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SYNTHESIS OF HETEROCYCLES VIA ENAMINES—X[1]

REACTIONS OF 1-SUBSTITUTED-4,4,6-TRIMETHYL-1,4-DIHYDROPYRIMIDINE-2(3H)THIONE DERIVATIVES WITH α-HALOGENATED CARBOXYLIC ACIDS AND KETONES

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Abstract—2,4-Dioxathiazolidine derivatives (7) have been obtained in synthetically useful yields by the condensations of easily available 1-substituted-4,4,6-trimethyl-1,4-dihydropyrimidine-2(3H) thione derivatives (4) and α-halogenated carboxylic acids in aqueous medium. The condensations of 4 with α-haloketones in ethanol containing conc HCl furnish 2-oxa-4-thiazolines (8). The condensations of N,N-dialkyl-N'-arylthioureas or aryl thiourethanes with α-chlorocarboxylic acids and α-haloketone in presence of conc HCl furnish 7 and 8 respectively.

A typical enamine character is demonstrated by biological pyrimidines viz uracil (I, R=H), thymine (I, R=Me) etc.[2,3] The electrophiles attack these pyrimidines either at C_5, forming imminium cation (2) as intermediates which by the loss of a proton give C_5 substituted products (3),[4] or at C_5, C_6-double bond to give adducts.[1] The nucleophiles react at C_6 of 1 and 2 resulting in ring cleavage followed by the formation of alternate cyclization products.[4,5] These reactions have been responsible for a variety of ring transformations in pyrimidine nucleosides and nucleotides.[6] The enamine character has also been elaborated in 1-substituted-4,4,6-trimethyl-1,4-dihydropyrimidine-2(3H) thione derivatives (4), and with HCl compounds 4 have been converted to 2-substituted amino-4,4,6-trimethyl-4H-1,3-thiazines (5) or 2-substituted amino-4,4,6-trimethyl-6H-1,3-thiazines (6) depending upon the reaction conditions.[7]

RESULTS AND DISCUSSION

Chloroacetic acid performs a facile conversion of 6-methyl-2-thiouracil to 6-methyluracil.[8] In continuation of our interest in the development of synthetic methodology for the conversion of $\rangle C{=}S$ to $\rangle C{=}O$,[9] we have performed the reactions of chloroacetic acid with 4. An aqueous solution of chloroacetic acid and 4 (R^2=C_6H_5) on refluxing furnished a product, m.p. 135° which analysed for molecular formula $C_9H_7NO_2S$ (MS, M⁺ *m/e* 193.043). It exhibited two CO absorption bands at 1680 and 1760 cm⁻¹ in the IR spectrum and ^{1}H NMR signals appeared at δ 4.20 (s, 2H) and 7.2–7.5 (m, 5H). From these data, it was assigned the structure, 3-phenyl-2,4-dioxathiazolidine (7, R^2=C_6H_5, R^3=H), which was also corroborated by the peaks at *m/e* 119 (M^+ –CH_2–S–C=O), 91 (119–CO), 77 (119–NCO), 74 (M^+ –Ph–NCO), 46 (74–CO) in the mass spectrum. Thus, in this reaction aqueous solution of chloroacetic acid did not oxidise $\rangle C{=}S$ to $\rangle C{=}O$.[10]

3-Substituted-2,4-dioxathiazolidine derivatives exhibit a broad spectrum of biological activities and have been synthesized from easily oxidisable thiol precursors.[11–14] Since the derivatives of 4 are easily available, it was planned to investigate the synthetic utility of the conversion of 4 and its derivatives to the corresponding 3-substituted-2,4-dioxathiazolidine derivatives and the results of the condensations of derivatives of 4 with chloroacetic acid and 2-chloropropionic acid are tabulated in Table 1. In all the cases the reaction proceeded smoothly except in the condensation of chloroacetic acid and 4 (R^2=H), where 13 (R^2=H) was formed. When the reaction of 4 (R^2=Ph) and chloroacetic acid was performed in ethanol, 7 (R^2=Ph, R^3=H), was formed in relatively poor yields. The reaction of 4 (R^2=Me) with ethylchloroacetate when performed in ethanol or ethanol containing conc HCl, gave a multitude of products.

A synthesis of 7 (R^2=$C_6H_4CH_3$ - *o*/$C_6H_4CH_3$ - *p*; R^3=H) has been reported by the condensations of symm. N,N' - di - *o* - tolylthiourea/N,N' - di - *p* - tolylthiourea with chloroacetic acid.[19] On repeating these condensations, it was found that instead of 7, actually 2 - *o* -

Table 1. 2,4-Dioxathiazolidine derivatives (7)

Product	4/R^2	ClCH(R^1)COOH R^1	m.p. (°C)	Yield[a] (%)
7a	CH_3	H	180[b]	90
7b	$C_6H_4CH_3$-*o*	H	98[c]	81
7c	$C_6H_4CH_3$-*p*	H	157[d]	81
7d	$C_6H_4NO_2$-*p*	H	128	81
7e	C_6H_5	H	135[e]	80
7f	H	CH_3	Yellow oil	81
7g	CH_3	CH_3	Yellow oil	50
7h	$C_6H_4CH_3$-*p*	CH_3	110[f]	80

[a]The yields of the derivatives of 7 obtained by the methods reported in literature are relatively poor.
[b]Lit. m.p. 36–9°.[15]
[c]Lit. m.p. 117–19°.[16]
[d]Lit. m.p. 160°.[16]
[e]Lit. m.p. 137°.[17]
[f]Lit. m.p. 108–32°.[18]

tolylimino - 3 - *o* - tolyl - 2,4 - dioxathiazolidine[16] and 2 - *p* - tolylimino - 3 - *p* - tolyl - 2,4 - dioxathiazolidine[16] were formed.

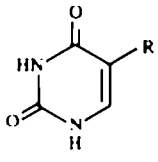
Amongst the two evident pathways, A and B, depicted in Scheme 1, for this reaction, the absence of the derivatives[7] of **10** in the reaction mixtures (TLC) at any stage during the reaction and isolation of **13** (R^2=H), supported the pathway B for the condensations of **4** with α-chlorocarboxylic acids. Thus the reactions of 1 - substituted - 4,4,6 - trimethyl - 1,4 - dihydropyrimidine - 2(3H) thione derivatives (**4**), with α-chlorocarboxylic acids through the sequence (i) initial reaction at sulphur, (ii) enamine hydrolytic cleavage of the pyrimidine ring, (iii) an alternate cyclization, (iv) hydrolysis of the exocyclic imino group, furnish 3-substituted-2,4-dioxathiazolidine.[20]

In the formation of **7**, in Scheme 1, the structural units, R–N–C=S of **4** and R'–CH–CO– of α-chlorocarboxylic acids were utilized and –N–C–CH–C– of **4** had been extruded. It was therefore argued that monoprotic thioureas could condense with α-chlorocarboxylic acid with the elimination of a secondary amine to form **7**. Consequently N,N-dimethyl-N'-phenylthiourea and N,N - diethyl - N' - *p* - tolylthiourea on condensation with chloroacetic acid in aqueous solution have been found to furnish **7** (R^2=Ph, R^3=H, 70%) and **7** (R^2=$C_6H_4CH_3$-*p*, R^3=H, 80%) respectively.

N,N - Dimethyl - N' - phenylthiourea on condensation with ethyl chloroacetate or chloroacetonitrile in an alcoholic solution, containing conc HCl, furnished 3 - phenyl - 2,4 - dioxathiazolidine as the major product. However, condensation of N,N - dimethyl - N' - phenylthiourea with chloroacetonitrile in ethanol gave 3 - phenyl - 4 - imino - 2 - thiazolidone (**14**) and 3 - phenyl - 2 - imino - 4 - thiazolidone (**15**).[21]

The reactions of 1 - substituted - 4,4,6 - trimethyl - 1,4 - dihydropyrimidine - 2(3H) thione (**4**) with α-chlorocarboxylic acids constitute a facile synthesis of 3 - substituted - 2,4 - dioxathiazolidine (**7**). It has been reported that condensation of 4,4,6 - trimethyl - 1,4 - dihydropyrimidine - 2(3H) thione (**4**, R^2=H) with phenacyl bromide in ethanol gives 2 - amino - 4 - phenylthiazole.[22] In the latter case, evidently the hydrolysis of the imino group has not taken place. It was argued that condensations of **4** with α-haloketones performed under acid catalysed hydrolytic conditions could constitute a synthesis of 3 - substituted - 4 - aryl - 2 - oxa - 4 - thiazoline derivatives. Thus **4** (R^2=H, Me, Ph, $C_6H_4CH_3$-*p*) have been condensed with phenacyl bromide in ethanol containing conc HCl to furnish **8** (R^2=H, Me, Ph, $C_6H_4CH_3$-*p* and R^4=Ph) respectively. The reaction would evidently follow a pathway depicted for similar condensation of **4** and chloroacetic acid (Scheme 1).

6-Methyl-2-thiouracil, on condensation with phenacyl bromide, *p*-bromo/chlorophenacyl chlorides, performed in ethanol containing conc HCl gave **8** (R^2=H, R^4=Ph, C_6H_4Br-*p* and C_6H_4Cl-*p*) respectively in 70–90% yields. However 6 - methyl - 2 - thiouracil on condensation with phenacylbromide in alcohol furnished 2 - amino - 4 - phenyl thiazole.[22]



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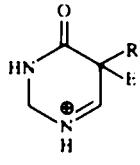

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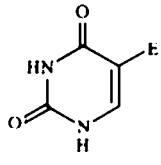

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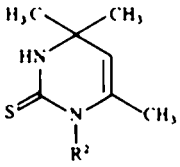

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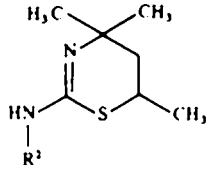

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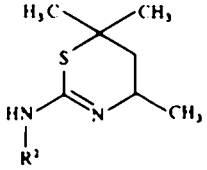

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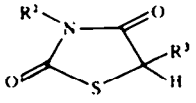

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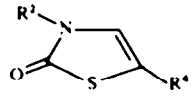
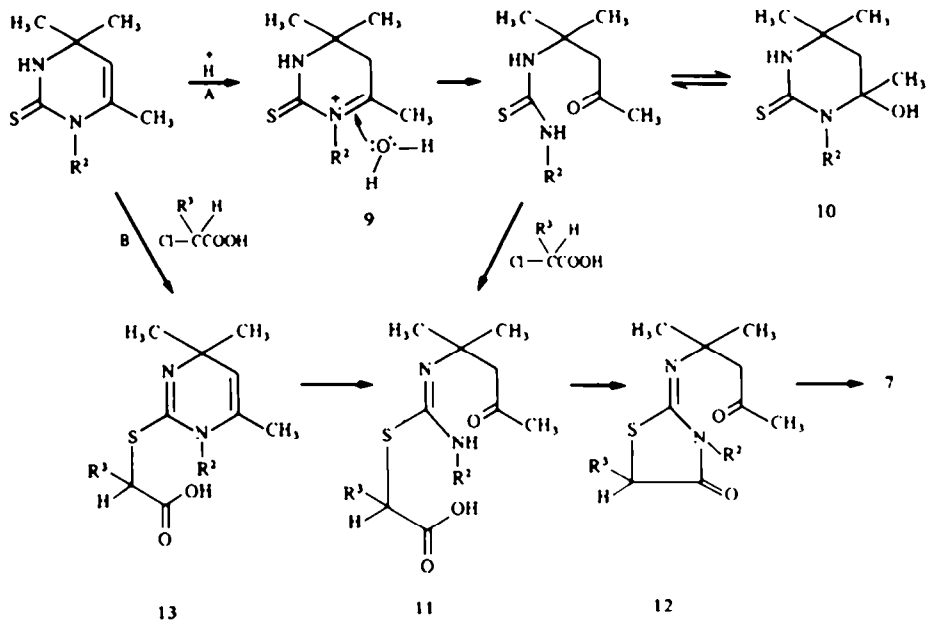


8

a, R^2=CH_3; R^3=H
b, R^2=$C_6H_4CH_3$–O, R^3=H
c, R^2=$C_6H_4CH_3$–P, R^3=H
d, R^2=$C_6H_4NO_2$–P, R^3=H
e, R^2=C_6H_5, R^3=H
f, R^2=H, R^3=CH_3
g, R^2=CH_3, R^3=CH_3
h, R^2=$C_6H_4CH_3$–P, R^3=CH_3

a, R^2=H, R^4=C_6H_5
b, R^2=CH_3, R^4=C_6H_5
c, R^2=C_6H_5, R^4=C_6H_5
d, R^2=$C_6H_4CH_3$–P, R^4=C_6H_5
e, R^2=H, R^4=C_6H_4Br–P
f, R^2=H, R^4=C_6H_4Cl–P

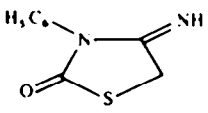
Scheme 1.



N,N - Dialkyl - N' - arylthioureas with phenacyl halides have been reported to furnish (i) arylisothiocyanates (ii) 2 - arylimino - 5 - aryl - 1,3 - oxathioles (iii) 3,4 - diaryl - 2 - arylimino - 4 - thiazolines and (iv) dialkylamine hydrochloride.[23] It was envisaged that the same condensation reactions when performed in ethanol containing conc HCl would provide derivatives of **8**. Thus the condensation of N,N - dimethyl - N' - phenylthiourea with phenacyl bromide performed in ethanol containing conc HCl gave 2 - phenylimino - 5 - phenyl - 1,3 - oxathiole (**16**, R^5=Ph, 25%) and 3,4 - diphenyl - 2 - oxa - 4 - thiazoline (**8**, R^2=R^4=Ph 52%). Similarly N,N - diethyl - N' - *p* - tolylthiourea and phenacyl bromide furnished 5 - phenyl - 2 - *p* - tolylimino - 1,3 - oxathiole (**16**, R^5=$C_6H_4CH_3$-*p*, 20%) and 3 - *p* - tolyl - 4 - phenyl - 2 - oxa - 4 - thiazoline (**8**, R^2=$C_6H_4CH_3$ - *p*, R^4=Ph, 54%). When the same reactions were performed in ethanol, the formation of corresponding 2 - arylimino - 5 - aryl - 1,3 - oxathioles (**16**) were noticed, but the reactions could not proceed to completion even on prolonged heating.

N,N - dialkyl - N' - arylthioureas with ethanol/sodium ethoxide formed arylthiourethanes.[24] We have now found that N,N - dialkyl - N' - arylthioureas with ethanol/conc HCl also furnish aryl thiourethanes. We argued that in the reactions of N,N - dialkyl - N' - arylthioureas with α-haloketones in ethanol containing conc HCl, **8**, might have been formed by the condensation of α-haloketones with aryl thiourethenes formed *in situ*. On monitoring the progress of the reactions, the formation of aryl thiourethanes could not be detected. Thus the reactions of N,N - dialkyl - N' - arylthioureas with α-haloketones might proceed through (i) the sequence depicted in the condensations of α-chlorocarboxylic acids and **4** or (ii) through the formation of aryl thiourethanes and subsequent condensations with α-haloketone. On performing the condensations of phenyl/*p* - tolyl - thiourethanes with phenacyl bromide in ethanol containing conc HCl, 3 - phenyl/3 - *p* - tolyl - 4 - phenyl - 2 - oxa - 4 - thiazolines were formed. However, the reaction of N,N - dimethyl - N' - phenylthiourea and phenacyl bromide run in ethanol containing sodium ethoxide also gave 2 - phenylimino - 5 - phenyl - 1,3 - oxathiole (20%) and 3,4 - diphenyl - 2 - oxa - 4 - thiazoline (56%).

As a consequence of the above observations, the condensation of 1 - phenyl - 4,4,6 - trimethyl - 1,4 - dihydropyrimidine - 2(3H) thione (**4**, R^2=Ph) with ethyl chloroformate might be expected to form β-lactam derivatives. But on performing the condensation of **4** (R^2=Ph) with ethylchloroformate, 1 - phenyl - 3 - ethoxycarbonyl - 4,4,6 - trimethyl - 1,4 - dihydropyrimidine - 2(3H) thione (**17**) was formed.



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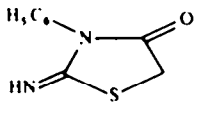

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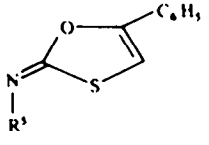

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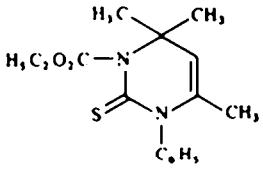

17

EXPERIMENTAL

M.ps were determined in capillaries and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Tesla BS 487C 80 MHz and Varian XL-100 instruments respectively by using TMS as internal standard. IR spectra were recorded with a Hungarian spektromom-2000 instrument. Mass spectra were run on a Hitachi/Perkin-Elmer RMU-60D instrument. Elemental analysis were performed at microanalytical laboratory, Calcutta University, Calcutta, India. For TLC, plates coated with silica

gel G were used, and spots were developed with I_2. The progress of the reactions were monitored through TLC of the portions of the reaction mixtures drawn at regular intervals.

2,4-Dioxathiazolidine derivatives (7)

General procedure. A suspension of appropriate 1 - substituted - 4,4,6 - trimethyl - 1,4 - dihydropyrimidine - 2(3H) thione (0.01 mole) in 7% aqueous chloroacetic acid or 2-chloropropionic acid (50 ml) was refluxed. After an hr, a clear soln was obtained. The reaction was completed in 3–4 hr (TLC). The mixture was allowed to stand overnight and the product separated out as needles, was collected and recrystallized. The filtrate was neutralized with $NaHCO_3$aq and extracted with $CHCl_3$. The extract was dried over Na_2SO_4, solvent distilled off and the residue was recrystallized. The data for the compounds obtained in this manner from appropriate 4 and chloroacetic acid/2-chloropropionic acid are given below:

Compound **7a** (R^2=Me, R^1=H). 90%, m.p. 180° (EtOH). IR (nujol): 1630 and 1690 cm^{-1} (>C=O). ^{1}H NMR (TFA): δ 3.35 (s, 3H, CH_3), 4.36 (s, 2H, CH_2). Mass: $M^{+\cdot}$ *m/e* 131, *m/e* 130 (131–H), 74 (131–CH_2–NCO), 73 (130–CH_2–NCO), 57 (131–CH_2–S–C=O), 56 (130–CH_2–S–C=O), 46 (74–CO), 45 (73–CO): 42 (74–S). (Found: C, 36.62, H, 3.85: N, 11.0. Calc for $C_4H_5NO_2S$: C, 36.64; H, 3.81; N, 10.68%).

Compound **7b** (R^2=$C_6H_4CH_3$-*o*, R^1=H). 81%, m.p. 98° (benzene–pet ether 2:1). IR ($CHCl_3$): 1690 and 1760 cm^{-1} (>C=O). ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H, CH_3), 4.12 (s, 2H, CH_2), 7.37 (m, 5H, ArH). Mass: M^+ *m/e* 207; *m/e* 133 (207–CH_2–S–C=O), 105 (133–CO), 91 (133–NCO), 74 (207 - *o*–CH_3–C_6H_4–NCO), 46 (74–CO). (Found: C, 57.86; H, 4.40; N, 6.80; S, 16.33. Calc for $C_{10}H_9NO_2S$: C, 57.99, H, 4.34; N, 6.76; S, 16.23%).

Compound **7c** (R^2=$C_6H_4CH_3$-*p*, R^1=H). 81%, m.p. 157° (benzene–pet ether, 2:1). IR ($CHCl_3$): 1700 and 1720 cm^{-1} (>C=O). ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3): 4.1 (s, 3H, CH_2), 7.07–7.55 (m, 4H, ArH). (Found: C, 57.65; H, 4.24; N, 6.70, S, 16.65. Calc for $C_{10}H_9NO_2S$: C, 57.99; H, 4.34; N, 6.76; S, 16.23%).

Compound **7d** (R^2=$C_6H_4NO_2$-*p*, R^1=H). 80%, m.p. 128° (benzene–pet ether, 2:1). IR ($CHCl_3$): 1640 and 1700 cm^{-1} (>C=O). ^{1}H NMR ($CDCl_3$): δ 4.7 (s, 2H, CH_2), 7.4 (m, 4H, ArH). Mass: M^+ *m/e* 238: *m/e* 164 (238–CH_2–S–C=O), 136 (164–CO), 122 (164–NCO), 74 (238-*p*–O_2N–C_6H_4–NCO), 46 (74–CO), (Found: C, 45.58: H, 2.52: N, 12.00. Calc for $C_9H_6N_2O_4S$): C, 45.38; H, 2.52: N, 11.70%).

Compound **7e** (R^2=Ph, R^1=H). 80%, m.p. 135° (benzene). IR ($CHCl_3$): 1680 and 1760 cm^{-1} (>C=O). ^{1}H NMR ($CDCl_3$): δ 4.2 (s, 2H, CH_2), 7.2–7.8 (m, 5H, ArH), Mass: M^+ *m/e* 193.043; *m/e* 119 (193–CH_2–S–C=O), 91 (119–CO), 77 (119–NCO), 74 (193–Ph–N=C=O), 46 (74–CO). (Found: C, 55.79; H, 3.62: N, 7.25. Calc for $C_9H_7NO_2S$: C, 55.96: H, 3.62; N, 7.25%).

Compound **7f** (R^2 = H, R^1 = Me). 81%, IR ($CHCl_3$): 1700 and 1750 cm^{-1} (>C=O), ^{1}H NMR ($CDCl_3$): δ 1.70 (d, 3H, CH_3), 4.37 (q, 1H, CH), Mass: $M^{+\cdot}$ *m/e* 131 ($C_4H_5NO_2S$): *m/e* 88 (131–HNCO), 87 (88–H), 60 (88–CO), 59 (87–CO), 43 (131–H_3C–C–S–C = O).
H

Compound **7g** (R^2 = Me, R^1 = Me). 50%, IR ($CHCl_3$): 1690 and 1740 cm^{-1} (>C=O). ^{1}H NMR ($CDCl_3$): δ 1.67 (d, 3H, CH_3), 3.07 (s, 3H, CH_3), 4.2 (q, 1H, CH). Mass: M^+ *m/e* 145 ($C_5H_7NO_2S$): *m/e* 88 (145–H_3C–NCO), 87 (88–H), 60 (88–CO), 59 (87–CO), 57 (145–H_3C–C–S–C = O), 29 (57–CO).
H

Compound **7i** (R^2 = $C_6H_4CH_3$-*p*, R^1 = Me). 80%, m.p. 110° (EtOH). IR ($CHCl_3$): 1685 and 1730 cm^{-1} (>C=O). ^{1}H NMR ($CDCl_3$): δ 1.75 (d, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.32 (q, 1H, CH), 7.13 (q, 4H, ArH). Mass: $M^{+\cdot}$ *m/e* 221; *m/e* 133 (221–H_3C–C–S–C = O), 105 (133–CO), 91 (133–NCO), 88 (221-*p*-$CH_3C_6H_4$–NCO), 87 (88–H), 60 (88–CO), 59 (87–CO). (Found: C, 59.71, H, 5.30. Calc for $C_{11}H_{11}NO_2S$: C, 59.72, H, 4.97%).
H

S - (4,4,6 - *trimethyl* - 1,4 - *dihydropyrimidine* - 2 - *yl*) *thioglycolic acid* (**13**, R^2=H). The reaction of **4** (R^2=H) and aqueous chloroacetic acid furnished **13** (R^2=H), 70%, m.p. 119° (EtOH). IR ($CHCl_3$) 1665 cm^{-1} (>C=O), ^{1}H NMR (TFA): δ 1.50 (s, 6H, gemdimethyl H), 2.25 (s, 3H, CH_3), 4.2 (s, 2H, CH_2), 4.38 (s, 1H,=C–H). Mass $M^{+\cdot}$ *m/e* 214 ($C_9H_{14}N_2O_2S$).

Reaction of **4**(R^2 = Ph) *with chloroacetic acid in alcoholic medium*

A suspension of **4** (R^2 = Ph) (0.01 mole) and chloroacetic acid (0.02 mole) is ethanol (25 ml) was refluxed. The reaction was completed in 3 days (TLC). After work up as described earlier the product was identified as **7** (R^2 = Ph, R^1 = H) (20%).

Reaction of **4** (R^2 = Me) *with ethyl chloroacetate*

A soln of **4** (R^2 = Me) (0.01 mole) and ethyl chloroacetate (0.02 mole) in anhyd EtOH/EtOH or EtOH containing conc HCl, on just warming for a few min on water bath, gave a multitude of products, which could not be isolated.

Reactions of N,N - *dimethyl* - N' - *phenylthiourea with chloroacetic acid*

An aqueous suspension of N,N - dimethyl - N' - phenylthiourea (0.01 mole) in 7% aqueous chloroacetic acid (50 ml) was refluxed for 7 hr. The mixture was kept overnight and a product separated out. It was filtered, dried and recrystallized from benzene. It was found to be identical with an authentic sample of **7** (R^2 = Ph, R^1 = H). The filtrate on work up gave an additional amount of the product and the combined yield was 70%.

Similarly N,N - diethyl - N' - *p* - tolyl - thiourea with chloroacetic acid gave **7** (R^2=$C_6H_4CH_3$-*p*, R^1=H), yield 80%.

Reaction of N,N - *dimethyl* - N' - *phenylthiourea with ethyl chloroacetate*

A soln of N,N - dimethyl - N' - phenylthiourea (0.01 mole) and ethykchloroacetate (0.02 mole) in EtOH (25 ml) containing conc HCl (5 ml) was refluxed for 2 hr. After work up the product was purified by chromatography on silica gel using benzene as eluent and was found to be identical with an authentic sample of **7** (R^2 = Ph, R^1 = H) (35%). On running the reaction for a longer time a multitude of products was formed.

Reaction of N,N - *dimethyl* - N' - *phenylthiourea with chloroacetonitrile*

(a) A soln of N,N - dimethyl - N' - phenylthiourea (0.01 mole) and chloroacetonitrile (0.02 mole) in EtOH (25 ml) containing conc HCl (5 ml) was refluxed for 8 hr. On work up, the major component (50%) isolated was found to be **7** (R^2 = Ph, R^1 = H).

(b) A soln of N,N - dimethyl - N' - phenylthiourea (0.01 mole) and chloroacetonitrile (0.02 mole) in EtOH was refluxed. The reaction was completed in 7 hr with the formation of two products (TLC). The solvent was distilled off and residue was chromatographed on silica gel by using benzene as eluent.

Compound **14** (*1st component*) 30%, m.p. 99° (EtOH). IR ($CHCl_3$): 1645 cm^{-1} (>C=O), 1730 cm^{-1} (>C=N-). ^{1}H NMR ($CDCl_3$): δ 3.92 (s, 2H, CH_2), 7.42 (m, 5H, ArH). Mass: $M^{+\cdot}$ *m/e* 192 ($C_9H_8N_2OS$).

Compound **15** (*2nd component*) 25%, m.p. 176–7° (EtOH) (lit. m.p. 178°).[21] IR ($CHCl_3$): 1645 cm^{-1} (>C=O), 1685 cm^{-1} (>C=N). ^{1}H NMR (TFA): δ 4.35 (s, 2H, CH_2), 7.6 (m, 5H, ArH). Mass: $M^{+\cdot}$ *m/e* 192 ($C_9H_8N_2OS$).

2-Oxa-4-thiazoline derivatives (**8**, R^4 = Ph)

General procedure. A suspension of a derivative of **4**

(0.01 mole) and phenacyl bromide (0.01 mole) in EtOH (50 ml) containing conc HCl (5 ml) was refluxed for 10–15 hr. The mixture was worked up as in the formation of derivatives of 7, the data of the compounds thus obtained are given below:

Compound **8a** (R^2 = H, R^4 = Ph). 75% m.p. 130° (pet. ether, 60–80°). IR ($CHCl_3$): 1640 cm^{-1} (>C=O). ^1H NMR (TFA): δ 6.77 (s, 1H, =C–H), 7.55 (m, 5H, ArH). Mass: M^+ *m/e* 177 (Found: C, 61.08; H, 3.90; N, 8.0); S, 18.4. Calc for $C_9H_{14}NOS$: C, 61.0; H, 3.95; N, 7.90; S, 18.07%).

Compound **8b** (R^2 = Me, R^4 = Ph). 47%, m.p. 115–7° (EtOH) (lit. m.p. 120–1°).[24] IR ($CHCl_3$): 1650 cm^{-1} (>C=O). ^1H NMR ($CDCl_3$): δ 3.22 (s, 3H, CH_3), 6.75 (s, 1H, =C–H), 7.50 (m, 5H, ArH). (Found: C, 62.70; H, 4.70; N, 7.50; S, 17.10. Calc for $C_{10}H_8NOS$: C, 62.82; H, 4.71; N, 7.32; S, 16.75%).

Compound **8c** (R^2 = $C_6H_4CH_3$-*p*, R^4 = Ph). 70%, m.p. 115° (pet. ether, 60–80°). IR ($CHCl_3$): 1640 cm^{-1} (>C=O). ^1H NMR ($CDCl_3$): δ 2.42 (s, 3H, CH_3), 6.8 (s, 1H, =C–H), 7.37 (m, 9H, ArH). Mass: M^+ *m/e* 267 (Found: C, 72.40; H, 5.00; N, 5.73; Calc for $C_{16}H_{13}NOS$: C, 71.91; H, 4.86; N, 5.24%).

Compound **8d** (R^2 = Ph, R^4 = Ph). 72%, m.p. 140° (EtOH) IR ($CHCl_3$): 1650 cm^{-1} (>C=O). ^1H NMR ($CDCl_3$): δ 6.70 (s, 1H, =C–H), 7.70 (m, 10H, ArH). (Found: C, 71.50; H, 4.72; N, 6.10; S, 10.71. Calc for $C_{15}H_{11}NOS$: C, 71.10; H, 4.34; N, 5.87; S, 10.22%).

2-Oxa-4-thiazoline derivatives (**8**, R^2 = H)

General procedure. A suspension of 6 - methyl - 2 - thiouracil (0.01 mole) and a phenacyl halide derivative (0.01 mole) in EtOH (50 ml) containing conc HCl (5 ml) was refluxed for 6–9 hr. The mixture was worked up as in the formation of derivatives of 7, and the data for the compounds thus obtained are given below:

Compound **8e** (R^2 = H, R^4 = C_6H_4Br-*p*). 82%, m.p. 270° (benzene-pet. ether, 2:1), (lit. m.p. 273°).[26]

Compound **8f** (R^2 = H, R^4 = C_6H_4Cl-*p*). 90%, m.p. 220° (lit. m.p. 224°).[26]

Reaction of 6 - methyl - 2 - thiouracil with phenacylbromide in ethanol

A suspension of 6 - methyl - 2 - thiouracil (0.01 mole) and phenacyl bromide (0.01 mole) in EtOH (50 ml) was refluxed for 7 hr. The solvent was distilled off and residue was treated with $NaHCO_3$aq. It was extracted with $CHCl_3$. The extract was dried over Na_2SO_4, solvent was distilled off and residue was purified by chromatography on silica gel by using benzene as eluent. The product was found to be identical with an anthentic sample of 2 - amino - 4 - phenylthiazole (70%).

Reactions of N,N - dialkyl - N' - arylthioureas with phenacyl bromide in alcoholic solution containing conc HCl/NaOEt

A soln of N,N - dimethyl - N' - phenyl thiourea (0.01 mole) and phenacyl bromide (0.01 mole) in EtOH (50 mol) containing conc HCl (25 ml) was refluxed. Two products started forming after 2 hr simultaneously and reaction was completed in 5 hr (TLC). The mixture was worked up and the products were separated on silica gel by using benzene-EtOAc (10:2) as eluent. The first component was identified as 2 - phenylimino - 5 - phenyl - 1,3 - oxathiole (yield 25%) and second component as 3,4 - diphenyl - 2 - oxa - 4 - thiazoline (yield 52%) by comparing with authentic samples.

Similarly, N,N - diethyl - N' - *p* - tolylthiourea and phenacyl bromide furnished 2 - phenylimino - 5 - *p* - tolyl - 1,3 - oxathiole (yield 20%) and 3 - *p* - tolyl - 4 - phenyl - 2 - oxa - 4 - thiazoline (yield 5.4%).

On using NaOEt (0.01 mole) instead of conc HCl in the above reactions, same products were formed in almost similar yields.

Reactions of aryl thiourethanes with phenacyl bromide

A soln of phenyl thiourethane (0.01 mole) and phenacyl bromide (0.01 mole) in EtOH (50 ml) containing conc HCl (10 ml), was refluxed for 5 hr and 3,4 - diphenyl - 2 - oxa - 4 - thiazoline was obtained in 67% yield. Similarly the reaction of *p*-tolylthiourethane[27] and phenacyl bromide gave 3 - *p* - tolyl - 4 - phenyl - 2 - oxa - 4 - thiazoline in almost same yields.

Reaction of **4** (R^2 = Ph) *with ethylchloroformate*

A soln of **4** (R^2 = Ph) (0.01 mole) and ethyl chloroformate (0.05 mole) was refluxed for 15 min. The solvent was distilled off and residue consisting of two components, was dissolved in $CHCl_3$ and chromatographed on neutral alumina using benzene as eluent. The faster moving component R_f 0.91 ($CHCl_3$–MeOH, 10:2) was found to be unchanged starting material (5%) and component R_f 0.75 was identified as 1 - phenyl - 3 - ethoxycarbonyl - 4,4,6 - trimethyl - 1,4 - dihydropyrimidine - 2(3H) thione, 80%, m.p. 129° (pet. ether, 60–80°). IR ($CHCl_3$): 1760 cm^{-1} (>C=O). ^1H NMR ($CDCl_3$): δ 1.0–1.6 (unresolved signals, 12H, CH_3), 4.0–4.6 (q, 2H, CH_2), 4.7 (d, 1H, =C–H), 7.2 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$): δ 13.706 (q, CH_3), 20.119 (q, CH_3), 20.295 (q, CH_3), 27.649 (q, CH_3), 27.825 (q, CH_3), 56.768(s), 64.122 (t, CH_2), 113.712 (d, –CH=C–) 128.598 (d, ArH), 129.186 (d, ArCH), 129.948 (d, ArCH) 133.657 (s, N–C–^{13}) 141.187 (s, ArC), 154.421 (s, >C=O), 178.831 (s, >C=S). (Found: C, 52.86; H, 6.25, N, 12.33; S, 14.09. Calc for $C_{15}H_{19}N_2O_2S$: C, 52.80; H, 6.20; N, 12.43; S, 14.50%).

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