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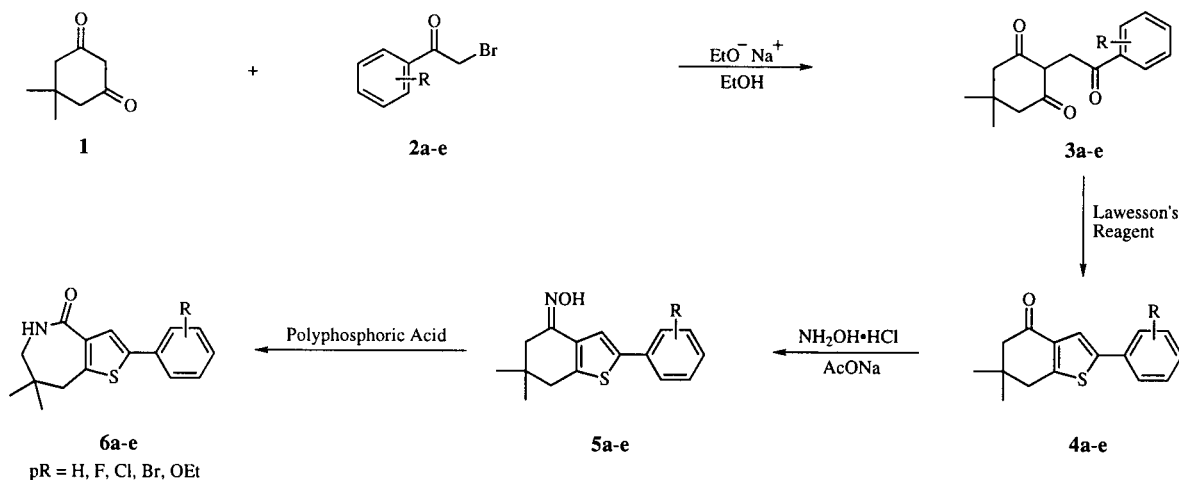
A novel synthesis of substituted thieno[3,2-*c*]azepinones is described. This new approach uses 5,5-dimethyl-1,3-cyclohexanedione (dimedone) as the starting material. Oxime intermediates are obtained in three steps from the aforementioned diketone. Using these intermediates, the title compounds are synthesized in moderate yields.

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There have been several reports on the biological aspects of benzazepines and its analogs. Some of these compounds are known to have activities as anticancerigen [3], calcium antagonists [4] and central nervous system depressor [5]. In spite of the fact that the thienozepines are analogs of benzazepines there are few reports about medicinal activities of thienozepines [6]. There are also few references for the preparation of this class of heterocycles. Usually the synthesis of this nucleus is accomplished in one step by ring cyclization of the corresponding 2,3-disubstituted thiophene or in two steps: first ring cyclization to thienocyclohexanone following by ring expansion of the Schmidt type [7]. Recently we have developed one method to get furo[3,2-*c*]azepinones or pyrrolo[3,2-*c*]azepinones using the 5,5-dimethyl-1,3-cyclohexanedione (dimedone) **1** as the starting material [8]. In the present study we applied the same approach to prepare a series of 2-aryl-7,7-dimethyl-5,6,7,8-tetrahydrothieno[3,2-*c*]azepin-4-ones **6a-e** (Scheme 1, R = Br, Cl, F, OEt, H). Compounds **2a-e** have been prepared following a

reported procedure [9]. The alkylation of 5,5-dimethylcyclohexane-1,3-dione with substituted 2-bromoacetophenones, in the presence of sodium ethoxide in ethanol [10], furnishes the corresponding tricarbonyl compounds **3a-e**. Reactions of **3a-e** with Lawesson's reagent in refluxing toluene [11] furnished tetrahydrobenzothiophen-4-ones **4a-e**. Structural assignment of **4a-e** derivatives was made on spectroscopic grounds. In the infrared spectra of **4a-e** the appearance of absorption bands at 1672-1666 cm^{-1} was consistent with the presence of a cyclic ketone group [8]. In the ^1H nmr spectra of **4a-e** derivatives the presence of a three-proton singlet at δ 1.13-1.18 confirmed the presence of the two methyl substituents at the C-6 position; two two-proton singlets at δ 2.40-2.43 and δ 2.89-2.94 were assigned to the methylene protons at C-5 and C-7. A downfield one-proton singlet at δ 7.52-7.59 was assigned to the methine proton attached to C-3. The remaining aromatic protons in compounds **4a-e** appeared at δ 7.27-7.54. Further evidence of the structure of **4a-e** is derived from their mass spectral data. All the compounds showed the

Scheme 1



molecular ion as their base peak. Treatment of **4a-e** with hydroxylamine hydrochloride in refluxing ethanol led directly to the formation of the corresponding mixture of oximes **5a-e** (*syn/anti*). The structure of this mixture followed from spectroscopic data; of particular note a one proton signal at δ 7.61-7.52 in the ^1H nmr spectrum of **5a-e** could be assigned to the 3-thiophene-proton of the *syn* oximes [12] while the 3-thiophene-proton of the *anti* oximes give rise to a signal at δ 7.54-7.34. The presence of molecular ions and m/z (M^+-16) and (M^+-30) fragments in the mass spectrum of compounds **5a-e** was consistent with their structures [13]. The *regiospecific* ring expansion to the desired thieno[3,2-*c*]azepinones **6a-e** was accomplished by reaction of **5a-e** with polyphosphoric acid at 80° (Beckman conditions). In agreement with the suggested structure, the ir spectra of all the compounds **6a-e** exhibited a strong amide carbonyl band at $1650\text{-}1640\text{ cm}^{-1}$. Its ^1H nmr spectra showed a singlet at δ 1.11 for the methyl protons of C-7 as well as one singlet of the proton attached to C-3 at δ 7.54. Two two-proton signals at δ 2.75 (singlet) and δ 3.92 (doublet, $J = 6\text{ Hz}$) were assigned to the methylene protons at C-8 and C-6. One proton signal at δ 6.35 (triplet, $J = 6\text{ Hz}$) was assigned to the NH-proton. The remaining aromatic protons appeared at δ 7.32-7.59. The mass spectrum of these compounds showed their molecular ions as their base peak and its fragmentation is according to the assigned structure.

Further investigations on the synthesis of novel compounds from 1,3-cyclohexanedione are presently being carried out.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Nicolet FT-55X spectrophotometer. The ^1H nmr spectra were determined on a Varian FT-200 and Varian FT-300 instrument. All nmr spectra were obtained with the pulse sequence as part of the spectrometer's software and was determined in deuteriochloroform solution containing tetramethylsilane as the internal standard with chemical shifts (δ) expressed downfield from tetramethylsilane. Mass spectra were recorded using Jeol SX-102 mass spectrometer using the direct inlet system with an ionization energy of 70 eV, an emission current of 100 μA and ion source temperature of 150° . Column chromatography was carried out on Merck Kieselgel 60 F_{254} . Thin layer chromatography was carried out on Merck Kieselgel 60 PF_{254} . All of the solvents used were dried over an appropriate drying agent.

The starting 4-*R*-2-bromoacetophenones **2a-e** were prepared following a reported procedure from 4-*R*-acetophenones and bromine in acetic acid [9]. The structures of compounds **2a-e** were supported by ir, ^1H nmr and mass spectral data which are similar to those reported. Compounds 2-[2'-(4-*R*-phenyl)-2'-oxoethyl]-5,5-dimethyl-1,3-cyclohexanediones **3a-e** have been prepared following our reported procedure [10] from dimedone

1 and 4-*R*-2-bromoacetophenones **2a-e**. They have not been previously obtained and their structures were supported by spectral data and elemental analyses.

2-[2'-(4-Bromophenyl)-2'-oxoethyl]-5,5-dimethyl-1,3-cyclohexanedione **3a**.

This compound was obtained as a colorless solid (46%), $148\text{-}150^\circ$; ir (chloroform): $1690\text{ (CO)}\text{ cm}^{-1}$; ms: m/z 336 (M^+ , 33%).

Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{O}_3\text{Br}$: C, 56.99; H, 5.08. Found: C, 57.04; H, 5.10.

2-[2'-(4-Chlorophenyl)-2'-oxoethyl]-5,5-dimethyl-1,3-cyclohexanedione **3b**.

This compound was obtained as a colorless solid (47%), $145\text{-}147^\circ$; ir (chloroform): $1692\text{ (CO)}\text{ cm}^{-1}$; ms: m/z 292 (M^+ , 100%).

Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{O}_3\text{Cl}$: C, 65.64; H, 5.85. Found: C, 65.68; H, 5.83.

2-[2'-(4-Fluorophenyl)-2'-oxoethyl]-5,5-dimethyl-1,3-cyclohexanedione **3c**.

This compound was obtained as a colorless solid (51%), $152\text{-}154^\circ$; ir (chloroform): $1691\text{ (CO)}\text{ cm}^{-1}$; ms: m/z 276 (M^+ , 33%).

Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{O}_3\text{F}$: C, 69.55; H, 6.20. Found: C, 65.60; H, 6.18.

2-[2'-(4-Ethoxyphenyl)-2'-oxoethyl]-5,5-dimethyl-1,3-cyclohexanedione **3d**.

This compound was obtained as a colorless solid (47%), $138\text{-}140^\circ$; ir (chloroform): $1690\text{ (CO)}\text{ cm}^{-1}$; ms: m/z 302 (M^+ , 23%).

Anal. Calcd. for $\text{C}_{18}\text{H}_{22}\text{O}_2$: C, 71.50; H, 7.34. Found: C, 71.54; H, 7.32.

2-[2'-Phenyl-2'-oxoethyl]-5,5-dimethyl-1,3-cyclohexanedione **3e**.

This compound was obtained as a colorless solid (47%), $170\text{-}172^\circ$; ir (chloroform): $1686\text{ (CO)}\text{ cm}^{-1}$; ms: m/z 258 (M^+ , 30%).

Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{O}_3$: C, 74.39; H, 7.02. Found: C, 74.40; H, 7.03.

Synthesis of 2-(4-*R*-Phenyl)-6,6-dimethyl-4,5,6,7-tetrahydrobenzothiophen-4-ones **4a-e**.

2-(4-Bromophenyl)-6,6-dimethyl-4,5,6,7-tetrahydrobenzothiophen-4-one **4a**.

General Procedure ($R = \text{bromo}$).

A solution of 0.1 g of **3a** (0.29 mmole) and 0.08 g of Lawesson's reagent (0.19 mmole) in toluene (5 ml) was heated under reflux for 6 hours. After removal of the solvent *in vacuo*, the residual oil was chromatographed on silica gel column. Elution with hexane/dichloromethane, 90/10 afforded **4a** as a colorless solid (hexane) (0.04 g, 40%), mp $130\text{-}132^\circ$; ir (chloroform): $1672\text{ (CO)}\text{ cm}^{-1}$; ^1H nmr: δ 1.18 (s, 6H, 2 x $\text{CH}_3\text{-C}_6$), 2.43 (s, 2H, H5), 2.94 (s, 2H, H7), 7.59 (s, 1H, H3), 7.45-7.54 (m, 4H, Ar-H); ms: m/z 334 (M^+ , 100%).

Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{OSBr}$: C, 57.32; H, 4.51. Found: C, 57.35; H, 4.50.

2-(4-Chlorophenyl)-6,6-dimethyl-4,5,6,7-tetrahydrobenzothiophen-4-one **4b**.

This compound was obtained as a colorless solid (hexane) (50%), mp $128\text{-}130^\circ$; ir (chloroform): $1665\text{ (CO)}\text{ cm}^{-1}$; ^1H nmr: δ 1.11 (s, 6H, 2 x $\text{CH}_3\text{-C}_6$), 2.40 (s, 2H, H5), 2.91 (s, 2H, H7),

7.52 (s, 1H, H3), 7.34-7.48 (m, 4H, Ar-H); ms: m/z 290 (M⁺, 100%).

Anal. Calcd. for C₁₆H₁₅OSCl: C, 66.08; H, 5.20. Found: C, 66.11; H, 5.18.

2-(4-Fluorophenyl)-6,6-dimethyl-4,5,6,7-tetrahydrobenzothio-phen-4-one **4c**.

This compound was obtained as a colorless solid (hexane) (45%), mp 98-100°; ir (chloroform): 1667 (CO) cm⁻¹; ¹H nmr: δ 1.15 (s, 6H, 2 x CH₃-C6), 2.43 (s, 2H, H5), 2.90 (s, 2H, H7), 7.56 (s, 1H, H3), 7.49-7.52 (m, 4H, Ar-H); ms: m/z 274 (M⁺, 100%).

Anal. Calcd. for C₁₆H₁₅OSF: C, 70.04; H, 5.51. Found: C, 70.07; H, 5.50.

2-(4-Ethoxyphenyl)-6,6-dimethyl-4,5,6,7-tetrahydrobenzothio-phen-4-one **4d**.

This compound was obtained as a colorless solid (hexane) (45%), mp 115-117°; ir (chloroform): 1669 (CO) cm⁻¹; ¹H nmr: δ 1.16 (s, 6H, 2 x CH₃-C6), 1.5 (t, J = 7.3 Hz, 3H, CH₃-CH₂), 2.42 (s, 2H, H5), 2.90 (s, 2H, H7), 4.06 (q, J = 7.3 Hz, 2H, -CH₂-O-), 7.50 (s, 1H, H3), 7.25-7.45 (m, 4H, Ar-H); ms: m/z 300 (M⁺, 100%).

Anal. Calcd. for C₁₈H₂₀O₂S: C, 71.96; H, 6.71. Found: C, 72.0; H, 6.70.

2-Phenyl-6,6-dimethyl-4,5,6,7-tetrahydrobenzothio-phen-4-one **4e**.

This compound was obtained as a colorless solid (hexane) (49%), mp 124-126°; ir (chloroform): 1668 (CO) cm⁻¹; ¹H nmr: δ 1.13 (s, 6H, 2 x CH₃-C6), 2.41 (s, 2H, H5), 2.90 (s, 2H, H7), 7.56 (s, 1H, H3), 7.27-7.53 (m, 4H, Ar-H); ms: m/z 256 (M⁺, 100%).

Anal. Calcd. for C₁₆H₁₆OS: C, 74.96; H, 6.29. Found: C, 74.99; H, 6.30.

Synthesis of 2-(4-R-Phenyl)-6,6-dimethyl-4,5,6,7-tetrahydrobenzothio-phen-4-one Oximes (*syn/anti*) **5a-e**.

2-(4-Bromophenyl)-6,6-dimethyl-4,5,6,7-tetrahydrobenzothio-phen-4-one Oxime **5a**.

General Procedure (R = Br).

To a solution of **4a** (0.1 g, 2.9 mmoles) dissolved in 50 ml of ethanol was added a solution of 1.08 g (15 mmoles) of hydroxylamine hydrochloride dissolved in 30 ml of 5 M sodium acetate and the mixture was stirred on a steam-bath for two hours. Removal of the solvent under reduced pressure gave an amorphous solid that was separated by column chromatography (silica gel, dichloromethane) to give 0.082 g (85%) of **5a** mp 225-226°; ir (chloroform): 3288 (OH) cm⁻¹; ¹H nmr: δ 1.07 (s, 6H, 2 x CH₃-C6, *syn*), 1.08 (s, 6H, 2 x CH₃-C6, *anti*), 2.59 (s, 2H, H5, *syn*), 2.68 (s, 2H, H5, *anti*), 2.38 (s, 2H, H7), 7.34 (s, 1H, H3, *anti*), 7.52 (s, 1H, H3, *syn*), 7.41-7.47 (m, 4H, Ar-H); ms: m/z 350.2701 (M⁺, 100%).

2-(4-Chlorophenyl)-6,6-dimethyl-4,5,6,7-tetrahydrobenzothio-phen-4-one Oxime **5b**.

This compound was obtained as a colorless solid (hexane) (90%), mp 208-210°; ir (chloroform): 3231 (OH) cm⁻¹; ¹H nmr: δ 1.05 (s, 6H, 2 x CH₃-C6, *syn*), 1.06 (s, 6H, 2 x CH₃-C6, *anti*), 2.33 (s, 2H, H5, *syn*), 2.58 (s, 2H, H5, *anti*), 2.30 (s, 2H, H7), 7.35 (s, 1H, H3, *anti*), 7.54 (s, 1H, H3, *syn*), 7.39-7.59 (m, 4H, Ar-H); ms: m/z 305.8142 (M⁺, 100%).

2-(4-Fluorophenyl)-6,6-dimethyl-4,5,6,7-tetrahydrobenzothio-phen-4-one Oxime **5c**.

This compound was obtained as a colorless solid (hexane) (97%), mp 230-232°; ir (chloroform): 3276 (OH) cm⁻¹; ¹H nmr: δ 1.09 (s, 6H, 2 x CH₃-C6, *syn*), 1.10 (s, 6H, 2 x CH₃-C6, *anti*), 2.43 (s, 2H, H5, *syn*), 2.52 (s, 2H, H5, *anti*), 2.32 (s, 2H, H7), 7.36 (s, 1H, H3, *anti*), 7.51 (s, 1H, H3, *syn*), 7.42-7.50 (m, 4H, Ar-H); ms: m/z 289.3612 (M⁺, 100%).

2-(4-Ethoxyphenyl)-6,6-dimethyl-4,5,6,7-tetrahydrobenzothio-phen-4-one Oxime **5d**.

This compound was obtained as a colorless solid (hexane) (80%), mp 201-203°; ir (chloroform): 3355 (OH) cm⁻¹; ¹H nmr: δ 1.11 (s, 6H, 2 x CH₃-C6, *syn*), 1.13 (s, 6H, 2 x CH₃-C6, *anti*), 1.19 (t, J = 7.3 Hz, 3H, CH₃-CH₂), 2.61 (s, 2H, H5, *syn*), 2.66 (s, 2H, H5, *anti*), 2.37 (s, 2H, H7), 4.0 (q, J = 7.3 Hz, 2H, -CH₂-O-), 7.34 (s, 1H, H3, *anti*), 7.51 (s, 1H, H3, *syn*), 7.42-7.49 (m, 4H, Ar-H); ms: m/z 315.4211 (M⁺, 100%).

2-Phenyl-6,6-dimethyl-4,5,6,7-tetrahydrobenzothio-phen-4-one Oxime **5e**.

This compound was obtained as a colorless solid (hexane) (90%), mp 210-212°; ir (chloroform): 3283 (OH) cm⁻¹; ¹H nmr: δ 1.08 (s, 6H, 2 x CH₃-C6, *syn*), 1.09 (s, 6H, 2 x CH₃-C6, *anti*), 2.35 (s, 2H, H5, *syn*), 2.44 (s, 2H, H5, *anti*), 2.34 (s, 2H, H7), 7.54 (s, 1H, H3, *anti*), 7.61 (s, 1H, H3, *syn*), 7.32-7.42 (m, 4H, Ar-H); ms: m/z 271.3712 (M⁺, 100%).

Synthesis of 2-(4-R-Phenyl)-7,7-dimethyl-5,6,7,8-tetrahydrothieno[3,2-c]azepin-4-ones **6a-e**.

2-(4-Bromophenyl)-7,7-dimethyl-5,6,7,8-tetrahydrothieno[3,2-c]azepin-4-one **6a**.

General Procedure (R= Br).

To a mixture of phosphorus pentoxide (1.8 g, 7.0 mmoles) and phosphoric acid (1 ml) was added 0.05 g (0.14 mmole) of **5a** and the mixture was mechanically stirred at 80-100° for 3 hours. The mixture was treated with ice-water, neutralized with sodium carbonate and extracted with methylene chloride (3 x 5 ml); the combined organic extracts were washed with water (2 x 10 ml) and dried (sodium sulfate). Removal of the solvent under reduced pressure gave an amorphous solid that was separated by column chromatography (silica gel, methylene chloride) to give 0.025 g (50%) of **6a** mp 245-247°; ir (chloroform): 1665 (CO) cm⁻¹; ¹H nmr: δ 1.11 (s, 6H, 2 x CH₃-C7), 2.75 (s, 2H, H8), 2.92 (d, 2H, J = 6 Hz, H6), 6.35 (t, 1H, 6 Hz, NH), 7.54 (s, 1H, H3), 7.42-7.49 (m, 4H, Ar-H); ms: m/z 349 (M⁺, 100%).

Anal. Calcd. for C₁₆H₁₆ONSB: C, 54.96; H, 4.61; N, 4.0. Found: C, 54.99; H, 4.60; N, 4.02.

2-(4-Chlorophenyl)-7,7-dimethyl-5,6,7,8-tetrahydrothieno[3,2-c]azepin-4-one **6b**.

This compound was obtained as a colorless solid (50%), mp 232-234°; ir (chloroform): 1664 (CO) cm⁻¹; ¹H nmr: δ 1.08 (s, 6H, 2 x CH₃-C7), 2.76 (s, 2H, H8), 2.92 (d, 2H, J = 6 Hz, H6), 6.25 (t, 1H, J = 6 Hz, NH), 7.55 (s, 1H, H3), 7.37-7.48 (m, 4H, Ar-H); ms: m/z 305 (M⁺, 100%).

Anal. Calcd. for C₁₆H₁₆ONSCl: C, 62.84; H, 5.27; N, 4.58. Found: C, 62.87; H, 5.26; N, 4.60.

2-(4-Fluorophenyl)-7,7-dimethyl-5,6,7,8-tetrahydrothieno[3,2-*c*]-azepin-4-one **6c**.

This compound was obtained as a colorless solid (60%), mp 210-212°; ir (chloroform): 1667 (CO) cm^{-1} ; ^1H nmr: δ 1.09 (s, 6H, 2 x CH_3 -C7), 2.76 (s, 2H, H8), 2.92 (d, 2H, J = 6 Hz, H6), 6.50 (t, 1H, J = 6 Hz, NH), 7.52 (s, 1H, H3), 7.04-7.49 (m, 4H, Ar-H); ms: m/z 289 (M^+ , 100%).

Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{ONS}$: C, 66.41; H, 5.57; N, 4.84. Found: C, 66.44; H, 5.56; N, 4.86.

2-(4-Ethoxyphenyl)-7,7-dimethyl-5,6,7,8-tetrahydrothieno[3,2-*c*]-azepin-4-one **6d**.

This compound was obtained as a colorless solid (60%), mp 220-222°; ir (chloroform): 1663 (CO) cm^{-1} ; ^1H nmr: δ 1.22 (s, 6H, 2 x CH_3 -C7), 1.60 (t, J = 7.3 Hz, 3H, CH_3 -CH₂), 2.70 (s, 2H, H8), 2.89 (d, 2H, J = 6 Hz, H6), 4.07 (q, J = 7.3 Hz, 2H, CH_2 -O-), 6.80 (t, 1H, J = 6 Hz, NH), 7.52 (s, 1H, H3), 7.35-7.46 (m, 4H, Ar-H); ms: m/z 315 (M^+ , 100%).

Anal. Calcd. for $\text{C}_{18}\text{H}_{21}\text{O}_2\text{NS}$: C, 68.54; H, 6.71; N, 4.44. Found: C, 68.56; H, 6.70; N, 4.46.

2-Phenyl-7,7-dimethyl-5,6,7,8-tetrahydrothieno[3,2-*c*]azepin-4-one **6e**.

This compound was obtained as a colorless solid (50%), mp 247-249°; ir (chloroform): 1669 (CO) cm^{-1} ; ^1H nmr: δ 1.25 (s, 6H, 2 x CH_3 -C7), 2.70 (s, 2H, H8), 2.88 (d, 2H, J = 6 Hz, H6), 6.75 (t, 1H, J = 6 Hz, NH), 7.55 (s, 1H, H3), 7.34-7.49 (m, 4H, Ar-H); ms: m/z 271 (M^+ , 100%).

Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{ONS}$: C, 70.81; H, 6.32; N, 5.16. Found: C, 70.83; H, 6.30; N, 5.17.

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