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Synthesis of thiazol, thiazinan, thiadiazin, thiazolidin, triazine, thioxo-pyrimidin and thioxo-imidazolidine by inter-intra molecular cyclization

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Syntheses of five and six membered heterocyclic derivatives by the reaction of disubstituted thiocarbamides with inter-intramolecular cyclizations in catalyst free condition have been reported. The simple product isolation without column, good yields under mild condition, and applicable green matrix are the advantages of present protocol.

Keywords: Thiocarbamides, thiazol, thiazinan, thiadiazin, thiazolidin, triazine, thioxo-pyrimidin, thioxo-imidazolidine

Thiazols, triazines, imidazolidines, thiadiazines, thiazolidines and thiones are key structural motif and attracted considerable attention because of their applications in pharmaceutical and biological systems. Many of the scaffolds interestingly exhibits anti-proliferative[1], anti-asthmatic[2-4], anti-inflammatory[5,6], anti-tubercular[7], anti-depressant[8-11], anti-cancer[12,13], anti-viral[14], anti-ulcers[15], anti-hypertensives[16], anti-histaminics[17], anti-diabetic, anti-protozoal[18,19], neuroprotective, anti-oxidant[20], and molluscicidal[21-27] activities. Furthermore, literature explorations revealed that, much work have been reported on inter molecular cyclization reaction of thiourea with phenacyl bromide[28-31], chloroacetic acid[32-35], chloroacetyl chloride[36], and α,β-unsaturated acid[37] in various reaction condition. Synthesis of aza-heterocycles from N,N'-disubstituted thioureas[38] and 2-phenyl-amino-thiazolines from (2-hydroxyethyl)-phenylthioureas[39] have been reported by intra molecular cyclization using TsCl/NaOH.

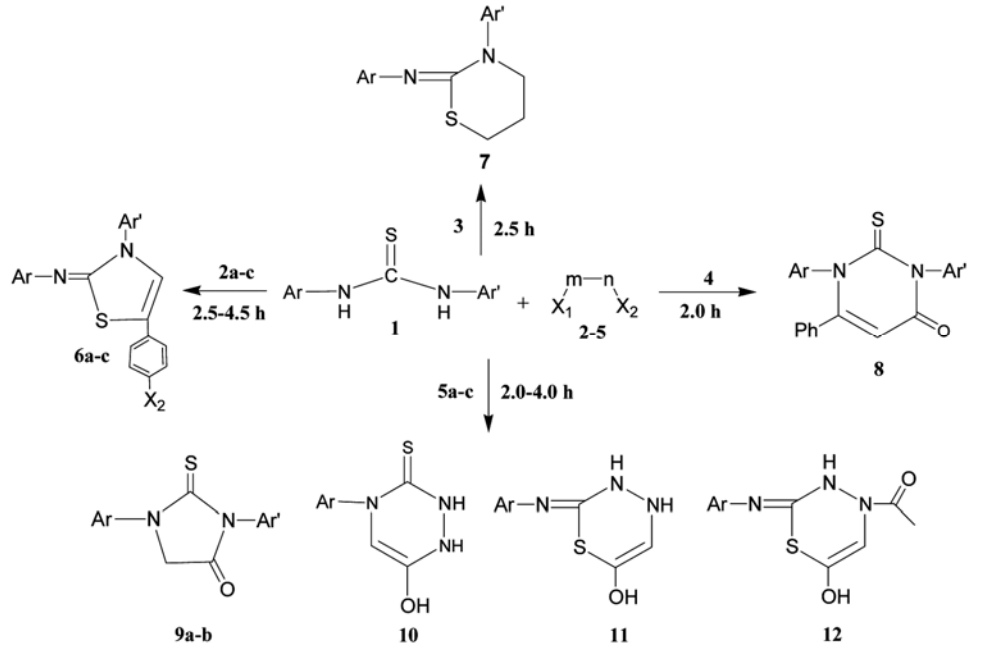
The development of useful organic transformations from simple starting materials with few synthetic steps to unite compounds to form highly functionalized and diversified molecules while keeping environmental aspects with interesting properties is highly desirable and have great synthetic challenge for chemists[40-42]. Although various methods for the syntheses of heterocyclic compounds have been reported many of them exhibit one or other limitations such as use of more quantity of organic solvents, catalysts, formation of hazardous waste product, and carbon emission during chemical reaction that have serious environmental threats[43,44].

To reduce the environmental damage by developing the synthetic plan includes minimum quantity of environment benign solvents and or dilute acid solution with catalyst free conditions. Therefore, the development of environmentally benign, catalyst free condition and green chemistry matrix remains a main objective for the synthesis of heterocyclic derivatives[45,46]. To best of our knowledge, we wish to report the environmental benign synthesis of heterocyclic compounds which affords good yields under mild and catalyst free condition (Scheme I and Scheme II).

Results and Discussion

We have found that, synthesis of heterocyclic derivatives by monitoring reaction under mild conditions can be achieved. Regarding the optimization of reaction conditions, we have applied basic concept to reduce more quantity of organic solvents, hazardous catalyst, longer reaction time and to enhance yield with green chemistry matrix.

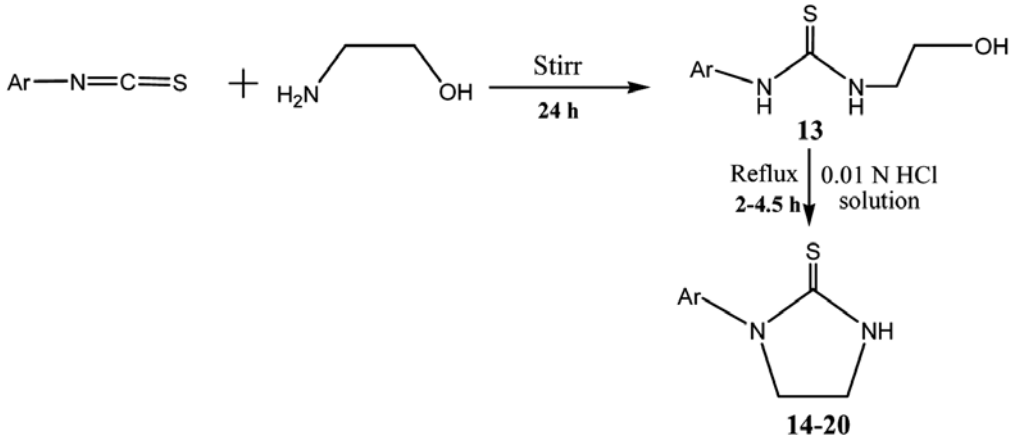
We examined reaction of **6a** by the interaction of diphenyl thiourea with phenacyl bromide under stirring, refluxing and or microwave irradiation methods. In initial experiment, we have studied the reaction in aqueous medium due to environmental impact for organic synthesis but water did not give any desirable impact (Table I, Entry **1**). We have



Reflux in 75% C_2H_5OH solution

Reactant	Ar	Ar'	X_1	X_2	m	n	Product
2a	C_6H_5	C_6H_5	Br	H	$COCH_2$	C_6H_4	6a
2b	C_6H_5	C_6H_5	Br	Br	$COCH_2$	C_6H_4	6b
2c	$4CH_3OC_6H_4$	$2CH_3C_6H_4$	Br	H	$COCH_2$	C_6H_4	6c
3	C_6H_5	C_6H_5	Br	Br	CH_2	CH_2-CH_2	7
4	C_6H_5	C_6H_5	OH	C_6H_5	CO	CH=CH	8
5a	C_6H_5	C_6H_5	Cl	OH	CH_2	CO	9a
5b	$4CH_3OC_6H_4$	$4CH_3C_6H_4$	Cl	Cl	CH_2	CO	9b
5a	$4CH_3C_6H_4$	NH_2	Cl	OH	CH_2	CO	10
5b	$4ClC_6H_4$	NH_2	Cl	Cl	CH_2	CO	11
5b	C_6H_5	$NHCOCH_3$	Cl	Cl	CH_2	CO	12

Scheme I



Ar	Product	Ar	Product	Ar	Product
C_6H_5	**14**	$(CH_3)_3C$	**15**	$4ClC_6H_4$	**16**
$4CH_3C_6H_4$	**17**	$4CH_3OC_6H_4$	**18**	C_6H_5-CH_2	**19**
C_6H_4-CO	**20**				

Scheme II

changed our strategy towards polarity and high boiling point of organic solvents like ethylene glycol which offered only 25% yield on stirring for 24 h, 42% of yield on refluxing for 7 h while 45% on MW irradiation for 30 min (Table I, Entry **2**). Further, we have optimized the reaction in comparatively low boiling solvents, to reduce environmental damage; interestingly the reaction was most effectively carried out in 75% aqueous ethanol, which furnishes the product with 90% yield on refluxed for 3 h (Table I, entry **4**) as compared to ethanol (Table I, Entry **3**), while acetone and DCM did not put enviable impact on yield of products (Table I, Entry **5**-**6**) with stretching reaction time. The optimization results clearly indicated that, aqueous ethanol as a reaction medium play an imperative role for completion of reaction in different methods with comparable yields for rest of the reactions.

In continuation of our research to optimize the reaction conditions we have studied the model reaction by taking diphenyl thiourea with chloroacetic acid which offered **9a**. The same reaction was monitored with different solvents such as water, ethylene glycol, ethanol, acetone and DCM using conventional or MW irradiation methods. The low yield of product was obtained when water, ethylene glycol or acetone was used as solvents (Table I, entry **1**, **2** and **5**) under conventional or MW irradiation. The model reaction did not put any progressive impact in DCM by conventional method but same reaction was unsuccessful under MW irradiation (Table I, entry **5**). A further optimization revealed that best result 91% was obtained in 75% aqueous ethanol for 3 h (Table I, entry **4**) under refluxed condition as compared to absolute ethanol (Table I, entry **3**). Therefore, 75% aqueous ethanol was a suitable media for rest of the transformations under refluxing condition and results of which are given in Table II.

Another model reaction by using the intramolecular cyclization of isothiocyanates and ethanolamine, **14** was performed and results are summarized in Table III. In this study the variety of dehydrating agents under conventional and MW conditions have been tested. We first optimized the same reaction with conc. H_2SO_4 gave 22% of product for 24 h on stirring while 50% yield of

Table I — Optimization of **6a** and **9a** with different reaction conditions

Entry	Solvent	Conventional Method[d]				Conventional Method[e]				MWI			
		Time (h)	Yield[f] (%)	Time (h)	Yield[g] (%)	Time (h)	Yield[f] (%)	Time (h)	Yield[g] (%)	Time (Min)	Yield[f] (%)	Time (Min)	Yield[g] (%)
1	Water	24	20	24	28	8.0	30	6.0	45	30	40	30	34
2	Ethylene glycol	24	25	24	32	7.0	42	5.0	38	30	45	30	37
3	Ethanol	24	25	24	30	5.0	83	3.5	86	30	42	30	34
4	75% Ethanol	24	28	24	35	5.0	90	3.0	91	30	52	30	40
5	Acetone	24	22	24	25	5.5	32	5.0	43	30	44	30	25
6	DCM	24	---[h]	24	---[h]	6.5	25	6.0	29	30	---[h]	30	---[h]

d- Stirring at RT; e- Refluxing; MWI- Microwave irradiation; f-reaction for **6a**; g-reaction for **9a**; h- no reaction; h-time in hours; Min-time in minutes.

Table II — Formation of target molecules

Entry	Ar	Ar'	X	Product	Time (h)	Yield (%)	DT	m.p. (°C)
1	C_6H_5	C_6H_5	H	6a	4.5	90	j	277
2	C_6H_5	C_6H_5	Br	6b	2.5	83	j	300
3	4-$CH_3OC_6H_4$	2-$CH_3C_6H_4$	H	6c	3.5	93	j	140
4	C_6H_5	C_6H_5	−	7	2.5	82	j	108
5	C_6H_5	C_6H_5	−	8	2	87	k	120
6	C_6H_5	C_6H_5	OH	9a	3	91	k	170
7	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	Cl	9b	4	88	k	68
8	4-$CH_3C_6H_4$	NH_2	OH	10	2	90	k	230(dec)
9	4-ClC_6H_4	NH_2	Cl	11	2	86	k	180(dec)
10	C_6H_5	NH-$COCH_3$	Cl	12	2.5	85	j	115

DT-desulfurization test; j-negative; k-Positive; dec- decomposed.

product on refluxing for 12 h but on MW irradiation mixture of reactant and product was obtained (Table III, entry **1**). We have tried another reagent PTSA with same reaction conditions but did not afford the progressive yield (Table III, entry **2**). The same reaction was optimized with conc. HCl, gave 29% of product on stirring for 24 h, 50% on refluxing for 12 h while MWI did not give any precious impact but product with traces of reactant (Table III, entry **3**). Conc. mineral acids did not give valuable impact for optimization hence we have tried with different concentration of acids solution. We have optimized the same reaction with various concentrations of HCl solution like, 5N, 2N, 1N & 0.1N; the progressive yield was obtained (Table III, entry **4-7**). The good result was recorded when reaction underwent with 0.01N solution of HCl under refluxing condition but MWI was unable to give the desired product (Table III, entry **8**). Hence 0.01 N solution of HCl was the best choice for further synthesis of rest of the organic transformations with good yields and results are summarized in Table IV.

All synthesized products were well characterized using ^{1}H NMR, ^{13}C NMR and MS and the products showed good agreements with their spectral data. The involvement of sulfur in cyclic system is confirmed by a desulphurization test. The positive desulfurization test has clearly indicated that sulfur was not involved in ring system whereas, negative desulfurization test indicated sulfur in the ring system.

Finally, to demonstrate the efficiency and potential of the present protocol the results have compared with principles of green chemistry in term of green chemistry metrices such as smaller E factor, good mass intensity, mass productivity,% effective mass yield, maximum reaction mass efficiency, high atom economy/atom utilization and highest carbon efficiency for the synthesis of **6-12** & **14-20**. The green chemistry matrices have established the minimum reaction waste, higher environmental compatibility and sustainability of present protocol (Table V, see details calculations in supplementary file).

Experimental Section

Melting points were taken in open capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR were recorded on a Bruker DSX-300/AV-III-400L NMR spectrometer in $CDCl_3$ and DMSO-d_6 solution with TMS as an internal reference. The ESI-MS spectra were recorded using QUATRO MICRO API-WATER mass spectrometer. TLC was performed on Merck 60 F_{254} pre coated silica plates and spot were located under UV chamber and by charring with suitable charring agents. All chemicals were purchased from Merck and Sigma Aldrich and used without further purifications.

General experimental procedure for 1 and 13

The mixture of aliphatic or aromatic amines (2 mmol) and aryl isothiocyanates (2 mmol) was stirred without solvent at RT for 24 h. The progress of reaction was monitored by TLC. After completion of the reaction, a solid product appeared. The solid product was first washed with aq. HCl to remove unreacted amine followed by aq. $NaHCO_3$ and water. The final crude product was purified by recrystalization using ethanol with excellent yield.

Table III — Optimization of 14 with different reaction conditions

Entry	Dehydrating agents	Conventional Method[d]		Conventional Method[e]		MWI	
		Time (h)	Yield (%)	Time (h)	Yield (%)	Time (Min)	Yield (%)
1	Conc. H_2SO_4	24	22	12	50	30	--[i]
2	PTSA	24	19	12	32	30	--[i]
3	Conc. HCl	24	29	12	50	30	--[i]
4	5N HCl	24	32	5.0	58	30	24
5	2N HCl	24	36	4.0	66	30	37
6	1N HCl	24	40	3.5	73	30	42
7	0.1N HCl	24	45	3.0	80	30	48
8	0.01N HCl	24	52	2.5	93	30	55

d- Stirring at RT; e- Refluxing; MWI- Microwave irradiation; PTSA- *p*-Tolylsulphonic acid; i-mixture of product and reactant; h-time in hours; Min- time in minutes.

General experimental procedure for 6-12

A mixture of 1,3-disubstituted thiocarbamides (0.001 mol) and halogenated and or unsaturated active compounds (0.001 mol) in ethanol (1 mL) was refluxed in round bottom flask for 2-4.5 h. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured in ice cold water to precipitate the crude product. The crude product was isolated by simple filtration and further purified by recrystallization with a good to excellent yield.

N-(3,5-Diphenyl-3*H*-thiazol-2-ylidene)-phenylamine, 6a: Brown solid. Yield 90%. m.p.277°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34-6.90 (m, 15H, Ar-H), 6.20 (s, 1H, CH=C); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.21, (C=S) 151.24 (N-C=CH), 139.11 (Ar-C_6), 137.74 (Ar-C_5), 131.04 (Ar-C_4), 129.10-127.161 (Ar-C_3), 122.63 (Ar-C_2), 120.87 (Ar C_1), 97.20 (N-CH=C); ESI-MS: *m/z* 328.00 $[M]^+$. Anal. Calcd for $C_{21}H_{16}N_2S$: C, 76.80; H, 4.91; N, 8.53; S, 9.76. Found: C, 76.77; H, 4.95; N, 8.50; S, 9.73%.

N-[5-(4'-Bromo-phenyl)-3-phenylthiazol-(3*H*)-2-ylidene]-phenylamine, 6b: Pale brown solid. Yield 83%. m.p.300°C;^{1}H NMR (400 MHz, DMSO-d_6): δ 7.62-7.13 (m, 14H, Ar-H), 7.03 (s, 1H), 3.47-3.45 (d, J=7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 140.23(C=N), 133.87 (C-N), 132.03-123.23 (Ar-C), 121.50(-C=CH), 105.30 (-C=CH); ESI-MS: *m/z* 406.00 $[M]^+$, 407.98 $[M+2]^+$. Anal. Calcd for $C_{21}H_{17}BrN_2S$: C, 61.62; H, 4.19; Br, 19.52; N, 6.84; S, 7.83. Found: C, 61.59; H, 4.18; Br, 19.47; N, 6.82; S, 7.80%.

N-[5-Phenyl-3-(2'-methylphenyl)-3*H*-thiazol-2-ylidene]-(4'-Methoxy)-phenylamine, 6c: Brown solid. Yield 93%. m.p.140°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.25-7.12(m, 9H, Ar-H), 6.97-6.84 (m, 4H, Ar-H), 6.40 (s, 1H, CH=C), 6.42-6.40 (d, J= 9.2 Hz, 1H) 3.73 (s, 3H, Ar –OCH_3), 2.07 (s 3H, Ar-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.38 (C=S), 139.57-122.32 (C-Ar), 114.78-114.05 (CH=C), 97.76 (C=CH), 55.24 (Ar-OCH_3), 17.50 (CH_3-Ar); ESI-MS: *m/z* 372.00 $[M]^+$. Anal. Calcd for

Table IV — Formation of target molecules

Entry	Ar	Product	Time (h)	Yield (%)	DT	m.p. (°C)
1	C_6H_5-	14	2.5	93	j	160
2	$(CH_3)_3C$-	15	2.0	95	j	89
3	4-Cl-C_6H_4-	16	3.0	89	k	140
4	4-CH_3-C_6H_4-	17	2.0	83	j	125
5	4-CH_3O-C_6H_4-	18	2.0	88	k	115
6	C_6H_4-CH_2-	19	2.5	91	k	112
7	C_6H_4-CO-	20	2.5	93	k	159

DT-desulfurization test; j-negative; k-Positive.

Table V — Green Chemistry Metrics applied to Organic synthesis

P	% AE	Kernel RME	CurzonRME	Andrus RME	MI	MP	% EMY	% CE	E factor	% AU	SCEI
6a	76.86	0.6917	0.6917	0.2590	3.860	25.90	165.01	100	0.3012	76.86	0
6b	80.46	0.6687	0.6687	0.3024	3.306	30.24	146.55	100	0.2428	80.46	0
6c	79.01	0.7348	0.7348	0.2839	3.522	28.39	187.14	100	0.2656	79.01	0
7	62.38	0.5115	0.5115	0.2112	4.735	21.18	132.93	100	0.6029	62.38	0
8	94.68	0.8237	0.8237	0.2928	3.414	29.28	--	100	0.0561	94.68	0
9a	83.12	0.7564	0.7564	0.2306	4.336	23.06	283.94	100	0.2030	83.12	0
9b	81.07	0.7134	0.7134	0.2548	3.924	25.48	276.60	100	0.2334	81.07	0
10	80.24	0.7222	0.7222	0.1982	5.045	19.82	234.16	100	0.2462	80.24	0
11	76.82	0.6607	0.6607	0.2092	4.780	20.92	214.01	100	0.3017	76.82	0
12	74.14	0.6302	0.6302	0.2118	4.721	21.18	220.72	100	0.3487	74.14	0
14	90.82	0.8447	0.8447	0.1493	6.700	14.93	--	100	0.1010	90.82	--
15	89.78	0.8529	0.8529	0.1348	7.420	13.48	--	100	0.084	89.78	--
16	92.19	0.8205	0.8205	0.1731	5.777	17.31	--	100	0.084	92.19	--
17	91.44	0.7589	0.7589	0.1591	6.284	15.91	--	100	0.093	91.44	--
18	92.04	0.8100	0.8100	0.1701	5.423	17.01	--	100	0.084	92.04	--
19	91.44	0.8348	0.8348	0.1591	6.284	15.91	--	100	0.093	91.44	--
20	91.96	0.8553	0.8553	0.1688	5.926	16.87	--	100	0.087	91.96	--

Where Product (P), Atom economy (AE); Reaction mass efficiency (RME), Mass intensity (MI); Mass productivity (MP); Effective mass yield (EMY); Carbon efficiency (CE); Environmental factor (E factor); Atom utilization (AU); Solvent and Catalyst Environmental Impact(SCEI).

$C_{23}H_{20}N_2OS$: C, 74.16; H, 5.41; N, 7.52; S, 8.61. Found: C, 74.12; H, 5.39; N, 7.49; S, 8. 58%.

Phenyl-(3-phenyl-[1,3]-thiazinan-2-ylidene)-amine, 7: White solid. Yield 82%. m.p.108°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.58-6.66 (m, 10H, Ar-CH), 3.71-3.70 (t, J=5.76 Hz, 2H), 3.04-3.01 (t, J=12.6, Hz), 2.23-2.23 (d, J=8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.90(C-S), 149.01C=N), 147.31C-N), 128.61-120.51 (Ar-H), 50.82 (CH_2-N), 30.06 (CH_2-S), 27.20 (-CH_2); ESI-MS: *m/z* 269.00 [M+1]. Anal. Calcd for $C_{16}H_{16}N_2S$: C, 71.60; H, 6.01; N, 10.44; S, 11.95. Found: C, 71.54; H, 6.01; N, 10.41; S, 11.91%.

1,3,6-Triphenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one, 8: Colourless solid. Yield 87%. m.p.120°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.53-6.92 (m, 15H, Ar-H), 6.82 (s, 1H, CH=C); ^{13}C NMR (100 MHz, DMSO-d_6): δ 179.61 (C=S), 163.59 C=O), 163.50 C-N), 152.52-118.04 (Ar-C); ESI-MS: *m/z* 357.20 $[M+1]^+$. Anal. Calcd for $C_{22}H_{16}N_2OS$, Calcd C, 74.13; H, 4.52; N, 7.86; S, 9.00. Found: C, 74.07; H, 4.51; N, 7.84; S, 8.97%.

1,3-Diphenyl-2-thioxo-imidazolidin-4-one, 9a: Colourless solid. Yield 91%. m.p.170°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.05-6.89 (m, 10H, Ar-H), 3.89 (s, 2H, -CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.46 (C=S), 154.98 (C=O), 148.13 (C-N), 129.41-120.94 (Ar-C), 32.91 (-CH_2); ESI-MS: *m/z* 268.10 $[M]^+$, (Calcd 268.07). Anal. Calcd for $C_{15}H_{12}N_2OS$, Calcd; C, 67.14; H, 4.51; N, 10.44; S, 11.95. Found: C, 67.07; H, 4.50; N, 10.42; S, 11.91%.

1-(4'-Methoxy-phenyl)-2-thioxo-3-(4'-methylphenyl)-imidazolidin-4-one, 9b: White solid. Yield 88%. m.p.68°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.25-7.23 (d, J=6.7 Hz, 2H), 7.11-7.09 (d, J=8.04 Hz, 2H), 7.01-6.99 (d, J=6.8Hz, 2H, Ar-H); 6.81- 6.79 (d, J= 8.2Hz, 2H ,Ar-H), 3.94 (s, 3H, ArO-CH_3), 2.29 (s, 2H, CH_2-C=O), 2.21 (s, 3H, Ar-CH_3), ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.69-171.59 (C=S), 159.73 (C=O), 154.97- 114.35- (Ar-C), 55.47 (Ar -OCH_3), 32.78 (H_2C-C=O), 20.95 (Ar- CH_3); ESI-MS: *m/z* 312.10 $[M]^+$. Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97; S, 10.26. Found: C, 65.29; H, 5.14; N, 8.94; S, 10.24%.

6-Hydroxy-4-(4'-methylphenyl)-1,2-dihydro-1,2,4-triazine-3(4*H*)-thione, 10: White solid. Yield 90%. m.p.230 °(dec); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.46-7.44 (d, J=8 Hz, 2H,Ar-H), 7.12 -7.10 (d, J=8.04 Hz, 2H Ar-H), 4.02 (s, 1H, NH-C=S), 3.34 (s, 2H, O=C-CH_2-NH), 2.29 (s, 3H, Ar -CH_3), 1.23 (s, 1H, NH-CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.99 (C=S), 165.31 (C=O) 164.33 (C-N), 137.94 (Ar-CH), 130.94 (Ar-CH), 128.51 (Ar-CH), 61.18 (CH_2-NH), 20.52 (Ar-CH_3); ESI-MS: *m/z* 221.00 $[M]^+$. Anal. Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99; S, 14.49. Found: C, 54.21; H, 5.00; N, 18.97; S, 14.47%.

2-(4-Chloro-phenylimino)-3,4-dihydro-2*H*-[1,3,4]thiadiazin-6-ol, 11: White solid. Yield 86%. m.p.180 °(dec); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.04 (s, 1H, OH), 7.65-7.63 (d, J=8 Hz, 2H, Ar-H), 7.29-7.27 (d, J=8.4 Hz, 2H,Ar-H), 3.50 (s, 1H, –NH), 1.24(s, 1H,-CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.66 (C=S), 139.94 (C-OH), 129.85-118.25 (Ar-C-H), 61.22 (C-N); ESI-MS: *m/z* 241.10$[M]^+$, 242.20 [M+2]. Anal. Calcd for $C_9H_8ClN_3OS$: C, 44.72; H, 3.34; Cl, 14.67; N, 17.39; S, 13.27. Found: C, 44.68; H, 3.32; Cl, 14.64; N, 17.36; S, 13.25%.

1-(5-Hydroxy-2-phenylimino-2,3-dihydro-[1,3,4]thiadiazin-4-yl)-ethanone, 12: Colourless solid. Yield 85%. m.p.115°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.45 (s, 1H, NH), 7.60-6.94 (m, 5H, Ar-H), 4.89(s, 2H, CH_2), 2.64 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.10 (C=O), 156.33(C=N), 129.78-117.37 (Ar-C), 99.49 (-CH_2), 42.83 (CO-CH_3); ESI-MS: *m/z* 249.10 $[M]^+$. Anal. Calcd for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45; N, 16.86; S, 12.86. Found: C, 52.95; H, 4.43; N, 16.84; S, 12.84%.

General procedure for the syntheses of 14–20

A mixture of 1-(2/3-hydroxyethyl)-3-aryl/alkyl thiocarbamides (0.001 mol) and aq. HCl solution (1 mL 0.01N) was refluxed in round bottomed flask for 2-3 h. During this time, the progress of the reaction was monitored by TLC. After completion of the reaction, a solid mass appeared. The solid mass was washed with aq. $NaHCO_3$ followed by water. Finally the crude product was purified by recrystallization with aqueous ethanol to give the pure compound in good to excellent yield.

N-(Thiazolidin-2-ylidene)-benzenamine, 14: White solid. Yield 93%. m.p.160°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.79 (s, 1H, N-H), 7.45-7.43 (d, 2H, J=7.6Hz, 2,6-Ar-H), 7.21-7.18 (dd, 2H, J=2Hz & 6.4Hz, 3,5-Ar-H), 6.91-6.87 (t, 1H, J=7.4 Hz, 4-Ar-H), 3.95-3.91 (t, 2H, J=7.4 Hz, CH_2), 3.26-3.23 (t, 2H,

J=7.4 Hz, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.83 (C=N), 144.27 (Ar-C_1), 128.83 (Ar-$C_{2,6}$), 121.30 (Ar-$C_{3,5}$), 118.50 (Ar-C_4), 58.17 (CH_2-N), 32.60 (CH_2-S); ESI-MS: *m/z* 178.1 $[M]^+$. Anal. Calcd for $C_9H_{10}N_2S$: C, 60.64; H, 5.65; N, 15.72; S, 17.99. Found: C, 60.63; H, 5.66; N, 17.71; S, 17.98%.

2-Methyl-N-(thiazolidin-2-ylidene)-propan-2-amine, 15: White needle. Yield 95%. m.p.89°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.23 (s, 1H, N-H), 4.06-4.02 (t, 2H, J=7.3Hz, CH_2), 3.23-3.21 (t, 2H, J=7.3Hz, CH_2), 1.36 (s, 9H, $3CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.98 (C=N), 62.08 (CH_2-N), 34.72 (CH_3-C), 29.07 (CH_2-S); ESI-MS: *m/z* 158.1 $[M]^+$. Anal. Calcd for $C_7H_{14}N_2S$: C, 53.12; H, 8.92; N, 17.70; S, 20.26. Found: C, 53.13; H, 8.91; N, 17.71; S, 20.27%.

1-(4-Chlorophenyl)-imidazolidine-2-thione, 16: White needle. Yield 89%. m.p.140°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33 (s, 1H, N-H), 7.23-7.21 (d, 2H, J=6.6Hz, 2,6Ar-H), 7.01-6.99 (d, 2H, J=6.7Hz, 3,5Ar-H), 3.75-3.71 (t, 2H, J=7.0Hz, CH_2), 3.30-3.27 (t, 2H, J=7.0Hz, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.42 (C=S), 147.16 (Ar-C_1), 128.97, 128.26 (Ar-$C_{2,6}$), 126.65 (Ar-C_4), 122.66 (Ar-$C_{3,5}$), 49.13 (CH_2-N), 31.36 (CH_2-S); ESI-MS: *m/z* 212.1 $[M]^+$, 214.1 [M+2]. Anal. Calcd for $C_9H_9ClN_2S$: C, 50.82; H, 4.26; Cl, 16.67; N, 13.17; S, 15.08. Found: C, 50.83; H, 4.26; Cl, 16.68, N, 13.18; S, 15.07%.

1-(4-Methylphenyl)-imidazolidine-2-thione, 17: White solid. Yield 83%. m.p.125°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.25 (s, 1H, N-H), 7.08-7.06 (d, 2H, J=8.2Hz, 2,6Ar-H), 7.01-6.98 (d, 2H, J=8.2Hz, 3,5Ar-H), 3.78-3.74 (t, 2H, J=7.0Hz, CH_2), 3.27-3.24 (d, 2H, J=7.0Hz, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.91 (C=S), 145.1 (Ar-C_1), 132.65, (Ar-$C_{3,5}$), 129.33 (Ar-$C_{2,6}$), 121.17 (Ar-C_4), 50.64 (CH_2-NH), 31.93 (CH_2-S), 20.85 (CH_3-Ar); ESI-MS: *m/z* 192.2 $[M]^+$. Anal. Calcd for $C_{10}H_{12}N_2S$: C, 62.46; H, 6.29; N, 14.57; S, 16.68. Found: C, 62.44; H, 6.30; N, 14.58; S, 16.70%.

1-(4-Methoxyphenyl)-imidazolidine-2-thione, 18: White needle. Yield 88%. m.p.115°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.26 (s, 1H, N-H), 7.01-7.00 (d, 2H, J=5.5Hz, ,6Ar-H), 6.84-6.82 (d, 2H, J=5.6Hz, 3,5Ar-H), 3.95 (s, 3H, CH_3O-Ar), 3.77-3.73 (t, 2H, J=7.5Hz, CH_2), 3.27-3.24 (t, 2H, J=7.0Hz, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.38 (C=S), 155.86 (Ar-C_4), 141.17, (Ar-C_1), 122.65 (Ar-$C_{3,5}$), 114.20 (Ar-$C_{2,6}$), 55.46 (CH_3O-Ar), 50.35 (CH_2-NH), 31.86 (CH_2-S); ESI-MS: *m/z* 208.0 $[M]^+$. Anal. Calcd for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.81; N, 13.45; S, 15.40. Found: C, 57.68; H, 5.80; N, 13.46; S, 15.41%.

Phenyl-N-(thiazolidin-2-ylidene)-methanamine, 19: Colourless solid. Yield 91%. m.p.112°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.32-7.08 (m, 5H, Ar-H), 3.39-3.36 (t, 2H, J= 7.2 Hz, CH_2), 3.26-3.23 (t, 2H, J=7.1Hz, CH_2), 2.93 (s, 2H, CH_2-Ar), 2.54 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.94 (C=N), 133.87 (Ar-C_1), 129.11, (Ar-$C_{2,6}$), 126.35 (Ar-$C_{3,5}$), 122.21 (Ar-C_4), 61.67 (CH_2-Ar), 56.42 (CH_2-NH), 28.15 (CH_2-S); ESI-MS: *m/z* 191.9 $[M]^+$. Anal. Calcd for $C_{10}H_{12}N_2S$: C, 62.46; H, 6.29; N, 14.57; S, 16.68. Found: C, 62.45; H, 6.30; N, 14.58; S, 16.67%.

Phenyl-(2-thioxoimidazolidin-1-yl)-methanone, 20: White solid. Yield 93%. m.p.159°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.17 (s, 1H, N-H), 7.8-7.85 (d, 2H, J= 7.6 Hz, CH_2), 7.65-7.61 (t, 1H, J=7.2Hz & 7 Hz, CH), 7.54-7.50 (t, 2H, J=7.2Hz & 7.4 Hz, CH_2-Ar), 3.94 (s, 4H,). Anal. Calcd for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58; S, 15.55. Found: C, 58.25; H, 4.89; N, 13.58; S, 15.57%.

Conclusion

In summary, we have reported the greener protocol for the synthesis of heterocyclic derivatives with minimum quantity of environmentally benign solvent under mild condition. The simple workup, inexpensive, high to moderate atom economy, reduced reaction times, good yields, and purification without column have been reported. Furthermore, broad scope of applicability, avoidance of the use of metal containing catalyst and hazardous solvents the method can be treated as environmentally friendly.

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