Tetrahedron Letters 55 (2014) 6791–6794

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of α-aryl-diazophosphonates via palladium-catalyzed cross-coupling of aryl iodides with diethyl diazomethylphosphonate

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A R T I C L E I N F O

Article history:
Received 25 June 2014
Revised 19 September 2014
Accepted 8 October 2014
Available online 17 October 2014

Keywords:
Diazo compounds
Phosphonates
Cross-coupling
Palladium catalysis
Phosphorylated compounds

A B S T R A C T

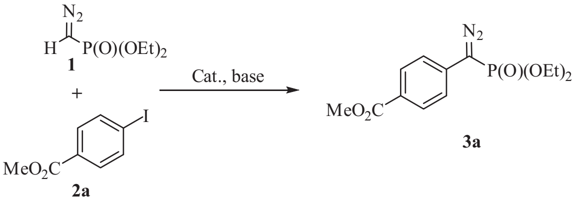
An efficient procedure for the Pd-catalyzed arylation of diethyl α-diazomethylphosphonate with aryl iodides is described. It can serve as a pathway for the generation of arylated diazophosphonates, which are typically difficult to access. The significance of this methodology was demonstrated via further synthetic transformations of newly synthesized diazo compounds in cyclopropanation, epoxidation, N–H and O–H insertion reactions.

Transition-metal-catalyzed transformations of α-diazo compounds have become a standard method in organic synthesis. They are traditionally used for carbene generation in reactions such as X–H insertion (X = C, N, O, S), cyclopropanation, cycloaddition to nitriles and carbonyl compounds, and amongst other reactions.[1,2] Despite the fact that α-diazophosphonates have received less attention in organic synthesis than diazocarboxylates, they are widely used for the preparation of different derivatives of phosphonic acids, such as cyclopropanes,[3] aziridines,[4] phosphonoketones,[5] aminophosphonates,[6] and α,β-unsaturated phosphonates.[7]

It is known that the diazocarbonyl species has considerable nucleophilicity and the hydrogen at the α-position can be successfully substituted with an electrophile using the Arndt–Eistert reaction.[8] Moreover, ethyl diazoacetate has been utilized for the $Pd(PPh_3)_4$-catalyzed cross-coupling with vinyl- and aryl iodides with retention of the diazo function.[9] Having in mind this procedure, we have modified it in order to explore more readily available and inexpensive palladium catalysts, and have applied it for the synthesis of diazophosphonates.

The coupling of methyl 4-iodobenzoate (**2a**) with diethyl diazomethylphosphonate (**1**) was selected as a model reaction (Scheme 1, Table 1).

Screening of catalytic systems, solvents, and bases revealed that application of the zero-valent palladium catalyst $Pd_2(dba)_3$ led to rapid decomposition of the diazo compound (Table 1, entry 1).



Scheme 1.

Despite the fact, that $Pd(PPh_3)_4$ gave a slightly better yield than $PdCl_2(PPh_3)_2$ [45% vs 36% (entries 2 and 3)], the latter was chosen for further exploration because this palladium complex is regarded as being much cheaper and easy to handle.

The reaction was more favored in acetonitrile than in the other tested solvents. DBU appeared to be the best base for this coupling, whereas other bases such as triethylamine, pyridine, and inorganic bases were found to be ineffective (entries 8–11). It was found that one equivalent of DBU was insufficient for complete conversion. The use of two equivalents of DBU relative to ArI increased the yield of **3a** two-fold (entry 12). Formic acid was used as a reducing agent to generate a Pd(0) species and its amount appeared to be highly important for product yield. When 10 mol % of HCO_2H was used, **3a** was formed in only 65% yield, whereas the application of 70 mol % resulted in a significant increase in the amount of product (entry 14). Finally it was found that the most favorable temperature was 45 °C; under these conditions the isolated yield of **3a** reached 95%. Other temperatures resulted in reduced yields of **3a**.

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http://dx.doi.org/10.1016/j.tetlet.2014.10.048

Table 1
Yield of the hydroarylation product **2a** produced via Scheme 1[a]

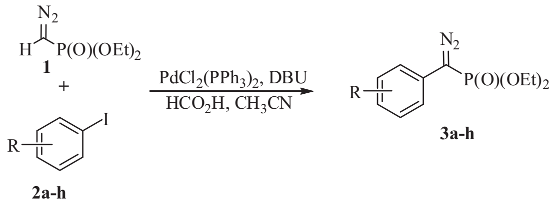
Entry	Catalyst (mol %)	Additive (mol%)	Base	Solvent	Yield (%)
1	$Pd_2(dba)_3$ (5)	PPh_3 (10)	DBU	CH_3CN	0
2	$Pd(PPh_3)_4$ (5)	–	DBU	CH_3CN	45
3	$Pd(PPh_3)_2Cl_2$ (10)	HCO_2H (10)	DBU	CH_3CN	36
4	$Pd(PPh_3)_2Cl_2$ (10)	HCO_2H (10)	DBU	Benzene	25
5	$Pd(PPh_3)_2Cl_2$ (10)	HCO_2H (10)	DBU	Acetone	0
6	$Pd(PPh_3)_2Cl_2$ (10)	HCO_2H (10)	DBU	DMF	10
7	$Pd(PPh_3)_2Cl_2$ (10)	HCO_2H (10)	DBU	CH_2Cl_2	30
8	$Pd(PPh_3)_2Cl_2$ (10)	HCO_2H (10)	Et_3N	CH_3CN	5
9	$Pd(PPh_3)_2Cl_2$ (10)	HCO_2H (10)	Pyridine	CH_3CN	0
10	$Pd(PPh_3)_2Cl_2$ (10)	HCO_2H (10)	K_2CO_3	CH_3CN	Trace
11	$Pd(PPh_3)_2Cl_2$ (10)	HCO_2H (10)	Cs_2CO_3	CH_3CN	Trace
12	$Pd(PPh_3)_2Cl_2$ (10)	HCO_2H (10)	DBU[b]	CH_3CN	65
13	$Pd(PPh_3)_2Cl_2$ (10)	HCO_2H (10)	DBU[b]	CH_3CN	73
14	$Pd(PPh_3)_2Cl_2$ (10)	HCO_2H (70)	DBU[b]	CH_3CN	86
15	$Pd(PPh_3)_2Cl_2$ (10)	HCO_2H (140)	DBU[b]	CH_3CN	15
16	**$Pd(PPh_3)_2Cl_2$ (10)**	**HCO_2H (70)**	**DBU**[b,c]	**CH_3CN**	**95**

Bold indicates the best reaction conditions.
[a] Reaction conditions: **2a** (1 mmol); **1** (1.5 mmol); base (1 mmol), Pd catalyst, 40 °C.
[b] 2 mmol of DBU used.
[c] Reaction at 45 °C.

Various aryl iodides were subjected to three-component arylation under the optimized reaction conditions[10] (Scheme 2). The scope of the method was examined by varying the substituents on the iodides (Table 2). A significant influence from the electronic effects was observed. In the case of aryl iodides containing electron-withdrawing groups, the reaction proceeded smoothly giving high yields (up to 95%) (Table 2, entries 1–5). Good yields were also obtained in the cases with unsubstituted phenyl or arenes containing weak electron-donating groups (entries 6 and 7), however, the *p*-MeO-substituted substrate gave an unsatisfactory yield (entry 8). The reaction was not affected significantly by steric hindrance from the substituents on the benzene ring, as confirmed by the production of diazophosphonate **3e**. Aryl bromides and aryl chlorides were ineffective in the presented cross-coupling.

The proposed mechanism for the hydroarylation is presented in Scheme 3. The palladium dichloride complex can be easily reduced by formic acid resulting in a Pd(0) species. The catalytic cycle starts with oxidative addition to form arylpalladium iodide complex **A**. Then coordination of diazo compound to this complex generates the complex **B**. Base-assisted removal of HI affords the intermediate **C**. Finally, reductive elimination provides the aryl-diazoacetate product with simultaneous regeneration of the Pd(0) species.

The arylation of diazomethylphosphonate reported in this work represents a simple method for the preparation of a wide range of new diazophosphonates, which possess high synthetic potential in phosphorus-organic chemistry. Their synthetic utility was demonstrated via the preparation of a new family of phosphonate-containing substances starting from diazo compound **3c** (Scheme 4).

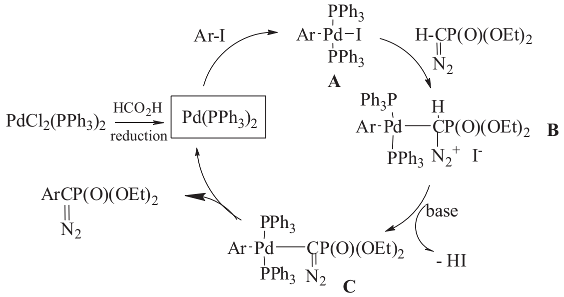


Scheme 2.

Table 2
Cross-coupling of aryl iodides with **1** via Scheme 2[a]

Entry	ArI	Product	Time (h)	Yield (%)[b]
1	*p*-MeO_2C-C_6H_4I	**3a**	1	95
2	*m*-MeO_2C-C_6H_4I	**3b**	2	75
3	*p*-O_2N-C_6H_4I	**3c**	0.5	94
4	*m*-O_2N-C_6H_4I	**3d**	2	76
5	*o*-O_2N-C_6H_4I	**3e**	1.5	70
6	PhI	**3f**	5	60
7	*m*-Me-C_6H_4I	**3g**	7	66
8	*p*-MeO-C_6H_4I	**3h**	12	25

[a] Reaction conditions: aryl iodide (1 mmol), **1** (1.5 mmol), base (2.5 mmol), HCO_2H (1.5 mmol), Pd catalyst (0.05 mmol), 80 °C.
[b] Isolated yield.



Scheme 3.

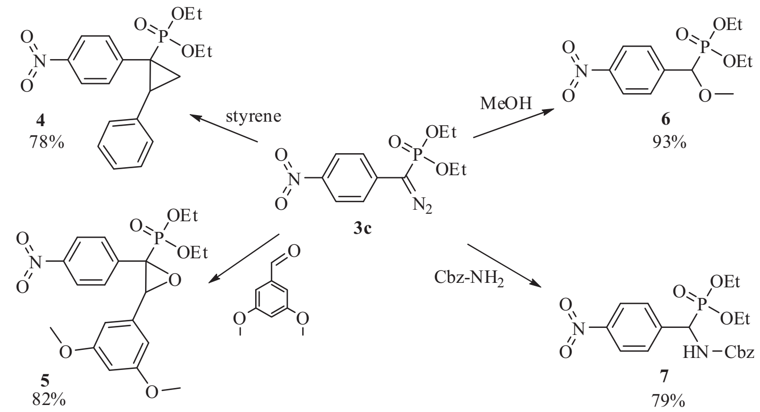
We found that 0.5 mol % of $Rh_2(OAc)_4$ catalyzed the cycloaddition of **3c** to styrene smoothly in DCE at 60 °C to furnish cyclopropane **4** in 78% yield after two hours. Compound **4** was isolated as a mixture of *Z*/*E* isomers (dr 3:97 *Z*/*E*), as determined by ^1H and ^{31}P NMR spectroscopy. The structure of product **4** was further confirmed by elemental analysis and from spectral data. The assignment of the relative configuration of **4** was deduced from the ^1H–^{31}P HOESY spectrum (Fig. 1).

NOE correlations were found for the phosphorus signal at 24.5 ppm and the two *cis*-configured protons of the cyclopropane ring of **4-major** (Fig. 2) at 2.8 ppm (C*H*Ar) and 1.8 ppm (CH_2, H_{cis}), respectively. This fact evidenced the proximity of these protons to the P atom indicating the *anti* configuration of the molecule (Fig. 1).

Addition of **3c** to 3,5-dimethoxybenzaldehyde afforded epoxide **5** in 82% yield under the same reaction conditions as described above. The epoxide is a somewhat unusual product of this transformation. It is well known that 1,3-dioxolanes are typically furnished as the main products resulting from the reaction of two molecules of an aldehyde with one fragment of a diazo compound under metal catalysis.[11]

A single diastereomer of epoxide **5** was detected by ^{31}P NMR spectroscopy and isolated by column chromatography. ^1H–^1H NOE correlations were found between the doublet of the epoxide proton (4.0 ppm) and signals *A* at 7.7 ppm and 8.2 ppm corresponding to the 4-nitrophenyl moiety (Fig. 3). Additionally, multiplet signals due to the OCH_2 protons of the diethoxyphosphoryl group (3.7–3.8 ppm, signal *B*) correlated with the signals at 6.8 ppm and 6.9 ppm corresponding to the aromatic protons in the 3,5-dimethoxyphenyl fragment (Fig. 3) The spatial proximity of these groups indicated the *syn* configuration of **5**.

Both OH- and NH-insertion reactions of metal carbenoid intermediates derived from their corresponding diazo compounds have found widespread use in the synthesis of biologically active compounds, including the construction of bicyclic β-lactams,



Scheme 4.

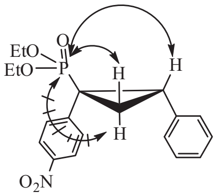


Figure 1. ^{1}H–^{31}P HOESY correlations of compound **4**.

amino and α-hydroxy acids, peptides, depsipeptides, etc. We examined the reactivity of diazophosphonate **3c** in such transformations under rhodium-catalyzed conditions. It was found that heating **3c** with methanol or benzyl carbamate in DCE in the presence of Rh$_2$(OAc)$_4$ afforded α-methoxyphosphonate **6** and aminophosphonate derivative **7**, respectively, in high yields.

In conclusion, we have reported an efficient procedure for the Pd-catalyzed arylation of diethyl α-diazomethylphosphonate with aryl iodides. The described reaction can serve as a pathway for the generation of difficult to access arylated diazophosphonates. The significance of this methodology was demonstrated via further synthetic transformations of the newly synthesized diazo compounds **3c** in cyclopropanation, epoxidation, and N–H and O–H insertion reactions.

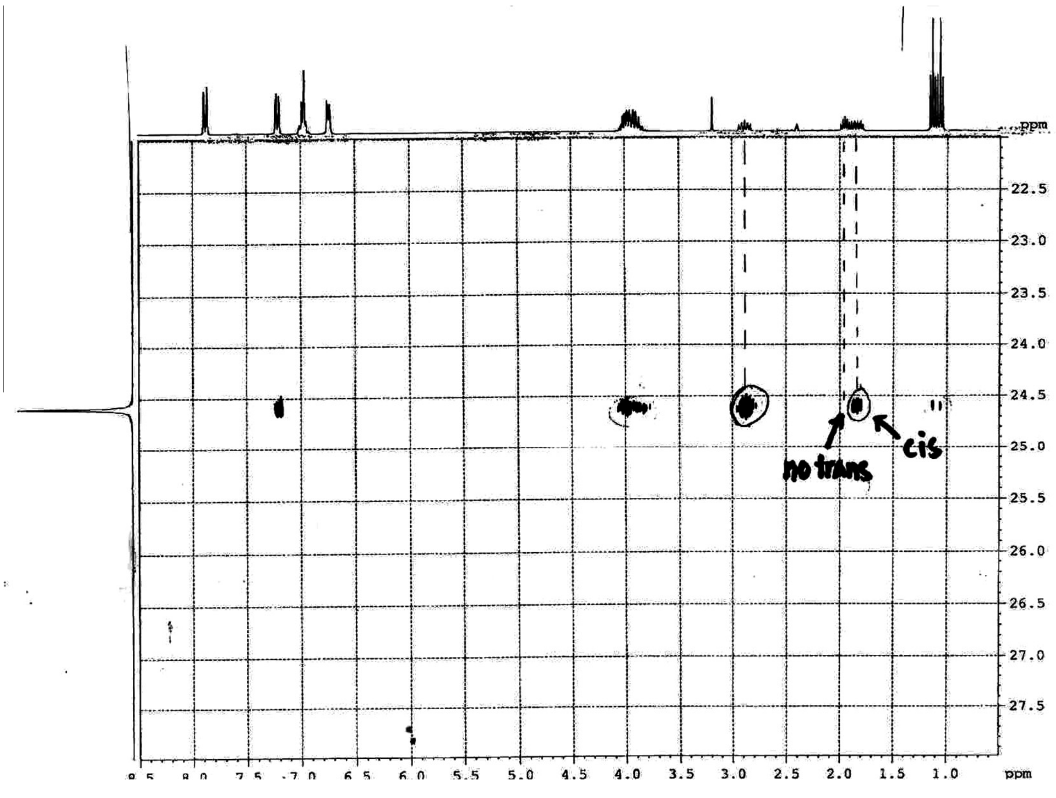


Figure 2. ^{1}H–^{31}P HOESY spectrum of compound **4**.

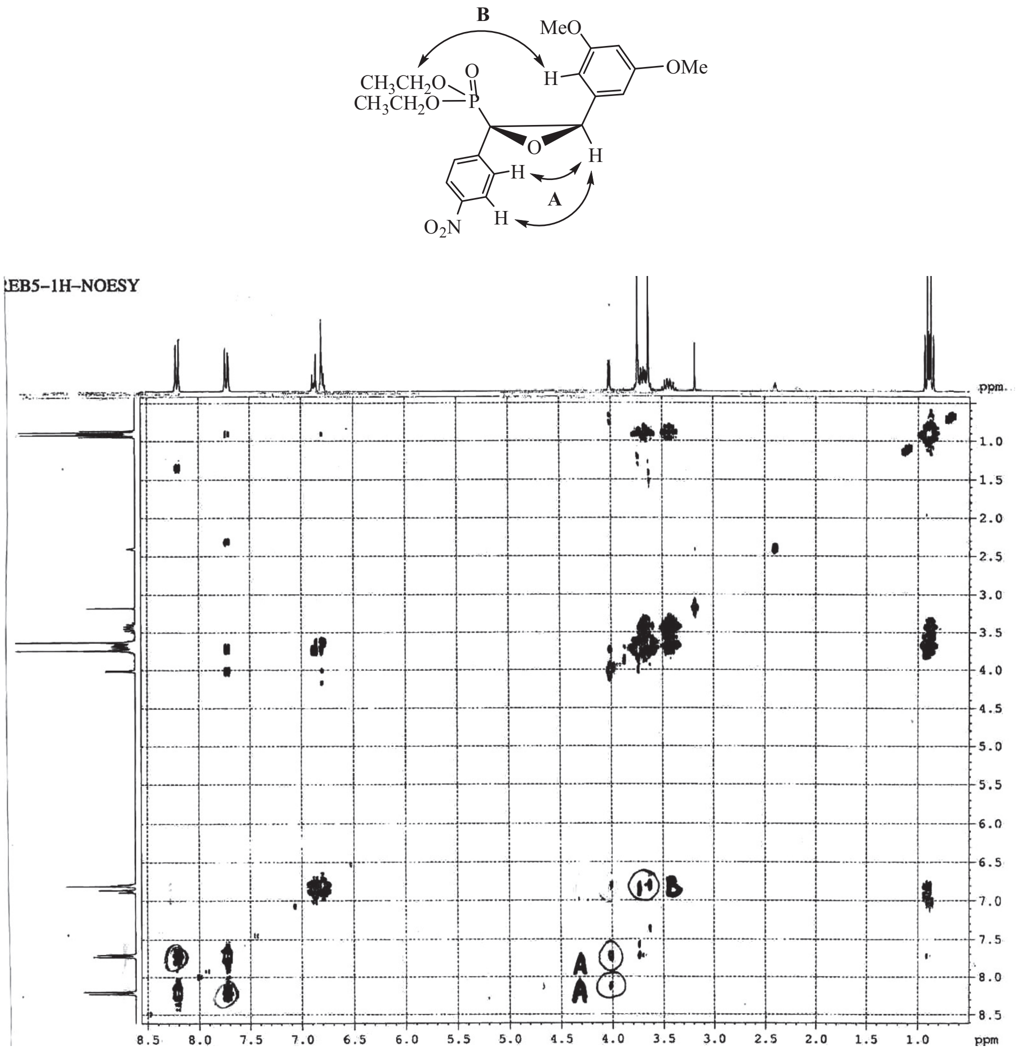


Figure 3. ^1H–^1H NOESY spectrum of compound **5**.

Acknowledgements

This work was supported by a Grant-in-Aid of the Russian Foundation for Basic Research and NFFD of Ukraine (No. 14-03-90404). The authors thank Dr. R. A. Novikov for his contribution in registration of NMR spectra.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.048.

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10. *Typical procedure for the Pd-catalyzed cross-coupling*: To a mixture of aryl iodide **2a–h** (1 mmol) and $PdCl_2(PPh_3)_2$ (36 mg, 0.05 mmol) in a Schlenk flask under an argon atmosphere DBU (304 mg, 2 mmol) and formic acid (32 mg, 0.7 mmol) in CH_3CN (10 mL) were added. The mixture was stirred and heated at 45 °C, then compound **1** (267 mg, 1.5 mmol) in CH_3CN (2 mL) was added in small portions over 10–20 min. The mixture was stirred at the same temperature until compound **2** had been consumed (monitored by TLC, the total heating time is indicated in Table 2). The solvent was evaporated in vacuo. Purification of the mixture by column chromatography (EtOAc/hexane, 1:1 v/v) gave pure product **3a–h**.
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