Chapter 1

Introduction

1.1 Introduction

Heterocyclic compounds, especially nitrogen, oxygen and sulfur containing biologically active molecules are important as medicines, pesticides, agro-chemicals, bioelectronic materials etc.\(^1\) The biological activities of these heterocyclic compounds are determined by the position and nature of suitably positioned functional groups on the heterocycles. So it is the main challenge to synthetic organic chemists to synthesize molecules with appropriate functional groups at suitable position of the carbon skeleton. In this aspect synthetic investigations are conducted for designing the structure of molecules with desired properties and developing novel strategies for synthesizing heterocyclic compounds. Thus day to day addition of new reaction strategies for the synthesis of functionalized heterocyclic compounds is the prime requirement to synthetic chemistry to emerge into other fields of science. The present thesis describes the reactions of \(\alpha\)-formylketene dithioacetals leading to the synthesis of functionalized heterocyclic compounds like furans, pyrazoles, annulated pyrazoles and thiopyranones.

\(\alpha\)-Oxoketene dithioacetals are versatile bielectrophilic synthons, which found wide applications in the synthesis of a variety of heterocyclic compounds.\(^2\) The Vilsmeier-Haack reaction of \(\alpha\)-oxoketene dithioacetals led to the formation of \(\alpha\)-formylketene dithioacetals, however synthetic potential of these compounds remained unexplored.\(^3\) Rudorf \textit{et al} synthesized them modifying the existing method of synthesis of aroylketene dithioacetals and made attempts to explore the synthetic utility of these
multifunctionalized synthons in synthesizing thiophenes and thienothiophenes. Recently, we have developed new methods for synthesizing nicotininonitriles, isoazoles, 2-pyridones, and pyrimidines from \(\alpha\)-formylketene dithioacetals. A brief review on the synthesis and applications of \(\alpha\)-formylketene dithioacetals are given in the following sections.

1.2 Synthesis of \(\alpha\)-formylketene dithioacetals

Usually \(\alpha\)-formyl derivatives of ketene dithioacetals are obtained indirectly from the corresponding bis(methylsulfanyl)ethylene esters via a reduction-oxidation process. This is exemplified by the oxidation of \(\beta\)-hydroxyketene dithioacetal 2, synthesized by the lithium aluminium hydride reduction of bis(methylsulfanyl)ethylene ester to afford formylketene dithioacetal 3 (Scheme 1.1). \(^9\)

![Scheme 1.1]

Rudorf et al have reported the synthesis of formylketene dithioacetals from aroylacetaldehydes using usual procedure for the synthesis of \(\alpha\)-oxoketene dithioacetals 6 (Scheme 1.2). \(^10\) In their reactions the formylketene dithioacetals were obtained in 40-50% yields.

![Scheme 1.2]
Recently, we have developed a new method for synthesizing \( \alpha \)-formylketene dithioacetals 8 from aroylketene dithioacetals 7 by treating them with well-known Vilsmeier-Haack reagent prepared from phosphorous oxychloride and N,N-dimethylformamide (Scheme 1.3).\(^3\)

![Scheme 1.3](image)

The Vilsmeier-Haack reaction is a widely used method for the formylation of activated aromatic and heteroaromatic compounds.\(^{11}\) In Chapter 2 of the thesis, we have explained important iminoalkylations by the Vilsmeier-Haack reagent, leading to the synthesis of formylated intermediates or nitrogen-containing heterocyclic compounds.

1.3 Applications of \( \alpha \)-formylketene dithioacetals in the synthesis of heterocyclic compounds

Rudorf et al have initiated attempts to explore the synthetic utility of these compounds in the synthesis of functionalized heterocycles such as pyridinethiones 9, which could then be converted into imidazolinyl substituted heterocycles 12 (Scheme 1.4).\(^{10}\)

![Scheme 1.4](image)
Using various alkylating agents like methyl iodide, ethyl iodide, dibromoethane, phenacyl bromide, bromoacetone etc they synthesized a variety of formylketene dithioacetals. When the alkylation of the dithiolate anion 5 was carried out with two equivalents of α-haloketones or α-halonitriles, the resulted formylketene dithioacetals were \textit{in situ} cyclized to form corresponding substituted thiophenes 13 and thienothiophenes 14 (Scheme 1.5).

![Scheme 1.5](image)

**Scheme 1.5**

Recently, we have explored the synthetic utility of this valuable synthon in synthesizing heterocycles like 2-pyridones 16 (Scheme 1.6)\textsuperscript{3,7}, nicotinonitriles 17 & 18 (Scheme 1.7)\textsuperscript{5}, isoxozoles 19 (Scheme 1.8)\textsuperscript{6} and pyrimidine carbaldehydes 20 (Scheme 1.9).\textsuperscript{8}

![Scheme 1.6](image)

**Scheme 1.6**

![Scheme 1.7](image)

**Scheme 1.7**
Further investigations on the reactions of α-formylketene dithioacetals led to develop new methods for synthesizing furans, differently substituted and annulated pyrazoles and thiopyranones are described in Chapter 3, Chapter 4, Chapter 5 and Chapter 6 of the thesis.

1.4. Synthesis of 2,3,5-trisubstituted furans from α-formylketene dithioacetals

Furans are key structural units in many natural products, pharmaceuticals and a broad spectrum of biologically active molecules. Most known methods for the construction of furan scaffold proceed through the electrophilic cyclization of unsaturated compounds which has proven to be an efficient method for one-step construction and functionalization of furans and other oxygen containing heterocycles. As a part of ongoing research work in our laboratory, we have investigated the reactions of 2-aryloyl-3,3-bis(alkylsulfanyl)acrylaldehydes with phosphorous ylides to afford (E)-2-[bis(alkylsulfanyl)methylene]-1-aryl-4-phenyl-3-buten-1-ones, which in turn were converted to substituted furan on reaction with N-bromosuccinimide. Besides, 2-aminofurans were prepared from the furans on refluxing them with ethylamine in ethanol (Scheme 1.10). The
results of our investigations on these reactions are discussed in Chapter 3 of the thesis.

\[\begin{align*}
\text{Scheme 1.10}
\end{align*}\]

1.5. Synthesis of pyrazoles from $\alpha$-formylketene dithioacetals

Pyrazoles, an important class of nitrogen-containing aromatic heterocycles, are widely used in pharmaceutical and agrochemical industries. A number of pyrazole derivatives with potential medicinal properties such as analgesic, anti-inflammatory, anti-bacterial, anti-fungal and anti-cancer activities have been identified. They constitute the core structure of the blockbuster drugs such as Viagra, Celebrex, Acomplia etc. The reaction of 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes 8 with phenylhydrazine hydrochloride, 2,4-dinitrophenylhydrazine, hydrazine hydrate and semicarbazide hydrochloride resulted in the formation of differently substituted pyrazoles 24, 25 & 26 (Scheme 1.11). These results and their experimental details are described in Chapter 4 of the thesis.
1.6. Aryl-[3-(alkylsulfanyl)-1-phenyl-1H-pyrazol-4-yl]methanones:
Valuable precursors for the synthesis of pyrazolopyridones,
pyrazolopyrimidinones and aminopyrazoles

Functionalized pyrazoles are important substrates for further
modifications to biologically important heterocyclic compounds. They
provide scaffolds, on which pharmacophores can arrange to yield potent and
selective drugs. We envisioned that the reaction of aryl-[3-(alkylsulfanyl)-1-
phenyl-1H-pyrazol-4-yl]methanones with different 1,3-binucleophiles would
provide an easy access to annulated pyrazoles. The results of our
investigations on the annulation of aryl-[3-(alkylsulfanyl)-1-phenyl-1H-
pyrazol-4-yl]methanones with cyanoacetamide or guanidine hydrochloride
leading to the synthesis of pyrazolopyridones 27 or pyrazolopyrimidinones 28 respectively are explained in the Chapter 5. Besides, aryl-[3-(alkylsulfanyl)-1-phenyl-1H-pyrazol-4-yl]methanones were converted to aminopyrazoles 29 treating them with primary amines (Scheme 1.12) and results of these reactions are also explained.

Scheme 1.12

1.7. Reactions of α-formylketene dithioacetals with ethyl bromozincioacetate: Synthesis of thiopyranones

Junjappa and Ila\textsuperscript{15} have reported the synthesis of dienes from α-oxo ketene dithioacetals by Reformatsky reaction with ethyl bromozincioacetate. In light of the above report α-formylketene dithioacetals were treated with ethyl bromoacetate and zinc to get ethyl (2E)-4-aryloxy-5,5-bis(methylsulfanyl)-2,4-pentadienoate 30. The pentadienoate was reluctant to react with ammonium acetate/acetic acid or cuprous iodide to afford pyridones or pyranones. However, when the acrylaldehyde was treated with the Reformatsky reagent in the presence of CuI, the thiopyranones 31 were formed along with the pentadienoate 30 (Scheme 1.13). The results of our investigations on these reactions are discussed in the Chapter 6.
A wide spectrum of biological activities and industrial importance are associated with thiopyrans and their derivatives. Several tetrahydro-4H-thiopyran-4-ones are reported to possess fungicidal, antibacterial, parasitic, sedative, and anti-inflammatory activities. Some of them are intermediates in the synthesis of pyrilium dyes. The thiopyranone ring is a synthetic equivalent of 3-pentanone as the sulfur bridge is easily removed by Raney-Nickel. Thus the synthesis of thiopyrones is an interesting area of organic chemistry for synthetic chemists.

1.8. Conclusion

α-Formylketene dithioacetals, on reaction with Wittig reagent afforded butadiene intermediates, which on cyclization in the presence of NBS afforded furans while on reaction with Reformatsky reagent in the presence of CuI afforded thiopyranones. The synthetic utility of α-formylketene dithioacetals was explored by reacting them with hydrazine derivatives and semicarbazide leading to the synthesis of pyrazoles, which were further annulated to pyrazolopyridines and pyrazolopyrimidinones. Thus we found that the α-formylketene dithioacetals are versatile intermediates in synthesizing functionalized furans, pyrazoles, and thiopyranones.
References


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