Journal of Multidisciplinary Engineering Science and Technology (JMEST)
ISSN: 2458-9403
Vol. 4 Issue 8, August - 2017

Synthesis of Acetamide Derivatives Using Microwave-Assisted Method

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***Abstract*—A new convenient and efficient transition synthesis of acetamides through reaction of substituted thiazolidines and some amines is reported. The characteristic signals in their NMR spectra show the relationships between the structure and positions of the substituted groups in the products obtained. Some acetamides derivatives were tested for their antibacterial and antifungal activities in vitro against *Staphylococcus aureus, Enterobacter aerogenes and Candida albicans* by agar diffusion method.**

Keywords— Acetamide; solvent-free; microwave-assisted method.

I. INTRODUCTION

Many organic reactions have been heated using traditional heat transfer equipment such as oil bath, sand bath and heating jacket. These heatings are however rather slow and temperature gradients can develop within the sample. In addition, local overheating can lead to product, reagent and substrate decomposition. In contrast, in microwave dielectric heating, the microwave energy is introduced into the chemical reaction remotely and direct access by the energy sources to the reaction vessels is obtained. The microwave radiation passes through the walls of the vessels and heats only reactants and not the reaction vessel itself.

Its specific heating method attracts extensive interest because of rapid volumetric heating, suppressed side reactions, energy saving, direct heating, decreased environmental pollutions, and safe operations. Another area of interest which has been under focus recently is to avoid the use of organic solvent, which leads to wastage and is detrimental to the environment. Microwave heating for carrying out reactions in solven free has also attracted considerable attention in recent years. [1,2].On the other hand, acetamide derivatives bearing azole hetro aromatic are nowadays an important group of organic compounds that are used as antimicrobial, antiviral, anti-inflammatory [3,4]. Thiazole can be synthesized by methods such as Cook-Heibron, and many Modification of Cook-Heibron menthods. This paper describes the condensation reaction of some amines **3** with Synthesis of 2-chloro-*N*-[2-(6- substituted -2-oxo-2*H*-chromen-3-yl)-1,3-thiazol-5-yl]acetamide **2** under microwave irradiation. Futhermore, the synthesized acetamides were screened for antimicrobial and antifungal activities.

II. EXPERIMETAL

A. General experimetal procedures

Melting point was measured by using Thiele's apparatus in capillary and uncorrected. The FTIR-spectra were recorded on Magna 760 FT-IR Spectrometer (NICOLET, USA) in form of mixing with KBr and using reflex-measure method. ^{1}H-NMR (500 MHz), ^{13}C-NMR (125 MHz) spectra were recorded on an AVANCE AMX 500 FT-NMR Spectrometer (BRUKER, German) at 500.13 MHz, using DMSO-d6 as solvent and TMS as an internal reference, δ in ppm. Bioassays were carried out in Hospital 19-8, Hanoi, Vietnam.

*B. Synthesis of 2-chloro-N-[2-(6- substituted -2-oxo-2H-chromen-3-yl)-1,3-thiazol-5-yl]acetamide (**2**)*

3-(5-aminothiazol-2-yl)-6- substituted-2*H*-chromen-2-one **(1)** (0.01 mole) was dissolved in 50 ml of Glacial acetic acid and 5 ml of saturated solution of Sodium acetate. In case the substance did not dissolve completely, the mixture was slightly warmed. The solution was cooled in ice bath with stirring. To this stirred solution, chloroacetyl chloride (0.12 mole) solution added drop wise [5]. To prevent the occurrence of vigorous reaction the temp was maintained at 0^{o}C then reaction was heated for 30 mins after this cool the mixture and pour over crushed ice white product was separated by filtration. The product was washed with 50% aqueous acetic acid and finally with water. It was recrystallized from ethanol [6,7]. M.P (Fig. 1).

*C. Synthesis of N-(2-(6-substituted-2-oxo-2H-chromen-3-yl)thiazol-5-yl)-2-(arylamino)acetamide (**4**)*

A mixture of 0.01 mole of each 2-chloro-*N*-[2-(6-substituted -2-oxo-2*H*-chromen-3-yl)-1,3-thiazol-5-yl]acetamide (**2**) and to this different secondary amines (**3**) [8,9]. were taken in a porcelain crucible with lid and irradiated by using the MW irradiation power of 120W, irradiation times of 3-5 min. After completion of the reaction, the mixture was treated with water (10mL), and the precipitate was washed with water (50 mL)

several times; washed and crystallized from 96% ethanol (30 mL) to give pure Acetamides **4a-e**.

- **Compound 2a (R^1=H)**

^{1}HNMR (DMSO-d_6, δ, ppm): 11.5 (s -1H, NH); 8.06 (d, 1H, *J* = 7.2 Hz, H-4); 7.95 (s, 1H, H-N thiazole); 7.85 (d, 1H, *J* = 7.6 Hz, H-5); 7.66 (m, 1H, H-7); 7.55 (d, 1H, *J* = 7.2 Hz, H-8); 7.35 (m, 1H, H-6); 4.5 (s, 2 H, CH_2; (^{13}C NMR (DMSO-d_6, δ, ppm): 166.3 (C=O amide); 165.1 (C=N); 162.1 (C-2); 152,5 (C-b); 150.2 (C-NH); 145.0 (C-4); 141.3 (C-N); 130.5 (C-3); 128.5 (C-7) 128.0 (C-5); 126.1 (C-6); 121.0 (C-a); 115.5 (C-8); 43.5 (C-CH_2Cl).

- **Compound 2b (R1= Cl)**

^{1}HNMR (DMSO-d_6, δ, ppm): 11.5 (s-1H, NH); 8.07 (s, 1H, H-5); 8.03 (d, 1H, *J* = 7.6 Hz, H-4); 7.95 (s, 1H, H-N thiazole); 7.65 (m, 1H, H-7); 7.55 (d, 1H, *J* = 7.2 Hz, H-8); 4.25 (s, 2 H, CH_2; ^{13}C NMR (DMSO-d_6, δ, ppm): 166.4 (C=O amide); 164.3 (C=N); 162.0 (C-2); 151,3 (C-b); 150.1 (C-NH); 146.1 (C-4); 141.3 (C-N); 132.1 (C-6); 129.5 (C-3); 129.3 (C-7) 126.5 (C-5); 123.0 (C-a); 119.5 (C-8); 42.7 (C-CH_2Cl).

- **Compound 2c (R^1= Br)**

^{1}HNMR (DMSO-d_6, δ, ppm): 11.5 (s-1H, NH); 8.07 (s, 1H, H-5); 8.05 (d, 1H, *J* = 7.5 Hz, H-4); 7.97 (s, 1H, H-N thiazole); 7.65 (m, 1H, H-7); 7.30 (d, 1H, *J* = 7.4 Hz, H-8); 4.25 (s, 2 H, CH_2; ^{13}C NMR (DMSO-d_6, δ, ppm): 165.5 (C=O amide); 164.1 (C=N); 161.1 (C-2); 152,0 (C-b); 150.6 (C-NH); 146.1 (C-4); 142.2 (C-N); 130.5 (C-5); 129.5 (C-3); 129.3 (C-7) 123.0 (C-a); 122.1 (C-6); 119.5 (C-8); 42.7 (C-CH_2Cl).

- **Compound 4a (R^1=H, R^2 = C_7H_8BrN)**

^{1}HNMR (DMSO-d_6, δ, ppm): 11.9 (s-1H, H-a); 8.07 (s, 1H, H-4''); 8.03 (d, 1H, *J* = 7.6 Hz, H-4); 7.87(d, 1H, *J* = 7.6 Hz, H-5''); 7.65 (m, 1H, H-7''); 7.55 (d, 1H, *J* = 7.2 Hz, H-8'');7.39 (m,1H, H-6'') 7.03 (d, 1H, *J* = 7.3 Hz, H-4'''); 6.95 (d, 1H, *J* = 7.3 Hz, H-3'''); 3.25 (s, 2 H, CH_2); 2.55 (s, 3H, H-CH_3); ^{13}C NMR (DMSO-d_6, δ, ppm): 169.1 (C=O amide); 165.2 (C-2); 162.1 (C-2''); 154.2 (C-O); 151.3 (C-5); 146 (C-4''); 142.6 (C-2'''); 135.1 (C-6'''); 130.1 (C-5'''); 129.9 (C-3''); 129.3 (C-4'''); 128.5 (C-7''); 127.9 (C-7''); 126.5 (C-6); 143.3 (C-4) 116.4 (C-8''); 115.5 (C-3'''); 55.1 (C-CH_2); 20.5 (C-CH_3).

- **Compound 4b (R^1=H, R^2 = $C_7H_5F_3N_2O_2$)**

^{1}HNMR (DMSO-d_6, δ, ppm): 12.2 (s, 1H, H-a); 8.05 (s, 1H, H-4''); 8.01 (d, 1H, *J* = 7.2 Hz, H-4'''); 7.97 (s, 1 H, H-4); 7.88 (d, 1H, *J* = 7.6 Hz, H-5'''); 7.70 (m, 1H, H-7''); 7.45 (d, 1H, *J* = 7.2 Hz, H-8''); 7.42 (m, 1H, H-6''); 7.35 (1H- H-2'''); 6.98 (s, 1 H, H-b); 6.79 (d, 1H, *J* = 7.2 Hz, H-6'''); 3.5 (s, 2H, H-CH_2); ^{13}C NMR (DMSO-d_6, δ, ppm): 169.5 (C=O); 165.1 (C-2); 162.1 (C-2''); 155.5 (C-1'''); 153.5 (C-O); 151.1 (C-5); 157,5 (C-4''); 143.5 (C-4); 137.5 (C-4'''); 129.5 (C-3''); 128.3 (C-7''); 128.1 (C-5''); 126.3 (C-6''); 125.9 (C-5'''); 125.5 (C-3'''); 123.5 (C-CF_3); 116.5 (C-8''); 112.3 (C-2'''); 55.5 (C-CH_2).

- **Compound 4c (R^1=Cl, R^2 = C_7H_8BrN)**

^{1}HNMR (DMSO-d_6, δ, ppm): 12,1 (s, 1H, H-a); 8.06 (s, 1H, H-4''); 8.03 (s, 1 H, H-5''); 7.95 (s,1 H, H-4); 7.55 (d, 1H, *J* = 7.5 Hz, H-7''); 7.45 (d, 1H, *J* = 7.6 Hz, H-8''); 7.34 (s, 1 H, H-6'''); 7.03 (m, 1 H, H4'''); 5.55 (m, 1 H, H-3'''); 6.74 (s, 1H, H-b); 3.79 (s, 2H- CH_2); 2,56 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, δ, ppm):169.3 (C=O); 165.1 (C-2); 162.8 (C-2); 152.5 (C-O); 151.2 (C-5); 147.5 (C-4''); 143.9 (C-2'''); 142.8 (C-4); 134.5 (C-6'''); 132.5 (C-6''); 130.0 (C-3'''); 129.5 (C-7''); 129.0 (C-5'''); 127 (C-5''); 120.0 (C-8''); 115.2 (C-3'''); 114.1 (C-1'''); 54.5 (C-CH_2); 21.5 (C-CH_3).

- **Compound 4d (R^1=Cl, R^2 = $C_7H_5F_3N_2O_2$)**

^{1}HNMR (DMSO-d_6, δ, ppm): 12.05 (s, 1H, H-a); 8.07 (s, 1H, H-4''); 8.02 (s, 1 H, H-5''); 8.01 (d, *J* = 7.7 Hz 1H, H-5'''); 7.95 (s, 1H, H-4); 7.55 (d, *J* = 7.2 Hz 1H, H-7''); 7.35 (d, *J* = 7.2 Hz, H-8''); 7.32 (s, 1H, H-2'''); 6.85 (d, *J* = 7.2 Hz, H-6'''); 3.8 (s, 2H, H-CH_2); 6.98 (s, 1H, H-b); ^{13}C NMR (DMSO-d_6, δ, ppm): 169.5 (C=O); 165.2 (C-2); 162.9 (C-2''); 154.5 (C-1'''); 151.5 (C-O); 150.5 (C-5); 147.5 (C-4''); 143.5 (C-4); 137.5 (C-4'''); 135.5 (C-5''); 129.5 (C-7''); 128.5 (C-3''); 125.5 (C-5'''); 124(C-3'''); 123.5 (C-F); 120.5 (C-8'') 112.0 (C-2'''); 55.5 (C-CH_2).

- **Compound 4e (R^1=Br, R^2 = C_7H_8BrN)**

^{1}HNMR (DMSO-d_6, δ, ppm): 12,5 (s, 1H, H-a); 8.05 (s, 1H, H-4''); 8.01 (s, 1 H, H-5''); 7.95 (s,1 H, H-4); 7.54 (d, 1H, *J* = 7.5 Hz, H-7''); 7.50 (d, 1H, *J* = 7.6 Hz, H-8''); 7.34 (s, 1 H, H-6'''); 7.05 (m, 1 H, H4'''); 5.55 (m, 1 H, H-3'''); 6.74 (s, 1H, H-b); 3.79 (s, 2H- CH_2); 2,36 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, δ, ppm):169.3 (C=O); 166.1 (C-2); 163.8 (C-2); 156.3 (C-O); 153.2 (C-5); 145.5 (C-4''); 142.5 (C-2'''); 142.5 (C-4); 135.5 (C-6'''); 132.5 (C-6''); 130.0 (C-3'''); 129.5 (C-7''); 129.0 (C-5'''); 127 (C-5''); 121.4 (C-8''); 115.5 (C-3'''); 112.5 (C-1'''); 54.5 (C-CH_2); 22.5 (C-CH_3).

- **Compound 4f (R^1=Br, R^2 = $C_7H_5F_3N_2O_2$)**

^{1}HNMR (DMSO-d_6, δ, ppm): 12.05 (s, 1H, H-a); 8.07 (s, 1H, H-4''); 8.05 (s, 1 H, H-5''); 8.02 (d, *J* = 7.7 Hz 1H, H-5'''); 7.97 (s, 1H, H-4); 7.55 (d, *J* = 7.2 Hz 1H, H-7''); 7.35 (d, *J* = 7.2 Hz, H-8''); 7.32 (s, 1H, H-2'''); 6.85 (d, *J* = 7.2 Hz, H-6'''); 3.75 (s, 2H, H-CH_2); 6.88 (s, 1H, H-b); ^{13}C NMR (DMSO-d_6, δ, ppm): 169.5 (C=O); 165.2 (C-2); 161.8 (C-2''); 154.5 (C-1'''); 151.5 (C-O); 150.5 (C-5); 147.5 (C-4''); 143.5 (C-4); 137.5 (C-4'''); 135.5 (C-5''); 129.1 (C-7''); 128.5 (C-3''); 125.5 (C-5'''); 124 (C-3'''); 121.5 (C-F); 120.5 (C-8'') 112.5 (C-2'''); 55.3 (C-CH_2).

III. RESULTS AND DISCUSSION

The derivatives of *N*-(2-(6-substituted-2-oxo-*2H*-chromen-3-yl)thiazol-5-yl)-2-(arylamino)acetamide **(4)** could be easily synthesized by corresponding 2-chloro-*N*-[2-(6- substituted -2-oxo-2*H*-chromen-3-yl)-1,3-thiazol-5-yl]acetamide (**2**) and to this different secondary amines **(3).** this reaction using microwave-assisted methods. We have found that the solvent-free conditions under microwave irradiation offers several

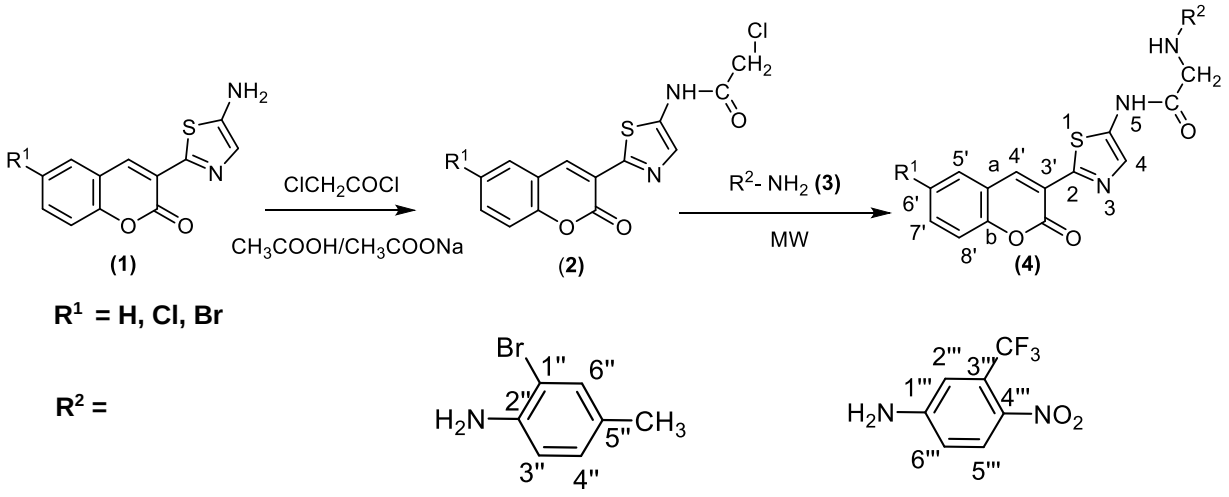

Fig. 1. *Synthesis of acetamide derivatives.*

advantages because solvents are often expensive, toxic, difficult to remove in case of aprotic dipolar solvents with high boiling point, and are environmentally polluting agents. when the reaction takes place in a microwave oven. The reactions were usually completed within 3 – 5 minutes and gave improved yield (55 – 74%) over conventional methods in a shorter time. Moreover, the work-up procedure is simply reduced to the recrystallization of product from an appropriate solvent. In the IR spectra showed characteristic bands at 1674–1641 ($\gamma_{C=O}$), 3322–3210 (γ_{N-H}), 1564, 1557, 1511, 1495 ($\gamma_{C=N}$), 1050–1051 (γ_{C-O}). The synthetic processes could be represented in Table. I.

TABLE I. PHYSICAL PARAMETERS OF COMPOUNDS **4A-F**

Entry	Mp (°C)	Yield (%)	IR spectrum (cm^{-1})			
			$\nu_{C=O}$	$\nu_{C=N}$	ν_{C-O}	ν_{N-H}
4a	178-179	74	1720	1556	1121	3102
4b	196-197	70	1707	1523	1023	3320
4c	221-222	65	1724	1561	1205	3215
4d	189-190	55	1697	1533	1256	3121
4e	192-193	63	1751	1572	1275	3106
4f	210-211	56	1751	1656	1203	1325

The ^{1}H-NMR spectra showed resonance signals which are specific for protons in amide - NH groups at δ = 11.56–12.05 ppm. Proton H-4'' in thiazole cycle has its chemical shift at δ = 7.19–8.01 ppm in singlet, The resonance signal of H-4'' in chromene cycle appeared as a singlet at δ = 8.02–8.06 ppm. Signals of aromatic protons appeared at δ = 6.89 – 7.96 ppm. while ethyl signals at δ = 2.35 – 3.80 ppm. The ^{13}C-NMR spectra showed signals of the carbonyl C=O, C=N shifted downfield at δ 165.0- 169.5 ppm. In addition, there were resonance peaks in upfield region at δ = 42.7 – 55.4 ppm that indicated the presence of ethyl groups and δ = 146.93 – 158.34 ppm belonged to C=C. Compounds **4a**-**f** were screened for their antibacterial and antifungal activities in vitro against *E. aerogenes, Staphylococcus, Candida albicans* by agar diffusion method. All acetamides have significant biological activities against *Staphylococcus* and *C. albicans*. Compounds 4a–f showed highest antibacterial activity against C. albicans. Almost all compounds 4 have remarkable biological activity, except compound 4a which exhibited no activity against *E. aerogenes* in two concentrations. Table. II:

TABLE II. RESPONSE OF VARIOUS MICRO-ORGANISMS TO SUBSTITUTED ACETAMIDES **4A-F**

Entry	Diameter of zone inhibition (mm)					
	E. aerogenes		*S. aureus*		*C. albicans*	
	100 µg/ml	150 µg/ml	100 µg/ml	150 µg/ml	100 µg/ml	150 µg/ml
4a	0	0	15	18	25	25
4b	18	22	16	22	25	30
4c	23	24	21	28	25	29
4d	12	16	18	24	35	32
4e	13	15	22	26	22	32
4f	15	17	15	18	28	25

ACKNOWLEDGMENT *(Heading 5)*

Financial support for this work was provided by Scientific Research Fund- Hanoi University of Industry.

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