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Highly Stereoselective and General Synthesis of (*E*)-Stilbenes and Alkenes by Means of an Aqueous Wittig Reaction

James McNulty*[a] and Priyabrata Das[a]

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The chemoselective formation of trialkyl(benzylidene) ylides in water and their Wittig reaction with aromatic and aliphatic aldehydes provides a practical, stereoselective and environmentally benign route to valuable (*E*)-stilbenes and alkenes. The synthesis of the phytoalexin resveratrol is described. In addition, the method allows for a gram-scale synthesis of the anticancer agent DMU-212 utilizing no organic solvent at any stage.

Introduction

The Wittig reaction[1] has evolved over the last half-century to become one of the most strategic, widely applicable carbon–carbon olefin bond forming processes available in organic synthesis.[2–4] This reliable reaction allows for olefination with complete positional selectivity, predictable chemoselectivity and may be conducted in many cases with reliable and high stereocontrol. The reaction has been the subject of extensive experimental[2–5] and theoretical[5a] investigations and has been comprehensively reviewed.[2,4,5b] Two major drawbacks of the reaction are the lack of stereocontrol achieved in certain cases, for example in the synthesis of valuable stilbenes from semi-stabilized ylides[6] and the practical issue of phosphane oxide side-product removal.

Principal methods for the synthesis of stilbenes involve the Wittig[6–7] reaction for (*Z*)-stilbenes and the Wittig–Horner olefination reaction for (*E*)-stilbenes.[6b,6c] Both reactions typically require the use of dry organic solvents under inert conditions by using a strong, non-aqueous base. The Wittig reaction employing a triphenyl(benzylidene) ylide is still the most direct route to (*Z*)- and (*E*)-stilbenes,[7] despite suffering from poor to moderate stereocontrol. Removal of the phosphane oxide as well as separation of the stereoisomers generally requires column chromatography. The use of water as a solvent for organic reactions is highly desirable for environmental, economical, safety and chemical processing reasons.[8,9] Significant rate enhancements have also been observed when using water as a media for organic reactions.[10,11] Water has been used as the reaction media for the Wittig reaction of stabilized ylides[12] giving unsaturated esters. The use of triphenyl-substituted semi-stabilized ylides reacting with aromatic aldehydes has also been reported in water,[13] providing stilbenes with poor configurational selectivity requiring chromatographic separation and removal of triphenylphosphane oxide. Further advances involving the use of carboxyl- and sufonyl-substituted Wittig reagents in water and methanol have been reported.[14] These methods allow for easier phosphane oxide removal; however, the funtionalized triarylphosphanes employed require multi-step syntheses and stereocontrol in the Wittig reaction is quite low.

Surprisingly, the Wittig reaction of semi-stabilized ylides derived from trialkyl(benzyl)phosphonium salts (such as **2**, Scheme 1) containing small alkyl groups has never been investigated in water. Chemoselective deprotonation at the benzylic[15a] position (b) over the alkyl positions (a) in a trialkyl(benzyl)phosphonium salt was reported in organic media. Similar chemoselectivity was also demonstrated with trialkyl(allyl)phosphonium salts.[15b–15d] The use of trialkylphosphane-derived ylides in Wittig olefination is of limited applicability but typically provides a higher ratio of (*E*)-olefins.[4] Phosphane oxides containing small alkyl groups, such as trimethyl- and triethylphosphane oxide, are highly soluble in water. Hence, the demonstration of the process outlined in Scheme 1 in water could potentially open a stereoselective route to (*E*)-stilbenes as well as allow rapid purification through simple filtration. Herein we report on the success of this process and advance a direct "green" organic solvent-free synthesis of (*E*)-stilbenes and related olefins exclusively in aqueous media. Semi-stabilized triethyl(benzylidene) ylides are shown to be formed chemoselectively in water by using sodium or lithium hydroxide and to react with aromatic aldehydes in water, yielding (*E*)-stilb-

[a] Department of Chemistry, McMaster University,
1280 Main Street West, Hamilton, Ontario, L8S 4M1, Canada
Fax: +1-905-522-2509
E-mail: jmcnult@mcmaster.ca
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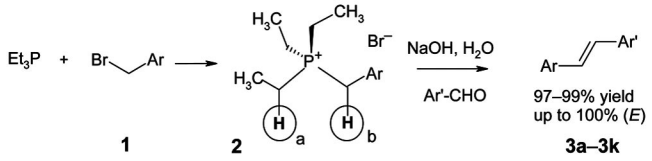
enes with high stereocontrol. The entire process is conducted in water, the product (*E*)-stilbene is isolated by simple filtration and washing with water.



Scheme 1. Synthesis of stilbenes **3a**–**3k** by aqueous Wittig chemistry.

(*E*)-Configured stilbenes constitute the central nucleus in a range of valuable materials including pharmaceuticals,[16–22] light-emitting diodes[23] and dye-sensitized photovoltaic solar cells.[24–27] In terms of pharmaceuticals, the stilbenes resveratrol and DMU-212 (**4** and **5**, Figure 1), have been shown to modulate diverse biological phenomena. Resveratrol **4**, a naturally occurring phytoalexin, has been associated with a diverse array of biological activities.[16–18]

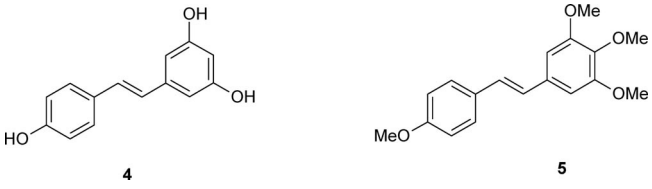


Figure 1. Structures of resveratrol **4** and DMU-212 **5**.

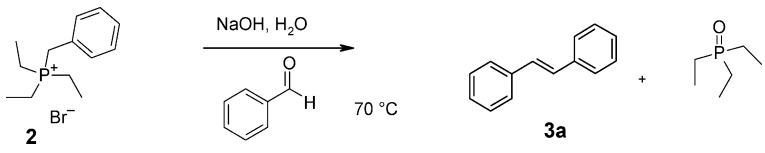
DMU-212 (**5**), a synthetic derivative of resveratrol, was shown to be more antiproliferative than resveratrol in human colon cancer cells.[19] Other valuable (*E*)-stilbenes have recently been shown to bind to myelin and to be useful as molecular imaging probes in positron emission tomography (PET).[20–22] (*E*)-Configured stilbenes are also key components in both light-emitting diodes (LEDs),[23] and photovoltaic solar cells.[24] The potential of photoelectrochemical cells in the direct conversion of sunlight into electrical energy,[25,26] and in mediating the conversion of water to hydrogen and oxygen is immense.[27]

Results and Discussion

A model reaction involving the synthesis of unsubstituted (*E*)-stilbene **3a** was first investigated and is shown in Scheme 2. Benzyltriethylphosphonium bromide (**2**) was prepared in situ through the direct 1:1 reaction of triethylphosphane with benzyl bromide. The salt was dissolved in water, and sodium hydroxide and benzaldehyde were added to yield an emulsion. Upon warming, the product (*E*)-stilbene slowly precipitated from the solution. The reaction rate proved dependent on the concentration of sodium hydroxide and phosphonium salt. We settled upon the use of 4.0 equiv. of NaOH and a salt concentration of 2.5 M as a standard condition. From this reaction (*E*)-stilbene **3a** was isolated in 99% yield and with an (*E*)/(*Z*) ratio of 4:1 by simply cooling the aqueous suspension, filtering and washing with water. NMR analysis showed the solid product to be free from triethylphosphane oxide and demonstrated that 1-phenylpropene was not formed, indicating high chemoselectivity in the ylide formation through benzylic CH deprotonation. We also note that no Cannizzaro side products were detected as might have been anticipated under these basic conditions. This same reaction, conducted by using lithium hydroxide, provided (*E*)-stilbene **3a** in 99% yield and a selectivity of (*E*)/(*Z*) = 99:1 (Table 1, Entry 2).

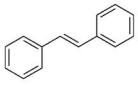
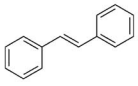
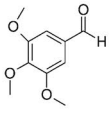
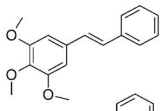
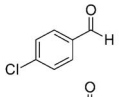
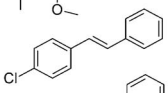
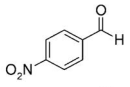
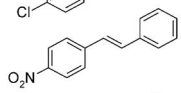
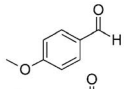
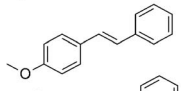
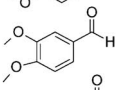
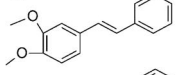
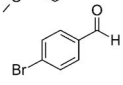
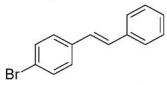
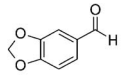
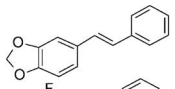
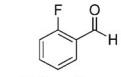
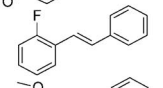
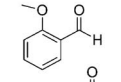
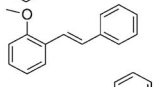
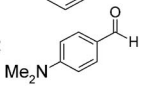
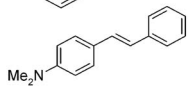
This aqueous Wittig reaction proved to be very general. The ylide formed in situ from benzyltriethylphosphonium bromide in purely aqueous base reacted successfully with a wide range of aldehydes exhibiting varying electronic and steric demands as shown in Table 1. The product yields are almost quantitative in all cases investigated so far. The stereoselectivity is high favouring the (*E*)-stilbene isomer, although electron-withdrawing groups on the aldehyde appear to lower this stereoselectivity somewhat.

The synthesis of both resveratrol (**4**) and DMU-212 (**5**) were readily achieved through the analogous process by employing the reaction of triethylphosphane with 4-methoxybenzyl bromide under solvent-free conditions, which provided the 4-methoxyphenyl salt **2b**. Under these conditions the salt **2b** is formed cleanly [$\delta(^{31}P)$ = 37.4 ppm]. Dissolution in aqueous sodium hydroxide (2.5 M) and addition of 3,5-dimethoxybenzaldehyde followed by warming to 70 °C for 3 h, chilling, suction filtration and washing with water yielded the trimethyl ether of resveratrol in 95% yield and with an (*E*)/(*Z*) ratio of 95:5. Demethylation with BBr_3 then gave resveratrol **4** in 80% yield (m.p. 256–258 °C).[28] Likewise, the reaction of the basic solution of **2b** with 3,4,5-trimethoxybenzaldehyde (70 °C, 3 h), cooling, filtering and washing with water allowed for a gram-scale synthesis of the potent anticancer agent DMU-212 (**5**) directly in 96% isolated yield with an (*E*)/(*Z*) ratio of 99:1.[29] Visually, the salt (2.5 M) and base (4.0 equiv.) form a slightly cloudy aqueous suspension. After addition of the aldehyde and warming, the stilbene product crystallizes from the aqueous medium. After cooling and filtration, NMR analysis of the aqueous filtrate shows triethylphosphane oxide alone [$\delta(^{31}P)$ = 54.9 ppm], and the filtered solid proved to be essentially the pure (*E*)-stilbene DMU-212 (**5**), with no cross-



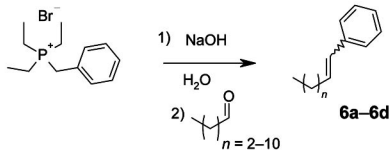
Scheme 2. Synthesis of stilbene **3a** by aqueous Wittig reaction.

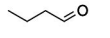
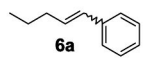
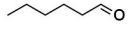
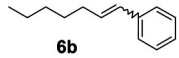
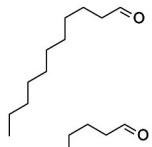
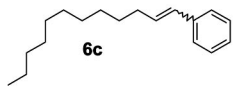
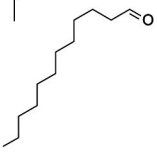
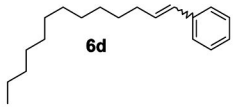
Table 1. Synthesis of stilbene derivatives from the reaction of various aldehydes.

Entry	ArCHO	Stilbene	% Yield	(*E*)/(*Z*)
1		 **3a**	99	80:20
2		 **3a**	99[a]	99:1
3		 **3b**	97	95:5
4		 **3c**	99	90:10
5		 **3d**	99	80:20
6		 **3e**	98	95:5
7		 **3f**	98	95:5
8		 **3g**	98	90:10
9		 **3h**	97	95:5
10		 **3i**	99	90:10
11		 **3j**	98	95:5
12		 **3k**	99	99:1

[a] LiOH was used as base.

Table 2. Synthesis of 1-phenylalkenes from enolizable aliphatic aldehydes.



Aldehyde	1-Phenylalkene	% Yield	(*E*)/(*Z*)
	 **6a**	65	2:3
	 **6b**	70	6.2:3.8
	 **6c**	72	7:3
	 **6d**	77	3:1

contamination. No purification is required to remove triethylphosphane oxide from the stilbene in all of the cases thus far investigated (Table 1).

The aqueous Wittig reaction was also successfully extended to the reaction with enolizable aliphatic aldehydes. At the outset, a major concern was the possibility of a competing Cannizzaro and/or homo-aldol reaction of such aldehydes, given that the reaction is performed under classic conditions known to effect these processes. Nonetheless, addition of NaOH to a suspension of butanal in the presence of benzyltriethylphosphonium bromide (**2**) provided 1-phenyl-1-pentene (**6a**) (Table 2, Entry 1) as the major product. Traces of polar products were observed; however, chromatographic purification gave the olefin in 65% isolated yield. The process was successfully extended to a series of aliphatic aldehydes **6a**–**6d**.

Interestingly, both isolated yield and (*E*)-olefin content increased proportionally with the aliphatic chain length. We attribute the higher yields to a lipophilic effect possibly involving micelles (vide infra). The higher (*E*)-olefin stereoselectivity ist likely due to enhanced reactivity via the (*E*)-oxaphosphetane intermediate.

Although the mechanism of the aqueous Wittig reaction is speculative, we note the formation of an emulsion from the suspension of the phosphonium salt and aldehyde in water. No reaction occurs until the base is added. The emulsion slowly disappears and the product precipitates. We connect these observations to the remarkable chemoselectivity that is observed. Cannizarro and homo-aldol products are suppressed with both reactive aliphatic and aromatic aldehydes in the presence of classic reagents for these reactions. We believe that these results are most likely due to the formation of micelles, surface-stabilized by the phosphonium salt, partitioning the organic materials from the aqueous basic environment. This partitioning is the most likely explanation for the protection of the aldehyde from the expected basic side reactions. The aldehyde is subject to a locally selective reaction environment with the in-situ generated ylide. Rapid and reversible ylide generation occurs through deprotonation of the phosphonium salt at the interface. The neutral dipolar ylide is translocated to the lipophilic interior where the Wittig reaction takes place. The water-soluble phosphane oxide would be expected to diffuse out of the micelles to the aqueous phase. Precipitation or crystallization of the olefin product occurs as its concentration accumulates to the saturation point within the micelle. As the reaction nears completion and phosphonium salt and aldehyde are consumed, the micelles disappear leaving only a suspension of the olefin in water.

Conclusion

We show that semi-stabilized ylides can be formed solely in aqueous media from the reaction of a trialkylbenzylphosphonium salts and a metal hydroxide and that these ylides react with aromatic aldehydes in water to precipitate (*E*)-stilbenes with high selectivity. As the triethylphosphane oxide side product is water-soluble, we also show that the (*E*)-stilbene product can be isolated pure simply by filtration and washing with water. The same ylides react with enolizable aliphatic aldehydes providing 1-phenylalkenes with good selectivity. Overall, this direct, high-yielding synthesis of (*E*)-stilbenes and alkenes in aqueous media is technically simple, general and provides high yields of valuable pharmacological and photo-active materials with high configurational selectivity under environmentally benign conditions. In fact, the aqueous stilbene synthesis elevates the Wittig reaction of trialkylphosphane-derived semi-stabilized ylides into the realm of "Click" chemistry, satisfying most of the stringent criteria.[30] Extension of the scope of the aqueous Wittig chemistry and mechanistic investigations are under study.

Experimental Section

Synthesis of DMU-212 (5): Into a flame-dried flask, containing a magnetic stirring bar was weighed 4-methoxybenzyl bromide (1.21 mL, 8.4 mmol) under argon. Triethylphosphane (1.24 mL, 8.4 mmol) was then added slowly at 0 °C. The reaction mixture was slowly warmed to room temp. and stirred for 30 min. Distilled water (3.4 mL) was added to make a 2.5 M solution. The mixture was stirred at room temp. for 15 min, whereupon LiOH (814.3 mg, 34 mmol) was added slowly. After 2 min, 3,4,5-trimethoxybenzaldehyde (1.65 g, 8.4 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask cooled to room temp. Water (80 mL) was added to the reaction mixture, and the flask was stirred for 10 min. The slurry was vacuum-filtered, washed with water and dried to yield 2.42 g (96%) of DMU-212 (**5**) as a yellow solid. M.p. 156–157 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 3.85 (s, 3 H), 3.91 (s, 6 H), 6.88 (d, J_{HH} = 16.1 Hz, 1 H), 6.89 (J_{HH} = 8.8 Hz, 2 H, 2 H), 6.99 (d, J_{HH} = 16.1 Hz, 1 H), 7.43 (d, J_{HH} = 8.8 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.2, 56.0, 60.8, 103.1, 114.3, 126.5, 127.5, 127.7, 129.9, 133.3, 137.4, 153.3, 159.1 ppm. HRCI MS: calcd. for $C_{18}H_{20}O_4$ [M^+] 300.1362, found 300.1346.

Supporting Information (see footnote on the first page of this article): General details, synthetic protocols and characterization data for phosphonium salts, compounds **4** and **5** and the materials reported in Tables 1 and 2.

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