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AQUEOUS BASE INDUCED SELECTIVE TRANSFORMATIONS OF 3-(2-OXOALKYL) THIAZOLIUM CATIONS

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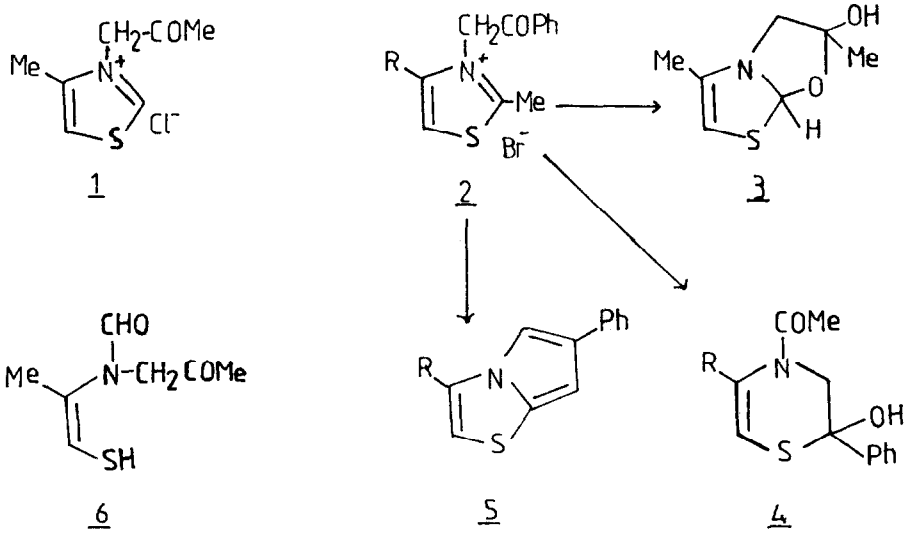
Abstract : The title compounds react with aqueous sodium hydroxide (i) 2%, 1 equiv., (ii) 2%, 2 equiv., and (iii) 8%, 2 equiv., to give 2-hydroxy-2-alkyl/aryl-4-formyl-2, 3-dihydro-1, 4-thiazines (**7**), 2-alkyl/aryl-4-formyl-1, 4-thiazines (**8**) and 2-aroylthiazoles (**9**), respectively. **7** and **8** with 8% aqueous sodium hydroxide form **9**, but **7** with 2% aqueous sodium hydroxide or TFA give **8**.

Hydrolytic ring opening of thiazolium cation of thiamine to a formyl amino thiol species[1] has prompted a variety of investigations of synthetically useful transformations of thiazolium cations[2,3,4]. In one category of these studies, 3-acetonyl-4-methylthiazolium chloride (**1a**) with aqueous sodium hydroxide and 2-methyl-3-phenacylthiazolium chloride (**2** ; R=H) with aqueous sodium hydrogen carbonate and with aqueous sodium or potassium hydroxide are reported[5] to form the bicyclic compound(**3**), 2-hydroxy-2-phenyl-4-acetyl-2, 3-dihydro-1, 4-thiazine (**4**; R=H)[6] and 3-phenylpyrrolo [1, 2-b] thiazole (**5**; R=H)[7], respectively. Now, we have found that the use of appropriate amount and concentration of aqueous sodium hydroxide solution directs the transformations of 3-(2-oxoalkyl) thiazolium cations in synthetically useful manner to 1, 4-thiazines or 2-aroylthiazole derivatives selectively.

3-Acetonyl-4-methylthiazolium chloride (**1a**) with 2% aqueous sodium hydroxide (1 equiv.)- methanol solution gives a product, 76%, m.p. 115°C, M^+ m/z 173. It could be assigned either of the three isomeric structures **7a**, **3** or **6**. The appearance of one carbonyl absorption band at 1660 cm^{-1} in its i.r. spectrum rules out structures **6** and **3** for this compound. Its ^1H NMR spectrum, which is quite similar to the one reported[8] for the compound **3** shows two signals at δ 8.00 and 8.68 in 1 : 3 ratio due to CHO group. The ortho ester H of the structure **3** is not expected to appear at such a downfield chemical shift. Similarly, its ^{13}C NMR spectrum, shows two downfield signals at δ 159. 50 and 160. 60 for C=O carbon(s). These data apparently corroborate structure 2-hydroxy-2, 5-dimethyl-4-formyl-2, 3-dihydro-1, 4-thiazine (**7a**) for this product. Further in the ^1H and ^{13}C NMR spectra, the presence of two signals each for C(2)-CH_3 (δH 1.67, 1.71 ; δC 20. 90, 20.95), N-CH_3 (δ H 2.19, 2.29; δC 27.50, 27.52), CH_2 (δH 3.08, 4.70 and 3.20, 3.62 AB quartets; δC 49.76, 51.00) and CHO groups (δH 8.00, 8.68 ; δ C 159.50, 160.60) shows that compound **7a** exists in two isomeric forms which stem from hindered rotation of formyl group around amide bond (fig. 1).

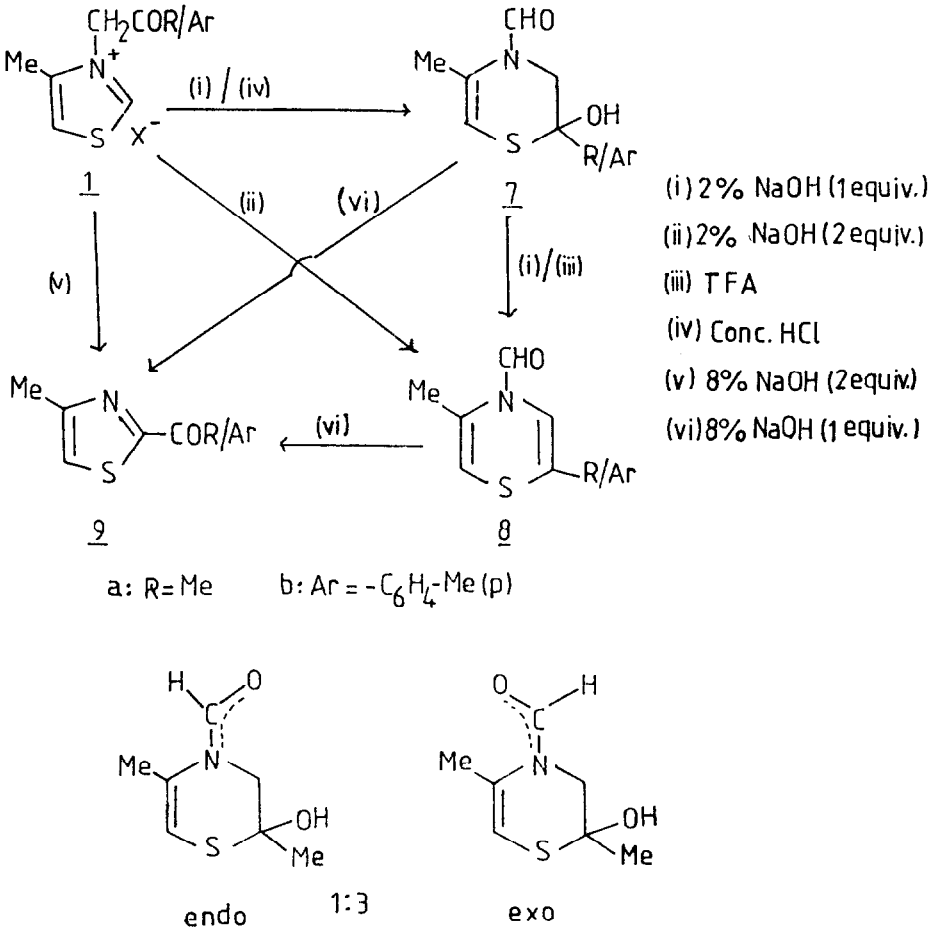
Compound **1a**, even on stirring in aqueous methanol or in aqueous sodium hydroxide (0.1-1%, 1 equiv.) - methanol or in concentrated HCl-methanol solution provides compound **7a** in 72-82% yields. However, **1a** with 2 equiv. of 2% aqueous sodium hydroxide in methanol gives a product, 69%, m.p. 68°C, M^+m/z 155. Its ^1H NMR

spectrum shows the presence of two CH_3, two olefinic H and one CHO group. Its off resonance proton decoupled ^{13}C NMR spectrum exhibits two quartets (CH_3) at δ 20.07 and 27.32, three doublets (CH) at δ 102.30, 117.22, and 155.92. Form these data, it could be assigned the structure, 2, 5-dimethyl-4-formyl-1, 4-thiazine (**8a**) which has also been obtained by reaction of **7a** either with 2% aqueous sodium hydroxide (1equiv.)-methanol or with trifluoroacetic acid (TFA). On keeping, compound **8a** partially changes to **7a**. Further, **1a** with 8% aqueous sodium hydroxide (2 equiv.)-methanol solution gives a product, a liquid, M^+ m/z 141 in 74% yield. Its ^1H NMR spectrum displays two CH_3 singlets at δ 2.50 and 2.70 alongwith olefinic 'H' at δ 7.20, but shows absence of olefinic 'H' present in compound **8a**. From these data, it could be assigned the structure 2-acetyl-4-methylthiazole (**9a**)[9] which could also be obtained by stirring compound **7a** or **8a** in 8% aqueous sodium hydroxide (1 equiv.)-methanol solution.



Similarly, 3-(4-methylphenacyl)-4-methylthiazolium chloride (**1b**) on stirring in methanol solution containing (i) aqueous 2% sodium hydroxide (1 equiv.), (ii) aqueous 2% sodium hydroxide (2 equiv.) and (iii) aqueous 8% sodium hydroxide (2 equiv.) gives compounds **7b**, **8b** and **9b**, respectively. Also **7b** and **8b** with 8% aqueous sodium hydroxide (1 equiv.) in methanol solution give **9b**. Compound **7b** on stirring in 2% aqueous sodium hydroxide (1 equiv.)-methanol or TFA gives **8b**.

From these results it may be concluded that 3-acetonyl/3-phenacylthiazolium halides (**1a/1b**) with 1 equiv. aqueous sodium hydroxide (2%) undergo ring opening followed by recyclisation to six membered ring, which subsequently in the presence of another equivalent of NaOH undergoes dehydration and in concentrated sodium hydroxide solution is further deformylated to 2-alkyl/aryl-5-methyl-1, 4-thiazine which are not isolated but undergo autooxidation and rearrangement to compounds **9**, in a manner reported[10] earlier for similar compounds. However, by the proper choice of concentration and the amount of sodium hydroxide solution, products 2-hydroxy-2-alkyl/aryl-4-formyl-5-methyl-2, 3-dihydro-1, 4-thiazine (**7**), 2-alkyl/aryl-4-formyl-5-methyl-1, 4-thiazine (**8**) and



(fig-1)

2-acetyl/aroyl-4-methylthiazole (**9**) could be formed in a selective manner.

2-Methyl-3-phenacyl-4-(p-tolyl) thiazolium chloride (**2** : R=-C_6H_4-CH_3(p)) on reaction with 2% aqueous sodium hydroxide (1 equiv.)-methanol or even with weak base viz. aqueous $NaHCO_3$ (5%), NaOH (1%) solutions forms only (**5** : R=-C_6H_4-CH_3 (p)). However, 2-phenyl-3-phenacyl-4-methylthiazolium bromide under similar conditions undergoes dephenacylation to provide 2-phenyl-4-methylthiazole.

Therefore, contrary to the observation of Doughty et al.[5] that the thiazolium cation **1a** undergoes intramolecular cyclisation to give bicyclic compound **3a**, we have found that **1a** and **1b** in aqueous methanolic sodium hydroxide solution undergo ring opening and recyclisation to give 1, 4-thiazine/thiazole derivatives (**7**, **8**, **9**). However, 2-substituted-3-phenacylthiazolium salts undergo alternate reactions.

EXPERIMENTAL

^1H and ^{13}C NMR were recorded on Bruker AC 200 NMR spectrometer and IR spectra were recorded on Spectromom 2000 instrument. Mass spectra (70 ev) were taken on JEOL JMS-D 300 instrument. M.ps are uncorrected. Silica gel coated plates and columns were used for monitoring the reactions and purification of the products, respectively.

Synthesis of 3-(2-oxoalkyl) thiazolium cations (1,2) General Procedure

A mixture of thiazole (0.01 mol) and ∝-haloketone (0.01 mol) was heated in an oil bath at 100-110°C. On completion of the reaction, the reaction mixture turned into a solid (8-10h). The crude product was washed with dry ether (15ml). The solid obtained was crystallised from anhydrous methanol.

3-Acetonyl-4-methylthiazolium chloride (1a)[5]: 94%; m.p. 201°C; δ H(TFA) 2.57 (diffused s, 6H, 2x-CH_3), 4.21 (s, 1H, C(5)-H), 5.60 (s, 2H, CH_2) and 7.61 (s, 1H, C(2)-H); $\nu_{max.}$(KBr) 1715 (C=O) cm^{-1}.

3-(4-Methylphenacyl)-4-methylthiazolium chloride (1b) : 90%; m.p. 194°C; δ H(TFA) 3.56 (s, 6H, 2x-CH_3), 6.06 (s, 2H, CH_2) and 7.20-8.00 (m, 6H, ArH); $\nu_{max.}$ (KBr) 1710 (C=O) cm^{-1}.

2-Methyl-3-phenacyl-4-(p-methylphenyl) thiazolium chloride[11] : (**2** : R= -C_6H_4-CH_3 (p)) : 82%; semi-solid; δ H(TFA) 2.35 (s, 3H, CH_3), 2.97 (s, 3H, CH_3) and 6.90-8.10 (m, 12H, ArH and -CH_2-); $\nu_{max.}$ (neat) 1685 (C=O) cm^{-1}.

4-Methyl-2-phenyl-3-phenacylthiazolium bromide[11]: 83%; semi-solid; δ H(TFA) 2.35 (s, 3H, CH_3) and 7.10-8.95 (m, 13H, ArH and -CH_2-);$\nu_{max.}$ (neat) 1695 (C=O) cm^{-1}.

Synthesis of 2-aryl/alkyl-2-hydroxy-4-formyl-5-methyl-2, 3-dihydro-1, 4-thiazines (7) :

Method A : To a solution of 3-substituted thiazolium halide (**1**) (0.004 mol) in methanol (10-15 ml), aqueous sodium hydroxide (1-2%, 0.004 mol) or water (20-25 ml) was added in separate experiments. The reaction mixture was stirred at room temperature for 15-20 minutes. The solid separated was filtered off and filtrate was extracted with chloroform. The extract was dried (Na_2SO_4) and chloroform was distilled off. The residue was combined with solid product and was crystallised from $CHCl_3$: hexane (1 : 2) to give **7**.

Method B : To a solution of **1** (0.004 mol) prepared in methanol (15-20 ml), conc. HCl (5-7 ml) was added. The reaction mixture was refluxed for 14-16 h. It was cooled, diluted with water and was neutralised with aqueous sodium bicarbonate solution. The product obtained after the extractive work up was crystallised.

2-Hydroxy-4-formyl-2, 5-dimethyl-2, 3-dihydro-1, 4-thiazine (7a) : (A) 76-85% ; (B) 72%; m.p. 115°C; M^+ m/z 173 (50%), 154 (18%) 139 (100%), 130 (20%), 126 (4%), 113 (5%), 100 (45%) and 72% (5%); δ H($CDCl_3$) 1.67 (s, 1/4x 3H, CH_3), 1.71 (s, 3/4x 3H, CH_3), 2.19 (s, 3/4x 3H, CH_3), 2.29 (s, 1/4x 3H, CH_3), 2.93 (s, 1H, OH, exchanges with D_2O), 3.08, 4.70 (AB quartet, J=12Hz, Δ AB=324Hz, 3/4x2H, CH_2), 3.20, 3.62 (AB quartet, J=6Hz, Δ AB=64Hz, 1/4x 2H, CH_2), 5.03 (s, 1H, C(5)-H), 8.00 (s, 1/4x 1H, CHO) and 8.69 (s, 3/4x 1H, CHO); δ C($CDCl_3$) 20.90(q, CH_3)*, 27.50 (q, CH_3)* 27.59 (q, CH_3)*, 49.76 (t, CH_2)*, 51.00 (t, CH_2)*, 75.98 (s, ArC-2). 100.81 (d, ArC(6)-H), 159.50 (d, CHO)* and 160.60 (d, CHO)*; $\nu_{max.}$ (KBr)1660 (C=O) and 3300 (OH) cm^{-1}; $\lambda_{max.}$ 251nm (ε 41, 600)) (C, 48.9; H, 6.9; N, 7. 6. $C_7H_{11}NO_2S$ requires C, 48.27; H, 6.89; N, 8.04%).

2-Hydroxy-4-formyl-2-(4-methylphenyl)-5-methyl-2, 3-dihydro-1, 4-thiazine (7b) : (A) 69-75% ; (B) 74% ; m.p. 129°C ; M^+ m/z 247 (20%), 231 (2%), 203 (3%), 190 (3%), 130 (2%), 119 (80%), 100 (95%) and

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*Due to the existence of two rotamers, two signals each of C(2)-CH_3 (for **7a**), C(3), C(5)-CH_3 and CHO are observed in ^{13}C NMR spectra.

72 (3%); δ H($CDCl_3$) 1.25 (s, 1.4x 1H, OH, exchanges with D_2O), 1.42 (s, 3/4x 1H, OH, exchanges with D_2O), 2.20 (s, 3/4x 3H, CH_3), 2.27 (s, 1/4x 3H, CH_3), 2.34 (s, 3/4x 3H,C(5)-CH_3), 2.40 (s, 1/4x 3H, C(5)-CH_3), 3.15, 4.94 (AB quartet, J=14Hz, Δ AB= 336Hz, 3/4x 2H, CH_2), 3.37, 3.70 (AB quartet, J=12Hz, Δ AB=68Hz, 1/4x 2H, CH_2), 5.28 (s, 1/4x 1H, C(6)-H), 7.15-7.90 (m, 4H, ArH), 8.26 (s, 1/4x 1H, CHO) and 8.68 (s, 3/4x 1H, CHO); δ C($CDCl_3$), 21.27 (q, CH_3)*, 21.16 (q, CH_3)*, 21.95 (q, CH_3)*, 50.16 (t, CH_2)*, 56,.63 (t, CH_2)*, 79.67 (s, ArC), 101.48 (d, C(6)-H)*, 106.95 (d, C(6)-H)*, 125.95 (d, ArCH), 128.53 (s, ArC), 129.43 (d, ArCH), 160.90 (d, CHO)* and 163.56 (d, CHO)* ; $\nu_{max.}$ (KBr) 1660 (C=O) and 3450 (OH) cm^{-1}; $\lambda_{max.}$ 245nm (ε 48, 250) (C, 62.2; H, 6.1; N, 5.2 $C_{13}H_{15}NO_2S$ requires C, 62.65; H, 6.02; H, 5.62%).

Synthesis of 2-Aryl-4-formyl-1, 4-thiazines (8)

Method A : A solution 3-substituted-4-methylthiazolium halide (**1**) (0.004 mol) in methanol (15-20 ml) was treated with aqueous sodium hydroxide (2%; 15ml) and small amount of solid separated was redissolved by adding methanol (10-15ml). The reaction mixture was stirred at room temperature. After the completion of the reaction (tlc) (20-24h), the reaction mixture was diluted with water and extracted with chloroform. The extract was dried over Na_2SO_4 and $CHCl_3$ was distilled off. The residue was crystallised from $CHCl_3$: hexane (1:1) to get the pure product.

Method B : A solution of compound **7** (0.004 mol) in methanol (20-25 ml) was treated with 2% aqueous sodium hydroxide (8ml, 1 equiv.) and was stirred for 20-24h. The reaction mixture was worked up as above.

Method C : Compound **7** (0.004 mol) was dissolved in minimum quantity of trifluoroacetic acid (3-5 ml) and was allowed to stand at room temperature for 5-10 mts. It was diluted with water and was neutralised with sodium bicarbonate. The product was obtained by extractive work up as given above.

4-Formyl-2, 5-dimethyl-1, 4-thiazine (8a) : (A) 69% (B) 68% (C) 73%; m.p. 68°C; M^+ m/z 154 (10%), 139 (99%), 113(5%) and 72(15%); δ H($CDCl_3$) 2.30 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 5.23 (s, 1H, C(6)-H), 7.29 (s, 1H, C(3)-H) and 8.69 (s, 1H, CHO); δ C($CDCl_3$) 20.07 (q, CH_3), 27.32 (q, CH_3), 102.30 (d, C(6)-H), 117.22 (d, C(3)-H) and 155.92 (d, CHO); $\nu_{max.}$ (KBr) 1660 (C=O) cm^{-1}; $\lambda_{max.}$ 251nm (ε 25,600).

4-Formyl-2-(4-methyphenacyl)-5-methyl-1, 4-thiazine (8b) : (A) 67% (B) 68% (C) 63%; m.p. 78°C, M^+ m/z 231 (2.1%), 216 (20%), 203 (2%) 190(4%), 188 (30%),118 (100%), 90(50%), and 72(4%); δ H($CDCl_3$) 2.23 (s, 3H, CH_3), 2.47(s, 3H, CH_3), 5.37 (s, 1H, C(6)-H), 6.89 (s, 1H, C(3)-H), 7.30 7.85 (AB quartet, J=8Hz, Δ AB=33Hz, 4H, ArH) and 8.62 (s, 1H, CHO); $\nu_{max.}$ (KBr) 1655 (C=O)cm^{-1}; $\lambda_{max.}$ 248nm (ε 59, 800).

Synthesis of 2-acetyl/aroyl-4-methylthiazoles (9)

Method (A) : A solution of 3-substituted-4-methylthiazolium chloride (**1**) (0.004 mol) in methanol (15-20 ml) containing aqueous 8% sodium hydroxide (3.8 ml, 2 equiv.) was stirred at ambient temperature (20-24h). After the completion of the reaction, it was extracted with chloroform and extract was dried (Na_2SO_4) and the solvent was distilled off. The thick liquid residue could not be crystallised from $CHCl_3$: hexane (1 : 1) or methanol : diethyl ether (1 : 1).

Method B : A solution of compound **7** (0.004 mol) in methanol (20-25 ml) was mixed with aqueous sodium hydroxide (8%, 1 equiv., 2 ml) and was stirred for 22-26h. The product was obtained as described above.

Method C : A solution of compound **8** (0.004 mol) in methanol (20-25 ml) was mixed with aqueous 8% sodium hydroxide (2.2ml, 1 equiv.) and was stirred for 22-24 h. The product was obtained as given in method A.

2-Acetyl-4-methylthiazole (9a)[9] : (A) 74%; (B) 72% (C) 74%; M^+ m/z 141 (78%), 98(100%) and 90 (70%) ; δ H($CDCl_3$) 2.50 (s, 3H, CH_3), and 7.20 (s, 1H, C (5)-H); $\nu_{max.}$ (neat) 1660 (C=O) cm^{-1}.

2-(Methylbenzoyl)-4-methylthiazole (9b): (A) 71%, (B) 73%, (C) 72%; M^+ m/z 218 (5.6%), 217 (31%) 189 (60%) 119 (100%) and 91 (38%); δ H($CDCl_3$) 2.40 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 7.22 (s, C(5)-H), 7.28, 8.38 (AB quartet, J=8Hz, Δ AB=200Hz, 4H, ArH); δ C($CDCl_3$) 17.21 (q, CH_3), 21.59 (q, CH_3), 121.00 (d, ArCH), 128.93 (d, ArCH), 131.40 (d, ArCH), 132.55 (s, ArC), 144.21 (s, ArC), 155.10 (s, ArC), 166.86 (s, ArC) and 183.36 (s, CO); $\nu_{max.}$ (neat) 1660 (C=O) cm^{-1}; $\lambda_{max.}$ 310nm (ε 38,000).

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