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SYNTHESIS OF INTERNAL ALKYNES USING NEW PALLADIUM *N*-HETEROCYCLIC CARBENE CATALYTIC SYSTEM

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ABSTRACT
Alkyne is a recurring functional group in a wide range of natural products and other bioactive compounds. It is as well a versatile intermediate in synthesis. A direct method for incorporating a triple bond in molecules is termed Sonogashira reaction, and it typically employs palladium and copper catalysts. However, the use of copper catalysts mediates homocoupling of terminal alkynes. In order to address the homocoupling problem, copper-free reactions are considered. In this study, a new palladium-N-heterocyclic carbene-pyridine complex was synthesized and tested as catalysts in the coupling reaction of aryl iodides with terminal alkynes. The catalyst was synthesized by alkylation of imidazole to yield N-methylimidazole (H2), which was further alkylated to yield dialkyl imidazolium salt (H4). The dialkyl imidazolium salt was further reacted with palladium bromide ($PdBr_2$) in 3-methylpyridine using potassium carbonate (K_2CO_3) as a base to yield the Palladium N-Heterocyclic carbene pyridine complex (H10). The products obtained were characterized using ^{1}HNMR and FT-IR spectroscopic techniques which supported their proposed structures. The elemental compositions were established on the basis of C, H, N elemental analysis. Using H10 as catalyst, a mild protocol for the Sonogashira coupling reaction was developed. Using 1.0 mol% catalyst loading, acetonitrile-water (1:1) as a solvent system, KOH as a base, and room temperature were found as a suitable condition for the synthesis of internal alkynes from the reaction of aryl halides with aryl alkynes. The new catalytic system was compatible with various functional groups and worked effectively with unactivated, activated and deactivated aryl iodides.
Key-words: Palladium-N-heterocyclic carbenes, Sonogashira reactions, Internal alkynes.

INTRODUCTION

Alkynes are organic compounds containing carbon-carbon triple bond. The reactivity of the carbon-carbon triple bond renders such compounds of high synthetic value both as building blocks and intermediates for many reactions (Shivalinga & Sanjay, 2016; Chinchilla & Najera, 2011; Jana *et al*., 2011)..). A versatile method for incorporating a triple bond in organic molecules is termed Sonogashira reaction, which typically employs palladium and copper as catalysts to couple a terminal alkyne with an aryl or vinyl halide (Chinchilla and Najera, 2007).The Sonogashira coupling of terminal acetylenes with aryl or vinyl halides provides a powerful tool for C-C bond formation (Seechurn*et al*., 2012). Typical procedures for the Sonogashira coupling utilize catalytic palladium with a metal cocatalyst and a base (Sonogashira*et al.,* 1975). The most widely employed cocatalysts are copper salts, which mediates homocoupling of terminal alkynes when the copper acetylide is exposed to oxidative agents or air (Santra*et al*., 2013). This homocoupling side reaction usually makes the internal acetylenes difficult to obtain (Bakherad*et al.,* 2010). The use of other cocatalysts such as zinc, tin, boron, aluminum, Ag_2O, and AgOTf have been developed to address this issue, but additional steps are needed to make these agents. In order to avoid this undesired reaction, it is necessary to run the reaction in an inert atmosphere, and hence the copper-free Sonogashira reaction has been developed as a modified protocol. However, efficient, stable palladium catalysts are still needed to achieve the Sonogashira coupling reaction with low catalyst loading under copper-free conditions (Dogan *et a*l., 2011; Aktas*et al.,* 2013; Chen *et al.,* 2009). One of the most rapid fields of growth in the last twenty years is the investigation of Pd-NHC complexes in cross coupling (Akkoc *et al.,* 2016). The strong sigma electron donation combined with the steric bulkiness of the NHC results in Pd complexes that are particularly well suited for cross coupling (Mudi *et al*., 2015).

As a result of these properties, Pd-NHC complexes have been some of the most active catalysts in C-C and C-heteroatom cross coupling reactions as reported in the literature (Rullah*et al.,* 2019; (Hermann *et al.,* 1995). *N*-heterocyclic carbenes (NHC's) are among the most remarkable ligands for homogeneous catalysis. The use of different metal-NHC complexes has led to important innovations in homogeneous catalysis, thusnumerous metal-NHC derivatives including Ag, Co, Fe, Cu, Ni, Ru, Ir, Rh, and Pd complexes, have been prepared (Dogan*et al*., 2011). Although there is numerous metal-carbene complexes, the most prominent are the Pd-NHC complexes, this is likely due to their catalytic efficiency and resistance against air, moisture, and high temperature. As a result of these properties, Pd-NHC complexes have been some of the most active catalysts in C-C and C-heteroatom cross-coupling reactions (Hopkinson *et al.,* 2014). As part of an effort to uncover catalysts that are highly active and work under mild reaction conditions, this research was focused on the synthesis of new Pd-NHC pyridine complex and the investigation of its catalytic performance in a copper-free Sonogashira coupling reaction.

MATERIALS AND METHODS

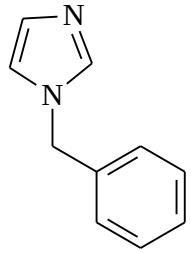
Materials and Instrumentation

All chemicals were obtained from Sigma Aldrich and used as received. All solvents used were of analytical grade and were used without further purification. The products were purified either using microcolumn chromatography or by washing with the appropriate solvent.

The ^{1}H and ^{13}C NMR spectral data were recorded on either Bruker 400MHz or 500 MHz NMR machine (Joel 1500 model). Chemical shifts were recorded in ppm using tetramethylsilane as reference and $CDCl_3$ as solvent. Fourier transform infrared (FT-IR) spectra were recorded using an Agilent technology FT-IR spectrophotometer in wavenumber (cm^{-1}). Elemental analysis was obtained with a PerkinElmer Series 11 (CHNS/O) Analyzer 2400.

Synthesis of *N*-Benzyl Imidazole (H2)

Imidazole (10.0 mmol, 0.68 g), potassium hydroxide (12.0 mmol, 0.67 g), and acetonitrile (80.0 ml) were added to a 250 ml two necked round bottom flask and stirred for 1 hour at room temperature. To the stirred mixture, alkyl bromide (11.0 mmol) was added, and the mixture refluxed under magnetic stirring at 80 ^{0}C for 24 hours. After the completion of the reaction, the solvent was allowed to evaporate in a fume hood and the crude product was extracted twice with ethyl acetate (30 ml) and distilled water (20 ml). The separated organic layer was dried and washed several times with *n*-hexane to obtain thick brown oil. The product obtained as thick brown oil was further purified using silica gel column chromatography using ethylacetate / diethyl ether (70:30) (Ibrahim *et al.,* 2018).



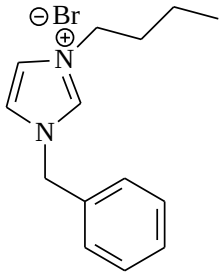
***N*-Benzyl Imidazole (H2)**

Thick brown oil; 0.97 g, Yield (61%); **^{1}H NMR** ($CDCl_3$)δ(ppm): 5.01 (*s*, 2H NC*H*$_2$), 6.83 (d, 1H NC*H*C), 7.01 (d, 1H CC*H*N), 7.26 ($CDCl_3$), 7.28-7.07 (m, 5H Ar-*H*), 7.49 (s, 1H NC*H*N). **FT-IR**(*v* cm^{-1}); C=N 1659.34, C=C aromatic 1451.48, =C-H aromatic 3029.87, C–N 1033.50, C–N 1074.27, mono substituted benzene 713.11. Anal.Calcd for ($C_{10}H_{10}N_2$) Calc.; C (75.94), H (6.32), N (17.70). Found; C (77.01), H (6.21), N (17.14).

Synthesis of *N*-Benzyl-*N*-Butyl Imidazolium Bromide (H4)

N-benzylimidazole, **H2** (1.64 mmol, 0.26 g), Butylbromide (2.0 mmol. 0.21 ml) and anhydrous THF (5 ml) were added into a 50 ml round bottom flask fitted with a magnetic stir bar and a reflux condenser. The mixture was refluxed for 24 hours at 80 ^{0}C. After the completion of the reaction, the mixture was cooled to room temperature, the product obtained as an oily mass was allowed to settle and the THF was decanted. The product was washed several times with THF to obtain gummy brown oil (Muskawar *et al*., 2016).

_N_-Benzyl-_N_-Butyl Imidazolium Bromide (H4)



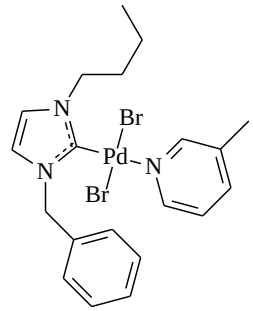
Brownish gummy oil, 0.38 g, Yield (79 %); ^{1}H-NMR ($CDCl_3$) δ(ppm); 1.10 (t, 3H C*H*$_3$), 1.60-1.54 (m, 2H.C*H*$_2$), 2.20-2.12 (m, 2H C*H*$_2$), 4.69 (t, 2H NC*H*$_2$-Aliphatic), 5.01 (s, 2H NC*H*$_2$-Aromatic), 6.83 (d, 1H CC*H*N), 7.26 ($CDCl_3$), 7.28-7.01 (m, 5H Ar-*H*), 7.49 (d, 1H NC*H*C), 11.68 (s, 1H NC*H*N). FT-IR (*ν cm^{-1}*); C=N 1666.33, C=C aromatic 1451.41, =C-H aromatic 3029.77, C–N 1033.75, C–N 1078.66, C–H aliphatic 2925.80, mono substituted benzene 702.27. Anal.Calcd for ($C_{14}H_{19}N_2Br$) Calc.; C (56.94), H (6.44), N (9.49). Found; C (56.78), H (6.69), N (9.27).

Synthesis of Palladium _N_-Heterocyclic Carbene Pyridine Complex (H10)

Under Nitrogen atmosphere, *N*-benzyl*N*-butylimidazolium Bromide, **H4** (0.94 mmol, 0.19g), palladium bromide (0.94 mmol, 0.25 g), potassium carbonate (4.0 mmol, 0.28 g) and 3-methylpyridine (5 ml) were added in an oven dried 25ml round bottom flask. The mixture was stirred at 90^{o}C for 30 hours on a hotplate equipped with a magnetic stir bar. The resulting product was dried and then dissolved in dichloromethane (5 ml) and passed through a micro column packed with silica gel, the eluent was dried and washed several times with diethyl ether (Ibrahim *et al.*, 2016).

Dibromido[(1-benzyl-3-butylimidazole2-ylidene)(3 methylpyridine)palladium (II)] (H10)

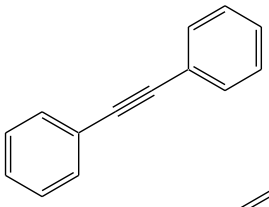
Yellow crystals, 0.22g, Yield (41 %); **FT-IR** (*ν cm^{-1}*) C=C aromatic 1439.72, C=C aromatic 1477.76, C–H aliphatic 2921.84, C–H aliphatic 2951.85, mono substituted benzene 702.50.



Procedure for the Sonogashira Cross-Coupling Reaction Using the Preformed Complex (H10)

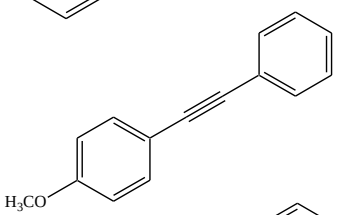
H10 complex (0.010 mmol, 0.0048 g) was dissolved in the appropriate solvent (4 ml). aryl iodide (1.0 mmol), alkyne (1.2 mmol) and base (2.0 mmol) were added to the mixture and stirred at the required temperature for the required time. The product obtained at the end of the reaction was partitioned between ethyl acetate (20 ml) and distilled water (10 ml). The combined ethyl acetate extracts was dried using anhydrous magnesium sulphate, and the solvent evaporated to afford a crude product which was further purified using the thin-layer chromatography technique. The spectral data of the alkynes synthesized in this study were found to correspond with those reported in the literature (Ibrahim *et al.,* 2015); (Buchmeister*et al.,* 2011); (Bakherad&Jajarmi, 2013); (Bruce *et al.,* 2008) and (Liang *et al.,* 2005).

Diphenylacetylene(3a):



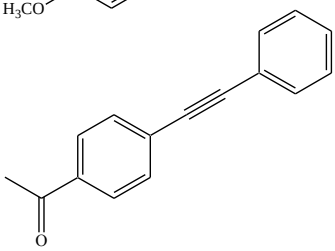
Yellow solid, 78 % Yield, ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm):7.60-7.56 (m, 5H), 7.45-7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 131.6, 128.3, 128.2, 123.2, 89.3; FT-IR(Neat) (*ν cm^{-1}*); C≡C alkyne 2218.82, C=C aromatic 1451.77, C–H aromatic 3026.96

1-Methoxy-4-(phenylethynyl)benzene(3b):



Yellow solid, 88 % Yield, ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.49 (d, *J* = 5.8 Hz, 2H), 7.45 (d, *J* = 8.9 Hz, 2H), 7.30 (d, *J* = 7.3 Hz, 3H), 6.86 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm):138.2, 133.0, 131.4, 128.4, 127.9, 123.6, 113.9, 55.3, FT-IR(Neat) (*ν cm^{-1}*); C≡C alkyne 2218.94, C=C aromatic 1461.52, C–O 1249.54, CH_3 stretching 2851.84.

1-[4-(Phenylethynyl)phenyl]ethanone(3c):



Yellow solid, 95 % Yield, ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.92 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.54 - 7.52 (m, 2H), 7.35 - 7.34 (m, 3H), 2.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm):197.3, 136.1, 131.7, 131.6, 128.8, 128.4, 128.3, 128.2, 128.1, 122.6, 92.7, 88.6, 26.6; FT-IR(Neat) (*ν cm^{-1}*); C≡C alkyne 2218.73, C=C aromatic 1443.61, C=O 1678.40, CH_3 stretching 2851.58.

RESULTS AND DISCUSSION

Synthesis and Characterization of Palladium *N*-Heterocyclic Carbene Pyridine Complex (H10)

The synthesis of Palladium N-heterocyclic carbene pyridine complex (H10) was successfully achieved via a 3-step procedure. First by the reaction of imidazole in slight excess benzyl bromide using KOH as a base and anhydrous acetonitrile as a solvent which yielded thick brown oil (*N*-benzylimidazole) in good yield (61%). It is necessary to start making the sp^2 nitrogen more nucleophilic by deprotonation through constant stirring at room temperature prior to adding the benzyl bromide into the mixture so as to avoid getting the benzyl group being attached to the SP nitrogen instead. The purity of the synthesized product was checked by subjecting it to thin layer chromatography and the pure product was obtained through silica gel micro column chromatography.

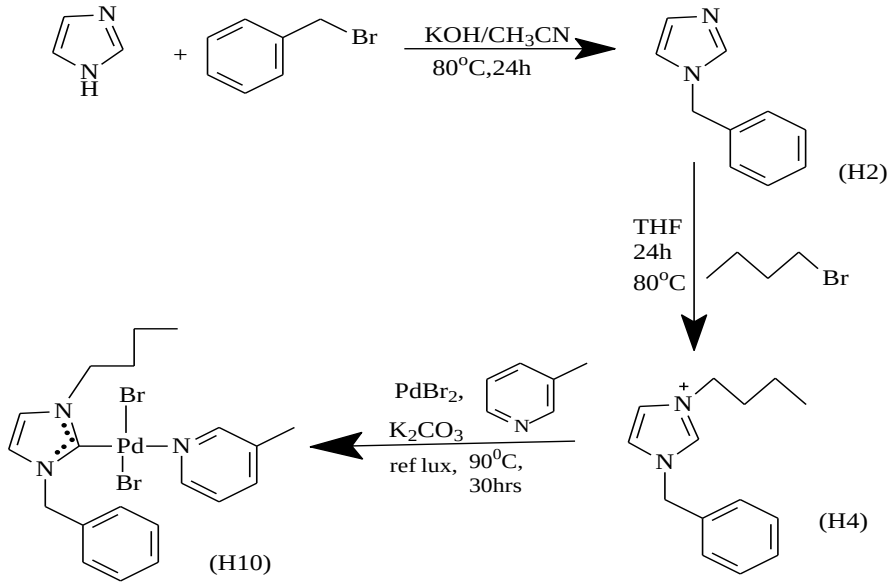
In the ^{1}HNMR spectrum of *N*-methylimidazole (H2), the protons on the methylene carbon of the benzyl group were found to resonate at 5.019 ppm and also appeared as singlet peak. This indicates the successful *N*-benzylation of the imidazole. Also, the chemical shifts at 7.014-7.280 ppm indicated the presence of aromatic protons. The result obtained from the elemental analysis shows consistency between the experimental values and the theoretical values. The results obtained were found to be in consistent with the literature when compared.

The purified product was further reacted with butyl bromide in order to obtain the imidazolium salt, *N*-benzyl-*N*-butyl imidazolium bromide (H4), which was obtained as thick brown oil in excellent yield of 79 %.

In the ^{1}H NMR spectrum of the compound H4, formation of the *N*-benzyl-*N*-butylimidazolium bromide was confirmed by the presence of a downfield signal at 11.681 ppm which was assigned to the acidic proton NC*H*N. The alkylation of the butyl group on the Nitrogen atom (NCHN) yields a quaternary N which makes the C2 (N*C*HN) more acidic, hence more de-shielded. This can further be confirmed when compared to the N-benzylimidazole spectrum were the NC*H*N proton signal was found at 7.492 ppm. More so, the presence of multiple signals around 2.200 - 1.081 ppm assigned to the CH_3 and CH_2 of the butyl group, which was absent in the *N*-benzylimidazole spectrum confirms the formation of *N*-benzyl-*N*-butylimidazium bromide.

The Imidazolium salt obtained was further reacted with K_2CO_3 and $PdBr_2$ in 3-methylpyridine as described in section 2.4 above, to obtain the targeted Palladium *N*-heterocyclic carbene pyridine complex. The reaction is a one pot synthesis; the first step involves the deprotonation of the acidic proton in the imidazolium bromide by a strong base (K_2CO_3) forming the carbene (in-situ), this is then followed by the coordination of the Pd (II) metal with the carbene forming the corresponding palladium *N*-heterocyclic carbene pyridine complex. The purified complex was characterized using FT-IR and elemental analysis.

The elemental analysis of the compound obtained shows no significant difference between the theoretical and the experimental values. The variation in the FT-IR spectral data of the complex compared to that of the pre carbene further confirms the formation of the complex.

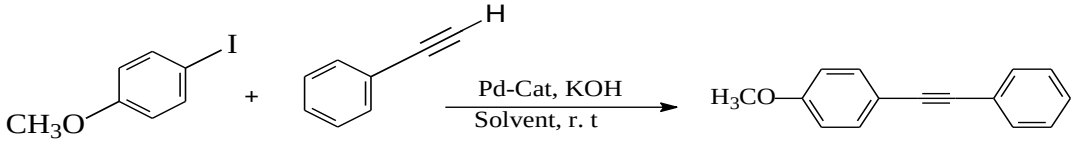


Scheme 1: Synthetic route for the Pd-NHC pyridine complex (H10)

Synthesis of Alkynes via Pd-catalyzed Sonogashira Cross Coupling Reaction

The synthesized imidazolium based Pd-NHC pyridine complex was used to develop a mild protocol for the synthesis of some internal alkynes.

Table 1: Optimization of the Reaction Conditions for Palladium Catalyzed Sonogashira Coupling Reaction of 4-Iodoanisole with Phenylacetylene



Entry	Catalyst	Solvent	Base	Time	Yield
1	**H10**	H_2O	KOH	2	No reaction
2	**H10**	CH_3CN	KOH	2	13
3	**H10**	DMF	KOH	2	10
4	**H10**	CH_3CN/H_2O (1:1)	KOH	2	88
5	**H10**	DMF/H_2O (1:1)	KOH	2	30
6	**H10**	CH_3CN/H_2O (1:1)	KOH	1	48
7	**H10**	CH_3CN/H_2O (1:1)	K_2CO_3	2	29
8	**H10**	CH_3CN/H_2O (1:1)	Et_3N	2	45
9	**H10**	CH_3CN/H_2O (1:1)	-	2	No reaction
10	**$PdBr_2$**	CH_3CN/H_2O (1:1)	KOH	2	61
11	**No Catalyst**	CH_3CN/H_2O (1:1)	KOH	2	No reaction

Reaction conditions; Catalyst loading (1 mol%), 4-iodoanisole (1.0mmol), phenylacetylene (1.5 mmol), base (2.0 mmol), solvent (4 ml).

The optimization reactions were carried out in order to determine the most ideal reaction conditions, the results obtained were summarized in Table 1. Several experiments were performed using 4-iodoanisole and phenylacetylene as model substrates at a catalyst loading of 1 mol%. The effect of varying the solvent was investigated using an H10 catalyst at room temperature. No reaction was observed using water as the solvent (Table 1, entry 1), only 13 % and 10 % yield of the product was observed using acetonitrile and DMF respectively, as solvents (Table 1, entries 2 and 3). Using a mixture of acetonitrile and water gave a much better yield (Table 1, entry 4) and moderate yield with DMF-H_2O (Table 1, entry 5). Hence, a mixture of acetonitrile and water proves to yield an excellent result when the reaction is carried out at room temperature and was adopted as an optimum solvent system.

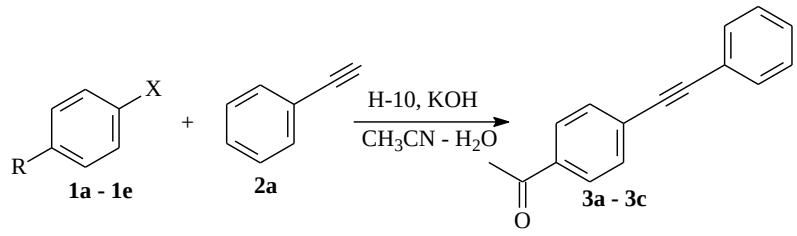
The presence of a base is essential for the Pd-catalysed Sonogashira coupling reaction [12]. Three different bases, KOH, K_2CO_3, and Et_3Nwere used. Low yield (29 %) was observed with K_2CO_3 (Table 1, entry 7) and moderate yield with Et_3N (Table 1, entry 8). KOH was observed to give an excellent yield of 88 % (Table 1, entry 4) and therefore, was adopted as an optimum base. No product was obtained in the absence of any base (Table 1, entry 9). Upon variation of time, better conversion of the product (88 %) was observed at 2 hours (table 1, entry 4). A decrease in the yield (48 %) was recorded when the reaction time was reduced to 1 hour (Table 1, entry 6).

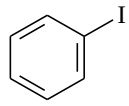
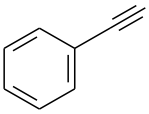
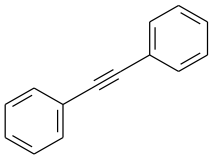
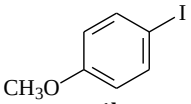
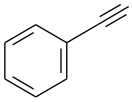
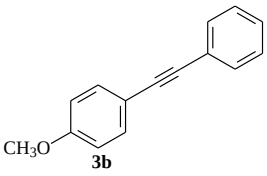
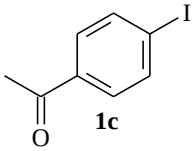
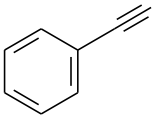
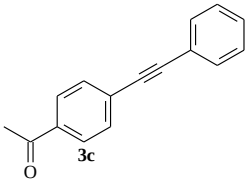
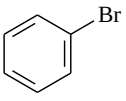
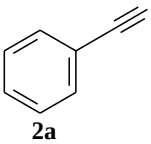
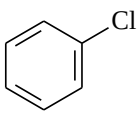
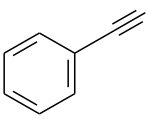
From the optimization of the reaction conditions, it was revealed that carrying out the reaction using a mixture of acetonitrile and water (1:1), KOH as the base at room temperature for 2 hours led to the most excellent isolated yield of 88 % (Table 1, entry 4). This optimized reaction condition was adopted and the effects of various catalysts were studied. $PdBr_2$ was moderately active and yielded 61% (Table 1, entry 10), of the expected coupling product. These interesting results reveal that the synthesized catalyst (H10) is more active than the precursor used in their synthesis ($PdBr_2$). Finally, as expected, a reaction without catalyst (Table 1, entry 11) does not yield any product.

Sonogashira Coupling Reaction of Aryl Iodides with PhenylacetyleneCatalyzed By H10 Complex:

Using the optimized reaction conditions [H10 catalyst (1mol%), aryl halide (1mmol), phenylacetylene (1.2mmol), KOH (2.0mmol), CH_3CN (2ml), H_2O (2ml), room temperature, time (2hours)], various aryl iodides were reacted with phenylacetylene (Table 2). Aryl iodides with an electron withdrawing and an electron donating substituents (**1a – 1c**) were reacted with phenylacetylene (**2a**) to yield their corresponding internal alkynes (**3a - 3c**) in good to excellent yields (78 – 95%). The reaction of phenylacetylene with an unactivated aryl iodide (Table 1, entry1) afforded an internal acetylene in good yield. The coupling reaction of both the activated aryl iodide (Table 2, entry 2) and the deactivated aryl iodide (Table 2, entry 3) with phenylacetylene yielded internal acetylene in excellent yields (88 and 95%) respectively. However, upon reacting the phenylacetylene with aryl bromide (Table 2, entry 4) and aryl chloride (Table 2, entry 5) under the same reaction conditions (at room temperature), no reaction was observed, even after raising the temperature to 100°C.

Table 2: Effect of Alkyl Halide in the Sonogashira coupling reaction of arylhalides with phenylacetylene



Aryl halide (1a – 1d)	Alkyne (2a)	Coupling Product (3a – 3c)	Isolated Yield (%)
 1a	 2a	 3a	78
 1b	 2a	 3b	88
 1c	 2a	 3c	95
 1d	 2a	---	
 1e	 2a	---	

Reaction Conditions: H_{10} catalyst (1mol%), aryl halide (1mmol), phenylacetylene (1.2mmol), KOH (2.0mmol), CH_3CN (2ml), H_2O (2ml), room temperature, time (2hours).
*Does not react even at 100°C.

CONCLUSION

The synthesis of *N*-heterocyclic carbene precursor and its corresponding *N*-heterocyclic carbene pyridine complex was achieved. The new *N*-heterocyclic carbene pyridine complex was found to be effective catalyst for the Sonogashira coupling reactions of phenylacetylene with various aryl halides and was found to show better catalytic property compared to other commercially available palladium precursors.

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