ABSTRACT
ABSTRACT of the thesis submitted to the University of Pune, for the degree of Doctor of Philosophy in Organic Chemistry.

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Title of the Thesis "Synthesis of Heterocyclic compounds Using Vilsmeier - Haack Reaction"

The thesis entitled "Synthesis of Heterocyclic Compounds Using Vilsmeier - Haack Reaction" is divided into seven chapters.

CHAPTER - I

APPLICATIONS OF VILSMIEIER - HAACK REACTION

A review of the Vilsmeier-Haack reaction and its synthetic applications are presented in the first chapter with up-to-date references. Evidence for V-H complex, reaction conditions, reagents, and the effect of solvent are discussed.

In the second part of this chapter, synthetic utility of the Vilsmeier-Haack reaction is reviewed. Herein the reactions involving simple formylation, formylation of olefins, ketones, diformylation, formylation with aromatization, regiospecific formylation, formylation with dimerization and miscellaneous V-H reactions are discussed with suitable examples and updated references. The synthesis of several heterocyclic systems from the intermediate products of the Vilsmeier-Haack reaction are also presented.

At the end of the chapter, the aim of the present work is briefed.
CHAPTER - II

VILSMEIER-HAACK REACTION OF 2-ARYLIMINO THIAZOLID-4-ONES

Formylation of 2-arylimino thiazolid-4-ones (3b-h) using DMF/POCl$_3$ is achieved to give 4-chloro-2-arylamino thiazol-5-carboxaldehydes, (4b-h). The compounds having reactive methylene group (3b-h) required for this purpose were synthesised from primary aromatic amines (1b-h) using literature procedures via arylthioureas (2b-h) (Scheme-I).

The structures of chloroaldehyde intermediates (4b-h) are supported by IR and PMR spectra.

Two plausible mechanisms (Scheme II and III) for the above Vilsmeier-Haack formylation reaction are suggested.

The reaction of 2-arylimino thiazolid-4-one (3b-h) with POCl$_3$ forms iminyl chloride (7b-h) which tautomerises to the activated aromatic species (9b-h) through enamine (8b-h). The enamine (9b-h) acts as nucleophiles towards a reactive intermediates obtained from DMF/POCl$_3$ to form (10b-h). These on hydrolysis with NaOH furnish (4b-h) (Scheme-II). This mechanism is supported by actual isolation and characterisation of intermediates 10f (m.p. 130°C) 10g (m.p. 125°C) and 10h m.p. (156°C).

An alternative mechanism is suggested in which 3 affords 8. Activation by chlorine gives formylation at C$_5$ which affords (4b-h) (Scheme-III).
Scheme I

1. Addition of HCl to Ar-NH to give Ar-NH-C-NH₂
2. Reaction of Cl·CH₂·COOH with NaOAc, EtOH under reflux
3. Reaction of Ar-NH-C-NH₂ with DMF/POCl₃ at 5-10°C
4. Further reactions with specific Ar groups for b-h, c, d, e, f, g, and h

b, Ar = \( \text{Ph} \)

10f, 10g, 10h, 236

10f, Ar = \( \text{Ph-CH₃} \)

10g, Ar = \( \text{Ph-Cl} \)

10h, Ar = \( \text{Ph-CH₃} \)
CHAPTER - III

SYNTHETIC UTILITY OF 4-CHLORO-2-ARYLAMINO THIAZOLE-5-CARBOXALDEHYDES

In the third chapter we have demonstrated the considerable synthetic potential of the intermediate chloroaldehydes for the preparation of various fused and condensed heterocyclic compounds and Schiff's bases.

The versatile intermediate chloroaldehydes B and C (Scheme IV) were reacted with equimolar quantities of phenylhydrazine, hydrazine, hydroxylamine, thiourea, urea and o-phenylenediamine to form 1-phenyl-5-arylamino pyrazole [4, 3-d] thiazoles (1b-c), 5-arylamino pyrazolo [4,3-d] thiazoles (3b-c), 5-arylamino thiazolo [5, 4-d] isoxazoles (4b-c), 5-mercapto-2-arylamino thiazolo [4, 5-d] pyrimidines (7b-c), 5-hydroxy-2-arylamino thiazolo [4,5-d] pyrimidines (9b-c) and 2-phenylimino thiazole [4,5-e] (1,4) benzodiazepines (12b-c) respectively.

Condensation of chloroaldehydes B and C with ethylenediamine, o- and p-phenylenediamine and hydrazine in 2:1 molar ratio in refluxing ethanol formed heterocyclic Schiff’s bases N, N’-bis-(4-chloro-2-arylimino thiazol-5-yl-methylene) ethylenediamines (16b-c), N,N’-bis-(4-chloro-2-aryliminothiazol-5-yl-methylene) -o-phenylenediamines (18b-c), N,N’-bis-(4-chloro-2-aryliminothiazol-5-yl-methylene)-p-phenylenediamines (20b-c) and N,N’-bis-(4-chloro-2-phenylimino thiazol-5-yl-methylene) azine (21b-c) respectively (Scheme-V). The structures were supported by elemental analysis, IR and PMR spectra.
Scheme IV
\[ \text{Scheme V} \]
The synthetic utility of versatile intermediate 4-chloro-2-arylamino-5-carboxaldehyde (4a-f) is further extended for the preparation of furano ring system (7a-f) (Scheme VI).

Hydrolysis of (4a-f) using 6N HCl resulted in displacement of chlorine to form 4-oxo-5-formyl-2-arylamino thiazoles (5a-f), which on treatment with ethyl chloroacetate in presence of sodium acetate yielded aryloxy esters (6a-f). These were then modified to furan ring systems (7a-f) using fused sodium acetate in acetic anhydride by cyclisation. Elemental analysis and IR spectral data were used to confirm the functional group changes in the sequence of reactions.

CHAPTER - V

SYNTHESIS OF 5-OXO-2-ARYLAMINO THIAZOL [4, 5-d] PYRANS

In the fifth chapter a synthesis of 5-oxo-2-arylamino-thiazol [4, 5-d] pyrans (10a-f) is described.

Initially (E)-5-(4-oxo-arylamino thiazolyl) acrylic acids (8a-f) were prepared from 4-oxo-2-arylimino thiazole-5-carboxaldehyde (5a-f) using perkin's reaction.

The acrylic acids (8a-f) were heated with PPA at 245°C to intermediates (9a-f) (not isolated) which on hydrolysis with cold alkali yielded 5-oxo-2-arylamino thiazol [4, 5-d] pyrans (10a-f) (Scheme - VII).
SCHEME - VI

\[
\begin{align*}
40-f & \xrightarrow{\text{6N, HCl}} \text{NH}_2 \text{CHO} \\
50-f & \xrightarrow{\text{CH}_3 \text{COONa, Ac}_2 \text{O/ HOAc}} \text{NH}_2 \text{CHO} \\
60-f & \xrightarrow{(\text{CH}_3 \text{CO})_2 \text{O}(i) \text{ CH}_3 \text{COOK}} \text{NH}_2 \text{CHO} \\
70-f & \xrightarrow{(ii) \text{ H}_2 \text{O, HCl}} \text{Perkin's reaction} \\
80-f & \xrightarrow{\text{PPA, 2h, 245 °C}} \text{NH}_2 \text{CH}_2 \text{COOH} \\
90-f & \xrightarrow{\text{Aq. NaOH}} \text{NH}_2 \text{CHO} \\
100-f & \xrightarrow{\text{Cl}} \text{NH}_2 \text{CHO} \\
\end{align*}
\]

SCHEME - VII

- a, Ar = -
- b, Ar = -
- c, Ar = -
- d, Ar = -
- e, Ar = -
- f, Ar = -
The methods of synthesis of seven membered heterocyclic compounds, 2-arylimino thiazole [4, 5-e] (1,4) diazepines C9a-f from chlorocarbaxaldehydes (4a-f) and ethylenediamine using two different routes were investigated.

In the first route the chlorocarboxaldehydes 4a-f were condensed with equimolar quantities of ethylenediamine in 1-propanol in the presence of formic acid at pH (3-5).

In the second route the intermediate chlorocarboxaldehydes (4a-f) were refluxed with sodium iodide in acetonitrile to form 4-iodo-2-arylamino thiazole-5-carboxaldehyde (8a-f). These compounds were then cyclized into seven membered heterocyclic diazepines by refluxing with equimolar quantities of ethylenediamine in ethanol. The second method requires less time and forms products with good yields.

It is worth while to mention here that the second route is far superior to the first one. Hence, it could be the preferred method for the synthesis of the above compounds. Both the routes are shown in (Scheme - VIII).

CHAPTER - VII

BIOLOGICAL TESTING OF THE COMPOUNDS

The results of the biological testings of the compounds described in Chapter III are presented in this Chapter. These compounds were screened for antibacterial activity against S. aureus and E. coli using disc diffusion method.

243
Two compounds viz., 5-(2-methyl phenyl amino) pyrazolo-[4,3-d] thiazole, 3b and 2-(2-methyl phenylimino) thiazole [4,5-e] (1,4) benzodiazepine, 12b, were found active against S. aureus as well as E. coli. The compound N, N'-bis-[4-chloro-2-(2-methyl phenylimino) thiazol-5 yl- methylene] -o-phenylenediamine, 18b, was found active only against S. aureus.

Other compounds such as 1-phenyl-5-(4-methyl phenylamino) pyrazolo-[4, 3-d] thiazole, 1c, 5-(2-methyl phenylamino) thiazolo [5, 4-d] isoxazole, 4b, 5-(4-methylphenylamino) thiazolo [5,4-d] isoxazole, 4c, 5-mercapto-2-(4-methyl phenylamino) thiazolo [4, 5-d] pyrimidine, 7c, 2-(4-methylphenylimino) thiazolo [4,5-e] (1,4) benzodiazepine, 12c and N,N'-bis- [4-chloro - 2 - (2-methyl- phenylimino) thiazol-5- yl-methylene]-p-phenylenediamine, 20b were found active against E. coli.

\[
\begin{align*}
\text{Refluxed in n propanol} & \quad \text{pH (3-5)} & \quad 16 \text{ hrs} \\
\end{align*}
\]

ROUTE-I

\[
\begin{align*}
\text{Reflux in Acetonitrile} & \quad \text{Reflex for 1-5 hrs.} \\
\end{align*}
\]

ROUTE-II

SCHEME-VIII