobu–Claisen protocol with two further microwave-assisted steps (alkene reduction and phenol oxidation) in a rapid route to such natural products. There is ample precedent for microwave-assisted alkene reduction,[1] but as far as we are aware there are no reports of oxidation of simple phenols to 1,4-benzoquinones under microwave conditions, although hydroquinones and anilines have been subject to microwave-assisted oxidation to 1,4-benzoquinones.[16,17] Therefore, we undertook a preliminary study using 2-methoxy-6-pentyl- and -pentadecyl phenols (**4a**,**b**), prepared as previously described.[11] As summarized in Table 2, a range of reagents/conditions that are known to oxidize phenols were adapted for use in a focussed microwave reactor. Thus, $PhI(OAc)_2$,[18] $PhI(OCOCF_3)_2$,[19] Jones' reagent,[20] Fremy's salt,[21] oxygen/salcomine,[22,23] hydrogen peroxide/methyltrioxorhenium(VII)[24] and air/copper(II) chloride[25] were all investigated, as were three other oxidants that although not known to oxidize phe-

Table 2. Microwave-assisted oxidation of 2-methoxyphenols to 1,4-benzoquinones

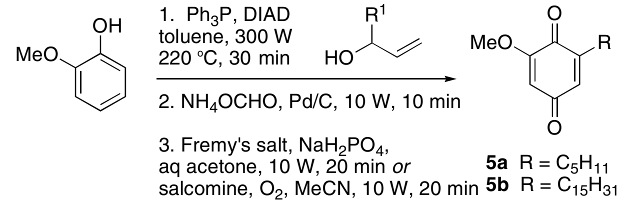


4a R = n-C_5H_{11}
4b R = n-$C_{15}H_{31}$

5a R = n-C_5H_{11}
5b R = n-$C_{15}H_{31}$

Conditions[a]	Yield (%)	
	R = n-C_5H_{11}	R = n-$C_{15}H_{31}$
$PhI(OAc)_2$, TFA, aq AcOH, 300 W, 40 °C, 20 min	54	28
$PhI(OCOCF_3)_2$, TFA, aq AcOH, 300 W, 40 °C, 20 min	41	[b]
CrO_3, H_2SO_4, aq acetone, 10 W, 80 °C, reflux, 20 min	66	12
Fremy's salt, NaH_2PO_4, aq acetone, 10 W, reflux, 20 min	82	53
O_2, salcomine, MeCN, 10 W, 90 °C, reflux, 10 min	[b]	45
$MeReO_3$, 30% H_2O_2, EtOH, 10 W, reflux, 15 min	Trace	[b]
$CuCl_2$, [bmim]Cl,[c] aq n-BuOH, 10 W, reflux, 40 min	0	[b]
$(NH_4)_2Ce(NO_3)_6$, aq MeCN, 10 W, 80 °C, reflux, 20 min	55	16
TEMPO, $Mn(NO_3)_2$, $Co(NO_3)_2$, AcOH, 10 W, reflux, 10 min	26	[b]
Magtrieve,[TM,d] toluene, 100 W, reflux, 30 min	12	34

[a] Reflux refers to use of a flask with an open reflux condenser; all other reactions carried out in sealed tubes at the specified temperature.
[b] Not attempted.
[c] 1-Butyl-3-methylimidazolium chloride.
[d] DuPont trademark for the oxidant based on CrO_2.



Scheme 1.

nols to quinones appeared adaptable for use under microwave conditions, namely cerium(IV) ammonium nitrate,[26] TEMPO[27] and Magtrieve™.[28,29] Although none of the reactions are particularly high-yielding, with two exceptions they all proceed rapidly and give the corresponding quinones **5**, and were deemed suitable for use in a synthetic sequence.

Hence using a combination of microwave-assisted reactions, the benzoquinone natural products primin **5a** and 2-methoxy-6-pentadecyl-1,4-benzoquinone **5b** were synthesized from guaiacol in four reaction steps—the combined Mitsunobu–Claisen process, catalytic transfer hydrogenation[30,31] and phenol oxidation—with a total reaction time of 1 h in overall yields of 43% and 28%, respectively (Scheme 1).

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