One Pot Synthesis of Aryledene Substituted Phenylamino/Hydrazino Methyl 2,4-Dithiazolidinones

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Abstract
Derivatives of novel aryledene substituted phenylamino/hydrazino methyl-2,4-dithiazolidinones 5(a-e) and 6(a-e) were synthesized by a single step through Mannich base. 2,4-dithiazolidinones were condensed with substituted aromatic aldehydes/propanal 2(a-e) and aniline (3) / hydrazine hydrate (4) in methanol as solvent and added a catalytic amount of acetic acid in one pot to yield corresponding title compounds. Chemical structures of these compounds were confirmed by means of FTIR, $^1$H NMR, $^{13}$C NMR mass spectra and their elemental analysis.

Keywords: 2,4-dithiazolidinones, aromatic aldehydes, Mannich base, aniline and hydrazine hydrate.

Introduction
The number of life threatening infections caused by multidrug resistant has reached in alarming level hospital and the community. Infections caused by these organisms create a serious challenge to the scientific community and the need for effective therapy has lead to a reach for novel antimicrobial agents. Over the years excessive use of antimicrobial drugs has to lead to a worldwide phenomenon of antibacterial resistance. This has resulted into an increase in morbidity and mortality and has become a worldwide health issue. As a consequence, the development of new antimicrobial agents is in constant demand. The compounds bearing thiazolidinone nucleus are well known to exhibit versatile range biological activities such as hypnotic activity [1, 2], anti-tubercular [3], anti-convulsant [4, 5], antibacterial [6, 7], anti-cancer [8, 9], anti-histaminic [10, 11], anti-fungal [12], anti-inflammatory [13], anti-viral [14]. A Mannich base is a beta amino ketone, which is formed in the reaction of an amine, formaldehyde and a carbon acid. The Mannich base is an end product in the Mannich reaction which is nucleophilic addition reaction of an non-enalozable aldehyde and any $^1$ and $^2$ amine to produce resonance stabilized imines. The addition of a carbanion from -CH acidic compound to the imine give the Mannich base. The literature reports on the result of a number of biological activities when the substituent and their positions on the thiazolidine ring are changed [15]. In this case, medicinal chemistry is an important aid in the discovery of new active molecules using small heterocyclic rings to increase the biological activity of certain nuclei [16]. Due to the importance of the core of the thiazolidinone ring our research group introduced some of the Mannich base compounds have been synthesized by the reaction of thiazolidinone, aromatic aldehyde and aromatic amines.
Experimental

Materials and Reagents

Melting points were recorded on a Stuart SMP30 melting point apparatus and were uncorrected. Column chromatography was performed using silica–gel (100–200 mesh size) purchased from Thomas Baker, and thin layer chromatography (TLC) was carried out using aluminium sheets pre-coated with silica gel 60F254 purchased from Merck. IR spectra (KBr) were obtained using a Perkin Elmer Spectrum100 FTIR Spectrometer. 1H NMR (400 MHz) and 13C NMR (100 MHz) spectra were recorded on a Bruker WM-400 spectrometer in DMSO-d6 with TMS as an internal standard. Mass spectra (ESI) were carried out on a JEOL SX-102 spectrometer. CHN analysis was done by Carlo Erba EA 1108 automatic elemental analyzer. The chemicals and solvents used were of commercial grade and were used without further purification unless otherwise stated.

Synthesis of Mannich Bases of arylidene substituted phenylamino/hydrazino methyl 2,4-dithiazolidinones (5a–e) and 6(a–e): To a solution of compound 1 (0.01mmol) in dry methanol (10mL), substituted aromatic aldehyde/propanal (2a-e) (0.02mmol) and substituted amine (3)/hydrazine hydrate (4) (0.01mmol) are added slowly at RT with a period of 0.5 h. Then the reaction mixture was heated to reflux for 6 to 8 h (monitored by TLC). After completion of the reaction the reaction was poured into ice cold water solid separated, filtered of and washed with hot water than recrystallized with methanol.

5-Benzylidene-3-(phenyl(phenylamino)methyl)thiazolidin-2,4-dione (5a): Yield: 62 %; IR (KBr, cm⁻¹): 3341, 3031, 2785, 2489, 1736, 1698; 1H NMR (DMSO-d6,400 MHz): δ 6.25 (s, 1H, -CH), 6.98-7.02 (dd, 2H, Ar-H), 7.30-7.34 (m, 5H, Ar-H), 7.40-7.44 (m, 5H, Ar-H), 7.50-7.67 (m, 3H, Ar-H), 8.26 (s, 1H, -CH), 13.02 (s, 1H,-NH) ppm. 13C NMR (DMSO-d6,100 MHz): δ 81.4, 114.5, 117.4, 121.2, 126.2, 126.8, 128.0, 129.2, 129.5, 129.9, 130.6, 132.2, 136.4, 145.2, 149.5, 174.2 ppm. ESI–MS (m/z): 387(M+1). Anal. Calcd. for C26H18N2O2S: C,71.48; H,4.69; N, 7.25; Found: C, 71.40; H, 4.62; N, 7.21.

5-(4-methoxybenzylidene)-3-(4-methoxyphenyl)(phenylamino)methyl)thiazolidin-2,4-dione (5b): Yield: 72.0 %; IR (KBr, cm⁻¹): 3394, 3042, 2984, 1737, 1706; 1H NMR (DMSO-d6,400 MHz): δ 3.89 (s,3H-OCH3), 3.92(s,3H-OCH3), 6.62 (s,1H,CH),6.72-6.78 (dd,2H,Ar-H), 6.89-7.02(dd,2H, Ar-H),7.04-7.08 (dd,2H,Ar-H), 7.28-7.31 (dd, 2H,Ar-H), 7.42-7.46 (dd, 2H,Ar H), 7.80-7.84 (dd, 2H, Ar-H), 8.17 (s,1H,CH) ppm; 13C NMR (DMSO-d6,100 MHz): δ 56.2,56.4, 81.2, 112.4, 114.5, 115.2, 117.0, 121.8, 129.4, 130.2,132.7, 134.6, 137.4, 150.2, 159.4, 162.4, 167.4, 175.2 ppm. ESI–MS (m/z): 447(M+1). Anal. Calcd. for C28H22N2O2S: C,67.25; H,4.97; N, 6.27; Found: C, 69.18; H, 4.89; N, 6.21.

5-(2,3-Dichlorobenzylidene)-3-(2,3-dichlorophenyl)(phenylamino)methyl)thiazolidin-2,4-dione (5c): Yield: 65.0 %; IR (KBr, cm⁻¹): 3385, 3042, 2982, 1747, 1710; 1H NMR (DMSO-d6,400 MHz): δ 6.12 (s, 1H,-CH), 6.82-6.92 (m, 3H, Ar- H), 7.10-7.14 (dd, 2H, Ar- H),7.20-7.24 (dd,2H,Ar-H), 7.26-7.28 (t, 1H, Ar-H),7.30-7.34 (m, 2H, Ar- H), 7.82 (dd,1H,Ar-H), 8.19 (s, 1H,-CH) ppm; 13C NMR (DMSO-d6,100 MHz): δ 79.2, 114.2, 117.2, 121.5, 122.2, 126.4, 127.9, 129.6, 129.9, 130.2, 130.4, 131.4, 133.4, 135. 9, 135.7, 144.5, 146.7, 148.4, 149.2, 167.2, 174.5 ppm; ESI–MS (m/z): 522 (M+1). Anal. Calcd. For C32H18Cl2N2O2S: C, 52.69; H, 2.69; N, 5.34; Found: C, 52.52; H, 2.57; N, 5.21.

5-(2-Hydroxyphenylidene)-3-(2-hydroxyphenyl)(phenylamino)methyl)thiazolidin-2,4-dione (5d):Yield: 69.0 %; IR (KBr, cm⁻¹): 3417, 3029, 2798, 1726, 1686; 1H NMR (DMSO-d6,400 MHz): δ 6.12 (s, 1H,-CH), 6.74-6.82 (m, 3H, Ar-H), 6.89-7.10 (m, 4H, Ar-H), 7.12-7.16 (dd, 2H,Ar-H), 7.29-7.32 (m, 3H, Ar-H), 7.62-7.64 (dd, 2H, Ar-H). 8.24 (s, 1H,-CH) ppm; 13C NMR (DMSO-d6,100 MHz): δ 76.8, 114.5, 115.2, 116.7, 117.2, 118.4, 121.0, 121.6, 122.4, 127.5, 129.4, 129.9, 130.2, 137.5, 147.4, 148.4, 156.2, 156.5, 168.4, 174.4 ppm. ESI–MS (m/z): 419 (M+1). Anal. Calcd. For C26H16N2O2S: C, 66.01; H, 4.32; N, 6.69; Found: C, 65.92; H, 4.32; N, 6.73.

3-(1-Phenylamino)propyl)-5-propyldenetiothiazolidin-2,4-dione (5e):Yield: 59.0 %; IR (KBr, cm⁻¹): 3402, 3014, 2842, 1715, 1690; 1H NMR (DMSO-d6,400 MHz): δ 1.04 (t, 3H, -CH3), 1.14 (t, 3H, -CH3), 1.65 (m, 2H,-CH2), 2.14 (m, 2H,-CH2), 4.62 (t, 1H, -CH), 6.75-6.78 (dd, 2H, Ar- H), 6.80-6.85 (dd,-2H,Ar- H), 7.28-7.32 (dd, 2H, Ar-H), 6.72
(t, 1H, -CH) ppm. $^{13}$C NMR (DMSO-d$_{4}$,100 MHz): $\delta$ 12.4, 13.2, 19.6, 26.7, 80.4, 114.2, 121.8, 127.4, 130.5, 143.2, 148.6, 174.2 ppm. ESI–MS (m/z): 291 (M+1). Anal. Calcd. For C$_{13}$H$_{18}$N$_{2}$O$_{2}$S: C, 62.04; H, 6.25; N, 9.65; Found: C, 61.94; H, 6.23; N, 9.62.

5-Benzylidene-3-(hydrazinyl) phenylmethyl-thiazolidin-2,4-dione (6a): Yield: 71.0 %; IR (KBr, cm-1): 3354, 3380, 3015, 2902, 1720, 1684; $^1$H NMR (DMSO-d$_{4}$,400 MHz): $\delta$ 6.15 (s, 1H, -CH), 6.98-7.04 (d, 2H, Ar-H), 7.30-7.34 (m, 3H, Ar-H), 7.40-7.44 (m, 2H, Ar-H), 7.50-7.67 (m, 3H, Ar-H), 8.16 (s, 1H, -CH), 13.02 (s, 1H, -NH) ppm. $^{13}$C NMR (DMSO-d$_{4}$,100 MHz): $\delta$ 81.4, 117.4, 126.2, 126.8, 128.0, 129.2, 129.5, 130.4, 138.4, 145.2, 145.2, 146.5, 165.2 174.2 ppm. ESI–MS (m/z): 326(M+1). Anal. Calcd. for C$_{17}$H$_{15}$N$_{2}$O$_{2}$S: C,62.75; H,4.65; N, 12.91; Found: C, 62.71; H, 4.60; N, 12.87.

3-(Hydrazinyl)-(4-methoxybenzylidene)thiazolidin-2,4-dione (6b): Yield: 63.0 %; IR (KBr, cm-1): 3350, 3310, 3015, 2902, 1724, 1684; $^1$H NMR (DMSO-d$_{4}$,400 MHz): $\delta$ 3.65 (s, 3H,-OCH$_3$), 3.88 (s,3H,-OCH$_3$), 6.14 (s, 1H,-CH), 7.40-7.45 (dd, 2H, Ar-H), 6.82-6.85 (dd, 2H, Ar-H), 6.99-7.02 (d, 2H, Ar-H), 7.54-7.68 (dd, 2H, Ar-H) 8.10 (s, 1H, -CH) ppm. $^{13}$C NMR (DMSO-d$_{4}$,100 MHz): $\delta$ 56.2, 56.5, 84.2, 115.2, 115.4, 115.9, 117.4, 128.2, 128.4 129.6, 131.2, 136.8, 145.2, 159.5, 162.4, 165.4, 174.2 ppm. ESI–MS (m/z): 386(M+1). Anal. Calcd. for C$_{19}$H$_{19}$N$_{2}$O$_{2}$S: C,59.21; H,4.97; N, 10.90; Found: C, 59.17; H, 4.95; N, 10.87.

5-(2,3-Dichlorobenzylidene)-3-(2,3-dichlorophenyl)(hydrazinyl)methyl)thiazolidin-2,4-dione (6c): Yield: 70.0 %; IR (KBr, cm-1): 3382, 3374, 3052, 1747, 1705; $^1$H NMR (DMSO-d$_{4}$,400 MHz): $\delta$ 6.10 (s, 1H,-CH), 7.12-7.19 (dd, 2H, Ar-H), 7.45-7.49 (d, 1H,Ar-H), 7.52-7.54 (m, 2H, Ar-H), 7.38-7.40 (t,1H,Ar-H),10.82 (s,1H,-CH), 10.98 (s, 2H,-NH$_2$), 13.02-13.04 (br,s,-NH) ppm. $^{13}$C NMR (DMSO-d$_{4}$,100 MHz): $\delta$ 78.2, 117.4, 122.4, 126.0, 127.4, 128.2, 128.7, 129.0, 129.2, 129.6, 130.4, 134.2, 138.4, 143.5, 145.2, 145.7, 167.2, 174.5 ppm. ESI–MS (m/z): 462 (M+1). Anal. Calcd. for C$_{18}$H$_{11}$Cl$_{3}$N$_{2}$O$_{2}$S: C, 44.08; H, 2.39; N, 9.07; Found: C, 44.02; H, 2.34; N, 9.02.

3-Hydrazinyl)-(2-hydroxyphenyl)methyl)-5-(2-hydroxybenzylidene)thiazolidin-2,4-dione (6d): Yield: 57.0 %; IR (KBr, cm-1): 3386, 3354, 3226, 3040, 1720, 1686; $^1$H NMR (DMSO-d$_{4}$,400 MHz): $\delta$ 6.08 (s, 1H,-CH), 6.92-7.02 (m, 4H, Ar-H),7.04-7.16 (dd,2H,Ar-H), 7.26-7.28 (t, 1H, Ar-H), 7.52-7.58 (dd, 1H, Ar-H), 8.30 (s, 1H,-CH) ppm. $^{13}$C NMR (DMSO-d$_{4}$,100 MHz): $\delta$ 117.4, 117.9, 118.3, 119.8, 122.4, 126.9, 127.3, 128.4, 129.2, 129.5, 130.3, 132.4, 145.2, 156.4, 159.8, 166.5, 174.9 ppm. ESI–MS (m/z): 357(M+1). Anal. Calcd. For C$_{18}$H$_{11}$N$_{2}$O$_{2}$S: C, 57.13; H, 4.23; N, 11.76; Found: C, 57.08; H, 4.19; N, 11.72.

3-(1-Hydrazinylpropyl)-5-propylidenethiazolidin-2,4-dione (6e): Yield: 75.0 %; IR (KBr, cm-1): 3348, 3302, 3018, 1714, 1692; $^1$H NMR (DMSO-d$_{4}$,400 MHz): $\delta$ 1.12 (t,3 H, CH$_3$),1.19 (t, 3H,-CH$_3$), 1.84 (m, 2H,-CH$_2$), 2.12 (m, 2H,-CH$_2$), 4.74 (t, 1H,-CH), 6.62 (t, 1H,-CH), $^{13}$C NMR (DMSO-d$_{4}$,100 MHz): $\delta$ 12.6, 13.4, 19.6, 24.4, 82.4, 117.5, 127.4, 143.5,167.4, 174.5 ppm. ESI–MS (m/z): 230 (M+1). Anal. Calcd. For C$_{9}$H$_{18}$N$_{2}$O$_{2}$S: C, 47.14; H, 6.59; N, 18.33; Found: C, 47.10; H, 6.57; N, 18.28.

Results and Discussion:

The reaction sequence employed for the synthesis of aryledene substituted phenylamino/hydrazino methyl-2,4-dithiazolidinones 5(a-e) and 6(a-e) in Figure 1. In this thiazolidine-2,4-dione (1) condensed with various substituted benzaldehyde/propanal 2(a-e) and aniline/ hydrazine hydrate (4) in methanol solvent and a catalytic amount of acetic acid to form corresponding compounds. The structures of synthesized compound 5(a-e) and 6(a-e) were confirmed by their elemental analysis and IR spectra (cm$^{-1}$) absorption bands at 3417-3402 (-NH), 3386-3308 (NH-NH$_2$) and 1747-1686 (-CONH$_2$). Some additional peaks appear due to substitution in aromatic ring showing absorption band at 3341 cm$^{-1}$ (-OH), and 760 cm$^{-1}$ (C-Cl). $^1$H NMR spectra common signals that appear are singlet at $\delta$ 3.82-3.92 correspond to –OCH$_3$, a singlet at $\delta$ 6.25-6.08 for -CH, a multiplet at $\delta$ 6.62-8.30 corresponds to aromatic protons.
Figure 1 Synthesis of aryledene substituted phenylamino/hydrazino methyl-2,4-dithiazolidinones

R = 2a: -C₆H₅; 2b: -C₆H₄-OMe; 2c: -Cl-C₆H₄; 2d: -C₆H₄-OH; 2e: CH₃CH₂-

Conclusions

In conclusion, we developed a series of novel aryledene substituted phenylamino/hydrazino methyl-2,4-dithiazolidinones 5(a-e) and 6(a-e) compounds through Mannich base from 2,4-dithiazolidinones, aromatic aldehydes, aniline/ hydrazine hydrate in a single step. All the synthesized compounds were characterized from IR, ¹H NMR and ¹³C NMR, Mass spectrometry and their elemental analysis.

Acknowledgements

The authors would like to thank the University Grants Commission (UGC-JRF) New Delhi for the financial support to do the research. And also grateful to the Chairman Dr. Ch.V. Purushotham Reddy and Principal Dr K. Veeravenkatiah, Chaitanya Post Graduate College (Autonomous) Hanamkonda, Warangal (TS) for providing research facilities.

References


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