

REVIEW ARTICLE ON VILSMEIER-HAACK REACTION

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ABSTRACT

This review article represents a survey covering the literatures on Vilsmeier-Haack reaction, glutarimides and dihydropyridines. This short review also provides an update on recent reports and demonstrates the usefulness and the efficiency of this approach. The data on the methods of synthesis, chemical reactions, and biological activity of these heterocycles published over the last years are reviewed here for the first time.

Keywords: Vilsmeier-Haack reaction, Glutarimides, dihydropyridines.

INTRODUCTION

The application of the Vilsmeier-Haack (VH) reagent (POCl₃/DMF) for the formylation of a variety of both aromatic and heteroaromatic substrates is well documented¹. The Vilsmeier-Haack reagent is an efficient, economical and mild reagent for the formylation of reactive aromatic and heteroaromatic substrates². It is now used as a powerful synthetic tool for the construction of many heterocyclic compounds³.

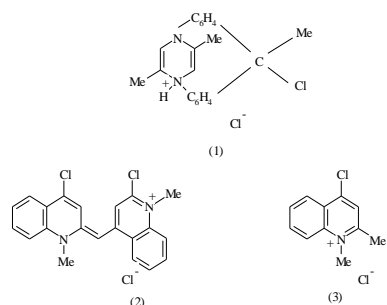
The classical Vilsmeier-Haack reaction⁴, however, involves electrophilic substitution of an activated aromatic ring with a halomethyleniminium salt to yield the corresponding iminium species, which facilitates easy entry into various nitrogen and oxygen based heterocycles^{5,3a,d}. Vilsmeier reagent serves not only as a formylating agent⁶, but also as an activating reagent for carboxylic acids to give esters⁷, amides⁸ and acid chlorides⁹ and for alcohols to give alkyl chlorides¹⁰, esters¹¹, alkyl aryl sulfides¹² and imides¹³. Besides this, the reagent has also been extensively used for effecting various chemical transformations with other classes of compounds.

There is a growing interest in formylation as an interesting strategy to form intermediate carboxaldehydes, due to their

intrinsic pharmacological properties and chemical reactivity¹⁴. Formylation reactions have been described for pyrido[2,3-*d*]pyrimidines as a key step for the introduction of functionalities via the intermediate carboxaldehydes¹⁵.

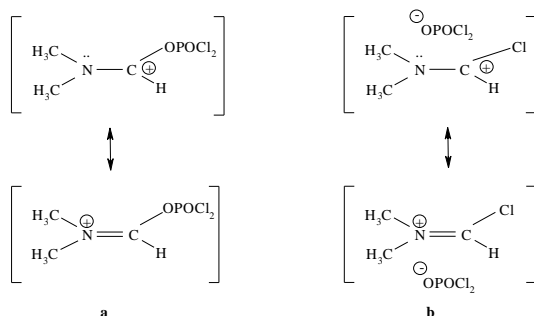
The Vilsmeier-Haack reaction can also be applied to introduce an acetyl group on activated aromatic or hetero aromatic compounds, many other conversions can be achieved with this technology. In general, N,N-dimethylformamide (DMF) and phosphorus oxychloride (POCl₃) are used to generate a halomethyleniminium salt used in the synthesis of a large number of heterocyclic compounds¹⁶⁻¹⁹.

In 1896, Friedel noted the formation of a red dye on treatment of N-methylacetanilide with phosphoryl chloride to which he assigned the problematic structure (1)²⁰. This was corrected by Fischer, Miller and Vilsmeier in 1925²¹ who assigned the cynine-dye structure (2) and argued cogently that this product derived from the self condensation of the quinolinium salt (3). It was the realization by Vilsmeier & Haack²² that one molecule of N-methylacetanilide had acetylated a second molecule prior to cyclisation that led to the discovery of the Vilsmeier-Haack formylation using N-dimethylformanilide.



The formyl group thus, introduced in to a substrate is, of course, a highly reactive species and the versatility of this reaction, to a large extent, is due to the variety of synthetically useful transformations that may subsequently be performed. The V.H. reaction has been extensively studied and reviewed²³.

The structure of the electrophilic adduct has aroused much interest. The behavior of the adduct appears to be consistent with an ionic character rather than a covalent character²⁴. The structures a & b were considered most likely for the DMF/ POCl_3 adduct.



Structure of the Vilsmeier-Haack Complex

Phosphorous oxychloride reacts with tertiary amides to give adduct which exhibits salt like properties. These adducts have been referred to as the Vilsmeier complexes²⁵.

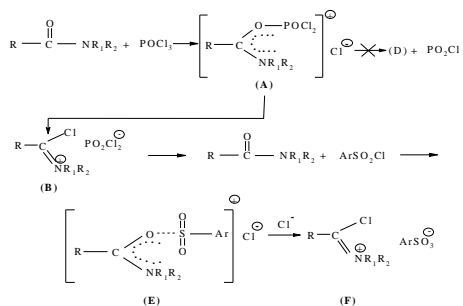
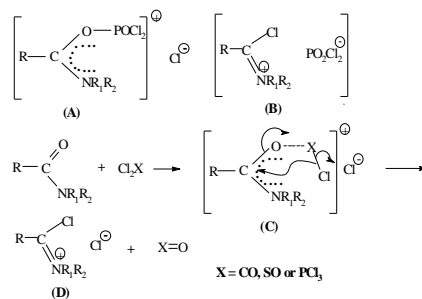


CHART-1 Nature of Vilsmeier-Haack Reagent

Recent studies on the NMR spectra of the DMF/ POCl_3 complex pointed to the imidoyl chloride salt structure (B)²⁶⁻²⁸ (Chart-1). Challis and Challis²⁹ suggested that O-acyl structure (A) might be more stable for POCl_3 than for other halides such as SOCl_2 , COCl_2 and PCl_5 .



The Vilsmeier complexes are generally prepared at low temperatures (<25°C). If the reaction with nucleophile is carried out at low temperature (<30°C) the rearrangement of (A) and (B) does not seem to be favoured. Furthermore, the Vilsmeier complex undergoes a much wide range of nucleophilic substitution reactions.

Reagents

The Vilsmeier complexes employed in the formylation reactions are usually derived from NN-disubstituted amide and POCl_3 . N-Methyl formamide and NN-dimethyl formamide are commonly used. N-Methyl formamide, N-formylpiperidine²⁷ and N-formylindoline²⁸ have also been used. The use of unsubstituted formamide has also been investigated³⁰, but the complex was found to be less reactive than the DMF / POCl_3 or MFA / POCl_3 complexes.

Other amides such as N,N-dimethyl acetamide, N-methyl acetamide, N,N-dimethyl benzamide, N,N', ∞ , ∞ , ∞ -pentamethyl acetamide, etc. have been employed in the presence of POCl_3 but these amides are prone to undergo self condensation. Acid chlorides other than POCl_3 have also been used in the Vilsmeier reactions. They are COCl_2 ³¹, SOCl_2 ³², ClOCl ³³, CH_3COCl ³⁴, ArCOCl ^{34,35}, ArSO_2Cl ³⁵, PCl_5 ³⁶, $\text{Me}_2\text{NSO}_2\text{Cl}$ ³⁷ and $\text{RO}_2\text{CNH SO}_2\text{Cl}$ ³⁸.

Solvents

In the case of amides like DMF, dimethyl acetamide, N-methyl pyrrolidone, etc. which are liquids, an excess of the amide can be used as solvent. Other solvents like chloroform, methylchloride, benzene, toluene, o-dichlorobenzene, dioxane and tetrahydrofuran have also been used.

Temperatures

Normally the reactions are carried out at room temperature or between 60° and 80°C. Reactions at temperature as high as 120°C have also been described³⁹. The Vilsmeier reaction has been the subject of many review articles of varying scope and length. Some of the reviews are enlisted here in chronological order. Vilsmeier (1951)⁴⁰, Bayer (1954)⁴¹, Brederick et al. (1959)⁴², Eilingsfeld, Seefeder and Weidinger (1960)⁴³, Minkin and Darofeenko (1960)⁴⁴, Oda and Yamamoto (1960)⁴⁵, De Maheas (1962)⁴⁶, Hofner et al. (1963)⁴⁷, Gore (1964)⁴⁸, Hazebroucq (1966)⁴⁹, Jutz (1968)⁵⁰, Ulrich (1968)⁵¹, Kuehne (1969)⁵², Seshadri (1973)²⁴, Jutz (1976)⁵³, Meth-cohn and Tarnowski (1982)⁵⁴, Smichen (1983)⁵⁵, Marson (1992)⁵⁶, Meth-cohn and Stanforth (1991)⁵⁷ and Meth-cohn (1993)⁵⁸, Arumugam S. (1994)⁵⁹, Duduzile M. M. (2007)⁶⁰, Carsten Borek (2008)⁶¹, Jones G. and Stanforth S. P. (1997)⁶², Kantlehner (1976)⁶³ has reviewed adducts from acid amides and acylation reagents and also the preparation and reaction of chloromethyliminium salt with nucleophiles. Liebscher and Hartmann (1979)⁶⁴ have published an article relating to vinylogous chloroiminium salts. These excellent reviews deal with the Vilsmeier reaction, its mechanism and the structure of the various electrophilic reagents. In this study we have restricted our coverage to important concepts rather than reiterate all the literature material.

Synthetic Applications of the Vilsmeier-Haack Reaction

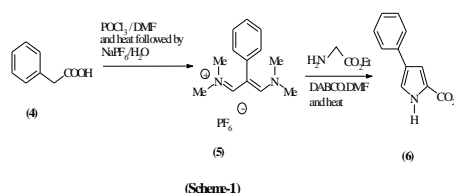
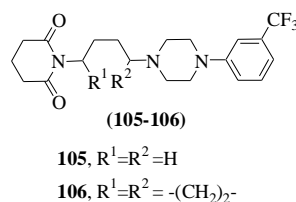
- i) Formylation of aromatic hydrocarbons, phenols, phenolethers, olefins, ketones, Beta-chlorovinylaldehydes.
- ii) Diformylation reactions.
- iii) Formylation with aromatization.

- iv) Regiospecific formylation.
- v) Oxygen and nitrogen nucleophiles are also reactive towards Vilsmeier reagent.
- vi) Formylation with dimerization.
- vii) Transformation of iminium salt into product other than aldehyde.
- viii) Miscellaneous V-H reactions.

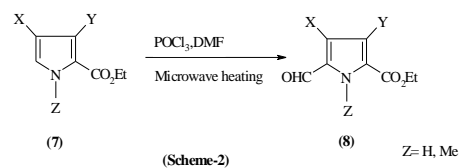
In view of the vastness of the literature, we have endeavored in this review to demonstrate the powerful potential of Vilsmeier-Haack reaction in the synthesis of different compounds. Only few representative reactions are illustrated under the following titles.

A) Synthesis of Pyrroles

Gupton J. T. et al.⁶⁵ have studied and reported the synthesis of 4-Aryl-2-carbethoxypyrrole (6) from compound (4) with POCl₃, DMF and heat followed by NaPF₆/H₂O via formation of Vinylogous iminium salt (5) (Scheme-1).

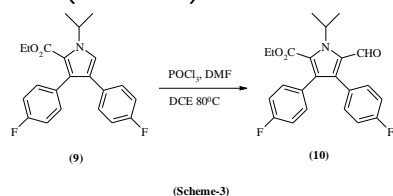


They have also reported microwave accelerated Vilsmeier-Haack formylation of pyrrole (7) into formyl pyrrole (8) (Scheme-2).

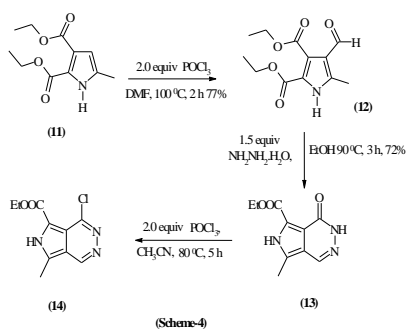


Pfefferkorn J. A. et al.⁶⁶ have described formylation of pyrrole (9) under Vilsmeier-

Haack conditions into pyrrole carboxaldehyde (10) as a part of development of an efficient and scalable second generation synthesis of novel, pyrrole-based HMG-C₀A reductase inhibitors (Scheme-3).

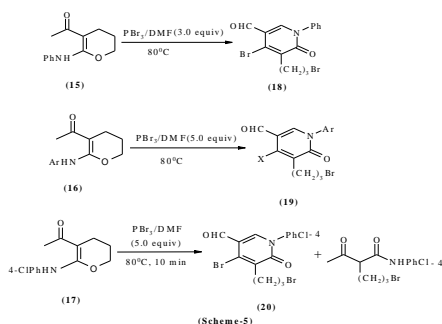


Cho T. P. et al.⁶⁷ have discovered the series of novel pyrrolopyridazine derivatives by carrying out synthesis of pyrrolopyridazine (14) from pyrrole diesters (11) by using V-H reagents (Scheme-4).



B) Synthesis of Functionalized Pyridines

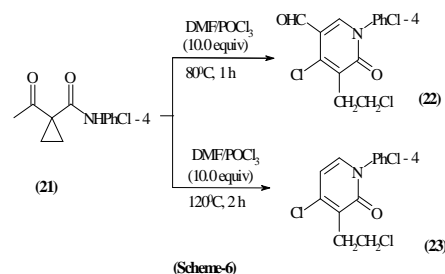
Xiang D. et al.⁶⁸ developed a facile and efficient one-pot synthesis of highly substituted pyridin-2(1*H*)-ones (18), (19) and (20) via Vilsmeier-Haack reactions of readily available 2-arylamino-3-acetyl-5,6-dihydro-4*H*-pyrans (15), (16) and (17) respectively (Scheme-5).



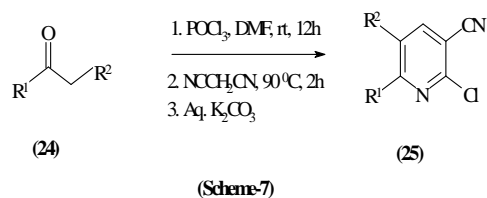
Pan W. et al.⁶⁹ also reported the synthesis of functionalized pyridine-2(1*H*)-ones (22) and (23) from 1-acetyl, 1-carbamoyl cyclopropanes (21) by using POCl₃ and DMF

under different temperature conditions (Scheme 6).

Functionalized pyridine-2(1*H*)-ones and their benzo/hetero-fused analogues represent an important class of organic heterocycles for their presence in numerous natural products and synthetic organic compounds along with diverse bio-physico and pharmacological activities⁷⁰⁻⁷¹.

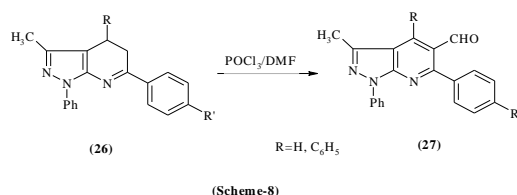


Asokan C. V. et al.⁷² have reported the conversion of enolizable ketones such as acetophenones and benzal acetones (24) into 2-chloronicotinitriles (25) upon treatment with malononitrile under Vilsmeier-Haack reaction conditions. (Scheme-7).

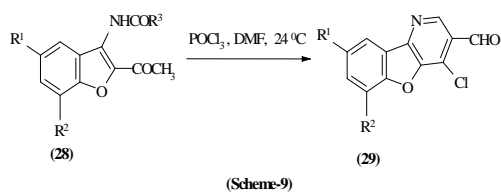


Quiroga J. et al.¹⁷ formylated pyrazolopyridine (26) into pyrazolo[3,4-*b*]pyridine-5-carbaldehyde (27) by using DMF and POCl₃ (Scheme-8).

They have concluded that, the formylation on the pyridine ring only takes place when there is a dihydroderivative on the appropriate pyrazolo-fused system. They have also observed that the use of the Vilsmeier-Haack condition developed a fast and efficient method for the formation of pyrazolo[3,4-*b*]pyridine-5-carbaldehyde (27)

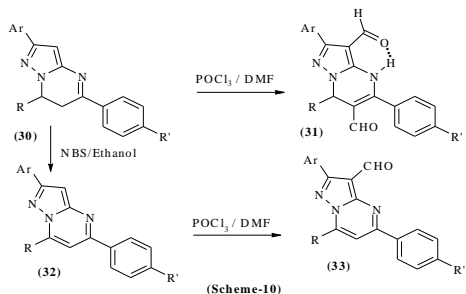


Tabuchi Y. et al⁷³ used Vilsmeier-Haack condition for the synthesis of 4-chloro-3-formylbenzo[*b*]furo[3,2-*b*] pyridine (29) from 2-acetyl-3-acylamino benzo[*b*] furans (28) (Scheme-9).

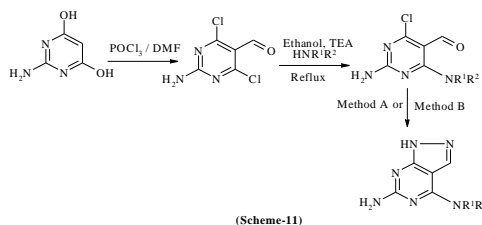


C) Synthesis of Pyrimidines

Quiroga J. et al¹⁷ suggested the regioselective formylation of pyrazolo [1,5-*a*] pyrimidine system using Vilsmeier-Haack conditions. They have synthesized pyrazolo [1,5-*a*] pyrimidine-3,6-dicarbaldehyde (31) from 6,7-dihydroderivatives (30). They have also converted 6,7-dihydroderivative (30) into aromatic pyrazolo pyrimidine (32) which was formylated with DMF & POCl₃ and afforded pyrazolopyrimidine-3-carbaldehyde (33) (Scheme-10).



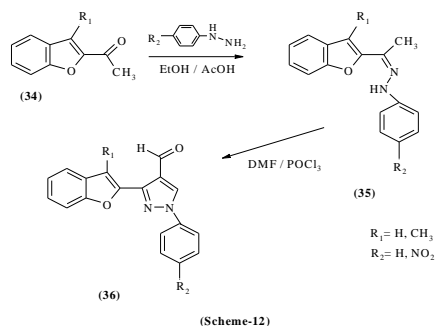
Quiroga J. et al⁷⁴ extended their work & carried out microwave assisted synthesis of pyrazolo[3,4-*d*]pyrimidines from 2-amino-4,6-dichloropyrimidine-5-carbaldehyde under solvent free conditions (Scheme-11).



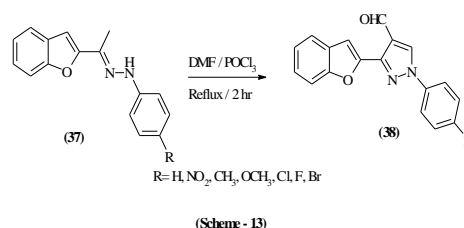
D) Synthesis of Pyrazoles

Aruna kumar D. B. et al⁷⁵ converted benzofurans (34) into benzofuran phenyl hydrozone (35) by treatment with phenyl

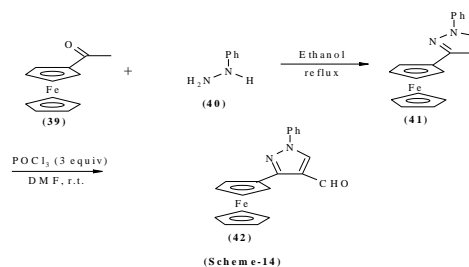
hydrazine in ethanol and acetic acid. The intermediate phenyl hydrazone (35) when subjected to Vilsmeier-Haack reaction condition, cyclized to afford substituted pyrazoles (36) which are well documented to possess antihypertensive, antibacterial, anti-inflammatory and antitumor activities⁷⁶ (Scheme-12).



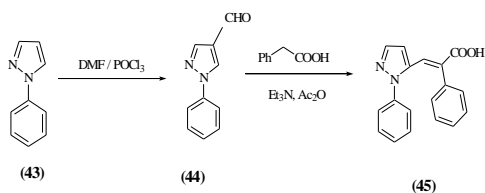
Goudarshivannanavar B C et al⁷⁷ have reported that, 2-acetyl benzofurohydrozones (37) on reaction with Vilsmeier-Haack reagent at appropriate molar ratio, underwent smooth cyclization followed by formylation afforded 3-(1-benzofuran-2-yl)-1-(substituted phenyl)-1*H*-pyrazole-4-carbaldehyde (38) (Scheme-13).



Damljanovic I. et al⁷⁸ reported that the condensation of acetylferrocene (39) with phenyl hydrazine (40) followed by intramolecular cyclization of the intermediate hydrazone (41) under Vilsmeier-Haack conditions formed 1*H*-3-ferrocenyl-1-phenyl pyrazole-4-carboxaldehyde (42) (Scheme-14)⁷⁹.



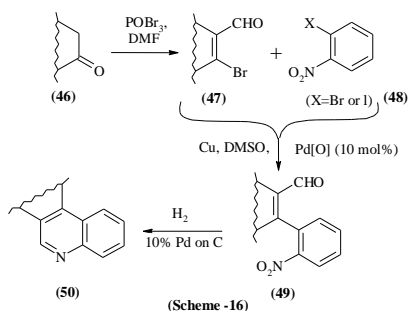
Vera-Divaio M. A. F. et al⁸⁰ illustrated Vilsmeier-Haack formylation of compound (43) into 1-Phenyl-1*H*-pyrazole-4-carboxaldehyde (44) in 65% yield. The aldehyde functional group has been utilized to synthesize corresponding acid (45) (Scheme-15).



(Scheme-15)

E) Synthesis of Quinolines

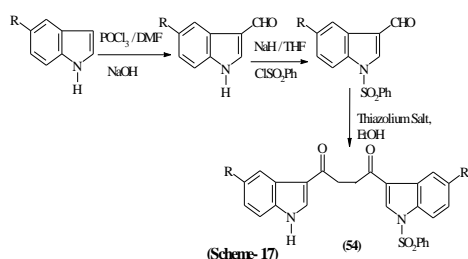
Some S. et al⁸¹ developed a new protocol for the preparation of quinolines (50) involving the subjecting of certain enolizable ketones (46) to a Vilsmeier-Haack haloformylation reaction (Scheme-16)⁸².



(Scheme-16)

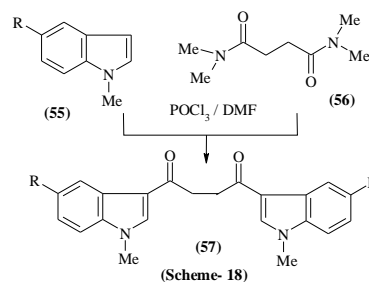
F) Synthesis of Indoles

Diana P. et al⁸³ have reported a rapid access to 1,4-Bis-indolyl-diketones (54) using Vilsmeier-Haack reaction (Scheme-17).



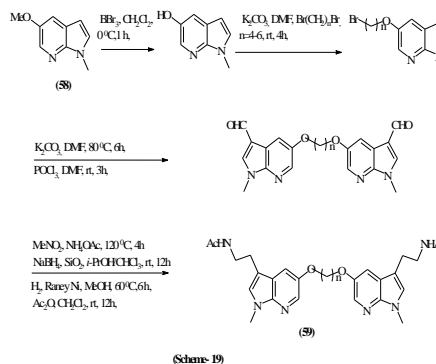
(Scheme-17)

They have also converted N-methyl derivatives (55) into 1,4-diketones (57) by Vilsmeier-Haack reaction using phosphorous oxychloride and tetramethyl succinamide (56) (Scheme-18).



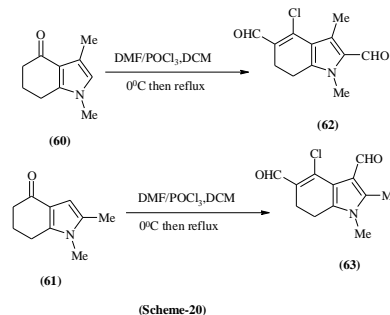
(Scheme-18)

Popowycz F. et al⁸⁴ have prepared dimer (59) from 5-Methoxy-1-methyl-7-azaindole (58) using Vilsmeier-Haack reaction conditions (Scheme-19).



(Scheme-19)

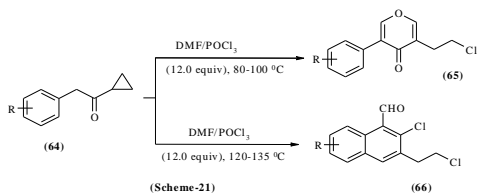
Barraja P. et al⁸⁵ have synthesized choro-bis-formylated derivatives (62) and (63) from substituted tetrahydroindolones (60) and (61) by using DMF/POCl₃ and DCM at 0°C (Scheme-20).



(Scheme-20)

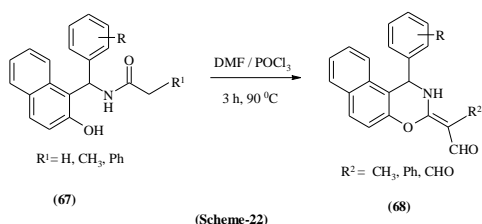
G) Synthesis of Pyranones and Naphthaldehydes

Xiang-Ying Tang and Min shi⁸⁶ have developed a convenient and efficient method to synthesize 3-(2-Chloroethyl)-5-aryl-4*H*-pyran-4-ones (65) and 2-Chloro-3-(2-chloroethyl)-1-naphthaldehydes (66) in moderate to good yields via the Vilsmeier-Haack reaction of readily available 1-Cyclopropyl-2-aryl ethanones (64) at different temperatures (Scheme 21).

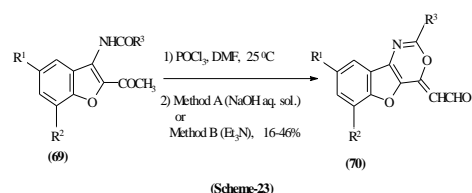


H) Synthesis of Oxazines

Damodiran M. et al⁸⁷ have reported the synthesis of highly functionalized oxazines (68) by Vilsmeier-cyclization of amidoalkyl naphthols (67) (Scheme-22).

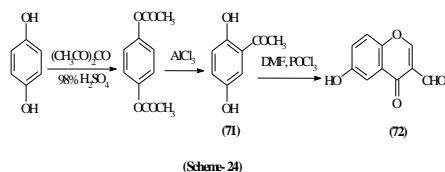


Tabuchi Y. et al⁷³ have suggested, the ring closure reaction of 2-acetyl-(E)-3-aryl-Kenylcarbonylaminobenzo[b] furans (69) using Vilsmeier reagent which generated oxazine (70) (Scheme-23).



I) Synthesis of Chromones

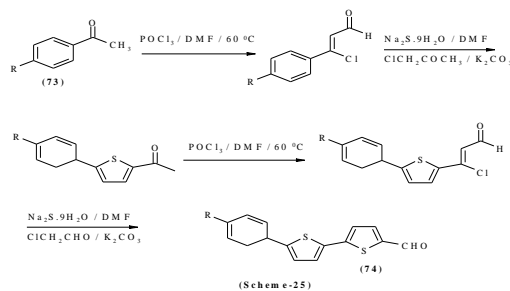
Wang B. D. et al⁸⁸ have prepared the 6-hydroxy-3-carbaldehyde chromone via Vilsmeier-Haack reaction. The compounds 6-hydroxy-4-chromone-3-carbaldehydes (72) were easily prepared by the reaction of 2,5-dihydroxy acetophenone (71) with DMF in POCl₃ solution (Scheme-24).



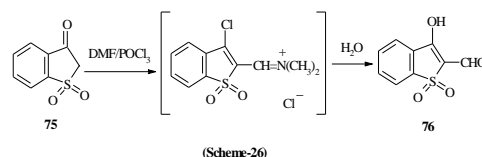
J) Synthesis of Bithiophenes and Benzothiophene dioxides

Herbivo C. et al⁸⁹ synthesized a series of formyl substituted 5-aryl-2,2-bithiophenes (74) starting from acetophenones (73)

using Vilsmeier-Haack reaction (Scheme-25). Formyl thiophene derivatives are versatile "Crossroads" intermediates.

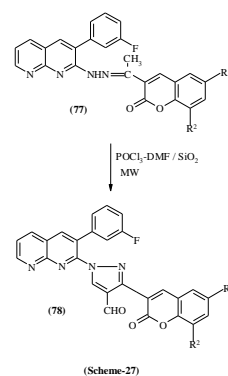


Bhatti H.S. and Seshadri S.⁹⁰ formylated benzo[b] thiophene-3(2H)-one-1,1-dioxide (75) by using DMF and POCl₃ to give (76) (Scheme 26).



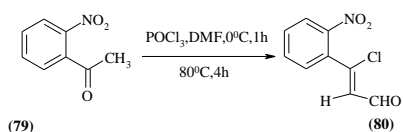
K) Synthesis of Naphthyridinepyrazoles

Mogilaiah K. et al⁹¹ used V-H reaction condition to develop a simple and efficient method for the synthesis of 1-[3-(3-fluorophenyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2H-chromenyl)-H-4-pyrazolecarbaldehydes (78) from (77) (Scheme 27).



L) Synthesis of Quindolines

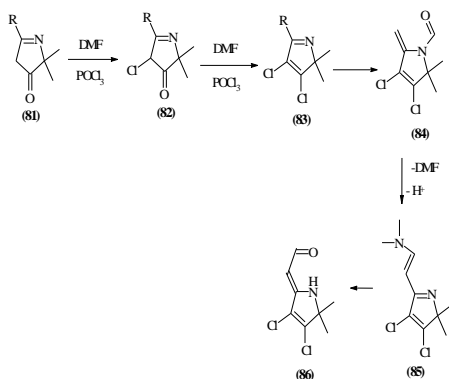
Dutta B. et al⁹² have reported the V-H formylation of 2-nitroacetophenone (79) with POCl₃ in DMF, to produce the β-Chlorocinnamaldehyde (80) (Scheme 28).



(Scheme-28)

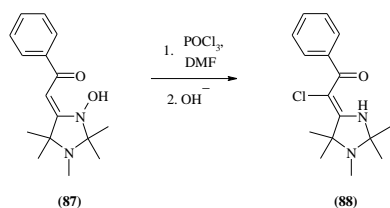
M) Formylation of Pyrrolones

Becker C. et al⁹³ have used Vilsmeier-Haack reaction conditions for the synthesis of enaminoimine (85) and enaminoaldehyde (86) starting from Pyrrolin-3-on-1-oxide derivatives (81) (Scheme 29).



(Scheme-29)

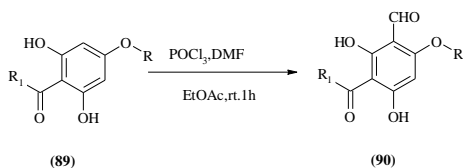
They have also reported, the reaction of exo-cyclic enhydroxylaminone (87) with the Vilsmeier reagent to form chlorosubstituted compound (88) (Scheme 30).



(Scheme-30)

N) Formylation of Phloroglucinols

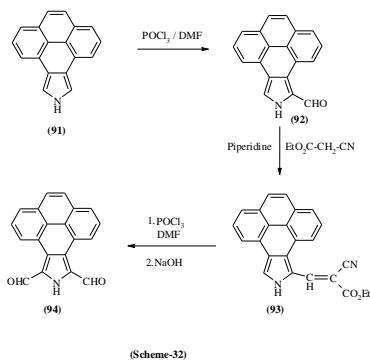
Naturally occurring phloroglucinol compounds have shown diverse range of biological activities⁹⁴. Bharate S. B. et al⁹⁵ formylated monoacyl phloroglucinol (89) to acylphloroglucinols (90) using V-H reaction (Scheme 31).



(Scheme-31)

O) Formylation of Pyrenopyrrole

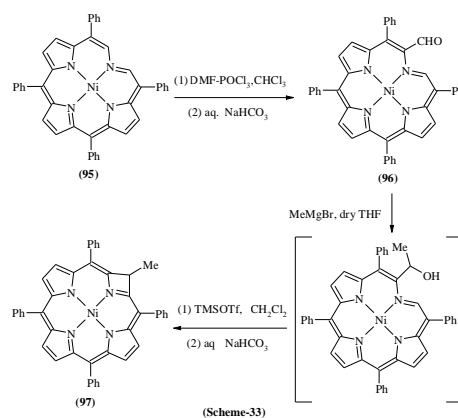
Gandhi V. et al⁹⁶ carried out, Vilsmeier-Haack formylation of pyrenopyrrole (91) to afford monoaldehyde (92) which after protection of pyrrole and further treatment with POCl_3 -DMF afforded the dialdehyde (94) (Scheme 32).



(Scheme-32)

P) Synthesis of Azeteochlorins

Banerji S. et al⁹⁷ have reported the formation of chlorophin monoaldehyde (96) from chlorophin (95) upon treatment with DMF/ POCl_3 in CHCl_3 followed by addition of aq. NaHCO_3 . The reaction of (96) with methyl-Grignard, followed by an acid-catalyzed ring-closure reaction, generated the compound [meso-tetraphenyl-2-methylazeteo-chlorinato] Ni (II) (97) in good yields (Scheme 33).

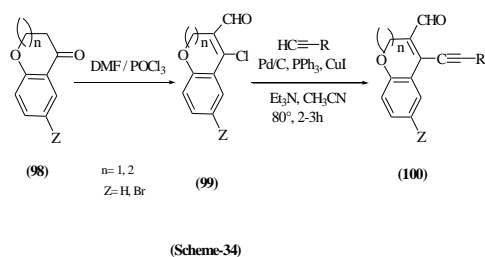


(Scheme-33)

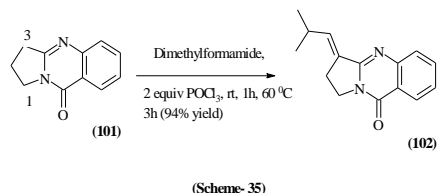
Q) Miscellaneous V-H reactions

Bera R. et al⁹⁸ used Vilsmeier-Haack reaction condition for alkylation of β -chloroacroleins. β -chloroacroleins(99) were readily prepared from the corresponding Ketones (98) by a Vilsmeier-Haack-Arnold reaction, which were then treated with terminal alkynes in acetonitrile

in the presence of 10% Pd/C, PPh₃, CuI and Et₃N under nitrogen to afford 4-alkynyl-2*H*-chromene-3-carbaldehydes (100) (Scheme 34).



Bubenyak M. et al⁹⁹ showed that, Deoxyvasicinone (101), upon Vilsmeier-Haack formylation using two equiv. of POCl₃ in DMF at 60°C for 3 hrs. gave the 3-dimethylaminomethylene derivative (102) in 94% yield (Scheme-35).

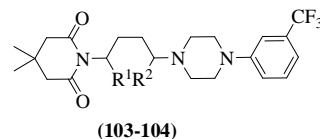


Glutarimides

Piperidine-2,6-diones (glutarimides, cyclic imides) have various biological activities¹⁰⁰ and the 2,6-piperidinedione moiety constitutes an important substructure in several new anticancer agents which have recently been introduced into experimental chemotherapy^{101,102}. Furthermore, these have been used as precursors in the synthesis of a variety of heterocyclic compounds¹⁰³. Therefore, the synthesis of piperidine-2,6-dione derivatives have attracted considerable attention of synthetic chemists and several methods have been reported in the literature¹⁰⁴⁻¹¹², most of which have used multi-step reactions using harsh reaction conditions. Many compounds possessing a cyclic imide moiety exhibit pharmacological activity such as antitumor¹¹³, immunosuppressive¹¹³, sedative¹¹³, anxiolytic¹¹³, anticonvulsive¹¹⁴ and others¹¹⁵.

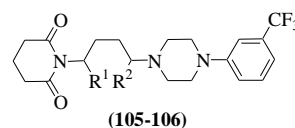
Paluchowska M. H. et al¹¹⁶ have showed that, the glutarimides 103 and 105 demonstrated anxiolytic activity while the

glutarimides 103, 104 and 106 demonstrated antidepressant like activity in the four-plate and the swim tests in mice, respectively. These glutarimides also inhibited the locomotor activity of mice. The antidepressant-like effect of 106 was reported significantly stronger than that induced by imipramine used as a reference antidepressant.



103, R¹=R²=H

104, R¹=R² = -(CH₂)₂-

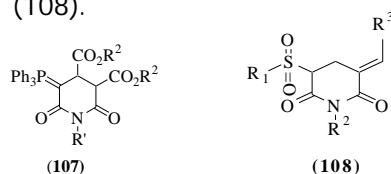


105, R¹=R²=H

106, R¹=R² = -(CH₂)₂-

Shaabani A. et al¹¹⁷ have synthesized fully functionalized *N*-alkyl-2-triphenyl phosphora-hylidene glutarimides (107) and concluded that these glutarimide derivatives constitute an essential part of many natural products with antibacterial, antitumor or fungicidal activity.

Chen C. Y. et al¹⁰⁷ have reported one-pot facile synthesis of *N*-alkyl 3-(*E*)-alkylidene-5-substituted sulfonylpiperidine-2,6-dione (108).

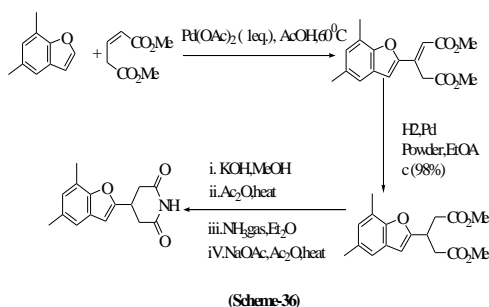


Kiyota H. et al¹¹⁸ suggested the synthesis of actiketal (RK-441S) (109) as a new acetal type glutarimide antibiotic¹¹⁹ which is expected to be a new anti-cancer agent and an immunosuppressant because of its low cytotoxicity^{119,120}.

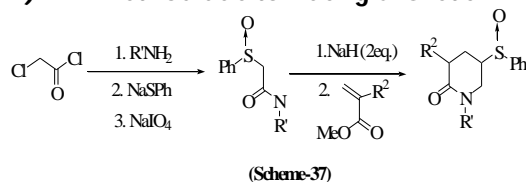
In recent years Fu R. et al¹²¹ have developed protected (*R*) and (*S*)-glutarimides (110) as a versatile building blocks^{122,123} for the asymmetric synthesis of substituted 3-piperidinol containing alkaloids and pharmaceutically relevant molecules.

In view of these useful pharmacological properties, biological activities and synthetic applications of glutarimides, various methods have been developed for their synthesis. Some of the important methods are described in the following schemes.

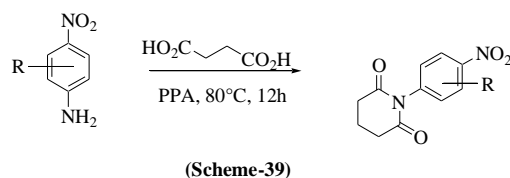
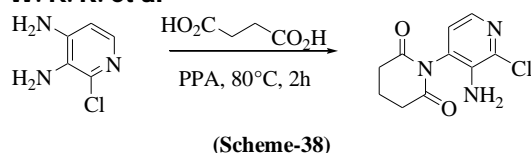
1) Method due to Kiyota H. et al¹¹⁸



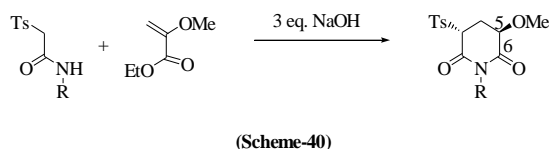
2) Method due to Huang C. G. et al¹²⁴



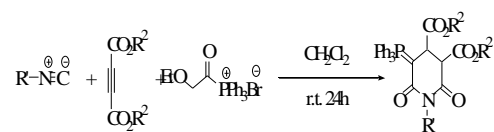
3) Methods due to Mederski Werner W. K. R. et al¹²⁵



4) Method due to Chen B. F. et al¹²⁶



5) Method due to Shaabani A. et al¹¹⁷



(Scheme-41)

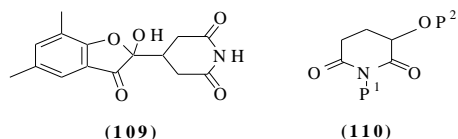
Dihydropyridines

1,4-dihydropyridines and their derivatives are an important class of bioactive molecules in the pharmaceutical field¹²⁷. The dihydropyridine heterocyclic ring is a common feature of a variety of bioactive compounds including anticonvulsant, antidiabetic, antianxiety, antidepressive, antitumor, analgesic, sedative, vasodilator, bronchodilator, hypnotic and anti-inflammatory agents¹²⁸.

Dihydropyridines are reported as calcium channel blockers¹²⁹ and are clinically useful agents for the treatment of cardiovascular diseases such as angina pectoris¹³⁰ and hypertension¹³¹. These are also used as antioxidants and are important for developing drugs. However, these are relatively difficult to synthesize.

During the years 1980-1990 considerable importance was acquired by derivatives of 1,4-dihydropyridines, as the first representatives of highly effective vasodilators and antihypertensive agents, the calcium channel blockers (Nicardipine, Nifedipine, Felodipine, etc)¹³²⁻¹³⁴. Many derivatives of 1,4-dihydropyridines with more valuable pharmacological properties¹³⁵⁻¹³⁷, which make further searches in the 1,4-dihydropyridine series extremely urgent. Till date an enormous number of symmetrical and unsymmetrical derivatives of 1,4-dihydropyridine with various functional substituents have been synthesized, and a great number of methods of obtaining them (including microwave) have been developed by further conversions and aromatization¹³⁸⁻¹⁴².

Scientists from the Latvian Institute of Organic Synthesis have carried out the systematic synthesis of numerous derivatives of 1,4-dihydropyridines with the aim of searching for new cardiotonic and ionotropic preparations, and clarification of structure-activity relationships¹⁴³⁻¹⁴⁵. In addition to this formyl group present on pyridine and

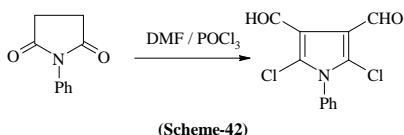


dihydropyridine molecules make them promising precursors for further synthetic transformations.

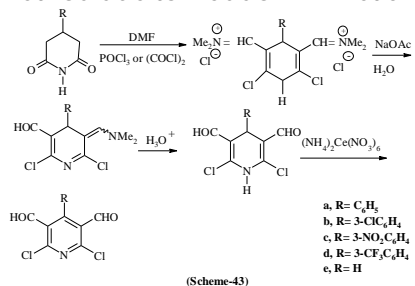
The use of formylation reaction as synthetic strategy to form versatile carboxaldehyde intermediates is still of interest, due to both their intrinsic pharmacological properties and chemical reactivity¹⁴⁶. Formylation reactions have been described for pyrazoles¹⁴⁷, pyridines¹⁴⁸ and pyrimidines¹⁴⁹ as a key step to the introduction of functionalities via the intermediate carboxaldehydes, and further cyclization to fused heterocycles. Vilsmeier–Haack reaction carried out on methylene-active compounds leads mainly to the formation of β -halo-carboxaldehyde derivatives, which are useful precursors in the construction of different heterocyclic compounds by means of numerous transformations¹⁵⁰⁻¹⁵¹. We have concentrated much of our recent work on the preparation of bioactive nitrogen-containing heterocycles.

By considering the importance of formyl pyridines different researchers have developed the various methods for the synthesis of chloroformylation of pyridines and dihydropyridines as described in the following schemes.

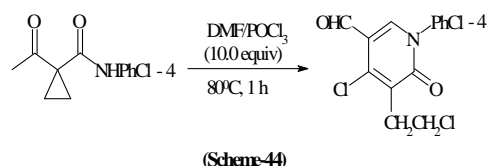
1. Method due to Kvitko I. Y. et al.¹⁵



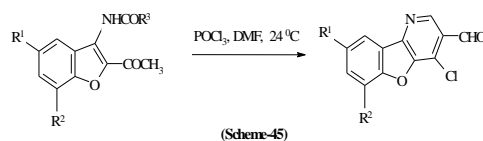
2. Method due to Maddox M. L. et al.¹⁵³



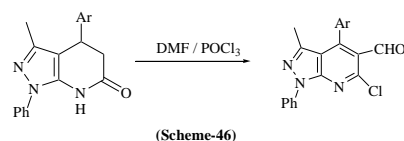
3. Method due to Pan W. et al.⁶⁹



4. Method due to Tabuchi Y. et al.⁷³



5. Method due to Quiroga J. et al.¹⁵⁴

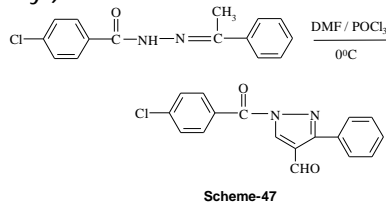


Rajput A. P.¹⁵⁵ have synthesized 1,4-diazepine type compounds and reported their useful

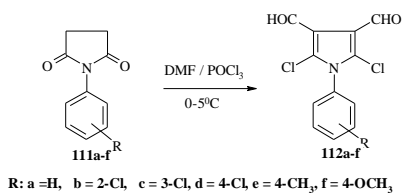
biological activities, pharmaceutical properties and therapeutic applications.

Rajput A. P.¹⁵⁶ have formylated 2-Aryliminothiazolid-4-ones using V-H reagent. The formylated synthones were used to synthesize various fused heterocyclic ring systems containing thiazole moiety and some heterocyclic Schiff bases to get some compounds of interesting biological activities

Rajput A. P. and Rajput S. S.¹⁵⁷ have reported that, the condensation of 4-chlorophenyl carboxylic acid hydrazide with different acetophenones and acetaldehydes afforded the corresponding acetophenones/acetaldehydes 4-chlorophenyl carbonyl hydrazones which on V-H reaction formylated the compound 1-(3-aryl/alkyl-4-formyl pyrazole-1-carbonyl)-4-chlorobenzenes.



They¹⁵⁸ have also prepared various dichloro, diformyl derivatives of pyrrole on formylation using V-H reagent from various succinimide derivatives.



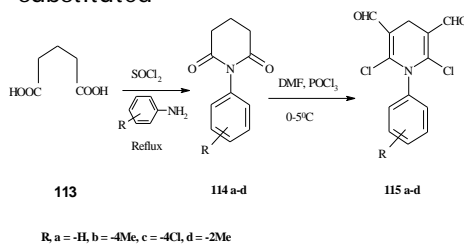
(Scheme-48)

Rajput A. P. and Rajput S. S.¹⁵⁹ have formylated benzaldehyde substituted

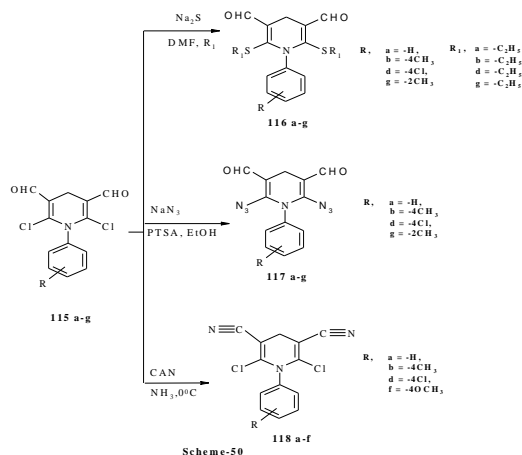
phenyl carbonyl hydrazones by using V-H reaction.

Rajput A. P. and Bhadane S. J.¹⁶⁰ have carried out formylation of N-substituted phenyl succinimides. From these compounds various heterocyclic compounds have been synthesized.

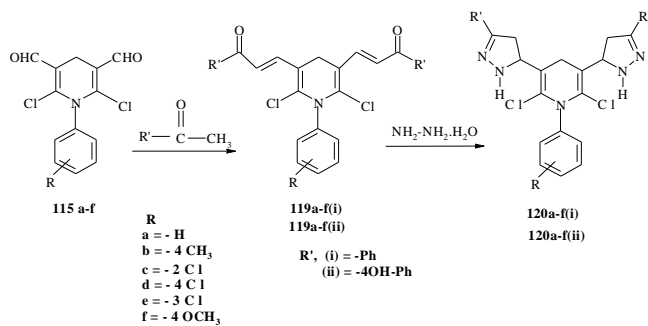
Rajput A. P. and Girase P. D.¹⁶¹⁻¹⁶⁶ have reported the synthesis, characterization and microbial screening of various nitrogen, oxygen and sulphur heterocyclic compounds from 2,6-dichloro 3,5-diformyl (N-substituted Phenyl)-4-hydropyridines.



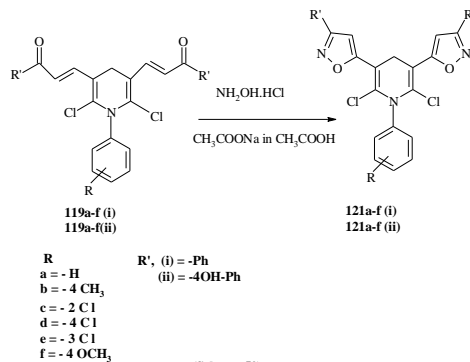
(Scheme-49)



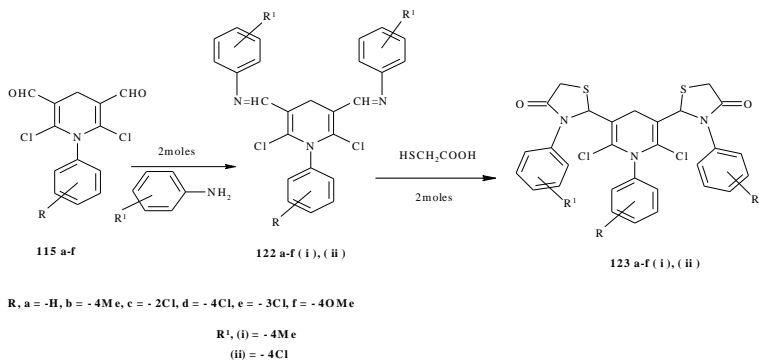
Scheme-50



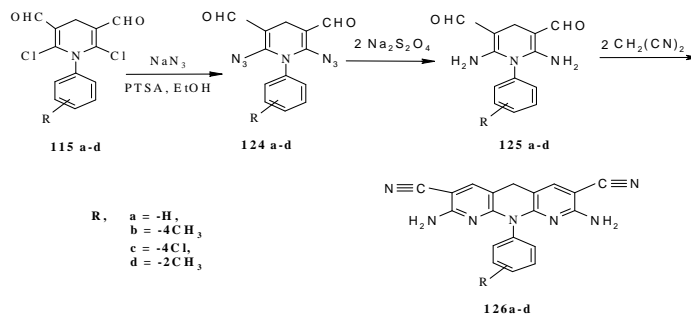
(Scheme-51)



(Scheme-52)



Scheme-53



(Scheme-54)

CONCLUSIONS

This review has attempted to summarize the synthetic methods and reactions of glutarimides and dihydropyridines. Many biologically active heterocyclic compounds have been synthesized from that heterocycle. These reactions greatly extended synthetic possibilities in organic chemistry.

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