SUMMARY
SYNTHESIS OF HETEROCYCLIC COMPOUNDS

“Photochemical Synthesis of Xanthenones and Solid supported reagent based Synthesis of some Benzothiazoles, Pyrazoles and Bis(indolyl)methanes”

Chemical reactions commonly need an initial input of energy to begin the process. The energy forms supplied to the chemical reactions include heat, photochemical, microwave, ultrasonic waves etc. The main objective of researchers is the optimization of this energy supply to accomplish the target molecules in shorter reaction time, with increased yield under cleaner reaction conditions. In this pursuit, the work being presented in the thesis focuses on the applications of photochemical vis-à-vis reagent based protocols for the synthesis of heterocyclic compounds.

One area of our interest is photochemistry i.e. chemical processes initiated by the light. Photochemical transformations make the use of electromagnetic radiations ($\lambda=200-800$ nm) to carry out chemical changes. These reactions occur through electronically excited states. A molecule gets energized selectively at a particular section called chromophore which is followed by energy redistribution. Photochemistry has provided a great wealth of novel reactions (like cycloadditions, dimerisations, inter and intramolecular H-abstractions, molecular rearrangements and fragmentations, isomerisations around double bonds etc.) of synthetic applications.

Another area of our interest is the fulfilling of the energy pathway/requirements of reaction by use of appropriate reagent. A reagent effects the rate by providing a low energy pathway to initiate the reaction. Therefore, the use of solid supported reagents has been made in a quest to design new methods to synthesize molecules of synthetic importance. Over recent years, supported reagents occupy an important place in the realm of synthetic organic chemistry, mainly because of the advantages over unsupported reagents such as cleaner reactions, easier work up, high yield, milder conditions, reduced reaction times, and above all environmentally benign.

The present work involves (i) the use of photochemical reactions for the synthesis of complex heterocyclic compounds i.e. xanthenones and (ii) the use of solid supported reagents for the synthesis of benzothiazoles, pyrazoles and bis(indolyl)methanes.
The whole work has been distributed in five chapters which opens up with the introduction as chapter I. The results of research work carried out have been described in four chapters II-V.

**Chapter I** present information, obtained through glimpse of literature describing scope of photochemistry with emphasis on phototransformations of chromenones and advantages and utility of solid supported reagents in synthesis of heterocyclic compounds (pyrazoles, bis(indolyl)methanes and benzothiazoles.

**Chapter II**, concerns with results of study pertaining to photolytic behavior of 3-propargyloxy-2-(furan-3-yl)-4\(H\)-chromen-4-ones 1 (a-d) (Scheme I) producing the xantheneones, the O-containing heterocycle. Xanthene derivatives are of utmost importance due to their applications in medicinal chemistry as well as molecular biology. In the recent past, research investigation on photochemical transformation of 3-propynyloxychromenones carried out in our laboratory and a diverse array of angular tri- and tetracyclic photoproducts was produced by Norrish type II process. Extensive study on the photochemical behavior of furan and additionally, photochemically active acetylene pendant along with C=O group containing \(\gamma\)-hydrogen prompted us to further investigate 3-propargyloxychromenones with furan-3-yl tethered to 2-position. Here, besides products obtained from H-abstraction, formation of xantheneones 2 and tetracyclic products 3 and 4 has been observed.

**Scheme I: Photochemical transformation of chromenones 1(a-d) to xantheneones (2-4)**

In these photoconversions, the regioselectivity for ring formation exclusively at 2’-position (furyl moiety) with no ring formation at 4’-position has been observed. The reason for this may be that the clipping at C-4’ requires the involvement of the Dewar
furan type moiety which is not possible probably due to high energy requirements ($S_0$ energy = 78 kcal mol$^{-1}$), but this type of ring formation has been observed in case of photoirradiation of the thienylchromenones with the intermediacy of Dewar thiopene ($S_0$ energy = 65 kcal mol$^{-1}$). The clipping at 2'-position is also supported by the calculations made from 3D-structure (MM2 programme) for the furylchromenones substrates. The –O–CH$_2$– and the 2'-position (the two clipping atoms for ring formation) have been observed in close proximity (Figure 1) with contact averaged at 3.449 Å as compared to 5.090 Å for clipping of –O–CH$_2$– and the 4'-position.

![Energy minimized structure of 1](image)

**Figure 1: Energy minimized structure of 1**

The formation of product 2 from chromenones 1 can be envisioned to occur through the initial photochemical sigmatropic 1,3-H shift in chromenone to furnish allenloxy chromenone 1A which cyclizes to 2A. The support for formation of allenloxy chromenone intermediate 1A can be derived from the former interpretation made in conjugated acetylenic carbonyl compounds, where the acetylenic compounds have been rearranged to the allenes photochemically. The intermediate 2A is converted to 2B by sigmatropic 1,5-H shift that subsequently gives 2 (through 1,3-H) (scheme II).
Summary

Scheme II: A proposed mechanism for the formation of furoxanthenones 2

The formation of 3 and 4 from 1 can be visualized to occur through the formation of 1,4-biradical via γ-hydrogen abstraction mechanism (Scheme III). The products formed may be rationalized through bond formation between –O-CH- radical with the 2'-position of the furan ring regioselectively, which is followed by ketonization and H-migration to C-11b (1,5-H migration).

Scheme III: Mechanism for formation of furoxanthenones 3 and 4

Chapter III incorporates the solid supported reagent mediated synthesis of benzothiazoles 7(a-v) using SiO2-HNO3 and NH2CONH2-HNO3 as catalysts in solvent-free conditions (Scheme IV). The reaction conditions were optimized by using different amount of catalyst using different solvents at different conditions of temperature. It was observed that the reaction condition SiO2-HNO3 (2% wt of aldehydes) at room temperature in solvent free condition was best optimized condition and urea nitrate under solvent-free conditions (1.5% wt of aldehyde) at room temperature proved
to be a very effective and efficient catalyst. All benzothiazoles were synthesized using these optimized conditions. Both of these reagents were proved to be very useful in terms of reaction time, product yield and cost. The synthesized benzothiazoles were screened for their in vitro antimicrobial activity. From the observations as well as literature it was found that 2-(hydroxyphenyl) benzothiazoles were found ineffective toward tested microbes. These synthesized hydroxyphenyl benzothiazoles were further subjected to alkylation by reacting with different alkylating agents in the presence of dry acetone, freshly dried K$_2$CO$_3$ and n-Bu$_4$N$^+$I as a phase transfer catalyst to observe the effect of alkylation on their antimicrobial activities (Scheme V). After alkylation, the derivatives 8a, 9a and 10b found to be more effective in the direction of antimicrobial activities. On the basis of these observations, it is derived that antibacterial activity of hydroxyl phenyl substituted benzothiazoles increases significantly when alkylated with branched alkylating agent having C=C bond, as compared to saturated analogs. This effect was observed at o- and p- position and thus seems to be site-specific.

Scheme IV: Synthesis of 2-substitued benzothiazoles 2.13-2.34 using catalyst SiO$_2$-HNO$_3$ and NH$_2$CONH$_2$.HNO$_3$

Scheme V: Alkylation of hydroxyphenyl benzothiazoles 7

A possible mechanism was proposed for the SiO$_2$-HNO$_3$ and NH$_2$CONH$_2$.HNO$_3$ mediated synthesis of benzothiazoles as outlined in scheme VI. It involves the initial condensation of amino group (-NH$_2$) on carboxaldehyde group (C=O), activated by
SiO$_2$-HNO$_3$ catalyst, to form Schiff base (benzothiazoline) which on subsequent oxidation furnished the products 7.

Scheme VI: Possible mechanism for the SiO$_2$-HNO$_3$ or NH$_2$CONH$_2$HNO$_3$ mediated synthesis of benzothiazole 7

Chapter IV describes the synthesis of 3,5-diaryl-N-(p-nitrophenyl)pyrazoles 13(a-i) and 3,5-diaryl-N-phenylpyrazoles 12(a-i) by oxidative aromatization of 4,5-dihydro-1,3,5-triaryl-1$H$-pyrazoles 11(a-i) by developing a protocol using SiO$_2$-HNO$_3$ (Scheme VII). The reaction conditions were optimized by using different amounts of catalyst using different solvents at different conditions of temperature. The results indicate that the oxidative aromatization of 4,5-dihydro-1,3,5-triaryl-1$H$-pyrazoles with SiO$_2$-HNO$_3$ (300% wt of pyrazoline) in dichloromethane at room temperature is the best optimized condition and oxidative aromatization of all of the pyrazolines were carried out under optimized conditions. This synthetic approach appears to be convenient and useful due to its operational simplicity, practical application, eco-friendly nature, mild reaction
conditions, easy workup and high yield. All the synthesized compounds have been evaluated *in vitro* for their antimicrobial activity against two gram positive bacterium strains i.e. *Bacillus subtilis* and *Staphylococcus aureus*, two gram negative bacterium strains i.e. *Escherichia coli* and *Pseudomonas aeruginosa* and antifungal activity against two yeasts i.e. *Candida albicans* and *Saccharomyces cerevisiae*.

Scheme VII: Transformation of 4,5-dihydro-1,3,5-(triaryl)-1H-pyrazoles 11 into 1,3,5-triarylsubstituted pyrazoles 12 and 13

The formation of the oxidation products 12 and 13 (Scheme VIII) may be envisioned to occur via two mechanisms:

(i) The imine nitrogen of the pyrazoline nucleus may attack first on the nitrate ion of SiO₂·HNO₃ to trigger the oxidative aromatization (Scheme VIII, path A) resulting into the formation of 3,5-diaryl-1-phenyl pyrazoles 12. This pyrazole may furnish the nitro product 13 on further reaction and/or

(ii) Firstly the nitration occurs on the *p*-position of N-phenyl ring (more active) followed by the oxidative aromatization (Scheme VIII, path B) to form the 3,5-diaryl-1-(*p*-nitrophenyl) pyrazoles 13.

To establish the exact mechanistic pathway(s), we performed an experiment of the nitration (Scheme IX) of 1,3,5-triphenylpyrazole 12 with SiO₂·HNO₃ under the optimised conditions. But, no formation of the nitro derivative 13 was observed with SiO₂·HNO₃. Therefore, the formation of 12 and 13 takes place via two independent routes. Hence, it may be concluded that second mechanism i.e. the nitration followed by oxidative aromatization is the most plausible mechanism (Scheme X) for the formation of nitration product 13 while the first mechanism is operative (Scheme IX) for the formation of simple pyrazole 12.
Summary

Scheme VIII: Oxidative aromatization of pyrazolines 11 to pyrazoles 12 and 13.

Scheme IX: Nitration of 1,3,5-triarylpyrazoles 12

Chapter V incorporates the development of SiO$_2$-HNO$_3$ mediated synthesis of bis(indolyl)methanes 16 and 19 both from the unsubstituted indole 14 as well as
substituted indoles 17. The reaction conditions were optimized by using different amount of catalyst using different solvents at different conditions of temperature. It is manifested from the results obtained that for unsubstituted indoles SiO₂-HNO₃ under solvent-free conditions (1.5 wt% of aldehyde) at 70 °C proved to be a very effective and efficient catalyst. So, in case of unsubstituted indoles the synthesis of bis(indolyl)methanes 16 was carried out in solvent-free conditions at 70 °C temperature while with substituted indoles 17 it was carried out in solution-phase conditions using THF as solvent at room temperature. Thus, silica supported HNO₃ proved to be an efficient catalyst in terms of easy preparation, yield, reaction time, easy work up and cost for obtaining the bis(indolyl)methanes.

\[
\begin{align*}
\text{2} & \quad \begin{array}{c}
\text{RCH} \quad \text{N} \\
\text{H} \quad \text{H}
\end{array} & \quad \text{SiO}_2\text{-HNO}_3 & \quad \text{solvent free} & \quad \begin{array}{c}
\text{N} \\
\text{H} \quad \text{H}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{R} = & \quad \text{a. C}_6\text{H}_{12}; \quad \text{b. 2-OCH}_3\text{C}_6\text{H}_4; \quad \text{c. 2-NO}_2\text{C}_6\text{H}_4; \quad \text{d. 4-ClC}_6\text{H}_4; \quad \text{e. 4-CH}_3\text{C}_6\text{H}_4; \\
& \quad \text{f. 3,4,5-(OCH}_3)_3\text{C}_6\text{H}_4; \quad \text{g. 2-OCH}_3\text{C}_6\text{H}_4; \quad \text{h. 4-OCH}_3\text{C}_6\text{H}_4; \quad \text{i. C}_6\text{H}_5\text{CH=CH(CH)}_3; \\
& \quad \text{j. C}_6\text{H}_5\text{CH}=\text{CH}; \quad \text{k. C}_6\text{H}_4\text{N}; \quad \text{l. (C}_6\text{H}_5)_2\text{C}_2\text{H}_2
\end{align*}
\]

\textbf{Scheme X: Synthesis of bis(indolyl)methanes 16}

\[
\begin{align*}
\text{H}_2\text{C=CH}_2 & \quad \begin{array}{c}
\text{N} \\
\text{N} \quad \text{H} \quad \text{H}
\end{array} & \quad \begin{array}{c}
\text{R} \\
\text{H}_2\text{C=CH}_2
\end{array} & \quad \text{SiO}_2\text{-HNO}_3 & \quad \text{THF} & \quad \begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{R} = & \quad \text{a. H; b. CH}_3; \quad \text{c. OCH}_3; \quad \text{d. F; e. Cl}; \quad \text{f. NO}_2
\end{align*}
\]

\textbf{Scheme XI: Synthesis of bis(indolyl)methanes 19(a-f)}

A plausible mechanism for formation of bis(indolyl)methanes 16 and 19 in presence of SiO₂-HNO₃ is represented in scheme XII. The indole possibly reacts with aldehydes in presence of SiO₂-HNO₃ to produce “A” as an intermediate. This intermediate can undergo further addition with second indole molecule to produce target compound.
Scheme XII: Plausible mechanism for synthesis of Bis(indolyl)methanes 16 and 19

The structures of the synthesised compounds have been derived from their spectral parameters (IR, $^1$H NMR, $^{13}$C NMR and Mass spectrometry). The assistance of molecular mechanics program (MM2) has also been sought to corroborate the results achieved in some photochemical transformations. The experimental procedures for the synthesis of substrates (reactants) and their products have also been given at the appropriate places.