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Novel synthesis and antimicrobial screening of 3-(6-Methoxycarbonylamino-pyridine-3-ylethynyl)-4-methyl-benzoic acid methyl ester by Sonogashira reaction

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ABSTRACT
Synthesis of 3-(6-Methoxycarbonylamino-pyridine-3-ylethynyl)-4-methyl-benzoic Acid methyl ester synthesized by using (5-Iodo-pyridine-2-yl)-carbamic acid methyl ester with presence of triethylamine, copper(I)iodide, N,N,dimethylformamide, and bis (triphenylphosphone)) palladium(II) chloride. All synthesized compound are active antimicrobial agents.
Keywords: *3-(6-Methoxycarbonylamino-pyridine-3-ylethynyl)-4-methylbenzoic acid methyl ester, Sonogashira Reaction, antimicrobial screening.*

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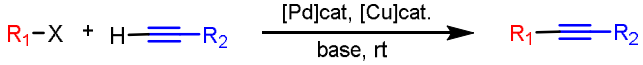
INTRODUCTION

Cross-coupling reactions mediated by transition metals are among the most essential methods for forming new carbon-carbon bonds [1-4]. The Sonogashira coupling reaction (palladium-catalyzed coupling of terminal alkyne with aryl halide) [5] has become a very attractive and powerful tool for the C(sp)-C(sp) bond forming reactions over the last 30 years [6].



The Sonogashira coupling is a palladium catalyzed C-C bond formation method that couple a terminal sp hybridized carbon from an alkyne to a sp2 carbon of an aryl or vinyl halide. This discovery came serval months after Cassar [7] Dieck and Heck [8]. Among that only palladium catalysis could be used to conduct this coupling at high temperatures. The reaction was named after Sonogashira, Thoda, and Hagihara who discovered in 1975 that this procedure could be carried out readily at room temperature utilizing a palladium source as PdCl2(PPh3)2 as catalyst and a co-catalytic quantity of CuI in an amine as solvent [9]. Sonogashira and Hagihara reported that addition of a catalytic amount of copper(I) Iodide greatly accelerates the reaction, thus enabling performance of the alkynylation at room temperature [10], an observation related to the already known coupling between copper acetylides and phenyl or vinyl halides (the so-called Stephens Castro reaction) [11].Therefore, the Sonogashira-Hagihara protocol (more often simply known as Sonogashira coupling) became procedure for the alkynylation of aryl or alkenyl halides. Because of its utility forming carbon-carbon bonds, the Sonogashira cross-coupling reaction has been used in a wide range of applications. The Sonogashira cross-coupling reaction can be carried out at mild conditions, such as at room temperature, in aqueous medium, and with gentle base, allowing it to be used in the synthesis [12-21]. The situations are considerably more encouraging in active (electron-poor) organic halides [22]. Modified nucleoside, nucleotides, and nucleic acids have many new applications in chemical biology, nanotechnology, and bioanalysis, as well as diagnostic and organic catalysis. Nucleic acids with reporter moieties, for example, can be employed to improve their intrinsic characteristics as well as to impart wholly new qualities for usage in a variety of biochemical applications [23,24]. Many metabolites and pharmaceutically significant scaffolds in nature contain alkyne or enyne groups, the Sonogashira

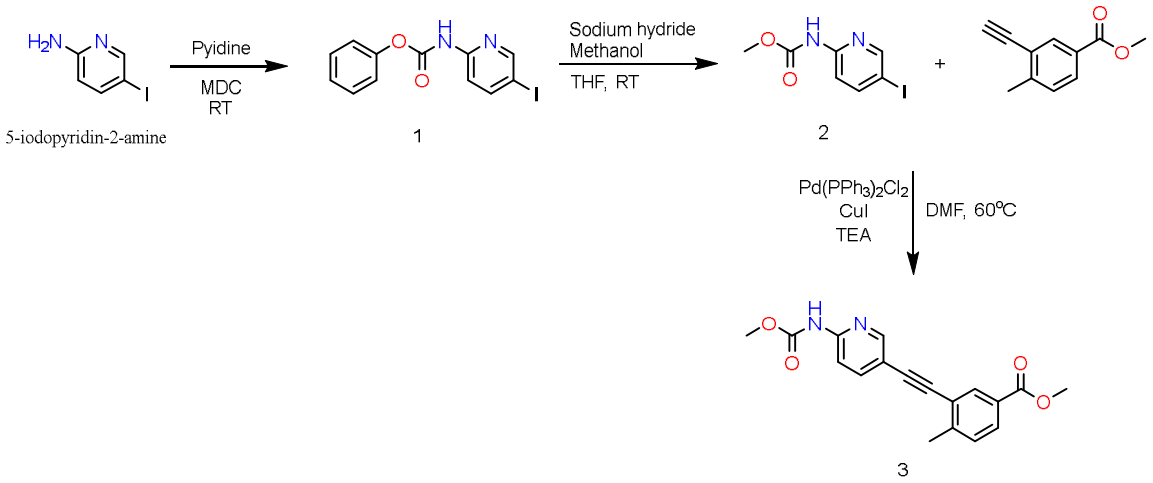
reaction has been widely used to synthesis them. To achieve this, some of the most current and promising uses of the Sonogashira coupling technology were used. So, the Sonogashira reaction produces a variety of compounds That can be used in a variety of ways. The sonogashira reactions product have application in dye, sensor, electronics, polymers, guest-host complex, among other fields of chemistry. It may be used to make wide range of chemical, including heterocycle, natural product, and pharmaceuticals [25-26]. The Sonogashira process has also been used to oligomers and polymers, in addition to natural products [27-29]. The importance of sp-sp bond formation in organic synthesis stems from the usefulness of natural products as medicinal chemistry targets and inspiration for methodological breakthroughs.

MATERIAL AND METHODS

All chemicals were indented from Merck laboratories. ^{1}H NMR spectra were recorded on bruker avance II (400MHz) spectrometer using DMSO as a solvent. TMS was taken as a standard and chemical shift data were reported in parts per million (ppm). Mass spectra were recorded in LCMS (Direct mass). Reaction was monitored by TLC silica gel 60 F_{254}. Melting point was recorded on melting point apparats mp 30 by capillary and was uncorrected. IR spectra were recorded on Schimadzu SX400 model.

RESULTS AND DISCUSSION

Synthesis of 3-(6-Methoxycarbonylamino-pyridine-3-ylethynyl)-4-methyl-benzoic acid methyl ester through Sonogashira reaction by coupling (5-Iodo-pyridine-2-yl)-carbamic acid methyl ester (2) & 3-ethynyl-4-methylbenzoate in good yield. (5-Iodo-pyridine-2-yl)-carbamic acid methyl ester synthesized by reaction of (5-Iodo-pyridine-2-yl)-carbamic acid phenyl ester with NaH in methanol & THF which was previously synthesized by coupling 5-Iodopyridine-2-amine & phenyl chloroformate. The structures of all synthesized compounds were confirmed by ^{1}H NMR analyses.



Synthesis of (5-Iodo-pyridine-2-yl)-carbamic acid phenyl ester (1)

To a solution 5-Iodopyridine-2-amine (2g, 9.09mmol) in 20ml MDC were added phenyl chloroformate (1.38ml,11.8mmol) and pyridine (0.88ml,11.8mmole). The reaction mixture was stirred for 3hr. at room temperature. The reaction was monitored by TLC & complies. The reaction mixture was concentrated. 25ml diisopropyl ether added & stirred for 15 min. The solid precipitate was filtered and washed using diisopropyl ether. The solid residue was dried at 50^{0}C for 2hr under high vacuum. (Yield: 1.4 g, 78%), White solid, m.p 150-157^{0}C, IR spectrum, ν, cm^{-1}: 3356(NH), 2911(CH), 1701(C=O), 1575 (NH Bend), 1541,1507(C=C), 1318 (CN), 1108 (CO), 1018,937,853,781,749,696,631,601,526(C-I). 1H NMR (400MHz, DMSO, δ ppm): 10.09 (s,1H,-NH), 8.59 (d, 1H, J=1Hz,C_6-H), 8.17 (dd, 1H, J1=6.2Hz, J2=2.3hz, C_4-H), 7.74 (d, 1H, J=8.8Hz, C_3-H), 7.49 (t, 2H, J=8.15Hz, $C_{3,5}$-H), 7.35 (t,1H, J=7.41Hz, C4-H), 7.28 (d, 2H, J=7.41Hz, C_6,2-H), exact mass of the compound was 340, and LCMS (Direct mass) base peak at 340.82. Found, % C 42.35; H 2.69; N 8.36; O 9.44. $C_{12}H_9IN_2O_2$. Calculated, %: C 42.38; H 2.67; N 8.36; O 9.41.

Synthesis of (5-Iodo-pyridine-2-yl)-carbamic acid methyl ester (2)

Sodium hydride (60% dispersion in mineral oil), (0.81g, 20.5mmol) was added to a stirred mixture of methanol (0.71ml, 17.64mmol) in 30ml THF. (5-Iodo-pyridine-2-yl)-carbamic acid phenyl ester (2g, 5.8mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 2hr. The reaction was monitored by TLC & complies. The reaction mixture was concentrated, the residue quenched was using 50ml DM water and extracted in 50ml ethyl acetate. The organic layer was dried over sodium sulphate and concentrated under high vacuum at 40 ^{0}C. The crude product was purified by column

chromatography on silica gel using to yield the solid. Solid was dried under high vacuum. (Yield: 1.3 g, 65%), white solid, m.p 128-132^{0}C, IR spectrum, ν, cm^{-1}: 3339(NH), 3023(CH), 1675(C=O), 1596,1576 (C=C), 1449 (CH3), 1314 (CN), 1215,1195 (C-O), 1111,1073,994,811,758,692,650,606,575(C-I). ^{1}H NMR (400MHz), DMSO, δ ppm); 10.31(s, 1H, -NH), 8.48 (d, 1H, J=1.89Hz, C_6-H), 8.11 (dd, 1H, J1=6.5Hz, J2=2.24HZ, C_4-H), 7.73 (d, 1H, J=8.89Hz, C_3-H), 3.70 (s, 3H), Exact mass of the compound was 277, and LCMS (Direct mass) base peak at 277.42 Found%: C 30.22; H 2.55; N 10.11; O 11.52. $C_7H_7IN_2O_2$. Calculated, %: C 30.24; H 2.52; N 10.08; O 11.51.

Synthesis of 3-(6-Methoxycarbonylamino-pyridine-3-ylethynyl)-4-methyl-benzoic acid methyl ester (3):

Copper(I) iodide (0.034g, 0.1798mmol), bis(triphenylphosphine) palladium (II) dichloride (0.094g, 0.1348mmol), (5-Iodo-pyridine-2-yl)-carbamic acid methyl ester (0.500g, 1.798mmol) with methyl 3-ethynyl-4-methylbenzoate (0.31g, 1.798mmol) were suspended in a 5ml DMF. Trimethylamine (0.49ml, 3.5mmol) was added in reaction mixture at room temperature, The reaction mixture was heated to 60^{0}C for 4hr under nitrogen atm. Reaction was monitored by TLC & complies. The reaction mixture was concentrated and the residue was quenched using 50ml DM water and extracted in 50 mL MDC. MDC layer was washed using 50ml distilled water. Org. layer dried over Sodium sulphate and concentrated. The resultant residue was purified using column chromatography using (5% Methanol in MDC) to yield the solid. Solid was dried under high vacuum (yield: 0.245 g, 49%), m.p 170-175 ^{0}C. IR spectrum, ν, cm^{-1}: 3349(NH), 3089,3064 (CH), 2294 (C≡C), 1688(C=O), 1530(NH), 1449 (CH3), 1342(CN), 1143(C-O), 996, 848, 783, 752, 726, 683, 594, 568, 516. ^{1}H NMR (400MHz, DMSO, δ ppm): 10.58 (s, 1h, -NH), 8.57 (s, 1H, C_2-H), 8.09 (s, 1H, C_2-H), 8.05 (d, 1H, J=7.81Hz, C_6-H), 7.96 (d, 1H, J=8.89Hz, C_4-H), 7.93 (d, 1H, J=8.05Hz, C_5-H), 7.55 (d, 1H, J=7.7Hz, C_5-H), 3.91 (s, 3H, CH_3), 3.75 (s, 3H, CH_3). Exact mass of compound 324, and LCMS (Direct mass) molecular ion peak at 324.88 found, %: C 66.67; H 4.95; N 8.66; O 19.73. $C_{18}H_{16}N_2O_4$. Calculated, %: C66.66; H 4.94; N 8.64; O 19.74.

Antimicrobial Activity: The Antimicrobial activity of compound was evaluated & compared with standard drugs. All the compound were tested for their antibacterial activity. Against Staphylococuus aureus (gm +Ve) & Escherichia coli (gm -Ve) using cup plate method at (100 ppm) (10 mg/ml) concentration in DMF (dichloromethane) solvent. Amplicillin was used as standard drug. All compound showed excellent activity against both strain (Table)

Pharmacology: Anti-bacterial activity of all synthesized compound was tested in vitro in bacterial strain of Staphylococuus aureus (gram +ve), Escherichia coli (gram -ve) were used, using serial agar dilution (cup plate method). The microorganisms were cultured in dishes containing agar medium, cup (8 mm) was put onto the dished and each compound (0.1 ml) was added into the cups under aseptic condition. Then the dishes were incubated at 37^{o}C for 24h. The zone of inhibition of the growth of the bacteria, which were produced by diffusion of the compound from the cup into the surrounding medium, was measured to evaluate the antibacterial activity. Each experimental was repeated twice. Ampicillin was used as a positive control for the experiments. Compare to control all compound showed higher antibacterial activity.

Table: *In Vitro* antibacterial activity of synthesized compounds

MIC of antibacterial agent (μM)			
Sr No.	Compound	S.aureus	E coli
01	1	16 mm	29 mm
02	2	10 mm	19 mm
03	3	15 mm	26 mm
04	Amplicillin	10 mm	12 mm

S.*aureus*: staphylococcus aureus, **E.coli:** Escherichia coli

Compound 1: (5-Iodo-pyridine-2-yl)-carbamic acid phenyl ester

Compound 2: (5-Iodo-pyridine-2-yl)-carbamic acid methyl ester

Compound 3: 3-(6-Methoxycarbonylamino-pyridine-3-yl ethynyl)-4-methyl-benzoic acid methyl ester \

CONCLUSION

Developed Sonogashira coupling provides an excellent mechanism & % yield for the creation of C-C networks, as we show here (sp-sp) bonds that has been widely used in the pharmaceuticals intermediate. All synthesized entities screened for antimicrobial activity & found potent against S. aureus & E.coli microorganisms.

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