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Use of a new hydrophilic phosphonic phosphines (DPPA).

Heck Reaction in Aqueous Medium under Microwave Irradiation.

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Abstract: The Heck reaction is efficiently and rapidly obtained by a palladium-catalysed reaction in water performed in a Teflon autoclave under microwave irradiation with a commercial microwave oven. Water soluble phosphine-ligand catalysts and phase transfer catalysis conditions are used.

Keywords: Heck reaction, Microwaves, Phase-transfer catalysis, Water-soluble phosphine, LogP, DPPA

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1. Introduction

The Heck type reaction is a powerful tool for carbon-carbon bond formation [1]. This palladium-catalysed reaction needs a stoichiometric use of base, high temperature (100°C) and long time (24 hrs) for complete conversion. Some alternative conditions, such as high pressure [2], phase-transfer conditions [3] or water-soluble phosphine-ligand catalysts were proposed and many Heck arylations are known to proceed smoothly in water or in water/organic solvent mixtures [4].

The Heck reaction is generally catalysed by palladium and occurs in dry solvents. Few examples about this type of reaction in aqueous medium are reported in presence of water-soluble phosphines (i.e. sulphonated phosphines). Triarylphosphine with meta or paraphosphonic acid moiety is more soluble than the sulphonated analogue [5], also we investigated the use of paraphosphonic triphenylphosphine as water-soluble ligand in Heck reaction in aqueous medium under phase transfer conditions according to Tuyet Jeffery [6]. The use of water as solvent is very attractive because of the economy and safety induced.

Microwave activation is very useful because of its important rate accelerating effect (i.e. reduction of reaction times) and thus high electricity economy is involved. Although many organometallic complexes were efficiently obtained under microwave radiations [7], reactions homogeneously catalyzed by organometallic complexes were up to now scarcely investigated [8,10,11]. The air-sensitive complexes have been prepared by Mingos using commercially available Teflon autoclaves designed for mineralisation under commercial microwave-oven irradiation.

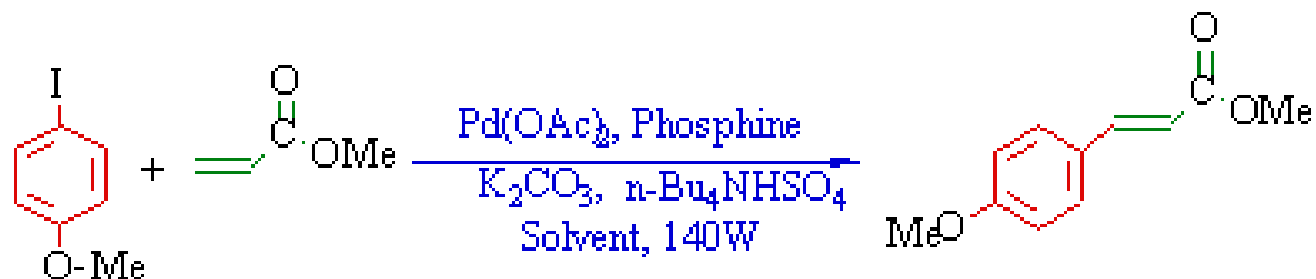
We report in this paper a new efficient method for Heck coupling reaction in a Teflon autoclave using a new water-soluble phosphine-ligand as catalyst [DPPPA, 4-(Diphenylphosphinyl)phenylphosphonic acid], phase transfer conditions and activation by microwave irradiation.

During this work papers about the Heck reactions under microwave irradiation were published. Hallberg et al. [12] used normal conditions (tributylamine and DMF as solvent) and Diaz-Ortiz [13] performed this reaction in triethylamine as solvent. The scopes of our work are the use of a new water-soluble triarylphosphine with paraphosphonic acid moiety (DPPPA) and aqueous conditions.

2. Results and Discussion

We first studied the Heck reaction of 4-iodoanisole with methyl acrylate under Jeffery's conditions (Scheme-1) in the presence of phosphines.

Scheme-1



Various phosphines were used in order to compare their effect on the arylation of methyl acrylate in the presence of palladium acetate and water as solvent or co-solvent (Table-1). The results show that triarylphosphine with a paraphosphonic acid moiety (DPPPA) gave the best yield (entry 8) in 8 min at 140 W in water as solvent.

With triphenylphosphine under Jeffery conditions in a hexane-water two-phase system a yield of 80% was obtained (entry 1). With the homogeneous mixture (acetonitrile and water) as a solvent the yield increased to 93% (entry 3) but in the absence of any phase-transfer reagent the yield was very poor (entry 2). In water without solvent the situation is quite different, the yield with triphenylphosphine or tritolyphosphine was not very good (entry 4 and 5). The use of water-soluble phosphine (TPPS, triphenylphosphinesulphonic acid or DPPPA) improved the yield and upon doubling the irradiation time to 8 min a yield similar to that observed in the presence of acetonitrile was obtained in water (entry 8).

Table-1 Heck reaction of 4-iodoanisole in water-organic medium or in water

4-iodoanisole/methyl acrylate/n-Bu₄NHSO₄/phosphine/Pd(OAc)₂ = 1/1.2/1/0.1/0.05

Entry	Phosphine	Solvent	Time (min)	Yielda (%)
1	PPh ₃	hexane / H ₂ O (1:1)	4	80
2	PPh ₃	MeCN / H ₂ O (1:1)	4	5b
3	PPh ₃	MeCN / H ₂ O (1:1)	4	93
4	PPh ₃	H ₂ O	4	38
5	(O-Tolyl) ₃ P	H ₂ O	4	40
6	TPPDS _c	H ₂ O	4	50
7	DPPPA _d	H ₂ O	4	63
8	DPPPA _d	H ₂ O	8	93

4-Iodoanisole, 0.1g (0.5 mmol); methyl acrylate, 0.06ml (0.6 mmol, 1.3 eq.); Pd(OAc)₂, 5 mg (5% molar); phosphine, (10% molar); K₂CO₃, 0.17g (2.5 eq.); n-Bu₄NHSO₄, 0.17 g (1 eq.), solvent, 2 ml. Irradiation at 140 W during the time indicated. **a** Isolated yields. **b** without n-Bu₄NHSO₄. **c** Disodium diphenyl-3,3'-phosphinediylbis-(benzenesulphonate). **d** 4-(Diphenylphosphinyl)phenylphosphonic acid.

In the second study, we performed the reaction between various iodoarenes and methyl acrylate (Scheme-2), the yield reported in Table-2 appears to depend on the solubility of the iodoarene in water.

Scheme-2

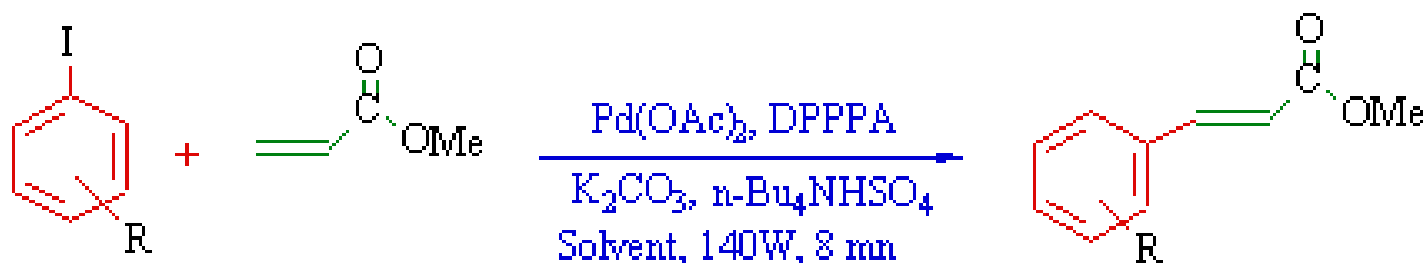


Table-2 Attempted of correlation of Heck coupling yields of aryl iodides with methyl acrylate and LogP in the presence of **DPPPA** in water

ArI/methyl acrylate/n-Bu₄NHSO₄/**DPPPA**/Pd(OAc)₂ = 1/1.2/1/0.1/0.05

Entry	R	LogPa	Yield ^b (%)
1	4-iPr	4.50	30
2	4-Me	3.77	55
3	H	3.30	78
4	4-OMe	3.05	93
5	3-CO ₂ Me	3.03	79
6	2-OH	3.02	95
7	4-NH ₂	2.52	96

Aryl iodide, (0.5 mmol); methyl acrylate, 0.06ml (0.6 mmol, 1.3 eq.); Pd(OAc)₂, 5 mg (5% molar); phosphine (**DPPPA**), (10% molar); K₂CO₃, 0.17g (2.5 eq.); n-Bu₄NHSO₄, 0.17 g (1 eq.); solvent, 2 ml of degassed water.

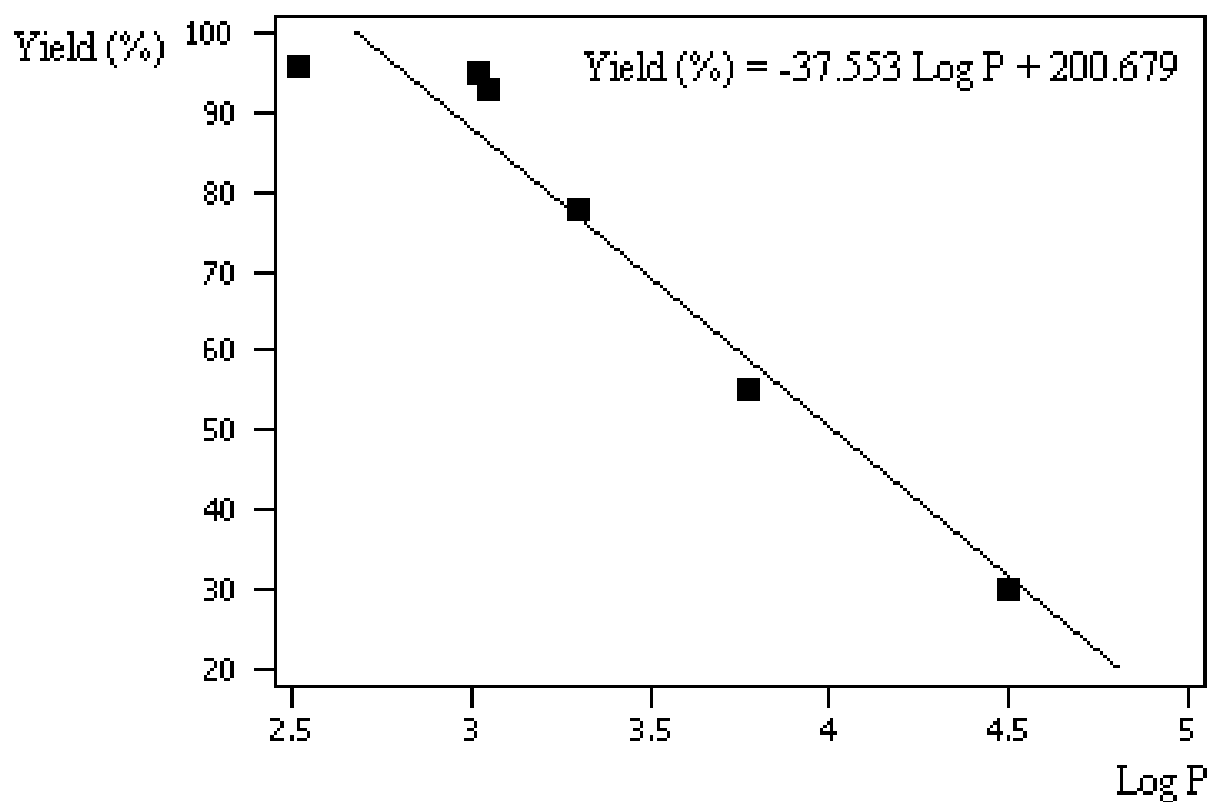
a Calculated with the program ChemPlus. **b** Isolated yields.

We used the hydrophobic parameter (LogP) in order to quantify the solubility of the iodoarenes in water. LogP is an experimental value of a substrate partition between two phases, generally n-octanol and water. This parameter developed by Hansch [9] is widely used in therapeutical chemistry for Structure-

Reactivities studies, but to our knowledge scarcely in organic chemistry. At present owing to molecular modelisation softwares, LogP values can be easily calculated. Iodoarenes molecules were built in 3D by HyperChem and after minimisation with AM1 method, the LogP values were calculated using the ChemPlus extension [10] and Ghose's method [11].

We observed a linear correlation between the LogP of the iodoarene and the yield of the reaction (Scheme 3). Thus with 4-iodoisopropylbenzene (LogP = 4.50) 30% were obtained and 96% when 4-iodoaminobenzene (LogP = 2.52) was used.

Scheme-3: Correlation between the yield and LogP of the substrate



$$a = -37.554 \pm 4.895 ; b = 200.679 \pm 16.736 ; SSE = 228.96 ; R^2 = 0.936$$

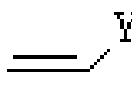

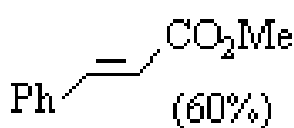

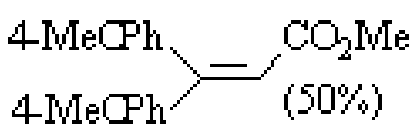

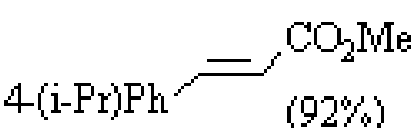

In the third study, we used **DPPPA** in acetonitrile-water solution, the results are reported in table-3. Bromobenzene gave a not as good yields (60%) as the iodoarenes (entry 1, table-3). In the case of 4-iodoanisole, it is possible to substitute the two b-hydrogens in the methyl acrylate (entry 2, table 3), however it is not the case with more hindered 4-iodoisopropylbenzene (entry 3, table 3). When methyl acrylate was substituted by allylic alcohol (entry 4), a mixture two aldehydes was obtained.

3. Conclusions

DPPPA [4-(**D**iphenylphosphinyl)phenylphosphonic acid] is a new water soluble phosphine which allows Heck reaction in water under microwave irradiation. **DPPPA** is more efficient in the case studied than the disulfonic analogue. We have also obtained a linear correlation between the LogP of the iodoaryle and the yield of the Heck reaction in water. Log P seems to be a convenient available parameter to quantify the solubility of a substrate for studying reaction in water.

Table-3 Arylation with different aryl halides in acetonitrile-water with **DPPPA**.

ArX/methyl acrylate/n-Bu₄NHSO₄/phosphine/Pd(OAc)₂ = 1/1.2/1/0.1/0.05 in CH₃CN/H₂O=1/1

Entry	PhX		Conditionsa	Product (yield %) ^b
1	PhBr		DPPPA n-Bu ₄ NCl	 (60%)
2	2 (4-MeOPhI)		(o-tol) ₃ P, n-Bu ₄ NCl	 (50%)
3	4-(i-Pr)PhI		DPPA n-Bu ₄ NCl	 (92%)
4	PhI		(o-tol) ₃ P, n-Bu ₄ NCl	Ph-(CH ₂) ₂ CHO (73%) ^c Ph-CH(CH ₃)CHO (16%) ^c

a 140 W during 10 minutes. **b** Isolated yields or as indicated. **c** According to ¹H NMR. **d** GC yields.

4. Experimental

¹H and ¹³C NMR (reference from internal Me₄Si) were recorded on a Bruker AC 250 instrument in CDCl₃ solution. ³¹P NMR spectra of the phosphines (reference from external H₃PO₄) were recorded on a Bruker WP80 SY. Mass spectra were recorded on a Nermag R10 10H spectrometer. FT IR spectra were recorded on a Perkin-Elmer 16 PC spectrometer. G.C. yields were obtained on a Shimadzu GC-8A apparatus fitted with an OV17 column and a catharometer detector which is connected to a Spectra Physics integrator-recorder. Microwave irradiations were carried out on a Toshiba microwave oven ER 7620 operating at 2450 MHz. All reactions were performed in a Teflon Savilex

autoclave under argon atmosphere. Water and all solvents were degassed before use.

Phosphines were prepared by phosphonation of the monobrominated phosphine followed by hydrolysis [14] for the DPPPA and according to Hermann's method [15] for the TPPDS by sulfonation of PPh₃ using H₂SO₄ and oleum mixture.

4.1.G.C. analysis

Column: OV17 1.5 m, oven temperature = programming from 140 to 240 °C (10 °C per minute), injector and detector temperature = 270 °C, gas flow (H₂) = 50 ml.min⁻¹. Retention time for E-methyl (4-methoxycinnamate) = 1.54 min.

4.2. Typical Experiment

In a typical experiment, Pd(OAc)₂ (5 mg), n-Bu₄NHSO₄ (0.5 mmol), K₂CO₃ (1.2 mmol) and phosphine (DPPPA) (10 mg, 6% molar) were placed in a Savilex autoclave under argon. A mixture of 4-iodoanisole (0.5 mmol) and methyl acrylate (0.6 mmol, 1.2 eq.) in 2 ml of Me₃CN/water (1/1) was added under argon atmosphere and the mixture was irradiated during 2 minutes at 140 W, then 6 times 1 minute. After cooling, the product was extracted with ether and filtered over Celite. Ether was distilled off and the residue was chromatographed on a silica gel column with CH₂Cl₂ as eluent; R_f (CH₂Cl₂) = 0.36. We obtain a white solid. MP 87-89 °C (Lit : 90 °C)¹⁵; ¹H NMR (CDCl₃) : 3.79 (s, 3H, CO₂CH₃); 3.84 (s, 3H, OCH₃); 6.31 (d, 3J_{HH} = 16 Hz, 1H, C=CH); 6.91 (d, 3J_{HH} = 8.8 Hz, 2H, Harom); 7.48 (d, 3J_{HH} = 8.8 Hz, 2H, Harom); 7.65 (d, 3J_{HH} = 16 Hz, 1H, HC=C); ¹³C NMR (CDCl₃) : 51.54 (CO₂CH₃); 55.43 (O-CH₃); 114.46 (Carom); 115.49 (C=C); 127.33. 129,76 (Carom); 144.55 (C=C); 161.54 (C-OCH₃, Carom); 167.75 (CO₂CH₃); IR (KBr) cm⁻¹ : ν(C=C) (1636); ν(C=O) (1718); ν(C-O) (1288, 1176)

5. Notes and References

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Comments

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