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Efficient synthesis, X-ray diffraction study and antimicrobial activity of some novel thiazolidin-4-ones and perhydro-1,3-thiazin-4-ones

Abstract: Condensations of thiosemicarbazones **1** derived from 1-tetralones with chloroacetic acid and 2-bromopropionic acid in the presence of *N*-methylpyridinium *p*-toluenesulfonate (an ionic liquid) yield the corresponding 2-substituted 4-thiazolidinones **2**. The reactions of **1** with 3-chloropropionic acid afford perhydro-1,3-thiazinan-4-ones **3** in excellent yields. The structures of compounds **2** and **3** were established on the basis of elemental analysis, IR, NMR and mass spectral data. X-Ray crystallographic studies of compound **2a** are reported. Compounds **1–3** were investigated for antimicrobial activities against *Bacillus subtilis, Staphylococcus aureus* (Gram-positive bacteria) and *Pseudomonas aeruginosa*, *Escherichia coli* (Gram-negative bacteria) and the fungi *Aspergillus niger, Candida albicans* and *Aspergillus fumigatus*. Thiazolidin-4-ones were found to be more active than perhydrothiazin-4-ones.

Keywords: antimicrobial activities; ionic liquid; perhydro-1,3-thiazin-4-ones; 4-thiazolidinones; thiosemicarbazones.

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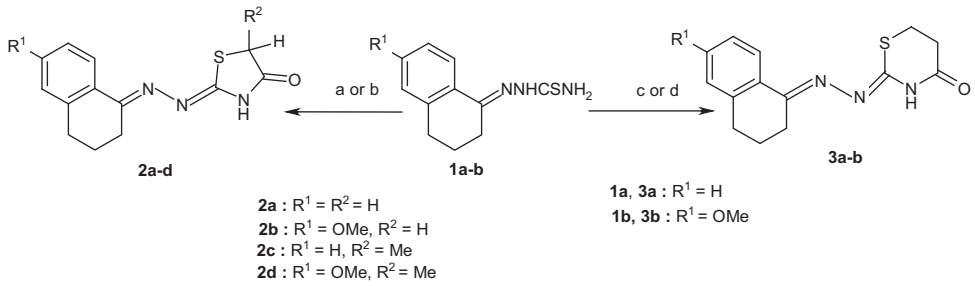
Introduction

4-Thiazolidinones and perhydro-1,3-thiazin-4-ones have been exploited in the past few decades for their wide range of biological activities such as antifungal, anticonvulsant [1], anti-HIV [2], analgesic, diuretic, antiviral, antiprotozoal [3], antibacterial [4, 5], anticancer [6], anti-inflammatory [7–9], cytotoxic [10], antitumor [11] and antituberculosis [12–14] properties. Recently, 4-thiazolidinones have been considered as a new class of antidiabetic drugs and potent aldose reductase inhibitors. They also have potential for treating diabetic complications such as nephropathy, neuropathy and cataract [15]. Several methods for preparation of 4-thiazolidinones have been reported in the literature. The commonly employed methods involve either a one-pot, three-component cyclocondensation of amines, carbonyl compounds and mercaptoacetic acid, or a two-step synthesis of Schiff base intermediates followed by their cyclocondensation with mercaptoacetic acid. The reported methods involve hazardous solvents and a long reaction time of 10–20 h with moderate to poor yields. There are reports of using *N,N′*-dicyclohexylcarbodiimide (DCC) [16], anhydrous $ZnCl_2$ [17, 18], Dean-Stark apparatus and molecular sieves for removal of water from the reaction mixture. In continuation of our work on the search for environmental friendly methods of synthesis of 4-thiazolidinones [19, 20], we now report a two-component cyclocondensation of thiosemicarbazones with halo acids yielding 2,5-disubstituted 4-thiazolidinones and perhydro-1,3-thiazin-4-ones under solvent-free conditions (Scheme 1).

Results and discussion

The synthesis and spectral characterization of compound **2a**, obtained by reaction of **1a** with chloroacetic acid, by conventional and solvent-free methods was reported [19] earlier by our group. In this paper, we report the X-ray crystallographic studies of compound **2a** (Figure 1). Compound **2a** crystallizes in the triclinic system having space group P-1 with the following parameters: a = 7.7239(13) Å, b = 8.746(2) Å, c = 11.1093(19) Å, α = 103.801(17)°, β = 95.285(14)°, γ = 116.05(2)°. The crystallographic data of compound **2a** are reported in Table 1. The CIF file of compound **2a** has been deposited with the Cambridge Structural Database and CCDC, no. 885668. The selected bond lengths and bond angles of **2a** are reported in Table 2.

The reaction of 1-tetralone with thiosemicarbazide in ethanol containing a catalytic amount of hydrochloric acid gave hydrazinecarbothioamide **1a**. Heating of **1a** under reflux with 2-bromopropionic acid in the presence of anhydrous sodium acetate in absolute ethanol for 12 h



Scheme 1 Reagents and conditions: (a) $ClCH_2COOH$ or $CH_3CH(Br)COOH$, NaOAc, anhydrous EtOH; (b) $ClCH_2COOH$, $CH_3CH(Br)COOH$, *N*-methylpyridinium *p*-toluenesulfonate; (c) $Cl(CH_2)_2COOH$, NaOAc, AcOH, Ac_2O; (d) $Cl(CH_2)_2COOH$, *N*-methylpyridinium *p*-toluenesulfonate.

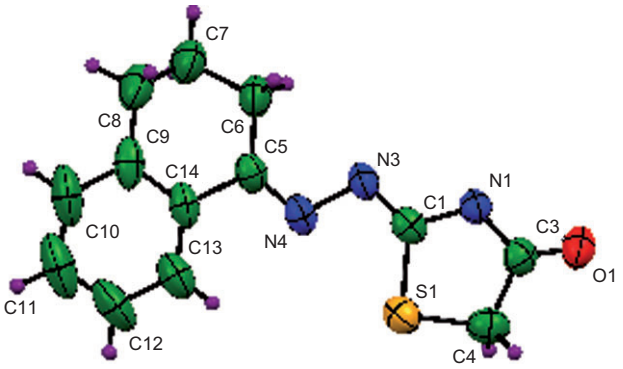


Figure 1 ORTEP drawing indicating molecular structure and atomic labeling of the (*Z*)-2-[(*E*)-(3,4-dihydronaphthalen-1(2*H*)ylidene) hydrazono]-thiazolidin-4-one (**2a**).

Table 1 Crystal data and structure refinement of (*Z*)-2-[(*E*)-(3,4-dihydronaphthalen-1(2*H*)ylidene)hydrazono]-thiazolidin-4-one (**2a**).

CCDC no.	885668
Empirical formula	$C_{13}H_{13}N_3OS$
Formula weight	259.32
Temperature (K)	293 (2)
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	
a (Å)	7.7239(13)
b (Å)	8.746(2)
c (Å)	11.1093(19)
α (°)	103.801(17)
β (°)	95.285(14)
γ (°)	116.05(2)
Volume (Å^3)	637.9(2)
Z	2
Density (calculated) (mg/m^3)	1.340
Absorption coefficient (mm^{-1})	0.244
Crystal size (mm^3)	0.28 × 0.26 × 0.18
Theta range for data collection	2.8994–29.0408
Reflections collected	2813
Independent reflections	2344
Data/restraints/parameters	2813/0/165
Goodness-of-fit on F^2	1.118
Final R indices [I > 2σ(I) = 2591 data]	R_1 = 0.1272, wR_2 = 0.1943
R indices (all data)	R_1 = 0.0651, wR_2 = 0.1868
Largest diff. peak and hole (eÅ^{-3})	-0.441, 0.822

gave **2c** (Scheme 1) in 56% yield (conventional method). Compound **2c** was obtained in 78% yield by cyclocondensation of **1a** with 2-bromopropionic acid in the presence of an ionic liquid, *N*-methylpyridinium *p*-toluenesulfonate, at 100°C for 4 h (Table 3). The analog **2d** was similarly prepared by adopting the procedure for **2c**. The structures of **2c,d** were established by elemental analysis and spectral (IR, NMR and mass) data.

Heating of compound **1a** under reflux with 3-chloropropionic acid in the presence of anhydrous sodium acetate and acetic anhydride in glacial acetic acid for 14 h furnished product **3a** in 48% yield (conventional method). Compound **3a** was obtained in 75% yield under solvent-free conditions using an ionic liquid (Table 3). The analog **3b** was obtained in a similar way. The structures of **3a,b** were established by elemental analysis and spectral data. The time of reaction and yields for the formation of compounds **2** and **3** by conventional methods as well as by solvent-free methods are reported in Table 3. The ionic liquid, *N*-methylpyridinium *p*-toluenesulfonate, was synthesized according to the literature [21]. The recovery of the ionic liquid was also attempted and it was found that it can be reused in two more cycles.

Antimicrobial studies

The antimicrobial screening of the synthesized compounds **2a–d** and **3a**,**b** was carried out using the disc

Table 2 Selected geometrical parameters of (*Z*)-2-[(*E*)-(3,4-dihydronaphthalen-1(2*H*)ylidene)hydrazono]-thiazolidin-4-one (**2a**).

Entry	Bond length (Å)	Entry	Bond angle (°)
S(1)-C(1)	1.767(5)	C(1)-S(1)-C(4)	90.7(3)
S(1)-C(4)	1.802(6)	C(5)-N(4)-N(3)	113.7(5)
N(4)-N(3)	1.410(6)	C(1)-N(1)-C(3)	116.3(5)
N(3)-C(1)	1.280(7)	C(6)-N(3)-N(1)	110.3(5)
C(3)-O(1)	1.221(7)	N(1)-C(3)-C(4)	112.3(5)
C(1)-N(3)	1.364(7)	N(3)-C(1)-N(1)	122.0(5)
C(1)-N(1)	1.279(7)	N(3)-C(1)-S(1)	125.5(4)
C(5)-C(6)	1.512(8)	S(1)-C(1)-N(1)	112.3(4)
C(10)-C(11)	1.397(11)	C(6)-C(5)-C(14)	119.7(5)
C(14)-C(13)	1.503(10)	C(5)-C(14)-C(13)	120.9(5)

Table 3 Synthesis of 4-thiazolidinones **2a–d** and perhydro-1,3-thiazinan-4-ones **3a–b** by conventional and solvent-free methods.

Compound	Solvent-free method		Conventional method	
	Reaction time (h)	Yield (%)	Reaction time (h)	Yield (%)
2a	2.5	90 [19]	5	63
2b	2.5	88 [19]	5	64
2c	`4	78	12	56
2d	4	76	12	56
3a	6	75	14	48
3b	6	74	14	44

diffusion method [22] by measuring the zone of inhibition. All compounds were screened *in vitro* for their antimicrobial activity against bacteria *Bacillus subtilis*, *Staphylococcus aureus* (Gram-positive bacteria) and *Pseudomonas aeruginosa* and *Escherichia coli* (Gram-negative bacteria) and fungi *Aspergillus niger, Candida albicans* and *Aspergillus fumigatus* at 40 μg/mL concentration. The standard drug, ampicillin trihydrate, was used for comparison purposes. Compounds **2a**, **2c** and **2d** showed the highest activity against Gram-positive bacteria *B. subtilis* and *S. aureus*. Compounds **2b**, **3a** and **3b** exhibited mild to moderate antibacterial activity in terms of the zone of inhibition (Table 4). Compounds **2a–d** and **3a,b** were also screened for antifungal activity and the results are reported in Table 5.

Conclusion

A convenient and efficient method for the synthesis of 2-substituted 4-thiazolidinones and perhydro-1,3-thiazin-4-ones under solvent-free conditions using ionic liquid is reported. The reaction times are markedly reduced and the yields of the products are greater in comparison to the classical procedure. Thazolidine-4-ones were found to be more active than perhydro-1,3-thiazinan-4-ones as antimicrobial agents.

Table 4 Antibacterial activity of 4-thiazolidinones **2a–d** and perhydro-1,3-thiazin-4-ones **3a,b**.

Compound	Zone of inhibition (mm)			
	Gram-positive		Gram-negative	
	B. subtilis	*S. aureus*	*P. aeruginosa*	*E. coli*
2a	22	23	18	19
2b	16	15	12	14
2c	18	19	17	18
2d	17	16	16	17
3a	14	12	10	11
3b	12	13	12	11
Ampicillin trihydrate	26	28	24	21
DMSO	0	0	0	0

Table 5 Antifungal activity of 4-thiazolidinones **2a–d** and perhydro-1,3-thiazin-4-ones **3a,b**.

Compound	Zone of inhibition (mm)		
	A. niger	*C. albicans*	*A. fumigates*
2a	18	15	17
2b	11	12	14
2c	16	17	17
2d	20	19	18
3a	16	13	16
3b	13	14	13
Ampicillin trihydrate	24	25	22
DMSO	0	0	0

Experimental

All chemicals were obtained from Sigma and used without further purification. Melting points were determined in open capillaries and are uncorrected. Elemental analysis was done on a Carlo-Erba 1108 elemental analyzer. Mass spectra were recorded on TOF MS ES+ 2.44e 4 instrument. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance II 400 NMR spectrometer using tetramethylsilane (TMS) as internal standard. IR spectra were recorded on an ABB FTIR spectrometer. Thin layer chromatography (TLC) was performed on silica gel G-coated plates using iodine vapor as visualizing agent. General procedures for synthesis of compounds **1a,b** and **2a,b** have been previously reported by our group [19]. X-Ray diffraction analysis was performed on an X Calibur EOS Oxford diffractometer. Compound **2a** [19] was crystallized from ethyl acetate by the slow evaporation method to obtain a pale yellow crystal for single crystal X-ray diffraction studies.

Synthesis of *N*-methylpyridinium *p*-toluenesulfonate (ionic liquid)

Pyridine (0.55 mol) was added to methyl *p*-toluenesulfonate (0.5 mol) at 0–10°C and the mixture was stirred at room temperature for 1 h. The resultant solid of *N*-methylpyridinium *p*-toluenesulfonate was filtered, washed with ethyl acetate to remove unreacted substrates and dried. The physical parameters of the ionic liquid were in good agreement with those reported in the literature [21].

Solvent-free procedure for synthesis of 2

A mixture of **1** (0.025 mol), 2-bromopropionic acid (3.8 g, 0.025 mol) and the ionic liquid (2.0 g) was stirred at 100°C for 4 h. After the reaction was completed, as monitored by TLC, the mixture was poured into ice-cold water. The resultant precipitate of **2** was filtered, dried and crystallized from ethanol (Table 3).

Conventional procedure for synthesis of 2

A mixture of **1** (0.015 mol), 2-bromopropionic acid (2.3 g, 0.015 mol), anhydrous sodium acetate (2.46 g, 0.03 mol) and absolute ethanol (5 mL) was heated under reflux for 10 h. The mixture was cooled to room temperature and then poured into ice-cold water. The separated solid was filtered, washed with water and crystallized from ethanol (Table 3).

2-{(*E*)-[3,4-Dihydro-2*H*-naphthalen-(1*E*)-ylidene]-hydrazono}-5-methylthiazolidin-4-one (2c) Mp 158–160°C; IR: ν 3132 (NH), 1713 (N-C=O), 1612 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 1.68 (d, 3H, CH_3, J = 7 Hz), 1.90 (m, 2H, CH_2), 2.81 (t, 2H, CH_2, J = 6 Hz), 2.89 (t, 2H, CH_2, J = 7 Hz), 4.06 (q, 1H, SCH, J = 7 Hz), 7.15 (d, 1H, ArH, J = 7 Hz), 7.23 (d, 1H, ArH, J = 7 Hz), 7.30 (t, 1H, ArH, J = 7 Hz), 8.21 (dd, 1H, ArH, J = 7 Hz, J = 1 Hz); ^{13}C NMR ($CDCl_3$): δ 175.9 (C=O), 162.2 (C=N), 140.9, 132.12, 130.25, 128.7, 126.4, 125.5 (ArC), 42.5 (SCH), 29.8 (CH_2), 27.5 (CH_2), 22.1 (CH_2), 19.1 (CH_3); MS: m/z 274 ($M+H^+$, 100%). Anal. Calcd for $C_{14}H_{15}N_3SO$: C, 61.53; H, 5.49; N, 15.38; S, 11.72. Found: C, 61.58; H, 5.60; N, 15.49; S, 11.83.

2-{(*E*)-[6-Methoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene]-hydrazono}-5-methyl-thiazolidin-4-one (2d) Mp 172–174°C; IR: ν 3070 (NH), 1705 (N-C=O), 1597 cm^{-1} (C=N); ^1H NMR (DMSO-d_6): δ 1.58 (d, 3H, CH_3, J = 7 Hz), 1.87 (t, 2H, CH_2, J = 6 Hz), 2.80 (m, 4H, $2CH_2$), 3.81 (s, 3H, OCH_3), 3.99 (q, 1H, SCH, J = 7 Hz), 6.66 (s, 1H, ArH), 6.75 (d, 1H, ArH, J = 9 Hz), 8.08 (d, 1H, ArH, J = 9 Hz); ^{13}C NMR (DMSO-d_6): δ 181.7 (C=O), 165.5 (C=N), 164.9 (C-OCH_3), 147.2, 131.7, 130.1, 117.9, 117.3 (ArC), 60.0 (OCH_3), 34.9 (SCH), 34.9 (CH_2), 32.0 (CH_2), 27.0 (CH_2), 24.1 (CH_3); MS: m/z 304 ($M+H^+$, 100%). Anal. Calcd for $C_{15}H_{17}N_3O_2S$: C, 59.40; H, 5.61; N, 13.86; S, 10.56. Found: C, 59.49; H, 5.69; N, 13.91; S, 10.86.

Solvent-free procedure for synthesis of 3

An equimolar mixture of **1** (0.025 mol) and 3-chloropropionic acid (2.71 g, 0.025 mol) and the ionic liquid (2.0 g) was stirred at 100°C for 6 h. After the reaction was completed, as monitored by TLC, the mixture was poured into ice-cold water. The resultant precipitate of **3** was filtered, dried and crystallized from ethanol (Table 3).

Conventional procedure for synthesis of 3

A mixture of **1** (0.005 mol), 3-chloropropionic acid (0.54 g, 0.005 mol), anhydrous sodium acetate (0.8 g, 0.010 mol), glacial acetic acid (3.0 mL) and acetic anhydride (1.0 mL) was heated under reflux for 10–14 h. The mixture was cooled to room temperature and poured into ice-cold water. The gummy product obtained was extracted with ethyl acetate (2 × 25 mL). The extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid residue of **3** was crystallized from ethyl acetate.

2-{(*E*)-[3,4-Dihydronaphthalene-1(2*H*)-ylidene]hydrazono}-perhydro-1,3-thiazin-4-one (3a) Mp 154–156°C; IR: ν 1697 (N-C=O) 1589 (C=N), 1543 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): δ 1.89 (m, 2H, CH_2), 2.79–3.07 (m, 8H, $4CH_2$), 7.15 (t, 1H, ArH, J = 7 Hz), 7.21–7.34 (m, 2H, ArH), 8.24 (dd, 1H, ArH, J = 7 Hz, J = 2 Hz), 9.72 (br, 1H, NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$): δ 169.4 (C=O), 162.4 (C=N), 140.9, 132.5, 130.3, 128.8, 126.3, 125.4 (ArC), 34.3 (SCH_2), 29.9, 27.4, 23.2, 22.7, 22.1 (CH_2); MS: m/z 274 $(M+H)^+$ (20), 233 (34), 231 (100%). Anal. Calcd for $C_{14}H_{15}N_3SO$: C, 61.53; H, 5.49; N, 15.38; S, 11.72. Found: C, 61.45; H, 5.44; N, 15.32; S, 11.80.

2-{(*E*)-[6-Methoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene] hydrazono}-perhydro-1,3-thiazin-4-one (3b) Mp 139–140°C; IR: ν 1697 (N-C=O), 1589 (C=N), 1551 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): δ 1.85–2.17 (m, 2H, CH_2), 2.76–3.16 (m, 6H, $3CH_2$), 3.83 (s, 3H, OCH_3), 6.65 (m, 1H, ArH), 6.78–6.81 (dd, 1H, ArH, J = 6 Hz, J = 3 Hz), 8.17 (m, 1H, ArH), 9.74 (br, 1H, NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$): δ 169.5 (C=O), 162.6 (C=N), 140.8, 132.1, 130.1, 127.2, 125.1, 123.4 (ArC), 58.9 (OCH_3), 33.4 (SCH_2), 28.9, 27.2, 23.1, 22.4, 22.6 (CH_2); MS: m/z 304 $(M+H)^+$ (20%). Anal. Calcd for $C_{15}H_{17}N_3O_2S$: C, 59.40; H, 5.61; N, 13.86; S, 10.56. Found: C, 59.33; H, 5.56; N, 13.78; S, 10.45.

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