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Synthesis of 5-(3-aryl-1-phenyl-*1H*-pyrazol-4-y1)-*1H*-tetrazole by using $AgNo_3$ catalyst

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ABSTRACT

An efficient and convenient method has been developed for the synthesis of 5- (3-Aryl-1-Phenyl-1H – Pyrazol-4-y1)-1H-tetrazoles form the (3+2) cycloadition of 3-Aryl-1Phenyl-1H – pyrazole -4- carbonitrile with sodium azide using $AgNo_3$ as a catalyst. The corresponding 5-(3-Aryl-1–phenyl-1H-pyrazol-4-y1)-1H –tetrazoles were formed in good yields.

Keywords: Pyrazole nitriles, sodium azide, $AgNo_3$, tetrazoles, Alzheimer's disease.

INTRODUCTION

Tetrazoles, being an interesting class of heterocyclic compounds find a wide range of applications as drugs in pharamaceuticals[1,2], explosives[3], propellants and in photography[4]. Tetrazoles are found in agriculture as plant growth regulators and in crop protection[5]. Tetrazole derivatives play a key role as herbicides and fungicides[6].

Pyrazoles are also a class of heterocyclic compounds that exhibit a broad spectrum of biological activities such as antiinflammatory, antimicrobial and antitumor[7]. Alzheimer's disease is a chronic neurodegenerative disorder and one the most frequent causes of mental impairment in the elderly[8,9] cholinesterase inhibitors[10] and monoamine oxidase inhibitors[11] might also be important for the treatment of Alzheimer's disease.

1H- Pyrazole ring present in the molecule is involved in interactions with enzyme.1H – Pyrazole ring is active against AchE and MAO[12].

All These facts regarding the tetrazole and 1H-pyrazole ring molecules motivated us for the synthesis of 5- (3-Aryl-1-phenyl-1H-pyrazol-4-y1)-1H-tetrazole compounds.

On the other hand various methods were developed for the synthesis of tetrazole derivatives involved in cyclo addition of nitriles with NaN_3 using Zn(II) salts[13], Fe(OAC)2[14], Cu_2O[15], $CuFe_2O4$[16] nanoparticles, Lewis acids such as AlCl3[17], BF_3. Et_20[18], Fecl3[19].

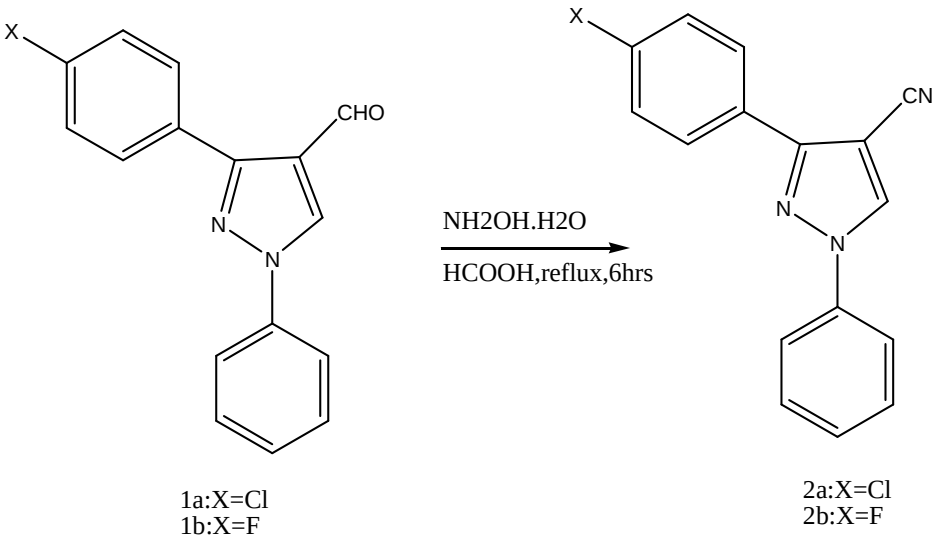
However many of the above mentioned protocols have some disadvantages like use of toxic metals, strong Lewis acids , expensive reagents and harsh reaction conditions.

MATERIALS AND METHODS

All the starting materials and reagents used were of analytical grade and utilized without any further purification. The reactions were checked by Thin layer chromoto-graphy (TLC) using silica gel G as stationary phase. IR spectra were recorded with perkinelemer IR Spectrophotometer (KBr disks). H^1NMR spectra were obtained using Bruker Avance 400 MHZ NMR Instrument : chemical shifts are expressed as values (δppm). Mass spectra were recorded on shimadzu GC-MS QP 2010 Gas Chromatography. TLC was performed on silica gel G using Ethylacetate: Hexane solvent system.

Synthesis of 3-Aryl-1-Phenyl-1H–Pyrazole-4-carbadehydes (1a,1b):
Synthesis of 3-Aryl-1-Phenyl-1H–Pyrazole-4-carbardehydes(1a,1b) were achieved using previously published method[20].

General procedure for the synthesis of 3-Aryl-1-Phenyl-1H–Pyrazole-4-Carbonitriles (2a,2b):
The reaction mixture of the pyrazole aldehydes (1a,1b) (10 mmol L-1) with hydroryl amine and methanoic acid (15 ml) was maintained under reflux for 6 hrs. The progress was monitored by TLC (Ethyl acetate:hexane,1:1).After the complete conversion of the substrate, the reaction mixture was poured in cold water and the precipitate formed was filtered out washed with Ehtanol and recrystallized from Ethanol/water to afford crystals.

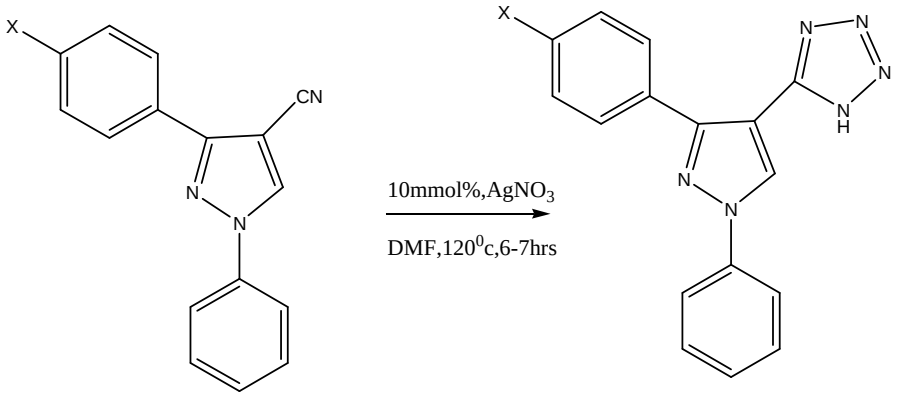


1a:X=Cl
1b:X=F

2a:X=Cl
2b:X=F

Reaction scheme of 3-Aryl-1-Phenyl-1H – Pyrazole-4-carbonitriles(2a,2b)

General procedure for the synthesis of 5-(3-Aryl-1-Phenyl-1H–Pyrazol-4-y1)-1H-tetrazoles (3a, 3b):
Sodium azide (0.05 mmol) was added to a solution of $AgNo_3$ (10mmol) in DMF (5 ml) and reaction mixture was stirred for 10 min. To this stirred solution 3-Aryl-1-Phenyl-1H – Pyrazole-4-carbonitrile (2a, 2b) (0.03mmol) was added at room temperature and stirred for 15 min at the same temperature and then heated at 120^{o}c for 6-7 hrs. The progress was monitored by TLC. After consumption of (2a, 2b), The reaction mixture was cooled to room temperature and chilled by adding crushed ice in to the reaction mixture followed by addition of 2NHCl till the reaction mixture reached to PH 2 . The reaction mixture was then extracted with ethylacetate. The organic layer was dried with anhydrous Na_2SO_4 and concentrated to obtain tetrazole derivatives (3a, 3b).



2a:X=Cl
2b:X=F

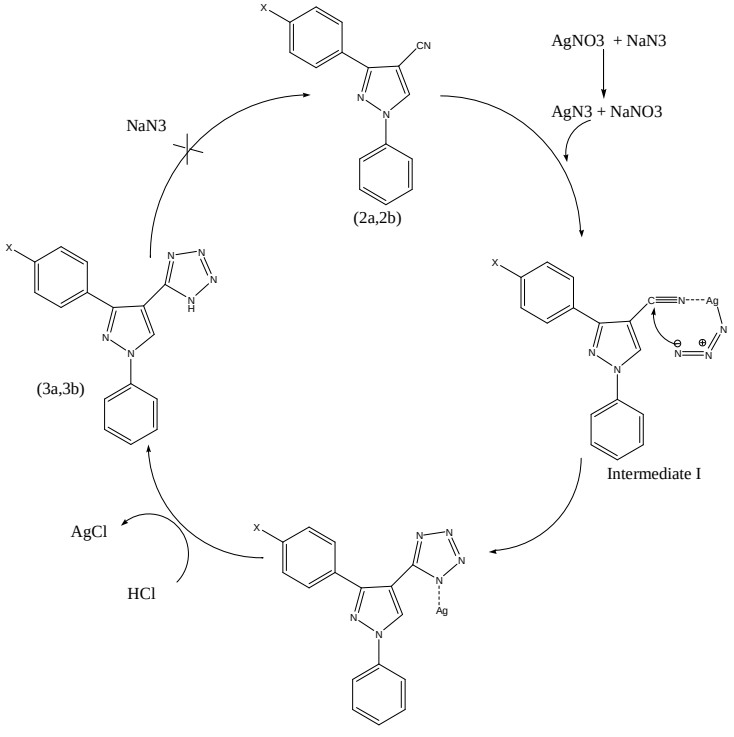
3a:X=Cl
3b:X=F

Reaction scheme of 5- (3-Aryl-1-Phenyl-1H – Pyrazol-4-y1)-1H-tetrazoles (3a, 3b)

RESULTS AND DISCUSION

The 5- (3-Aryl-1-Phenyl-1H – Pyrazol-4-y1)-1H-tetrazole has been synthesized from the discovery of effortful new structure escorts. The 1H –pyrazole ring is active against AchE and MAO[21,22,23]

Initially, $AgNo_3$ reacts with NaN_3 to produce AgN_3Catalytic species. The (3+2) cyclo addition between the CN bond of 3-Aryl-1-Phenyl-1H – Pyrazole-4-carbonitrile and AgN_3 takes place to form the Intermediate- I. Precoordination of the nitrogen atom of the CN group of (2a, 2b) with AgN_3 to Form the Intermediate – II would accelerate This cyclization step.protonolysis of the intermediate – II by 2 N HCl (maintained at PH 2) affords the 5- (3-Aryl-1-Phenyl-1H – Pyrazol-4-y1)-1H-tetrazoles (3a, 3b) andAgcl, as white solid was recovered at the end of the reaction through filtration only.



Plausible mechanism for the synthesis of tertrazole compounds (3a, 3b)

If the reaction is carried out with (1 equiv) of (2a, 2b) and NaN_3 (1.5 equiv) in DMF at 120°c For 12hrs, then the reaction did not proceed at all. This accounts for the absence of in situ generated AgN_3 catalyst required for the cyclo addition in tetrazoles formation. The starting materials (2a, 2b) were recovered in 70-80 % yield. These results clearly indicated that AgN_3 is a key catalytic species which enables the (3+2) cycloaddition with (2a,2b)to produce tetrazole salts which on protonolysis affords desired products (3a, 3b) in good yields.

The results obtained from various spectral data are discussed below:

3-(4'- Cholrophenyl)-1-Phenyl-1H Pyrazole -4 Carbonitrile (2a):

IR(KBr,cm^{-1})υ_{max}: 3020(Ar-CH), 2200(CN),1664(C= N)1490, 1450, 1114 (-C=C), (-C-N), (-N-N). H^1NMR (400 MHZ, $CDCl_3$, δppm): 8.5(S,1H, pyrazole – CH), 7.15-7.85 (m, 9H, Ar-H). mass: m/z -280.

3-(4'- Fluorophenyl)-1Phenyl-1H Pyrazole -4 Carbonitrie (2b):

IR(KBR,cm^{-1})υ_{max}: 3010(AR-CH), 2180(CN),1665(C= N)1492, 1452, 111 (-C=C), (-C-N), (-N-N). H^1NMR (400 MHZ, $CDCl_3$, δppm): 8.53(S,1H, pyrazole – CH), 7.21-7.87 (m, 9H, Ar-H). mass:m/z -263.

5-(3'-4"- Cholrophenyl)-1Phenyl-1H Pyrazole -4- y1- 1H-tetrazole (3a):

IR(KBR,cm^{-1})υ_{max}: 3021,1664,1535,1490,1450,1270,1114,744.H^1NMR (400 MHZ, $CDCl_3$, δppm): 8.51(S,1H, pyrazole – CH), 7.21-7.82 (m, 9H, Ar-H). mass:mlz -323.

5-(3'-4"- Fluorophenyl)-1Phenyl-1H Pyrazole -4- y1- 1H-tetrazole (3b):

IR(KBR,cm^{-1})υ_{max}: 3015,1660,1535,1540,1495,1265,1111,730.H^1NMR(400 MHZ, $CDCl_3$, δppm): 8.52(S,1H, pyrazole – CH), 7.25-7.87 (m, 9H, Ar-H). mass:m/z -306.

CONCLUSION

In the present study we report silver nitrate as a s highly efficient, convenient catalyst for the synthesis of 5-(3-Aryl-1-Phenyl-1H–Pyrazol-4-y1)-1H-tetrazoles via the (3+2) cyclo addition of pyrazole nitrile and sodium azide in refluxing DMF in good yields . The reaction proceeds through the insitu formation of silver azide which act as a catalytic species. The easy availability of catalyst, elimination of toxic hydrazoic acid, a simple work up procedure and better yields are significant advantages over other existing methods.

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