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SYNTHESIS OF 2 – (1, 3 – SUBSTITUTED – 1 H- PYRAZOL-4-Y1) – 1H- BENZO (D) OXAZOLES BY USING AMMONIUM CHLORIDE; AS A MILD AND EFFICIENT CATALYST

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ABSTRACT

An efficient and simple procedure has been developed for the synthesis of 2- (1,3- substituted–1H- pyrazol–4-y1)–1H -benzo(d)oxazoles from the condensation of 3–Aryl-1- Phenyl –1H – pyrazole – 4- carabaldehyde with 2- aminophenol using ammonium chloride, which is a very inexpensive, metal free, readily available reagent. The target compounds were obtained in good yields under fairly mild reaction conditions at room temperature.

KEYWORDS: *Pyrazole aldehydes, 2-aminophenol, ammonium chloride, 1H- Benzo (d)oxazoles, Alzheimer's disease.*

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INTRODUCTION

Alzheimer's disease is a chronic neurodegenerative disorder and one of the most frequent causes of mental impairment in the elderly[1,2]. Alzheimer's disease is caused by several factors including amyloid-β deposits, oxidative stress and low levels of acetylcholine. Cholinesterase inhibitors[3] and monoamine oxidase inhibitors (IMAOS) [4] might also be important for the treatment of Alzheimer's disease.Multipotent ligands able to inhibit cholinesterases as well as monomine oxidases[5]. 1H-pyrazole ring present in the molecule is involved in interactions with enzyme. 1H- pyrazole ring is active against AChE and MAO[6]. By keeping above facts in mind various 1H-pyrazole derivatives have been designed. Benzoxazole derivatives have been characterized as antitumor agents[7], Amyloidgenesis inhibitors[8]and cytotoxic natural products salvianen[9]. All the things regarding the benzoxazole molecules motivated us for the synthesis of 2-(1, 3 – substituted -1H – pyrazol – 4 – y1) – 1H – Benzo (d) oxazole compounds. On the other hand the most general synthetic approach for synthesis of Benzoxazole derivatives involved in condensation of aldehydes with 2–aminophenols using DDQ[10],O2/activated carbon[11], PIFA under microwave irradiation[12]. However, many of these procedures are associated with one or more disadvantages such as the use of toxic, expensive hazardous solvents.

EXPERIMENTAL MATERIALS AND METHODS

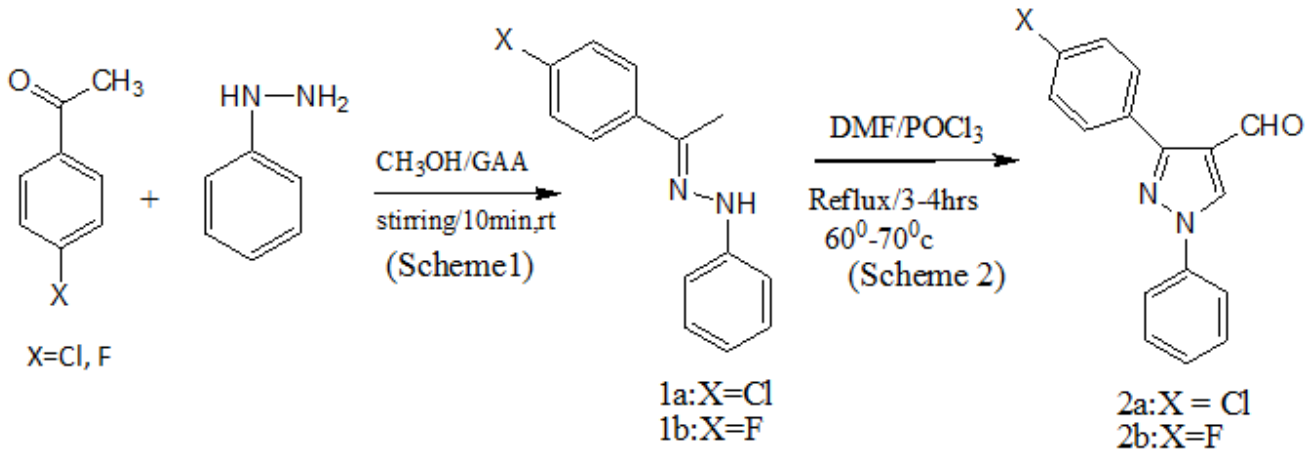
All the starting materials and regents used were of analytical grade and utilized without any further purification. The melting points were determined with Decibel melting point apparatus. The reactions were checked by thin layer chromatography (TLC) using silica gel G as Stationary phase. IR spectra were recorded with perkinelmer IR spectrophotometer (KBr disks). H^1NMR spectra were obtained using BrukerAvance 400 MHz NMR Instrument; chemical shifts are expressed as values δ (PPM).Mass spectra were recorded on shimadzu GC-MS QP 2010 Gas Chromatogrphy.TLC was performed on silica gel G using Ethyl acetate: Hexane solvent system.

Procedure for the synthesis of phenylhydrazones (1a, 1b) :- (Scheme-1)

To a solution of the appropriate acetophenone (0.08 mol)in 40ML methanol, phenyl hydrazine (0.08 mol) and glacial acetic acid (2 ml) were added. The resulting solution was shaken for 20 minutes at room temperature. The precipitates of hydrazones were filtered and washed with sufficient amount of methanol.

Procedure for the synthesis of 3-aryl –1- phenyl – 1H – pyrazole – 4 – carbaldehydes (2a, 2b): (Scheme -2)

$POCl_3$ (0.03 mol) was added drop wise to an ice-cold stirred solution of hydrazones (1a, 1b) (0.02 mol) in anhydrous DMF (25ml) following complete addition of $POCl_3$, the reaction mixture was allowed to attain room temperature and then heated at 60-70^{o}c for 3-4 hours[13]. The resulting mixture was poured on to crushed ice, neutralized with dilute NaOH. The precipitate obtained were filtered, washed with sufficient quantity of water and recrystallized from chloroform.



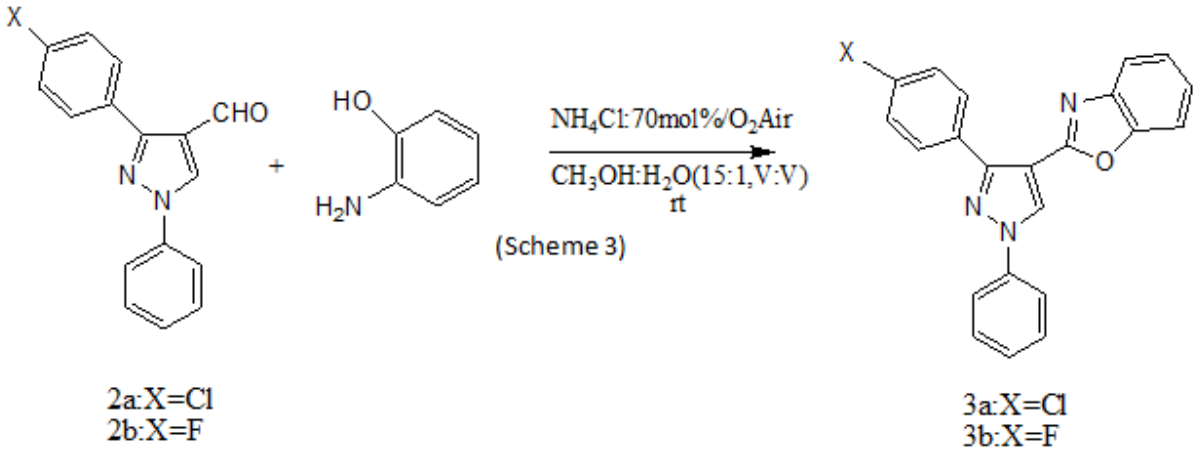
Table

Characteristics of 3-aryl –1- phenyl – 1H – pyrazole – 4 – carbaldehydes(2a,2b)

Sl.No	Name of the compound	X	Molecular formula	Molecular weight	Melting point	% of yield
1.	2a	Cl	$C_{16}H_{11}ClN_2O$	282.72	106-108	90
2.	2b	F	$C_{16}H_{11}FN_2O$	266.27	110-112	86

Procedure for the synthesis of 2-(1, 3 –substituted–1H- pyrazol–4–yl)-1H-Benzo (d) oxazoles: (Scheme-3)

To a stirred solution of pyrazole aldehydes (2a, 2b) 1mmol in 5ml methanol/water (15:1, V: V), 2-aminophenol (1.2 mmol) and ammonium chloride (70 mol %) were added. The mixture was stirred at room temperature for 40-50 minutes. The progress was monitored by TLC (Ethylacetate: hexane, 2:8). After the complete conversion of the substrate, 5ml water was added to the reaction mixture and was allowed to stand at room temperature for 15 min. During this time pure products formed which were collected by filtration. The residue was recrystallized from ethanol (5ml) to obtain the pure products (3a, 3b).



Reaction scheme of 2- (1, 3–substituted –1H–pyrazole –4 –yl)– 1H-Benzo (d) oxazoles

RESULTS AND DISCUSSION

The 2-(1, 3 – substituted – 1H – pyrazol – 4- yl) – 1H – Benzo (d) oxazoles has been synthesized from the discovering of effortful new structure escorts. The inhibitory activities compound (2a, 2b) against AChE and MAO[14-16]. Ammonium chloride is a very inexpensive, ecofriendly and easily available catalyst; it has been reported as the catalyst for synthesis of various organic compounds. Here, we report a very simple synthesis of 2- (1, 3 – disubstituted – 1H- pyrazole -4 yl)–1H– Benzo (d) oxaoles [3a, 3b] by the condensation of pyrazole aldehydes with 2- Aminophenol under mild conditions at room temperature. It is important to mention that, when the same reaction with ammonium chloride was carried out under nitrogen atmosphere (in absence of oxygen). The reactions stopped at the Benzoxazoline stage, which never proceeded to products (3a, 3b). This surely proves that aerial oxygen is essential for the oxidation step leading to the formation of product (3a, 3b).

The results are obtained from various spectral data are discussed below

3-(4 – chlorophenelyl) – 1 – phenyl -1H – pyrazole – 4 – carbaldehyde (2a):IR (KBr, Cm^{-1})υ_{Max}: 3042 (Ar-CH), 1664 (C=N), 1450, 1493, 1114 (-C=C), –(C=N), (-N-N) pyrazole; H^1 NMR (400 MHz, $CDCl_3$, δ PPM) : 10.02 (s, 1H, - CH=0), 8.5 (s, 1H, Pyrazole – CH), 7.11-7.88 (m, 9H Ar-H).Mass:m/z- 283

3-(4 – fluorophenyl)- 1 – phenyl - 1H – pyrazole – 4 – carbaldenyde (2b):IR (KBr, Cm^{-1})υ_{max}: 3040 (Ar- CH), 1665 (C=N), 1451, 1491, 1111 (-C=C) (-C=N),(-N-N) pyrazole : H^1NMR (400 MHz; $CDCl_3$, δ ppm): 10.05 (S, 1H, -CH=0), 8.51 (S, 1H, pyrazole – CH), 7.21 7.87 (m, 9H, Ar-H). Mass: m/z -266

2- (3'– (4"- chlorophenyl) – 1'- phenyl – 1H – pyrazole – 4-yl) –1H- Benzo (d) oxazole (3a):IR (kBr, cm^{-1}) υ_{Max}: 3147, 3057, 2997, 1629, 1593, 1554, 1496, 1340, 1114, 702. H^1NMR (400 MHz, $CdCl_3$, δppm): 8.7(s, 1H, pyrazole-CH), 7.2-7.8(m, 9H, Ar-H of 1-phenylpyrazole and 3-phenylpyrazole), 7.1-7.7(m, 4H of benzoxazole).Mass: m/z-388

2- (3'– (4"- fluorophenyl) – 1'- phenyl – 1H – pyrazole – 4-yl) –1H- Benzo (d) oxazole (3a):IR (kBr, cm^{-1}) υ_{Max}:3124,3025,2985,1640,1590,1490,1250,1111,690. H^1NMR (400 MHz, $CdCl_3$, δppm): 8.8(s, 1H, pyrazole-CH), 7.3-7.8(m, 9H, Ar-H of 1-phenylpyrazole and 3-phenylpyrazole), 7.1-7.8(m, 4H of benzoxazole).Mass: m/z-371

CONCLUSION

In conclusion, we have developed an economically and environmentally friendly catalyzed process for simple and efficient synthesis of 2-[1, 3 – substituted – 1H- pyrazole – 4 – yl] – 1H – Benzo (d) oxazoles at mild reaction conditions.

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