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Deigned Synthesis of N-(5-(4-methoxyphenyl) thiazol-2-yl) benzamide analgueous Promoted by Imidazoles as a catalyst

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ABSTRACT:

An efficient and convenient method has been explained for N-(5-(4-methoxyphenyl) thiazol-2-yl) benzamide derivatives that can be obtained from the reaction of 5-(4-methoxyphenyl) thiophen-2-amine and substituted aromatic carbonyl halides in the presence of Imidazoles and MDC solvent at reflux. 5-(4-methoxyphenyl) thiophen-2-amine can be prepared from 2-bromo-1-(4-methoxyphenyl) ethan-1-one with thiourea in the presence of sodium acetate and acetic acid at 35^0C. All the compounds were evaluated by advanced spectroscopic data (^{1}H NMR, ^{13}C NMR and LCMS) and the structural determination was evaluated by elemental analysis. Besides to this, all the newly synthesized compounds were examined for their antibacterial activities and antifungal activity by disc diffusion method against the organism of Aspergillus Niger and Candida albicans.

1. INTRODUCTION:

Amide group is an important key functional group in synthetic intermediates organic chemistry and medicinally chemistry and also its widespread occurrence in peptide and non-peptide natural products, therapeutic small molecules, and new polymeric materials [1–4]. The most general way for synthesizing amides bond involves the activation of the carboxylic function by means the conversion of carboxylic acids into the corresponding acid chlorides [5–8]. Hence this reactive derivative is coupled with the appropriate substituted amine to yield the corresponding amide. Alternatively, carboxylic acids, by the use of activating reagents, can be transformed into reactive acylating intermediates which directly react in situ with the suitable substituted amines without their preliminary isolation and purification [9–12]. The use of coupling reagents is the only practicable way when the reagents useful for obtaining acid chlorides from carboxylic acids are not compatible with other chemical functions or protecting groups present on the substrate.

The importance of amides bond has promoted the improvement of new protocols and reagents based on these approaches and alternative methods for amide bond formation [13–16]. The direct formation of amides by condensing no activated carboxylic acids and amines is extremely attractive because of its low environmental impact. Using metal-based catalysis in direct amide synthesized, as an alternative to coupling reagents, has been reported [17–19]. The main focus on the synthetic catalysts employed for direct amidation are boronic acids and esters together with Lewis acid metal complexes. Boron-based compounds are reported as catalysts promoting the condensation of carboxylic acids and amines in refluxing toluene [20, 21]. In addition amidation reaction protocols by using boronic acid and ester catalysts were also developed for the formation of dipeptide systems [22–24].

We reported the present work highly an efficient versatile and appropriate method for the synthesis of titled derivatives and with help of $TiCl_4$ as a catalyst. Our research perfectly and progressively the catalytic properties of magnetically separable Lew's acid several organic transformations has scaffold us to the identification that the effectiveness of these catalysts for the synthesis of Tited analogous has not been previously reported.

2. METHODS AND MATERIALS:

2.1. EXPERIMENTAL:

All the chemicals, synthetic reagents, and solvents were purchased from commercially and they were used without further purification. The standard procedures were used to follow by dry solvents and reaction mixture were checked by thin-layer chromatography (n-hexane: Ethyl acetate) on silica gel plates coated with alumina. The melting points of the desired compounds were determined in open capillary tubes and were uncorrected. ^{1}HNMR and ^{13}C-NMR spectrum were recorded titled derivatives on a Bruker Avance 400MHz and 100MHz instrument using $CDCl_3$ as a solvent. The mass spectra were obtained on a Shimadzu 2010A LCMS spectrometer. Elemental analysis of these analogous was recorded by the instrument.

2.2. GENERAL PROCEDURE OF 5-(4-METHOXYPHENYL) THIOPHEN-2-AMINE (3):

Take dry and clean 50mLRBF. The mixture of charge 2-bromo-1-(4-methoxyphenyl) ethan-1-one and Thiourea dissolved in the acetic acid and sodium acetate into RBF at room temperature which is also arranged on the magnetic stirrer possesses hot plate. The reaction mixture continuous carried the reaction for 2 hrs. at 55^0C .The progress of the reaction checked by the TLC (EtOAc : n-hexane = 6:4). After, all reactants were consumed, cooled the reaction mixture at RT. The crude extracted with ethyl acetate and washed with as saturated solution of $NaHCO_3$ and separated the ethyl acetate layer and also washed with water separated the organic layer. The organic layer can be distilled off under vacuums and solid compound obtained.

Characterization:

Palepinksolid; Rf-0.45 (Ethyl acetate: n-hexane-5:5); IR (KBr, cm^{-1}):5242, 3332, 3251, 3058, 1578, 1549, 1522. ^{1}HNMR (400MHz,$CDCl_3$)δppm: 7.745 (d, J = 9.6 Hz, 2H, Ar), 7.245 (d,J=8.0Hz,2H,Ar-H),6.956(s,1H,thiophene),6.195(s,2H,-NH_2),3.704(s,3H,-OCH_3);^{13}C NMR (100MHz,$CDCl_3$)ppm:167.94,143.02,128.59,128.03,127.73,125.26,119.58,56.04..LCMS(m/z): 206.85(M+);Molecularformulae:$C_{10}H_{10}N_2OS$: Elemental analysis: calculated: C- 58.23; H-4.89; N- 13.58.Obtained: C-58.16; H- 4.86; N- 13.65.

2.3. GENERAL PROCEDURE OF N-(5-(4-METHOXYPHENYL) THIAZOL-2-YL) BENZAMIDE ANALGUEOUS:

Take dry and clean 50mL RBF. The charge the methylene dichloride into RBF at room temperature which is also arranged on the magnetic stirrer which was contained hot plate. The charge a mixture of substituted aromatic amine and hetero aromatic acyl chloride (1mmol) with 5-(4-methoxyphenyl) thiophen-2-amines (1.1mmol) into RBF at mixture carried out 35^0C. Before, start the reaction, the strong base such as Imidazoles as catalyst and triethyl amine added into the reaction mixture and reaction continued in 5hrs at same temperature and monitored by TLC (ethyl acetate and n-hexane). After the completion of the reaction, crude poured in cold water and add 10 mL of 5% saturated solution of sodium bi carbonate added into the solution and charge with ethyl acetate. The organic layer separated and washed with solution of Brain. Finally separated the organic layer and distilled off. The desired product separated by column chromatography and also recrystallized with ethanol N-(5-(4-methoxyphenyl) thiazol-2-yl) benzamide.

CHARACTERIZATION:

2.3.1. N-(5-(4-methoxyphenyl) thiazol-2-yl) benzamide (5a):

White solid; M.p-215-217^0C ;Yield-87%; Rf-0.40 (Ethyl acetate: n-hexane-4:6);IR(KBr,cm^{-1}): 3092 , 1577, 1546, 1523, 1491,^{1}HNMR(400MHz,$CDCl_3$)δppm:11.547(s, 1H, -NHCO-), 7.942 (d, J = 7.2 Hz, 2H, Ar-H),7.716(dd,J=8.4Hz,2H,Ar-H),7.578(t,J=8.0Hz,2H,Ar-H),7.512(s,1H,thiophene,H),7.445(d,J=9.6Hz,2H,Ar-

H),7.158(d,J=6.8.0Hz,2H,Ar-H),7.087 (s,1H,thiophene),3.695(s,3H,-OCH_3);^{13}CNMR(100MHz,$CDCl_3$)ppm:165.06,158.76,155.41, 140.36,132.02,130.14,128.57,128.63,128.46,127.47,122.38,115.74,54.20;LCMS(m/z):311.58(M+H);Molecularformulae : $C_{17}H_{14}N_2O_2S$:Elemental analysis: calculated:C-65.79; H-4.55; N- 9.03.Obtained: C- 65.72 H- 4.54; N- 9.08.

2.3.2.4-Methoxy-N-(5-(4-methoxyphenyl) thiazol-2-yl) benzamide (5b):

Whitecompound;M.p-215-217^{0}C;Yield-87%;Rf-0.45(Ethylacetate:n-hexane-6:4);IR(KBr ,cm^{-1}):3077,3038,1584,1540,1522,1466,678.^{1}HNMR(400MHz,$CDCl_3$)ppm:11.508(s,1H,-NHCO-),7.913(d,J=7.2Hz,2H,Ar-H),7.697(d,J=8.8Hz,2H,Ar-H),7.525(s,1H,thiophene), 7.210-6.886(m,4H,Ar-H),3.714(s,3H,-OCH_3),3.670(s,3H,-OCH_3),^{13}CNMR(100MHz, $CDCl_3$) ppm:166.71,158.73,155.44,141.20,130.03,129.59,128.90,128.61,127.36,126.28,120.46, 118.09,116.07,55.52,52.24.LCMS(m/z):346.26(M+H);Molecularformulae:$C_{18}H_{16}N_2O_3S$: Elemental analysis: calculated: C-63.51; H-4.74; N- 8.23;lObtained:C-63.42,H- 4.72;N- 8.29.

2.3.3.4-Chloro-N-(5-(4-methoxyphenyl) thiazol-2-yl) benzamide (5c):

Whitesolid;M.p-233-235^{0}C;Yield-87%;Rf-0.45(Ethylacetate:n-hexane-4:6);IR(KBr,cm^{-1}): 3106,3040,1575,1534,1512,1490,688;^{1}HNMR(400MHz,$CDCl_3$)ppm:11.758(s,1H,-NHCO-), 7.792-7.514(m,6H,Ar-H),7.480(s,1H,thiophene,H),7.387-7.271(m,2H,Ar-H),3.812(s,3H,-OCH_3);^{13}CNMR(100MHz,$CDCl_3$)ppm:167.87,162.54,155.57,141.74,131.36,130.57,129.35, 128.90,128.41,128.05,126.64,123.28,55.80;LCMS(m/z):346.58(M+2);Molecularformulae:$C_{17}H_{13}ClN_2O_2S$:Elemental analysis: Calculated: C-59.22; H-3.80; N-8.20.Obtained: C- 59.14 H- 3.78;N- 8.20.

2.3.4 .4-Bromo-N-(5-(4-methoxyphenyl) thiazol-2-yl) benzamide (5d):

Pale compound;M.p-234-236^{0}C;Yield-85%;Rf-0.45(Ethylacetae: n-hexane-4:6);IR(KBr,cm^{-1}):3105,3040,1583,1532,1520,1490,695;^{1}HNMR(400MHz,$CDCl_3$)ppm:11.727(s,1H,-NHCO-),7.924(d,J=8.8Hz,2H,Ar-H),7.710(d,J=7.2Hz,2H,Ar-H),7.640(d,J=8.8Hz,2H,Ar-H),7.740 (s,1H,thiophene,H),3.614(s,3H,-OCH_3);^{13}CNMR(100MHz,$CDCl_3$)ppm:168.52,160.30,158. 87,140.54,130.27,129.21,128.80,128.20,127.76,126.41,122.47,55.16.LCMS(m/z):346.87 M+2):;Molecularformulae:$C_{17}H_{13}BrN_2O_2S$:Elementalanalysis: calculated: C-52.45; H-3.37; N- 7.20.Obtained: C- 52.36 H- 3.35; N- 7.29.

2.3.5. N-(5-(4-methoxyphenyl) thiazol-2-yl)-4-nitrobenzamide (5e):

Redsolid;M.p-228-230^{0}C;Yield-88%;Rf-0.51(Ethylacetate:n-hexane-4:6);IR(KBr,cm^{-1}): 30920,3044,1586,1539,1522,1491,684;^{1}HNMR(400MHz,$CDCl_3$)ppm:11.628(s,1H,-NHCO-),8.157(d,J=8.8Hz,2H,Ar-H),8.032(d,J=8.4Hz,2H,Ar-H),7.684(d,J=9.8Hz,2H,Ar-H),7.688 (d,J=9.2Hz,2H,Ar-H),7.066(d,J=7.2Hz,2H,Ar-H),3.662(s,3H,-OCH_3);^{13}CNMR(100MHz, $CDCl_3$)ppm:168.21,160.67,157.20,147.25,141.44,135.28,129.69,128.75,128.20,128.45,126. 68,121.22,56.74,LCMS(m/z):356.38(M+2):Molecularformulae:$C_{17}H_{15}N_3O_4S$:Elemental Analaysis: Calculated: C-57.46; H-3.69; N- 11.82.Obtained: C- 57.38 H- 3.67; N- 11.85.

2.3.6. N-(5-(4-methoxyphenyl) thiazol-2-yl) nicotinamide (5f):

White solid; M.p-235-237^{0}C ;Yield-89%; Rf-0.45 (Ethyl acetate: n-hexane-4:6);IR(KBr,cm^{-1}): 3087 , 3034, 1572, 1545, 1516,1491,^{1}HNMR(400MHz,$CDCl_3$)ppm:11.574(s,1H,-NHCO-),8.578(d,J=6.8Hz,2H,py),8.216(d,J=7.8Hz,2H,py),7.927(t,J=8.8Hz,2H,py), 7.842(t,J=8.8Hz, 2H,py),7.660(d,J=6.4Hz,2H,py),7.520(s,1H,thiophene,H),7.144(d,J=6.8Hz,2H,Ar-H),3.716 (s,3H,-OCH_3);^{13}CNMR(100MHz,$CDCl_3$)ppm:164.58,159.17,155.06,149.08,142.64,140.54,

135.65,128.87,128.08,127.74,125.31,122.39,120.64.LCMS(m/z):311.32(M+H);Molecular formulae:$C_{16}H_{13}N_3O_2S$:Elementalanalysis:calculated:C-61.72;H-4.21;N-13.50.Obtained:C-61.66,H- 4.20,N- 1358.

2.3.7. N-(5-(4-methoxyphenyl) thiazol-2-yl) thiophene-2-carboxamide (5g):

White solid;M.p-228-230^{0}C;Yield-88%; YRf-0.440 (Ethyl acetate: n-hexane-5:5);IR(KBr,cm-1): 3082 , 3056, 1572, 1542, 1518, 1496,^{1}HNMR(400MHz,$CDCl_3$)ppm:11.648 (s, 1H,-NHCO-),8.246(d,J=7.6Hz,1H,thiophene),7.887(d,J=8.0Hz,1H,thiophene),7.518 (s,1H, thiophene,H7.166(t,J=7.6Hz,2H,thiophene),7.088(d,J=7.0Hz,2H,Ar-H),7.114(d,J=7.6 Hz,2H, Ar-H),3.582(s,3H,-OCH_3)^{13}CNMR(100MHz,$CDCl_3$)ppm:164.84,160.66,156.71,141.72, 130. 64,129.84,128.55,127.66,127.14,126.46,121.44,54.84.LCMS(m/z):17.42(M+H);Molecular formulae:$C_{15}H_{12}N_2O_2S_2$: Elemental analysis: calculated: C-56.94; H-3.82; N-8.85. Obtained: C- 56.85 H- 3.81;N- 8.92.

3. BIOLOGICAL EVALUATION:

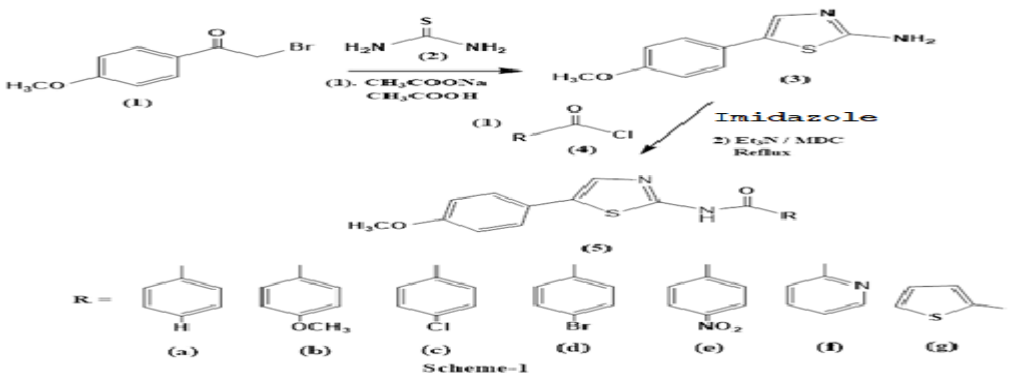
3.1. ANTIBACTERIAL ACTIVITY:100 mL sterile conical flask of nutrient broth was inoculated with the test organisms and incubated at 370 C overnight. By using a sterile pipette, 0.6 mL of the broth culture of each test organism was added to 60 mL of molten agar, mixed well and maintained at 450C. Sterile agar test plates of each test organism were prepared by pouring inoculated medium with uniform thickness. The agar was allowed to set and harden and wells of 4 mm diameter were cut at equidistant using a sterile cork borer. Agar plugs were removed. 100 lg/mL of test solutions were prepared in DMSO and were introduced into the wells using micropipette. The plates were kept at room temperature for 2 h for better diffusion of solution into the medium. The plates were incubated for 36h at370C. After incubation the diameter of inhibitory zones formed around each well was measured in millimeter (mm) using antibiotic zone scale. The assay was carried out in duplicate. DMSO was used as control and the antibacterial activity of the test compounds was compared with standard “Streptomycin”.

3.2. Antifungal activity:

Sterile molten potato dextrose agar (PDA) medium was inoculated with 50 lL of fungal spore suspension aseptically and maintained at 450Ctemperature. The inoculated medium was mixed well and poured immediately in sterilized petriplates. Then five wells of 6 mm diameter were punched using sterile borer and filled with 100 lg/mL of test compounds (4a-4j) as well as sterile DMSO 100% as negative control. Plates were incubated for 24 h at 370C. Antifungal activity was determined by measuring the zone of inhibition. The zones produced by the test compounds were compared with the “ketoconazole

4. RESULTS AND DISCUSSION:

4.1. Chemistry:



Scheme-1

Initially, we observed that the excellent result investigated the reaction is two steps, The first step of reaction 5-(4-methoxyphenyl) thiophen-2-amine from thiourea and 2-bromo-1-(4-methoxyphenyl) ethan-1-one in the presence of sodium acetate and acetic acid under conditions at reflux (Scheme -1). The second step of the reaction was N-(5-(4-methoxyphenyl) thiazol-2-yl) benzamide synthesized from the 5-(4-methoxyphenyl) thiophen-2-amine with various aromatic and hetero aromatic acyl halides in the presence of strong base such as triethyl amine and Imidazoles.

The advantages of the catalyst having some important features for the reaction conditions such as the simple work-up procedure, shortest reaction time, excellent product yields, and purification of products by non-chromatographic methods. It is particularly observed that various substituted aromatic amines possess electron-donating or electron-donating withdrawing substituents in para-positions lead good yield of the product. Here, we have observed that the reaction of aromatic amines having electron-withdrawing groups was rapid as compared to the reaction of aldehydes having electron donating groups.

4.2. Antifungal activity:

The in vitro antifungal activity of the desired compounds (5a-5g) was compared with standard drug" Ketonozole.'' as collected in (Table-II). The in vitro antifungal activity of the tested derivatives (5a-5g) was investigated against AspergillusNiger , Aspergillusfavus and Candida albicans using agar well diffusion assay and zones of inhibition of the test Compounds were expressed in mm as shown in Table-II. Compounds 5e showed excellent active potential activity against the fungal strain. The compound having "5f and 5g" was observed to be good active potential against tested fungal strain. Compounds such as 5c and 5d have demonstrated significant antifungal activity comparable to standard. From the results it is indicated that most of the compounds showed significant activity and few are moderately active as shown in Table -II. The remaining derivatives showed moderate potent activities against Aspergillusfavus. These results reveals that the compounds possess electron attracting groups exhibited moderate activity while the compounds having electron attracting groups exhibited good against the fungal stains..

Table-II: Antifungal activity of the synthesized compounds **(5a-5g):**

Zones of inhibition (mm)a of compounds **(5a–5g)** against tested fungal strains.

Entry	**Anti-Fungal Activity**		
	Aspergillus Niger	**Aspergillusfavus**	**Candida albicans**
5a	04	06	08
5b	11	12	10
5c	16	17	15
5d	14	15	14
5e	19	18	19
5f	15	15	14
5g	12	14	14
Ketonozole	22	22	22
DMSO			

5. CONCLUSIONS:

To find out this experiment, we prepared the seven derivatives N-(5-(4-methoxyphenyl) thiazol-2-yl) benzamide derivatives. The derivatives having electron donating groups and electron attracting groups including halogen containing derivatives .The percentage of the derivatives acquired electron donating group (92%) compared with electron withdrawing group of the compounds. As shown scheme-1, these compounds obtained using Imidazoles

an excellent coupling reagent. The compounds synthesized by using alkali base in non-polar solvent and derivatives of (5a-5g) synthesized by organic base (TEA) in non- polar solvent (DCM).In addition to antimicrobial activity of these derivatives exhibited various active potential in various as antifungal strains.

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