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Synthesis and Characterization of Pyrimidine, Pyridine and Chromen-2-One Analogues

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ABSTRACT

Some new of pyrimidine (5), pyridine (10) and chromen-2-one (15) analogues have been synthesized. The structures of target compounds were confirmed by spectroscopic techniques such as IR, ^{1}H NMR, mass and elemental analysis.

Keywords: pyrimidine, pyridine and chromen-2-one, synthesis, characterization.

INTRODUCTION

The chemistry of heterocyclic compounds continues to be an active field in the organic chemistry. Heterocyclic compounds bearing nitrogen and oxygen atoms were the reason for the activity of most of the drugs of natural origin leads to the discovery of the many synthetic drugs, which represent significant interest of heterocyclic compounds exist in numerous natural products displaying a wide range of biological and pharmaceutical activities [1,2]. Pyrimidine, pyridine and chromen-2-one are important building blocks in the construction of new molecular systems for biologically active molecules [3-9]. Considering these facts, and in continuation of our efforts to design heterocyclic compounds have nitrogen and oxygen atoms [10], we herein report the synthesis some new pyrimidine, pyridine and chromen-2-one derivatives.

MATERIALS AND METHODS

Chemicals were purchased from Sigma Aldrich Chemical Co. Melting points were determined on a Thomas Hoover capillary melting point apparatus with a digital thermometer. IR spectra were determined on FT-IR Shimadzu 8300 spectrophotometer. Column chromatography was performed n silica gel using suitable eluent, ^{1}H NMR was recorded on a Bruker 400 MHz NMR spectrophotometer in DMSO-d_6 /$CDCl_3$ and the chemical shifts were recorded in parts per million down fields from tetramethylsilane. Mass spectra were obtained with a VG70-70H mass spectrometer and important fragments are given. The results of elemental analyses were within ±0.4% to theoretical value.

Synthesis of *N*-(3-(trifluoromethyl)benzyl)pyrimidin-2-amine (3): To a solution of 2-bromo pyrimidine (**1**, 0.04 mol) and (3(trifluoromethyl)phenyl)methanol amine (**2**, 0.04 mol) in acetonitrile was added cesium carbonate and reaction mixture was heated to 120°C in microwave for 2 h. Completion of the reaction was checked by TLC. The reaction mixture was concentrated under reduced pressure to remove acetonitrile and dissolved in ethyl acetate and extracted with water, the organic layer was dried over sodium sulfate, filtered and concentrated to afford crude residue. The crude reaction mixture was purified by column chromatography using 230-400 mesh silica gel as a stationary phase. The column fractions were collected and concentrated to get pure product. Yield**:** 81%, obtained as a yellow solid; FT-IR: (KBr, cm^{-1}) 3233 (NH); ^{1}H NMR ($CDCl_3$): δ 5.03 (s, 2H, CH_2), 7.13-8.67 (m, 7H, Ar-H), 9.85 (s, 1H, NH), LC-MS m/z 254 (M+1). Anal.Calc. for $C_{12}H_{10}F_3N_3$: C, 56.92; H, 3.98; N, 16.59. Found: C, 56.64; H, 4.15; N, 16.39%.

Synthesis of 1-pyrimidin-2-yl-1-(3-trifluoromethyl-benzyl)-urea (5): To a solution *N*-(3-(trifluoro methyl) benzyl) pyrimidin-2-amine (**3**, 0.020 mol) in THF and chlorosulfonylisocyanate (0.020 mol) was added drop wise at -10°C under nitrogen atmosphere. The reaction mixture was stirred at same temperature for 2 h, and then formation of the intermediate was checked by UPLC, the reaction mixture was slowly quenched with water. The pH of water layer was made neutral and extracted with ethyl acetate (3×20 mL) and washed with brine solution. The combined organic layers were dried over sodium sulfate, filtered and concentrated to afford crude reaction mass and recrystalized from ethanol. Yield**:** 60%, obtained as white solid; FT-IR: (KBr, cm^{-1}): 1655 (C=O), 3375 (NH_2); ^{1}H NMR ($CDCl_3$): δ 4.21 (s, 2H, NH_2), 4.86 (s, 2H, CH_2), 7.22-8.16 (m, 7H, Ar-H), LC-MS m/z 297 (M+1). Anal.Calc. for $C_{13}H_{11}F_3N_4O$: C, 52.71; H, 3.74; N, 18.91. Found: C, 53.04; H, 3.51; N, 18.80%.

Synthesis of substituted triazole-4-carboxamide

Preparation of 5-(3-chloropyridin-4-yl)-3-methyl-3H-1, 2, 3-triazole-4-carboxylic acid (7): n-Butyl lithium (2.5 mol) was added drop wise to a mixture of 3-chloro-4-(1-methyl-1H-1,2,3-triazol-4-yl)pyridine (**6**, 0.026 mol) in THF under nitrogen atmosphere at -78°C and the reaction mixture was stirred at same temperature for 1 h to generate anion. To the reaction mixture added dry ice powder slowly with outlet in order prevent hazard due to pressure created by excess CO_2 liberation and after some time the reaction mixture was stirred at RT. Completion of the reaction was checked by TLC. The reaction mixture was slowly quenched with saturated ammonium chloride solution and pH was made basic by adding sodium bicarbonate solution and extracted with ethyl acetate, so that acid will remain in aqueous layer and impurities will dissolve in organic layer. The aqueous layer was acidified and extracted with ethyl acetate, so that acid will go to organic layer (3-15 mL). The organic layer was washed with brine solution and then combined organic layers were dried over sodium sulfate, filtered and concentrated to afford pure acid. Yield: 98%, obtained as yellowish solid; FT-IR: (KBr, cm^{-1}): 1695 (C=O), 3420 (OH); ^{1}H NMR (DMSO-d_6): δ 3.34 (s, 3H, CH_3), 7.54-8.72 (m, 3H, Ar-H), 12.25 (s, 1H, OH); LC-MS m/z 239 (M+1). Anal. Calc. for $C_9H_7ClN_4O_2$: C, 45.30; H, 2.96; N, 23.48. Found: C, 45.15; H, 3.26; N, 23.26%.

Synthesis of 5-(3-chloropyridin-4-yl)-3-methyl-3H-1,2,3-triazole-4-carbonyl chloride (8): To a solution of 5-(3-chloropyridin-4-yl)-3-methyl-3H-1,2,3-triazole-4-carboxylic acid (**7**, 0.01 mol) in DCM was added pinch of DMF and oxalyl chloride added drop wise under nitrogen atmosphere at 0°C and the reaction mixture was stirred at room temperature for 1 h to generate acyl chloride. As acyl chloride is unstable a portion of reaction mixture was quenched with methanol to form methyl ester and checked by TLC, and the reaction mixture was concentrated under reduced pressure to remove excess of oxalyl chloride under nitrogen condition. Yield: 76%, obtained as white solid; FT-IR: (KBr, cm^{-1}): 1675 (C=O); ^{1}H NMR (DMSO-d_6): δ 3.42 (s, 3H, CH_3), 7.49-8.63 (m, 3H, Ar-H); LC-MS m/z 258 (M+1). Anal.Calc. for $C_9H_6Cl_2N_4O$: C, 42.65; H, 2.35; N, 21.79. Found: C, 42.35; H, 2.47; N, 21.43%.

Synthesis of 5-(3-chloropyridin-4-yl)-N-(4-fluorophenyl)-N, 3-dimethyl-3H-1, 2, 3-triazole-4-carboxamide (10): A mixture of 5-(3-chloropyridin-4-yl)-3-methyl-3H-1,2,3-triazole-4-carbonyl chloride

(**8**, 0.01 mol) was heated with 4-fluoro *N*-methyl aniline (**9**, 0.01 mol) in 1,2 dichloro ethane and Et_3N at 80°C in seal tube for 16 h. The reaction mixture was extracted with water and DCM. The combined organic layers were dried over sodium sulfate, filtered and concentrated to afford crude reaction mass. The reaction mass was purified by column chromatography and product was eluted at 40% ethyl acetate in petroleum ether to afford pure product. Yield**:** 51%, obtained as off white solid; FT-IR: (KBr, cm^{-1}): 1665 (C=O); ^{1}H NMR: 400 MHz, $CDCl_3$: δ 3.45 (s, 3H, CH_3), 4.33 (s, 3H, CH_3), 6.44-8.61 (m, 7H, Ar-H); LC-MS m/z 346 (M+1). Anal.Calc. for $C_{16}H_{13}ClFN_5O$: C, 55.58; H, 3.79; N, 20.26. Found: C, 55.32; H, 3.48; N, 20.22%.

Synthesis of Coumarin derivative

7-Hydroxy-4-methyl-chromen-2-one (13): In a 250 mL three-necked round bottomed flask, fitted with a thermometer reaching to the bottom, and a dropping funnel is placed in concentrated sulfuric acid and nitrogen atmosphere. The flask is surrounded by an ice bath and when the temperature falls below 10^{o}C, a solution of resorcinol (**11**, 0.05 mol) in ethyl acetoacetate (**12**, 0.05 mol) was added drop wise. The mixture is stirred and the temperature is kept below 10^{o}C by means of ice and salt. After all the solution has been added the reaction mixture is set aside without further cooling. Reaction was monitored by TLC. After 2 h completion of the reaction, the mixture poured with vigorous stirring into a mixture of 180g of ice and 280 mL of water. The precipitate is collected on a filter and washed with two 10 mL portions of cold water. The crude product is then dissolved in 150 mL of 5% aqueous sodium hydroxide solution. The solution is filtered and the product is re-precipitated from the filtrate by the slow addition of dilute sulfuric acid. The product is collected, washed with cold water (3×10 mL) and dried. Yield: 71%, obtained as white solid; FT-IR: (KBr, cm^{-1}): 1655 (C=O); ^{1}H NMR: δ 2.30 (s, 3H, CH_3), 6.13-7.60 (m, 4H, Ar-H), 10.52 (s, 1H, OH); LC-MS m/z 177 (M+1). Anal. Calc. for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.23; H, 4.39%.

Synthesis of 4-methyl-7-acetoxycoumarin (14): A mixture of 4-methyl-7-hydroxycoumarin (**13**, 0.03 mol) and acetic anhydride refluxed under nitrogen atmosphere at 140^{o}C for 1.5 h, completion of the reaction was confirmed by TLC. Then reaction mixture was cooled to about 50^{o}C and poured with vigorous stirring into cold water. The precipitate was collected, washed, dried. The product was purified by recrystalization using ethanol. Yield**:** 85%, obtained as white solid; FT-IR: (KBr, cm^{-1}): 1695 (C=O); ^{1}H NMR: δ 2.30 (s, 3H, $COCH_3$), 2.43 (s, 3H, CH_3), 6.39-7.26 (m, 4H, Ar-H); LC-MS m/z 219 (M+1). Anal. Calc. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.17; H, 4.41%.

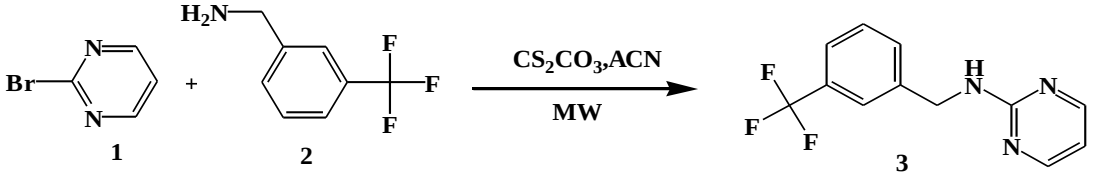
Synthesis of 4-methyl-7-hydroxy-8-acetylcoumarin (15): 4-methyl-7-acetoxycoumarin (**14,** 0.01mol) was treated with anhydrous aluminum chloride (0.02mol) as a catalyst at 150-170° C under without solvent condition for about 2-3 h. Then the reaction mixture was cooled to room temperature and quenched with 6 N hydrochloric acid in the presence of ice water. The reaction mixture was stirred for about 2-3 h, filtered the solid and recrystalized with methanol to obtain desired compound (**15).** Yield: 75%, obtained as bright yellow solid; FT-IR: (KBr, cm^{-1}): 1675 (C=O), 3350 (OH); ^{1}H NMR: δ 2.36 (s, 3H, $COCH_3$), 2.58 (s, 3H, CH_3), 6.22-7.72 (m, 3H, Ar-H), 11.56 (s, 1H, OH); LC-MS m/z 219 (M+1). Anal. Calc. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.25; H, 4.45%.

RESULTS AND DISCUSSION

The target compounds (3, 5, 10 and 15) were synthesized as illustrated in Schemes 1-4. All the compounds were characterized by analytical and spectroscopic IR, ^{1}H NMR, Mass, elemental analysis.

The starting material *N*-(3-(trifluoromethyl) benzyl)pyrimidin-2-amine (3) was prepared by heating corresponding 2-bromo pyrimidine (1) and (3-(trifluoromethyl)phenyl)methanol amine (2) in acetonitrile in the presence of cesium carbonate in the microwave (scheme 1). The IR spectra showed the N-H

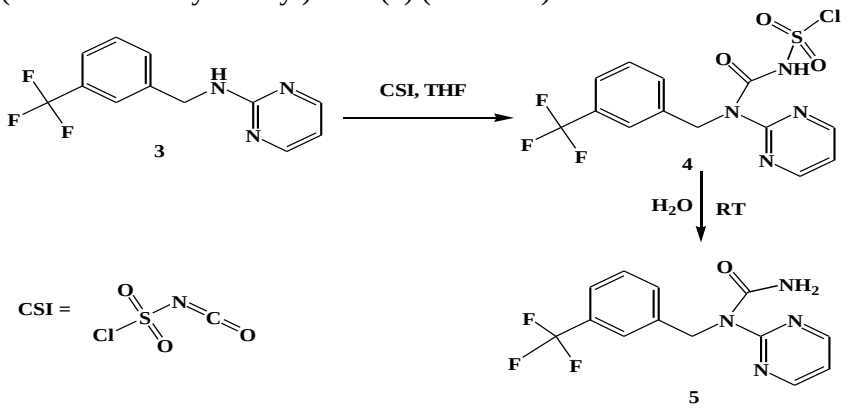
stretching absorption near 3140 cm^{-1}. In ^1H NMR, a singlet signal at δ 9.85 for NH proton was appeared which confirm the structure of compound (3).



1 2 3

Scheme 1

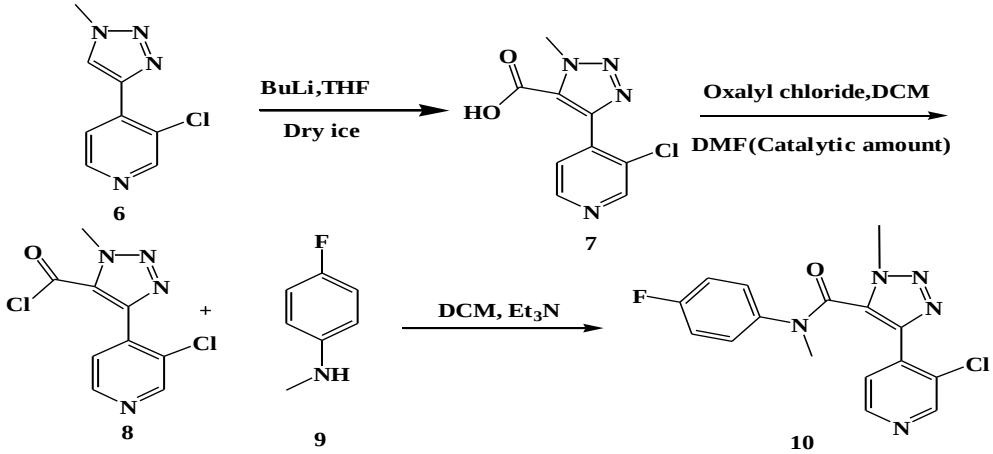
Compounds (3) was converted to the corresponding amide (4) by adding chlorosulfonylisocyanate in the presence of tetrahydrofuran which then undergo the hydrolysis to afforded the target compound 1-pyrimidin-2-yl-1-(3-trifluoromethyl-benzyl)-urea (5) (scheme 2).



Scheme 2

IR spectra of compound (5) showed absorption peak at 1655 cm^{-1} for carbonyl of amide. ^1H NMR, showed singlet at δ 4.21 for NH_2 protons and the mass spectra of compound **5** gave significant stable (M+1) peak at m/z 297.

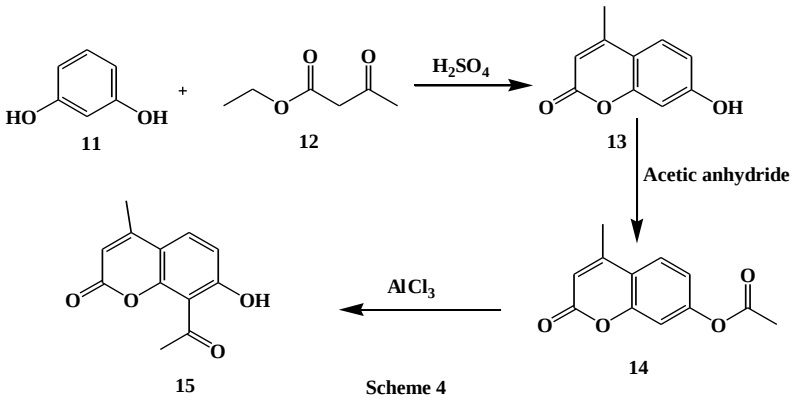
3-Chloro-4-(1-methyl-1H-[1,2,3]triazol-4-yl)-pyridine (6) was reacted with 2.5 M of n-Butyl lithium in presence of dry ice to afford 5-(3-Chloro-pyridin-4-yl)-3-methyl-3H-[1,2,3]triazole-4-carboxylic acid (7), reaction of carboxylic acid (7) with oxalyl chloride in the presence of catalytic amount of DMF gave compound (8) which on treating with (4-Fluoro-phenyl)-methyl-amine under basic conditions to afford compound (10) (scheme 3).



Scheme 3

Structure of compound(10**)** was confirmed in IR spectra by the appearance carbonyl of amide at 1655 cm^{-1}. ^1H NMR showed increase in four more aromatic protons with earlier aromatic proton peaks at δ 7.22-8.16, also the mass spectra gave significant stable (M+1) peak at m/z 346, which clearly evidence the formation of compound (10).

The synthesis of 7-hydroxy-4-methyl-chromen-2-one (13) was performed by the treatment of resorcinol with ethyl acetoacetate under nitrogen atmosphere. The compound (13) on treatment with acetic anhydride gave acetic acid 4-methyl-2-oxo-2H-chromen-7-yl ester (14). Further, Fries rearrangement of compound (14) with anhydrous aluminum chloride affords 8-acetyl-7-hydroxy-4-methyl-chromen-2-one (15) (scheme 4).



Scheme 4

In compound (**15**), the ^1H NMR showed singlet at δ 10.52 for OH proton, the target compound (**15**) also clearly confirmed by the mass spectra which showed significant stable (M+1) peak at m/z 177.

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REFERENCES

[1] S.M. Sondhi, M. Johar and S. Rajvanshi, Anticancer, Anti-inflammatory and Analgesic Activity Evaluation of Heterocyclic Compounds Synthesized by the Reaction of 4-Isothiocyanato-4-methyl pentan-2-one with Substituted o-Phenylenediamines and o-Diaminopyridine, *Aus. J. Chem*, **2001**, 54, 69-74.

[2] G.Bacolini, Topics Heterocycl. Syst, *Synth. React. Prop*, **1996**, 1, 103-110.

[3] A.E. Amr, M.S. Nermien, and M.M. Abdulla, Synthesis, reactions and anti-inflammatory activity of heterocyclic systems fused to a thiophene moiety using citrazinic acid as synthon, *Monatsh Chem*, **2007**, 138, 699-707.

[4] N. Fujiwara, T. Nakajima, Y. Ueda, H. Fujita and H. Kawakami, Novel piperidinylpyrimidine derivatives as inhibitors of HIV-1 LTR activation, *Bioorg. Med. Chem*, **2008**, 16, 9804-9816.

[5] R. Doshi, P. Kagthara and H. Parekh, Synthesis and biological evaluation of some novel isoxazoles and cyanopyridines, a new class of potential anti-tubercular agents, *Indian J. Chem*, **1999**, 38, 348-352.

[6] B.G. Mohammed, M.A. Hussein, A.M. Abdel-Alim and M. Hashem, *Arch. Pharm. Res*, 2006, 29, 26-33.

[7] G. T-Zitouni, Z.A. Kaplancikli, K. Erol and F.S. Kilic, Synthesis and analgesic activity of some triazoles and triazolothiadiazines, *Farmaco*, **1999**, 54, 218.

[8] A.A. Emmanuel-Giota, K.C. Fylaktakidou, D.J. Hadjipavlou-Litina, K.E. Litinas and Nicolaides, D.N. Synthesis and biological evaluation of several 3-(coumarin-4-yl)tetrahydroisoxazole and 3-(coumarin-4-yl)dihydropyrazole derivatives, *Hetero. Chem*, **2001**, 38, 717-722.

[9] M. Wang, L. Wang, Y. Li, Q. Li, Z. Xu and D. Qu, Antitumour activity of transition metal complexes with the thiosemicarbazone derived from 3-acetylumbelliferone, *Trans. Met. Chem*, **2001**, 26, 307- 310.

[10] M. Al‑Ghorbani, N.D. Rekha, Lakshmi V. Ranganatha, T. Prashanth, T. Veerabasappagowda and S. A. Khanum, Synthesis of oxadiazole–morpholine derivatives and manifestation of the repressed CD31 Microvessel Density (MVD) as tumoral angiogenic parameters in Dalton's Lymphoma, *Rus. J. Bio. Chem*, **2015**, 41, 5, 554–561.

[11] M. Al-Ghorbani, V. Vigneshwaran, V. Lakshmi Ranganatha, B.T Prabhakar and S. A. Khanum, Synthesis and biological efficacy of novel piperazine analogues bearing quinoline and pyridine moieties, *Bioorg. Chem*, **2011**, 46, 4853-4858.

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