Heterocyclic Letters
Vol. 9| No.3|273-277|May-July|2019
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS OF 2-(4-METHOXY-PHENYL)-3-(9-METHYL-5,6-DIHYDRO-4H-3-THIA-1-AZA-BENZO[E]AZULEN-2-YL)-THIAZOLIDIN-4-ONE AND DERIVATIVES FROM BENZOSUBERONES

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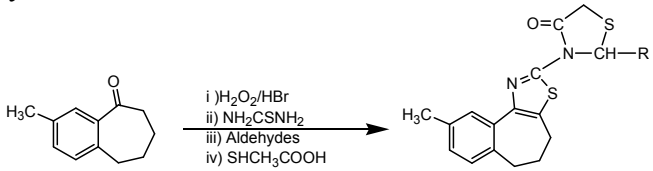
Abstract:
Reaction of 2-methyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one (**1**) with hydrogen bromide and hydrogen peroxide gave 6-bromo-2-methyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one (**2**). The compound **2** on cycloaddition with thiourea gave 5,6-dihydro-4*H*-benzo[6,7]cycloheptane[d][2,3]thiazol-2-amine (**3**). Compound **3**, when treated with various aromatic aldehydes in absolute ethanol and a few drops of glacial acetic acid, resulted the corresponding enamine derivatives **4a-f**. Compounds **4a-f** on cyclocondensation with thioglycolic acid in the presence of anhydrous zinc chloride resulting in the formation of thiazolidinone ring systems **5a-f**.



Key words: benzosuberone, thiazolidinone, fungicides, bactericide, type 2 diabetes mellitus.

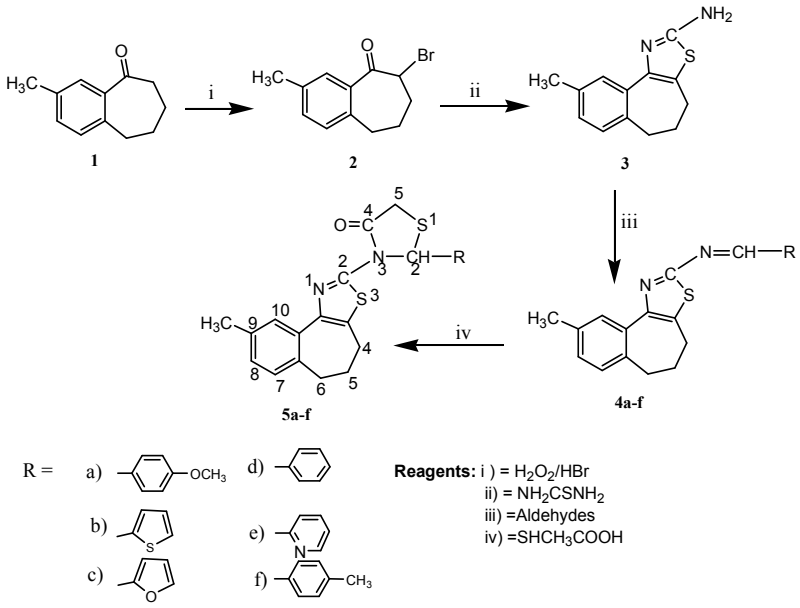
Introduction:

Thiazolidinones are important compounds due to their broad range of biological activities[I-V]. 2-Imino-thiazolidinone have been found to have anti-fungal activity[VI-VIII]. The rhodanines, 2-thioxo-4-thiazolidinones, appear to be 2-(4-Methoxy-phenyl)-3-(9-methyl-5,6-dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl)-thiazolidin-4-one and derivatives are very important as far as biocidal potency is concerned, the importance of which has been stressed in many fungicides and bactericide[IX-XII]. Joyeau *et al*[XIII]., have been synthesized pyrrolidinyl- and thiazolidinyl-dipeptide derivatives as inhibitors of the Tc 80 prolyl oligopeptidase from *Trypanosoma cruzi*. The thiazolidinones are a new class of compounds for treatment of type 2 diabetes mellitus. The efficacy of these drugs in decreasing plasma glucose levels is well established[XIV-XIX]. In view of the potential biological activity of 4-thiazolidinones[XX-XXV] and in continuation of our interest in the synthesis of biologically active fused heterocycles[XXVI-XXVIII]. It was thought worthwhile to prepare the title compounds with the hope that these new

ring systems may prove to be biologically active; the title compounds were prepared according to scheme I.

Results and Discussion :

Reaction of 2-methyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one (**1**) with hydrogen bromide and hydrogen peroxide gave 6-bromo-2-methyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one (**2**). The compound **2** on cycloaddition with thiourea gave 5,6-dihydro-4*H*-benzo[6,7]cycloheptane[d][2,3]thiazol-2-amine (**3**) in 70% yield. The IR spectrum of **3** showed characteristic band at 3282 cm^{-1} (NH_2) and also the disappearance of the C=O absorption band of **2**. Compound **3**, when treated with various aromatic aldehydes in absolute ethanol and a few drops of glacial acetic acid, resulted the corresponding enamine derivatives **4a-f**. Absorption band at 1595-1620 cm^{-1} (C=N) and the disappearance of NH_2 absorption bands at 3282 cm^{-1} in the IR spectrum and a sharp singlet at δ 9.10 (s, 1H, N=CH-Ar) in ^1H NMR spectrum clearly indicate the formation of the compounds **4a-f**. Compounds **4a-f** on cyclocondensation with thioglycolic acid in the presence of anhydrous zinc chloride resulting in the formation of thiazolidinone ring systems **5a-f**. IR spectrum of **5a-f** exhibited sharp absorption bands due to C=O (1691 cm^{-1}) and C-S (1172 cm^{-1}), which indicates the presence of β-thiolactum ring. Further, appearance of signals at δ 6.65 (1H, s, S-CH-Ar), 3.80 (1H, d, J = 16.60 Hz, S-CH_2) and 4.20 (1H, d, J = 16.60 Hz, S-CH_2) in the ^1H NMR spectrum confirms the presence of thiazolidinone ring.



Scheme-1

Experimental :

Melting points were determined using Gallankamp apparatus and are uncorrected. IR spectra were recorded on a FT-IR 1605 Perkin-Elmer; 1H NMR in CDCl3 on a Varian FT-80A spectrometer with TMS as an internal standard; and mass spectra on a VG-micro mass 7070H mass spectrometer. TLC was run on Silica gel G coated plates and iodine vapor as visualizing agent.

6-bromo-2-methyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one (2) : To a well stirred solution of hydrogen peroxide (70% aq 0.058 gm. 0.0017 mole) and hydrobromic acid (48%

aq 0.13 gm. 0.0017 mole) in methanol, 2-methyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one (**1**) (0.3 gm 0.0017 mole) in methanol was added drop by drop at 0-5^{0}C during 10 minutes. The reaction mixture was stirred at room temperature for 30 minutes and then refluxed for 24 hrs. The solution was concentrated to dryness in vacuo and the residue was dissolved in water extracted with chloroform. The organic layer was worked up in the usual way to give gummy compound which was purified by column chromatography using silica gel with ethyl acetate-petroleum ether as eluent (1:9) to give semi-solid **2**: yield: 50%; IR (KBr): 1730 cm^{-1}(C=O); ^{1}H NMR ($CDCl_3$): δ 1.90-2.05 (2H, q, 7-CH_2), 2.30 (3H, s, CH_3), 2.80-3.10 (4H, m, 8 & 9-CH_2), 4.85 (1H, t, Br-CH), 6.80 (1H, s, Ar-CH), 7.50 (1H, d, Ar-CH) 7.50 (1H, d, Ar-CH; Anal. Found: C, 56.97; H, 5.11. $C_{12}H_{13}OBr$ requires C, 56.99; H, 5.13%.

9-methyl-5,6-dihydro-4*H*-benzo[6,7]cycloheptane[d][2,3]thiazol-2-amine (3) : A mixture of compound **2** (0.00015 mole)**,** thiourea (0.00015 mole) in water (5 mL) was heated under reflux for 1 hr. After completion of the reaction as monitored by TLC, it was neutralized with 5% of ammonia and extracted with chloroform (20 mL). The organic layer was worked up in the usual way and the crude product was purified by column chromatography over silica gel with ethyl acetate-petroleum ether as eluent (1:9) to afford **3**: yield: 70%; m.p. 120-125^{0}C; IR (KBr): 3282 cm^{-1} (NH_2); ^{1}H NMR ($CDCl_3$): δ 2.00-2.18 (2H, m, 4-CH_2), 2.20-2.35 (3H, s, 9-CH_3), 2.70-2.90 (2H, m, 5-CH_2), 2.70-2.90 (2H, m, 6-CH_2), 4.80-5.10 (2H, bs, -NH_2), 6.80-6.90 (1H, s, Ar-CH), 7.60-7.70 (1H, d, Ar-CH) 7.60-7.70 (1H, d, Ar-CH; MS: m/z 230 ($M^{+\cdot}$); Anal. Found: C, 67.80; H, 6.06; N, 12.15. $C_{12}H_{14}N_2S$ requires C, 67.82; H, 6.08; N, 12.17%.

N-(9-methyl-5,6-dihydro-4*H*-benzo[6,7]cyclohepta[d][1,3]thiazol-2-yl)4-methoxy phenylmethanimine 4a-f : General procedure: A mixture of 9-methyl-5,6-dihydro-4*H*-benzo[6,7]cycloheptane [d][2,3]thiazol-2-amine (**3**) (0.0002 mole), 4-methoxy benzaldehyde (0.0002 mole) in ethanol and few drops of glacial acetic acid was refluxed for 10-12 hrs. After completion of the reaction, as monitored by TLC, the excess solvent was distilled off and residue was poured into ice-water. It was then extracted with chloroform, concentrated in vacuo and chromatographed over silica gel with ethyl acetate-petroleum ether as eluent (1:9) afforded **4a**: Yield: 50%; m.p. 118-120^{0}C; IR (KBr): 1595 (C=N), 1526 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$): δ 2.10-2.22 (2H, m, 4-CH_2), 2.30 (3H, s, 9-CH_3), 2.75-2.80 (2H, m, 5-CH_2), 2.95-3.00 (2H, m, 6-CH_2), 3.90 (3H, s, -OCH_3), 6.80-8.10 (7H, m, Ar-CH), 9.05 (1H, s, N=CH); Anal. Found: C, 72.39; H, 5.72; N, 8.02. $C_{21}H_{20}N_2SO$ requires C, 72.41; H, 5.74; N, 8.04%.

Compound 4b: Yield: 53%; m.p. 150-151^{0}C; Anal. Found: C, 66.64; H, 4.91; N, 8.62. $C_{18}H_{16}N_2S_2$ requires C, 66.66.90; H, 4.93; N, 8.64%. **Compound 4c**: Yield: 58%; m.p. 170-172^{0}C; Anal. Found: C, 70.10; H, 5.17; N, 9.07. $C_{18}H_{16}N_2OS$ requires C, 70.12; H, 5.19; N, 9.09%.

Compound 4d: Yield: 55%; m.p. 158-160^{0}C; Anal. Found: C, 75.45; H, 5.64; N, 8.78. $C_{20}H_{18}N_2S$ requires C, 75.47; H, 5.66; N, 8.80%.

Compound 4e: Yield: 50%; m.p. 160-162^{0}C; Anal. Found: C, 71.45; H, 5.30; N, 13.14. $C_{19}H_{17}N_3S$ requires C, 71.47; H, 5.32; N, 13.16%.

Compound 4f: Yield: 45%; m.p. 150-152^{0}C; Anal. Found: C, 70.88; H, 6.00; N, 8.41. $C_{21}H_{20}N_2S$ requires C, 75.90; H, 6.02; N, 8.43%.

3-(9^1-methyl-5^1,6^1-dihydro-4*H*-benzo[6^1,7^1]cyclohepta[d][1,3] thizol-2-yl)2-(4^{11}-methoxy phenyl)-1,3-thiazolan-4-one 5a : General procedure: To a stirred solution of **5a** (0.00055 mole) in absolute ethanol, containing a pinch of anhydrous $ZnCl_2$ and thioglycolic acid (0.0011 mole) was refluxed for 1 hr. The excess

solvent was removed in vacuo and diluted with water. The reaction mixture was then extracted with chloroform and evaporated to give a crude residue which was purified by column chromatography over silica gel with ethyl acetate-petroleum ether (1:9) as eluent to afford **5a**.Yield: 50%; m.p. 68-70^{0}C; IR (KBr): 1610 (C=N), 1691 (C=O), 1172 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.90-2.00 (2H, m, 4-CH_2), 2.20 (3H, s, 9-CH_3), 2.65-2.75 (2H, m, 5-CH_2), 2.82-3.00 (2H, m, 6-CH_2), 3.76 (3H, s, OCH_3), 3.82-3.90 (1H, d, *J*=16.60-S-CH_2), 4.10-4.19 (1H, d, *J*=16.60-s-CH_2), 6.65 (1H, s, S-CH), 6.81-7.42 (7H, m, Ar-CH); MS: m/z 422 ($M^{+\cdot}$); Anal. Found: C, 65.38; H, 5.19; N, 6.62. $C_{23}H_{22}N_2O_2S_2$ requires C, 65.40; H, 5.21; N, 6.63%.

Compound 5b: Yield: 54%; m.p.150-153^{0}C; IR (KBr): 1610 (C=N), 1696 (C=O), 1171 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.00-2.20 (2H, m, 4-CH_2), 2.25 (3H, s, 9-CH_3), 2.70-2.80 (2H, m, 5-CH_2), 2.95-3.15 (2H, m, 6-CH_2), 3.75-3.85 (1H, d, *J*=16.60-S-CH_2), 4.15-4.25 (1H, d, *J*=16.60-S-CH_2), 6.50 (1H, s, -S-CH), 6.90-7.70 (6H, m, Ar-CH); MS: m/z 398 ($M^{+\cdot}$); Anal. Found: C, 60.28; H, 4.50; N, 7.01. $C_{20}H_{18}N_2S_3O$ requires C, 60.30; H, 4.52; N, 7.03%.

Compound 5c: Yield: 53%; m.p.160-162^{0}C; IR (KBr): 1613 (C=N), 1689 (C=O), 1172 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.00-2.10 (2H, m, 4-CH_2), 2.20-2.30 (3H, s, 9-CH_3), 2.70-2.80 (2H, m, 5-CH_2), 2.90-3.01 (2H, m, 6-CH_2), 3.65-3.81 (1H, d, *J*=16.60-S-CH_2), 4.19-4.25 (1H, d, *J*=16.60-S-CH_2), 6.30 (1H, s, -S-CH), 6.40-7.65 (6H, m, Ar-CH); MS: m/z 382 ($M^{+\cdot}$); Anal. Found: C, 62.80; H, 4.68; N, 7.30. $C_{20}H_{18}N_2S_2O_2$ requires C, 62.82; H, 4.71; N, 7.32%.

Compound 5d: Yield: 40%; m.p. 91-92^{0}C; IR (KBr): 1654 (C=N), 1696 (C=O), 1171 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.85-1.95 (2H, m, 4-CH_2), 2.10-2.30 (3H, s, 9-CH_3), 2.65-2.78 (2H, m, 5-CH_2), 2.82-3.10 (2H, m, 6-CH_2), 3.81-3.95 (1H, d, *J*=16.60-S-CH_2), 4.15-4.20 (1H, d, *J*=16.60-S-CH_2), 6.65 (1H, s, -S-CH), 6.85 (1H, s, Ar-CH), 7.20-7.50 (8H, m, Ar-CH); Anal. Found: C, 67.32; H, 5.08; N, 7.12. $C_{22}H_{20}N_2S_2O$ requires C, 67.34; H, 5.10; N, 7.14%.

Compound 5e: Yield: 44%; m.p.150-152^{0}C; IR (KBr): 1617 (C=N), 1686 (C=O), 1170 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.90-2.20 (2H, m, 4-CH_2), 2.10-2.40 (3H, s, 9-CH_3), 2.65-2.80 (2H, m, 5-CH_2), 2.85-3.15 (2H, m, 6-CH_2), 3.70-3.80 (1H, d, *J*=16.60-S-CH_2), 4.25-4.40 (1H, d, *J*=16.60-S-CH_2), 6.60 (1H, s, -S-CH), 6.80-7.80 (6H, m, Ar-CH) and 8.60 (1H, d, N=CH); Anal. Found: C, 64.10; H, 4.81; N, 10.66. $C_{21}H_{19}N_3S_2O$ requires C, 64.12; H, 4.83; N, 10.68%.

Compound 5f: Yield: 43%; m.p.125-127^{0}C; IR (KBr): 1620 (C=N), 1695 (C=O), 1172 (C-S) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.85-2.05 (2H, m, 4-CH_2), 2.10-2.25 (3H, s, 9-CH_3), 2.30-2.40 (3H, s, Ph-CH_3), 2.68-2.80 (2H, m, 5-CH_2), 2.89-3.05 (2H, m, 6-CH_2), 3.80-3.90 (1H, d, *J*=16.60-S-CH_2), 4.08-4.18 (1H, d, *J*=16.60-S-CH_2), 6.65 (1H, s, -S-CH), 6.80-7.40 (7H, m, Ar-CH); Anal. Found: C, 67.96; H, 5.39; N, 6.87. $C_{23}H_{22}N_2S_2O$ requires C, 67.98; H, 5.41; N, 6.89%.

Acknowledgments: This work was funded of Srizanta Bio Lab, Hyderabad,Telangana State, India.

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Received on May 27, 2019.