Synthesis and structures of some new thiazolidin-4-ones and thiazolin-4-ones of anticipated biological activity

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Abstract
The condensation of *ω*-(4-formylphenoxy)acetophenone **(3a)** and its 4-bromo derivative **(3b)** with 2-thioxo-1,3-thiazolidin-4-one **(4a)** and 1,3-thiazolidin-2,4-dione **(4b)** in refluxing acetic acid in the presence of sodium acetate gave new *E*-5-arylmethylene-2-thioxo-1,3-thiazolidin-4-one (**5a** and **5b**) and *E*-1,3-thiazolidin-2,4-dione (**5c** and **5d**) derivatives in good yields, respectively. However, treatment of *E*-(**5a** and **5b**) with piperidine (or morpholine) in refluxing ethanol afforded new *E*-5-arylmethylene-2-piperidinyl (or morpholinyl)-1,3-thiazolin-4-one derivatives (**6a-d**). The structures of all new compounds were established from microanalytical and spectral data.

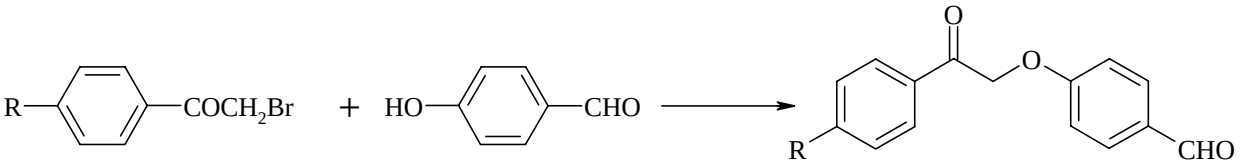
Keywords: 2-Thioxo-1,3-thiazolidin-4-one derivatives, 1,3-thiazolidin-2,4-dione derivatives, 1,3-thiazolin-4-one derivatives

Introduction

Thiazolidin-4-ones and thiazolin-4-ones have been reported to demonstrate a wide range of pharmacological activities, which include antibacterial [1,2], antifungal [2], antimicrobial [3-5], antiviral [6], and anticonvulsant [7] effects. In continuation of our previous studies [8-11] on thiazolidin-4-ones and thiazolin-4-ones, we report here the synthesis of some new thiazolidin-4-one **(5)** and thiazolin-4-one **(6)** derivatives of anticipated biological activity.

Results and Discussion

The aldehydes **3a** and **3b** were prepared by etherfication of *ω*-bromoacetophenone **(1a)** and its 4-bromo derivative **(1b)** with 4-hydroxybenzaldehyde **(2)** in refluxing dry acetone in the presence of anhydrous K_2CO_3.

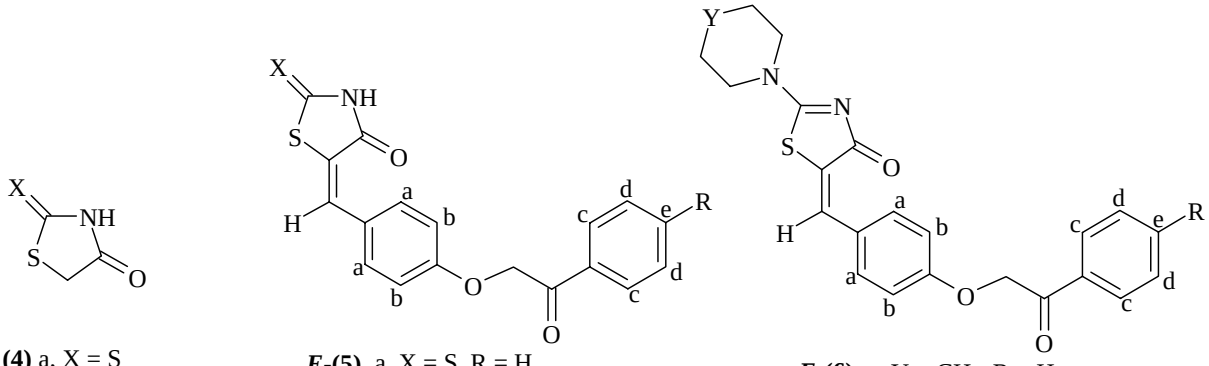


(1) a, R = H
b, R = Br

(2)

(3) a, R = H
b, R = Br

The aldehydes **3a** and **3b** were allowed to condense with 2-thioxo-1,3-thiazolidin-4-one **(4a)** and 1,3-thiazolidin-2,4-dione **(4b)** in refluxing glacial acetic acid in the presence of sodium acetate for 6 h to afford *E*-5-arylmethylene-2-thioxo-1,3-thiazolidin-4-one (**5a** and **5b**) and *E*-5-arylmethylene-1,3-thiazolidin-2,4-dione (**5c** and **5d**) derivatives, respectively, in good yields.



(4) a, X = S
b, X = O

***E*-(5)** a, X = S, R = H
b, X = S, R = Br
c, X = O, R = H
d, X = O, R = Br

***E*-(6)** a, Y = CH_2, R = H
b, Y = CH_2, R = Br
c, Y = O, R = H
d, Y = O, R = Br

The structures of compounds *E*-**(5a-d)** were substantiated from microanalytical and spectral data. Thus, the infrared spectra showed absorptions characteristic for NH, C=O and C=S groups in addition to other absorptions correlated to the assigned structures. Further, the ^{1}H NMR spectra showed signals corresponding to methylene, olefinic, aromatic and NH protons. Also, the EI-MS showed correct molecular ion peaks beside some of the abundant fragments. In addition, evidence to support the structural assignment was gained from the ^{13}C NMR spectrum of compound **5a**.

The reaction of compounds *E*-(**5a** and **5b**) with piperidine and morpholine in refluxing ethanol gave *E*-5-arylmethylene-2-piperidin-1-yl-1,3-thiazolin-4-one *E*-(**6a** and **6b**) and *E*-5-arylmethylene-2-morpholin-4-yl-1,3-thiazolin-4-one *E*-(**6c** and **6d**) derivatives, respectively, in very good yields.

The structures of compounds *E*-(**6a-d**) were elucidated from micro-analytical and spectral data. Thus, the infrared and ^{1}H NMR spectra showed absorptions correlated with the assigned structures. Moreover, the EI-MS showed correct molecular ion peaks in addition to some of the abundant peaks.

The formation of compounds *E*-(**6a-d**) can be explained on the basis of a nucleophilic attack of piperidine or morpholine upon the C=S group followed by elimination of hydrogen sulfide.

The *E*-configuration was assigned to structures **5** and **6** on the basis that a previous study [8] from this laboratory had identified the *E*- and *Z*-isomers of analogous 5-arylmethylene compounds. It was shown that, the olefinic proton of the *Z*-configured isomers were more deshielded by the 4-oxo group of the thiazole moiety as compared with the *E*-counterparts and appeared at lower field ($\delta \approx$ 8.00-8.20 ppm) relative to the *E*-isomer ($\delta \approx$ 7.50-7.80 ppm).

Experimental Section

General Procedures. Melting points are uncorrected. IR spectra were measured on a Unicam SP 1200 spectrometer as KBr discs. Unless otherwise stated, the ^{1}H and ^{13}C NMR spectra were measured in DMSO-d_6 on a Varian Gemini instrument at 200 and 50 MHz, respectively; in both cases, chemical shifts are given in ppm down-field from internal TMS. Mass spectra were recorded on a Shimadzu GC-MS Qp 1000 EX instrument operating at 70 eV.

Etherfication of *ω*-bromoacetophenone (1a) and its 4-bromo derivative (1b) with 4-hydroxybenzaldehyde (2). *ω*-Bromoacetophenone (**1a**) or its 4-bromo derivative (**1b**) (10 mmol) was added to a mixture of 4-hydroxybenzaldehyde (**2**) (1.22 g, 10 mmol) and anhydrous K_2CO_3 (2.90 g, 30 mmol) in dry acetone (50 ml). The mixture was refluxed on a water bath for 5-6 h, poured into iced cold water and then extracted with ether. The ether layer was dried by anhydrous Na_2SO_4 and rotatory evaporated to give **3a** and **3b**.

***ω*-(4-Formylphenoxy)acetophenone (3a).** Brown viscous oil, 2.16 g (90% yield. IR ($CHCl_3$): $\overline{\nu}$ = 3057 (CH_{arom}), 2940, 2913 and 2850 (CH_{aliph}), 1695 (C=O), 1589 and 1515 (C=C), 820 ($\delta_{2\text{-}H}$), 750 and 690 cm^{-1} ($\delta_{5\text{-}H}$).

***ω*-(4-Formylphenoxy)-4-bromoacetophenone (3b).** Brown viscous oil, 2.93 g (92% yield). IR ($CHCl_3$): $\overline{\nu}$ = 3069 (CH_{arom}), 2958, 2928 and 2869 (CH_{aliph}), 1699 (C=O), 1598 and 1510 (C=C), 826 cm^{-1} (δ_{2-H})

Condensation of aldehydes 3a and 3b with 2-thioxo-1,3-thiazolidin-4-one (4a) and 1,3-thiazolidin-2,4-dione (4b). To a solution of **4a** or **4b** (10 mmol) in glacial acetic acid (25 ml) and anhydrous sodium acetate (2.10 g, 30 mmol) was added aldehyde **3a** or **3b** (10 mmol). The reaction mixture was refluxed for 6 h, cooled and then poured into iced cold water. The precipitated solid was filtered off and recrystalised from the proper solvent to give *E*-(**5a-d**).

***E*-5-[(4-Benzoylmethoxy)phenylmethylene]-2-thioxo-1,3-thiazolidin-4-one (5a).** Pale yellow crystals, 2.30 g (65% yield), m.p.: 235-237°C (acetic acid). IR: $\overline{\nu}$ = 3240 (NH), 2920 (CH_{arom}), 2840 and 2740 (CH_{aliph}), 1710 (sh) and 1690 (C=O), 1585 (C=C), 1205 (S–CS–N), 830 ($\delta_{2\text{-}H}$), 760 and 680 cm^{-1} ($\delta_{5\text{-}H}$). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.39 (s, CH_2), 7.15 (dd, 2, H_b, J = 7.4 and 1.2 Hz), 7.55 (dd, 2, H_a, J = 7.4 and 1.2 Hz), 7.58 (apparent t, 2, H_d, J = 8.0 Hz), 7.59 (s, =CH), 7.71 (apparent t, 1, H_e, J = 8.0 Hz), 8.09 (dd, 2, H_c, J = 7.6 and 1.2 Hz), 13.75 (brs, NH,

exchangeable with D_2O). EI-MS m/e (%): 357 ($M^{+\cdot}$ + 2, 10), 356 ($M^{+\cdot}$ + 1, 36), 355 ($M^{+\cdot}$, 39), 270 (5), 269 (23), 268 ($M^{+\cdot}$ – HNCS & CO, 19), 149 (9), 106 (8), 105 ($C_6H_5CO^{+\cdot}$, base), 89 (12), 77 (35). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 71.8 (CH_2), 117.3, 127.4, 129.3, 130.4, 133.0, 134.0, 135.4 and 135.7 (sp^2 carbons), 161.5 (C=O), 195.5 (C=S). Anal. Calcd. for $C_{18}H_{13}NO_3S_2$ (355.430) requires : C, 60.82; H, 3.68; N, 3.94; S, 18.04%. Found: C, 60.61, H, 3.57; N, 3.68; S, 17.89%.

***E*-5-[4-(4-Bromobenzoylmethoxy)phenylmethylene]-2-thioxo-1,3-thiazo-lidin-4-one (5b).** Pale yellow crystals, 3.0 g (70% yield), m.p.: 253-254°C (ethanol). IR: $\bar{\nu}$ = 3175 (NH), 3085 (CH_{arom}), 2918 and 2850 (CH_{aliph}), 1706 (C=O), 1587 (C=C), 1210 (S-CS-N), 820 cm^{-1} ($\delta_{2\text{-H}}$). ^{1}H NMR (DMSO-d_6): δ 5.73 (s, CH_2), 7.02 (dd, 2, H_b, J = 7.6 and 1.2 Hz), 7.43 (dd, 2, H_a, J = 7.6 and 1.2 Hz), 7.50 (s, =CH), 7.61 (dd, 2, H_d, J = 7.6 and 1.2 Hz), 7.99 (dd, 2, H_c, J = 7.6 and 1.2 Hz), 13.20 (brs, NH, exchangeable with D_2O). EI-MS m/e (%): 435 ($M^{+\cdot}$ + 2, 16), 433 ($M^{+\cdot}$, 18), 348 (18), 346 ($M^{+\cdot}$ –HNCS & CO, 16), 186 (10), 185 (72), 184 (14), 183 (4-$BrC_6H_4CO^{+\cdot}$, base), 157 (17), 155 (13), 152 (16), 151 (96), 133 (11), 90 (11), 79 (11), 77 (31), 76 (28), 75 (22), 74 (13), 65 (22), 64 (44), 63 (43), 62 (15), 61 (14). Anal. Calcd. for $C_{18}H_{12}BrNO_3S_2$ (434.322) requires: C, 49.77; H, 2.78; N, 3.22; S, 14.76. Found: C, 49.63; H, 2.75; N, 3.09; S, 14.58%.

***E*-5-[(4-Benzoylmethoxy)phenylmethylene]-1,3-thiazolidin-2,4-dione (5c).** pale yellow crystals, 2.44 g (72% yield), m.p.: 212-214°C (ethanol). IR: $\bar{\nu}$ = 3160 (NH), 3030 (CH_{arom}), 2910, 2840 and 2770 (CH_{aliph}), 1728, 1710 (sh) and 1690 (C=O), 1585 (C=C), 830 ($\delta_{2\text{-H}}$), 755 and 690 cm^{-1} ($\delta_{5\text{-H}}$). ^{1}H NMR (DMSO-d_6): δ 5.62 (s, CH_2), 7.17 (dd, 2, H_b, J = 7.8 and 1.2 Hz), 7.55 – 7.76 (m, 6, 2H_a, 2H_d, H_e and =CH), 8.05 (dd, 2, H_c, J = 8.0 and 1.2 Hz), 13.06 (brs, NH, exchangeable with D_2O). EI-MS m/e (%): 341 ($M^{+\cdot}$ + 2, 5), 340 ($M^{+\cdot}$ + 1, 24), 399 ($M^{+\cdot}$, 27), 269 (10), 268 ($M^{+\cdot}$ – HNCO & CO, 16), 149 (5), 106 (8), 105 ($C_6H_5CO^{+\cdot}$, base), 77 (32). Anal. Calcd. for $C_{18}H_{13}NO_4S$ (339.370) requires: C, 63.70; H, 3.86; N, 4.12; S, 9.44%. Found: C, 63.58; H, 3.74; N, 4.03; S, 9.27%.

***E*-5-[4-(4-(4-Bromobenzoylmethoxy)phenylmethylene]-1,3-thiazolidin-2,4-dione (5d).** Pale yellow crystals, 3.13 g (75% yield), m.p.: 220-222°C (benzene/ethanol). IR: $\bar{\nu}$ = 3250 (NH), 3037 (CH_{arom}), 2921 and 2852 (CH_{aliph}), 1729 (sh) and 1703 (C=O), 1610 (C=C), 815 cm^{-1} ($\delta_{2\text{-H}}$). ^{1}H NMR (DMSO-d_6): 5.58 (s, CH_2), 7.15 (dd, 2, H_b, J = 7.8 and 1.2 Hz), 7.54 (dd, 2, H_a, J = 7.8 and 1.2 Hz), 7.60 (s, =CH), 7.70 (dd, 2, H_d, J = 7.8 and 1.2 Hz), 8.12 (dd, 2, H_c, J = 7.8 and 1.2 Hz), 13.45 (brs, NH, exchangeable with D_2O). EI-MS m/e (%): 419 ($M^{+\cdot}$ + 2, 31), 418 ($M^{+\cdot}$ +1, 13), 417 ($M^{+\cdot}$, 16), 348 ($M^{+\cdot}$ + 2 – HNCO & CO, 16), 346 ($M^{+\cdot}$–HNCO& CO, 24), 342 (18), 221 (25), 200 (37), 198 (17), 186 (10), 185 (60), 183 (4-$BrC_6H_4CO^{+\cdot}$, 63), 157 (50), 162 (11), 156 (14), 155 (35), 151 (19), 150 (C_6H_6OS, base), 135 (12), 134 (10), 121 (13), 115 (15), 89 (14), 76 (13), 75 (14), 69 (18), 60 (70). Anal. Calcd. for $C_{18}H_{12}BrNO_4S$ (418.262) requires: C, 51.68; H, 2.89; N, 3.34; S, 7.66%. Found: C, 51.53; H, 2.81; N, 3.29; S, 7.48%.

Reaction of 2-thioxo-1,3-thiazolidin-4-one derivatives *E*-(5a and 5b) with piperidine and morpholine. Piperidine or morpholine (6 mmol) was added to a solution of *E*-**(5a)** or *E*-**(5b)** (5 mmol) in ethanol (30 ml). The mixture was refluxed on a water bath until evolution of hydrogen sulfide ceased (5-6 h), whereupon it was cooled and then concentrated to afford *E*-**(6a-d)**.

***E*-5-[(4-Benzoylmethoxy)phenylmethylene]-2-piperidin-1-yl-1,3-thiazolin-4-one (6a).** Orange crystals, 1.66 (82% yield), m.p.: 164-166°C (ethanol). IR: $\bar{\nu}$ = 3070 (CH_{arom}), 2950 and 2880 (CH_{aliph}), 1710 and 1690 (C=O), 1605 (C=N), 1570 (C=C), 830 (δ_{2-H}), 760 and 690 cm^{-1} (δ_{5-H}). ^{1}H NMR (DMSO-d_6): δ 1.66 (brs, 6, $-(CH_2)_3-$), 3.44 (brs, 2, N–CH_2), 3.82 (brs, 2, N–CH_2), 5.65 (s, 2, CH_2), 7.06 (dd, 2, H_b, J = 9.0 and 1.8 Hz), 7.54 (dd, 2, H_a, J = 8.7 and 1.8 Hz), 7.56 (s, 1, =CH), 7.75 (dd, 2, H_d, J = 8.7 and 1.8 Hz), 7.89 (apparent t, 1, H_e, J = 8.7 Hz), 7.92 (dd, 2, H_c, J = 8.7 and 1.8 Hz). EI-MS m/e (%): 408 ($M^{+\cdot}$ + 2, 3), 406 ($M^{+\cdot}$, 59), 268 ($M^{+\cdot}$ – $C_7H_{10}N_2O$, 54), 150 (13), 105 ($C_6H_5CO^{+\cdot}$, base), 77 (45). Anal. Calcd. for $C_{23}H_{22}N_2O_3S$ (406.502) requires: C, 67.95; H, 5.45; N, 6.89; S, 7.88%. Found: C, 67.63; H, 5.21; N, 6.58; S, 7.74%.

***E*-5-[4-(4-Bromobenzoylmethoxy)phenylmethylene]-2-peperidin-1-yl-1,3-thiazolin-4-one (6b).** Orange crystals, ≈ 2.0 g (85% yield), m.p.: 178-180°C (ethanol). IR: $\bar{\nu}$ = 3050 (CH_{arom}), 2945, 2850 and 2760 (CH_{aliph}), 1705 and 2690 (C=O), 1603 (C=N), 1559 (C=C), 825 cm^{-1} (δ_{2-H}). ^{1}H NMR (DMSO-d_6): δ 1.62 (brs, 6, -$(CH_2)_3$-), 3.43 (brs, 2, N-CH_2), 3.85 (brs, 2, N-CH_2), 5.71 (s, 2, CH_2), 7.10 (dd, 2, H_b, J = 8.2 and 1.2 Hz), 7.62 (dd, 2, H_a, J = 8.0 and 1.2 Hz), 7.73 (s, 1, =CH), 7.79 (dd, 2, H_d, J = 8.7 and 1.6 Hz), 8.38 (dd, 2, H_c, J = 8.4 and 1.8 Hz). EI-MS m/e (%):486 ($M^{+\cdot}$ + 2, 25), 484 ($M^{+\cdot}$, 25) ,348 (41), 347 (47), 346 ($M^{+\cdot}$ – $C_7H_{10}N_2O$, 47), 289 (12), 288 (41), 185 (29), 183 (4-$BrC_6H_4CO^{+\cdot}$, 24), 151 (11), 150 (C_8H_6OS, base), 149 (28), 121 (11), 110(12), 109(15), 91(11), 76(11), 69(12), 55(11). Anal. Calcd. for $C_{23}H_{21}BrN_2O_3S$ (485.394) requires : C, 56.91; H, 4.36; N, 5.77; S, 6.60%. Found: C, 56.68; H, 4.29; N, 5.53; S, 6.41%.

***E*-5-[4-(Benzoylmethoxy)phenylmethylene]-2-morpholin-4-yl-1,3-thiazolin-4-one (6c).** Orange crystals, 1.69 g (83% yield), m.p.: 191-193°C (ethanol). IR: $\bar{\nu}$ = 3060 (CH_{arom}), 2940, 2870 and 2750 (CH_{aliph}), 1710 and 1695 (C=O), 1605 (C=N), 1560 (C=C), 836 (δ_{2-H}), 760 and 695 cm^{-1} (δ_{5-H}). ^{1}H NMR (DMSO-d_6): δ 3.50 (brs, 2, N-CH_2), 3.72 (brs, 4, OCH_2 and N-CH_2), 3.82 (brs, 2, OCH_2), 5.71 (s, 2, CH_2), 7.12 (dd, 2, H_b, J = 8.7 and 1.2 Hz), 7.65 (dd, 2, H_b, J = 8.7 and 1.2 Hz), 7.73 (s, 1, =CH), 7.93 (dd, 2, H_d, J = 8.7 and 1.2 Hz), 8.03-8.16 (m, 3, H_c and H_e). EI-MS m/e (%): 410 ($M^{+\cdot}$ + 2, 1), 408 ($M^{+\cdot}$, 34), 268 ($M^{+\cdot}$ – $C_6H_8N_2O_2$, 65), 150 (18), 105 ($C_6H_5CO^{+\cdot}$, base), 77(60). Anal. Calcd. for $C_{22}H_{20}N_2O_4S$ (408.458) requires : C, 64.69; H, 4.93; N, 6.85; S, 7.84%. Found: C, 64.43; H, 4.82; N,6.71; S, 7.59%.

***E*-5-[4-(4-Bromobenzoylmethoxy)phenylmethylene]-2-morpholin-4-yl-1,3-thiazolin-4-one (6d).** Orange crystals, ≈ 2.0 g (84% yield), m.p.: 220-223°C (ethanol). IR: $\bar{\nu}$: 3063 (CH_{arom}), 2920 and 2853 (CH_{aliph}), 1698 and 1687 (C=O), 1598 (C=N), 1553 (C=C), 820 cm^{-1} (δ_{2-H}). ^{1}H NMR (DMSO-d_6): δ 3.62 (brs, 2, NCH_2), 3.71 (brs, 4, NCH_2 and OCH_2), 3.83 (brs, 2, OCH_2), 5.61 (s, 2, CH_2), 7.11 (dd, 2, H_b, J = 9.0 and 1.8 Hz), 7.57 (dd, 2, H_a, J = 9.0 and 1.8 Hz), 7.61 (s, 1, =CH), 7.80 (dd. 2, H_d, J = 8.4 and 1.8 Hz), 7.95 (dd, 2, H_c, J = 8.4 and 1.8 Hz). EI-MS m/e (%): 488 ($M^{+\cdot}$ +2, 20), 486 ($M^{+\cdot}$, 21), 349 (18), 348 (55), 347 (14) 346 ($M^{+\cdot}$ – $C_6H_8N_2O_2$, 67),

345 (34), 291 (11), 290 (31), 186 (15), 185 (14), 182 (19), 171 (15), 152 (10), 151 (12), 150 (C_8H_6OS, base), 121 (15), 112 (16), 90 (10), 89 (15). Anal. Calcd. for $C_{22}H_{19}BrN_2O_4S$ (487.370) requires: C, 54.21; H, 3.92; N, 5.74; S, 6.57%. Found: C, 54.05; H, 3.73; N, 5.51; S, 6.32%.

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