Asian Journal of Chemistry; Vol. 31, No. 10 (2019), 2245-2248

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2019.22118

Ultrasound Aided Expedient Synthesis, Characterization and Antimicrobial Studies of Fluorenyl-Hydrazono-Thiazole Derivatives

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Received: 5 April 2019; *Accepted*: 19 May 2019; *Published online*: 30 August 2019; AJC-19530

Ultrasound assisted facile synthesis of fluorenyl-hydrazonothiazoles (**4a-d**) in quantitative yields by the condensation of 2-(9*H*-fluoren-9-ylidene)hydrazinecarbothioamide (**2**) with substituted phenacyl bromides in presence of dimethyl formamide has been reported. The reaction of carbothioamide **2** with α-haloacids resulted in to fluorenyl-hydrazonothiazolidin-4-ones (**3**). The structural characterization of the cyclized products have been established by elemental analysis and spectral data (IR, NMR and mass). The antimicrobial studies of the synthesized compounds are also reported.

Keywords: Thiazole, Halo acid, Fluorenone, Phenacyl bromide, Antimicrobial activity.

INTRODUCTION

In last few decades, heterocyclic compounds have been found immensely useful in biological and industrial arena. They have secured a highly remarkable position among pharmaceutically important natural and synthetic materials. Thiazoles are well known heterocyclic compounds which own important features of a variety of medicinal agents. In addition to vitamin B_1 (thiamine), the thiazole ring is found in many potent biologically active agents such as penicillins (antibacterial drugs), sulfathiazole (antimicrobial drug), ritonavir (antiretroviral drug) and meloxicam (anti-inflammatory drug). Compounds containing thiazole moiety have been reported to manifest wide spectrum of biological activities such as for treatment of allergies [1], hypertension [2], inflammation [3], schizophrenia [4], HIV infection [5,6], tumour [7-9] and convulsions [10-12]. The scrutiny for new biologically active analogues continues to be a zone of intensive research in medicinal chemistry [13,14]. In the present investigations, some new fluorenyl-hydrazono-thiazole derivatives have been synthesized under ultrasonic conditions. The synthesis method is very fast and efficient as the products are obtained in quantitative yields. The structures of all the synthesized compounds have been validated with elemental analysis and spectral data. All these compounds have also been screened for their antimicrobial activities.

EXPERIMENTAL

Fluorenone and other chemicals were procured from Merck and were used without further purification. Melting points were determined in a melting point apparatus in open capillaries and are reported without any correction. Proton and carbon NMR spectra were recorded in DMSO-d_6 on BRUKER AVANCE II 400 MHz spectrometer. Tetramethylsilane (TMS) was used as an internal standard and the chemical shifts are reported in ppm. IR spectra were obtained on Perkin Elmer (RZX) FTIR spectrometer and the frequencies are reported in cm^{-1}. Euro EA 3000 Elemental Analyzer was employed for element analysis. Molecular weight analysis was performed on Shimadzu GC-MS QP 2010 Ultra spectrometer. Thin layer chromatography (TLC) was accomplished on silica gel G coated plates and using iodine vapours as visualizing agent. Ultrasonication experiments were performed on Cole Parmar CPX500, 20 KHz and 500 Watt ultrasonicator.

General procedure for synthesis of compound 2: A mixture of 9-fluorenone (**1**) (1.0 mmol) and thiosemicarbazide (1.0 mmol) in absolute ethanol (20 mL) containing 2-3 drops of conc. HCl was stirred for 3-4 h at ambient temperature. The progress of reaction was monitored by TLC. After the completion of reaction, the reaction mixture was poured in to ice cold water and filtered the crude product. The crude solid was recrystallized from ethanol.

2-(9*H*-Fluoren-9-ylidene)hydrazinecarbothioamide (2): Yellow crystalline solid, yield 78 %; m.p.: 198-99 ºC (Lit. m.p. 202-203 ºC [Ref. 15,16]). IR (KBr, ν_{max}, cm^{-1}): 1618 (C=N), 1221 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.25 (t, 2H, C_6H_5, J = 7.4 Hz), 7.35-7.49 (m, 4H, C_6H_5), 7.56 (t, 2H, C_6H_5, J = 7.4 Hz), 8.51 (br, 1H, NH), 10.5 (br, 1H, NH); mass: *m/z* 253 (M^+, 48 %).

General procedure for the synthesis of compound 3: A mixture of carbothioamide **2** (0.005 mol), chloroacetic acid/ 2-chloropropionic acid (0.005 mol), anhydrous sodium acetate (0.8 g, 0.01 mol), glacial acetic acid (3.0 mL) and acetic anhydride (1.0 mL) was heated under reflux for 4 h. The reaction mixture was cooled to room temperature and then poured into ice cold water. The resultant solid was filtered, washed with water and recrystallized from ethanol.

(*Z*)-2-((9*H*-Fluoren-9-ylidene)hydrazono)thiazolidin-4-one (3a): Pale yellow crystalline solid, yield 88 %, m.p.: 211-215 ºC. IR (KBr, ν_{max}, cm^{-1}): 1705 (C=O), 1620 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.84 (s, 2H, SCH_2), 7.35-7.38 (m, 2H, ArH), 7.47-7.53 (m, 2H, ArH), 7.78-7.85 (m, 3H, ArH), 8.57 (d, 1H, ArH, J = 7.6 Hz), 13.13 (br, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 178.2 (C=O), 162.5 (C=N), 158.0 (C=N), 142.4 (thiazole-CS), 141.6, 135.6, 131.8, 130.9, 129.9, 128.3, 122.2, 120.5 (Ar-C). Mass: [M^+, 293] (42 %). Anal. calcd (found) % for $C_{16}H_{11}N_3OS$: C, 65.51 (65.82); H, 3.78 (4.01); N, 14.32 (14.56); S, 10.93 (11.28).

(*Z*)-2-((9*H*-Fluoren-9-ylidene)hydrazono)-5-methylthiazolidin-4-one (3b): Dark yellow solid, yield 78 %, m.p.: 202-204 ºC. IR (KBr, ν_{max}, cm^{-1}): 1698 (C=O), 1628 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.56 (q, 1H, CH_3), 3.88 (d, 1H, SCH), 7.38-7.41 (m, 2H, ArH), 7.45-7.5 (m, 2H, ArH), 7.8-7.82 (m, 4H, ArH), 12.15 (br, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 175.8 (C=O), 165.6 (C=N), 159.2 (C=N), 143.6 (thiazole-CS), 142.3, 139.7, 133.5, 132.6, 128.3, 126.9, 124.7, 122.6 (Ar-C), 25.8 (CH_3). Mass: [M^+, 307] (36 %). Anal. calcd. (found) % for $C_{17}H_{13}N_3OS$: C, 66.43 (66.66); H, 4.26 (4.53); N, 13.67 (13.80); S, 10.43 (10.28).

General procedure for the synthesis of compound 4: A mixture of carbothioamide **2** (0.001 mol) and *p*-substituted phenacyl bromide (0.001 mol) in 5 mL of DMF was kept under ultrasonication and the progress of the reaction was monitored with TLC. The reaction was completed in 5-8 min. After the completion of reaction, the mixture was poured in to ice cold water. The solid thus obtained was filtered and recrystallized from ethanol-DMF (3:1) mixture.

2-(2-(9*H*-Fluoren-9-ylidene)hydrazinyl)-4-phenylthiazole (4a): Pale yellow fluffy solid, yield 82 %, m.p.: 155-157 ºC. IR (KBr, ν_{max}, cm^{-1}): 1632 (C=N), ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.82 (s, 1H, =CH), 7.0 (t, 2H, C_6H_5, J = 7.4) 7.34-7.44 (m, 3H, Ar), 7.51(t, 2H, C_6H_5, J = 6.8), 7.63-7.69 (m, 4H, Ar), 7.77-7.85 (m, 2H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.6 (C=N), 158.5 (C=N), 146.6, 145.2, 144.3, 144.1, 142.6, 136.9, 134.2, 128.5, 126.3, 122.5, 120.4; Mass: *m/z* 353 (16 %, M^+). Anal. calcd. (found) % for $C_{22}H_{15}N_3O_2S$: C, 74.76 (74.92); H, 4.28 (4.43); N, 11.89 (12.15); S, 9.07 (9.28).

2-(2-(9*H*-Fluoren-9-ylidene)hydrazinyl)-4-(4-chlorophenyl)thiazole (4b): Greenish fluffy solid, yield 80 %, m.p.: 182-184 ºC. IR (KBr, ν_{max}, cm^{-1}): 1632 (C=N), ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.93 (s, 1H, =CH), 7.41 (d, 2H, Ar, J = 7.6 Hz), 7.52 (d, 42H, Ar, J = 7.2 Hz), 7.54-7.59 (m, 4H, ArH), 7.8-7.85 (m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 160.2, 157.4 (C=N), 147.1, 146.3, 140.2, 140.6, 138.7, 132.4, 127.6, 125.3, 123, 122.8, 121.5; Mass: *m/z* 387 (18 %, M^+), 389 (5 %, M+2). Anal. calcd. (found) % for $C_{22}H_{14}N_3SCl$: C, 68.12 (68.27); H, 3.64 (3.53); N, 10.83 (10.62); S, 8.27 (8.11).

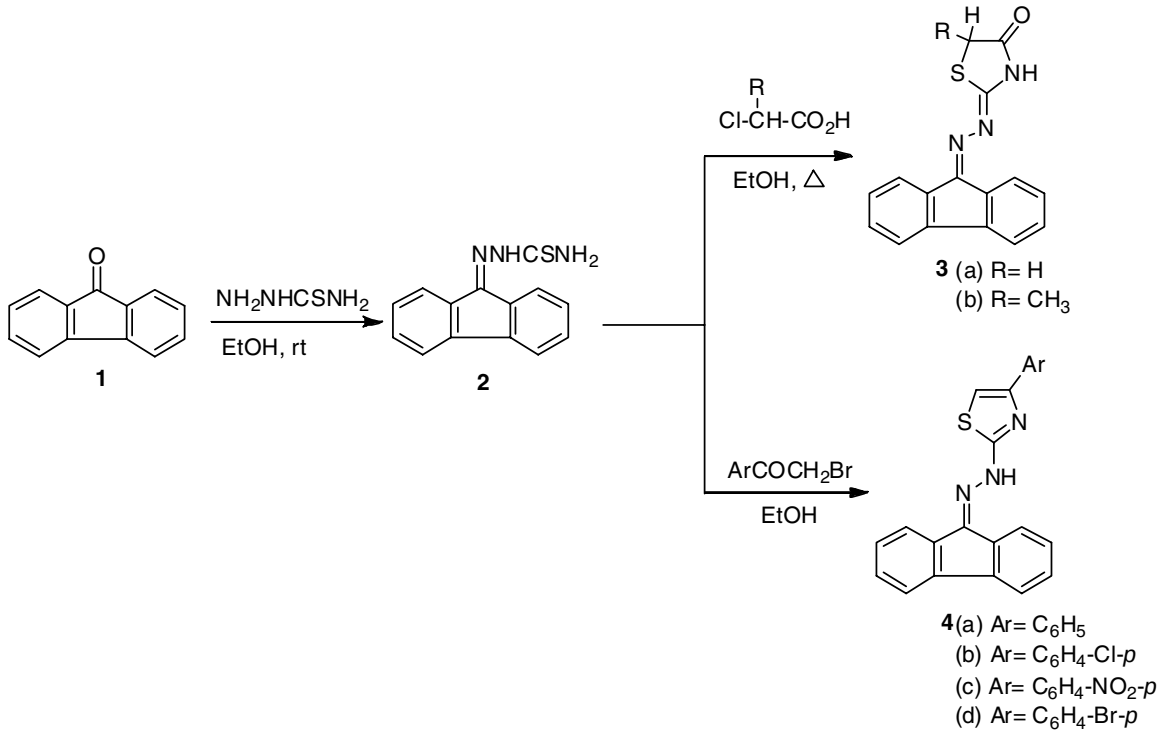
2-(2-(9*H*-Fluoren-9-ylidene)hydrazinyl)-4-(4-nitrophenyl)thiazole (4c): Yellowish fluffy solid, yield 83 %, m.p.: 232-234 ºC. IR (KBr, ν_{max}, cm^{-1}): 1638 (C=N), ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.12 (s, 1H, =CH), 7.46 (d, 2H, Ar, J = 8.2 Hz), 7.5 (d, 2H, Ar, J = 7.8 Hz), 7.6-7.63 (m, 5H, ArH), 7.9-7.95 (m, 3H, ArH); ^{13}C NMR (100 MHz, DMSOd_6) δ: 167.6, 159.3 (C=N), 148.3, 146.5, 143.9, 142.5, 139.8, 136.1, 129.3, 127.8, 125.2, 124, 122.2; Mass: *m/z* 398 (25 %, M^+). Anal. calcd. (found) for $C_{22}H_{14}N_4SO$: C, 66.32 (66.57); H, 3.54 (3.73); N, 14.06 (13.87); S, 8.05 (8.21).

2-(2-(9*H*-Fluoren-9-ylidene)hydrazinyl)-4-(4-bromophenyl)thiazole (4d): Yellowish green solid, yield 81 %, m.p.: 220-222 ºC. IR (KBr, ν_{max}, cm^{-1}): 1627 (C=N), ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.89 (s, 1H, =CH), 7.5 (m, 3H, ArH), 7.65 (d, 2H, Ar, J = 7.4 Hz), 7.64-7.66 (m, 4H, ArH), 7.82-7.85 (m, 3H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.3, 157.4 (C=N), 146.2, 145.3, 144.8, 141.6, 140, 135.6, 130.4, 128.8, 127.3, 125.1, 121.7; Mass: *m/z* 432 (29 %, M^+), 434 (25 %, M+2). Anal. calcd. (found) for $C_{22}H_{14}N_3SBr$: C, 61.12 (61.37); H, 3.26 (3.54); N, 9.72 (9.88); S, 7.42 (7.22).

RESULTS AND DISCUSSION

9-Fluorenone (**1**) on stirring with thiosemicarbazide in ethanol and conc. HCl at ambient temperature for 3 h furnished 2-(9*H*-fluoren-9-ylidene)hydrazinecarbothioamide (**2**). The melting point of carbothioamide derivative **2** is well in agreement with the reported literature [15,16]. IR spectrum of compound **2** showed absorption bands at 1618 and 1221 cm^{-1} associated with C=N and C=S functionalities, respectively. ^{1}H NMR spectrum of compound **2** exhibited broad singlets at δ 8.51 ppm and δ 10.5 ppm due to two NH groups. Finally, the mass spectrum, showed a peak at *m/z* 253 (48 %) corresponding to the molecular ion. Condensation of carbothioamide **2** with chloroacetic acid and 2-bromopropionic acid in presence of anhydrous sodium acetate and acetic acid furnished 2-((9*H*-fluoren-9-ylidene)hydrazono)thiazolidin-4-one (**3a**) and 2-((9*H*-fluoren-9-ylidene)hydrazono)-5-methylthiazolidin-4-one (**3b**) (**Scheme-I**), respectively. The IR spectrum of compound **3a** displayed peaks at 1705 and 1620 cm^{-1} due to C=O and C=N groups, respectively. ^{1}H NMR spectrum of compound **3a** exhibited a singlet of two protons at δ 3.84 ppm, which was assigned to SCH_2 group of thiazolidin-4-one ring. Aromatic protons appeared between δ 7.35-8.57 ppm. ^{13}C NMR showed C=O and C=N peaks at δ 178.2 and 162.5 ppm, respectively. The mass spectrum of compound **3a** exhibited molecular ion peak at *m/z* 293 (42 %). The structure of compound **3b** was also similarly established spectrally.

A pilot reaction of carbothioamide **2** with phenacyl bromide was carried out under reflux conditions, grinding in neat conditions and under ultrasonic conditions in different solvents. The



Scheme-I: Synthesis of fluorenyl-hydrazonothiazole derivatives

progress of the reaction was monitored by TLC and the yield of the product was estimated and reported in Table-1. It is clear that under ultrasonic conditions, the reaction is quick and the yield is quantitative. Compounds **4a-d** was obtained accordingly under ultrasonic conditions. The structure of the synthesized thiazole derivatives have been established by analytical and spectral data. In ^{1}H NMR spectrum of compound **4a**, the signal for methine CH of thiazole ring appears at δ 6.82 ppm authenticating the formation of thiazole ring. All other protons appear in aromatic region between δ 7.0-7.85 ppm. ^{13}C NMR spectrum of compound **4a** displayed two peaks at δ 162.6 ppm and δ 158.5 ppm attributed to C=N groups. Methine carbon appeared at 120.4 ppm in carbon NMR of compound **4a**. The mass spectrum of compound **4a** exhibited molecular ion peak at *m/z* 353 (16 %). The structure of other fluorenyl-hydrazono-thiazole derivatives (**4b-d**) was similarly assigned on the basis of spectral data.

Antimicrobial activity of compounds 3 and 4: Compounds **3** and **4** were assayed for their *in vitro* antibacterial and antifungal activity. *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* stains were employed for antibacterial screening. For *Aspergillus niger*, *Aspergillus fumigates* and *Candida albicans* strains were used for antifungal screening. Both microbial studies were assessed by minimum inhibitory concentration (MIC) by serial dilution method [17]. Ciprofloxacin and miconazole were used as reference drugs. The results of the screening experiments are presented in Table-2. All the compounds show bacterial inhibition in broad range. MIC values of derivatives **4b** and **4d** demonstrated the highest antibacterial activity.

TABLE-1
OPTIMIZATION OF REACTION PARAMETERS

Solvent	Condition	Time (min)	Yield (%)[a]
Ethanol	Room temp stirring	120	30
Ethanol	Reflux	30	62
DMF	Reflux	15	65
–	Grinding	30	56
Ethanol	Ultrasonic	15	68
DMF	Ultrasonic	5	82

[a]Yields are reported for **4a** and for others please refer experimental section.

TABLE-2
BIOLOGICAL ASSAY OF COMPOUNDS **3** AND **4**

Compd.	Antimicrobial activity (MIC, µg/mL)					
	Antibacterial activity			Antifungal activity		
	S. aureus	*E. coli*	*P. aeruginosa*	*A. niger*	*C. albicans*	*A. fumigates*
3a	50	50	25	25	25	25
3b	25	6.25	25	12.5	12.5	12.5
4a	25	25	25	12.5	25	50
4b	12.5	25	12.5	12.5	50	50
4c	25	25	12.5	12.5	50	50
4d	12.5	12.5	25	12.5	50	50
Ciprofloxacin	6.25	6.25	6.25	–	–	–
Miconazole	–	–	–	6.25	6.25	6.25

Compound **3b** (MIC = 12.5 µg/mL) demonstrated very good antifungal activity against *A. niger*, *C. albicans* and *A. fumigates*.

Conclusion

A simple and highly efficient protocol for the synthesis of thiazole derivatives from carbothioamide derivative and phenacyl bromides under ultrasonic conditions has been developed. High yields and easy work up are benefits of the present synthetic protocol.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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