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NI (II) PINCER COMPLEX CATALYZED SONOGASHIRA COUPLING OF 3-IODO-1*H*-INDAZOLE WITH TERMINAL ALKYNES CUI AS CO-CATALYST

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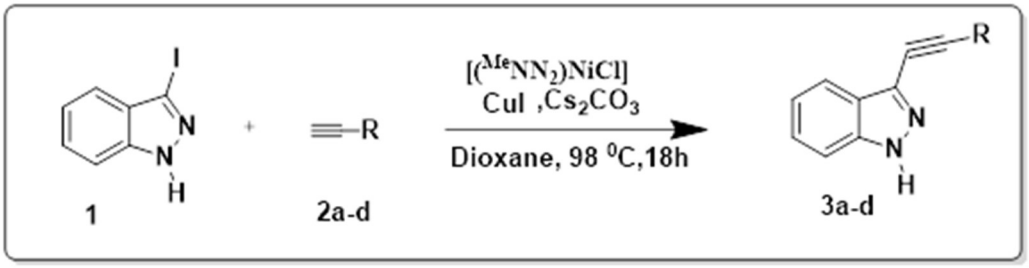
Abstract: Herein, we report the coupling of 3-iodo-1*H*-indazole **1** with a series of terminal alkynes **2a-d** to give desired 1*H*-indazoles **3a-d** with promising yields through C-C single bond formation via Sonogashira coupling in the presence of Ni (II) pincer complex as catalyst, whereas CuI as co-catalyst. The reaction did not occur under metal free conditions.

Keywords: 3-iodo-1*H*-indazole, Sonogashira coupling, Ni pincer complex, CuI.



Scheme I. Synthetic path way for compounds **3a-d**

1. INTRODUCTION

Numerous organic compounds, bioactive chemicals, and natural products all contain substituted alkynes as organic materials [1]. In addition, they are adaptable synthetic intermediates [2-3]. Over the past few years, Sonogashira coupling has emerged as one of the most popular techniques for adding alkynyl functionality to organic molecules. The struggle between C-C coupling and C -H elimination is further hampered by their sub-stoichiometric presence in relation to the substrates.

As a consequence, there have only been two prior reports of successful Sonogashira coupling of such substrates, in contrast to recent developments in other cross-coupling methods of non-activated alkyl halides [5]. Fu *et al*. [4] and later Glorius *et al*. [6]. Demonstrated the coupling of alkyl iodides and bromides utilizing Pd (NHC) catalysts in their key pioneering investigations.

A potent and adaptable technique for the production of acetylene is the Sonogashira-Hagihara [9] reaction of terminal alkynes with aryl halides catalyzed by Pd complexes in the presence of a catalytic quantity of CuI and an amine base. Natural compounds, [10] biologically active molecules, [11] new organic materials for optical and microelectronic applications, [12] dendrimeric, oligomeric, and polymeric materials, [13] macrocycles with acetylene links, [14] polyalkynylated molecules have been accomplished using this method. [15]

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2. EXPERIMENTAL SECTION

2.1General information

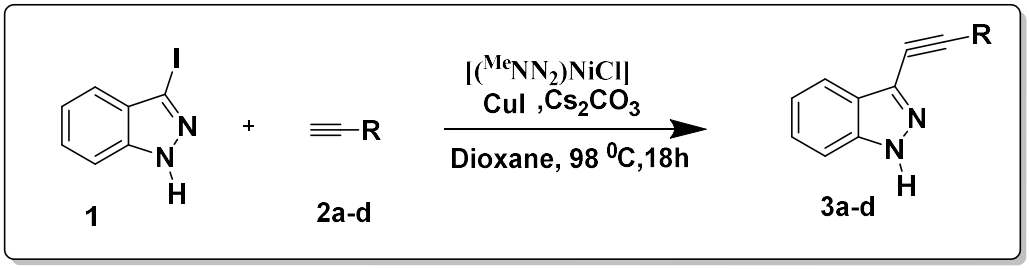
Electro thermal apparatus was used to record the melting point of synthesized compounds and are uncorrected. Thin-layer chromatography (TLC) was performed by using Merck silica gel 60 F254 precoated plates (0.25 mm) and column chromatography was performed by using Silica gel (particle size 100-200 mesh). ^{1}H NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer. ^{13}C NMR spectra were recorded on a Bruker AMX 100 MHz spectrometer. Chemical shift values were given in ppm (δ) with TMS as an internal standard. Mass spectra were determined on Agilent LC-1100 (LC-MS) series instrument.

2.2 General procedure for the synthesis of series of substituted 1*H*-indazole 3a-d:

In this context, coupling of 3-iodo-1*H*-indazole **1** with a series of terminal alkynes **2a-d** used as a test reaction. After exploring a wide range of conditions to give promising yield in dioxane using a 5 mol % loading of our previously reported Ni II pincer complex [7-8]as the catalyst, 3 mol % CuI as the co-catalyst, and 1.4 equiv of Cs_2CO_3 as the base (Scheme I). The best results were obtained at 98 °C. Other combinations of solvents, bases, and co-catalysts led to give desired 1*H*-indazole **3a-d**.

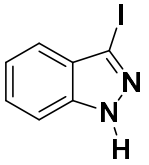
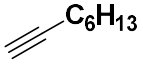
3. RESULTS AND DISCUSSIONS

A different series of substituted-1*H*-indazoles 3a-d viz, Sonogashira coupling followed by Ni (II) pincer complex as the catalyst, 3 mol % CuI as the co-catalyst, and 1.4 equiv of Cs_2CO_3 as the base . The best results were obtained at 98 °C. Other combinations of solvents, bases, and co-catalysts led to promising yields described in Scheme I (**Table 1 & 2).**



Scheme I

Table: 1 Structures and Name of the compounds:

Entry	Structure	IUPAC Name
1		3-iodo-1*H*-indazole
2a		Hex-1-yne
2b		Oct-1-yne

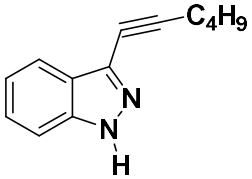
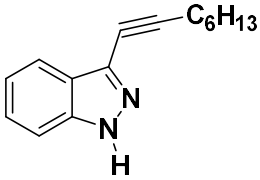
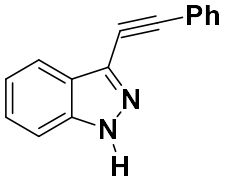
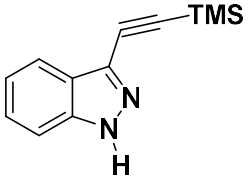
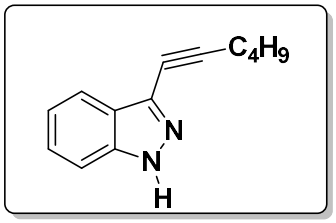
2c		Ethynyl benzene
2d		Ethynyl trimethylsilane
3a		3-(hex-1-yn-1-yl)-1*H*-indazole
3b		3-(oct-1-yn-1-yl)-1*H*-indazole
3c		3-(phenylethynyl)-1*H*-indazole
3d		3-((trimethylsilyl)ethynyl)-1*H*-indazole

Table: 2 Yield (%) and Mass values of synthesized compounds 3a-d:

Entry	MF	Yield (%)	$(M+H)^+$ ESI
3a	$C_{13}H_{14}N_2$	80	199.12
3b	$C_{15}H_{18}N_2$	68	227.15
3c	$C_{15}H_{10}N_2$	84	219.08
3d	$C_{12}H_{14}N_2Si$	72	215.09

3-(hex-1-yn-1-yl)-1*H*-indazole 3a:



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.7 Hz, 1H), 7.42 – 7.10 (m, 3H), 2.38 (d, *J* = 5.3 Hz, 2H), 1.52 (dt, *J* = 10.2, 7.9 Hz, 4H), 1.00 (t, *J* = 6.5 Hz, 3H).**^{13} C NMR (100 MHz, $CDCl_3$):** δ 145.26, 126.68, 126.29, 122.38, 119.88, 114.62, 112.69, 111.65, 60.81, 29.74, 21.47, 17.08, 14.01.

3-(oct-1-yn-1-yl)-1*H*-indazole 3b:

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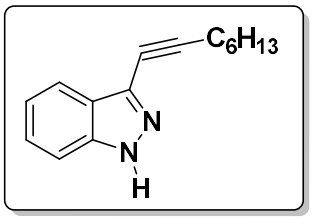
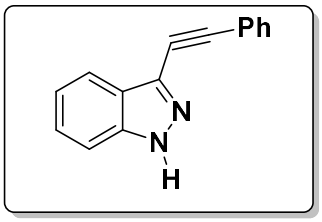


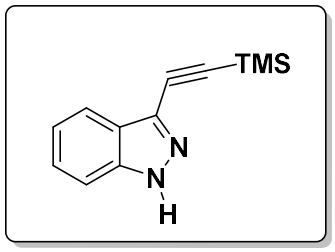
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.44 – 7.14 (m, 3H), 2.31 (t, *J* = 8.0 Hz, 2H), 1.56 (dd, *J* = 15.8, 7.9 Hz, 2H), 1.33 (dt, *J* = 15.3, 8.6 Hz, 6H), 0.99 (t, *J* = 6.4 Hz, 3H).**^{13} C NMR (100MHz, $CDCl_3$):** 145.26, 126.68, 126.29, 122.38, 119.88, 114.62, 112.69, 111.65, 60.81, 31.64, 29.19, 28.50, 22.93, 18.78, 14.01.

3-(phenylethynyl)-1*H*-indazole 3c:



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.45 (dd, *J* = 5.4, 2.0 Hz, 2H), 7.42 – 7.36 (m, 2H), 7.32 (td, *J* = 7.2, 2.1 Hz, 1H), 7.26 – 7.19 (m, 3H).**^{13} C NMR (100 MHz, $CDCl_3$):** δ 145.26, 131.41, 128.59, 126.68, 126.29, 123.33, 123.09, 122.38, 119.88, 112.69, 78.51.

3-((trimethylsilyl) ethynyl)-1*H*-indazole 3d:



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.3 Hz, 1H), 7.34 (dt, *J* = 22.5, 11.2 Hz, 3H), 0.38 (s, 9H). ^{1}HNMR N-H proton signal disappears in the presence of $CDCl_3$ solvent.**^{13} C NMR (100 MHz, $CDCl_3$):** δ 145.26, 126.68, 126.29, 122.38, 119.88, 112.69, 109.42, and 97.45.

4. CONCLUSION

In summary, a novel, cost-effective and practical method was developed to synthesize the series of 1*H*-indazoles **3a-d**. The advantages of this method include a simple reaction set-up not requiring specialized equipment's, low-toxicity of the reagent, moderate reaction times, and high product yields with excellent purity.

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