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Mechanistic Studies and Advanced Applications of Specific Three Component Heterocyclization Reactions

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Abstract. *Multicomponent reactions are considered as the powerful tool in synthetic organic chemistry. They are efficient and one-pot reactions employing more than one starting materials leading to the formation of a final product. A wide range of heterocyclic compounds have been synthesized via multi-component reactions. In a mechanistically interesting MCR between amino triazoles, different carbonyl compounds and aromatic aldehydes, a mixture of isomeric heterocycles are obtained in good yields. Multicomponent reactions (MCRs) of H_2S with different carbonyl compounds, amines and hydrazines have been carried out to get a variety of new types of sulphur and nitrogen containing heterocycles of immense medicinal importance. In a microwave assisted three-component reaction of 2,6-diaminopyrimidin-4-one, 4-hydroxycoumarin and aromatic aldehydes in DMF, Chromenopyridopyrimidines are formed in excellent yields .However, addition of acetic acid to the same reaction mixture leads to the formation of a different compound. This article focuses on the recently proposed mechanisms for a series of multicomponent heterocyclization reactions. A wide range of advanced applications of the heterocycles synthesized via MCRs have also been discussed.*

Keywords: *Heterocyclic compounds; Aminotriazoles; Aromatic aldehydes; Hydrazines; Chromenopyridopyrimidines.*

1. Introduction

Multi-component reactions are economical and convenient methods in the eco-friendly and diversity-oriented synthesis of heterocycles. Notably, the transition metal-catalysed multi-component reactions have received considerable interest (D'Souza & Müller , 2007). Besides the familiar advantages of multicomponent reactions, as availability of starting materials and low consumption of solvents, there is possibility of increasing the variety of the compounds synthesized (Ruijter et al., 2011; Biggs-Houck et al., 2010).Three-component reactions of substrates may take place by different routes leading to the fact that stoichiometric ratio of reactants (Sha & Huang, 2009) or the sequence of adding them (Suzuki et al., 2009), show a marked influence on the selectivity of multicomponent reactions. Additionally, the possibility of parallel reactions increases while using polyfunctional starting materials containing more than one reaction centers.These factors contribute to the effect that multicomponent reactions are characteristic for multicomponent heterocyclizations (Isambert & Lavilla 2008; Chen et al., 2009). The power of forming multiple bonds in one-pot via a multicomponent reaction furnishes an innovative and justifiable method in drug discovery (Bagley & Lubinu, 2006).

Moreover, MCRs follow simple purification procedures and faster reactions recommending chemo and regioselectivity in some cases (Kappe & Stadler, 2005; Lei et al., 2011). The pharmaceutical industry has noticed a significant push in drug synthesis via

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multicomponent approaches (Abdelraheem et al., 2018; Sunke R, et al., 2014), including the synthesis of atorvastatin. Now chemists have focused on developing greener synthetic methods for the construction of several pharmacophores which can prove to be vital in a drug discoveryprocess (Laxmikeshav et al., 2020; Maddirala et.al., 2016; Tokala et al., 2019, Sharma et al., 2017, Nekkanti et al., 2016). Medium-sizedN-containing heterocycles are key structures of various structurally remarkable natural products but the direct formation of these ring sizes from acyclic precursors is disfavoured due to various factors .However , in a unique MCR,a variety of medium size heterocycles have been synthesized by the action of activated alkynes (Voskressensky et al., 2004; Voskressensky et al., 2008). Organic chemists predominantly utilize multicomponent reactions in the design and preparation of complex polycyclic molecules. These reactions minimize the by-product formation, reduce reaction times, result excellent yields and enhance selectivity. Fundamentally, the combination of one-pot multicomponent approaches with distinct methodologies accelerate the synthesis of biologically pertinent heterocycles (Domling. & Ugi, 2000; Rotstein et al, 2014; Ghashghaei et al., 2019, Zhu et al., 2015 ; Müller 2014).

In this article authors have developed a range of mechanisms for a varied number of multicomponent heterocyclization reactions. Although the compounds are known but the proposed mechanisms have not been discussed earlier as revealed by the exhaustive literature survey. Apart from this, broad spectrum of applications of these reactions have also been debated in this article.

2. Discussion

A multicomponent reaction involves the construction of products from countless starting materials in a single-step procedure. These reactions can be employed to synthesize highly functionalized, biologically active heterocyclic compounds including various polycyclic structures. In a multicomponent reaction (MCR) between amino triazoles (**1**), different carbonyl compounds (**2**) and aromatic aldehydes (**3**), a mixture of isomeric heterocyclic products (**4**) and (**5**) are obtained in good yields. Most probably the formation of different intermediates influenced by various electronic and steric factors coupled with multiple reactive centers leads to the formation of two isomeric products. Furthermore, the stoichiometric ratio of reactants or the sequence of adding them influences significantly on the selectivity of multicomponent reactions. (Desenko et al., 1993; Khan & Khan.M.M,2011)- Figure 1.

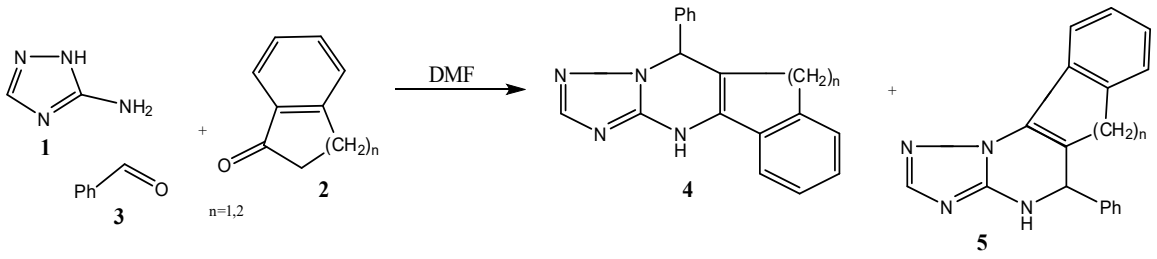
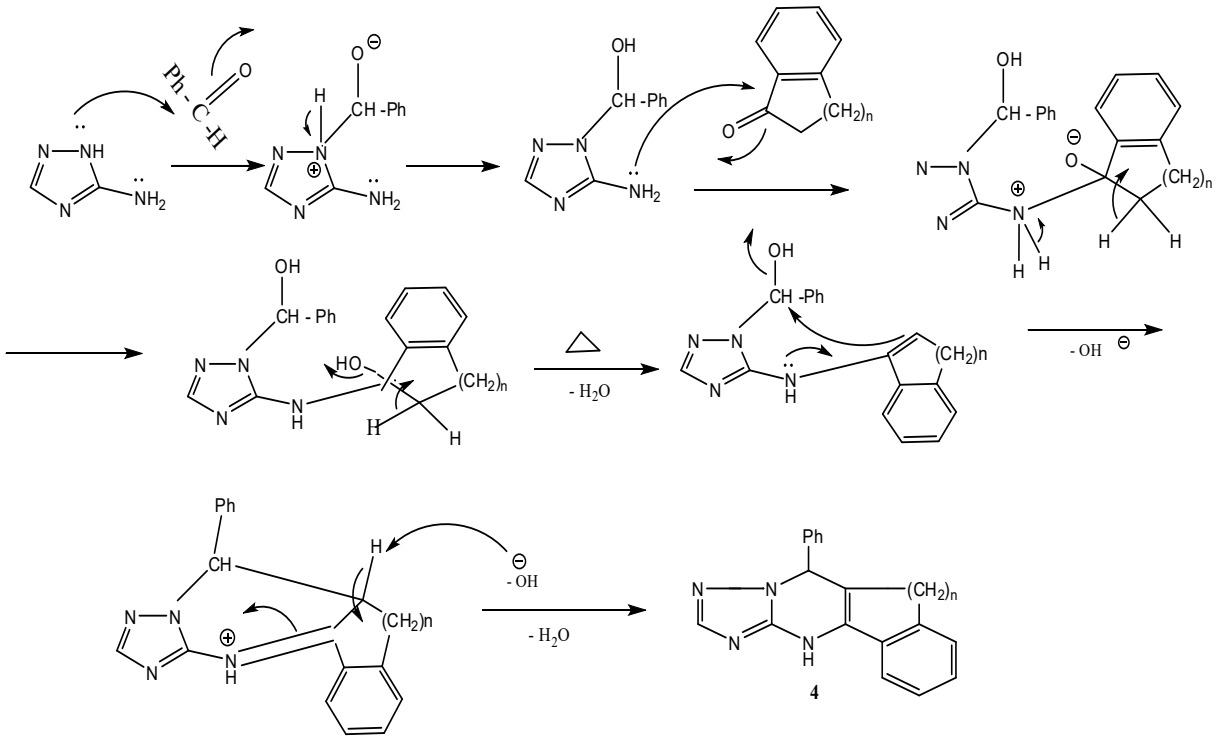


Figure 1. Formation of isomeric heterocycles 4 and 5

Plausible mechanism developed for the formation of heterocycles (**4**) and (**5**) can be rationalized as below –Figure 2.

(I)



(II)

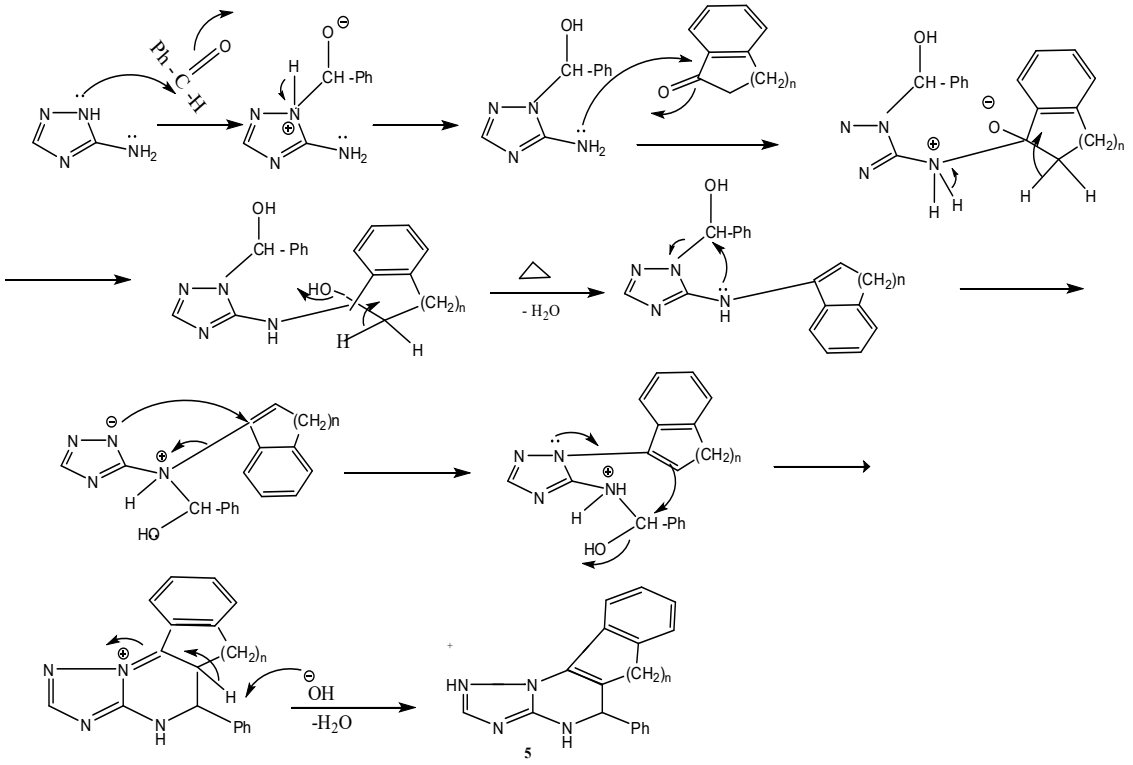


Figure 2. Mechanism developed for the formation of isomeric products **4** and **5**

In a similar multicomponent reaction between 1,2-diazoles (pyrazoles) (**6)** , 1,3-dicarbonyl compounds (**7)** and aromatic aldehydes (**3)** , non-isomeric compounds (**8)** and(**9)** are formed (Drizin.I,et.al.2002)- Figure 3.

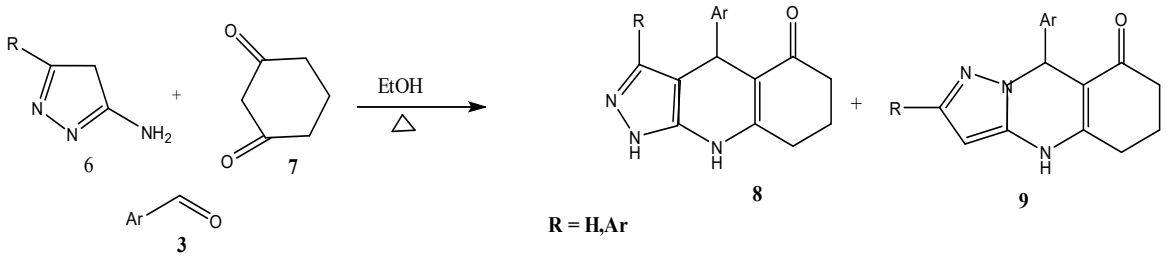
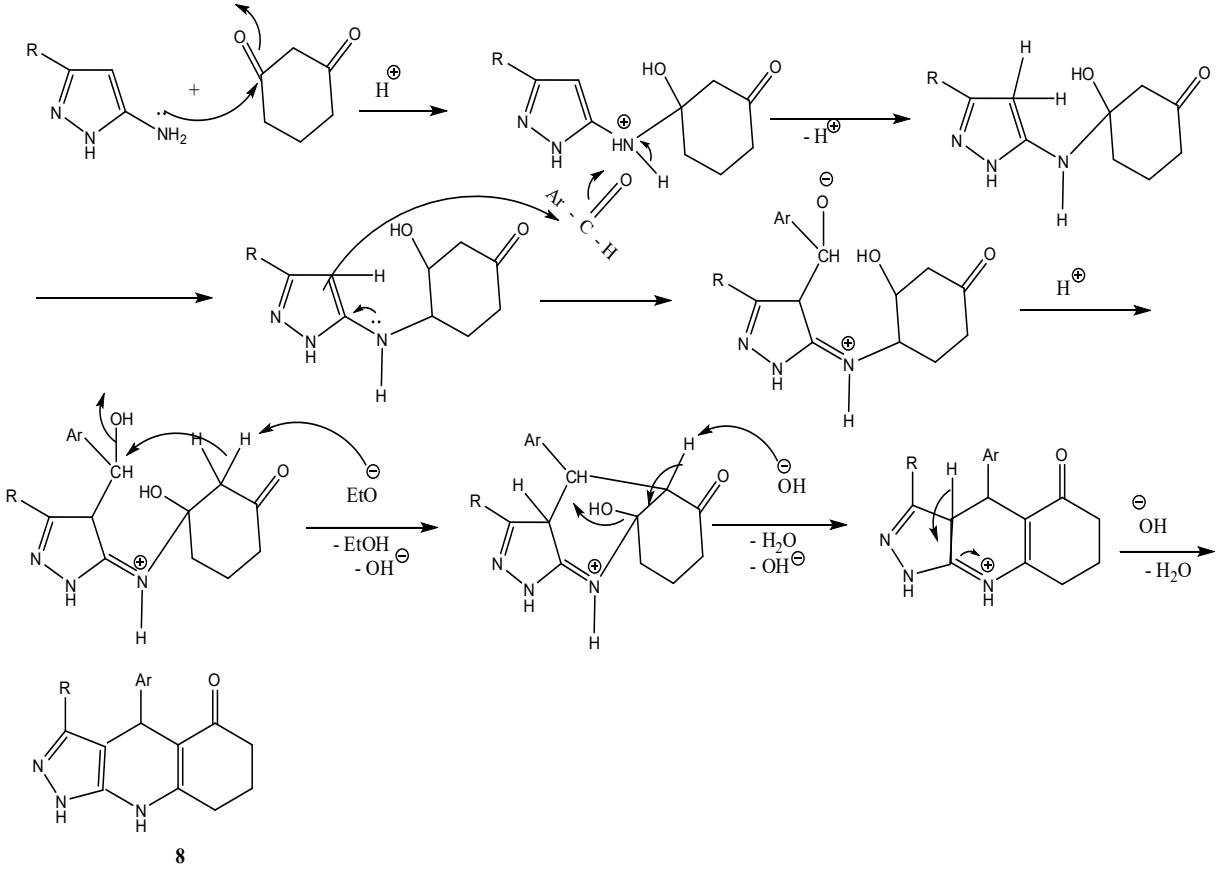


Figure 3. Formation of non-isomeric compounds **8** and **9**

Most feasible mechanism proposed for the formation of non-isomeric heterocycles **(8)**and (**9)** can be delineated as below-Figure 4.

(I)



(II)

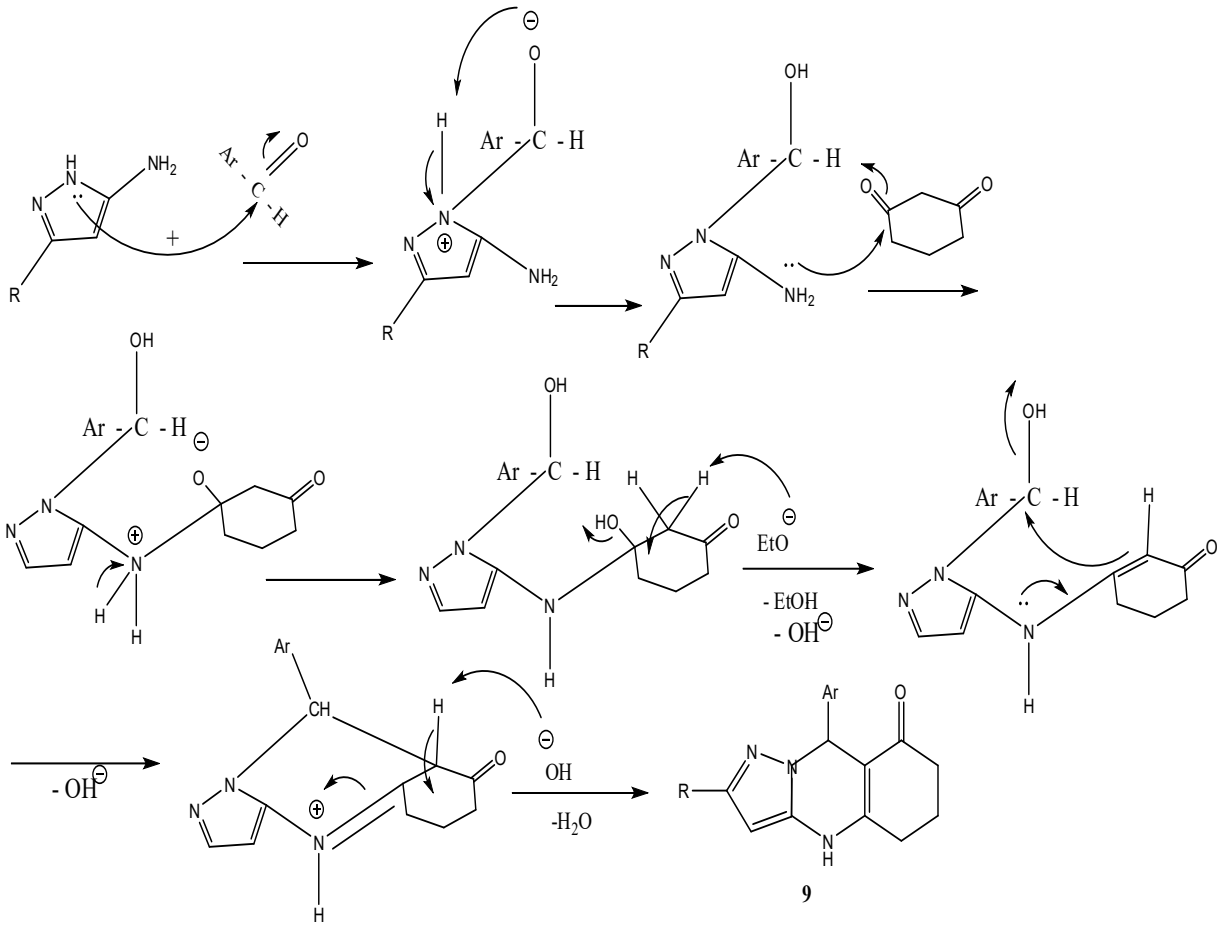


Figure 4. Mechanism proposed for the formation of non-isomeric heterocycles **8** and **9**

Multi-component reactions of H_2S with different carbonyl compounds, amines and hydrazines have been carried out to get a variety of new types of sulphur and nitrogen containing heterocyclic compounds. These compounds are of immense importance as potential antibacterial and antivirus preparations (Khafizova.S.R ,et al.2004; Akhmetova.V.R.etal.2004)-Figure 5.

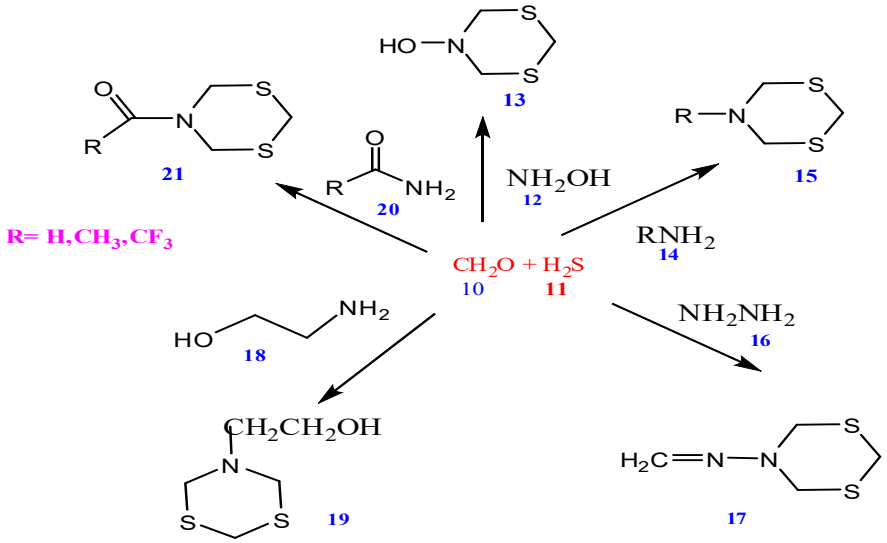
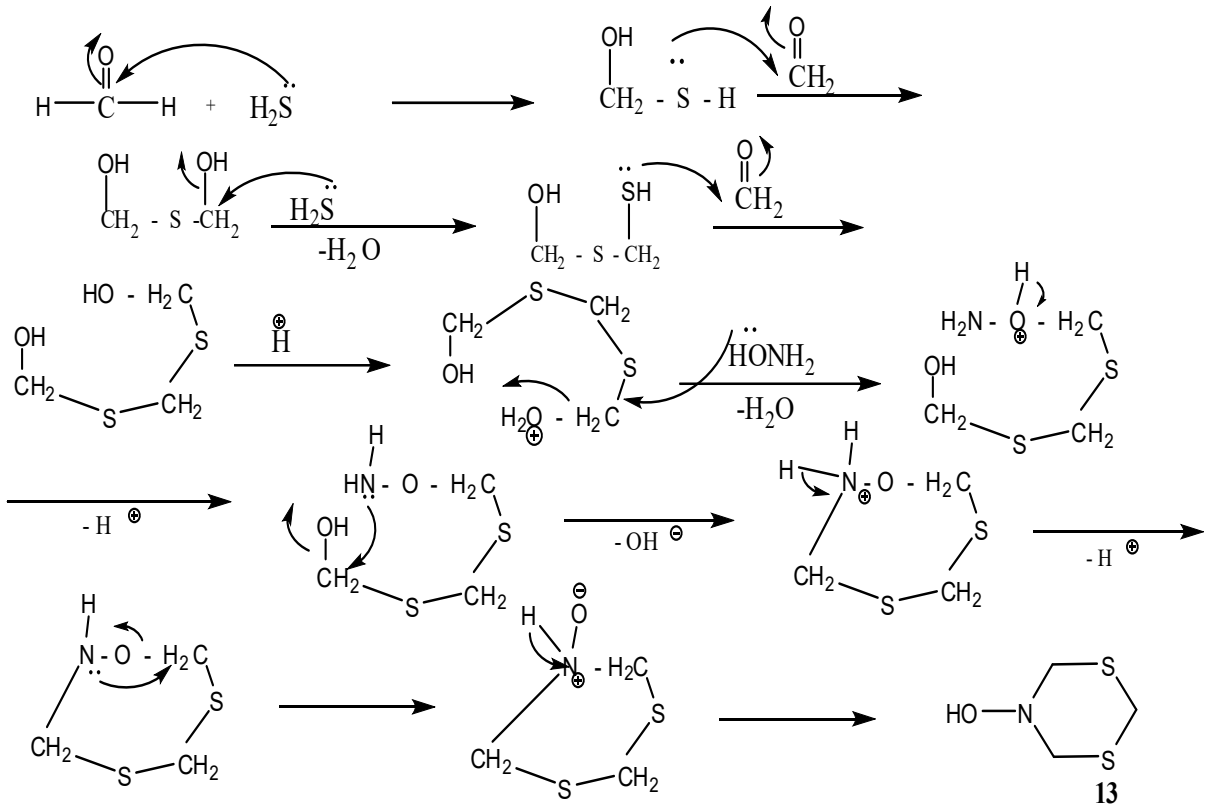


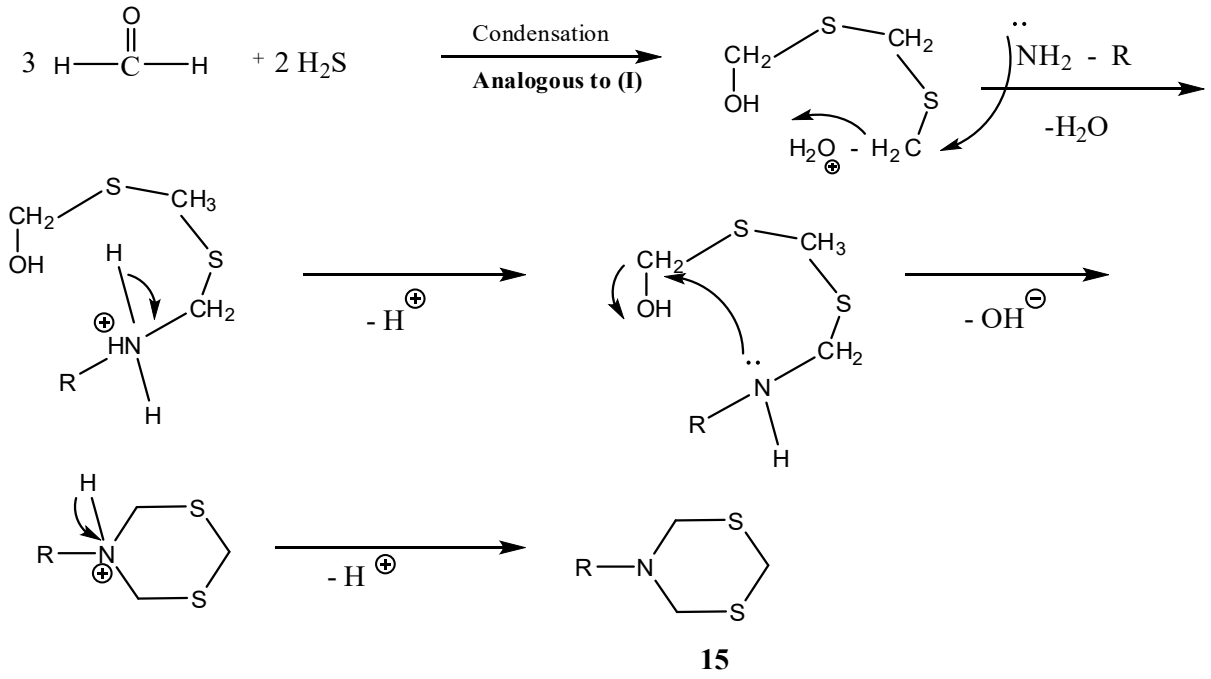
Figure 5. Multi-component reactions of H_2S with different carbonyl compounds, amines, and hydrazines

Probable mechanism suggested for the formation of heterocycles (**13,15,17,19)** and (**21)** can be outlined as below-Figure 6.

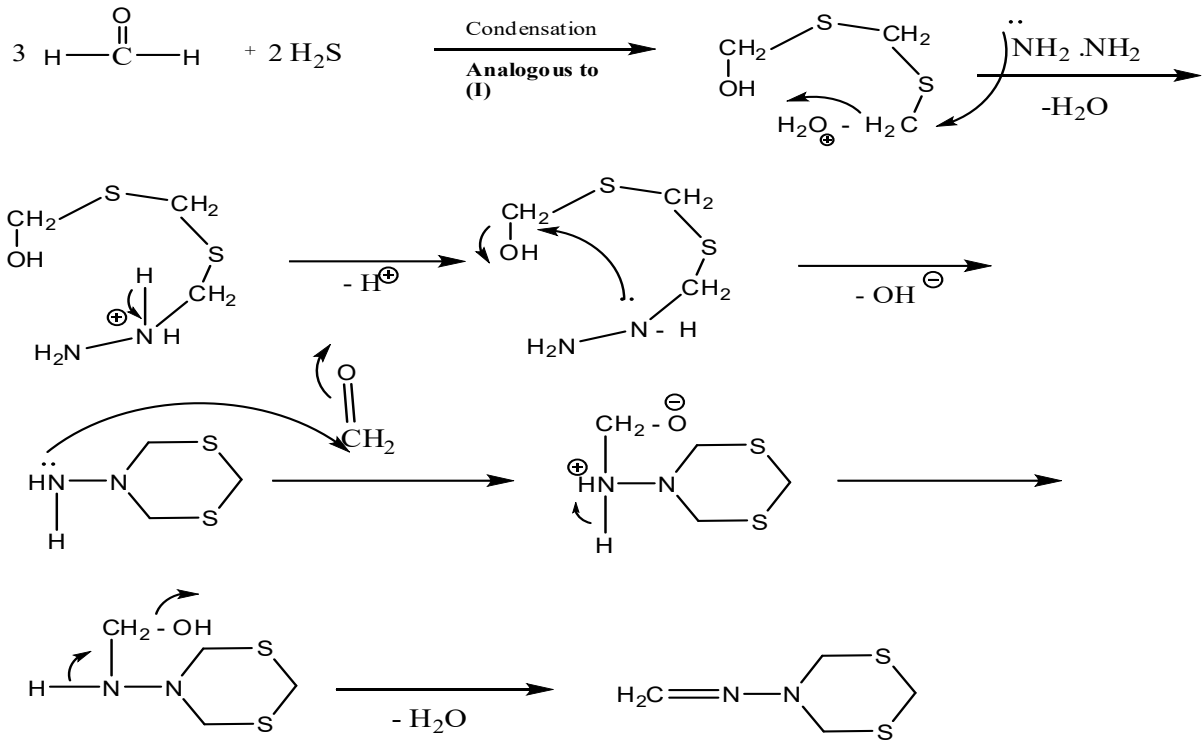
(I)



(II)

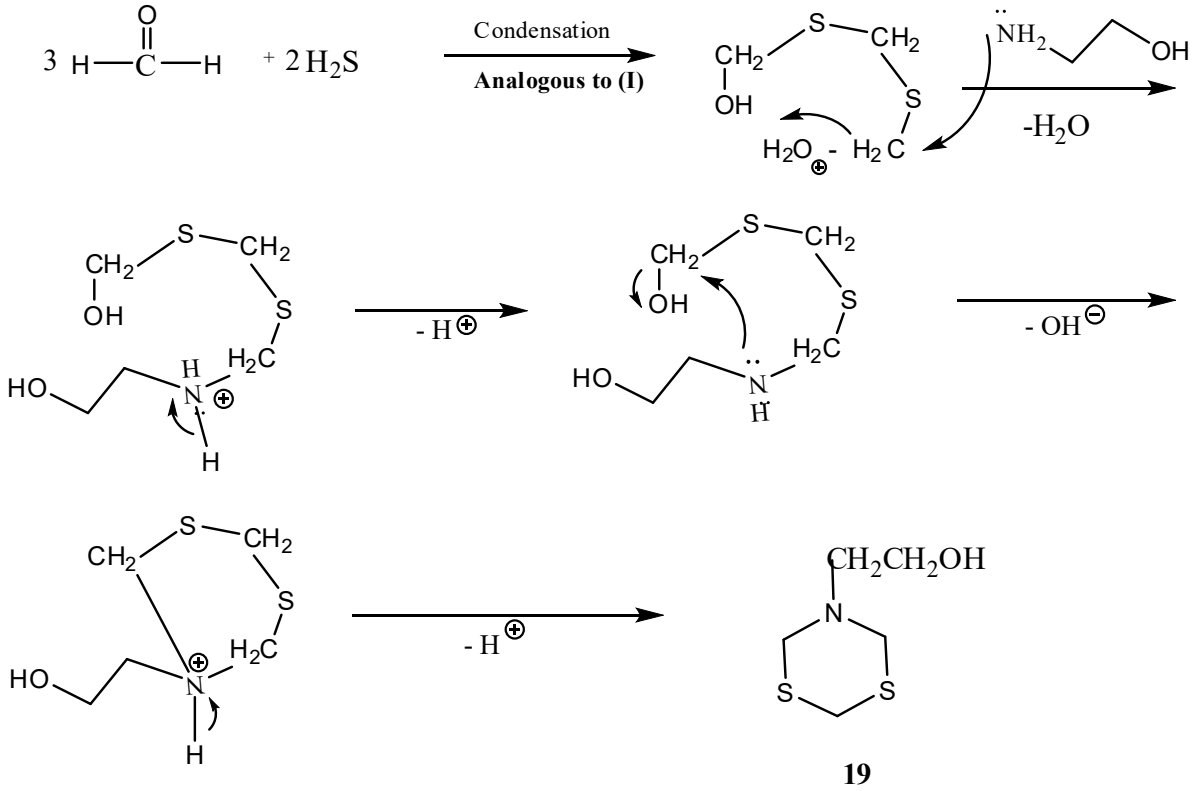


(III)


Condensation
Analogous to (I)
-H2O
- H+
- OH-
- H2O

17

(IV)


Condensation
Analogous to (I)
-H2O
- H+
- OH-
- H+

19

(V)

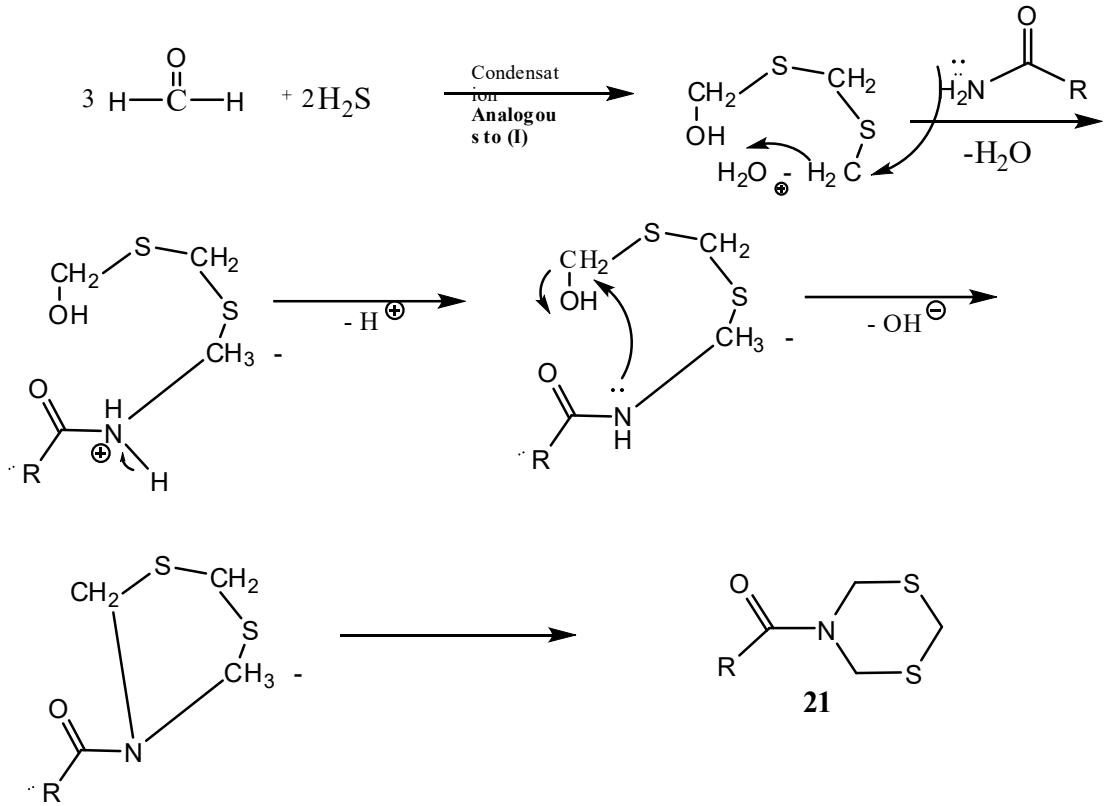


Figure 6. Mechanism suggested for the formation of heterocycles **13,15,17,19** and **21**

In a microwave assisted three-component reaction of 2,6-diaminopyrimidin-4-one, 4-hydroxycoumarin and aromatic aldehydes in DMF at 140^{0}C , Chromenopyridopyrimidines (**24)** are formed in excellent yields(Tu.S,Li.C,et.al.2008).However, addition of acetic acid to the reaction mixture at 150^{0}C leads to formation of a different heterocyclic compound (**25)**-Figure 7

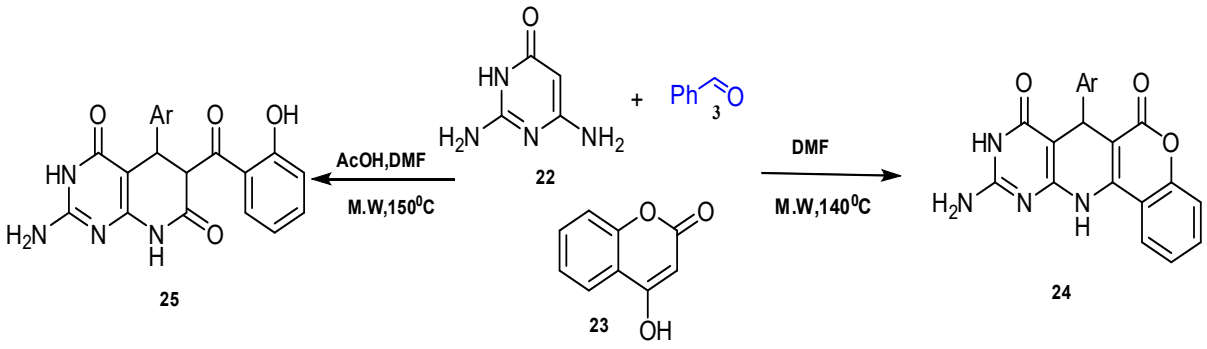


Figure 7. Microwave assisted three-component reaction

Literature reveals that the mechanism for the formation of compounds (**24)** and (**25)** has not been developed earlier, therefore, the possible mechanism suggested for these heterocycles can be discussed as-Figure 8

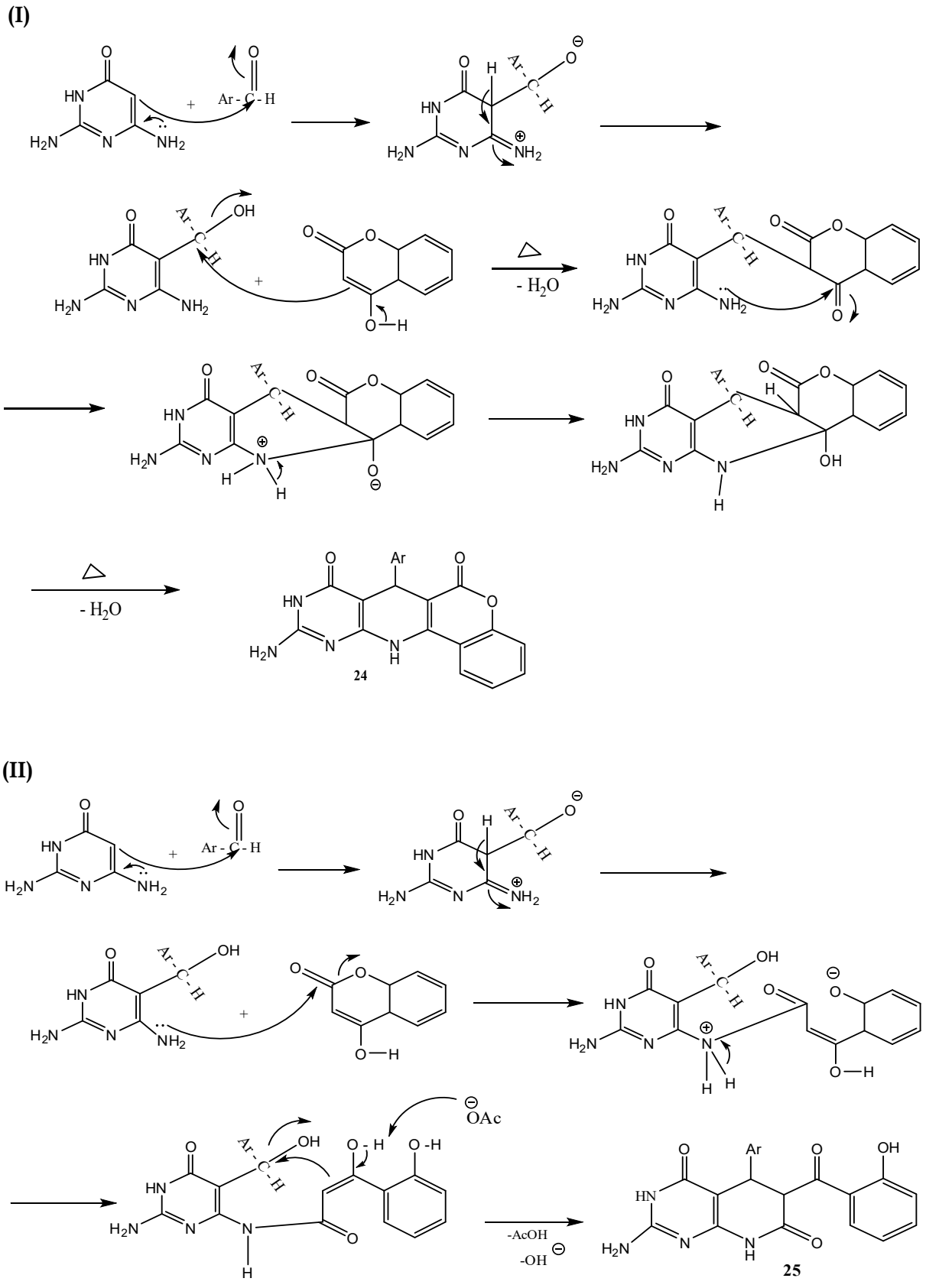
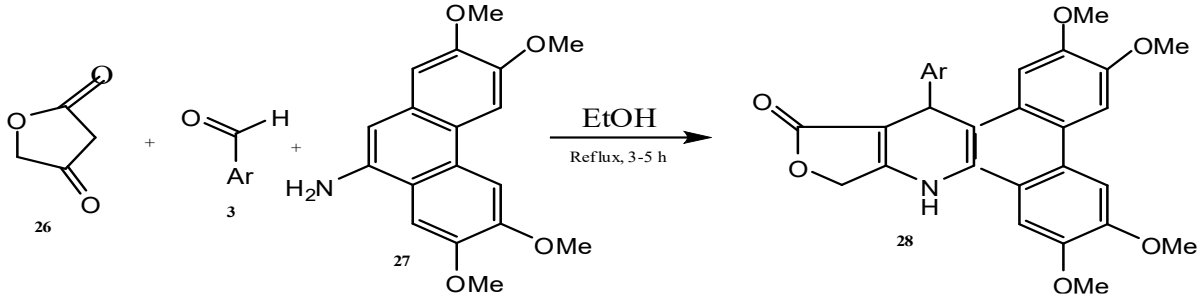


Figure 8. Probable mechanism developed for the formation of heterocycles **24** and **25**

A convenient method for the synthesis of 4-aza-2,3-dihydropyridophenanthrene derivatives (**28)** has been achieved through domino reactions of tetronic acid (**26)**, aryl

aldehydes(**3)** and 2,3,6,7- tetramethoxyphenanthrene-9-amine (**27)** when refluxed in ethanol(Kumar.N.P,et.al.2017)-Figure 9.



Ar= Ph,H,4-OMe,4-Me,4Cl, 3-CF_3, 3-OH etc.

Figure 9. Synthesis of 4-aza-2,3-dihydropyridophenanthrene derivatives

Most probable mechanism developed for the formation of 4-aza-2,3 dihydropyridophenanthrene derivatives (**28)** can be depicted as below- Figure 10.

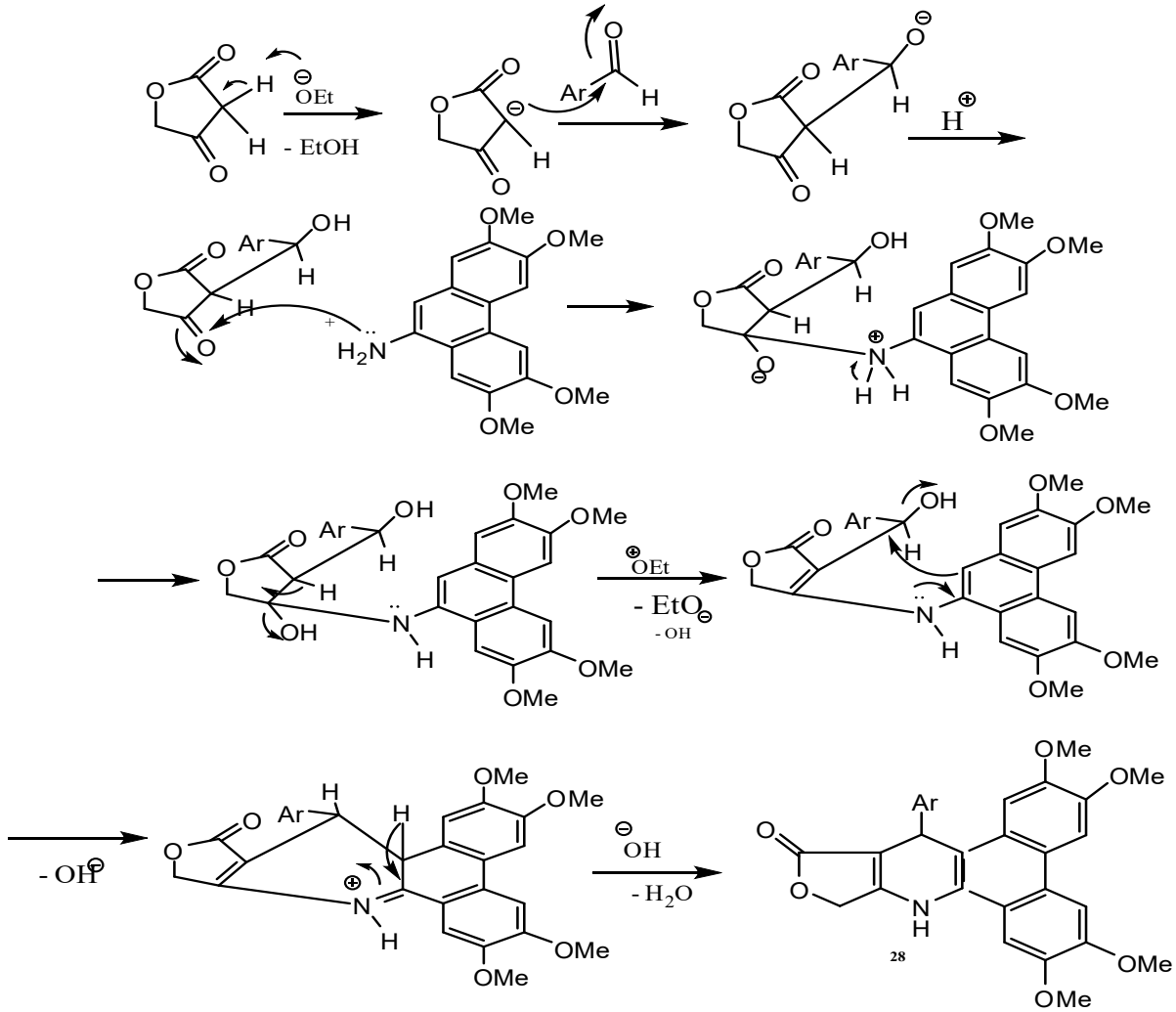


Figure 10. Mechanism developed for the formation of 4-aza-2,3-dihydropyridophenanthrene derivatives **28**

2-Amino-4*H*-chromenes (**31) h**ave been synthesized by the condensation of aldehydes (**3)** and malononitrile (**29)** with alpha and beta-naphthols (**30)**.The procedure for

synthesizing 2-amino-4*H*-chromenes (**31)** is very simple, efficient and clean as it is solvent free and does not require any toxic catalyst(Kaupp.G.2005; Kemnitzer.W , et.al.2005)-Figure 11

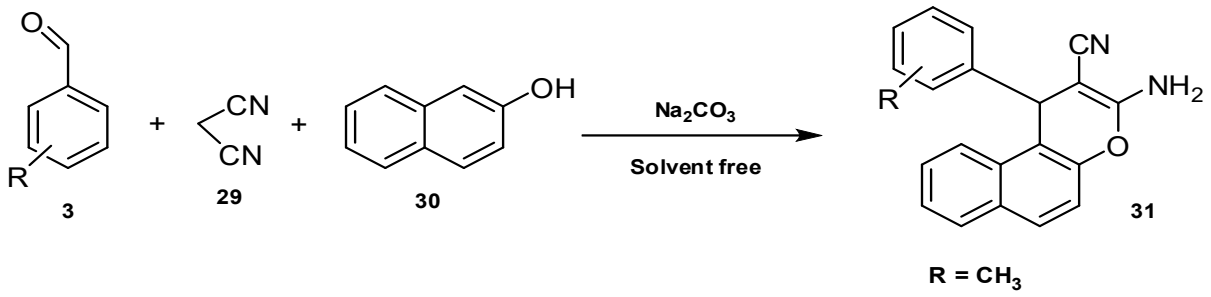


Figure 11. Formation of 2-Amino-4*H*-chromenes **31**

Most reasonable mechanism proposed for the formation of 2-amino-4*H*-chromenes (**31)** can be justified as below-Figure 12

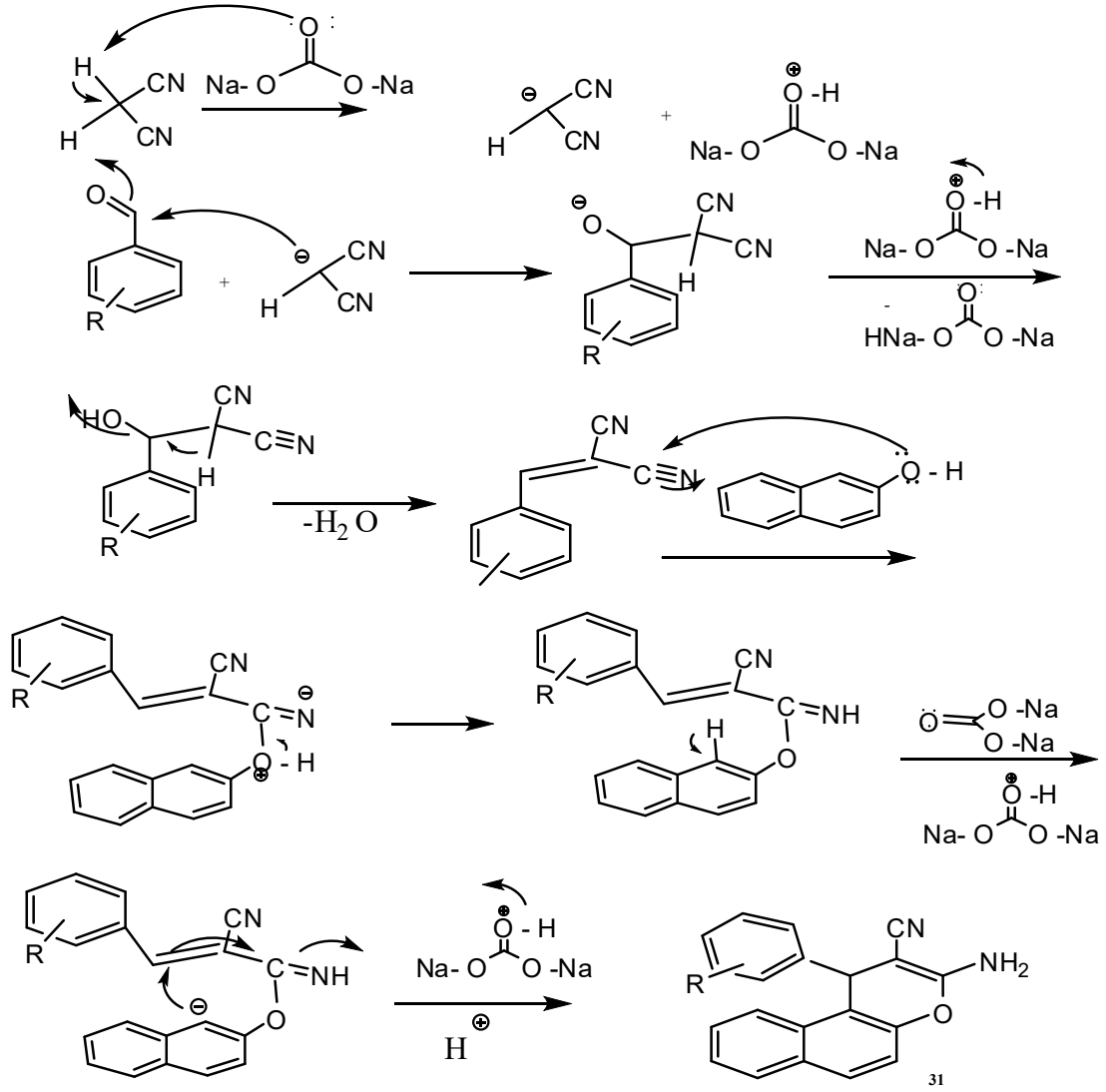


Figure 12. Mechanism developed for the formation of 2-amino-4*H*-chromenes **31**

3. Advanced applications of multicomponent heterocyclization reactions

The utility of MCRs in promoting the synthesis of multiple chemical structures has been widely recognized .These reactions can be employed to synthesize highly functionalized, biologically active molecules as well as polycyclic structures. The pharmaceutical industry has observed a substantial rise in drug synthesis via multicomponent strategies including the synthesis of atorvastatin. Dihydroquinoline lactone derivatives have been synthesized via a MCR involving tetronic acids, aryl anilines and aromatic aldehydes in ethanol. These compounds showed antibacterial activity under laboratory conditions against various bacterial strains and are specifically effective against Gram-negative bacteria. In a multicomponent reaction involving substituted isatins , β-nitrostyrene and benzylamine under microwave irradiation , a series of spirooxindoleshave been synthesized**.**

These molecules displayed marvellous antimicrobial activity against *Escherichia coli*, *Candida tropicalis* and *Pseudomonasaeruginosa*.Naphthopyrans are reported as potential non-purine xanthine oxidase inhibitors. A silicated fluoroboric acid-catalyzed three-component cycloaddition method involving acyclic 1,3-diketones, β-naphthol and aldehyde has been explored for the synthesis of substituted naphthopyrans under microwave irradiation (Sharma.S,et.al,2014). A plethora of compounds proved to be active as xanthine oxidase inhibitors. Synthetic possibilities of multi-component reactions of H_2S with different carbonyl compounds, amines and hydrazines have been investigated to produce new types of heterocyclic compounds, viz. substituted thiadiazinanes , dithiadiazacyclooctanes , thiadiaza and dithiadiazabicyclanes.These sulphur and nitrogen-containing heterocycles are of special interest as potential antibacterial and antivirus preparations and also as selective sorbents. 5-aza-7-deazapurine molecules used as antiviral and cytotoxic agents are synthesized by a one-pot three-component reaction involving cyanamide, 2-amino-4-phenylimidazole and triethyl orthoformate in ethyl acetate. Microwave- assisted synthesis of steroidal pyridines has been demonstrated using steroidal ketones , aldehydes , malononitrile ,methyl cyanoacetate and ammonium acetate as structural units and MgO nanoparticles as a catalyst in ethanol solvent. Heterocycles having pyridine nucleus are pharmacologically important as they can act as potent anticancer, antibacterial and antiviral agents.

A three-component microwave-assisted reaction of substituted benzimidazole-linked aminopyridine aldehyde and isocyanide using $Sc(OTf)_3$ as the catalyst under solvent-free conditions has been carried out to afford substituted benzimidazole- imidazo[1,2-a]pyridines in excellent yields.(Fadime.M-B,et.al,2012).The imidazo[1,2-*a*]pyridine nucleus is found in numerous drugs like Zolpidem,Alpidem and Olprinone . They are also favourable antiviral, antiulcer and anxiolytic agents. Quinoline and its derivatives are important both from synthetic as well as biological view point due to their surplus pharmacological activities. They are potent anticancer, antimicrobial and anticonvulsant agents .An efficient synthetic approach involving a multicomponent reaction for the synthesis of 2,4-diarylquinolines using substituted amines **,** aldehydes and alkynes as substrates has been carried out under microwave irradiation and solvent-free conditions. A one-pot multicomponent reaction under microwave irradiation for the synthesis of substituted purine-based quinazolinone derivatives has been achieved utilizing amines and amino benzoic acids as substrates with PCl_3 as a cyclising agent followed by the continuous

addition of adenine in the presence of K_2CO_3 .These quinazolinone derivatives exhibit various pharmacological properties like anticancer , antihypertensive and anti-inflammatory.

Conclusion

In conclusion multi-component reactions have received extensive interest due to their efficient. rapid and eco-friendly synthetic approaches for the formation of heterocyclic compounds in a single synthetic step. This article highlights a range of unknown mechanisms suggested/proposed for a series of multicomponent heterocyclization reactions. All the mechanisms presented in this manuscript have been developed by authors and not adapted from the literature at any place. Moreover, a broad spectrum of advanced applications of the heterocycles synthesized via multi-component reactions have also been deliberated.

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Conflict of interest

The authors declare no conflict of interest. No one outside the authors has any role in the design of the study; in the collection, Visualization, Investigation or in the writing of the manuscript.

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