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Synthesis of novel 1,2,3-triazole derivatives containing oxadiazole, trifluoromethyl pyridine

Vijay V. Dabholkar*, S. N. Gandhale and N.B. Shinde

Organic Research Laboratory, Department of Chemistry, Mumbai University, K.C. College, Churchgate, Mumbai, India

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ABSTRACT

4 (trifluoromethyl) pyridine-3-carbohydrazide (4) reaction with chloroacetic acid in presence of $POCl_3$ 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, 4, 5-trisubstitued 1, 2, 3-triazole (7). On reaction of (7) with hydroxyl amine hydrochloride gave its oxime derivative (8) which on treatment with different substituted aromatic benzyl chloride offered corresponding novel 1, 4, 5-trisubstitued 1, 2, 3-triazol oxime ether derivatives (9a-c) respectively.

Keywords*:* 1, 2, 3-triazole, 1, 3, 4-oxadiazole, oxime ether, antibacterial, antifungal.

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]. Oxime 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]. On the other hand, it is well known that the introduction of fluorine atoms or a fluoroalkyl group can greatly modify the physico-chemical features and thus the biological properties of a molecule [9-12].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.

MATERIALS AND METHODS

Chemicals and Instrumentation:

All air and moisture sensitive reactions were carried out in flame dried, N_2-flushed, double-neck round bottom flask sealed with rubber septa. The reagents were injected with a syringe. Melting points of all synthesized compounds 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 $CDCl_3$/DMSO-d_6 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 4-(trifluoromethyl) 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 100^0c 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 ^{0}c 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 4-(trifluoromethyl)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: 73%; m.p.164-167°C IR (KBr): 1316 (C-N), 1634 (C=N), 1654 (C=O), 3305 (NH) ; ^{1}H NMR((CDCl3-,δ/ ppm): 4.175 (s, 2H, NH2),), 7.135 (s, 1H, NH),7.616 (d, 1H, pyH), 8.838 (s, 1H, pyH), 8.903 (d,1H, pyH), GCMS; m/z 205 ; 205.98 (20%), 173.92 (100%), 145.90(70%) Anal. Calcd for $C_7H_6F_3N_3O$; C, 40.98; H, 2.95;F, 27.78; N ,20.48;O, 7.80 % . Found: C, 40.5; H, 2.65; F, 27.15; N, 20.02; O, 7.57 %..

Synthesis of 3-(**5-(chloromethyl)-1,3,4-oxadiazol-2-yl)-4-(trifluoromethyl)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^{0}c 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 $NaHCO_3$ solution. The product was extracted by ethyl acetate, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting residue was recrystallised from ethanol.

Pale yellow solid ,Yield: 71%; m.p.60-64^{0}C,IR (cm-1): 1151(C-O-C), 1572 (C=C),1686 (C=N),1H NMR((CDCl3-,δ/ ppm): 4.822 (s, 2H, CH_2), 7.769 (d, 1H, pyH), 9.020 (s, 1H, pyH), 9.357 (d,1H, pyH), GCMS; m/z 262 ; 262.96 (90%), 213 (75%),173.98(85%), 145.97(100%) Anal.Calcd for $C_9H_5ClF_3N_3O$: C ,41.01;H, 1.91;Cl, 13.45;F ,21.62;N ,15.94;O, 6.07 % . Found: C, 41.00;H ,1.75,Cl, 13.05; F ,21.15 ; N ,15.15 ;O, 6.03 %.

***Synthesis of 3*-(5-(azidomethyl)-1,3,4-oxadiazol-2-yl)-4-(trifluoromethyl)pyridine (6)**
A 3-(5-(chloromethyl)-1,3,4-oxadiazol-2-yl)-4-(trifluoromethyl)pyridine (5) (0.01 mol) and dry dimethylacetamide (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 ^{0}c 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 Na_2SO_4 and evaporated under reduced pressure. The crude product was further purified by column chromatography (n-Hexane: Ethyl acetate =85:15)

Yellow solid, Yield: 68%; m.p.115-119°c(With decomposition), IR (cm^{-1}): 2109 (N_3), ^{1}H NMR($CDCl_3$-,δ/ ppm): 4.922 (s, 2H, CH_2), 7.789 (d, 1H, pyH), 9.220 (s, 1H, pyH), 9.457 (d,1H, pyH), LCMS: m/z: 270; Anal.Calcd for $C_9H_5F_3N_6O$: C ,40.01;H, 1.87; F ,21.10 ; N ,31.1; O, 5.92 % . Found: C, 40.80;H ,1.75,; F ,21.01 ; N ,30.21 ;O, 5.54 %.

***Synthesis of* 1-(1-((5-(4-(trifluoro methyl)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)-4-(trifluoromethyl) 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: 62%; m.p.129-133^{0}C,IR (cm-1): 1675(C=O), ^{1}H NMR((CDCl3-,δ/ ppm): δ 2.68 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 5.875 (s, 2H, CH_2), 7.743 (d, 1H, pyH), 9.010 (d, 1H, pyH), 9.311 (s,1H, pyH), GCMS; m/z 352 ; 352.96 (10%) , 324 (50%) , 173.98 (100%), 145.97(50%) ; Anal.Calcd for $C_{14}H_{11}F_3N_6O_2$: C ,47.71;H, 3.15 ;F ,16.18; N, 23.86;O, 9.08 % . Found: C ,47.25 ;H ,3.01 ; F ,16.02; N, 23.15 ;O,8.85 %.

***Synthesis of* (1*E*)-1-[5-methyl-1-({5-[4-(trifluoro methyl)pyridin-3-yl]-1,3,4-oxadiazol-2-yl} methyl)-1*H*-1,2,3-triazol-4-yl]ethanone oxime (8)**

In cold solution of hydroxyl amine hydrochloride (0.01 mol) and methanol (50 ml) were added sodium hydroxide 30% solution (0.0105mol) under stirring at 5-10^{0}c.The reaction mass was stirred for 15 minute. Then start drop wise addition of 1-(1-((5-(4-(trifluoromethyl)pyridin-3-yl)-1,3,4-oxadiazol-2-yl) methyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethanone(7) (0.01mol) in (10ml) methanol under dry nitrogen atmosphere was added dropwise. After the addition is completed, the reaction mass was refluxed for 5-7 hrs. The completion of reaction was monitored by TLC. The mixture was poured in ice water and the product was extracted by ethyl acetate. On evaporation under reduced pressure the crude product was used as such for next step.

Off white solid ,Yield: 77%; m.p.169-173°C,IR (cm^{-1}): 3228 (OH), ^{1}H NMR((CDCl3-,δ/ ppm): 1.25 (s, 1H, OH), 2.41 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 5.855 (s, 2H, CH_2), 7.739 (d, 1H, pyH), 9.020 (d, 1H, pyH), 9.300 (s,1H, pyH), LCMS; m/z: 367; Anal.Calcd for $C_{14}H_{12}F_3N_7O_2$: C ,45.78;H ,3.29 ;F ,15.52 ;N, 26.69;O; 8.71 % . Found: C ,45.25 ;H ,3.01 ; F ,15.12 ; N, 26.15 ; O,8.05 %.

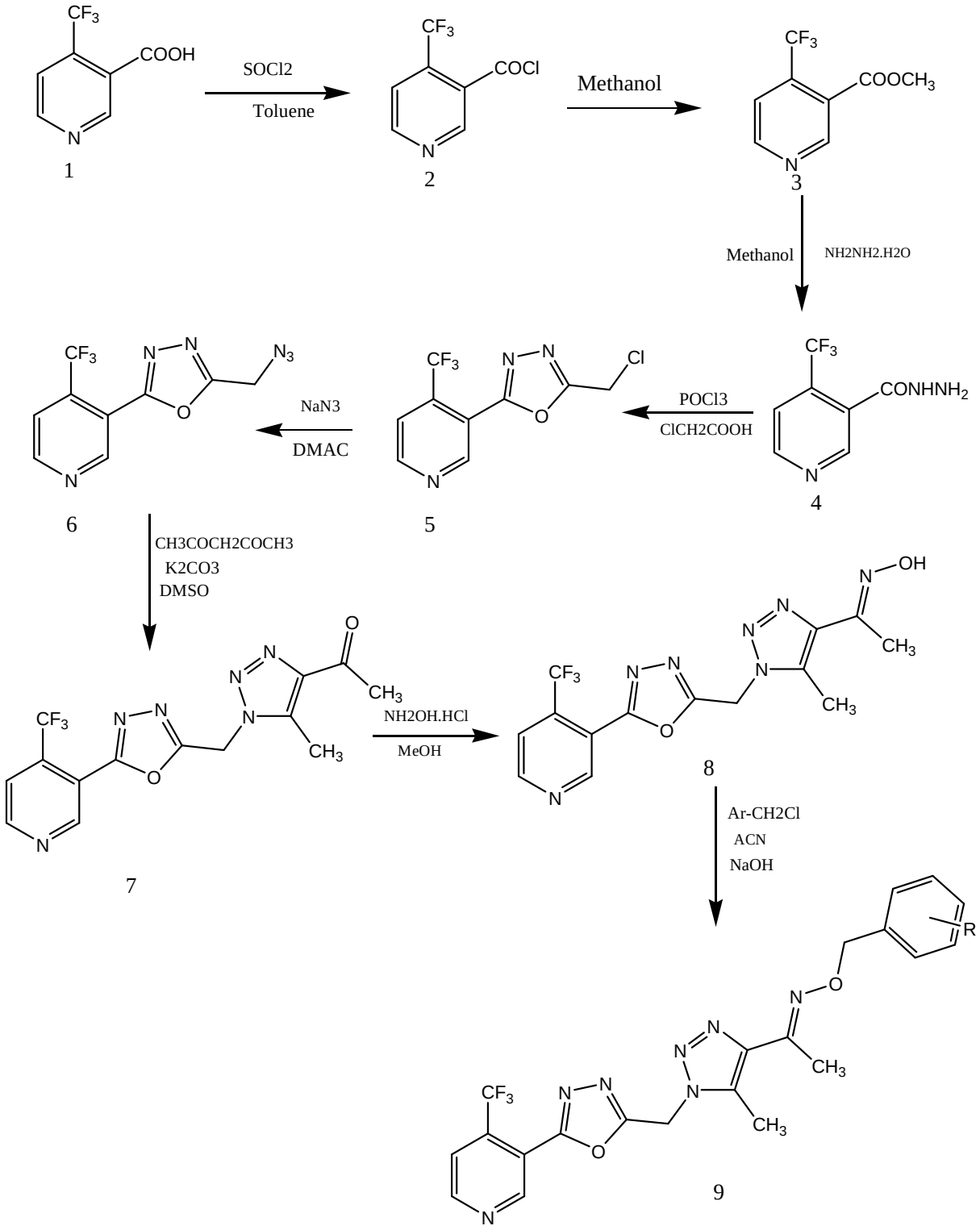
General procedure for the synthesis of compound (9 a-c)

In a three-neck flask charged dry acetonitrile (50 ml) and sodium hydroxide powder (0.01 mol) and stirred for 10-15 minute and 1-(1-((5-(4-(trifluoromethyl)pyridin-3-yl)-1,3,4-oxadiazol-2-yl)methyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethanone oxime 8 (0.01mol)in anhydrous CH_3CN (15ml) was added dropwise. After vigorous stirring for 25-30 minutes, a solution of substituted aryl methyl chloride (0.01 mol) in anhydrous CH_3CN (10ml) was added drop wise. After addition completed, the reaction mass was refluxed for 5-7 hrs. The completion of reaction was monitored by TLC. Upon Completion of the reaction mixture was concentrated under vacuum and poured into ice-cold water. The product was extracted by ethyl acetate and dried over sodium sulphate. 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 (9a-c).

(1*E*)-1-[5-methyl-1-({5-[4-(trifluoro methyl)pyridin-3-yl]-1,3,4-oxadiazol-2-yl}methyl)-1*H*-1,2,3-triazol-4-yl]ethanone O-benzyl-oxime (9a)

Yellowish coloured solid,Yield : 57%; m.p.111-115°C ,IR (cm^{-1}): 1589,1560 (C=N),Ar 1455,1432,1375,N-O-C 1025.^{1}H NMR(DMSO-d_6,δ/ ppm): 2.40 (s, 3H, CH3), 2.49 (s, 3H, CH3), 5.178 (s, 2H, CH2), 5.824 (s, 2H, CH2), 7.25-7.32 (m, 5H, Ar-H)7.730 (d, 1H, pyH), 8.990 (d, 1H, pyH), 9.286 (s,1H, pyH), LCMS; m/z: 457 ; Anal.Calcd for $C_{21}H_{18}F_3N_7O_2$; C ,55.14;H ,3.97 ;F ,12.46 ;N, 21.44;O; 7.00 % . Found: C ,55.02 ;H ,3.35 ; F ,12.12 ; N, 21.15 ; O,6.75 %.

SCHEME-1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COOH
N
1
SOCl2
Toluene
CF3
COCl
N
2
Methanol
CF3
COOCH3
N
3
Methanol
NH2NH2.H2O
CF3
CONHNH2
N
4
POCl3
ClCH2COOH
CF3
N
N
Cl
O
N
5
NaN3
DMAC
CF3
N
N
N3
O
N
6
CH3COCH2COCH3
K2CO3
DMSO
CF3
N
N
N
N
O
CH3
O
CH3
N
7
NH2OH.HCl
MeOH
CF3
N
N
N
N
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CH3
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OH
CH3
N
8
Ar-CH2Cl
ACN
NaOH
CF3
N
N
N
N
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CH3
N
O
CH3
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R
9

(1*E*)-1-[5-methyl-1-({5-[4-(trifluoromethyl)pyridin-3-yl]-1,3,4-oxadiazol-2-yl}methyl)-1*H*-1,2,3-triazol-4-yl]ethanone O-(2-chloro benzyl)--oxime (9b)

Pale yellow coloured solid, Yield: 63%; m.p.85-90^{0}C:.,IR (cm-1): 1580,1550 (C=N),Ar 1465,1442,1385,N-O-C1015, 1H NMR(DMSO-d6,δ/ ppm): 2.40 (s, 3H, CH3), 2.49 (s, 3H, CH3), 5.178 (s, 2H, CH2), 5.824 (s, 2H, CH2), 7.25-7.32 (m, 5H, Ar-H)7.730 (d, 1H, pyH), 8.990 (d, 1H, pyH), 9.286 (s,1H, pyH), LCMS; m/z: 492 ; Anal.Calcd for $C_{21}H_{17}ClF_3N_7O_2$; C ,51.28;H ,3.48; Cl, 7.21 ;F ,11.59 ;N, 19.93;O; 6.51 % . Found: C ,50.88 ;H ,3.05 ; Cl, 6.85; F ,11.12 ; N, 19.15 ; O,6.05 %.

(1*E*)-1-[5-methyl-1-({5-[4-(trifluoromethyl)pyridin-3-yl]-1,3,4-oxadiazol-2-yl}methyl)-1*H*-1,2,3-triazol-4-yl]ethanone O-(2-methyl benzyl)-oxime (9c)

Off white solid,Yield: 53%; m.p.133-136^{0}C:.,IR (cm-1): 1569,1540 (C=N), Ar 1465,1438,1379,N-O-C 1017,1H NMR(DMSO-d6,δ/ ppm): 2.40 (s, 6H, 2CH3), 2.49 (s, 3H, CH3), 5.178 (s, 2H, CH2), 5.824 (s, 2H, CH2), 7.25-7.32 (m, 5H, Ar-H)7.730 (d, 1H, pyH), 8.990 (d, 1H, pyH), 9.286 (s,1H, pyH), LCMS; m/z: 471 ; Anal.Calcd for $C_{22}H_{20}F_3N_7O_2$; C ,56.04;H ,4.28 ;F ,12.09 ;N, 20.80;O; 6.79 % . Found: C, 55.82; H, 3.85; F, 11.72; N, 20.50; O, 6.45 %.

Antibacterial Evaluation

The newly synthesized representative compounds were tested for their antimicrobial activity against the following microorganisms: (a) Gram-negative: Escherichia coli, Pseudomonas putide; (b) Gram-positive: Bacillus subtilis, Streptococcus lactis. The preliminary screening of the investigated compounds was performed using the filter paper disc-diffusion method. The compounds were tested at a concentration of 100 µg/mL. The zone of inhibition was measured in mm and compared with reference standard ampicillin trihydrate (100 µg/mL). The compounds tested displayed good activity towards Gram positive bacteria, but were less active against Gram-negative bacteria. The results of antibacterial screening studies are reported in Table I.

Table I: Antibacterial *in vitro* activity of compounds 5,7,8 & 9a-9c

Compounds	Zone of Inhibition (in mm)			
	Gram Positive		Gram Negative	
	S.aureus	***C.diphtheria***	***P.aeruginosa***	**E.coli**
5	09	10	09	11
7	19	18	16	18
8	14	15	17	16
9a	18	17	16	14
9b	19	20	19	15
9c	19	18	20	16
Ampicillin trihydrate	26	27	23	21
DMSO	00	00	00	00

Diameter of the disc was 6 mm, concentration of the compounds taken was about 100 µg/ml..

RESULTS AND DISCUSSION

Scheme 1 shows the synthetic pathways to prepare the target compounds(4-9). The key substrate 3-(5-(chloromethyl)-1,3,4-oxadiazol-2-yl)-4-(trifluoromethyl)pyridine (5) was synthesized from the reaction of 4-(trifluoromethyl)pyridine-3-carbohydrazide derivative (4) (prepared from 4-

(trifluoromethyl)pyridine-3-carboxylic acid (1) and chloroacetic acid in presence of phosphorus oxychloride (Scheme). The IR spectrum of compound (5) showed strong absorption bands at 1151 for (C-O-C), 1572 for (C=C) and 1686 (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 9.02 ppm due to Pyridine-H .The 3-(5-(chloromethyl)-1,3,4-oxadiazol-2-yl)-4-(trifluoromethyl)pyridine (5) was treated with sodium azide in dimethyl acetamide to form 3-(5-(azidomethyl)-1,3,4-oxadiazol-2-yl)-4-(trifluoromethyl)pyridine(6) compound which was confirmed by absence of chloride against silver nitrate test and IR spectra showed strong absorption bands at 2109 (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-(4-(trifluoromethyl)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. 1H NMR spectrum displayed also a singlet at 2.68 ppm and 2.70 ppm assigned for two CH_3 group and singlet at 5.875 assigned for CH_2 group .Treatment of compound (7) with hydroxylamine hydrochloride afforded oxime (8). The IR spectrum of compound (8) showed strong absorption bands at 3228 for (OH). ^{1}H NMR spectrum displayed also a singlet at 1.35 ppm assigned for OH group. The compound (8) reacted with various arylmethyl chlorides in the basic conditions to get the final compound (E)-N-(1-(1-((5-(4-(trifluoro methyl) pyridin-3-yl)-1,3,4-oxadiazol-2-yl) methyl) -5-methyl-1H-1,2,3-triazol -4-yl)ethylidene)(phenyl)methanamine (9).The structures of the compounds (9) were confirmed by IR, ^{1}H NMR, LCMS/MS and elemental analysis. The IR spectrum of compound (9) showed strong absorption bands at 1589, 1586 for (C=N). 1H NMR spectrum displayed a signal at 2.40 ppm and 2.49 ppm assigned for two CH_3 group, 5.178 ppm and 5.824 signals for two CH_2 group and 7.25-7.32 ppm multiplet for aromatic ring hydrogen . Also 7.730 ppm, 8.990 ppm and 9.286 ppm for pyridine hydrogen. Presence of C=N bond probably existed as Z and E-isomers in compound 9a-d.In 13C NMR spectra , the CH_3 group of E isomer is shifted towards up field at 12.706 ppm relative to that of Z isomer(21-22 ppm). In this paper both of compounds (8) and (9a-c) are in E configuration. In ^{1}H NMR spectra, the CH_3 protons of E isomer signal at 2.40 ppm.

CONCLUSION

A number of novel 1, 4, 5-trisubstitued 1, 2, 3-triazole compounds containing trifluoromethylpyridine and 1,3,4-oxadiazole ring were prepared in moderately yield, some representative compounds were further screened for their antimicrobial activity which have showed good activity against gram positive as well as gram negative bacteria..

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