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An Efficient Palladium-Catalysed Coupling of Terminal Alkynes with Aryl Halides under Jeffery's Conditions

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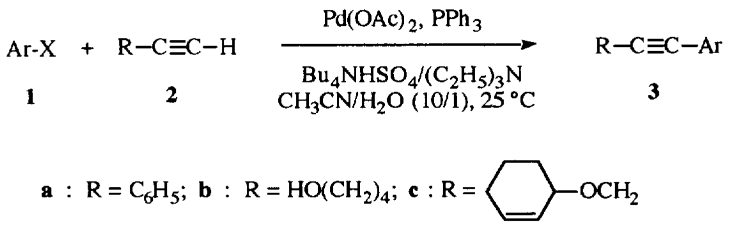
Abstract: Palladium-catalysed coupling of terminal alkynes with aryl halides occurs at room temperature in quite good yields in the presence of a quaternary ammonium salt and a base in a acetonitrile-water solution, without any added cuprous iodide. Copyright © 1996 Elsevier Science Ltd

Palladium-catalysed coupling of terminal acetylenes with organic halides is now widely used in organic synthesis.[1] Generally the reaction proceeds under mild conditions in the presence of copper iodide, in anhydrous organic solvents, involving the intermediate formation of a copper acetylide.[2] Recent developments in this type of reaction are directed towards the use of palladium-catalyst without the addition of cuprous iodide, although it is known terminal alkynes undergo an easy insertion reaction in the absence of cuprous iodide,[3] there are some examples of such coupling without cuprous iodide.If the early examples needed high temperatures,[4a-b] the use of piperidine or pyrrolidine as the base and $Pd(PPh_3)_4$ as the catalyst[4c] or of palladium complexes containing water-soluble ligands such as tppts (or triphenylphosphinotrisulfonate sodium salt) in a mixture of acetonitrile na water[5] allowed the reaction to occur without addition of cuprous iodide. The recent report of Beletskaya *et al.*[6] about the catalytic coupling of terminal acetylenes with iodoarenes and diaryliodonium salts in aqueous K_2CO_3 under very mild conditions using $PdCl_2(PPh_3)_2$ and CuI as catalyst prompts us to report that aryl or vinyl halides react very rapidly at room temperature with terminal alkynes *without addition of cuprous iodide* to give high yields of enynes and arylacetylenes using $Pd(OAc)_2$ and PPh_3 in the presence of a base and a phase transfer reagent, the so-called Jeffery's conditions.[7]



$$\underset{\mathbf{1}}{\text{Ar-X}} + \underset{\mathbf{2}}{\text{R}-\text{C}\equiv\text{C}-\text{H}} \xrightarrow[\text{Bu}_4\text{NHSO}_4/(\text{C}_2\text{H}_5)_3\text{N}\;\; \text{CH}_3\text{CN/H}_2\text{O (10/1), 25 °C}]{\text{Pd(OAc)}_2,\ \text{PPh}_3} \underset{\mathbf{3}}{\text{R}-\text{C}\equiv\text{C}-\text{Ar}}$$

a : R = C_6H_5; **b** : R = $HO(CH_2)_4$; **c** : R = $-OCH_2$

Scheme 1

Investigation of the coupling reaction between phenyl iodide **1** and phenylacetylene **2a** (Scheme 1; Table 1) in the presence of a catalytic amount of palladium acetate and triphenylphosphine in acetonitrile-water (10/1) in the presence of a combination of ammonium salt and potassium carbonate or triethylamine has shown that the reaction occurred very efficiently even at room temperature ***without added CuI***, the most efficient base being sodium carbonate. The reaction was complete in less than 2 h. It has to be noticed that the coupling reaction occurred even in the absence of added ammonium salt (entry 5), although the reaction rate was slower. Due to some solubility problems, we used for the next experiments the combination NEt_3/Bu_4NHSO_4.

Table 1. Influence of Additives on the Efficiency of the Reaction of C_6H_5I with $C_6H_5C{\equiv}CH$.[a]

Entry	Added salt	Base	Time (h)	Yield (%)[b]
1	Bu_4NHSO_4	Et_3N	1.5	89
2	Bu_4NHSO_4	Na_2CO_3	0.75	78
3	Bu_4NBr	Et_3N	1.25	86
4	Bu_4NBr	Na_2CO_3	0.5	79
5	none	Et_3N	2.0	83

[a] $[C_6H_5I]$:[**2a**]:$[Pd(OAc)_2]$:$[PPh_3]$:[base]:[salt] = 20:10:1:2:25:10; CH_3CN-H_2O (10:1); 25 °C.

[b] Isolated yields of pure compouds.

Table 2. Reaction of Ar-X **1** with Various Alkynes **2**.[a]

Entry	Ar-X	Alkyne	Time (h)	Yield of **3** (%)[b]
1	C_6H_5I	**2a**	1.5	89
2	*p*-$O_2NC_6H_4Br$	**2a**	1.25	69
3			2.0[c]	70
4	*p*-$CH_3OC_6H_4Br$	**2a**	3.0	62
5			4.0[c]	66
6	2-BrC_5H_4N	**2a**	2.5	70
7	2-BrC_4H_3S	**2a**	1.5	82
8	C_6H_5I	**2b**	1.5	92
9	*p*-$O_2NC_6H_4Br$	**2b**	1.5	86
10	*p*-$CH_3OC_6H_4Br$	**2b**	3.0	81
11	C_6H_5I	**2c**	1.0	88
12	*p*-$O_2NC_6H_4Br$	**2c**	1.25	82
13	*p*-$CH_3OC_6H_4Br$	**2c**	3.0	73

[a] [ArX]:[**2**]:$[Pd(OAc)_2]$:$[PPh_3]$:$[Et_3N]$:$[Bu_4NHSO_4]$ = 20:10:1:2:25:10; CH_3CN-H_2O (10:1); 25 °C.

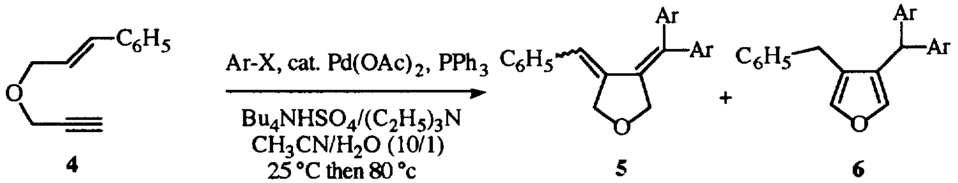
[b] Isolated yields of pure compouds.

[c] [ArX]:[**2**]:$[Pd(OAc)_2]$:$[PPh_3]$:$[Et_3N]$:$[Bu_4NHSO_4]$ = 50:25:1:2:25:62.5.

We examined then the coupling reaction of various haloarenes with different acetylenic compounds under these conditions (Table 2). The coupling products were obtained with quite good yields; however a noticeable difference in reactivity was observed using bromoarenes with an electron-donating group or an electron-withdrawing group (compare entries 2 and 4, 9 and 10, 12 and 13). Heterocyclic bromides such as bromopyridine or bromothiophene never poisoned the palladium catalyst, the coupled products being isolated in high yields. These transformations occurred also using a smaller amount of palladium as the catalyst (2.5 % *vs* 10 %), although the reaction times were slightly higher for the completion of the reaction (entries 3 and 5).

It should be noticed that in the case of compound **2c**, only coupling at the acetylenic carbon atom occured under these conditions (entries 11-13).

These results prompt us to apply these conditions in a cascade reaction (Scheme 2). Reaction of the acetylenic compound **4** in the presence of an excess of an aryl halide **2** at room temperature gave the coupling product which was not isolated. An increase of the reaction temperature to 80 °C gave, as expected, the product of cyclisation **5**, resulting from an intermolecular Heck reaction followed by the cyclisation of the intermediate σ-complex. This product, which is a mixture of *(E)* and *(Z)* stereomers (approximatively 1/1), was sometimes contaminated by product **6** resulting from the aromatisation of compound **5**, for longer reaction times.



Ar-X	Time (h)	Yield (%)	
C_6H_5-I	15	46	
p-$O_2NC_6H_4Br$	40	36	24
p-$CH_3OC_6H_4Br$	24	53	

Scheme 2

In conclusion, these results show clearly that aryl halides are efficiently coupled with terminal alkynes in a water-acetonitrile mixture under Jeffery'conditions, ***without any addition of CuI***. Under these conditions, the sequence "Sonogashira reaction, Heck reaction and cyclisation" occured in a one-pot. Further studies and particularly the sequential one-pot introduction of various substituted aryl halides are in progress in our laboratory.

Typical Experimental Procedure : A solution of $Pd(OAc)_2$ (44.5 mg, 0.2 mmol) and PPh_3 (104.9 mg, 0.4 mmol) in 5 mL of H_2O-CH_3CN (1/10) in a Schlenk tube under nitrogen was added to a well-stirred mixture of the alkyne (2 mmol), the halide (4 mmol), Et_3N (700 µL, 5 mmol) and Bu_4NHSO_4 (645 mg, 2 mmol) in 5 mL of H_2O-CH_3CN (1/10). Stirring was continued at room temperature until the disparition of the starting alkyne (observed by TLC). The mixture was then hydrolysed by 10 mL H_2O and extracted with 3x30 mL diethyl ether. Removing of the solvent *in vacuo* followed by column chromatography gave the expected product.

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