An improved procedure for the synthesis of aryl phosphonates by palladium-catalysed cross-coupling of aryl halides and diethyl phosphite in polyethylene glycol

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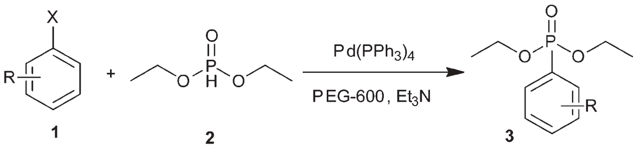
A general and greener protocol for the synthesis of aryl phosphonates by the cross-coupling of aryl halides and diethyl phosphite using tetrakis(triphenylphosphine)palladiume/triethylamine/polyethylene glycol 600 [$Pd(PPh_3)_4$/Et_3N/PEG 600] as an efficient catalytic system has been developed. This procedure also avoids hazardous solvents and is therefore an eco-friendly alternative to the existing methods.

Keywords: Hirao reaction, aryl phosphonates, polyethylene glycol

Aryl phosphonates and their derivatives have received attention recently because of their wide range of applications in polymers, medicinal chemistry, catalysis and photoelectric materials.[1] Phosphonates play an important role in organometallic catalysis[2] and organocatalysis.[3] Various approaches to the synthesis of aryl phosphonates have been explored over the past few years.[4–7] The transition-metal-catalysed Hirao reaction[8] is one of most widely-used methods for the synthesis of arylphosphonates. Some improved procedures by the cross-coupling of aryl halides,[9–12] triflates,[13] tosylates,[14] boronic acids[15–16] imidazolylsulfonates[17] and azoles[18] with dialkyl phosphites have also been developed to construct C(sp^2)–P bonds. Although these methods are suitable for certain syntheses, some of these procedures have one or more disadvantages such as the use of volatile and hazardous organic solvents, the requirement for expensive ligands and a microwave oven. Thus, the development of a more practical and economical procedure for the preparation of these compounds is still highly desirable.

The use of polyethylene glycol as a reaction medium has gained considerable interest in organic synthesis due to its many advantages from environmental, economical, and safety standpoints. It is noncorrosive, nonvolatile, stable, non-toxic, inexpensive, biologically acceptable and eco-friendly, and allows many useful organic transformations to be performed under mild reaction conditions.[19–25] In continuation of our research program for the development of environmentally benign methodologies,[26–32] we now report the synthesis of aryl phosphonates by cross-coupling of aryl halides and diethyl phosphite in PEG 600 (Scheme 1).

In order to achieve a practical protocol for the synthesis of aryl phosphonates, the effect of a number of parameters such as catalysts, bases, and solvents were screened for a model reaction employing *N*-(3-iodobenzyl)acetamide and diethyl phosphonate. The results are shown in Table 1. Among various catalysts it was found that $Pd(PPh_3)_4$ was the most effective. A concentration of 5 mol% was sufficient to complete the reaction with maximum yield (Table 1, entry 4). The reaction did not proceed smoothly in the absence of the catalyst and only a trace of the product was formed. To identify the best medium for the reaction, we also performed the model reaction with different solvents such as THF, DMF, 1,4-dioxan, EtOH, MeCN, CH_2Cl_2, toluene and PEG 600. PEG 600 was found to be the best reaction medium. Further examination of the conditions indicated that Et_3N was the optimal base. Other organic and inorganic bases were poorer at promoting this cross-coupling of the model substrates. The influence of the reaction temperature was also optimised. Increasing or reducing the reaction temperature from 130 °C led to a lower yield of **3a**.



Scheme 1 Palladium-catalysed synthesis of aryl phosphonates in PEG 600.

We then examined the reaction of representative aryl halides and diethyl phosphite under these optimised reaction conditions (5 mol% $Pd(PPh_3)_4$, Et_3N, PEG 600, 130 °C). The reaction proceeded efficiently with aryl iodides and gave the corresponding aryl phosphonates in high to excellent yields without the formation of any by-products (Table 2, entries 1–3). This method was found to be equally effective for conversion of aryl bromides with electron-withdrawing and electron-donating groups. Aryl halides having electron-withdrawing groups gave higher yields compared to those containing electron-donating groups. Steric hindrance had a negative influence on the reaction. The corresponding products were obtained in slightly lower yield and required longer reaction times when the substituent groups was present in the *ortho* position of the benzene ring. More importantly, aryl chlorides were successfully employed to afford the desired product with moderate to high yields. This procedure was also compatible with the presence of a variety of functional groups such as ester, ketone, aldehyde, nitro, dialkylamine, amides, and hydroxy in the substrates.

In summary, we have successfully developed a convenient protocol for the synthesis of aryl phosphonates by the cross-coupling of aryl halides and diethyl phosphite using a catalytic system that employs $Pd(PPh_3)_4$ along with triethylamine as the base in PEG 600. The operational simplicity, and the use of commercially available $Pd(PPh_3)_4$ with no need for any other ligands, and the wide range of substrates make this approach a useful as an alternative to the existing synthetic methodologies.

Experimental

All chemicals were purchased and used without further purification. Melting points were determined on an X-4 apparatus and are uncorrected. IR spectra were recorded using a Bruker-TENSOR 27 spectrophotometer. NMR spectra were taken with a Bruker DRX-500 spectrometer at 500 MHz (^1H), 125 MHz (^{13}C) and 201 MHz (^{31}P) using $CDCl_3$ as the solvent with TMS as internal standard. Elemental analyses were obtained on a Vario EL III CHNOS elemental analyser.

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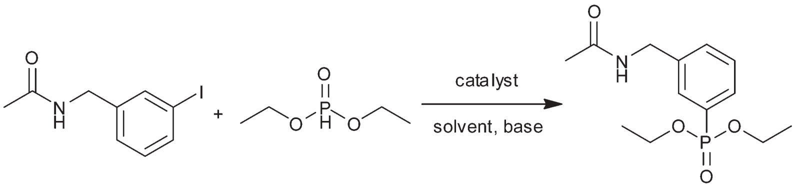
Table 1 Effect of reaction parameters on the synthesis of diethyl (3-(acetamidomethyl)phenyl)phosphonate (**3a**)[a]



Entry	Catalyst	Solvent	Base	Temperature /°C	Time/h	Yield/%[b]
1	CuI	PEG 600	Et_3N	130	45	15
2	$Pd(OAc)_2$	PEG 600	Et_3N	130	17	60
3	$Pd(PPh_3)_2Cl_2$	PEG 600	Et_3N	130	40	62
4	$Pd(PPh_3)_4$	PEG 600	Et_3N	130	15	95
5	$Pd(PPh_3)_4$	THF	Et_3N	Reflux	20	35
6	$Pd(PPh_3)_4$	DMF	Et_3N	Reflux	19	74
7	$Pd(PPh_3)_4$	1,4-dioxane	Et_3N	Reflux	20	25
8	$Pd(PPh_3)_4$	EtOH	Et_3N	Reflux	23	39
9	$Pd(PPh_3)_4$	MeCN	Et_3N	Reflux	27	56
10	$Pd(PPh_3)_4$	CH_2Cl_2	Et_3N	Reflux	26	68
11	$Pd(PPh_3)_4$	toluene	Et_3N	Reflux	25	45
12	$Pd(PPh_3)_4$	PEG 600	Na_2CO_3	130	22	60
13	$Pd(PPh_3)_4$	PEG 600	K_2CO_3	130	22	15
14	$Pd(PPh_3)_4$	PEG 600	NaF	130	21	Trace
15	$Pd(PPh_3)_4$	PEG 600	NaOAc	130	22	25
16	$Pd(PPh_3)_4$	PEG 600	KOAc	130	22	15
17	$Pd(PPh_3)_4$	PEG 600	KOH	130	23	10
18	$Pd(PPh_3)_4$	PEG 600	NaOH	130	23	13
19	$Pd(PPh_3)_4$	PEG 600	$NaHCO_3$	130	21	16
20	$Pd(PPh_3)_4$	PEG 600	DMAP	130	23	5
21	no	PEG 600	Et_3N	130	45	Trace
22[c]	$Pd(PPh_3)_4$	PEG 600	Et_3N	130	15	71
23[d]	$Pd(PPh_3)_4$	PEG 600	Et_3N	130	15	95
24	$Pd(PPh_3)_4$	PEG 600	Et_3N	110	15	73
25	$Pd(PPh_3)_4$	PEG 600	Et_3N	120	15	80
26	$Pd(PPh_3)_4$	PEG 600	Et_3N	140	15	85

[a] Reaction conditions: *N*-(3-iodobenzyl)acetamide (1 mmol), diethyl phosphite (1.5 mmol), base (4.0 mmol), catalyst (0.05 mmol), solvent (5 mL).
[b] Isolated yields.
[c] Reaction was performed using 2 mol % catalyst.
[d] Reaction was performed using 10 mol % catalyst.

Table 2 Synthesis of aryl phosphonates

Entry	Aryl halide	Product	Time/h	Yield/%[a]	M.p./°C
1	$3\text{-}CH_3CONHCH_2C_6H_4I$	**3a**	15	95	Oil
2	$2\text{-}CH_3OOCC_6H_4I$	**3b**	16	86	Oil[33]
3	$3\text{-}CH_3COOC_6H_4I$	**3c**	15	93	Oil[33]
4	C_6H_5Br	**3d**	15	83	Oil[14]
5	$2\text{-}CH_3C_6H_4Br$	**3e**	16	65	Oil[14]
6	$4\text{-}CH_3C_6H_4Br$	**3f**	16	81	Oil[14]
7	$3\text{-}OHC_6H_4Br$	**3g**	20	76	68–70 (67–69)[34]
8	$4\text{-}OHC_6H_4Br$	**3h**	18	78	95–96 (93–94)[34]
9	$3\text{-}NH_2C_6H_4Br$	**3i**	18	80	49–50 (47–50)[34]
10	$4\text{-}NH_2C_6H_4Br$	**3j**	20	78	117–118 (115–119)[34]
11	$3\text{-}NO_2C_6H_4Br$	**3k**	15	83	Oil[34]
12	$4\text{-}NO_2C_6H_4Br$	**3l**	15	85	Oil[34]
13	$4\text{-}AcC_6H_4Br$	**3m**	15	90	Oil[15]
14	$4\text{-}CH_3OOCC_6H_4Br$	**3n**	20	85	Oil[14]
15	$2\text{-}BrC_6H_4CHO$	**3o**	25	72	Oil[35]
16	$3\text{-}BrC_6H_4CHO$	**3p**	25	82	Oil[36]
17	$4\text{-}BrC_6H_4CHO$	**3q**	21	88	Oil[33]
18	$4\text{-}CH_3CONHC_6H_4Cl$	**3r**	21	61	Oil[8]
19	$4\text{-}CNC_6H_4Cl$	**3s**	20	70	32–33 (30–32)[8]
20	$3\text{-}NO_2C_6H_4Cl$	**3t**	23	68	Oil[12]
21	$4\text{-}NO_2C_6H_4Cl$	**3k**	20	73	Oil[12]
22	$4\text{-}AcC_6H_4Cl$	**3l**	20	70	Oil[15]
23	$4\text{-}CH_3OOCC_6H_4Cl$	**3m**	20	72	Oil[14]
24	$2\text{-}ClC_6H_4CHO$	**3n**	25	60	Oil[35]
25	$3\text{-}ClC_6H_4CHO$	**3o**	25	65	Oil[36]
26	$4\text{-}ClC_6H_4CHO$	**3p**	21	79	Oil[33]

[a] Isolated yields.

Synthesis of aryl phosphonates; typical procedure

A mixture of *N*-(3-iodobenzyl)acetamide (1 mmol), diethyl phosphite (1.5 mmol), triethylamine (4.0 mmol), and Pd(PPh$_3$)$_4$ (0.05 mmol) in PEG 600 (5 mL) was stirred in an oil bath at 130 °C for an appropriate time under the nitrogen. The progress of the reaction was followed by TLC. After the completion of the reaction, the resulting mixture was cooled to room temperature and extracted with diethyl ether (10 mL). The ether layer was washed with brine, and then dried with anhydrous Na$_2$SO$_4$. The solvent was removed *in vacuo*, and the crude reaction mixture was purified by chromatography on silica gel to give pure diethyl (3-(acetamidomethyl)phenyl)phosphonate (**3a**): Oil; IR (KBr): 3280, 2981, 2362, 1651, 1558, 1423, 1238, 968, 788, 567 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): 1.30 (t, J = 7.0 Hz, 6H, CH$_3$), 2.02 (s, 3H, CH$_3$), 4.02–4.14 (m, 4H), 4.44 (d, J = 5.5 Hz, 2H), 6.23 (br s, 1H), 7.39–7.43 (m, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.64–7.67 (m, 1H), 7.69 (d, J = 7.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): 16.2 (d, $^{3}J_{\text{c-p}}$ = 6.4 Hz), 22.9, 42.9, 62.2 (d, $^{2}J_{\text{c-p}}$ = 15.6 Hz), 128.2 (d, $^{1}J_{\text{c-p}}$ = 187.0 Hz), 128.8 (d, $^{2}J_{\text{c-p}}$ = 15.5 Hz), 130.3 (d, $^{3}J_{\text{c-p}}$ = 9.4 Hz), 130.6 (d, $^{3}J_{\text{c-p}}$ = 10.6 Hz), 131.8 (d, $^{4}J_{\text{c-p}}$ = 3.1 Hz), 139.4 (d, $^{2}J_{\text{c-p}}$ = 14.5 Hz), 170.6 ppm; ^{31}P NMR (201 MHz, CDCl$_3$): 18.9 ppm; Anal. Calcd.for C$_{13}$H$_{20}$NO$_4$P: C, 54.73; H, 7.07; N, 4.91. Found: C, 54.65; H, 6.89; N, 5.10%.

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