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Efficient synthesis of 2,4-disubstituted thiazoles and 2-substituted 4-thiazolidinones under solvent free conditions

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Abstract

Condensation of thiosemicarbazones **2** derived from 1-tetralones (**1**) with chloroacetic acid in presence of *N*-methylpyridinium tosylate (an ionic liquid) yields 2-substituted-4-thiazolidinones **3**. The reaction of **2** with α-halo carbonyl compounds at room temperature under grinding conditions yields 2,4-disubstituted thiazoles **4** in excellent yields. The structures of compounds **2–4** have been established on the basis of elemental analysis, IR, NMR and mass spectral data.

Keywords: grinding; ionic liquid; thiazoles; thiosemicarbazones; 4-thiazolidinones.

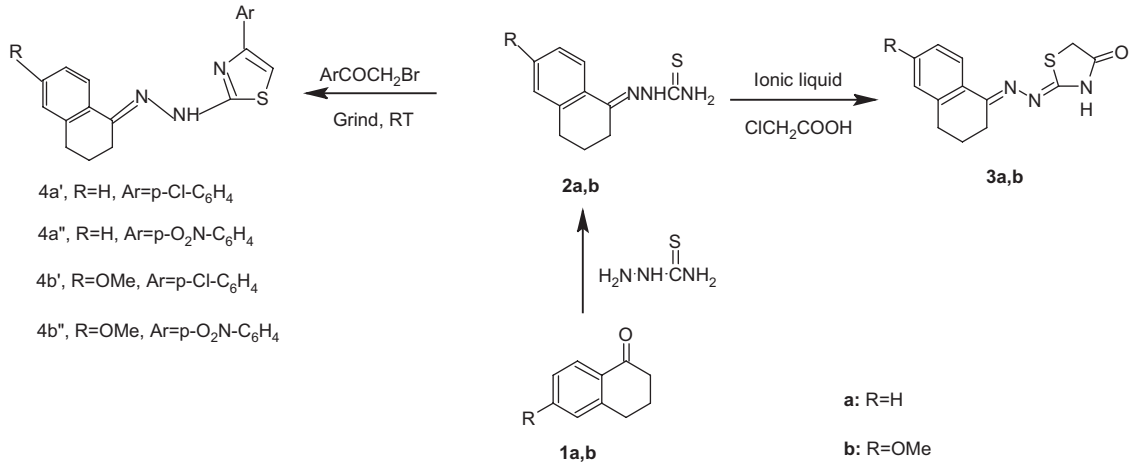
Introduction

Thiazoles and 4-thiazolidinones have been exploited in the past few decades for their wide range of biological activities such as anti-fungal, anti-convulsant (Gursoy and Terzioglu, 2005), anti-HIV (Rawal et al., 2007), analgesic, diuretic, anti-viral, anti-protozoal (Tenorio et al., 2005), anti-bacterial (Bonde and Gaikwad, 2004; Kucukguzel et al., 2006), anti-cancer (Gududuru et al., 2005), anti-inflammatory (Wilson et al., 2001; Ottana et al., 2005), cytotoxic (Brantley et al., 2005), anti-allergic (Hargrave et al., 1983) and anti-tuberculotic (Kachhadia et al., 2005) activities. Several methods for the 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 two-step synthesis via Schiff base intermediates followed by their cyclocondensation with mercaptoacetic acid. The two-step approach involves hazardous solvents and long reaction times with moderate to poor yields. In these reactions various desiccants such as N,N'-Dicyclohexylcarbodiimide (DCC) (Srivastava et al., 2002), anhydrous $ZnCl_2$ (Sharma and Kumar, 2000; Desai and Desai, 2006), Dean-Stark apparatus and molecular sieves are employed for removal of water from the reaction mixture. In the present paper, a convenient two component cyclocondensation using an ionic liquid for obtaining 2-substituted-4-thiazolidinones with excellent yield is reported. Also in this article we describe a highly efficient synthesis of 2,4-disubstituted thiazoles by grinding thiosemicarbazones with α-halo carbonyl compounds without any solvent at room temperature in excellent yields (Scheme 1).

Results and discussion

Reaction of 1-tetralone with thiosemicarbazide in ethanol containing a catalytic amount of concentrated HCl gave hydrazinecarbothioamide **2a**. Compound **2a** was allowed to react with chloroacetic acid in the presence of sodium acetate (conventional method) and in the presence of an ionic liquid (*N*-methylpyridinium tosylate) affording thiazolidinone **3a** in moderate yield (Table 1). The IR spectrum of **3a** displayed the presence of a carbonyl group peak at 1705 cm^{-1}. The ^1H NMR spectrum of **3a** exhibited a sharp singlet at δ 3.79 for the SCH_2 group in the thiazolidinone unit, suggesting that cyclization had occurred. Two triplets at δ 2.80 (J=6.2 Hz), δ 2.88 (J=6.6 Hz) and one multiple at δ 1.85–1.91 integrating for two protons each in ^1H NMR spectrum of **3a** were assigned to the tetrahydronaphthalene ring. The mass spectrum of **3a** showed the $[M+H]^+$ peak at m/z 260 (100%). Thiazolidinone **3a** was also obtained under solvent free conditions by heating **2a** and chloroacetic acid in the presence of ionic liquid at 80–90°C for 3 h (Table 1). Analogues **2b** and **3b** were similarly obtained by adopting the same procedure.

Compound **2a** was also allowed to react with p-chlorophenacyl bromide by stirring in absolute ethanol or by grinding in the absence of solvent at room temperature to give thiazole **4a'**. The IR spectrum of **4a'** exhibit absorption at 3204, 1605, 1481 cm^{-1} attributed to the respective NH, C=N, C=C functional groups. The ^1H NMR spectrum of **4a'** exhibits a singlet at δ 6.75 for the =CH proton of the thiazole ring. The analogues **4a''**, **4b'** and **4b''** were similarly prepared by adopting the same procedure and their structures were confirmed by elemental analysis and spectral (IR and NMR) data (Scheme 1). The reaction times and yields for the formation of compounds **3** and **4** by conventional method as well as by solvent free method are reported (Table 1). The ionic liquid, *N*-methylpyridinium tosylate was synthesized by the literature method. The recovery of the ionic liquid was also attempted and we found that it could be re-used for two more cycles.



Scheme 1

Conclusion

A convenient and efficient method for the synthesis of 2,4-disubstituted thiazoles under grinding and synthesis of 4-thiazolidinones under solvent free conditions using ionic liquid is described. The yields of the products under solvent free conditions are almost quantitative.

Experimental section

The chemicals were obtained from Sigma (Sigma, Bangalore, India) 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 a TOF MS ES+2.44e 4 instrument. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded in $CDCl_3$ on a Bruker AVANCE II 400 NMR spectrometer using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on ABB FTIR spectrometer. Thin layer chromatography (TLC) was performed on silica gel G coated plates and using iodine vapor as visualizing agent.

Synthesis of ionic liquid

Pyridine (1.1 mol) was added to a methyl-4-toluene sulfonate (1.0 mol) at 0–10°C. After completion of the addition, the mixture was stirred at room temperature for 1 h. The solid of *N*-methylpyridinium tosylate was filtered. The product was then washed with ethyl acetate and dried. The physical parameters of the ionic liquid are in good agreement with those reported in the literature (Kroutil and Budesinsky, 2007).

General procedure for synthesis of 2

A mixture of **1** (0.03 mol), thiosemicarbazide (2.73 g, 0.03 mol) and concentrated HCl (0.8 ml) in absolute ethanol (40 ml) was stirred at room temperature for 3 h. The mixture was poured into ice cold water. The resultant white solid was filtered, dried and crystallized from ethanol.

(*E*)-2(3,4-Dihydronaphthalen-1(2*H*)-ylidene)hydrazinecarbothioamide (2a): Bright white needles; m.p. 202–206°C; yield 91%; IR: ν 3410, 3217, 3140 (NH), 1597 (C=N), 1489 (C=C), 1288 cm^{-1} (C=S); ^{1}H NMR δ 1.95–2.01 (m, 2H, CH_2), 2.61 (t, 2H, CH_2, J=6.6 Hz), 2.79 (t, 2H, CH_2, J=6.2 Hz), 6.51 (br, 1H, NH exchanged with D_2O), 7.15–7.32 (m, 3H, C_6H_5), 7.40 (br, 1H, NH_2 exchangeable with D_2O), 7.99 (dd, 1H, C_6H_5), 8.80 (br, 1H, NH_2 exchangeable with D_2O). Analysis: found for $C_{11}H_{13}N_3S$: C, 60.22%; H, 5.90%; N, 19.22%; S, 14.58. Calculated: C, 60.27; H, 5.98%; N, 19.12%; S, 14.62%.

(*E*)-2-(6-Methoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazinecarbothioamide (2b): Light brown crystals, m.p. 198–200°C, yield 86.5%. IR: ν 3433, 3194, 3117 (NH), 1582 (C=N), 1489 (C=C), 1250 cm^{-1} (C=S); ^{1}H NMR δ 1.87–1.93 (m, 2H, CH_2), 2.49 (t, 2H, CH_2, J=6.6 Hz), 2.68 (t, 2H, CH_2, J=6.2 Hz), 3.75 (s, 3H, OCH_3), 6.30 (br, 1H, NH exchangeable with D_2O), 6.59 (d, 1H, C_6H_5, J=2.6 Hz), 6.70–6.73 (m, 1H, C_6H_5), 7.28 (br, 1H, NH_2 exchangeable with D_2O), 7.85 (d, 1H, C_6H_5, J=8.8 Hz), 8.66 (br, 1H, NH_2 exchangeable with D_2O). Analysis: found for $C_{12}H_{15}N_3SO$: C, 57.80; H, 5.98; N, 16.82; S, 12.81. Calculated: C, 57.91; H, 6.05; N, 16.88; S, 12.86%.

Solvent free general procedure for synthesis of 3

An equimolar mixture of **2** (0.025 mol) and chloroacetic acid (0.23 g, 0.025 mol) in premolten ionic liquid (2.0 g) was stirred at 80–90°C for 3–4 h. The reaction was monitored by TLC. The mixture was poured into ice cold water and the resultant solid was filtered, dried and crystallized from ethanol.

Table 1 Synthesis of 2,4-disubstituted thiazoles and 4-thiazolidinones by a conventional method and under solvent free conditions.

Entry	Solvent-free method		Conventional method	
Compound	Reaction time	Yield (%)	Reaction time	Yield (%)
3a	2.5 h	90	5 h	63
3b	2.5 h	88	5 h	64
4a'	10 min	95	15 min	65
4a''	12 min	92	20 min	64
4b'	10 min	94	15 min	63
4b''	12 min	93	20 min	64

Conventional procedure for synthesis of 3

A mixture of **2** (0.005 mol), chloroacetic acid (0.47 g, 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 crystallized from ethanol.

(*Z*)-2-((*E*)-(3,4-Dihydronaphthalen-1(2*H*)ylidene)hydrazono)-thiazolidin-4-one (3a): Light yellow crystals; m.p. 206–208°C; IR: ν 2800 (NH), 1705 (N-C=O), 1605 cm^{-1} (C=N); ^1H NMR δ 1.85–1.91 (m, 2H, CH_2), 2.79 (t, 2H, CH_2, J=6.2 Hz), 2.86 (t, 2H, CH_2, J=6.6 Hz), 3.79 (s, 2H, SCH_2), 7.14 (d, 1H, C_6H_5, J=7.5 Hz), 7.22–7.32 (m, 2H, C_6H_5), 8.21–8.24 (m, 1H, C_6H_5); ^{13}C NMR δ 173.5 (C=O), 162.5 (C=N), 162.1 (C=N), 140.9, 132.3, 130.1, 128.6, 126.3, 125.5 (C_6H_5), 33.1 (SCH_2), 29.9 (CH_2), 27.4 (CH_2), 22.2 (CH_2); EIMS: m/z 260 ($M+H^+$, 100%), 144 ($M-C_3H_3N_2SO$, 29%). Analysis: found for $C_{13}H_{13}N_3SO$: C, 60.20; H, 5.04%; N, 16.18; S, 12.32. Calculated: C, 60.32; H, 5.11; N, 16.24; S, 12.38%.

(*Z*)-2-[(*E*)-(6-Methoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene]hydrazono)thiazolidin-4-one (3b): Shining white crystals; m.p. 224–226°C; IR: ν 3124 (NH), 1697 (N-C=O), 1597 cm^{-1} (C=N); ^1H NMR δ 1.78–1.84 (m, 2H, CH_2), 2.72–2.78 (m, 4H, $2CH_2$), 3.72 (s, 2H, SCH_2), 3.76 (s, 3H, OCH_3), 6.64 (d, 1H, C_6H_5, J=2.5 Hz), 6.72–6.75 (m, 1H, C_6H_5), 8.01 (d, 1H, C_6H_5, J=8.6 Hz); ^{13}C NMR δ 173.5 (C=O), 160.3 (C=N), 159.5 (C=N), 142.0, 126.5, 125.0, 128.6 (C_6H_5), 54.9 (OCH_3), 32.7 (SCH_2), 29.7 (CH_2), 26.8 (CH_2), 21.8 (CH_2). Analysis: found for $C_{14}H_{15}N_3O_2S$: C, 58.10; H, 5.14; N, 14.56%, S, 11.02. Calculated: C, 58.23; H, 5.22; N, 14.58; S, 11.17%.

Solvent-free general procedure for synthesis of 4

A mixture of **2** (0.001 mol) and p-substituted phenacyl bromide (0.001 mol) was grinded in a pestle mortar without a solvent for 15–20 min at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was extracted with ethyl acetate. The solvent was removed under reduced pressure to obtain the crude solid that was crystallized from ethanol.

Conventional procedure for synthesis of 4

A mixture of **2** (0.001 mol) and p-substituted phenacyl bromide (0.001 mol) in absolute ethanol (5.0 ml) was stirred at room temperature for 15 min. The resultant solid was filtered, washed with ethanol and crystallized from ethanol.

(*E*)-4-(4-Chlorophenyl)-2-(2-(3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)thiazole (4a′): Dark brown needles; m.p. 232–235°C; IR: ν 3204 (NH), 1605 (C=N), 1481 (C=C), 733 cm^{-1} (C-Cl); ^1H NMR δ 2.02–2.05 (m, 2H, CH_2), 2.81 (t, 2H, CH_2, J=6.1 Hz), 2.91 (t, 2H, CH_2, J=6.6 Hz), 6.75 (s, 1H, CH), 7.19–7.70 (m, 7H, C_6H_5), 8.07–8.09 (m, 1H, C_6H_5), 12.59 (br, 1H, NH exchangeable with D_2O). Analysis: found for $C_{19}H_{16}N_3SCl$: C, 64.56; H, 4.56; N, 11.84; S, 9.04. Calculated: C, 64.48; H, 4.62; N, 11.92; S, 9.14%.

(*E*)-2-(2-(3,4-Dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)-4-(4-nitrophenyl)thiazole (4a″): Light yellow needles; m.p. 195–197°C; IR: ν 3310 (NH), 1597 (C=N), 1558, 1335 (NO_2), 1504 cm^{-1} (C=C); ^1H NMR δ 1.97–2.03 (m, 2H, CH_2), 2.59 (t, 2H, CH_2, J=6.6 Hz), 2.78 (t, 2H, CH_2, J=6.2 Hz), 7.12 (s, 1H, CH), 7.14–8.27 (m, 8H, C_6H_5), 8.80 (br, 1H, NH exchangeable with D_2O). Analysis: found for $C_{19}H_{16}N_4SO_2$: C, 62.65; H, 4.36; N, 15.32; S, 8.76. Calculated: C, 62.76; H, 4.44; N, 15.38; S, 8.89%.

(*E*)-4-(4-Chlorophenyl)-2-(2-(6-methoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)thiazole (4b′): White crystals; m.p. 218–220°C; IR: ν 3040 (NH), 1620 (C=N), 1497 (C=C), 748 cm^{-1} (C-Cl); ^1H NMR δ 1.87 (t, 2H, CH_2, J=6.2 Hz), 2.50 (t, 2H, CH_2, J=6.0 Hz), 2.66–2.74 (m, 4H, $2CH_2$), 3.76 (s, 3H, OCH_3), 6.63 (d, 1H, C_6H_5, J=2.0 Hz), 6.73–6.76 (m, 1H, C_6H_5), 7.12 (s, 1H, CH), 7.35 (d, 1H, C_6H_5, J=8.4 Hz), 7.62 (d, 1H, C_6H_5, J=8.0 Hz), 7.71 (d, 2H, C_6H_5, J=8.5 Hz), 7.98 (br, 1H, NH exchanged with D_2O). Analysis: found for $C_{20}H_{18}N_3SClO$: C, 62.62; H, 4.64; N, 10.92; S, 8.32. Calculated: C, 62.76; H, 4.69; N, 10.98; S, 8.41%.

(*E*)-2-(2-(6-Methoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene)-hydrazinyl)-4-(4-nitrophenyl)thiazole (4b″): Light brown crystals; m.p. 211–212°C; IR: ν 3348 (NH), 1597 (C=N), 1558, 1342 (NO_2), 1512 cm^{-1} (C=C); ^1H NMR δ 1.84–1.90 (m, 2H, CH_2), 2.50 (t, 2H, CH_2, J=6.1 Hz), 2.64–2.72 (m, 4H, $2CH_2$), 3.75 (s, 3H, OCH_3), 6.61 (1H, d, C_6H_5, J=2.4 Hz), 6.72–6.75 (m, 1H, C_6H_5), 7.33 (s, 1H, CH), 7.93 (d, 1H, C_6H_5, J=8.8 Hz), 8.00 (d, 2H, C_6H_5, J=2.0 Hz), 8.16 (d, 2H, C_6H_5, J=2.2 Hz), 10.87 (br, 1H, NH exchanged with D_2O). Analysis: found for $C_{20}H_{18}N_4O_3S$: C, 60.89; H, 4.52; N, 14.18; S, 8.09. Calculated: C, 60.94; H, 4.62; N, 14.12; S, 8.14%.

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