

Improvements in the synthesis of terminal alkynes via coupling of arylbromides with 2-methylbut-3-yn-2-ol

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Abstract

The palladium/copper (Pd/Cu)-catalyzed cross-coupling of bromobenzene and 2-methylbut-3-yn-2-ol has been investigated to ascertain the factors influencing the reaction rate. Most usefully, the reaction is carried out using Pd(acetate)₂ as catalyst precursor in combination with PPh₃ and a copper salt. A primary or a cyclic amine is best suited as the reaction solvent. Under these conditions, substrate to palladium ratios of 2000 can be used. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Arylacetylenes; Cross-coupling; Aryl bromides; Palladium/copper catalysts

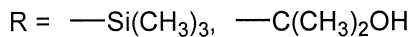
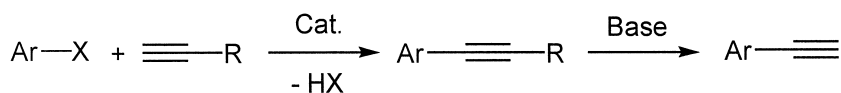
1. Introduction

The palladium/copper (Pd/Cu)-catalyzed cross-coupling of 1-alkynes with aryl halides is one of the most powerful synthetic methods to prepare internal arylacetylenes and their derivatives [1–3]. This procedure can be modified to prepare terminal arylacetylenes by using trimethylsilylacetylene [4] or 2-methylbut-3-yn-2-ol [5] as protected acetylenes (Scheme 1).

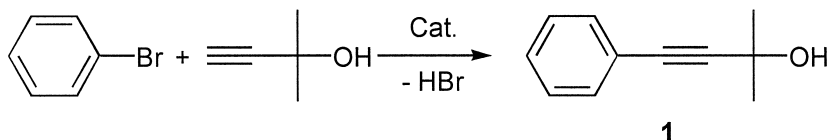
The reaction is usually carried out in the presence of 1–5 mol% of PdCl₂(PPh₃)₂ promoted with copper (I) iodide. An aliphatic amine is used as the solvent and as HX scavenger.

Moreover, a number of different modifications of this procedure have been developed. For example, the reaction has been carried out in the presence of the catalytic system, Pd(CH₃-COO)₂/PPh₃ [6], without copper-based promoters. Alternatively, Pd(PPh₃)₄, either in the presence of Cu₂Br₂ [7] or in the absence of copper salts [8], has been employed as catalyst. Recently, Herrmann et al. have reported the use of some phospho-palladacycles [9] and palladium-carbene complexes [10] which catalyse the reaction in the absence of copper salts. Finally, it should be mentioned that the reaction can be carried out in water using either a Pd/C–CuI–K₂CO₃ catalytic system [11] or a homogeneous system prepared from Pd(0) [12] or Pd(II) [13] and sulphonated triphenylphosphine.

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Scheme 1.



Scheme 2.

Since we are engaged in a project aimed at the synthesis of fine chemicals via carbonylation of terminal alkynes [14,15], we need a procedure for the synthesis of 1-alkynes not resorting to sophisticated or air-sensitive catalysts. Therefore, we have investigated the title cross-coupling reaction to ascertain the role played by the components of the catalytic system and to enhance the productivity of the reaction still maintaining the original simple catalyst preparation and formulation.

2. Results and discussion

For our investigations, we chose as model reaction the coupling of bromobenzene with 2-methylbut-3-yn-2-ol which yields 2-hydroxy-2-methyl-4-phenylbut-3-yne (**1**) (Scheme 2).

Our attention was first given to the role played by the palladium complex used to formulate the catalytic system. The results obtained with some Pd(II) and Pd(0) catalyst precursors are reported in Table 1.

From the data of Table 1, it appears that among the Pd(II) species, the most effective is Pd(CH₃COO)₂ when used in the presence of three equivalents of PPh₃. Pd(PPh₃)₄ is the most effective among the Pd(0)-based catalysts. The fact, that Pd(PPh₃)₄ and Pd(CH₃COO)₂/PPh₃ display an almost equal catalytic activity,

is not surprising since it is well-known that Pd(CH₃COO)₂ in the presence of triphenylphosphine and protic solvents affords Pd(0) species [16,17]. In this connection, the low activity observed when the catalytic experiments are carried out in the presence of oxygen is easily accounted for. Much more surprising is the difference in catalytic activity displayed by Pd(PPh₃)₄ and the system, Pd₂(dba)₃/PPh₃ (dba = dibenzylideneacetone) (Table 1).

Even if the catalytic activities of Pd(PPh₃)₄ and Pd(CH₃COO)₂ are practically equivalent, in our opinion, the employment of latter species offers two distinct advantages: (i) it is not an air-sensitive species with an endless shelf-life; (ii) it allows a simple way to a fine-tuning of

Table 1

Influence of the catalyst

Bromobenzene 5.0 mmol, 2-methylbut-3-yn-2-ol 5.0 mmol, CuI 0.05 mmol, Pd 0.025 mmol, substrate/Pd = 200, diethylamine 10 ml, T 55°C, reaction time 3 h.

Entry	Catalyst	PPh ₃ (mmol)	1 yield (%)
1	PdCl ₂ (PPh ₃) ₂	0	37
2	PdCl ₂ (PPh ₃) ₂	0.025	40
3	Pd(CH ₃ COO) ₂	0	4 ^a
4	Pd(CH ₃ COO) ₂	0.075	72
5	Pd(CH ₃ COO) ₂	0.075	31 ^b
6	Pd ₂ (dba) ₃	0.050	36
7	Pd ₂ (dba) ₃	0.075	41
8	Pd(PPh ₃) ₄	0	69
9	Pd/C	0.075	4

^aReaction time 6 h.

^bReaction carried out in the presence of O₂.

Table 2

Influence of the phosphine

Bromobenzene 5.0 mmol, 2-methylbut-3-yn-2-ol 5.0 mmol, Pd(CH₃COO)₂ 0.025 mmol, Pd/P 1/3 ratio, CuI 0.05 mmol, substrate/palladium = 200, diethylamine 10 ml, T 55°C.

Entry	Phosphine	1 yield at 6 h (%)	1 yield at 16 h (%)
1	triphenylphosphine (PPh ₃)	80	92
2	tri- <i>n</i> -butylphosphine (PBU ₃)	16	34
3	(2-pyridyl)diphenylphosphine [P(2-Py)Ph ₂]	32	52
4	1,3-bis(diphenylphosphino)propane (DPPP)	38	67
5	1,4-bis(diphenylphosphino)butane (DPPB)	44	73

the catalytic activity by choosing the nature of the phosphorous ligand. Accordingly, Table 2 shows the results obtained with some different phosphines. The data, achieved at two different reaction times, indicate that the most effective ligand is PPh₃. A more basic ligand such as P(*n*-C₄H₉)₃ gives a lower reaction rate. Chelating P–P and P–N ligands also result to be less effective (entries 3–5).

Table 3

Influence of the cocatalyst

Bromobenzene 5.0 mmol, 2-methylbut-3-yn-2-ol 5.0 mmol, cocatalyst 0.05 mmol, Pd(CH₃COO)₂ 0.025 mmol, PPh₃ 0.075 mmol, substrate/Pd = 200, diethylamine 10 ml, T 55°C, reaction time 3 h.

Entry	Cocatalyst	1 yield (%)
1	none	5
2	CuI	72
3	NaI	4
4	CuBr	74
5	CuCl	75
6	CuCl ₂ · 2H ₂ O	74
7	Cu(CH ₃ COO) ₂ · H ₂ O	76

Table 4

Influence of the amount of cocatalyst

Bromobenzene 5.0 mmol, 2-methylbut-3-yn-2-ol 5.0 mmol, Pd(CH₃COO)₂ 0.025 mmol, PPh₃ 0.075 mmol, substrate/Pd = 200, diethylamine 10 ml, T 55°C, Reaction time 6 h.

Entry	CuI (mmol)	1 yield (%)
1	0	12
2	0.05	80
3	0.10	74
4	0.15	24

The data in Table 3 indicate that the presence of a copper salt is necessary in order to observe high reaction rates. NaI was used to test the effect of a simple salt not containing copper. Surprisingly, it appears that neither the nature of the copper salt nor its oxidation state influences the catalytic activity. It is interesting to note that the use of anhydrous salts is unnecessary.

Table 5

Influence of the amine

Bromobenzene 5.0 mmol, 2-methylbut-3-yn-2-ol 5.0 mmol, Pd(CH₃COO)₂ 0.025 mmol, PPh₃ 0.075 mmol, substrate/Pd = 200, CuI 0.05 mmol, amine 10 ml, T 55°C, reaction time 1 h.

Entry	Amine	pK _b	1 yield (%)
1	di- <i>iso</i> -propylamine	1.95	20
2	diethylamine	3.02	29
3	triethylamine	3.24	7
4	<i>n</i> -butylamine	3.39	90
5	benzylamine	4.63	61
6	aniline	9.42	0
7	piperidine	2.79	87
8	pyrrolidine	2.89	84

Table 6

Influence of the reaction time

Bromobenzene 25.0 mmol, 2-methylbut-3-yn-2-ol 25.0 mmol, CuI 0.025 mmol, Pd(CH₃COO)₂ 0.0125 mmol, PPh₃ 0.0375 mmol, substrate/Pd = 2000, *n*-butylamine 50 ml, T 78°C.

Entry	Reaction time (h)	1 yield (%)
1	1	37
2	3	65
3	6	78
4	12	90
5	24	99

Table 7

Influence of the amount of phosphine

Bromobenzene 25.0 mmol, 2-methylbut-3-yn-2-ol 25.0 mmol, CuI 0.025 mmol, Pd(CH₃COO)₂ 0.0125 mmol, substrate/Pd = 2000, *n*-butylamine 50 ml, *T* 78°C, reaction time 1 h.

Entry	PPh ₃ /Pd	1 yield (%)
1	1	7
2	2	25
3	3	37
4	4	30
5	10	13

The data obtained using different Cu/Pd molar ratios are collected in Table 4; the highest activity is obtained using a 2/1 ratio.

Usually the reaction is carried out in an amine that serves both as solvent and as scavenger of HBr. The results of experiments carried out with a number of different amines are collected in Table 5. In order to obtain comparable data, these investigations were carried out at the boiling point of diethylamine (55°C).

It appears that the nature of the amine plays a very important role in determining the reaction rate. A sum of electronic and steric factors seems to be operative. As a matter of fact, the highest rates are achieved using basic no sterically demanding amines, i.e., primary aliphatic amines as *n*-butylamine. We have no rationalisation for the very good reaction rates obtained using cyclic amines such as pyrrolidine and piperidine.

Amines, having higher boiling points, allow to favourably increase the reaction temperature. Thus, in an experiment carried out in refluxing

n-butylamine (78°C) using a bromobenzene/Pd ratio of 200, the substrate conversion was 95% in 1 h and complete in 3 h. Under these conditions, the catalytic system properly works even with bromobenzene/Pd ratios as high as 2000 providing 78% of substrate conversion in 6 h, and total conversion in 24 h (Table 6).

Unfortunately, at higher substrate/Pd ratios, the reaction rate decays; e.g., an experiment carried out in boiling *n*-butylamine using bromobenzene/Pd = 5000 yields only 32% of 1 in 72 h.

Table 7 shows the results obtained using variable triphenylphosphine/palladium ratios.

The best results are obtained using a P/Pd ratio of 3; the use of lower or greater amounts of phosphine leads to a decrease in the reaction rate. It is interesting to note that while using a P/Pd ≤ 4, the reaction mixture is yellow, at P/Pd ratios greater than 4, the reaction mixture becomes colourless. This finding suggests that at higher P/Pd ratios, some subtle modifications of the catalytic system are produced. The stoichiometry of the two reactants also influences the reaction as it can be deduced from the data of Table 8; the use of excess alkyne leads to a decrease in the catalytic activity. On the contrary, the use of excess arylbromide enhances the reaction rate. Although this finding can be significant as far as mechanistic considerations are concerned, it seems less useful from a synthetic point of view since the arylbromide is usually the most valuable reagent.

Finally, having optimised the conditions for the cross-coupling of bromobenzene with bu-

Table 8

Influence of the bromobenzene/alkyne ratio on the reaction rate

CuI 0.025 mmol, Pd(CH₃COO)₂ 0.0125 mmol, PPh₃ 0.0375 mmol, substrate/Pd = 2000, *n*-butylamine 50 ml, *T* 78°C.

Entry	Bromobenzene (mmol)	2-Methylbut-3-yn-2-ol (mmol)	Reaction time (h)	1 yield (%)
1	25.0	25.0	1	37
2	25.0	25.0	3	65
3	25.0	12.5	1	48
4	25.0	12.5	3	80
5	25.0	50.0	1	31
6	25.0	50.0	3	56

tynol, we have investigated if other Ar–X compounds can be used instead of the arylbromides. The experiments show that phenyltriflate displays a reactivity very close to that of bromobenzene, while no reaction is observed using chlorobenzene.

3. Conclusions

The experiments carried out have confirmed the synthetic utility of the cross-coupling of arylbromides with 2-methylbut-3-yn-2-ol; synthetic runs with substrate to palladium ratios as high as 2000 can be carried out to completion in 18–24 h. A variety of palladium species can be used to formulate the catalytic system. In our opinion, the most convenient catalyst precursor is Pd(II) acetate, owing to its high activity, availability and long-term stability. The best-suited phosphorous ligand is the cheap and readily available PPh_3 . The presence of a copper salt is necessary to obtain high reaction rates; however, both the oxidation state of copper and the nature of the associated counter ion do not affect the reaction rate.

The catalytic activity is strongly influenced by the nature of the amine which serves as solvent; the highest reaction rates are obtained in the presence of basic primary amines such as *n*-butylamine or in the presence of cyclic amines such as piperidine or pyrrolidine.

4. Experimental

Melting point was determined with a Büchi 510 apparatus. Infrared (IR) spectrum was recorded with a Perkin Elmer 881 spectrophotometer. ^1H (200 MHz) and ^{13}C (50 MHz) NMR spectra were recorded in CDCl_3 on a Varian Gemini instrument. MS spectrum was obtained at 70 eV with a Carlo Erba QMD 1000 spectrometer.

Pd(II) acetate was purchased from Engelhard. Ten percent Pd on activated carbon was purchased from Aldrich. $\text{Pd}(\text{PPh}_3)_4$ [18] and

$\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ [19] were prepared by literature methods. Bromobenzene, 2-methylbut-3-yn-2-ol and the other chemicals were commercial products (Aldrich and Fluka) and used as received.

4.1. Cross-coupling reaction and analysis of the reaction crudes

All reactions, unless otherwise stated, were carried out under nitrogen atmosphere using Schlenk-type glassware.

In a typical experiment (entry 5 of Table 5), Pd(II) acetate (5.4 mg, 0.025 mmol), triphenylphosphine (19.8 mg, 0.075 mmol) and bromobenzene (800 mg, 5.0 mmol) were placed in a 50-ml two-necked flask under nitrogen atmosphere to give a yellow solution. After 10 min, CuI (9.5 mg, 0.05 mmol) was added. Finally, after 20 min, 2-methylbut-3-yn-2-ol (420 mg, 5.0 mmol) and *n*-butylamine (10 ml) were added. The resulting pale yellow solution was heated at 55°C for 1 h, then cooled to 0°C. An amount of 5 N HCl was added until the pH of the aqueous phase became 3. The mixture was extracted with diethyl ether (2×10 ml) and methylene chloride (2×10 ml). The organic phase was washed with NaHCO_3 and brine, and dried over anhydrous Na_2SO_4 .

The reaction yield was determined by the ratio of the signals at 1.52 ppm (methyl groups of the starting alkyne) and at 1.61 ppm (methyl groups of the reaction product) in the ^1H -NMR.

2-Hydroxy-2-methyl-4-phenylbut-3-yne can be purified by flash column chromatography on silica gel eluting with a 95:5 hexane:ethyl acetate mixture. Mp: 51°C. IR (CDCl_3): 3600, 3000, 2930, 1715, 1370, 1330, 1160, 1115 cm^{-1} . MS m/z (%): 160 (M^+ , 17), 159 (30), 145 (100), 129 (8), 128 (10), 127 (10), 117 (13), 115 (27), 107 (8), 102 (12), 91 (10), 86 (39), 84 (62), 77 (10), 51 (9). ^1H -NMR (CDCl_3 , ppm) δ : 1.61 (s, 6H), 2.15 (br s, 1H), 7.24–7.34 (m, 3H), 7.36–7.44 (m, 2H). ^{13}C -NMR (CDCl_3 , ppm) δ : 31.48 (2C), 65.64, 82.15, 93.75, 122.73, 128.27 (3C), 131.65 (2C).

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