Original Article: Ammonium Chloride Catalyzed Green Synthesis, Characterization of Substituted 1-*H*-Indazole Derivatives

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ABSTRACT

We have demonstrated novel and eco-friendly acceptable green methods for the synthesis of numerous 1-*H*-indazole by grinding protocol using NH_4Cl milder acids in an EtOH solvent. The substituted 1-*H*-indazole synthesized from the grinding of *ortho*-hydroxybenzaldehyde with hydrazine hydrate in an Ethanol solvent and NH_4Cl milder acids. The methods give good yield within less time. The protocol is practically green, milder, higher yield, with short reaction times.

Introduction

Indazole is aheterocyclicaromaticorganic compound1. Indazole derivatives spread a broad variety of biological activities.[1] heteroatom compounds moiety has resulted in the finding of potent HIV protease agonist [2], aldolreductase inhibitors, serotonin receptor antagonists, and acetylcholinesterase inhibitors[3], anti-inflammatory[4], antitumor [5], and anticancer [6] agents, and serotonin 5-HT3 receptor antagonists [7]. The numerous methods for the synthesis of indazole have been reported in the literature. Indazole with cyclohexanone ring show antimicrobial antitubercular activity Brian S. Brown *et al.,* [8], Indazole derivatives with aryl group on the 5 or

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6 position have been synthesized and analyzed as potent, inhibitors of proteins kinase[9] or selective glucocorticoid receptor agonists and antagonists[10]. The indazole scaffolds are one of the significant bioactive molecules, drug, and natural products.

Some of the natural products and biologically active indazole Show in (**Figure 1**).

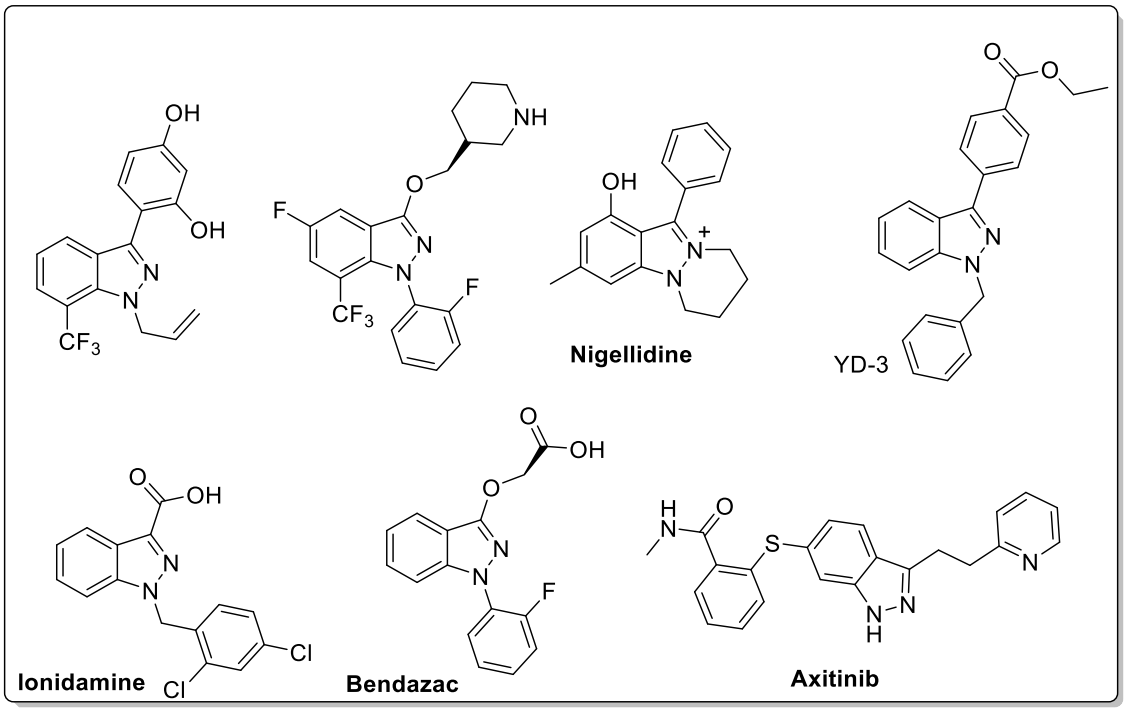


Figure 1. Biologically active various molecules with an indazole moiety

Synthesis of indazole by cyclization of hydrazone of substituted acetophenones and benzophenones in polyphosphoric acid PPA [11].Use of Michael reaction for the preparation of indazole achieved by *1,3-dipolar cycloaddition of nitrile imines to benzyne is described by John et al 2010* [12]. Diels alder reaction synthesized indazole by 3+2 cycloaddition between arynes generated from silylaryltriflates and various diazomethane derivatives,it shows different yields at different substituent[13]. A immense variety of substituted indazoles were prepared via palladium-catalyzedintramolecularamination of aryl halides. Similarly, natural products Nigellidine, Nigeglanine, and Nigellidine are prepared by palladium catalyzed cyclisation.[14, 15] The treatment of $FeCl_3/O_2$ with hydrazones derivative, the formation of 1H indazole proceed via the C-H activation and new C-N bond generation. From this activation reaction, the corresponding 1,3-diaryl-substituted indazoles are produced with a very good yield with milder reaction condition[16]. The indazole also prepared via the coupling reaction using $CuBr_2$ the condensation reaction followed by coupling/deacylation with the help of $CuBr_2$ and L-proline catalyst get substituted 3-aminoindazoles the present protocol is normal with moderate yield[17] Next the substituted novel derivatives also prepared via the 3+2 diels alder reaction between the arynes with hydrazones. The various condition was used for the for the 3+2 diels reaction with -tosylhydrazones and N-aryl/alkyl hydrazones, the yields of indazole was moderate to good[18]. We have synthesized various 1-*H*-indazole derivatives by our methods[19]. In the pursuit of developing novel antimicrobial agents, herein we demonstrate the preparation of some novel hybrids indazole moiety to investigate their potential antimicrobial activities. Our research

group is always interested in finding new heterocyclic compounds for biological testing [20-28]. The main objective of our continuous research is to find out new leads molecules with potential antimicrobial activities.

Experimental

Materials and methods:

All the General reagents were easily available and applied for research without purification. The required chemicals and catalysts were obtained from, Alfa Aesar Sigma, Avra chemical, across organics and fine chemicals. the purification of compounds was performed over the chromatography using silica gel (100-200 mesh). The spectral data generation tetramethylsilane (TMS) was used as internal for NMR. The spectrometer was used for the FT-IR data collection. The AcquityQda detector, 2489 UV/ Vis detector was used to measure the Mass of new compounds. For the measuring GC-MS data Autoinjector Shimadzu GC/MS machine was used.

Step I:- Typical procedure for the synthesis of hydrazone derivatives A

A mixture of 1-(2-hydroxyphenyl)propan-1-one (1 Equiv.), hydrazine hydrates(2 Equiv.) in EtOH was taken in silica dish and reaction mixture grinder properly for 30 min. The reaction was monitored over the TLC and checked for the reaction finished. Once the TLC indicate the completion of the reaction the reaction mixture was poured into the cold water and mixed well the formed solid which was the filter, recrystallized from appropriate solvent to afford pure hydrazone derivatives.

Step II:- Typical procedure for the synthesis of 1H-Indazole derivatives.

Hydrazone derivatives1-(2-hydroxyphenyl)propan-1-one 1mole in EtOH and NH_4Cl (2 Equiv.), the reaction mixture grinder properly for 30 min. The complication of the experiment was checked by TLC, the crude whole reaction mass was poured into the ice-cold water and purified ethanol to afford pure 3-ethyl 1*H*-indazole.

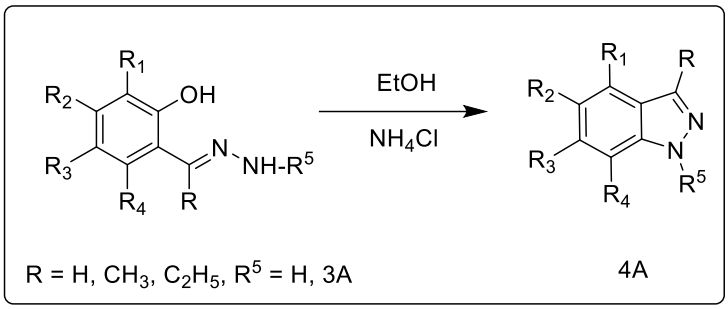
3-ethyl-1H-indazole (4C)colorless solid, mp 75-78°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (brs, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.15 (t, J = 4.0 Hz, 1H), 6.98 (t, J = 6.0 Hz, 1H), 2.85 (q, J = 6.0 Hz, 2H), 1.43(t, J = 6.0 Hz, 3H); ES-MS (m/z) 147.0924. $[M+1]^+$.

Synthesis of 5-Methyl-3-phenyl-1H-indazole(4H):, 1.59 g, 80% yield. ^{1}H NMR (DMSO-d_6) δ 8.21 (d, 2H), 8.21 (br s, 1H), 7.65-7.78 (m, 3H), 7.43 (t, 1H), 7.30 (d, 1H), 2.50 (s, 3H); ES-MS (m/z) 209 $[M+1]^+$.

Result and Discussion

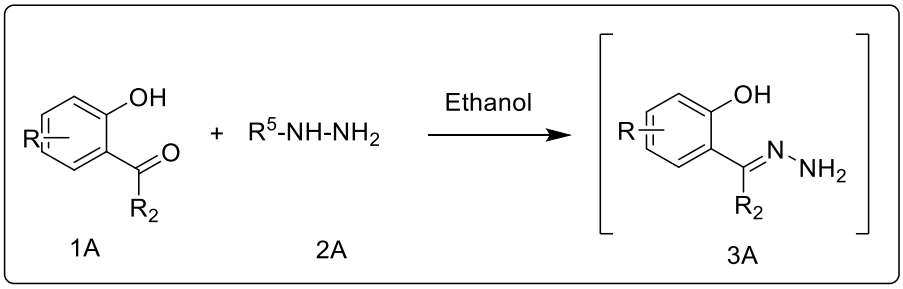
The initial precursor hydrazone derivatives **1A-4A** were prepared by the reaction ortho-hydroxyl-aldehyde or ortho-Chloro-aldehyde with hydrazine hydrate in an ethanol solvent (**Scheme 1**). Then, we move towards the synthesis of 1*H*-indazole , The hydrazone derivatives further grinded with ammonium chloride in ethanol solvent to afford desired compounds. Initially, when the hydrazone derivatives were grinded with 0.25 Equiv. of ammonium chloride (Table 2, entry 2), TLC shows the formation of the new spot was generated, mean conversion of reactant into compounds was generated. All the novel synthesized moieties were refined by chromatographic techniques and all novel new, pure compounds are analyzed by using spectral techniques like NMR IR, Mass, and GC-MS methods. The NMR spectra of 4A displayed a clear NMR peak at 8.21 ppm for 1H and no peak was observed for the OH proton. Next, the carbon ^{13}C, NMR spectrumshowed the distinguished sharp peak it was the absence of one C=O group, which means the desired compounds were observed. The detailed characterization of the spectral analysis indicates the generation of compound 4A with 40% yield (Tabe1, Entry 4). later, we had to apply 50% ammonium chloride (NH_4Cl) at room temperature to give 55% of product 2A (Table 1, entry 4). Increasing the mole% of NH_4Cl up to 200% at room temperature produced the desired product with 85% yield (Table 1, entry 4).

Table 1. Optimization reaction condition for the conversion of 3A to 4A

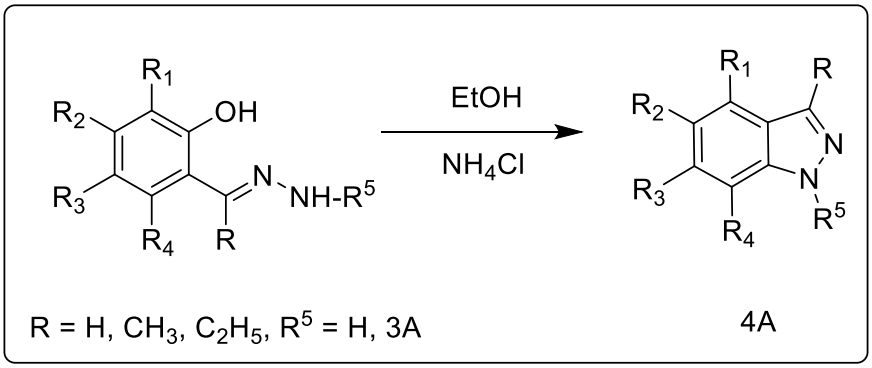


Sr/No	Reagent	Equiv.	solvent	Product
1	NH_4Cl	-	**Ethanol**	no
2	NH_4Cl	0.25	Ethanol	30
3	NH_4Cl	0.25	Methanol	20
4	NH_4Cl	0.50	Ethanol	55
5	NH_4Cl	0.50	Methanol	32
6	NH_4Cl	1.00	Ethanol	70
7	NH_4Cl	2.00	Methanol	45
7	NH_4Cl	2.00	Ethanol	85

When the experiment was performed with methanol solvent, we found that the indazole product was quite less as compared to the ethanol solvent. When, the 0.25 Equiv, of ammonia, grinded win the presence 0.25 Equiv. of NH_4Cl produce indazole with 20% similarly, increasing in the mole % of ammonium chloride, When the 2.00 Equiv. of NH_4Cl was used for the conversation of hydrazone to indazole, 45% yield was observed.



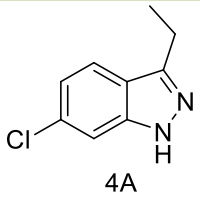
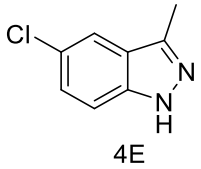
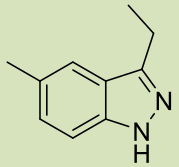
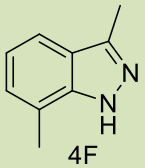
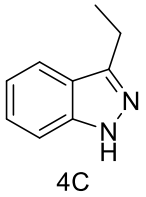
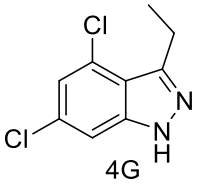
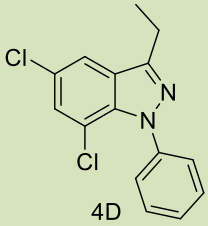
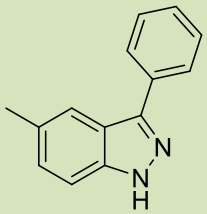
Scheme 1. Preparation of hydrazone derivatives



Scheme 2. Preparation of 1*H*-Indazole derivatives

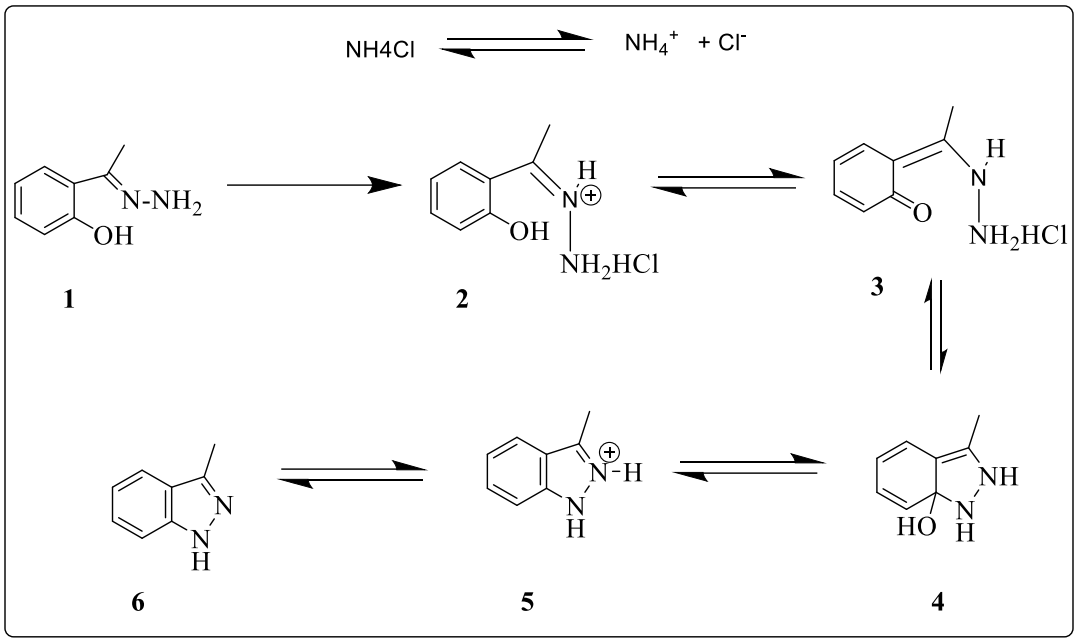
Finally, the developed protocol conditions in our hand, with the help of obtained methodology, we moved towards the finding the scope of the protocol with a variety of ortho-hydroxy aldehyde. The series of ortho-hydroxy aldehyde having various substituents, group on the aryl rings was grinded with the developed methodology for up to 30 min of reaction time, obtaining expected final compounds with 80-88% yield. Accordingly, substrates bearing halogen methylsubstituentsoffered excellent yields (up to 88%) (Table 2, 3). The present protocol was new for the synthesis of novel series of substituted 1*H*-indazole derivatives as compared with the literature reported methods., this methods is greater in terms of yields time, handling, temperature, and efficiency[10]. The application of these compounds in the designing of new biologically important molecules is underway.

Table 2. Physicochemical data of 1-*H*-indazole derivatives

Sr/No	Product	M.P.	Yield	Sr/No	Product	M.P.	Yield
1	 4A	128-130	80	5	 4E	168-171	92
2	 4B	140-141	89	6	 4F	112-115	83
3	 4C	133-136	79	7	 4G	225-228	89
4	 4D	142-144	88	7	 4H	182-185	92

Mechanism

The mechanism was predicted based on the literature [29-30], Here the ammonium chloride initiate the reaction of aldehyde and hydrazine hydrate produce compound 1. The acidic nature of ammonium chloride, triggers the activation of the aldehydic carbonyl group. The ammonium chloride a mild acid can activate the carbonyl group via hydrogen bonding to enhance the nucleophilic attack of hydrazine hydrate to give 2 hydrazone intermediate (Scheme 3) [29]. Under the milder acidic condition, the phenolic group undergoes tautomerization gives to a keto-hydrazine 3. Compound 3 undergoes dehydrogenation subsequently giving the desired product **6** (Scheme 3).



Scheme 3. Mechanism of indazole formation

Conclusions

This study demonstrates a novel, efficient, method for the synthesis of 1H-indazole derivatives. We have synthesized a series of 1*H*-indazole derivatives by the classical method. The required indazole was prepared by the reaction of hydrogen derivatives with NH_4Cl milder acid under ethanol solvent conditions. Along with, The methods has many benefits like a generality, high yields with pure compounds, fewer reaction times, ecofriendly-greener, low-cost, easy experimental procedure, normal work-up, and procedures.

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Conflict of Interest

The authors declared that they do not have any conflict of interest regarding this research article

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