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LETTERS

Wittig Reactions in Water. Synthesis of New Water-Soluble Phosphonium Salts and Their Reactions with Substituted Benzaldehydes

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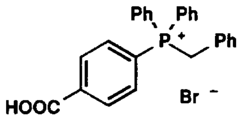
***Abstract*:** We report the synthesis of new phosphonium salts which are soluble and stable in basic aqueous solution. The Wittig reactions of these phosphonium salts with substituted benzaldehydes in aqueous sodium hydroxide are discussed. These reactions exclude the use of any organic solvents and the products are isolated by a simple filtration.

Synthetic organic chemistry in water has been widely studied in recent years and there are extensive reviews on the subject;[1-5] these reviews outline reactions, for example, organometallic reactions, which had previously been thought unlikely to proceed in the presence of water. More recently, there have been efforts to design water-compatible reagents, *e.g.* water-soluble phosphines (which are widely used in industry as ligands in organometallic reactions),[6,7] polyether-substituted tin hydrides[8] and manganese porphyrin complexes.[9]

We have designed several aqueous base-soluble phosphonium salts as potential reagents for aqueous Wittig reactions. These are triphenylbenzylphosphonium salts with solubilising groups attached to the phenyl rings; specifically, we have synthesised phosphonium salt **1** (with one *p*-COOH substituent) and phosphonium salts **2** and **3** (with one or two hydroxyl groups in different positions relative to phosphorus). These substituents were chosen as they will be deprotonated in basic solution and the resulting ionic species should dissolve. Phosphonium salt **1** was our initial choice as the –COO⁻ group should have little electronic effect on the molecule.[10]



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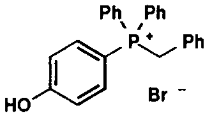
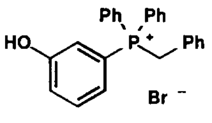


2a



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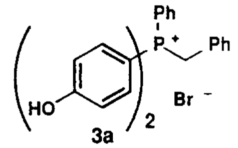
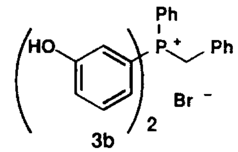


3a



3b

Phosphonium salt **1** was synthesised from phosphine **4** and benzyl bromide in refluxing toluene. Phosphine **4** was made by a modified literature procedure;[11] the Grignard reagent derived from phosphine **5** was reacted with carbon dioxide to give the required phosphine **4** in 62% yield after recrystallisation. Phosphonium salt **1** was obtained in 37% yield over the three steps.

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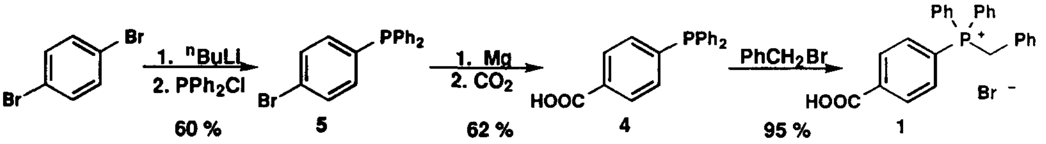


Phosphonium salts **2** and **3** were synthesised in three steps from the corresponding bromoanisoles **6**. The Grignard reagent generated from each bromoanisole was quenched with chlorodiphenylphosphine (for **2**) or dichlorophenylphosphine (for **3**). We opted to synthesise the phosphonium bromides **7**; subsequent demethylation gave the hydroxyl-substituted phosphonium salts **2** and **3** (Table 1). An unexplained oxidation during the work-up of the Grignard reaction of **6b** with $PhPCl_2$ gave the phosphine oxide **9**. Reduction with polymethylhydrosiloxane[12] and subsequent alkylation gave the appropriate phosphonium salt **3b**.

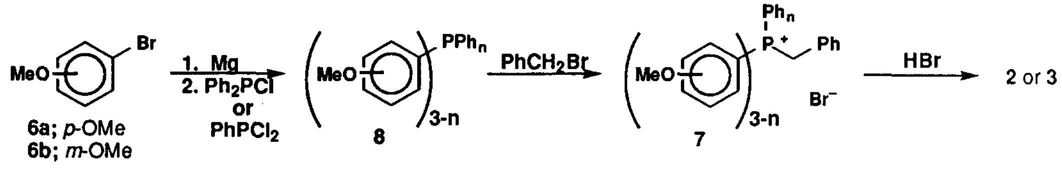
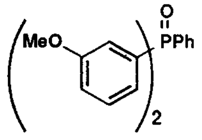


Table 1: Yield of hydroxyl-substituted phosphonium salts

starting material	n	yield **8** (%)	yield **7** (%)	product	yield (%)
6a	1	86	97	**2a**	99
6b	1	55	87	**2b**	95
6a	2	76	87	**3a**	95
6b	2	0[a]	81[b]	**3b**	40

[a] no phosphine was isolated; phosphine oxide **9** was obtained in 100 % yield.

[b] yield calculated from one-pot reduction-alkylation method of phosphine oxide **9**.

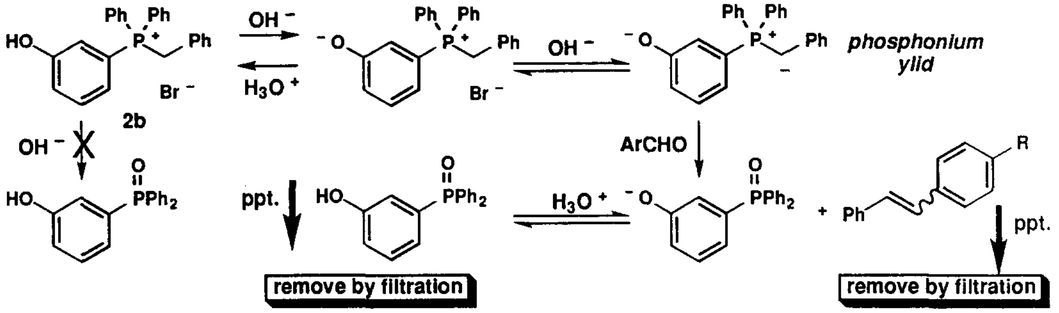


9

Wittig reactions[13] and Horner-Wadsworth-Emmons reactions[14-16] in the presence of water have been reported previously although these were carried out in biphasic solutions using phase transfer catalysis. There are, however, a few isolated examples of Wittig reactions in water which exclude organic solvents: vitamin A acetate is synthesised industrially in water,[17] and nitrostyrenes[18] and *p*-carboxystyrene[19] have been synthesised in water by reaction of aqueous formaldehyde with the corresponding ylids, generated in aqueous base from the phosphonium salts. Attempted Wittig reactions with less reactive aldehydes resulted in hydrolysis of the phosphonium salts instead.[20]

Phosphonium salts **1**, **2** and **3** are all insoluble in water at pH 7 but dissolve easily in 10 % aqueous NaOH. Addition of aqueous acid to these solutions caused the phosphonium salts to precipitate and they could be recovered quantitatively by filtration, indicating that hydrolysis of the phosphonium salts to phosphine oxides is slow. The presence of an oxido or $-COO^-$ group in basic solution may inhibit the hydrolysis of these phosphonium salts.

Aqueous sodium hydroxide was added to a premixed *suspension* of aldehyde and phosphonium salt in water. Addition of aqueous base caused the suspension to dissolve and the mixture was stirred overnight at room temperature. A white precipitate (the stilbenes) appeared. In most cases, simple filtration and an aqueous wash gave mixtures of *E* and *Z* stilbene products (Table 2); reactions with phosphonium salt **1**, however, did not give clean precipitates and, in these cases, the stilbenes were isolated by extraction with dichloromethane. Acidification of the filtrate with aqueous hydrochloric acid gave a second precipitate, which was also isolated by filtration and identified as the phosphine oxide by-product of the Wittig reaction. A representative Wittig reaction between phosphonium salt **2b** and a substituted benzaldehyde is shown.



10; R = OMe 12; R = H
11; R = Cl 13; R = NO_2

Table 2: Wittig reactions of phosphonium salts with substituted benzaldehydes

	yield and isomer ratio of stilbenes **10-13** upon reaction with substituted benzaldehydes							
	4-methoxybenzaldehyde		4-chlorobenzaldehyde		benzaldehyde		4-nitrobenzaldehyde	
P+ salt	yield **10** (%)	*E*:*Z*[a]	yield **11** (%)	*E*:*Z*[a]	yield **12** (%)	*E*:*Z*[a]	yield **13** (%)	*E*:*Z*[a]
1	43	45:55[b]	58	50:50[b]	91	46:54[b]	100[b]	
2a	40	79:21	91	72:28	40	100:0[c]	76	63:37
2b	72	68:32	87	74:26	28	100:0[c]	98	60:40
3a	0[d]		0[d]		17[d]	100:0[c]	6[d]	91:9
3b	24	100:0	81	86:14	45	100:0[c]	73	82:18

[a] crude ratio measured by ^1H NMR.
[b] products were recovered by extraction with dichloromethane.
[c] only *E*-stilbene can be recovered by filtration.
[d] phosphonium salt recovered.

The *E*:*Z* ratios observed are likely to be partly a consequence of the workup procedure rather than any stereochemical properties of the reaction. The synthesis of stilbene **12** itself represents a special case; *E*-stilbene is a solid, whereas Z-stilbene exists as a liquid under standard conditions. The precipitates from the Wittig reactions of benzaldehyde were pure *E*-isomers. Extraction of the aqueous filtrate with CH_2Cl_2 allowed *more E*-stilbene and also Z-stilbene to be recovered. This partial solubility of stilbene in water may prove a hindrance to an efficient Wittig process. Nevertheless, moderate to good yields of substituted stilbenes are obtained by filtration only without extraction (Table 2).

Wittig reactions with phosphonium salt **1** gave disappointingly poor results. The reactions proceeded sluggishly and so required longer reaction times. Recovery of the products also required the use of organic solvent and thus the yields and stereochemical ratios cannot be compared to the reactions of phosphonium salts **2** and **3**.

Greater success was achieved with phosphonium salts containing hydroxyl groups (**2** and **3**). The stilbene products precipitated from basic solution and were recovered with simple filtration. In most cases, an increase in yield was observed when changing from the *para*-hydroxyl series to the *meta*-hydroxyl series (**a** to **b**). This is much more pronounced in phosphonium salts **3**. Presumably, the greater electron-donating potential of the *p*-oxido group[10] reduces the positive charge on phosphorus and increases the pK_a value of the oxidophosphonium salt.

Reactions of phosphonium salt **3a** were consistently poor; electron donation from *two para*-oxido groups onto phosphorus may lower the equilibrium ylid concentration considerably; in the reactions of phosphonium salt **3b**, the addition of a second hydroxyl group seems not to help (and possibly to hinder) the reaction. Note, however, that hydrolysis of the phosphonium salts does not occur either; the unsuccessful reactions with phosphonium salt **3a** always gave a good recovery of starting material. Indeed, it was recovered by filtration in *basic* solution. This would imply that a simple analysis of pK_a values cannot be the whole answer. In addition to the phosphonium salt and the ylid, there are two other intermediates (where one or both hydroxyl groups are deprotonated prior to ylid formation). If one or more of these intermediates is insoluble in aqueous base further deprotonation to give the ylid will not occur.

These new phosphonium salts **1–3** are soluble and resistant to hydrolysis in aqueous base (5-10% NaOH). Wittig reactions in water gave unsymmetrical stilbenes (predominantly *E*) in high yields from benzaldehydes containing electron-donating or electron-withdrawing groups. Both the stilbene products and the phosphine oxide by-products of the reaction are isolated by simple filtration. Phosphonium salt **2b** gives the best results under these conditions.

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