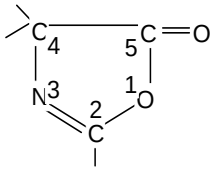
PART (I)

SYNTHESIS AND CHEMICAL REACTIONS OF 5(4)-OXAZOLONES

Oxazolones are five possible types; the most important of these are the 5(4)-oxazolones.

The 5(2)-oxazolones are represented by few compounds, few examples of 2(3)-oxazolones are known. There is one doubtful example of 4(5)-oxazolones and no 2(5)-oxazolone are yet discovered. The five possible types of oxazolones can be represented as follow.



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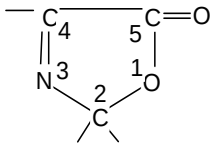

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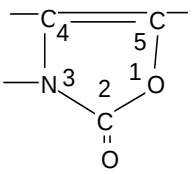

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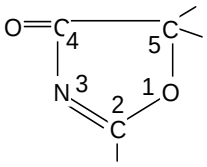

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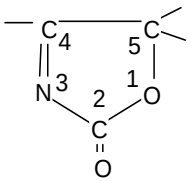
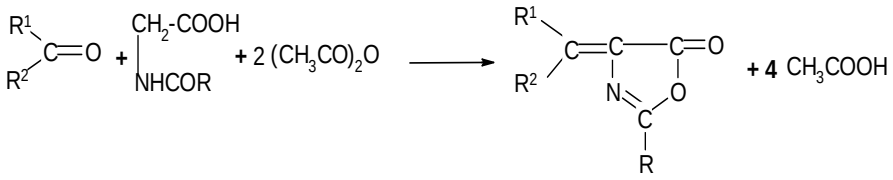


2(5)

SYNTHESIS OF OXAZOLONES

(1) Erlenmeyer synthesis:

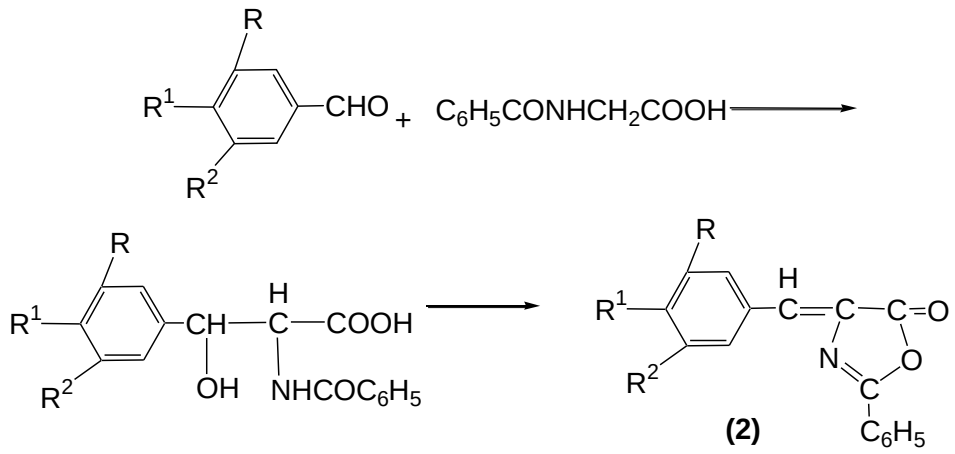
This is the oldest method for the preparation of oxazolones, it mainly involves the interaction of acylglycine and carbonyl compound in acetic anhydride to give 4-alkylidene-5(4)-oxazolone (1).



(1)

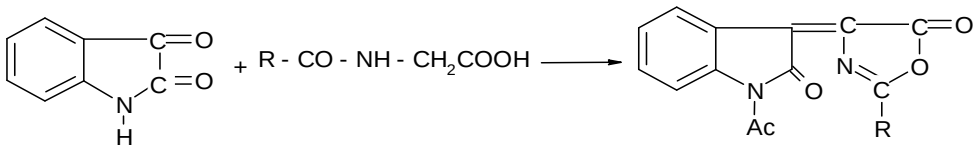
Erlenmeyer and kunlin [1], prepared 2-phenyl-4-isobutylidene-5(4)-oxazolone via the reaction of hippuric acid and isobutylaldehyde in acetic anhydride and sodium acetate.

Also it was reported that [2,3], the synthesis is a special case of Perkin condensation, according to the following scheme.



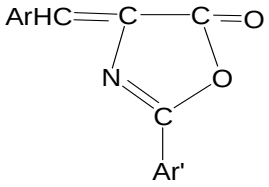
(2)

Kandile et al. [4], reported that the condensation of isatin with acylglycines under Perkin conditions gave the corresponding oxazolone (3).



(3)

El-Hashash et al. [5], synthesized 2-aryl-4-arylidene-5(4)-oxazolones (4) and 2-aryl-4-phthalyldiene-5(4)-oxazolone (5) from condensation of aromatic aldehyde and aroylglycine.



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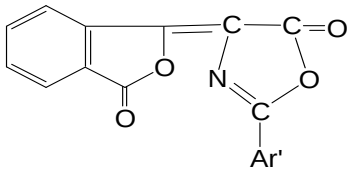
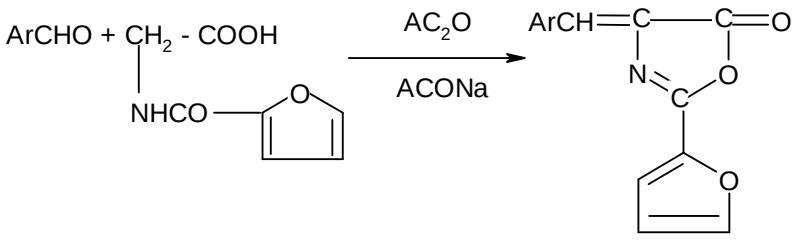


(5)

Fahmy et al.[6], have prepared 4-arylidene-2-(2'-furyl)-5(4)-oxazolone (6) via Erlenmeyer synthesis.



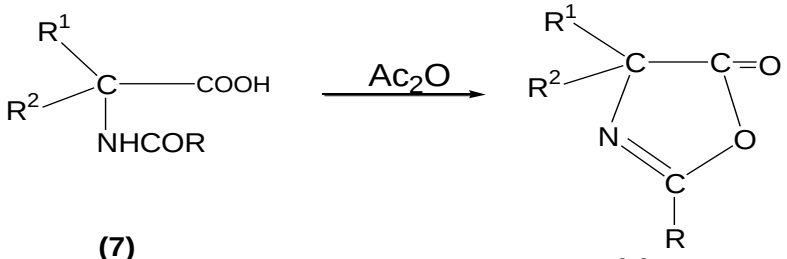
(6)

Whereas, 4-isopropylidene-2-(2'-furyl)-5(4)-oxazolone was obtained by the reaction of 2-furylglycine with acetone in presence of acetic anhydride and sodium bicarbonate.

(2) From α- acylamino acids:

Pyrolysis of α-benzamidocinnamic acid as reported by Erlenmeyer [7] gives 2-phenyl -4-benzylidene-5(4)-oxazolone.

However, oxazolones (1) are prepared by dehydration of α-acylamino acids (7), in the presence of pyridine or acetic anhydride, to give the corresponding oxazolone (1).

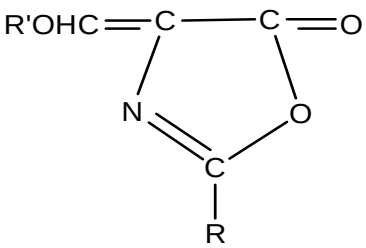


(7) **(1)**

(3) Dehydration of β-alkoxy or β-acyloxy-α-acylamino acids:

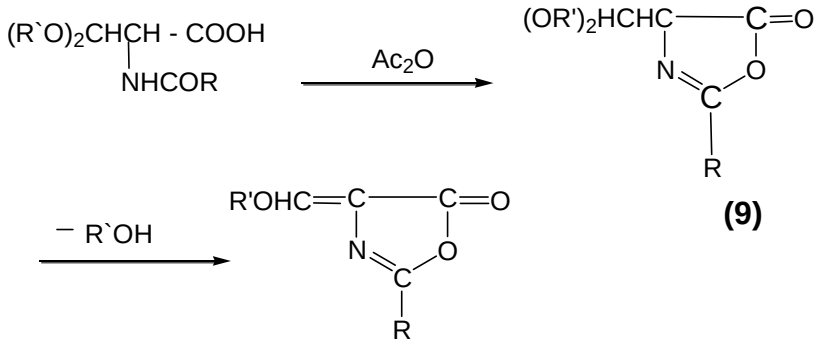
Carter and others [8-10], reported that unsaturated oxazolones were obtained from β-alkoxy and β-acyloxy-α-acylamino acids by using dehydrating agent as acetic anhydride.

Unsaturated azlactone which is difficult to obtain by Erlenmeyer method, is easily prepared via this method and it is the basis of general synthesis of 4-alkoxymethylene-5(4)-oxazolones (8) from penaldic acid acetals [11].



(8)

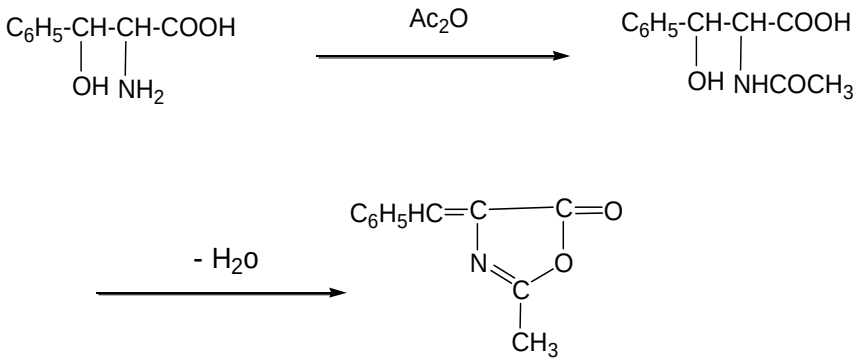
It was reported [12], that the saturated oxazolone (9) is first formed as an intermediate and by loss of alcohol it gave alkoxymethylene oxazolone (8).



(8)

(4) Dehydration of β-hydroxy- β-acylamino acids:

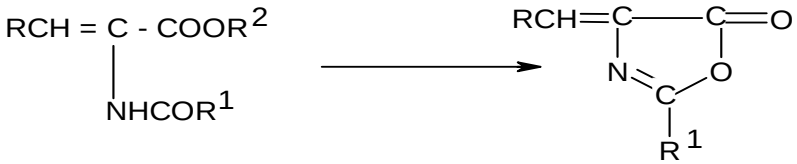
2-methyl-4-benzylidene-5(4)-oxazlone (10) was prepared by Erlenmeyer and Frustuck [2], by action of acetic anhydride on phenyl serine.



(10)

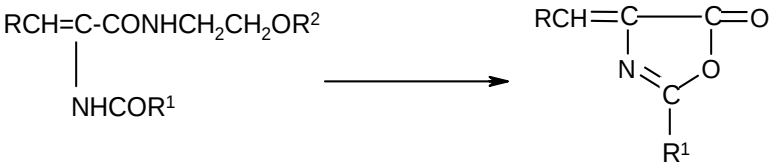
(5) From α-acylamino esters and amides:

Cyclization of α-acylamino esters (11) using acetic anhydride, acid chloride, thionyl chloride [13], and phosphorous pentachloride [14] to give the corresponding oxazolones (12).



(11) **(12)**

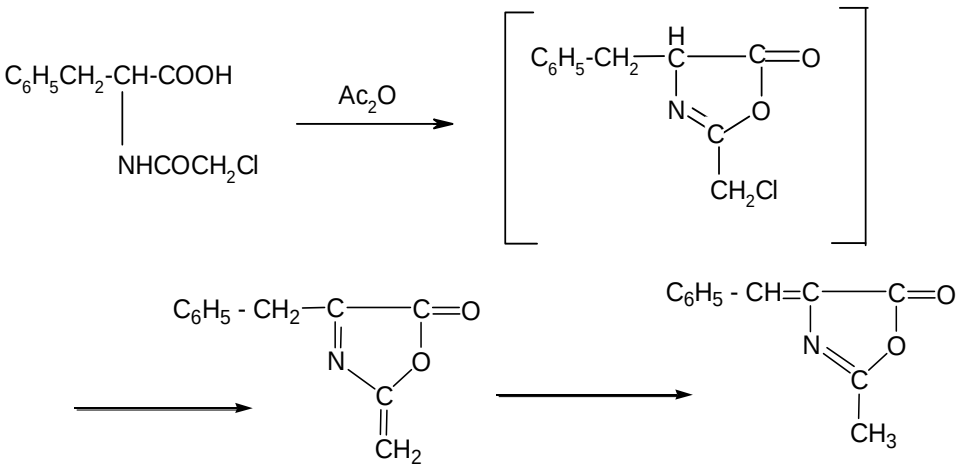
Also, oxazolones (12) were prepared from α-acylamino amide derivatives (13) under the same reaction conditions [13].



(13) **(12)**

(6) Bergmann synthesis:

Bergmann and stern [15], reported that N-chloroacetylphenyl alanine reacted with acetic anhydride to give 2-methyl-4-benzylidene-5(4)-oxazolone (10). However they suggested that, the synthesis proceeds via 5(2)-oxazolone.

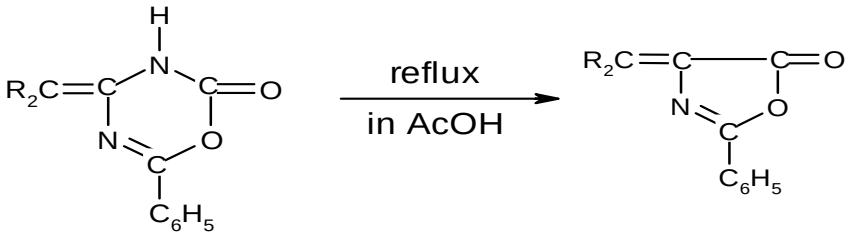


5 (2) - OXAZOLONE **(10)**

(7) Miscellaneous synthesis:

(a) From 4-alkylidene and 4-arylidene-2-oxo-l,3,5-oxadiazines:

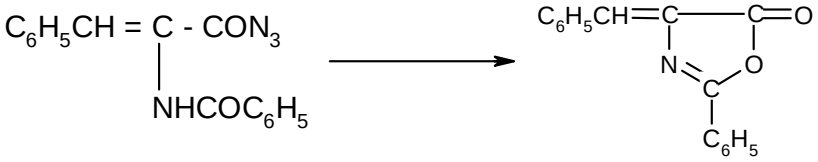
It was reported [16] that, 4-alkylidene and 4-arylidene-5(4)-oxazolones were obtained from 4-alkylidene and 4-arylidene-6-phenyl-2-oxo-l,3,5-oxadiazines (14) by heating in glacial acetic acid .



(14)

(b) From arylidene hippuric azides:

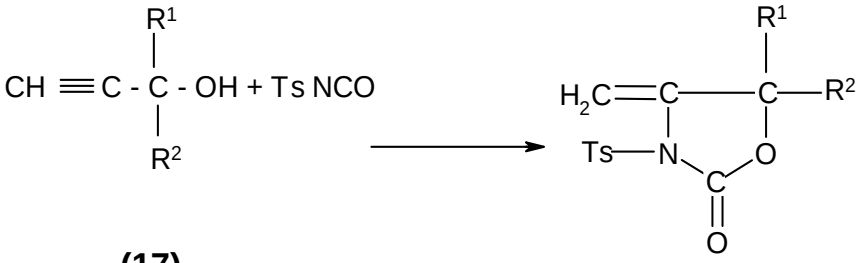
It was reported that [17], when α-benzamidocinnamic acid azide (15) was heated in alcohol or pyridine 2-phenyl-4-benzylidene-5(4)-oxazolone (16) are formed.



(15) **(16)**

(c) From propargylic alcohols and p- toluenesulfonyl isocyante:

Reaction of propargyl alcohol and p-toluenesulfonylisocyante in dichloromethane containing catalytic amounts of cuprous iodide and triethylamine at room temperature afforded 4-methylene -3-tosyl oxazolidin-2-one (18) [18].



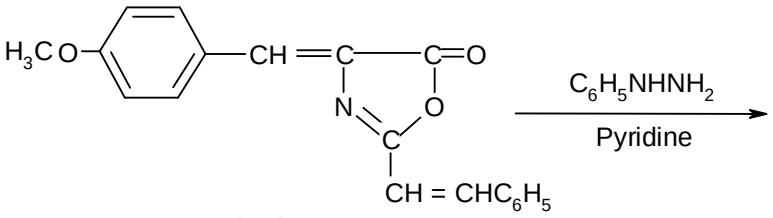
(17) **(18)**

Ts = tosyl

CHEMICAL REACTIONS OF OXAZOLONES

(1) Hydrazinolysis:

It was stated [19] that, the reaction of the 4- anisylidene -2- styryl-5(4)-oxazolones (19) with phenyl hydrazine gave (20). However when 4-benzylidene-2-styryl-5(4)-oxazolone (21) reacted with p-nitro phenyl hydrazine to give hydrazide (22).



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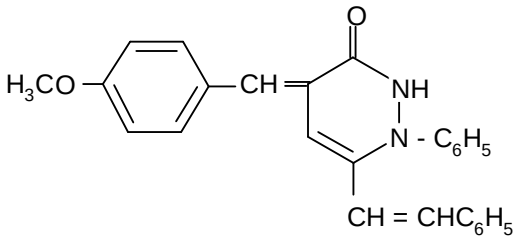
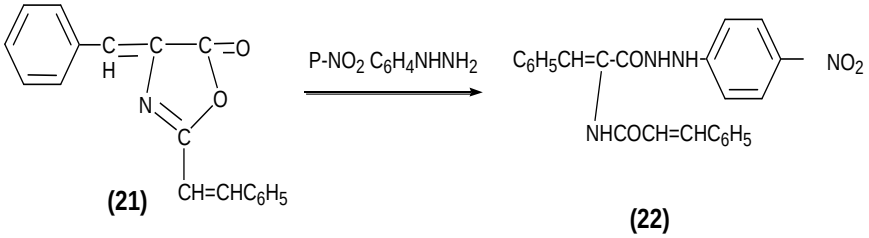
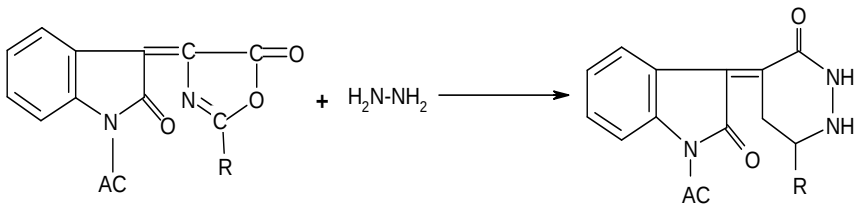


(20)



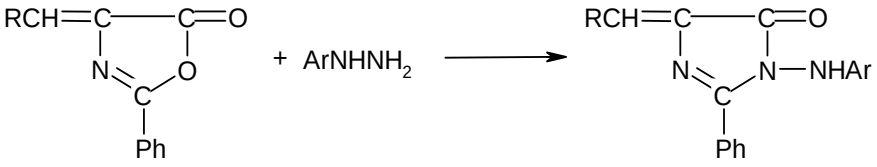
(21) **(22)**

Kandile et al [4], found the hydrazinolysis of oxazolone (3) with hydrazine at room temperature gave cyclic hydrazides (23).



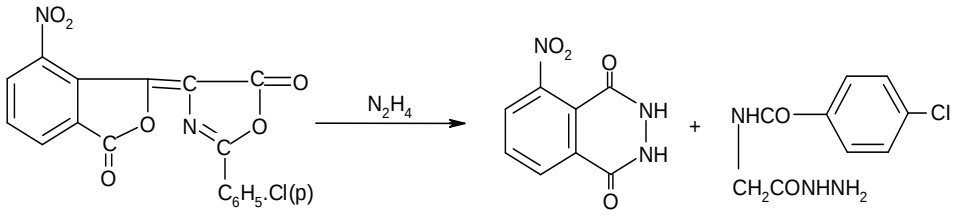
(3) **(23)**

Also the reaction of s-(benzothiazolyl-2)mercaptoacetyl hydrazides with oxazolone gave 1-N-benzothiazol-2-thioacetamido-4-arylidene-2-phenylimidazol-5-ones (24)[20].

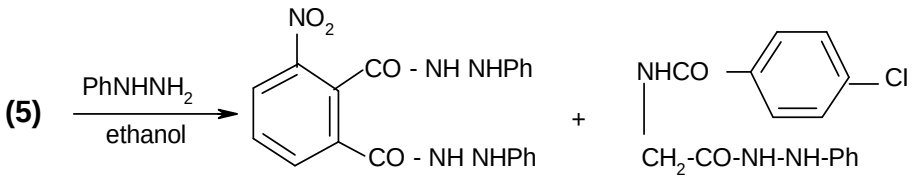


(24)

The reaction of (5) [5] with excess hydrazine hydrate gave a mixture of 5-nitrophthalazin-l,4-dione (25) and p-chlorobenzoylglycine hydrazide (26), but the reaction of oxazolone (5) with excess phenylhydrazine in boiling ethanol yielded a mixture of 3-nitrophthalic acid bis-phenylhydrazine (27) and p-chlorobenzoylglycine-N-phenylhydrazide (28).



(5) **(25)** **(26)**

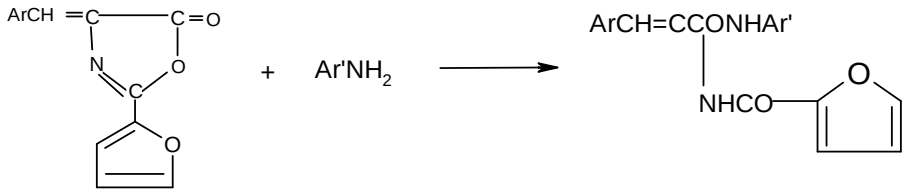


(27) **(28)**

(2)Aminolysis:

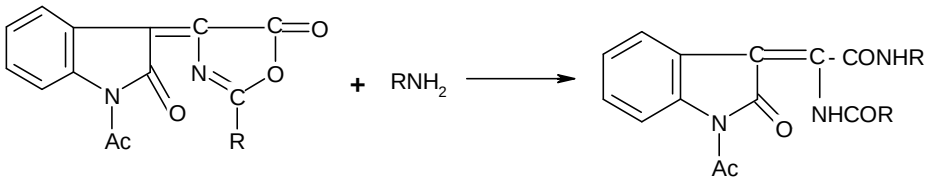
Reaction of oxazolones with amines takes place at C-5 except with some 4-heteromethylene oxazolone, most of the 5(4)-oxazolone reacted easily with primary amines than with secondary amines.

It was reported [19] that, the aminolysis of 4-arylidene-2-(2'-furyl)-5(4)-oxazolone (6) with aromatic amines in benzene gave α-(2-furamido)-N-substituted cinnamides (29).



(6) **(29)**

Kandile et al. [4], found that the aminolysis of oxazolone (3) with H_2NR, (R = NHPh, CH_2 Ph, Ph) gave amides (30).

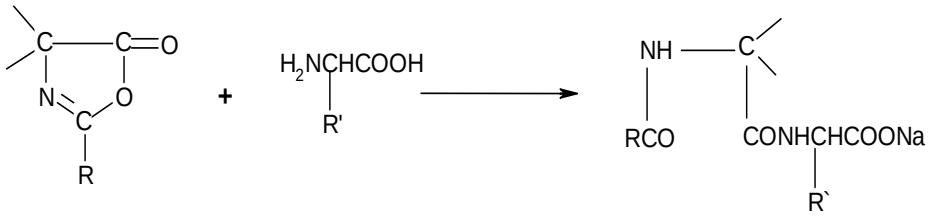


(3) **(30)**

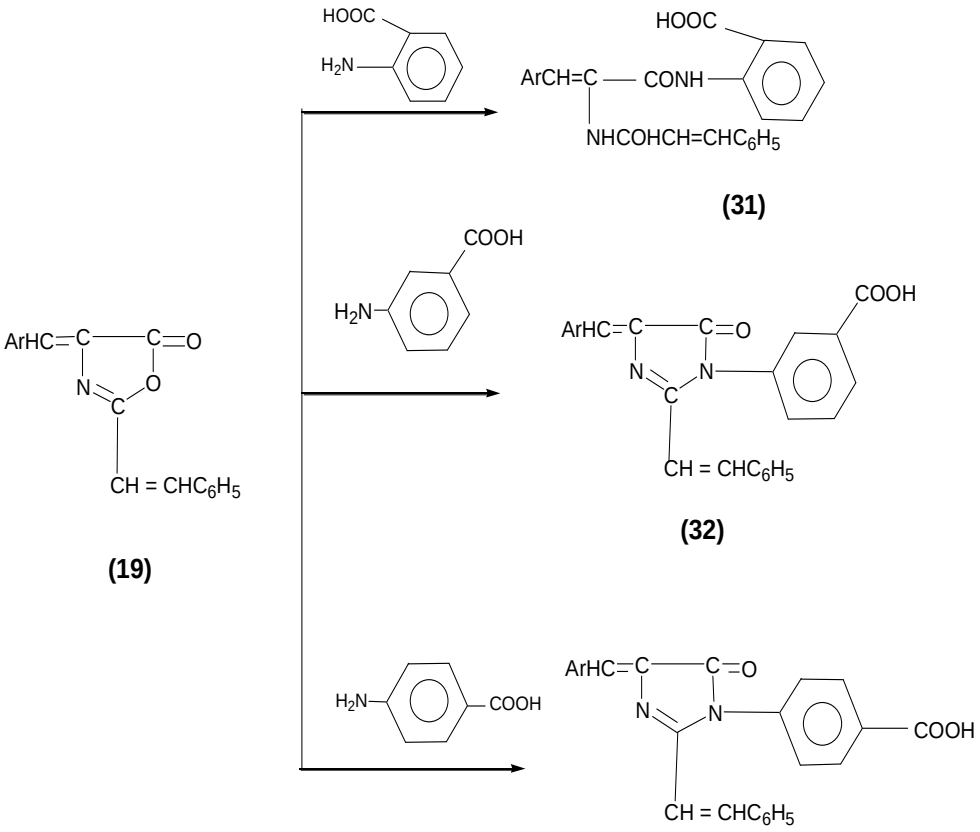
(3) Action of amino acids:

The use of oxazolones for the synthesis of peptides was originated by Mohr [2l] and others [22-24] to give compounds have antibiotics which have ant tumor properties.

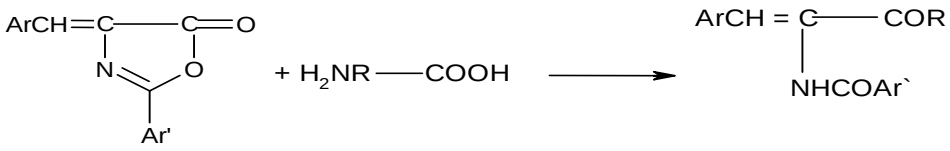
The oxazolone (which may be saturated or unsaturated at C-4 behaves as an acid anhydride in the reaction with α- amino acid. Aqueous acetone is the common medium and sodium hydroxide is added to neutralize the acid liberated.



It was stated [19] that the reaction of oxazolones (19) with o- amino benzoic acid gave anilides (31) while m- and p- amino benzoic acids gave the corresponding imidazolones (32) and (33) respectively.



Also it was[5], stated that the reaction of oxazolones (4) with 3-amino propionic acid, DL-leucine and DL-phenyl alanine, in boiling aqueous pyridine gave o-(o-chlorobenzoylamino)-ß-(p-chlorophenyl)-N-(alkyl/or aralkyl) acryl amide (34).



(4) **(34)**

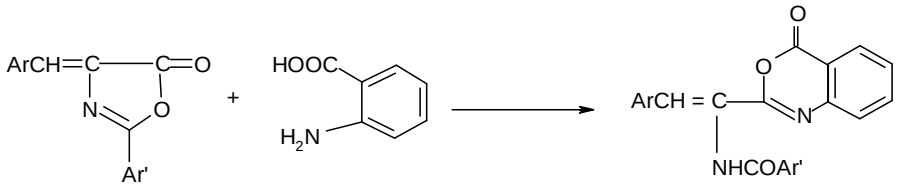
R =

a) $NHCH_2CH_2COOH$

b) $NHCH(COOH)-CH_2CH(CH_3)_2$

c) $NH-CH(COOH)-CH_2C_6H_5$

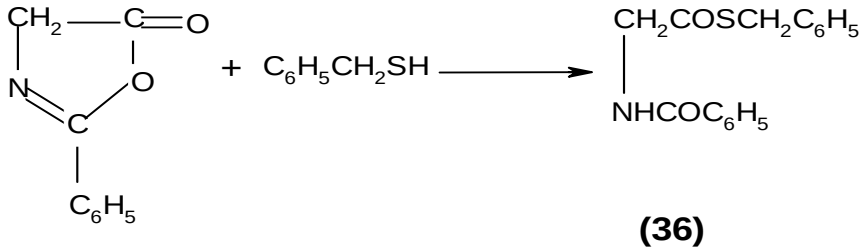
On the other hand when oxazolones (4) reacted with anthranilic acid in refluxing n-butanol it gave the corresponding benzoxazinone (35).



(4) **(35)**

(4) Thiolysis:

Oxazolones reacted with thiol to give the corresponding thioester. It was reported [25] that, the reaction of 2-phenyl-5(4)-oxazolone with benzyl-mercaptan gave benzylthiohippurate (36).



(36)

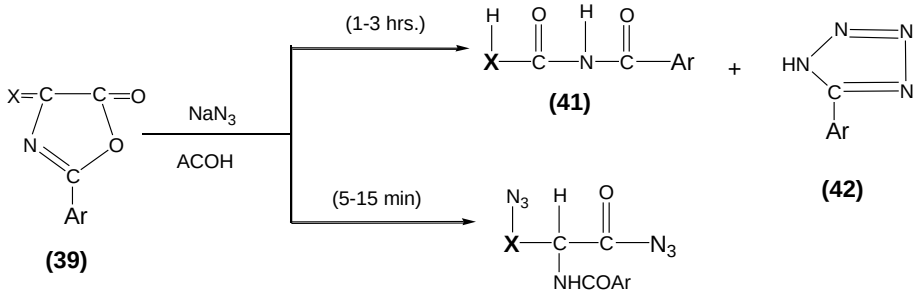
Hashash [26] stated that 4-cinnamylidene-2-phenyl-5(4)-oxazolone (37) reacted with aromatic thiols to give thioester (38).

(37) **(38)**

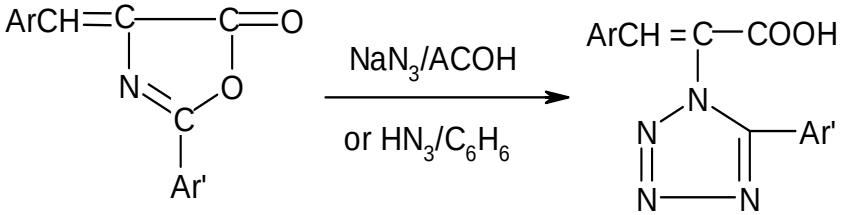
Ar =
a) C_6H_5-
b) $C_6H_5CH_2$ -
c) - $C_6H_4.CH_3$ (P)

(5) <u>Azidolysis</u>:

It was reported [16,27], that there are two possible routes for ring opening during azidolysis of 4-alkylidene-2-aryl-5(4)-oxazolones (39) and only one route for ring opening during azidolysis of 4-arylidene-2-aryl-5(4)-oxazolone (40). When treated oxazolones (39) with sodium azide in acetic acid for (1-3 hrs.), it gave a mixture of N-acyl-benzamide (41) and 5-aryl-tetrazoles (42) but when the reaction was carried out for short time (5-15 min) diazido compounds (43) were obtained.



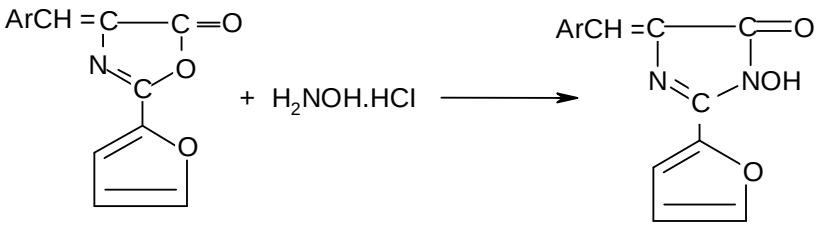
However when oxazolone (40) reacted with sodium azide in acetic acid or hydrazoic acid solution in benzene α-tetrazolo cinnarnic acid [16,19,27] (44) was formed only.



(6) Action of hydroxylamine hydrochloride:

Reaction of oxazolone with hydroxylamine hydrochloride takes place via carbonyl oxygen fission followed by cyclization.

Treatment of 4-arylidene-2-(2'-furyl)-5(4)-oxazolones (6) with hydroxylamine hydrochloride gave 4-arylidene-2-(2'-furyl)-5-imidazolones (45) [6] .

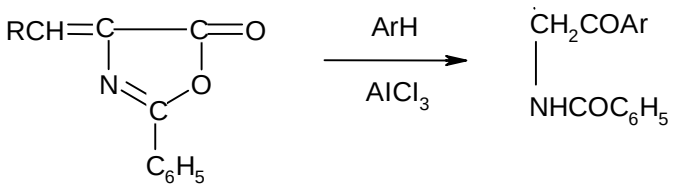


(6) **(45)**

(7) Miscellaneous reactions:

(a) Friedel-Crafts reaction:

It was stated [28], that 2-phenyl-4-benzylidene-5(4)-oxazolone (46) reacted with benzene, toluene, m-xylene or chlorobenzene by action of anhydrous aluminium chloride via the procedure adopted by Filler et al.[29] gave the 2-benzamidoacetophenones (47) instead of the expected 2-phenyl-4-dipheny-lmethyl-5(4)-oxazolone. The same product was obtained when (46) was replaced by any substituted arylidene oxazolones [30-33] .

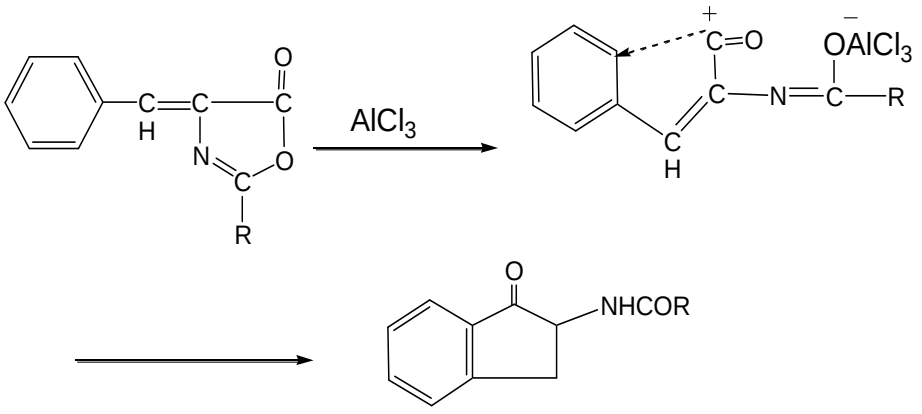


(46) **(47)**

R	Ar
C_6H_5	a) C_6H_5
$C_6H_4.Cl(O)$	b) $C_6H_4.CH_3(P)$
	c) $C_6H_3(CH_3)_2$ (3,5)
	d) $C_6H_4Cl(P)$

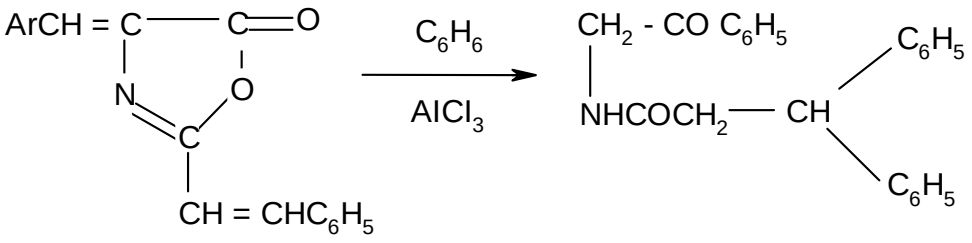
The similarity of the melting points of the products whether the starting material is benzylidene oxazolone or substituted arylidene oxazolones indicates that the solvent is involved in the reaction, and the reaction can not take place by 1,4-addition as proposed by Filler and Hebron[29], but by elimination of the arylidene group.

Filler and Hebron [29], reported that no 2-benzamidoindenone (48) was obtained from this reaction but Awad [28] obtained this compound by inter-molecular cyclization of the corresponding benzylidene oxazolone in acetylene tetrachloride [34] at 60 °C according to the following scheme.



(48)

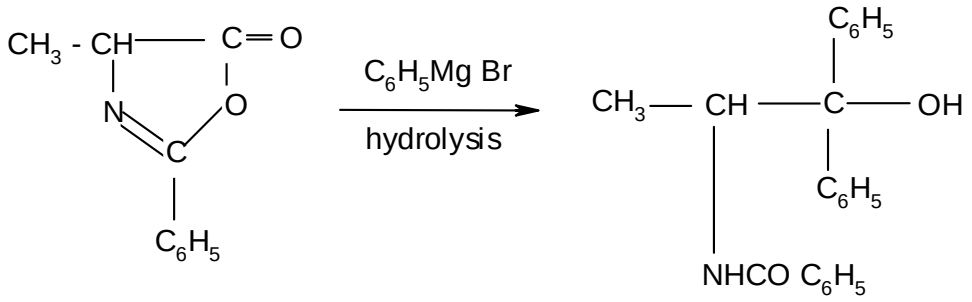
Similarly, 4-arylidene-2-styryl-5(4)-oxazolones (19) react under Friedel-Crafts condition with benzene in presence of anhydrous aluminium chloride to give ß,ß-diphenlypropianamidoacetophenone [19](49).



(19) **(49)**

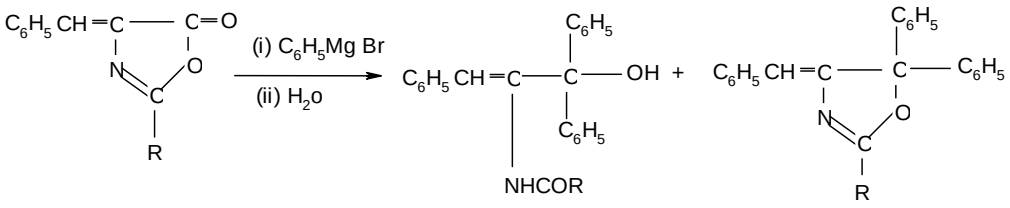
(b) Action of Grignard reagents:

It was reported [35] that, 2-phenyl-4-methyl-5(4)-oxazolone (50) reacted with excess phenyl magnesium bromide to give 1,1-diphenyl-2-benzamido-1-propanol (51).



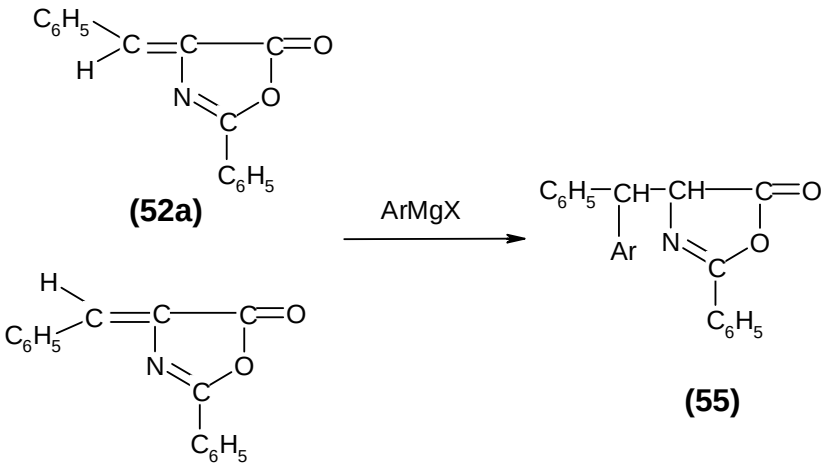
(50) **(51)**

It was stated [36] that, the action of some Grignard reagents on unsaturated azlactones as the reaction with 2-phenyl-4-benzylidene-5(4)-oxazolone (52) afforded l,l-diphenyl-2-benzamido-cinnamoyl alcohol (53) as described by authors[37,38] and small quantity of 2,5,5-triphenyl-4-benzylidene-2-oxazoline (54).



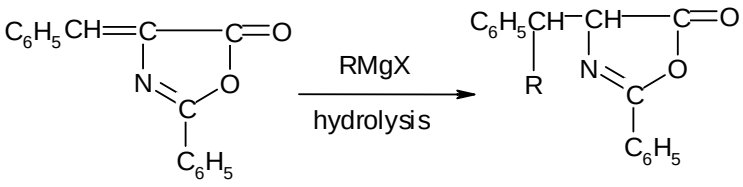
(52) **(53)** **(54)**

Peterson et al. [39] stated that, the labile geometrical isomer of (52) reacts with aryl Grignard reagent to give (55).



(52a) **(52b)** **(55)**

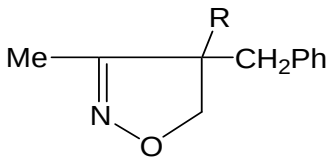
Treatment of 4-benzylidene-2-phenyl-5(4)-oxazolone (52b) with Grignard reagents gave 2-phenyl-5(4)-oxazolone (56) [26-29].



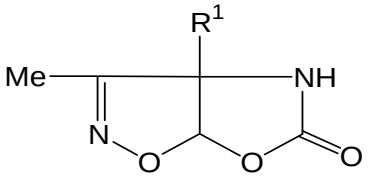
(52b) **(56)**

(c) Reaction with azo derivatives:

It was found [40] that, the reaction of oxazolone (57) (R = H) with $Me_3CCO_2N{:}NCO_2CMe_3$ in CH_2Cl_2 and Et_3N gave oxazolone (57).($R=Me_3CCO_2NNHCO_2CMe_3$) which on reductive cyclization with ($NaBH_4$-EtOH) gave oxazoloisoxazoles (58).



(57)

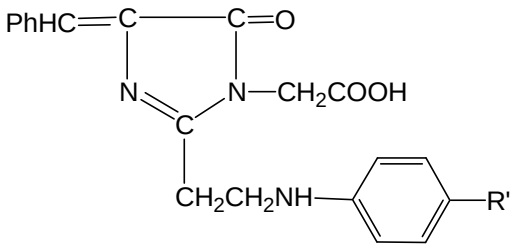


(58)

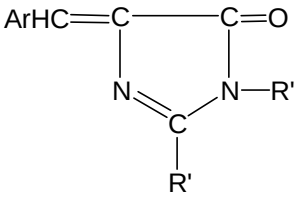
(8) BIOLOGICAL ACTIVITY OF OXAZOLONE DERIVATIVES

Oxazolone nucleus has been employed as a basis for the synthesis of chemotherapeutic agents and a large number of its derivatives have been reported to possess various biological properties such as fungicides, herbicides and antibacterial.

A large number of oxazolone derivatives especially imidazolone derivatives (58), (59) showed highest biological activity and safety such as anti-inflammatory activity [41] and antibacterial [42].

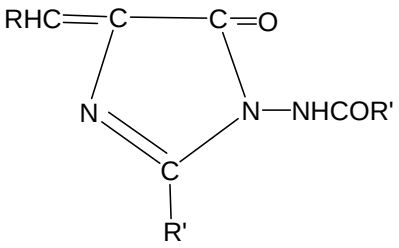


(58)



(59)

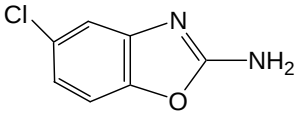
Benzoyl-benzylidenimidazolinones (60) (R = unsubstituted phenyl, pyridyl; R' =Ph, Me) exhibited good anticonvulsant activity[43] against pentylenetetrazole.



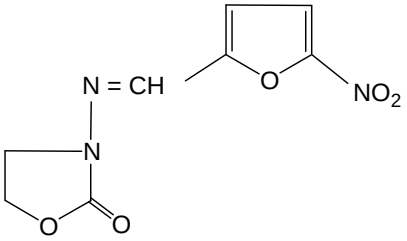
(60)

It was reported [44] that, oxazolidine derivatives used as sedative, muscle-relaxant and show promise as appetite depressants.

Also it used in treatment of enteric infection as oxazolamine (61) and furazodidone (62).

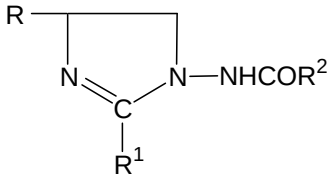


(61)



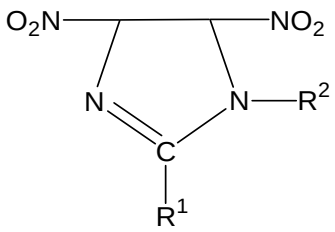
(62)

Several new l-acylamino-2-alkyl-4-arylimidazoles (63),(R= phenyl, substituted phenyl; R^1= methyl, CH_2Ph; R^2 =Me, OEt) have antimicrobial activity[45] which inhibited the development of staphylococcusaureus.



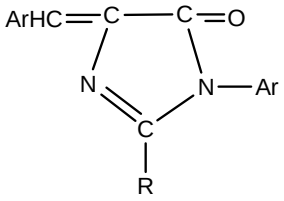
(63)

Nitroimidazole derivatives (64), (R = H, Me; $R^2 = CH_2COR$; R^1= 2-$C1C_6H_4$, 2,4-$Cl_2C_6H_3$, 3,4-$Cl_2C_6H_3$) possess antibacterial and antifungicidal activity[46].



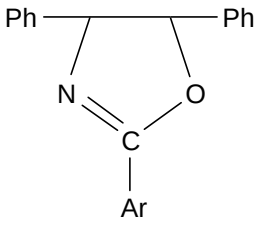
(64)

Some substituted benzylidenimidazolones (65) used as anticonvulsant agent [47].



(65)

Moreover 4,5-diphenyloxazole (66) used in most potent platelet aggregation inhibitor [48].



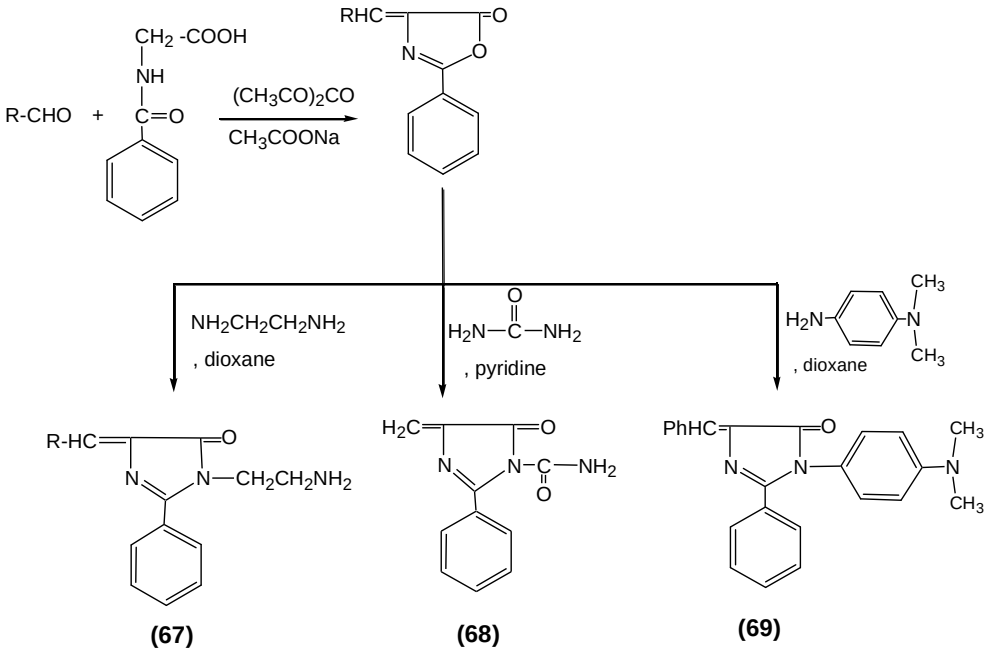
(66)

Part (II)

SYNTHESIS OF IMIDAZOLES AND IMIDAZOLONES

(1) From carboxylic acid derivatives:

Imidazolone derivatives were synthesized via Erlenmeyer synthesis [1-6,49] by the reaction of 4-substituted oxazolone with the appropriate amine in dioxine / pyridine.

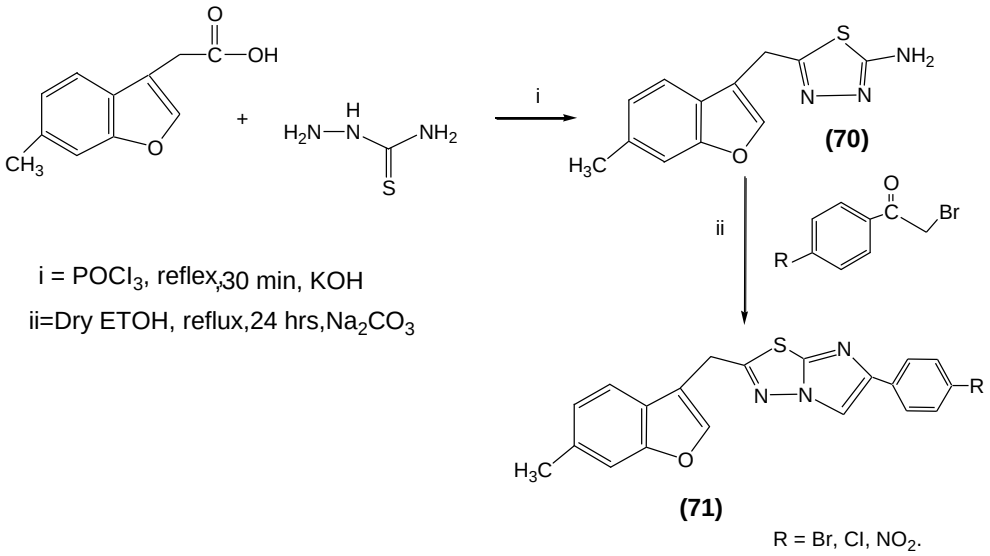


(67) **(68)** **(69)**

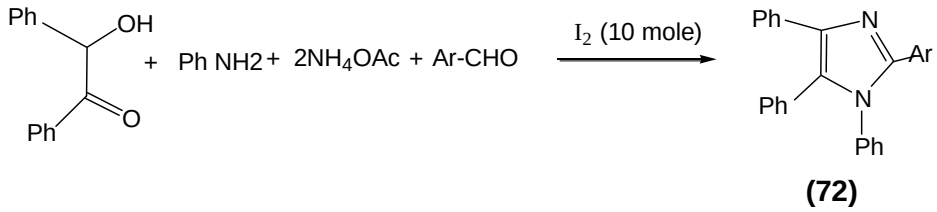
R = p-$MeOC_6H_5$, p-OH C_6H_4, p-$(Me)_2NC_6H_3$,m-$NO_2C_6H_4$, C_2H_5,C_3H_7.

R= C_6H_5, 4-Cl C_6H_5, 4- BrC_6H_5, 4-$MeOC_6H_5$,4-MeC_6H_5, 4-$NO_2C_6H_5$.

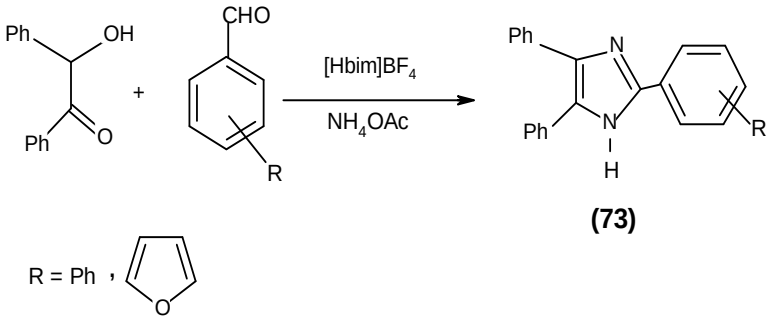
Imidazole derivatives were prepared by condensation of acid derivatives with α-bromoarylketone under reflux in dry ethanol [50].



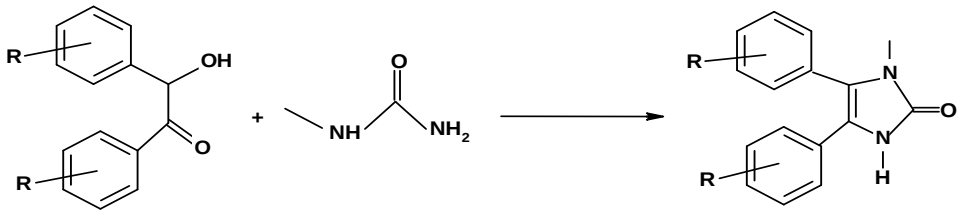
One-pot procedure for the synthesis of 1,2,4,5-tetraryl-imidazoles using iodine as a catalyst, at room temperature[51].



S. A. Siddiqui et al. [52] have reported imidazole derivatives using carboxylic acid derivatives.



Also, imidazolones were synthesized using carboxylic acids illustrated by the following scheme [53].

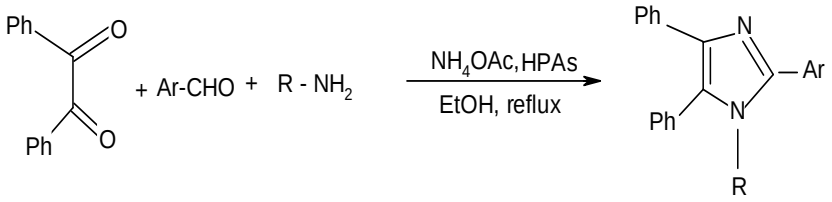


(74)

R = H, Me

(2) From diketones:

One-pot synthesis of imidazole derivatives by four component condensation of benzyl, benzaldehyde derivatives, primary amine, ammonium acetate catalyzed by keggin heteropolyacids (HPAs)[54] such as: $H_3[PW_{12}O_{40}]$, $H_4[SiW_{12}O_{40}]$.



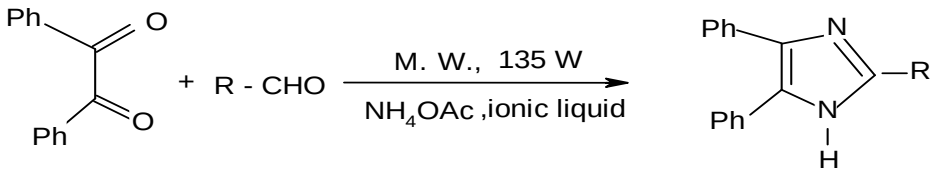
(75)

Ar = Ph , 4 - Meph, 4 - Brph,

R = Me, ph , $phCH_2$.

Also, a typical acid-catalyzed reaction in organic solutions, could be conducted successfully with good to excellent yields in a neutral ionic liquid l-methyl-3-heptylimidazolium tetrafluoroborate ([HeMlM] BF4), under solvent free and microwaves-assisted conditions in absence of any acid as a catalyst [55]

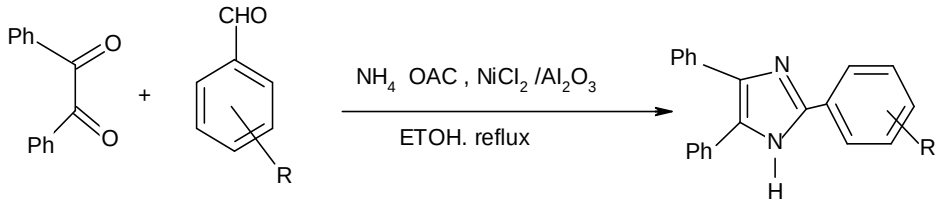
.



(76)

R=C_6H_5,4-FC_6H_4,4-ClC_6H_4,4-BrC_6H_4,4-$CF_3C_6H_4$

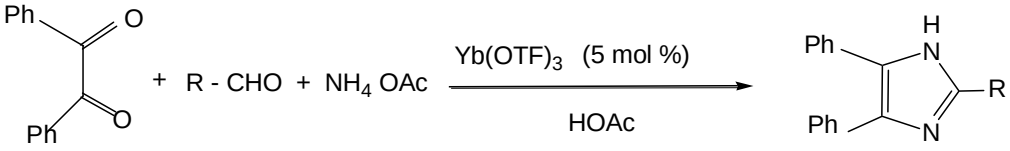
M.M. Heravi et al. [56] synthesized benzimidazoles under heterogeneous system using $NiCl_2.6H_2O$/ $A1_2O_3$ as a catalyst.



(77)

R = C_6H_5, 4-Cl C_6H_5, 4-Br C_6H_5, 4-MeO C_6H_5, 4-Me C_6H_5,4-$NO_2C_6H_5$.

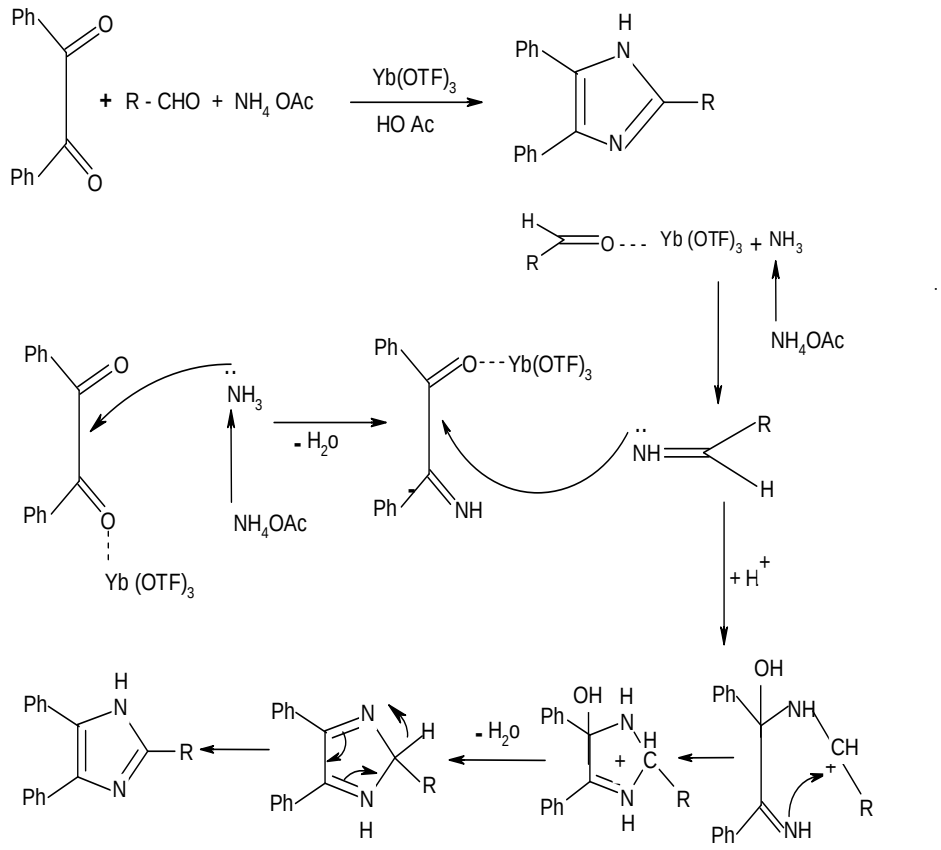
When using the rare earth metal compounds, the model reaction of the following mixture proceeded smoothly to afford the corresponding adduct in good to excellent yield [57]. Among them Yherbium triflate $Yb(OTf)_3$ was the most effective catalyst (which is strong Lewis acid).



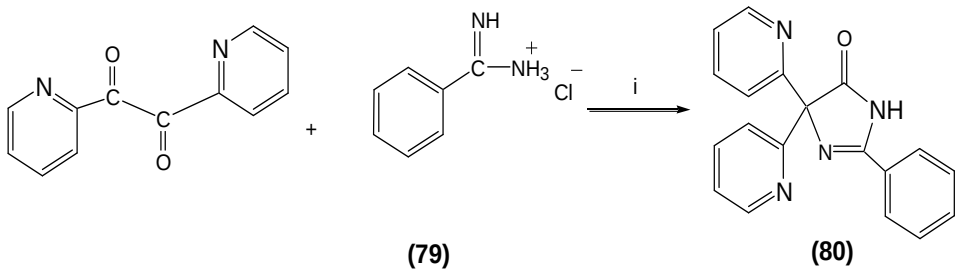
(78)

R = p-$MeOC_6H_5$, p-OHC_6H_4. p-$(Me)_2NC_6H_3$, m-$NO_2C_6H_4$, C_2H_5,C_3H_7.

A probable mechanism for synthesis may be postulated as shown below:



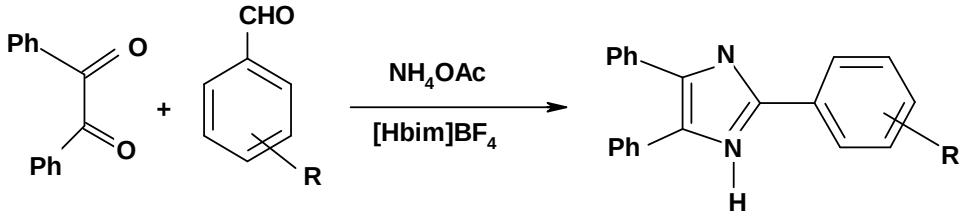
Imidazolone ring could be established via Pinacol-like rearrangement [59] arising from the reaction of 2,2'-pyridyl **(79)** and benzamidine/HCl **(80)**.



(79) **(80)**

i =EtOH, NaOH . reflux . 2 hrs.

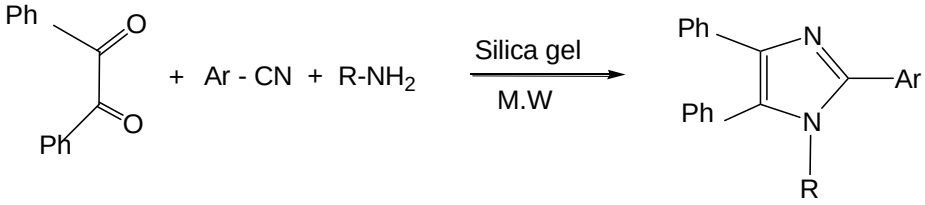
S. A. Siddiqui et al. [52] generated a variety of imidazoles by the reaction of l,2-difuran-2-yl-ethane-l,2-dione with benzaldehydes at 100°C.



(81)

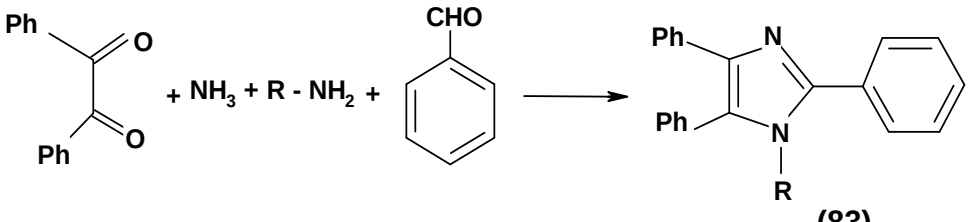
R =H, p-MeO, o-OH,p-OH , p-Cl, p-Br, o-OH, m-Me , p-OH,p-NO_2.

S.Balalaie et al.[59] reported that, the one-pot, three-component condensation of benzil, benzonitrile derivatives and primary amines on the surface of silica gel with acidic character under microwave irradiation as a new efficient method to produce 1,2,4,5-tetra substituted imidazoles.



(82)

Also, 1,2-diketones have been used to prepare imidazoles via cyclocondensation reactions [60].

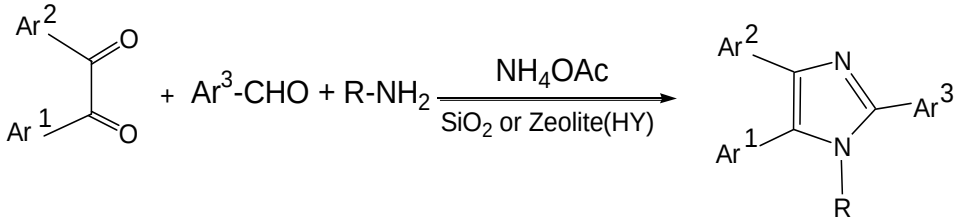


(83)

R=Bn, $C_6H_{11}.CH_2$-(o)

Primary amines and ammonium acetate have also been employed in synthesis of imidazoles. The significant shortfall of this methodology is the

necessity to use symmetrical benzil due to a lack of regiocontrol for the 4- and 5-positions in the process [61,62].

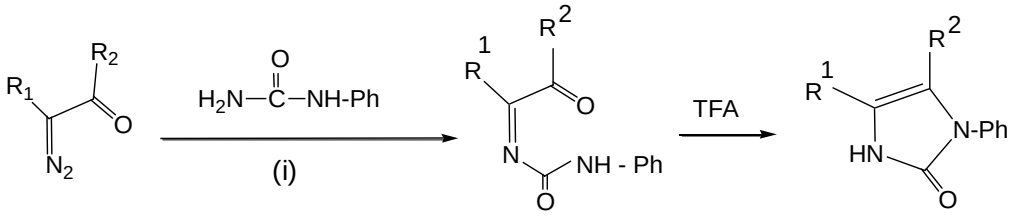


(84)

$Ar^1 = Ar^2$

(3) From amide derivatives:

The synthesis of highly substituted imidazoles and imidazolones from various diazocarbonyls with primary ureas results in regioselective formation of N-H insertions product of type **(85)** .In the presence of acid, the latter undergo ring closure to afford imidazolones **(86)** [63].



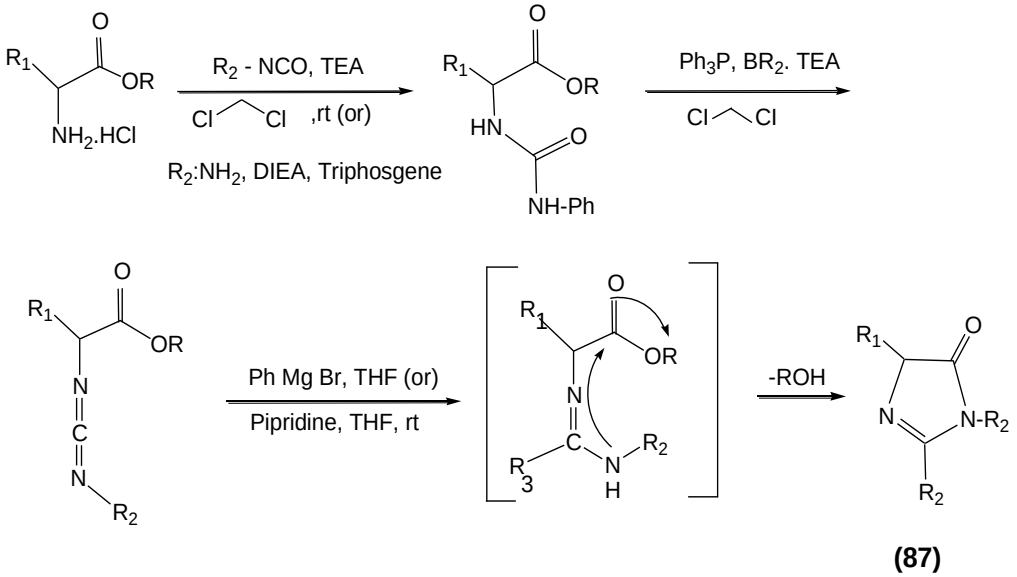
(85) **(86)**

R_1 = H, Et, COPh, $PO(O\text{-}Et)_2$, SO_2Me;

R_2=Ph, OEt .

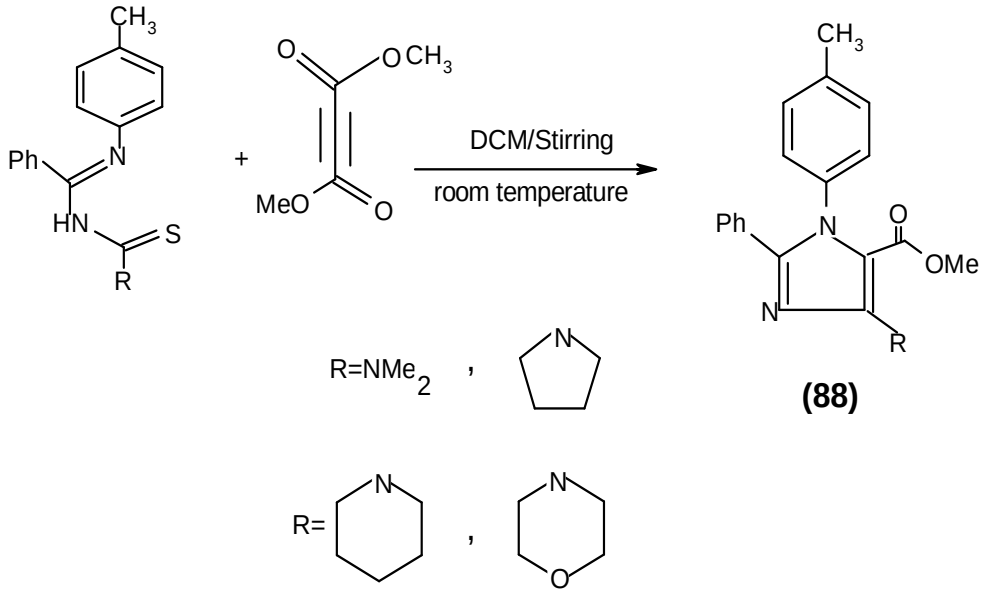
(i) = Rh_2 (O-CO-heptyl)$_4$, (Cat.), Toluene /DCE (1:1)

Via tandem chemoselective addition reaction on carbodiimide cyclization [64,65] was used for the synthesis of 2-substituted imidazolones as the following scheme.



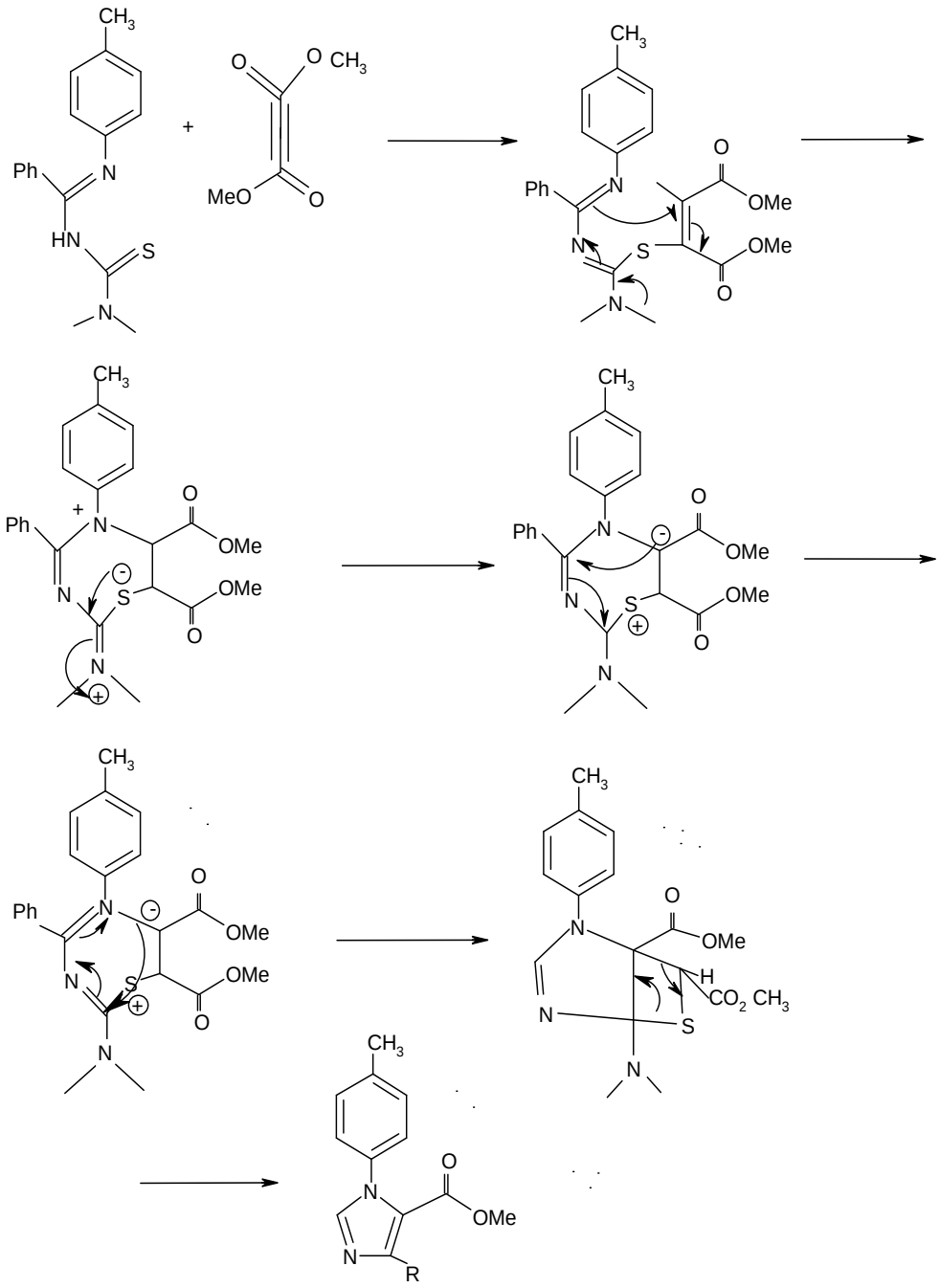
(87)

A. Marwaha et al. [66], Single-pot synthesis of functionalized imidazole derivatives by the reaction of thioamides **(87)** with di-methylacetylene dicarboxylate via sequential cycloaddition-cycloreversion-cycloaddition reactions.

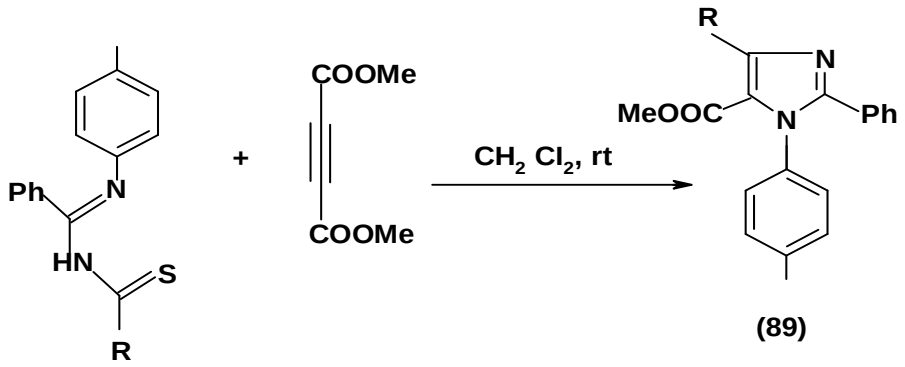


(88)

A plausible mechanism underlying the formation of the imidazole derivatives.



Also, imidazoles were concisely synthesized in 65-71 % yield by the reaction of thioamide with dimethylacetylene dicarboxylate in CH_2Cl_2 at room temperature [67]

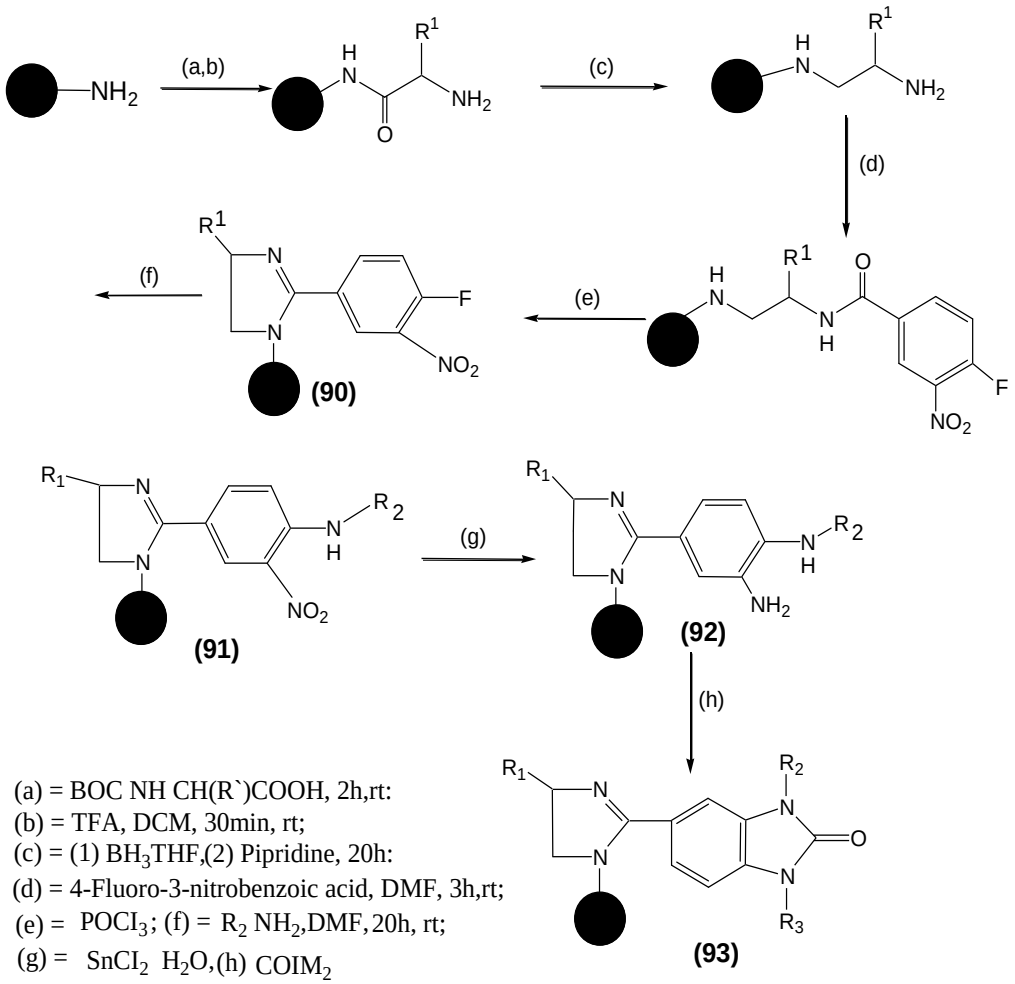


(89)

R = NMe_2 , $N(CH_2)_4O$

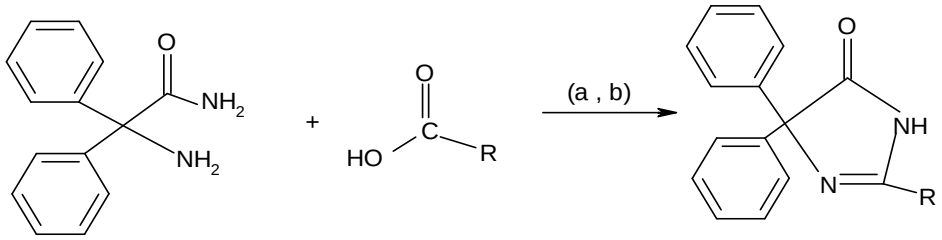
R= $N(CH_2)_4$, $N(CH_2)_5$

Acharya et al. [68-73], described the solid-phase synthesis of substituted 4,5-dihydro-(lH-imidazole-2-yl)-l,3-dihydro-2H-benzimidazol-2-ones.



(a) = BOC NH CH(R`)COOH, 2h,rt:
(b) = TFA, DCM, 30min, rt;
(c) = (1) BH_3THF,(2) Pipridine, 20h:
(d) = 4-Fluoro-3-nitrobenzoic acid, DMF, 3h,rt;
(e) = $POCl_3$; (f) = R_2 NH_2,DMF, 20h, rt;
(g) = $SnCl_2$ H_2O,(h) $COIM_2$

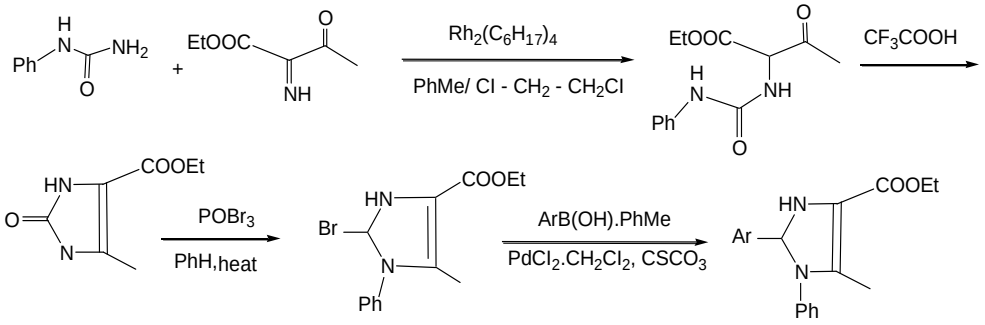
Also, imidazolone ring was synthesized by treatment of amine with a polymer-supported carbodiimide reagent in the presence of excess carboxylic acid or acyl chloride afforded α-amidoamide as intermediate [74-75].



(94)

(a) = P -EDC resin , CH_2Cl_2 rt, 24h.;
(b)=NaOH ,EtOH,rt, 2h.

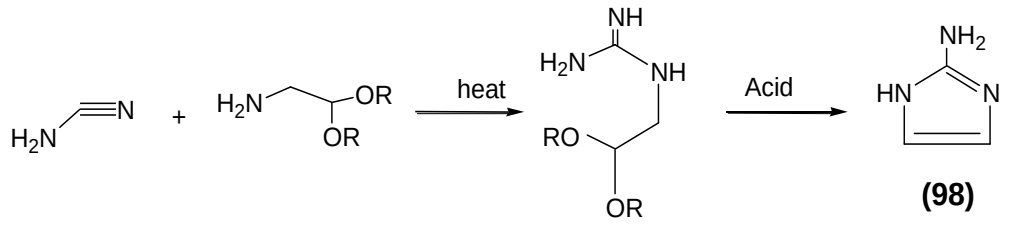
Recently [76], Clapham and co-workers disclosed a two and four step-reaction sequence for the synthesis of imidazolone and imidazoles using amides compounds as starting material.



(95) **(96)** **(97)**

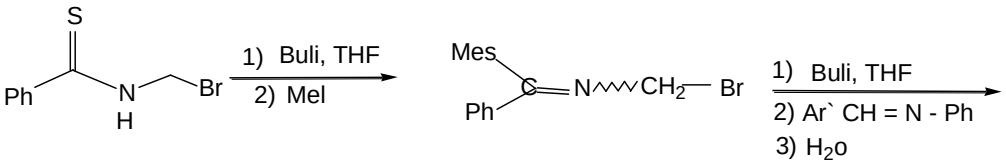
Ar=4-$MeOC_6H_4$.
Ar=4-$EtOOCC_6H_4$.
Ar=4-$TBDMSOC_6H_4$.

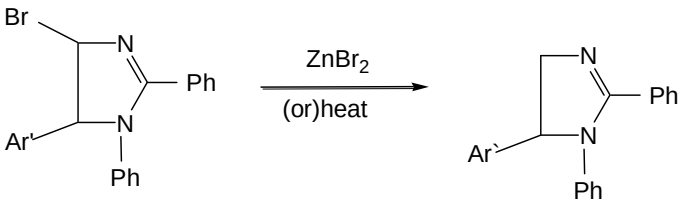
Reaction between cyanamide and 2-aminoacetaldehydeacetales followed by an acid catalyzed cyclization which was found by Lawson [77].



(98)

Imidazoles have also been prepared via a multi-steps process in which N-(benzotriazol-l-ylmethyl) thiobenzamide was the starting material [78].

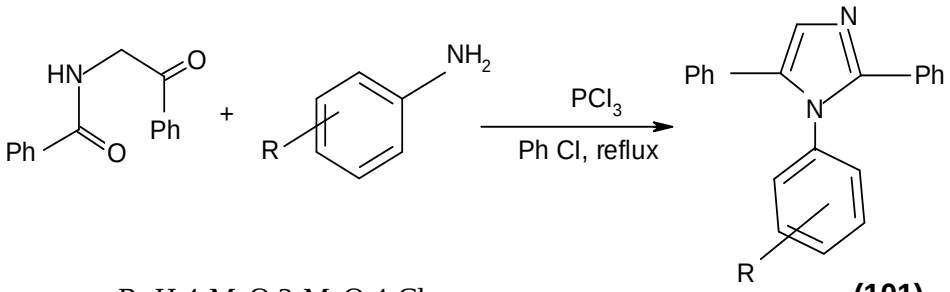




(99) **(100)**

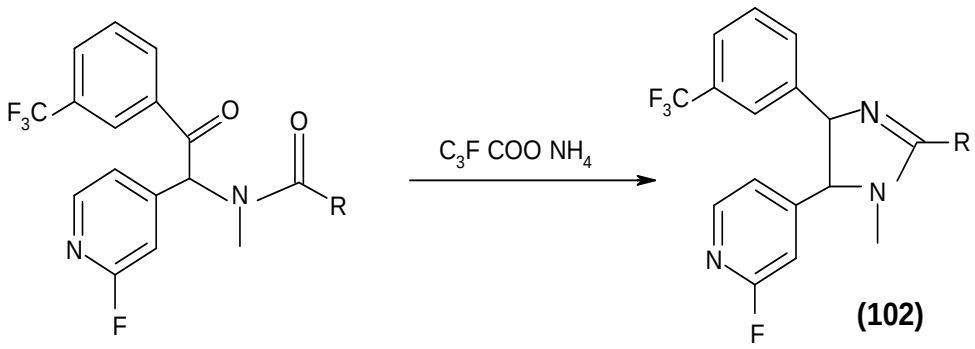
Ar'=Ph,4-MeC$_6$H$_4$.

Popilin and Tiscenko reported [79] that, the treatment of benzamido-acetophenone with PCl_3 and arylamines in boiling chlorobenzene gives imidazoles.



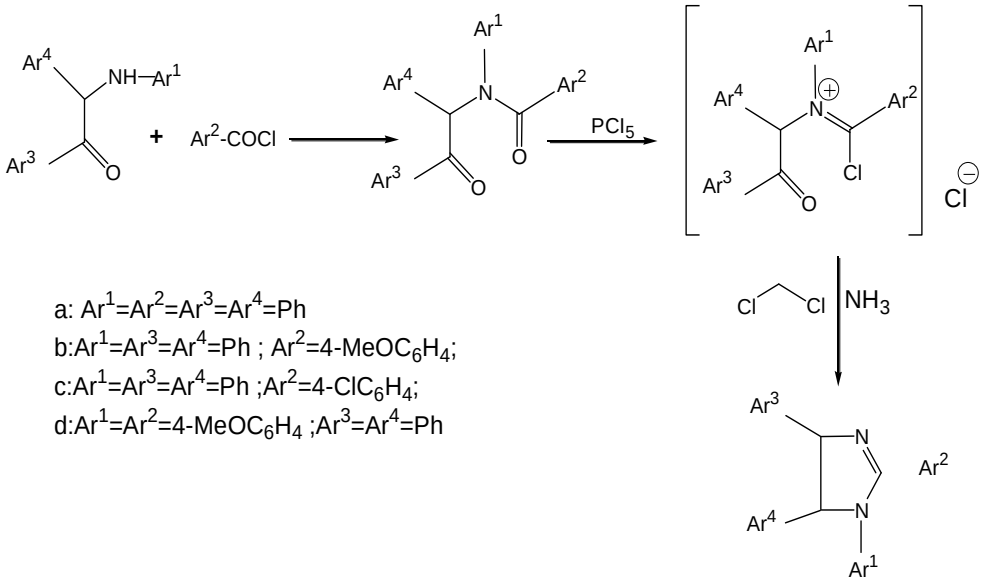
R=H,4-MeO,2-MeO,4-Cl. **(101)**

Also, imidazoles were efficiently prepared by thermal cyclo-condensation of N-alkyl-N-(ß-keto) amides with ammonium trifluoro-acetate [80].



(102)

Heinze and co-workers [81] developed a three-step procedure for the synthesis of imidazoles from the required desylamines and aroyl chlorides in presence of PCl_5.



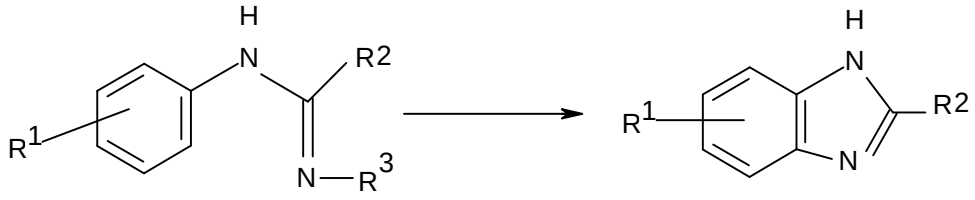
a: $Ar^1=Ar^2=Ar^3=Ar^4=Ph$
b:$Ar^1=Ar^3=Ar^4=Ph$; $Ar^2=4\text{-}MeOC_6H_4$;
c:$Ar^1=Ar^3=Ar^4=Ph$;$Ar^2=4\text{-}ClC_6H_4$;
d:$Ar^1=Ar^2=4\text{-}MeOC_6H_4$;$Ar^3=Ar^4=Ph$

(103)

(4) From amidine and related compounds:

The formation of imidazoles from *N*-arylamidines was first reported by Partiridge and Turner [82] who obtained them by allowing the hydroxyl derivatives to react with benzene-sulfonyl chloride in pyridine or triethylamine under anhydrous conditions.

Generally, yields are good and the methods can be used for the synthesis of variety of derivatives.

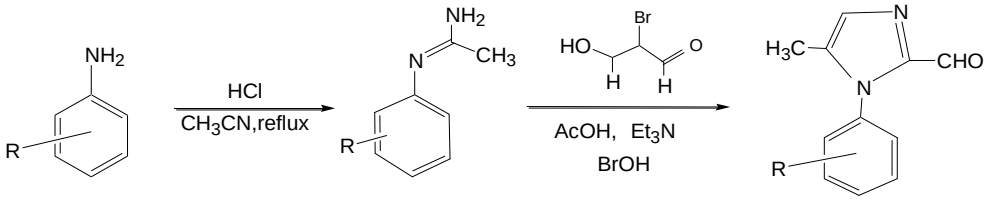


(104)

a,=R^1=alkyl,alkoxy; R^2=Ph; R^3=OH
b,=R^1=H; R^2=4-thiazolyl,Ph,Et; R^3=H
c,=R^1=H; R^2=4-thiazolyl,Ph,Et; R^3=Cl

Subsequently, Grenda et al. [83] showed that, such products could be obtained from the parent amidine by oxidation with sod-hypochlorite under basic conditions. N-chloro derivatives were suggested to be intermediates in these reactions.

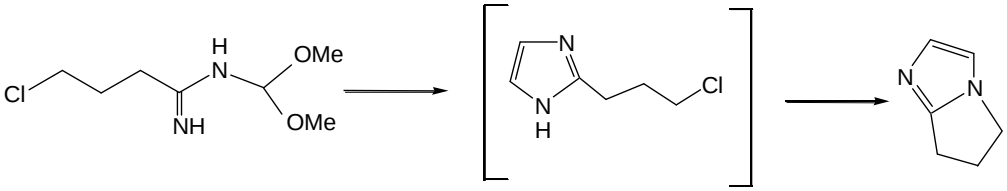
S. B. Ferreira et al. [84] were prepared and utilized N-aryl-amidines as the starting materials for the synthesis of N-substituted-phenylimidazole-5-carbaldehyde.



R=H, 4-Cl, 4-F, 4-NO_2, 4-CF, 4-CN, 4-CH_3,

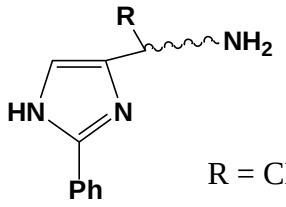
(105)

H.C.Kan et al. [85], synthesized bicyclicimidazolium ionic liquids by intramolecular-cyclization of the corresponding amidines.



(106)

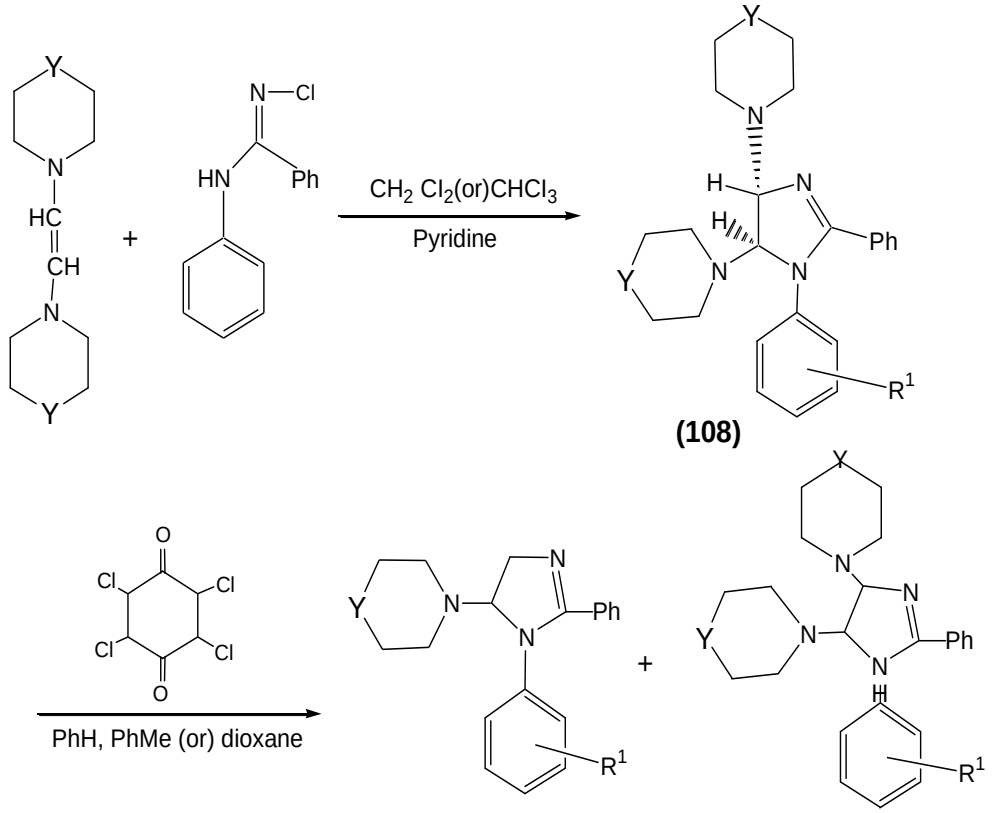
F. Bures et al. [86-87], published the synthesis of chiral derivatives of 2-phenylimidazole by the condensation of benzamidine with α-bromo-ketones in the solvent / base system, THF, water and K_2CO_3.



R = CH_3, $(CH_3)_2$, CH- , $(CH_3)CHCH_2$-

(107)

Several years ago, imidazoles were synthesized by the reaction of diamin-oethane with *N*-aryl-*N*-chlorobenzamidines in boiling CH_2C1_2 or $CHCl_3$ in presence of an equimolar amount of pyridine, followed by oxidation with chloroanil [88-89].



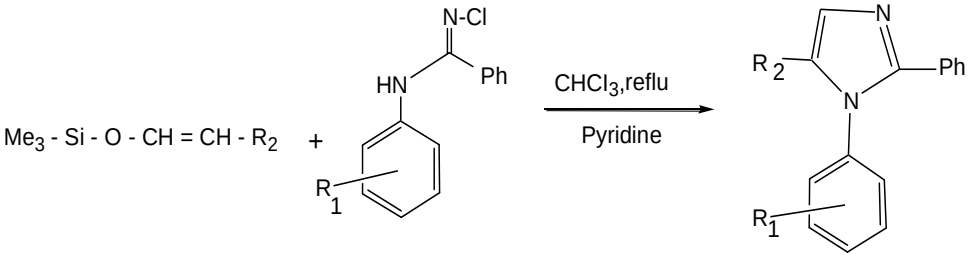
[Y=O, CH_2; R_1=H, 2-Me, 4-F, 4-B]

(108)

(109)

(110)

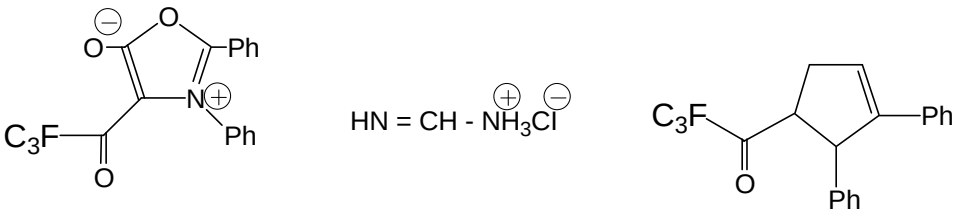
On the other hand, imidazoles were synthesized in 55-57% yield by the reaction of silylenol ethers with *N*-chloro-*N*-aryl-benzamidines in refluxing $CHCl_3$ in the presence of pyridine [90]



(111)

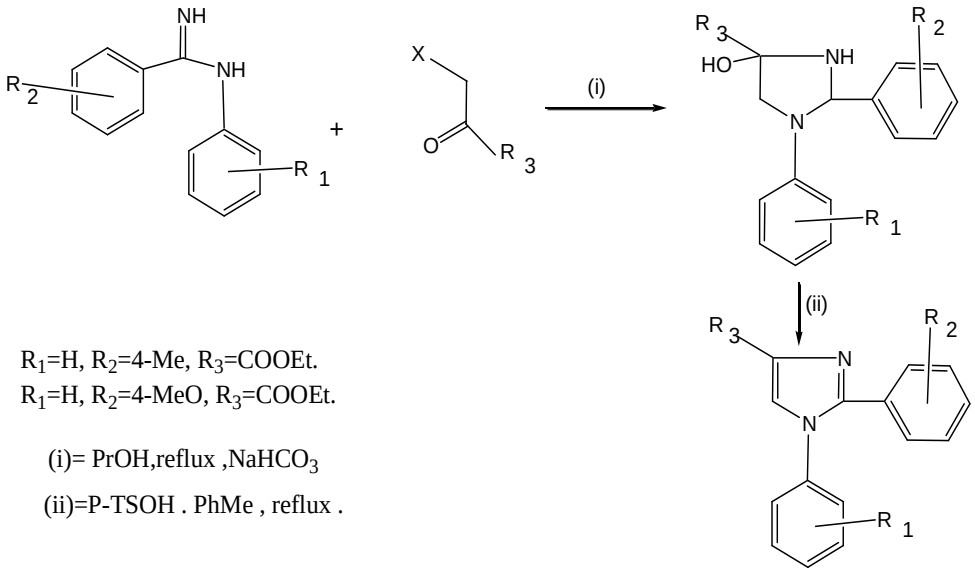
R_1 =H, 4-Me, 4-F, 4-Br.
R_2 =H, Me, Et, Br.

In 1994, kawase reported [91] that, the treatment of the meso ionic 4-trifluoroacetyl-l,3-oxazolium-5-olate(l) with formamidine hydro-chloride (2) and K_2CO_3 in DMF provides imidazoles (112).



(1) **(2)** **(3)** **(112)**

In recent years, a large number of imidazoles have been synthesized by a strategy involving treatment of amidine derivatives with 2-halomethylketone and $NaHCO_3$ in refluxing in isopropanol, followed by acid-catalyzed dehydration [92-97].



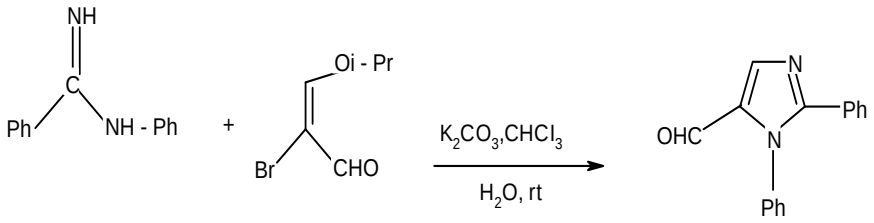
R_1=H, R_2=4-Me, R_3=COOEt.
R_1=H, R_2=4-MeO, R_3=COOEt.

(i)= PrOH,reflux ,$NaHCO_3$

(ii)=P-TSOH . PhMe , reflux .

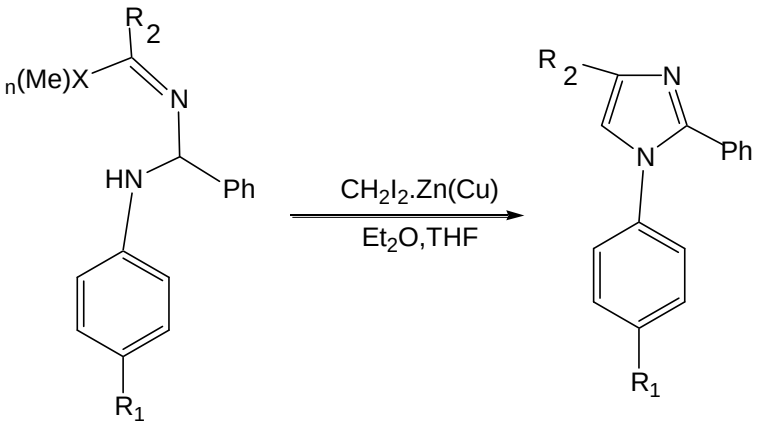
(113)

In 1997, an alkylation-cyclization sequence involving the use of amidine and α-bromoaldehyde was employed to prepare imidazole highly regioselectivity in 56% yield [(98)].



(114)

The Mahajan group had previously shown that a variety of imidazoles can be prepared in good yields by treatment of 1 -aryl-4-secondary amino-4-methylthio/methyl-2-phenyl-l,3-diazobuta-l ,3-dienes with the Simmons-smith reagent generated from diiodo-methane and zinc-copper couple in ether[(99)].



R_1 =H, Me **(115)**

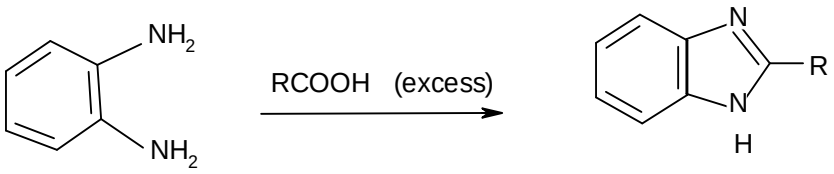
R_2 =Me, NMe_2, $N(CH_2)_4$,$N(CH_2)_5O$,$N(CH_2)_4$.

X = S, N

n = 1 for (S), 2 for (N)

(5) From diamine derivatives and related compounds:

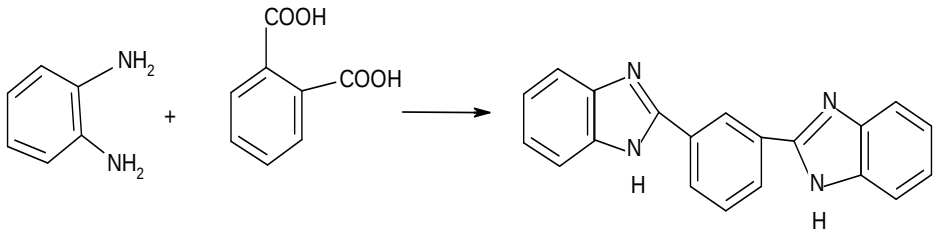
Fisher [100-105] reported that heating of o-phenylenediamine with excess of the acid gave the corresponding imidazoles.



(116)

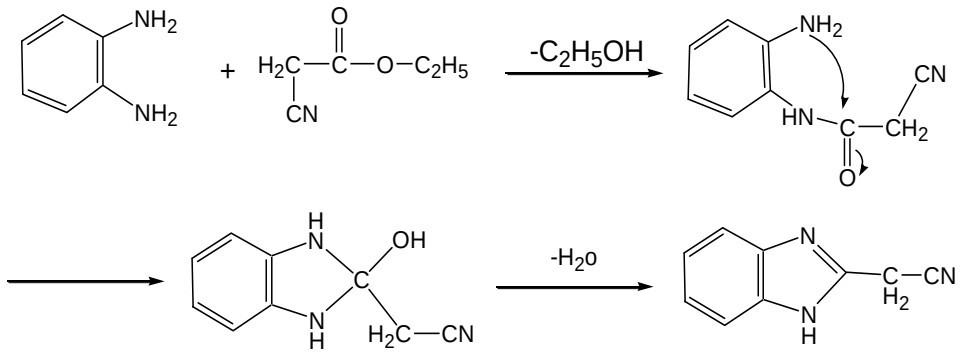
R = CH_3, $CH_3CH(OH)$-, $phCH_2$-

It was also reported that the reaction of o-phenylenediamine with aromatic acid is more suitable [106]. Thus, it reacted with isophthalic acid to give 1,3-bis(2-benzimidazolyl)benzene [107].



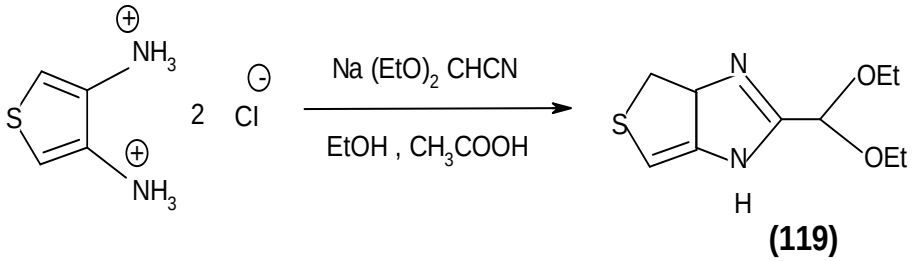
(117)

The acid derivatives such as acylchloride [108], ester [109], anhydride [110,111] were also used in the synthesis of imidazole ring, thus condensation of o-phenylenediamine with ethylcyanoacetate under reflux gave 2-cyanomethylbenzimidazole.



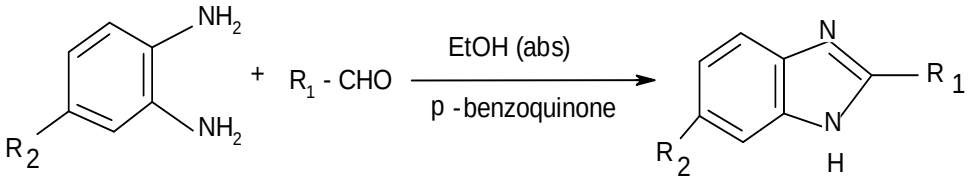
(118)

Reaction of diethoxyacetonitrile and diaminothiophene dihydrochloride in the presence of sod.ethoxide at room temperature afforded thienoimidzoles diethylacetal [112-114].



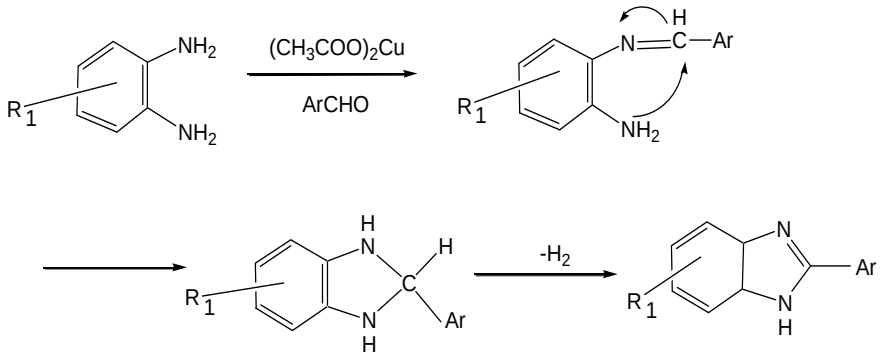
(119)

K.starceuic et al. [115-116] reported that, the imidazoles were synthesized by condensation of corresponding aldehyds and p-benzoquinone in absolute ethanol.



(120)

Weidenhagen [117] reported that, heating of o-phenylene-diamine derivatives with aldehyde in aqueous cupric-acetate or aqueous alcohol gave benzimidazole.

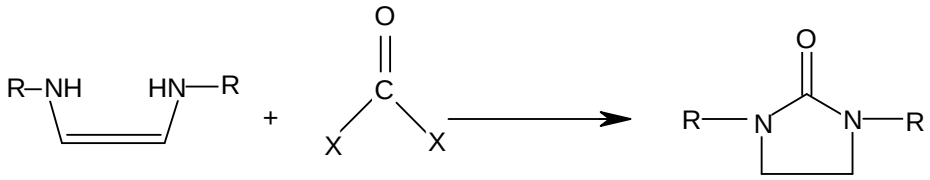


(121)

R =Cl , NO_2 Me

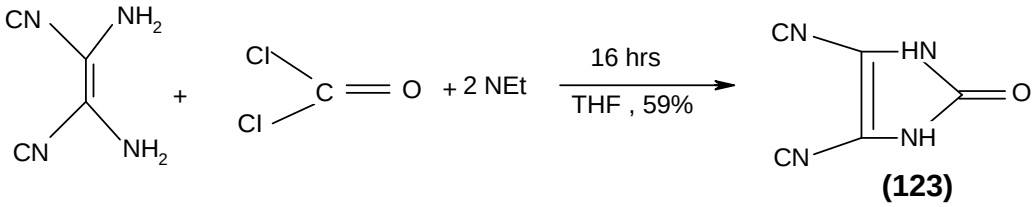
R=Ph , $C_6H_4OCH_3$(p), $N(Me)_2C_6H_3$ (p)

Also, the construction of imidazolone ring using diamine was accomplished by cyclization and carbonylation steps [118,119].



(122)

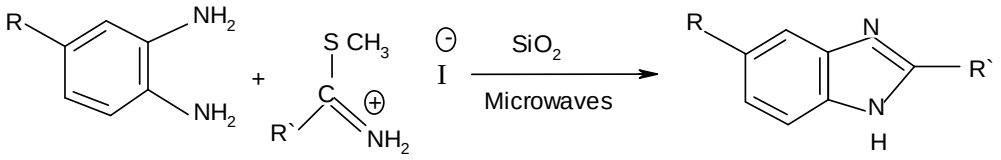
Imidazolone was also prepared by reaction DAMN (diamino-malonoitrile) with phosgene [121-,22].



(123)

Condensation of o-phenylenediamine with cyanide in the presence of acetic anhydride gave 2-acetylaminobenzimidazole [123].

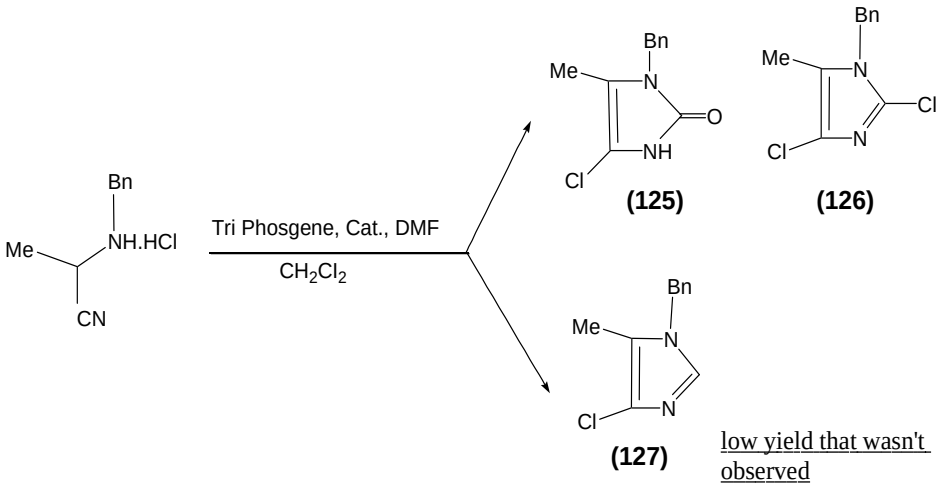
Imidazoles were prepared under dry conditions by the condensation of o-phenylenediamine with 5-methylisothioamide-hydroiodides on silica gel under microwave irradiation [124,125].



(124)

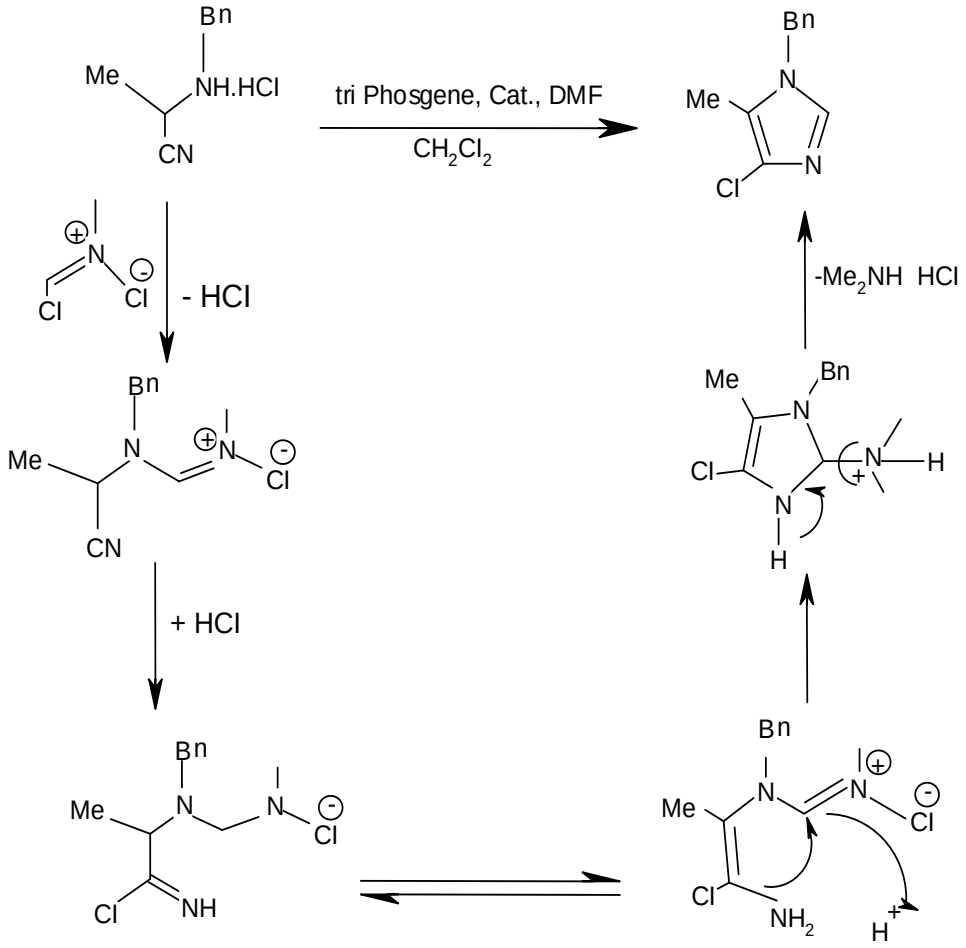
(6) From nitrile compounds:

The synthesis that were expecting the formation of chloroimidazolidione or dichloromidazoles upon treating α-aminonitriles with phosgene equivalents. However the formation of l,5-disubstituted-4-chloroimidazoles was observed in very low yields upon treating α-aminonitrile with triphosgene in the presence of catalytic amount of DMF [126,127].

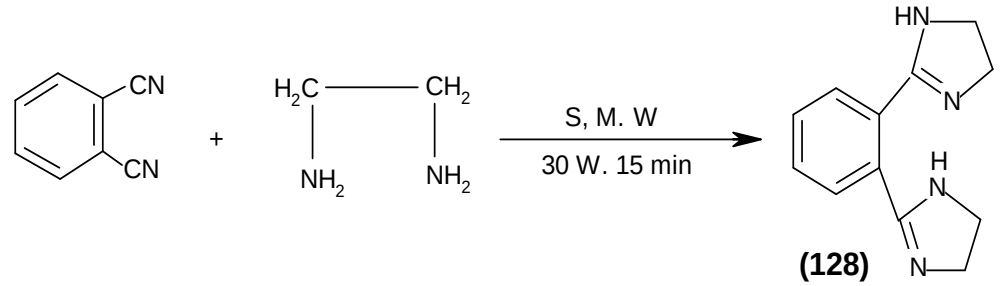


The formation of this product can be only explained by the involvement of the Vilsmeier reagent formed in situ.

The proposed mechanism for the formation of imidazoles is shown.

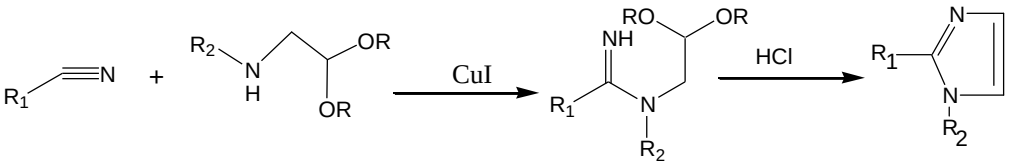


The imidazoline and imidazole ring was built by cyclization of appropriate nitrile with ethylenediamine in the presence of sulfur under solvent free conditions [128].



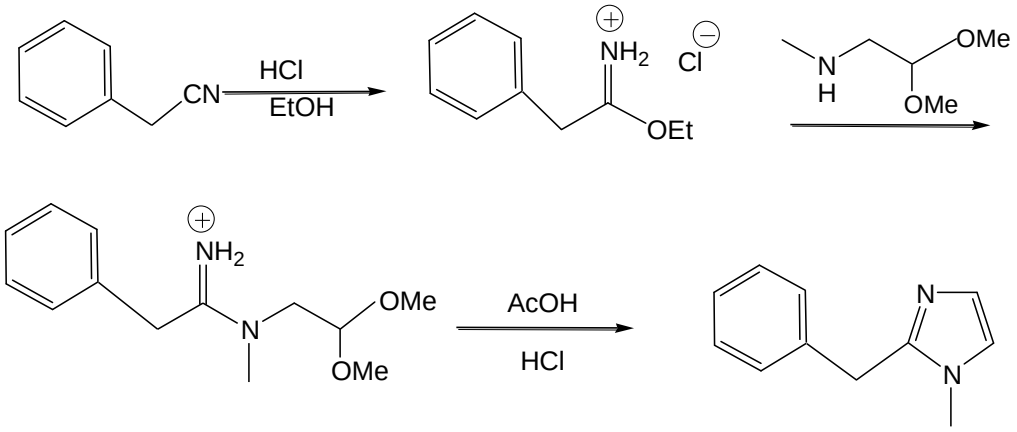
(128)

The preparation of imidazoline has previously been performed by electrophilic diamination of functionalized alkenes,[129] reaction of aziridine with platinum II nitriles [130], and reaction of aromatic nitriles with ethylene diamines by the action of elemental sulfur[131], copper Salt[132], phosphates or silica gel [133].Direct synthesis of imidazoles from nitriles and α-amino-acetals [134].



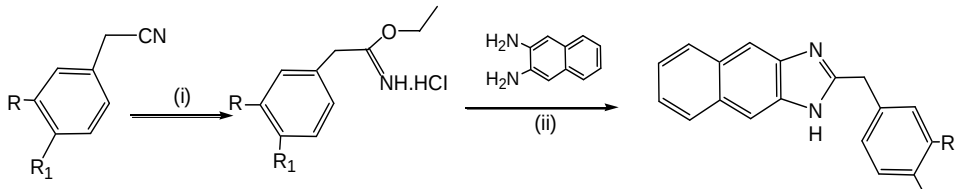
(129)

R.P. frutos et al., synthesized imidazoles using nitrile and *α*-aminoacetal [135,136].The formation of imidate salts often required prolonged reaction times (up to weak).



(130)

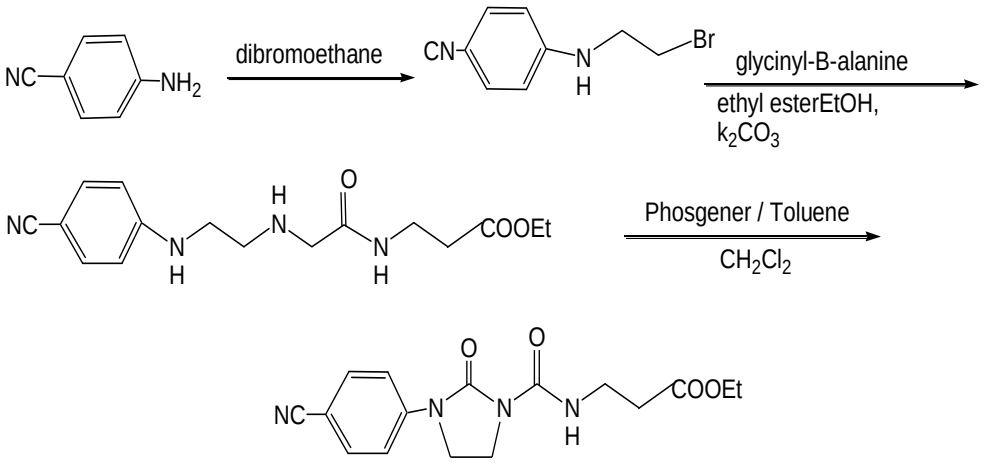
G. E. Grella et al [137], developed that, the treatment of requisite phenylacetonitriles with HCl gas and absolute ethanol in chloroform afforded imidates. The reaction of imidates with the 2,3-diamino-naphthalene gave targets.



(131)

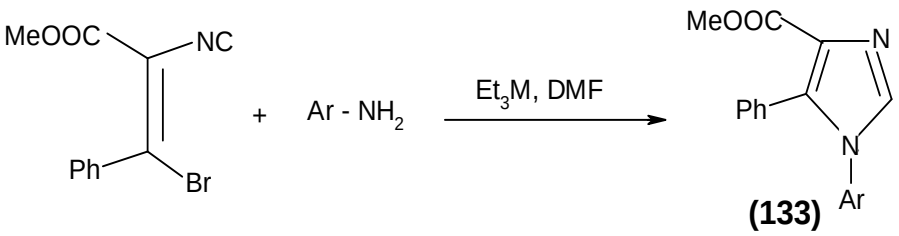
(i)=HCl(g), absolute EtOH/dry $CHCl_3$;
(ii)= MeOH

The new synthesis routs using aminobenzonitrile for the construction of imidazolone [120].



(132)

A few years later, imidazoles were synthesized by the reaction of methyl(Z)-3-brorno-2-isocyano-3-phenylacrylate with arylamine in DMF in the presence of Et_3N.[138] .

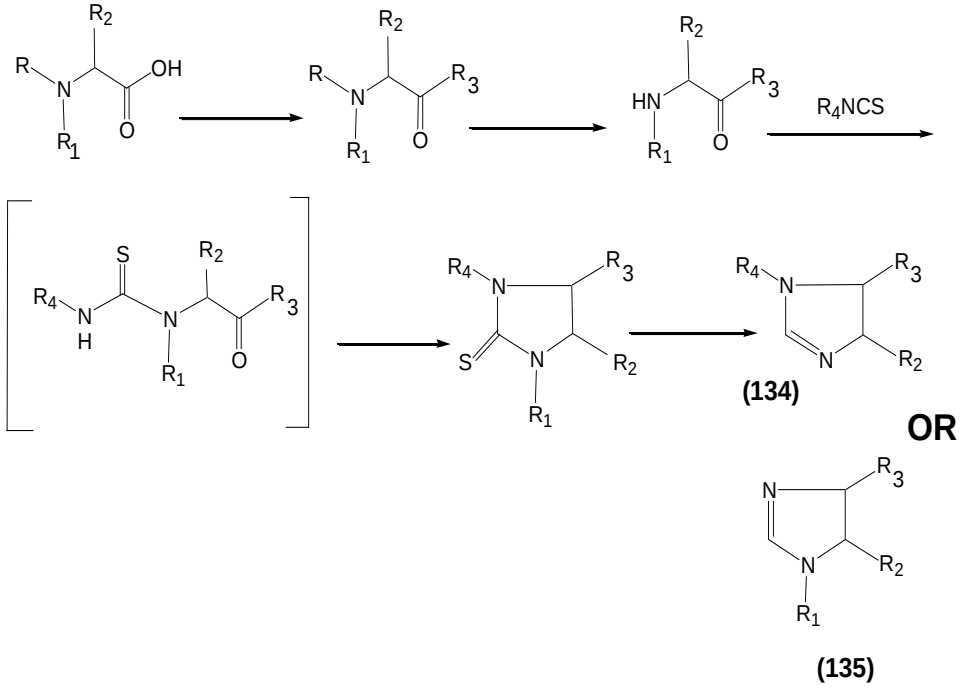


(133)

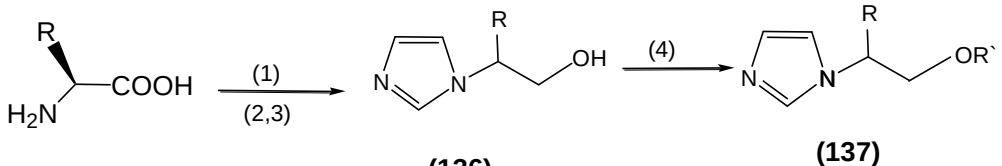
Ar= ph,4-$MeOC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, 4-ClC_6H_4,4-$MeOC_6H_4$.

(7) From amino acid compounds:

The Marckwald synthesis could be expanded to prepare regiospecific *N*-substituted imidazoles from α-amino acids [139,140].



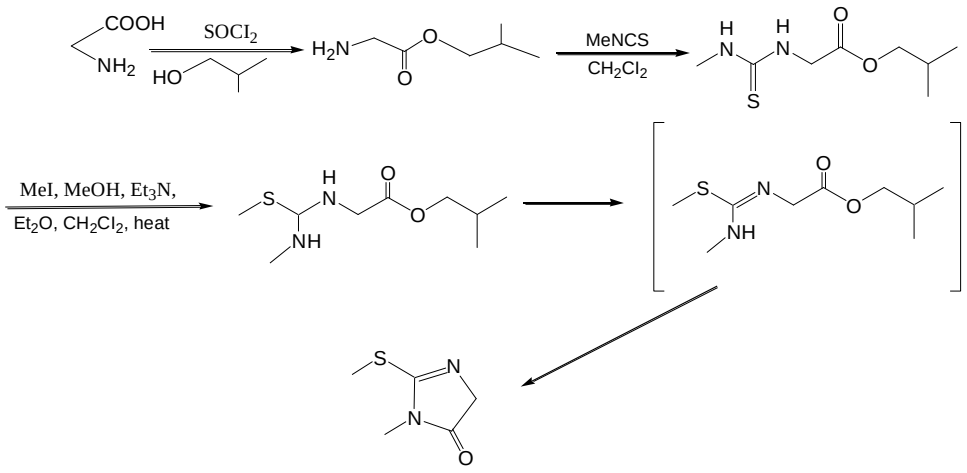
The lipophilic chiral imidazoles were synthesized according to the procedures outlined in scheme using L-alanine, L-phenyl alanine and L-glutamic acid [141].



R	CH_2ph	CH_3	CH_2CH_2COOH
R`	C_4H_9	$C_{12}H_{25}$	$C_{14}H_{29}$

(1)= $NH_3,H_2O.NaOH.H_2O$ (2)= $SOCl_2$, CH_3OH
(3)= $NaBH_4,C_2H_5OH$ (4)= NaH,THF,R'Br

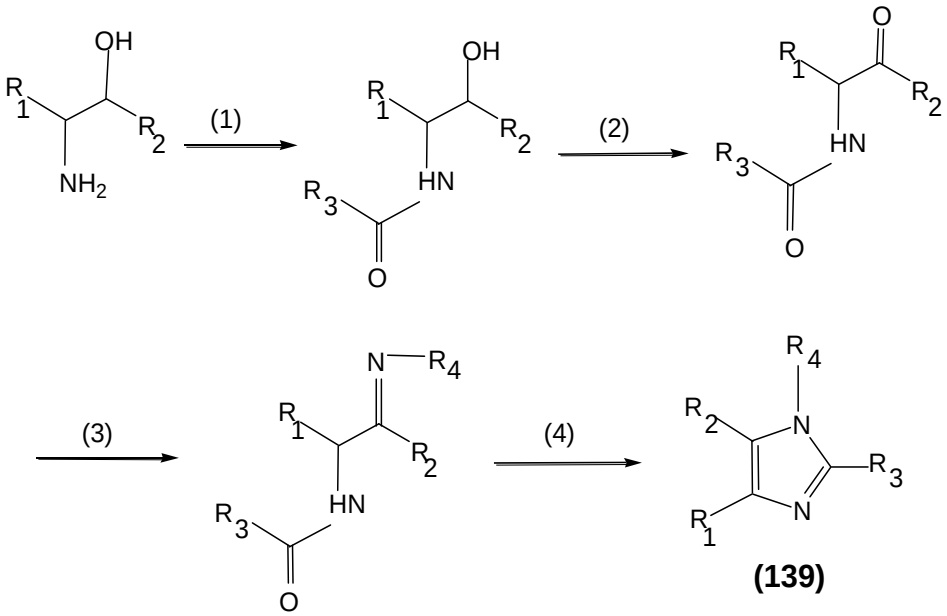
Following scheme shows the route for the cheap preparation of imidazolones compounds through "five-steps" using amino acid under microwave heating [142].



(138)

(8) From amino alcohols:

One approach to substituted imidazole involves the use of α-amino alcohol [143]. Treatment of these systems with reagent such as [PCl_5; $POCl_3$], that allow for conversion of the amide to its corresponding chloroimine, results in cyclization to the imidazole.

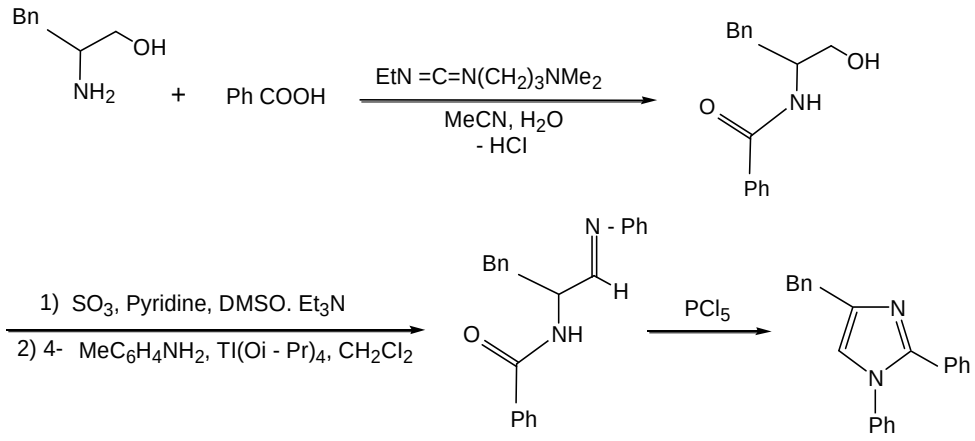


(139)

(1)= R_3-CO_2H, EDCl, CH_3CN, H_2O;
(2)= SO_2, Pyridine, DMSO,Et_3N;
(3)= R_4-NH_2, $Ti(iO\text{-}Pr)_4$, CH_2Cl_2;
(4)= PCl_5

The rout developed by Engel and Steglish [144], the α-amidoimines were derived from acid precursors via a Dakin-west rearrangement.

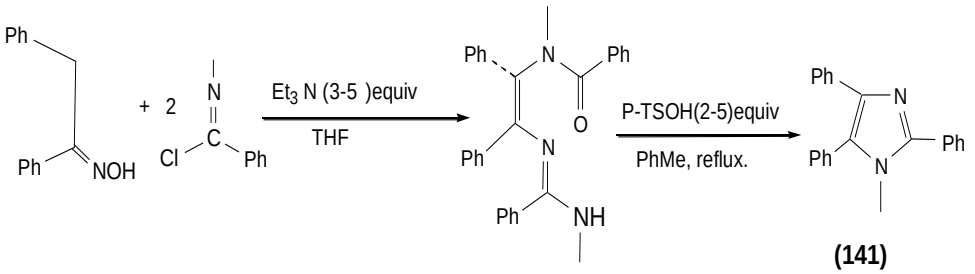
In 2004, Trisubstituted imidazole was synthesized in 65% overall yield via a four step procedure involving *N*-acylation of amino alcohol with benzoic acid , oxidation of the resulting compound , formation of imine and followed by cyclization[145].



(140)

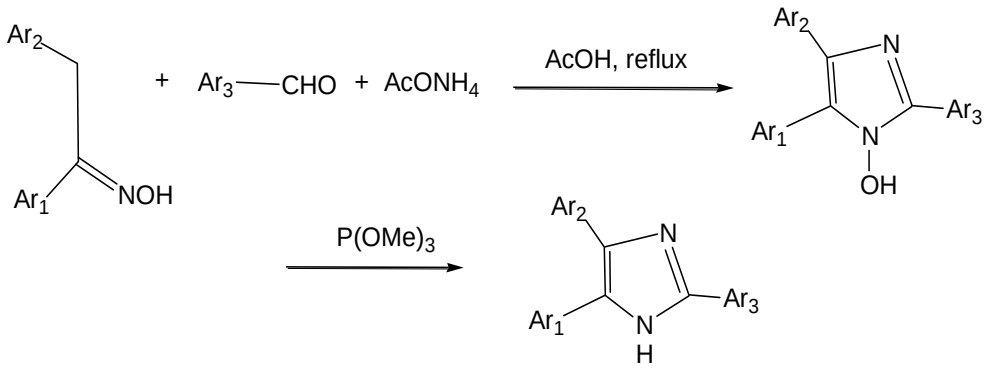
(9) From oxime compounds:

In 1993, a hetero-cope rearrangement was used as key reaction of a two step synthesis of imidazoles [146].



(141)

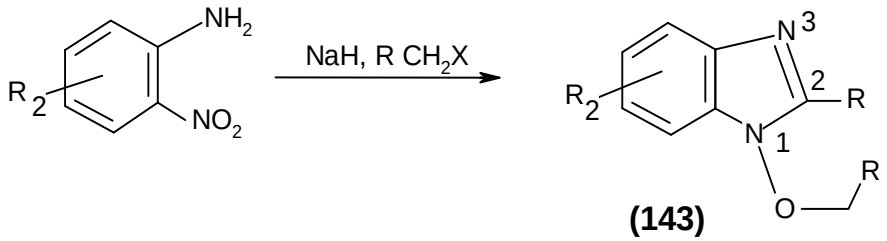
On the other hand, Gallagher and co-workers [147] synthesized imidazole by using a strategy that involves the cyclocondensation reaction of ketoximes with aldehydes and ammonium acetate.



(142)

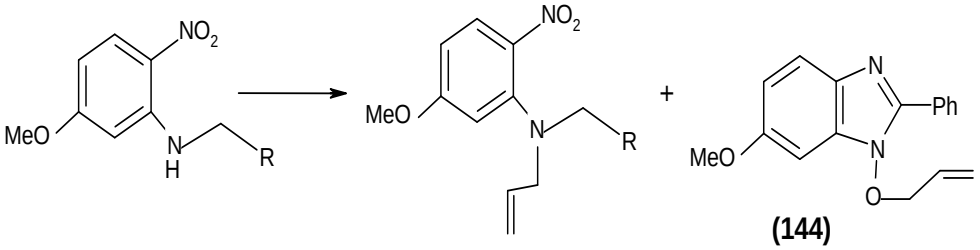
(10) From nitroaniline and related compounds:

Treatment of *N*-alkylnitroaniline with sodium hydride in the presence of various alkylating agents did lead to formation of the desired benzimidazole derivatives [148].



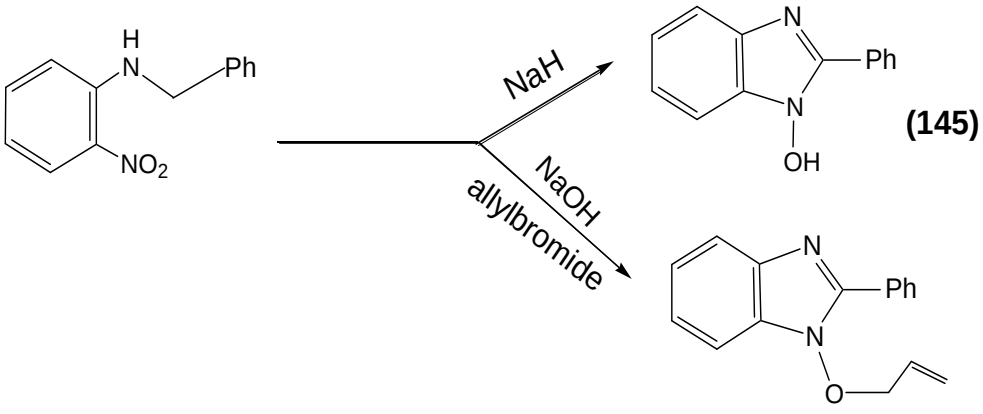
(143)

Also, *N*-benzylated substrate was reacted with alkylbromide to afford the corresponding benzimidazole along with *N*,*N*-dialkylated product (2:1) ratio.



(144)

In the absence of alkylating agent, the heterocyclization proceeded yielding the *N*-hydroxybenzimidazole [149].

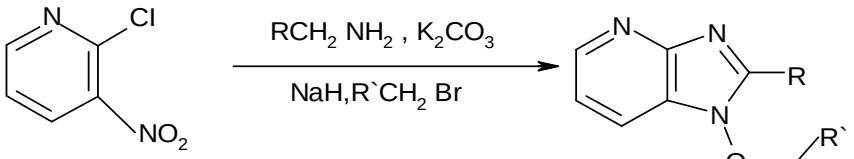


(145)

(146)

(11) From nitro-pyridine derivatives:

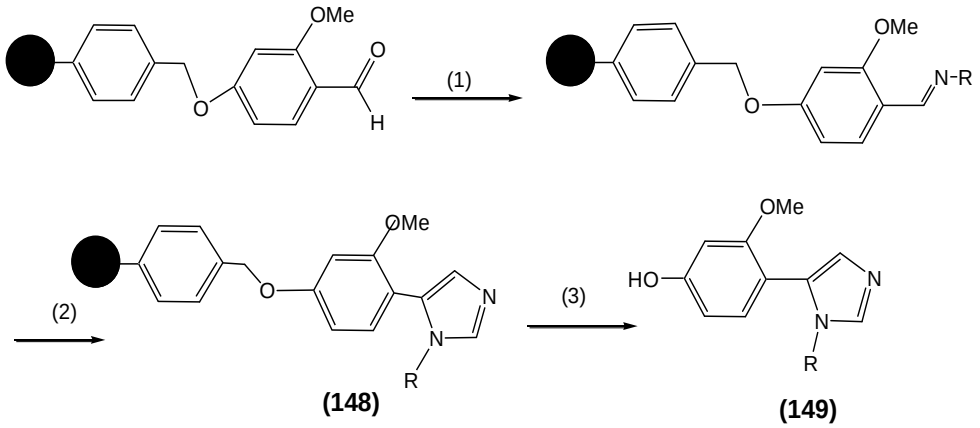
2-chloro-3-nitropyridine as starting material to provide a number of new *N*-alkoxypyrimidazoles [149].



(147)

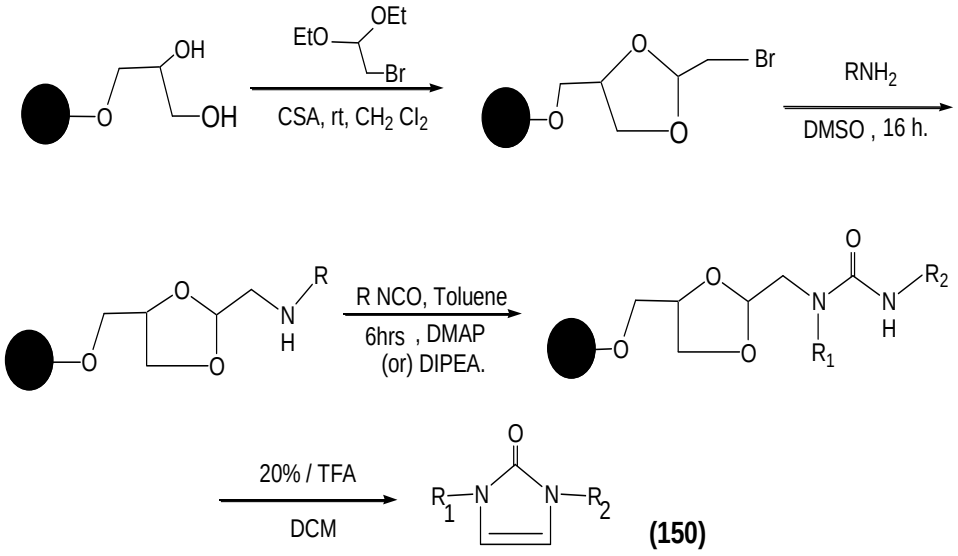
(12) From polymer bound compound:

Translation of 1,3-dipolar cycloaddition reaction to the polymer bound 3-methoxy-4-hydroxybenzaldehyde afforded imidazole ring [150] .



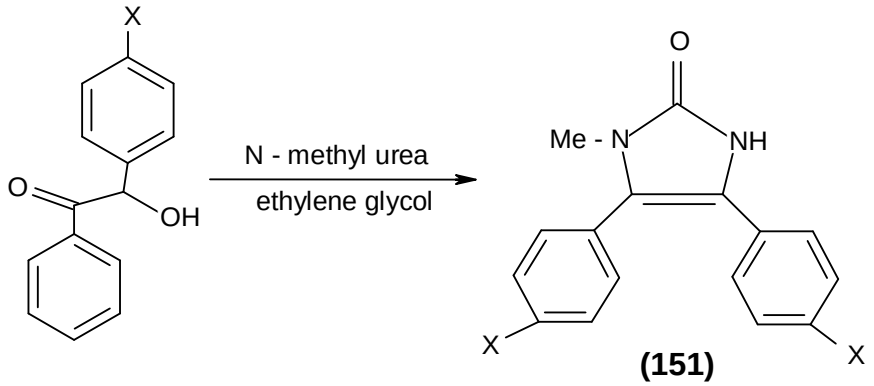
(1)= $CH(OMe)_3$, DMF
(2)= 4 -$CH_3C_6H_4SO_2$, CH_2NC, DMF20 min.
(3)= TFA/CH_2Cl_2,rt,1.5h.

Upon deprotection of the polymer bound acetal functionality under acidic conditions, the released amide or (urea) aldehyde intermediate would spontaneously undergo cyclization to form an *N*-acyliminium ion that would deprotonated.



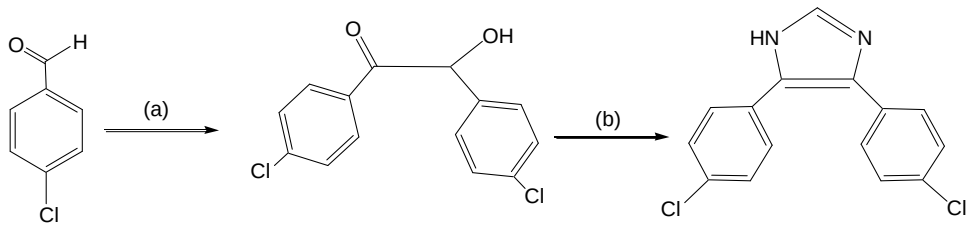
(13) From benzoin compound:

Preparation of the imidazolone derivatives, started with the thermal cyclization of benzoin with *N*-methylurea in ethylene glycol at l80°C [(156)].



(151)

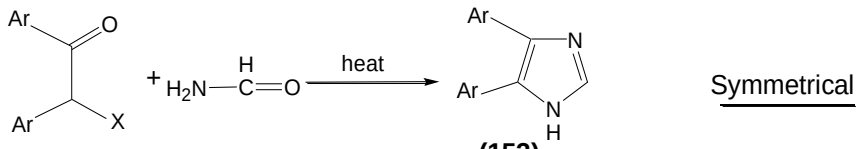
Also, C. W. Plummer et al.[53], synthesized imidazole via the following scheme.



(152)

(a)= NaCN, H_2O, EtOH
(b)= p-Formaldhyde, Formamide.

Brodereck and Theiling reported that symmetrical and unsymmetrical imidazoles respectively could be synthesized by reaction of very large molar excess of formamide with the appropriate benzoin [157], or/ 2-amino-l,2-diarylethanone [158].

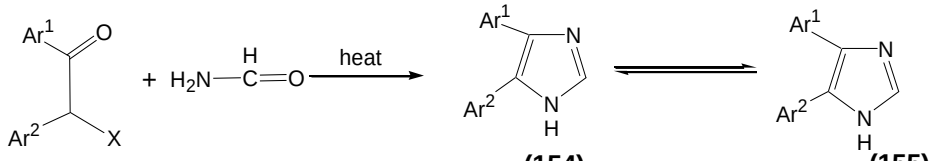


(153)

Symmetrical

X=OH

X=NH_2

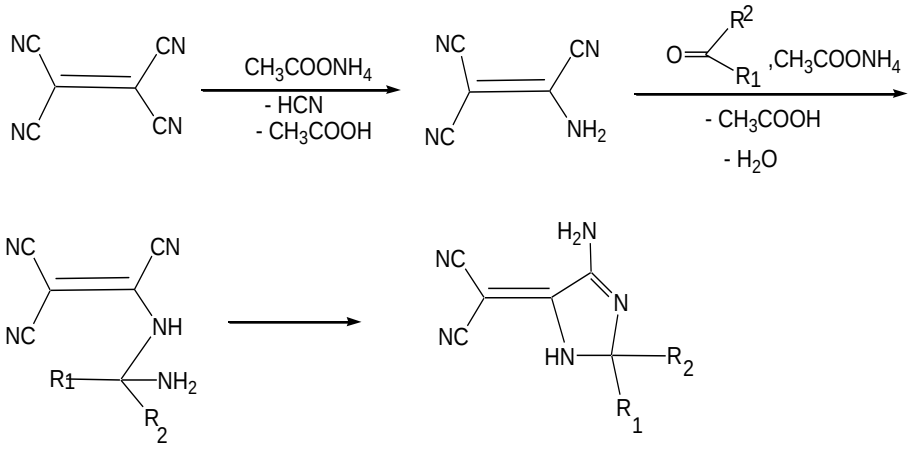


(154) **(155)**

Unsymmetrical

(14) From tetracyanoethylene:

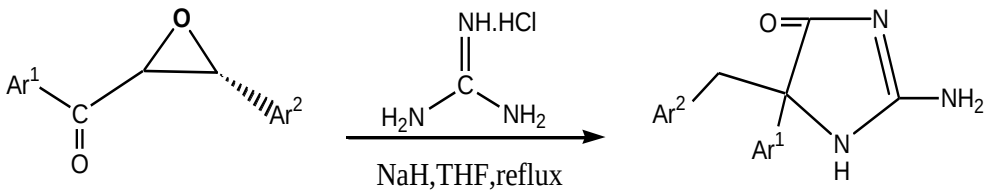
A new method via [3+2]heterocyclization reaction for the preparation of imidazoles using tetracyanoethylene as starting material [159-161].



(156)

(15) From Epoxydiphenylene:

2,3-Epoxydiphenylketone react with guanidine or urea to form 2-amino-4H-imidazol-4-ones and analogous hydonations via a novel one potrearrangement[162].

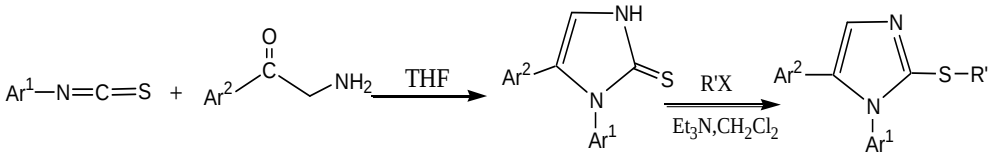


(157)

Ar	C_6H_4.OMe(4)	C_6H_4.Cl(4)	C_6H_5
Ar	C_6H_3.$(OMe)_2$(3,4)	Ph	Ph

(16) From β-aminoketones compounds:

In 2002, a combinational library of imidazole was synthesized by alkylation with imidazole-2-thiones obtained via reaction of arylisothiocyanates [163].



(158)

Ar^1= Ph,C_6H_4.OMe(3)

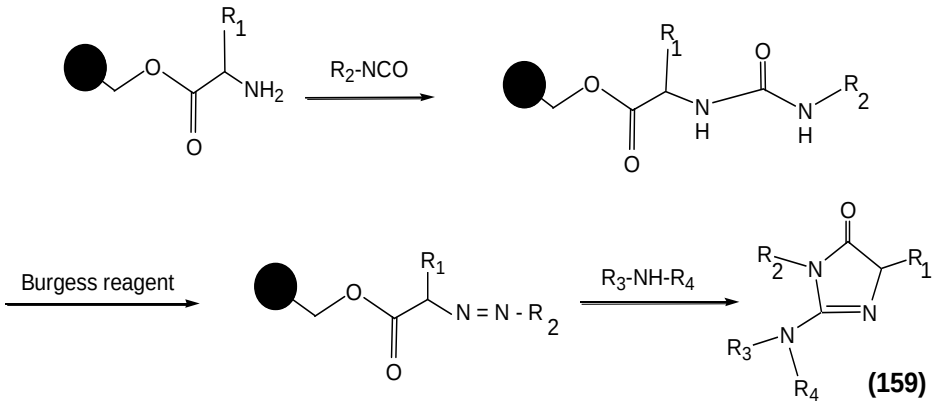
Ar^1= Ph,C_6H_4.OMe(4)

R^1= CH_2(3-indolyl),2-NO_2Bz,CH_2NEt,

CH_2CH_2(1-pyrrolyl),CH_2(2-NO_2 furyl),

CH_2CH=CH-Me

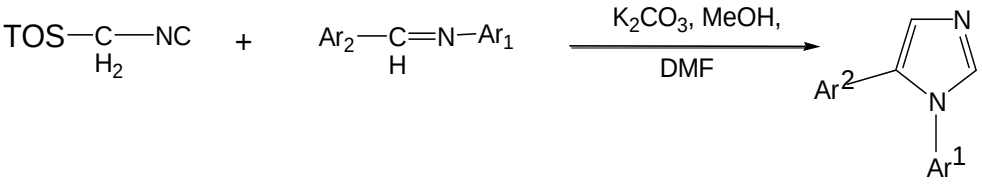
Starting from inexpensive Merifield resin which reacted with urea and an aryl isocyanate lead to formation of imidazolones [164-172]



(159)

(17) From schiffs base:

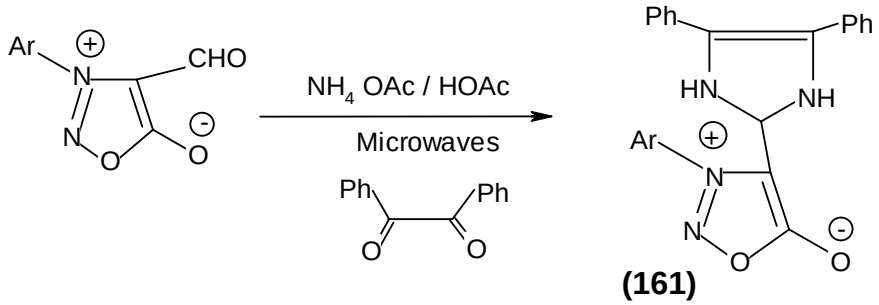
In particular, the vanleusen group found that the base-induced [3+2]cycloaddition of *p*-toluene sulfonyl isocyanide to *N*-(arylidene)anilines in aprotic medium occurs with concomitant elimination of *p*-toluene sulfinic acid to give imidazole [173-176] .



(160)

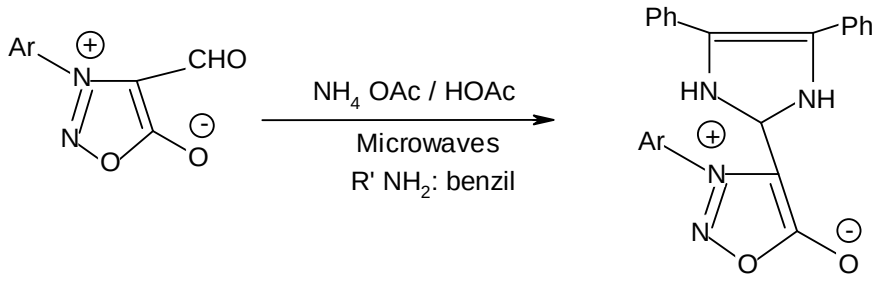
(18) By using microwaves:

Via the one pot condensation of 3-aryl-4-formylsydanones with symmetrical 1,2-dicarbonyl compounds; including benzil in glacial acetic acid using ammonium acetate under microwave irradiation.



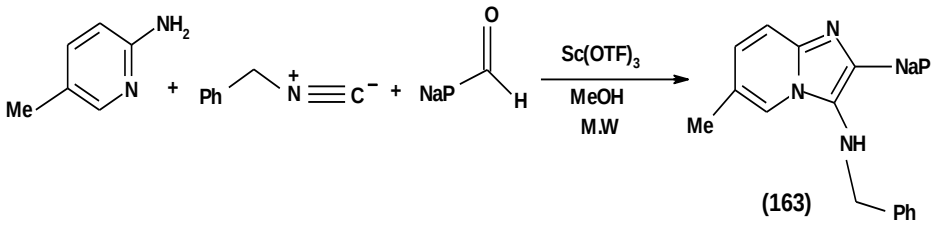
(161)

The same condition with 4,4' -dimethoxy, 4,4` -difluorobenzil and 2-dithienylethanedione used to synthesis imidazole derivatives. A similar treatment yields imidazoles by condensation with primary amine under microwave conditions [177].



(162)

Microwave assisted vgi3cc reaction of 2-amino-5-methyl-pyridine with benzyl isocyanide and 2-naphthaldehyde [178].

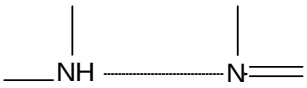


(163)

CHEMICAL REACTION OF IMIDAZOLES AND IMIDAZOLONES

Properties of imidazoles and imidazolones:

When Hunter and Marriot [181] carried out some crescopic structure of a series of imidazoles, they found that *N*-unsubstituted imidazoles were highly associated, but the association is prevent by replacement of the iminohydrogen. It was believed that the association involves hydrogen bond [182] between the imino group of one molecule and the tertiary nitrogen of another molecule.



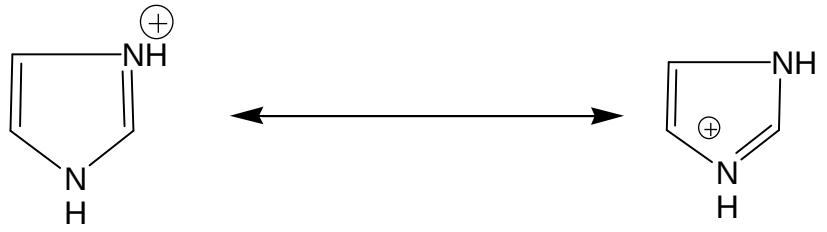
Reaction of neutral imidazoles:

Imidazole can be considered as having properties similar to both pyrrole and pyridine. In consequence one would expect that electrophilic agents would attack by electrophilic radical and nucleophilic species. Substitution reactions, which do not destroy the aromatic character, are predominant while the imidazol ring susceptible the electrophilic attack on an annular carbon. It is much less likely to involve in nucleophilic substitution reactions unless there is a strongly electron withdrawing substituent elsewhere in the ring.

Basicity of imidazole:

Imidazole is the most basic of the azoles and forms salts with a wide variety of the acid both organic and inorganic. Thus, hydro-chloride and nitrate salts were well defined, although they may be hygroscopic. Salts of organic acids, e.g., oxalate and picrates from readily and their relatively low solubilities in aqueous medium have made them extremely useful for the isolation and purification of imidzoles.

The stability of an imidazolium salt is a function of the symmetrical cation which is resonance stabilized.



(164) **(165)**

Methyl and other alkyl substitution exert a weak base. Aromatic substituent decrease basic strength while groups attached to these aryl rings exert their normal behavior.

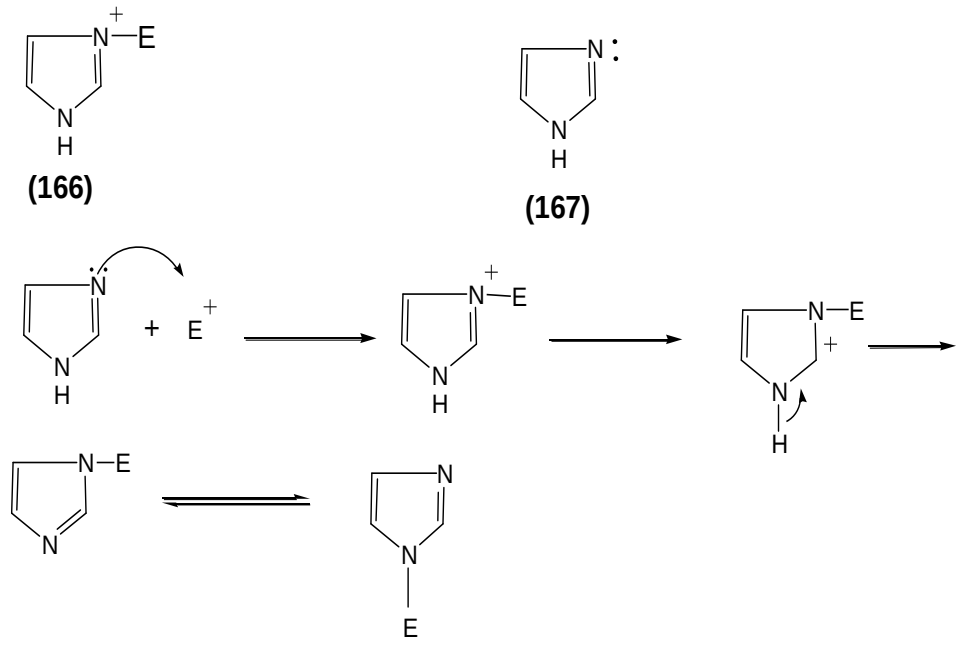
Acidity of imidazole:

The N-H proton in simple imidazoles is weakly acidic. Thus, the compounds are able to form salts with a number of metals. The anion which forms on loss of the proton is again symmetrical and highly susceptible to attack by electrophiles.

1- Electrophilic attack

A- Electrophilic attack on nitrogen:

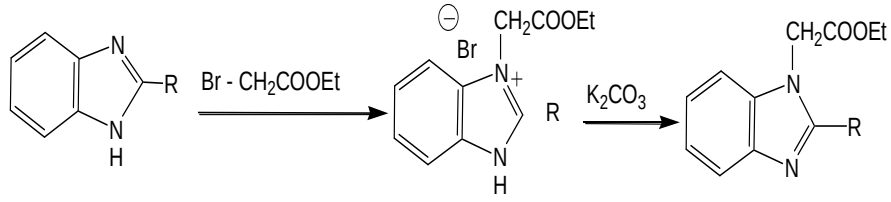
Reaction with the N-H nitrogen would require the use of the electrons from the 6 π system will disturb the aromaticity. For this reason the transition state **(166)** would be energetically more favorable than **(167)** and in consequence reactions with the imidazole neutral molecule follow the following sequence:



(166) **(167)**

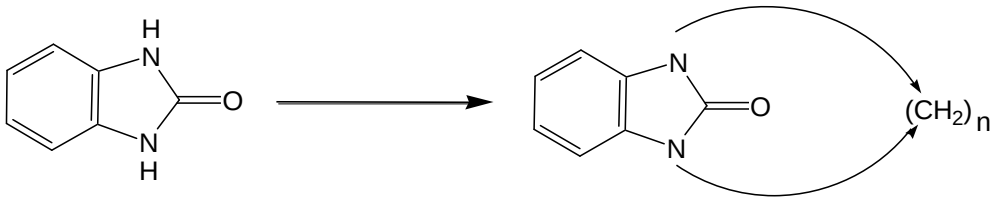
1) Alkyl halides and related compounds:

The quaternization of substituted imidazole and imidazolone is a facile reaction which leads to a stable quaternary salt there are number examples of quaternizing alkylations of imidazoles and imidazolones using alkyl, alkenyl, ethylhaloacetate, phenacylbromide or dimethylsulphoxide[(183)], for instance ethyl-1-benzimidazolyl-acetate and their 2-alkyl derivatives were easily obtained by reaction of benzimidazoles with ethyl/methylbromoacetate in DMF containing anhydrous K_2CO_3 [(184-185)].



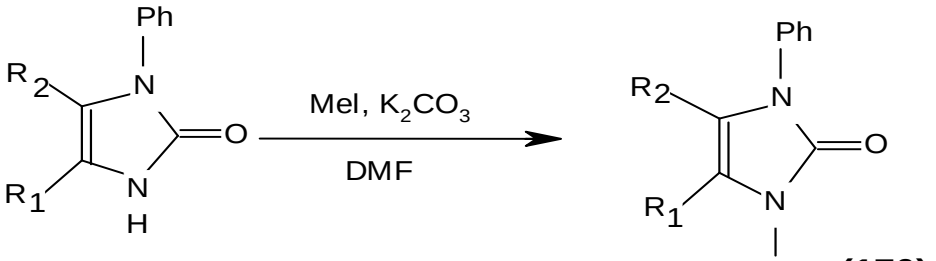
R = H, alkyl group **(168)**

2-Benzimidazolinone was alkylated using dibromoalkanes in a basic medium giving 1,3-polymethylenebenzimidazolinone [(186)].



(169) n = 10 - 12

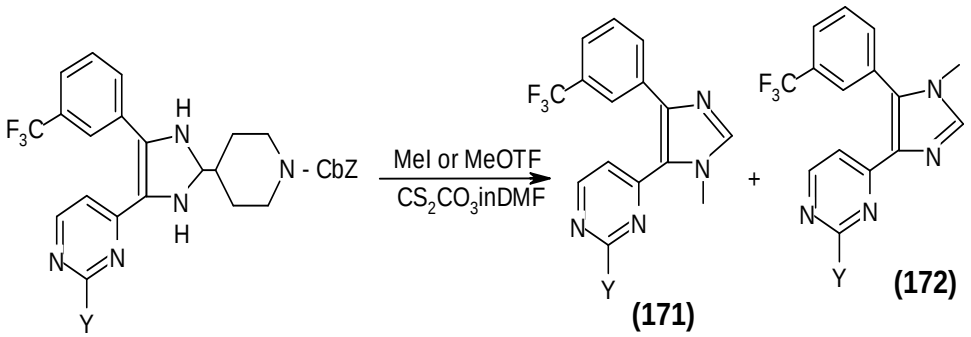
Also, Alkylation of imidazolone using MeI and K_2CO_3 were described [65].



(170)

R_1	E	E	CONHPh	$CONMe_2$	COPh
R_2	Ph	Me	Ph	Me	Me

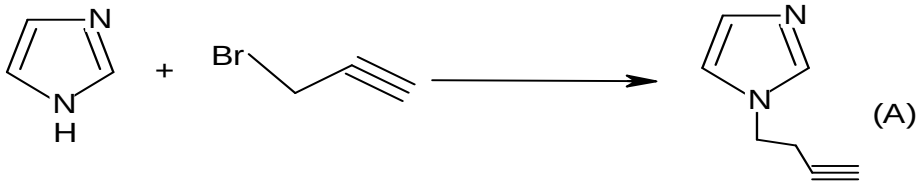
However, methylation of imidazole using iodomethane, Cs_2CO_3 in DMF furnished the undesired regioisomer, together with less than 5% of the required product and this result wasn't altered using methyl triflate as electrophile [187].



Y=SMe
Y=SO_2Me

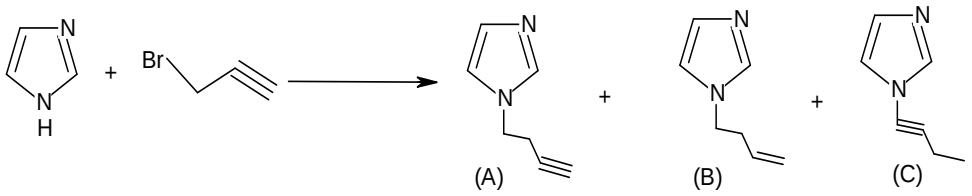
(171) **(172)** Major product

Alkylation of imidazole with propargl bromide under microwave radiation [188].



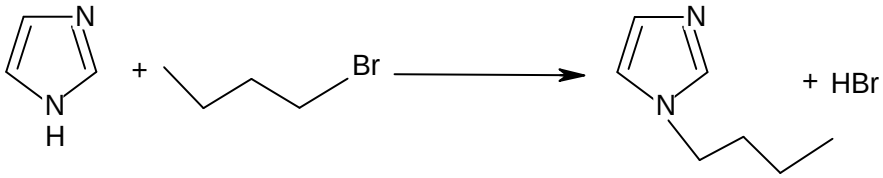
(173)

But usually, in basic media the reaction affords a mixture of *N*-ally and *N*-propargl (C) derivatives [189-190].



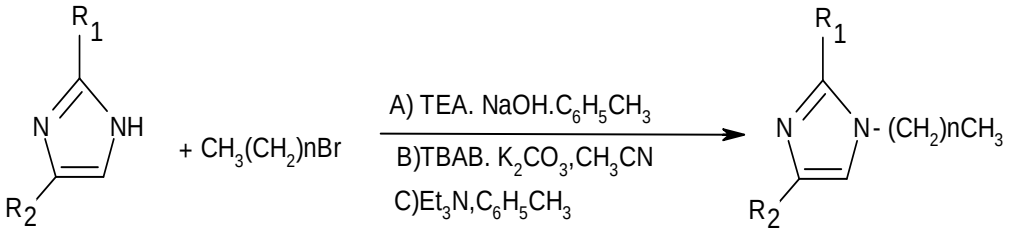
(174) **(175)** **(176)**

Also, imidazole was alkylated using 1-bromobutane using activated carbons as a catalyst [191].



(177)

Different azole compounds were reacted with appropriate alkyl bromides in an alkaline media, at reflex temperature and in the presence of (TEAI) or (TBAB) as phase transfer catalysts by A,B,C [192] **.**

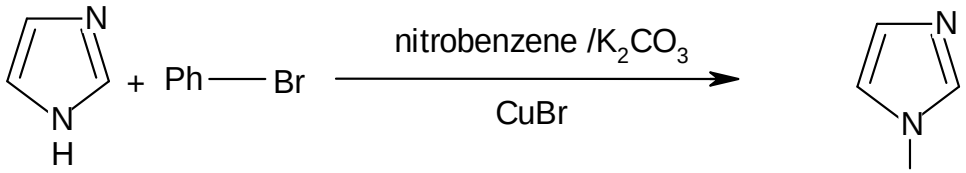


(178)

R_1=H,CH_3
R_2=H,NO_2

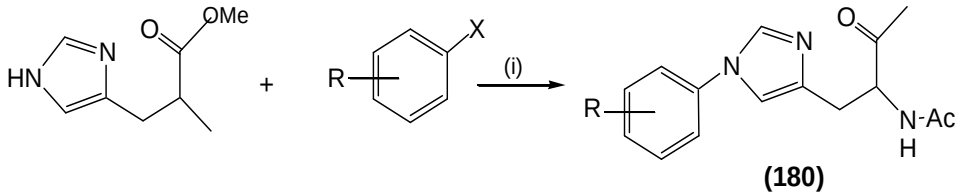
2) Aryl halide and related compounds:

Arylation at ring nitrogen was not simple procedure because halides are not usually susceptible to nucleophilic displacement of halogen group. A modified ullmann-type reaction an imidazole using bromobenzene in the presence of potassium carbonate in nitro-benzene and copper bromide gave a reasonable yield of 1-arylimidazole [193].



(179)

Also, Kiyomori et al. [195], described a modified ullmann-type coupling of simple imidazoles with aryl iodides or bromides using $Cu(OTF)_2$. PhH as a catalyst in the presence of o-phenanthraline, dibenzylidene acetone and cesium-carbonate in hot xylene, direct flash chromatography afforded clean products [196-197].



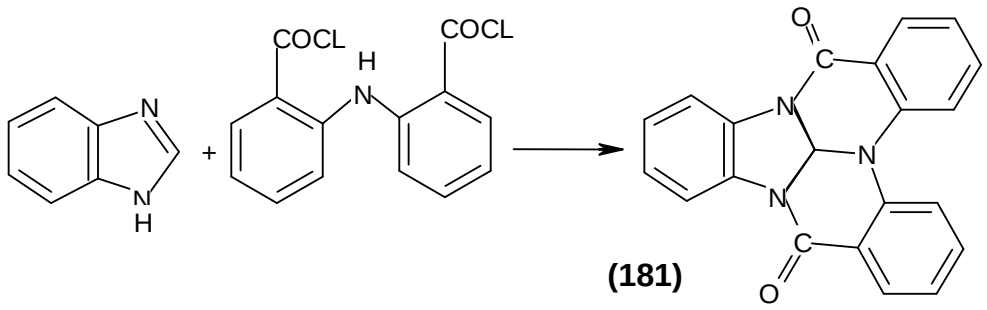
(180)

(i)=Cu(1),O-Phen/LiOH;
CS_2CO_3, DMF, hot, xylene .

R = H , p-Br , m-Br , p-Cl, p-CH_3, m-CH_3, p-OCH_3

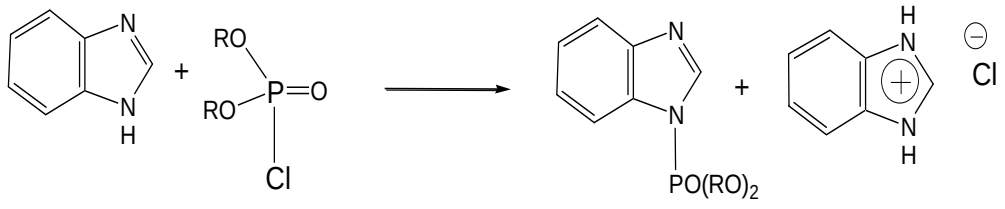
3) Aroyl halides and related compounds:

Imidazoles are readily acylated, arylated and may be converted to quanternary salts. In one such reaction the imidazole eventually partially dearomatized compounds to reaction with bis-(chloroformyl)diphenyl amine [198].



(181)

Reaction of benzimidazole with dialkylphosphorylchloride gave 1 - dialkylphosphorylbenzimidazole [199].

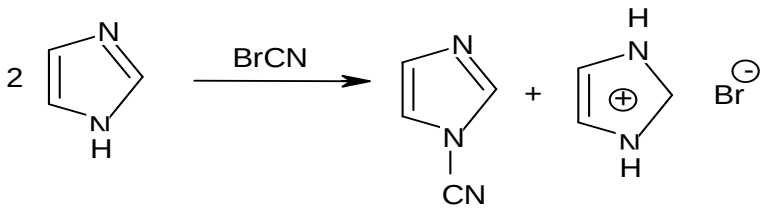


(182)

4) Other electrophiles:

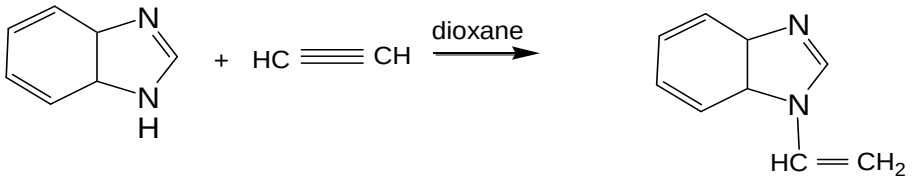
-Reaction of cyanogens bromide with imidazole:

Having a free NH group gave the corresponding *N*-cyano derivatives [200].

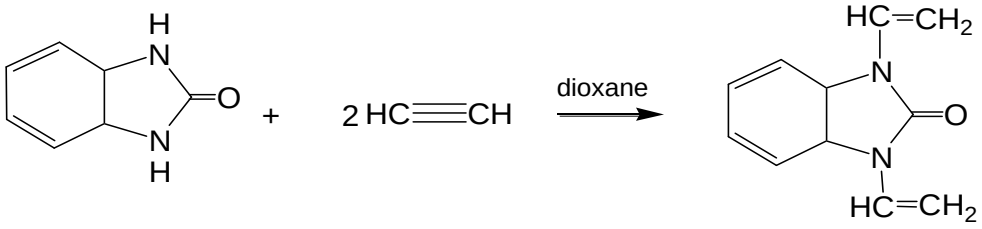


(183)

Also, addition of acetylene in aqueous dioxane to imidazole and imidazolinone afforded 1-vinylbenzimidazole and benzimidazolinone respectively [200].



(184)

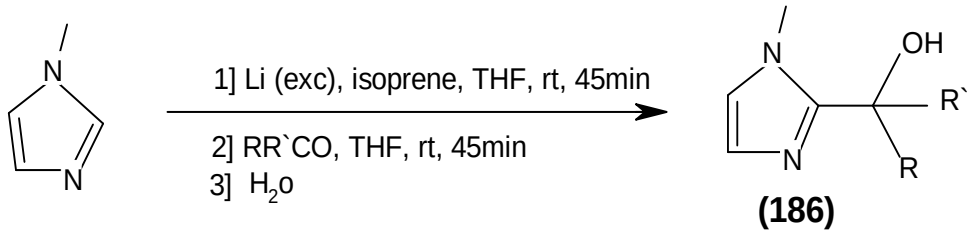


(185)

B- Electrophilic attack on carbon:

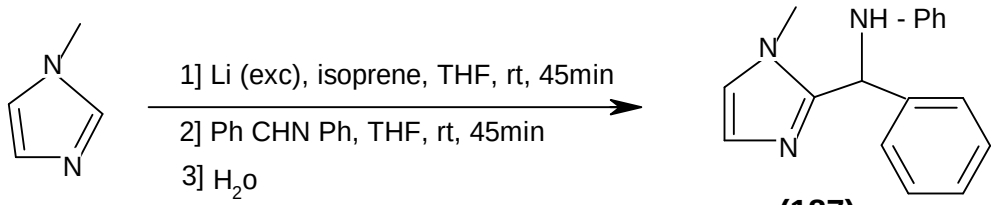
1) Alkyl halide and related compounds:

Imidazoles could be treated with different carbonyl compounds as electrophiles using lithium metal and isoprene in DMF at room temperature [201-203].



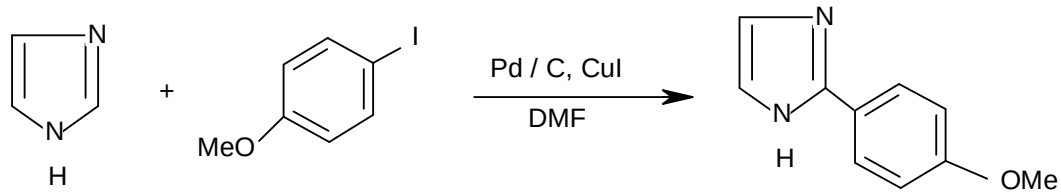
(186)

Also, it was reacted with different arylaldimines as electrophiles in situ [204].



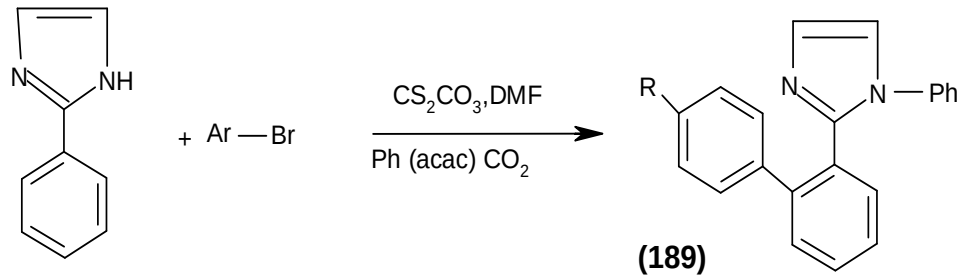
(187)

More recently, there was established that, the regioselective C-2 arylation of imidazole with aryliodides can conveniently be performed in DMF in the presence of CuI using Pd $(OAc)_2$ as the catalyst [205-207]



(188)

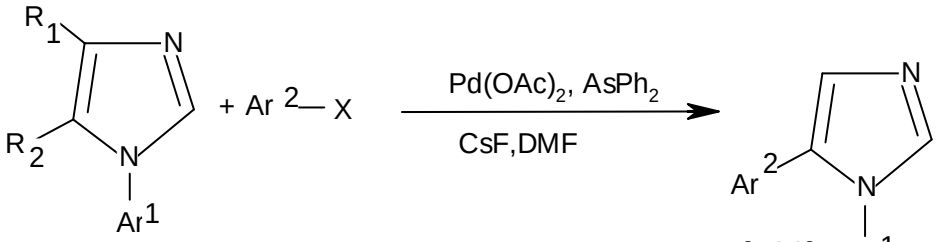
In fact, in 2003, it was claimed that imidazole can undergo a highly regio-selective C-2 arylation reaction by treatment of an aryl bromide in DMF in presence of'CS_2CO_3 [208].



(189)

Ar	Ph	4-$MeOC_6H_4$	4-$CF_3C_6H_4$
R	H	4-$MeOC_6H_4$	4-$CF_3C_6H_4$

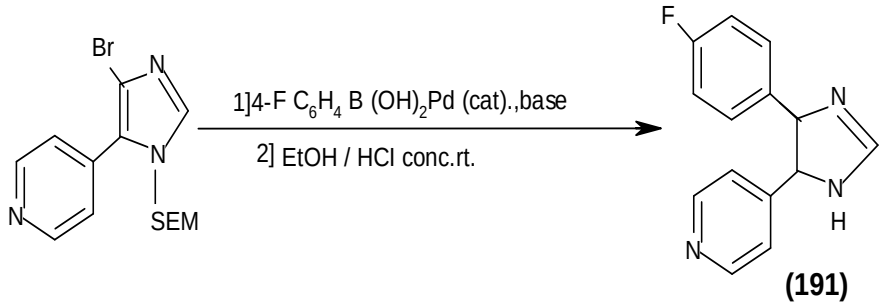
Also, Direct arylation of imidazoles with aryl halides [209]. The reaction conditions most suitable for a highly regioselective C-5 arylation of imidazole.



(190)

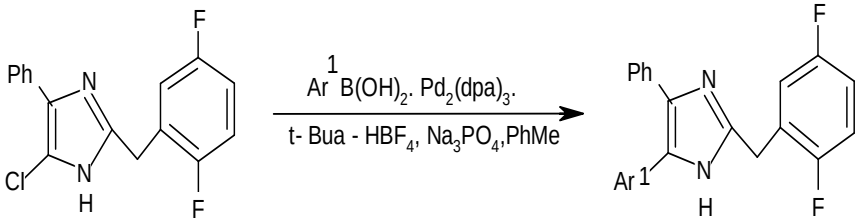
Ar^1 = ph
R_1=R_2= H

On the other hand, the C-4 arylation of imidazole was performed by a Suzuki-type reaction with 4-fluorophenylboronic acid [210].



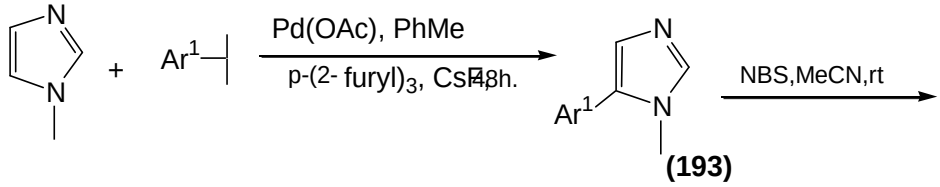
(191)

Also, Pd-catalyzed Suzuki-coupling involving the use of the unprotected 5-chloroimidazole [213] as the substrate has also been described.

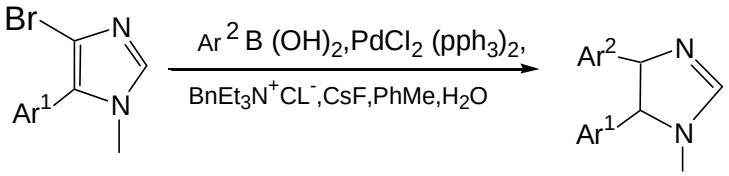


(192)

Suzuki-type coupling reactions under phase-transfer condition have also been described [213].

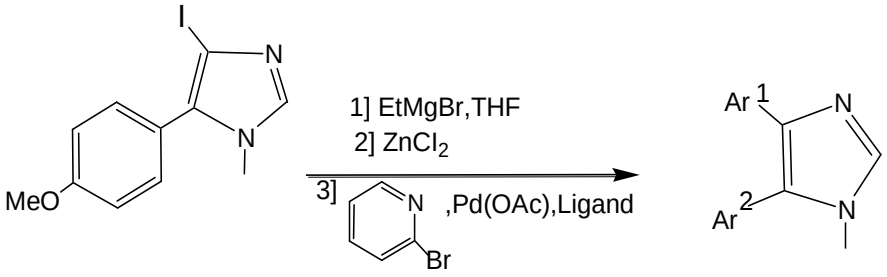


(193)

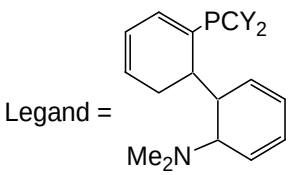


(194) **(195)**

A pd-catalyzed Negishi-type reaction cross-coupling reaction was employed on imidazole using bromopyridine [214].



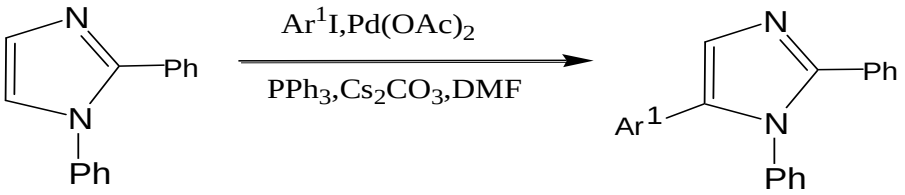
(196)



Ar^1 = 2-pyr,

Ar^2 = 4-$MeOC_6H_4$

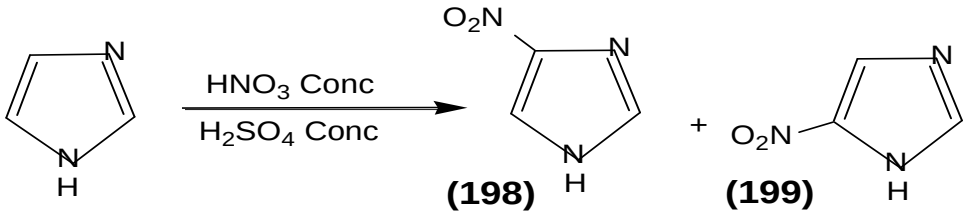
C-5 arylation of imidazoles with required aryl iodides under the optimized conditions originally reported by Miura [215-216].



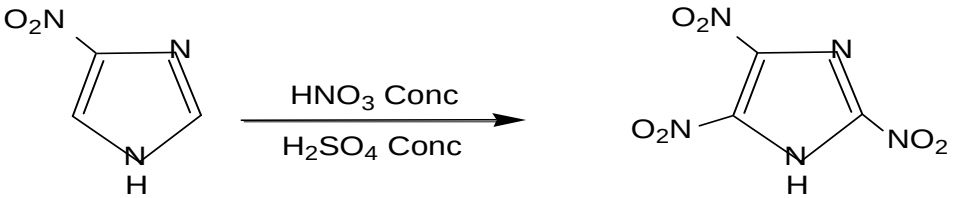
(197)

2) <u>Nitration</u>:

Nitration of imidazole [217] with a mixture of concentrated nitric and sulfuric acids gave the corresponding 4-nitro and 5-nitro derivatives. There is no substitution at C-2, therefore the important antibiotic 2-nitroimidazole (azomycine) can not be prepared by direct nitration. Variations in reaction conditions such as heating imidazole with sulfuric acid, addition in mixed acid gives sucessifly 4-nitroimidazole and 5-nitroimidazole and 2,4,5-trinitroimidazole can be prepared by nitration of 2,4-dinitroimidazole [218].

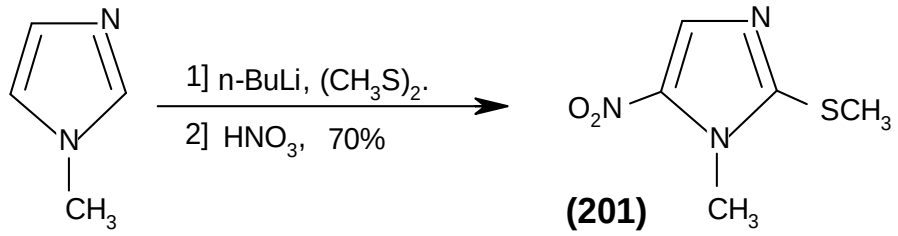


(198) **(199)**



(200)

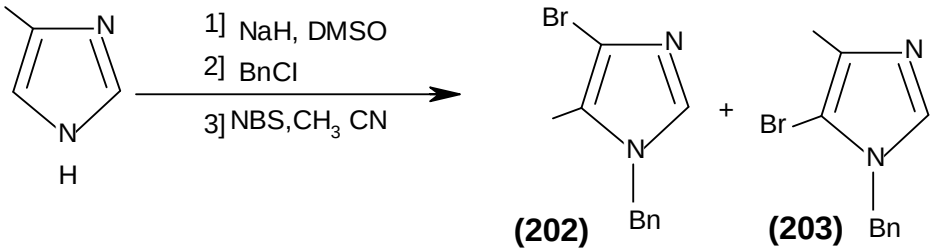
The reaction of imidazole with n-butyl lithium at 30^0C and subsequent addition of dimethyldisulfide and then nitration of the product compound afforded the corresponding 5-nitroimidazole [219].



(201)

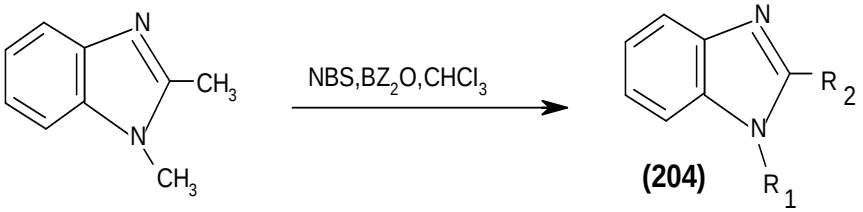
3) <u>Bromination</u>:

Treatment of imidazole with NaH and BnCl [(220)] and then Brominated with NBS to afford bromoimidazoles [(221-222)].



(202) **(203)**

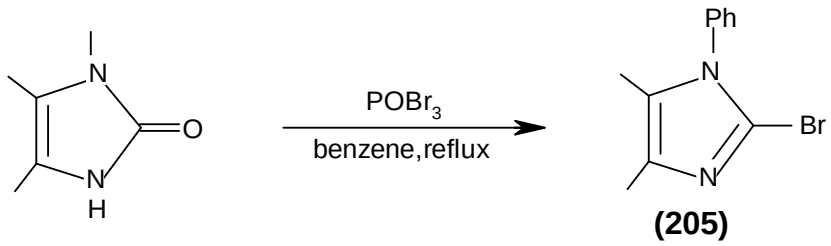
Also, imidazole was brominated with *N*-bromosuccinimide under free radical substitution condition gave brominated imidazoles [(223)].



(204)

a=R_1=R_2=CH_3Br, R_3=R_4=H
b=R_1=$CHBr_2$, R_2=CH_2Br, R_3=Br, R_4=H
c=R_1=R_2=CH_3, R_3=Br, R_4=Br,H

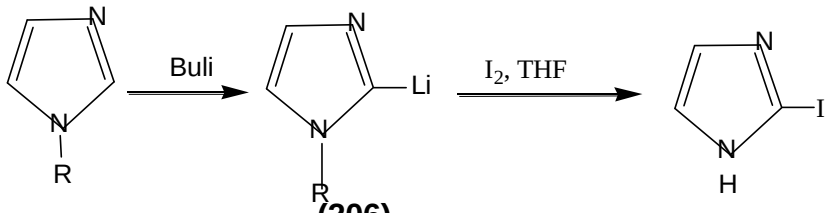
Also, chlorination [(53)], Bromination of imidazolone were done [(63)].



(205)

4) Iodination:

In alkaline medium imidazoles are subjected iodination on ring nitrogen, giving 1-iodoimidazole was prepared via the lithiation of imidazole [224].



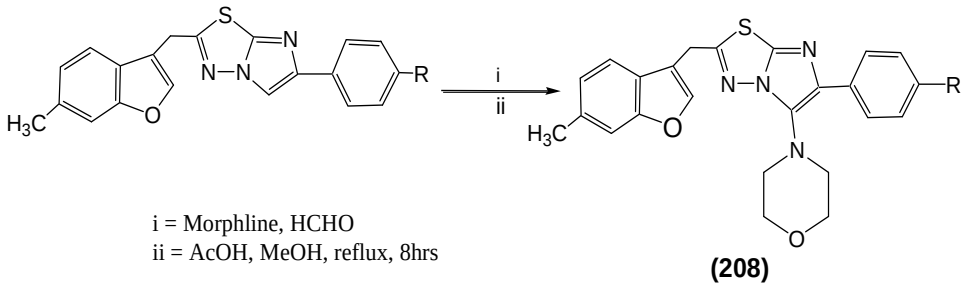
(206) **(207)**

R = SO_2Ph
R = CPh_3

5) Reaction with aldehydes and ketones:

Mannich reaction:

Imidazoles undergo Mannich reaction with cyclic secondary amine namely, (morpholine and formaldehyde) in presence of catalytic amount of acetic acid [50].

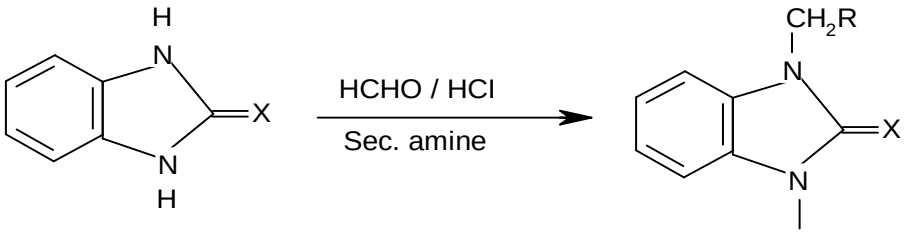


i = Morphline, HCHO
ii = AcOH, MeOH, reflux, 8hrs

R = Br, CI, NO_2

(208)

Also, it was done on 2-benzimidazlinone and benzimidazoline thiones [225].



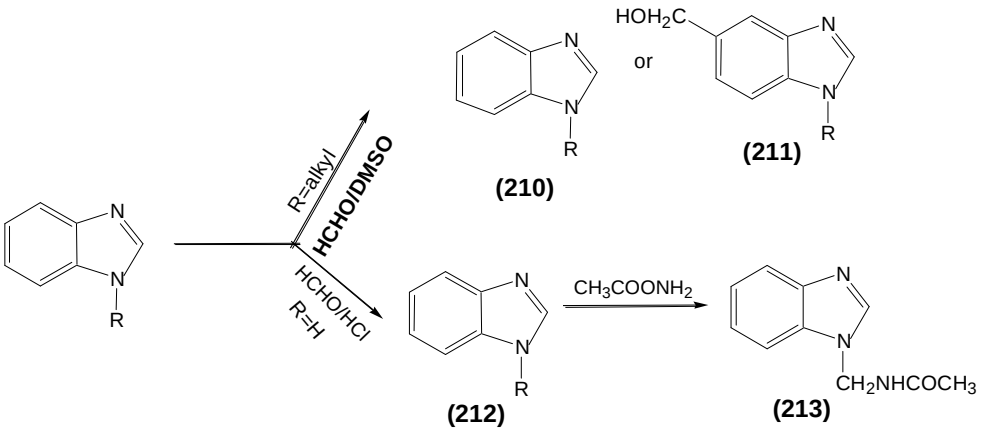
(209)

X =O, S

R = Piperidine , morpholine . Et_2N ,OH

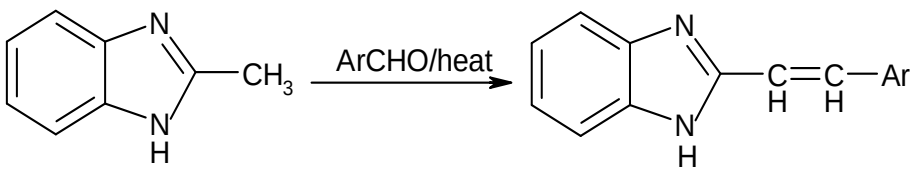
When imidazoles or benzimidazoles substituted on nitrogen treated with formalin or in a solvent such as DMSO, hydroxy-methylation takes place at C-4 or at (C-5).

Also, reaction of benzimidazole with p-formaldehyde in presence of conc. HCl gave 1-hydroxymethylbenzimidazole [226] which upon treatment with acetamide [200].



(210) **(211)** **(212)** **(213)**

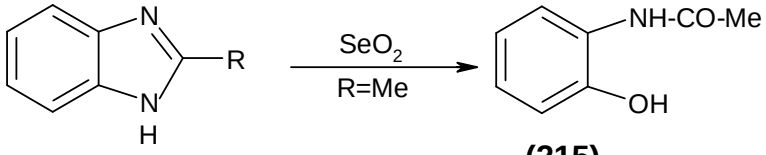
On the other hand, thermal condensation of 2-methyl benzimidazole with substituted benzaldehyde afforrded the chalcone analogues [227] .



(214)

6) Oxidation:

Imidazole oxidized using selenium dioxide in dioxone [199].



(215)

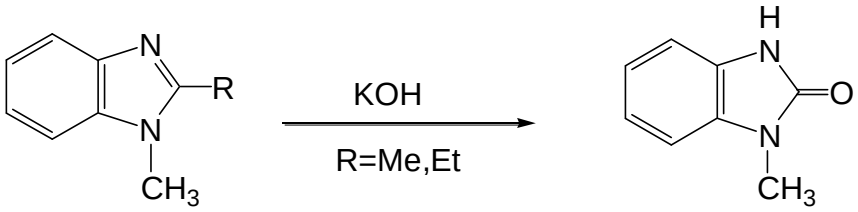
Nucleophilic attack:

Imidazoles and imidazolones are usually resistant to nucleophilic substitution unless the molecules are activated with an electron withdrawing group. While, its condensed analogue like benzimidazoles are rather more susceptible to nucleophilic attack, especially in the 2-position. Indeed, both imidazole and its condensed analogue are most likely to react at this site.

A-Nucleophilic attack on carbon atom :

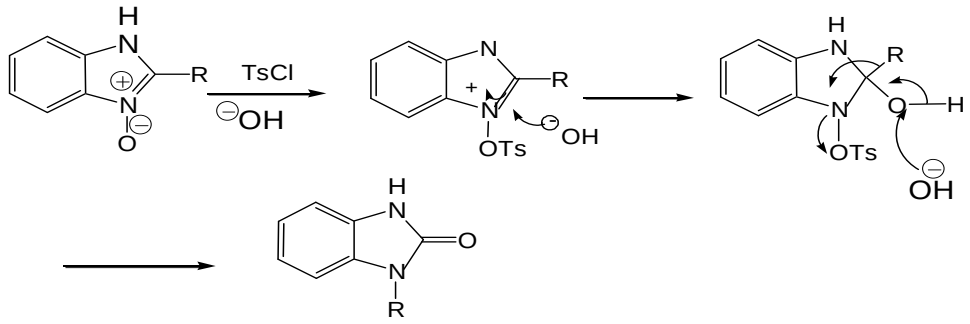
1) Hydroxide ion and other O-Nucleophiles:

At high temperature (250ºC) 2-alkyl and 2-aryl groups of condensed imidazole can be replaced by hydroxyl group. Thus, heating of 2-alkylbenzimidazole with KOH gave 2-benzimidazolone [228].



(216)

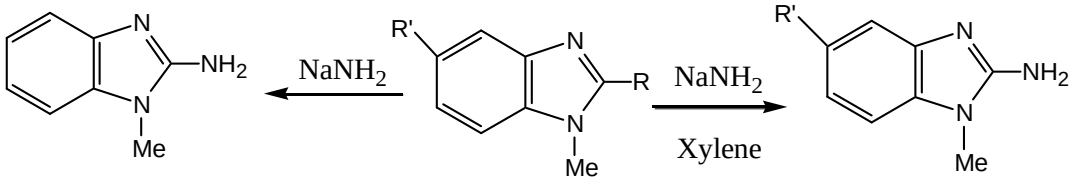
On the other hand, benzimidazol-N-oxides with tosyl-chloride gave benzimidazolinone [228] as sole product which formed as follow:



(217)

2) Amines and amide ions:

Usually amines are too weak nucleophiles to react with imidazoles. Unless there are activating groups present elsewhere in the molecule, imidazole itself can not be directly aminated at C-2. In reaction with alkaline hydroxylamine, l,2-dimethyl-4-nitroimidazole and l,2-dimethyl-5-nitroimidazole gave the 4- and 5-amino derivatives respectively. Thus, the-"chichibabin reaction"- [229] of 5-methoxymethylbenzimidazole gave good yield of the 2-amino product under vigorous conditions ($NaNH_2$, 250°C). So, 2-alkyl or 2-aryl group of 1-methylbenzimidazoles can be replaced by amino group [230] although other products are also formed as shown:

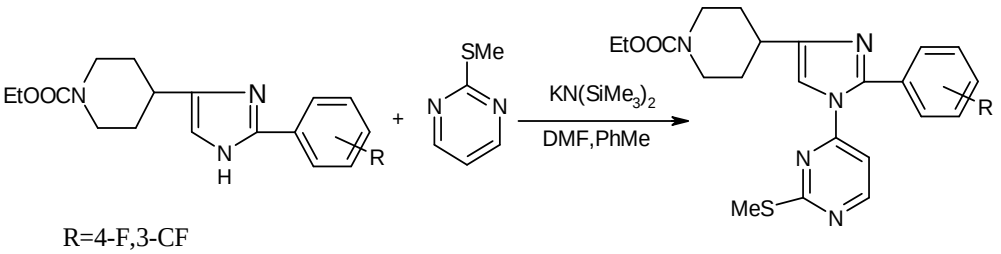


(218) **(219)**

R'=MeO,R=H
R'H,R=alkyl,ph

B- Nucleophilic attack at nitrogen atom:

In 2004, imidazoles were undergoing classical nucleophilic substitution reaction by Revesz and co-workers [231].



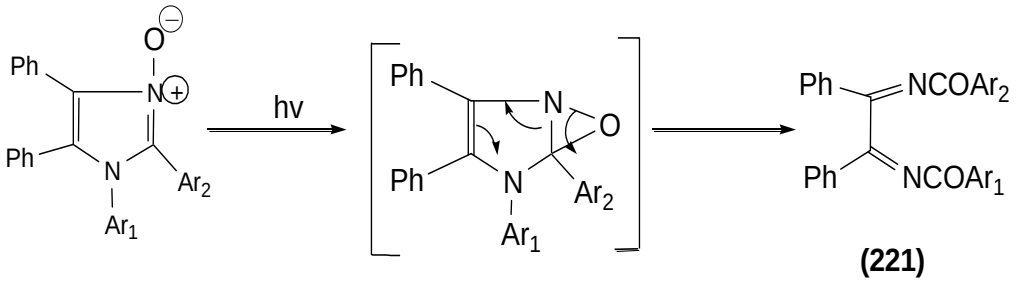
R=4-F,3-CF

(220)

3- Thermal and photochemical reactions:

a) Fragmentation

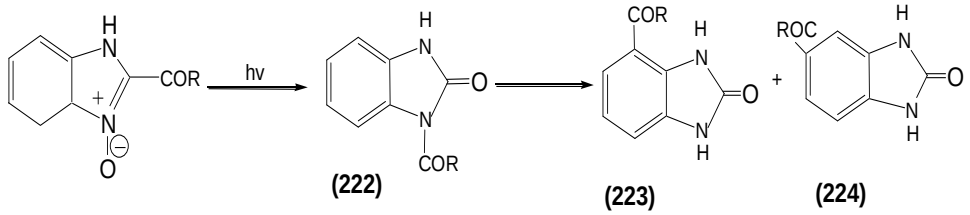
Imidazoles in general are very stable to heat. The parent molecule decomposed at 590°C by unknown process, which may be similar to the mass spectral fragmentation. The reported stabilities of the thermal rearrangement products of 1-substituted imidazoles at temperatures as high as 650°C give some doubt on the above decomposition temperature. When imidazole-3-oxides are photolyzed the products are unsymmetrical benzyldiimines [232]. This reaction is believed to proceed via a fused oxaziridine intermediate.



(221)

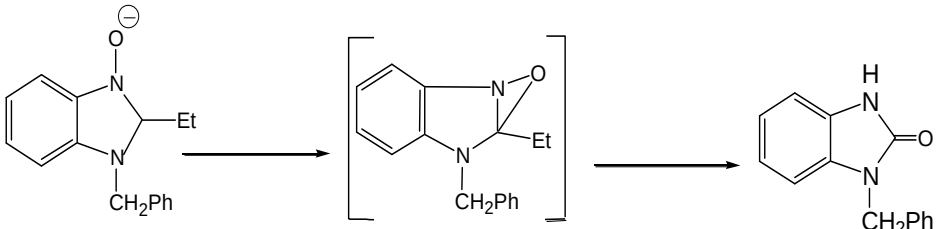
b) Rearrangement

Imidazoles are undergoing the photo-fires rearrangement. Photolysis of 2-acylbenzimidazol-l-oxide gave the *N*-acyl derivatives which undergoes photo-fires rearrangement in benzene to give the 4- and 5-transpositions products [233].



(222) **(223)** **(224)**

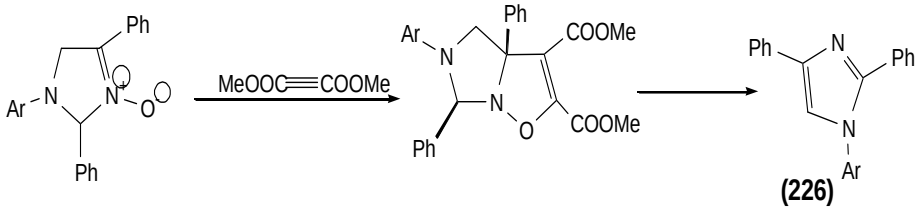
Photo-rearrangement of l-benzyl-2-ethylbenzimdazole-3-oxide gave l-benzyl-3-ethylbenzimidazolinone [(234)] .



(225)

c) Ring opening reaction

A thermal ring opening reaction of imidazoisoxazoles obtained by disteroselective-cycloaddition of dimethylacetylene-dicarboxylate (DAD) with Δ^3-imidazoline [(235)].

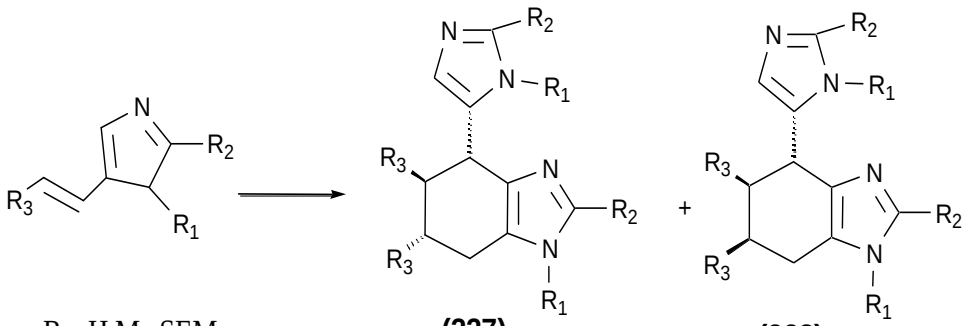


(226)

4- Miscellaneous reaction:

a) Diels-Alder dimerization:

Diels-Alder dimerization of imidazole derivatives, as the diene component with active dienophiles such as *N*-phenylmaleimide or 4-phenyl-l,2,4-traizoline-3,5-dione [(236-238)].



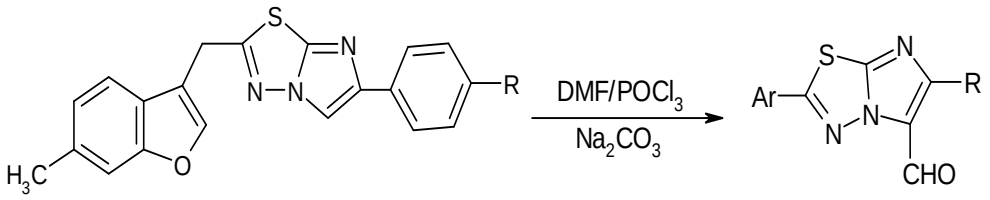
R_1=H,Me,SEM,
R_2=H,SPh,TBS,
R_3=H,CO_2ET,$CONH_2$.

(227) **(228)**

Homonucleur (4 π + 2π) cycloaddition.

b) Vilsmeier -Haack reaction

Vilsmeier-Haack reaction of imidazothiadiazole in DMF and $POC1_3$ furnished 5-formyl derivatives [239, 50].

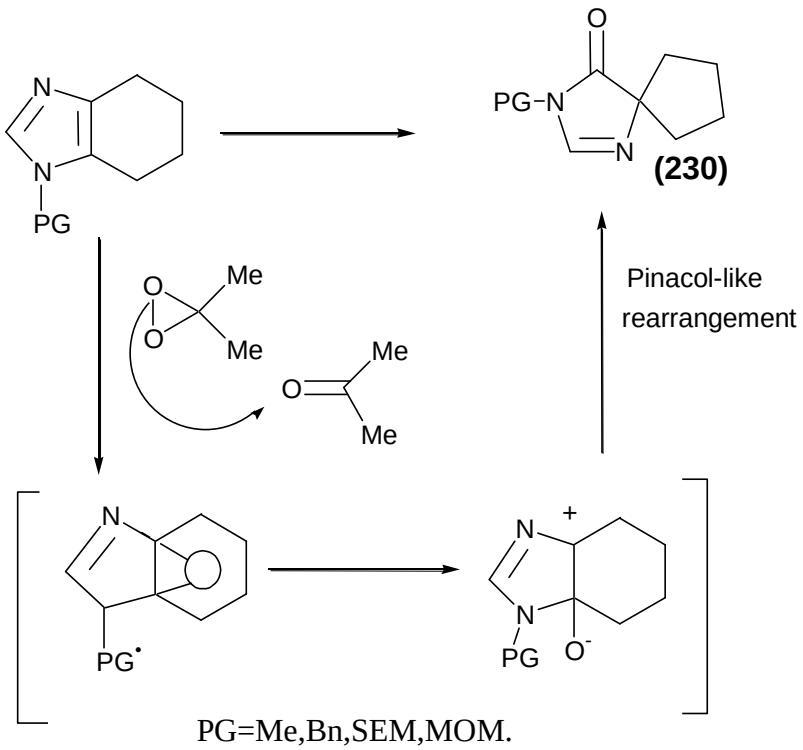


R=Br,Cl,NO_2

(229)

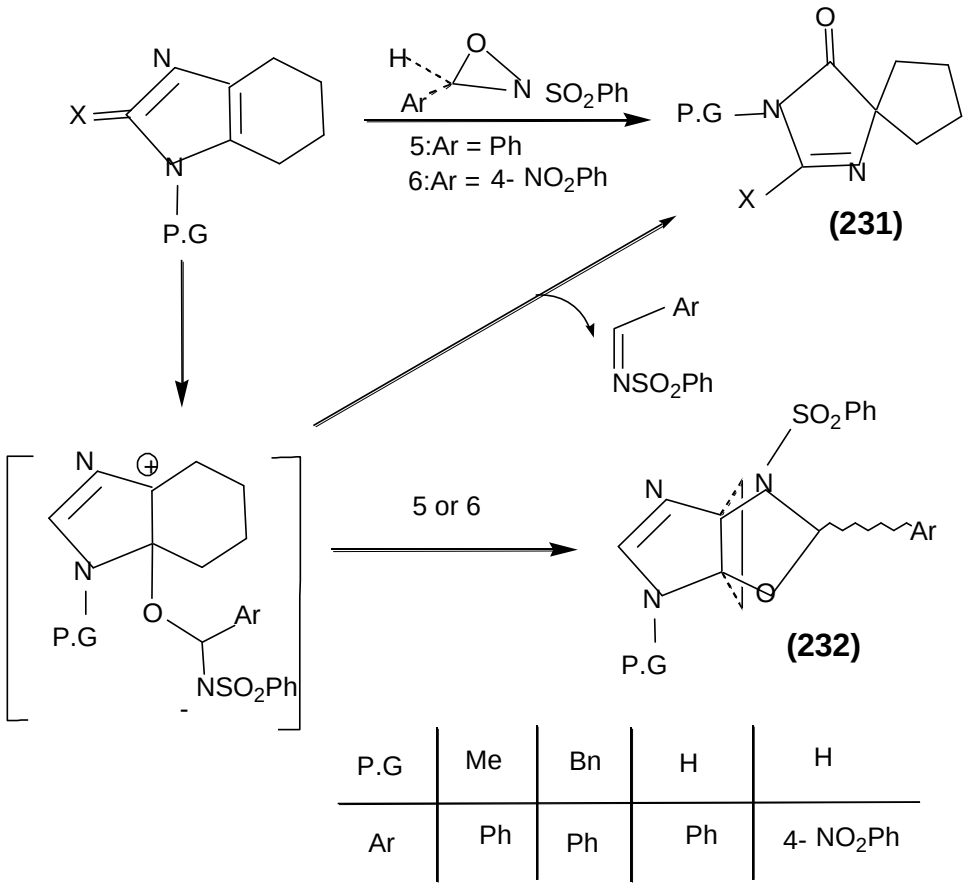
c) Pinacol- like rearrangement reaction

Rearrangement reaction of tetrahydrobenzimidazoles (THB's) leading to the formation of spiro fused 5-imidazolones upon treatment with DMDO [240-243].



PG=Me,Bn,SEM,MOM.

R. Sivappa et al. [(244)] sought to identify alternative oxidants that would effect this rearrangement. Among several possibilities, N-sulfonyloxaziridine as it share many common characteristics with dioxiranes. Therefore, it occurred that this reagent may offer a self stable alternative to DMDO.



P.G	Me	Bn	H	H
Ar	Ph	Ph	Ph	4- NO_2Ph