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Water is an efficient medium for Wittig reactions employing stabilized ylides and aldehydes

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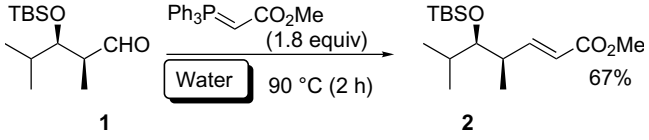
Abstract—Water is demonstrated to be an excellent medium for the Wittig reaction employing stabilized ylides and aldehydes. Although the solubility in water appears to be an unimportant characteristic in achieving good chemical yields and *E*/*Z*-ratios, the rate of Wittig reactions in water is unexpectedly accelerated.

For over 50 years, the Wittig reaction[1] has excelled as one of the most popular and powerful methods to create carbon–carbon double bonds in synthetic chemical methodology.[2] The use of stabilized or nonstabilized ylides in the presence of aldehydes to provide access to alkenes with either high *E*- or *Z*-geometrical selectivity has been studied extensively over many years.[2c] Traditional olefination reaction conditions that provide an excess of the *E*-alkenes generally include a stabilized ylide and an aldehyde, often in solvents ranging from hexane to DMF or DMSO. The Wittig reaction is known to proceed at a slow reaction rate when nonpolar solvents are employed.[3] Consequently, in order to improve the Wittig reaction, a number of variations of reaction conditions have been reported, for example, increasing temperature[4] or pressure,[5] presence of additives,[6] irradiation with microwaves[7] or light,[8] sonication,[9] use of silica gel[3] or ionic solvents.[10] Although water has been applied as a solvent for Wittig reactions employing elegantly modified water-soluble phosphonium salts,[11a] to our knowledge, the application of water as the essential medium for performing Wittig reactions utilizing poorly water-soluble stabilized ylides is unprecedented in the literature.[11]

Demonstrated herein is the Wittig reaction utilizing stabilized ylides conducted in water as an efficient medium.



Scheme 1.

Although the starting materials and products appear to be poorly soluble in the medium, the rate of the reaction is unexpectedly fast in water. Thus, in the course of the preparation of enoate **2** as an instrumental template for the synthesis of macrolide antibiotics (Scheme 1), the Wittig product (**2**) was obtained in 67% yield[12] after conducting the olefination reaction in water at 90 °C for 2 h. This reaction is faster in water in comparison to the reported Wittig reaction employing aldehyde **1** and the same ylide in conventional organic solvents such as refluxing CH_2Cl_2 (70%, 4 weeks!)[13] or refluxing CH_3CN (95%, 18 h).[14]

Motivated by the surprising impact of water in the Wittig reaction, we decided to conduct a broader investigation of this reaction by utilizing various phosphoranes and aldehydes. Indeed, good yields as well as very high *E*/*Z*-isomeric ratios of the olefination products were obtained, particularly when aromatic carboxaldehydes were employed (Table 1).

The impact of water is noticeable in the formation of products **4**–**7** (20 °C, 1 h) and particularly in the formation of chalcone (**3**) (entry 1), which has been

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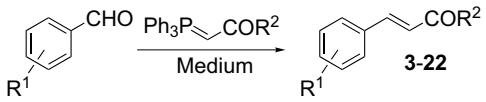
Table 1. Wittig reactions of various aromatic aldehydes and stabilized ylides in water[a]



Entry	R^1	Medium	Ylide, R^2	Equiv	Temperature (°C)	Time	Yield,[b] {lit.} (%)	*E*/*Z*[c]	Product
1	H	**Water**	Ph	1.5	**20**	**1 h**	**91**	**90:10**	**3**
2	H	Benzene	Ph	NR	~80[d]	3 days	{>70}[d]	NR	**3**
3	H	**Water**	OMe	1.2	**20**	**1 h**	**88**	**93:7**	**4**
4	H	Methanol	OMe	1.2	20	1 h	89	3:1	**4**
5	H	**Water**	O-*t*-Bu	1.2	**20**	**1 h**	**97**	**92:8**	**5**
6	H	**Water**	OTroc	1.2	**20**	**2 h**	**93**	**94:6**	**6**
7	H	**Water**	Me	1.2	**20**	**1 h**	**85**	**98:2**	**7**
8	H	[Bmim][BF_4]	Me	1.1	60	2.5 h	{82}[e]	97:3	**7**
9	4-NO_2	**Water**	Ph	1.5	**90**	**2 h**	**93**	**84:16**	**8**
10	4-NO_2	**Water**	Me	1.5	**90**	**2 h**	**96**	**87:13**	**9**
11	2-NO_2	**Water**	OMe	1.2	**90**	**1 h**	**92**	**88:12**	**10**
12	4-CN	**Water**	OMe	1.5	**90**	**2 h**	**86**	**83:17**	**11**
13	2-Cl	**Water**	OMe	1.2	**20**	**5 min**	**97**	**81:9**	**12**
14	F_5	**Water**	OMe	1.2	**20**	**5 min**	**86**	**99:1**	**13**
15	4-Cl, 3-F	**Water**	OMe	1.5	**20**	**1 h**	**95**	**96:4**	**14**
16	4-Br	**Water**	OMe	1.5	**90**	**20 min**	**78**	**89:11**	**15**
17	4-Br	Methanol	OMe	NR	30	3 h	{84}[f]	NR	**15**
18	4-OMe	**Water**	OMe	1.2	**20**	**4 h**	**66**	**92:8**	**16**
19	4-OMe	**Water**	OMe	1.2	**90**	**30 min**	**90**	**92:8**	**16**
20	4-OMe	CH_2Cl_2	OMe	1.0	~50[g]	4 h	{8}[g]	93:7	**16**
21	4-OMe	Benzene	OMe	1.0	~80[h]	2 days	{73}[h]	93:7	**16**
22	4-OMe	[Bmim][BF_4]	OMe	1.1	60	3 days	{82}[f]	96:4	**16**
23	3,4-OMe	**Water**	OMe	1.5	**90**	**1 h**	**90**	**>99:1**	**17**
24	3,4-OMe	Benzene	OMe	NR	~80[i]	0.5 day	NR[i]	>90:10	**17**
25	4-OH	**Water**	OMe	1.5	**90**	**1 h**	**92**	**95:5**	**18**
26	4-OH	CH_2Cl_2	OMe	1.0	~50[g]	4 h	{10}[g]	97:3	**18**
27	4-OH	Benzene	OMe	1.0	~80[h]	2 days	{89}[h]	93:7	**18**
28	4-NMe_2	**Water**	OMe	1.5	**90**	**2 h**	**81**	**90:10**	**19**
29	4-NMe_2	Methanol	OMe	1.5	20	5 h	78	3:1	**19**
30	4-NMe_2	CH_2Cl_2	OMe	1.0	~50[g]	4 h	{0}[g]	—	**19**
31	2-OBn	**Water**	OMe	1.2	**90**	**1 h**	**91**	**73:27**	**20**
32	3-OBn	**Water**	Me	1.5	**90**	**2 h**	**98**	**95:5**	**21**
33	3,4-OCH_2O	**Water**	O-*t*-Bu	1.2	**90**	**1 h**	**98**	**95:5**	**22**

NR = not reported.

[a] The reactions were conducted on a 1.0 mmol scale in 5.0 mL deionized water.

[b] Isolated purified material.

[c] *E*/*Z*-Ratio. Crude reaction mixtures analyzed by 500 MHz ^{1}H NMR.

[d] Reflux benzene. See Ref. 15.

[e] See Ref. 10.

[f] See Ref. 16a.

[g] Reflux CH_2Cl_2. See Ref. 5a.

[h] Reflux benzene. See Ref. 5a.

[i] Reflux benzene, reported 'good yield'. See Ref. 17.

reported to undergo a similar Wittig reaction in refluxing benzene for 3 days (entry 2).[15] Thus, methyl (triphenylphosphoranylidene)acetate undergoes a rapid Wittig reaction with benzaldehyde in water at room temperature to form 88% of methyl cinnamate (**4**) in 60 min (entry 3). As a comparison, when substituting water as a medium with MeOH to provide homogenous reaction conditions (entry 4), a complete conversion of benzaldehyde to product was obtained, but the *E*/*Z*-ratio was significantly depleted to 3:1 for cinnamate **4**. These initial results demonstrate that water is a very useful medium for the olefination reaction and does not jeopardize the *E*/*Z*-selectivity.

The Wittig reaction in water is a straightforward protocol that works favorably between ylides and aromatic carboxaldehydes having electron donating or electron withdrawing groups present. Indeed, the effect of electron donating groups has been reported to reduce the rate of the Wittig reaction in MeOH.[16] The presence of electron withdrawing groups increased the reaction rates of the Wittig reactions conducted in water. Employing an elevated reaction temperature when using solid aldehydes such as *p*-cyano- (entry 12) or *p*-bromobenzaldehyde (entry 16) provided high yields of the corresponding products. The observed *E*/*Z*-ratios of the products were generally slightly lower when utilizing some of the *ortho*-substituted benzaldehydes. Steric effects appear to be crucial for *ortho*-substituted aldehydes, but electronic effects cannot be ruled out. Thus, *o*-nitro-substituted benzaldehyde (entry 11) gave 92% of the Wittig product after conducting the reaction in

water at 90 °C for 1 h. As expected, pentafluorobenzaldehyde underwent a very fast olefination reaction with ylides in water and the *E*/*Z*-ratio of product **13** was very high (99:1), in contrast to the *E*/*Z*-ratio obtained utilizing the *o*-chloro substituted benzaldehyde (entry 13).

Also, in water we observed that *p*-anisaldehyde reacts slowly with ylides at room temperature, for example, a 66% yield of product **16** was obtained after 4 h at 20 °C (entry 18). At the same time, heating the reaction to 90 °C for 30 min increased the yield of **16** to 90% without affecting the *E*/*Z*-ratio (entry 19). The efficiency of water is evident, since this Wittig reaction has previously been reported utilizing the identical ylide in refluxing CH_2Cl_2 (4 h, 8%),[5a] in refluxing benzene (2 days, 73%),[5a] or in an ionic liquid at 60 °C (3 days, 82%)[10] (entries 20–22). As a comparison, the Wittig reaction conducted in water using the corresponding 3,4-dimethoxybenzaldehyde gave cinnamate **17** in 90% yield and excellent *E*/*Z*-ratio after 1 h at 90 °C (entry 23). It is also noteworthy that the relatively unreactive *p*-Me_2N-substituted benzaldehyde did not react with the ylide in water at 20 °C, but after 2 h at 90 °C afforded product **19** in 81% yield (entry 28). When conducted in MeOH, this reaction provided 78% yield of **19** at 20 °C after 5 h, but the *E*/*Z*-ratio was significantly diminished to 3:1 (entry 29). The corresponding reaction in CH_2Cl_2 (reflux 4 h)[5a] was fruitless (entry 30).

Furthermore, conducting the Wittig reaction in water is advantageous with substrates having unprotected acidic functional groups. Consequently, *p*-hydroxybenzaldehyde gave the corresponding cinnamate product **18** in 92% yield (entry 25).

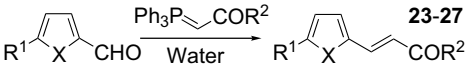
Heterocyclic aromatic carboxaldehydes, such as thiophene-, pyrrole-, quinoline-, and pyridine- (Table 2) provide high yields of the corresponding products (**23**–**30**) when conducting the Wittig reactions in water. The *E*/*Z*-ratio was modest employing 3-pyridinecarboxaldehyde (entry 8), but it was excellent when using 2- or 4-quinolinecarboxaldehyde (entries 6–7).

The Wittig reaction in water is also applicable to aliphatic aldehydes (Scheme 2). Thus, high yields of the corresponding α,β-unsaturated methyl-, *tert*-butyl-, and *troc*-esters were obtained from the olefination reaction utilizing various ylides. Notably, the yield of products **31**–**33** increased as the alkyl chain for the aliphatic aldehyde was extended. Although the α-branched aliphatic aldehydes reacted slower for the olefination reactions, it is nevertheless feasible to obtain high yields of the Wittig reaction products in water.[18] Hence, *troc*-ester **35** was prepared in 73% yield at 20 °C for 18 h.

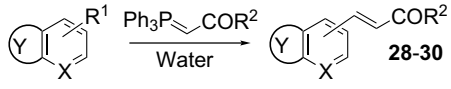
The desire to use water as a 'solvent' in organic chemistry[19] stems from the fact that water is extremely inexpensive and straightforward, and represents no environmental concerns. Although the inherent ability of water to force nonpolar molecules to associate, the *hydrophobic effect*,[20] is a process instrumental in biological systems, water is generally ignored in organic reactions due to solubility problems and its amphoteric nature. Recently, Sharpless[21] demonstrated that indeed water is an ideal medium for many organic transformations even if starting materials and products appear to be insoluble.

Water may be considered to enhance reactivity in Wittig reactions due to its ability to stabilize the polar transition state of the reaction, a phenomenon that a nonpolar medium is less capable of facilitating. Water may also be disposed to participate in the Wittig reaction based on its protic nature. This was concluded from the results obtained after conducting the reaction in D_2O. A Wittig reaction utilizing benzaldehyde with methyl (triphenylphosphoranylidene)acetate in D_2O resulted in 90% product having 90% deuterium incorporation at the

Table 2. Wittig reactions of various heterocyclic aromatic aldehydes and ylides in water[a]

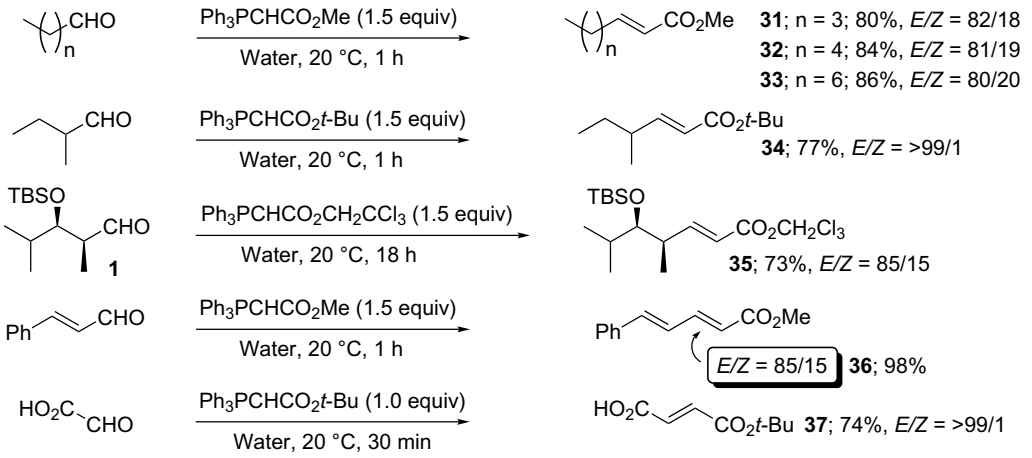


Entry	R^1	X	Ylide, R^2	Equiv	Temperature (°C)	Time	Yield,[b] (%)	*E*/*Z*[c]	Product
1	H	S	OMe	1.2	20	1 h	95	92:8	**23**
2	Br	S	OMe	1.5	20	5 min	89	91:9	**24**
3	Me	S	O-*t*-Bu	1.5	20	1 h	97	90:10	**25**
4	NO_2	S	O-*t*-Bu	1.5	90	1 h	94	86:14	**26**
5	H	NH	O-*t*-Bu	1.5	90	2 h	84	>99:1	**27**



Entry	R^1	X	Y	Ylide, R^2	Equiv	Temperature (°C)	Time	Yield,[b] (%)	*E*/*Z*[c]	Product
6	2-CHO	N	C_4H_4	Ph	1.5	90	2 h	89	>99:1	**28**
7	4-CHO	N	C_4H_4	OMe	1.5	90	2 h	92	>99:1	**29**
8	3-CHO	N	H,H	OMe	1.5	20	1 h	88	81:19	**30**

[a] The reactions were conducted on a 1.0 mmol scale in 5.0 mL deionized water.
[b] Isolated purified material.
[c] *E*/*Z*-Ratio. Crude reaction mixtures analyzed by 500 MHz ^{1}H NMR.



Scheme 2. Wittig reactions in water applied to aliphatic aldehydes.

α-carbon of ethyl cinnamate.[22] Thus, a very fast deuterium exchange occurs, which is in accordance with what has been postulated by Bestmann using EtOD.[23]

Water has been illustrated as an efficient medium for the Wittig reaction employing stabilized ylides and aldehydes. This work demonstrates that solubility of the reagents and substrates is not of a paramount nature, even though pronounced hydrophobic entities are present. Since water has its own distinctive place among possible solvent systems, water should always be considered as a possible medium in the improvement and development of new organic reactions. Not only is water shown as an extremely useful medium for the synthesis of carbon–carbon double bonds, but this letter also exemplifies advances toward the synthesis of alkenes using an environmentally friendly approach. Further development of the aqueous Wittig reaction is currently under investigation in our laboratory.

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Supplementary data

Experimental procedures and spectral data (^{1}H NMR and ^{13}C NMR) for pertinent compounds (PDF). Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.04.105.

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