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SYNTHESIS AND ANTI-MICROBIAL ACTIVITY OF NOVEL-1-SUBSTITUTED 5-(1-(PYRIDYL-4-YL)-CYCLOPROPYL-*1H*-TETRAZOLES

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Abstract:
A new, simple and convenient procedure for the synthesis of novel 1-substituted-5-(1-(pyridyl-4-yl)-cyclopropyl-*1H*-tetrazoles **4(a-f)** has been developed by the reaction of dibromoethane reacted with 4-pyridyl carbonitrile **(1)** under phase transfer conditions to give 1-(pyridyl-4-yl) cyclopropyl carbonitrile **(2).** The compound **(2)** was treated with sodium azide, than followed by alkylation/ acylation to form corresponding title compounds **4(a-f)**. All the synthesized compounds were investigated for their antimicrobial activities against Gram positive *S. Aureus* bacteria, Gram negative *E.Coli* bacteria and fungi *C. Albicans* and *A. Niger* in comparison with standard drugs. Some of the tested compounds showed significant antimicrobial activity.

Keywords: Tetrazoles, sodium azide, phase transfer catalyst, antimicrobial activity

INTRODUCTION:

Tetrazoles are in increasingly popular skeleton[I] with wide ranging applications. The synthesis of novel tetrazole derivatives and the investigation of their chemical and biological behavior have gained more importance in the recent decades for biological and pharmaceutical reasons. Recently, several biologically relevant substances incorporating a tetrazole moiety have been developed, for example Losartan is an angiotensin II receptor antagonist [II], Tomelukast (L-171883) mimics the cysteinyl glycine terminus of growth hormone LTD 4, also functions as a potent anti-asthmatic drug [III] and BMS-317180 is a potent oral agonist of the human growth hormone secretagogue (GHS) receptor [IV]. They have found use in pharmaceuticals as lipophilic spacers and carboxylic acid surrogates, which improves oral absorption [V]. Substituted-1,2,3,4-tetrazoles were reported to possess antineoceceptive activity [VI-X], anti bacterial [XI], anti fungal[XII-XIV], anti-viral [XV], anti-inflammatory [XVI-XVII] and anti-ulcer [XVII-XIX] activities. Some of 5-(Pyridyl)-2H-tetrazol-2-aceticacid esters shown anti inflammatory activity[XX]. The tetrazole function is metabolically stable this featured a close similarity between the acidic character of the tetrazole group have inspired medicinal chemists to synthesize substituted tetrazoles as potential medicinal agents. Therefore, as part of our program aimed for the synthesis of new heterocycles in ionic liquids[XXI],we herein report an efficient synthesis of 1-substituted-5-(1-(pyridyl-4-yl)-cyclopropyl-*1H*-tetrazoles and their antimicrobial activity.

EXPERIMENTAL SECTION:

General methods: Melting points were recorded on a Stuart SMP30 melting point apparatus and were uncorrected. Column chromatography was performed using silica–gel (100–200 mesh size) purchased from Thomas Baker, and thin layer chromatography (TLC) was carried out using aluminium sheets pre-coated with silica gel 60F254 purchased from Merck. IR spectra (KBr) were obtained using a Perkin Elmer Spectrum100 FTIR Spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker WM-400 spectrometer in DMSO-d_6 with TMS as an internal standard. Mass spectra (ESI) were carried out on a JEOL SX-102 spectrometer. CHN analysis was done by Carlo Erba EA 1108 automatic elemental analyzer. The chemicals and solvents used were of commercial grade and were used without further purification unless otherwise stated.

Synthesis of (1-(pyridyl-4-yl)-cyclopropanecarbonitrile (2):

To a mixture of 4-pyridylcarbonitrile **(1)** (0.1 mmol) in 50% NaOH solution (5mL), added TBAB (0.04 mmol) as phase transfer catalyst than stirred for few min at room temperature. To this mixture added slowly dibromoethane (0.3 mmol) and stirred at room temperature for overnight (monitored by TLC). After completion of reaction,diluted with water than extracted with EA, washed with brine solution, dried over anhydrous Na_2SO_4, concentrated under vacuo to afford the compound **2** with 54% yield.

IR (KBr, cm^{-1}) ν = 3142, 2224; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.78 (t,2H,-CH_2), 0.96 (t, 2H,-CH_2), 7.12-7.15 (dd 2H, Py-H), 8.42-8.46 (dd, 2H, Py-H); ^{13}C NMR ((DMSO-d_6,75MHz,): δ 12.2, 16.6, 118.9, 121.7, 152.4; MS (*m/z)*:145 [M+1]; Anal. Calcd. for $C_9H_8N_2$: C, 74.98; H, 5.59; N, 19.43. Found: C, 74.92; H, 5.47; N, 19.39.

Synthesis of (1-(pyridyl-4-yl)-cyclopropyl-*1H*-tetrazoles (3):

To a mixture of (1-(pyridyl-4-yl)-cyclopropanecarbonitrile **(2)** (1 mmol) in [Bmim]BF4 (3 mL), stirred at room temperature for few min, NaN_3 (1.2 mmol) was added portion wise to the reaction mixture and then it was stirred at 80 ^{o}C for appropriate time. After completion of the reaction (monitored by TLC), it was cooled to RT and poured into ice cold water and carefully acidified (pH <5) with conc. HCl, the solid separated was filtered, washed with water, dried and purified by re-crystallization from methanol afforded compound **3**.

IR (KBr, cm^{-1}) ν = 3390, 3048, 1664; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.89 (t,2H,-CH_2), 1.02(t, 2H,-CH_2), 7.24-7.28 (dd 2H, Py-H), 8.45-8.52(dd, 2H, Py-H); ^{13}C NMR ((DMSO-d_6,75MHz,): δ 15.9, 17.2, 122.8, 152.2, 158.1, 160.1; MS (*m/z)*:188 [M+1]; Anal. Calcd. for $C_9H_8N_5$: C, 57.74; H, 4.85; N,37.41. Found: C, 57.68; H, 4.83; N, 37.39.

Synthesis of 1-substituted-5-(1-(pyridyl-4-yl)-cyclopropyl-*1H*-tetrazoles 4(a-f) :

To a solution of compound (1-(pyridyl-4-yl)-cyclopropyl-*1H*-tetrazoles **(3)** (1.0 mol) in anhydrous DMF (50 mL) was added K_2CO_3 (3.0 mol), then stirred for 30 minutes and added slowly the compounds alkyl/acyl chlorides (1.2 mol) at room temperature. The reaction mixture was refluxed for 7-8 h (the reaction was monitored by TLC), after completion of the

reaction, the reaction mixture poured into ice-cold water than purified by column chromatography (DCM: MeOH) to get title compounds.

1-(5-(1-(pyridin-4-yl)-cyclopropyl-*1H*-tetrazole-1-yl)ethanone (4a):

IR (KBr, cm^{-1}) ν = 3057, 1708; 1654; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.92(t, 2H,-CH_2), 1.10 (t,2H,-CH_2), 7.18-7.22 (dd 2H, Py-H), 8.38-8.45 (dd, 2H, Py-H); ^{13}C NMR ((DMSO-d_6,75MHz,):δ 15.2, 17.0, 26.2, 123.4, 150.9, 159.6, 163.4. 168.2; MS (*m/z)*:230[M+1]; Anal. Calcd. for $C_{11}H_{11}N_5O$: C, 57.63; H, 4.84; N, 30.55. Found: C, 57.56; H, 4.82; N, 30.42

Phenyl (1-(5-(1-(pyridin-4-yl)-cyclopropyl-*1H*-tetrazole-1-yl) methanone (4b):

IR (KBr, cm^{-1}) ν = 3048, 1710; 1654; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.98 (t, 2H,-CH_2), 1.12 (t,2H,-CH_2), 7.20-7.24 (dd 2H, Py-H), 7.65-7.78(m, 5H, Ar-H), 8.32-8.36 (dd, 2H, Py-H); ^{13}C NMR (DMSO-d_6,75MHz,): δ 16.2, 22.2, 122.4, 131.0, 132.5, 135.4, 138.9, 150.4, 158.9, 160.4. 166.8; MS (*m/z)* :292 [M+1]; Anal. Calcd. for $C_{16}H_{13}N_5O$: C, 65.97; H, 4.50; N, 24.05. Found: C, 65.92; H, 4.45; N, 24.02.

(5-(1-(pyridin-4-yl)-cyclopropyl-*1H*-tetrazole-1-yl) (p-tolyl)methanone (4c):

IR (KBr, cm^{-1}) ν = 3052, 1712; 1652; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.98 (t, 2H,-CH_2), 1.10 (t,2H,-CH_2), 7.26-7.30 (dd 2H, Py-H), 7.46-7.48(dd, 2H, Ar-H),7.58-7.62(2H, dd, Ar-H), 8.35-8.38 (dd, 2H, Py-H); ^{13}C NMR (DMSO-d_6,75MHz,): δ 17.4, 22.4. 23.7, 120.2, 128.5, 129.2, 130.5, 145.4, 148.9, 158.3, 161.3, 166.2; MS (*m/z)*:306 [M+1]; Anal. Calcd. for $C_{17}H_{15}N_5O$: C, 66.87; H, 4.95; N, 24.92. Found: C, 66.85; H, 4.91; N, 24.89.

(4-(1-(1-benzyl-*1H*-tetrazol-5-yl) cyclopropyl) pyridine(4d):

IR (KBr, cm^{-1}) ν = 3110,1656; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.92 (t, 2H,-CH_2), 1.09 (t,2H,-CH_2),5.82(s, 2H, -CH_2),7.23-7.28 (dd 2H, Py-H), 7.32-7.42 (m, 5H, Ar-H), 8.30-8.34 (dd, 2H, Py-H); ^{13}C NMR (DMSO-d_6,75MHz,): δ 18.2, 24.4, 43.2, 122.6, 126.7, 128.4, 129.2, 137.4, 139.5,150.6, 161.3; MS (*m/z)*:278 [M+1]; Anal. Calcd. for $C_{16}H_{15}N_5$: C, 69.29; H, 5.45; N, 25.25. Found: C, 69.18; H, 5.41; N, 25.17.

(4-(1-(1-ethyl-*1H*-tetrazol-5-yl) cyclopropyl) pyridine(4e):

IR (KBr, cm^{-1}) ν = 3110,1662; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.89 (t, 2H,-CH_2), 1.12 (t,2H,-CH_2),1.32 (t, 3H, -CH_3), 3.45 (q, 2H,-CH_2), 7.25-7.28 (dd 2H, Py-H), 8.30-8.35 (dd, 2H, Py-H); ^{13}C NMR (DMSO-d_6,75MHz,): δ 16.2, 16.9, 24.2, 42.0, 122.8, 151.2, 159.4, 160.3; MS (*m/z)*:216 [M+1]; Anal. Calcd. for $C_{11}H_{13}N_5$: C, 61.38; H, 6.09; N, 32.54. Found: C, 61.26; H, 6.02; N, 32.52.

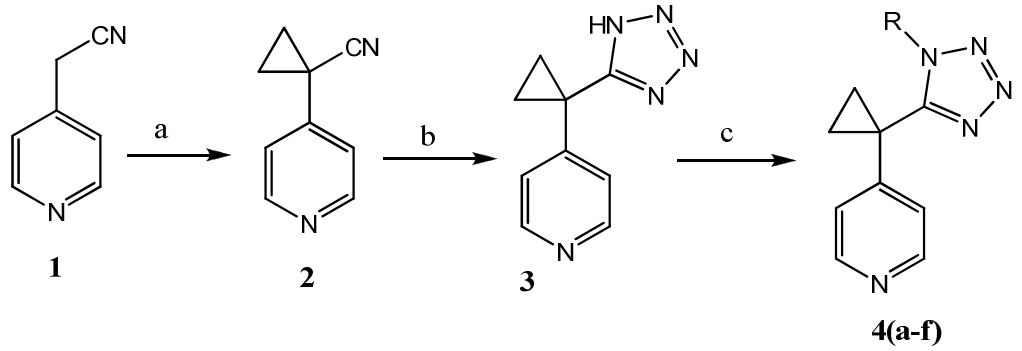
(4-(1-(1-methyl-*1H*-tetrazol-5-yl) cyclopropyl) pyridine(4f):

IR (KBr, cm^{-1}) ν = 3112,1659; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.85 (t, 2H,-CH_2), 1.10 (t,2H,-CH_2), 3.24 (s, 3H,-CH_3), 7.22-7.28 (dd 2H, Py-H), 8.32-8.38 (dd, 2H, Py-H); ^{13}C NMR (DMSO-d_6,75MHz,): δ 16.8, 24.2, 33.4, 122.6, 150.2, 158.4, 160.2; MS (*m/z)*:202 [M+1]; Anal. Calcd. for $C_{10}H_{11}N_5$: C, 59.69; H, 5.51; N, 34.80. Found: C, 59.62; H, 5.47; N, 34.75.

RESULTS AND DISCUSSION

In recent times, ionic liquids have attracted increasing interest in the context of green synthesis. These ILs have shown great promise as an alternative to conventional solvents due to their unique properties of non volatility, non-flammability, thermal stability, recyclability, and controlled miscibility. Butylimidazolium salts [ILs] have already been demonstrated as efficient catalysts and solvents for various organic transformations. Our literature survey revealed that till now there were no methods reported in the literature for the synthesis of 5-(1-(pyridyl-4-yl)-cyclopropyl-*1H*-tetrazoles using ionic liquids. As part of our ongoing research work, we herein, report a simple and efficient procedure for the synthesis of novel 1-substituted-5-(1-(pyridyl-4-yl)-cyclopropyl-*1H*-tetrazoles from 4-pyridyl acetonitrile (**1)** in the presence of [Bmim]BF_4 ionic liquid at 80 ^{0}C to afford title compounds in good yields **(Scheme-1).** The compound 4-pyridyl acetonitrile (**1)** is treated with dibromoethane under phase transfer conditions to form (1-(pyridyl-4-yl)-cyclopropanecarbonitrile **(2)** which were reacted with sodium azide than followed by treated with acyl/alkyl halides to give corresponding desired compounds **4(a-f)**. The structures of all the newly synthesized compounds were elucidated on the basis of their spectral (IR, NMR and mass) and elemental analyses data. The synthesized compounds **4(a-f)** were also assayed for their antimicrobial activity.

Scheme-1:



a)1,2-dibromoethane, 50% NaOH, PTC conditions, b) NaN_3/IL c) alkyl/acylchlorides, K_2CO_3/ acetone, reflux

4a) –$COCH_3$; 4b) –COPh; c) –CO-Ph-CH_3; d)-CH_2-Ph; e) –CH_2-CH_3; f) –CH_3

ANTIMICROBIAL ACTIVITY:

Antimicrobial activities of synthesized compounds **4(a-f)** were tested using the agar disc diffusion method. They were dissolved in DMSO. Final inoculums of 20 µl suspension of each bacterium and fungus used. Nutrient agar (antibacterial activity) and sabouraud's dextrose agar medium (antifungal activity) was prepared and sterilized by an autoclave and transferred to previously sterilized petridishes. The solidified plates were then seeded with 20 µl bacterial suspensions (freshly prepared in saline). Cups were cut in the solidified medium using sterile cork borer about 10 mm diameter. Sample solution (50 µl) of 125µg/ml concentration (calculated from tube dilution method) was loaded in each cup under sterile condition. The plates were left for 30 min to allow the diffusion of compounds at room

temperature. Antibiotic of ciprofloxacin (50µl) and fluconazole (50 µl) were used as positive control, while DMSO used as negative control. Then the plates were incubated for 24 h at 37 ± 1°C for antibacterial activity and 48 h at 37 ± 1°C for antifungal activity. The zone of inhibition was calculated by measuring the minimum dimension of the zone of no microbial growth around the each disc.

All the synthesized compounds have shown positive antibacterial activity against *S. Aureus, E. Coli,* but they are less active as compared to standard ciprofloxacin. The compound **4c, 4d, 4e** and **4f** shows greatest activity against *S. Aureus and E. Coli* respectively and show positive activity against *C. Albicans and A Niger*. The compounds **4b, 4d** and **4f** showed the greatest activities among the synthesized compounds and they have less activity as compared to standard fluconazole.

Table-1: Minimum inhibitory concentration (MIC, µg/ml) of synthesized compounds 4(a-f)

	Bacterial strains (+ Ve and –Ve)		**Fungal strains**	
Compound	***S. aureus***	***E. coli***	***C. albicans***	***A. niger***
4a	12	10	7	9
4b	12	10	12	16
4c	15	17	8	10
4d	16	18	12	13
4e	18	20	10	11
4f	17	21	14	16
Ciprofloxacin	25	25		
Flucanazole			18	18

CONCLUSION:

In conclusion, we synthesized a series of 1-substituted-5-(1-(pyridyl-4-yl)-cyclopropyl-*1H*-tetrazoles from 4-pyridyl carbonitrile. All the synthesized compounds characterized from IR, ^{1}H NMR and ^{13}C NMR spectroscopy and Mass spectrometry and screened for antimicrobial activity against S. *Aureus and E.Coli* and fungi *Candida albicans and A. Niger*. Some compound shows greatest activity.

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