



RAPID COMMUNICATION

Conceptual approach to the synthesis of symmetrical 1,3-diynes from β -bromo vinyl carboxylic acids

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Abstract. A conceptual route has been developed for the synthesis of 1,3-diyne from β -bromo vinyl carboxylic acids. The reaction of the β -bromo vinyl carboxylic acid with palladium catalyst is conceptually similar to the decomposition of 2-diazoniumbenzoic acid to benzyne. In the presence of palladium catalyst, the β -bromo vinyl carboxylic acid undergoes a fragmentation to generate terminal alkyne. The terminal alkyne undergoes dimerisation in the presence of palladium catalysts to produce the product 1,3-diyne.

Keywords. β -bromo vinyl carboxylic acid; palladium; benzyne; terminal alkyne; 1,3-diyne.

1. Introduction

1,3-Diynes are an important class of organic building blocks and they found applications in organic synthesis, materials science as well as in pharmaceutical science.¹ 1,3-Diynes serve as the important scaffold to the synthesis of different natural products,² organic conductors,³ supramolecular switches,⁴ macrocyclic annulenes⁵ and various electron-rich materials.⁶ Considering their importance, tremendous effort has been taken for the development of efficient and cost-effective methodology in recent years.⁷

The dimerisation of terminal alkynes are the classical approach to the synthesis of 1,3-diynes and Glaser coupling,⁸ Hay coupling⁹ and Eglinton coupling¹⁰ are the pioneering work in this field. These coupling reactions involve copper-catalyzed dimerisation of terminal alkynes where the metal or aerial oxygen acts as the oxidant. Recently, various groups have developed efficient dimerisation methodologies in the presence or absence of metal catalysts. Wang *et al.*, have reported the synthesis of 1,3-diynes *via* cross-coupling of terminal alkynes with 1-bromoalkyne in the presence of CuI catalyst.¹¹ The cross-coupling of alkynyl bromide with alkynyl boronic acid also produces 1,3-diynes in the presence of CuFe₂O₄

nanoparticles.¹² Huang and co-workers have reported the synthesis of 1,3-diynes *via* copper-catalyzed decarboxylative coupling of substituted potassium propiolates with 1,1-dibromo-1-alkenes.¹³ The literature reports resolve that the 1,3-diyne synthesis involves the requirement of either one or two terminal alkynes. Herein, we are reporting a conceptual approach to the synthesis of 1,3-diynes from β -bromo vinyl carboxylic acids. To the best of our knowledge, we are the first ones reporting the synthesis of 1,3-diyne in a catalytic way without the requirement of any prefunctionalized alkyne unit(s).

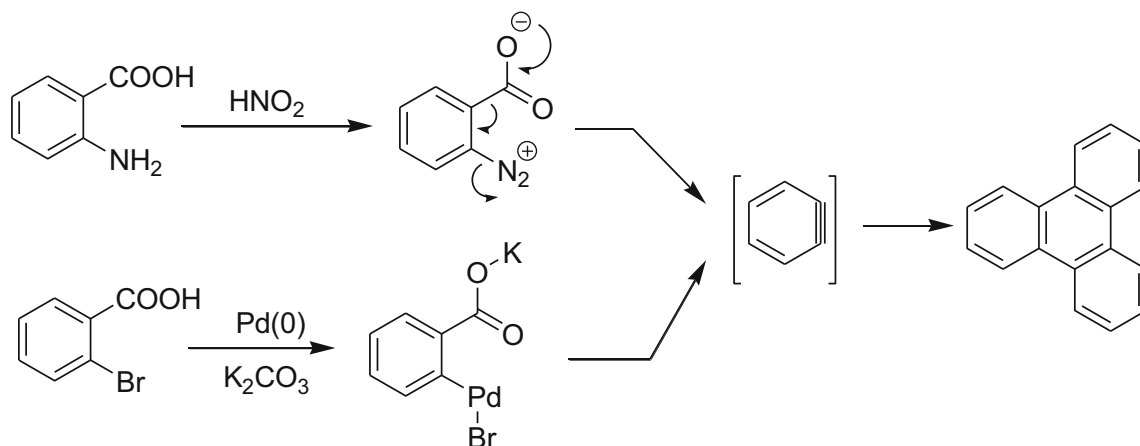
2. Experimental

The diazocoupling reaction of 2-aminobenzoic acid is a classical approach for the synthesis of benzyne (Scheme 1).¹⁴ Recently Kim *et al.*, have reported that 2-bromobenzoic acid produces benzyne in presence of palladium catalyst.¹⁵ However, in both the case, the *in situ* generated benzyne undergo [2+2+2] cycloaddition to form triphenylene (Scheme 1).

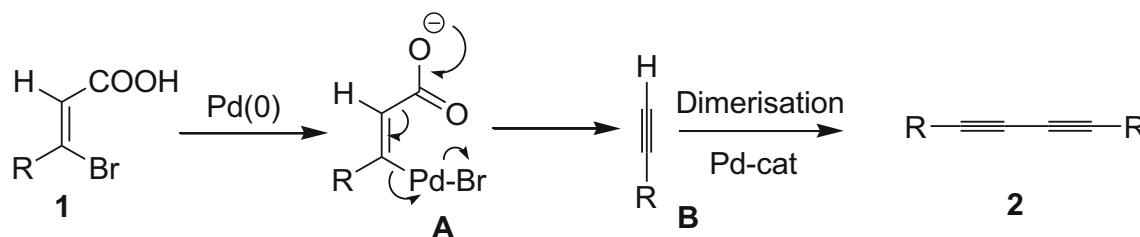
We envisioned that the reaction of β -bromo vinyl carboxylic acids with palladium catalyst will produce a similar intermediate palladium complex, which will undergo a rearrangement to form terminal alkyne. This terminal

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Scheme 1. Synthetic background: Synthesis of benzyne from 2-aminobenzoic acid.

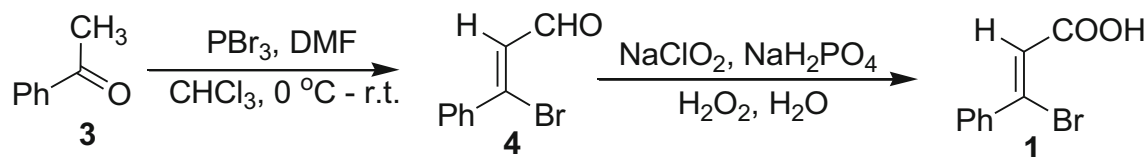
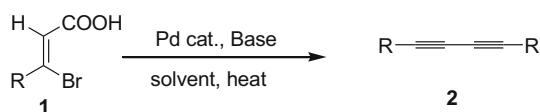


Scheme 2. Conceptual approach towards the synthesis of 1,3-diyne.

alkyne will dimerise to produce 1,3-diyne under the reaction conditions in the presence of palladium catalyst (Scheme 2).

At first, we have focused on the synthesis of β -bromo vinyl carboxylic acids starting from acetophenone derivatives. The Vilsmeier-Haack type reaction of acetophenone gives β -bromo vinyl aldehyde derivative (4), which produces our desired scaffold β -bromo vinyl carboxylic acid (1) after Pinnick oxidation (Scheme 3).¹⁶

After synthesizing the scaffold β -bromo vinyl carboxylic acid, we reacted it with different catalysts in various solvents and the results are shown in Table 1.



Scheme 3. Synthesis of scaffold.

3. Results and Discussion

At the beginning, we have reacted the substrate β -bromo vinyl carboxylic acid with palladium acetate and sodium carbonate in dimethylformamide solvent. In this case, we have observed the formation of 1,4-diphenyl-1,3-diyne in 21% of yield. Then we varied the catalysts to improve the reaction yield. We observed that $\text{Pd}(\text{PPh}_3)_4$ gave the highest yield and PdCl_2 did not promote the reaction. Then we employed different bases and found that Cs_2CO_3 distinctly improved the yield. Among the various solvents, DMF gave good results. On increasing the reaction temperature the yield remained unchanged; however, decreasing of temperature to 60 °C required longer reaction time with a lower yield. Therefore, the screened reaction conditions were β -bromo vinyl

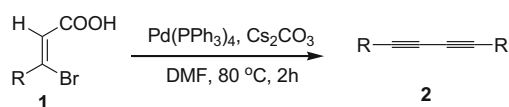
Table 1. Screening of the reaction conditions.^a

Sl. no.	Solvent	Catalyst	Additive	Temperature (°C)	Yield (%) ^b
1	DMF	Pd(OAc) ₂	Na ₂ CO ₃	80	21
2	DMF	PdCl ₂	Na ₂ CO ₃	80	0
3	DMF	PdCl ₂ (PPh ₃) ₂	Na ₂ CO ₃	80	41
4	DMF	Pd(PPh ₃) ₄	Na ₂ CO ₃	80	50
5	DMF	Pd(PPh ₃) ₄	K ₂ CO ₃	80	47
6	DMF	Pd(PPh ₃) ₄	Cs ₂ CO ₃	80	63
7	DMF	Pd(PPh ₃) ₄	NaOAc	80	52
8	DMA	Pd(PPh ₃) ₄	Cs ₂ CO ₃	80	56
9	DMSO	Pd(PPh ₃) ₄	Cs ₂ CO ₃	80	57
10	DMF	Pd(PPh ₃) ₄	Cs ₂ CO ₃	100	63
11	DMF	Pd(PPh ₃) ₄	Cs ₂ CO ₃	60	60 ^c

^aReaction conditions: scaffold β -bromo vinyl carboxylic acid (0.5 mmol), catalyst (5 mol%), base (1 equivalent), solvent (3 mL) and heated for 2 h.

^bIsolated yield.

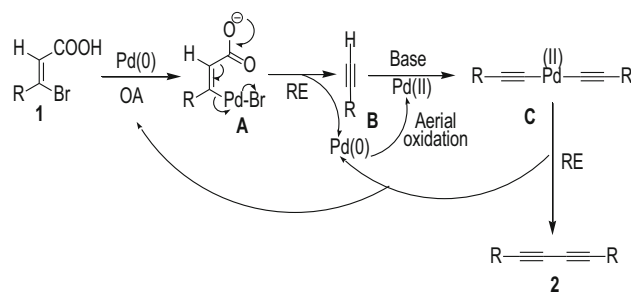
^cSubstrate vanished after 6 h.

Table 2. Examination of the substrate scope.^a

Entry	Substrate	Product	Yield (%) ^b
1			63
2			61
3			60
4			55
5			61
6			62
7			74

^aReaction conditions: scaffold β -bromo vinyl carboxylic acid (0.5 mmol), Pd(PPh₃)₄ (5 mol%), Cs₂CO₃ (1 equivalent), DMF (3 mL) and heated at 80 °C for 2 h.

^bIsolated yield.

**Scheme 4.** Probable reaction mechanism.

carboxylic acid (0.5 mmol), Pd(PPh₃)₄ (5 mol%), Cs₂CO₃ (1 mmol) heated at 80 °C in DMF solvent for 2 h.

After getting the screened reaction conditions, we have employed it on different substituted β -bromo vinyl carboxylic acid derivatives and the results are shown in Table 2. We have used substrates with various substituted aryl rings and found that the presence of electron-donating groups on the phenyl ring decreases the yield of the reaction (Table 2, entry 2–4). When we performed the reaction with electron-deficient aryl ring, then the yield was good (Table 2, entry 7). The overall yield of the reaction was moderate.

In this reaction, the *in situ* generated terminal acetylene immediately dimerises in the presence of palladium catalyst. Probably the reaction goes in a similar way as reported by Yang and co-workers and then Gazvoda *et al.*, in a copper-free Sonogashira reaction mechanism.¹⁷ The probable reaction mechanism is shown in Scheme 4.

At first, the Palladium (0) catalyst undergoes oxidative addition with C-Br bond in β -bromovinyl

carboxylic acid derivative (Scheme 4, Compound 1). Then decarboxylation along with reductive elimination of Pd(II) gives the terminal alkyne B. Then Pd(0) catalyst undergoes aerial oxidation to Pd(II) which binds with two alkyne ions generated in the presence of the base. The reductive elimination of this dialkyne Pd(II) species produces the final product 1,3-diyne and Pd(0) catalyst regenerated.

4. Conclusions

In conclusion, we have developed a conceptual approach for the synthesis of terminal alkynes from β -bromo vinyl carboxylic acids using palladium catalyst.¹⁸ The generated terminal alkyne dimerises in situ in the presence of palladium catalyst under the same reaction conditions. Finally, the product 1,4-diarylbuta-1,3-diyne was formed in moderate to good yields.

Supplementary Information (SI)

General reaction procedures, analytical data and NMR spectra of the compounds are available at www.ias.ac.in/chemsci.

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 18. General reaction condition: β -bromo vinyl carboxylic acid (0.5 mmol), $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (1 mmol) were taken in a two neck round bottomed flask and then 3 mL of dimethylformamide (DMF) solution was added. The reaction mixture was then heated at 80 °C for 2 h. After completion of the reaction, mixture was allowed to cool to room temperature and then diluted with water. Then the product was extracted with ethyl acetate (3 x 20 mL). The combined organic layer was evaporated under reduced pressure and the crude product was purified by column chromatography using silica gel (60–120 mesh) and hexane/ethyl acetate as eluent