Chapter three

3. Discussion

3.1 Synthesis of chalcones:

The chalcone were made by select the α,β unsaturated carbonyl group disconnection using as d^2 synthon and aromatic aldehyde.

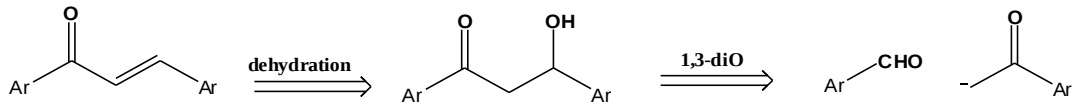


Figure 3.1: Retrosynthesis of chalcone

Chalcone is a product of condensation of aromatic aldehydes with aromatic ketones. The reactive intermediate enolates would formed by deprotonation of α-H of aromatic ketones at basic condition, then attack the aldehyde making aldol, which underwent E1cB elimination forming the desired chalcone **(**Clayden et al, 2009).

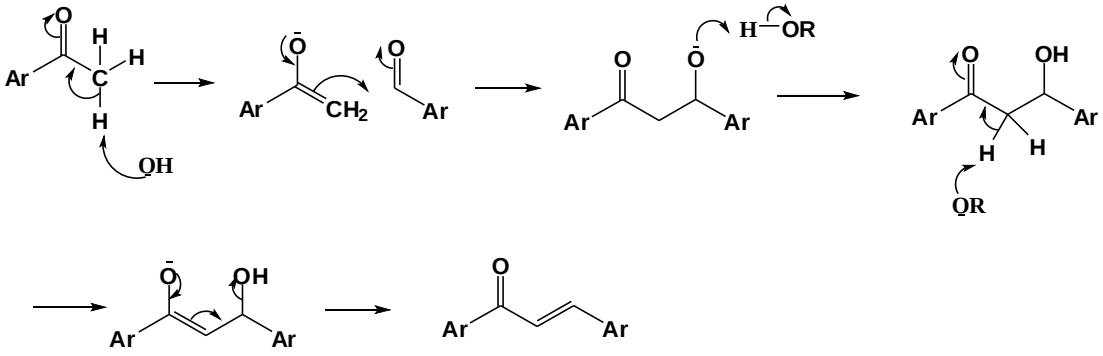


Figure 3.2: Mechanism of reaction of chalcone formation

Chalcones were prepared using ultrasound irradiation to promote the condensation reaction. It is carried using acetophenone and its derivatives, *p*- bromoacetophenone and *p*-noirtoacetophenone, with aromatic aldehyde as shown in Scheme 2.1-3. The products included 1-aryl-3-phenyl-2,propen-1-ones, 1-aryl-3-(*p*-bromophenyl)-2,

propen-1-ones and 1-(*p*-nitrophenyl-3-aryl-2, propen-1-ones product were obtained in good yield, presented in Table 2.2.1.

The reactions were performed under ultrasound irradiation which provides rapid and clean reaction in very short period of time of 1 hour, the reaction also has catalyzed by NaOH in the presence of ethanol as solvent. The majority of the products were well recrystallized from pair of solvent acetone-water as shown in Table 2.2.1.

3.2 Ultrasound-assisted microwave synthesis:

In this work study ultrasound and microwave irradiation in combination was developed as powerful technique for synthesis of six and five membered heterocycles. The ultrasound irradiation used for solvation and homogenization of the reactants, while microwave used for increasing the rate of heterocycles synthesis in subsequence steps.

To adopt this condition two pot containing chalcone VII and three equivalent amount of hydrazine sulfate were prepared in ethanol, then either sonocated for 15 minutes or put directly in microwave oven for 10 minutes. The direct injection at GC-MS after only sonication shown no reaction has occurred at all, while only microwave irradiation shown a 32.8% of the product. The ultrasound assisted microwave synthesis has shown a 50.7% of the product. That is due to increasing of the total solid surface of the chalcone in contact with ethanol by ultrasound, and to knowledge no other method of sample treatment can produce such effects (Santos et al, 2009).

Ethanol is a choice for this work because of it is safety and it is also could stabilize the entire products due to the presence of polarized bond, but it is not good for solvation of every chalcone. The sonication, the problem is the poor property of ethanol to solvate the chalcones which solved by ultrasound irradition. The attempt of hetero-synthesis under microwave irradiation after sonication has shown completion

after 20 minutes. It is very clear here the role of ultrasound in the enhancement of chalcone solvation in the reaction mixture, this approach provides fast, clean and safety synthesis.

3.3 Synthesis of pyrimidine derivatives:

The approach of retrosynthetic analysis of pyrimidine is built on carbon-nitrogen disconnection to guanidine and suitable electrophilic enone.

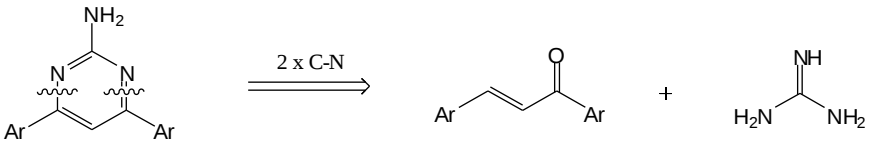


Figure 3.3: Retrosynthesis of pyrimidine heterocycle

Heterocycles in general are thermodynamic products. Cyclization of enone using guanidine leads to pyrimidine. The reaction is either starts with conjugate addition to alkene of enone group, followed by intramolecular imine formation, which underwent aromatization to the required product as shown in figure 3.4., or starts with imine

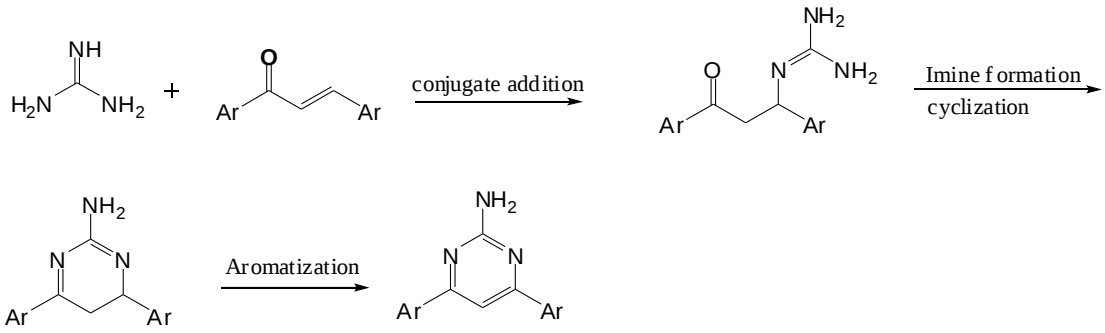


Figure 3.4: Mechanisms of reaction of pyrimidine synthesis

formation at carbonyl group followed by intramolecular conjugate addition to alkene of enone group, which underwent aromatization to the required product as shown in figure 3.5 **(**Clayden et al, 2009; Joule and Mills, 2010).

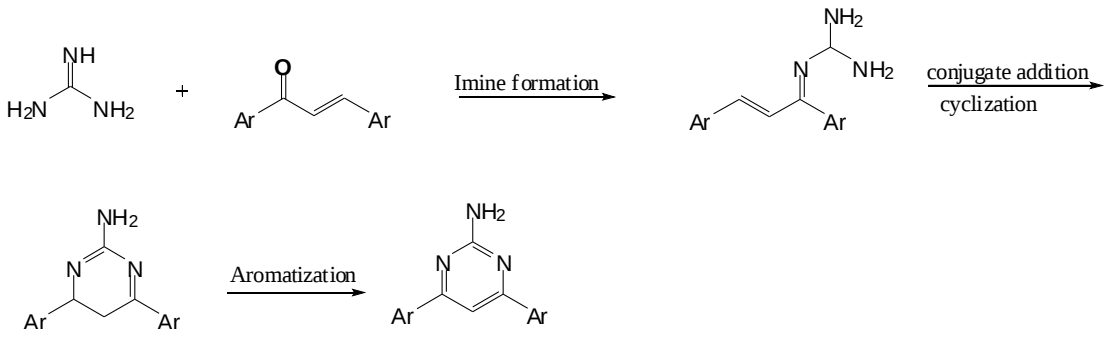


Figure 3.5: The second approach; mechanisms of reaction of pyrimidine synthesis

Whatever reaction goes there is no regioselectivty problem, due to symmetry at guanidine reagent, and hence one product will produced.

Normally conjugate addition occurs at high temperature while direct addition, here imine formation, is a kinetic product. Aromatization is carrying out at air in thermodynamic condition.

The majority of the products were shown completion at the first 20 minutes. The compounds which have N,N dimethyl groups and further alkene group conjugated with enone shown longer reaction times and failures in some cases, that may be due to kinetic problem in addition to the solvent effect.

Compound XV result from chalcone I, which has a good solubility in ethanol, were gave the highest yield % of 88 followed by 79 for XVII. The lowest yield % of XXI for XXI is the product of chalcone IV which have a least solubility in ethanol at normal condition.

3.4 Synthesis of pyrazoles derivatives

The disconnection of pyrazole at C-N bonds provides reliable reagents of hydrazine and a suitable electrophilic enone as shown in Figure 3.6.

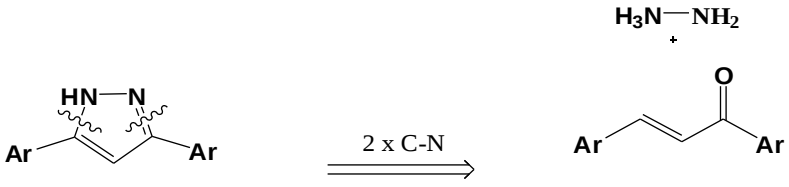


Figure 3.6: Retrosynthesis of pyrazole heterocycle

Cyclization of enone using hydrazine leads to pyrazole. The reaction starts with conjugate addition to alkene of enone group, followed by intramolecular imine formation and aromatization and vice versa without regioselectivty problem (Figure 3.7) **(**Clayden et al, 2009; Joule and Mills, 2010).

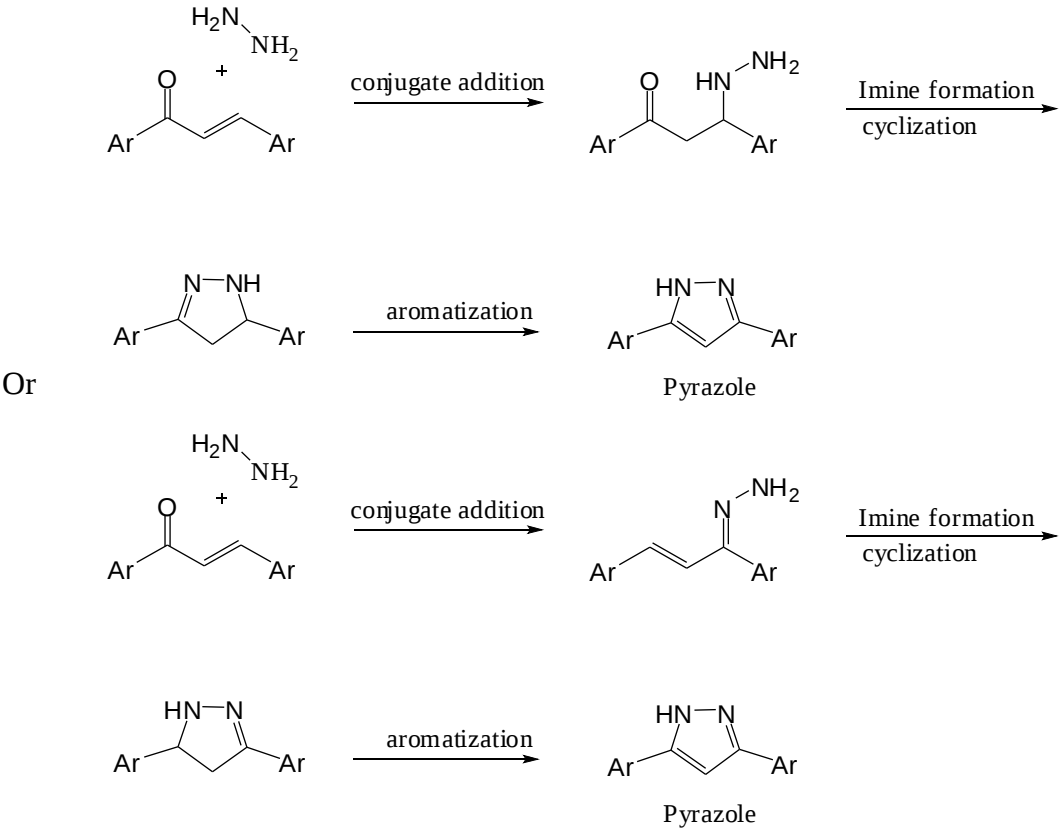


Figure 3.7: Mechanism of reaction of pyrazole synthesis

Pyrazole is a five membered ring containing two nitrogen in nearby, ultrasound and microwave in combination has also showed successfully synthesis of the series of 3,5 diaryl pyrazoles (scheme 2.5). The reactions were carried out using chalcones and hydrazine sulfate at basic sodium acetate as catalyst and ethanol as solvent. The reactions have completed during the first twenty minutes for the most of synthetic pyrazole except XXVI, XXVIII and XXXIII which need more time. In general, a good to moderate yield have been gotten (Table 2.2.3). As in pyrimidine the solvent effect has appeared clearly, the most soluble chalcone give a high yield % and vice versa.

3.5 Synthesis of isoxazole derivatives:

The disconnection at C-N and C-O bonds in isoxazole leads to a suitable reagents of hydroxylamine hydrochloride and electrophilic enone as shown in figure 3.8 below **(**Clayden et al, 2009; Joule and Mills, 2010).

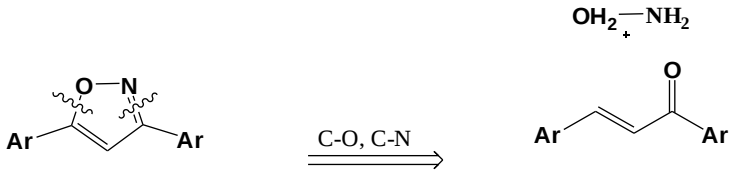
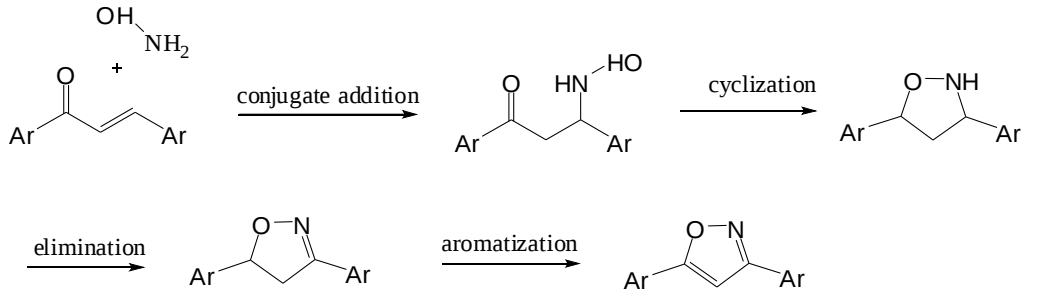
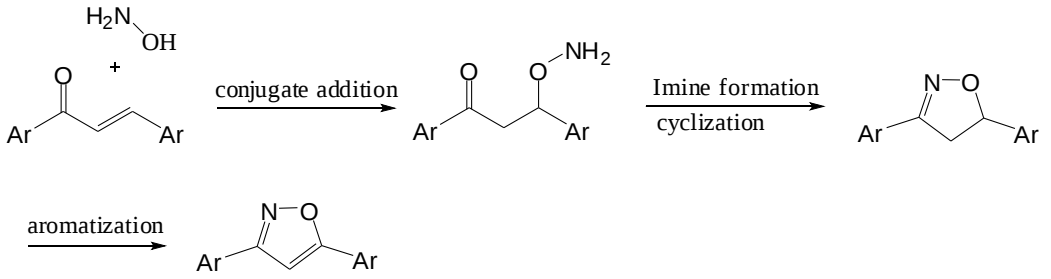


Figure 3.8: Retrosynthesis of isoxazole heterocycle

Hydroxylamine have two nucloephiclic site, oxygen and nitrogen, when it is react with unsymmetrical enone two isomeric products are possible. The mechanisms illustrated in Figure 3.9.





Or:

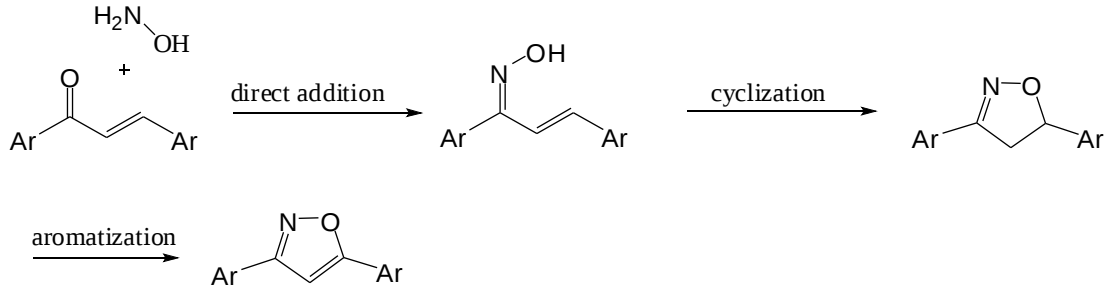


Figure 3.9: Mechanism of reaction of isoxazole synthesis

The attempt of ultrasound assisted microwave synthesis for preparation of isoxazoles leads generally to regioisomer and dihydroisoxazole products observed by GC-MS (Scheme 2.6-7). Compounds XXXIV and XLIV were gotten in yield% of 91 and 33 respectively. The higher yield of compound XXXIV is due to the same reason of the corresponding pyrimidine and pyrazole. XLIV has made in clean and high regioselectivity.

The reaction of hydroxylamine and XIV lead to stable 4,5 dihydroxazole and isoxazole XLVII-a, both of these compounds were isolated using preparative TLC and identified (Tables 2.2.4-5). The stable oxime XXXVII-b has also observed and isolated which is a product of chalcone IV.

3.5. Spectral data of the prepared compounds:

3.5.1. Infrared spectroscopy:

In chalcones the conjugated alkene st.vib. showed in most cases two peaks in range of 1570 and 1590 cm^{-1} while carbonyl st.vib.is slightly higher at 1650 cm^{-1}. The nitro group st.vib. asy and sym 1330 and 1515 cm^{-1}. Monosubstituted and parasubstituted gave a clear two peaks at range of 690 and 750 cm^{-1} for out of plane bending monosubstituted and one peak at 810 cm^{-1} for parasubstituted (Table 2.3.1).

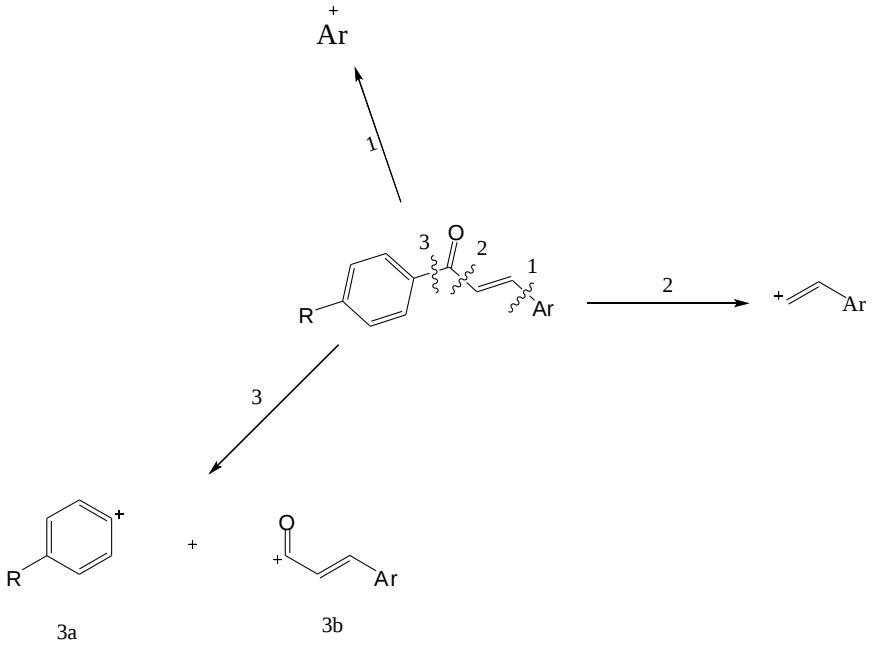
The IR spectra of pyrimidines showed the symmetric and assymmetric stretching of NH_2 group at position 2 on pyrimidine ring at 3190 and 3330 cm^{-1}. Bending vibration of mono and para substituted aryl is slightly different from starting chalcones but a strong band at 770 nm clearly due to bending vibration of the C-H attached at position five on pyrimidine ring.

In pyrazoles, the IR spectra have showed week and broad band for N-H on its ring at range of 3134-3240 cm^{-1}, the weakness is due to tautomerism properties. It is also showed broad and strong band at 772 cm^{-1} this is a result of bending vibration of the C-H at position four on pyrazole ring, the others out of plane bending vibration look like that of chalcones with some interference of the expected monosubstituted band at region of 1750 cm^{-1} with the pand of pyrazole (Table 2.3.3).

The most important band for isoxazole on IR is the out of plane bending vibration at near to 772 cm^{-1}, this is band of C-H at position four on isoxazole ring, it has also observed on the spectra of 4,5 di hydro isoxazole compound XLVII-b. The absence of this band on spectra of the isolated oxime compound XXXVII-b give another evidence for the importance of this band on vibration region.

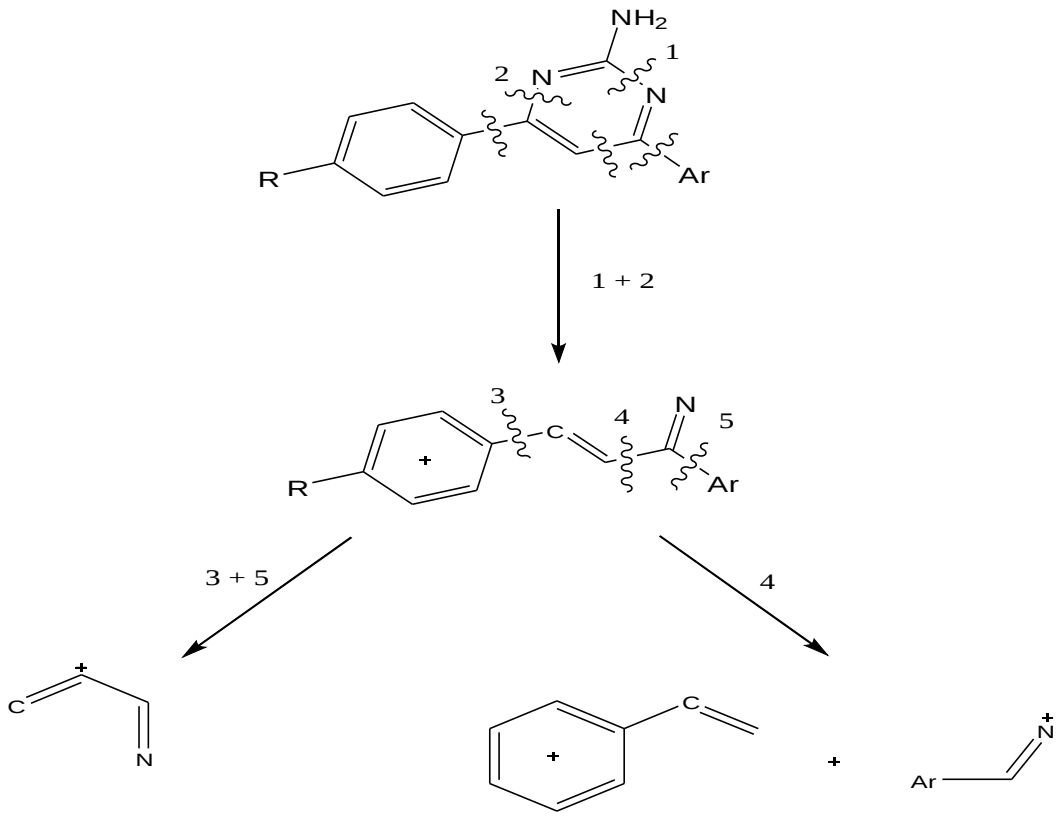
3.5.2. Mass spectroscopy:

The mass spectroscopy results provide the exact mass of target chalcones, in addition to fragment observed in all the synthetic chalcone, this fragment of aryl group with two carbons and two hydrogen atoms as shown in pathway 2 (Scheme 3.10), another fragment observed in all of the chalcone for aryl group of ring A due to cleavage through pathway 3 and formation of 3b ion, the corresponding ion 3a has also observed except when the strong electron-withdrawing nitro group is attached to ring A. Also a common fragment results from pathway 1 for ring B has observed except with the presence of the furfural ring exactly compounds VIII and XIII (Table 2.4.1). Another specific fragment such as miss out of the bromine has been observed.



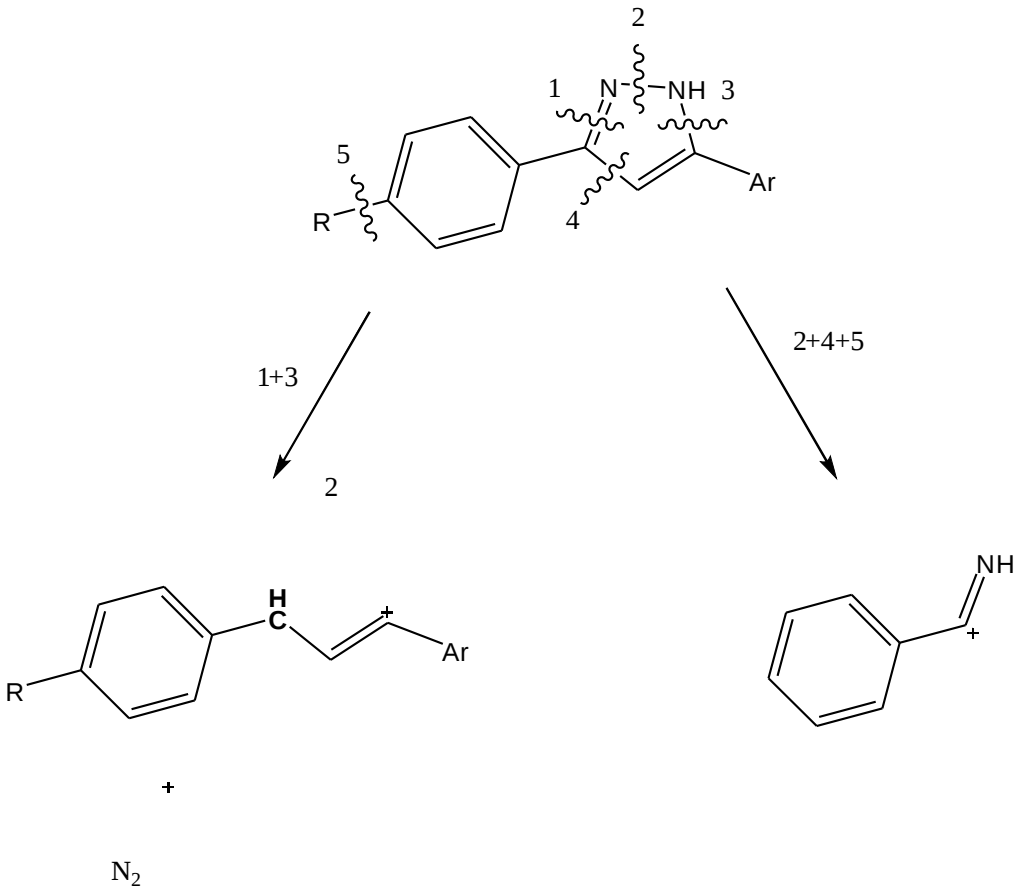
Scheme 3.10: General fragmentation pathways of the prepared chalcones

For pyrimidines, the mas spectroscopy gas chromatography has solved the half of synthetic compounds, non-resolved pyrimidines XV, XVI, XVII, XIX, XX have a higher mass, higher malting point and/or higher susceptibility to make hydrogen bond. In general, the molecular ion has observed as a base beak, and the fragmentation ion has illustrated in Scheme 2.8. The most important ion is a result from the loss of nitrogen in the position 1 with carbon 2 and the NH_2 group (pathway 1+2), this fragment has observed in all resolved compounds, the same fragment would undergo fragmentation through pathways of 3+5 and 4, these ions have also observed in the entire of the products (Scheme 3.11 and Table 2.4.2).



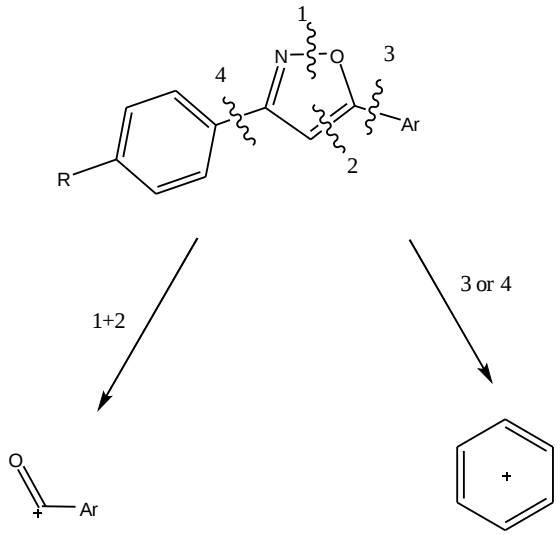
Scheme 3.11: General fragmentation pathways of the prepared pyrimidines

The interpretation of pyrazole using mass spectroscopy has provides the required mass of all gotten compounds. The most important recorded ion results from the loss of N_2 through pathway 1+3 as shown in Scheme 3.12, this ion has observed in all compounds except those containing bromine. Another fragment ion with mass of 104 appeared at all compounds due to cleavage through pathway 2+4+5.

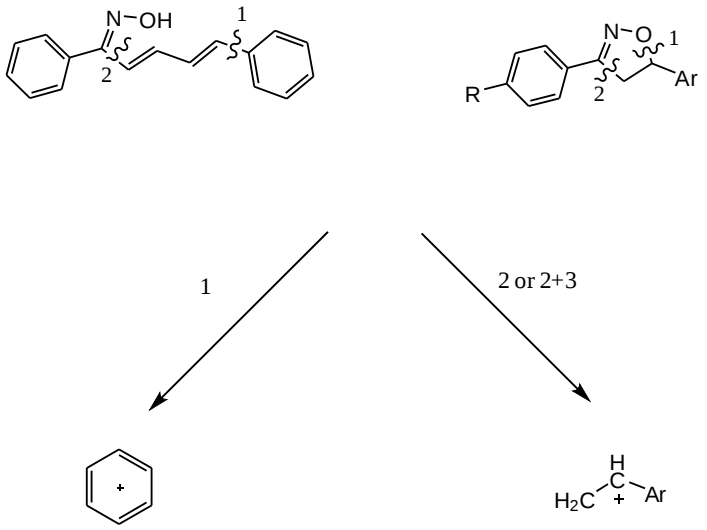


Scheme 3.12: General fragmentation pathways of the prepared pyrazoles

The mass spectroscopy has shown the exact mass of all synthetic isoxazoles and isoxazole intermediates. The most important fragment is a result of the cleavage through pathway 1+2 this fragment has appeared in all synthetic isoxazoles and it's a good guide to identify the regioisomers (Scheme 3.13 and Table 2.4.4-6). The major fragment on the intermediates is slightly different, the cleavage occur through pathway 2 or 2+3 (Scheme 3.14, Tables 2.4.4 and 2.4.5).



Scheme 3.13: General fragmentation pathways of the prepared isoxazoles



Scheme 3.14: General fragmentation pathways of the prepared isoxazole intermediate

3.5.3. Proton nuclear magnetic resonance:

The ^{1}H NMR is the most important analysis tool of chalcones characterization. The high stereoselectivity of making Trans chalcones were observed by ^{1}H NMR. due to the presence of band with high J constant of about 15 Hz, this band is the most important distinctive mark for chalcones appeared as doublet of the two protons of enone at about 7.2 – 7.7 ppm. Further ^{1}H NMR provides clearly the presence of such functional group of MeO, MeN_2 in specific chalcones.

^{1}H NMR is also useful for characterization of pyrimidines heterocycles, it has showed a singlet chemical shift of NH_2 at about 5.1 ppm, as a marker to entire the products. Another singlet chemical shift at about 7.4 ppm belong to the proton at position 5 in pyrimidine ring was observed, with some interference in some compounds, and it is also showed shielding features to 7.1 ppm when the pyrimidine ring is conjugated with ethane at compounds XXI and XXIV (Schemes 2.4).

The pyrazoles has also a particular sign of singlet beak for N-H, this peak has a chemical shift about 6.8 ppm. It has appeared at all synthetic pyrazoles. But the proton at position four has resolved only in four compounds of XXVI, XXVIII, XXXI and XXXII (Schemes 2.6) with chemical shift around 7.5 ppm. The interpretation of all synthetic pyrazole has presented in Table 2.5.7.

Isoxazole gives the expected number of protons, multiplicity and coupling constant values. But there is no particular assignment share with all (Table 2.5.4). The isoxazole intermediate demonstrated has also resolved very well, the diastereotopic CH_2 of compound XXXVII-b give a nice double doublet at 3.24 and 3.60 ppm (Table 2.5.5).

3.5.4. Ultraviolet spectroscopy:

Chalcones showed Two λ_{max} at UV-Vis spectra, it were found generally around 227 nm and higher than 300nm due to π-π^* and n-π^* respectively. The presence of NMe_2 group lowers the energy of transition in significant amount (Table 2.6.1).

UV-Vis spectra of pyrimidines were presented it Table 2.6.2. Two major beaks have observed, the highest energy transition is due to π-π^* on pyrimidine chromosphere, the λ_{max} of these transition appears at near to the excitation of the normal benzene, because of conjugation with electrons donating group of amine and aryl groups. The lowest energy is due to excitation of nonbonding electrons at nitrogen on the ring of pyrimidine.

Pyrazoles has shown to two λ_{max} in the majority of compounds, due to π-π^* and n-π^* of pyrazoles chromophore and nonbonding electrons of nitrogen on pyrazole ring respectively. Compounds XXV, XXVII and XXIX shown one λ_{max} at the region of benzene ring, the n-π^* does not observed (Table 2.4.6).

Isoxazoles chromophore has shown λ_{max} near to that of pyrazoles, which results from π-π^*. The n-π^* has observed in compound XLIV, as expected due to presence of NMe_2. The dihydroisoxazole compound XLVII-b has also showed two λ_{max} at 250, 214 nm (Table 2.6.4 and 2.6.5).

3.6 Determination of reaction mechanism:

The isolation and characterization of 1,5-diphenyl (2E,4E)-pentadien-1-oxime, compound (XLVII-b) (Figure 3.10d) has shown insight chemistry about the mechanism of reaction, this compound is the intermediate of the compound (XLVII-a) 3-phenyl-5-(ethenyl-2-phenyl)-isoxazole (Figure 3.10a).

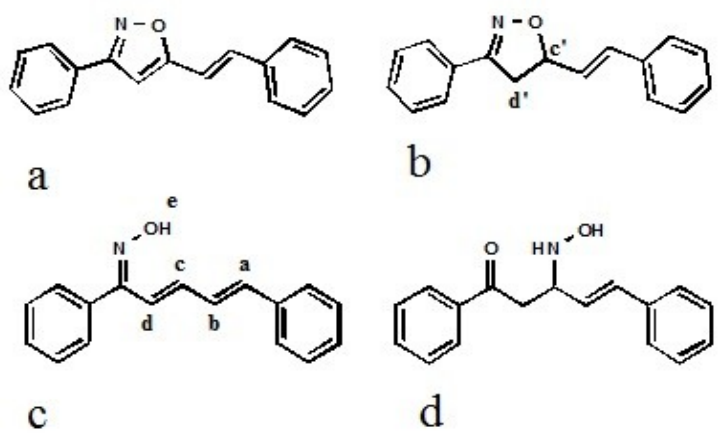


Figure 3.10: Structure of 3-phenyl-5-(ethenyl-2-phenyl)-isoxazole and their intermediates.

EI-MS provide a mass of 249 slightly higher than the mass of the target compound of 247, this mass is equal to the mass of dihydroisoxazole (Figure 3.10b), hence it has suggested as the product, but the incompatible IR spectra has shown a broad band at OH region. There are only two possible intermediates with a OH group (Figure 3.10c and d) result of the direct or conjugate addition respectively. The intermediate d have a high molecular weight than the expected one, therefore the product is the intermediate c. This observation has supported by ^{1}H NMR and UV-Vis analysis. The UV-Vis spectroscopy gives two λ_{max} at 254 and 321 nm due to π-π^{*} and n-π^{*}. Moreover, the clear evidence has shown in the ^{1}H NMR spectra, the 10 protons attached to the two phenyls gives a multiple pand at the region of 7.27-7.65 ppm, which may less concerned as it found in both of the intermediate and the target compound. The spectra of the remaining five protons is the more interested, the integration has shown three protons in the unsaturated region and two protons in the saturated one (Figure 3.2a), while we need to see four and one at the unsaturated and saturated regions respectively, and this insuper-paradox is the point of matter, it has solved using the coupling constant, the more deshielded proton a 7.19 (1H, d, J = 15.64 Hz) ppm has coupled with proton b 6.61 (dd, J = 10.74 & 15.64 Hz) ppm (Figure 3.11A) which has also coupled with proton c: 6.98 (0.74 H, dd, j = 10.74 & 15.45 Hz) ppm. Proton d 6.66 (d, j = 15.45 Hz) ppm has coupled with proton c, and overlapped with proton b, their bands has distinguished with two circles. The highly observation herein is that the NMR feels quantitatively with three protons instead of

four! And proton e 3.64 (s, 0.46 H) ppm of the OH group appears as a half of proton; 1.5 H has missed out!? In fact, the loss of area under peak occurred at protons e, c and d, is very reasonable as these protons are the site of hetrocyclization to produce the dihydroisoxazole (Figure 3.10b), and the first triplet and overlapped double doublet (Figure 3.11B) is due to the formation of the diastereotopic protons d' and the last multiple pand due to the appearance of the proton c'.

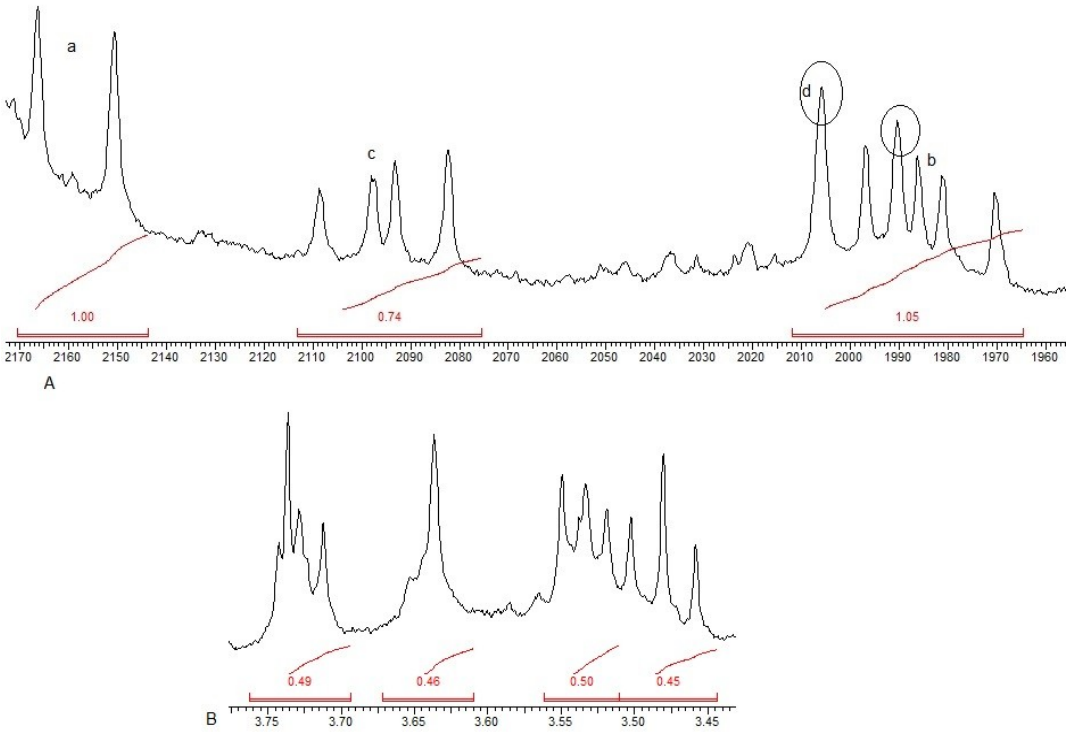


Figure 3.11: Interested parts of ^{1}H NMR of 1,5-diphenyl (2E,4E)-pentadien-1-oxime

These results established that heterocyclization products of ultrasound assisted microwave synthesis are kinetic products, not a thermodynamic as the heterocycles produced by a conventional chemistry. The heterocyclization to the dihydroisoxazole or unsaturated form in general is a reversible, and could presence in two forms (Figure 3.12) with special focus to C3; the lowest electrophilicity the more oxime product and vice versa, this shown the obvious role of the structural feature of the enone in the determination of the last product. The hard controlling of regioisomers produced by the enone with C1 and C3 has approximately the same electrophilicity.

Figure 3.12: 1,5-diphenyl (2E,4E)-pentadien-1-oxime and its possible regioisomer

The attempt of heterocyclization of compound XIV leads to one of the following dihydroisoxazoles (Figure 3.13), but the only the product of direct addition has observed, it well characterized by ^{1}H NMR (Table 2.5.5) . The formation of this compound also proves that the reaction is carried out through the kinetic process, and the important role of the structural features of starting materials.

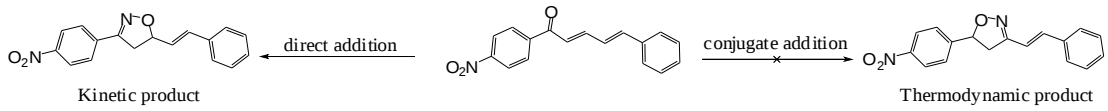


Figure 3.13: 1-(*p*-nitrophenyl)-5-phenyl-(2E,4E)-pentadiene-1-one and its possible products of conjugate and direct addition.