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Synthesis and Characterization of Indazole Derivative via Suzuki Coupling Reaction

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Abstract: Suzuki coupling reaction used for preparation of methyl 4-(5-methyl-1H-indazole-4-) benzoate. A derivative of 5-methyl-4-phenyl-1H-indazole are prepared with excellent yield by acid amine reaction and cyclization using T_3P (propanephosphonic acid anhydride) and Triphosgene serve as catalyst, respectively. The prepared derivatives 4-(5-methyl-1H-indazol-4-yl)-N-(1-phenylpropyl) benzamide and 5-(4-(5-methyl-1H-indazol-4-yl) phenyl)-1, 3, 4-oxadiazol-2(3H)-one are characterized by ESI mass spectroscopy and1HNMR.

Keywords: Acid-Amine coupling, Indazole, Triphosphosgene, Suzuki coupling, Tetrakis

Introduction

Heterocycles compound contains two dissimilar elements in place of members of its ring(s). Heterocyclic chemistry is the branch of organic chemistry which are deal with the synthetic properties, and applications of these heterocyclic compounds. Other elements along with carbon such as nitrogen, sulphur and oxygen it can be included in the rings, the compounds are called heterocyclic compounds. The heterocycle is named that means there is at least one or more than one hetero atom is present in the ring and its cyclic moieties. Heterocyclic compounds conceivably constitute the prime and utmost diverse family of organic compound. Moreover, every single carbocyclic complex, irrespective of structure and functionality, principle used for collection of heterocyclic analogues compound by substituting one or additional of the ring carbon molecules with a unlike element. Even if we restrict our consideration to oxygen, nitrogen and sulphur (mostly heterocyclic elements), the variations and mixtures of such replacement are frequent. Polycyclic ring structure and higher number of non-cumulative double bonds disturbed nomenclature of two-dimensional reprehensive structure. In addition, this system may be bridged, or involved in assemblies or Spiro systems (not covered by these rules). The fusion of two atoms and one bond may derivative since the two rings as separate entities used for nomenclature of compound.

Heterocyclic ring is preferred as the parent compound and fused ring is committed as a prefix. Indazole is organic, heterocyclic, aromatic, bicyclic compound consists of the fusion of benzene and pyrazole. It is a colourless solid. In medicinal chemistry its have own important pharmacophore and honoured structure. Now a day's moiety of choice which possesses many pharmacological properties. The Indazoles are one of the most important classes of nitrogen-containing heterocyclic compounds behave as a bicyclic ring structure synthesized pyrazole and benzene ring. Generally indazole comprises two tautomeric forms: 1H and 2H-indazole. The nitrogen-containing heterocycles are important building blocks for many bioactive natural products and commercially available drugs. As pharmacologically important scaffolds, they have attracted considerable attention from chemists [1]. Indazoles are one of the most important classes of nitrogen-containing heterocyclic compounds behaviour of bicyclic moieties completed up of a pyrazole ring and benzene ring. Indazole generally contains two tautomeric forms: 1H-indazole and 2H-indazole. Subsequently 1H-indazole is more thermodynamically stable than 2H-indazole, there is the prime tautomer [2]. Indazole derivatives hardly occur in nature, but this particular nucleus in a variability of synthetic moiety keeps wide range of pharmacological actions, such as anti-inflammatory, antiarrhythmic, antitumor, antifungal, antibacterial, and anti-HIV activities [3–8]. Distinctly relieved indazole-containing complexes well-appointed with dissimilar functional groups denote important pharmacological activities and serve used as structural motifs in drug molecules. For example, niraparib 1 (Figure 2) has been widely used as an anticancer drug for the treatment of recurrent epithelial ovarian, fallopian tube or primary peritoneal, breast and prostate cancer

[9]. Pazopanib 2(Figure 2) is a tyrosine kinase inhibitor, which has been approved by the FDA for renal cell carcinoma [10]. Benzydamine 4 and Bendazac 3 are commercially used as an anti-inflammatory drugs, which refuge 1H-indazole scaffold (Figure 2) [11]. Iindazole scaffolds display broad spectrum light with pharmacological activities and numerous approaches have been established these heterocycles with healthier biological activities.

There are many research spotted on novel indazole-containing derivatives its synthesis and their biological properties [12–13]. Tesaro was develop an orally active compound namely Niraparib (trade name Zejula) serve as PARP inhibitor used for ovarian cancer treatment [1]. US FDA providing approval to this drug for those patient who gave partial response towards platinum-based chemotherapy that used to treatment of adult patients with recurring fallopian tube, epithelial ovarian or primary peritoneal cancer. Pazopanib (trade name Votrient) known as selective and effective multi-targeted tyrosine kinase inhibitor used to inhibits angiogenesis and prevent tumour growth. Nonsteroidal anti-inflammatory drug Bendazac (or bendazolic acid), plasticised for medication in treatment of joint and muscular pain and irregular renal cell carcinoma. Another Nonsteroidal anti-inflammatory drug Benzydamine (alias as Tantum Verde and registered in certain states as Difflam and Septabene) with anti-inflammatory treatment for mouth and throat as well as local anaesthetic and analgesic properties for pain relief.

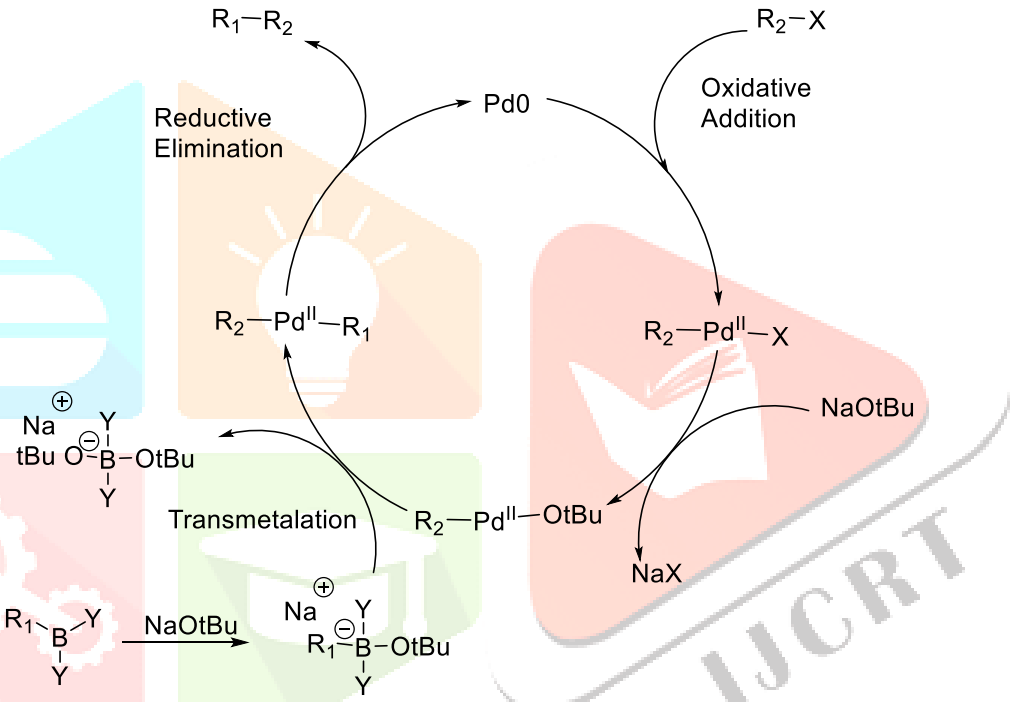

Figure-1: Suzuki Coupling

Suzuki reaction is an organic reaction, classified as a coupling reaction, where the coupling partners are a boronic acid and an organohalide catalyzed by a palladium (0) complex.8, 10, 11 It was first published in 1979 by Akira Suzuki and he shared the 2010 Nobel Prize in Chemistry with Richard F. Heck and Ei-ichi Negishifor their effort for discovery and development of palladium-catalyzed cross couplings in organic synthesis [12]. Several publication wrote this reaction as Suzuki–Miyaura reaction which is also known to as the Suzuki coupling.

Acid-Amine coupling reaction is an organic reaction.in this reaction acid and amine couple to each other and get amide (-CONH) bond using T3P, HATU, HBTU, EDC+ HOBt, EDC+DMAP, DCC, BOP, PyBOP, CDI, Mixed Anhydrides and Succinimidyl Esters this are the reagent use in this reaction and TEA, DIEA as a Base

General Reaction:-

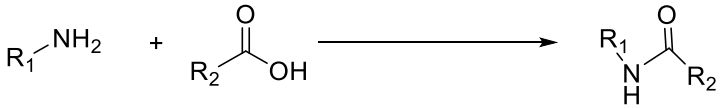

Figure-2: Acid Amide

Mechanism:-

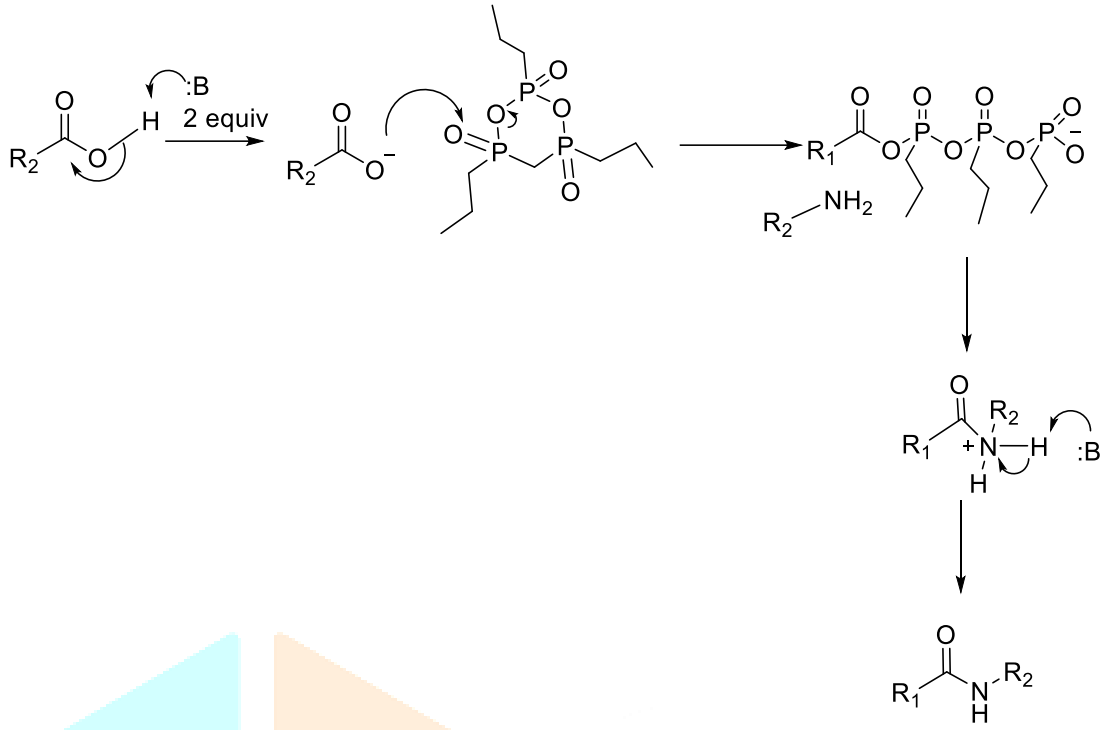

Figure-3: Acid Amide Reaction Mechanism

Cyclisation reaction

Based on bonding distances or bond angles of the reaction intermediate Baldwin's rules led feasibility of cyclisation reaction of carbanions. This rules mostly apply on ring closer elements produced 3 to 7 membered rings contained compound in second period of reaction. According to this reaction three factor that affect reaction at various stage mainly,

1. The ring strain of the reaction reflected due to different size of newly develop rings.
2. Relative direction of the bond was changed due to anion attached on electron deficient receptor of exo/endo newly formed rings.
3. During the reaction period the electron deficient part (diagonal, trigonal, tetrahedral) was affected by tereostructure.

Disadvantage

1. One of the raw material phosgene is highly toxic/hazardous chemical that adversely affect the production environments as well as transport system. Moreover, off-gas containing phosgene reaction more dangerous, required process safety and higher labour protection
2. High number of phosgene is generate by decomposing of diphosgene (colourless liquid) at high temperature and pressure
3. Between the reaction small amount of trichloromethyl carbonate (triphosgene) have characters like colourless crystals, highly toxic with phosgene like odour was discharged which is mainly used as a substitute for phosgene,

Nowadays, in industry feed components were altered by using diphosgene and triphosgene but during feeding operation negligible amount of highly toxic phosgene was liberated. Several country face second level risk because of multi-layer solid phosgene, led improper disposal as well as caused mass casualties.

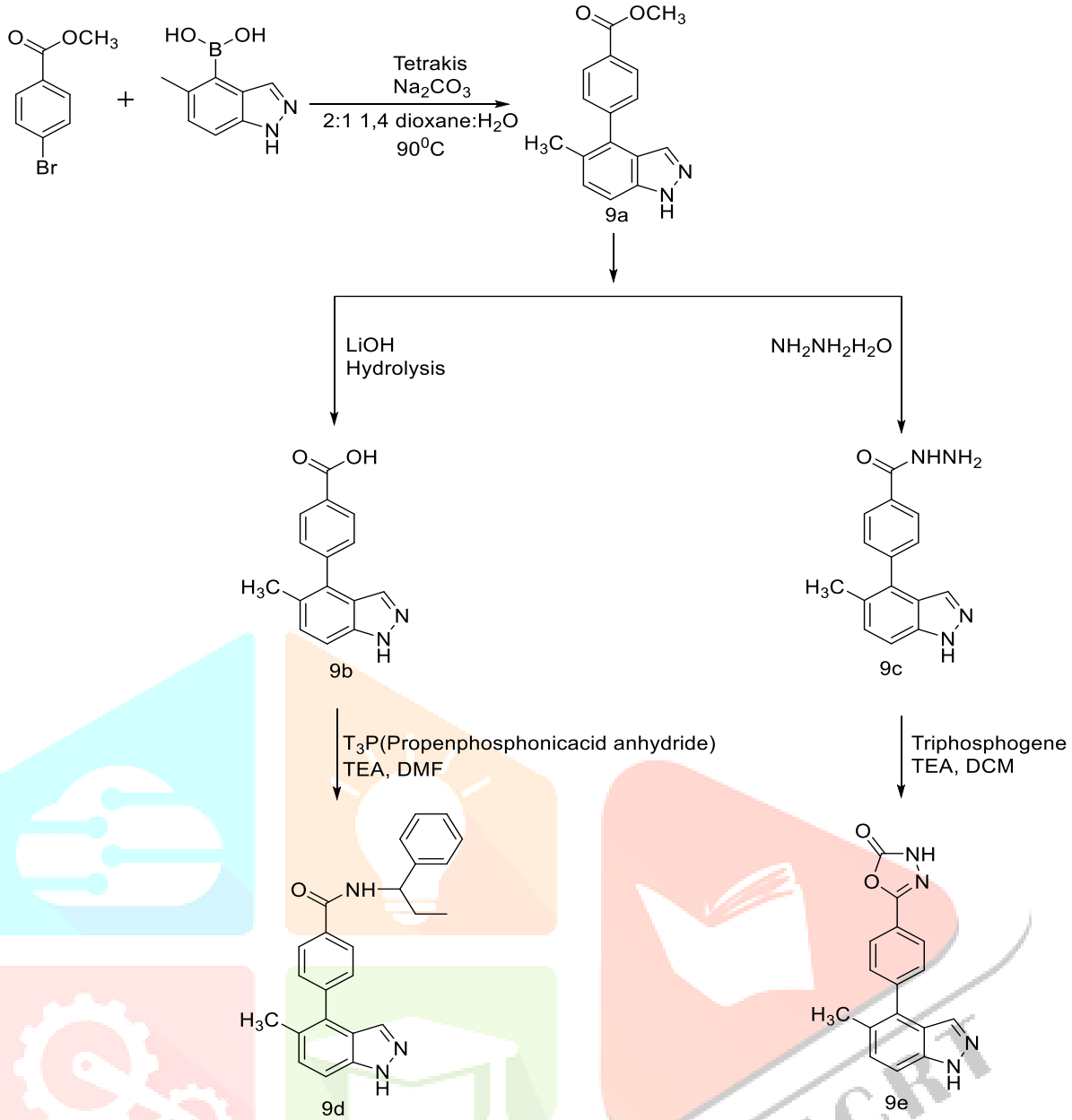

Figure-4: Route of Reaction

Synthesis

Synthetic route of 9(a): The synthetic route of present series is shown in the scheme. 500 mg methyl 4-bromobenzoate and 615 mg boronic acid dissolve in 2:1 ratio (12 ml) 1, 4 dioxane + water. After one hour dropwise add 740 mg saturated Na_2CO_3 solution with constant stirring. Then add 269 mg Tetrakis catalyst get 90ºC temperature. TLC performed in 30% E.A-Haxene.

Work Up (Ethyl-Water): Organic layer taken and brian solution was added in this layer and again separate the upper organic layer. After that sodium sulphate was added and then concentrate on Rotavapor.

Synthetic route of 9(b): 200 mg compound-9(a) was taken and dissolved in 10 ml MeOH then 1M LiOH was added in this reaction mixture. Then put it for stirred at room temperature overnight. TLC performed in 40% Ethyl-Hexane system.

Work Up (Ethyl-Water): Neutralized the LIOH with HCl, Organic layer taken and brine solution was added in this layer and again separate the upper organic layer. After that sodium sulphate was added and then concentrate on Rotavapour.

Synthetic route of 9(C): 200 mg compound-9(b)[methyl4-(5-methyl-1H-indazole-4-yl) benzoate] was taken and dissolved in 7.52 ml Ethanol and add 4ml $NH_2NH_2.H_2O$ (Hydrazide hydrate) With continuous degassing and get the stir at room temperature of overnight. TLC performed in 40% Ethyl-Hexane system.

Work Up (Ethyl-Water): Organic layer taken and brine solution was added in this layer and again separate the upper organic layer. After that sodium sulphate was added and then concentrate on Rotavapour.

Synthetic route of 9(d):140mg compound-9(c) [4-(5-methyl-1H-indazole-4-) benzoic acid and 80.65mg INT-2 (1-phenylpropane-1-amine) dissolve in DMF solvent and add TEA (Triethyl amine) at 0ºC

and dissolve T_3P (propanephosphonic acid anhydride) in and add this solution in above mixture.stirr the mixture at room temperature of overnight. TLC performed in 40% Ethyl-Hexane system.

Work Up (Ethyl-Water): Organic layer taken and brine solution was added in this layer and again separate the upper organic layer. After that sodium sulphate was added and then concentrate on Rotavapour.

Characterization By: NMR (DMSO) δ: 8.94 (s, 1H), 8.04 (d, 2H), 7.60 (s, 1H), 7.53 (m, 5H), 7.32 (m, 3H), 7.23 (d, 1H), 5.21 (t, 1H), 2.66 (s, 3H), 1.23 (q, 2H), 1.16 (t, 3H) **MS (ES+):** Molecular ion Peak 370

Synthetic route of 9(e): 50mg compound 9(d) [5-(4-(5-methyl-1H-indazole-4-yl) phenyl)- 1,3,4-oxadiazole-2(3H)-one dissolve in 2.0 ml DCM solvent and add TEA (Triethyl amine) at 0ºC and Triphosgene in DCM and add the above mixture at 0ºC. stirred the mixture at room temperature of overnight. TLC performed in 40% Ethyl-Hexane system.

Work Up (Ethyl-Water): Organic layer taken and brine solution was added in this layer and again separate the upper organic layer. After that sodium sulphate was added and then concentrate on Rotavapour.

Characterization By: NMR (DMSO) δ: 13.23 (s, 1H), 12.60 (s, 1H), 7.91 (dd, 2H), 7.68 (s, 1H), 7.53 (dd, 2H), 7.32 (d, 1H), 7.23 (d, 1H), 2.39 (s, 3H)
MS (ES+): M+1 Peak (293.16)

Conclusion:

In summary, we have described derivative of indazole by Suzuki Reaction using tetrakis catalyst. The main advantage of this reaction is good yields, simple work up, operational simplicity without any anhydrous condition. The yield obtained using tetrakis catalyst is 32%. The indazole ring is an important pharmacophore in modern drug discovery. Attention has been increasingly given to the synthesis of indazole derivatives as a source of new antimicrobial agents. The indazole derivatives are a resource for medicinal research. The knowledge gained by various researches has suggested that substituted indazoles and heterocycles possess pharmacological activity with lower toxicities. Since now, researchers have been attracted toward designing more potent indazole derivatives having wide diverse of biological activity.

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