Coupling of terminal acetylenes in water-ethyl acetate biphasic solvent under green reaction conditions

Prasenjit Shit and Raju Singha*

Department of Chemistry, Panskura Banamali College (Autonomous), Panskura R.S., Purba Medinipur-721 152, West Bengal, India

E-mail: rajusingha70@gmail.com

A green reaction protocol has been developed for the coupling of terminal acetylenes to 1,3-diynes in aqueous-organic biphasic medium. Aromatic terminal acetylenes are easily dissolved in organic medium and then transferred to aqueous medium along with phase transfer catalyst. The coupling occurs in aqueous medium in presence of palladium catalyst and aerial oxygen and then the product 1,3-diyne again returns to organic medium. The developed reaction conditions are highly acceptable from the green chemistry point of view because of its water as the green solvent, recyclable catalytic paths, aerial oxidation, ambient reaction temperature, easy to handle and economically cheap reagents and solvents.

Keywords: Green chemistry, biphasic reaction, palladium catalyst, terminal alkyne, aerial oxidation, 1,3-diyne.

Introduction

1,3-Diynes is one of the promising class of organic compounds found applications in academic organic synthesis, pharmaceutical science and also in materials chemistry[1]. 1,3-Diyne building blocks are used in the synthesis of different pharmaceutically important compounds, organic conductors[2], natural products[3], macrocyclic annulenes[4], supramolecular switches[5] and different electron-rich materials[6]. Because of such multipurpose applications of 1,3-diyne building blocks, a remarkable attention has been taken by the various scientists to the development of even more efficient, cost-effective, and environmentally friendly reaction methodology in last few decades[7].

The classical approach for the construction of 1,3-diynes involved homocoupling/heterocoupling of terminal alkyne bonds. The pioneering works in this field are Hay coupling[8], Glaser coupling[9], Eglinton coupling[10] and Cadiot-Chodkiewicz reaction[11]. In these coupling reactions, the coupling between two terminal alkynes is catalyzed by mainly copper catalyst or palladium catalyst and aerial oxygen or different metals serve as the oxidant. In the last two decades, various groups are involved in the development of such coupling methodologies to obtain greener reaction pathways.

Jia and coworkers have reported a facile CuI/I_2 mediated methodology for synthesizing 1,3-diynes via coupling between terminal alkyne carbons in DMF solvent at 80°C where molecular iodine acts as the oxidizing agent[12]. Jiang *et al.* have synthesized 1,3-diynes via homocoupling of terminal acetylenes by using layered CuAl-LDH complex and TMEDA acts as the ligand in acetonitrile solvent[13]. Recently Kesavan *et al.* have developed a room temperature homocoupling methodology for terminal acetylenes in presence of $Cu(OAc)_2$ catalyst and pipyridine base in dichloromethane solvent. Various groups also tried to avoid organic solvents for the green chemistry practice and they performed the homocoupling reactions in PEG, alcohol and also in ionic liquid as the reaction medium[14]. Herein, we have developed an environment friendly green reaction methodology for the homocoupling of aryl-substituted terminal acetylenes in water-ethyl acetate (H_2O-EtOAc) biphasic solvent mixture in presence of palladium chloride ($PdCl_2$) catalyst and aerial oxygen (O_2) as the oxidant.

At first, we know that organic solvent is require to dissolve the nonpolar acetylenes and then a phase transfer catalyst (PTC) may bring them in aqueous medium where the coupling reaction will occur. Accordingly, we have per-

Table 1. Optimization of the reaction parameters[a]
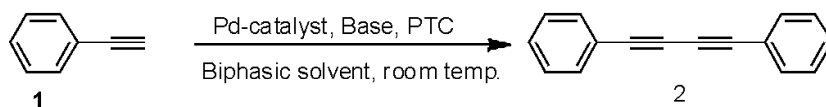
Sl. No.	Catalyst	Solvent mixture	Base	PTC	Time (h)	Yield (%)[b]
1.	PdCl$_2$	H$_2$O-Hexane	Na$_2$CO$_3$	TBAC	48	47
2.	PdCl$_2$	H$_2$O-Toluene	Na$_2$CO$_3$	TBAC	48	42
3.	PdCl$_2$	H$_2$O-DCM	Na$_2$CO$_3$	TBAC	48	18
4.	PdCl$_2$	H$_2$O-CHCl$_3$	Na$_2$CO$_3$	TBAC	48	17
5.	PdCl$_2$	H$_2$O-EtOAc	Na$_2$CO$_3$	TBAC	48	84
6.	PdCl$_2$	H$_2$O-Et$_2$O	Na$_2$CO$_3$	TBAC	48	63
7.	Pd(OAc)$_2$	H$_2$O-EtOAc	Na$_2$CO$_3$	TBAC	48	76
8.	PdCl$_2$	H$_2$O-EtOAc	K$_2$CO$_3$	TBAC	48	75
9.	PdCl$_2$	H$_2$O-EtOAc	Na$_2$CO$_3$	TBAB	24	92
10.[c]	PdCl$_2$	H$_2$O-EtOAc	Na$_2$CO$_3$	TBAB	48	90
10.	PdCl$_2$	H$_2$O	Na$_2$CO$_3$	TBAB	48	42

[a]Reaction conditions: Substrate (0.5 mmol), Pd-cat. (5 mol%), base (1 equiv.), PTC (1 equiv.) and 3 mL of H$_2$O-solvent (5:1) stirred at room temperature with air bubbling throughout the reaction. [b]Isolated yield. [c]H$_2$O-EtOAc (1:1).

formed the reaction to screen the reaction conditions. We have chosen phenylacetylene as the model substrate and performed the reaction in water-hexane (5:1) solvent mixture in presence of palladium chloride catalyst and tetrabutylammonium chloride (TBAC) as the PTC and we have isolated the homo-coupling product in 47% yield. Then we have used different solvent mixtures and found that chlorinated solvents DCM, CHCl$_3$ (Table 1, Entry 3, 4) gave poor yields whereas the highest yield was obtained from water-ethyl acetate mixture of solvents (Entry 5). There was no improvement on changing the catalyst and base, however, the yield was improved to 92% on using TBAB as the phase transfer catalyst (Entry 9). The solvent mixture H$_2$O-EtOAc (1:1) or alone water gave lesser yield. Hence, the optimized reaction conditions are phenylacetylene (0.5 mmol), Na$_2$CO$_3$ (0.5 mmol.), PdCl$_2$ (5.0 mol%), and 3.0 ml of H$_2$O-EtOAc (5:1) and stirred at room temperature in presence of air bubbling at aqueous layer.

After getting the optimized reaction conditions we have employed it on various substituted phenyl acetylenes and the results are shown in Table 2. Acetylene derivatives containing large nonpolar (naphthyl) groups also gave good yield and this became possible due to the biphasic solvents. The overall yield of the reactions was good to excellent.

Table 2. Examination of substrate scope[a,b]
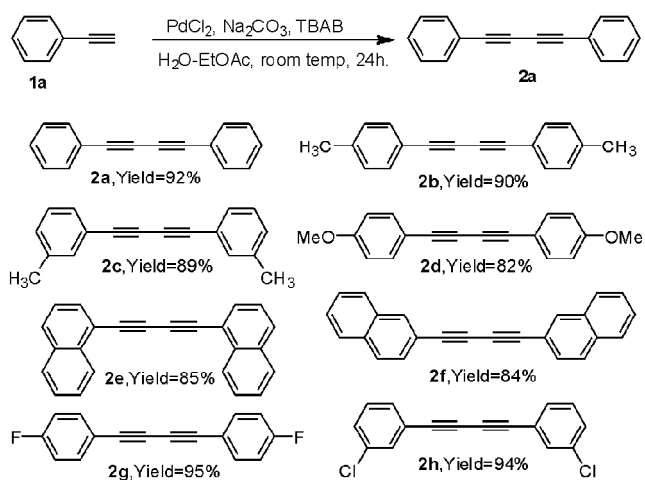
[a]Reaction conditions: Substrate (0.5 mmol), PdCl$_2$ (5 mol%), Na$_2$CO$_3$ (1 equiv.), TBAB (1 equiv.) and 3 mL of H$_2$O-EtOAc (5:1) stirred at room temperature with air bubbling throughout the reaction. [b]Isolated yield.

After getting the homo-coupling products, we had tried to apply this methodology for the heterocoupling synthesis. The reaction of phenylacetylene and 4-methoxyphenylacetylene (1:1) gave three products 1,4-diphenylbuta-1,3-diyne (**2a**), 1,4-bis(4-methoxyphenyl)-1,3-butadiyne (**2d**) and 1-methoxy-4-(4-phenyl-buta-1,3-diynyl)-benzene (**3a**) in almost equimo-

**Table 3.** Application of methodology for heterocoupling reactions

MeO—⬡—≡ + ≡—⬡ →[PdCl$_2$, Na$_2$CO$_3$, TBAB / H$_2$O-EtOAc, room temp, 24h.] MeO—⬡—≡—≡—⬡

0.5 mmol   2 mmol

3a: Y = 73%
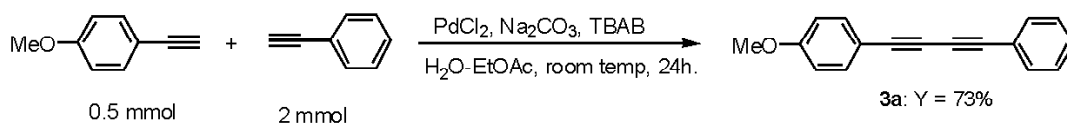
^{a}*Reaction conditions:* Substrate (0.5 mmol, 4-methoxyphenylacetylene), PdCl$_2$ (5 mol%), Na$_2$CO$_3$ (1 equiv.), TBAB (1 equiv.) and 3 mL of H$_2$O-EtOAc (5:1) stirred at room temperature with air bubbling throughout the reaction. ^{b}Isolated yield with respect to 4-methoxyphenylacetylene.

lar ratio. Then we performed the reaction with 4-methoxy-phenylacetylene and excess of phenylacetylene (1:4) to get the higher yield of the heterocoupling product. We had isolated the heterocoupling product 1-methoxy-4-(4-phenyl-buta-1,3-diynyl)-benzene in 73% yield along with other homocoupling products (Table 3).

A plausible reaction mechanism is shown in Scheme 1. The organic alkyne is dissolve in the organic layer (**A**). Then PTC brings the acetylene to aqueous layer (**B**) where they bind with Pd(II) catalyst (**C**). The reductive elimination of palladium complex (S-Pd-S, in C) gives the 1,3-diyne product (S-S, D) which again returns to the organic layer. The palladium(0) catalyst is reoxidized to palladium(II) by dissolved oxygen in the aqueous layer and the catalytic cycle is completed. The literature reports say that palladium catalyst first converted to nanoparticles and then participate in the catalytic cycle[15].

To check the recyclability of the catalyst we have performed an experiment where after completing the reaction, we gently removed the EtOAc layer containing the product using needle and syringe. Then we added 0.5 mL EtOAc containing phenylacetylene (0.5 mmol) to the remaining aqueous layer. These process were repeated three times. From Table 4, we can conclude that the catalytic cycle is recyclable whereas the efficiency of the catalyst gradually decreases.
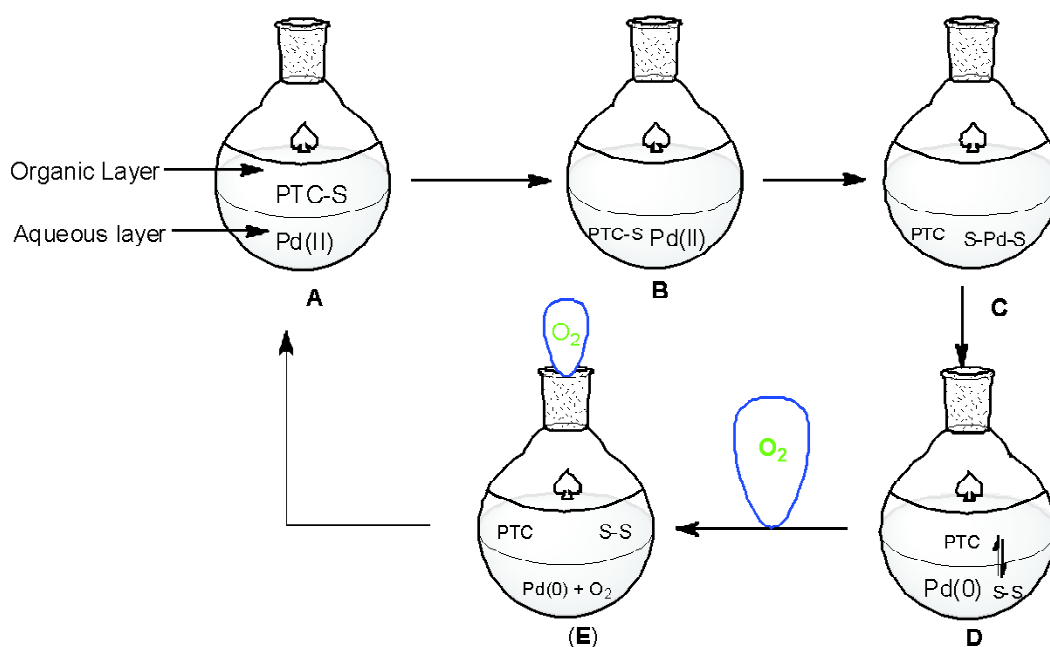
PTC: Phase Transfer Catalyst (TBAB), S: substrate (Phenyl acetylene) and PTC-S: substrate is captured by PTC. S-S: dimer of phenyl acetylene.

Scheme 1. Plausible reaction mechanism for the homocoupling.

No. of cycle	Time (h)	Yield (%)
Table 4. Recyclability of the catalytic cycle		
1	24	92
2	24	85
3	48	62

Conclusions

We have developed a green reaction methodology for the construction of 1,3-diynes via homocoupling of terminal acetylenes. The homocoupling of highly nonpolar terminal alkyne derivatives occurred in presence of biphasic reaction conditions. The oxidation of the palladium catalyst is carried out by aerial oxygen. The developed reaction methodology will be highly acceptable by the chemical community because of its ambient reaction conditions, recyclability of the catalyst, aerial oxidation and finally excellent yield in the green catalytic pathway.

General reaction procedure

In a two neck flask, the catalyst PdCl$_2$ (5 mol%), Na$_2$CO$_3$ (1 equivalent) and TBAB (1 equivalent) were taken and then 2.5 ml water and 0.5 ml EtOAc were added to it. Then 0.5 mmol of aryl acetylene was added to the reaction vessel and stirred at ambient temperature with continuous air bubbling through a syringe. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (20 mL×3). Then combined organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated at reduced pressure. Finally, the crude product was purified by column chromatography using silica gel (60–120 mesh) as stationary phase and 2% ethyl acetate in hexane as the eluent.

Supporting information (Spectral data of the compounds)

1,4-Diphenyl-1,3-butadiyne (2a):

White solid compound; melting point: 85–86°C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 7.31–7.40 (6H, m), 7.52–7.54 (4H, m); ^{13}C NMR (CDCl$_3$, 50 MHz) δ: 76.6, 81.8, 121.9, 128.6, 129.4, 132.7.

1,4-Bis(4-methylphenyl)-1,3-butadiyne (2b):

White solid compound; melting point: 183–184°C; ^{1}H NMR (CDCl$_3$, 200 MHz) δ: 2.36 (6H, s), 7.14 (4H, d, *J* 8.0 Hz) 7.41 (4H, d, *J* 8.0 Hz); ^{13}C NMR (CDCl$_3$, 50 MHz) δ: 21.8, 73.7,

81.8, 119.0, 129.4, 132.6, 139.7.

1,4-Bis(3-methylphenyl)-1,3-butadiyne (2c):

Pale yellow solid compound; melting point: 73–74°C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 2.34 (6H, s) 7.17–7.24 (4H, m), 7.33–7.35 (4H, m); ^{13}C NMR (CDCl$_3$, 50 MHz) δ: 21.4, 73.9, 81.8, 121.8, 128.5, 129.8, 130.3, 133.2, 138.3.

1,4-Bis(4-methoxyphenyl)-1,3-butadiyne (2d):

Yellow solid compound; melting point: 139–140°C; ^{1}H NMR (CDCl$_3$, 200 MHz) δ: 3.82 (6H, s), 6.85 (4H, d, *J* 8.8 Hz), 7.46 (4H, d, *J* 8.8 Hz); ^{13}C NMR (CDCl$_3$, 50 MHz) δ: 55.4, 73.0, 81.3, 113.9, 114.2, 134.1, 160.3.

1,1´-(1,3-Butadiyne-1,4-diyl)bis-naphthalene (2e):

Yellow solid compound; ^{1}H NMR (CDCl$_3$, 400 MHz,) δ: 7.45–7.49 (2H, m) 7.55–7.58 (2H, m), 7.63–7.66 (2H, m), 7.84 (2H, d, *J* 7.2 Hz), 7.88–7.91 (4H, m), 8.44 (2H, d, *J* 8.4Hz); ^{13}C NMR (CDCl$_3$, 50 MHz) δ: 78.9, 81.2, 119.4, 125.5, 126.4, 126.9, 127.5, 128.7, 130.0, 132.3, 133.3, 134.1.

2,2´-(1,3-Butadiyne-1,4-diyl)bis-naphthalene (2f):

Yellow solid compound; ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 7.51–7.58 (6H, m), 7.80–7.84 (6H, m), 8.10 (2H, s); ^{13}C NMR (CDCl$_3$, 50 MHz) δ: 74.6, 82.4, 119.3, 127.0, 127.5, 128.0, 128.1, 128.4, 128.7, 133.0, 133.3, 133.4.

1,4-Bis(4-fluorophenyl)-1,3-butadiyne (2g):

White solid compound; melting point: 190-191°C; ^{1}H NMR (CDCl$_3$, 200 MHz) δ: 6.99–7.00 (4H, m), 7.48–7.55 (4H, m); ^{13}C NMR (CDCl$_3$, 50 MHz) δ: 73.7, 80.6, 116.1 (d, *J* 22.0 Hz), 118.0, 134.7 (d, *J* 8.5 Hz), 163.3 (d, *J* 250.0 Hz).

1,4-Bis(3-chlorophenyl)buta-1,3-diyne (2h):

White solid; melting point: 72–73°C ^{1}H NMR (CDCl$_3$, 200 MHz) δ: 7.23-7.44 (6H, m), 7.50–7.51 (2H, m); ^{13}C NMR (CDCl$_3$, 50 MHz) δ: 74.9, 80.7, 123.5, 129.9, 130.8, 132.4, 134.5.

1-Methoxy-4-(4-phenyl-buta-1,3-diynyl)-benzene (3a):
White solid; ^{1}H NMR (CDCl$_3$, 200 MHz) δ: 3.86 (3H, s), 6.88–6.93 (2H, m), 7.37–7.42 (3H, m), 7.50–7.52 (1H, m), 7.54–7.60 (3H, m); ^{13}C NMR (CDCl$_3$, 50 MHz) δ: 55.5, 73.0, 74.4, 81.2, 82.0, 113.9, 114.4, 122.2, 128.6, 129.2, 132.6, 134.3, 160.6.

lege-295, 18th November, 2015), New Delhi, Govt. of India for sponsoring college research facilities.

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