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Dimethyl aminomethylene ketones and α, β-unsaturated ketones with thiazolyl substituted 4-thiazolidinone framework: versatile reactive intermediates to synthesize a variety of medicinally potent heterocycles

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Abstract

The reactive intermediates i.e. dimethyl aminomethylene ketones (NJ-2016-004) and α,β-unsaturated ketones (NJ-2016-005a-d) possessing thiazolyl substituted 4-thiazolidinone framework have been synthesized from the reaction of thiazolyl substituted 4-thiazolidinones with N,N-dimethylformamide dimethylacetal (DMF DMA) and substituted benzaldehydes respectively. Schematic reaction schemes are presented as Reaction Scheme: NJ-01 and Reaction Scheme: NJ-02. Formation of the compounds was ensured on the basis of analytical IR, NMR and MS spectral data.

Keywords: *N,N*-dimethylformamide dimethylacetal, Substituted benzaldehydes, Dimethyl aminomethylene ketones, *α,β*-Unsaturated ketones, 4-Thiazolidinones.

Introduction

Thiazoles are known to possess different biological properties. In view of their cyclooxygenase inhibitory activities[1], these are used as thromboembolic agents and possess significant importance due to their presence in vitamin B_1 and co-enzyme carboxylase as structural component[2]. Literature survey depicts that thiazoles have been reported as anti-viral[3], anti-inflammatory[4], anti-microbial, anti-hypertensive and anti-convulsant agents[5]. Many heterocyclic compounds having thiazole molecular framework play an important role in the treatment of challenging diseases, therefore, thiazole moiety (Figure-1a) is embedded as an active pharmacophore in various medicines.

4-Thiazolidinones are five-membered heterocycles with a thioether and amine entities at the first and third positions respectively (Figure-1b). 4-Thiazolidinones have been widely investigated for their broad spectrum of applications as medicinally potent pharmacophores and as privileged molecular frameworks to synthesize a variety of heterocycles as active and safe drugs. 4-Thiazolidinones are also known as magic moiety which holds almost all type of biological activities. Some of biological activities are mentioning here as anti-microbial[6], anti-tubercular[7], anti-inflammatory[8], analgesic[9], anti-convulsant[10], anti-HIV[11] and hypoglycemic activity[12].

Dimethyl aminomethylene ketones or enaminones are extremely firm compounds which are using as reactive intermediates to synthesize a variety of organic compounds including five-, six- and seven-membered heterocycles. The dimethyl aminomethylene ketones can be prepared simply starting from economical and easily obtainable preliminary materials. Therefore, dimethyl aminomethylene ketones or enaminones are outstanding intermediates in organic synthesis. The dimethyl aminomethylene ketones or enaminones consist an >N- group linked with C=C-C=O moiety (Figure-1c). The chemistry of enaminones has been received extensive attention in recent years. The enaminones are synthetic intermediates with ambident nucleophilicity of enamines and electrophilicity of enones. The enaminones act as push-pull templates in which the amine group pushes and the carbonyl group pulls electron density[13-14]. These types of frameworks contain four nucleophilic sites and two electrophilic sites to provide unique platform for the preparation of newer compounds including heterocycles such as pyrazoles, isoxazoles, pyrimidines, diazepines, oxazepines and thiazepines. In addition, an assortment of enaminones were establish to reveal various biological activities like anti-tumor, anti-bacterial, P-gp modulator and anti-convulsant agents[15-16].

α,β-Unsaturated ketones or chalcones have a keto carbonyl moiety with α,β-unsaturation (Figure-1d). The chalcones may be synthesized *via* Claisen-Schmidt condensation of aromatic aldehydes and acetophenones with acid or base. The α,β-unsaturated ketones are also versatile and convenient intermediates to synthesize widespread range of heterocyclic compounds. Reactions of α,β-unsaturated ketones with bidentate nucleophiles generally result in the formation of polycyclic ring system due to inductive polarization of carbonyl group at the β-arrangement[17].

The dimethyl aminomethylene ketones and chalcones both offer unique opportunity to a chemist for the production of an extensive diversity of heterocycles. This arouses our interest in the synthesis of hetero ring fused dimethyl aminomethylene ketones and chalcones from thiazolyl substituted 4-thiazolidinones. In view of these previous conclusions and in prolongation of our interest in the functionalization of 4-thiazolidinone condensed dimethyl aminomethylene ketones and chalcones, some newer dimethyl aminomethylene ketones and chalcones derivatives containing thiazolyl substituted 4-thiazolidinone moieties have been synthesized in the present work. To our information, no effort has been made in the literature to examine the feasibility of the preparation of the dimethyl aminomethylene ketones and chalcones possessing thiazolyl substituted 4-thiazolidinones.

Materials and methods

Starting materials were procured from different companies. Solvents were used after purification. Melting points were taken in glass capillaries and are uncorrected. Reactions were monitor by thin layer chromatography plates using various solvent systems. Column chromatography was performed for purification of the compounds synthesized. IR spectra were taken on Bruker FT-IR Alpha-T model. ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL 400 MHz NMR spectrometer using $CDCl_3$ and DMSO-d_6. Chemical shifts are presented in δ ppm relative to signal for TMS. MS spectra were recorded on Xevo G2-SQT mass spectrometer. The elemental analysis (C, H, N, O and S) were done on Perkin Elmer 2400 elemental analyzer. Physical and analytical data of the compounds are given in the Table-1.

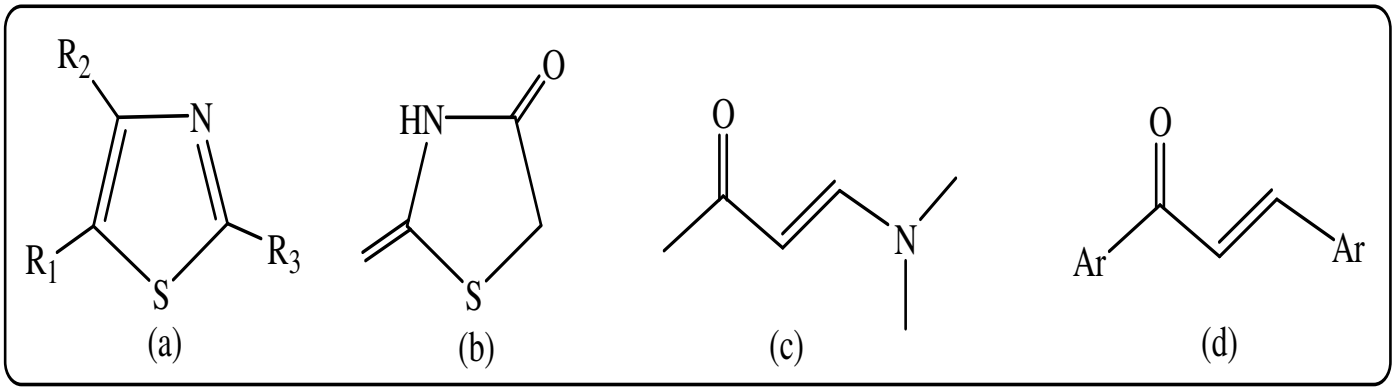


Figure-1: Thiazole, 4-Thiazolidininone, Dimethyl aminomethylene ketones and α, β-Unsaturated ketones moieties.

Table-1: Physical and analytical data of the synthesized compounds

Compound Codes	Molecular Formula	Mol. Wt.	Yield (%)	M.P (°C)	% of Elemental Analysis of C, H, N, S and O Calculated (Exp.)				
					C	**H**	**N**	**S**	**O**
NJ-2016-002	$C_5H_5ClN_2OS$	176.62	88	160-162	34.00 (34.04)	2.85 (2.80)	15.86 (15.82)	18.15 (18.12)	9.06 (9.02)
NJ-2016-003	$C_6H_5N_3OS_2$	199.25	70	190-192	36.17 (36.14)	2.53 (2.49)	21.09 (21.06)	32.19 (32.15)	8.03 (8.00)
NJ-2016-004	$C_9H_{10}N_4OS_2$	254.33	65	236-238	42.50 (42.46)	3.96 (3.92)	22.03 (22.00)	25.22 (25.19)	6.29 (6.25)
NJ-2016-005a	$C_{13}H_8N_4O_3S_2$	332.36	78	243-245	46.98 (46.95)	2.43 (2.40)	16.86 (16.82)	19.30 (19.27)	14.44 (14.41)
NJ-2016-005b	$C_{13}H_8ClN_3OS_2$	321.81	80	228-230	48.52 (48.50)	2.51 (2.49)	13.06 (13.01)	19.93 (19.90)	4.97 (4.94)
NJ-2016-005c	$C_{13}H_9N_3OS_2$	287.36	81	202-204	54.34 (54.31)	3.16 (3.12)	14.62 (14.59)	22.32 (22.30)	5.57 (5.53)
NJ-2016-005d	$C_{14}H_{11}N_3O_2S_2$	317.39	73	264-266	52.98 (52.95)	3.49 (3.45)	13.24 (13.22)	20.21 (20.23)	10.08 (10.06)

Experimental Section: Synthesis of 2-chloro-N-(thiazol-2-yl) acetamide (NJ-2016-002): Reaction of 2-aminothiazole **(NJ-2016-001)** (1.00g, 0.01mol.) with chloroacetyl chloride (2.24ml, 0.02mol) in DMF (5ml) at rt for 2hrs. Reaction progress was checked by TLC. After completion of the reaction, the reaction mixture was poured on crushed ice. Precipitated solid was filtered, washed with distilled water, dried and recrystallized from ethanol to give pure creamy white coloured product. IR (cm^{-1}): 3305 (N-H), 3050 (C-H), 1695 (C=O), 1550 (C=C), 1432 (C-H), 1297 (C=N), 1171 (C-N), 767 (C-Cl), 690 (C-S) cm^{-1}; ^{1}H NMR (δ): 9.10 (s,1H,NH), 7.57 (d,1H,ArH), 7.31 (d,1H,ArH), 4.28 (s,2H,CH_2); ^{13}C NMR (δ): 163.4 (C of amide), 162.1 (C of thiazole ring), 131.6 (C of thiazole ring), 111.1 (C of thiazole ring), 43.4 (C of CH_2 group); MS m/z (%): 176.26 (69%), 160.24 (80%), 149.94 (100%), 124.76 (53%), 102.44 (65%), 65.66 (42%).

Synthesis of (E)-2-(thiazol-2-ylimino)thiazolidin-4-one (NJ-2016-003): A mixture of 2-chloro-*N*-(thiazol-2-yl)acetamide **(NJ-2016-002)** (1.76g, 0.01mol.) dissolved in dry ethanol (15ml) with ammonium thiocyanate (1.76g, 0.01mol.) was heated under reflux condition for about 4hrs. The reaction progress was checked by TLC. After completion of reaction, the reaction mixture was left undisturbed overnight. Excess ethanol was distilled off under reduced-pressure and the residue was stirred with water. The solid was filtered, washed with water and dried. Product obtained was recrystallized with ethanol to give the yellow-brown compound. IR (cm^{-1}): 3306 (N-H), 3076 (C-H), 2990 (C-H), 1706 (C=O), 1487(C=C), 1316 (C-H), 1252 (C=N), 1186 (C-N), 725 (C-S-C); ^{1}H NMR (δ): 8.01 (s,1H,NH), 7.97 (d,1H,ArH), 7.50 (d,1H,ArH), 3.80 (s,2H,CH_2); ^{13}C NMR (δ): 172.8 (C of amide), 170.8 (C of thiazole ring), 156.8 (C of imine group), 139.4 (C of thiazole ring), 116.6 (C of thiazole ring), 33.5 (C of CH_2 group); MS m/z (%): 199.65 (70%), 190.87 (55%), 180.7 (52 %), 150.5 (48 %), 110.2 (35%), 65.76 (20%).

Synthesis of (2E,5Z)-5-{(dimethylamino)methylene-2-thiazol-2-ylimino}thiazolidin-4-one (NJ-2016-004): A mixture (E)-2-(thiazol-2-ylimino)thiazolidin-4-one **(NJ-2016-003)** (1.99g, 0.01mol.) was taken with *N,N*-dimethylformamide dimethylacetal (15ml) to reflux for 2hrs. The progress of the reaction was checked by the TLC. The reaction mixture was filtered, washed and recrystallized with ethanol to give red coloured compound. IR (cm^{-1}): 3218 (N-H), 2918 (C-H), 1674 (C=O), 1424 (C=C), 1285 (C=N), 1199 (C-N), 731 (C-S-C) cm^{-1}; ^{1}H NMR (δ): 8.09 (s,1H,NH), 7.96 (d,1H,ArH), 7.50 (d,1H,ArH), 6.80 (d,1H,CH), 3.09 (s,6H,$N(CH_3)_2$); ^{13}C NMR (δ): 173.2 (C of amide group), 170.8 (C of thiazole ring), 162.7 (C of imine group), 156.8 (C of ethylene moiety), 139.4 (C of thiazole ring), 117.7 (C of thiazole ring), 100.8 (C of ethylene moiety), 43.0 (C of methyl group); MS m/z (%): 254.0 (46%), 129.0 (48%), 128.0 (55%), 115.1 (38%), 101.0 (35%), 74.0 (47%).

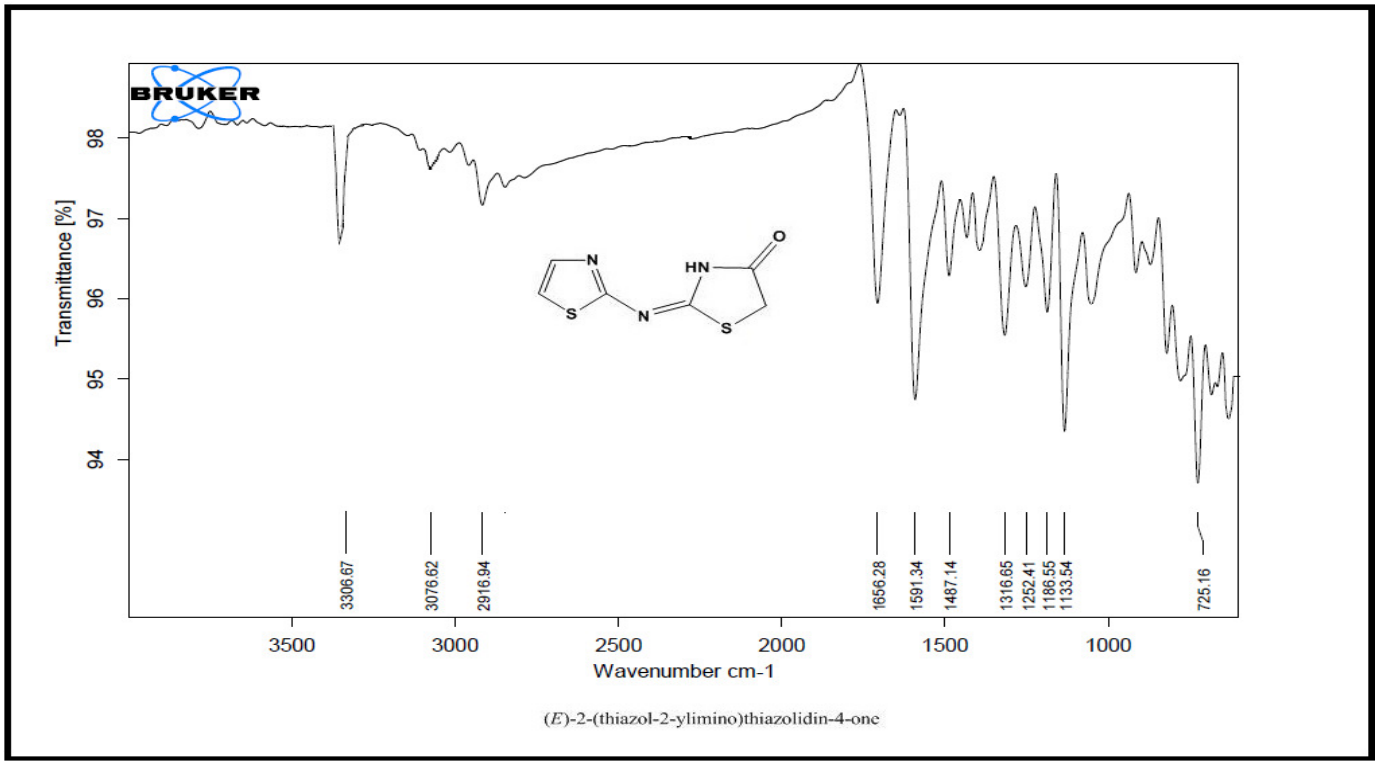


Figure-2: IR spectrum of *(E)-2-(thiazol-2-ylimino) thiazolidin-4-one* (NJ-2016-003)

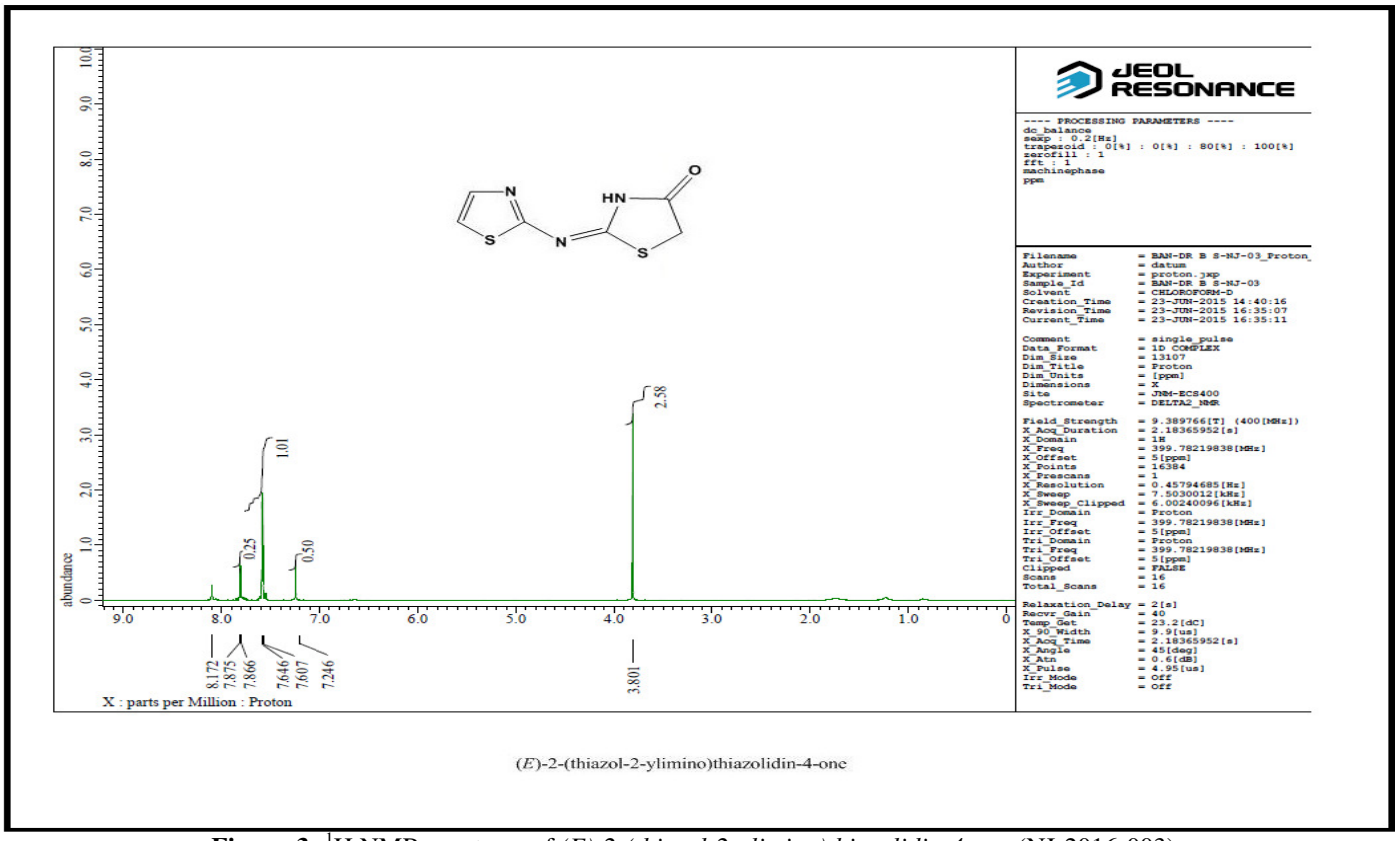


Figure-3: ^{1}H NMR spectrum of *(E)-2-(thiazol-2-ylimino)thiazolidin-4-one* (NJ-2016-003)

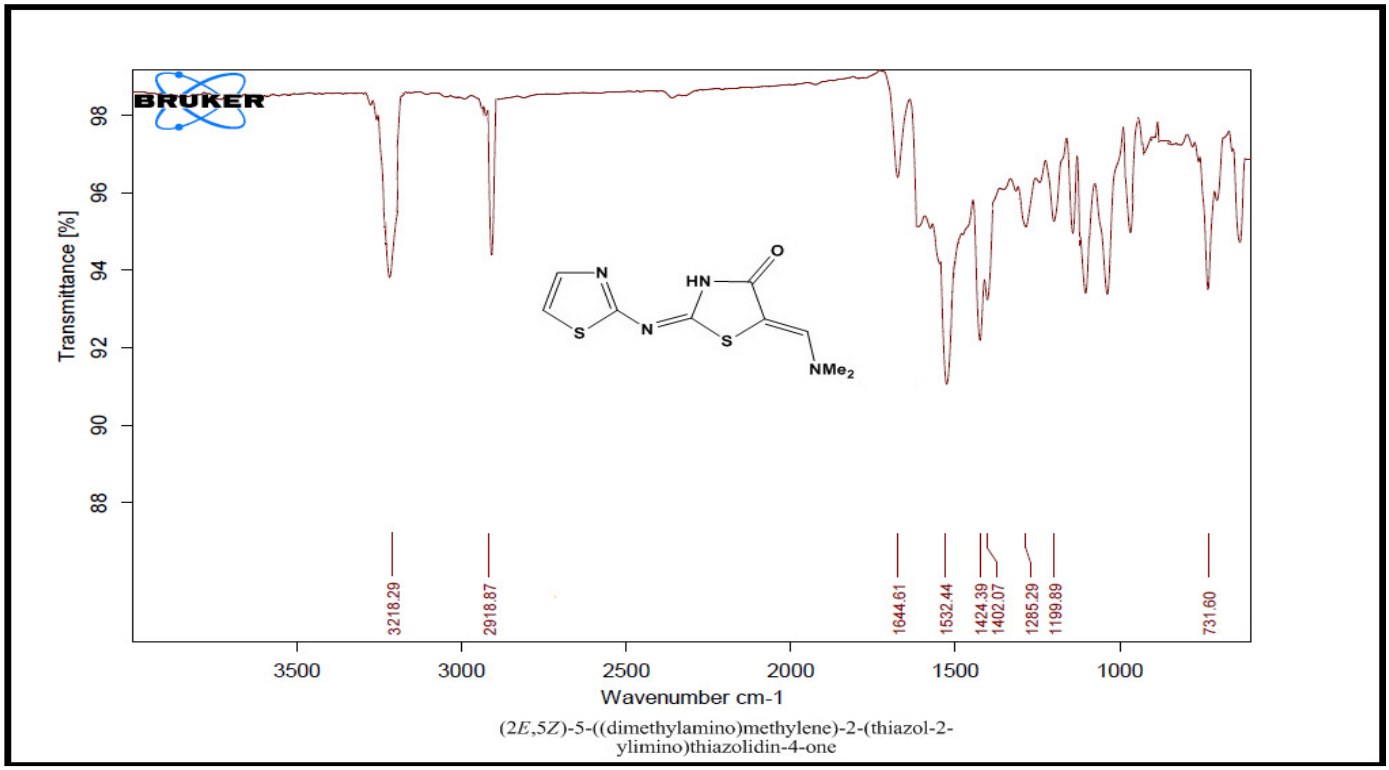


Figure-4: IR spectrum of *(2E,5Z)-5-((dimethylamino)methylene-2-(thiazol-2-ylimino)thiazolidin-4-one* (NJ-2016-004)

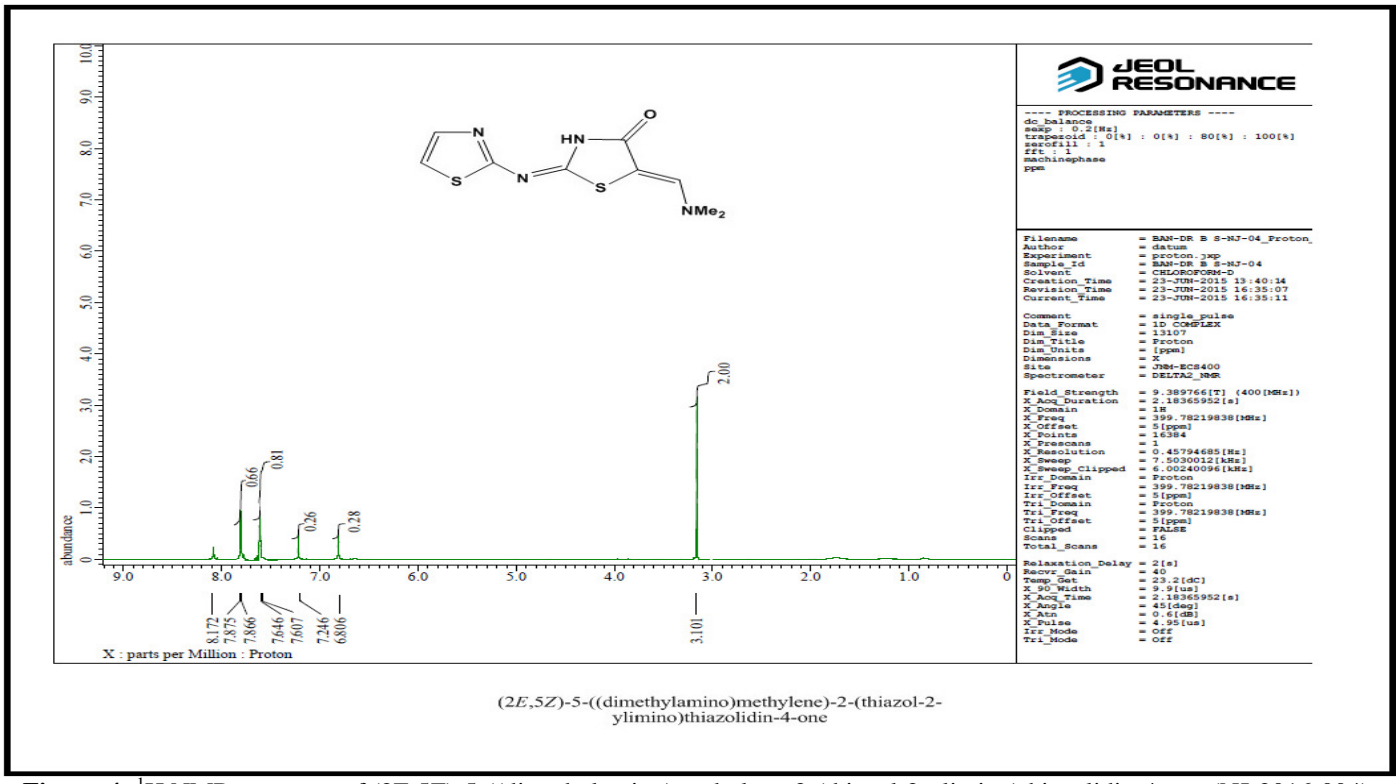


Figure-4: ^{1}H NMR spectrum of (2E,5Z)-5-((dimethylamino)methylene-2-(thiazol-2-ylimino)thiazolidin-4-one (NJ-2016-004)

Synthesis of (2E,5Z)-5-(4-substituted benzylidene)-2-(thiazol -2-ylimino) thiazolidin-4-ones (NJ-2016-005a-d): The chalcones were prepared *via* base catalyzed Claisen-Schmidt condensation reaction of substituted aromatic aldehydes. A mixture of aromatic aldehydes (0.001mol.) and (E)-2-(thiazol-2-ylimino) thiazolidin-4-one **(NJ-2016-003)** (0.001mol.) was dissolved in 30ml ethanol. Then 10ml NaOH solution (1g in 10ml water) was added drop wise to the reaction mixture on vigorous stirring for 30 minutes. The reaction temperature was maintained between 10-15˚C. After completion of the reaction, reaction mixture was neutralized by 0.1N HCl to precipitate the products. On filtering off, the crude solids were collected, dried and recrystallized by ethanol to give **NJ-2016-005(a-d)**.

(2E,5Z)-5-(4-Nitrobenzylidene)-2-(thiazol-2-ylimino) thiazolidin-4-one(NJ-2016-005a): Red-yellow coloured solid. IR (cm^{-1}): 3339 (N-H), 3072 (C-H), 1716 (C=O), 1515 (C=C), 1181(C=N), 1068 (C-N), 726 (C-S); ^{1}H NMR (δ): 8.06-8.29 (d,4H,ArH), 8.0 (s,1H,NH), 8.04 (s,1H,CH), 7.71 (d,1H,ArH), 7.64 (d,1H,ArH); ^{13}C NMR (δ) 173.8 (C of amide group), 172.6 (C of thiazole ring), 156.8 (C of imine group), 147.8 (C of benzene ring), 146.2 (C of ethylenic moiety), 140.6 (C of benzene ring), 139.4 (C of thiazole ring), 127.7 (C of benzene ring), 127.2 (C of benzene ring), 125.6 (C of benzene ring), 125.3 (C of benzene ring), 118.6 (C of thiazole ring), 114.6 (C of ethylenic moiety); MS m/z (%): 331.9 (48%), 298.0 (100%), 215.7 (88%), 186.7 (70%), 130.7(60%), 65.76 (45%).

(2E,5Z)-5-(4-Chlorobenzylidene)-2-(thiazol-2-ylimino) thiazolidin-4-one (NJ-2016-005b): Yellow coloured solid. IR: 3320 (N-H str.), 3060 (C-H str.), 1714 (C=O str.), 1554 (C=C str.), 1265 (C-N str.), 1170 (C=N str.), 710 (C-S str.), 690 (C-Cl str.); ^{1}H NMR (δ): 8.0 (s,1H,NH), 7.91 (d,1H,ArH), 7.80 (s,1H,CH), 7.45-7.69 (d,4H,ArH), 7.80 (s,1H,CH), 7.67(d,1H,ArH); ^{13}C NMR (δ): 174.0 (C of amide group), 171.8 (C of thiazole ring), 156.3 (C of imine group), 143.3 (C of ethylenic moiety), 140.5 (C of thiazole ring), 132.5 (C of benzene ring), 131.3 (C of benzene ring), 129.4 (C of benzene ring), 129.0 (C of benzene ring), 128.7 (C of benzene ring), 128.4 (C of benzene ring), 119.1 (C of thiazole ring), 115.9 (CH of ethylenic moiety); MS m/z (%): 386.55 (72%), 296.44 (72%), 240.79 (61%), 202.62 (100%).

(2E,5Z)-5-Benzylidene-2-(thiazol-2-ylimino) thiazolidin-4-one (NJ-2016-005c): Golden yellow coloured solid. IR (cm-^{1}): 3335 (N-H), 3026 (C-H), 1720 (C=O), 1554(C=C), 1215 (C-N), 1150 (C=N), 657 (C-S); ^{1}H NMR (δ): 8.0 (s,1H,NH), 7.89 (d,1H,ArH), 7.85 (s,1H,CH), 7.69 (d,1H,ArH), 7.39-7.65 (m,5H,ArH); ^{13}C NMR (δ): 175.2 (C of amide group), 174.3 (C of thiazole ring), 159.1 (C of imine group), 143.9 (C of ethylenic moiety), 141.4 (C of thiazole ring), 138.9 (C of benzene ring), 127.9 (C of benzene ring), 127.7 (C of benzene ring), 127.6 (C of benzene ring), 127.4 (C of benzene ring), 127.2 (C of benzene ring), 118.2 (C of thiazole ring), 113.4 (C of ethylenic moiety); MS m/z (%): 287.16 (70%), 250.33 (60%), 210.24 (100%), 174.79 (53%), 132.65 (45%), 69.12 (47%).

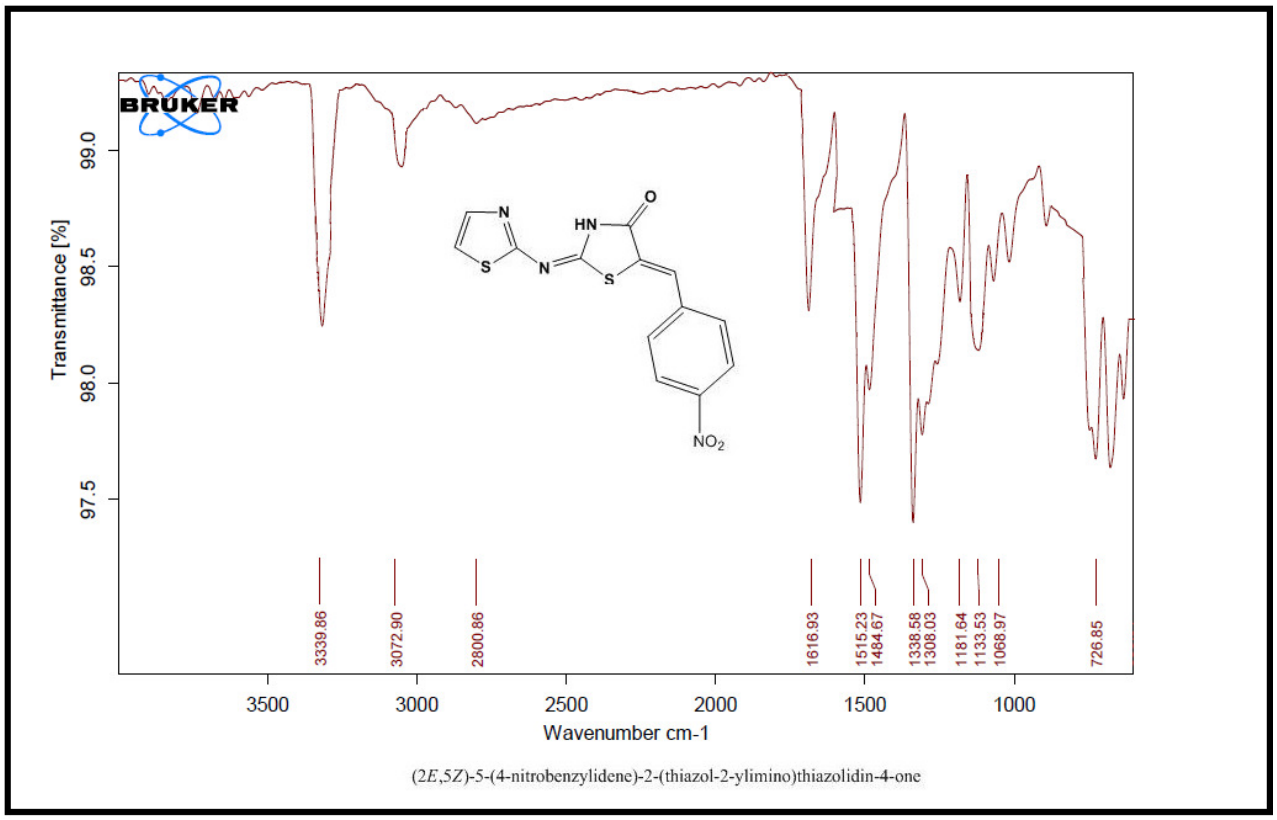


Figure-5: IR spectrum of *(2E,5Z)-5-(4-nitrobenzylidene)-2-(thiazol-2-limino)thiazolidin-4-one* (NJ-2016-005a)

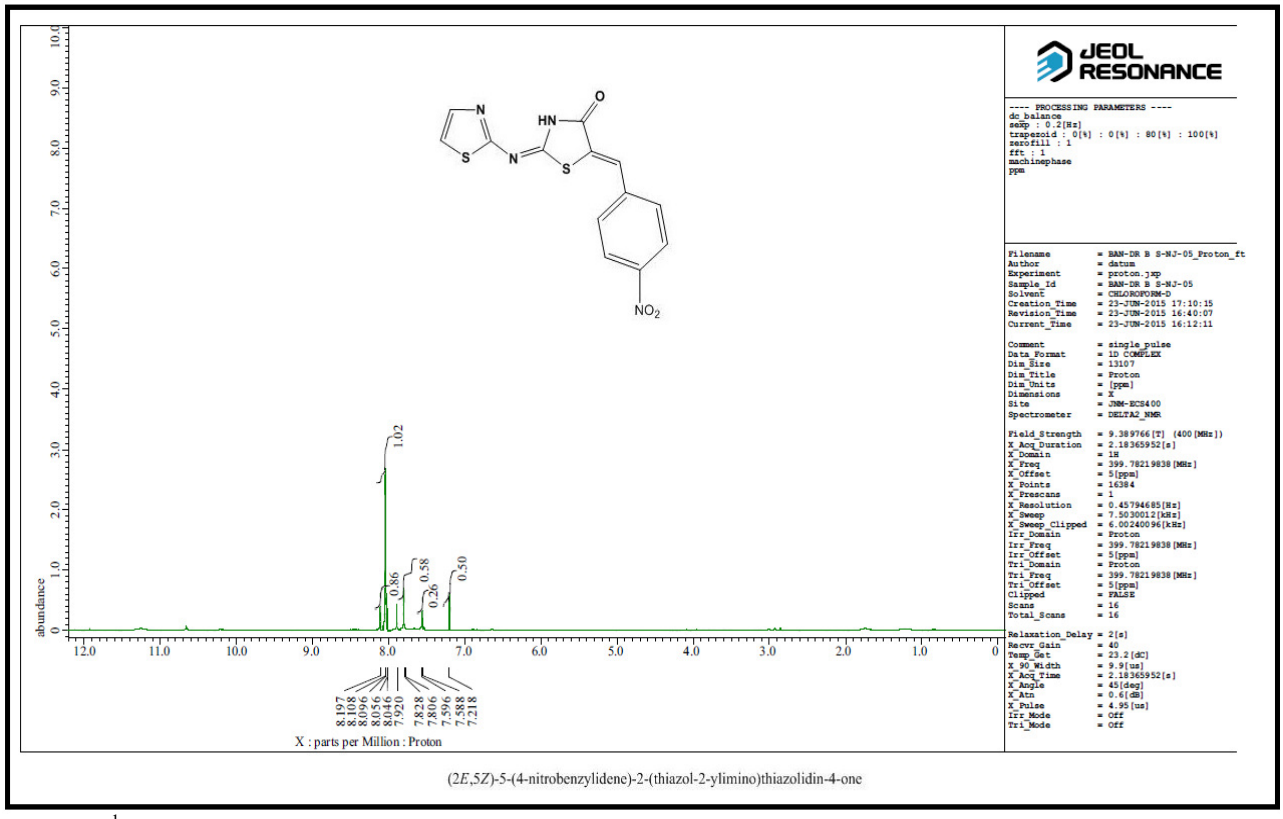


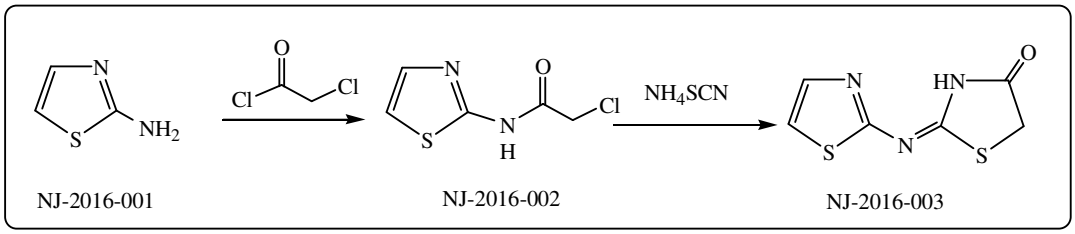
Figure-6: ^{1}H NMR spectrum of *(2E, 5Z)-5-(4-nitrobenzylidene)-2-(thiazol-2-limino) thiazolidin-4-one* (NJ-2016-005a)

(2E,5Z)-5-(4-Methoxybenzylidene)-2-(thiazol-2-ylimino) thiazolidin-4-one (NJ-2016-005d): Dark orange- yellow coloured solid. IR (cm^{-1}): 3366 (N-H), 3091(C-H), 1711(C=O), 1170 (C=N), 1551 (C=C), 1245 (C-N), 657 (C-S); ^{1}H NMR (δ): 8.0 (s,1H,NH), 7.84 (d,1H,ArH), 7.81 (s,1H,CH), 7.66 (d,1H,ArH), 6.94-7.62 (d,4H,ArH), 3.83 (s,3H,CH_3); ^{13}C NMR (δ): 172.1 (C of amide group), 170.2 (C of thiazole ring), 163.4 (C of benzene ring), 157.1 (C of imine group), 144.2 (C of ethylenic moiety), 142.9 (C of thiazole ring), 133.2 (C of benzene ring), 131.5 (C of benzene ring), 127.5 (C of benzene ring), 119.1 (C of thiazole ring), 117.7 (C of ethylenic moiety), 112.4 (C of benzene ring), 111.4 (C of benzene ring), 55.1 (C of aliphatic CH_3); MS m/z (%): 317.19 (59%), 290.44 (100%), 228.81 (60%), 194.16 (43%), 112.54 (75%), 55.76 (52%).

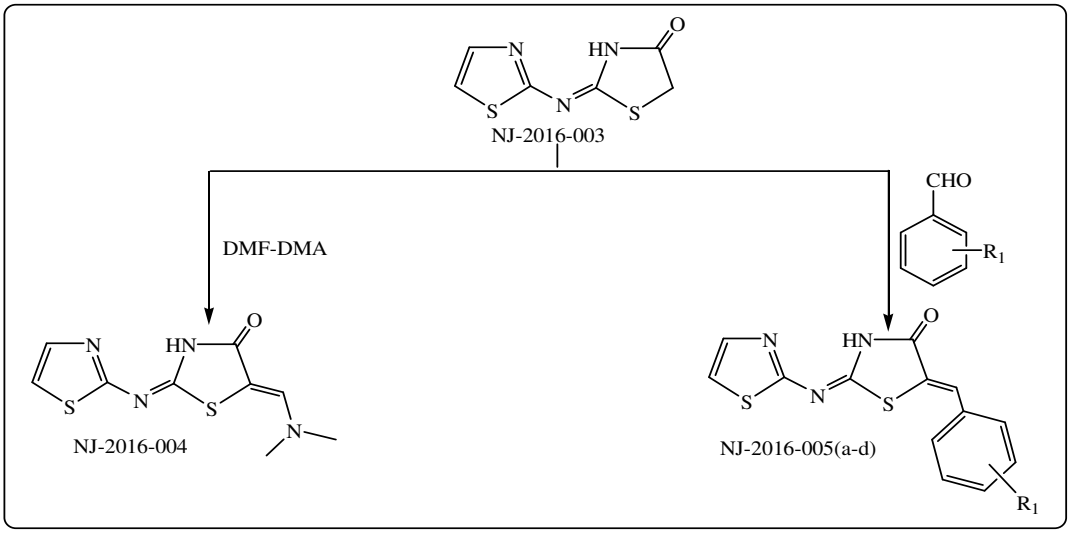
Results and discussion

The literature survey revealed that active synthons such as the dimethyl aminomethylene ketones and α,β-unsaturated ketones are accessible for very facile synthetic entry to the synthesis of five-, six- and seven-membered heterocyclic ring systems on their reactions with nucleophilic moieties. Thes synthons are readily available from the reactions of appropriate reagents with the compounds containing $COCH_2$ group in their molecular framework. In the present work, novel dimethyl aminomethylene ketones (NJ-2016-004) and α,β-unsaturated ketones (NJ-2016-005a-d) were synthesized from thiazolyl substituted 4-thiazolidinones (NJ-2016-003) through condensation reactions with *N,N*-dimethylformamide dimethylacetal and aromatic aldehydes respectively.

The formation of these compounds was confirmed on the basis of disappearance of the IR peaks and ^{1}H NMR signals of CH_2 group of 4-thiazolidinone moiety in the compounds NJ-2016-004 and NJ-2016-005a-d. The 4-Thiazolidinone (NJ-2016-003) is the key compound to synthesize reactive intermediates NJ-2016-004 and NJ-2016-005a-d. Compound (NJ-2016-003) was prepared from 2-chloro-*N*-(thiazol-2-yl)acetamide (NJ-2016-002) by reaction with ammonium thiocyanate. The compound NJ-2016-002 was synthesized from 2-aminothiazole treated with chloroacetyl chloride in DMF.



Scheme-1: NJ-01: Synthesis of Thiazolyl substituted 4-Thiazolidinone



Codes of Compounds	Substituents R_1
NJ-2016-005a	NO_2
NJ-2016-005b	Cl
NJ-2016-005c	H
NJ-2016-005d	OMe

Reaction Scheme: NJ-02: Synthesis of Thiazolyl substituted 4-Thiazolidinones possessing Dimethyl aminomethylene ketone and α,β-Unsaturated ketone motifs.

Conclusion

The research work was designed and executed to obtain thiazole substituted and 4-thiazolidinone containing dimethylaminomethylene ketone or enaminone and α,β-unsaturated ketone or chalcone intermediates from the reactions of *N,N*-dimethylformamide dimethylacetal (DMF DMA) and substituted benzaldehydes *via* cyclo-condensation reactions. Formation of the compounds were confirmed on the basis of analytical and spectral data of the synthesized compounds. These reactive intermediates are the key intermediates to synthesize a variety of medicinally potent five-, six- and seven-membered heterocycles.

Acknowledgement

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