CHAPTER III

REACTION OF ACYLKETENE S,N-ACETALS WITH MALONYL CHLORIDE: SYNTHESIS OF NOVEL 1,5-SUBSTITUTED 4-HYDROXY-6-METHYLTHIO-2(1H)-PYRIDONES AND 6,8-SUBSTITUTED 4-HYDROXY-7-METHYLTHIO-2,5-DIOXO-5,6-DIHYDRO-2H-PYRANO[3,2-e]PYRIDINES*

III.1 INTRODUCTION

Preparation and properties of α-oxoketene S,N-, N,N-, and α-nitroketene S,N-acetals of general formula 2, 8 and 5 respectively have been extensively investigated1,2,3. They can easily be prepared in excellent yields by displacement of one of the methylthio groups in α-oxoketene dithioacetals with either primary or secondary amines4,5,6. They can also be prepared from active methylene ketones by reacting their enolate anions with appropriate isothiocyanates followed by alkylation4,7-10,11. Thus a large number of active methylene ketones can be considered as primary precursors

for the synthesis of these compounds. They are stable crystalline compounds and are comparatively less susceptible to hydrolytic conditions than the corresponding enamines. The Chemistry of these compounds has been extensively investigated and their applications as three carbon fragments exploiting the 1,3-electrophilic centres has led to the synthesis of a variety of amino heterocycles\textsuperscript{1,3,12}. On the other hand by virtue of amino functionality in the $\beta$-position, these compounds can display pronounced enamine properties and increased electrophilicity at $\beta$-carbon. Also these class of compounds can function as enamines by participating as two carbon fragments in the reaction with Michael acceptors as well as 1,3-electrophilic components to yield many heterocycles\textsuperscript{13,14,15,16}.

A number of examples of synthetic applications of these enamines to prepare a variety of important heterocyclic systems have been reported\textsuperscript{13,14,15,16}. Some of these selected applications of $\alpha$-oxoketene S,N-2 and N,N-acetals\textsuperscript{8} as enamines have been briefly described in the following section.

**III.1.2 $\alpha$-OXOKETENE-S,N-AND N,N-ACETALS AS ENAMINES IN NENITZESCU INDOLE SYNTHESIS\textsuperscript{14}**

The reaction of p-benzoquinone with ethyl 3-amino crotonate in refluxing acetone to yield ethyl 5-hydroxy-2-methylindole-3-carboxylate was discovered by Nenitzescu\textsuperscript{17} in 1929. This method was reinvestigated in the seventies and a number of structural variants in enamine components were introduced to make the method more versatile\textsuperscript{18}. However, the Chemistry of enamines employed in these developments remained within the traditional methods.
Scheme 1

Ar = C6H5, 4-BrC6H4, 4-MeOC6H4
R1 = Ph, Et
R2 = Ph, Et
R = Ph, Et
X = SMe, NHPh

AcOH / Δ

1, 9, 10: R1 = COPh, R2 = Ph
b: R1 = COPh, R2 = Et
c: R1 = NO2, R2 = Ph
d: R1 = NO2, R2 = Et
Subsequently Junjappa, Ila and co-workers introduced the $\alpha$-oxoketene $S,N-2$, $\alpha$-nitro $S,N-5$ and $N,N$-acetals $8$ (Scheme 1) as new class of enamines for the synthesis of 5-hydroxy indoles$^{14}$. Thus p-benzoquinone $1$ was reacted with $\alpha$-oxoketene $S,N$-acetals $2$ in acetic acid to yield the corresponding 2-amino-3-aryloxy-5-hydroxybenzofuran $3$ (Scheme 1) along with hydrolysed Michael adduct $4$. However, when the nitroketene $S,N$-acetals $5$ were reacted with $1$ in refluxing acetic acid, the expected 1-aryl/alkyl 2-methylthio-3-nitro-5-hydroxy indole $6$, and the corresponding 2-methylthio-3-nitro-5-hydroxybenzofuran $7a$ or 2-anilino-3-nitro-5-hydroxybenzofuran $7b$ were formed (Scheme 1). Similarly the $N,N$-acetals $8$ reacted with p-benzoquinone $1$ to yield a mixture of the corresponding 5-hydroxyindole $9$ and the benzofurans $10$ (Scheme 1). The cyclic $N,N$-acetals $11$ also reacted with p-benzoquinone $1$ to yield the tricyclic indole $12$ (Scheme 2). The $\alpha$-oxoketene $S,N$- and $N,N$-acetals therefore have synthetic potential as functionalized enamines.

III.1.3 REACTION OF $\alpha$-OXOKETENE $S,N$- AND $N,N$-ACETALS WITH DIMETHYLACETYLENE DICARBOXYLATE$^{15}$

The $\alpha$-oxoketene $S,N$-acetals $2$ were reacted with dimethylacetylene dicarboxylate $13$ to exploit the nucleophilic $\alpha$-carbon reactivity towards Michael acceptors. Thus when $S,N$-acetal $2$ was reacted with DMAD $13$, indeed the first Michael adducts $14$ were formed in high yields. However, on further heating the adducts $14$ failed to undergo cyclization to the corresponding pyridones $15$ (Scheme 2)$^{15}$. Apparently the electron withdrawing carboethoxy group and nucleophilic the amino group preferentially occupy the trans position, which prohibits the intramolecular condensation to yield the corresponding pyridones $15$ (Scheme 2). This limitation of geometrical barrier was circumvented when the $\alpha$-oxoketene $N,N$-acetals
were reacted with DMAD, which underwent facile intramolecular condensation to give the corresponding pyridones (Scheme 2). The \( \alpha \)-carbon in the \( N,N \)-acetals is apparently more nucleophilic than that in the corresponding \( S,N \)-acetals due to the presence of two amino groups at the \( \beta \)-carbon.

### III.1.4 REACTION OF \( \alpha \)-OXOKETENE \( S,N \)-AND \( N,N \)-ACETALS WITH BENZOYL ISOThIOCYANATE

The enamine like properties of \( S,N \)-acetals which can be considered as enaminones were further exploited in this laboratory by reacting them with aroyl isothiocyanates to give the corresponding thiopyrimidines in high yields (Scheme 3). The nitroketene \( S,N \)-and \( N,N \)-acetals \( S \) (\( X=\text{PhNH} \)) though condensed with aroyl isothiocyanates through \( \alpha \)-carbon to yield the corresponding adducts \( S \) (\( X=\text{PhNH} \)) and \( S \) failed to cyclize intramolecularly to yield the corresponding nitropyrimidines (Scheme 3). However, under oxidative conditions with bromine, and \( S \) yielded the corresponding isothiozolines in good yields (Scheme 3).

### III.1.5 CYCLOCONDENSATION OF \( \alpha \)-OXOKETENE \( S,N \)-AND \( N,N \)-ACETALS WITH MALEIC ANHYDRIDE AND MALEIMIDE

The synthetic applications of the \( \alpha \)-oxoketene \( S,N \)-and \( N,N \)-acetals as enaminones were further exploited in this laboratory by reacting them with maleic anhydride. Thus the \( S,N \)-acetals in refluxing acetonitrile reacted with maleic anhydride to give the corresponding pyrrolinone acetic acids (Scheme 4). These pyrrolinones underwent smooth cyclization in the presence of acetic anhydride, when the corresponding 2,4-substituted-3-methylthio-1,6-dioxo-2,3-dihydropyran \( \{3,4-\} \) pyrroles were formed in high yields (Scheme 4).
Scheme 4

R₁=CsH₅, 4-MeOC₆H₄, 4-ClCsH₄, 4-MeC₆H₄; R₂=Me, Et, PhCH₂

R₁=c₆H₅ R₂=Et

R₁=C₆H₅, 4-MeOC₆H₄, 4-ClC₆H₄, 4-MeC₆H₄, Me;
R₂=Me, Et, PhCH₂, C₆H₅

R₁=Me, Et, PhCH₂, C₆H₅

R₁=c₆H₅, 4-ClC₆H₄, 4-MeOC₆H₄, Me, X=S, NH

CH₃CN/Ac₂O Δ 90% 30 min

Δ 8 h 75–88% 79–88%
In an alternative experiment, condensation of S,N-acetals 2 and maleic anhydride 25 in the presence of acetic anhydride directly afforded the corresponding 2-substituted-3-methylthio-4-aryl-1,6-dioxo-2,3-dihydropyrano [3,4-c] pyroles 27 in excellent yields (Scheme 4). Similarly, the reaction of cyclic S,N-acetals 28 (X=S) and N,N 11 acetics (X=NH) with maleic anhydride 25 in refluxing acetonitrile gave the corresponding pyrrolo [2,1-b] thiazoles 29 (X=S) and pyrrolo [1,2-a] imidazoles 29 (X=NH) respectively in good yields.

III.1.6 Reactions of α-Oxoketene Dithioacetals with Aminoacetaldehyde Diethylacetal and α-Oxoketene S,N-Acetals with Bromoacetaldehyde Diethylacetal

The α-oxo and α-nitro ketene dithioacetals 30 react with aminoacetaldehyde diethylacetal to yield the functionalized enamines 31. Such S,N-acetals 31 were shown to undergo facile acid catalysed ring closure to the corresponding 2-methylthio-3-substituted pyroles 32 in good yields (Scheme 5).20,21 It may be noted here that the nucleophilic α-carbon of S,N-acetals 31 attacks the electrophilic carbon (diacetal carbon) intramolecularly to give 32 (Scheme 5), when the method was extended to the corresponding N-substituted pyroles 34 the yields of the S,N-acetals were apparently poor due to reduced basicity of the amino group. Thus, an alternative approach was developed through the reaction of α-oxo 2 and α-nitro 5 ketene S,N-acetals and bromoacetaldehyde diethylacetal 33 in hot DMF to yield the desired N-substituted pyroles 34 (Scheme 5).21 The method was equally facile when the cyclic S,N-acetals 28 were reacted with 33 under similar reaction conditions to yield the annulated pyroles 35 (Scheme 5).
III.1.7 REACTION OF ENAMINONES AND ENAMINES WITH MALONYL CHLORIDE\textsuperscript{22,23}

The enaminones \textsuperscript{36} derived from \(\beta\)-ketoesters have been reacted with malonyl chloride \textsuperscript{37} to yield the corresponding 4-hydroxy pyridones \textsuperscript{38} in high yields (Scheme 6)\textsuperscript{22}. The method is extended to substituted malonyl chloride \textsuperscript{42} as well to yield the corresponding pyridones \textsuperscript{41} and \textsuperscript{43} (Scheme 6)\textsuperscript{23}. Interestingly in these systems, initially the carbonyl carbon of acid chloride is attacked by the lone pair of the nitrogen \textsuperscript{40} followed by cyclization through nucleophilic \(\alpha\)-carbon.

Becher and co-workers have reported\textsuperscript{25} the reaction of ethyl acetone dicarboxylates \textsuperscript{44} with arylisothiocyanates in the presence of sodium ethoxide and Dimethyl Sulfoxide to afford the intermediate pyridones \textsuperscript{45}, which were S-methylated to give the thiomethyl pyridone \textsuperscript{46} (Scheme 7).

In a series of papers Becher et al reported\textsuperscript{24,25} that the enolates of penten-1,5-diones \textsuperscript{48} as well as those of glutanaldehyde in a general reaction with organic isothiocyanates yielded 3-acyl or 3-formyl \(2(1H)\) pyridinethiones \textsuperscript{49} (Scheme 7).

In the preceding section a brief account of the Chemistry of \(\alpha\)-oxoketene S,N-acetals \textsuperscript{2} which display the properties of enamines has been discussed. It is therefore, possible to exploit these acetals to construct many important and highly functionalized heterocycles. Our literature survey revealed that the existing methods available for the synthesis of pyridones are not satisfactory particularly when the structural diversity is considered. Thus, the synthesis of pyridones \textsuperscript{38}, from the classical enamine components \textsuperscript{36} derived from \(\beta\)-ketoesters, suffer from one of the serious limitations involving the product formation with alkyl
III.2 RESULTS AND DISCUSSION

In the present study, the known $\alpha$-oxoketene S,N-acetals 2a-k (Scheme 8) were prepared according to the reported procedures $^1$-$^5$, while hitherto unknown S,N-acetal 2l (Scheme 8) was prepared by reacting the $\alpha$-oxoketene dithioacetal derived from acetone, with methylamine in boiling ethanol. The structures of all the S,N-acetals 2a-1 were fully confirmed with the help of analytical and spectral data before they were used as starting materials.

In one of the experiments, the $\alpha$-oxoketene S,N-acetal 2a was reacted with one equivalent of malonyl chloride 37 in the presence of triethylamine in benzene and work-up of the reaction mixture yielded a white crystalline solid (m.p. 267-268$^\circ$C) in 89% yield, which was characterized as 5-benzoyl-4-hydroxy-6-methylthio-1-N-phenyl-2(1H)-pyridone 50a (Scheme 8) on the basis of its analytical and spectral data. Thus, pyridone 50a was analysed for $C_{19}H_{15}NO_3S$ and its mass spectrum showed the molecular ion peak at m/z 337(11%). Its i.r. spectrum (KBr) exhibited sharp peaks at 1660 cm$^{-1}$ and 1635 cm$^{-1}$, which could be assigned to amide carbonyl and benzoyl carbonyl respectively. Its structure was further confirmed by its $^1$H n.m.r. spectrum (CDCl$_3$/DMSO-d$_6$). Thus, the singlet at $\delta$ 1.82(3H) was assigned to three protons of the methylthio group, while the other singlet at $\delta$ 5.84(1H) was assigned to the ring H-3 proton. The multiplet
Scheme 8
around 6 7.15-7.70(8H) was assigned to the eight aromatic protons, the other multiplet between 6 7.83-8.03(2H) was assigned to two aromatic protons. Under similar reaction conditions the other α-oxoketene S,N-acetals 2b-l underwent smooth cyclization with one equivalent of malonyl chloride 37 to yield the corresponding pyridones 50b-l in 71-91% overall yields. The analytical and spectral data of these compounds are in conformity with their assigned structures and are given in the experimental section.

Since pyridones 50 can easily be converted to their enolates and could be reacted further with another mole of malonyl chloride 37 to yield the corresponding pyrano [3,2-c] pyridones 51 (Scheme 9) attempts were made to react 2 with excess of 37.

Thus when α-oxoketene S,N-acetal 2e was reacted with three equivalent of malonyl chloride 37 in the presence of triethylamine in tetrahydrofuran, after work-up the reaction mixture yielded a white crystalline solid (m.p. 202-203°C) different from pyridone 50e in 36% yield (Scheme 9) which was characterized as 8-benzoyl-4-hydroxy-6-methyl-7-methylthio-2,5-dioxo-5,6-dihydro 2H-pyran [3,2-c] pyridine 51e (Scheme 9) on the basis of its analytical and spectral data. Thus 51e was analysed for C_{17}H_{13}NO_{5}S and its mass spectrum showed the molecular ion peak at m/z 343 (38%). Its i.r. spectrum (KBr) exhibited peaks at 1735 cm^{-1} which was assigned to pyrano ring carbonyl whereas broad band at 1670 cm^{-1} was assigned to both benzoyl carbonyl as well as amide carbonyl stretching vibrations. Further structural proof for 51e was obtained from its $^1$H n.m.r. spectrum (CDCl$_3$/DMSO-d$_6$) which showed two singlets at 6 2.26(3H) and 6 3.88(3H) which were attributed to the methylthio protons
respectively. The H-3 proton of the pyranoring appeared as another singlet at $\delta 5.45(1H)$. The multiplets between $\delta 7.48-7.85(3H)$ and between $\delta 7.97-8.17(2H)$ were assigned to the aromatic protons.

The other $\alpha$-oxoketene S,N-acetals $2_g$, $1$, $m$, similarly reacted with excess of malonyl chloride $37$ in the presence of triethylamine in tetrahydrofuran to yield the corresponding pyrano [3,2-\(\alpha\)] pyridines $51_g$, $1$, $m$ (Scheme 9) in $38-44\%$ overall yields. The structures of all the products were confirmed by their analytical and spectral data, which are described in the experimental section.

The S,N-acetals $5_g$, cyclic S,N-acetals $28$ derived from nitromethane and acetophenone respectively did not yield the expected pyridones $52$ and $53$ respectively (Scheme 10). Also the reaction of N,N-acetal $8$ with malonyl chloride $37$ did not afford any identifiable products (Scheme 10).

It may be noted that the overall yields of annulated pyridines $51$ are modest. However, reports on the synthesis of the annulated pyridines with these structural features are very scanty in the literature. The only reference that could be traced out was reported by Schmidt and co-workers in 1978$^{26}$. The strategy of the synthesis was based on the reaction of pre-constructed 4-hydroxy pyridones $55$ with ethoxymethylene malononitrile $56$ in the presence of a base. Moderate to good yields of pyranopyridines $58$ (Scheme 11) were obtained when the reaction was carried out in ethanol at 50-60°C using NaOEt as the base.

The reaction provides a simple method for the synthesis of hitherto unreported pyranopyridones from readily accessible starting materials. In the absence of satisfactory routes for the synthesis of these class of compounds the present method could be considered as an important
Scheme 10
addition despite the moderate yields, though the optimization of yields has not been studied.

III.3 EXPERIMENTAL

General

Melting points were determined on Thomas Hoover apparatus and are uncorrected. The i.r. spectra were recorded on a 'Perkin-Elmer 297' Spectrophotometer and the $^1$H n.m.r. spectra were recorded on a Varian EM-390, 90 MHz Spectrometer using tetramethyl silane (TMS) as internal standard and chemical shifts values are expressed in $\delta$(ppm). $^{13}$C n.m.r. spectra were recorded on a Brucker WH-270 spectrometer. The mass spectra were recorded on a Jeol D-300 mass spectrometer and carbon, hydrogen, nitrogen analysis were done at Central Drug Research Institute, Lucknow, India.

Starting Materials

The commercial samples of the various acetophenones and benzene, tetrahydrofuran, triethylamine were purified before use. Malonyl chloride was prepared by the reported procedure. Of the various $\alpha$-oxoketene S,N-acetals used $2a-k$ were prepared by the reported procedure and their structures were confirmed by comparing their analytical and spectral data with the reported ones. The unknown $\alpha$-oxoketene S,N-acetal $2i$ was prepared by extending the reported procedure, and structure was confirmed by the spectral and analytical data which is given below.

3-Methylamino-3-methylthio-1-methyl-2-propen-1-one (2i) was obtained as viscous oil (TLC single spot); yield 76%; i.r. (CCl$_4$): $\nu_{\text{max}}$ = 3435, 1757 cm$^{-1}$; $^1$H n.m.r.(CCl$_4$): 6.1.98(s,3H;CH$_3$); 2.37(s,3H;SCH$_3$); 3.05(d, 3H,NHCH$_3$); 4.75(s,1H olefin); 11.30(brs,1H,NH). (Found: C,49.51; H,7.63; N,9.58; Calc. for C$_6$H$_{11}$NOS(145.1): C,49.62; H,7.58; N,9.65%).
1-Alkyl/aryl-5-aryloxy-6-methylthio(2H)-pyridones (50a-l);

General Procedure:

To a well stirred and ice cooled solution of S,N-acetal 2 (10 mmol) and dry triethylamine (2.02 g, 20 mmol) in dry benzene (30 ml), a solution of malonyl chloride (1.41 g, 10 mmol) in benzene (15 ml) was added slowly during 15 min. and the reaction mixture was further stirred for 3 h. The reaction mixture was poured into crushed ice (150 g), neutralized with solid NaHCO₃ (10 g), and it was allowed to warm up to room temperature. The light brown solid separated was collected by suction filtration and recrystallized from boiling ethanol to give pure pyridones 50a-1 as white crystalline solids.

5-Benzoyl-4-hydroxy-6-methylthio-1-phenyl-2-pyridone (50a) was obtained as white crystalline solid (ethanol); yield 89%; m.p. 267-268°C; i.r. (KBr): δ max = 1660, 1635 cm⁻¹; ¹H n.m.r. (CDCl₃/DMSO-d₆): δ 1.82 (s, 3H, SCH₃); 5.84 (s, 1H, H-3); 7.15-7.70 (m, 8H arom); 7.93-8.03 (m, 2H arom). (Found: C, 67.35; H, 4.43; N, 4.13; Calc. for C₁₉H₁₅NO₃ (337.4): C, 67.65; H, 4.45; N, 4.15%). m/z 337(M⁺,11); 209(12).

5-(4-Chlorobenzoyl)-4-hydroxy-6-methylthio-1-phenyl-2-pyridone (50b) was obtained as white crystalline solid (ethanol); yield 81%; m.p. 211-212°C; i.r. (KBr): δ max = 1660, 1638 cm⁻¹; ¹H n.m.r. (CDCl₃/DMSO-d₆): δ 1.85 (s, 3H, SCH₃); 5.93 (s, 1H, H-3); 7.14-7.60 (m, 7H arom); 7.78-8.13 (m, 2H arom). (Found: C, 61.13; H, 3.74; N, 3.75; Calc. for C₁₉H₁₄ClNO₃ (371.8): C, 61.37; H, 3.76; N, 3.76%). m/z 371(M⁺,12).

4-Hydroxy-5-(4-methoxybenzoyl)-6-methylthio-1-phenyl-2-pyridone (50c) was obtained as white crystalline solid (ethanol); yield 83%; m.p. 270°C; i.r. (KBr): δ max = 1665, 1640 cm⁻¹; ¹H n.m.r. (CDCl₃/DMSO-d₆):
5-Benzoyl-4-hydroxy-6-methylthio-1-(4-methylphenyl)-2-pyridone (50d) was obtained as white crystalline solid (ethanol); yield 91%; m.p. 286-287°C; i.r. (KBr): $\nu_{\text{max}} = 1660, 1640 \text{ cm}^{-1}$; $^1$H n.m.r. (CDCl$_3$/DMSO-d$_6$): $\delta$ 1.82 (s, 3H, SCH$_3$); 2.37 (s, 3H, CH$_3$); 5.97 (s, 1H, H-3); 7.00-7.70 (m, 7H arom); 7.82-8.10 (m, 2H arom). (Found: C, 65.12; H, 4.61; N, 3.81%. Calc. for C$_{20}$H$_{17}$NO$_3$S(367.4): C, 65.39; H, 4.63; N, 3.81%). m/z 367 (M$^+$, 9).

5-Benzoyl-4-hydroxy-1-methyl-6-methylthio-2-pyridone (50e) was isolated as white crystalline solid (ethanol); yield 73%; m.p. 270-271°C; i.r. (KBr): $\nu_{\text{max}} = 1660, 1635 \text{ cm}^{-1}$; $^1$H n.m.r. (CDCl$_3$/DMSO-d$_6$): $\delta$ 2.20 (s, 3H, SCH$_3$); 3.60 (s, 3H, NCH$_3$); 5.77 (s, 1H, H-3); 7.40-7.60 (m, 3H arom); 7.72-7.92 (m, 2H arom). (Found: C, 60.87; H, 4.71; N, 5.06. Calc. for C$_{14}$H$_{13}$NOS(275.3): C, 61.09; H, 4.72; N, 5.09%). m/z 275 (M$^+$, 30).

5-(4-Chlorobenzoyl)-4-hydroxy-1-methyl-6-methylthio-2-pyridone (50f) was obtained as white crystalline solid (ethanol); yield 71%; m.p. 229-230°C; i.r. (KBr): $\nu_{\text{max}} = 1670, 1650 \text{ cm}^{-1}$; $^1$H n.m.r. (CDCl$_3$/DMSO-d$_6$): $\delta$ 2.26 (s, 3H, SCH$_3$); 3.70 (s, 3H, NCH$_3$); 6.01 (s, 1H, H-3); 7.35-7.86 (m, A$_2$B$_2$, 4H arom). (Found: C, 54.01; H, 3.85; N, 4.50. Calc. for C$_{14}$H$_{12}$ClNO$_3$S(309.8): C, 54.28; H, 3.87; N, 4.52%). m/z 309 (M$^+$, 27).

5-Benzoyl-1-ethyl-4-hydroxy-6-methylthio-2-pyridone (50g) was obtained as white crystalline solid (ethanol); yield 76%; m.p. 279-280°C; i.r. (KBr): $\nu_{\text{max}} = 1660, 1640 \text{ cm}^{-1}$; $^1$H n.m.r. (CDCl$_3$/DMSO-d$_6$): $\delta$ 1.22 (t, 3H, J=7Hz, CH$_3$CH$_2$); 2.30 (s, 3H, SCH$_3$); 4.23 (q, 2H, J=7Hz, CH$_3$CH$_2$); 6.85 (s, 1H, H-3); 7.40-7.95 (m, 5H arom). (Found: C, 62.06; H, 5.17; N, 4.82. Calc. for
5-(4-Chlorobenzoyl)-1-ethyl-4-hydroxy-6-methylthio-2-pyridones (50h)

was obtained as white crystalline solid (ethanol); yield 74%, m.p. 264-265°C; i.r. (KBr): \( \nu_{\text{max}} = 1670, 1640 \text{ cm}^{-1} \); \( ^1\text{H} \) n.m.r. (CDCl\(_3/\)DMSO-d\(_6\)):
- 1.22(t, 3H, J=7Hz, \( \text{CH}_3\text{CH}_2\));
- 2.30(s, 3H, \( \text{SCH}_3\));
- 4.22(q, 2H, J=7Hz, \( \text{CH}_3\text{CH}_2\));
- 5.82(s, 1H, H-3);
- 7.35-7.98(m, \( \text{Ar} \), 4H).

(Found: C, 55.3%; H, 4.3%; N, 4.29. Calc. for \( \text{C}_{15}\text{H}_{14}\text{ClNO}_3\text{S}\)): C, 55.6%; H, 4.32; N, 4.32%.

m/z 323(M\(^+\), 16).

1-Benzyl-5-benzoyl-4-hydroxy-6-methylthio-2-pyridone (50i)

was obtained as white crystalline solid (ethanol); yield 77%; m.p. 211-212°C; i.r. (KBr): \( \nu_{\text{max}} = 1660, 1630 \text{ cm}^{-1} \); \( ^1\text{H} \) n.m.r. (CDCl\(_3/\)DMSO-d\(_6\)):
- 2.02(s, 3H, \( \text{SCH}_3\));
- 5.48(s, 2H, \( \text{C}_6\text{H}_5\text{CH}_2\));
- 5.98(s, 1H, H-3);
- 7.10-8.05(m, 10H, \( \text{Ar} \)).

(Found: C, 68.18; H, 4.82; N, 3.97. Calc. for \( \text{C}_{20}\text{H}_{17}\text{NO}_3\text{S}\)): C, 68.37; H, 4.84; N, 3.98%.

m/z 351(M\(^+\), 29).

1-Benzyl-4-hydroxy-5-(methoxybenzoyl)-6-methylthio-2-pyridones (50j)

was obtained as white crystalline solid (ethanol); yield 78%; m.p. 209-209°C; i.r. (KBr): \( \nu_{\text{max}} = 1660, 1640, 1600 \text{ cm}^{-1} \); \( ^1\text{H} \) n.m.r. (CDCl\(_3/\)DMSO-d\(_6\)):
- 2.00(s, 3H, \( \text{SCH}_3\));
- 3.83(s, 3H, \( \text{OCH}_3\));
- 5.50(s, 2H, \( \text{C}_6\text{H}_5\text{CH}_2\));
- 5.98(s, 1H, H-3);
- 6.84-7.45(m, 7H, \( \text{Ar} \));
- 7.76-7.92(m, 2H, \( \text{Ar} \)).

(Found: C, 65.87; H, 4.97; N, 3.66. Calc. for \( \text{C}_{21}\text{H}_{19}\text{NO}_4\text{S}\)): C, 66.14; H, 4.98; N, 3.67%.

m/z 381(M\(^+\), 10).

5-Benzoyl-4-hydroxy-6-methylthio-1-n-propyl-2-pyridone (50k)

was obtained as white crystalline solid (ethanol); yield 76%; m.p. 230-231°C; i.r. (KBr): \( \nu_{\text{max}} = 1667, 1640 \text{ cm}^{-1} \); \( ^1\text{H} \) n.m.r. (CDCl\(_3/\)DMSO-d\(_6\)):
- 0.90(t, 3H, \( \text{J=6.5Hz}, \text{CH}_3\text{CH}_2\text{CH}_2\));
- 1.66(sext, 2H, \( \text{J=6.5Hz}, \text{CH}_3\text{CH}_2\text{CH}_2\));
- 2.27 \( \text{t}, \text{J=6.5Hz}, \text{CH}_3\text{CH}_2\text{CH}_2\));
- 4.11(t, 2H, \( \text{J=6.5Hz}, \text{CH}_3\text{CH}_2\text{CH}_2\));
- 5.84(s, 1H, H-3);
- 7.37-7.90
123

(m,5\textsubscript{H}\textsubscript{arom}). (Found: C,63.15; H,5.59; N,4.60. Calc. for C\textsubscript{16}H\textsubscript{17}NO\textsubscript{3}S(303.4): C,63.36; H,5.61; N,4.62%). m/z 303(M\textsuperscript{+},10).

5-Acetyl-4-hydroxy-1-methyl-6-methylthio-2-pyridone (501) was obtained as colorless crystalline solid (ethanol); yield 75%; m.p. 224-225°C; i.r.(KBr): \(\nu\text{max} = 1700, 1640, 1600\text{ cm}^{-1}\); \(^1\)H n.m.r. (CDCl\textsubscript{3}/DMSO-d\textsubscript{6}): 6 2.32(s,3H,\textit{SCH}_3); 2.40(s,3H,\textit{CH}_3); 3.60(s,3H,\textit{NCH}_3); 5.87(s,1H,H-3).

(Found: C,50.47; H,5.14; N,6.54. Calc. for C\textsubscript{9}H\textsubscript{11}NO\textsubscript{3}S(213.25): C,50.64; H,5.16; N,6.56%). m/z 213(M\textsuperscript{+},55).

6-Alkyl/Benzyl-9-benzoyl/acetetyl-4-hydroxy-7-methylthio-2,5-dioxo-5,6-dihydro 2\textsubscript{H}-pyrano [3,2-c] pyridines (5le,g,i,m); General Procedure:

To a well stirred solution of S,N-acetal 2 (10 mmol) and dry triethylamine (6.06g, 60 mmol) in dry tetrahydrofuran (15 ml), malonyl chloride (4.23g, 30 mmol) was added slowly during 15 min. and the mixture was further stirred for 25 hr. at room temperature. The mixture was poured onto crushed ice (150g), neutralized with solid sodium bicarbonate(10g), extracted with chloroform (3x100 ml) washed with water (3x100 ml), dried over sodium sulfate and evaporated to give a dark colored viscous residue, which on column chromatography on silica gel (chloroform/hexane 1:3 eluent) gave pure pyrano pyridones 5le,g,i,m as pale colored solids (ethanol).

8-Benzoyl-4-hydroxy-6-methyl-7-methylthio-2,5-dioxo-5,6-dihydro-2H-pyrano [3,2-c] pyridine (5le) was obtained as pale yellow crystalline solid (ethanol); yield 36%; m.p. 202-203°C; i.r.(KBr): \(\nu\text{max} = 1735, 1670\text{br}\text{ cm}^{-1}\); \(^1\)H n.m.r. (CDCl\textsubscript{3}/DMSO-d\textsubscript{6}): 6 2.36(s,3H,\textit{SCH}_3); 3.88(s,3H,\textit{NCH}_3); 5.45(s,1H,H-3); 7.48-7.85(m,3H); 7.98-8.17(m,2H). (Found: 59.30; H,3.77; N,4.06. Calc. for C\textsubscript{17}H\textsubscript{13}NO\textsubscript{5}(343.5): C,59.41; H,3.79; N,4.08%). m/z 343(M\textsuperscript{+},38).
8-Benzoyl-6-ethyl-4-hydroxy-7-methylthio-2,5-dioxo-5,6-dihydro-2H-pyrano [3,2-e] pyridine (50g) was obtained as pale yellow crystalline solid (ethanol); yield 44%; m.p. 202-203°C; i.r. (KBr): $\nu_{\text{max}} = 1740, 1675 \text{ cm}^{-1}$; $^1$H n.m.r. (CDCl$_3$/DMSO-d$_6$): $\delta$ 1.35 (t, 3H, J=7Hz, CH$_3$CH$_2$); 2.38 (s, 3H, SCH$_3$); 4.45 (q, 2H, J=7Hz, CH$_3$CH$_2$N); 4.56 (s, 1H, H-3); 7.40-7.75 (m, 3H aromatic); 7.88-8.08 (m, 2H aromatic); 13C n.m.r. (DMSO-d$_6$; 100 MHz): 13.70 (CH$_3$CH$_2$); 20.50 (CH$_3$S); 41.69 (CH$_3$CH$_2$); 89.35 (C-3); 101.73 (C-8); 119.85 (C-4a); 129.06, 129.55, 134.55 (CH aromatic); 136.03 (C-1' of phenyl); 145.21 (C-4); 158.62 (C-8a); 159.77 (C-7); 163.01 (CN-C=N); 167.9 (C=O); 188.56 (Ar-C=O). (Found: C,60.56; H,4.24; N,4.01. Calc. for C$_{18}$H$_{15}$NO$_5$S (357.4): C,60.44; H,4.19; N,3.91%). m/z 357($M^+$,100).

6-Benzyl-8-benzoyl-4-hydroxy-7-methylthio-2,5-dioxo-5,6-dihydro-2H-pyrano [3,2-e] pyridines (51i) was obtained as pale yellow solid (ethanol); yield 38%; m.p. 200°C; i.r. (KBr): $\nu_{\text{max}} = 1732, 1660$ (br) cm$^{-1}$; $^1$H n.m.r. (CDCl$_3$/DMSO-d$_6$): $\delta$ 2.11 (s, 3H, SCH$_3$); 5.45 (s, 1H, H-3); 5.65 (s, 2H, C$_6$H$_5$CH$_2$); 7.01-8.02 (m, 10H aromatic). (Found: C,66.03; H,3.97; N,3.39. Calc. for C$_{23}$H$_{17}$NO$_5$S (419.4): C,65.80; H,4.05; N,3.34%). m/z 419($M^+$,57).

8-Acetyl-6-ethyl-4-hydroxy-7-methylthio-2,5-dioxo-5,6-dihydro-2H-pyrano [3,2-e] pyridine (51m) was obtained as pale yellow crystalline solid (ethanol); yield 35%; m.p. 165-166°C; i.r. (KBr): $\nu_{\text{max}} = 1740, 1705, 1665$ cm$^{-1}$; $^1$H n.m.r. (CDCl$_3$/DMSO-d$_6$): $\delta$ 1.33 (t, 3H, J=7.5Hz, CH$_3$CH$_2$); 2.54 (s, 3H, SCH$_3$); 2.60 (s, 3H, CH$_3$); 4.44 (q, 2H, J=7.5Hz, CH$_3$CH$_2$N); 5.47 (s, 1H, H-3). (Found: C,53.02; H,4.48; N,4.67. Calc. for C$_{13}$H$_{13}$NO$_5$S (295.3): C,52.82; H,4.40; N,4.74%). m/z 295($M^+$,79).
References