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Heck-type Reactions in Water

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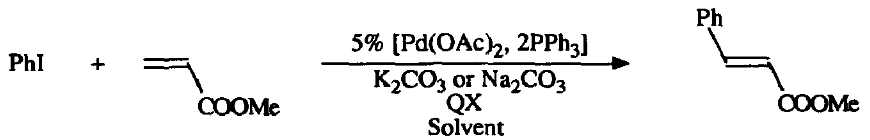
Abstract : The presence of water is determining for the efficiency of quaternary ammonium salt (QX) in palladium-catalysed vinylation of organic halides using an alkali metal carbonate as the base, whether QX is a chloride, a bromide or a hydrogensulfate. The [Pd/M_2CO_3/QX] catalyst system can even be used for performing the reactions in neat water, without organic solvent.

Palladium-catalysed vinylation of organic halides (Heck-type reactions[2]) fulfils an ever increasing role in organic synthesis. Tetraalkylammonium chloride has proved highly useful for enhancing the rate and selectivity of this type of reactions.[3] In contrast, tetraalkylammonium hydrogensulfate has generally been found ineffective[4-7] although its presence has sometimes been observed to be slightly beneficial when compared to reactions performed in its absence.

We wish to report herein (i) that not only can tetraalkylammonium hydrogensulfate be highly efficient in combination with an alkali metal carbonate, but also (ii) that water has a determining influence on the efficiency of the quaternary ammonium salt (QX), whatever the nature of the anion (X= Cl, Br or HSO_4) and (iii) that reactions can even be realised in neat water.

Investigation of the arylation of methyl acrylate in the presence of a combination of tetra-n-butylammonium salt and potassium (or sodium) carbonate and catalytic amounts of palladium acetate and triphenylphosphine (scheme) has shown (Table 1) that in dry acetonitrile,[8] while n-$Bu_4NCl.xH_2O$ [9] has an important accelerating effect (entry 2), neither n-Bu_4NHSO_4, non hydrated n-Bu_4NCl nor n-Bu_4NBr have any significant influence (entries 3-5). In contrast, when the reaction was performed in a mixture of water and acetonitrile, an important increase in the reaction rate was observed upon addition of any tetra-n-butylammonium salt, whether the latter was n-Bu_4NHSO_4, non hydrated n-Bu_4NCl or n-Bu_4NBr (entries 6-9). The determining role of water is confirmed by the fact that n-$Bu_4NCl.xH_2O$ loses its efficiency when the reaction is performed in the presence of a dehydrating agent such as magnesium sulfate (entry 10 compared to entry 2).



QX= n-Bu_4NCl, n-Bu_4NBr or n-Bu_4NHSO_4

Scheme

Table 1 : Influence of water on the efficiency of the [Pd/M_2CO_3/QX] catalyst system in the arylation of methyl acrylate. a)

Entry	Solvent	Added salt	Conversion b) (%)	Yield b) (%)
1	dry CH_3CN c)	none	15	15
2	"	n-$Bu_4NCl.xH_2O$ d)	99	97
3	"	n-Bu_4NHSO_4	12	12
4	"	n-Bu_4NCl e)	10	10
5	"	n-Bu_4NBr	5	5
6	1:10 H_2O-CH_3CN	none	5	5
7	"	n-Bu_4NHSO_4	98	96
8	"	n-Bu_4NCl e)	98	96
9	"	n-Bu_4NBr	99	97
10	dry CH_3CN c)	n-$Bu_4NCl.xH_2O$ d) (+$MgSO_4$)	1	1
11	1:10 H_2O-CH_3CN	LiCl	15	15
12	"	KCl	15	15

a) $Pd(OAc)_2$ (0.05 equiv.) was added to the well-stirred mixture of phenyl iodide (1 equiv.), methyl acrylate (2 equiv.), PPh_3 (0.1 equiv.), K_2CO_3 (2.5 equiv.) and added salt (1 equiv.) in the solvent indicated (1 ml/1mmol of PhI). Stirring was continued for 2h at 50°C. b) GLC yields. c) ACS grade solvents were used as dry solvents. d) "Tetrabutylammonium chloride hydrate 98%" from Aldrich. e) "Tetra-n-butylammonium chloride 98%" from Lancaster.

The influence of water, which is crucial whether QX is a chloride, a bromide or a hydrogensulfate, has also been observed whether the solvent was acetonitrile or N,N-dimethylformamide and whether the inorganic base was potassium or sodium carbonate.

The fact that tetraalkylammonium hydrogensulfate can be highly effective while neither lithium nor potassium chloride has been efficient (entries 11-12) clearly shows that the increase of the reaction rate is directly dependent upon the presence of a quaternary ammonium cation.

The role of water could be similar to that observed in many "solid-liquid" phase-transfer catalysed organic processes in which the importance of water has been well evidenced.[10-13]

The results presented in Table 2 show that palladium-catalysed arylation of methyl acrylate in the presence of an alkali metal carbonate can even be performed in water alone, without any organic solvent, under mild conditions (50°C or room temperature), upon addition of a tetraalkylammonium salt, whether the latter is a chloride, a bromide or a hydrogensulfate.

Table 2 : Influence of tetraalkylammonium salts on Pd-catalysed arylation of methyl acrylate in neat water, in the presence of potassium or sodium carbonate as the base.[a)]

Entry	Base	QX	Temperature/Time	Yield [b)] (%)
1	K_2CO_3	None	50°C/2h	5
2	"	n-Bu_4NCl [c)]	"	98
3	"	n-Bu_4NBr	"	95
4	"	n-Bu_4NHSO_4	"	98
5	Na_2CO_3	n-Bu_4NHSO_4	"	95
6	K_2CO_3	n-Bu_4NCl [c)]	25°C/24h	98
7	"	n-Bu_4NHSO_4	"	98

a) K_2CO_3 (2.5 equiv.), tetraalkylammonium salt (1 equiv.), water (1 ml/1mmol) and $Pd(OAc)_2$ (0.05 equiv.) were successively added to the well-stirred mixture of phenyl iodide (1 equiv.), methyl acrylate (2 equiv.) and PPh_3 (0.1 equiv.). Stirring was continued for the time and at the temperature indicated. b) GLC yields. c) hydrated or non hydrated tetra-n-butylammonium chloride.

Heck-type reactions in aqueous media have been described, involving substrates having carboxy groups which can form water-soluble intermediates with alkali metal salts.[14] Reactions have also been effected in a mixture of water and acetonitrile using water-soluble sulfonated phosphines.[15,16] The results reported herein

indicate that reactions involving water-insoluble substrates and phosphine ligand can be efficiently realised in water, provided that they are performed in the presence of a combination of an alkali metal carbonate and a quaternary ammonium salt, whether the latter is a chloride, a bromide or a hydrogensulfate.

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