Summary

Reaction of 2-[4-(4-chlorobenzylidene)-5-oxo-4,5-dihydroxoazol-2-ylmethyl]isoindole-1,3-dione **(1)** with 4-aminoacetophenone gave the imidazole derivative**(2)** , which treatment with 4-chlorobenzaldehyde in alcoholic potassium hydroxide afforded 2-(4-(4-chlorobenzylidene)-1-(4-[4-chlorophenyl)-but-2-enoyl]phenyl]-5-oxo-4,5-dihydro-*1H*-imidazol-2-ylmethyl)isoindole-1,3-dione**(3)**. The reactivity of compound **3** towards nitrogen nucleophiles was investigated.

Thus, the reaction of compound **(3)** with hydrazine hydrate or/ semicarbazide afforded the pyrazole derivatives **(4a,b)**. Meanwhile, the reaction of **(3)** with hydroxylamine hydrochloride in refluxing pyridine gave the isoxazole derivative **(5)**.Treatment of **(3)** with urea or/ thiourea in refluxing sodium ethoxide solution gave the pyrimidine derivatives **6(a,b)**.The reaction of **(3)** with aromatic amines namely,aniline, *p*-toluidine and *p*-anisidine gave the imidazole derivatives **7(a-c)** respectively. Also, the reaction of **(3)** with active methylene compounds *viz* ethyl cyanoacetate and malononitrile gave pyridine derivatives **8(a,b)**.

Moreover, treatment of **(3)** with hydrogen peroxide in presence of methanol gave 2-(4-(4-chlorobenzylidene)-1-(4-[3-chlorobenzyl)oxirane carbonyl]benzyl)-5-oxo-4,5-dihydro-*1H*-imidazol-2-ylmethyl)isoindole -1,3-dione **(9)** .

The work was extended to study the behavior of oxarine derivative **(9)** toward some nitrogen nucleophiles. Thus, reaction of **(9)** with hydrazine hydrate afforded t pyrazole derivatives **10(a,b)** ,

while treatment of **(9)** with hydroxylamine hydrochloride gave isoxazole derivative **(11)**. Furthermore, refluxing of **(9)** with thiourea in DMF gave 2-{1-{4-[4-(4-chlorobenzyl)-2-thioxoxazolidine-5-carbonyl] benzyl}-4-[2-(4-chlorophenyl)ethylidene]-5-oxo-4,5-dihydro-*1H*-imidazol-2-ylmethyl}isoindole-1,3-dione **(12)**. Treatment of **(9)** with glycine in DMF gave the morpholine derivative **(13) .**

Condensation of **(1)** with glycine yielded imidazolyglycine **(14)** which on treated with thionyl chloride followed by addition of ammonium thiocyanate afforded [4-(4-chlorobenzylidene)-2-(1,3-dioxo-1,3-dihydroisoindol-2-ylmethyl)-5-oxo-4,5-dihydroimidazol-1-yl] acetylisothiocyanate **(15)** .

Reaction of **(15)** with phenylhydrazine in dry acetone gave traizole derivative **(16)**, whereas reaction of **(15)** with o-aminophenol gave thiourea derivative **(17)**, which upon heating in acetic anhydride afforded 2-[4-(4-chlorobenzylidene)-2-(1,3-dioxo-1,3-dihydroisoindol-2-ylmethyl)-5-oxo-4,5-dihydroimidazol-1-yl]-*N*-(*3H*-indol-2-yl)]acetamide **(18)**. Also, reaction of **(15)** with anthranilic acid in dry acetone gave thiourea derivative **(19),** which was boiled in acetic anhydride gave quinazoline derivative **(20)**.

Finally, oxadiazine derivatives **(21)**, **22(a-c)** were obtained in good yields from the cyclocondensation of **(15)** with phenylisothiocyanate and Schiff bases, respectively.

Also, compound **(15)** was reacted with active methylene compounds gave **23(a,b)** and **(24)** . It was reacted with thioglycolic acid gave compound **(25)** which cyclized in acetic anhydride gave **(26)**. Compound **(14)** was reacted with hydrazine hydrate gave compound **(27**).

Synthesis of 2-(*N*-phthalimidomethyl)-4-phthalidene-5(4)-oxazolone**(28)** and its chemical character towards base catalysed or/ acid catalysed ring opening reaction was studied. It was found that **(28)** reacted with aromatic amine and amino carboxylic acid, amino derivatives gave imidazolone derivatives.

Compouned **(28)** reacted also with hydrazine hydrate gave a mixture of 1,4-phthalazindione (**32**) and cin namic acid hydrazide derivative(**33**) and with phenyl hydrazine gave mixture of *N*-anilinophthalimide (**34**)and cinnamic acid hydrazid derivative (**35**) and with hydroxyl amine hydrochloride gave **(36)** .

The reaction of **(28)** with aluminum chloride in presence of reactive aromatic substrates namely, toluence, o-xylene, m-xylene gave *N*-phthalmidoacetamidomethylarylketone **37(a-c)** were also investigated.

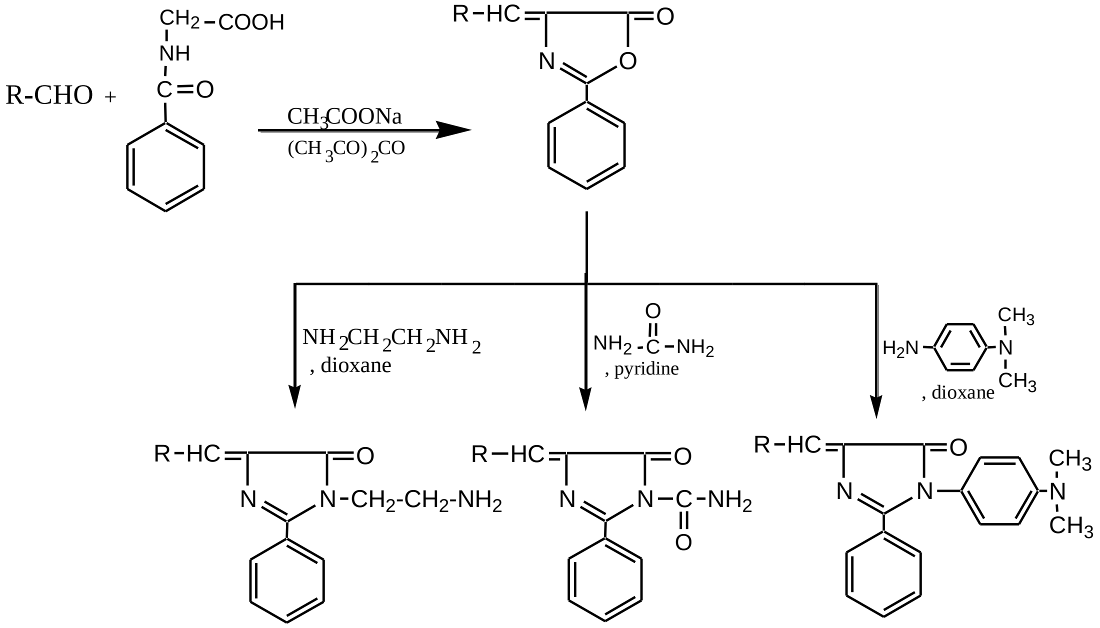
The structure of all the synthesized derivatives is established by: (**i**) elemental analysis, (**ii**) IR, (**iii**) NMR, (**iv**) Mass spectra.

Biological activity of the synthesized compounds have been investigated and the result are cited in test.

SYNTHESIS OF IMIDAZOLES AND IMIDAZOLONES

(1) From carboxylic acid derivatives :

Imidazolone derivatives were synthesized via Erlenmeyer synthesis (1-8) by the reaction of 4-substituted oxazolone with the appropriate amine in dioxine / pyridine.

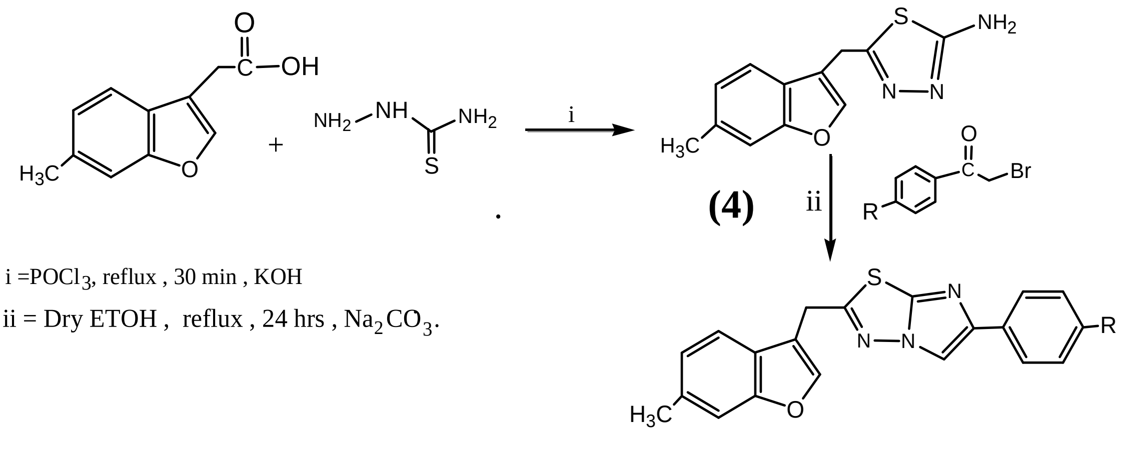


(1) (2) (3)

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

Imidazole derivatives were prepared by condensation of an acid derivatives with α-bromoarylketone under reflux in dry ethanol (9).



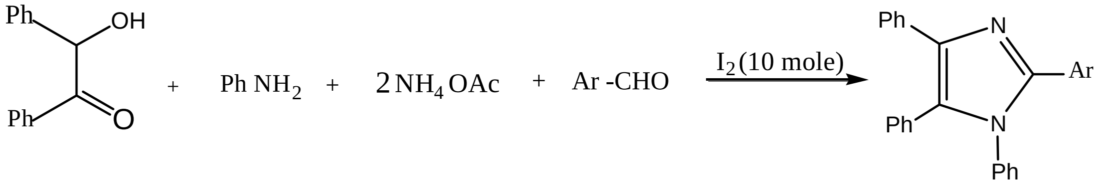
i =$POCl_3$, reflux , 30 min , KOH

ii = Dry ETOH , reflux , 24 hrs , Na_2CO_3.

(4)

(5) R = Br ,Cl , NO_2.

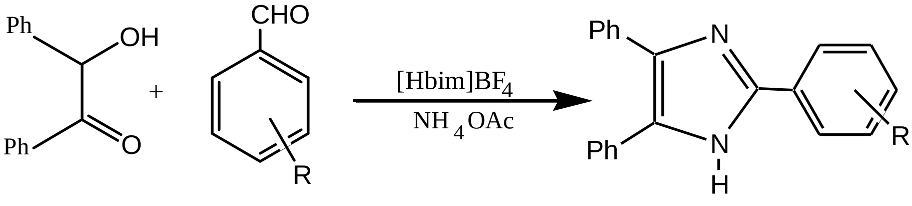
One-pot procedure for the synthesis of 1,2,4,5-tetrarylimidazoles using iodine as a catalyst , at room temperature **(10)** .



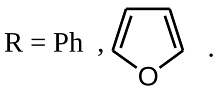
(6)

Ar = C_6H_4 , C_6H_4MeO(p) , C_6H_4OH (o) ,C_6H_4OH (P) , $C_6H_4NO_2$ (P) .

S. A. Siddiqui et al **(11)** ., have reported imidazole derivatives using carboxylic acid derivatives.

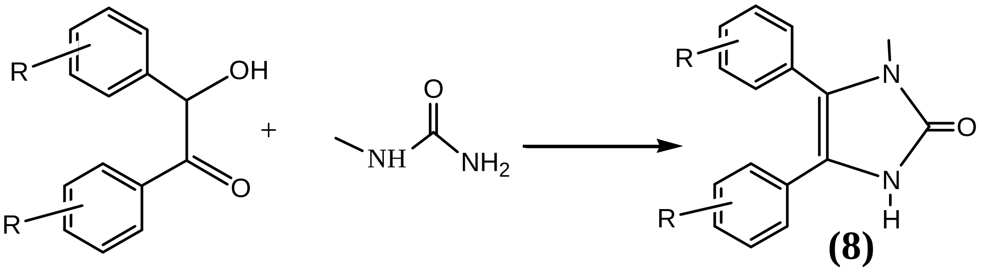


(7)



R = Ph , .

Also, imidazolones were synthesized using carboxylic acids illustrated by the following scheme (12) .

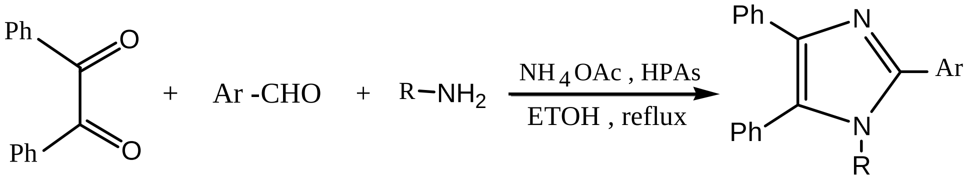


(8)

R = H , Me .

(2) From diketones :

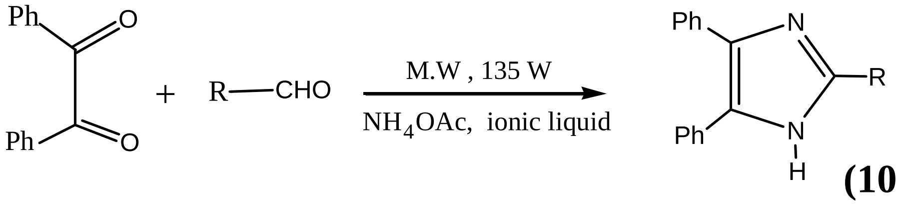
One-pot synthesis of imidazole derivatives by four component condensation of benzil, benzaldehyde derivatives, primary amine, ammonium acetate catalysed by keggin heteropolyacids (HPAs) (13) such as: **$H_3 [PW_{12} O_{40}]$, $H_4 [SiW_{12} O_{40}]$.**



(9)

Ar = Ph , 4-Meph , 4- Brph ;
R = Me , ph , $phCH_2$.

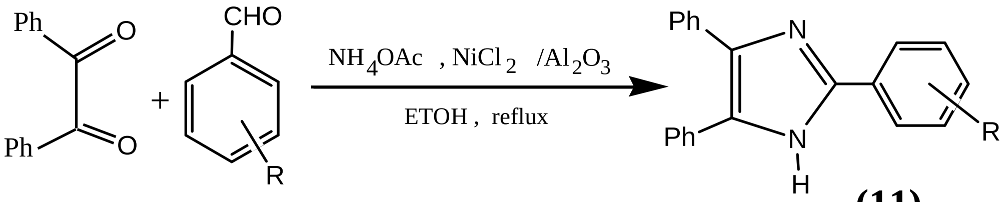
Also, a typical acid-catalyzed reaction in organic solutions, could be conducted successfully with good to excellent yields in a neutral ionic liquid 1-methyl-3-heptylimidazolium tetrafluoroborate ($[HeMIM]BF_4$), under solvent free and microwaves-assisted conditions in a absence of any acid as a catalyst (14) .



(10)

R = C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_3$.

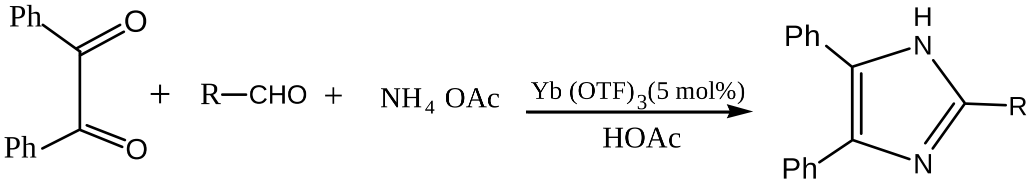
M. M. Heravi et al [(15)]., synthesized benzimidazoles under heterogeneous system using $NiCl_2.6H_2O/Al_2O_3$ as acatalyst.



(11)

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-$NO_2C_6H_5$.

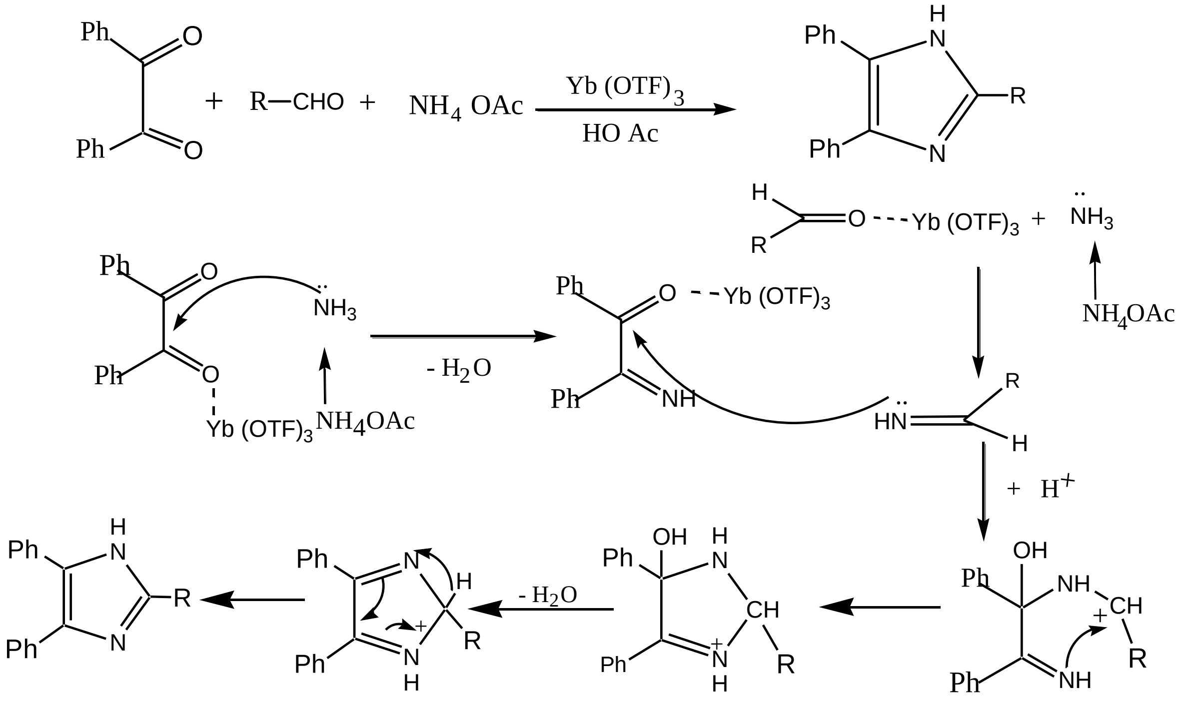
When using the rare earth metal compounds, the model reaction of the following mixture proceeded smoothly to afford the corresponding adduct in good to excellent yield [(16)]. Among them Yherbium triflate $Yb(OTf)_3$ was the most effective catalyst.(which is strong lewis acid).



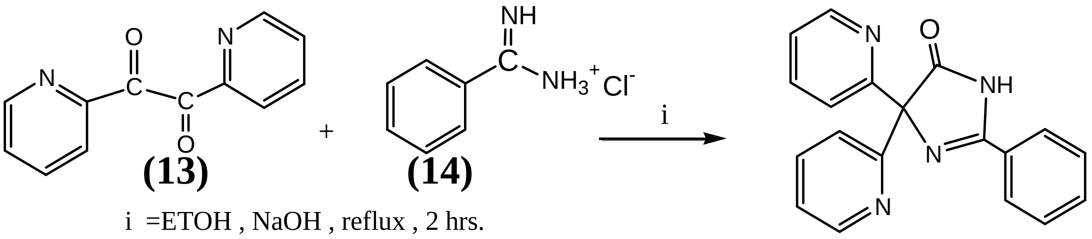
(12)

R = p-MeO C_6H_5, p-OH C_6H_4, p-$(Me)_2NC_6H_3$, m-$NO_2C_6H_4$,
C_2H_5, C_3H_7.

Aprobable mechanism for synthesis may be postulated as shown below:



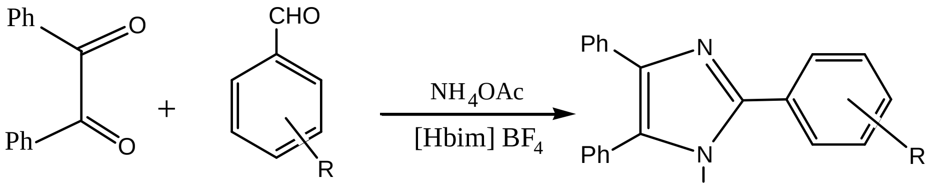
Imidazolone ring could be established via Pinacol-like rearrangement [17] arising from the reaction of 2,2`-pyridyl **13** and benzamidine/ HCl **14** .



(13) **(14)**

i =ETOH , NaOH , reflux , 2 hrs.

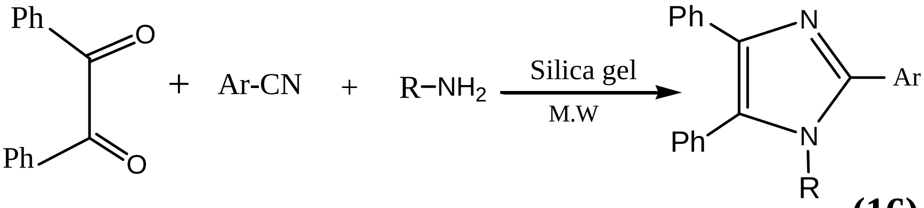
S. A. Siddiqui et al [11]**.**, generated a variety of imidazoles by the reaction of 1,2-difuran-2-yl-ethane-1,2-dione with benzaldehydes at 100°C.



(15)

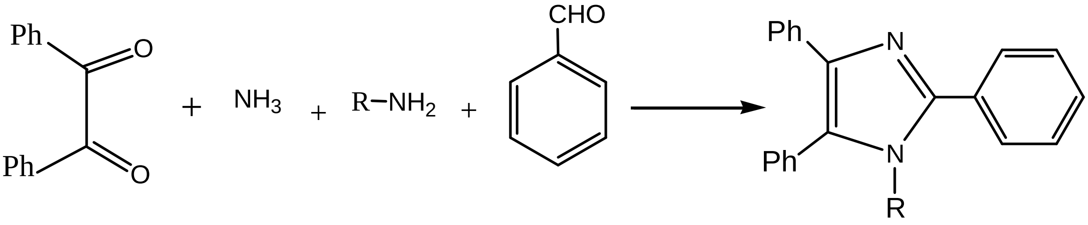
R =H , p-MeO , o-OH , p-OH , p-Cl , p-Br , o-OH , m-Me , p-OH , p-NO$_2$.

S.Balalaie et al (18)., 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.



(16)

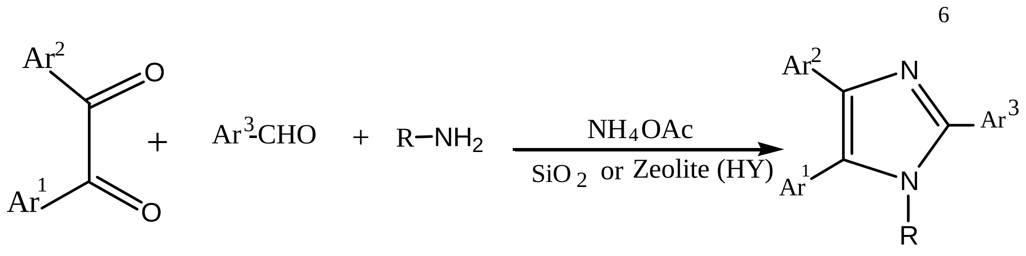
Also, 1,2-diketones have been used to prepare imidazoles via cyclocondensation reactions (19) .



(17)

R = Bn , c-$C_6H_{11}CH_2$ -

Primary amine and ammonium acetate have also been employed in the 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 (20-21) .

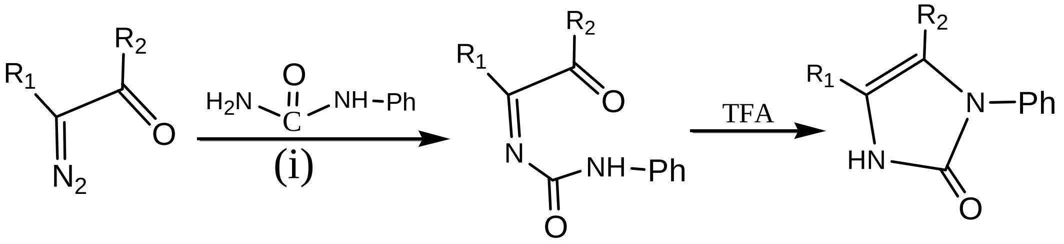


(18)

$Ar^1 = Ar^2$

<u>(3) From amide derivatives</u> :

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 **(19)** .In the presence of acid, the latter undergo ring closure to afford imidazolones **(20)** **(22)** .

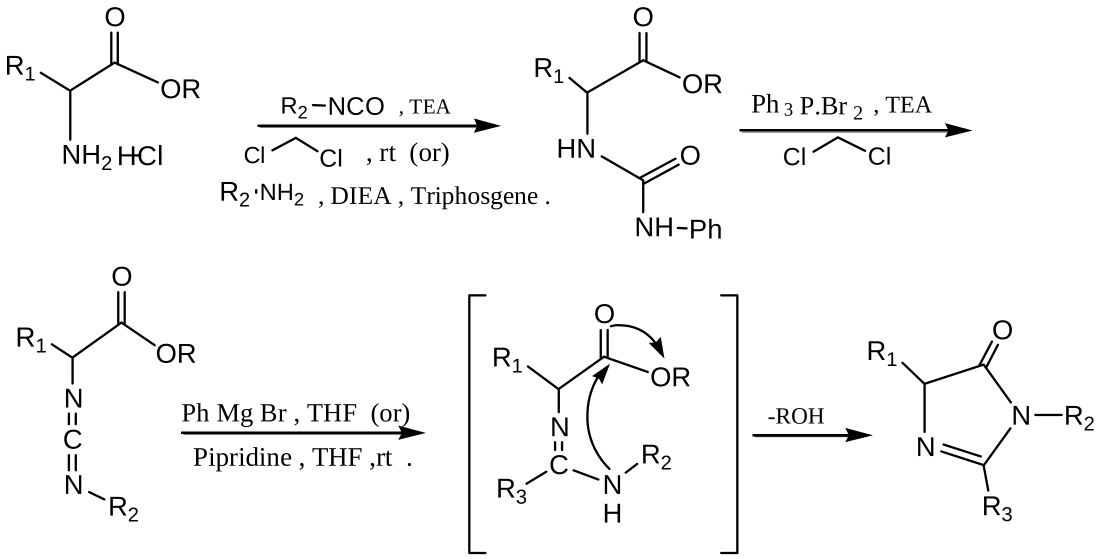


(19) **(20)**

R^1 = H , E , COPh , $PO(O\text{-}Et)_2$, SO_2 Me ;
R^2 = Ph , OEt .

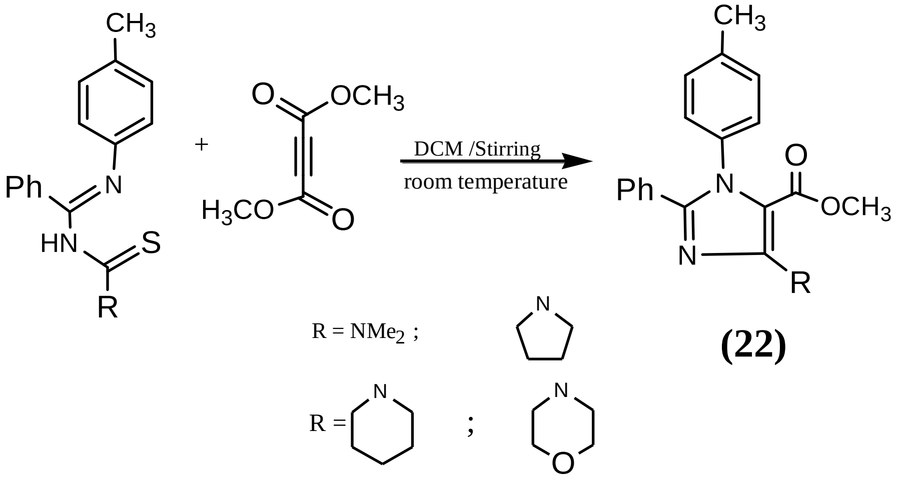
(i) = $Rh_2(O\text{-}CO\text{-}heptyl)_4$, (Cat.) , Toluene /DCE (1:1)

Via tandem chemoselective addition reaction on carbodiimide cyclization **(23-24)** was used for the synthesis of 2-substituted imidazolones as the following scheme.



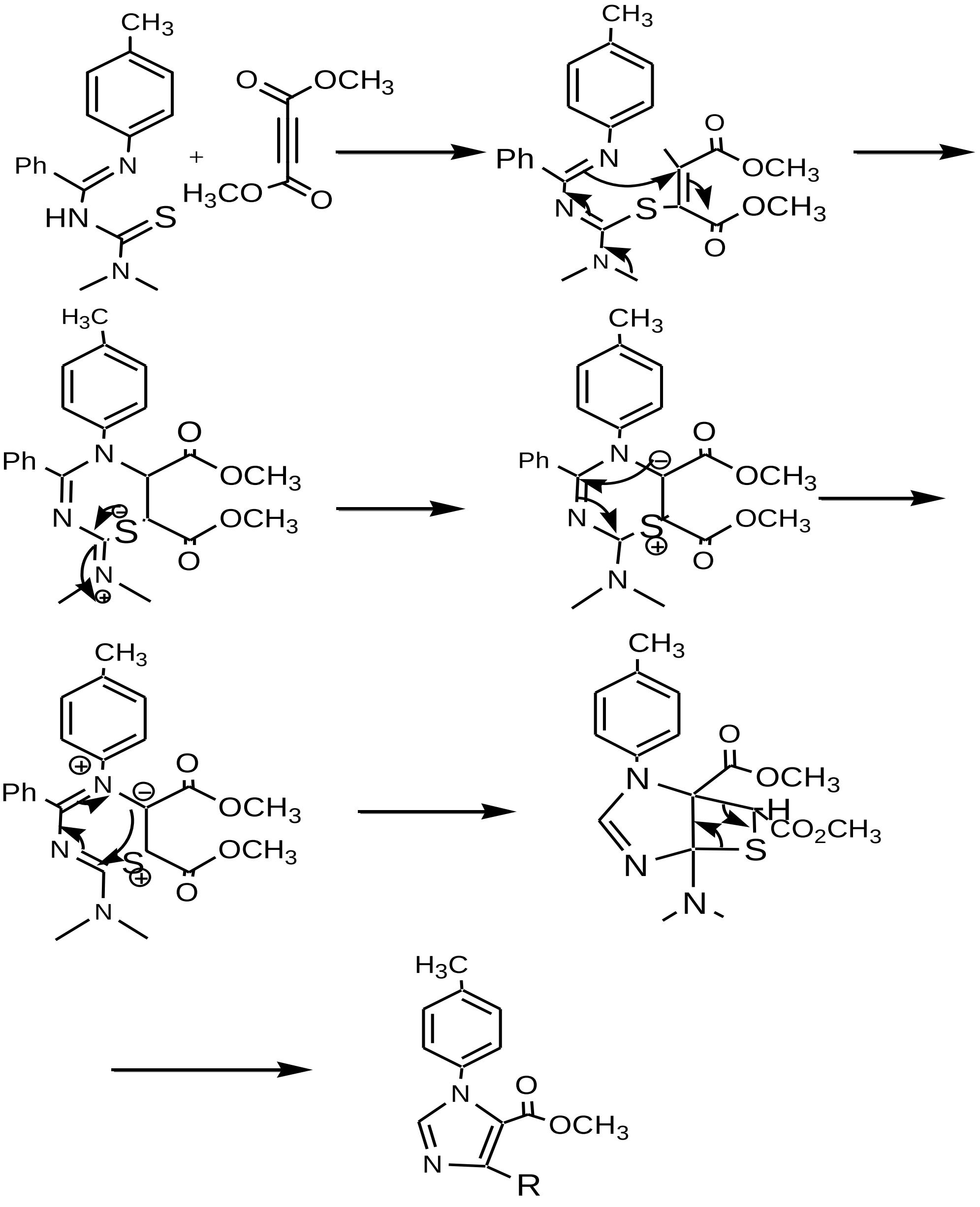
(21)

A. Marwaha et al [(25)] ., Single-pot synthesis of functionalized imidazole derivatives by the reaction of thioamides with di-methylacetylene dicarboxylate via sequential cycloaddition-cyclore-version-cycloaddition reactions.

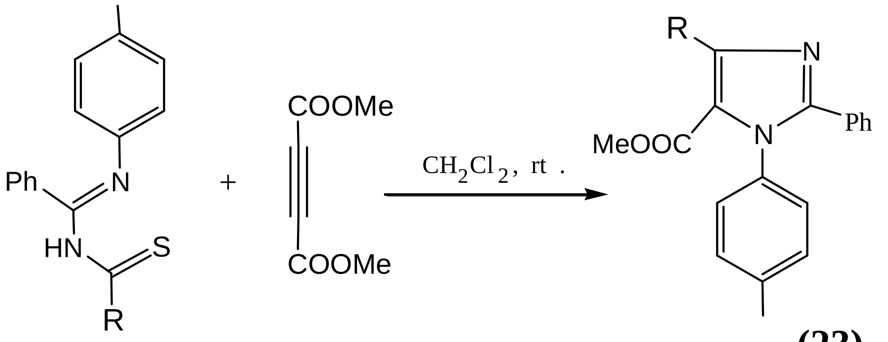


(22)

A plausible mechanism underlying the formation of the imidazole derivatives.



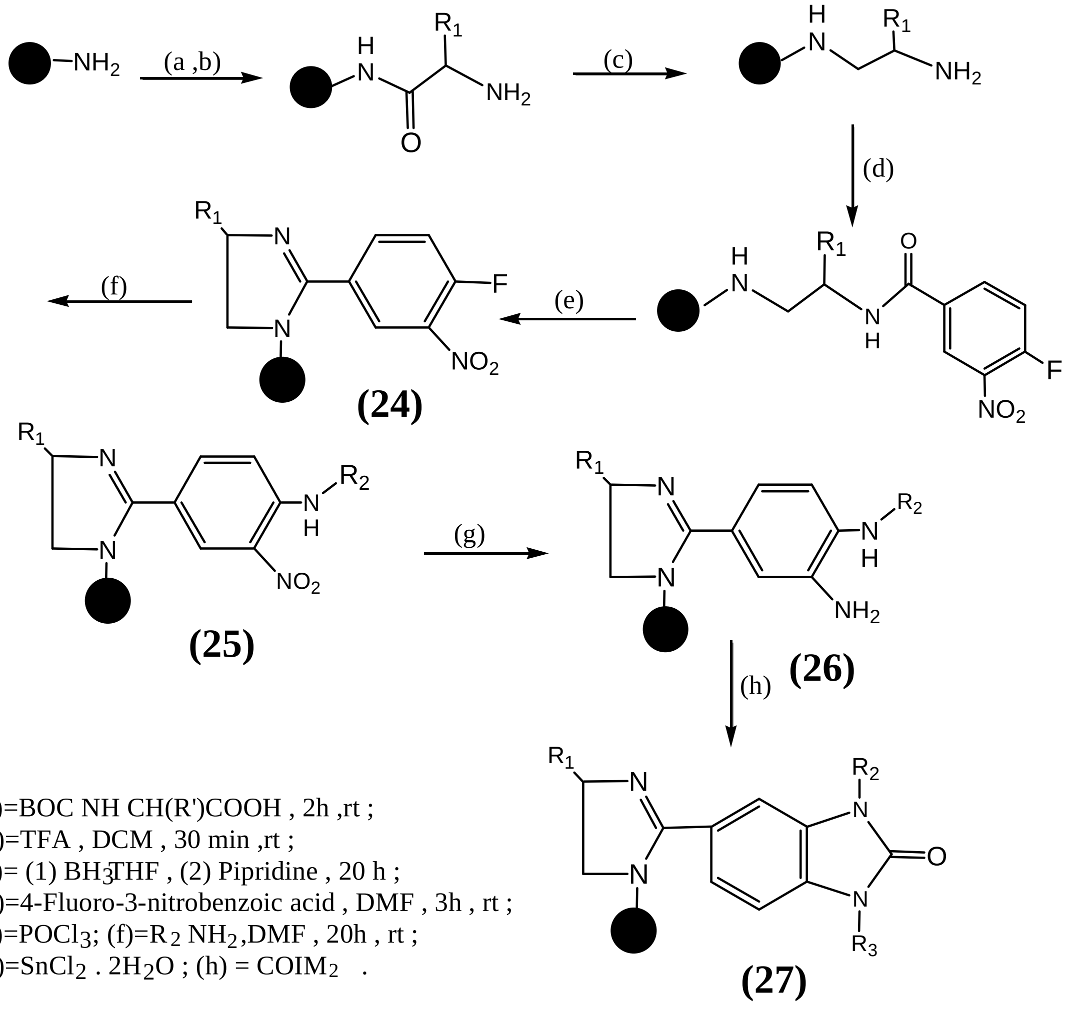
Also, imidazoles were concisely synthesized in 65-71% yield by the reaction of thioamide with dimethyl acetylenedicarboxylate in CH_2Cl_2 at room temperature **(26).**



(23)

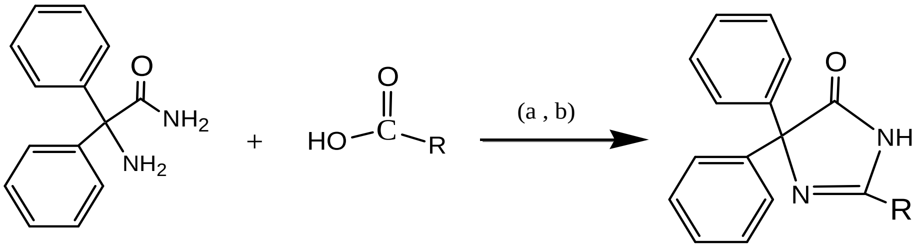
R = NMe_2 , $N(CH_2)_4O$
R = $N(CH_2)_4$, $N(CH_2)_5$.

Acharya et al [(27-32)] ., described the solid-phase synthesis of substituted 4,5-dihydro-1H-imidazole-2-yl)-1,3-dihydro-2H-benzimidazol-2-ones.



(a)=BOC NH CH(R')COOH , 2h ,rt ;
(b)=TFA , DCM , 30 min ,rt ;
(c)= (1) BH_3THF , (2) Pipridine , 20 h ;
(d)=4-Fluoro-3-nitrobenzoic acid , DMF , 3h , rt ;
(e)=$POCl_3$; (f)=R_2NH_2,DMF , 20h , rt ;
(g)=$SnCl_2 . 2H_2O$; (h) = $COIM_2$.

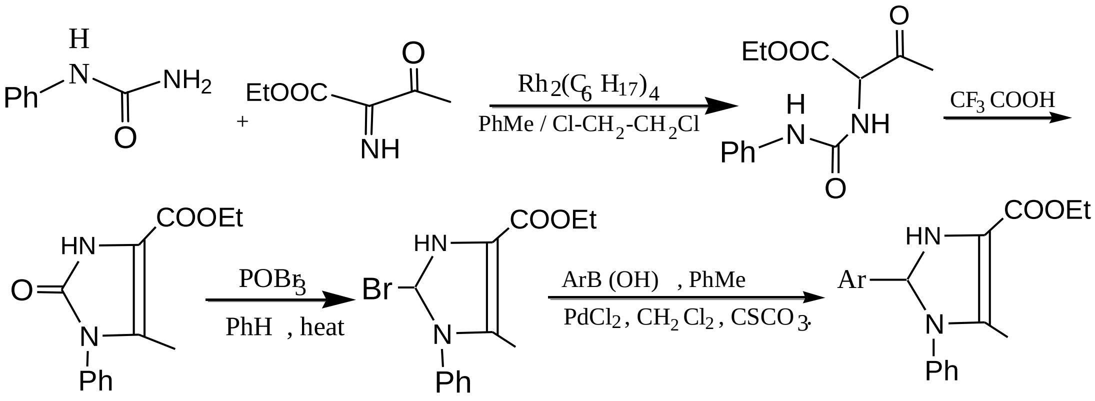
Also, imidazolone ring was synthesized by treatment of amine with a polymer-supported carbodiimide reagent in the presence of excess carboxylic acid or acyl chloride afforded α-amidoamide as intermediate (33-34) .



(a) = P -EDC resin , CH_2CL_2 , rt , 24h .;
(b)=Na OH , ETOH , rt , 2h .

(28)

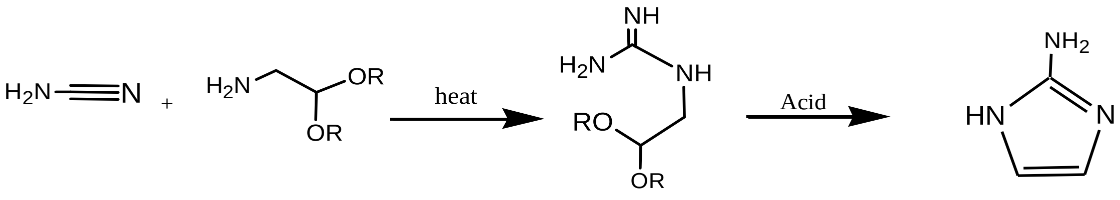
Recently (35), clapham and co-workers disclosed a two and four step-reaction sequence for the synthesis of imidazolone and imidazoles using amides compounds as starting material.



(29) **(30)** **(31)**

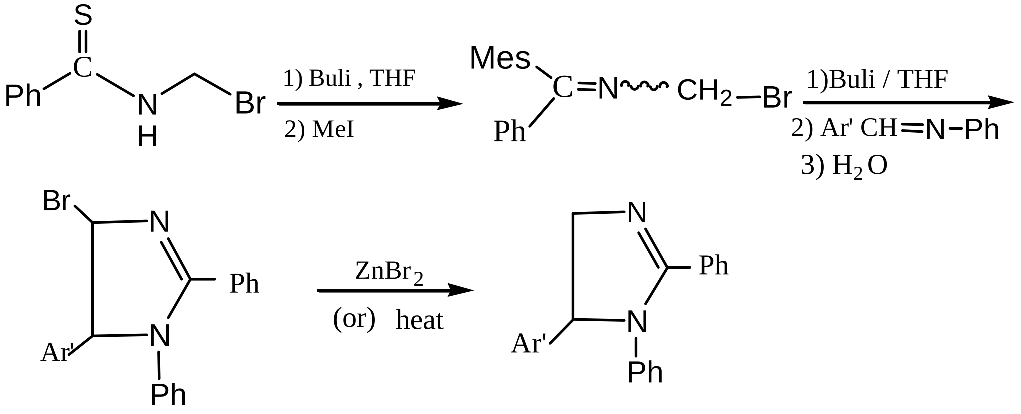
Ar = 4-MeO C_6H_4.
Ar = 4-EtOOC C_6H_4.
Ar = 4-TBDMSO C_6H_4.

Reaction between cyanamide and 2-aminoacetaldehyde-acetales followed by an acid catalysed cyclization which was found by lowson (36).



(32)

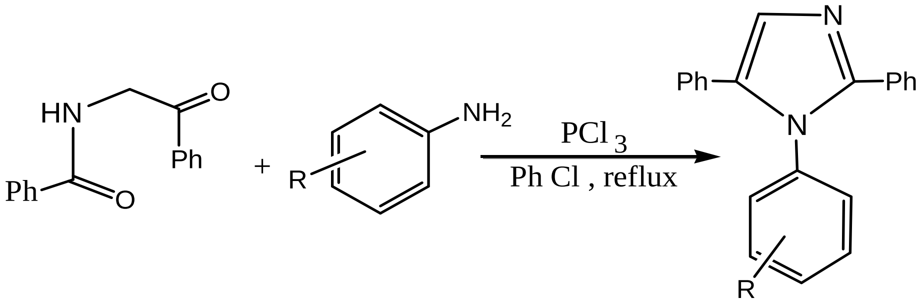
Imidazoles have also been prepared via amulti-step process in which *N*-(benzotriazol-l-ylmethyl)thiobenzamide was the starting material **(37)** .



(33) **(34)**

Ar' =ph , 4-Me C_6H_4 .

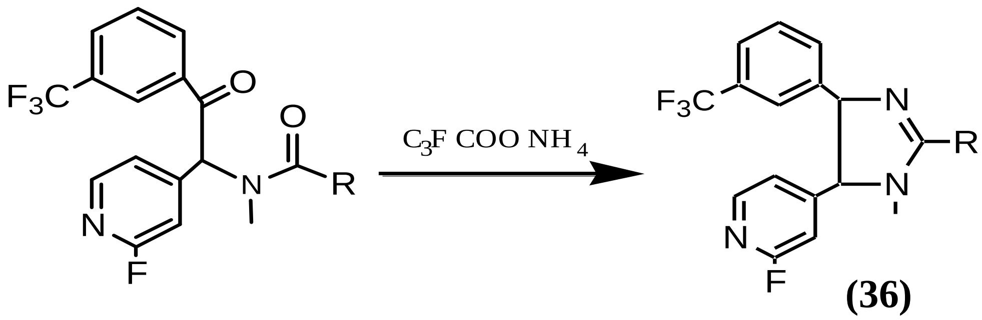
Popilin and Tiscenko reported **(38)** that treatment of benzamido-acetophenone with PCl_3 and arylamines in boiling chlorobenzene gives imidazoles.



R = H , 4-MeO , 2-MeO , 4-Cl .

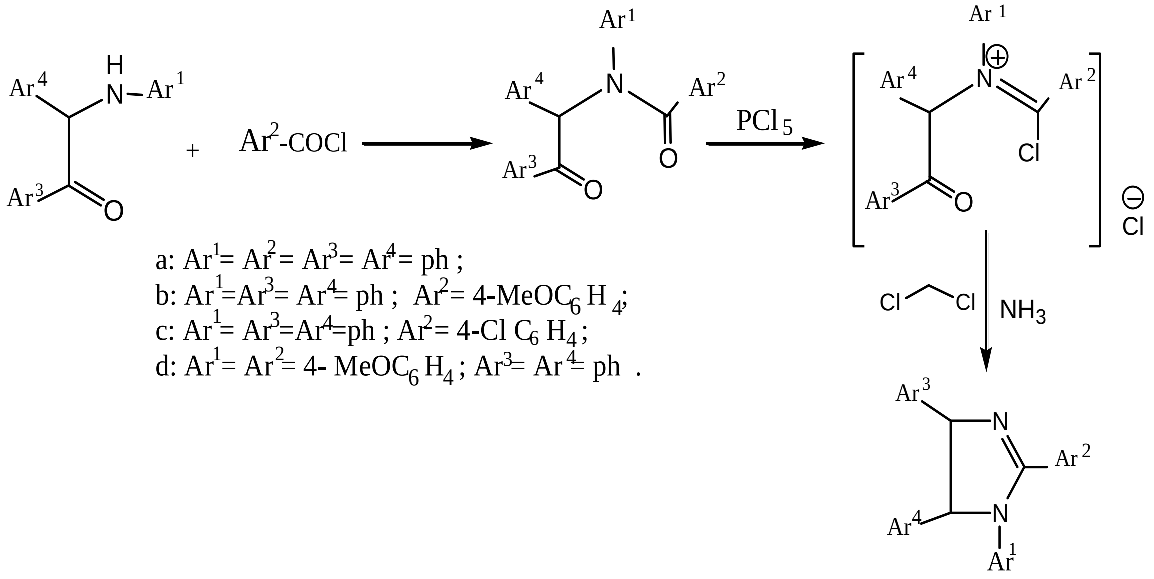
(35)

Also, imidazoles were efficiently prepared by thermal cyclo-condensation of *N*-alkyl-*N*-(β-keto)amides with ammonium trifluoroacetate **(39)**.



(36)

Heinze and co-workers (40) developed a three-step procedure for the synthesis of imidazoles from the required desylamines and aroyl chlorides in presence of PCl_5.



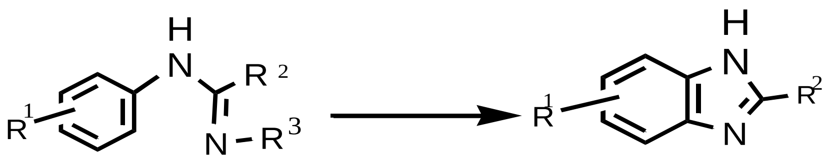
a: $Ar^1 = Ar^2 = Ar^3 = Ar^4 =$ ph ;
b: $Ar^1 = Ar^3 = Ar^4 =$ ph ; $Ar^2 =$ 4-$MeOC_6H_4$;
c: $Ar^1 = Ar^3 = Ar^4 =$ ph ; $Ar^2 =$ 4-Cl C_6H_4;
d: $Ar^1 = Ar^2 =$ 4- $MeOC_6H_4$; $Ar^3 = Ar^4 =$ ph .

(37)

(4) From amidine and related compounds :

The formation of imidazoles from *N*-arylamidines was first reported by partiridge and turner (41) 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.

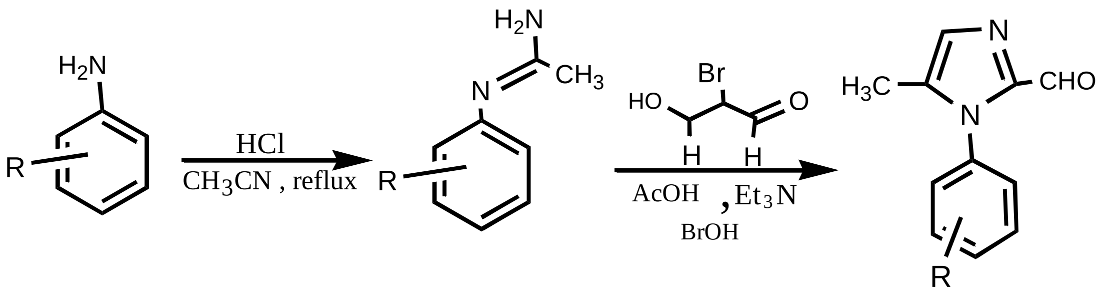


(38)

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 [(42)]., showed that such products could be obtained from the parent amidine by oxidation with sod-hypochlorite under basic conditions. *N*-chloro derivatives was suggested to be intermediates in these reactions.

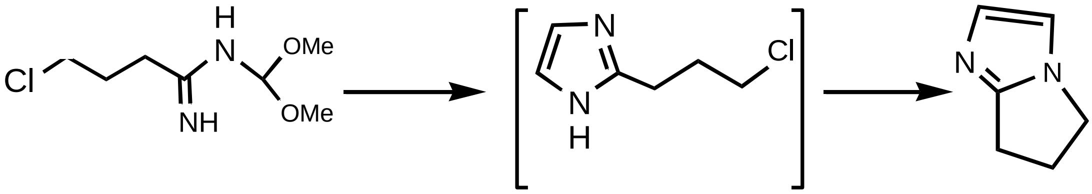
S. B. Ferreira et al [(43)] ., were prepared and utilized *N*-aryl-amidines as the starting materials for the synthesis of *N*-substituted-phenylimidazole-5-carbaldehyde.



R = H , 4-Cl , 4-F , 4-NO_2 , 4-CF , 4-CN , 4-CH_3
,4-OCH_3 , 2,6-F ,CH_3 .

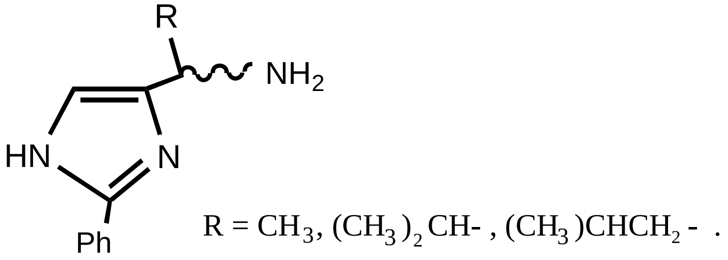
(39)

H.C.Kan et al [(44)]., synthesized bicyclicimidazolium ionic liquids by intramolecular-cyclization of the corresponding amidines.



(40)

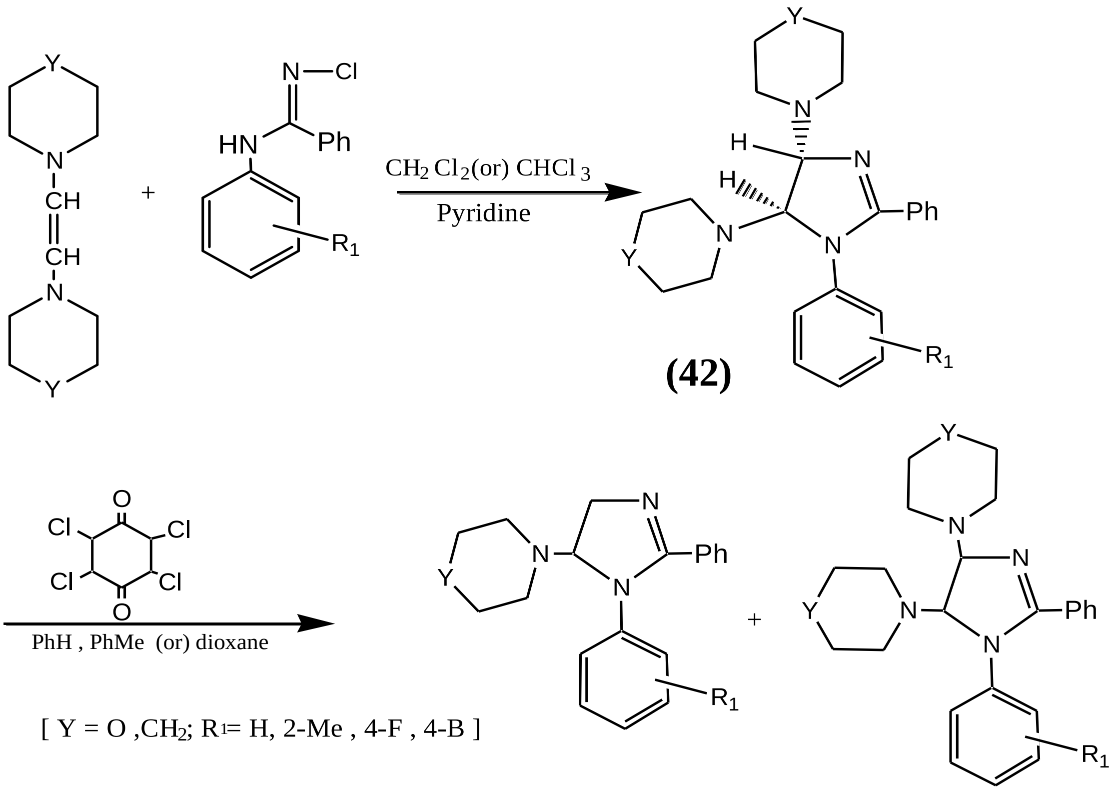
F. Bures et al [(45-46)] ., puplished the synthesis of chiral derivatives of 2-phenylimidazole by the condensation of benzamidine with α-bromoketones in the solvent / base system, THF, water and K_2CO_3.



R = CH_3, $(CH_3)_2CH$- , $(CH_3)CHCH_2$- .

(41)

Several years ago, imidazoles were synthesized by the reaction of diaminoethane with *N*-aryl-*N*-chlorobenzamidines in boiling CH_2Cl_2 or $CHCl_3$ in presence of an equimolar amount of pyridine, followed by oxidation with chloroanil [(47-48)].

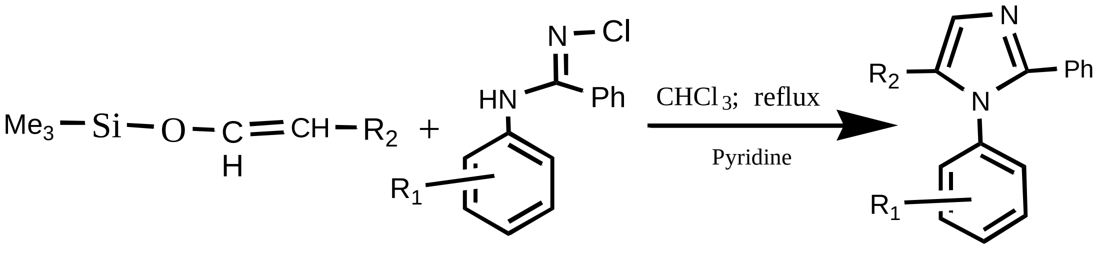


(42)

[Y = O ,CH$_2$; R$_1$= H, 2-Me , 4-F , 4-B]

(43) **(44)**

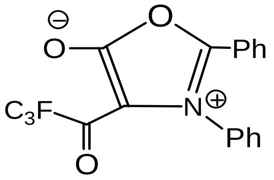
On the other hand, imidazoles were synthesized in 55-57% yield by the reaction of silylenol ethers with *N*-chloro-*N*-aryl-benzamidines in refluxing CHCl$_3$ in the presence of pyridine [(49)].



R$_1$= H , 4-Me , 4-F , 4-Br .
R$_2$= H , Me , Et , Br .

(45)

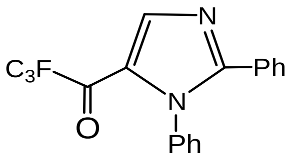
In 1994, kawase reported (50) that treatment of the mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olate(**1**)with formamidine hydrochloride (**2**) and K_2CO_3 in DMF provides imidazoles (**3**).



(1)

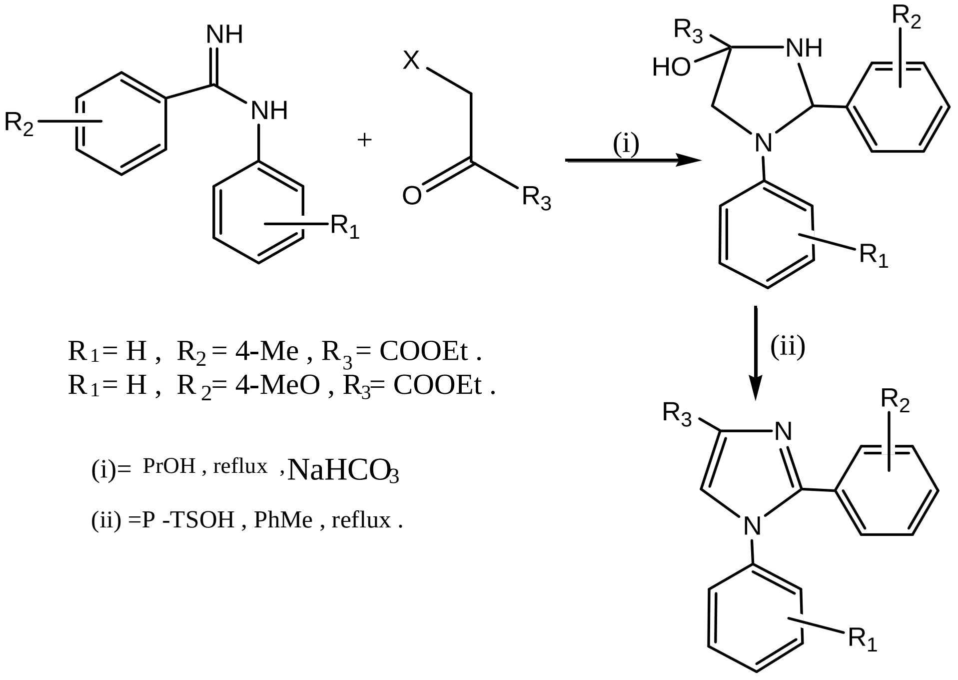
$H\!N{=}CH{-}\overset{\oplus}{N}H_3\overset{\ominus}{Cl}$

(2)



(3)

In recent years, a large number of imidazoles have been synthesized by a strategy involving treatment of an amidine derivatives with 2-halomethylketone and $NaHCO_3$ in refluxing in isopropanol, followed by acid-catalyzed dehydration (51-56) .



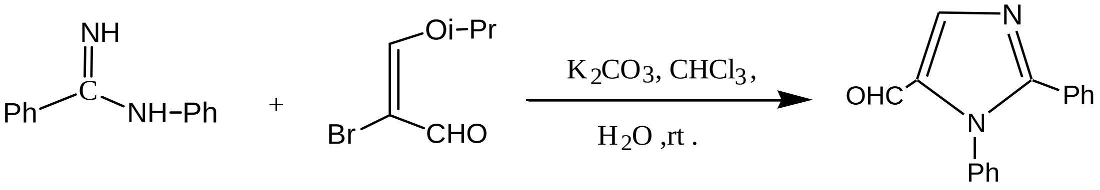
R_1= H , R_2 = 4-Me , R_3= COOEt .
R_1= H , R_2= 4-MeO , R_3= COOEt .

(i)= PrOH , reflux ,$NaHCO_3$

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

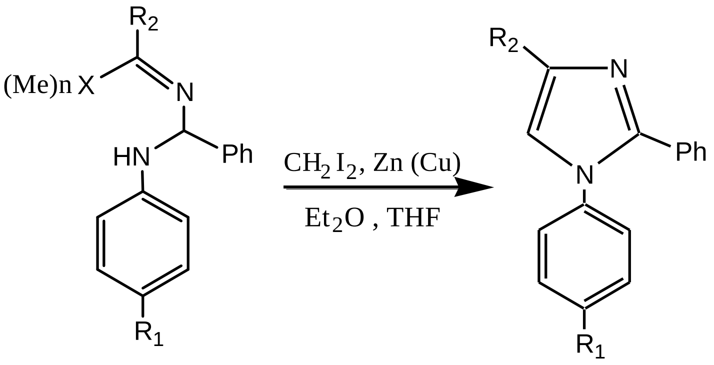
(46)

In 1997, an alkylation-cyclization sequence involving the use of amidine and α-bromoaldehyde was employed to prepare imidazole highly regioselectivity in 56% yield (57) .



(47)

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-1,3-diazobuta-1,3-dienes with the simmons-smith reagent generated from diiodo-methane and zinc-copper couple in ether (58) .



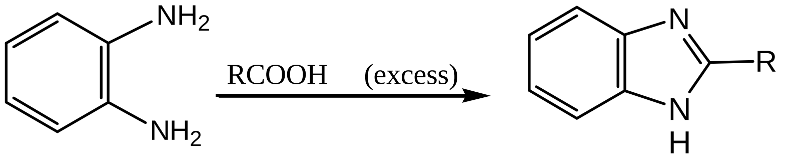
(48)

R_1 = H , Me .
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 :

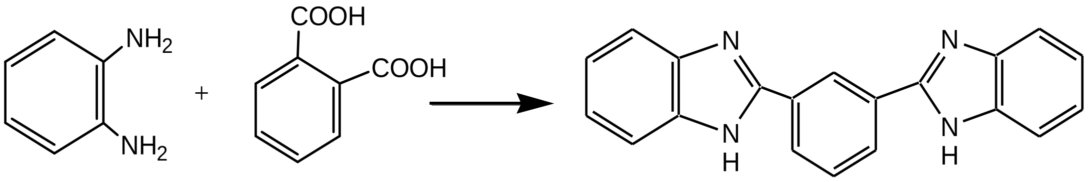
Fisher (59-64) reported that heating of o-phenylenediamine with excess of the acid gave the corresponding imidazoles.



(49)

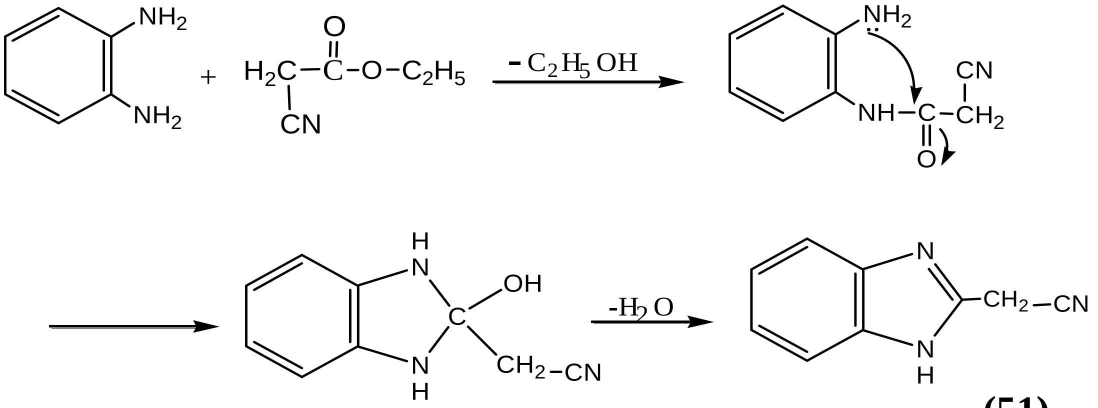
R = CH_3, $CH_3CH(OH)$- , phCH_2-

It was also reported that the reaction of o-phenylenediamine with aromatic acid is more suitable (65). Thus, it reacted with isophthalic acid to give 1,3-bis(2-benzimidazolyl)benzene (66) .



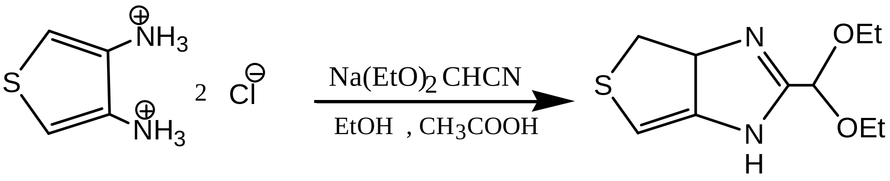
(50)

The acid derivatives such as acylchloride (67), ester (68), anhydride (69-70) were also used in the synthesis of imidazole ring, thus condensation of o-phenylenediamine with ethyl cyanoacetate under reflux gave 2-cyanomethylbenzimidazole.



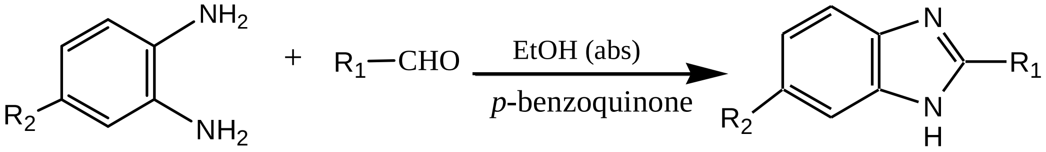
(51)

Reaction of diethoxyacetonitrile and diaminothiophene dihydrochloride in the presence of sod.ethoxide at room temperature afforded thienoimidzoles diethylacetal (71-73) .



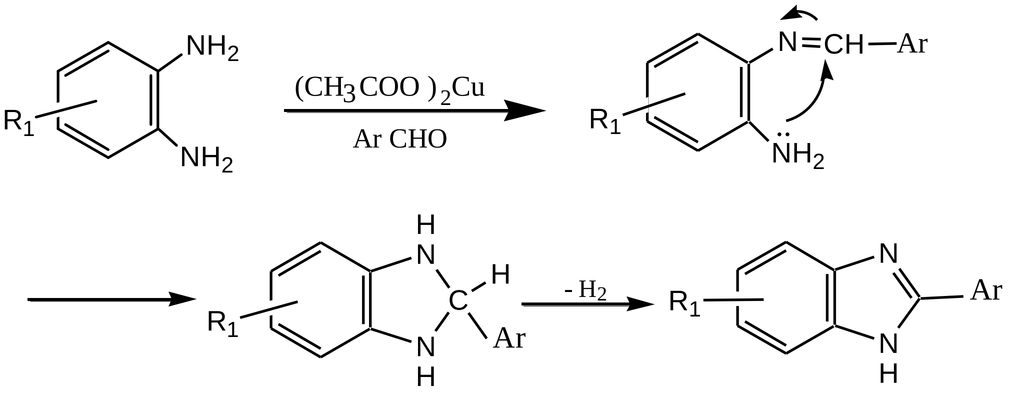
(52)

k.starceuic et al (74-75) ., reported that the imidazoles were synthesized by condensation of corresponding aldehydes and *p*-benzoquinone in absolute ethanol.



(53)

Weidenhagen (76) reported that, heating of o-phenylene-diamine derivatives with aldehyde in aqueous cupric acetate or aqueous alcohol gave benzimidazole.

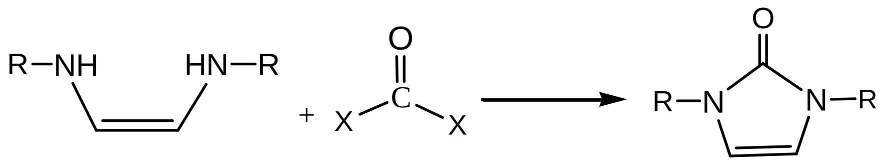


R =Cl , NO2 Me

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

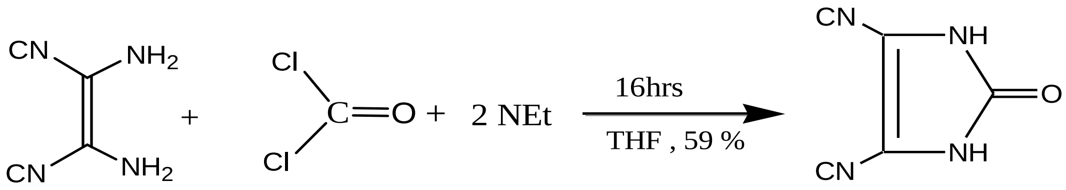
(54)

Construction of imidazolone ring using diamine was accomplished by cyclization and carbonylation steps (77-78) .



(55)

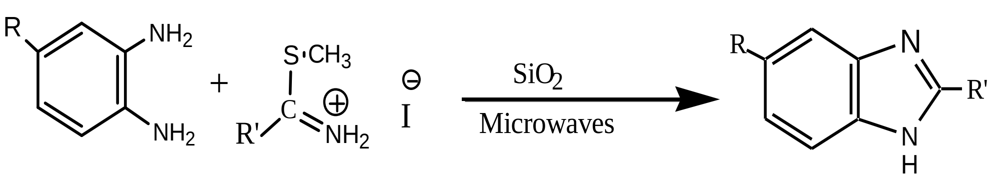
Imidazolone was also prepared by reaction DAMN (diamino-malononitrile) with phosgene (80-81) .



(56)

Condensation of o-phenylenediamine with cyanide in the presence of acetic anhydride gave 2-acetylaminobenzimidazole (82).

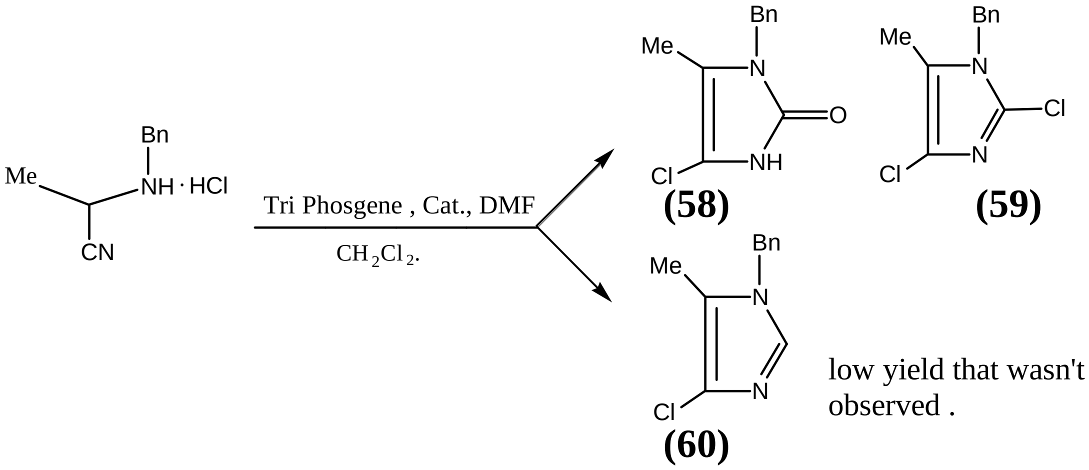
Imidazoles were prepared under dry conditions by the condensation of o-phenylenediamine with 5-methylisothioamide-hydroiodides on silica gel under microwave irradiation (83-84) .



(57)

<u>(6) From nitrile compounds</u> :

The synthesis that were expecting the formation of chloro-imidazolidione or dichloromidazoles upon treating α-aminonitriles with phosgene equivalents. However the formation of 1,5-disubstituted-4-chloroimidazoles was observed in very low yields upon treating α-aminonitrile with triphosgene in the presence of catalytic amount of DMF **(85-86)**.

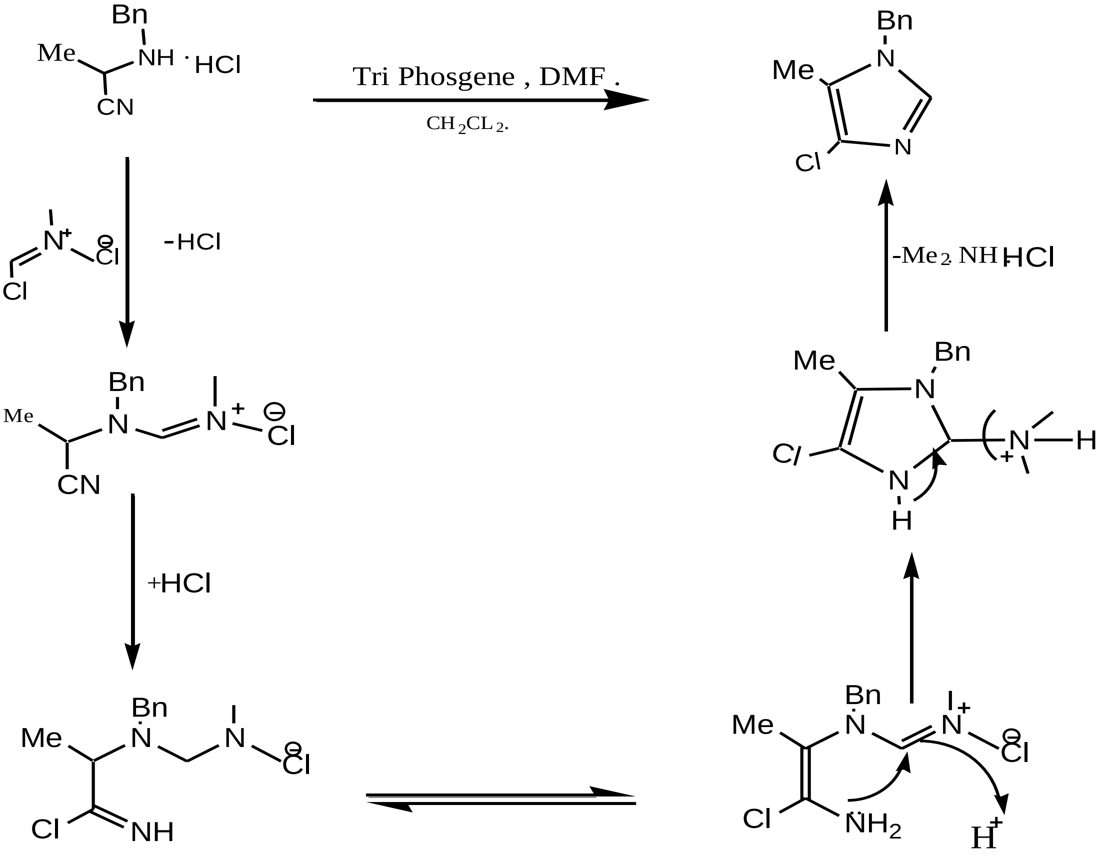


(58) **(59)** **(60)**

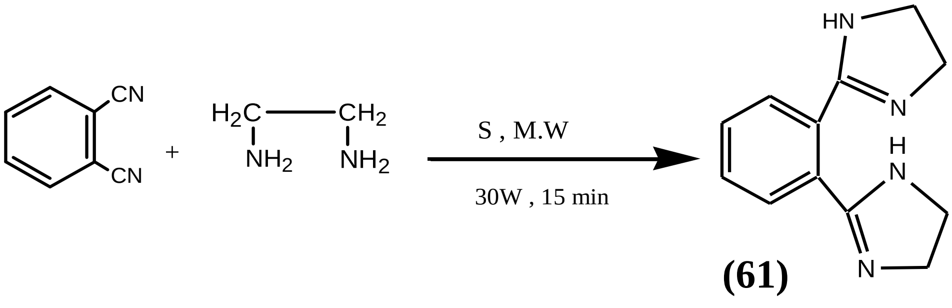
low yield that wasn't observed .

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.



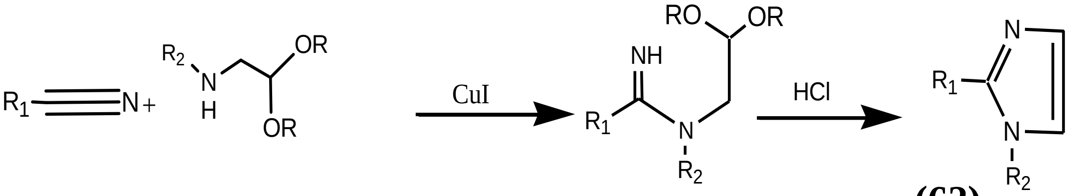
The imidazoline and imidazole ring was built by cyclization of appropriate nitrile with ethylenediamine in the presence of sulfur under solvent free conditions (87) .



(61)

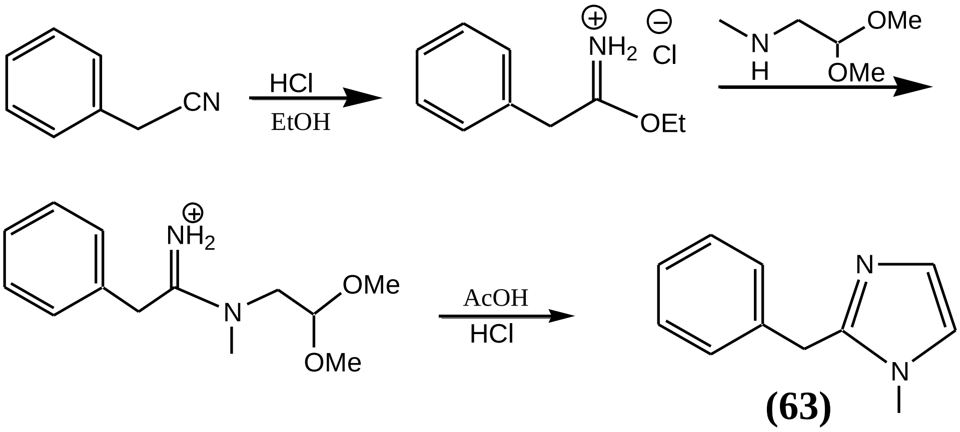
The preparation of imidazoline has previously been performed by electrophilic-diamination of functionalized alkenes, (88) reaction of aziridine with platinum II nitriles (89), and reaction of aromatic nitriles with ethylenediamines by the action of elemental sulfur (90), copper Salt (91), phosphates or silica gel (92).

Direct synthesis of imidazoles from nitriles and α-aminoacetals (93).



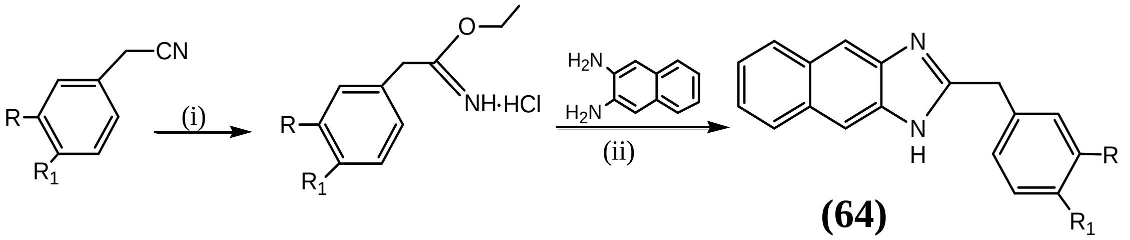
(62)

R.P. frutos et al., synthesized imidazoles using nitrile and α-aminoacetal (94-95).The formation of imidate salts often required prolonged reaction times (up to weak).



(63)

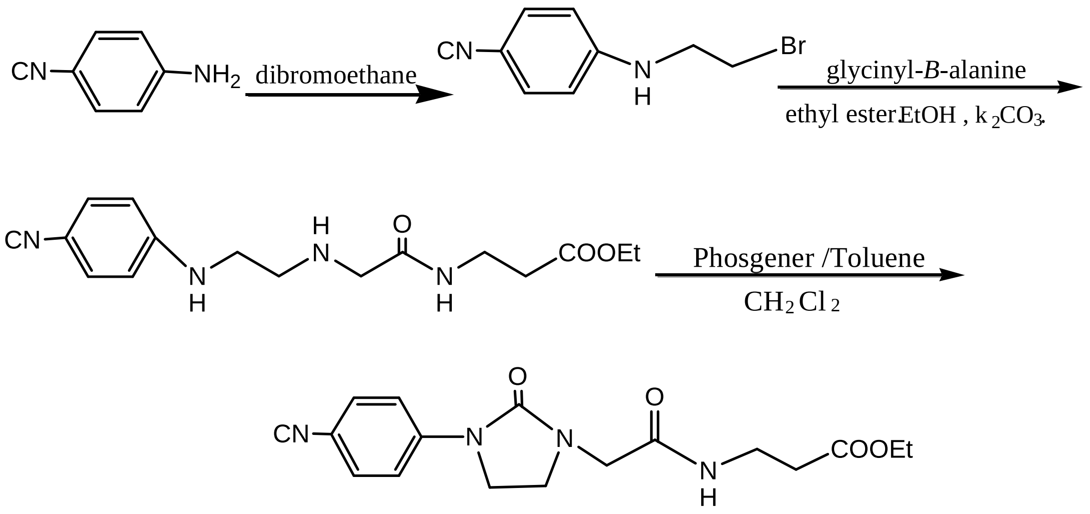
G. E. Grella et al (96) ., developed that, the treatment of requisite phenylacetonitriles with HCl gas and absolute ethanol in chloroform afforded imidates. The reaction of imidates with the 2, 3-diaminonaphthalene gave targets.



(64)

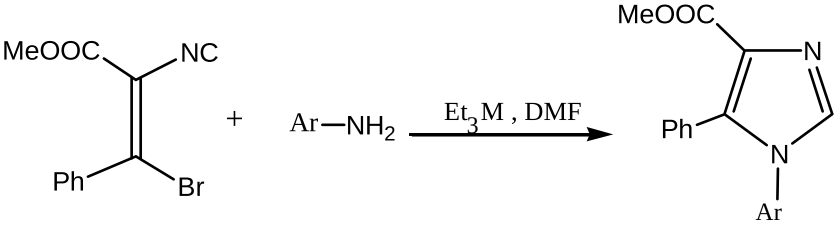
(i) = HCl (g) , absolute EtOH /dry $CHCl_3$;
(ii) = MeOH .

The new synthesis rout using aminobenzonitile for the construction of imidazolone (79) .



(65)

A few years later, imidazoles were synthesized by the reaction of methyl(*Z*)-3-bromo-2-isocyano-3-phenylacrylate with arylamine in DMF in the presence of Et_3N (97) .

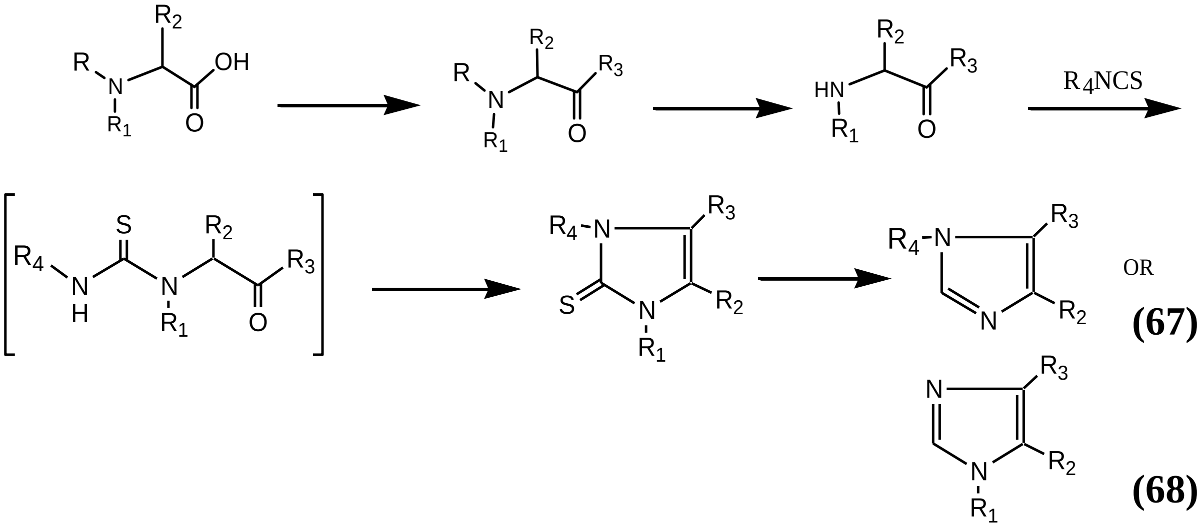


(66)

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 :

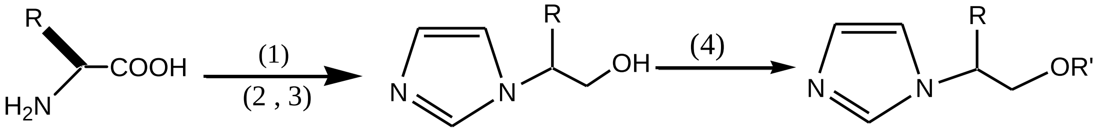
The Marckwald synthesis could be expanded to prepare regiospecific *N*-substituted imidazoles from α-amino acids $^{(98-99)}$.



(67)

(68)

The lipophilic chiral imidazoles were synthesized according to the procedures outlined in scheme using L-alanine, L-phenyl alanine and L-glutamic acid $^{(100)}$.



(69) **(70)**

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

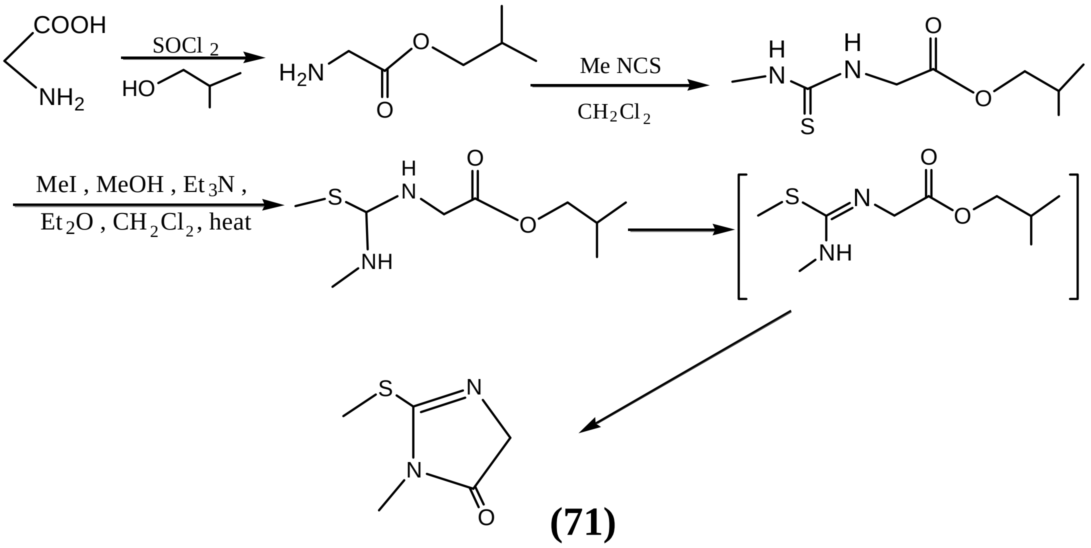
(1)=NH_3,H_2O . NaOH. H_2O .

(2) =$SOCl_2$, CH_3OH .

(3)= $NaBH_4$ .C_2H_5OH .

(4) =NaH , THF , R'Br .

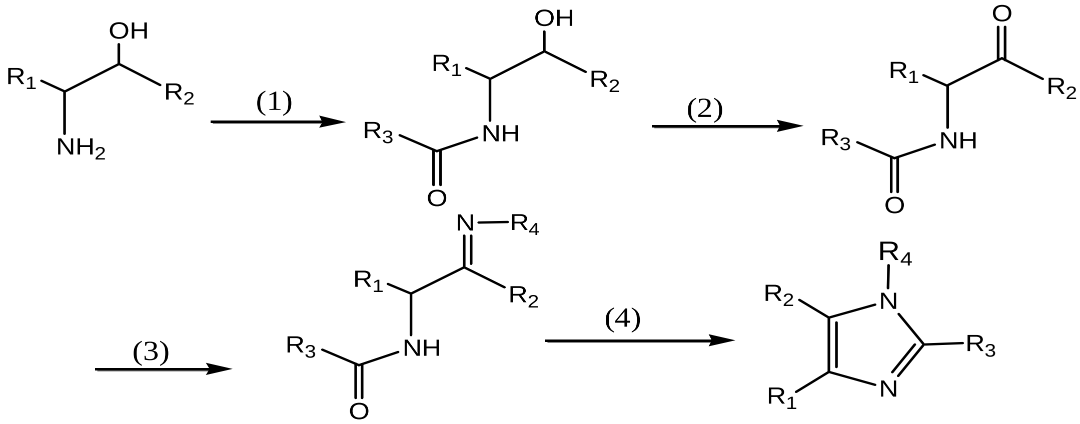
Following scheme shows the route for the cheap preparation of imidazolones compounds through " five-steps" using amino acid under microwave heating **(101)** .



(71)

(8) From amino alcohols :

One approach to substituted imidazole involve the use of α-amino alcohol **(102)** . Treatment of these system 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.

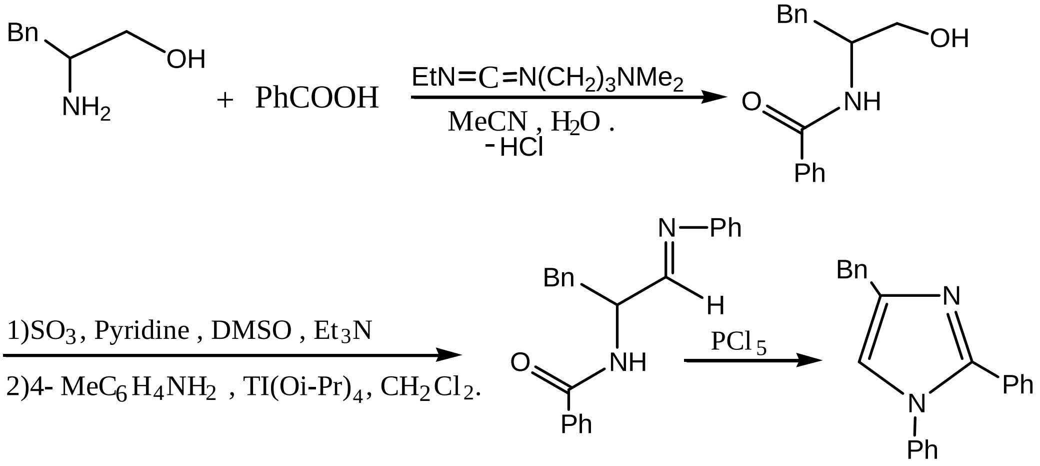


(1) =R^3-CO_2H , EDCl , CH_3CN , H_2O ;
(2) =SO_3, Pyridine , DMSO , Et_3N ;
(3) =R^4- NH_2, Ti (iO- Pr)$_4$, CH_2Cl_2;
(4) = pCl_5.

(72)

The rout developed by Engel and steglish (103) , the α-amidoimines were derived from acid precursors via a Dakin-west rearrangement.

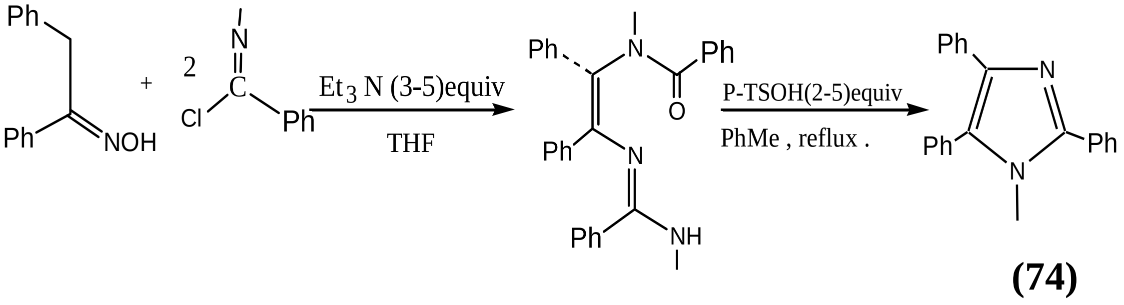
In 2004, the trisubstituted imidazole was synthesized in 65% overall yield via a four step procedure involving *N*-acylation of amino alcohol with benzoic acid , oxidation of the resulting compound , formation of imine and followed by cyclization (104) .



(73)

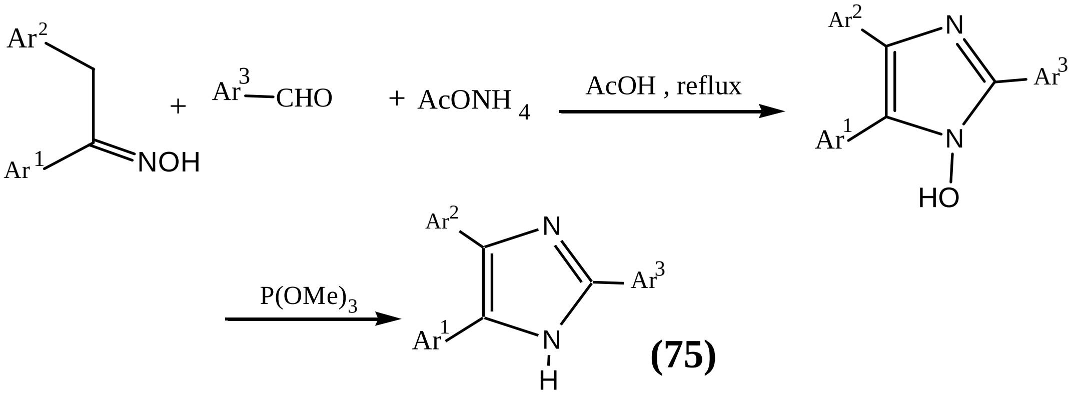
(9) From oxime compounds :

In 1993, a hetero-cope rearrangement was used as key reaction of a two step synthesis of imidazoles (105) .



(74)

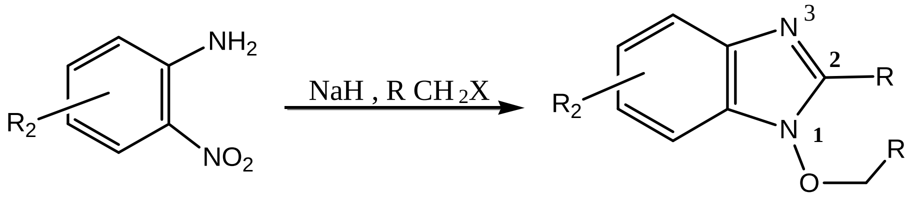
On the other hand , Gallagher and co-workers **(106)** synthesized imidazole by using a strategy that involves the cyclocondensation reaction of ketoximes with aldehydes and ammonium acetate.



(75)

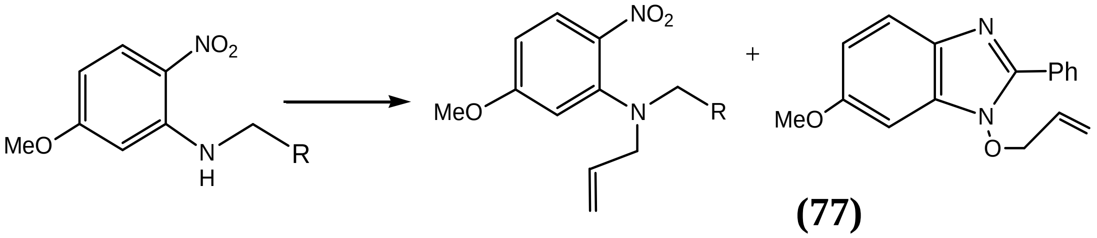
(10) From nitroaniline and related compounds :

Treatment of *N*-alkylnitroaniline with sodium hydride in the presence of various alkylating agents did lead to formation of the desired benzimidazole derivatives **(107)** .



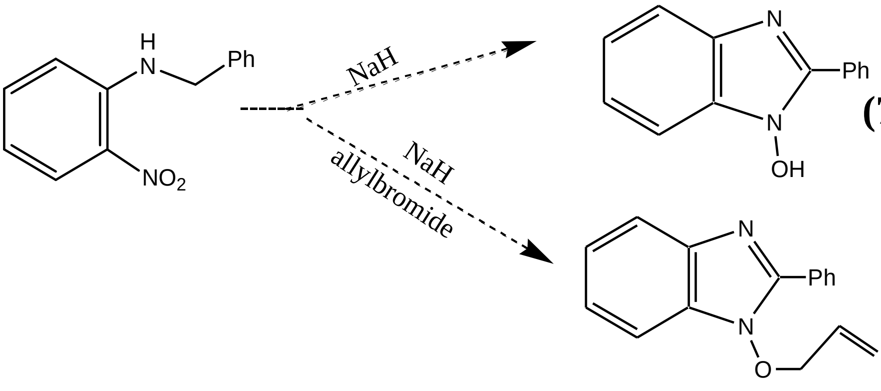
(76)

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



(77)

In the absence of alkylating agent, the heterocyclization proceeded yielding the *N*-hydroxybenzimidazole (108).

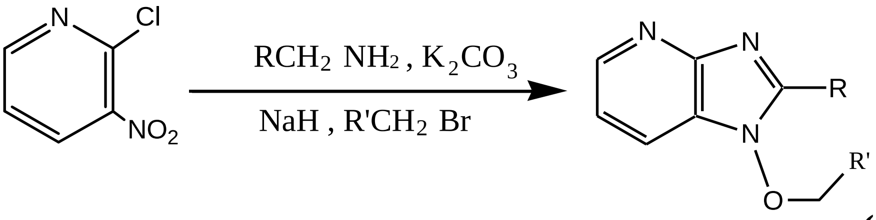


(78)

(79)

(11) From nitropyridine derivatives :

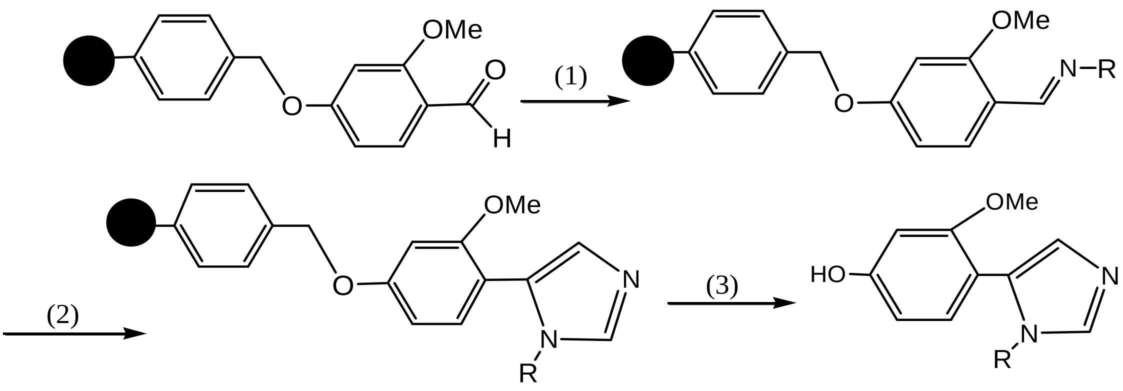
2-chloro-3-nitropyridine as starting material to provide a number of new *N*-alkoxypyrimidazoles (108).



(80)

(12) From polymer bound compound :

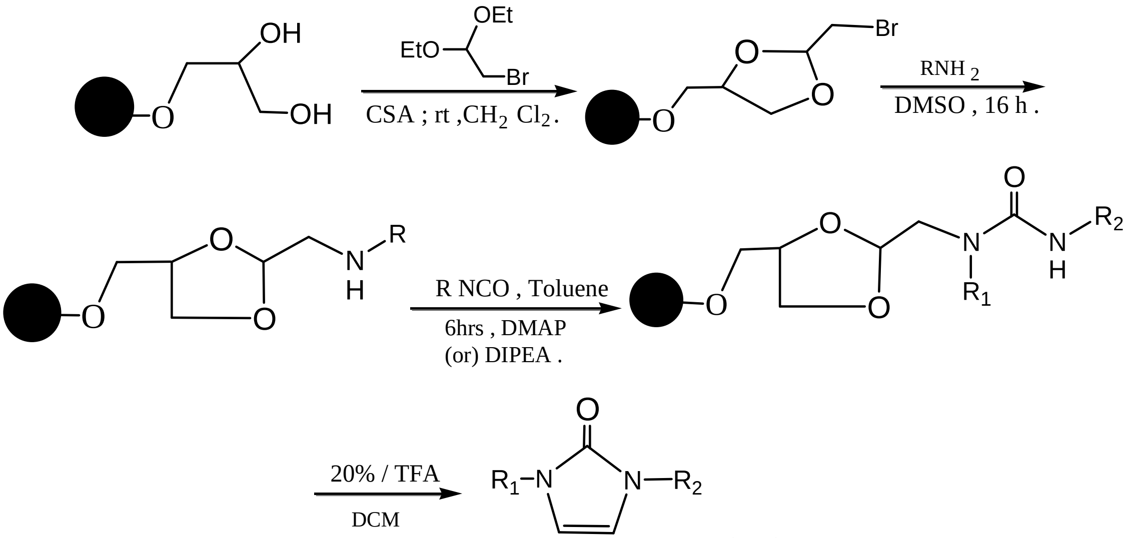
Translation of 1,3-dipolar cycloaddition reaction to the polymer bound 3-methoxy-4-hydroxybenzaldehyde afforded imidzole ring (109).



(1) =CH(OMe)$_3$, DMF .
(2) =4-CH$_3$C$_6$ H$_4$SO$_2$CH$_2$NC , DMF , 20 min .
(3) =TFA /CH$_2$ Cl$_2$, rt ,1.5h .

(81) **(82)**

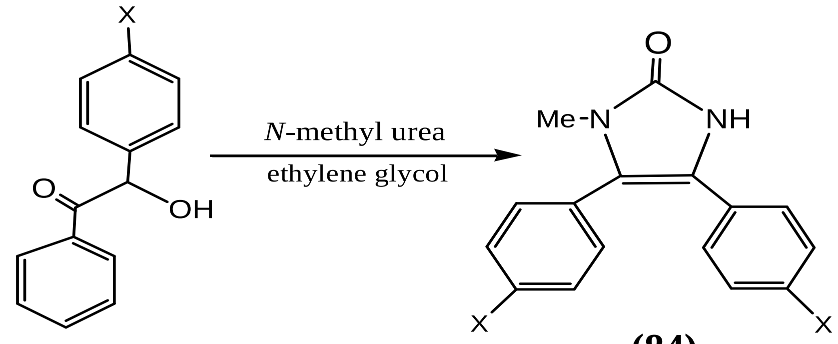
Upon deprotection of the polymer bound acetal functionality under acidic conditions, the released amide or (urea)aldehyde intermediate would spontaneously undergo cyclization to form an *N*-acyliminium ion that would deprotonated .



(83)

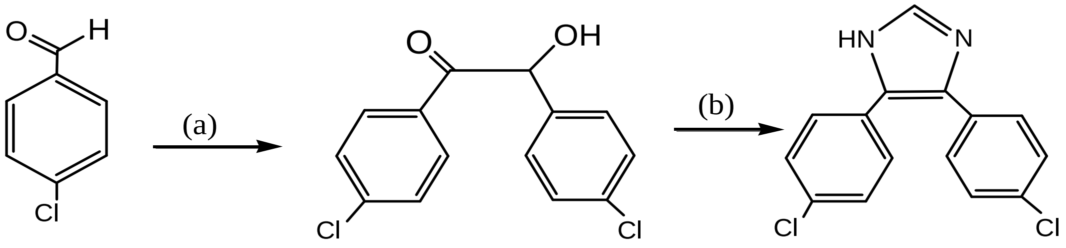
(13) From benzoin compound :

Preparation of the imidazolone derivatives, started with the thermal cyclization of benzoin with *N*-methylurea in ethylene glycol at 180°C (115) .



(84)

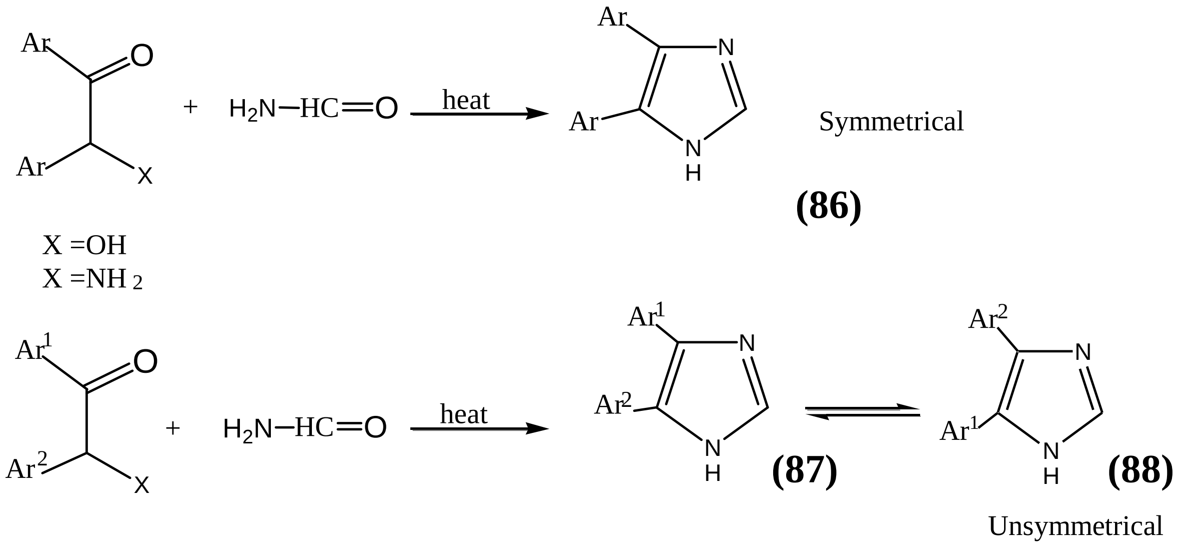
Also, C. W. Plummer et al (12) ., synthesized imidazole via the following scheme.



(85)

(a) =NaCN , H_2O , EtOH ;
(b) =*P*-Formaldehyde ; 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 (116) , or/ 2-amino-1,2-diarylethanone (117) .

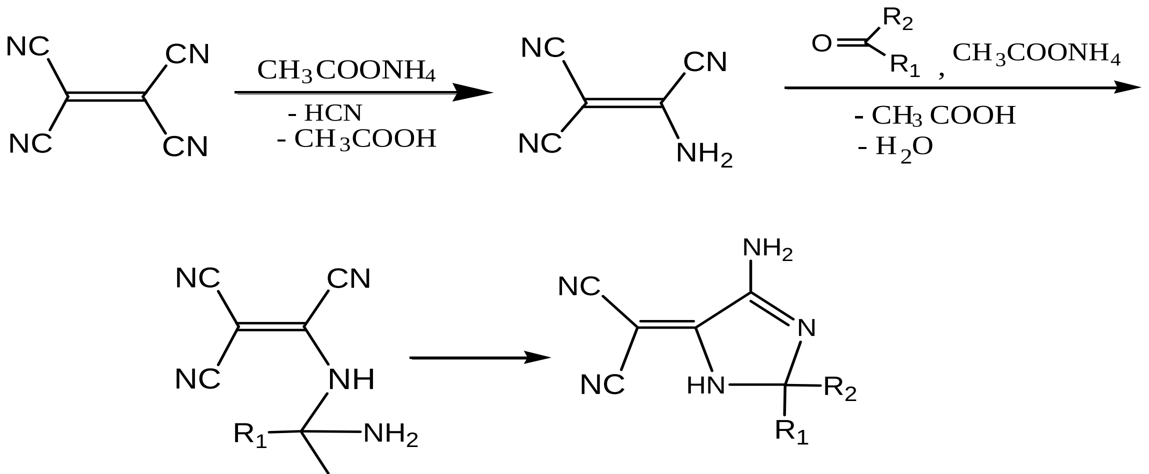


(86)

(87) **(88)**

(14) From tetracyanoethylene :

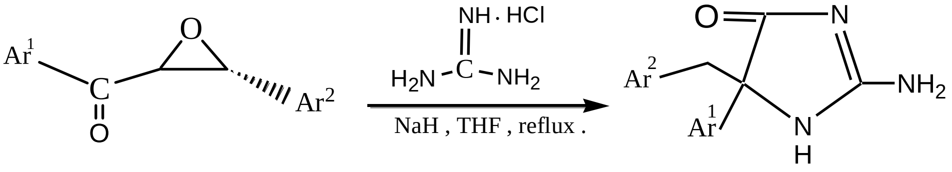
A new method via [3+2]heterocyclization reaction for the preparation of imidazoles using tetracyanoethylene as starting material (118-120) .



(89)

(15) From Epoxydiphenylketone :

2,3-Epoxydiphenylketone react with guanidine or urea to form 2-amino-4H-imidazol-4-ones and analogour hydontions via a novel one pot-rearrangement (121) .

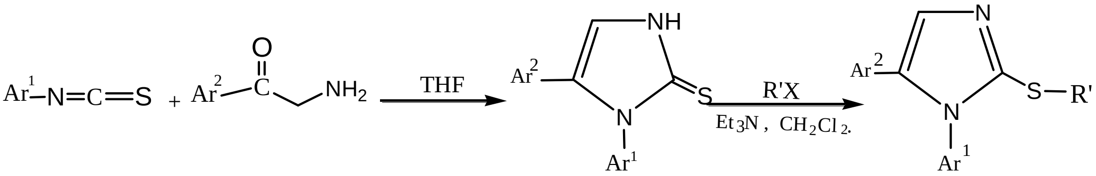


(90)

Ar	4-MeOC$_6$H$_4$	4-ClC$_6$H$_4$	C$_6$H$_5$
Ar	3,4-(MeO)$_2$C$_6$H$_3$	Ph	Ph

(16) From β-aminoketones compounds :

In 2002, acombinational library of imidazole was synthesized by alkylation with imidazole-2-thiones obtained via reaction of aryl-isothiocyanates with β-aminoketons (122) .

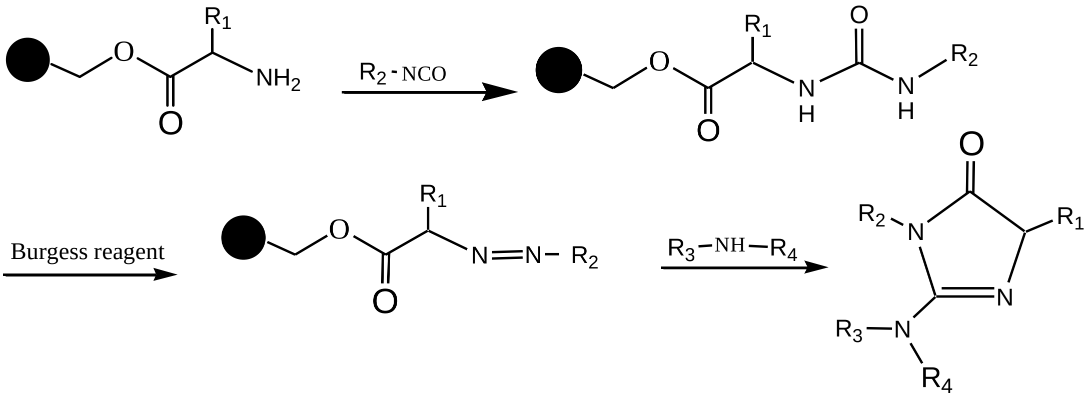


(91)

Ar^1= ph , 3-MeOC$_6$H$_4$
Ar^1= ph , 4-MeOC$_6$H$_4$
R^1 = CH$_2$(3-indolyl) , 2-NO$_2$ Bz , CH$_2$NEt ,
CH$_2$CH$_2$(1-pyrrolyl) , CH$_2$(2-NO$_2$ furyl) ,
CH$_2$CH=CH-Me

Starting from inexpensive Merifield resin which reacted with urea and an arylisocyanate lead to formation of imidazolones (123-131)

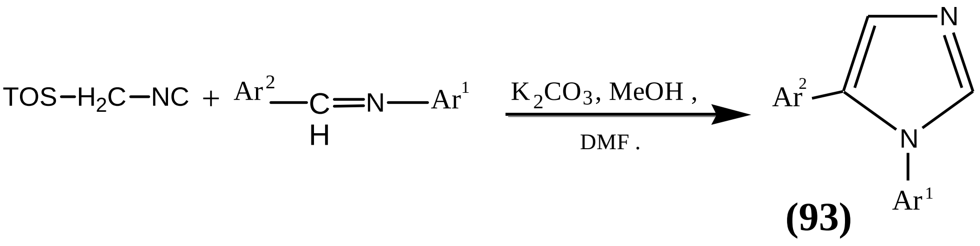
.



(92)

(17) From schiff's base :

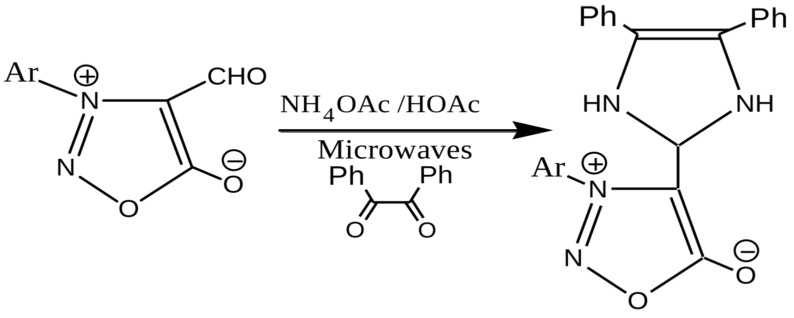
In particular, the van Leusen group found that the base-induced [3+2]cycloaddition of *p*-toluene sulfonylmethylisocyanide to *N*- (arylidene)anilines in aprotic medium occurs with concomitant elimination of *p*-toluene sulfinic acid to give imidozole (132-135) .



(93)

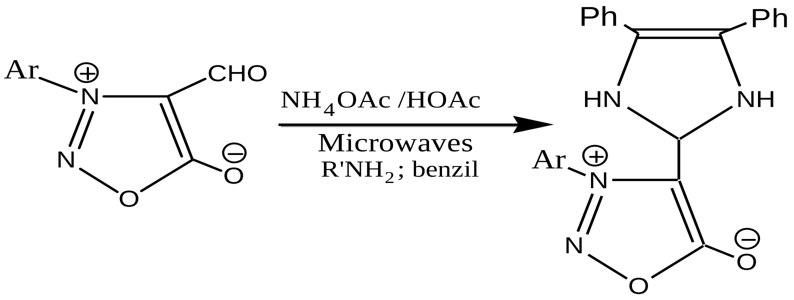
(18) By using microwaves :

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 imidazole was synthesised.



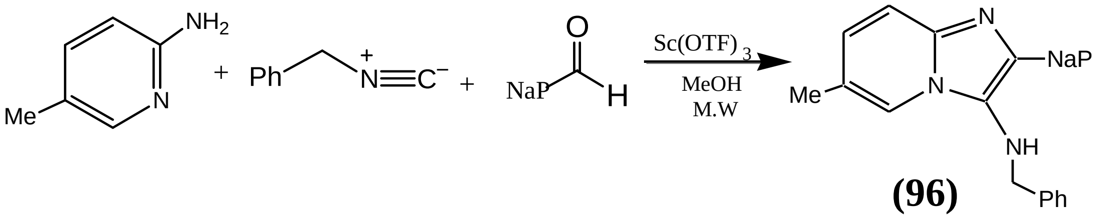
(94)

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 (136).



(95)

Microwave assited vgi3cc reaction of 2-amino-5-methyl-pyridine with benzylisocyanide and 2-naphthaldehyde (137).

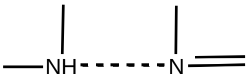


(96)

CHEMICAL REACTIONS OF IMIDAZOLES AND IMIDAZOLONES

Properties of imidazoles and imidazolones.

When Hunter and Marriot **(138)** 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 imino hydrogen. It was believed that the association involves hydrogen bond **(139)** between the imino group of one molecule and the tertiary nitrogen of another molecule.



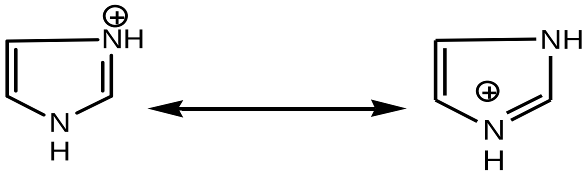
Reaction of neutral imidazoles:

Imidazole can be considered having properties similar to both pyrrole and pyridine. In consequence one would expect that electrophile agents would attack by electrophilic, radical and nucleophilic species. Substitution reactions, which do not destroy the aromatic character are predominant while the imidazol ring suscptilies 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, hydrochloride and nitrate salts were well defined, although they may be hygroscopic. Salts of organic acids, e.g., oxalate and picrates form 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.



(97) **(98)**

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

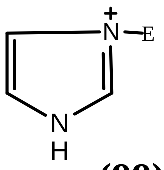
Acidity of imidazole :

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.

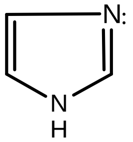
Electrophilic attack

A- Electrophilic attack on nitrogen:

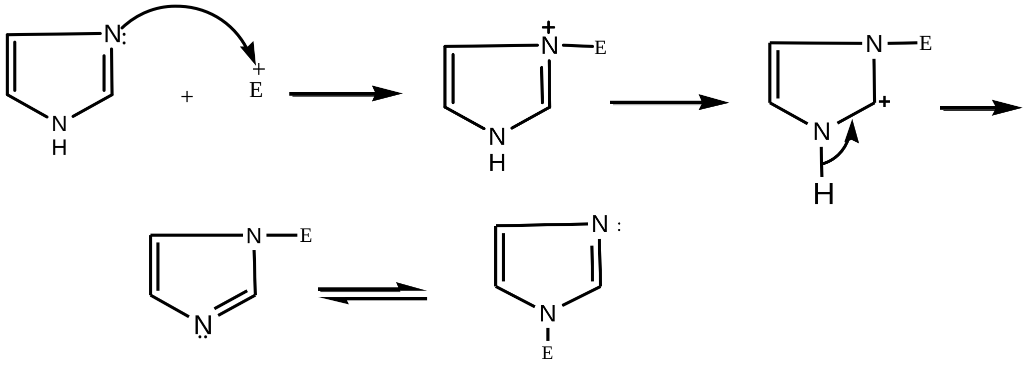
Reaction with the N-H nitrogen would require the use of the electrons from the 6 π system will disturb the aromaticity. For these reason the transition state(**99**) would be energetically more favorable than (**100**) and in consequence reactions with the imidazole neutral molecule follow the following sequence:



(99)

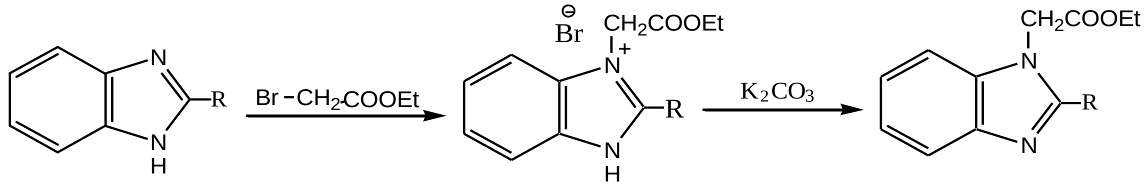


(100)



1) Alkyl halides and related compounds:

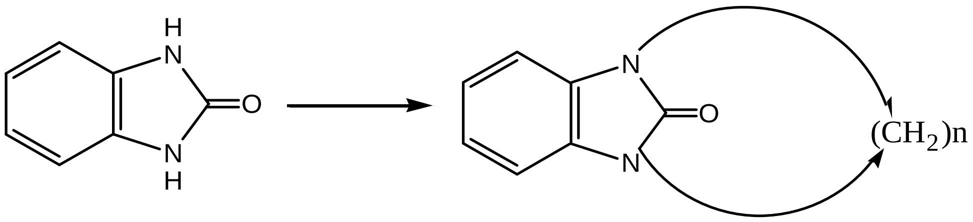
The quaternization of substituted imidazole and imidazolone is a facile reaction which leads to a stable quaternary salt there are number examples of quaternizing alkylations of imidazoles and imidazolones using alkyl, alkenyl, ethylhaloacetate, phenacylbromide or dimethylsulphoxide**(140)**, for instance ethyl-1-benzimidazolyl-acetate and their 2-alkyl derivatives were easily obtained by reaction of benzimidazoles with ethyl/methylbromoacetate in dry DMF containing anhydrous K_2CO_3 (141-142).



R =H ; alkyl group

(101)

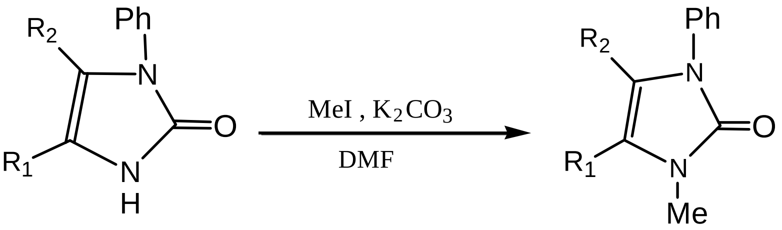
2-Benzimidazolinone was alkylated using dibromoalkanes in a basic medium giving 1,3-polymethylenebenzimidazolinone (143).



(102)

n = 10-12

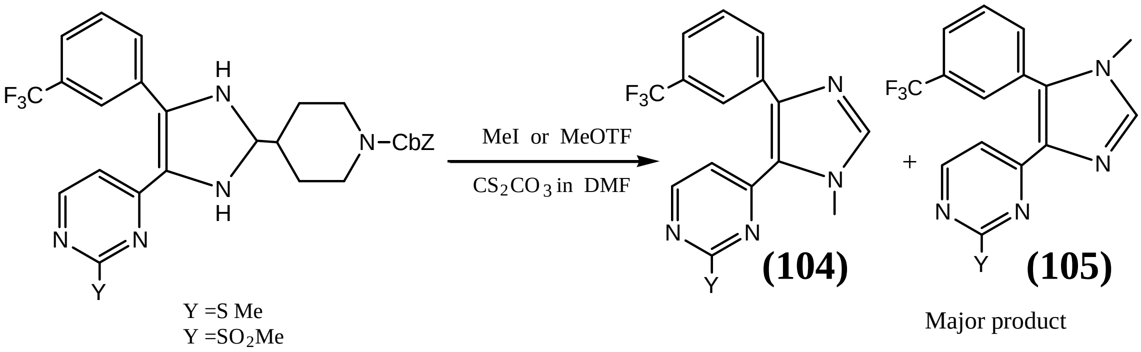
Also, Alkylation of imidazolone using MeI and K_2CO_3 in DMF were described (22).



(103)

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 undesirede regioisomer, together with less than 5% of the required product and this result wasn't altered using methyl triflate as electropile **(144)** .

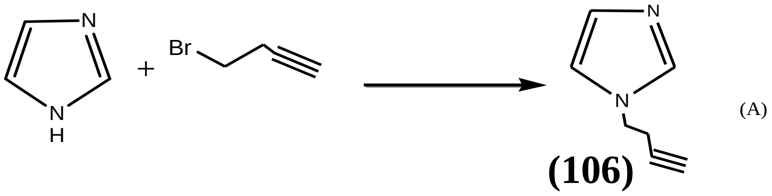


Y =S Me
Y =SO_2Me

(104) **(105)**

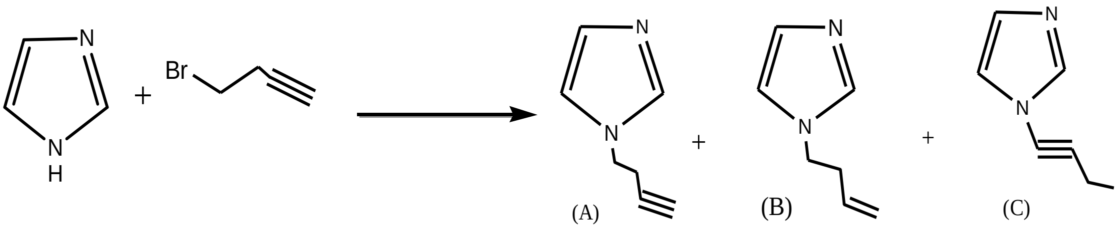
Major product

Also,alkylation of imidazole with propargylbromide under microwave radiation **(145)** .



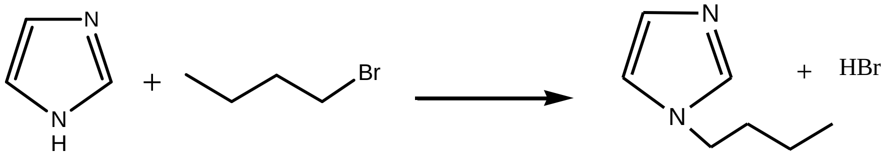
(106)

But usually, in basic media the reaction affords a mixture of *N*-ally (B) and *N*-propargyl (C) derivatives **(146-147)** .



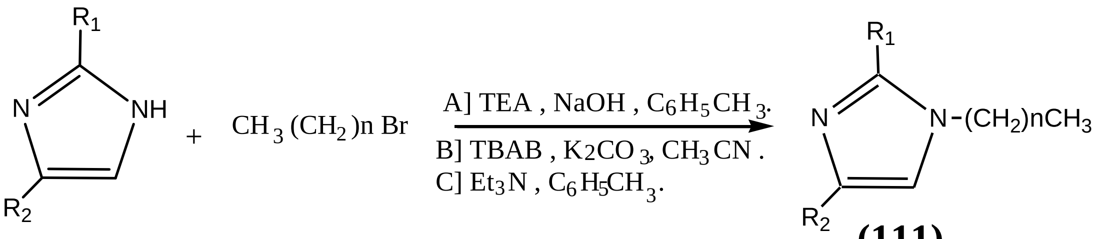
(107) **(108)** **(109)**

Also, imidazole was alkylated using 1-bromobutane using activated carbons as a catalyst **(148)** .



(110)

Different azole compounds were reacted with appropriate alkyl bromides in an alkaline media, at relfux temperature and in the presence of (TEAI) or (TBAB) as phase transfer catalysts by A,B, C (149) .

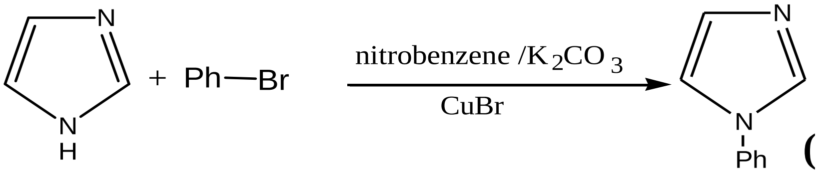


(111)

R_1= H , CH_3
R_2= H , NO_2 .

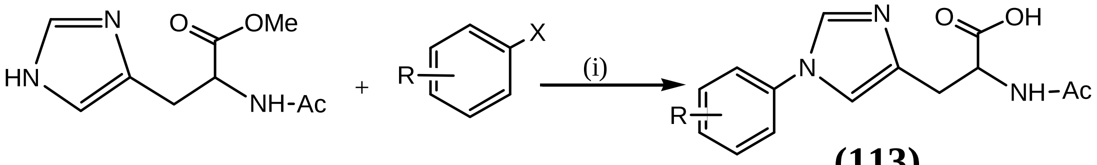
2) Aryl halide and related compounds :

Arylation at ring nitrogen was not simple procedure because halides are not usually susceptible to nucleophilic displacement of halogen group. Amodified ullmann-type reaction an imidazole using bromobenzene in the presence of potassium carbonate in nitrobenzene and copper bromide gave a reasonable yield of 1-arylimidazole (150) .



(112)

Also, kiyomori et al (151-152) ., described a modified ullmann-type coupling of simple imidazoles with aryliodides or bromides using $Cu(OTF)_2$. PhH as acatalyst in the presence of o-phenanthraline, dibenzylidene acetone and cesiumcarbonate in hot xylene, direct flash chromatography afforded clean products **(153-154)**.



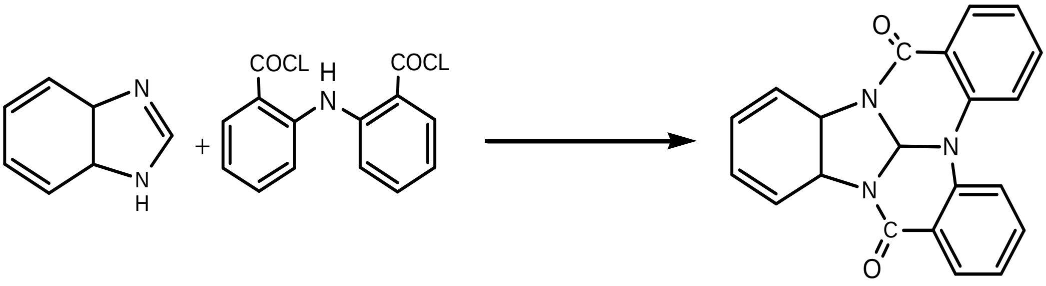
(113)

(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

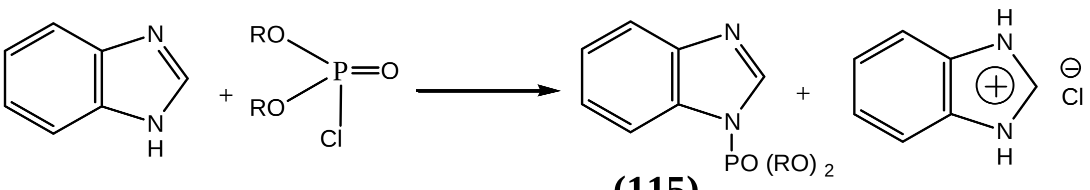
3) Aroyl halides and related compounds :

Imidazoles are readily acylated, arylated and may be converted to quanternary salts. In one such reaction the imidazole eventually partially dearomatized on to reaction with bis-(chloroformyl)diphenyl amine **(155)**.



(114)

Reaction of benzimidazole with dialkylphosphorylchloride gave 1-dialkylphosphorylbenzimidazole **(156)**.

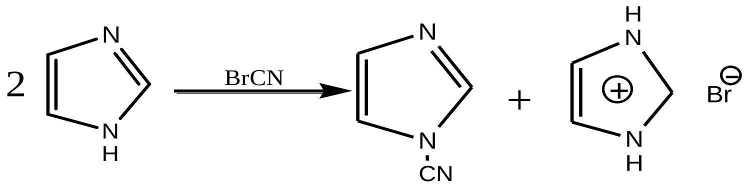


(115)

4) Other electrophiles :

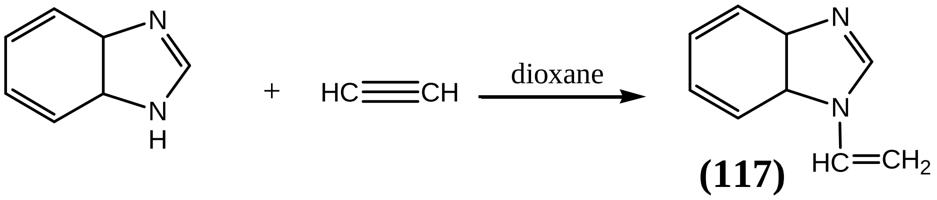
Reaction of cyanogens bromide with imidazole.

Having a free NH group gave the corresponding *N*-cyano derivatives (157) .

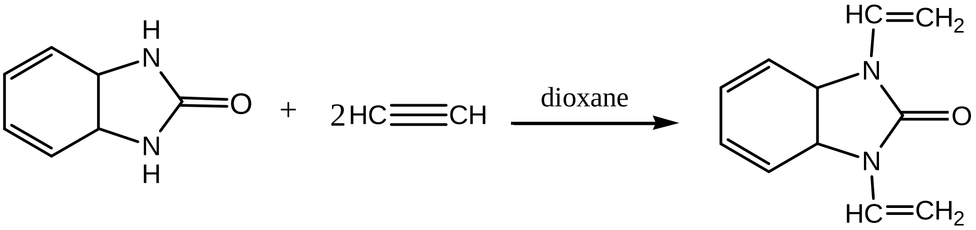


(116)

Also, addition of acetylene in aqueous dioxane to imidazole and imidazolinone afforded 1-vinylbenzimidazole and benzimidazolinone respectively (157) .



(117)

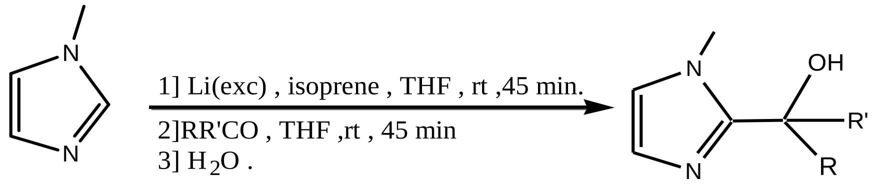


(118)

B- Electrophilic attack on carbon:

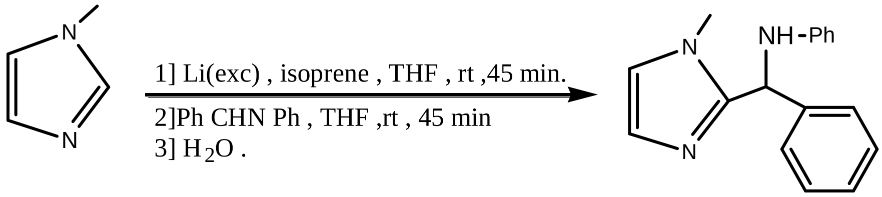
1) Alkyl halide and related compounds:

Imidazoles could be treated with different carbonyl compounds as electrophiles using lithium metal and isoprene in DMF at room temperature (158-160) .



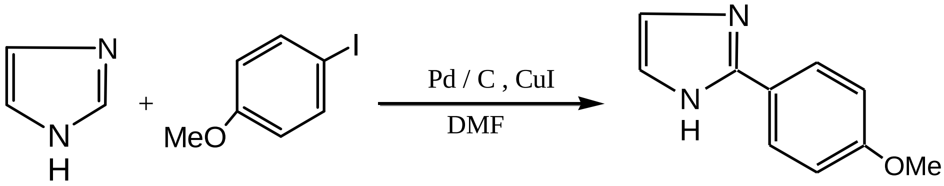
(119)

Also, it was reacted with different arylaldimines as electrophiles in situ (161) .



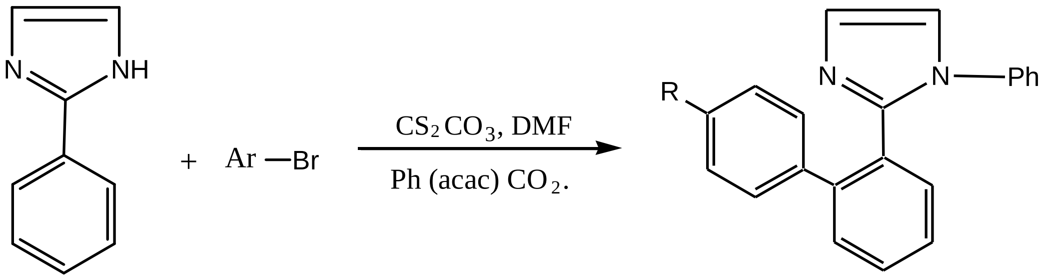
(120)

More recently, there was established that, the regioselective C-2 arylation of imidazole with aryl iodides can conveniently be performed in DMF in the presence of CuI using Pd $(OAc)_2$ as the catalyst (162-164) .



(121)

In fact, in 2003, it was claimed that imidazole can undergo a highly regioselective C-2 arylation reaction by treatment of an aryl bromide in DMF in presence of CS_2CO_3 **(165)** .

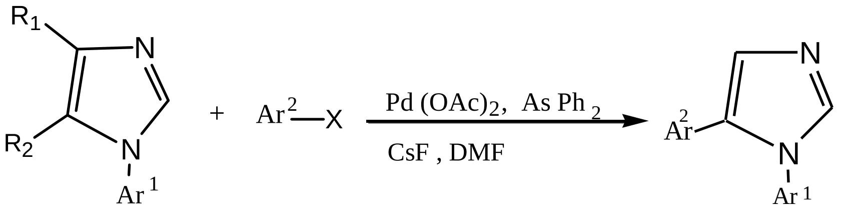


(122)

Ar	Ph	4-MeOC$_6$H$_4$	4-CF$_3$C$_6$H$_4$
R	H	4-MeOC$_6$H$_4$	4-CF$_3$C$_6$H$_4$

Also, Direct arylation of imidazoles with aryl halides **(166)** . The reaction conditions most suitable for a highly regioselective

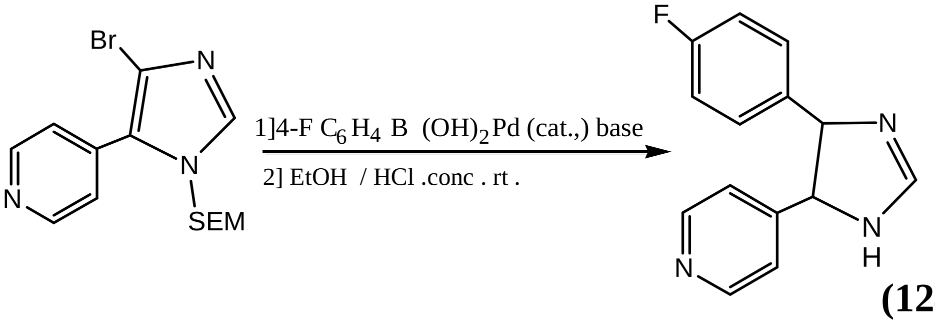
C-5 arylation of imidazole.



(123)

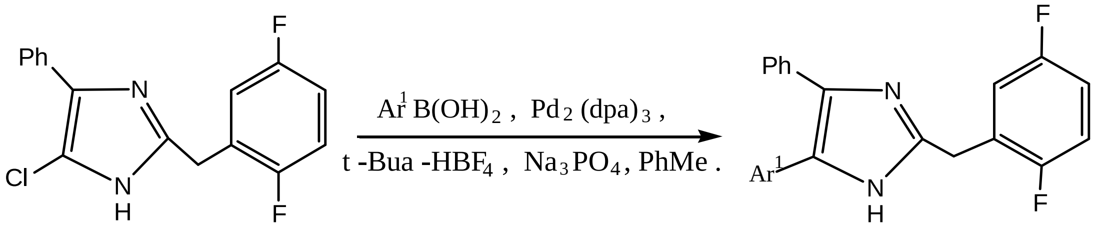
Ar^1 = ph
$R_1 = R_2$ = H

On the other hand, the C-4 arylation of imidazole was performed by a Suzuki-type reaction with 4-fluorophenylboronic acid **(167)** .



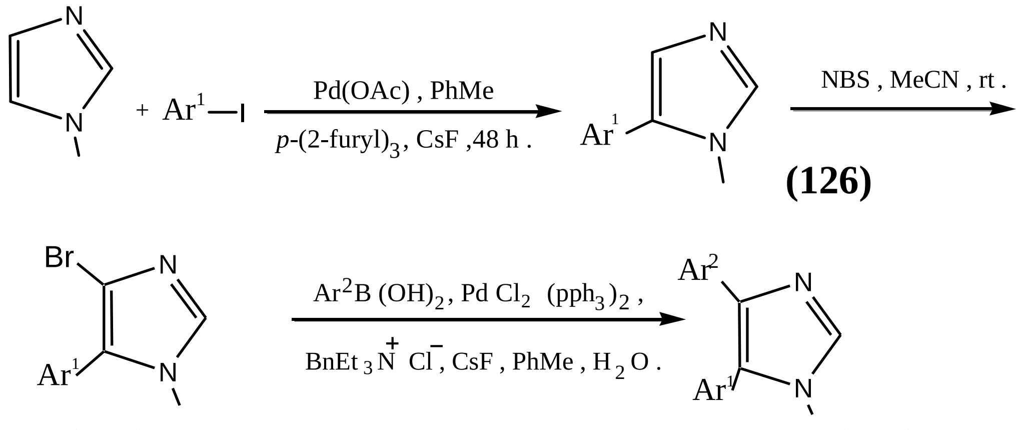
(124)

Also, Pd-catalyzed Suzuki-coupling involving the use of the unprotected 5-chloroimidazole (168) as the substrate have also been described.



(125)

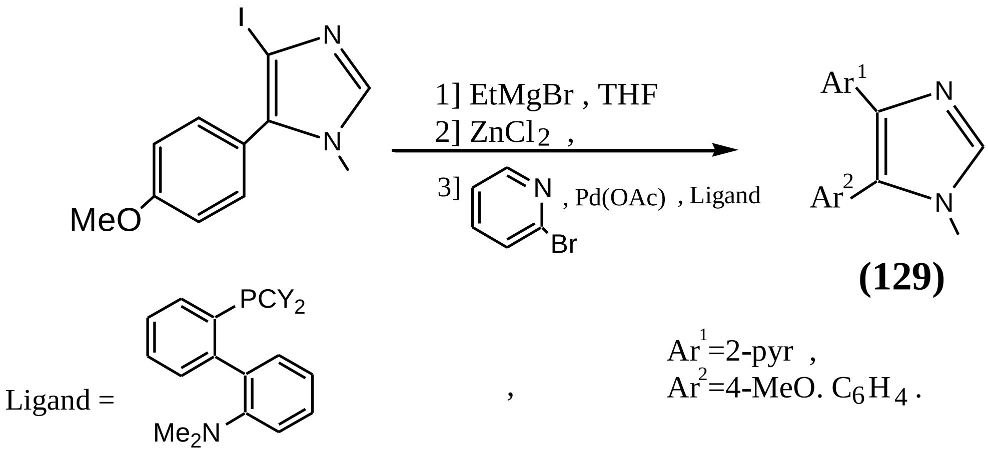
Suzuki-type coupling reactions under phase transfer condition have also been described (169-170) .



(126)

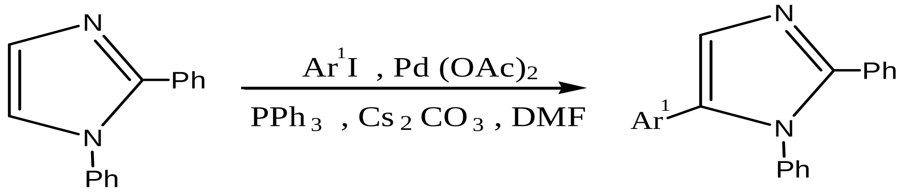
(127) **(128)**

A pd-catalyzed Negishi-type reaction cross-coupling reaction was employed on imidazole using bromopyridine (171) .



(129)

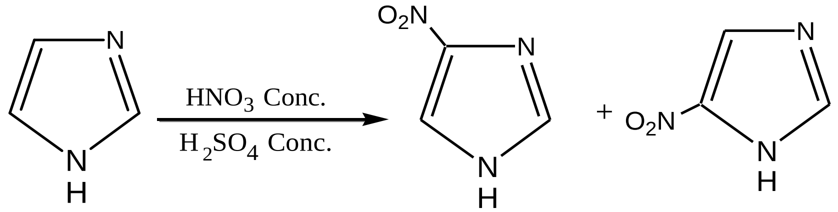
C-5 arylation of imidazoles with required aryliodides under the optimized conditions originally reported by Miura **(172-173)**.



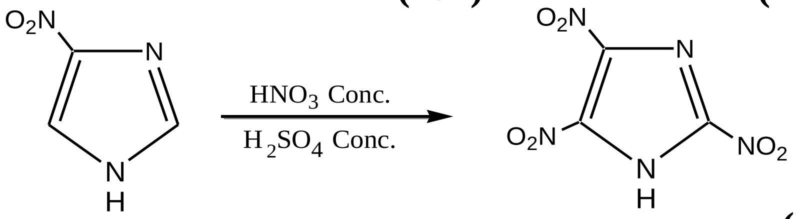
(130)

2) Nitration :

Nitration of imidazole **(174)** 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, 2,4,5-trinitroimidazole can be prepared by nitration of 2,4-dinitroimidazole **(175)**.

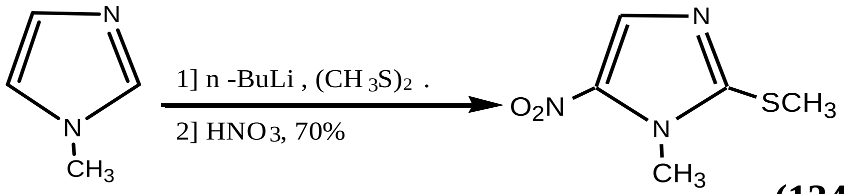


(131) **(132)**



(133)

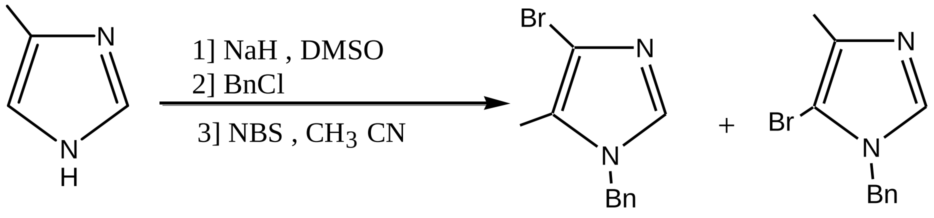
The reaction of imidazole with n-butyllithium at 30°C and subsequent addition of dimethyldisulfide and then nitration of the product compound afforded the corresponding 5-nitroimidazole$^{(176)}$.



(134)

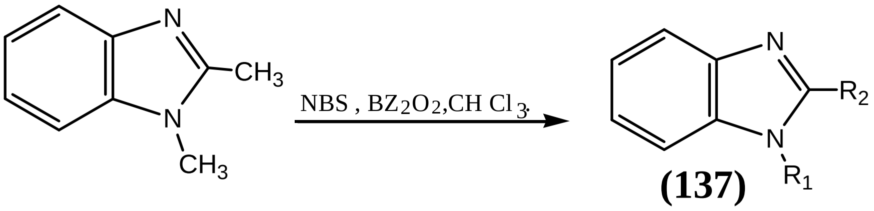
3) Bromination :

Treatment of imidazole with NaH and BnCl $^{(177)}$ and then Brominated with NBS to afford bromoimidazoles $^{(178-179)}$.



(135) **(136)**

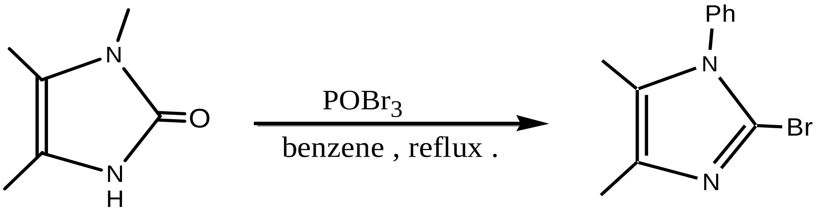
Also, imidazole was brominated with *N*-bromosuccinimide under free radical substitution condition gave brominated imidazoles (180) .



(137)

a.=R_1 =R_2=CH_3 Br , 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 .

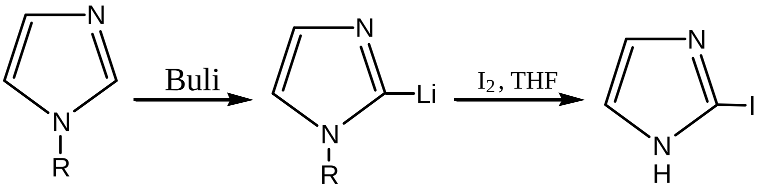
Also, chloroination (12, Bromination of imidazolone were done(22) .



(138)

4) Iodination :

In alkaline medium imidazoles are subjected iodination on ring nitrogen,giving 1-iodoimidazole was prepared via the lithiation of imidazole (181) .



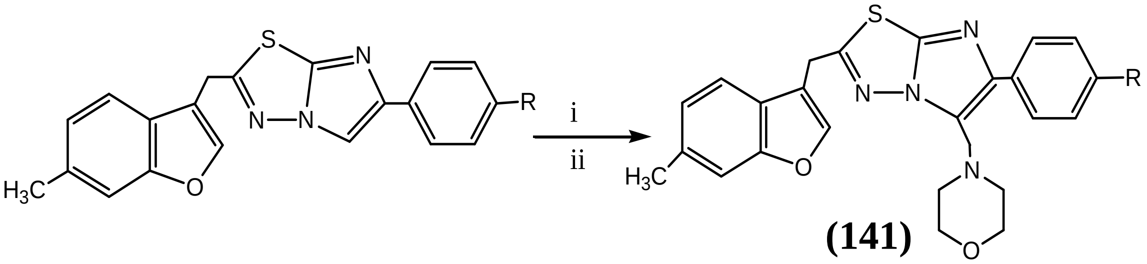
R =SO_2Ph
R =CPh_3

(139) **(140)**

5) Reaction with aldehydes and ketones :

Mannich reaction:

Imidazoles undergo Mannich reaction with cyclic secondary amine, (morpholine)and(formaldehyde) in presence of catalytic amount of acetic acid (9) .



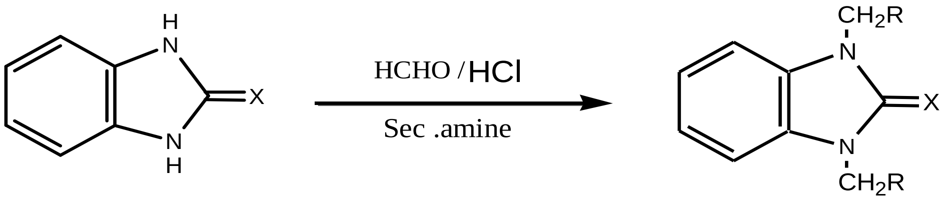
(141)

i = Morphline , HCHO

ii = AcOH , MeOH , reflux ,8hrs

R = Br , Cl , NO_2

Also, it was done on 2-benzimidazlinone and benzimidazoline thiones (182) .

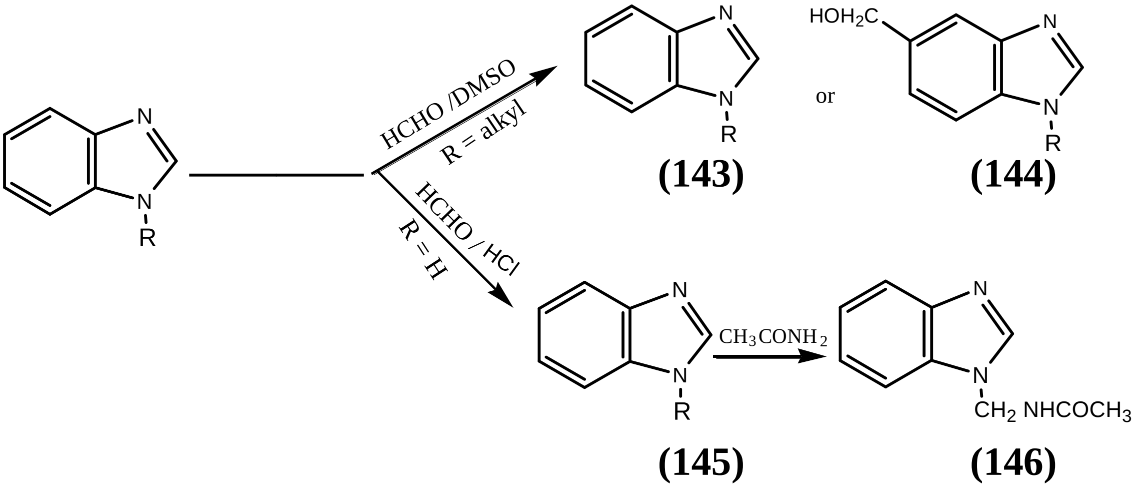


(142)

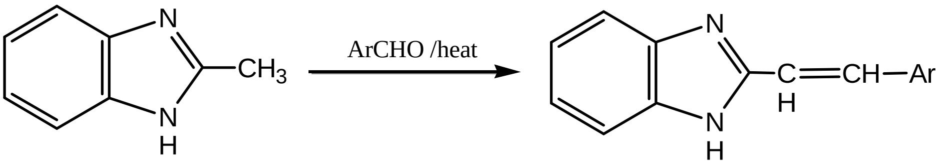
R = Piperidine , morpholine , Et_2N ,OH .
X = O, S

When imidazoles or benzimidazoles substituted on nitrogen treated with formaline 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 (183) (**144**), upon treatment with acetamide (157) afforded (**146**).



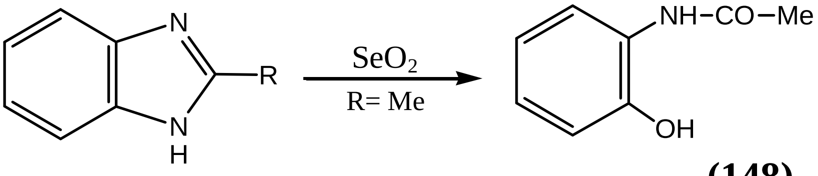
On the other hand, thermal condensation of 2-methyl benzimidazole with substituted benzaldehyde afforded the chalcone analogues (184) .



(147)

6) Oxidation:

Imidazole oxidized using selenium dioxide in dioxone (156) .



(148)

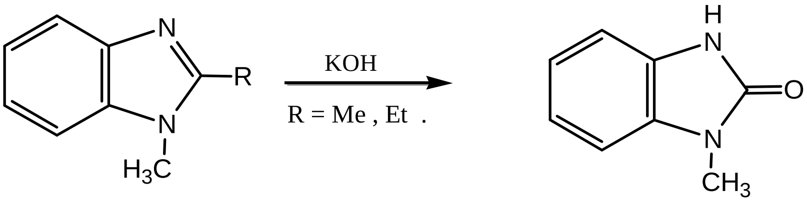
Nucleophilic attack :

Imidazoles and imidazolone 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 :

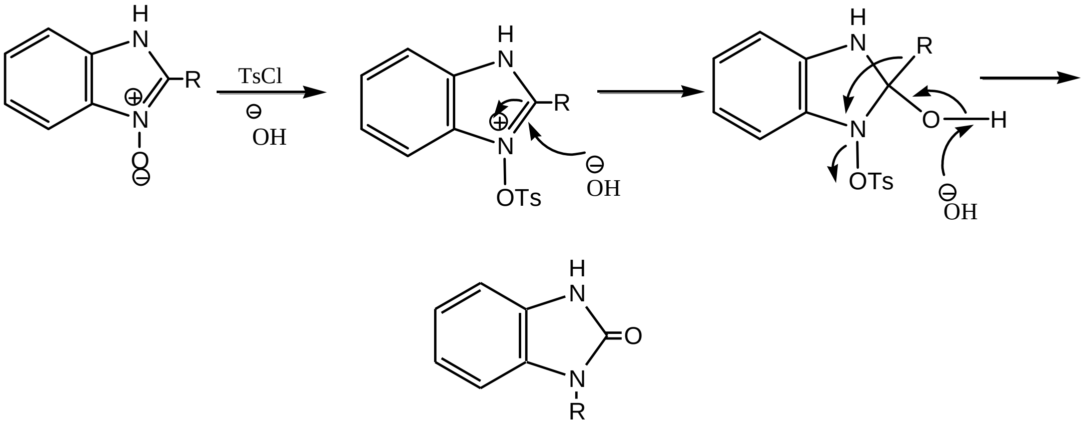
1) Hydroxide ion and other O-Nucleophiles:

At high temperature (250°C) 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 (185) .



(149)

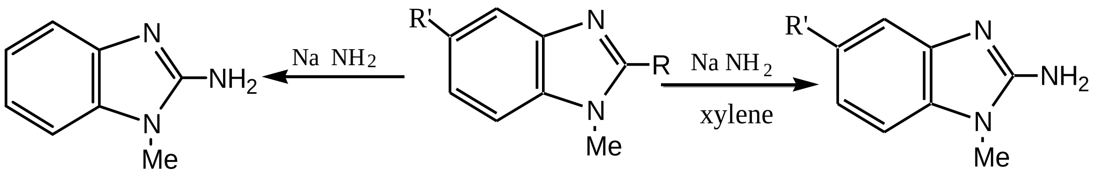
On the other hand, benzimidazole-*N*-oxides with tosylchloride gave benzimidazolinone (185) as sole product which formed as follow:



(150)

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, 1,2-dimethyl-4-nitroimidazole and 1,2-dimethyl-5-nitroimidazole gave the 4-and 5-amino derivatives respectively. Thus, "the chichibabin reaction"(186) 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 (187) although other products are also formed as shown:

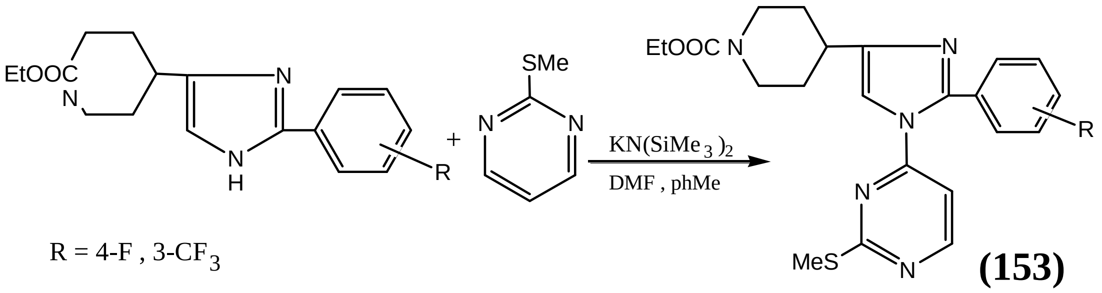


(151) **(152)**

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

B- Nucleophilic attack at nitrogen atom:

In 2004, imidazoles were undergo classical nucleophilic substitution reaction by Revesz and co-workers **(188)** .

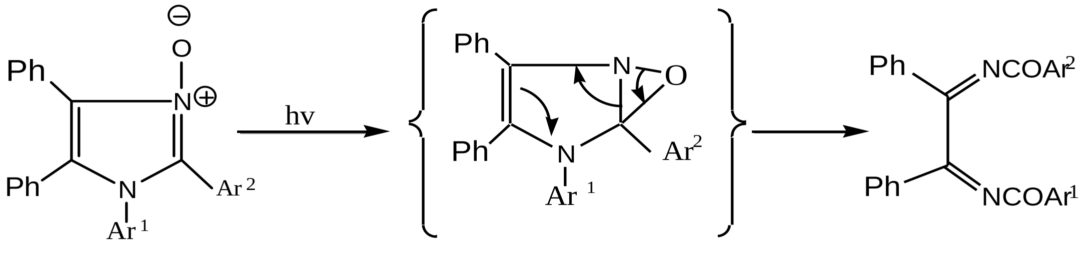


(153)

Thermal and photochemical reactions :

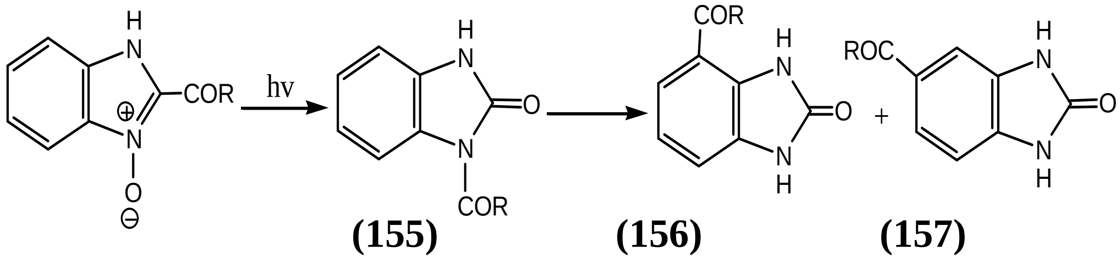
a) Fragmentation

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**(189)**.This reaction is believed to proceed via a fused oxaziridine intermediate.



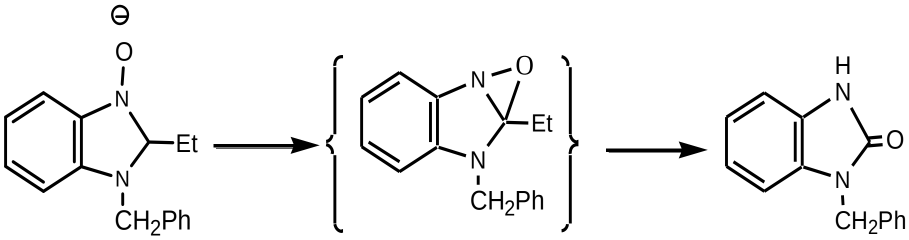
b) Rearrangement

Imidazoles are undergoing the photo-fires rearrangement. Photolysis of 2-acylbenzimidazol-1-oxide gave the *N*-acyl deriveatives which undergoes photo-fries rearrangement in benzene to give the 4- and 5-transpositions products **(190)** .



(155) **(156)** **(157)**

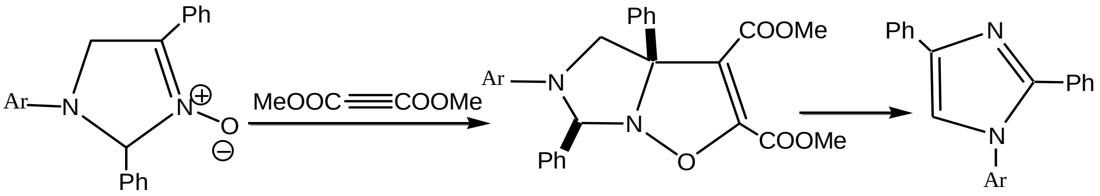
Photo-rearrangement of 1-benzyl-2-ethylbenzimdazole-3-oxide gave 1-benzyl-3-ethylbenzimidazolinone **(191)** .



(158)

c) Ring opening reaction

A thermal ring opening reaction of imidazoisoxazoles obtained by disteroselective-cycloaddition of dimethylacetylene-dicarboxylate (DAD) with Δ^3-imidazoline **(192)** .

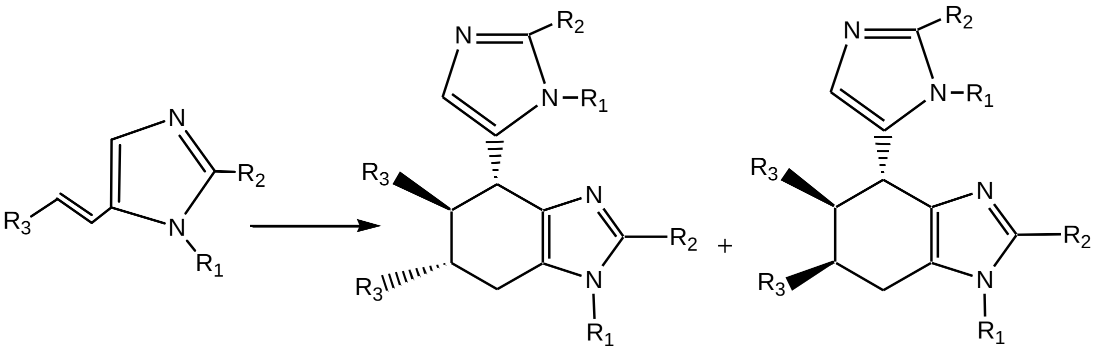


(159)

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-1,2,4-traizoline-3,5-dione (193-195) .



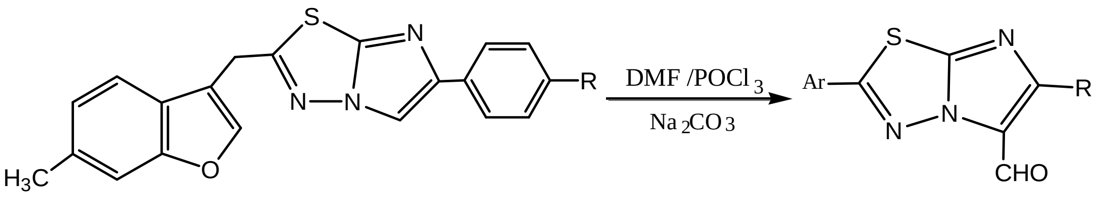
R_1= H , Me , SEM ,
R_2 = H , Sph , TBS ,
R_3= H , CO_2 Et , $CONH_2$

(160) **(161)**

Homonculear (4 π + 2 π) cycloaddition.

b) Vilsmeier -Haack reaction

Vilsmeier-Haack reaction of imidazothiadiazole in DMF and $POCl_3$ funished 5-formyl derivatives (196, 9) .

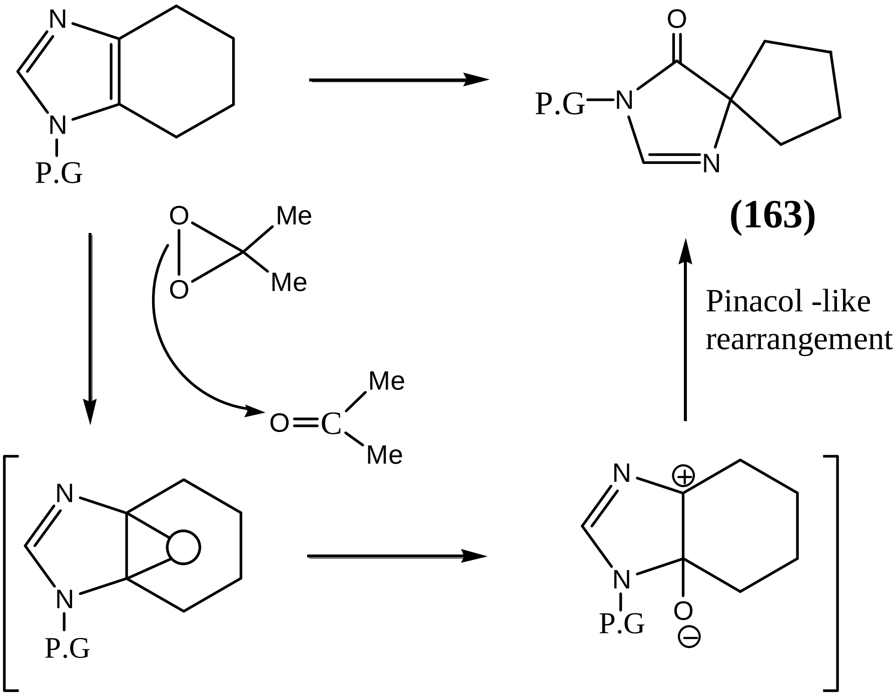


(162)

R = Br , Cl , NO_2

c) Pinacol- like rearrangement reaction

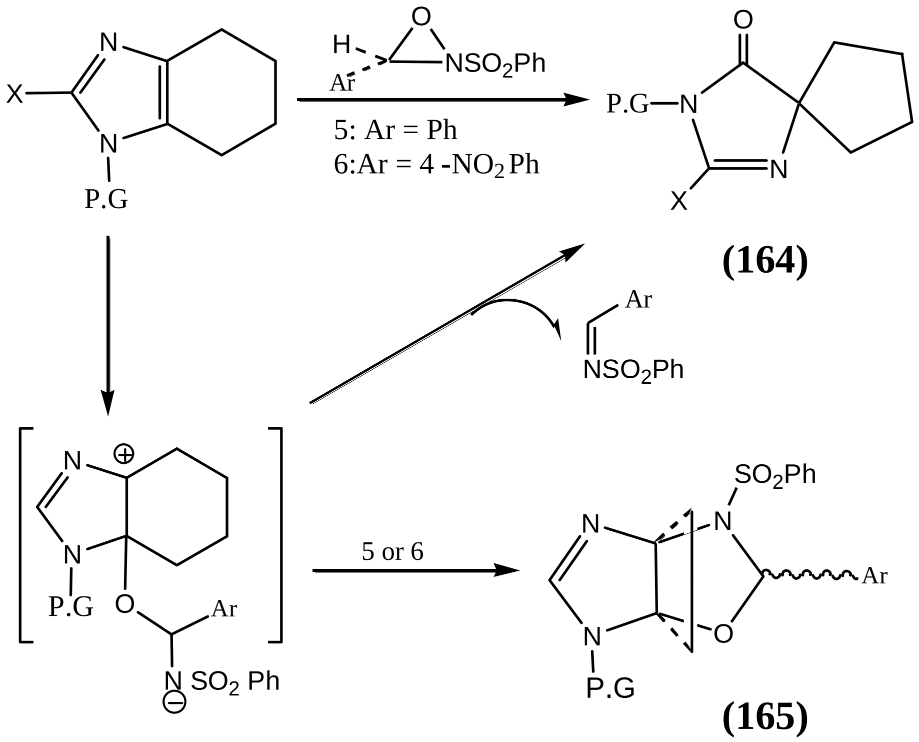
Rearrangement reaction of tetrahydrobenzimidazoles (THB's) leading to the formation of spiro fused 5-imidazolones upon treatment with DMDO **(197-200)** .



(163)

P.G = Me , Bn ,SEM , MOM.

R.Sivappa et al **(201)** .; 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 .



(164)

(165)

P.G	Me	Bn	H	H
Ar	Ph	Ph	Ph	4-NO$_2$Ph