SYNTHESIS OF α-FORMYLKETENE DITHIOACETAL MEDIATED NOVEL PYRAMIDINE DERIVATIVES

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A MINOR PROJECT WORK OF Dr. ANNIE MATHEWS
POSTGRADUATE DEPARTMENT OF CHEMISTRY
BASELIUS COLLEGE
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Annie
SYNTHESIS OF α-FORMYLKETENE DITHIOACETAL MEDIATED NOVEL PYRAMIDINE DERIVATIVES

In chemistry, organic synthesis is the purposeful execution of one or more chemical reactions in order to get a product or several products. An organic synthesis begins by selection of compounds that are known as reagents or reactants. The best chemical syntheses are those that use cheap starting materials, require only a few steps, and have a good output of product based on the amounts of starting chemicals. The starting materials for organic synthesis can be simple compounds removed from oil and natural gas or more complex chemicals isolated in large amounts from plant and animal sources. The goal of chemical synthesis is to make a particular product that can be used commercially, for example as a drug, a fragrance, a polymer coating, a food or a cloth dye, a herbicide or some other commercial or industrially useful products. Compounds are also synthesized to test a chemical theory, to make a new or better chemical or to confirm the structure of a material isolated from a natural source. Chemical synthesis can also be used to supplement the supply of a drug that is commonly isolated in small amounts from natural sources. Chemical synthesis has played an important role in eradicating one of the major infectious diseases associated with the tropical regions of the world- Malaria. Malaria is a disease that affects millions of people and is spread by mosquito bites and the discovery of the drug chloroquine was a boon against malaria.
Pyrimidines are single-ringed, crystalline organic base, C₄H₄N₂, that forms uracil, cytosine, or thymine- an integral part of the genetic materials DNA and RNA and is the parent compound of many drugs, including the barbiturates.¹ Pyrimidines also known as metadiazines, are heterocyclic compounds composed of four carbon atom and two nitrogen atoms, the nitrogen atoms are in the meta positions. Pyrimidine and its derivatives demonstrate a diverse array of biological and pharmacological activities including anticonvulsant, antibacterial, antifungal, antiviral and anticancer properties. In addition pyrimidines are important for many biochemical processes, including sucrose and cell wall polysaccharide metabolism² and also as drugs in medicinal chemistry.³ They possess antifoliate, antimicrobial, anticancer, anticonvulsant, antirubella and selective hepatitis B virus inhibiting activities.⁴ Dihydropyrimidinones, the products of the Biginelli reaction, are widely used in the pharmaceutical industry as calcium channel blockers.⁵ Pyrimidine-5-carbaldehydes are valuable precursors for the synthesis of drugs used for the treatment of Alzheimer disease.⁶ Some annulated pyrimidines are used in the treatment of cardiovascular diseases and insomnia.⁷

The increasing importance of pyrimidine and its derivatives as intermediates for the synthesis of biologically and industrially useful compounds prompted us to develop a new method for their synthesis from α-formylketene dithioacetals.⁸ It was reported that formylketene dithioacetals when treated with guanidine produced pyrimidine-5-carbaldehyde(Scheme-1).⁹
The presence of highly reactive formyl group on the above pyrimidinecarbaldehydes will make the compounds valuable precursors for the synthesis of highly functionalized and annulated heterocyclic compounds. Therefore in the project we investigated the reactivity of pyrimidine-5-carbaldehydes with malononitrile. The reactions of aldehydes or ketones with active methylene compounds like malononitrile, ethyl cyanoacetate when carried out in the presence of weak bases like an amine or a buffer of ammonium acetate / acetic acid afford corresponding condensation adducts, which can be insitu cyclized to form heterocyclic compounds especially functionalized pyridine derivatives. Therefore we planned a synthesis by the knoevenagel condensation reaction on pyrimidine-5-carbaldehyde with malononitrile so as the produce novel pyrimidine derivatives (Scheme-2).
The condensation products were further used for the synthesis of annulated pyrimidines (Scheme 3).

![Scheme 3](image_url)

Objective of the project was to prepare novel pyrimidine derivatives from α-formylketene dithioacetals. Different synthetic steps were used to obtain the final products. The main reaction was the synthesis of pyrimidine-5-carbaldehyde from α-formylketene dithioacetals using guanidine. It was followed by the Knoevenagel condensation reaction on pyrimidine-5-carbaldehyde with malononitrile to obtain condensation products. The condensation products were further used for the synthesis of annulated pyrimidines.

Literature survey revealed that substituted pyrimidines can be effectively transformed to useful fused heterocyclic systems. Such systems can be effectively used as number of materials. Therefore, the project with an objective to prepare highly substituted pyrimidines for possibility for further transformations can be of substantial interest.
Experiments, Results and Discussion.

Pyrimidines had been obtained from 1,3 bifunctional compounds by combining with proper 1,3- dinitrogen nucleophiles. Among the numerous synthetic routes to substituted pyrimidines the reaction with amidines is well known and has been much used. It thus seemed to be of interest to examine the behavior of guanidine with α-formylketene dithioacetals for the synthesis of useful pyrimidines. Thus we treated α-formylketene dithioacetals with guanidine and excellent yield of highly functionalized pyrimidines were obtained. The starting compounds could be prepared in quantitative yield from α-oxoketene dithioacetals by Vilsmeier-Haack reaction as reported by Asokan et al. As the synthesized substituted pyrimidines contained various reactive groups, it was further used for transformations to prepare annelated pyrimidines by treating with malononitrile.

PREPARATION OF α-OXOKETENE DITHIOACETAL

Ketones in presence of strong base can react with CS₂ and alkylating agent forming ketene dithioacetals(Table-1). Compounds were obtained as pure crystals after crystallization and column chromatography using 3:7 ethyl acetate-hexane mixture. Compounds were confirmed by comparing their Rf values with standard ketene dithioacetals.
The Vilsmeier-Haack reaction of α-oxoketene dithioacetals: Synthesis of Formylketene dithioacetals.

The benzoylketene dithioacetal 2 was dissolved in dry DMF and the solution was added to 1.5 equivalent Vilsmeier-Haack reagent, prepared by mixing phosphorous oxychloride and DMF at 0 °C. The reaction mixture was well stirred at room temperature for 12 hrs and worked up using aqueous potassium carbonate. The reaction
led to the formation of formylketene dithioacetals 3 as the single **product in 93% yield** (Scheme 5). The reaction was extended to various ketene dithioacetals to afford corresponding formylketene dithioacetals(Table-2). Compounds were obtained as pure semi solids after column chromatography using 2:3 ethyl acetate-hexane mixture. Compounds were confirmed by comparing their Rf values with standard formylketene dithioacetals.9

![Chemical structure](image)

**Scheme-5**

<table>
<thead>
<tr>
<th>6,7</th>
<th>Ar</th>
<th>Yield (%)</th>
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<tr>
<td>a</td>
<td>C₆H₅</td>
<td>90</td>
</tr>
<tr>
<td>b</td>
<td>4-CH₃C₆H₄</td>
<td>89</td>
</tr>
<tr>
<td>c</td>
<td>4-ClC₆H₄</td>
<td>85</td>
</tr>
<tr>
<td>d</td>
<td>4-BrC₆H₄</td>
<td>82</td>
</tr>
<tr>
<td>e</td>
<td>4-CH₃OC₆H₄</td>
<td>91</td>
</tr>
<tr>
<td>f</td>
<td>3,4- (CH₃O)₂C₆H₄</td>
<td>85</td>
</tr>
</tbody>
</table>

**Table-2**
Synthesis of pyrimidine-5-carbaldehydes

The starting compound, formylketene dithioacetal could be consider as a combination of ketene dithioacetal as well as a 1,3-dicarbonyl compound. There are number of reports for the preparation of pyrimidines from such compounds with amidines. Therefore the reaction of formylketene dithioacetal with amidines should readily generate substituted pyrimidines. The only major product formed was pyrimidine-5-carbaldehyde.

Formylketene dithioacetals were treated with guanidine with potassium carbonate as base in presence of acetonitrile to obtain pyrimidine-5-carbaldehyde. Compounds were obtained as pure solids after recrystalisation and column chromatography using 1:1 ethyl acetate-hexane mixture. Compounds were confirmed by comparing their Rf values with standard pyrimidine-5-carbaldehydes (Scheme-6). The reaction was extended to various formylketene dithioacetals to afford corresponding pyrimidine-5-carbaldehydes (Table-3).

\[ \text{Scheme-6} \]

7 \text{ R= NH}_2 \quad 8
Mechanism of formation of pyrimidinecarbaldehydes

The formation of substituted pyrimidines 8 from formylketene dithioacetal 7 using amidines can be rationalized according to the mechanism proposed by Topfl et al.\textsuperscript{14} Initially a sequential conjugated addition elimination of amidine to afford an acyclic N,S-acetal 9 followed by the intramolecular 1,2-nucleophilic addition to the carbonyl group of the intermediate 10 followed by elimination of water to produce the required pyrimidine 8. Among the carbonyl groups, the one near the aromatic ring system is more susceptible to the 1,2 intramolecular addition reaction (Scheme 7). Therefore a pyrimidine with a highly useful functional moiety was produced where the aldehyde remain unreacted.

<table>
<thead>
<tr>
<th>(7,8)</th>
<th>R</th>
<th>Yield (%)</th>
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<tr>
<td>a</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>70</td>
</tr>
<tr>
<td>b</td>
<td>4-CH\textsubscript{3}C\textsubscript{6}H\textsubscript{4}</td>
<td>75</td>
</tr>
<tr>
<td>c</td>
<td>4-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>76</td>
</tr>
<tr>
<td>d</td>
<td>4-BrC\textsubscript{6}H\textsubscript{4}</td>
<td>78</td>
</tr>
<tr>
<td>e</td>
<td>4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{4}</td>
<td>80</td>
</tr>
<tr>
<td>f</td>
<td>3,4- (CH\textsubscript{3}O)\textsubscript{2}C\textsubscript{6}H\textsubscript{3}</td>
<td>70</td>
</tr>
</tbody>
</table>

Table-3
KONEVENANGEL CONDENSATION REACTION ON PYRIMIDINE-5-CARBALDEHYDES WITH MALONONITRILE

Pyrimidine-5-carbaldehydes 8 had an aldehyde and –SCH$_3$ groups adjacent to each other. In order to produce fused pyrimidines, pyrimidine-5-carbaldehyde was treated with malononitrile, an active methylene compound. Generally the reactions of aldehydes or ketones with active methylene compounds like malononitrile, ethyl cyanoacetate are carried out in the presence of weak bases like an amine or a buffer of ammonium acetate / acetic acid.$^{15}$ In many cases such reactions afford corresponding condensation adducts, which can be $insitu$ cyclized to form heterocyclic compounds especially functionalized pyridine derivatives.$^{16}$ So when the 5-pyrimidinecarbaldehydes 8
were subjected to Knoevenagel condensation reaction with malononitrile using ammonium acetate / acetic acid as the buffer, the reaction afforded 2-{[2-amino-4-(methylsulfanyl)-6-phenyl-5-pyrimidinyl]methylene}malononitriles 11 in excellent yields (Scheme 8). The condensation products were heated with HCl/t-BuOH and also with sodium alkoxides and the reactions produced a mixture of compounds which couldn’t be separated to get pure compounds for analysis.

\[
\begin{align*}
\text{R} & \quad \text{NH}_2 \\
\text{N} & \quad \text{N} \\
\text{R} & \quad \text{SMe} \\
\text{CHO} & \\
\text{N} & \quad \text{N} \\
\text{SMe} & \quad \text{NH}_2 \\
\text{CN} & \quad \text{CN} \\
\text{NH}_4\text{COOCH}_3 / \text{CH}_3\text{COOH.} & \quad \text{Reflux 2h} \\
\end{align*}
\]

\[8,11\]

\[
\begin{array}{|c|c|c|}
\hline
\text{8,11} & \text{R} & \text{Yield}\% \\
\hline
\text{a} & \text{H} & 65 \\
\hline
\text{b} & 4-\text{CH}_3 & 70 \\
\hline
\text{c} & 4-\text{Cl} & 67 \\
\hline
\text{d} & 4-\text{Br} & 70 \\
\hline
\text{e} & 4-\text{OCH}_3 & 77 \\
\hline
\text{f} & 3,4-(\text{OCH}_3)_2 & 76 \\
\hline
\end{array}
\]

\[\text{Table-4}\]
Infrared spectrum, $^1$H and $^{13}$C NMR spectra of typical Knoevenagel condensation adduct of Pyrimidine-5-carbaldehyde and Malononitrile (11f)

Fig 1 - IR Spectrum of 11f
Fig 2 - $^1$H NMR Spectrum of 11f
The IR spectrum of the condensation product 11f (Figure 1) showed all the peaks of NH$_2$ group at 3379 cm$^{-1}$, 3309 cm$^{-1}$. 3182 cm$^{-1}$ peak represented aromatic C-C stretching vibrations. A sharp peak at 2229 cm$^{-1}$ indicated the presence of cyanide group in the product, clearly indicating the presence of condensation in the product. Aromatic - C= C- stretching vibration was seen at 1643 cm$^{-1}$. Carbon-Nitrogen stretching vibration
was seen at 1265 cm$^{-1}$. The $^1$H NMR spectrum of 11f (Figure 2) revealed a singlet peak at $\delta$ 2.60 representing three -SMe protons. Two singlets at $\delta$ 3.93 & 3.95 represented two methoxy groups in the phenyl ring. A broad peak at $\delta$ 5.05 represented two NH$_2$ protons, multiplet at $\delta$ 6.90-7.26 represented three phenyl protons and a sharp singlet at $\delta$ 7.92 represented vinylic proton. The aldehyde peak of pyrimidine-5-carbaldehyde was absent in the $^1$H NMR of the compound supporting the reaction site in the reagent. $^{13}$C NMR spectrum of 11f (Figure 3) reaffirmed the predicted structure. Peaks at $\delta$ 13.17, was of SMe carbon. Peak at $\delta$ 56.00, 56.12 were of the methoxy carbons. Peak at $\delta$ 88.15 was assigned to the carbon atom connected to the nitrile groups [(C-(CN)$_2$] , $\delta$ 111.35 and $\delta$ 111.85 were representing the two nitrile carbon atoms. Peak at $\delta$ 110.84 represented the C-5 carbon of pyrimidine ring. The six phenylic carbons were at $\delta$ 112.27, 113.23, 123.00, 129.09, 149.36 and 151.33. The vinylic carbon appeared at $\delta$ 156.25. The three other pyrimidine carbons were at $\delta$ 161.40, 165.81, 171.82. Peaks representing the two cyanide groups and the -SMe group revealed that no cyclization took place in the reaction and the product is only a condensation product of the pyrimidine and malononitrile. Analysis of the spectra of other systems was in agreement with the structure proposed.

**Cyclization reaction of Knoevenagel condensation adduct.**

As the condensation adduct contains reactive groups, we planned to cyclize the product in order to synthesize new annulated pyrimidines. Asokan et al had reported similar cyclisation reactions to produce pyridines.$^{16}$ Therefore we expected a pyridopyrimidine derivative. The condensation product was dissolved in t-BuOH and to
that solution, con HCl(acid medium) was added and heated in an oil bath at 120°C for 24 Hr. Cooled the reaction mixture and then added ice cold water. Extracted in dichloromethane, dried over anhydrous sodium sulphate and the solvent was evaporated. TLC revealed a mixture of products with close Rf values. Recrystallization from different solvents did not give any pure product. A similar reaction was carried out using sodium ethoxide(base) instead of HCl. There also a mixture of products were resulted.

**Reaction between pyrimidinecarbaldehyde( 8 )with hydroxylamine.**

In addition to the reaction with malononitrile, we tried to react the pyrimidines 8 with hydroxylamine hydrochloride in a view to synthesize isoxolopyrimidines 13. But we obtained only the oxime 12, by the reaction of aldehyde functionality and hydroxylamine (Scheme 9). The $^1$H NMR showed no aldehyde hydrogen peak and the alkysulfanyl protons were present in the spectrum (Fig. 5)
Scheme 9

\[
\begin{align*}
8 & \quad \text{CHO} & \text{NH}_2 \\
\text{R} & \quad \text{NH}_2 & \text{SMe} \\
\end{align*}
\]

+ \text{NH}_2\text{OH.HCl}

\[
\begin{align*}
\text{K}_2\text{CO}_3 / \text{CH}_3\text{CN} & \quad \text{Reflux 10h} \\
\text{R} & \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2 & \quad \text{SMe} \\
\text{R} & \quad \text{O} \\
\end{align*}
\]

8, 12

| Scheme 9 |
|---|---|---|
| 8, 12 | R | Yield % |
| a | 4-H | 60 |
| b | 3-OCH$_3$ | 74 |
| c | 4-CH$_3$ | 65 |

Table 5
Fig 4- IR Spectrum of the oxime with 5-pyrimidinecarbaldehyde 12b

Fig 5- $^1$H NMR Spectrum of the Oxime with 5-pyrimidinecarbaldehyde 12b
Fig 6  $^{13}$C NMR Spectrum of the Oxime with 5-pyrimidinecarbaldehyde 12b

The NH$_2$ peaks were present in the IR spectrum of the oxime of the pyrimidine 12b at 3287 and 3129 cm$^{-1}$. In addition of that the oxime OH peak was at 3479 cm$^{-1}$ (Figure 4). In the IR spectrum a sharp peak appeared at 979 cm$^{-1}$ due to N-O of aldoxime. The aldehyde peak was absent in the $^{1}$H NMR spectrum of the compound 12b (Figure 5). Peaks at δ 3.8 and 2.5 corresponded to -OMe and SCH$_3$ protons. NH$_2$ protons of the pyrimidine ring were at δ 5.8. Aromatic protons appeared as a multiplet at δ  6.96-6.99 and at δ7.42-7.45. A singlet at δ 7.94 was due to the aldoxime proton. These factors proved that only the oxime was formed in the reaction. $^{13}$C NMR spectrum of the
compound 12b (solvent CDCl$_3$) (Figure 8). Peaks at $\delta$ 13.1 and 55.4 corresponded to and SCH$_3$ and –OMe carbons. Peak at $\delta$ 88.07 was assigned to the carbon atom connected to the =NOH. The six phenylic aromatic carbons were at $\delta$ 111.3, 111.7, 113.2, 114.3, 1128.9 and 131.0. The pyrimidine carbons were at $\delta$ 156.1, 161.6, 165.8, 171.8. These factors proved that only the oxime was formed in the reaction.

**Conclusion**

In the project a facile and practical method for the synthesis of structurally diverse hitherto unreported pyrimidines from alpha-formylketene dithioacetals was carried out. Knoevenagel condensation on pyrimidine-5-carbaldehyde was carried out using malononitrile which generated novel pyrimidine derivatives with number of potential functional groups. The condensation products were further used for the synthesis of annulated pyrimidines by heating with HCl/t-BuOH and also with sodium alkoxides and the reactions produced a mixture of compounds which could not be separated to get pure compounds for analysis. The synthetic potential of the novel pyrimidines prepared are to be investigated further. Work is going on in the laboratory to prepare annulated pyrimidines. Crystal studies of the pyrimidine-5-carbaldehyde and of the condensation product with malononitrile are also going on.
Experimental

Melting points were determined on Buchi 530 melting point apparatus and were uncorrected. The IR spectra were recorded using KBr pellets on a Schimadzu IR-470 spectrometer and the frequencies are reported in cm\(^{-1}\). The \(^1\)H NMR spectra were recorded on a Brucker WM (500 MHz) spectrometer using TMS as internal standard and CDCl\(_3\) or DMSO as solvents. The \(^{13}\)C NMR spectra were recorded on a Brucker WM 300 (75.47 MHz) spectrometer using CDCl\(_3\) or DMSO as solvent. Both \(^1\)H NMR and \(^{13}\)C NMR values are expressed as \(\delta\) (ppm). The CHN analyses were done on an Elementar VarioEL III Serial Number 11042022 instrument.

All commercially available reagents were purified before use. The aroyl ketenedithioacetals were prepared by the known procedure.\(^{101}\) Anhydrous sodium sulphate was used as drying agent. All purified compounds gave a single spot upon TLC analyses on silicagel 7GF using an ethyl acetate/hexane mixture as eluent. Iodine vapors or KMnO\(_4\) solution in water was used as developing agent for TLC.

General procedure for the synthesis of ketene dithioacetals: Dry tetrahydro furan was added to sodium \(t\)-butoxide (0.1M) in the R.B flask and cooled to 0\(^\circ\)C. To the mixture, acetophenones (05M) dissolved in CS\(_2\) (4 ml, 0.05m) was added drop wise. And the reaction mixture was allowed to stir for 5-6hrs. Then a calculated volume of CH\(_3\)I (3ml, 0.1M) was added drop wise. The temperature should be of the order of 0-5\(^\circ\)C by using ice. The reaction mixture was allowed to stir for 10hrs. It was then poured to ice cold water to obtain the precipitate of \(\alpha\)-oxoketene dithioacetal. The product was extracted
using ethyl acetate and dried over anhydrous Na$_2$SO$_4$ and concentrated. The product was purified using column chromatography and confirmed by measuring Rf value using TLC.

2-Benzoylketene dithioacetal - yellow solid; yield -93%, M.P= 86-88°C

2-(4-methylbenzoyl)ketene dithioacetal - yellow solid; yield 90%, M.P= 90-92°C

2-(4-chlorobenzoyl)ketene dithioacetal - yellow colored solid; yield 93%, M.P= 92-94°C

2-(4-bromobenzoyl)ketene dithioacetal - yellow colored solid; yield (93%), M.P= 100-102°C

2-(4-methoxybenzoyl)ketene dithioacetal - yellow colored crystalline solid; yield 93%; mp 90-92 °C
2-(3,4-dimethoxybenzoyl)ketene dithioacetal - yellow colored crystalline solid; 85%; mp 108-110 °C.

General procedure for the synthesis of formylketene dithioacetals:

Vilsmeier–Haack reagent was prepared by adding phosphorousoxy chloride (0.67ml, 7mmol) to dimethyl formamide(6ml,70mmol) at 0°C and the mixture was left to stand for 30 minutes at room temperature. The α-oxo ketenedithioacetal (4.7 mmol) was added to this and the solution was stirred well for 10-12 hrs at room temperature. When the TLC analysis showed complete conversion of ketene dithioacetal, the reaction mixture was poured ice cold water and treated with saturated K₂CO₃ (36mmol) solution. The semisolid separated was extracted with ether(3X25ml). The combined organic phases were washed with water, dried and the solvent was evaporated off. The crude product obtained was filtered through a column using ethyl acetate-hexane(1:50) as eluent and silica gel as adsorbent. The compounds were confirmed by comparing with the reported ones.

2-Benzoyl-3,3-bis(methylsulfanyl)acrylaldehyde was obtained from the Vilsmeier-Haack reaction of 3,3-bis(methylsulfanyl)-1-phenyl-2-propen-1-one as yellow colored oil; yield 1.02g (90%).
3,3-Bis(methylsulfanyl)-2-(4-methylbenzoyl)acrylaldehyde was obtained from the Vilsmeier-Haack reaction of 3,3-bis(methylsulfanyl)-1-(4-methylphenyl)-2-propen-1-one as yellow colored oil; yield 1.14 g (89%).

3,3-Bis(methylsulfanyl)-2-(4-chlorobenzoyl)acrylaldehyde was obtained from the Vilsmeier-Haack reaction of 3,3-bis(methylsulfanyl)-1-(4-chlorophenyl)-2-propen-1-one as yellow colored oil; yield 1.12 g (85%).

3,3-Bis(methylsulfanyl)-2-(4-bromobenzoyl)acrylaldehyde was obtained from the Vilsmeier-Haack reaction of 3,3-bis(methylsulfanyl)-1-(4-bromophenyl)-2-propen-1-one as yellow colored oil; yield 1.2 g (82%).

3,3-Bis(methylsulfanyl)-2-(4-methoxybenzoyl)acrylaldehyde was obtained from the Vilsmeier-Haack reaction of 3,3-bis(methylsulfanyl)-1-(4-methoxyphenyl)-2-propen-1-one as yellow colored crystalline solid; yield 1.01 g (91%); mp 90-92 °C (reported mp, 91.5-93 °C).

3,3-Bis(methylsulfanyl)-2-(3,4-dimethoxybenzoyl)acrylaldehyde was obtained from the Vilsmeier-Haack reaction of 3,3-bis(methylsulfanyl)-1-(3,4-dimethoxyphenyl)-2-propen-1-one as yellow colored crystalline solid; yield 0.98 g (85%); mp 114-116 °C.
General procedure for the synthesis of pyrimidine-5-carbaldehyde[8].

Formylketene dithioacetal 7 (2mmol) was dissolved in CH₃CN at room temperature. To the above solution add guanidine hydrochloride (0.192g, 2mmol) and K₂CO₃ (0.55g, 4mmol) and refluxed for 15-20 hrs. Cooled the mixture and poured it to ice cold water. Semisolid obtained was extracted in DCM (3X25ml), dried and purified using column chromatography with ethyl acetate-haxane (3:7) mixture. The product was obtained as cream coloured solid.

| C₁₂H₁₁N₃OS | 2-Amino-4-(methylsulfanyl)-6-phenyl-5-pyrimidinecarbaldehyde was obtained from 2-Benzoyl-3,3-bis(methylsulfanyl)acrylaldehyde by reacting with guanidine hydrochloride. Cream coloured solid. Yield-70% IR (KBr, νmax) = 3480, 3276, 3125, 1636, 1524 cm⁻¹. ¹H NMR 500 MHz, CDCl₃ δ=2.5 (s, 3H, SCH₃), 7.22-7.5 (m, 5H, aromatic), 9.8 (s, 1H, CHO)., ¹³C NMR 75 MHz, CDCl₃ δ=13.4(-SCH₃), 128-160(m, 5H, aromatic), 188.7(CH). CHN Analysis; C-59.2, N-16.98; Mass (FAB); m/z = 246; Mp 198-200°C |
| C₁₃H₁₃N₃OS | 2-amino-4-(4-methylphenyl)-6-(methylsulfanyl)-5-pyrimidinecarbaldehyde was obtained from 3,3-Bis(methylsulfanyl)-2-(4-methylbenzoyl)acrylaldehyde by reacting with guanidine hydrochloride. Cream coloured solid. Yield- 75%, IR (KBr) νmax /cm⁻¹ 3390, 3276, |
3130, 1636, 1522, \(^1\)H NMR- 500 MHz, \(\text{CDCl}_3\) \(\delta = 2.4\) (s, 3H, SCH\(_3\)), 2.5 (s, 3H, CH\(_3\)), 5.9 (m, 2H, NH\(_2\)), 7.27 – 7.34 (m, 2H, aromatic), 7.47-7.50 (m, 2H, aromatic), 9.84 (s, 1H, CHO), \(^{13}\)C NMR 75MHz, \(\text{CDCl}_3\) \(\delta = 13.3\) (SCH\(_3\)), 21.4 (-CH\(_3\)), 116-172 (m, 4H, aromatic), 188.8 (CHO), CHN Analysis; C-59.57, N-15.89; Mass(FAB) m/z = 260, MP 190-192°C

2-amino-4-(4-chlorophenyl)-6-(methylsulfanyl)-5-pyrimidinecarbaldehyde was obtained from 3,3-Bis(methylsulfanyl)-2-(4-chlorobenzoyl)acrylaldehyde by reacting with guanidinehydrochloride. Cream coloured solid. Yield-76%, IR (KBr)\(\nu_{\text{max}}/\text{cm}^{-1}\) 3460, 3200, 1630, 1520, \(^1\)H NMR 500MHz, \(\text{CDCl}_3\) \(\delta = 2.5\) (s, 3H, SCH\(_3\)), 5.7 (b, 2H, NH\(_2\)), 7.2-7.5 (m, 4H, aromatic), 9.6 (s, 1H, CHO), \(^{13}\)C NMR 75 MHz \(\text{CDCl}_3\) \(\delta = 13.4\) (SCH\(_3\)), 116-175 (aromatic), 188 (CHO), CHN Analysis; C-51.67, N-14.35; Mp174-176°C

2-amino-4-(4-bromophenyl)-6-(methylsulfanyl)-5-pyrimidinecarbaldehyde was obtained from 3,3-Bis(methylsulfanyl)-2-(4-bromobenzoyl)acrylaldehyde by...
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<td>( \text{C}<em>{12}\text{H}</em>{10}\text{BrN}_{3}\text{OS} )</td>
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<td>( \text{C}<em>{13}\text{H}</em>{13}\text{N}<em>{3}\text{O}</em>{2}\text{S} )</td>
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<td>( \text{C}<em>{14}\text{H}</em>{15}\text{N}<em>{3}\text{O}</em>{3}\text{S} )</td>
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2927, 1639, $^1$HNMR, 300 MHz, Acetone $\delta =2.71$ (s, 3H, SCH$_3$), 3.74 and 3.76 (6H, (OCH$_3$)$_2$), 6.92-7.1 (m, 2H, NH$_2$ and 3H aromatic), 9.66 (s, CHO), $^{13}$C NMR, 75 MHz, acetone $\delta=13.2$ (SCH$_3$), 56.2 and 56.3 (two OCH$_3$), 111.95-175.27 (aromatic), 188.36 (CHO), Mp-156-158°C

**General procedure for the Knoevenagel condensation reaction of Pyrimidines with Malononitrile (11)**

A mixture of malononitrile (230 mg, 3.5 mmol), ammonium acetate (0.75 g, 10 mmol) and acetic acid (5ml) were heated to 70 °C. To this appropriate pyrimidine (2 mmol) was added, stirred for 2h at the same temperature and cooled to attain room temperature. The reaction mixture was diluted with ethyl acetate(100ml) and then added ice cold water, separate the organic layer, dried over anhydrous sodium sulphate and the solvent was evaporated. The crude product obtained was purified using column chromatography with ethyl acetate-hexane(3:7) mixture and the product was obtained as yellow solid.
2-[[2-amino-4-(methylsulfanyl)-6-phenyl-5-pyrimidinyl[methylene]] malononitrile was obtained by the Knoevenagel condensation reaction of 2-Amino-4-(methylsulfanyl)-6-phenyl-5-pyrimidinecarbaldehyde.

Deep yellow colored crystals; mp 184-186 °C; yield 0.38 g (65%); IR (KBr) $\nu_{\text{max}} / \text{cm}^{-1}$ 3454, 3295, 3188, 2230, 1627, 1573, 1535., $^1$H NMR (300 MHz, CDCl$_3$) $\delta = 2.6$ (s, 3H, SCH$_3$), 5.5 (b, 2H, NH$_2$), 7.48-7.5 (m, 5H, ArH), 7.93 (s, 1H, vinylic) ppm; $^{13}$C NMR (75MHz, CDCl$_3$) $\delta = 172.7$(2C pyrimidine), 167.1(4C pyrimidine), 162.4 (6C pyrimidine), 156.7(vinylic), 141.8, 133.2, 129.9, 130.19 ( phenyl carbons) ,113.4(5C pyrimidine), 111.5 (CN), 110.2 (CN), 88.1 (C(CN)$_2$), 13.0(SMe) ppm, Anal: Found: C, 61.40%; H, 3.80%; N, 23.82%; S, 10.98%.

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2-[[2-amino-4-(4-methylphenyl)-6-(methylsulfanyl)-5-pyrimidinyl[methylene]] malononitrile was obtained by the Knoevenagel condensation reaction 2-Amino-4-(4-methylphenyl)-6-(methylsulfanyl)-5-pyrimidinecarbaldehyde (520mg, 2 mmol) with malononitrile (230 mg, 3.5 mmol). Yellow colored crystals; mp 188-190 °C; yield 0.45g (70%); IR (KBr) $\nu_{\text{max}} / \text{cm}^{-1}$ 3415, 3324, 3207, 2229, 1634, 1573, 1518., $^1$H NMR (300 MHz, CDCl$_3$) $\delta = 2.3$ (s, 3H, Me), 2.57(s, 3H, SMe), 5.62 (s, 2H, NH$_2$), 7.25-7.38 (4H, Aromatic), 8.1 (s, vinylic) ppm., $^{13}$C NMR (75MHz, CDCl$_3$) $\delta = 171.7$(2C pyrimidine), 166.1(4C pyrimidine), 161.4 (6C pyrimidine), 156.0(vinylic), 141.0, 133.7, 129.4, 129.19 ( phenyl carbons), 113.1(5C pyrimidine), 111.76 (CN), 111.2 (CN), 88.2(C(CN)$_2$), 21.3(Me), 13.0(SMe) ppm., Anal: Found: C, 62.48%; H, 4.31%; N, 22.80%; S, 10.41%.
2-[[2-amino-4-(4-chlorophenyl)-6-(methylsulfanyl)-5-
pyrimidinyl]methylene] malononitrile was obtained by the
Knoevenagel condensation reaction of 2-Amino-4-(4-
chlorophenyl)-6-(methylsulfanyl)-5-pyrimidinecarbaldehyde
(0.56g, 2 mmol) with malononitrile (230 mg, 3.5 mmol). Deep
yellow colored crystals; mp 182-184 °C; yield 67%; IR (KBr) ν max / cm⁻¹ 3450, 3290, 3186, 2227, 1620, 1578, 1532, ¹H NMR (300
MHz, CDCl₃) δ = 2.6 (s, 3H, -SC₃H₃), 5.6 (b, 2H, NH₂), 7.37-7.7 (m,
4H, ArH), 7.9 (s, 1H, vinylic) ppm; ¹³C NMR (75MHz, CDCl₃) 
δ= 172.3 (2C pyrimidine), 167.5 (4C pyrimidine), 162.7 (6C
pyrimidine), 155.7 (vinylic), 140.8, 132.2, 128.9, 130.1 (phenyl
 carbons), 113.4 (5C pyrimidine), 111.0(CN), 110.3(CN), 88.2 (C(CN)₂)

2-[[2-amino-4-(4-bromophenyl)-6-(methylsulfanyl)-5-
pyrimidinyl]methylene] malononitrile was obtained by the
Knoevenagel condensation reaction 2-Amino-4-(4-
bromophenyl)-6-(methylsulfanyl)-5-pyrimidinecarbaldehyde
(645mg, 2 mmol) with malononitrile (230 mg, 3.5 mmol). Deep
yellow colored crystals; mp 182-184 °C; yield 70%; IR (KBr) ν max / cm⁻¹ 3467, 3363, 3244, 2221, 1631, 1585, 1519, ¹H NMR (300
MHz, CDCl₃) δ = 2.6 (s, 3H, SCH₃), 5.4 (b, 2H, NH₂), 7.3 (d, J=8.4
Hz, 2H, ArH), 7.6 (d, J=8.0 Hz, 2H, ArH), 7.9 (s, 1H, vinylic) ppm.
¹³C NMR (75MHz, CDCl₃) δ=172.4 (2C pyrimidine), 166.5 (4C
pyrimidine), 163.7 (6C pyrimidine), 154.7 (vinylic carbon),
141.8, 133.2, 129.8, 131.3 (phenyl carbons), 113.4 (5C
pyrimidine), 111.5(CN), 110.6(CN), 88.7 (C(CN)₂),
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<td>11e</td>
<td>2-[[2-amino-4-(4-methoxyphenyl)-6-(methylsulfanyl)-5-pyridinyl]methylen] malononitrile was obtained by the Knoevenagel condensation reaction 2-Amino-4-(4-Methoxyphenyl)-6-(methylsulfanyl)-5-pyrimidinecarbaldehyde (550mg, 2 mmol) with malononitrile (230 mg, 3.5 mmol). Yellow colored crystals; mp 192-194 °C; yield 77%; IR (KBr) $\nu_{\text{max}}$ / cm$^{-1}$ 3410, 3308, 3182, 2934, 2225, 1648, 1582, $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 2.5(s, 3H, SMe), 3.8 (s, 3H, OMe), 5.4 (s, 2H, NH$_2$), 6.94-6.96 ( d, J= 8.4 Hz, 2H, phenyl), 7.45-7.42( d, J= 8.7 Hz, 2H, Phenyl), 7.93(1H, Vinylic) ppm,. $^{13}$C NMR (75MHz, CDCl$_3$)$\delta$=171.8 (2C pyrimidine), 165.8(4C pyrimidine), 161.6 (6C pyrimidine), 161.4(vinylic carbon), 156.1, 131.0, 128.9, 114.3(phenyl carbons), 113.1 (CN), 111.78, (CN), 88.0(C(CN)$_2$), 55.41(OMe), 13.13(SMe) ppm,. Anal: Found: C, 59.50%; H, 4.071%; N, 21.68%; S, 9.88%.</td>
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<td>11f</td>
<td>2-[[2-amino-4-(3,4-dimethoxyphenyl)-6-(methylsulfanyl)-5-pyridinyl]methylen] malononitrile was obtained by the Knoevenagel condensation reaction 2-Amino-4-(3,4-dimethoxyphenyl)-6-(methylsulfanyl)-5-pyrimidinecarbaldehyde (610mg, 2 mmol) with malononitrile (230 mg, 3.5 mmol). Deep yellow colored crystals; mp 178-180 °C; yield 76%; IR (KBr) $\nu_{\text{max}}$ / cm$^{-1}$ 3412, 3305, 3182, 2221, 1631, 1577, 1531, $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 2.6(s, 3H, SCH$_3$), 3.93 (s, 3H, -OMe and 3.95 (s, 3H, -OMe), 5.48(s, 2H, NH$_2$), 6.9-7.1 (m, 3H, ArH), 7.9 (s, 1H,vinylic) ppm,. $^{13}$C NMR 75MHz, CDCl$_3$ $\delta$= 171.82 (2C pyrimidine), 165.81(4C pyrimidine), 161.40 (6C pyrimidine), 156.25(Vinylic), 151.33, 149.36, 129.09, 123.00, 113.21, 112.27, (phenylc), 111.85 (CN), 111.35 (CN), 110.84, (5C pyrimidine), 88.15 (C(CN)$_2$), 56.1, 56.0, ((OMe)$_2$), 13.17(SMe)., Anal: Found: C, 57.75%; H, 4.27%;</td>
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General procedure for the cyclization reaction of Knoevenagel condensation adduct.

1 mmol of condensation product was dissolved in t-BuOH and to the solution con HCl(acid medium) was added and heated in an oil bath at 120°C for 24 Hr. Cooled the reaction mixture and then added ice cold water. Extracted in dichloromethane, dried over anhydrous sodium sulphate and the solvent was evaporated. TLC revealed a mixture of products with close Rf values. Recrystallization from different solvents did not give any pure product. A similar reaction was carried out using sodium ethoxide( base) instead of HCl . There also a mixture of products resulted which were very difficult to separate.

General procedure for the reaction of Pyrimidines with Hydroxylamine hydrochloride(12)

A mixture of hydroxylamine hydrochloride (70 mg, 1 mmol), potassium carbonate (138mg, 1 mmol) and acetonitrile (10ml) were heated to 80 °C. To this appropriate pyrimidine-5-carbaldehyde(0.5mmol) was added, stirred for 10h at the same temperature and cooled to attain room temperature. The reaction mixture was diluted with dichloromethane(50ml) and then added ice cold water, separate the organic layer, dried over anhydrous sodium sulphate and the solvent was evaporated. Recrystallised from DCM/Hexane mixture.

2-amino-4(methylsulfanyl)-6-phenyl-5-pyrimidinecarbaldehyde oxime was obtained from 2-amino-4(methylsulfanyl)-6-phenyl-5-pyrimidinecarbaldehyde (144mg,0.5mmol) by the reaction of hydroxylamine hydrochloride(70mg,1mmol) as yellow solid. mp 130-132 °C; yield 0.083g (60%); IR (KBr) $\nu_{\text{max}}$ / cm $^{-1}$ 3487, 4326, 3371, 3317, 2923, 1654, 1566, 1014, $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ =2.6 (s, 3H, methylsulfanyl), 4.5 (b, NH$_2$,OH), 7.80( d, J = 8.7Hz, 2H, phenyl), 8.25(s, -
2-Amino-4-(3-methoxyphenyl)-6-(methylsulfanyl)-5-pyrimidinenealdehyde oxime was obtained from 2-Amino-4-(3-methoxyphenyl)-6-(methylsulfanyl)-5-pyrimidinenealdehyde (137 mg, 0.5 mmol) by the reaction of hydroxylamine hydrochloride (70 mg, 1 mmol) as pale white solid. mp 190-192 °C; yield 0.13 g (74%); IR (KBr) ν<sub>max</sub> / cm<sup>-1</sup> 3350, 3317, 3193, 2997, 1643, 1581, δ<sub>1H NMR</sub> (300 MHz, CDCl<sub>3</sub>, DMSO) δ = 2.6 (s, 3H, methylsulfanyl), 3.8 (s, 3H, OCH<sub>3</sub>), 5.1 (b, NH<sub>2</sub>, OH), 6.9-7.6 (m, phenyl protons), 8.27 (s, 1H, CH=N-)

2-Amino-4-(3-methylphenyl)-6-(methylsulfanyl)-5-pyrimidinenealdehyde oxime was obtained from 2-Amino-4-(3-methylphenyl)-6-(methylsulfanyl)-5-pyrimidinenealdehyde (129 mg, 0.5 mmol) by the reaction of hydroxylamine hydrochloride (70 mg, 1 mmol) as pale white solid. mp 230-232 °C; yield 0.10 g (65%); IR (KBr) ν<sub>max</sub> / cm<sup>-1</sup> 3506, 3328, 3244, 3193 1612, 1535, δ<sub>1H NMR</sub> (300 MHz, CDCl<sub>3</sub>, DMSO) δ = 2.5 (s, 3H, methylsulfanyl), 2.18 (s, 3H, -CH<sub>3</sub>), 5.1 (b, NH<sub>2</sub>, OH), 6.9-7.6 (m,4H, phenyl protons), 8.27 (-CH=N-)

References


15 Chakrasali, R.; Ila, H; Junjappa, H. Synthesis, 1988, 87