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Extraction and Synthesis

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New Pyrazole Derivatives

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Discovering Thoughts, Inventing Future

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Clove (Eugenia Caryophyllata) Extraction and Synthesis of New Pyrazole Derivatives from Eugenol

By S. Hamri, K. Rhazri, A. Hafid, H. Ouchetto, Y. Hajbi & M. Khouili

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Abstract- An efficient method for the preparation of novel 1,3,4-trisubstituted 4,5-dihydro-1H-pyrazoles via 1,3-dipolar cycloaddition has been described. Using this method, various pyrazole were synthesized from eugenol, a major phenolic constituent of clove bud essential oil, as dipolarophilic system and N-aryl-C-ethoxycarbonitrilimine: the (Z)-ethyl 2-bromo-2-(2-(4-chlorophenyl)-hydrazono) acetate.

Keywords: *clove (eugenia caryophyllata), eugenol, 1,3-dipolar cycloaddition, pyrazole, dipolarophile, nucleo-philic substitution (SN).*

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Clove (Eugenia Caryophyllata) Extraction and Synthesis of New Pyrazole Derivatives from Eugenol

S. Hamri [α], K. Rhazri [σ], A. Hafid [ρ], H. Ouchetto [ω], Y. Hajbi [¥] & M. Khouili [§]

Abstract- **An efficient method for the preparation of novel 1,3,4-trisubstituted 4,5-dihydro-1*H*-pyrazoles via 1,3-dipolar cycloaddition has been described. Using this method, various pyrazole were synthesized from eugenol, a major phenolic constituent of clove bud essential oil, as dipolarophilic system and N-aryl-C-ethoxycarbonitrilimine: the (*Z*)-ethyl 2-bromo-2-(2-(4-chlorophenyl)-hydrazono) acetate.**

Keywords: clove (eugenia caryophyllata), eugenol, 1,3-dipolar cycloaddition, pyrazole, dipolarophile, nucleophilic substitution (SN).

I. Introduction

According to the literature, the majority of natural products derived from plants by different extraction methods. In bibliography, eugenol extracted from clove, is cited as a substance similar to an odorous oil, having the same functional groups as those of the family of natural allyl phenols such as chavicol (A), estragol (B), and osmorhyzol (C) (fig. 1).[1]

This is also the main component of the oil of clove (Eugenia caryophyllata), also present in many herbs like cinnamon.[2]

Eugenol **1** is used as raw material in the manufacture of several drugs. Thus, in dentistry, it is employed as an antiseptic, disinfectant and also widely used as an analgesic.[3, 4] This is also the major active ingredient of rhizoma Acori graminei (RAG). Cited in the literature as a medicinal herb that has been used for epilepsy and forgetting in East Asia for centuries, down cytotoxicity $A\beta_{1\text{-}40}$-induced PC-12 cells in vitro.[10]

In cosmetic and food products, it is used as a flavoring, antimicrobial, and antioxidant agent.[5] In addition to these antioxidant properties,[6] it protects neurons in culture from toxic events.[7] It has activities of anti-convulsive[8] and hypothermic[9] agent.

Complex heterocyclic systems such as: isomerization in polar protic solvents,[11] the conversion into ferulic acid,[12] oxidation[13] and enzymatic glycosylation of eugenol by cultured cells of *E. perriniana*.[14] Much of the synthetic strategy is devoted to the preparation of heterocyclic compounds derived from medicinal plants.

As part of our research, we have synthesized new pyrazole derivative structure from eugenol **1**. In this case, the 4-allyl-2 methoxyphenol (eugenol) **1** has a high reactivity, attributed to the functional groups of the aromatic ring. Recently, considerable attention has been focused on the development of new methodologies to synthesize many kinds of substituted pyrazolic subunit.[15] Indeed, these compounds are now widely recognized as important materials showing interesting biological activities and also as intermediate on heterocyclic chemistry. Many pyrazoles derivatives known to exhibit a wide range of biological properties such as antihyperglycemic, analgesic, anti-inflammatory, antibacterial, hypoglycaemic, sedative-hypnotic activity.[16] Although many pyrazoles have pharmacological activities,[17] those who have found a practical application, their activities are due more to the various substituents that the intrinsic activity of the pyrazole ring itself.

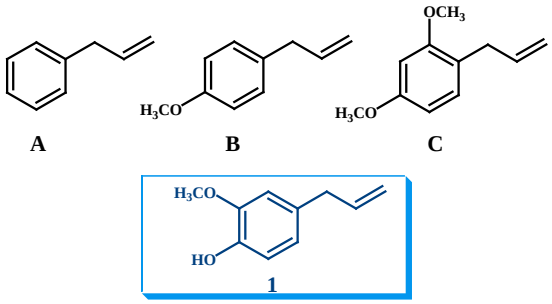

Fig. 1 : Names of allyl phenols natural

According to studies cited in the literature and those carried out in our laboratory for building five-membered pyrazole cycles prompted us to explore new methodologies for the synthesis of substituted 1-aryl-pyrazoles.[18]

According to studies cited in the literature and those carried in our laboratory for the construction of five-membered pyrazole cycles, we looked at the development of new methodologies for the synthesis of substituted 1-aryl-pyrazoles namely the 1,3-dipolar cycloaddition.[18] This is a process for the synthesis of several classes of azoles, such as isoxazoles, triazoles

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and pyrazoles.[19] Pyrazoles are part of heterocyclic structures most commonly used for the development of new drugs.[20, 21] Subsequently, David J. Babinski et *al.* have synthesized heterocyclic compounds containing the pyrazole skeleton, following a synthetic strategy based on pericyclic reactions for the preparation of pyrazoles 3,4,5-tri-substituted by a tandem catalytic cross-coupling/electrocyclization enol triflates and diazoacetates.[19-f]

Our investigation of this system is part of a current study on the synthesis of new pyrazole derivatives via 1,3-dipolar cycloaddition reaction. In this paper, we present the synthesis of 1-aryl-4,5-dihydro-1*H*-pyrazoles from eugenol, previously extracted of cloves, and different dipoles *N*-aryl-*C*-ethoxycarbonitrilimines.

II. Results and Discussion

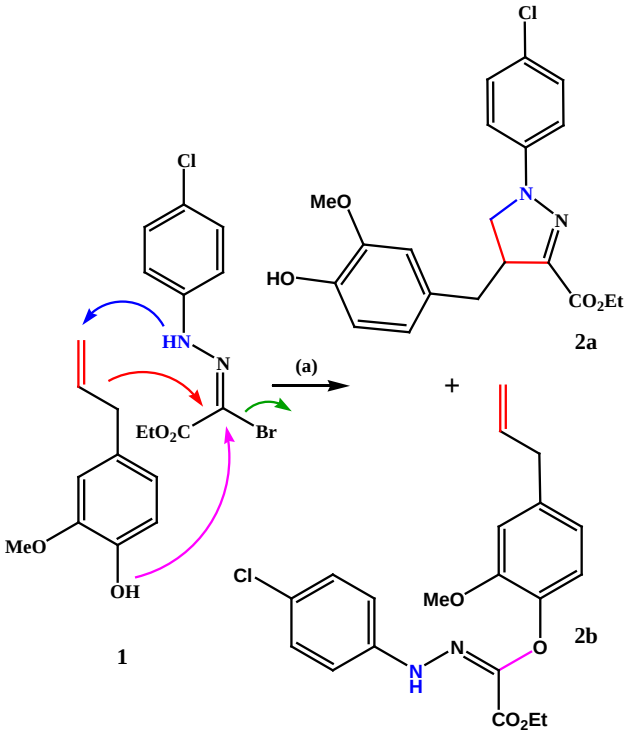
Clove (buds) was purchased commercially for extraction of essential oil eugenol. *Eugenia caryophyllata* buds were converted into powder by crushing and extracted by steam distillation of water for 4 hours.

The eugenol **1** will then be separated from the water by extraction with diethyl ether. The diethyl ether solution will then be dried and evaporated at a temperature not exceeding 40°C, to afford the eugenol oil. This oil was then purified by chromatography and identified by NMR ^{1}H and ^{13}C.[22]

Thereafter, new cycloaddition reactions with 4-allyl-2-methoxyphenol **1** as a dipolarophile were developed using the *N*-aryl-*C*-ethoxycarbonitrilimine derivative: the (*Z*)-ethyl 2-bromo-2-(2-(4-chlorophenyl)-hydrazono)acetate, who act as a dipole. The synthesis of the latter, was performed under conditions described by Hamilton et al.,[23] according to one reaction of diazonium chloride aniline with ethyl diazoacetate treated with a solution of bromine.

The 1,3-dipolar cycloaddition of 4-allyl-2-methoxy-phenol **1** with allyl group formed the corresponding pyrazole **2a**. Unfortunately, we have noted the presence of compound **2b** according *O*-alkylation reaction.[24] To avoid this side reaction, the 1,3-dipolar cycloaddition reaction was carried in different non-polar solvents.

The desired derivative **2a** (1-aryl-4,5-dihydro-1*H*-pyrazoles) was formed predominantly in relation to the derivative **2b** (*N*-aryl-*C*-ethoxy-carbonitrilimines). The latter product is derived from the condensation of phenol on the dipole *via* a nucleophilic substitution (*SN*) reaction (Scheme 1). The conversion rate, according to the results (Table 1), increases with the temperature without any degradation. We noted that the best conversion was obtained after 48 hours, when the reaction was carried out in refluxing toluene.

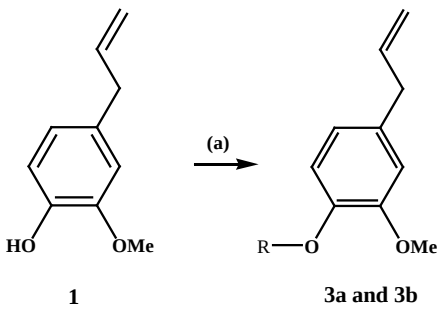


Scheme 1 : Reagents and conditions: (a) Et_3N, solvent, reflux, 48h

Table 1 : Reaction yields depending on solvent

Solvent	**2a** yield (%)	**2b** yield (%)
THF	6	11
Toluene	30	16
Xylene	20	1

To control the dipolar cyclization reaction and avoid the formation of the ether-oxides, first we initially protected the phenol by a simple nucleophilic substitution reaction with various alkyl halides, which also allow us studying the donor effect of the system. The *SN* reaction was carried out with K_2CO_3 in acetone (Scheme 2).



Scheme 2 : Reagents and conditions: (a) RX, K_2CO_3, Acetone, reflux, 4 h

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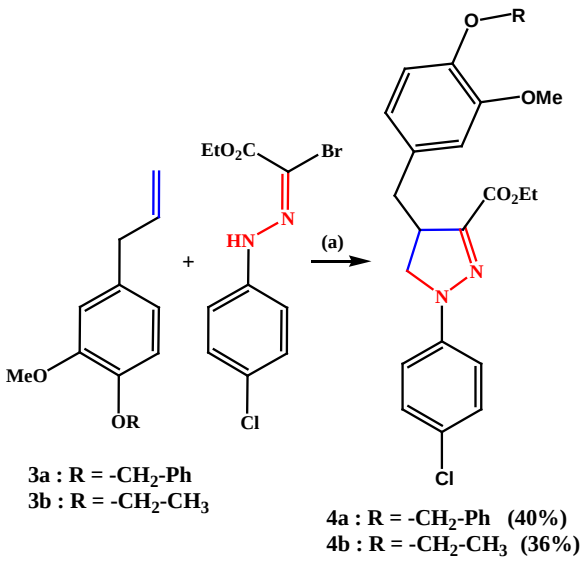
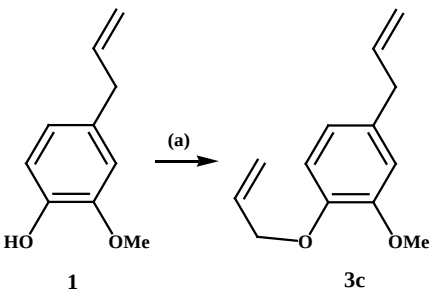
Table 2 : Synthesis, yields of compounds 3a and 3b

R	Compound	Yield (%)
Benzyl	**3a**	92
Ethyl	**3b**	90



Scheme 3 : Reagents and conditions: (a) Et_3N, Toluene, reflux, 48 h

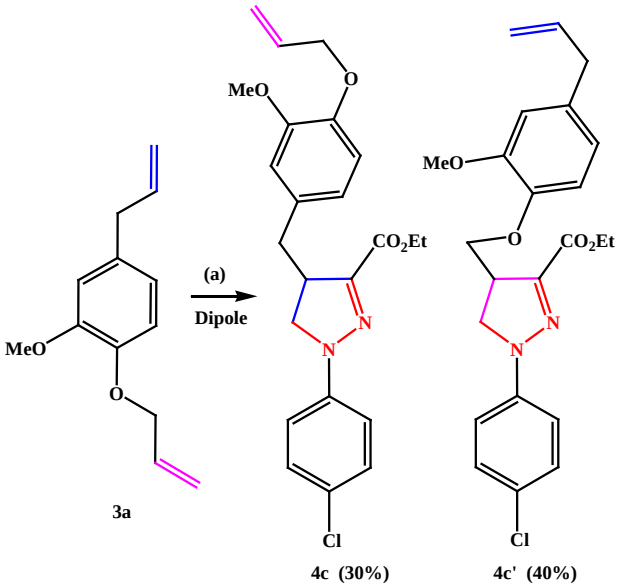
The desired compounds, **3a and 3b**, were isolated in good yields (Scheme 2, Table 2) and were subjected to condensation reaction with *N*-aryl-*C*-ethoxy-carbonitrilimine to afford only derivatives of 1-aryl-4,5-dihydro-1*H*-pyrazole, **4a** and **4b**, with average yields. This modest result is presumably due to the degradation of the *N*-aryl-*C*-ethoxycarbonitrilimine (Scheme 3).



Scheme 4 : Reagents and conditions: (a) allyl chloride, K_2CO_3, Acetone, reflux, 4 h

We envisioned the protection of the phenol with allyl group so as to examine the effect of the presence of two dipolarophile systems in our condensation reaction.

Thus, the eugenol **1** was engaged in *SN* reaction in presence of allyl chloride, according the conditions described for the preparation of **3a** and **3b**, to afford the compound **3c** in good yield (91%) (Scheme 4).The resulting allyl **3a** was heated in toluene at reflux for 48 hours in the presence of a dipole: the (*Z*)-ethyl 2-bromo-2-(2-(4-chlorophenyl)-hydrazono) acetate, to give two dipolar cycloadducts **4c** (30%) and **4c'** (40%). (Scheme 5) we noted that this 1,3-dipolar cycloaddition is not regioselective.



Scheme 5 : Dipole: (*Z*)-ethyl 2-bromo-2-(2-(4-chlorophenyl)-hydrazono) acetate; (a) Et_3N, Toluene, reflux, 48 h

III. Experimental Section

Melting points were taking for samples in capillary tubes with an electro-thermal apparatus and are uncorrected. ^1H NMR and ^{13}C NMR were recorded on a Bruker Avance DPX250 spectrometre (300 MHz ^1H, 75 MHz ^{13}C) using trimethylsilane as the internal standard, chemical shifts were reported in parts par million (ppm, δ units). Coupling constants were reported in units of hertz (Hz). Flash chromatography was performed on silica gel 60 (40–63 mesh). Thin layer chromatography (TLC) was carried out on Merck silica gel 60F254 precoated plates. Visualization was made with ultraviolet light. All organic solvents were distilled immediately prior to use.

a) General procedure for preparation of compound 2a and 2b

To a solution of 4-allyl-2-methoxyphenol 1 (1.22 mmol) in dry THF, toluene or xylene (10 mL); was added (3.4 mmol) the (*Z*)-ethyl 2-bromo-2-(2-(4-chlorophenyl)-hydrazono) acetate, and 0.52 mL of the triethylamine. The mixture was heated at solvent reflux for 48 hours. After cooling, the reaction mixture was extracted three times with dichloromethane. Organic phase was dried, evaporated and the crude was purified by column chromatography (eluent: ethyl acetate - hexane, 2: 8) to give **2a** and **2b**.

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b) Ethyl-5-(4-hydroxy-3-methoxybenzyl)-1-(4 chlorophenyl)-4,5-dihydro-1H-pyrazole-3-carboxylate 2a

This compound was obtained as a yellow solid. Yields from: THF (6%), toluene (30%), xylene (20%). Mp: 124-126°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (d, J = 9.1 Hz, 4H), 6.85 (d, J = 8.2 Hz, 1H), 6.65 (dd, J = 1.9 and 8.2 Hz,1H), 6.55 (d, J = 1.9 Hz ,1H), 5.55 (s, 1H), 4.82-4.55 (m, 1H), 4.3 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 3.19-2.62 (m, 4H), 1.35 (t, J = 7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.86, 146.75, 144.82, 140.96, 139.68, 129.39, 127.84, 126.36, 122.25, 116.03, 114.73, 112.02, 62.22, 61.35, 56.08, 36.97, 36.52, 14.45.

c) (4-Allyl-2-methoxy-phenoxy)-[(4-chloro-phenyl)-hydrazono]acetic acid ethyl ester 2b:

This compound was obtained as a yellow oil. Yields from: THF (11%), toluene (16%), xylene (1%). ^{1}H NMR (300MHz, $CDCl_3$): δ 9.80 (s, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 6.80-6.61 (m, 3H), 5.94-5.76 (m, 1H), 5.15-5.01 (m, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 3.39-2.22 (m, 2H), 1.25 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 158.6, 154.0, 151.3, 141.2, 140.0, 136.5, 131.1, 129.7, 124.3, 122.8, 117.7, 116.8, 114.5, 61.4, 56.2, 48.4, 13.8.

d) General procedure for preparation of compounds 3a-c

To a solution of 4-allyl-2-methoxyphenol **1** (0.3 g, 1.7 mmol) in dry acetone (10 ml) was added K_2CO_3 (0.67 g, 4.88 mmol). The reaction was stirred in oil bath at 50-80°C. After 1 hour, 1.7 mmol of the corresponding haloalkyl groups or allyl chloride was added to a previous solution and the mixture was heated for 4 hours. After complete conversion of the starting material, the reaction was evaporated to dryness and the residue was purified by column chromatography (eluent: ethyl acetate - hexane, 1: 9) to give the corresponding compounds **3a-c**.

e) 4-Allyl-1-(benzyloxy)-2-methoxybenzene 3a

The compound was obtained as a yellow oil (92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.19 (m, 5H), 6.78-6.58 (m, 3H), 6.10-5.90 (m,1H), 5.07 (s, 2H), 5.20-5.00 (m, 2H), 3.80 (s, 3H), 3.40-3.20 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.6, 146.5, 137.6, 137.4, 133.3, 128. 7, 127.7, 127.3, 120.46, 115.6, 114.3, 112.4, 71.2, 55.9, 39.8.

f) 4-Allyl-1-methoxy-2-ethoxybenzene 3b

The compound was obtained as a yellow oil (90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.60-6.70 (m, 3H), 5.90-5.80 (m, 1H), 5.00-4.90 (m, 2H), 4.00 (q, J = 6 Hz, 2H), 3.80 (s, 3H), 3.30-3.16 (m, 2H), 1.33 (t, J = 6 Hz, 3H, O-CH_2-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3, 146.7, 137.7, 132.6, 120.0, 115.5, 112.4, 112.2, 64.4, 55.8, 39.8, 14.9.

g) 4-Allyl-1-allyloxy-2-methoxybenzene 3c

The compound was obtained as a yellow oil (91%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90-6.70 (m, 3H), 6.20-5.90 (m, 2H), 5.48 (dd, J = 3.3 and 1.5 Hz, 1H), 5.4 (dd, J = 3.3 and 1.5 Hz, 1H), 5.36-5.24 (m, 2H), 5.15-5.05 (m, 2H), 4.69-4.51 (m, 2H), 3.85 (s, 3H), 3.38-3.26 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 149.7, 146.8, 136.5, 133.6, 130.8, 122.4, 117.2, 116.4, 115.2, 114.1, 72.3, 56.2, 48.2.

h) General procedure for preparation of 4a-c

To a solution of each compounds **3a-c** in dry toluene (10 mL) was added 1.2 equivalents of *N*-aryl-*C*-ethoxycarbonitrilimine and appropriate quantity of triethylamine. The mixture was stirred at reflux for 48 hours. After cooling, the mixture was extracted with dichloromethane. Organic phase was evaporated and purified by column chromatography (eluent: ethyl acetate - hexane, 2: 8) to give the corresponding compounds.

i) Ethyl-5-(4-Benzyloxy)-3-methoxybenzyl)-1-(4-chlorophenyl)-4,5-dihdro-1H-pyrazole-3-caboxylate 4a

This compound was obtained as a yellow solid (40%). Mp: 102-104°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.13 (m, 5H), 7.00 (d, J = 8.1 Hz, 2H), 6.80 (d, J = 7.9 Hz, 2H), 6.60 (d, J = 7.8 Hz, 1H), 6.57-6.48 (m, 1H), 6.00 (d, J = 7.8 Hz, 1H), 5.20 (s, 2H), 4.87-4.75 (m, 1H), 4.20 (q, J = 7.3 Hz, 2H), 3.75 (s, 3H), 3.40-3.20 (m, 2H), 1.40-1.60 (m, 2H), 1.10 (t, J = 7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172, 160, 150, 146, 142, 140, 136, 132, 129, 127, 120, 119, 117, 111, 65, 63, 56, 40, 15, 13.

j) Ethyl-5-(4-ethoxy-3-methoxybenzyl)-1-(4-chloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylate 4b

This compound was obtained as a yellow solid (36%). Mp: 124-126°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (d, J = 9.1 Hz, 2H), 7.2 (d, J = 9.1 Hz, 2H), 6.80 (d, J = 8.7 Hz, 1H), 6.68-6.56 (m, 1H), 5.99 (d, J = 8.7 Hz, 1H), 5.07-4.92 (m, 1H), 4.18 (q, J = 6.9 Hz, 2H), 4.00 (q, J = 7.2 Hz, 2H), 3.8 (s, 3H), 3.36-3.25 (m, 2H), 1.4-1.6 (d, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H), 1.10 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 149, 146, 142, , 136, 132, 130, 129, 120, 119, 115, 113, 112, 64, 63, 55, 40, 14.8, 13.6.

k) Ethyl-5-(4-(allyloxy)-3-methoxybenzyl)-1-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-3-carboxylate 4c

This compound was obtained as a yellow oil (30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.3 (d, J = 9.1 Hz, 2H), 7.2 (d, J = 9.1Hz, 2H), 6.82 (d, J = 8.1Hz, 1H), 6.68 (dd, J = 2.1 and 8.1 Hz, 1H), 6.6 (d, J = 2.1 Hz, 1H), 6.18-6.02 (m, 1H), 5.4 (dd, J = 1.5 and 17.4 Hz, 1H), 5.3 140 (dd, J = 1.5 and 10.2 Hz, 1H), 4.80-4.70 (m, 1H), 4.65-4.58 (m, 2H), 4.32 (q, J = 7.2, 2H), 3.85 (s, 3H), 3.22-2.65 (m, 4H), 1.38 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.08, 149.93, 147.46, 141.18, 139.9, 133.65, 129.18, 126.6, 121.81, 118.34, 116.26, 114.05, 113.38, 70.29, 62.34, 61.56, 56.37, 37.14, 36.79, 14.67.

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l) Ethyl-5-((4-allyl-2-methoxyphenoxy)methyl)-1-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-3-carbox-ylate 4c'

This compound was obtained as a yellow oil (40%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, *J* = 9.6Hz, 2H), 7.2 (d, *J* = 9.6 Hz, 2H), 6.75-6.65 (m, 3H), 6.2-5.88 (m, 1H), 5.12-5.05 (m, 2H), 4.95-4.85 (m, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.86-3.60 (m, 2H), 3.82 (s, 1H), 3.42-3.30 (m, 4H), 1.4 (t, *J* = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.91, 150.26, 146.29, 141.37, 140.61, 135.02, 129.64, 126.66, 120.93, 116.15, 115.40, 113.08, 68.79, 61.62, 60.54, 56.18, 40.13, 36.29, 14.67.

IV. Extraction of Eugenol

Commercially available plant material (buds) was purchased for the essential oil extraction. The buds of Eugenia caryophyllata were extracted by steam distillation for 4h. The distillation was extracted with diethyl ether, dehydrated with anhydrous sodium sulfate and solvent removed and by evaporation using a rotator evaporator at 40°C. The residual oil obtained was used for chemical analysis, further purification and biological assays. The extracted oil was purified by normal phase chromatography on silica gel with the eluent of n-hexane ; ethyl acetate (10 : 1). The eluate was collected in 30 fractions of 30ml, Fractions collected were evaporated and of the residual obtained is colorless oil was identified by ^{1}H-NMR (250 MHz, $CDCl_3$), ^{13}C-NMR (62,5MHz, $CDCl_3$).

V. Conclusion

New structure pyrazole derivatives have been prepared by 1,3-dipolar cycloaddition with eugenol as the starting material. The latter was extracted from cloves by steam distillation. The cycloaddition reaction with the compound (*Z*)-ethyl 2-bromo-2-(2-(4-chlorophenyl)-hydrazono) acetates, used as a dipole, was carried out with modest yields. In the case of the presence of dipolarophile: 4-allyl-1 (allyloxy)-2-methoxybenzene, the reaction proceeded with full conversion and 70%, with the formation of the two possible regioisomeric products, are: ethyl 4-(4-(allyloxy)-3-methoxybenzyl)-1-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylate (**4c**) and ethyl 4- ((4-allyl-2-methoxyphenoxy)methyl)-1-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylate (**4c'**). The two regioisomeric products were obtained in good yields. This method was used to prepare a variety of substituted 1-(4-aryl)-4,5-dihydro-1*H*-pyrazole. All synthesized compounds were purified and identified by conventional spectroscopic methods.

VI. Acknowledgements

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Synthesis and Applications of Pyrimidinethiones

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Abstract- One important class of pyrimidine is pyrimidinethione, which is also well known as mercapto or thioxopyrimidine compounds. This review deals with the synthesis and applicaions of pyrimidinethiones.

Keywords: *pyrimidinethiones, therapeutic applications.*

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Synthesis and Applications of Pyrimidinethiones

Mohamed Abdel-Megid [α σ], K. M. Elmahdy [α] & Aymn E. Rashad [σ ρ]

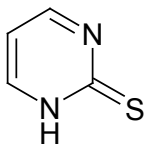
Abstract- One important class of pyrimidine is pyrimidinethione, which is also well known as mercapto or thioxopyrimidine compounds. This review deals with the synthesis and applicaions of pyrimidinethiones.

Keywords: pyrimidinethiones, therapeutic applications.

I. Introduction

Pyrimidine derivatives have been very well known in medicinal chemistry for their therapeutic applications. One possible reason for their activity is the presence of a pyrimidine base in thymine, cytosine and uracil, which are essential building blocks of nucleic acids, DNA and RNA. Pyrimidinethione derivatives have attracted substantial interest of synthetic-biochemists.[1]

Pyrimidinethiones exist in three possible structures, depending on the position of thione group. There are 2-pyrimidinethione (I), 4-pyrimidinethione (II) and 2,4-pyrimidinethione (III).



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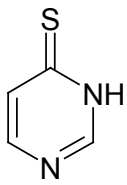
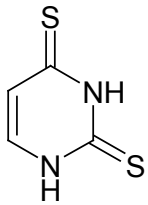
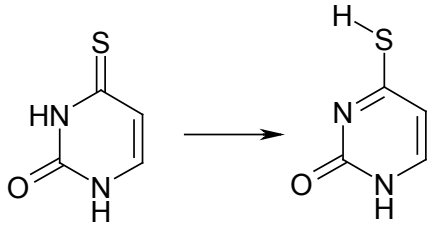


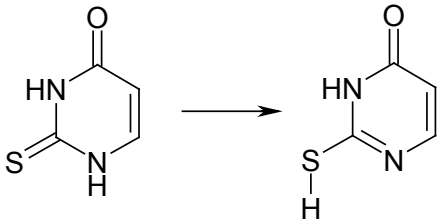
II



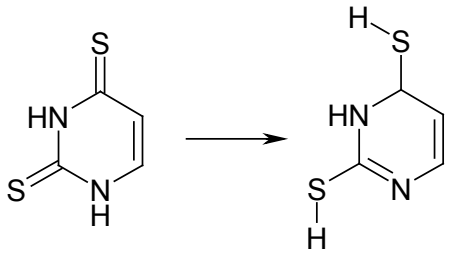
III

It was found that, upon UV irradiation of monomers of thione compounds isolated in low-temperature inert gas matrices, a proton from the N–H group was shifted to the C=S group placed in the α-position. That led to the conversion of the thione form of studied compounds into the thiol tautomer. Very recently, analogous unimolecular thione→thiol photo-tautomeric transformations were found to occur also for matrix-isolated monomers of 4-thiouracil and 2-thiouracil. For these species, the photoprocesses involving transfer of protons from the N–H groups to the thiocarbonyl (C=S) groups dominated strongly over the transfer of protons to the carbonyl (C=O) groups[2].





For 2,4-dithiouracil, the presence of two N–H and two C=S groups in a molecule opens the gate for more than one, simple pathway of the UV-induced thione→thiol phototautomeric reaction. The thiol–thione tautomers of the compound could be expected as products of a single-proton-transfer photoreaction and the dithiol tautomer can be photogenerated in a double-proton-transfer process. the dithiol tautomer of 2,4-dithio- uracil, generated by the transfer of both N–H protons to the thiocarbonyl C=S groups[2].



The crystal structure of 2,4-dithiouracil has been determined. The dimers of 2,4-dithiouracil are present in the structure. Every molecule is connected with two neighbouring molecules by means of two kinds of pair coupling hydrogen bonds. At the same time each molecule is a donor and an acceptor in four hydrogen bonds of the N–H·· ·S type[3].

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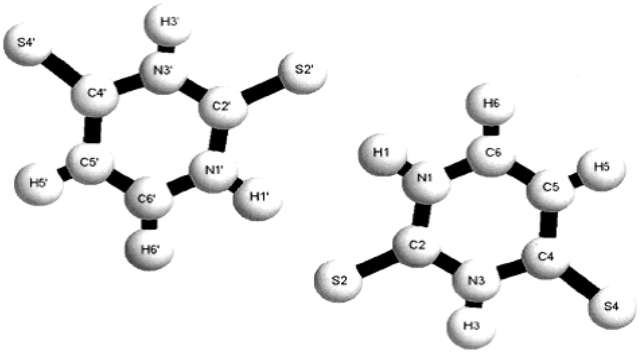
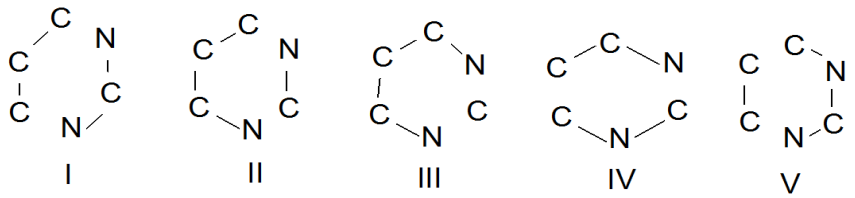


II. Synthesis of Pyrimidinethiones

Pyrimidinethiones were generally prepared by five types of ring synthesis (I, II, III, IV and V) according to the nature of the fragments which combine together to form pyrimidinethione nucleus.



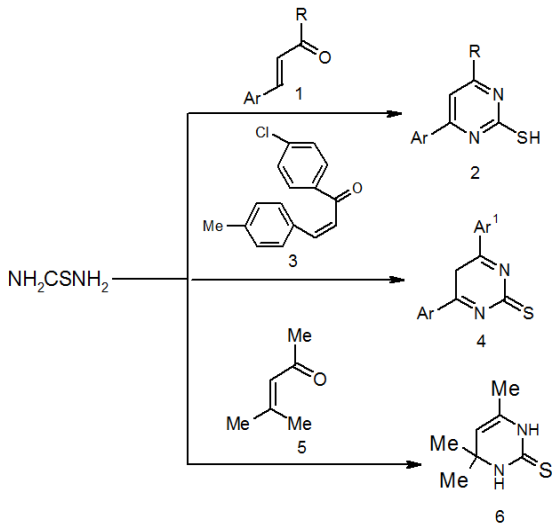
a) Synthesis from C-C-C and N-C-N fragments

i. *From thiourea and its derivatives*

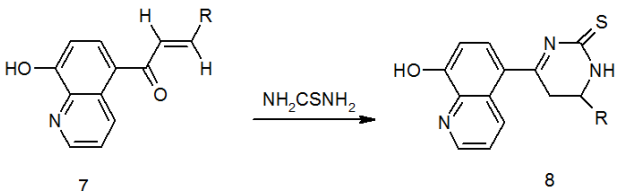
Thiourea and its derivatives considered as good synthons for the synthesis of 2-thiopyrimidine derivatives *via* their interaction with enones, 1,3-dicarbonyl-compounds, acetylenic compounds, arylidene, ethoxymethylene derivatives, acrylonitriles and enamines.

a. *With enone derivatives*

Reaction of thiourea with ethylenic ketone 1[4], benzoylethylene derivative 3[5] and mesityl oxide (5)[6]afforded pyrimidine derivatives 2, 4 and 6, respectively.



4-(8-Hydroxyquinolin-5-yl)-6-substituted-1,2,5,6-tetra-hydropyrimidine-2-thiones 8 were prepared from the reaction of compound 7 with thiourea in the presence of sodium ethoxide[7].



R = C_6H_5, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 2-furyl, C_3H_7 n

On the other hand, 5-chloro-4-formyl-3-methyl-1-phenylpyrazole (9) was condensed with 10 to form an α,β-unsaturated ketonic intermediates 11, which were then cyclocondensed with thiourea to give pyrimidine-2-thione derivatives 12[8].

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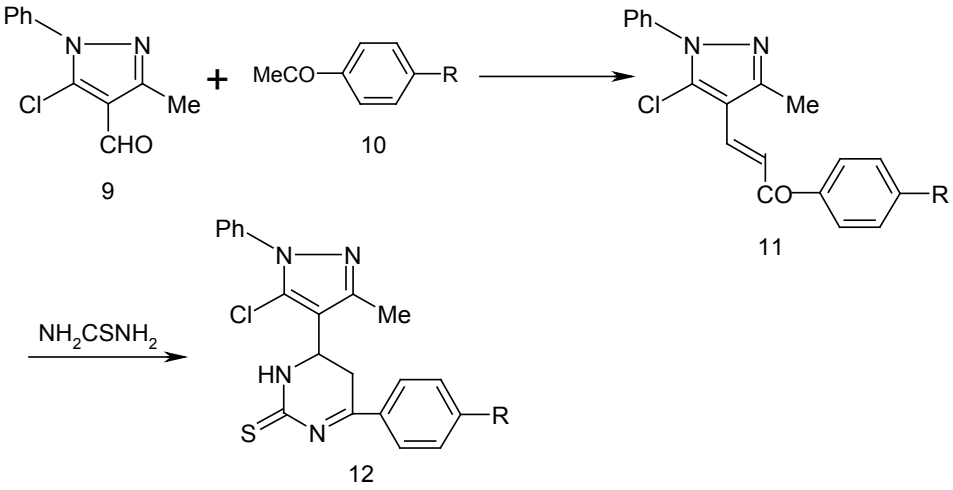
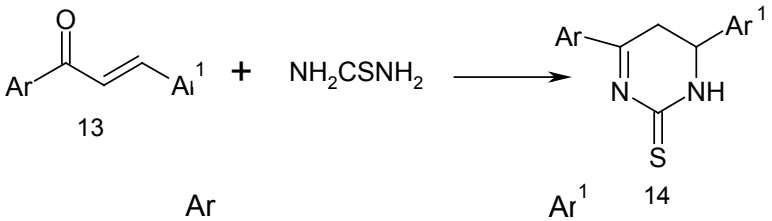
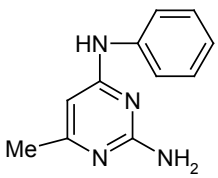


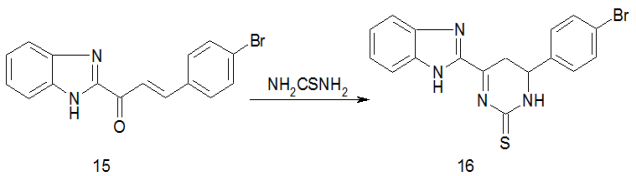
Reaction of chalcons 13 with thiourea afforded pyrimidine-2-thione derivatives 14[9-13].



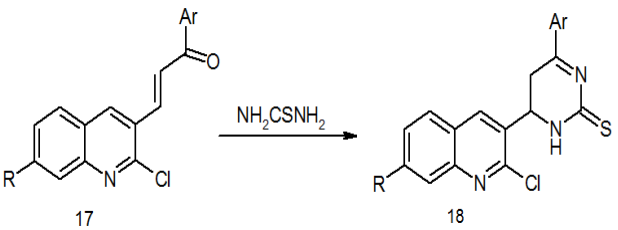
Ar	Ar^1
a, 2,4-$(Me)_2C_6H_3$	, 4-ClC_6H_4
b, 3,4-$(Me)_2C_6H_3$	, 4-ClC_6H_4
c, 2-OMe-4-MeC_6H_3	, 4-ClC_6H_4
d, C_6H_3-CH_2-C_6H_4	, C_6H_5
e, C_6H_5	
f, 2-ClC_6H_4	
g, 2-$MeOC_6H_4$	
h, 2,4-$(MeO)_2C_6H_3$	
i, 4-ClC_6H_4	
j, 3-$O_2NC_6H_4$	



4-[1-H-benzimidazol-2-yl]-6-(4-bromophenyl)-5,6-dihydropyrimidine-2(1H)thione (16) was prepared through cyclocondensation of 1-(benzimidazol-2-yl]-3-(4-bromophenyl)-2-propen-1-one (15) with thiourea[14].



Interaction of 3-(1-aryl-1-oxoprop2-2en-3-yl)-7-substituted -2-chloroquinoline (17) with thiourea in the presence of ethanolic sodium ethoxide afforded 4-aryl-6-(2-chloro-7-substituted-quinolin-3-yl)-5,6-dihydroprimidine-2(3H)thione (18)[15] .



Anisoyl vinylaryl quinazolines 19 was reacted with thiourea to give pyrimidine-2-thione derivatives 20[16,17].

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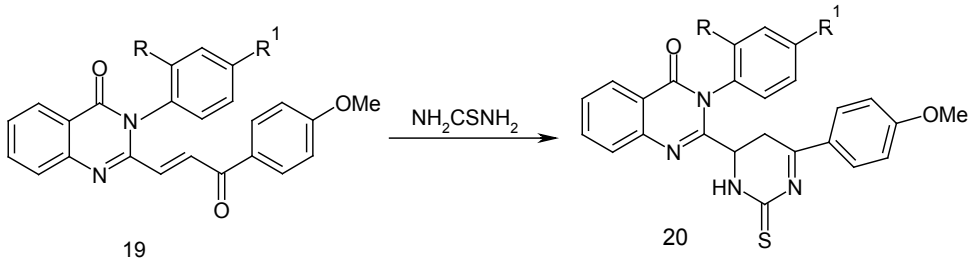
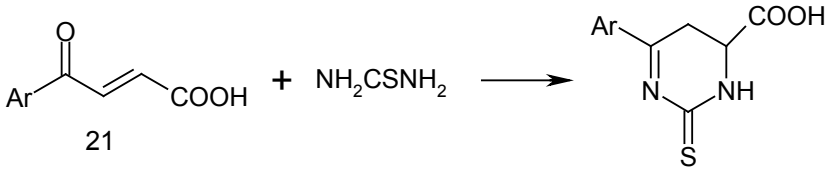


19 20

R = Me, R1 = H; R = H, R1 = NH2

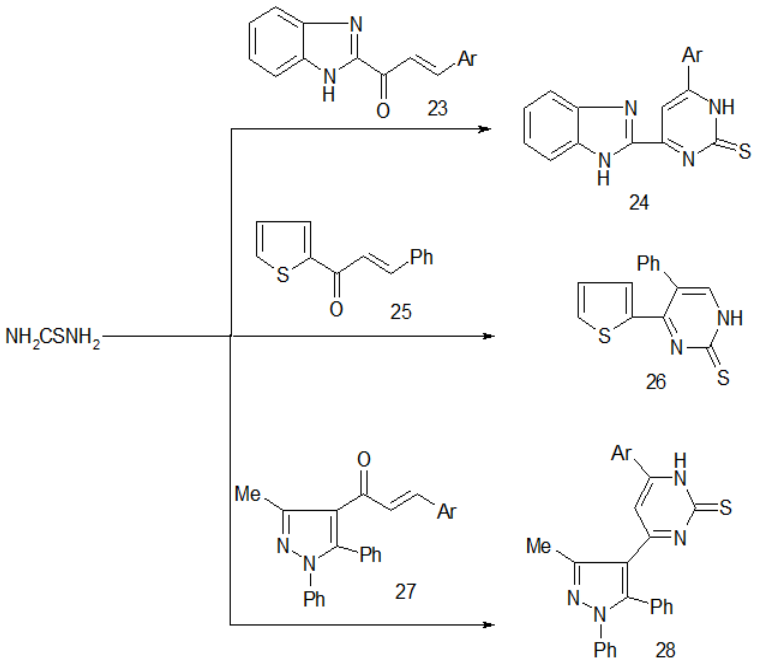
Reaction of β-aroylacrylic acids 21 with thiourea in the presence of ethanolic sodium ethoxide afforded the corresponding 6-aryl-4-carboxy-4,5-dihydropyrimidine-2(1H)-thiones 22[18].



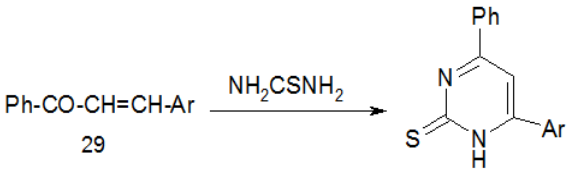
21 22

Ar = C_6H_5, 3,4-$Cl_2C_6H_3$ 2,5-C_6H_3(Me)(Cl)

Reaction of thiourea with 2-cinnamoyl benzimidazole (23), benzal-α-acetothienone (25) and 4-cinnamoyl-3-methyl-1,5-diphenylpyrazole (27) afforded pyrimidine-2-thiones 24, 26 and 28[19, 20, 21], respectively.



4,6-Disubstituted-2(1H)-pyrimidinethione 30[22] has been prepared by treatment of 4-nitrobenzylidene-acetophenone (29) with thiourea.



29 30

Ar = 4 -$O_2NC_6H_4$

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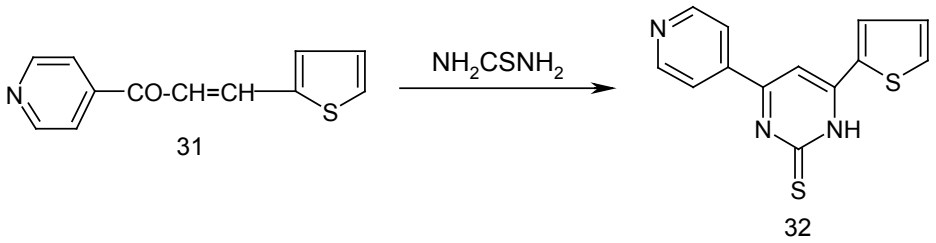
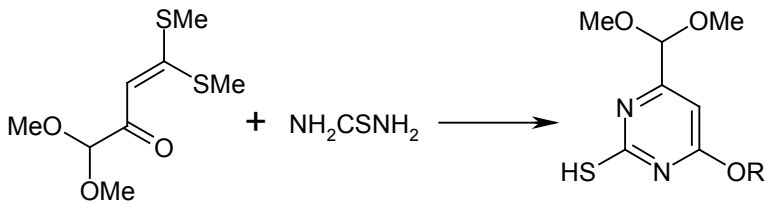
On the other hand, the chalcone 31 was reacted with thiourea to afford pyrimidinethione 32[23].



31 32

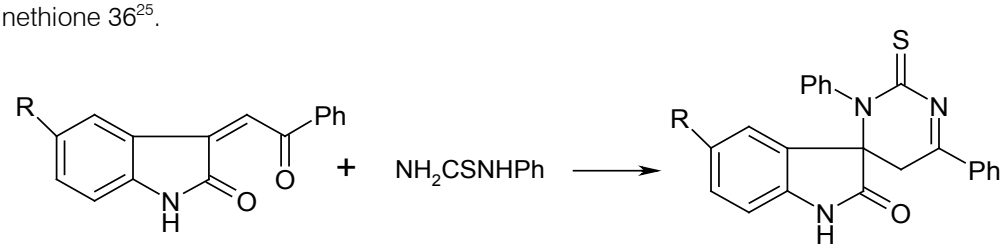
Treatment of α-oxoketene dithioacetal 33 with thiourea in the presence of sodium methoxide furnished the respective 6-alkoxy-4-[bis(methoxy)methyl]-2-mercaptopyrimidines (34) [24].



33 34

R = Me, Et

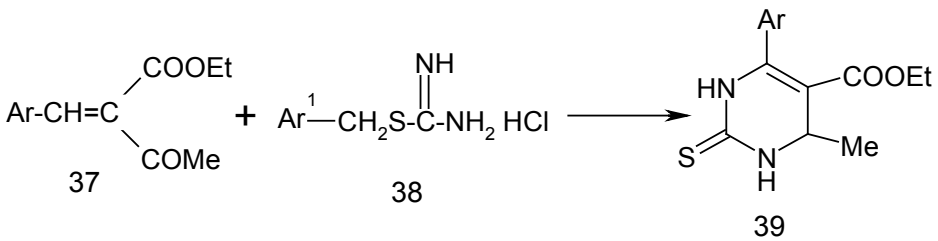
Condensation of compound 35 with phenylthiourea in ethanol under microwave irradiation yielded spiroindol pyrimidinethione 36[25].



35 36

R = Cl, Me

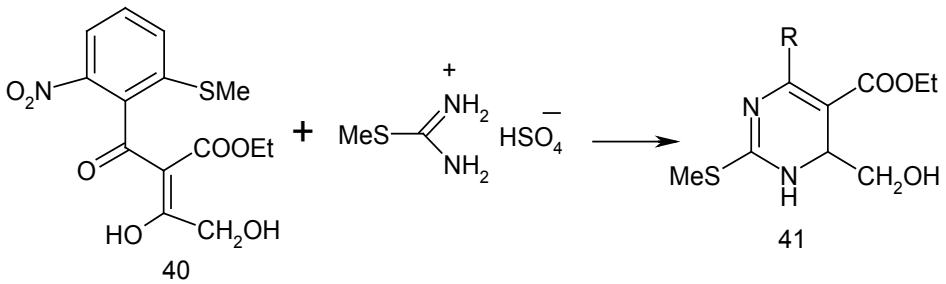
Treatment of *p*-nitrobenzylidine ethyl acetoacetate (37) with *p*-methoxybenzylthioamidine hydrochloride (38) gave pyrimidinethione 39[26].



37 38 39

Ar = 4- $O_2NC_6H_4$; Ar^1 = 4- $MeOC_6H_4$

Reaction of ethyl 4-(acetyloxy)-2-[2-(methylthio)-3-nitrophenyl methylene-3-oxobutanoate (40) and 2-methyl-2-thio pseudourea sulphate in the presence of sodium acetate afforded ethyl (hydroxymethyl) pyrimidine carboxylate derivative 41[27,28].



40 41

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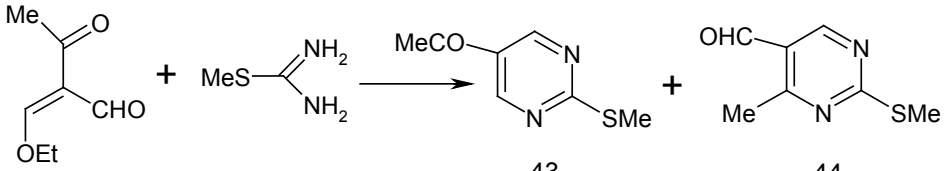
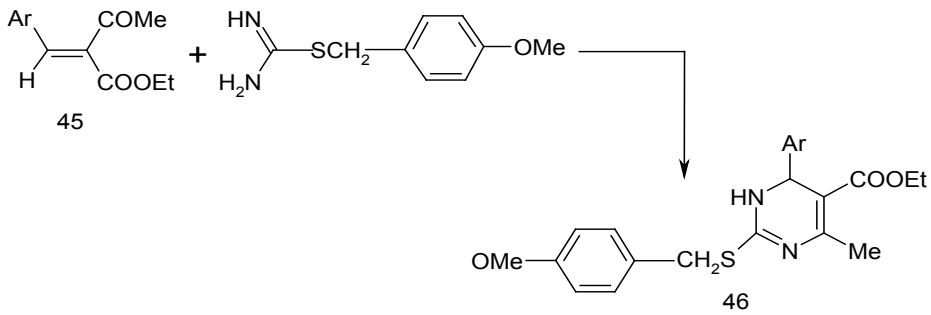
Condensation of 4-ethoxy-3-formyl-3-buten-2-one (42) with methyl thiourea afforded a mixture of 5-acetyl-2-methylthiopyrimidine (43) and 5-formyl-4-methyl-2-methylthiopyrimidine (44)[29,30].



42 43 44

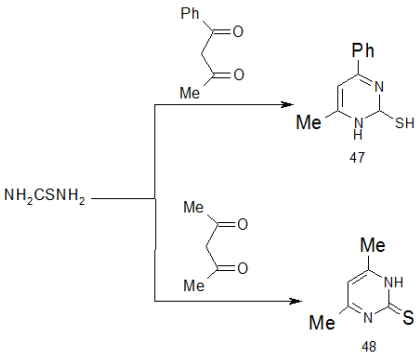
Treatment of α-acetylcinnamic esters 45 with S-(p-methoxybenzyl) thiourea in the presence of sodium hydroxide yielded 4-methyl-5-pyrimidine carboxylic acid esters 46[31].



45 46

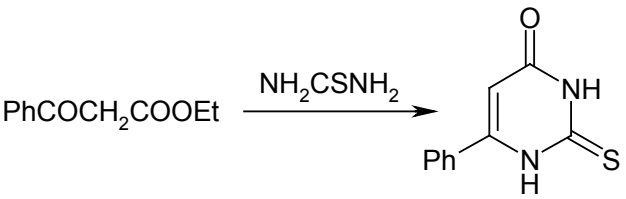
b. *With Dicarbonyl Compounds*

Reaction of thiourea with benzoylacetone[32] and acetylacetone[33,34,35] gave pyrimidine derivatives 47 and 48, respectively.



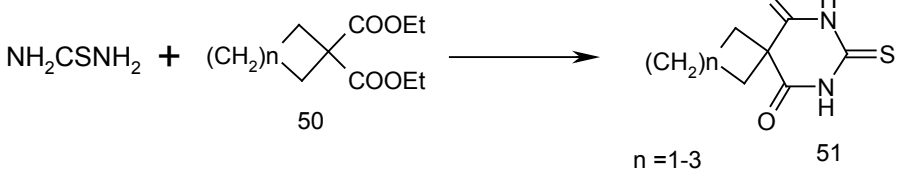
47 48

Reaction of ethyl benzoylacetate and thiourea in ethanolic sodium acetate afforded pyrimidinethione 49[36].



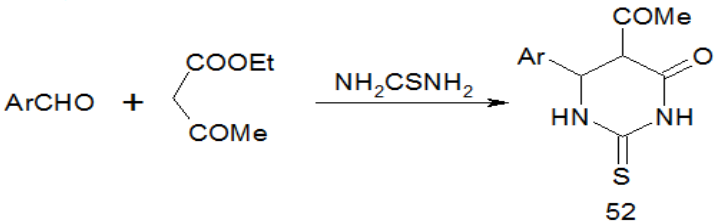
49

Interaction of thiourea with 1,1-cycloalkane-dicarboxylic acid diethyl esters (50) gave spiropyrimidinethione 51[37].



50 n =1-3 51

Ternary condensation of aromatic aldehyde, ethyl acetoacetate and thiourea produced tetrahydropyrimidine-2-thiones 52[38].



52

Ar = 4 -F-C_6H_4; 2,4 -F_2-C_6H_3

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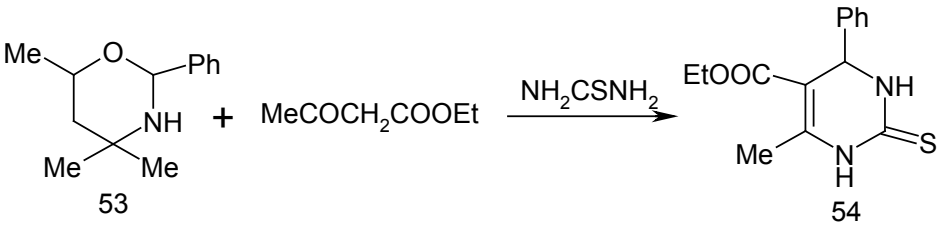
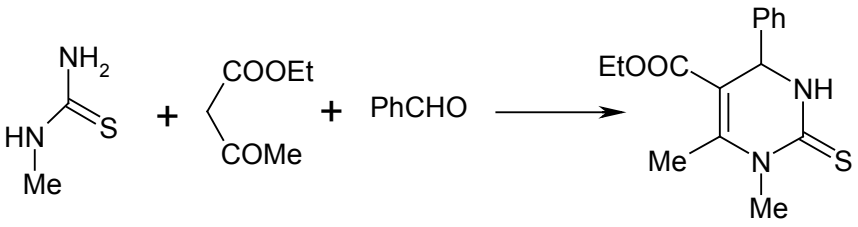
Reaction of oxazinane 53 with a mixture of ethyl acetoacetate and thiourea in the presence of anhydrous acetonitrile and trifluoroacetic acid furnished ethyl 6-methyl-4-phenyl-1,2,3,4-tetrahydropyrimidine-2-thione-5-carboxylate 54[39].



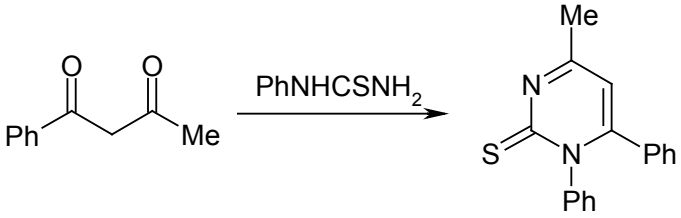
53 54

1,6-Dimethyl-4-phenyl-2-thioxo-3,4-dihydropyrimidine-5-carboxylic acid ethyl ester (55) was synthesized by condensation of ethyl acetoacetate, benzaldehyde and N-methylthiourea[40].



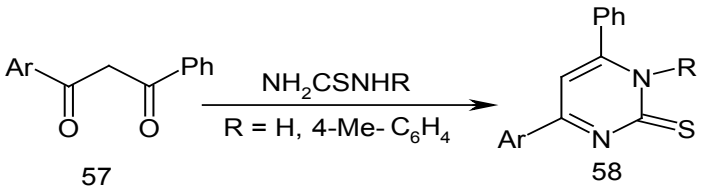
55

Further, 1-phenyl-1,3-butanedione was reacted with *N*-phenylthiourea in the presence of hydrochloric acid to produce 1,6-diphenyl-4-methyl-2-pyrimidinethione (56)[41].

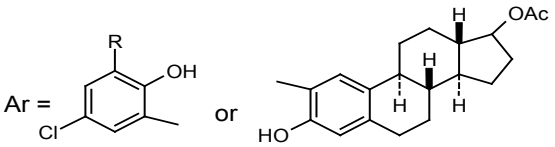


56

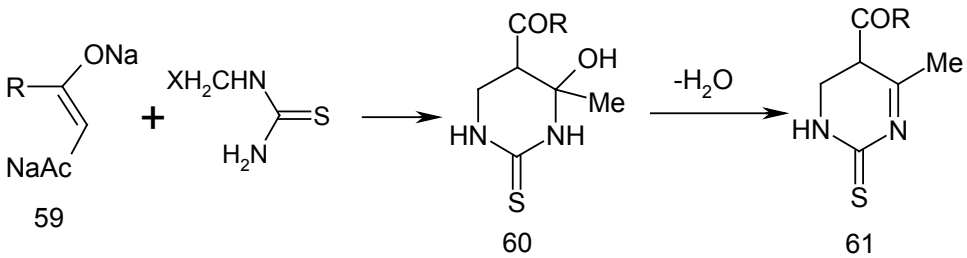
Diaroylmethane derivatives 78 were treated with thiourea to give pyrimidine-2-thione derivatives 79[18,42].



57 58



Heterocyclization of thiourea derivative with the enolate of 1,3-dicarbonyl derivative 59 yielded hydroxyhexahydropyrimidines 60 which underwent dehydration to afford tetrahydropyrimidines 61[43].



59 60 61

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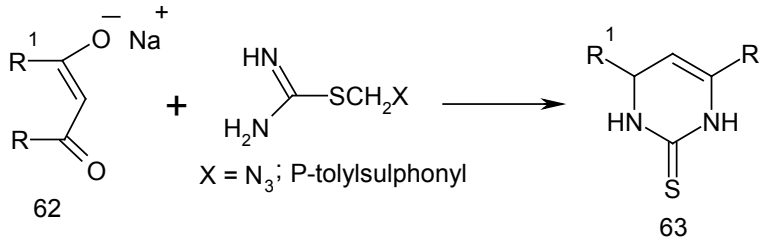
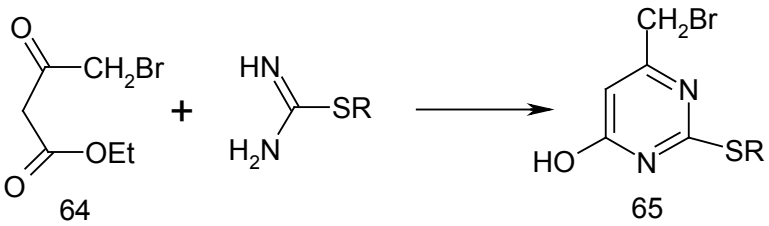
Reaction of 1,3-dicarbonyl compound 62 with (azidomethyl) thiourea or [(*p*-tolylsulphonyl)methyl] thiourea gave pyrimidine derivative 63[44].



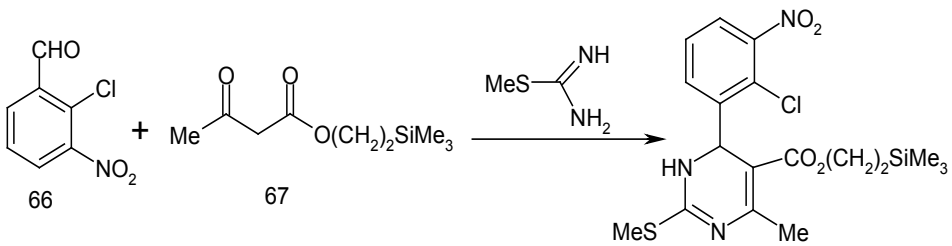
62 63

Condensation of ethyl γ-bromoacetoacetate 64 with S-methyl or S-benzyl isothiourea gave pyrimidine derivatives 65[45].



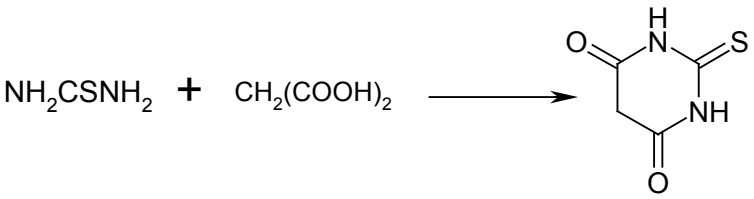
64 65

Condensation of 2-chloro-3-nitrobenzaldehyde 66 with acetoacetate derivative 67 and methyl thiourea yielded 3,4-dihydropyrimidine carboxylate 68[46].



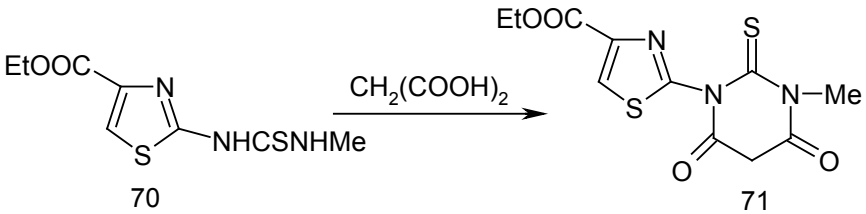
66 67 68

Dioxopyrimidinethione 69[47-49] was obtained by the reaction of thiourea with malonic acid.



69

Treatment of thioazolyl thiourea derivative 70 with malonic acid, in the presence of acetyl chloride, gave pyrimidine derivative 71[50].



70 71

c. *With Acetylenic Compounds*

Cyclocondensation of acetylene derivative 72 with thiourea produce pyrimidinethione 73[51].

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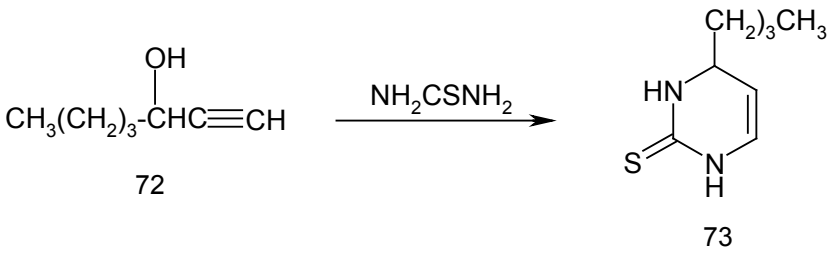
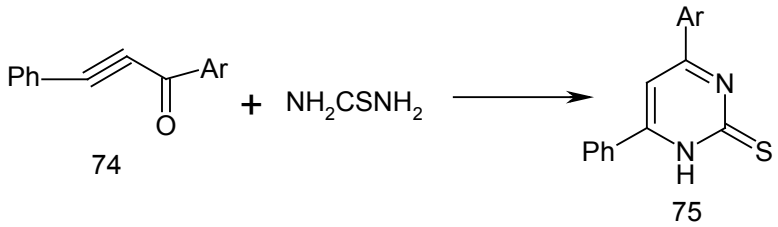


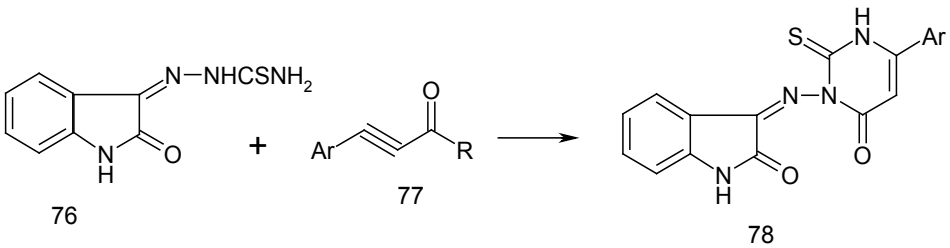
72 73

Reaction of aroylphenylacetylenes 74 with thiourea in the presence of ethanolic sodium ethoxide afforded 4-aryl-6-phenylpyrimidine-2(1H)thiones 75[52].



74 75

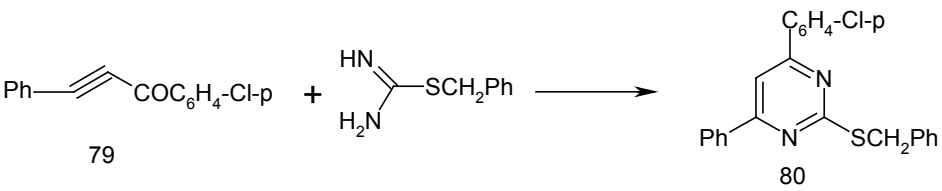
Treatment of isatin-3-thiosemicarbazone (76) with acetylenic ester 77 in the presence of ethanolic sodium ethoxide yielded 3-[2-oxo-2H,3H-benzo(b) pyrrolidine-3-iminyl]-4-oxo-2-thioxo-1,2,4-trihydropyrimidine (78)[53, 54].



76 77 78

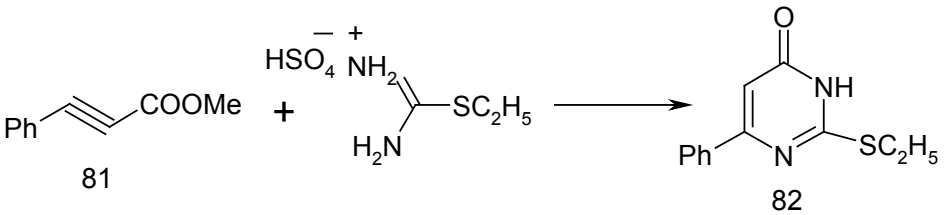
R = OMe, OEt ; Ar = 4-Cl- C_6H_4 , 4-MeO- C_6H_4

S-benzylisothiourea hydrochloride was reacted with p-chlorobenzoylphenylacetylene (79) to give 2-benzylthio-4-(*p*- chlorophenyl)-6-phenylPyrimidine(80)[4].



79 80

When S-ethylisothiourea sulphate was allowed to react with methyl propiolate 81, in the presence of sodium acetate, gave 1,6-dihydro-2-ethylthio-4-phenyl- pyrimidin-6-one (82)[55].



81 82

d. *With Arylidenes*

4-Amino-6-aryl-5-cyanopyrimidine-2(3H)-thiones 84[56,57] were obtained by the reaction of β-arylidene malononitrile 83 with thiourea in the presence of anhydrous potassium carbonate.

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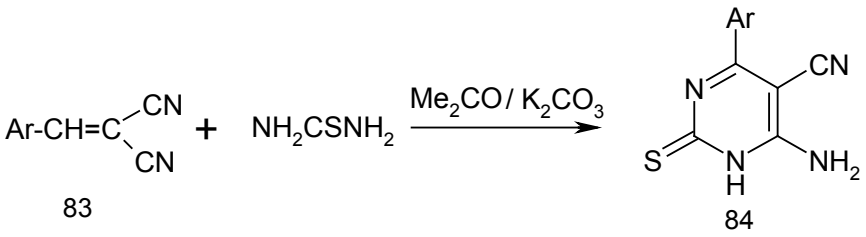
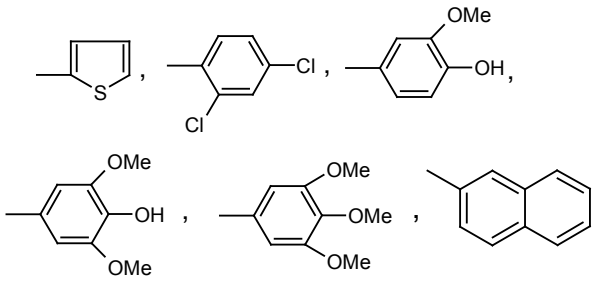
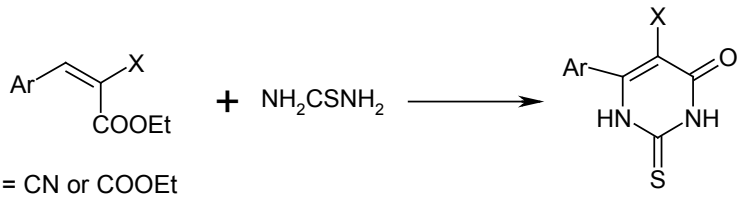


83 84

Ar =



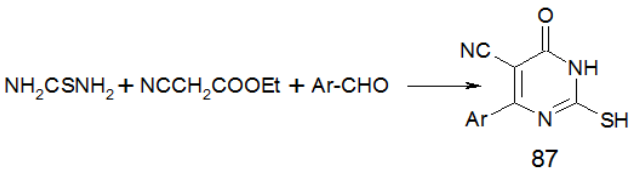
4-Oxo-2-thioxopyrimidine derivatives 86 were obtained by the reaction of arylidines 85[58,59] with thiourea.



X = CN or COOEt

85 86

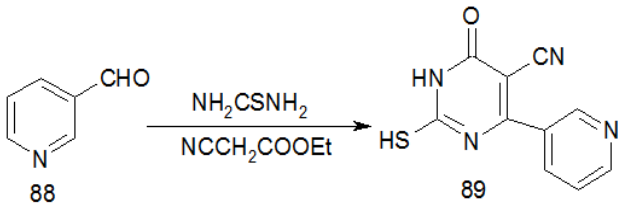
2-Mercapto-4-aryl-5-cyanopyrimidin-6(1H) ones (87)[60,61] were obtained by reaction of ethyl cyanoacetate, thiourea with aromatic aldehydes in ethanolic sodium ethoxide.



87

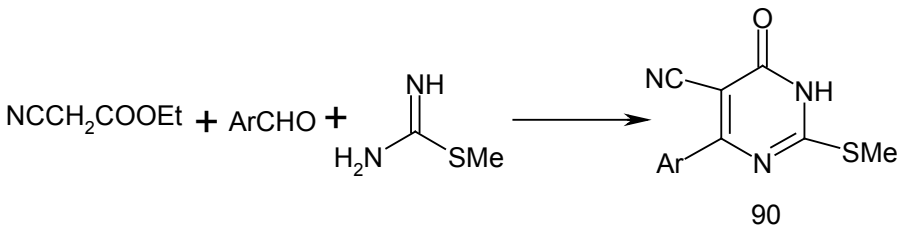
Ar = 2, 4-$Cl_2C_6H_3$, 4-$(Me)_2N$-C_6H_4

5-Cyano-2-mercapto-6(1H)pyrimidinone derivative 89[62] was obtained by reaction of 3-pyridine carboxyaldehyde (88), thiourea and ethyl cyanoacatate.



88 89

Reaction of ethyl cyanoacetate with aromatic aldehyde and methyl thiourea gave the corresponding 4-aryl-5-cyano-2-methylthio-6-oxopyrimidine derivative 90[63].



90

e. *With Ethoxymethylene Compounds*

Reaction of ethoxymethylene derivatives 91 with thiourea derivatives gave pyrimidine derivatives 92, 93, 94, 95 and 96 respectively[64].

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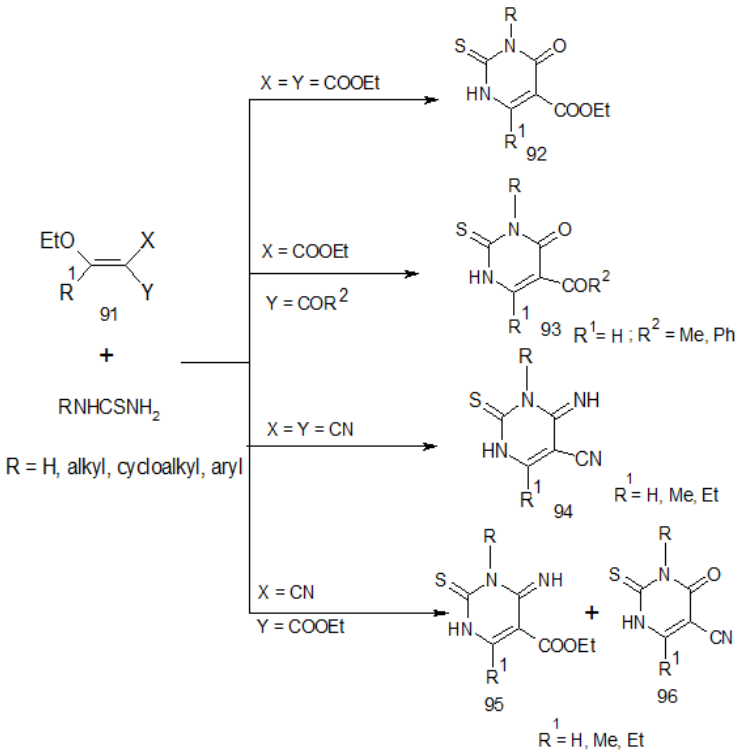
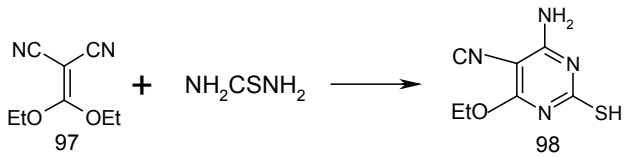
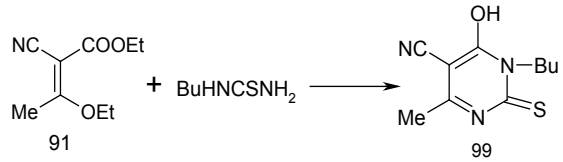


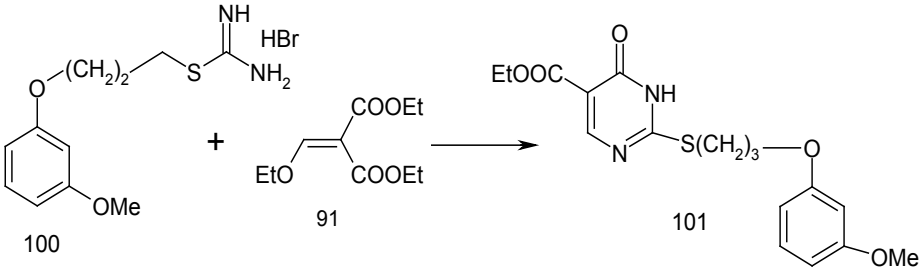
Reaction of diethoxymethylenemalononitrile (97) with thiourea afforded pyrimidine derivative 98[65,66].



Butyl-5-cyano-6-hydroxy-4-methyl-2-thiopyrimidine (99)[67] was synthesized by the reaction of ethyl α-ethoxyethylidinecyanoacetate (91) with *N*-butyl-thiourea.

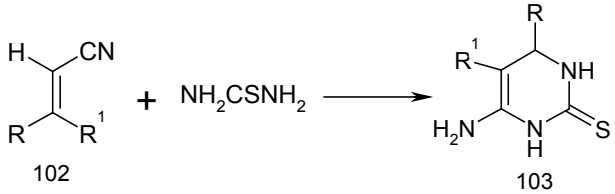


Treatment of S-[3-(methoxyphenoxy)propyl] isothiourea hydrobromide (100) with ethoxymethylidinemalonate (91) gave pyrimidine derivatives 101[68].

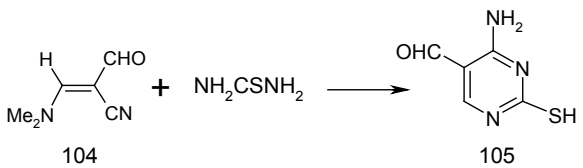


f. *With Acrylonitrile Derivatives*

Reaction of cyanoolefine 102 with thiourea gave the aminopyrimidine derivatives 103[69-71].



Interaction of acrylonitrile derivative 104 with thiourea yielded thiopyrimidine 105[72].



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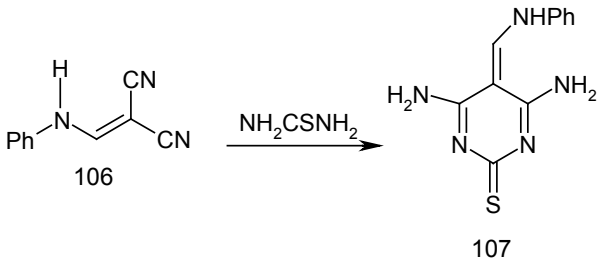
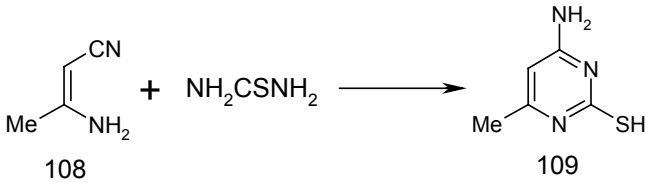
Pyrimidine-2-thione derivatives 107 was prepared via interaction between β-enaminonitrile 106 with thiourea[73,74].

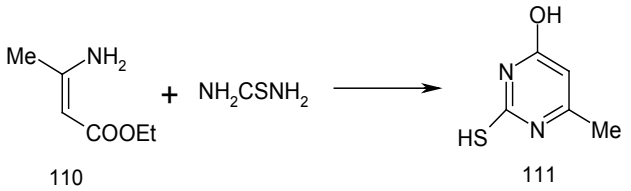


g. *With Enamine derivatives*

Reaction of 2-amino-1-cyanopropene (108) with thiourea gave thiopyrimidine 109[65].

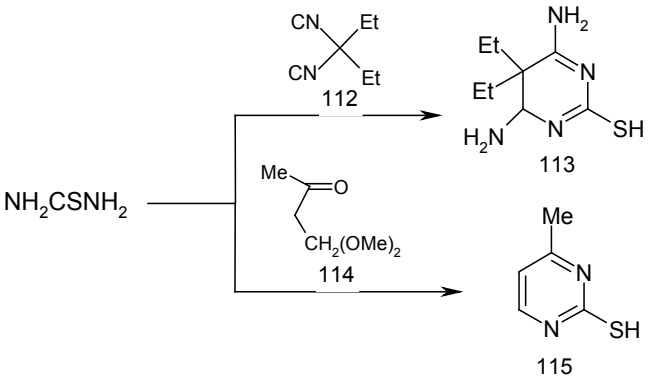


Also, interaction of 3-aminocrotonate (110) with thiourea gave thioxo-pyrimidine 111[75].

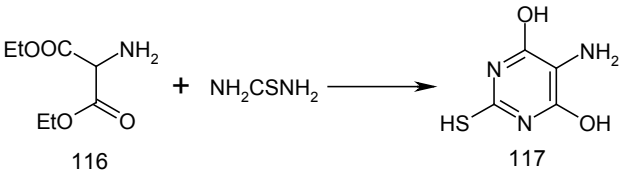


h. *With Different Compounds*

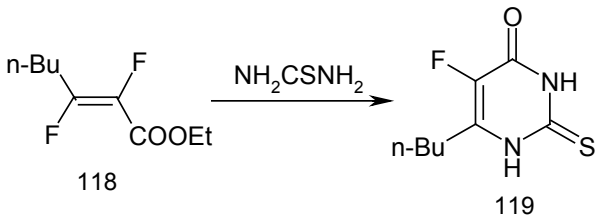
Reaction of thiourea with diethylmalononitrile (112)[69]and ketone derivative 114 afforded pyrimidine derivative 113 and 115 respectively.



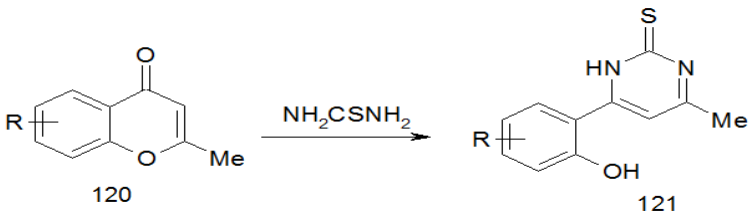
The condensation of thiourea with diethyl 2-aminomalonate 116 afforded 5-amino-2-mercapto-pyrimidine-4,6-diol (117)[76].



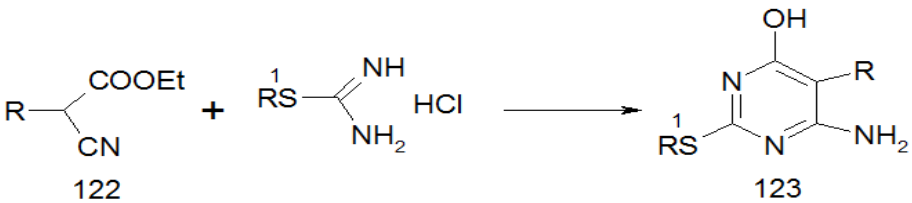
Reaction of ethyl 3-*n*-butyl-*trans*-2,3-difluoro-2-acrylate (118) with thiourea afforded the corresponding 6-*n*-butyl-5-fluoro-2-thiouracil (119)[77].



Condensation of 2-methylchromones 120 with thiourea afforded 4-methyl-6-substituted-phenyl-(1H) pyrimidinethiones 121[78].



Reaction of ethyl cyanoacetate derivatives 122 with S-alkyl thiourea derivatives yielded pyrimidine derivatives 123[79].



a, R = NHCOMe; b, R = $NHNH_2Ph$

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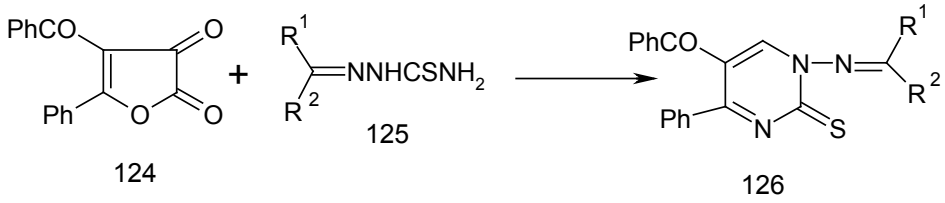
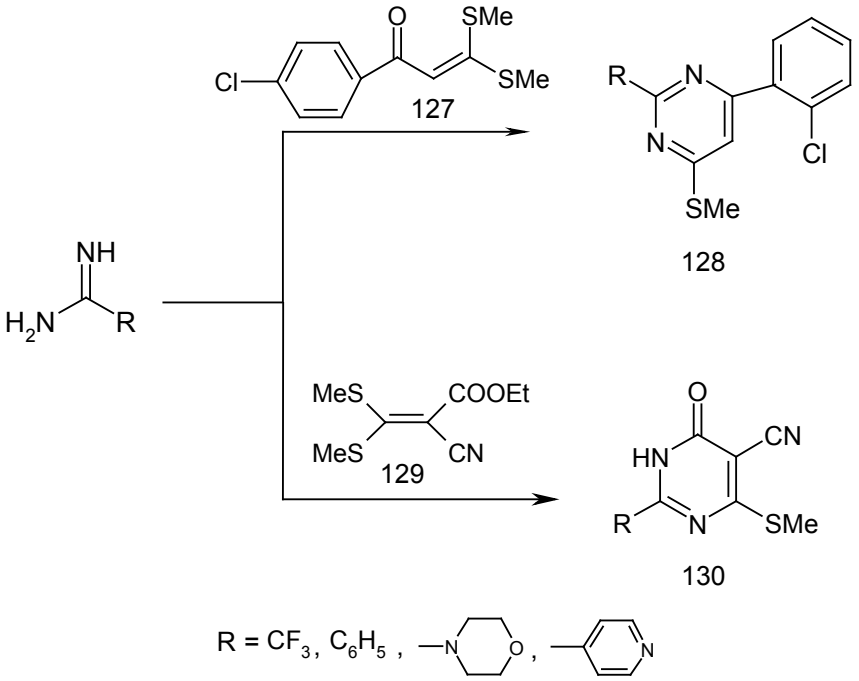
Furan-2,3-dione 124 and thiosemicarbazones 125 combined with loss of carbon dioxide and water to yield 1-methyleneaminopyrimidine-2-thione derivative 126[80].

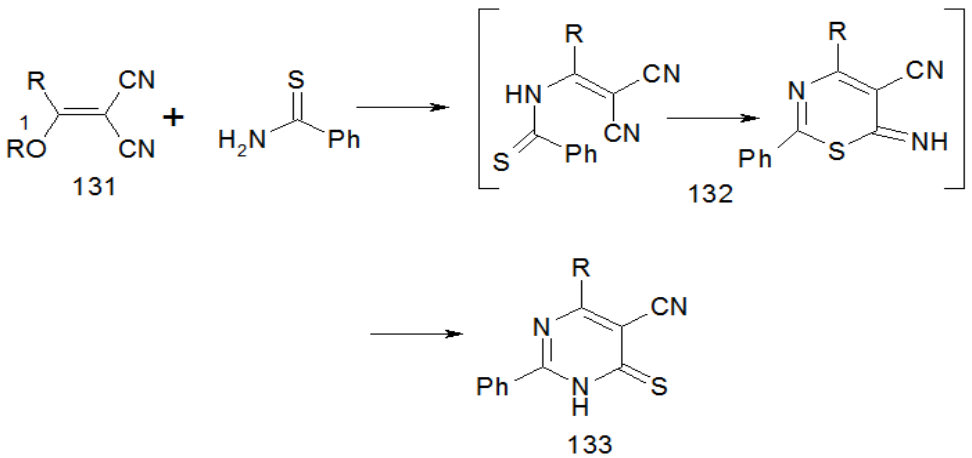


ii. *From Guanidine Derivatives*

Guanidine derivatives are considered as basic unit for the preparation of 4-thiopyrimidines. Thus, reaction of guanidine derivatives with benzoylethylene derivative 127 and acrylate derivative 129 afforded pyrimidine derivatives 128 and 130[81,82] respectively.



Treatment of 3-alkoxy-3-aryl(or alkyl)-2-cyanoacrylonitriles (131) with thiobenzamide and sodium isopropoxide in 2-propanol yielded 6-thioxo-3,4-dihydropyrimidine derivatives 133 through the formation of 3-aryl(or alkyl)-2-cyano-3-thiobenzamide cyanoacrylonitriles (132)[83].



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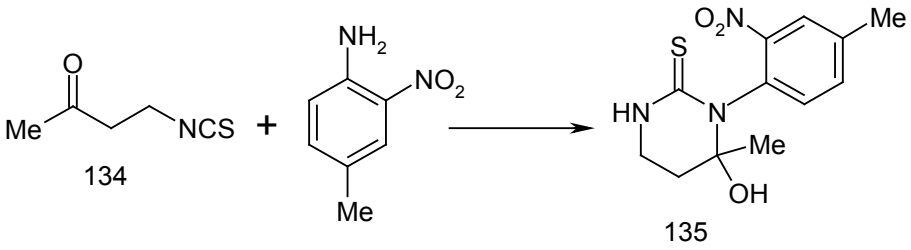
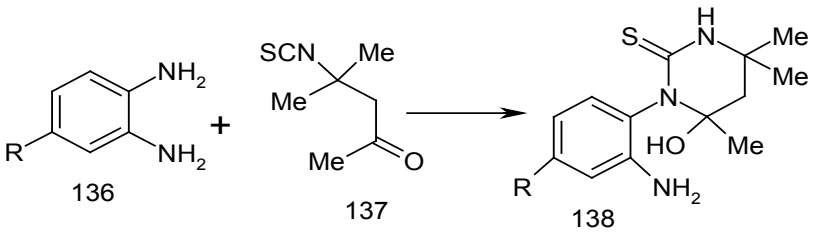
iii. *From Isothiocyanate Derivatives*

Isothiocyanate derivatives are used for the synthesis of 2- and 4-pyrimidinethiones. Thus, 1-(2-nitro-4-methylphenyl)-6-hydroxy-6-methyl-1,4,5,6-tetrahydropyrimidine-2(3H)thione (135)[84] was prepared by the reaction of 4-isothiocyanatobutan-2-one (134) with 4-methyl-2-nitroaniline.

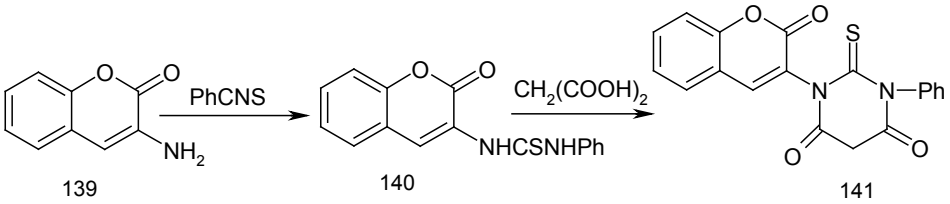


Phenylenediamines 136 was allowed to react with 4-isothiocyanato-4-methyl-2-pentanone (137) at room temperature to give aryltetrahydropyrimidine-2-thiones 138[85].

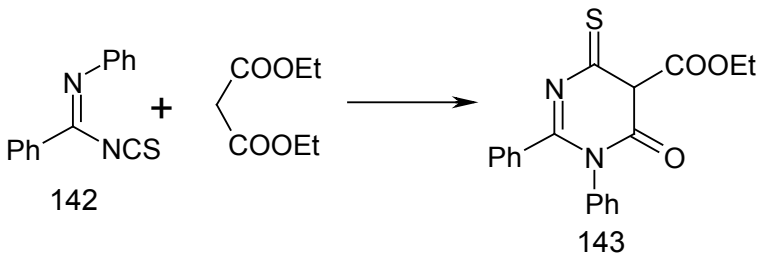


R = H, Me, OMe

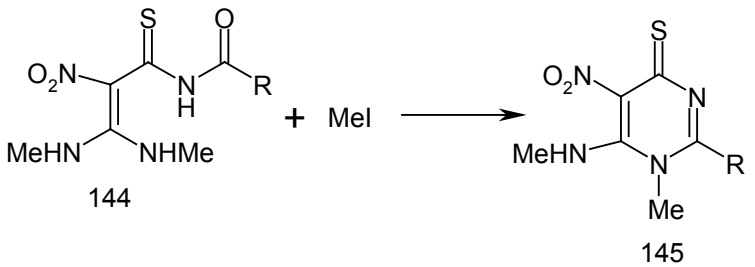
Treatment of 3-aminocoumarin (139) with phenyl isothiocyanate in ethanol afforded coumarinylphenylthiourea 140 which underwent cyclocondensation with malonic acid in acetyl chloride to give coumarnylphenylthiobarbituric acid 141[86].



When isothiocyanate derivative 142 was allowed to react with diethyl malonate gave pyrimidinethione 143[87].



2-Aryl-1-methyl-5-nitro-6-methylaminopyrimidine-4-thiones (145)[88] were synthesized by the reaction of nitrokenaminal acylisocyanate C-adducts 144 with methyl iodide.



R = C_6H_5 ; 4-ClC_6H_4 ; 4-MeO-C_6H_3-CH=CH- ; C_6H_4-CH=CH-

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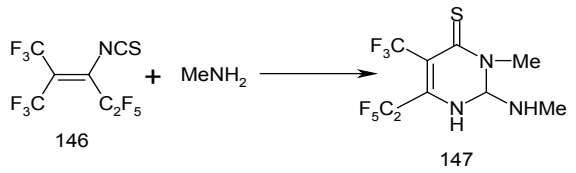
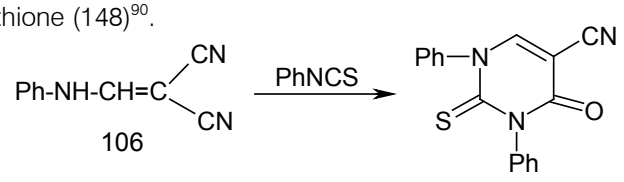
Treatment of perfluoro-2-methylpent-2-en-3-yl isothiocyanate (146) with methylamine afforded 3-methyl-2-methyl-amino-6-pentafluroethyl-5-trifluorome-thyl-3H-pyrimidine-4-thione (147)89.



146 147

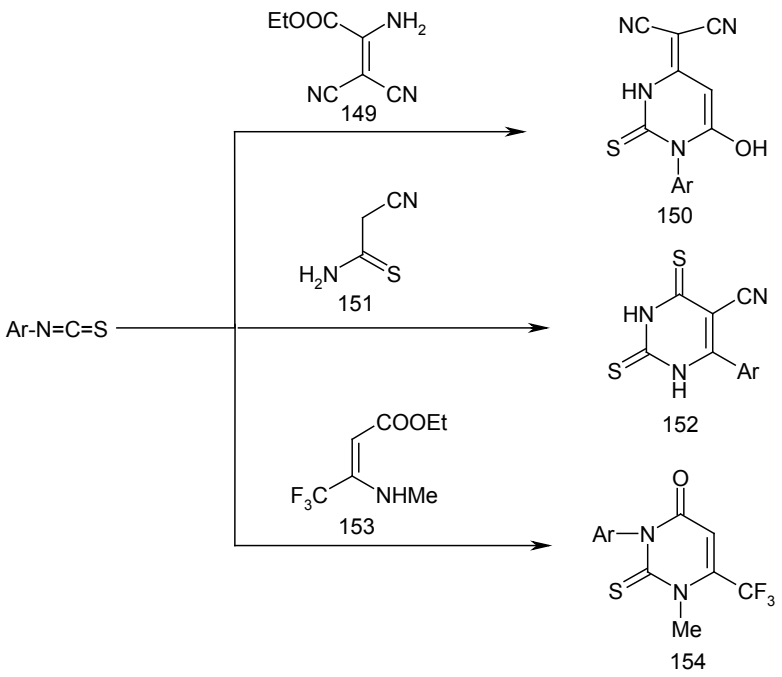
b) Synthesis from C-C-C-N and C-N fragments

Pyrimidinethiones synthesized by this manner may be contain thioxo group at 2 or 4 position. Thus, treatment of β-enaminonitrile 106 with phenyl isothiocyanate in ethanol containing sodium hydroxide furnished 5-cyano-1,3-diphenyl-4-oxo-pyrimidine-2-thione (148)[90].

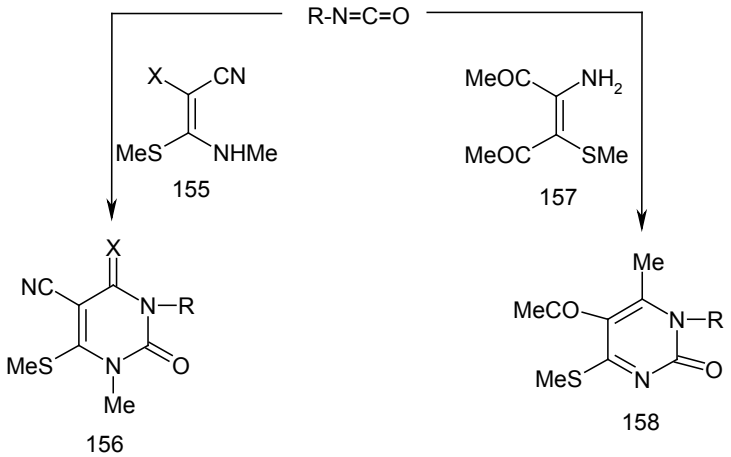


106 148

On the other hand, phenylisothiocyante derivatives was reacted with ethyl enaminonitrile 149[91], cyanothioacetamide 151[92] and methylamino acrylate 153 to give pyrimidinethio- ne derivatives 150, 152 and 154, respectively.



Reaction of isocyanate derivative with ketene S,N-acetals 155[93] and amino ethylene derivative 157[94] yielded pyrimidine derivatives 156 and 158, respectively.



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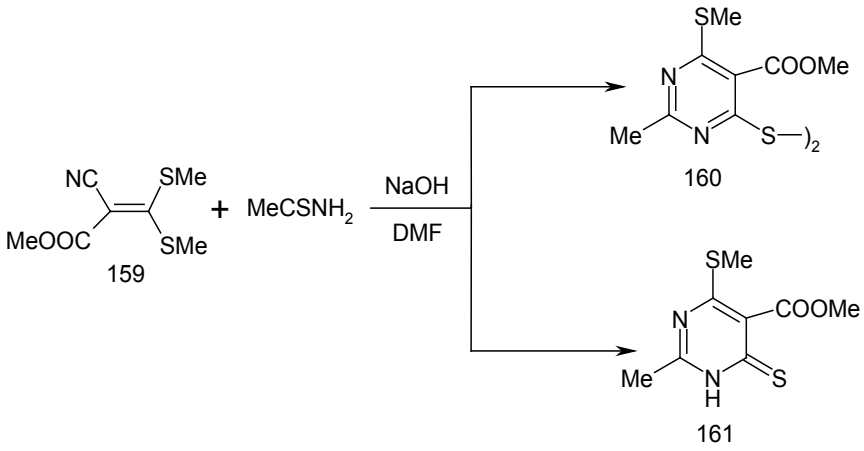
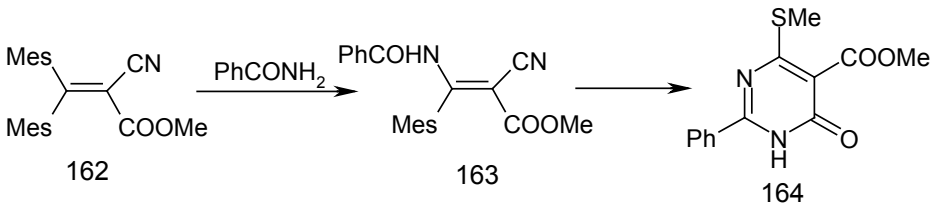
Treatment of methyl-2-cyano-3,3-bis[methylthio]propenate (159) and thioacetamide in NaOH/DMF afforded bis [5-(methoxycarbonyl)-2-methyl-6-methylthio-4-pyrimidine] disulphide (160) and 5-(methoxycarbonyl))-2-methyl-4-(methyllthio)-1(H)-pyri-midinethione 161[95].

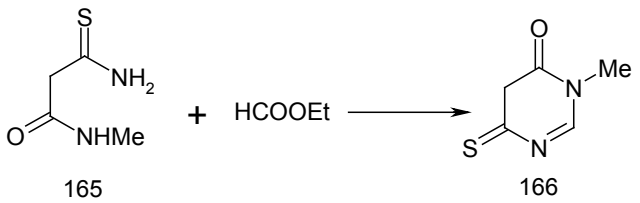


Reaction of methyl 2-cyano-3,3-bis(methylthio) acrylate (162) with benzamide in the presence of sodium hydride gave methyl 3-benzoylamino-2-cyano-3-(methylthio)acrylate (163), which readily converted to methyl 3,4-dihydro-6-(methylthio)-4-oxo-2-phenyl-pyrimidine-5-carboxylate (164)[96].

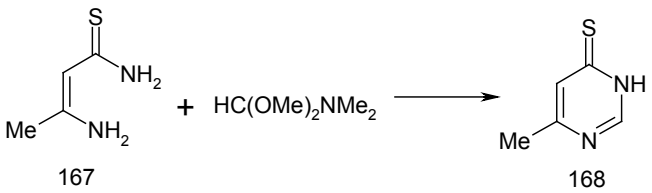


c) *Synthesis from N-C-C-C-N and C-fragments*

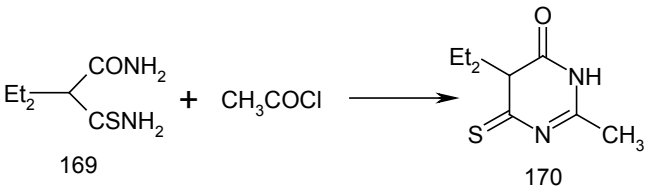
3-Amino-N-methyl-3-thioxopropanamide (165) allowed to react with ethyl formate to yield 3-methyl-6-thioxo-5,6-dihydropyrimidin-4-one (166)[97].



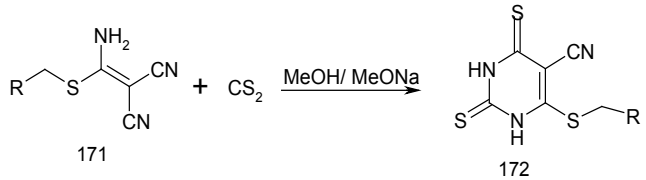
Cyclization of β-aminothiocrotamide (167) with dimethyl formamide dimethyl acetal afforded 6-methyl-4(3H)-pyrimidinethione (168)[98].



Treatment of 2-ethyl-2-thiocarbomylbutyramide (169) with acetyl chloride yielded pyrimidinethione 170[99].



Cyclocondensation of enaminonitrile 171 with carbon disulfide gave pyrimidinethione derivatives 172[100].



d) Synthesis from C-C-N and C-N-C fragments:

Reaction of acetylacetone with ammonia gave α,β-unsaturated aminoketone 173. When an equimolarcular amounts of 173 and aroylisothiocyanate were heated in dioxan afforded 4-mercapto-6-methyl-2-aryl-5-acetylpyrimidines 174[101-104].

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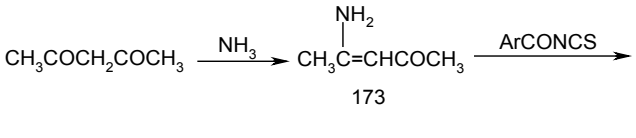
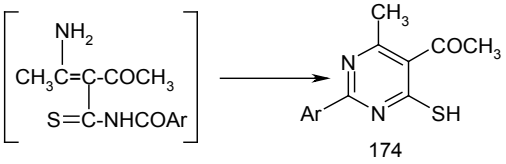
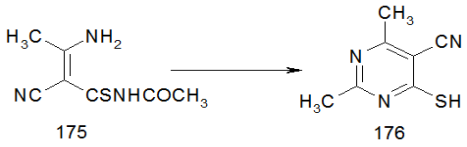


173



174

The adduct of β-aminocrotononitrile and acetylisothiocyanate 175 underwent base catalyzed cyclization to yield pyrimidine derivative 176[105,106].



175 176

Reaction of 177 with thiocyanate derivatives in acetone gave pyrimidinethiones 178[107].

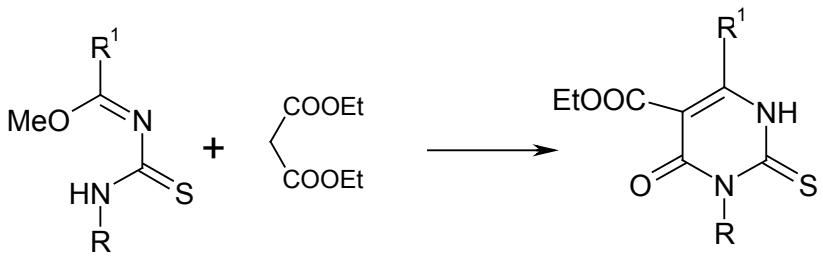


177 178

R = Ph, Me

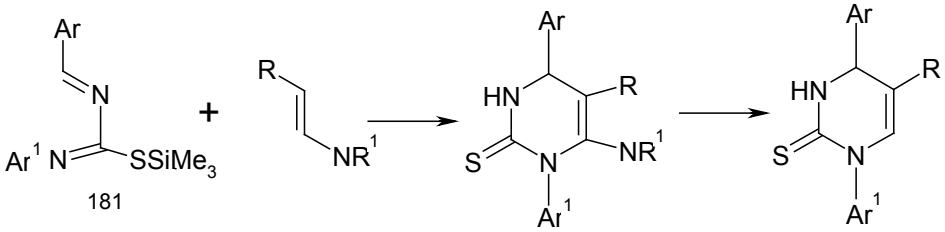
e) Synthesis from N-C-N-C and C-C fragments

Ethyl pyrimidine-5-carboxylate 180 was prepared by the reaction of 179 with diethyl malonate in the presence of ethanolic sodium ethoxide[108].



179 180

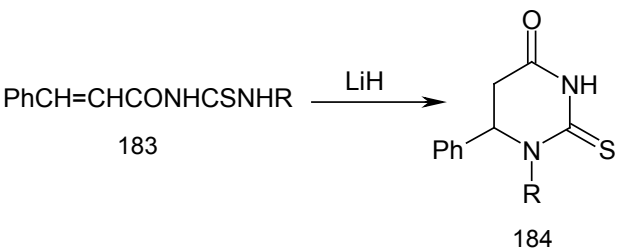
Reversed polarization in 2-trimethylsilylthio-1,3-diene 181 allows percyclic reaction with acyclic enamines to give pyrimidinethione 182[109].



181 182

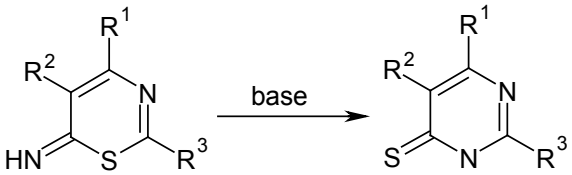
f) Miscellaneous Methods

cyclization of n-(4-substitutedphenyl)-n\-3-phenylprop enoylthiourea (183) with lithium hydride yielded thiouracil 184[110].



183 184

6-imino-6*H*-1,3-thiazines 185 underwent Dimroth rearrangement when treated with a base to form thioxopyrimidines 186[111].



185 186

III. Applications of Pyrimidinethiones

One important class of pyrimidine is 2-thiopyrimidine (2-TP) and its derivatives, which are also well known as 2-mercaptopyrimidine compounds. In 2-TP ring sulfur atom serves as an interesting replacement for the existing oxygen atom bonded to C-2 in uridine base. Studies evaluated primary activity of 2-TP

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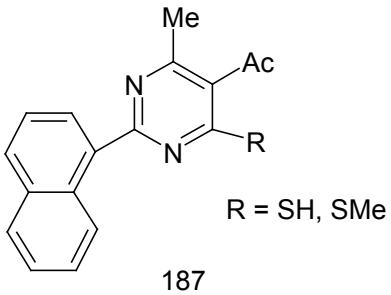
derivatives against Mycobacterium tuberculosis (Mtb). 2-TPs also serve as important precursors for asymmetric synthesis of allylic sulfides/sulfonates.

Recently, international applications revealed that, 2-TP derivatives possess potent activity against inflammation and immune disorders. Thus, search for novel, potent and selective 2-TP derivatives is desirable in order to substitute drugs having major side effects such as peptic-ulcer formation and gastro-intestinal damage. Various mono-, di-, tri- and tetra-cyclic, di/tetrahydro-2-TP derivatives have been synthesized and evaluated for anti-inflammatory and analgesic activity (both in *vivo* and in *vitro*)[1].

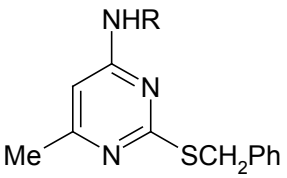
The widespread use of thiols as drugs, cosmetics, corrosion inhibitors, agents in photographic and vulcanization processes and chemical analysis of varied metal ions as well as different bio-oriented compounds[112].

Pyrimidine derivatives 187 exhibited bactericidal activity in vitro against *Salmonella spp*., *St. albus*, and *B. subtilis*[113].



187

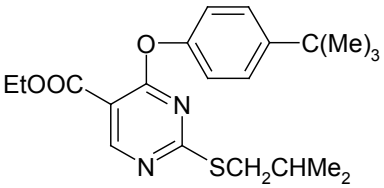
2-Benzylthio-4-substitutedamino-6-methylpyrimidines 188 were screened against selected bacteria which showed a moderate activity against *Bacillus subtilis* and *Neisseria*[114].



R = C_6H_5, 4 -Me-C_6H_5, 4 -Br-C_6H_4

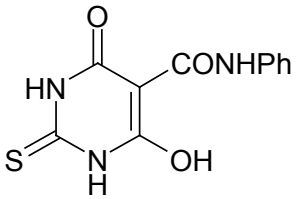
188

Phenoxypyrimidinecarboxylate 189 is a better herbicide against *Podosphaera lucotricha* on apples[115].



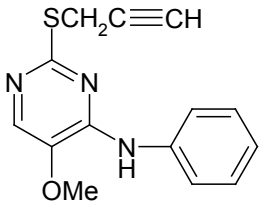
189

Pyrimidinecarboxanilide 190 is effective neoplasm inhibitors in vivo tests in mice[116].



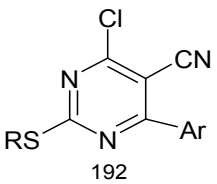
190

4-Anilinopyrimidine 191 at 60 ppm gave complete control of *Pseudo- cercosporella herbotrichoides* on wheat[117].



191

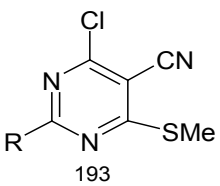
4-Chloropyrimidines 192 and 193 were submitted for preliminary evaluation of their in vitro activity against *M. tuberculosis*, human isolates of *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *S. faecalis*, *Staphylococcus aureus*, *E. coli* and antimycotic activity against *Candida albicans*, *Cryptococcus neoformans*, *Sporothrix schenckii*, *Aspergillus fumigatus* and *T. mentagrophytes*[118].



192

R = Me, Et, n-Pr, 4-Cl-$C_6H_4CH_2$

Ar = 2-thienyl, 2-furyl, 2,4- $F_2C_6H_3$, 3- FC_6H_4



193

R = SMe, S-$CH_2C_6H_5$

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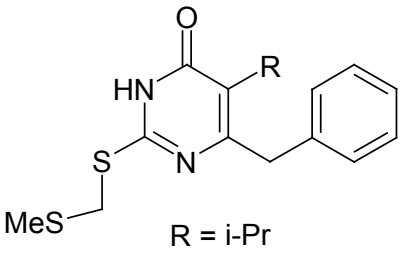
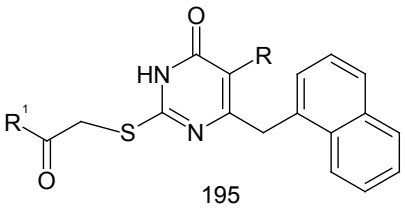
5-Isopropyl-2-[(methylthiomethyl)thio]-6-(benzyl) -pyrimidin-4-(1H)-one (194) elicited potent anti-HIV activity with an IC_{50} value less than 1 nM for inhibition of HIV replication[119].



194

6-(1-Naphthylmethyl) pyrimidin-4(3H)-ones 195 were evaluated for cytotoxicity and anti-HIV activity in MT-4 cells using the MTT method, which exhibited extremely potent inhibitory activity against HIV replication[120].



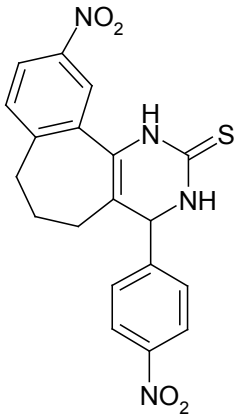
195

R = Me, Et, i-Pr

R^1 = Me, MeO, OEt, C_6H_5, 4- Cl- C_6H_4 ,

4- F- C_6H_4 , 4- Me- C_6H_4 , 4- MeO- C_6H_4

Antitumor activity screening for 10-nitro-4-(p-nitrophenyl)-1,3,4,5,6,7-hexahydro-2H-benzo[6,7] cyclo-hepta[1,2-d]-pyrimidine-2-thione (196) utilizing 59 different human tumor cell lines, representing leukemia, melanoma, and cancers of the lung, colon, brain, ovary, breast, prostate as well as kidney, was carried out. From the in vitro observed data it has been noticed that, compound 196 seem to be active against all the tested cell lines[121].



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Kinetics Studies and Mechanism Evolution of the Cyclization of Ethylene Diamine and Propylene Glycol over Alumina Supported Nanocrystalline Mn-Ferrite

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Abstract- Kinetics of Cyclization of propylene glycol and ethylene diamine to 2-methyl pyrazine has been studied over alumina-supported nanocrystalline $MnFe_2O_4$ catalyst in a differential flow fixed bed reactor in the temperature range 473 – 573 K. The partial pressures of propylene glycol and ethylene diamine were varied and rates were measured for the formation of 2 Methyl Pyrazine. Product selectivity as well as rate of formation of 2-methyl pyrazine was influenced by partial pressure of reactants. The rate equation R = k KP.KE PP PE / (1+ K P PP+K E PE) 2 deduced, on the basis of adsorption of PG and ED in gas phase represented the data most satisfactorily.

Keywords: cyclization, differential flow fixed bed reactor, adsorption, alumina-supported, nanocrystalline, 2 methyl pyrazine.

GJSFR-B Classification : FOR Code: 030299, 030703



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Kinetics Studies and Mechanism Evolution of the Cyclization of Ethylene Diamine and Propylene Glycol over Alumina Supported Nanocrystalline Mn-Ferrite

Rajeev Dixit

Abstract- Kinetics of Cyclization of propylene glycol and ethylene diamine to 2-methyl pyrazine has been studied over alumina-supported nanocrystalline MnFe2O4 catalyst in a differential flow fixed bed reactor in the temperature range 473 – 573 K. The partial pressures of propylene glycol and ethylene diamine were varied and rates were measured for the formation of 2 Methyl Pyrazine. Product selectivity as well as rate of formation of 2-methyl pyrazine was influenced by partial pressure of reactants. The rate equation R = k KP.KE PP PE / (1+ K P PP+K E PE) 2 deduced, on the basis of adsorption of PG and ED in gas phase represented the data most satisfactorily.

Keywords: *cyclization, differential flow fixed bed reactor, adsorption, alumina-supported, nanocrystalline, 2 methyl pyrazine.*

I. Introduction

Nanosize materials are known to exhibit certain properties that are different from their bulk counterparts [1] such materials possess higher surface area, band gap, coercivity, acidity / alkalinity and coordination of atoms. The chemical properties also vary because of the changes in the electron density as a function of particle size, resulting thereby in binding modes of the adsorbate molecules that are different than that observed in the case of corresponding bulk materials. Additionally, in case of supported catalysts, the electronic interaction between the nano-dispersed metal crystallites and the support materials are known to influence the chemisorptions properties. Providing support to the nanocrystalline metal oxides avoids their agglomeration in actual reaction conditions and helps achieve highly dispersed and uniform size particles. Anpo *at al*. and Maira *at al.* [2-3] In addition to large surfaces, support helps in the shape selectivity and also provides an inert envelope to protect from the chemical effect of the reaction medium.

2-MP is the pivotal intermediate for obtaining 2-cyanopyrazine, which on hydrolysis yields pyrazinamide, a well-known anti-tubercular drug. Conventionally, chromite catalysts are used for vapour phase synthesis of 2-MP. There are reports on the use of Palladized Zn-Cr oxide Forni *at al.* [4] ZSM-5 Kulkarni *at al.* [5] Modified copper-chromite Ilnam *at al.* [6] binary catalyst based on oxides of Zn and variable valence metals Balpanov *at al.* [7] Zn-modified zeolites Anand *at al.* [8] Zn-modified ferrite Anand *at al.* [9] and $CuO/ZnO/SiO_2$ Subramanyam *at al.* [10] as catalysts for synthesis of 2-MP from ED and PG. To the best of our knowledge, there is no report on the kinetics of cyclization of propylene glycol (PG) and ethylene diamine (ED) to produce 2-MP over alumina supported nanocrystalline manganese ferrite. The present problem of kinetic study of synthesis of 2-MP from PG and ED was therefore undertaken with a view (1) to collect data on the kinetics of the vapour phase synthesis of 2MP over alumina support Mn-ferrite (AMF) catalyst (2) to find a suitable rate law, which can explain the data satisfactorily, and (3) to predict a mechanism of the reaction. The catalyst has been characterized using IR, XRD, SEM, besides Surface Area measurement and Acidity measurement with the objective of understanding structure and nature of bonding over the catalyst surface.

In the present investigation of the kinetics of 2 MP synthesis over alumina supported catalyst, we have followed the usual procedure of calculation of partial pressure of reactants and rate of formation of 2-MP and subjected these data to different rate models based on surface reactions. From the derived rate equation, a tentative mechanism of the reaction has been suggested. An endeavour has also been made to support the present mechanism with the help of information to the author from literature.

II. Experimental

a) Catalyst Preparation

For preparation of alumina supported $MnFe_2O_4$, 16g of sized alumina (6/10 B.S.S. mesh size) was soaked in the dilute solution of manganese and iron salts (3.4 g of $MnCl_2.4H_2O$ and 4.3g of $Fe(NO_3)_3.9H_2O$ in 1 liter of water) for 3-4 hours. 1N NaOH was added to this system to allow precipitation of mixed hydroxides of the metals. The system was allowed to digest at 80°C for 4h. The catalyst was decanted and washed

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repeatedly with distilled water till free from chloride and nitrate ions. The material was oven dried and calcined at 500°C for 6h at atmospheric pressure to get alumina supported $MnFe_2O_4$ (AMF) catalyst.

b) Differential Reactor

In this reactor, only a small amount of catalyst is used so as to keep the conversion level low. This permits direct evaluation of reaction rates. Because of small contact time, the composition remains practically constant throughout the catalyst bed and rates obtained are initial rates. The initial rates obtained under these conditions are extremely helpful in simplifying rate equations. This technique is also helpful in dealing reactions with large heat effects.

The experimental set-up for kinetic measurement is similar to that described in chapter two. 0.1 g of catalyst was used for kinetic studies.

c) Experimental Procedure

The collection of data for kinetic studies of the vapour phase cyclization of ED and PG were collected at atmospheric pressure in a vertical, down flow, fixed bed reactor. The upper half of the reactor worked as pre-heater and the lower half as the reactor. The fresh catalyst was charged in the center of the reactor. Activation was attained by heating the catalyst in air at 773K for 4h and then cooling to the desired temperatures in a current of nitrogen and finally exposing to feed stream a mixture of ED, PG and water. Besides, functioning as a solvent, steam reduces the dealkylation of 2-MP to pyrazine, avoids charring, and reduces formation of aromatics. The liquid products were collected using a cold-water condenser. A blank run without any catalyst indicated negligible thermal conversion.

d) Identification and analysis of products

Before collecting data on a differential reactor few experiments were performed in a macro-reactor taking 10 g of catalysts and feeding ED, PG and water in the weight ratio of 1:1:2. About 50 ml of the product mixture was collected and was subjected to fractional distillation. The product boiling in the range 130-140°C was collected. A record of FT-IR spectrum of the distillate showed band in the region 2900-3200 cm^{-1}. Band appeared below 3000 cm^{-1} were assigned to C-H stretching modes of CH_3 group while those appeared above 3000 cm^{-1} were assigned to C-H stretching modes of ring hydrogen. There appeared medium to strong bands in the region 1000-1700 cm^{-1} characteristic of C-H / N-H bending modes and ring vibrations. These observations confirmed presence of 2-MP in the product. Further confirmation was made by comparing the FID retention time of 2-MP in the above mentioned distillate with that of standard 2-MP. Quantitative analysis was made on the basis of GLC peak area measurements. A Chemito model 7610 GLC machine was used for quantitative analysis. The analysis of product composition with differential reactor was made with GLC only.

e) Catalyst Characterization

The XRD records of alumina supported $MnFe_2O_4$ (AMF), $MnFe_2O_4$ (MF) were recorded over Rigaku X-ray powder diffractometer using Cu-K_α radiation as source are reproduced. The recordings confirm the crystallinity of the samples and appearance of most of the peaks of support as well as catalyst Cullity *at al*. [11] (Figure 1).

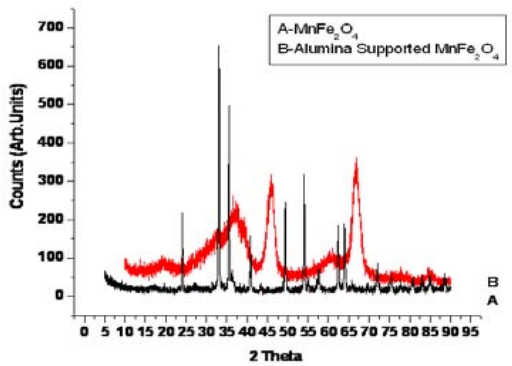

Figure 1 : X Ray Diffractogram of Mn Fe_2O_4 and Alumina supported $MnFe_2O_4$

Ammonia desorption experiments were carried out to measure the acidity of the catalyst using ammonia as an adsorbate. Detailed procedure is described elsewhere Cullity *at al.* [12] The BET surface areas were measured by N_2 adsorption at liquid N_2 temperature using BET surface area analyzer (Model SAA-2002, S.P.Consultant, Mumbai) and was found to be 206.6 $m^2 g^{-1}$. The FTIR spectrum of the alumina supported manganese ferrite catalyst was recorded on Perkin Elmer series 1600 FTIR spectrometer and are reproduced. Scanning electron microscopy (SEM) pictures were obtained using JEOL JSM-5600 instrument and are reproduced. (Figure 2 and 3).

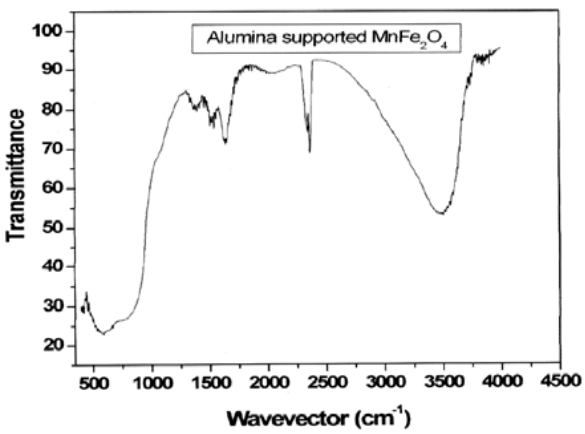

Figure 2 : FTIR Spectrum of Alumina supported $MnFe_2O_4$

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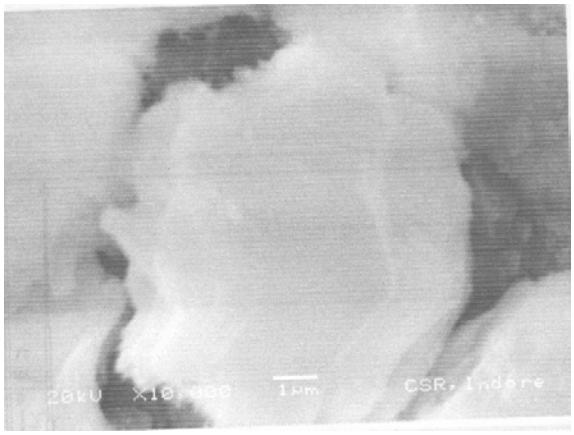

Figure 3 : SEM image of Alumina supported MnFeO4

III. Results and Discussion

a) Nomenclature

The reaction rates were calculated from the relation

$$R = F.\frac{Xp}{S}$$

Where F is the flow rate of reactants, Xp is the percent composition of particular product in the reaction mixture as obtained from GLC and S is the surface area of the catalyst.

P_p = partial pressure of propylene glycol

P_E = partial pressure of ethylene diamine

K_p = adsorption equilibrium constant for adsorption of propylene glycol

K_E = adsorption equilibrium constant of ethylene diamine

k = rate constant of the reaction

b) Effect of partial pressure of reactants on rates

All kinetic measurements were performed under low conversion (below 10 % conversion of PG). All measurements were taken after a study state condition was reached in the catalytic activity. Some standard experiments were performed from time to time to confirm that catalytic activity was constant and did not change with time. No reaction was observed at 350 °C in absence of catalyst even after several hours.

c) Effect of partial pressure of propylene glycol on rates

Effect of partial pressure of propylene glycol on rates was studied by varying the same while keeping the partial pressure of ethylene diamine constant. Total pressure was kept constant by introducing some amount of inert gas in the feed. The data thus obtained are presented at 473 K, 523 K and 573 K [Figure 4, Table 1].

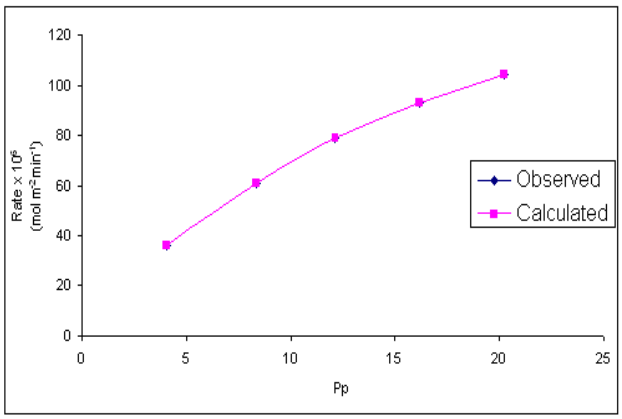

Figure 4 : Effect of Partial Pressure of Propyline Glycol (Pp) on rate of formation of 2 - MP Temp. 573 K

Table 1 : Effect of patial pressure of propylene glycol on rates

S.No.	Partial pressures of PG	Rate x 10^6 (moles s^{-1} m^{-2}) 473 K Observed	473 K Calculated	523 K Observed	523 K Calculated
1	4.05	2.11	2.11	17.70	17.70
2	8.10	3.60	3.60	29.38	29.38
3	12.15	4.72	4.72	37.67	37.67
4	16.21	5.58	5.58	43.86	43.86
5	20.26	6.23	6.23	48.65	48.65

Weight of catalyst : 0.1g, Partial pressure of ethylene diamine :9.11 kPa

None of the plots were linear between rate and partial pressure. All plots are bend towards pressure axis.

d) Effect of partial pressure of ethylene diamine on rates

Effect of variation of partial pressure of ethylene diamine on rates was studied at 473, 523 and 573 K under constant partial pressure of propylene glycol. The results are presented for the temperatures of 473 and 523. The graphical representation is shown for the temperature of 573 K .In this case also plots were not linear and bend towards pressure axis. (Figure 5 Table 2).

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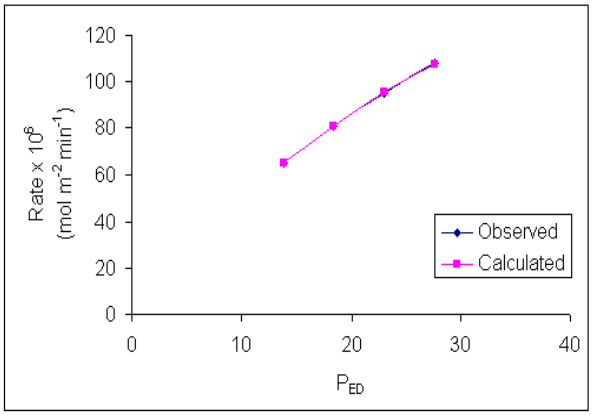

Figure 5 : Effect of Partial Pressure of Ethylene Diamine (P_{ED}) on rate of formation of 2 - MP Temp. 573 K

Table 2 : Effect of partial pressure of ethylene diamine on rates

S.No.	Partial pressures of ED	Rate x 10^6 (moles s^{-1} m^{-2}) 473 K		523 K	
		Observe	Calculated	Observed	Calculated
1	13.78	4.21	4.21	31.32	31.22
2	18.33	5.01	5.01	38.49	38.49
3	23.00	5.67	5.67	44.75	44.75
4	27.56	6.20	6.00	50.06	50.06

Weight of catalyst: 0.1g, Partial pressure of propylene glycol: 4.05 kPa

e) Effect of temperature on rates

Effect of temperature on rates is studied. Activation energy was calculated from arrhenius plot are shown. The rates increased with temperature. (Figure 6, Table 3).

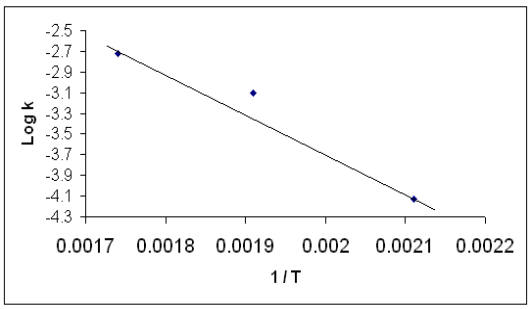

Figure 6 : Log k vs 1/T

Table 3 : Reaction rate constant and adsorption equilibrium constants

Temperature(K)	1/T	k	Log k	K_A	K_B
473	0.00211	0.000074	- 4.13	38.61	29.51
523	0.00191	0.00077	- 3.10	22.61	11.41
573	0.00174	0.0019	- 2.72	12.49	5.68

IV. Treatment of Rate Data

The activation energy was found to be 34.32 k cal. mol^{-1}. In the present study of the vapour phase kinetics of cyclization of propylene glycol and ethylene diamine to 2-methylpyrazine over alumina supported mangenese ferrite catalyst, we collected data under conditions that conversion was bellow 10 %. Rate data collected under this condition can be termed as initial rates. Besides we used only 0.1 g of catalyst so as to minimise mass transfer and diffusional effects. Since mass transfer from gas phase to the catalyst surface and diffusion through the catalyst bed were not rate controlling, the possibility of surface adsorption of reactants and surface reactions as rate controlling steps were left. We tested two most popular models applied for such cases namely Langmuir-Hinselwood model and Reidel model. The farmer assumes reaction between adsorbed PG and adsorbed ED, while the latter assumes reaction between an adsorbed reactant and another one remaining in gas phase. The rate laws derived on the basis of these two models are presented. (Table 4).

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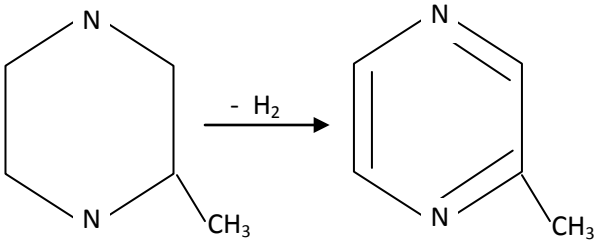
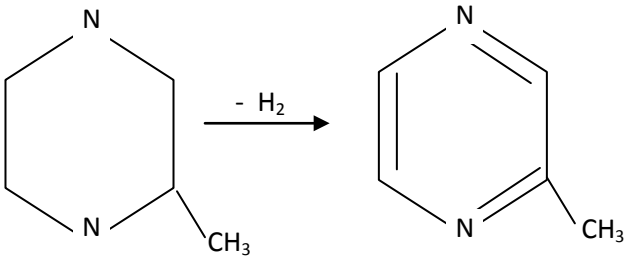
Table 4 : Models Tested for Cyclization of Propylene Glycol and Ethylenediamine

Model No.	Langmuir-Hinshelwood model	Resulting rate equation
1.	$CH_3\underset{\displaystyle OH}{\underset{|}{C}}H\text{-}CH_2\text{-}OH + S \rightarrow CH_3\text{-}\underset{\displaystyle OH}{\underset{|}{C}}H\text{-}CH_2OH\text{-}S$ $NH_2\text{-}CH_2\text{-}CH_2\text{-}NH_2 + S \rightarrow NH_2\text{-}CH_2\text{-}CH_2\text{-}NH_2\text{-}S$ $CH_3\underset{\displaystyle OH}{\underset{|}{C}}H\text{-}CH_2\text{-}OH\text{-}S + NH_2\text{-}CH_2\text{-}CH_2\text{-}NH_2\text{-}S \rightarrow$ 	$R=kK_PK_EP_PP_E/(1+K_pP_p+K_EP_E)^2$
2.	$CH_3\underset{\displaystyle OH}{\underset{|}{C}}H\text{-}CH_2OH + S \rightarrow CH_3\text{-}\underset{\displaystyle OH}{\underset{|}{C}}H\text{-}CH_2OH\text{-}S$ $CH_3\underset{\displaystyle OH}{\underset{|}{C}}H\text{-}CH_2\text{-}OH\text{-}S + NH_2\text{-}CH_2\text{-}CH_2\text{-}NH_2 \rightarrow$ 	$R= k\ K_P\ P_PP_E\ /\ 1+\ K_E\ (P_E)$

S = Surface, P_P = Partial pressure of Propylene Glycol, P_E = Partial pressure of Ethylene diamine, K = Equilibrium Constant, k = Rate Constant

As the rate constants are physical quantities their values can not be negative. An inspection of Table 4 reveals that positive constants are found only for Reidel model assuming one reactant adsorbed on the surface and another one remaining in gas phase. A plot of observed rates along with calculated rates obtained from reidel model are shown. (Figure 7).

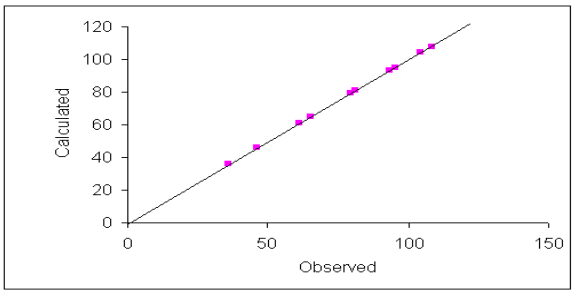


Figure 7 : Calculated Rates v/s Observed Rates

Reasonable agreement between observed rates and calculated rates confirm the validity of Reidel model. Further confirmation of the model was obtained by ploting observed rates vs calculated rates. The plot is found to be a straight line with an inclination of 45 degree passing through origin. This again confirms the validity of the model. A plot of observed rates vs. residuals is shown. The plot does not show any hetroscedic pattern (Figure 8).

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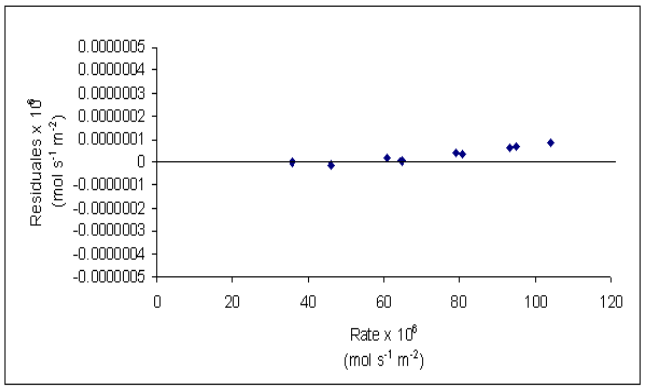

Figure 8 : Residuals v/s Calculated Rates

V. Mechanism of the Process

2-methyl pyrazine was found to be major product in the present study. Acetone was also detected in traces. When 2-methylpiperazine alone was passed over the catalyst in the reactor, 2-MP was found to be the only product. When PG alone was fed over the catalyst we obtained acetone as the major product. Passing hydrogen peroxide in the feed stream has no effect, indicating that free radical mechanism was not operative. Based on these observations, analysis of products and on the fact that kinetics follows a Reidel type of mechanism, an attempt is made here to predict a mechanism for the reaction.

Kulkarni et al [5] have proposed a mechanism for synthesis of 2-MP from PG and ED over ZSM –5 catalyst. According to these authors, PG is adsorbed over the catalyst, gets protonated, looses a molecules of water and is converted into carbonium ion. The carbonium ion looses a proton and produces propylene oxide. Propylene oxide can react with ED to produce 2-methyl piperazine, which is dehydrogenated to produce 2-methyl pyrazine. Although, this sounds well, it does not support the Reidel type of mechanism in which PG is adsorbed on the surface and reacts with ED present in Gas phase.

VI. Reaction Mechanism

The present catalyst contains both Lewis as well as Brönsted sites. While Lewis sites come from $MnFe_2O_4$, Brönsted sites come from hydroxyl group of alumina. It seems Lewis as well as Brönsted sites activate reaction of PG and ED. In case of Brönsted sites PG is adsorb first, gets protonated, looses a molecule of water and produces a carboniumion. The carbonium ion looses a proton and produces propylene oxide. Propylene oxide can react with ED to produce 2-methyl piperazine, which is dehydrogenated to produce 2-methyl pyrazine. In order to confirm this we passed 2-methylpiperazine alone over the catalyst in the reactor, and obtained 2-MP as the only product. Propylene oxide can also rearrange to produce acetone. In fact, when PG alone was fed over the catalyst we obtained acetone as the major product. This mechanism is consistent with the mechanism proposed by Kulkarni et.al [5] for synthesis of 2-MP from PG and ED over ZSM–5 catalyst. The mechanism over Brönsted sites is shown. Over Lewis acidic sites above type of mechanism is rather unlikely, because of (1) absence of, Brönsted sites (2) high possibility of ED over PG for adsorption over Lewis Sites (ED is stronger base then PG). However, because of much higher concentration of PG & H_2O over ED, it is possible that they displace few adsorbed ED molecules and produce Brönsted sites. Once such Brönsted sites are produced, the mechanism will follow the usual route of PG protonation, dehydration, formation of propylene oxide and reaction with ED to produce 2-methyl piperazine followed by its dehydrogenation to give 2-methyl pyrazine. This mechanism is consistent with the mechanism proposed by Forni and Paolo in their studies on TPD–TPR–MS Mechanistic study of the synthesis of 2-methylpyrazine over palladized Zn–Cr Oxide. The mechanism over Lewis sites is shown. When ED alone was fed over the catalyst ammonia and pyrazine were obtained. The mechanism of by products formation is shown. (Scheme 1 (a), (b) and (c)).

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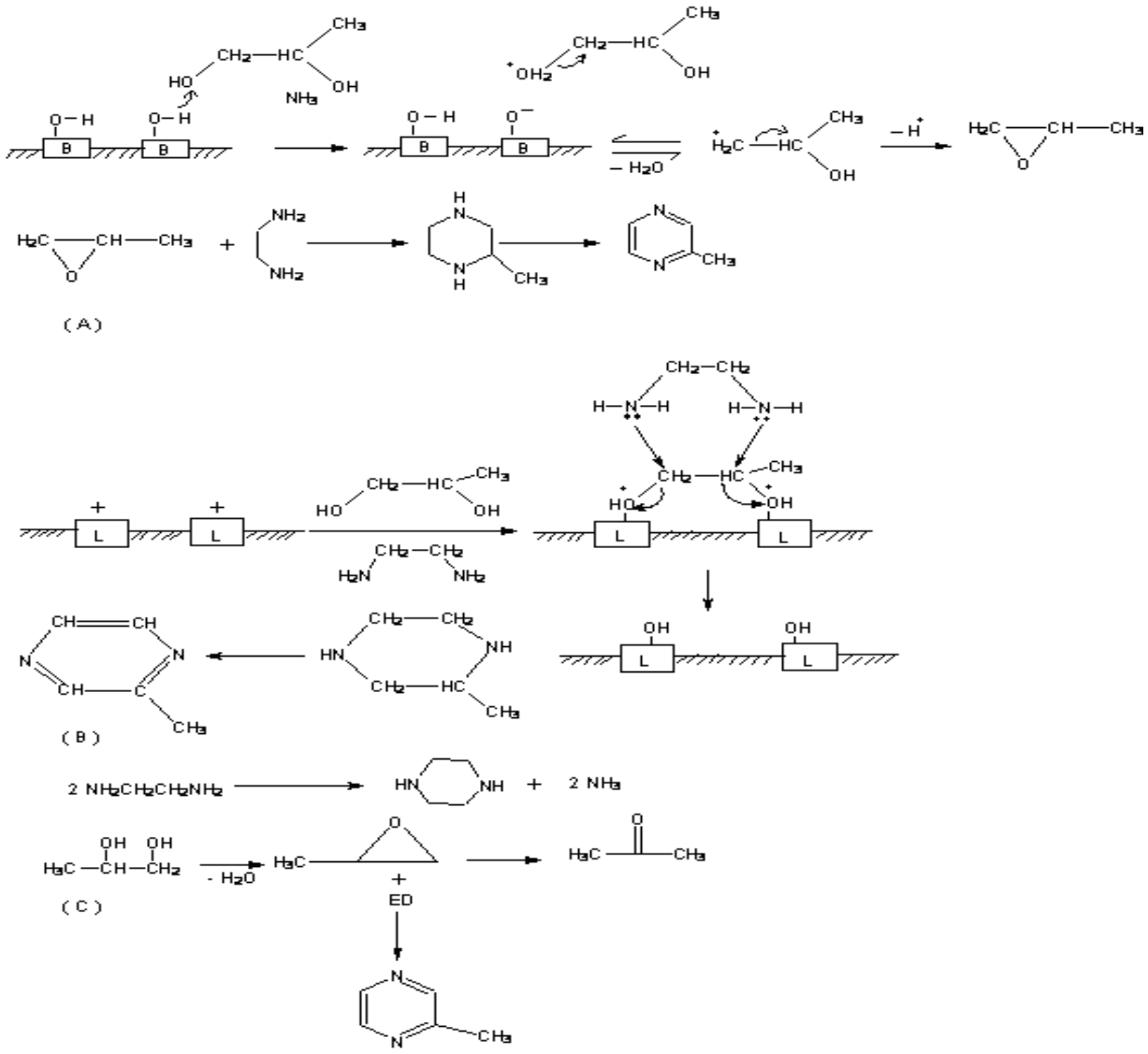

Scheme 1 : Reaction mechanism of vapour phase catalytic synthesis of 2-MP over alumina Supported manganese ferrite catalysts (a) bronsted sites (b) Lewis sites (c) formation of by products

VII. Acknowledgements

The Authors wish to express their appreciation to UGC-DAE-CSR, Indore for recording XRD, FTIR, and SEM measurements.

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Isolation and Characterization of a New Phytotoxic Molecule from Culture Fluids of Verticillium Dahliae

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Keywords : *verticillium dahliae, olive tree, new phototoxin, E and Z of cinnamyl acetate.*

GJSFR-B Classification : *FOR Code: 039999*



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I. Introduction

Phytotoxins are microbial metabolites which, at low concentration are harmful to plants. Many different fungi and bacteria are known to produce a wide range of metabolites in culture, which are toxic to plants. These include certain substance with varied biochemical structures, belonging to certain groups with height molecular weight such as quinines, polyketides, sterols, terpenoids, glycopeptides and glycoproteins (Mansoori and Smith, 2005; Buchner et al., 1987; Nachmias et al., 1982, 1987). Small molecules such as fusaric acid (Chawla and Wenzel 1987a; 1987b) eutypine and sterehirsutinal (Perrin-Cherioux et al., 2004) also have been described.

The most important disease of olive-tree growing in several Mediterranean Basin countries is Verticillium wilt (Zazzarini and Tosi, 1994; Cirulli et al., 1998; Tosi and Zazzarini, 1998; Vigouroux et al., 1975; Matallah et al., 1996; Saydam and Copu 1972; Ahmad et al., 1988), which is caused by Verticillium dahliae (Kleb). The later is a pathogenic agent of large variety of plants (Koike et al., 1995).

In Morocco, the disease was first observed in the region of Meknes (Serrhini, 1992). Since then, it has spread extensively in the main olive-growing belt of Morocco (Lachger and Sedra, 1996; Sedra, 2002). The very sensitive variety, "Picholine marocain", is widely cultivated, being approximately 98% of the total olive cultivation in Morocco and 5% of international cultivated territory of olive tree.

The difficulty of the verticillium dahliae control depends on the absence of host specificity and extreme pathogenicity's variability.

Most effective and economical means of reducing the disease impact are offered by varietal resistance. But, critical evaluation of olive trees and of segregating material for resistance to *V. dahliae* under field is time-consuming and expensive. In the same context, reports of the *in vitro* production of phytotoxins by *Verticillium* spp. (Green, 1954; Mc Lead, 1961; Malysheva and Zel'tser, 1968; Keen and Long, 1972; Cronshaw and Pegg, 1976; Nachmias *et al*., 1982), and their potential use as tools for rapid screening for resistance in different hosts (Michail and Can 1966; Irland and Leath, 1987) have been of great interest.

In this context, a toxic precipitate with acetone from the culture verticillium filtrate was obtained (Nachmias et al., 1982). This precipitate contains molecules with high molecular weight such as a protein-lipopolysaccharide toxin (Nachmias et al., 1985). The toxin with low molecular weight of this fungus had never been determined. The main objectives of this study were to show the presence of low molecular weight toxin in the filtrate after precipitation of all macromolecules by methanol. The filtrate was extracted with butanol and we have tested the toxicity of this fraction on stem cuttings of olive tree cultivar and compared with the toxicity of acetone precipitate obtained according to the method used by Nachmias in 1982.

II. Materials and Methods

a) Fungal Culture

V. dahliae (V10) was provided by the laboratory of INRA-Marrakech Phytopathology. A isolate kept in sterile sand was sown on PDA and incubated for 8 days at 25 ° C. Part of colony was suspended in sterile water. The Czapek medium (5 L) was made (for 1 L): 30 g of sucrose, 1 g of K2HPO4, 2 g of NaNO3, 0.5 g KCl, 0.5 g of MgSO4, 0.01 g of FeSO4. The pH was adjusted to 7 with NaOH and HCl. The medium was distributed as aliquots of 100 ml in 250 ml Erlenmeyer flasks which were then autoclaved at 121 ° C for 20 min. Each flask was inoculated with 1 ml of conidia suspension

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(10^6 conidia/ml) and incubated at room temperature (25 ° C) on a rotary shaker maintained at 80 rpm for 15 days. After centrifugation at 4200 g for 20 min and the supernatant was used for the butanol extraction. All chemicals and solvents were pure and were purchased from Sigma-Aldrich and Fluka.

b) Butanolic Extract (BE)

The obtained supernatant was evaporated under reduced pressure at 45 ° C to 250 ml. An equal volume of methanol was added and the mixture was kept for 48 hours at 4 ° C. The precipitate was filtered off and washed with methanol / water (1:1, v / v). The white precipitate was discarded, while the fractions resulting from filtrate and rinsing were mixed and evaporated under vacuum at 45 ° C to a volume of about 200 ml (F1). A glass column (3.5 x 60 cm) was filled with a mixture of 24 g of norite and 37.5 g of Celite homogenized in distilled water.

The concentrated fraction (F1, 200ml) was then passed through this column, and was washed with 100 ml of distilled water. The filtrates were collected (about 300 ml) and subjected to extraction with n-butanol (3 x 100 ml). The butanolic extract (BE) was evaporated to dryness, and gave 200mg of crude toxin (Figure 1). The later was subjected to purification by preparative TLC and analysed by GC-MS.

c) Acetone Precipitate (AP)

According to the procedure outlined by Nachmias et al. (1982, 1985), the crude toxin (AP) was obtained by precipitation with acetone from the in vitro culture of the V. Dahliae. A sterile Czapek liquid medium (100 ml) in Roux bottles was inoculated with 1 ml of conidia suspension (10^6conidia/ml) and incubated at room temperature (25°C) on a rotatory shaker maintained at 80 rpm for 15 days. The culture medium was centrifuged at 4200g for 20 mn, and the supernatant was concentrated under vacuum at 45°C in an evaporator. The concentrated fraction (one tenth of original volume) was dealt with four volumes of cold acetone (-18°C) and permitted to stand overnight at this temperature. The AP was collected by centrifugation at 10000g for 10 min at 5°C. The supernatant was discarded and the pellet was air dried and stored at 4°C.

d) Phytotoxin Bioassays

Stem cuttings were taken from the Picholine marocaine olive tree cultivar, which is susceptible to *V. dahliae* and represents about 98% of the cultivated varieties in Morocco. The bioassays were made according to the method described by Sedra (2002) and Amraoui (2005); the young stem were taken from olive tree susceptible to *verticillium dahliae* (Picholine marocaine), and then one stem was put in sterile glass test tubes, with the stem bases dipped in a *40 µg/ml* solution of the butanolic extract. The second assay was carried out in the same manner with the acetone precipitate (AP) at *50µg/ml as a positive control*. The tubes were kept at 25-27 °C in a growth chamber and were exposed to a 12 h photoperiodicity.

The tests were triplicated. The cuttings were rated after a 10 days period. Thereafter, appearance of symptoms of *Verticillium* wilt were observed: brown leaves, leaf necrosis, wilted stem with chlorosis, necrosis and leaf curl.

e) Preparative TLC and GC-MS Analysis of BE Fraction

A sample of the BE extract was purified on a silica gel TLC preparative plate (Kiesegel, 60 F 254) with a mixture of CH_2Cl_2/MeOH (9.5:0.5, v/v) as eluent. The silica gel band revelled with UV at 254 nm (Rf = 0.95) was scratched and the obtained powder was washed with methanol. The filtrate was analysed by gas chromatography on a Varian 3800 analyzer fitted with a fused silica capillary column BP5 (0.25 mm id, 25 m, 0.25 µm coating thickness), directly coupled to a Saturn 2000 MSD mass spectrometer. The GC/MSD was operated under the following conditions: injector temperature 220°C; transfer line 240°C; oven temperature programmed from 60 °C to 240 °C (3°C/min); carrier gas He at 1.0 ml/min; injection 0.1µl.

Compound identification was done by GC coupled to MS and a computer system that managed a library of mass spectra NIST (National Institute of Standards and Technology).

III. Results

a) Stem Cutting Assays

In susceptible reactions, cuttings displayed *Verticillium* wilt-like symptoms after uptake of the AP (acetone precipitate) and B.E (butanolic extract). The high toxicity of AP was obtained at 50 µg/ml, with 80% of mortality. The same toxicity symptoms observed with butanolic extract at 40 µg/ml with 80% of mortality (figure 2).

Leaves first became chlorotic, then developed necrosis that usually began at the margins of leaflets and progressed inward. Leaflets often curled inward or twisted around the midvein as they became necrotic and dried. Sometimes, leaflets or entire petioles abscised while the stem remained green and upright, and new green leaves emerged. The earliest symptoms were observed 5 days after treatment, and severe symptoms developed after 10 days. In contrast, no symptoms were observed on controls with water. These observations provide the first evidence that the butanolic extract is a toxic fraction composed with new phytotoxic compound present in the *Verticillium. dahliae* culture medium.

b) Extraction and Identification of the Natural Toxin

The purification of BE using the preparative TLC, according the method used by Akor and Anjori (2009), gave two major bonds (Rf = 0.95 and Rf=0.96

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after migration using 95/5 methylene chloride/methanol as solvent). These compounds were analysed by GC-Mass spectroscopy according to the method used by Imelouane (2009) for identification of essential oil of *Lavadula dentata* and thyme (*Thymis vilgaris*) from Eastern Morocco. The figure 3 shows the chromatographic profiles. The identification of these two compounds was based on the mass spectrum and confirmed by the data from library of mass spectra NIST (National Institute of Standards and Technology), and were assigned as: two isomers E and Z of cinnamyl acetate ($C_{10}H_{12}O_2$) with an abundance of 70% and 30% respectively (figure 4).

IV. Discussion

The BE have potential for use to induce symptoms of *verticillium dahliae*. Both the stem cutting assay could be reduce the time required for a selection compared with the currently used root-soak method.

Studies of metabolite production by *Verticillium albo-atrum* and *Verticillium dahliae* showed that they both produce high molecular weight toxic substances in liquid culture media (Nachmias *et al*., 1982, 1985, 1987; Riaan *et al*., 1994; Clovis *et al.,* 2006). Some of these toxins, are peptidic nature, were purified from culture fluids of potato isolates of *Verticillium dahliae* (Buchner *et al*., 1989), and induced interveinal chlorosis, followed by necrosis, when injected into excised leaves from disease-susceptible potatoes. In the present work, we showed that *Verticillium dahliae*, which is a plant pathogenic agent, is capable of producing a toxin that can able to induce the characteristic symptom of *verticillium dahliae* disease. Moreover, BE showed to be more toxic than either the AP fraction. The BE induced severe symptoms more rapidly. The purification of BE using the preparative TLC gave two major compounds which were analysed by GC-Mass spectroscopy and were assigned as two isomers E and Z of cinnamyl acetate ($C_{10}H_{12}O_2$) with an abundance of 70% and 30% respectively.

In our laboratory we have synthesised the major product, E-cinnamyl acetate (laouane 2011). This product was used in a screening program and we showed that 'Picholine Languedoc' has developed a susceptibility to the phytotoxin at 20 µg/mL, moreover, the same symptoms were obtained only at 10 µg/mL for 'Picholine Marocaine'.

This result suggests that the *verticillium dahliae* produces low molecular weight toxic substances in liquid culture. In addition, the stem cutting assay could provide an additional tool for screening plants for resistance to *verticillium dahliae*.

Susceptible olive tree (picholine marocaine) cutting treated with BE developed typical symptoms for *Verticillium Dahliae*-infected olive tree in the field (Lachger and Sedra, 1996, Serhini, 1992). This result supports that the BE is producing the same symptoms as those produced by fungal inoculation. Others host plants showed similar symptoms (Clovis S *et al* , 2006; Nachmias *et al.,* 1987; Scheffer, R. P., 1976; Irland, K. F. and K. T. Leath, 1987) when treated with toxins and fungal filtrate.

V. Conclusion

In the present study we described for the first time a protocol for the extraction and the determination of the structure of a new phytotoxin produced by a strain of Verticillium Dahliae which is pathogenic on olive tree. We have provided evidence that the butanolic fraction play a role in the development of the Verticillium wilt disease symptoms in susceptible olive tree more rapidily. The butanolic fraction showed the presence of two isomers: E-cinnamyl acetate (major product, VdT) and Z-cinnamyl acetate (minor product). The toxicity of E-cinnamyl acetate (major product, VdT) was confirmed on steam cutting olive tree.

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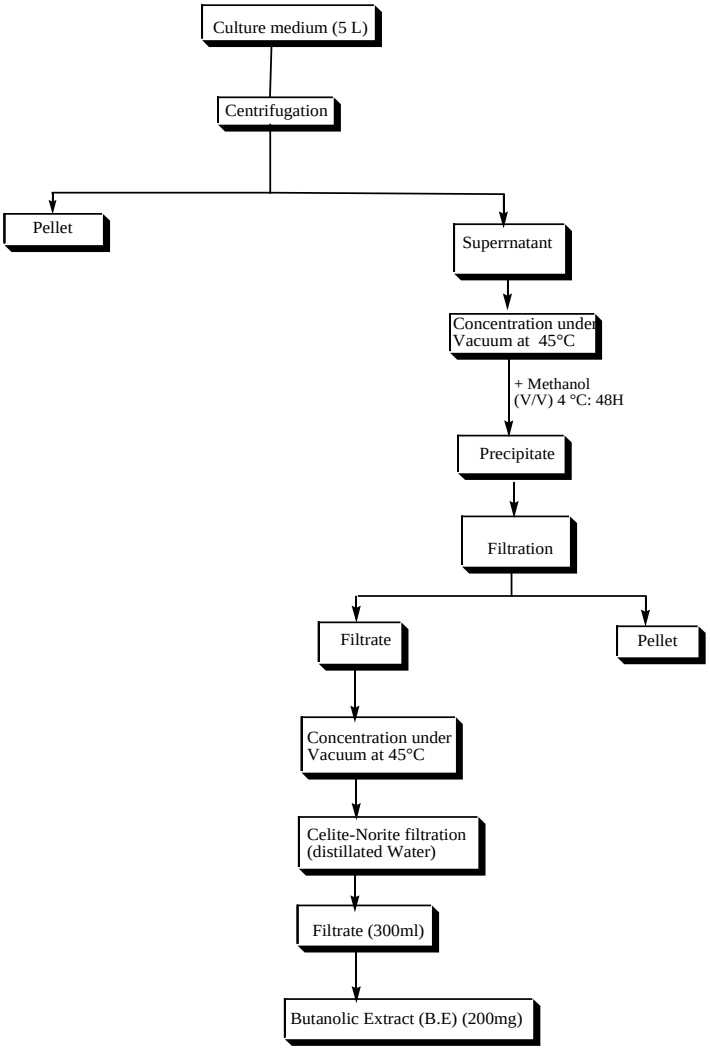

Figure1 : Protocol of phytotoxin extraction



Figure 2 : Appearance of cuttings of the susceptible olive variety (Picholine marocaine) 10 days after treatment with: BE, AP and control

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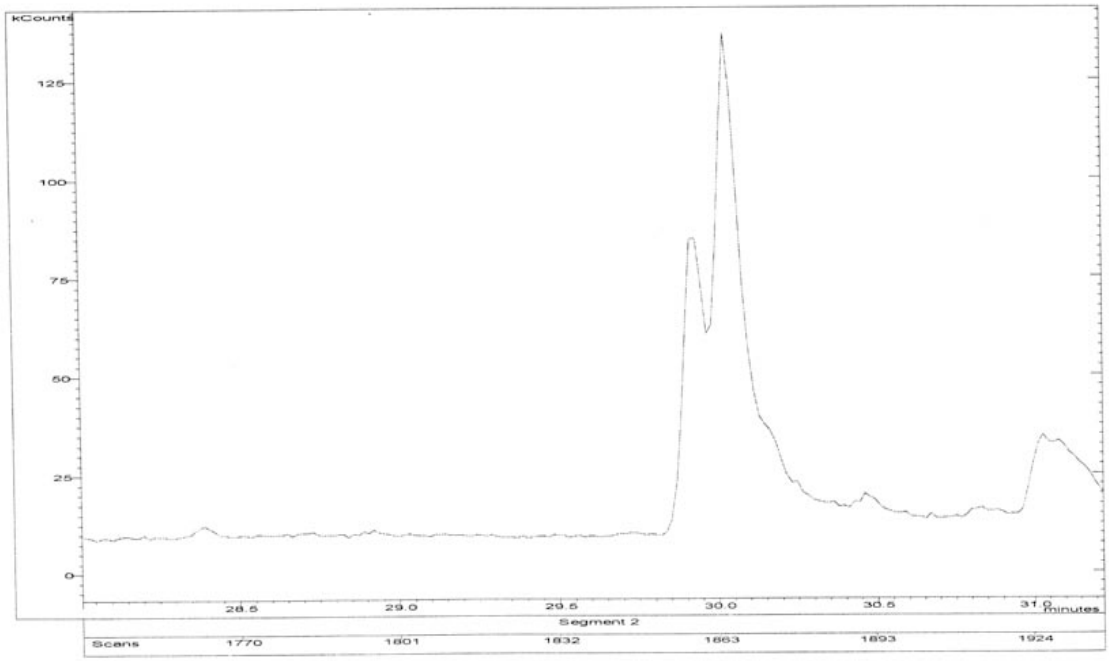

Figure 3 : chromatogram of two isomers compound extracted from *Verticillium dahliae* culture

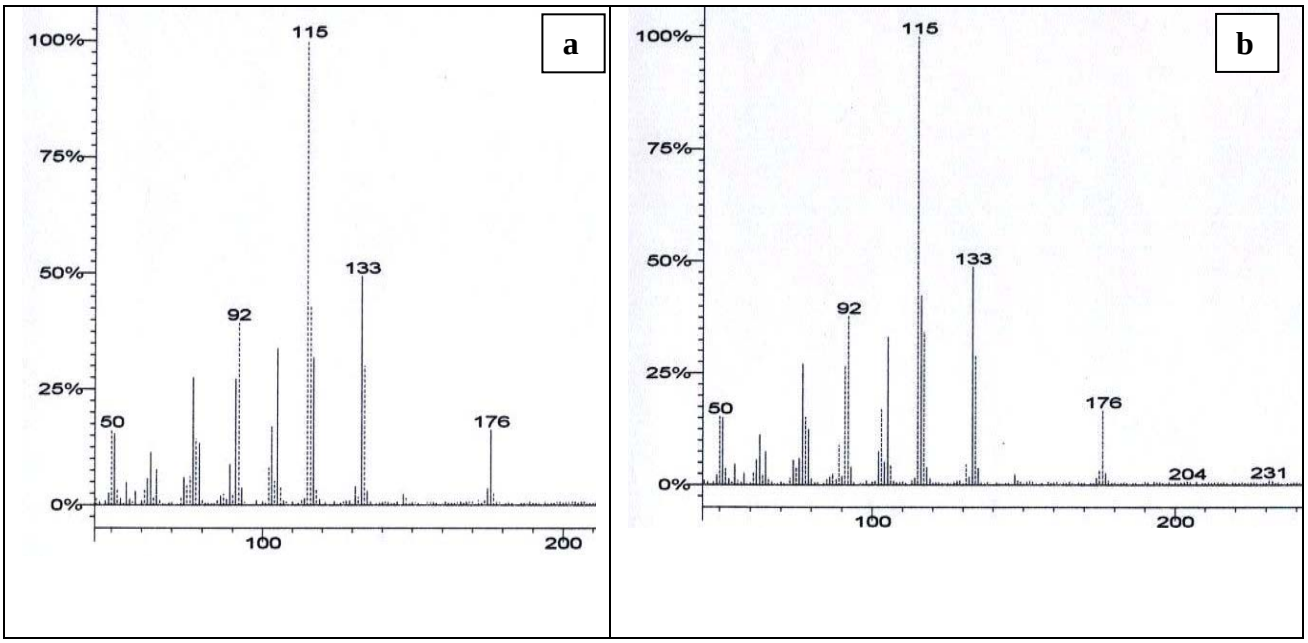

Figure 4 : **a)** Mass Spectrum of the first isomer, **b)** Mass Spectrum of the second isomer

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Methylation of Aniline over Mn-Cu Ferrites Catalysts

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Abstract- The structural and catalytic properties of the mixed spinel ferrite system $Mn_{1-x}Cu_xFe_2O_4$ (x=0, 0.25, 0.5,0.75, 1.0) have been investigated by X-Ray diffraction, Mössbauer and catalytic activity measurements. The variation of lattice parameter, crystallite size, and Mössbauer parameters of the product formed with the variation in the concentration of Cu has been studied. XRD Study revealed the formation of phase pure spinels with FCC cubic structure with particle size ranging from 5.21 nm to 20 nm. Lattice constant values showed constant decrease with increasing concentration. Mössbauer spectra showed the presence of Fe^{3+} at both octahedral and tetrahedral sites. These ferrites were used as catalysts in the alkylation of Aniline. A maximum conversion of 80.5 % of aniline with selectivity of 98.6 % towards N-methylaniline (NMA) has been obtained at a temperature 673 K, Methanol : Aniline molar ratio of 5:1 and weight hour space velocity (WHSV) of 0.2 h-1. It was found that the yield is maximum for $CuFe_2O_4$. The result is supported by acidity measurements.

Keywords: mn-cu ferrites; ferrospinel; methylation; aniline; cubic structure.

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METHYLATION OF ANILINE OVER MN-CU FERRITES CATALYSTS

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Methylation of Aniline over Mn-Cu Ferrites Catalysts

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Abstract- The structural and catalytic properties of the mixed spinel ferrite system $Mn_{1-x}Cu_xFe_2O_4$ (x=0, 0.25, 0.5,0.75, 1.0) have been investigated by X-Ray diffraction, Mössbauer and catalytic activity measurements. The variation of lattice parameter, crystallite size, and Mössbauer parameters of the product formed with the variation in the concentration of Cu has been studied. XRD Study revealed the formation of phase pure spinels with FCC cubic structure with particle size ranging from 5.21 nm to 20 nm. Lattice constant values showed constant decrease with increasing concentration. Mössbauer spectra showed the presence of Fe^{3+} at both octahedral and tetrahedral sites. These ferrites were used as catalysts in the alkylation of Aniline. A maximum conversion of 80.5 % of aniline with selectivity of 98.6 % towards N-methylaniline (NMA) has been obtained at a temperature 673 K, Methanol : Aniline molar ratio of 5:1 and weight hour space velocity (WHSV) of 0.2 h-1. It was found that the yield is maximum for $CuFe_2O_4$. The result is supported by acidity measurements.

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I. Introduction

Alkyl anilines are valuable intermediates for the manufacture of pharmaceuticals, drugs, dyes and agrochemicals. These compounds may be prepared by catalytic alkylation of aniline with various alkylating reagents: There are reports on alkylation of aniline in liquid phase under pressure[1], in vapour phase using oxides[2], Raney-Nickel[3], zeolites[4], AEL type molecular sieves[5], clays[6-10] and few spinels[11-14].

The unusual properties exhibited by nanoparticle and their promising technological applications have attracted much interest in recent years. [15]. There particles are shown to posses low saturation magnetization, Ms, enhance coercivity, H_c, and higher curie temperature, T_c, as compared to bulk materials, [16-21]. This phenomenon have been ascribed to random canting of surface spins [22], pinning of spins at particles surface or presence of a dead layer around magnetic core materials [23] and interparticle interactions [24]. It has been shown that certain ferrites with nanosized particles, posses metastable state and the cation distribution is different from that of bulk ferrites, where divalent metal occupies only tetrahedral, A, site and Fe^{+3} occupies only octahedral, B, site. In addition to these physical effects, nanoparticle ferrites are found to be excellent catalyst of alkylation and cyclization reactions with very high conversion and selectivity. The high performances of ferrite cata1yst have been attributed to cations distribution of different particles size, lattice parameters and acido-basic characters of ferrite catalyst. To the best of our know1edge, there is no report on the methylation of aniline over copper-manganese ferrites (Cu-Mn ferrite). The present problem of the methylation of aniline over Cu-Mn ferrites was there fore undertaken with a view to optimize the Cu-Mn-Fe composition and process conditions over the catalyst for maximum conversion of aniline. Besides these, catalysts have been characterized by XRD and Mössbauer spectroscopy, BET surface area and acidity measurements. The cation distribution obtained from Mössbauer study has been used to explain acidity and cata1ytic activity of the catalysts.

II. Experimental

a) Preparation of the Sample

Nanoparticle of $Cu_{1-x}Mn_x Fe_2O_4$ (x = 0, 0.25, 0.5, 0.75, 1.0) were prepared by co- precipitation method. Required quantities of $MnCl_2$, Fe $(NO_3)_3.9H_2O$ and $Cu(NO)_3.3H_2O$ were dissolved in excess of distilled water. The pH of the solution was adjusted to 9 with dilute solution of NaOH. Excess of water fast stirring and slow addition of NaOH solution are must for getting small size particles. The resulting mixture was heated at a temperature of 333 K along with stirring for one hour. Then, it was kept for settling in the heating mode at 333 K for half an hour for digestion. The product was washed by repeated decantation with 1.5 dm^3 portions of water until the supernatant is free of Cl^- (about 10-15 washings was required). The precipitate was filtered through Buchner funnel, dried in oven at 393 K and calcined at 673 K. The material was sieved through a 6/10 mesh sieve. After sieving the bigger size clusters were kept for acidity and catalytic activity evaluation while smaller size clusters obtained after sieving, were ground into fine powders and were used fur XRD and Mössbauer experiment.

b) Characterization of Samples

X-Ray diffraction pattern were recorded using Cu - K_α radiation (angle range 20° to 65°) as the source

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on a Rigaku X-Ray diffractometer. Diffraction patterns show the sharp lines corresponding to single-phase spinel for the samples as the entire peaks match well with the characteristic reflections of the corresponding ferrite. The average particle size was measured by broadening of the (311) peak and applying Debye - Scherer equation. Lattice cell parameters were also calculated using Bragg's equation.

c) Mössbauer Measurements

Samples were crushed to obtain fine powder in order to observe Mössbauer spectra. The Mössbauer absorber was prepared by spreading the paste of powdered sample and vacuum grease over perplex glass that is used as the sample holder. The absorption spectra were recorded in transmission geometry at room temperature with constant acceleration Mössbauer drive along with a 256 multichannel analyzer, using Austin Science Inc, USA Mössbauer. A single line source ^{57}Fe(Rh) with initial activity of 10 mCi was used. Several runs were taken in order to check the reproducibility of the spectra. Total counts collected were about 10^6 or more. The Mössbauer spectrometer was calibrated using a 0.001 inch enriched α-Fe foil. The outer lines are separated through 10.68 mm/s. This is an excellent agreement with an ideal absorption spectrum and calibration was done accordingly. The experimental data were computer fitted using the least square-fitting program assuming Lorentzian line shape with χ^2 minimization technique. The solid line through the data points is the result of the computer fit of the data.

d) Acidity Measurement

Acidity measurement were performed by ammonia desorption method. This experiment was carried out in order to measure the acidity of the ferrite catalyst using ammonia as an adsorbate. 1 g of the catalyst was packed in between two plugs of glass wool in a Pyrex tube down flow fixed bed reactor and heated to 773 K under a nitrogen gas flow rate of 0.5 cm^3/s for 1.5 hour. The reactor wag coo1ed to room temperature and adsorption was conducted at this temperature during which the sample was exposed to ammonia for 1.5 hours. In order to remove physically adsorbed ammonia from the purged sample again nitrogen gas was allowed to pass through it at the rate of 0.5 $cm^3\ h^{-1}$as the same rate at 353 K for 1 hour. The acid strength distribution was obtained raising the catalyst temperature from 353 K -773 K during the flow of nitrogen gas and absorbing the evolved ammonia in distilled water containing phenolphthalein as an indicator. Titrating the water solution with standard 0.1 M HCl solution in different temperature ranges lead to quantitative estimation.

e) Catalytic Activity

The alkylation unit consists of three parts i.e. feed system, reactor and product recovery unit. The reactor was charged with a known weight (5g) of catalyst and was clamped in the assembly holder. The tubular heater was also clamped in the stand. The reactor was then joined to the product recovery unit and syringe pump filled with known volume of reactant mixture. The catalyst was activated at 773 K by passing air and then brought down to desired temperature by cooling down in the current of N_2. The mixture of reactant was fed by a 10 ml syringe pump. The liquid product was condensed with the help of cold-water condenser, a cold trap and was analyzed by shimadzu gas chromatography using SE-30 column and FID detector.

III. Results and Discussion

a) XRD analysis

XRD patterns shown in Fig 3.1 reveals the formation of spinel phase of ferrite as all the composition showed the characteristic reflection of the spine1 phase. All the peaks of $MnFe_2O_4$ and $CuFe_2O_4$ matched well with those as reported for the same in JCPDS Card No.10-319; 3-864. The reflections at the planes (111), (220), (311), (222), (400), (422), (511), (440) can be detected with d values of 4.89, 2.97, 2.53, 2.42, 2.08, 1.71, 1.61, 1.49 respectively. Accordingly the lattice cell parameters were also calculated that matched well with the values as reported in the JCPDS card numbers given above. Lattice cell parameter shows a linear decrease from 8.49 A^0 to 8.39 A^0 with the introduction of Cu in $MnFe_2O_4$ as could be seen clearly from the fig 3.2 and may be attributed to the replacement of Mn^{2+} (0.80 A) by smaller Cu^{+2} (0.69 A). This also confirms the formation of solid solution. The mean crystallite size was calculated by broadening of the (311) diffraction peak and applying Scherer formula and the range is in between 7.2 nm - 20 nm. Surface area was also estimated from the crystallite size data assuming the crystallites to be of spherical shapes. They depend on the size of the particle as is clear from the reported values in Table 3.1. The average particle size and lattice cell parameter for the above mixed ferrite nanoparticles are also reported in Table 1.

b) Mössbauer

Mössbauer absorption spectra for the samp1es i.e. x = 0, 0.5, 1.0 were recorded at room temperature as shown in Fig. 3. The spectra were fitted using NORMOS fitting program and hyperfine parameters e.g. isomer shift δ, quadrupole splitting, Δ, line width, Γ, and hyperfine field, H_{int}, thus obtained are listed in Table 3.2. The Mössbauer spectra exhibit broad magnetic hyperfine sp1it sextets. In case of $MnFe_2O_4$ an additional doublet is seen which can be attributed to super paramagnetic behavior exhibited by smaller size

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particles. The doublet was fitted with two sub spectra . The isomer shift was found to be 0.24-0.27 mm/s which can be attributed to Fe^{3+} ions in tetrahedral and octahedral sites. The sextets were fitted with two sub spectra. One sextet is due to Fe^{3+} ion at the tetrahedral A site and the outer sextet is due to Fe^{3+} at the octahedra1 B sites, which indicates the ferrimagnetic behavior of the samp1es. All of them shows isomer shift values in the range 0.22 mm/s to 0.34 mm/s, which could be attributed to the Fe^{3+} ions present at both the A and B sites of the spinel structure. This indicates that Mn^{2+} is also distributed between tetrahedral site and octahedral site. Similar metastable structure has been proposed by Rath et al [25] in nanocrystalline Mn ferrite. However, the case is different in bulk ferrites where Mn^{2+} prefers tetrahedral site while Fe^{3+} prefers octahedral site.

Distribution of Mn^{2+} on both the sites has also been reported for $MnFe_2O_4$ nanoparticles by Mahmoud et al. [26]. On addition of Cu^{2+} which can occupy both the sites but prefers the octahedral site, slight broadening of the line width and reduction in the intensity of the central lines is observed. These results agree with those reported earlier in the literature. The tetrahedral and octahedral positions of iron in the ferrospinels could a1so be distinguished on the basis of Magnetic hyperfine field, MHF. It has been mentioned that the internal MHF field experienced at A sites is smaller than that exerted at B sites: Usually, contribution of Fe^{2+} to the hyperfine field is significantly smaller than that of Fe^{3+} i.e. ferric ions. Also the isomer shift values for ions located at the tetrahedral site are generally smaller than those at octahedral site. It has also been reported that Fe^{3+} ions are at A site while Fe^{3+}/ Fe^{2+} both can reside at B site alternately. The observed isomer shift value confirms the presence of Fe^{3+} ions at both the sites while no Fe^{2+} is present in any of the composition. The intensity ratio A and B sites gives the ratio of the number of Fe atoms at A and B sites respectively. Quadrupole splitting has value near by zero for both the sites. As in the presence of strong magnetic interaction, the distribution of quadrupole interaction that arises from chemical disorder, produces an appreciable broadening of the individual Zeeman lines for both tetrahedral and octahedral patterns, but doesn't produces an observable quadrupole line shifts. Data extracted from the fits are reported in table 2.

c) Effect of acidity and process variable

The performance of various Mn-Cu ferrite catalysts along with their acidity, XRD surface area, particle size, and lattice constants is presented in Table 3.1. It can be seen that conversion of aniline as well as acidity of different catalysts increase with increase in copper content of the ferrites. Similar trend can be seen for surface area. The increase XRD surface is due to decrease in particle size of the sample with increase in Cu content. Consistency in lattice parameters of all the ferrites confirms them to possess same lattice type as concluded in section.

The order of catalytic activity of ferrospinels towards overall conversion was found to be CF> MCF-3>MCF-2>MCF-l>MF. It can be concluded from these resu1ts that. catalytic performance of the ferrites under consideration is proportional to surface area as well as acidity. An examination of the acidity reveals CF to be the better catalyst as its acidity value is larger and it also increases with increasing x as is clear from the reported values in Table 3.1. It also shows CF to be the better catalyst, as its aniline conversion (%) is larger.

The effect of methanol to aniline mo1ar ratio on the performance of copper ferrite is depicted in Figure 3.4. The conversion increases at lower molar ratio and tends towards limiting conversion at higher molar ratio, Maximum conversion of 82 % of aniline was obtained at methanol to aniline mo1ar ratio of 5 with NMA selectivity of 80 %.

The temperature effect on alkylation for MF at constant molar ratio was also studied in the temp range 473-773 K and resu1ts are presented in Table 3.5. Negligible conversion can be seen below 473 K whi1e the conversion effectively occurs in the range 673 K - 700 K. The best performance by the catalyst was shown at temperature 673 K with conversion of 62 and 15 % for N-methyl aniline and N-N-dimethyl aniline respectively, and selectivity of 79 and 62 % for NMA and NNDMA respectively. Conversions decreased due to charring and deposition of carbon on the catalyst surface at temperature higher than 673 K.

IV. Conclusion

$Mn_{l-x}Cu_xFe_xO_4$ (x = 0., 0.25 0.5 0.75 1.0) mixed ferrite nanopartic1es were obtained in a broad range of Cu concentration 0.0 < x <1.0 by coprecipitation and digestion method. Room temperature Mössbauer spectra of these fine partic1es exhibit slightly high va1ue of hyperfine field and broadening of the zeeman spectral lines shows strong ferromagnetic behavior of the three compositions. The occupancy ratio between Fe cation at A and B sites of the spinel structured is deduced from the fitted data of the Mössbauer spectra.

These mixed ferrite spinel systems were also studied for the alkylation of aniline using methanol as the alkylating agent. These systems effectively alkyl ate aniline to N-methyl aniline and N-N-dimethyl aniline under optimized reaction condition. Highest activity is obtained for CF whereas MF and MCF-1 were mildly activated. Substitution of Cu in MF leads to the increase in va1ue of acidity and the aniline conversion. This behavior suggests for Mn-Cu mixed ferrite system to be a good catalyst.

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V. Acknowledgements

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Table 1 : Particle size, Lattice parameter, acidity and catalytic activity of Mn_{1-x} $Cu_xFe_2O_4$ catalyst. Temperature = 673 K, Mole ratio = 5.0

Composition	Aniline conversion	Particle Size (nm)	XRD Surface area (m^2/g)	Lattice parameter (A^0)	Acidity (m mole/g)
MF	28	13.9	86.16	8.49	1.2
MCF-1	32.2	20.9	56.15	8.45	1.2
MCF-2	40.4	14.6	78.67	8.43	1.3
MCF-3	58.0	13.9	81.29	8.40	1.4
CF	80.5	7.2	155	8.39	1.5

Table 2 : Mössbauer parameters extracted from the fitting for the composition $Mn_{1-x}Cu_xFe_2O_4$. Where I.S-Isomer shift, Q.S- Quadrupole splitting, MHF- Magnetic hyperfine field, H.L. W-half line width, RI -Relative intensity for A and B sites

Composition		Site	I.S (±0.03 mm/s)	Q.S (±0.02 mm/s)	MHF (± I T)	H.L.W. (± 0.01)	RI (%)
$MnFe_2O_4$	[D]	A	0.27	1.07	-	0.48	12.50
	[D]	B	0.24	0.82	-	0.36	12.50
	[S]	A	0.38	-0.212	50.12	0.47	37.50
	[S]	B	0.14	-0.12	50.00	0.41	37.50
$Mn_{0.5}Cu_{0.5}Fe_2O_4$	[D]	A	0.25	0.015	47.77	0.68	38
	[S]	B	0.32	-0.22	51.90	0.45	62
$Cu_{0.5}Fe_2O_4$	[S]	A	0.22	-0.04	48.15	0.71	45
	[S]	B	0.29	-0.1	51.14	0.67	55

Table 3 : Performance of various catalysts in the alkylation of aniline. Methanol/Aniline molar ratio = 5; Temperature = 673 K, WHSV = 0.2 h^{-1}.

Catalyst (%)	Aniline Conversion (%)	Product distribution		
		Aniline	NMA	NNDMA
MF	28.0	70.0	21.8	8.2
MCF-1	32.2	65.2	27.6	7.8
MCF-2	40.4	62.4	34.0	3.6
MCF-3	58.0	50.6	47.4	2.0
CF	80.5	19.4	79.4	1.2

Table 4 : Effect of mole ratio (Methanol to Aniline) on alkylation of Aniline Temperature = 673 K, WHSV = 0.2 h^{-1}, Catalyst = $CuFe_2O_4$

Mole ratio	Aniline Conversion (%)	NMA (yield)	NNDMA (yield)	NMA (Selectivity)	NNDMA (Selectivity)
2.5	64.2	20.6	10.0	67.3	32.7
5.0	82	61.2	15.3	80.0	20.0
7.5	79.2	63.6	8.2	88.5	11.5
1.0	73.4	71.2	5.2	93.2	6.8

Table 5 : Effect of temperature on alkylation of Aniline Methanol/aniline molar ratio = 5, WHSV = 0.2h^{-1}, Catalyst = $CuFe_2O_4$

Temperature	Aniline Conversion (%)	Product distribution (%)			
		Aniline	NMA	NNDMA	Others
473	06.0	96.0	-	-	4.0
573	38.2	51.2	20.8	22.0	6.0
673	80.1	23.2	62.4	14.4	-
773	42.8	39.8	42.2	18.0	-

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Figure Captions

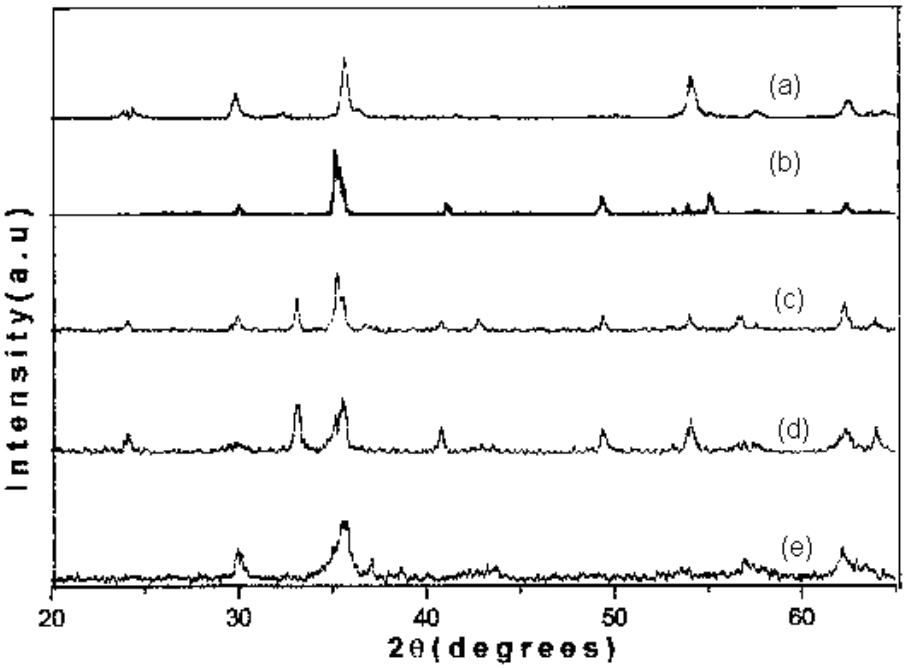

Figure 1 : XRD Pattern of Mn-Cu Ferrites

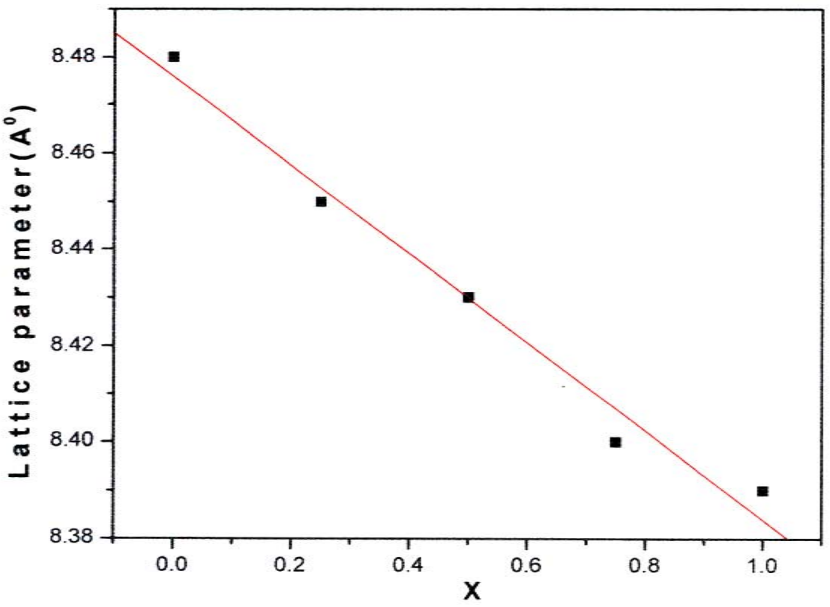

Figure 2 : Change in lattice parameter due to induction of Cu in Mn-ferrite

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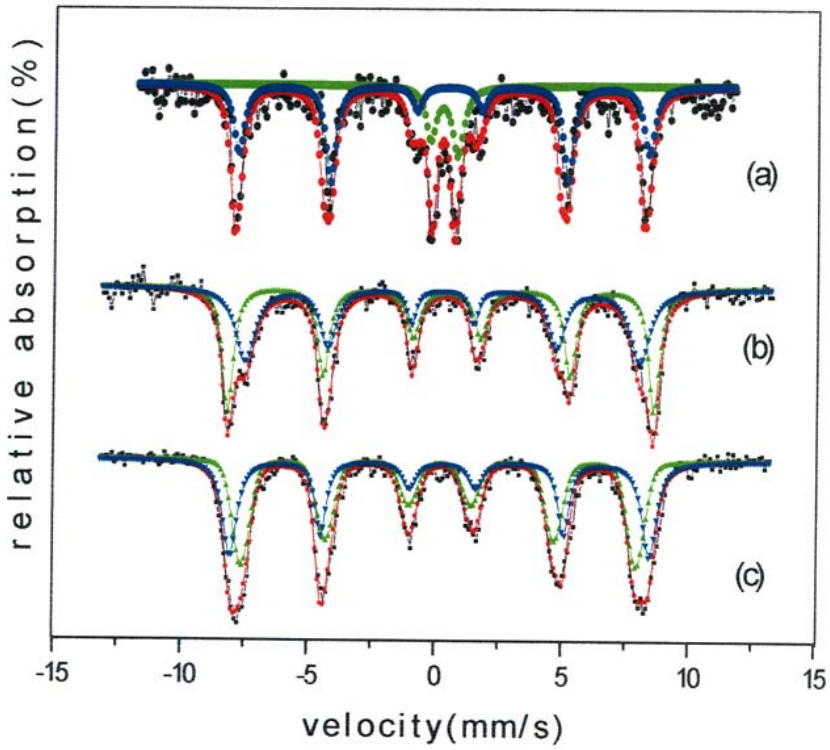

Figure 3 : Mössbauer Spetra of Samples

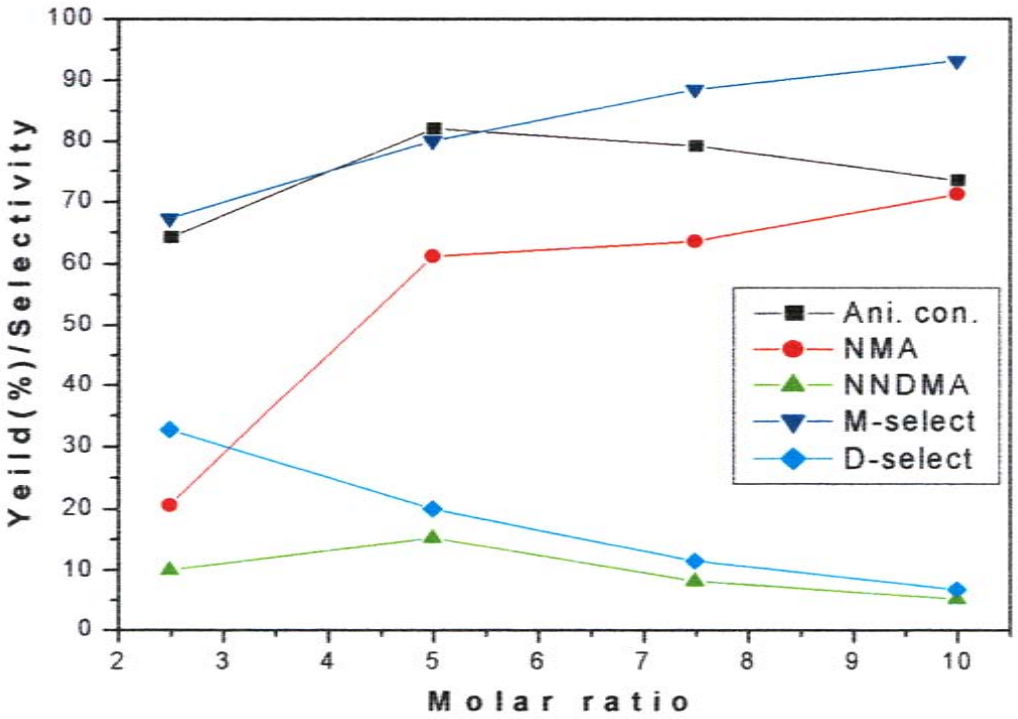

Figure 4 : Effect of molar ratio (methanol to aniline) on product selectivity

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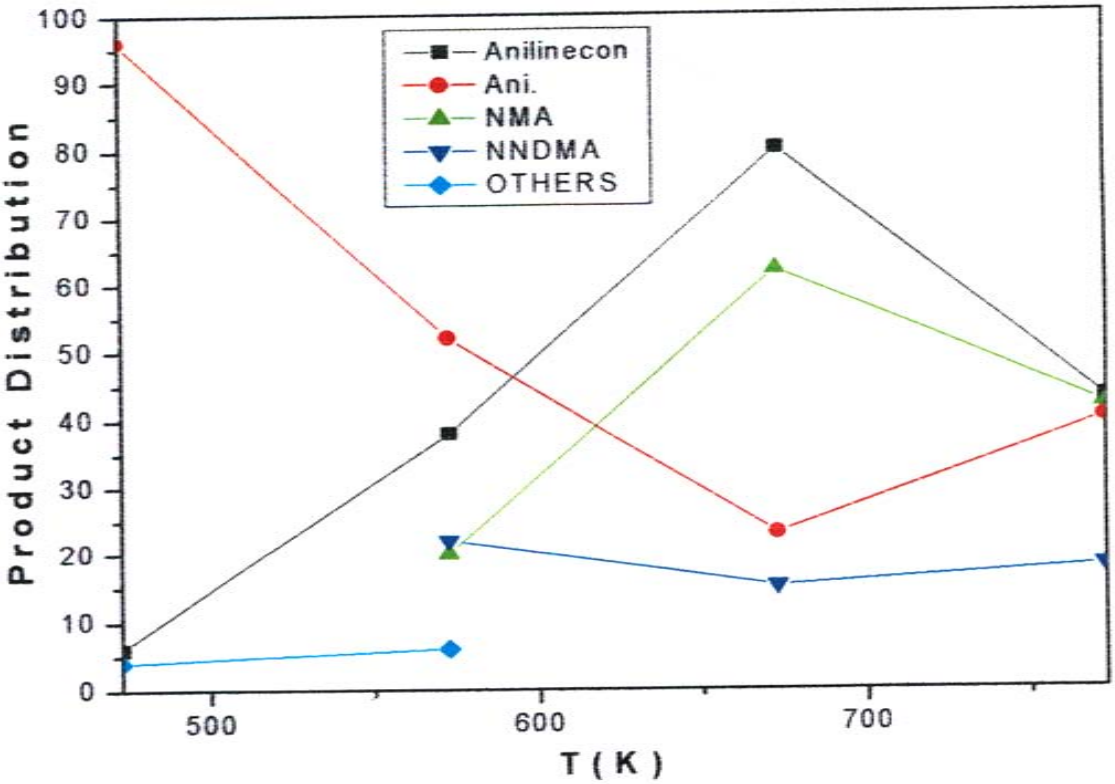

Figure 5 : Effect of temperature on product distribution

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4. Manuscript's Category,

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- To the point depiction of the research
- Consequences, including definite statistics - if the consequences are quantitative in nature, account quantitative data; results of any numerical analysis should be reported
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Approach:

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References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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