SYNTHESIS AND CHARACTERIZATION OF SOME 4-
SUBSTITUTED THIAZOLIDINONE DERIVATIVES

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This study is concerned with the synthesis and characterization of 4-thiazolidinone derivatives (3a-3h). These compounds were prepared by reacting mercaptoacetic acid with the appropriate Schiff bases (imines) by heating at 50-60 °C in chloroform with moderate yields (51-75 %). The structures of these 4-thiazolidinone derivatives were established on the basis of the spectral studies using IR, 1H-NMR, 13C-NMR, 13C-NMR DEPT and MS.

Introduction

Thiazolidinones are ketone derivatives of the saturated form of thiazole (called thiazolidine). 1,3-Thiazolidin-4-ones are five-membered heterocycles with one sulfur and one nitrogen atom (Figure 1).

Experimental part

The 1H-NMR spectra were recorded using VARIAN spectrophotometer (500 MHz), the 13C-NMR spectra were recorded using VARIAN spectrophotometer (75 MHz). The chemical shift values are expressed in δ(ppm), using tetramethylsilane (TMS) as internal standard and d6-DMSO as the solvent. The mass spectra were recorded at 70eV using HPLC-LCQ Fleet/Thermo Scientific mass spectrophotometer.

3-(4-Bromophenylimino)indolin-2-one (2a)

The compound was prepared by reacting 1.169 g (0.01 mol) of 4-bromoaniline and 1 g (0.01 mol) of indoline-2,3-dione (isatin). Yield = 75 %, m.p. = 273-275 °C, colour orange, IR (KBr disk) 1608 cm⁻¹ (C=N).

2-Chloro-N-(4-chlorobenzylidene)aniline (2b)

The compound was prepared by reacting 1.72 g (0.01 mol) of 2-chloroaniline and 1.4 g (0.01 mol) of 4-chlorobenzaldehyde. Yield = 71.7 %, m.p. = 225-228 °C, colour white, IR (KBr disk) 1614 cm⁻¹ (C=N).

2-(3-Ethoxy-2-hydroxybenzylideneamino)benzoic acid (2c)

The compound was prepared by reacting 0.825 g (0.01 mol) of 2-amino benzoic acid and 1 g (0.01 mol) of 3-ethoxy-2-hydroxybenzaldehyde. Yield = 87.5 %, m.p. = 208-209 °C, colour orange, IR (KBr disk) 1625 cm⁻¹ (C=N).

4-Bromo-2-(4-bromophenyliminomethyl)phenol (2d)

The compound was prepared by reacting 0.85 g (0.01 mol) of 4-bromoaniline and 1 g (0.01 mol) of 5-bromo-2-hydroxybenzaldehyde. Yield = 87.5 %, m.p. = 108-110 °C, colour yellow, IR (KBr disk) 1618 cm⁻¹ (C=N).

Figure 1. Thiazolidinone ring

1,3-Thiazolidin-4-ones belong to the most intensively investigated classes of five-membered heterocyclic compounds, the biological significance of this class of compounds attracted us to work on the synthesis of new derivatives because numerous 4-Thiazolidinones known for their versatile pharmacological activities such as hypnotic, anti-cancer, cardiovascular and antioxidant effect.

General procedure for the preparation of imines (2a-2h)*

Preparation of mono-imines (2a-2d).

In general, the mono-imines (2a-2d) were prepared by the reaction of the mixture of 0.01 mol amine with 0.01 mol aldehyde in 20 ml of methanol or ethanol and 4-6 drops of glacial acetic acid. The reaction mixture was refluxed for 0.5-9 h, and the progress of the reaction was followed by TLC using hexane:ethyl acetate 6:4 as eluent. After completion the reaction, the solvent was evaporated, and the residue was recrystallized from a suitable solvent.

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Preparation of bis-imines (2e-2h)

In general, the bis-imines (2e-2h) were prepared by the reaction of 0.01 mol diamine with 0.02 mol of aldehyde (20 ml) of methanol or ethanol and 4-6 drops of glacial acetic acid. The reaction mixture was refluxed for 1-9 h, with monitoring the progress of the reaction by TLC using hexane:ethyl acetate 6:4 as eluent. After completion the reaction, the solvent was evaporated and the product was recrystallized from a suitable solvent.

2,2’-[Benzene-1,4-diylbis[nitrilomethylidene]]bis(6-ethoxyphenol) (2e)

The compound was prepared by reacting 0.324 g (0.01 mol) of benzene-1,4-diamine with 1 g (0.02 mol) of 3-ethoxy-2-hydroxybenzaldehyde. Yield = 85 %, m.p. = 187-190 °C, colour orange, IR (KBr disk) 1624 cm⁻¹ (C≡N).

2,2’-[Naphthalene-1,5-diylbis[nitrilo(E)methylidene]]bis(6-ethoxyphenol) (2f)

The compound was prepared by reacting 0.452 g (0.01 mol) of naphthalene-1,5-diamine with 0.95g (0.02 mol) of 3-ethoxy-2-hydroxybenzaldehyde. Yield = 96 %, m.p. = 133-136°C, colour chartreuse, IR (KBr disk) 1618 cm⁻¹ (C≡N).

3’-(4-Bromophenyl)spiro[indoline-3,2’-thiazolidine]-2,4’-dione (3a)

The compound was prepared by reaction of 0.5 g (0.01 mol) of 3-((4-bromophenyl)imino)indolin-2-one (2a) and 0.153 g (0.115 ml, 0.01 mol) of thioglycolic acid. Yield=55 %, m.p.=180-182°C, colour: yellow. IR (KBr) 1654 (C=O of thiazolidinone ring ); 3024 cm⁻¹ (Ar-H), 2909 cm⁻¹ (C-H aliphatic), 1393 cm⁻¹ (C-N), 665 cm⁻¹ (C-S), 1H-NMR (500 MHz, DMSO-d₆) δ=4.4 (s, 2H, CH₂); 7.3-8.01 (m, 8H, ArH); 9.27(s, 1H, N-H). 13C NMR (75 MHz, DMSO-d₆) δ=36(s, -CH₂-), 49(s, -C-), 107-139(m, Ar-C); 177(s, CH₂-C=O); 179(s, N-H-C=O).

3-(2-Chlorophenyl)-2-(4-chlorophenyl)thiazolidin-4-one (3b)

The compound was prepared by reaction of 0.8 g (0.01 mol) of 2-chloro-N-(4-chlorobenzylidencyaniline (2b) and 0.29 g (0.02 mol, 0.01 mol) of thioglycolic acid. Yield=61 %, m.p.=248-251 °C, colour: orange. IR (KBr) 1681 (C=O of thiazolidinone ring), 3018 cm⁻¹ (Ar-H), 2930 cm⁻¹ (C-H aliphatic), 1396 cm⁻¹ (C-N), 667 cm⁻¹ (C-S). 1H-NMR (500 MHz, DMSO-d₆) δ=4.3s, (2H, CH₂), 7.2s, (1H, C₃H), 7.4-8.01 (m, 8H, ArH). 13C NMR (75 MHz, DMSO-d₆) δ =36.9(s, -CH₂-), 43(s, -CH-), 111-142(m, Ar-C), 175(s, CH₂-C=O).

2-(3-Ethoxy-2-hydroxyphenyl)-4-oxothiazolidine-3-ylbenzoic acid (3c)

The compound was prepared by reaction of 2-(3-ethoxy-2-hydroxybenzylidencyanilino)benzoic acid (2c) (0.5 g, 0.01 mol) and thioglycolic acid (0.16 g, 0.12 ml, 0.01 mol). Yield=70 %, m.p.=178-180 °C, colour: orange. IR (KBr) 1691 cm⁻¹ (C=O of thiazolidinone ring ); 3014 cm⁻¹ (Ar-H), 2945 cm⁻¹ (C-H aliphatic); 1399 cm⁻¹ (C-N); 637 cm⁻¹ (C-S). 1H-NMR (500 MHz, DMSO-d₆) δ=1.9s, (3H, -CH₂); 4.2 (s, 2H, C₃H); 4.4(s, 2H, -CH₂); 7.20(s, 1H, C₃H); 7.22-8.7 (m, 8H, ArH); 9.59 (s, 1H, O=CH=O). 13C NMR (75 MHz, DMSO-d₆) δ=28(s, CH₂); 35(s, -CH₂-); 40(CH₃O); 44(s, - CH-); 116-153 (m, Ar-C); 172(s, CH₂-C=O); 182(COOH).

2-(5-Bromo-2-hydroxyphenyl)-3-(4-bromophenyl)thiazolidin-4-one (3d)

The compound was prepared by reaction of 0.7 g (0.01 mol) of 4-bromo-2-(((4-bromophenyl)imino)methyl)phenol (2d) and 0.18 g (0.137 ml, 0.01 mol) of thioglycolic acid. Yield=78 %, m.p.=171-172 °C, colour: yellow. IR (KBr) 1685 cm⁻¹ (C=O of thiazolidinone ring ); 3052 cm⁻¹ (Ar-H), 2913 cm⁻¹ (C-H aliphatic); 1385 cm⁻¹ (C=N); 681 cm⁻¹ (C-S). 1H-NMR (500 MHz, DMSO-d₆) δ =4.48 (s, 2H, CH₂H);7.3(s, 1H, C₃H); 7.5-8.01(m, 8H, ArH); 9.62 (s, 1H, Ar-CH₂). 13C NMR (75 MHz, DMSO-d₆) δ=37(s, -CH₂-); 45(s, -CH-); 120-157(Ar-C); 172(s, CH₂-C=O).

Preparation of bis thiazolidinones (3e-3h)

A mixture of appropriate Schiff bases (0.02 mol) (2e-2h) and thioglycolic acid (0.02 mol, 0.40 ml) in a suitable solvent (50 ml) was refluxed for 10-30 h. Water formed during the reaction was removed azeotropically by a Dean-Stark apparatus.
The progress of the reaction was checked by TLC using hexane : ethyl acetate 6:4 as eluent. This mixture of reaction was treated with sodium bicarbonate solution to remove unreacted acid. The obtained solid was washed and purified by recrystallization from dichloromethane to give color powder.

3,3’-(1,4-Phenylene)bis(2-(3-ethoxy-2-hydroxyphenyl)thiazolidin-4-one) (3e)

The compound was prepared by reaction of 0.4 g (0.01 mol) of 2e and 0.18 g (0.139 ml, 0.02 mol) of thiglycolic acid. Yield=71 %, m.p.=155-157 ºC, colour: orange. IR (KBr) 1654 cm⁻¹ (C=O of thiazolidinone ring); 3014 cm⁻¹ (Ar-H), 2920 cm⁻¹ (C-H aliphatic); 1380 cm⁻¹ (C-N); 671 cm⁻¹ (C-S). 1H-NMR (500 MHz, DMSO-d₆) δ = 1.8(s, 6H,-CH₂); 4.0(s, 4H, -CH₂); 4.6 (s, 4H, C₆H); 7.2-8.04(m, 12H, Ar-H); 9.5(s, 2H, Ar-OH). 13C NMR (75 MHz, DMSO-d₆) δ = 29(d, -CH₃); 38(d, -CH₂); 42(d, CH₂O); 53 (d, -CH-); 113-153(m, Ar-C); 178(d, CH₂=C=O).

3,3’-(Naphthalene-1,5-diyl)bis(2-(3-ethoxy-2-hydroxyphenyl)thiazolidin-4-one) (3f)

The compound was prepared by reaction of 0.5 g (0.01 mol) of 2f and 0.1 g (0.153 ml, 0.02 mol) of thiglycolic acid. Yield=59 %, m.p.=154-157 ºC, colour: brown. IR (KBr) 1650 cm⁻¹ (C=O of thiazolidinone ring); 3030 cm⁻¹ (Ar-H), 2911 cm⁻¹ (C-H aliphatic); 1387 cm⁻¹ (C-N); 668 cm⁻¹ (C-S). 1H NMR (500 MHz, DMSO-d₆), δ=1.9(s, 6H, -CH₂); 4.11(s, 4H, -OCH₂); 4.7 (s, 4H, C₆H); 7.4(s, 2H, -C₂H₂); 7.58-8.1(m, 14H, Ar-H); 9.6 (s, 2H, Ar-OH).

2-(3-Ethoxy-2-hydroxyphenyl)-3-(4-(4-(2-(3-ethoxy-2-hydroxyphenyl)-4-oxothiazolidin-3-yl)benzyl)phenyl)thiazolidin-4-one (3g)

The compound was prepared by reaction of 0.5 g (0.01 mol) of 2g and 0.093 g (0.141 ml, 0.02 mol) of thiglycolic acid. Yield=76 %, m.p.=105-107 ºC, colour: orange. IR (KBr) 1654 cm⁻¹ (C=O of thiazolidinone ring); 3027 cm⁻¹ (Ar-H), 2915 cm⁻¹ (C-H aliphatic); 1390 cm⁻¹ (C-N); 672 cm⁻¹ (C-S). 1H-NMR (500 MHz, DMSO-d₆), δ=1.87(s, 6H, -CH₂); 2.9(s, 2H, -CH₂); 4.2(s, 4H, -OCH₂); 4.4 (s, 4H, C₆H); 7.39(s, 2H, -C₂H₂); 7.59-8.16(m, 14H, Ar-H); 9.58 (s, 2H, Ar-OH).

2-(5-Bromo-2-hydroxyphenyl)-3-(4-(4-(R)-2-(5-bromo-2-hydroxyphenyl)-4-oxothiazolidin-3-yl)benzyl)phenyl) thiazolidin-4-one (3h)

The compound was prepared by reaction of 0.4 g (0.01 mol) of 2h and 0.18 g (0.139 ml, 0.02 mol) of thiglycolic acid. Yield=73 %, m.p.=246-247 ºC, colour orange. IR (KBr) 1660 cm⁻¹ (C=O of thiazolidinone ring); 3032 cm⁻¹ (Ar-H), 2918 cm⁻¹ (C-H aliphatic); 1395 cm⁻¹ (C-N); 677 cm⁻¹ (C-S). 1H-NMR (500 MHz, DMSO-d₆), δ=2.8(s, 2H, -CH₂); 4.2(s, 4H, C₆H); 7.1(s, 2H, -C₂H₂); 7.59-8.16(m, 14H, Ar-H); 9.4 (s, 2H, Ar-OH).

RESULTS AND DISCUSSION

Thiazolidinones 3a-3h have been prepared by reaction of the appropriate Schiff bases (2a-2h) with thiglycolic acid in a suitable solvent (benzene or chloroform).

Analysis of infrared spectra

The IR spectra of thiazolidinones 3a-3h in KBr disk show six band groups correspond to the stretching vibration of the aromatic C-H, aliphatic C-H, carbonyl amid group, aromatic C=C, the C-N and bending vibration of S-C bonds, occur within the ranges 3107-2980, 2975-2887, 1691-1654, 1399-1361, 738-654, and 925-617 cm⁻¹ respectively.
The absorption frequencies are affected by substitution of the phenyl ring, and the substitution by electron-donating groups (methylic group decreases) while substitution by electron-withdrawing groups (bromo) increase the vibrational frequencies.

Analysis of $^{13}$C-NMR spectra

The $^{13}$C NMR spectrum of 3a showed thiazolidin-4-one ring signals at δ 36 ppm for C5 carbon 5) at δ 49.94 ppm for C2 atom. A multiplet for aromatic carbons at δ 107-139 ppm, a singlet of carbonyl group at δ 177.06 ppm and a signal for C4 carbon of the ring were observed at δ 179.78 ppm.

Analysis of mass spectra

The mass spectrum of 3a showed the molecular ion peak corresponding to the particular compound at 375 m/z. The fragmentation of 3a gave the peaks at 301, 283, 273, 205, 156, 117, 76 and 64 m/z which attributed to the fragments of $C_{10}H_{11}BrN_{2}O_{5}$, $C_{10}H_{11}N_{2}O_{5}$, $C_{10}H_{11}BrBrN_{2}O_{5}$, $C_{10}H_{11}N_{2}O_{5}$, $C_{10}H_{11}Br_{2}O_{4}$, $C_{10}H_{11}N_{2}O_{5}$, $C_{10}H_{11}O_{4}$, and $C_{10}H_{11}O_{5}$, respectively.

The mass spectrum of 3b showed the molecular ion peak corresponding to the particular compound at 359 m/z, and the fragmentation of 3b gave the peaks at 342, 314, 238, 210, 181 and 154 m/z which attributed to the fragments of $C_{10}H_{11}BrN_{2}O_{5}$, $C_{10}H_{11}NO_{3}$, $C_{10}H_{11}O_{3}$, $C_{10}H_{11}Br_{2}O_{4}$, $C_{10}H_{11}NO_{3}$, $C_{10}H_{11}O_{4}$, and $C_{10}H_{11}O_{5}$, respectively.

The mass spectrum of 3c showed the molecular ion peak corresponding to the particular compound at 429 m/z, and the fragmentation of 3c gave the peaks at 355, 183, 172, 156, 76, 64 m/z which attributed to the fragments of $C_{10}H_{11}Br_{2}O_{4}$, $C_{10}H_{11}BrN_{2}$, $C_{10}H_{11}O_{4}$, $C_{10}H_{11}Br_{2}O$, $C_{10}H_{11}O_{4}$, $C_{10}H_{11}O_{5}$, respectively.

Analysis of $^{13}$C-NMR DEPT spectra

$^{13}$C-NMR DEPT spectra of 3a showed thiazolidin-4-one ring signals at δ 36(negative) 49.94(positive) ppm for C5 carbon C2 carbons, respectively. Multiplet signals for aromatic carbons were observed at δ 107-139 (positive) ppm, while at δ 177.06(positive) and δ 179.78(positive) ppm the carbonyl γ-lactam C4 signals could be observed, respectively.

$^{13}$C-NMR DEPT spectrum of 3b showed the following signals: δ 28.67 (positive) ppm for -CH_{2}, δ 35.67(negative) ppm for C5, δ 40.82(positive) ppm for -OCH_{2}, and δ 44.94 ppm C2, multiplet signals for aromatic carbons at δ 106-153 (positive) ppm, δ 172.90 (positive) ppm for C4 and δ 183.02(positive) ppm for carbonyl of carboxylic group.

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References

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Section A - Research paper

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