Microwave Assisted Synthesis and Characterization of 2-Cyano-N-(4-Oxo-2-Substituted Thiazolidin-3-yl) Acetamide derivatives

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ABSTRACT

Green synthesis of (E)-N'-(substituted benzylidene)-2-cyanoacetohydrazides was achieved from 2-cyanoacetohydrazide and various aromatic aldehydes in good yields. 2-Cyano-N-(4-oxo-2-substituted thiazolidin-3-yl)acetamides were successfully obtained (E)-N'-(substituted benzylidene)-2-cyanoacetohydrazides and 2-mercaptoacetic acid employing conventional and microwave irradiation. The structures of new synthesized compounds were elucidated by FTIR, ^{1}H NMR spectral analysis.

KEY WORDS: 2-Cyanoacetohydrazides, Green synthesis, Microwave Irradiation (MWI), Thiazolidin-3-yl)acetamides.

1. INTRODUCTION

4-Thiazolidinones are the important group of heterocyclic compounds containing sulphur and nitrogen in a five member ring. 4-Thiazolidinone is considered as wonder nucleus because of different types of biological activities. 4-Thiazolidinone is very versatile molecule utilized in clinically active drugs and various synthetic pharmaceutical drugs that showed a wide scope of bioactivities such as, anti-tubercular (Waghmode, 2014), anti-bacterial (Solankee and Patel, 2013), anti-HIV (Patel, 2006) anti-inflammatory (Turgutet, 2010), anti-mycobacterial (Bouzroura, 2004), anti-convulsant (Mistry, 2004), anti-histaminic (Shah, 1993), anti-cancer (Ramalakshmi, 2009), anti-protozoan (Patel, 2007), analgesic (Vigoritaet, 2001) anticancer (Havrylyuk, 2010), antitubercular (Pathak, 2012), antibacterial (Mohamed, 2010), antifungal (Omar, 2010), antimicrobial (Joshi, 2013), cytotoxic (Mosula, 2009), antitumor (Asmaa, 2016), biopolymer (Chandran Ambily, 2012), anti-inflammatory, antioxidant and COX inhibitory activity (Singh, 1981). Synthesis of thiazolidinones could be achieved by conventional one or two pot, combinatorial syntheses methods and microwave syntheses (Cunico, 2007). The synthesis of 2-imino-4-thiazolidinones has been reported by Akerblom (1967) using thiourea and sodium salt of labelled monochloroacetic acid. The syntheses of 4-thiazolidinones using alkyl isothiocyanate, hydrazide or acetamide and the treatment with ethyl bromoacetate and sodium acetate were reported by Cesur (1994). 2, 2-Disubstituted-4-thiazolidinones were synthesized by Vicini (2006), utilizing 2-mercaptoacetic acid, Schiff's bases of ketones and amines. Desai (2006), has synthesized thiazolidinone from Schiff's base and thiolactic acid by microwave syntheses. The one-pot three-component synthesis of 4-thiazolidinones under microwave dielectric heating using DCC/DMAP catalyst was reported by Dubreuil (2003). Amit Verma (2008), has demonstrated various chemical and biological activities of the 4-thiazolidinone. Look (1996), has described various literature combinatorial protocols towards synthesis of 4-thiazolidinone core. Ebrahimi (2016), synthesized one pot 1, 3-thiazolidin-4-one derivatives using ammonium persulfate (APS) catalyst. Pai (2016) and Desai (2013), also reported the synthetic approaches of 4-thiazolidinones. The aim of the present work was to synthesize new 2-cyano-N-(4-oxo-2-substituted thiazolidin-3-yl)acetamide derivatives under the conventional and microwave conditions.

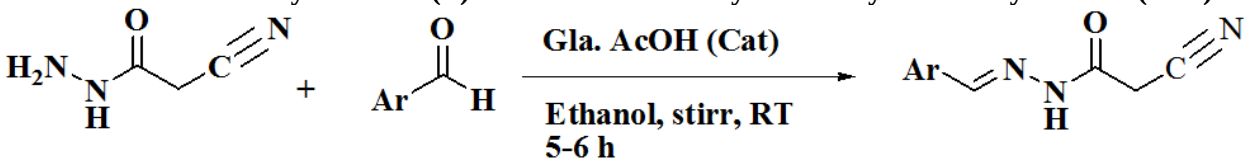
2. MATERIALS AND METHODS

All the chemicals and solvents were purified by standard literature procedures. The moisture was removed from the glass apparatus using $CaCl_2$ drying tubes. The melting points determined using Gallenkamp melting point apparatus in open capillary tubes and are uncorrected. FT-IR spectra recorded on Bruker FTIR-TENSOR II spectrophotometer using Platinum attenuated total reflection (Platinum ATR) discs. ^{1}H NMR spectra of 2-Cyano-N-(4-oxo-2-substituted thiazolidin-3-yl)acetamide were recorded on Bruker Ascend 500 NMR spectrophotometer at 500 MHz frequency in $CDCl_3$ or dimethyl sulfoxide (DMSO-d_6) using tetramethylsilane (TMS) as internal standard. Chemical shifts recorded in δ ppm and signals are given as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), or multiplet (m). Reactions were monitored by Thin Layer Chromatography (TLC) using silica gel 60 F_{254} (Merck) 0.2 mm plates under UV light (254 and 366 nm) for detection. The commercially available LR, AR grade chemicals were utilized without purification or prepared by standard literature protocols. All the compounds have been synthesized by conventional and MWI methods.

3. RESULTS AND DISCUSSION

Condensation of various aromatic aldehydes (4a-k) with 2-cyanoacetohydrazide 3 at room temperature afforded hydrazine derivatives (5a-k) (Akerblom, 1967; Cesur, 1994; Salman, 2013; 2016). FTIR spectrum of hydrazone5j exhibited showed stretching frequencies at 3128 cm^{-1} for NH and 2256 cm^{-1} for CN group respectively. ^{1}HNMR for 7a showed singlet at δ 3.98 ppm corresponding to CH_2CN group. The double doublet signal at δ 3.56 ppm was observed due to two diastereotopic methylene protons ($CO-CH_2-S$) of the 4-thiazolidinone as they coupled with each other and splited the signals of each other to show doublet of doublet.

Scheme.1. Synthesis of (E)-N'- substituted benzylidene-2-cyanoacetohydrazides (5a-k)

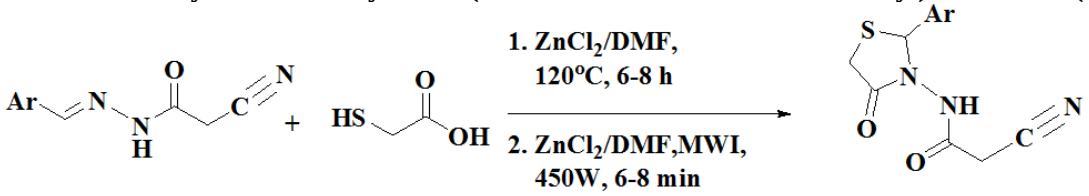


3 **4a-k** **5a-k**

Scheme 1: Singlet signal at δ 6.59 ppm for CH (S-CH-N), multiplet at δ 7.05 - 7.25 ppm for aromatic protons (Ar-H) and singlet at δ 10.89 ppm was observed for NH. Different substituents of aromatic aldehydes were utilized for the synthesis of 2-cyano-N-(4-oxo-2-substituted thiazolidin-3-yl)acetamides (**7a-k**) under conventional heating and microwave irradiation green protocol.

It was observed that the reaction rates were increased under MWI (Microwave Irradiation) green protocol than conventional heating method. In conventional heating method the yield is low as compared to microwave irradiation. Microwave irradiation (MWI) caused rapid reaction due to polarized molecule under irradiation.

Scheme.2. Synthesis of 2-cyano-N-(4-oxo-2-substituted thiazolidin-3-yl)acetamides (7a-k)



5a-k **6** **7a-k**

5, 7	Aryl	% Yield		5,7	Aryl	% Yield	
		Conv.	MW			Conv.	MW
a	Phenyl	69	72	**g**	2-hydroxyphenyl	66	72
b	4-methoxyphenyl	73	79	**h**	2-styryl	74	81
C	4-chlorophenyl	75	80	**i**	2-thiophenyl	76	82
d	4-hydroxy-3-methoxyphenyl	81	89	**j**	5-bromo-2-thiophenyl	61	77
e	3-nitrophenyl	75	79	**k**	3-methyl-1-phenyl-1H-pyrazol-5-yl	60	72
f	4-nitrophenyl	64	72				

Experimental: Synthesis of 2-Cyano-N-(4-oxo-2-phenylthiazolidin-3-yl)acetamide (7a):

Conventional method: In a round bottom flask, 2-mercaptoacetic acid (0.015 mol) and compound 5a (0.01 mol) were dissolved in 5 mL DMF. Anhydrous $ZnCl_2$ was added as a catalyst. The reaction mixture was stirred at 115°C for 10 hours. The progress of the reaction was monitored by Thin Layer Chromatography (TLC check, Chloroform: methanol 9:1). Then reaction mass was cooled, poured in ice-cold water and triturated with an excess of 10% sodium bicarbonate solution. The solid product obtained was recrystallized from ethanol-DMF (9:1) afforded compound 7a. Same procedure was followed for the synthesis of compounds 7b-k.

Microwave method: In a hard glass tube 5a (0.01 mol) and 2-mercaptoacetic acid (0.01mol), catalytic amount of $ZnCl_2$ (0.1 g) and DMF (0.5 mL) were added and mixed well to form pasty mass. This pasty was irradiated in domestic microwave oven till completion of the reaction. (TLC check, Chloroform: methanol 9:1). After the completion, reaction mixture was cooled to room temperature, poured in ice-cold water and triturated with an excess of 10% sodium bicarbonate solution. The solid product obtained was filtered and recrystallized from Ethanol: DMF (9:1) afforded compound 7a. Same procedure was employed for the synthesis of compounds 7b-k.

2-Cyano-N-(4-oxo-2-phenylthiazolidin-3-yl)acetamide (7a): Orange solid, Yield: Conv.69 % and MWI.72%, 0.360 g; m.p. 270°C;IR (KBr): 3321 (-NH str.),3054 (Ar-CH str.), 1735, 1681 (C=O, thiazolidine ring) 1613 (-CN str.) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.56 (s, 2H, SCH_2), 3.95 (s, 2H, CH_2CN), 6.59 (s, 1H, S-CH-N), 7.05-7.25 (m, 5H, ArH), 10.58 (s, 1H, NH)ppm; Anal. Calcd.for $C_{12}H_{11}N_3O_2S$ (261.3): C, 55.16; H, 4.24; N, 16.08; Found: C, 55.26; H, 4.27; N, 16.03.

2-Cyano -N-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)acetamide (7b): Yellow solid, Yield: Conv.73 % and MWI. 78%, 0.415 g; m.p. 170°C; IR (KBr)cm^{-1}: 3323 (-NH str.),3059 (Ar-CH str.), 1731, 1689 (C=O, thiazolidine ring) 1613 (-CN str.);^{1}H NMR (500 MHz, DMSO-d_6):δ 3.54 (s, 2H, SCH_2), 3.84 (s, 3H, OCH_3), 3.99 (s, 2H, CH_2CN), 6.56 (s, 1H, S-CH-N), 7.05 (d, 2H, ArH), 7.25 (d, 2H, ArH), 10.58 (s, 1H, NH)ppm; Anal. Calcd.for $C_{13}H_{13}N_3O_3S$ (291.33): C, 53.60; H, 4.50; N, 14.42; Found: C, 53.65; H, 4.52; N, 14.50.

2-Cyano -N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)acetamide (7c): Faint Yellow solid, Yield: Conv.75 % and MWI. 80%, 0.422 g; m.p. 200°C; IR (KBr)cm^{-1}: 3405-3323 (-NH str.),3054 (Ar-CH str.), 1735, 1689 (C=O, thiazolidine ring) 1613 (-CN str.);^{1}H NMR (500 MHz, DMSO-d_6): δ 3.58 (s, 2H, SCH_2), 3.99 (s, 2H, CH_2CN), 6.56 (s, 1H, S-CH-N), 7.25 (d, 2H, ArH), 7.71 (d, 2H, ArH), 10.59 (s, 1H, NH)ppm; Anal. Calcd.for $C_{12}H_{10}ClN_3O_2S$ (295.73): C, 48.73; H, 3.41; N, 14.21; Found: C, 48.70; H, 3.47; N, 14.11.

2-Cyano -N-(2-(4-hydroxy-3-methoxyphenyl)-4-oxothiazolidin-3-yl)acetamide (7d): Yellow solid, Yield: Conv.81% and MWI.84%, 0.473 g; m.p. 146°C; IR (KBr)cm^{-1}: 3405-3323 (OH, NH str.),3054 (Ar-CH str.), 1735, 1689 (C=O, thiazolidine ring) 1613 (-CN str.);^{1}H NMR (500 MHz, DMSO-d_6): δ 3.58 (s, 2H, SCH_2), 3.85 (s, 3H, OCH_3), 3.97 (s, 2H, CH_2CN), 6.58 (s, 1H, S-CH-N), 6.98 (m, 2H, ArH), 7.42 (m, 1H, ArH), 10.57 (s, 1H, NH), 11.07 (s, 1H, OH)ppm; Anal. Calcd.for $C_{13}H_{13}N_3O_4S$ (301.73): C, 50.81; H, 4.26; N, 13.67; Found: C, 50.60; H, 4.35; N, 13.72.

2-Cyano -N-(2-(3-nitrophenyl)-4-oxothiazolidin-3-yl)acetamide (7e): Yellow solid, Yield: Conv.75 % and MWI.79%, 0.452 g; m.p. 240°C; IR (KBr)cm^{-1}: 3405-3321 (NH str.), 3054 (Ar-CH str.), 2251 (CN), 1735, 1681 (C=O, thiazolidine ring) 1613 (-CN str.);^{1}H NMR (500 MHz, DMSO-d_6): δ 3.59 (s, 2H, SCH_2), 3.99 (s, 2H, CH_2CN), 6.58 (s, 1H, S-CH-N), 7.39 (m, 1H, ArH), 7.70 (m, 1H, ArH), 8.22 (m, 2H, ArH), 10.59 (s, 1H, NH)ppm; Anal. Calcd.for $C_{12}H_{10}N_4O_4S$ (306.30): C, 47.06; H, 3.29; N, 18.29; Found: C, 47.16; H, 3.39; N, 18.32.

2-Cyano-N-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)acetamide (7f): Orange solid, Yield: Conv.64 % and MWI.72%, 0.413 g; m.p. 172°C; IR (KBr)cm^{-1}: 3412-3321 (-NH str.), 3054 (Ar-CH str.), 2251 (CN), 1735, 1681 (C=O, thiazolidine ring) 1613 (-CN str.); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.58 (s, 2H, SCH_2), 3.99 (s, 2H, CH_2CN), 6.56 (s, 1H, S-CH-N), 7.65 (d, 2H, ArH), 8.32 (d, 2H, ArH), 10.59 (s, 1H, NH)ppm; Anal. Calcd.for $C_{12}H_{10}N_4O_4S$ (306.30): C, 47.06; H, 3.29; N, 18.29; Found: C, 47.11; H, 3.41; N, 18.37.

2-Cyano -N-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)acetamide (7g): Faint yellow solid, Yield: Conv.66 % and MWI. 72%, 0.173 g, m.p. 262°C; IR (KBr)cm^{-1}: 3411-3321 (OH, NH str.), 3054 (Ar-CH str.), 2251 (CN), 1739, 1685 (C=O, thiazolidine ring) 1619 (CN str.); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.58 (s, 2H, SCH_2), 3.99 (s, 2H, CH_2CN), 6.56 (s, 1H, S-CH-N), 6.98 (m, 2H, ArH), 7.12 (m, 2H, ArH), 7.42 (m, 2H, ArH), 10.57 (s, 1H, NH), 11.17 (s, 1H, OH)ppm; Anal. Calcd.for $C_{12}H_{11}N_3O_3S$ (277.30): C, 51.98; H, 4.00; N, 15.15; Found: C, 51.78; H, 4.10; N, 15.05.

2-Cyano-N-(4-oxo-2-styrylthiazolidin-3-yl)acetamide (7h): Faint yellow solid, Yield: Conv.74 % and MWI.81%, 0.400 g; m.p. 90-94°C;IR (KBr)cm^{-1}: 3410-3321 (-NH str.), 3054 (Ar-CH str.), 2251 (CN), 1735, 1681 (C=O, thiazolidine ring) 1613 (-CN str.); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.58 (s, 2H, SCH_2), 3.98 (s, 2H, CH_2CN), 6.98 (d, 1H, CH=C), 7.32 (d, 1H, C=CH), 7.45(s, 1H, S-CH-N), 7.25-7.46 (m, 5H, Ar-H), 10.57 (s, 1H, NH)ppm; Anal. Calcd.for $C_{14}H_{13}N_3O_2S$ (287.34): C, 58.52; H, 4.56; N, 14.62; Found: C, 58.32; H, 4.63; N, 14.82.

2-Cyano-N-(4-oxo-2-(thiophen-2-yl)thiazolidin-3-yl)acetamide (7i): Yellow solid, Yield: Conv.76% and MWI.82%, 0.400 g, m.p. 150°C; IR (KBr)cm^{-1}: 3410-3321 (-NH str.), 3054 (Ar-CH str.), 2251 (CN), 1735, 1681 (C=O, thiazolidine ring) 1613 (-CN str.); ^{1}H NMR (500 MHz, DMSO-d_6):δ 3.56 (s, 2H, SCH_2), 3.96 (s, 2H, CH_2CN), 6.78 (q, 1H, ArH), 7.12 (q, 1H, ArH), 7.25 (q, 1H, ArH), 7.47(s, 1H, S-CH-N), 10.59 (s, 1H, NH)ppm; Anal. Calcd.for $C_{10}H_9N_3O_2S_2$ (267.33): C, 44.93; H, 3.39; N, 15.72; Found: C, 44.83; H, 3.45; N, 15.92.

N-(2-(5-Bromothiophen-2-yl)-4-oxothiazolidin-3-yl)-2-cyanoacetamide (7j): Orange solid, Yield: Conv.61 % and MWI.77%, 0.423 g; m.p. 210°C; IR (KBr)cm^{-1}: 3410-3321 (-NH str.),3054 (Ar-CH str.), 2251 (CN), 1735, 1681 (C=O, thiazolidine ring) 1613 (-CN str.); ^{1}H NMR (500 MHz, DMSO-d_6):δ 3.56 (s, 2H, SCH_2), 3.96 (s, 2H, CH_2CN), 6.78 (d, 1H, ArH), 7.12 (d, 1H, ArH), 7.48 (s, 1H, S-CH-N), 10.56 (s, 1H, NH)ppm; Anal. Calcd.for $C_{10}H_8BrN_3O_2S_2$ (346.22): C, 34.69; H, 2.33; N, 12.14; Found: C, 34.69; H, 2.39; N, 12.14;

N-(2-(5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl)-2-cyanoacetamide (7k): Faint yellow solid, Yield: Conv.68 % and MWI.72%, 0.403 g; m.p. 172°C; IR (KBr)cm^{-1}: 3410-3321 (-NH str.), 3059 (Ar-CH str.), 2251 (CN), 1735, 1681 (C=O, thiazolidine ring) 1613 (-CN str.); ^{1}H NMR (500 MHz, DMSO-d_6):δ 3.58(s, 2H, SCH_2), 3.98 (s, 2H, CH_2CN), 7.25-7.36 (m, 5H, Ar-H), 10.57 (s, 1H, NH)ppm. Anal. Calcd.for $C_{16}H_{14}ClN_5O_2S$ (375.83): C, 51.13; H, 3.75; N, 18.63; Found: C, 51.33; H, 3.55; N, 18.55.

4. CONCLUSION

We have reported green synthesis of 2-cyano-N-(4-oxo-2-substituted thiazolidin-3-yl)acetamide derivatives from (E)-N'-(substituted benzylidene)-2-cyanoacetohydrazides. The microwave assisted chemical transformation affords excellent product yield, reduced reaction time and minimization or elimination of by-products. The results obtained confirmed superiority of microwave irradiation over the traditional heating method.

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