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Research Article

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Synthesis of new triazole and oxadiazole containing compound in the azide reaction as an antibacterial drug

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ABSTRACT

Triazole-containing compounds or oxadiazole as anti-bacterial always be used in pharmaceutical science. So our went to produce compound to be including both the imidazole and oxadiazole. pyridine-3-carbohydrazide (4) reaction with chloroacetic acid in presence of POCl3 gave chloro methyl 1, 3, 4 –Oxadiazole (5) derivative. Compound (5) on treatment with sodium azide yielded azidiomethyl- 1, 3, 4-oxadiazole (6). This azide (6) derivative further reacted with acetyl acetone in presence of potassium carbonate to form 1-(1-((5-pyridin-3-yl)-1,3,4-oxadiazol-2-yl) methyl)-5- methyl-1H-1,2,3-triazol-4-yl)ethanone (7).

Keywords: triazole, oxadiazole, ether, antibacterial

INTRODUCTION

Heterocyclic compounds containing nitrogen plays important role in agrochemical and pharmaceuticals. The basic heterocyclic rings present in the various medicinal agents are mainly 1, 2, 3-triazole and 1, 2, 4-triazole [1]. A large volume of research has been carried out on triazole and their derivatives, which has proven the pharmacological importance of this heterocyclic nucleus. In recent years 1, 2, 3-triazole chemistry developed very fast due to the discovery of the diverse biologically active triazole derivatives. The 1, 2, 3-triazole system has widespread uses, and it has been considered as an interesting component in terms of biological activity [2-6]. ether derivatives are very important class of compounds and receiving more and more attention because of their widespread biological activities which were found to be potent insecticidal [7], antifungal [8-12]. Moreover the presence of pyridyl ring into a parent compound may improve its properties and biological activities in the pharmaceutical and agrochemical compounds. And many pyridyl containing compounds are also known to possess a wide range of biological and pharmaceutical activities [13-20].Large number of oxadiazole derivatives reported in the literature possesses a broad spectrum of pharmacological activity. 1, 3, 4-oxadiazoles are biologically active, synthetically useful and important heterocyclic compounds [21-24].Similarly 2,5-Disubstituted-1,3,4-oxadiazole derivatives possess broad spectrum of activities like antifungal[25],anticonvulsant [26-27],anticancer [28] etc. Encouraged by these reports the present study has been undertaken.

EXPERIMENTAL SECTION

Chemicals and Instrumentation:
All air and moisture sensitive reactions were carried out in flame dried, N2-flushed, double-neck round bottom flask sealed with rubber septa. The reagents were injected with a syringe. Melting points of all synthesized compounds

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were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using CDCl3/DMSO-d6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). Mass spectra were recorded on Shimadzo GCMS. C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

Synthesis of pyridine-3-carbohydrazide (4)

Part-A: Preparation of acid chloride:

4-(trifluoromethyl)pyridine-3-carboxylic acid (1) (0.1 mol) and Toluene (100 ml) were dehydrated on a oil bath using Dean and Stark assembly. After removing of moisture thionyl chloride (0.1 mol) was added drop wise in presence of catalytic amount of dimethyl foramide at 100℃ temperature. After complete addition, refluxed reaction mass for 5-7 hrs . The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent (75ml) was removed under reduced pressure and the crude product (in presence of toluene) was used as such for next step .

Part-B: Preparation of methyl ester.

In another 4 neck RB flask charged methanol (150 ml) and cool to 10℃ and compound 4 added drop wise in cold solution of methanol. After addition completed, the reaction mixture was refluxed for 4-5 hrs. The progress of the reaction was monitored by TLC and conformed by GCMS. After completion of the reaction, the excess of solvent was removed under reduced pressure and the obtained crude product was used for next step.

Part-C: Synthesis of pyridine-3-carbohydrazide (4)

In RB flask charged methyl ester (0.1mol) Part-B and add 150 ml methanol add hydrazine hydrate 99 % (0.15mol) and reflux the reaction mass for 7-9 hrs. The progress of the reaction was monitored by TLC and conformed by GCMS. After completion of the reaction, the solvent was removed under reduced pressure and the crude product was further crystallized in ethanol.

White crystalline solid ,Yield: 70%; m.p.159-161□C IR (cm^{-1}): 1315 (C-N), 1627 (C=N), 1664 (C=O), 3300 (NH) ; 1H NMR((CDCl$_3$,δ/ ppm): 4.198 (s, 2H, NH2),), 7.125 (s, 1H, NH),7.597 (d, 1H, pyH), 8.80 (s, 1H, pyH), 8.92 (d,1H, pyH), GCMS; m/z 137 ; 205.0 (20%), 173.8 (100%), 145.86(70%) Anal. Calcd for $C_6H_7N_3O$; C, 40.5; H, 2.9;F, 27.6; N ,20.4;O, 7.80 % . Found: C, 40.0; H, 2.6; F, 27.21; N, 20.3; O, 7.8 %..

Synthesis of 3-(5-(chloromethyl)-1,3,4-oxadiazol-2-yl)- pyridine (5)

A mixture 4(trifluoromethyl)pyridine-3-carbohydrazide 4 (0.01mol) and chloro acetic acid (0.01mol) in presence of $POCl_3$ (25ml) were refluxed for 8-10hrs at 105-110℃ in an oil bath. The progress of the reaction was monitored by TLC and confirmed by GCMS After completion of the reaction, the solvent was removed under reduced pressure and the crude product was poured into crushed ice-water. It was neutralized with NaHCO3 solution. The product was extracted by ethyl acetate, dried over anhydrous Na2SO4 and evaporated under reduced pressure.

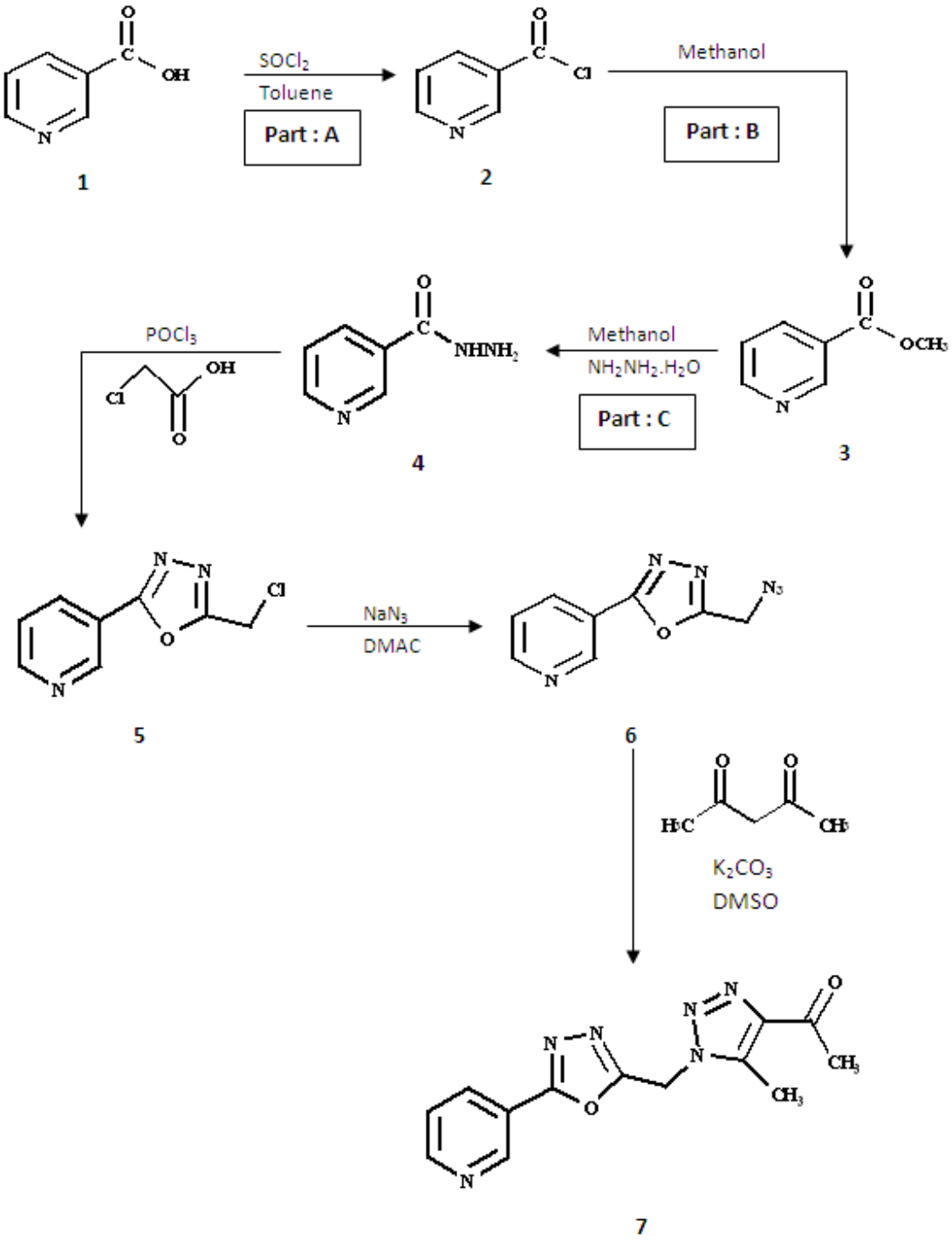
The resulting residue was recrystallised from ethanol.

Pale yellow solid ,Yield: 78.5%; m.p.60-62℃,IR (cm^{-1}): 1172(C-O-C), 1570 (C=C),1680 (C=N),^{1}H NMR((CDCl$_3$,δ/ ppm): 4.825 (s, 2H, CH2), 7.77 (d, 1H, pyH), 9.03 (s, 1H, pyH), 9.35 (d,1H, pyH), GCMS; m/z 195 ; 262.98 (90%), 218 (75%),173.96(85%), 145.93(100%) Anal.Calcd for $C_8H_6ClN_3O$: C ,42.01;H, 1.93;Cl, 13.49;F ,21.64;N ,15.90;O, 6.1 % . Found:C, 42.00;H ,1.74,Cl, 12.05; F ,21.11 ; N ,14.15 ;O, 6.09 %.

Synthesis of 3-(5-(azidomethyl)-1,3,4-oxadiazol-2-yl)- pyridine (6)

A 3-(5-(chloromethyl)-1,3,4-oxadiazol-2-yl)-4-(trifluoromethyl)pyridine (5) (0.01 mol) and dry imethylacetamide (30ml) was stirred at 20°C temperature for 10 min, start addition of sodium azide (0.015) solution in 10 ml water was added . Then stirred mass at 20 0c for 4-5 hrs. The progress of the reaction was monitored by TLC. Upon Completion, the reaction mixture was poured into ice-cold water (500ml). The product was extracted by ethyl acetate, dried over anhydrous Na2SO4 and evaporated under reduced pressure. The crude product was further purified by column chromatography (n-Hexane: Ethyl acetate =85:15)

Yellow solid, Yield: 49%; m.p.114-117°c(With decomposition), IR (cm^{-1}): 2100 (N_3), ^{1}H NMR(CDCl$_3$,δ/ ppm): 4.90 (s, 2H, CH2), 7.77 (d, 1H, pyH), 9.23 (s, 1H, pyH), 9.44 (d,1H, pyH), LCMS: m/z: 203; Anal.Calcd for $C_8H_6N_6O$: C ,40.01;H, 1.87; F ,21.11 ; N ,31.3; O, 5.94% . Found: C, 40.85;H ,1.77,; F ,21.0 ; N ,30.3 ;O, 5.6 %.



RESULTS AND DISCUSSION

Synthesis of 1-(1-((5-pyridin-3-yl)-1,3,4-oxadiazol-2-yl) methyl)-5- methyl-1H-1,2,3-triazol-4-yl)ethanone (7)

3-(5-(azidomethyl)-1,3,4-oxadiazol-2-yl)- pyridine (6) (0.01 mol) and acetyl acetone (0.01 mol) were added drop wise in dimethyl sulfoxide (50 ml) and powdered Potassium carbonate (0.03 mol) mixture . The mixture was stirred at room temperature for 8-10 hrs. under dry nitrogen. The progress of the reaction was monitored by TLC. Upon Completion, the reaction mixture was poured into ice-cold water (500ml). The product was extracted by ethyl

acetate, dried over anhydrous Na_2SO_4 . On evaporation under reduced pressure the crude product was further purified by column chromatography using n-Hexane and Ethyl acetate (60:40) to yield the desired product (7).

Orange solid ,Yield: 68%; m.p.127-135°C,IR (cm^{-1}): 1670(C=O), ^{1}H NMR(($CDCl_3$,δ/ ppm): δ 2.64 (s, 3H, CH3), 2.73 (s, 3H, CH3), 5.874 (s, 2H, CH2), 7.76 (d, 1H, pyH), 9.00 (d, 1H, pyH), 9.315 (s,1H, pyH), GCMS; m/z 286 ; 352.9 (10%) , 327 (50%) , 171.98 (100%), 145.7(50%) ; Anal.Calcd for $C_{13}H_{12}N_6O_2$: C ,47.74;H, 3.15 ;F ,16.12; N, 23.87;O, 9.05 % . Found: C ,47.35 ;H ,3.21 ; F ,16.22; N, 23.05 ;O,8.83 %.

Scheme 1 shows the synthetic pathways to prepare the target compounds(4-7). The key substrate 3-(5-(chloromethyl)-1,3,4-oxadiazol-2-yl)- pyridine (5) was synthesized from the reaction of pyridine-3-carbohydrazide derivative (4) (prepared from pyridine-3-carboxylic acid (1) and chloroacetic acid in presence of phosphorus oxychloride (Scheme 1). The IR spectrum of compound (5) showed strong absorption bands at 1172 for (C-O-C), 1570 for (C=C) and 1680 (C=N). ^{1}H NMR spectrum displayed also a singlet signal at 4.82 ppm assigned for CH_2 group, a doublet signal at 7.7 and 9.35 ppm due to Pyridine- H and singlet at 9.03 ppm due to Pyridine-H .The 3-(5-(chloromethyl)-1,3,4-oxadiazol-2-yl)-pyridine (5) was treated with sodium azide in dimethyl acetamide to form 3-(5- (azidomethyl)-1,3,4-oxadiazol-2-yl)-pyridine(6) compound which was confirmed by absence of chloride against silver nitrate test and IR spectra showed strong absorption bands at 2100 (for N_3) . By introducing azido-methyl group the aim is synthesis of novel five membered heterocyclic compounds. Thus, the reaction of compound (6) with acetylacetone in DMSO in the presence of anhydrous potassium carbonate to generate compound 1-(1-((5-pyridin-3-yl)-1,3,4-oxadiazol-2-yl)methyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethanone (7). The structures of the products were assigned on the basis of their spectral data and elemental analysis. ^{1}H NMR spectrum displayed also a singlet at 2.64 ppm and 2.73 ppm assigned for two CH_3 group and singlet at 5.874 assigned for CH_2 group .

CONCLUSION

A novel compounds of the pyridine containing 1, 2, 3-triazole and 1,3,4-oxadiazole ring were prepared in moderately yield . In many medical and pharmaceutical research, antibacterial effects triazole and oxadiazole derivatives positive [28-38]. Hence the research was to synthesize a compound that has both of these structures would be more susceptible to drug effects.

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