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Amidines: their synthesis, reactivity, and applications in heterocycle synthesis

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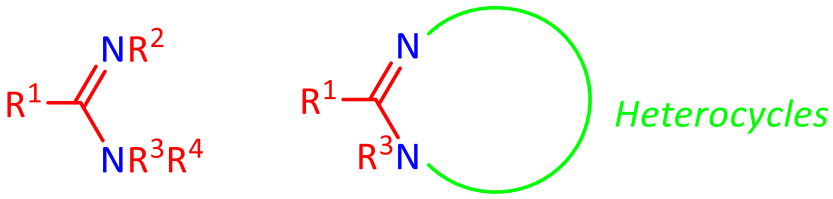
Abstract

The reactivity of amidines makes them valuable as building blocks for the synthesis of heterocyclic motifs of biological relevance, for functional materials, for organo-catalysts and as ligand in metal-complexes. As a large number of publications have recently reported on the reactivity of amidines, we compiled some features of these interesting molecules. Consequently, this article aims to review the preparation of functionalized amidines and to highlight their use as starting materials in the synthesis of various organic molecule classes, especially heterocyclic structures. In this review, we cover also related name reactions such as the Pinner reaction.



Keywords: Amidines, preparation, three-membered rings, four-membered rings, five-membered rings, heterocycles; secretase inhibitor; Pinner reaction; Pinner salt, amidinium salts; Baylis-Hillman

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1. Introduction

Compounds having amidine group **1a** have a structure analogue of carboxylic acids and esters **2** (Figure 1).[1] Either N^1 or N^3 in amidine **1a** can share with their lone of electrons and subsequently the resonated structure **1b** is formed (Figure 1).[2,3]

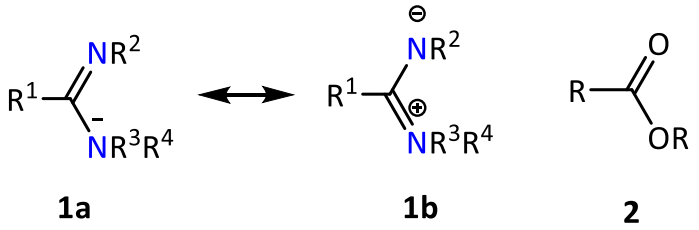


Figure 1. Resonance forms of amidines.

Amidines (imidamides) are described as strong organic bases (pK_a ranges from 5-12).[4,5] The amidinium ion **3** is stabilized by resonance. Deprotonation in strong alkaline solution enhances the formation of an anion **4** (Figure 2).[6-8]

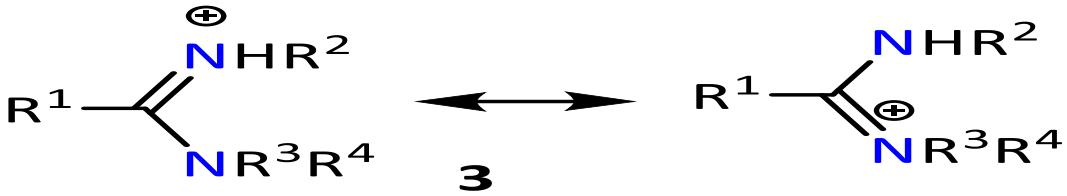
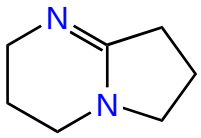


Figure 2. Protonation and deprotonation of amidines.

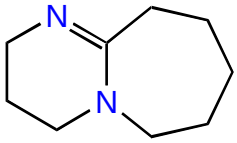
In addition, amidines served as well-suited hydrogen bond-donor acceptor pair with carboxylic acid and therefore are used in catalysis and materials sciences.

Well over one million amidines and around 30000 acyclic amidines are known (source: SciFinder), thus only a selection is covered in this review. Very prominent examples are DBU (over 8000 references) and DBN

(nearly 2000 references), The cyclic amidines such as DBN and DBU (Figure 3) are also very potent catalysts, for instance in Baylis-Hillman reactions. We do not include metal complexes with amidine ligands.



2,3,4,6,7,8-Hexahydropyrrolo[1,2-*a*]pyrimidine
(1,5-Diazabicyclo[4.3.0]non-5-ene, DBN)



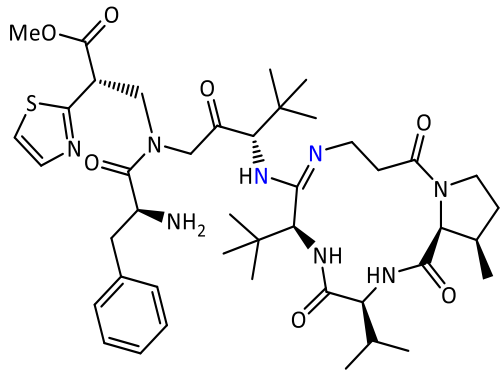
pK_a = 12

2,3,4,6,7,8,9,10-Octahydropyrimido[1,2-*a*]azepine
(1,8-Diazabicyclo[5.4.0]undec-7-ene, DBU)

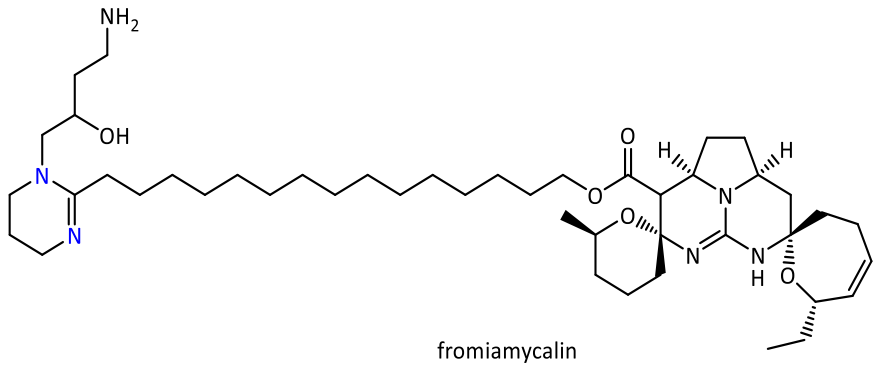
Figure 3. Structures of DBN and DBU.

2. Amidines as Naturally Occurring Compounds

As there is a long list of biologically active amidines, it is beyond the scope of this review to list and discuss them all. However, we would like to give prototypic examples. Functionalized amidines have been isolated as fermentation products of *Actinomycetes*. For example, bottromycin, a macrocyclic peptide with antibiotic activity, isolated from *Streptomyces bottropensis*,[9-11] Other amidines have been isolated from fungi, marine invertebrates and plants. Also complex amidines can be found in nature; fromiamycalin is an example for this, which was isolated from *Fromia monilis* (Figure 4).[12-14]



Bottromycin A2



fromiamycalin

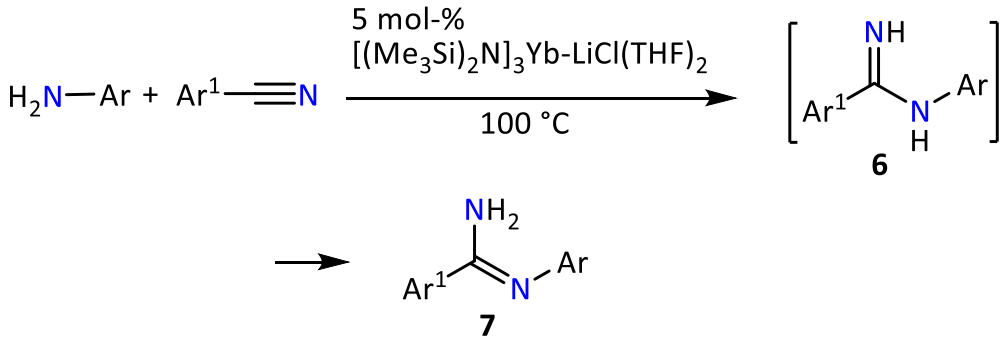
Figure 4. Some naturally-occurring amidine structures.

3. General Methods for the Preparation of Amidines

Substituted amidines are useful intermediates in the synthesis of many heterocyclic and alicyclic compounds. Consequently, numerous methods have been shown the preparation of this important class.[15]

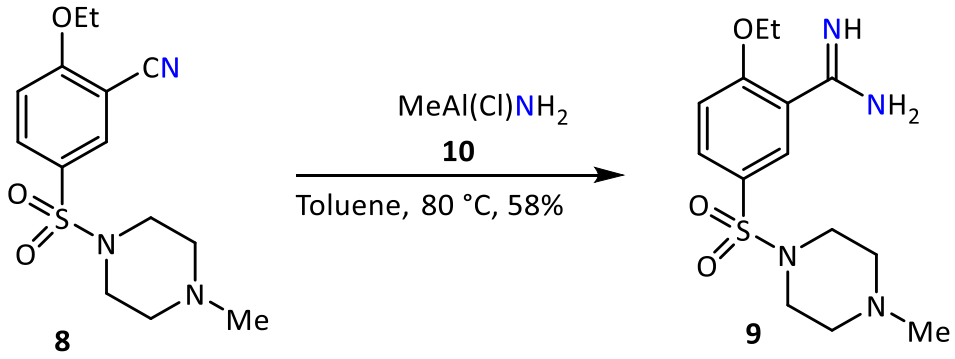
3.1. Amidines from nitriles

The addition of primary amines to nitriles catalyzed by ytterbium amides **5** furnished amidines **7**. The reaction is suggested to proceed via formation of intermediate **6** (Scheme 1).[16]



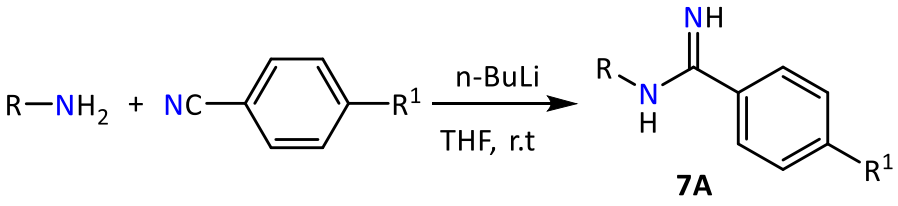
Scheme 1. Synthesis of amidines **7** from amines and nitriles in presence of ytterbium amides **5**

2-Ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)benzonitrile (**8**) was converted into the amidine **9** in 58% yield by reaction with methyl-chloroaluminum amide **10** (Scheme 2). [17]



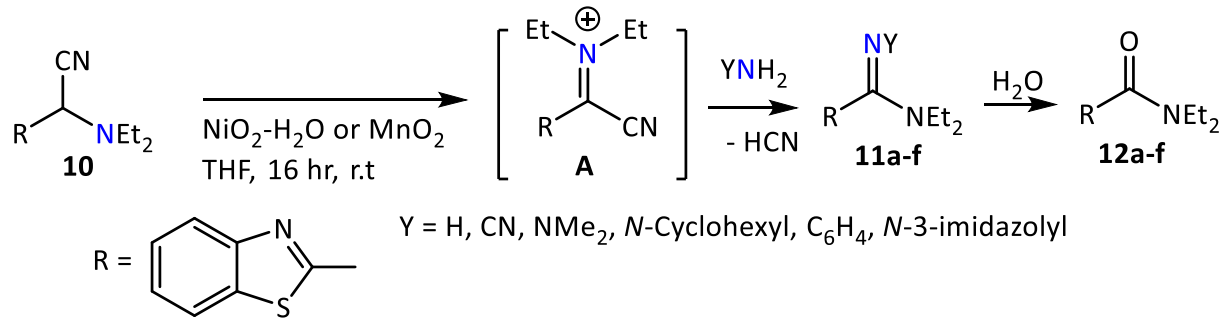
Scheme 2. Conversion of nitrile group in **8** into amidine in **9** in presence of catalyst **10**.

Previously, it was reported that primary amines were deprotonated with *n*-BuLi before addition of aryl nitriles.[18,19] A series of nitrile compounds were added under the same conditions, to the anion of amines. The amidines **7A** were obtained after acidic work up in moderate yields (Scheme 3).[20]



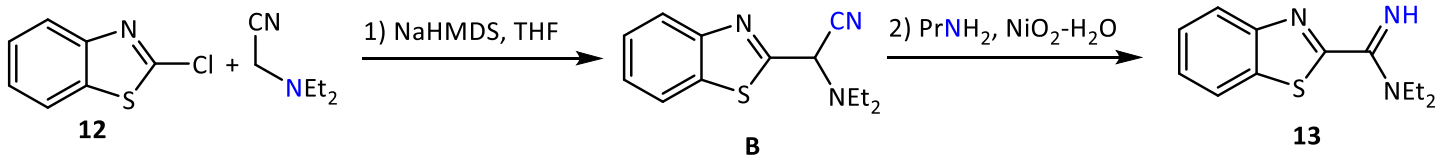
Scheme 3. Synthesis of amidines **7** from amines and nitriles in presence of BuLi.

The oxidation of heteroaryl aminoacetonitriles **10** using NiO_2-H_2O or MnO_2 in the presence of substituted amines afforded amidine derivatives **11a-f** (Scheme 4).[21] Side products of this reaction are diethyl arylamides **12a-f** (Scheme 4).[21] It was proposed that the reaction occurred *via* formation of intermediate **A**, which was trapped by a primary amine to form a *N,N,N'*-trisubstituted amidine.[21] Hydrolysis of **11a-f** by water present in the reaction medium gave also side products **12a-f** (Scheme 4).



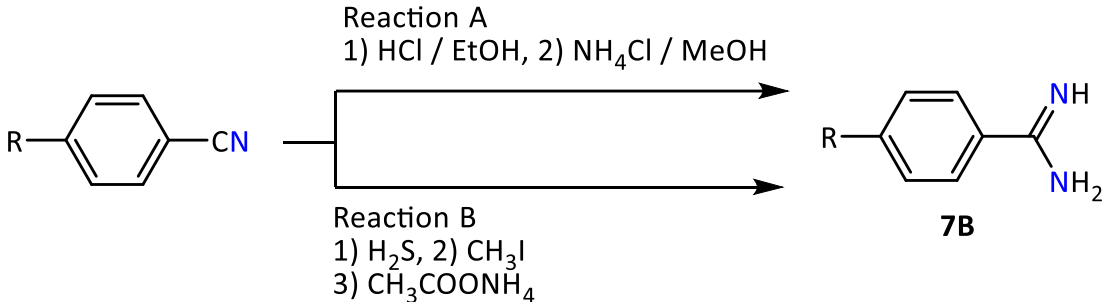
Scheme 4. Formation of benzothiazolylamidines **11**.

In the same article it was reported that when the anion of *N,N*-diethylaminoacetonitrile, prepared by deprotonation with NaHDMS in tetrahydrofuran (THF), was treated with 2-chlorobenzothiazole (**12**) to give intermediate **B.** Oxidation of **B** by NiO_2-H_2O in the presence of *n*-propylamine, afforded the benzothiazole amidine **13** in an isolated yield of 35% (Scheme 5).[21]



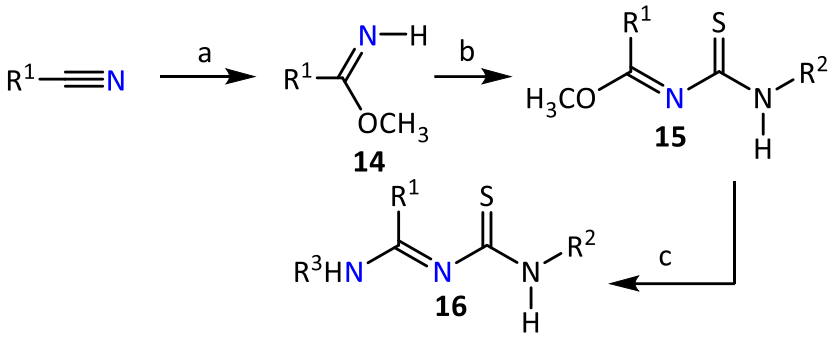
Scheme 5. Preparation of amidine **13**.

Aryl nitriles were converted into amidines **7B** by one of the reactions A or B as shown in (Scheme 6).[22]

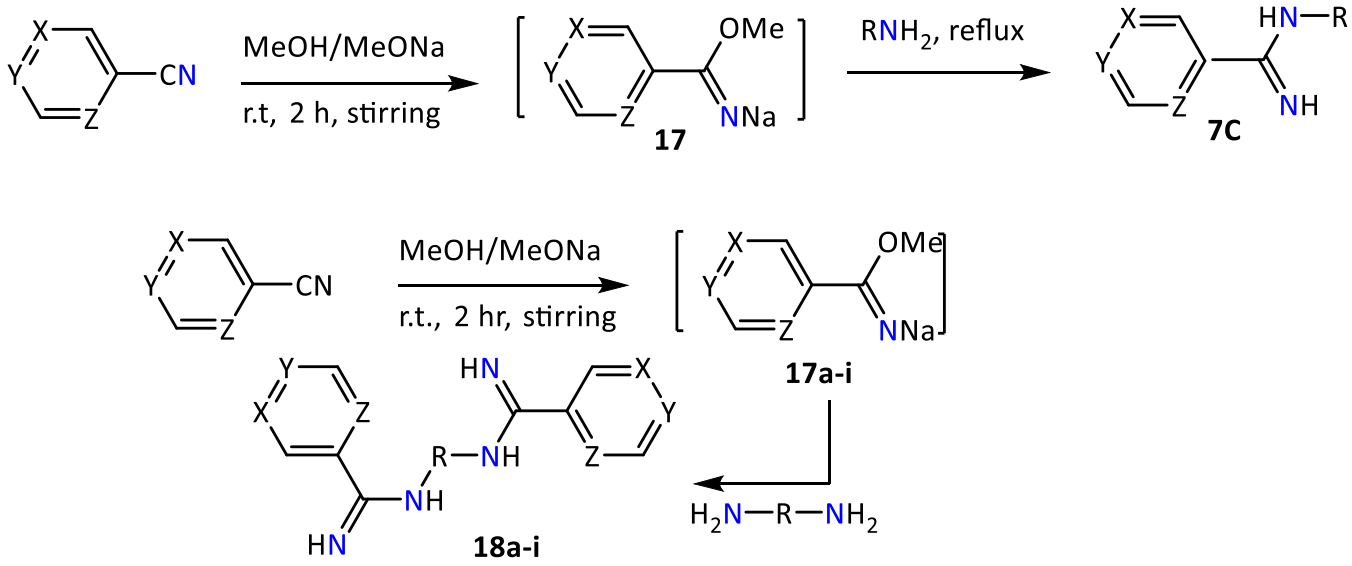


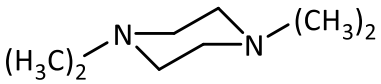
Scheme 6. Synthesis of amidines **7** from substituted nitriles.

Imidates **14** were synthesized by alcoholysis of aromatic and benzylic nitriles according to the well-known Pinner reaction by bubbling anhydrous HCl gas into an equimolar mixture of aromatic or benzylic nitrile derivatives and methanol according to the sequence of steps in Scheme 7. [23,24]



Scheme 7. Synthesis of thioamidoamidines **16.** a: MeOH, HCl(g)/Et_2O; NaOH (10%)/Et_2O; b: R^2NCS/THF; c: R^3NH_2/MeOH.

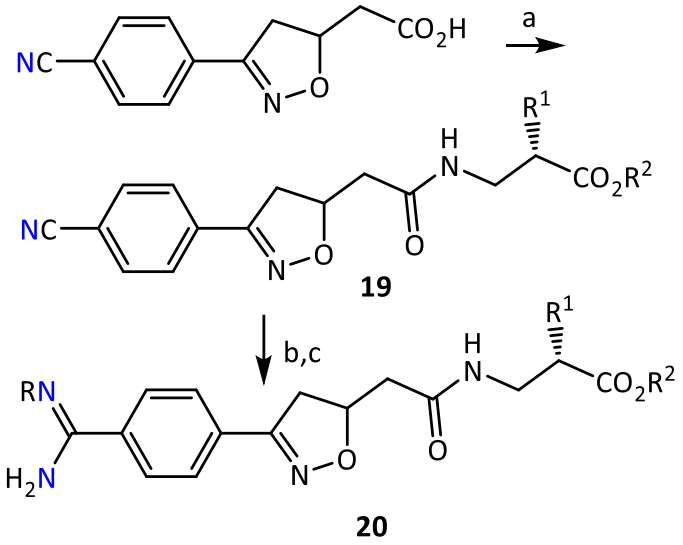


18	X	Y	Z	R
a	CH	CH	N	$(CH_2)_4$
b	CH	N	CH	$(CH_2)_4$
e	N	CH	N	$(CH_2)_4$
c	CH	CH	N	
d	CH	N	CH	
f	N	CH	N	C_6H_4-C_6H_4
g	CH	CH	N	C_6H_4-C_6H_4
h	CH	N	CH	C_6H_4-C_6H_4
i	N	CH	N	C_6H_4-C_6H_4

Scheme 8. Synthesis of amidines from reaction of nitriles with amines in presence of methoxide.

Condensation of various isothiocyanates to the imidates **14** in anhydrous tetrahydrofuran gave *N*-thioamidoimidates **15**.[23] Reaction of **15** with primary amines in anhydrous methanol, allowing *N*-thioamidoamidines **16** formation after the substitution of methoxy group by amino (Scheme 7).[23] Therefore and when nitriles reacted with sodium methoxide the reaction was proposed to give intermediate **17**, which underwent reaction with aliphatic amines under the conditions of Scheme 8, to give the corresponding amidine derivatives **7C** (Scheme 8).[24] Therefore, the synthesis of amidine derivatives was carried out by condensation of **17a-i** with primary diamine in 2:1 molar ratio, in the presence of sodium methoxide. This reaction gave amidine derivatives **18a-i** in good yields (Scheme 8).[25] When evaluated for anti-inflammatory activity and *in vitro* anticancer activity some amidines of type of **18a-i** exhibited good anti-inflammatory potency whereas others showed good breast (T47D), lung (NCI H-522), colon (HCT-15), ovary (PA-1) and liver (HepG2) anticancer activity.[25]

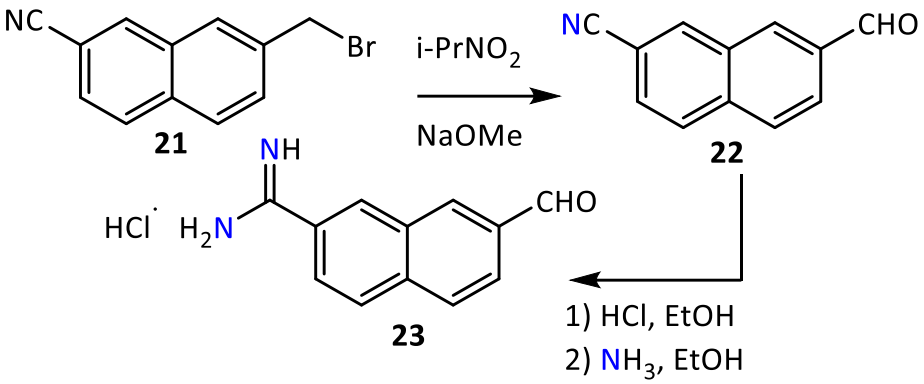
An isoxazoline nitrile was coupled with a substituted β-alanine derivative to afford the amido-nitrile intermediate **19**, which was converted into the substituated amidines by treatment with the appropriate alkyl or benzyl amine in ethanol after hydrolysis **20** (Scheme 9).[26]



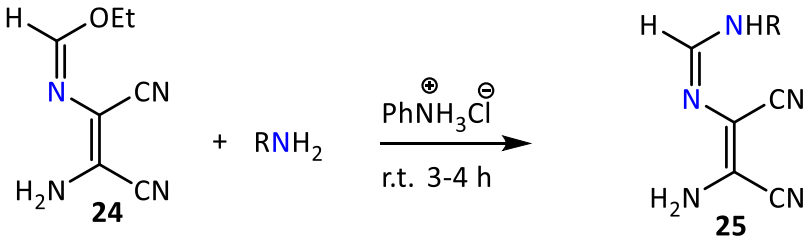
Scheme 9. Synthesis of amidines **20.** Reagents and conditions: (a) TBTU (2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate)/ Et_3N / DMF / α-substituted β-alanine; (b) EtOH / HCl, RNH_2 / EtOH; (c) LiOH / H_2O / MeOH.

Oxidation of bromide **21** with 2-nitropropane/sodium methoxide gave naphthaldehyde **22**, which was exposed to Pinner conditions to afford the formylnaphthylamidine hydrochloride **23** (Scheme 10).[27]

Starting from available ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate (**24**),[28-30] *N*-aryl (or benzyl-)-*N*′(-2-amino-1,2-dicyanovinyl)formamidines **25** were prepared in good yields by reaction with anilines (Scheme 11).[31]



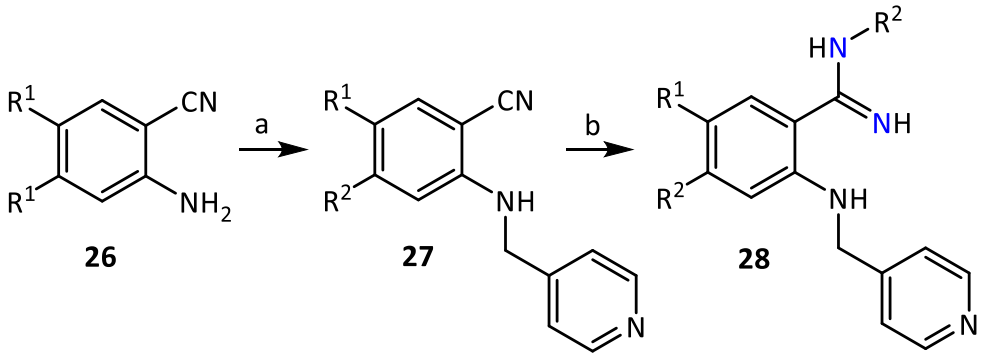
Scheme 10. Synthesis of amidine salts **23**.



25		Yield (%)
a	R = 2-ClC$_6$H$_4$CH$_2$	92
b	R = 3,4-(CH$_3$O)$_2$C$_6$H$_4$CH$_2$	94
c	R = 3,4-(CH$_3$O)$_2$C$_6$H$_3$	96
d	R = 4-CH$_3$OC$_6$H$_4$	93

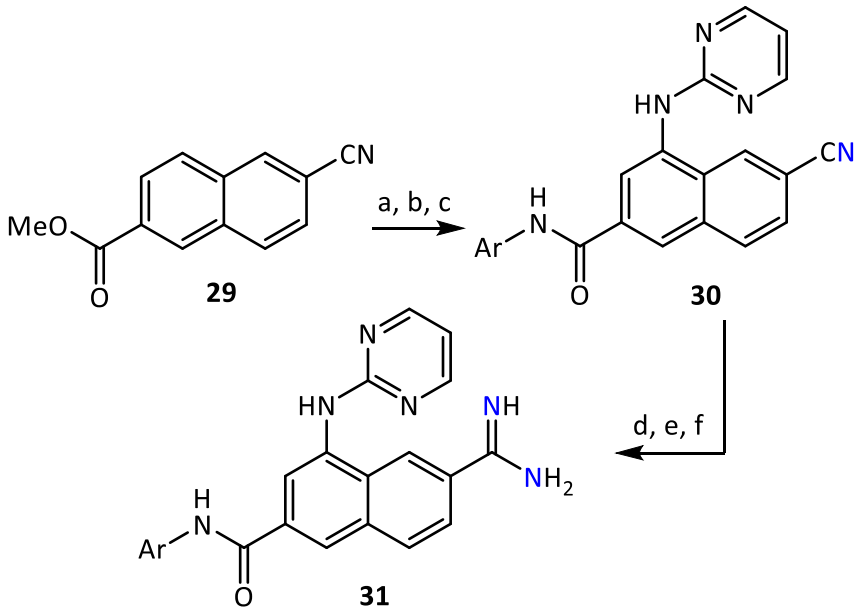
Scheme 11. Synthesis of amidines **25**.

The anthranilic amidines **28** were synthesized via reductive amination of **26** with 4-pyridine carboxaldehyde in the presence of $NaCNBH_3$, giving the corresponding benzonitriles **27**. Thereafter, reaction of **27** with various amines promoted by trimethylaluminum produced amidines **28** in moderate yields (Scheme 12).[32] Amidines **28** showed interesting biological activities as kinase inhibitors of Flt-1 and KDR (Kinase-insert domain-containing receptor), respectively.



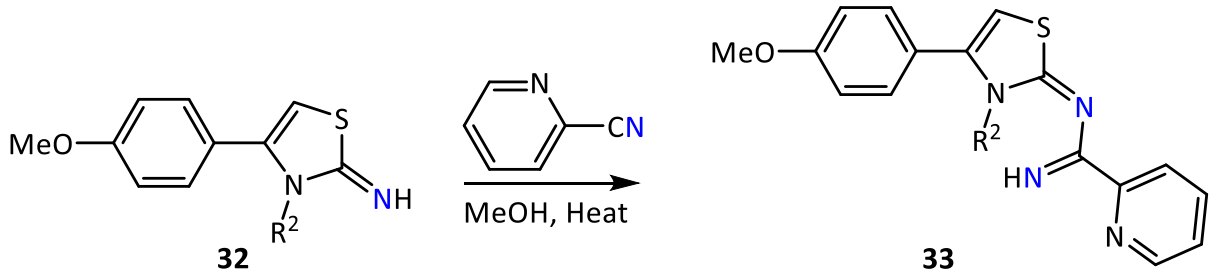
Scheme 12. Synthesis of amidines **28.** (a) 4-pyridinecarboxaldehyde, AcOH, MeOH, $NaCNBH_3$, RT; (b) RNH_2, $AlMe_3$, toluene, 28-80%.

8-(Aminopyrimidinyl)naphthalenes **31** were prepared via nitration of naphthalene **29** followed by reduction and then Pd-catalyzed amine coupling to 2-bromopyrimidine by the sequences shown in Scheme 13. The resulting ester **30** was then hydrolyzed and coupled to aniline to give amidonitriles, which were converted *via* thioamides to the amidines **31** in the presence of HATU (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate) along with Hünig's base (*N,N*-diisopropylethylamine, DIPEA) using DMF as solvent. That was followed by thioamide formation using H_2S and then amination (Scheme 13). The isolated amidines showed activity as inhibitors of the serine protease urokinase plasminogen activator (uPA).[33]



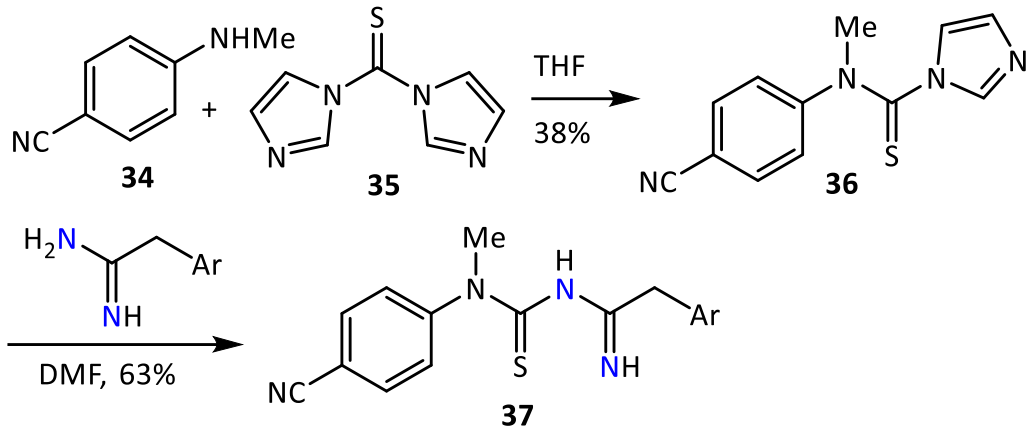
Scheme 13. Synthesis of amidines **31.** Reagents and Conditions: (a) KNO_3, H_2SO_4, 0 °C; (b) H_2, 10% Pd/C, EtOAc, THF; (c) 2-bromopyrimidine, Pd_2dba_3, BINAP, NaO-t-Bu, toluene, 80 °C; (d) LiOH, THF, H_2O; (e) aniline, HATU, DIPEA, DMF; (f) H_2S, TEA, pyridine, then MeI, acetone, then NH_4OAc, MeOH.

The reaction of 2-cyanopyridine with 3-(4'-methoxyphenyl)-4-phenyl-2-imino-4-thiazolines **32** gave the amidines **33** in good yield (Scheme 14).[34]



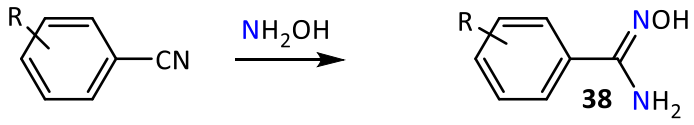
Scheme 14. Synthesis of amidines **33**.

Reaction of an aniline **34** with *N,N*[1] thiocarbonyldiimidazole (**35)** followed by displacement of the second imidazole with an acetamidine moiety produced as 2-aryl-[*N*-(*N*-4-cyanophenyl-*N*-methylthiocarbamoyl)]-acetamidines **37** in good yields (Scheme 15).[35]



Scheme 15. Synthesis of amidines **37**.

As a general method, nitrile groups (i.e. in arylnitriles) can be converted into hydroxyamidine derivatives **38** by their direct reaction with hydroxylamine (Scheme 16).[36-39] The latter can serve as precursors for amidines.



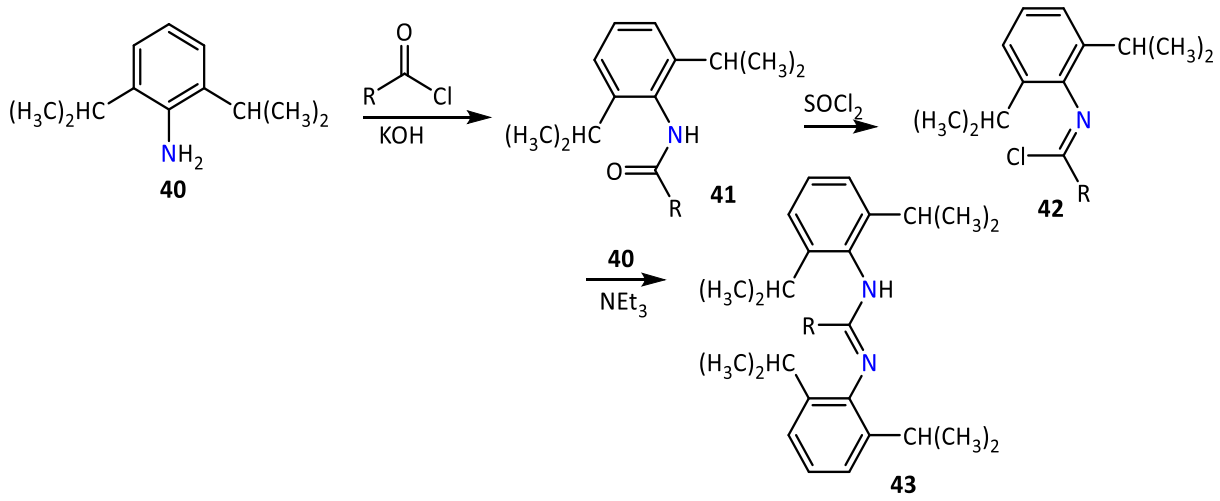
38	**a**	**b**	**c**	**d**	**e**
R	4-F	4-Me	3-Cl	4-CF_3	3-CF_3
Yield (%)	90	92	85	91	96

Scheme 16. Synthesis of hydroxyamidines **38**.

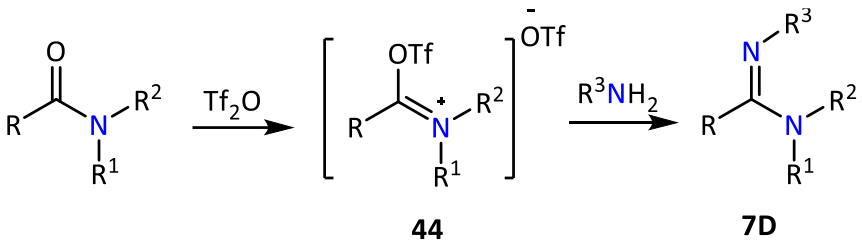
3.2. Amidines from amides

When 2,6-diisopropylaniline (**40**) was treated with one equivalent of aroyl chloride in an aqueous potassium hydroxide solution, the resulting amides **41** were formed (Scheme 18).[40] Subsequently, arylamides **41** were converted into the corresponding imidoyl chlorides **42**, which on treatment with **40** in the presence of triethylamine (Et_3N) gave *N,N*′-bis(2′,6′-diisopropylphenyl)aryl-diamide (**43**, Scheme 18).[40]

The synthesis of amidines was also achieved by the addition of amines to amides activated with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of pyridine. Various disubstituted and trisubstituted amidines **7D** were prepared via the formation of salt **44** (Scheme 19).[41,42]



Scheme 18. Synthesis of amidines **43.**

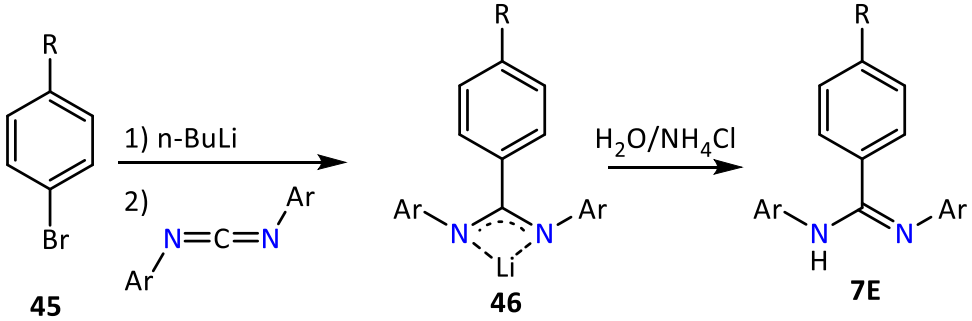


Scheme 19. Synthesis of amidines **7D** from amide derivatives.

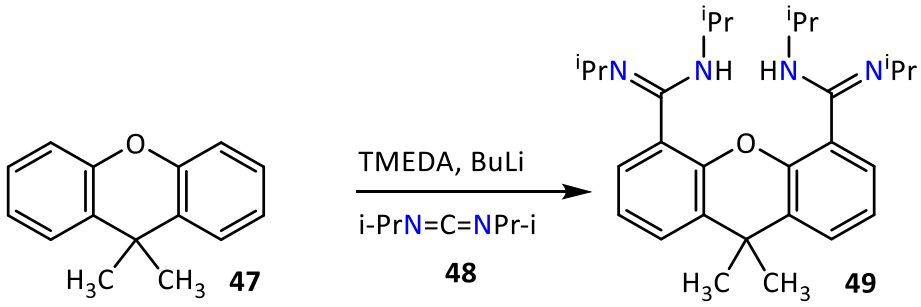
3.3. Amidines from carbodiimides

Bromoaryl derivatives **45** underwent lithio-debromination with *n*-BuLi, followed by reaction with a diaryl carbodiimide, to give the anion **46**. Hydrolysis of **46** gave the corresponding amidines **7E** (Scheme 20).[43]

ortho-Lithiation of 9,9-dimethyl-9*H*-xanthene (**47**) with BuLi in the presence of tetramethylethylene-diamine (TMEDA) in hexane has been used to generate the aryl dianion. Reaction under the previous conditions with a dimine moiety (e.g. *i*-PrN=C=N- *i*-Pr (DIC) **(48**) produced in good yield the *ortho*-bisamidine derivative **49** (Scheme 21).[44] For the synthesis of other bisamidines, see Section 3.12.



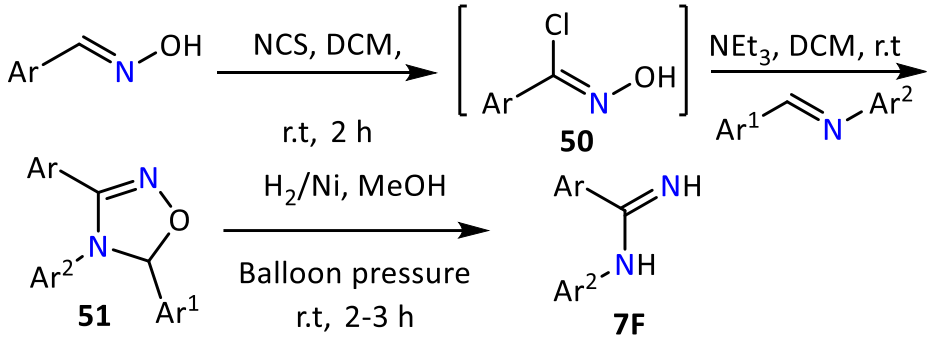
Scheme 20. Synthesis of amidines **7**.



Scheme 21. Synthesis of *ortho*-bisamidine **49.**

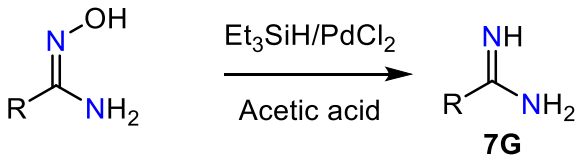
3.4. Amidines from aldoximes

Chlorination of azomethines of hydroxylamines by *N*-chlorosuccinimide in dichloromethane (DCM) afforded intermediates **50** (Scheme 22). 1,3-Dipolar cycloaddition of imines with nitrile oxides (resulting on treatment of **50** by trimethylamine) formed 4,5-dihydro-1,2,4-oxadiazoles **51**. Reduction of the N-O bond led to the formation of monosubstituted *N*-aryl amidines **7F** in good yield (Scheme 22).[45]



Scheme 22. Synthesis of amidines **7F** from aldoximes.

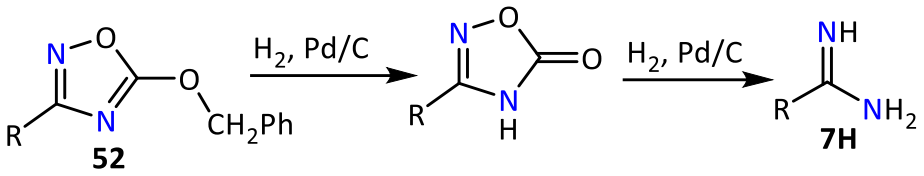
The reduction of amidoximes using triethylsilane (Et_3SiH) as a reducing agent with the aid of palladium chloride in the presence of acetic acid gave amidines **7G** (Scheme 23).[46]



Scheme 23. Synthesis of amidines **7G** using $Et_3SiH/PdCl_2$.

3.5. Amidines from 1,2,4-oxadiazol-5-ones

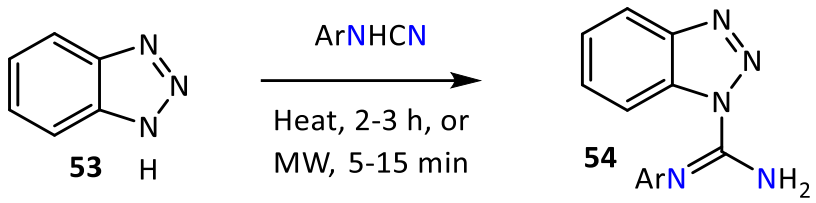
Amidines **7H** were prepared by the stepwise reduction of 5-benzyloxy-l,2,4-oxadiazole derivatives **52** using two equivalents of H_2 withPd/C (Scheme 24).[47] Decarboxylation yields the final compounds.



Scheme 24. Stepwise synthesis of amidines **7H** from 1,2,4-oxadiazole-5-one using reduction over Pd/C.

3.6. Amidines from 1,2,3-benzotriazole

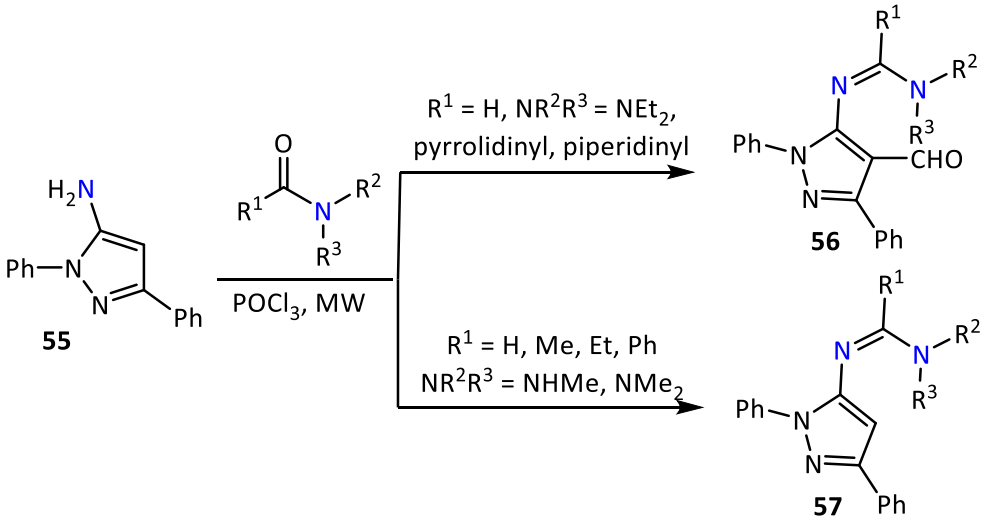
1,2,3-Benzotriazol-1-yl-(*N*-aryl)amidines **54** were synthesized by the reaction between 1,2,3-benzotriazole (**53**) and arylcyanamides (ArNHCN) under either thermal or microwave conditions (Scheme 25).[48]



Scheme 25. Synthesis of amidines **54**.

3.7. Amidines from aminopyrazoles

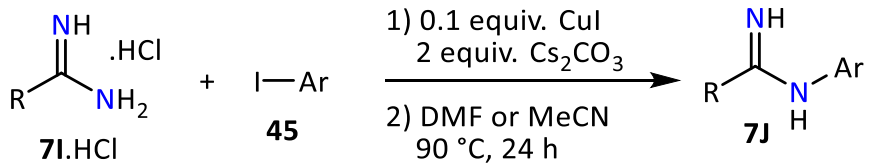
5-Amino-1,3-diphenylpyrazole (**55**) was reacted with various amide solvents, such as *N,N*-dimethylformamide (DMF), 1-pyrrolidinecarboxaldehyde, and 1-piperidinecarboxaldehyde under microwave heating gave the amidine aldehyde products **56** in 91-96% yields (Scheme 26).[49] However, in other amide solvents, including *N*-methylacetamide, *N*-methylformamide, *N*-methylpropanamide, *N,N*-dimethylbenzamide, the simple amidination products **57** were formed, again in good yields (Scheme 26).[49]



Scheme 26. Synthesis of amidines **56** and **57**.

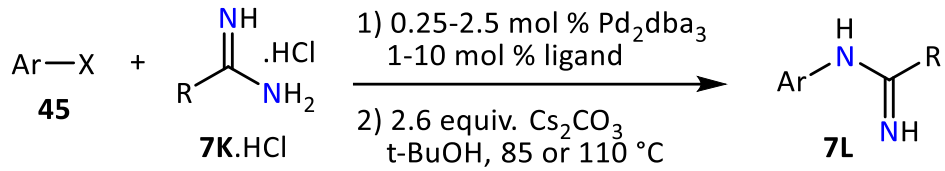
3.8. Amidines by arylation of amidine salts

Copper-catalyzed cross-coupling reactions of amidine salts **7I**.HCl with aryl iodides **45** gave monoarylated amidines **7J** in either DMF or acetonitrile as the solvent as shown in Scheme 27.[50]



Scheme 27. Arylation of amidine salts using CuI/Cs_2CO_3.

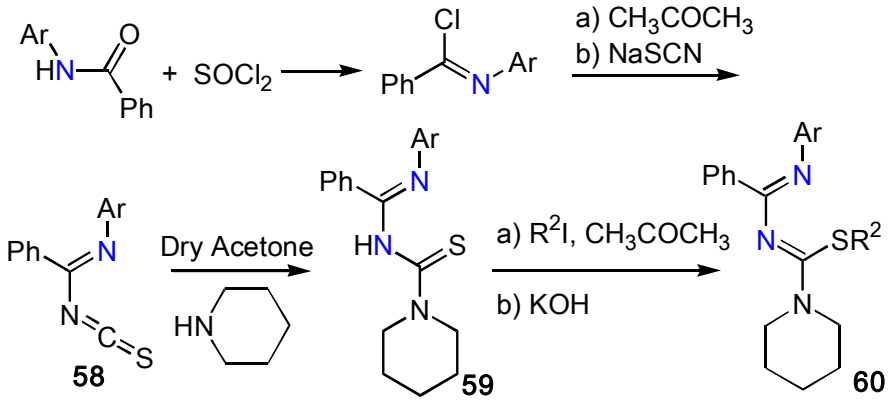
Similarly, Pd-catalyzed *N*-arylation of both aryl- and alkyl-amidine salts by aryl halides X (X= Cl, Br, I) is shown in (Scheme 28).[51]



Scheme 28. Arylation of amidine salts using Pd-catalyst.

3.9. Amidines by reaction of isothiocyanates with secondary amines

A series of 1-aryl-2-phenyl-4-piperidino-4-thioalkyl-1,3-diazabuta-1,3-dienes **60** was conveniently prepared starting from *N*-arylbenzimidoyl isothiocyanates **58**;.[52-54] Reaction first with secondary amines such as piperidine gave good yields of *N*-aryl-*N*′-(piperidin-1-yl-thiocarbonyl)benzamidines **59**, commonly referred to as thioureas. The alkylation of these thioureas with alkyl iodides resulted in excellent yields of amidines **60** (Scheme 29).[55]

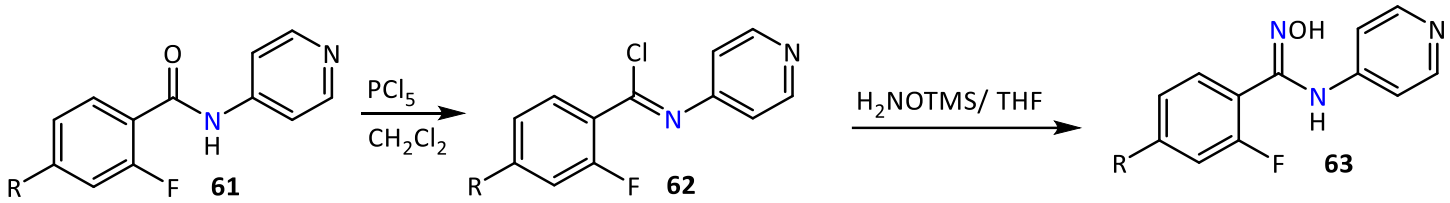


Scheme 29. Synthesis of amidines **60**.

4. Synthesis of Various Classes of Amidine

4.1. Synthesis of amidoximes

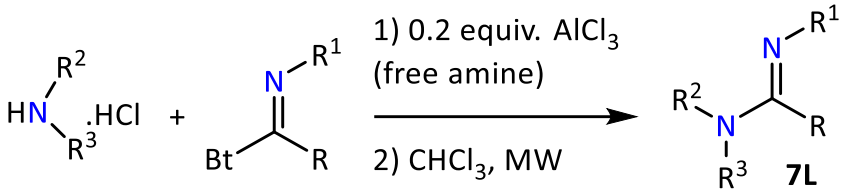
Reaction of amides **61** with phosphorus pentachloride (PCl_5) in dichloromethane produced imidoyl chlorides **62** (Scheme 30). On treatment of **62** with *O*-(trimethylsilyl)hydroxylamine (H_2NOTMS), the reaction yielded the corresponding amidoximes **63 (**Scheme 30).[56]



Scheme 30. Synthesis of amidines **63**.

4.2. Synthesis of polysubstituted amidines

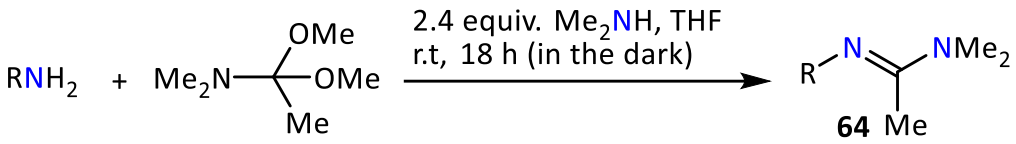
Microwave reactions of primary and secondary amines with imidoylbenzotriazoles (imidoyl-Bt) gave various *N*,*N*′-di- and *N*,*N*′,*N*′-trisubstituted amidines **7L** in good yields as shown in Scheme 31.[57]



Scheme 31. Synthesis of *N*,*N*′-di- and *N*,*N*′,*N*′-trisubstituted amidines **7L**.

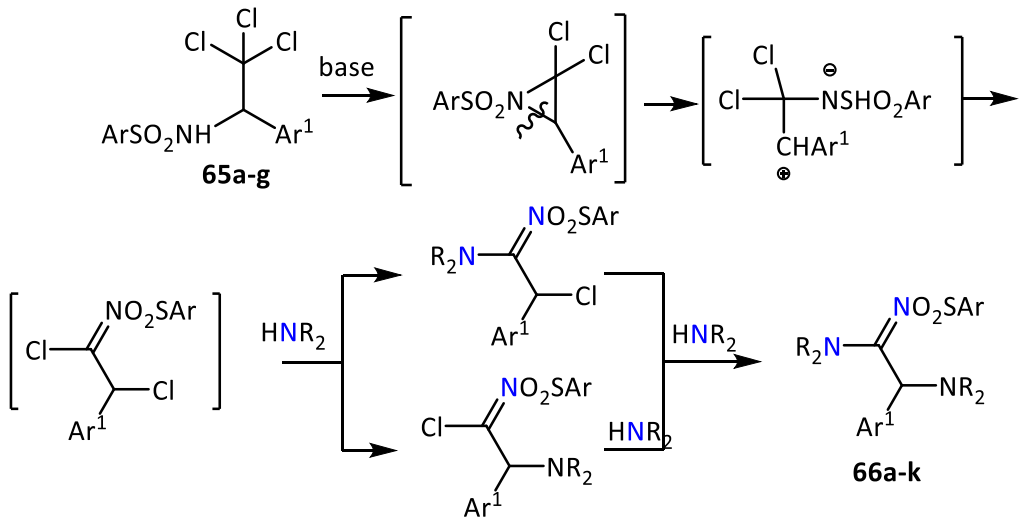
4.3. Synthesis of acetamidines

Reaction of primary amines, as shown in Scheme 32, with *N,N*-dimethylacetamide dimethylacetal in the presence of excess dimethyl amine, yielded acetamidines **64**.[58]



Scheme 32. Synthesis of amidines **64**.

Sulfonamide **65a-g** reacted with excess of a secondary amines or its salts in a dipolar aprotic medium in the presence of inorganic bases gave *N,N*-dialkyl-*N*′-arylsulfonyl-(*α*-dialkylamino-*α*-aryl)acetamidines **64a-k** (Scheme 33).[59]

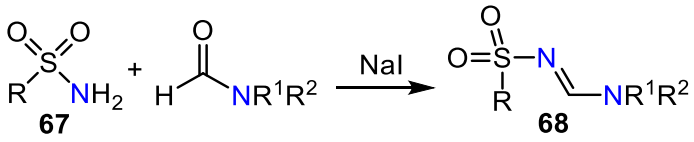


66	Ar	Ar^1	NR_2
a	4-ClC_6H_4	Ph	NEt_2
b	4-ClC_6H_4	4-MeC_6H_4	NEt_2
c	4-ClC_6H_4	4-ClC_6H_4	NEt_2
d	4-ClC_6H_4	4-FC_6H_4	NEt_2
e	4-ClC_6H_4	4-HOC_6H_4	NEt_2
f	4-ClC_6H_4	1-naphthyl	NEt_2
g	4-ClC_6H_4	4-MeC_6H_4	NMe_2
h	4-ClC_6H_4	4-MeC_6H_4	N-n-Pr_2
i	4-ClC_6H_4	4-MeC_6H_4	$N(CH_2CH_2)_2O$
j	4-MeC_6H_4	4-MeC_6H_4	NEt_2
k	4-MeC_6H_4	4-MeC_6H_4	$N(CH_2CH_2)_2O$

Scheme 33. Synthesis of acetamidines **66a-k**.

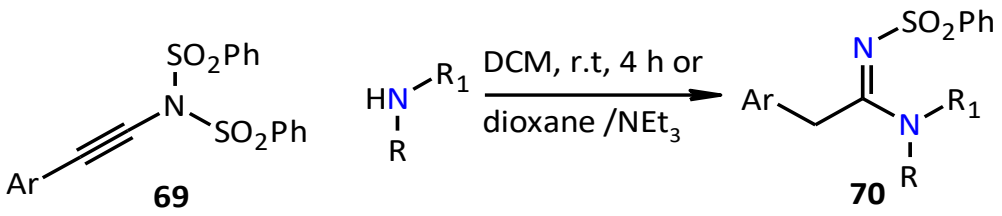
4.4. Synthesis of *N*-sulfonyl amidines

Iodide ions catalyze the direct condensation of sulfonamides **67** and formamides furnishing *N*-sulfonyl formamidines **68** in good yields (Scheme 34).[60]



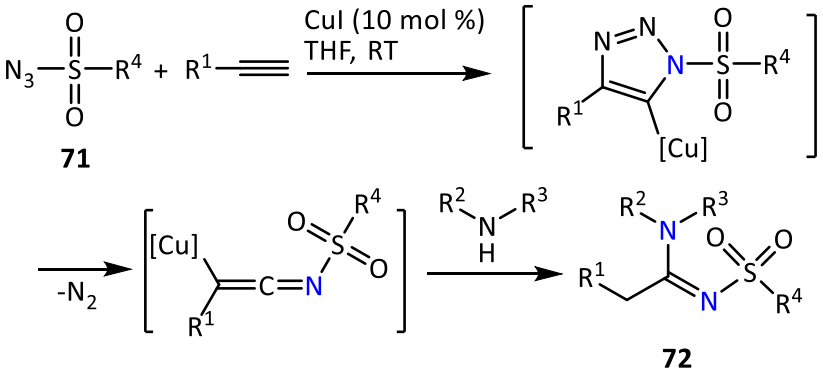
Scheme 34. Synthesis of *N*-sulfonyl amidines **68**.

A catalyst-free hydroamination of *N,N*-disulfonyl ynamides **69** with amines gives *N*-sulfonylamidines **70** (Scheme 35).[61]



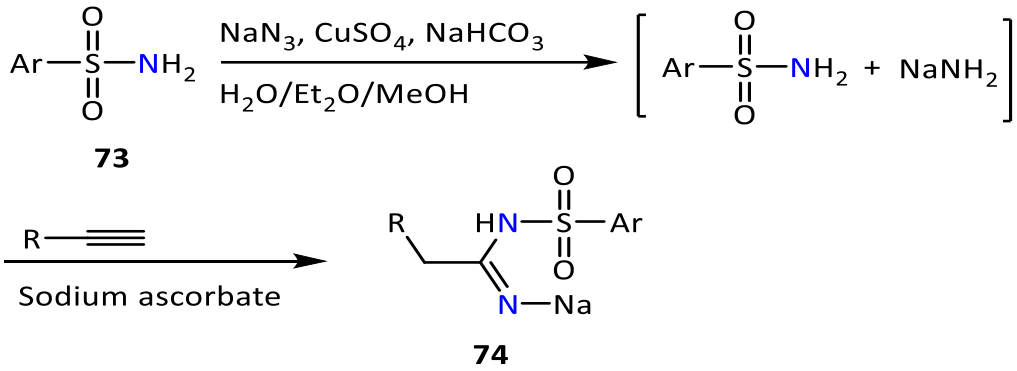
Scheme 35. Synthesis of *N*-sulfonyl amidines **70**.

Sulfonyl amidines **72** were synthesized from alkynes, amines and sulfonyl azide **71** in the presence of CuI catalyst at r.t. in 66-99% yields (Scheme 36).[62] The intermediate triazoles release nitrogen to produce sulfonyl iminoketenes which react with amines to give the target molecules.



Scheme 36. Synthesis *N*-sulfonyl amidines **72.**

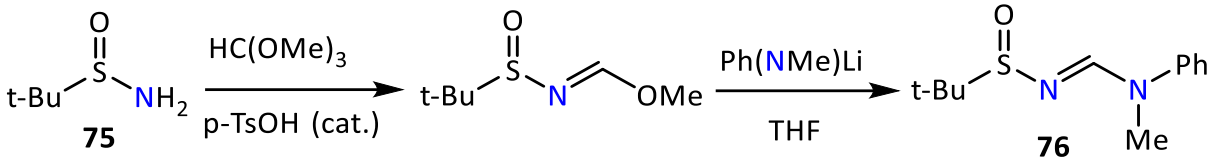
Sulfonyl amidines **74** were synthesized from sulfonylamides **73** by one-pot diazo-transfer and intermolecular copper (I)-catalyzed reaction with alkynes (Scheme 37).[63,64]



Scheme 37. Synthesis of *N*-sulfonyl amidines **74**.

4.5. Synthesis of *N*-imidoylsulfinylformamidines

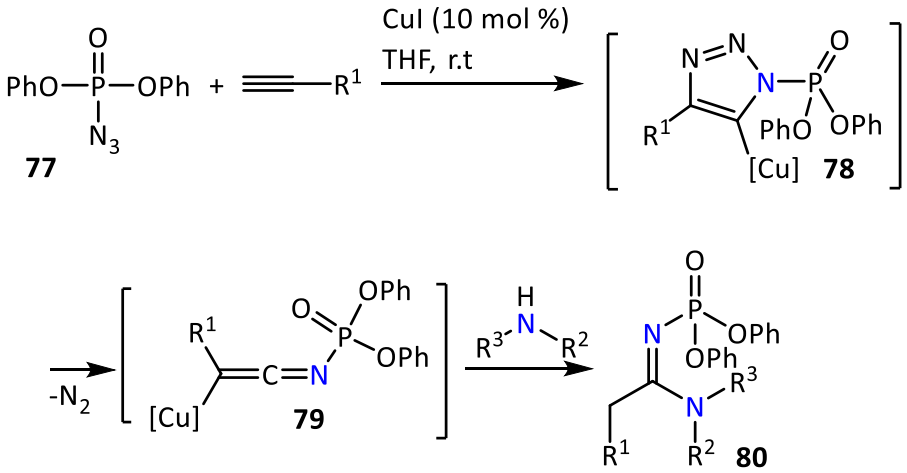
N-Imidoylsulfinylformamidines **76** were obtained by the reaction of a sulfinamide **75** with trimethyl orthoformate, followed by reaction with the lithium salt of *N*-methylaniline (Scheme 38).[65,66]



Scheme 38. Synthesis of *N*-imidoylsulfinformamidines.

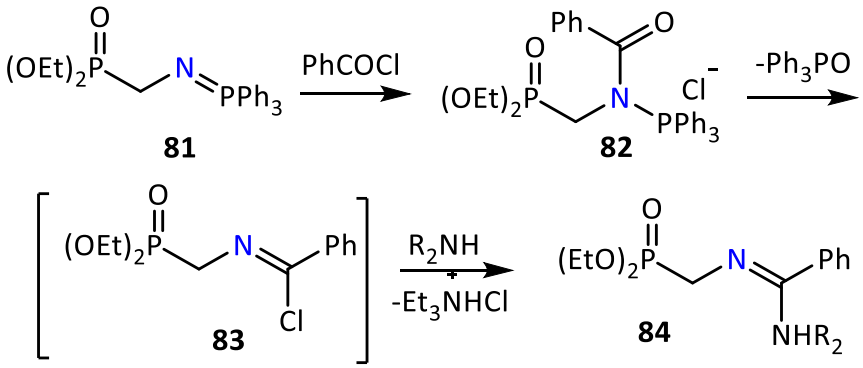
4.6. Synthesis of phosphoryl amidines

Reaction of phosphoryl azide **77** with alkynes in the presence of CuI/THF mixture (Scheme 39), produced a triazolo-Cu complex **78** as intermediate (Scheme 38). Rearrangement of **78** accompanied with elimination of nitrogen gave **79** as a tentative intermediate. Addition of amines as one-pot synthesis gave phosphoryl amidines **80** (Scheme 39).[67]



Scheme 39. Synthesis of phosphoryl amidines **80**.

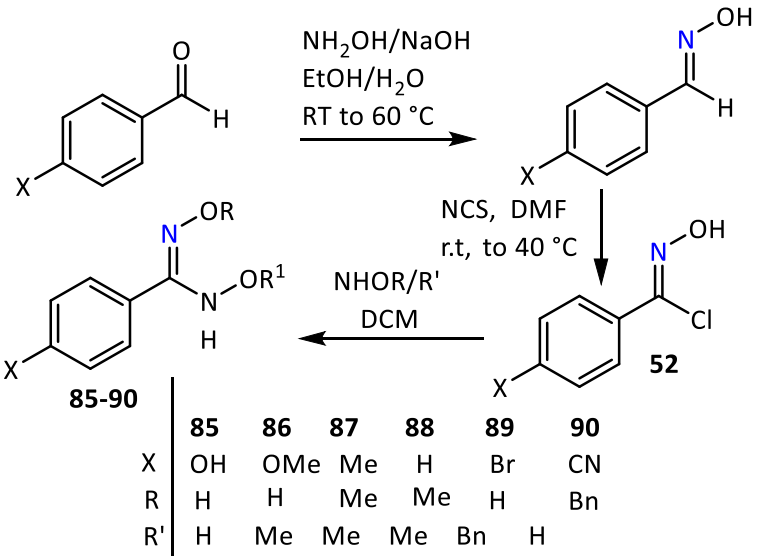
When phosphazene **81** was treated with benzoyl chloride in THF at room temperature,[68] the reaction proceeded *via* intramolecular loss of triphenylphosphane oxide,[69] to give unstable imidoyl chloride **83** (Scheme 40). The addition of amines in the presence of triethylamine then gave *N*-(phosphorylalkyl)amidines **84** (Scheme 40).[70]



Scheme 40. Synthesis of phosphoryl amidines **84**.

4.7. Synthesis of *N,N*-substituted amidines

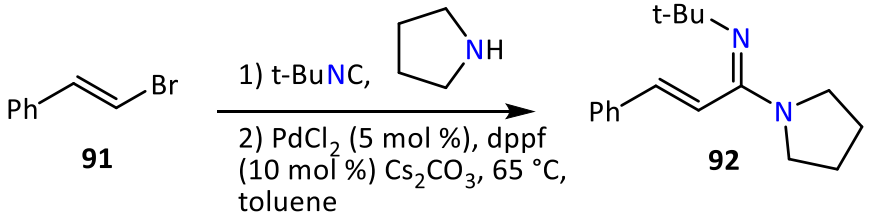
It is known that addition of *N*-chlorosuccinimide (NCS) to the *p*-substituted benzaldoximes gives directly the corresponding benzhydroxamic acid chlorides **52**, which on treatment with substituted hydroxylamines produce *N,N*-substituted amidines **85-90** (Scheme 41).[71,72]



Scheme 41. Synthesis of *N,N'*-substituted amidines **85-90**.

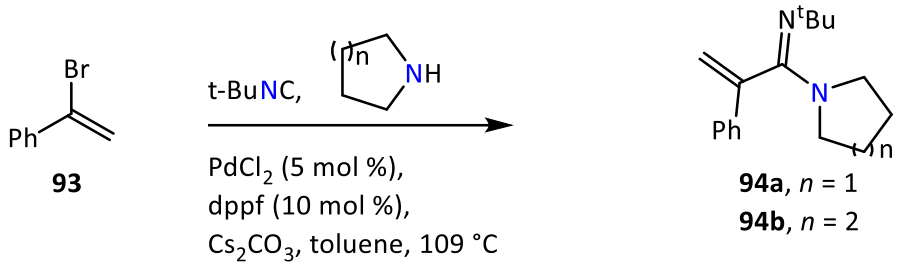
4.8. Synthesis of α,β-unsaturated amidines

Unsaturated amidines can be synthesized by coupling reaction between β-bromostyrene **91** with *tert*-butylisocyanide and pyrrolidine using the same conditions developed for coupling of aryl bromides (5 mol% $PdCl_2$, 10 mol% [1,1′-bis(diphenylphosphino)ferrocene (dppf), Cs_2CO_3, toluene). The desired amidine **92** was obtained in excellent yield (Scheme 42).[73]



Scheme 42. Synthesis of α,β-unsaturated amidines **92**.

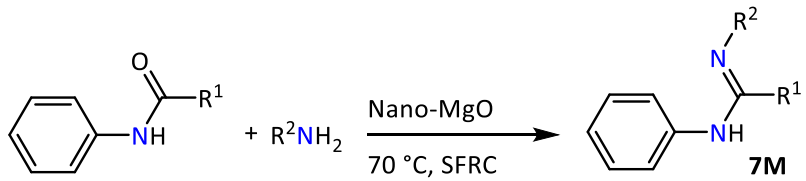
Under similar conditions, the reaction of α-bromostyrene (**93**) with *tert*-butylisocyanide and pyrrolidine or piperidine produced the isomeric methylidine amidines **94a**,**b** (Scheme 43).[63]



Scheme 43. Synthesis of α,β-unsaturated amidines **94a,b**.

4.9. Utility of nano-catalysis in the synthesis of amidine

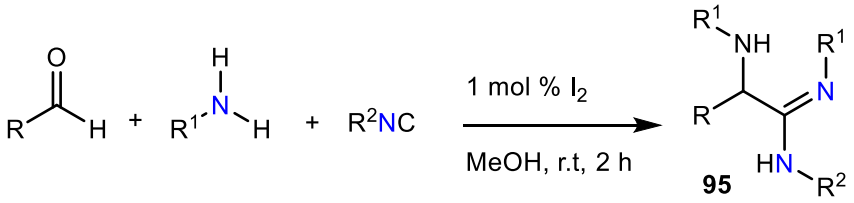
Amidines **7M** have been synthesized rapidly and in high yields from *N*-arylamides using Nano-MgO using solvent-free reaction condition (SFRC) as shown in Scheme 44.[74] It should be noted that these conditions suppress the transamidation.



Scheme 44. Nano-catalysis in amidine synthesis

4.10. Amidines through one-pot three component reactions

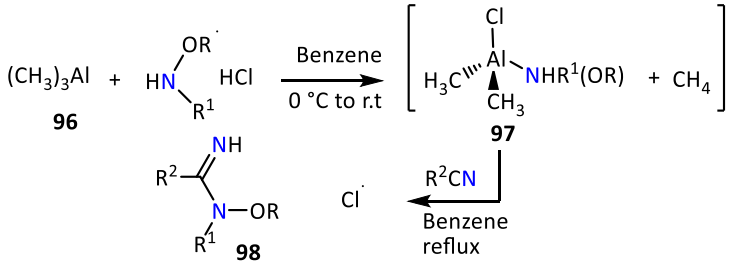
Reaction of an isocyanide (1 mmol), an aldehyde (1 mmol), and an amine (2 mmol) using 1 mol% of molecular iodine in methanol, gave amidines **95** in good yields (Scheme 45).[75]



95	R	R^1	R^2	Yield %
a	C_6H_5	C_6H_5	$(CH_3)_3C$	90
b	C_6H_5	C_6H_5	*c*-C_6H_{11}	93
c	2-Br-C_6H_4	C_6H_5	$(CH_3)_3C$	85
d	*c*-C_6H_{11}	C_6H_5	*c*-C_6H_{11}	86
e	*n*-C_8H_{17}	C_6H_5	*c*-C_6H_{11}	88
f	4-Cl-C_6H_4	C_6H_5	$(CH_3)_3C$	88
g	2-Furyl	C_6H_5	$(CH_3)_3C$	90
h	4-Cl-C_6H_4	4-CH_3O-C_6H_4	$(CH_3)_3C$	90
j	C_6H_5	4-CH_3-C_6H_4	$(CH_3)_3C$	86
i	4-F-C_6H_4	4-CH_3-C_6H_4	$(CH_3)_3C$	92

Scheme 45. One-pot reaction for the formation of amidines **95**.

4.11. Synthesis of *N*-alkoxy amidine salts



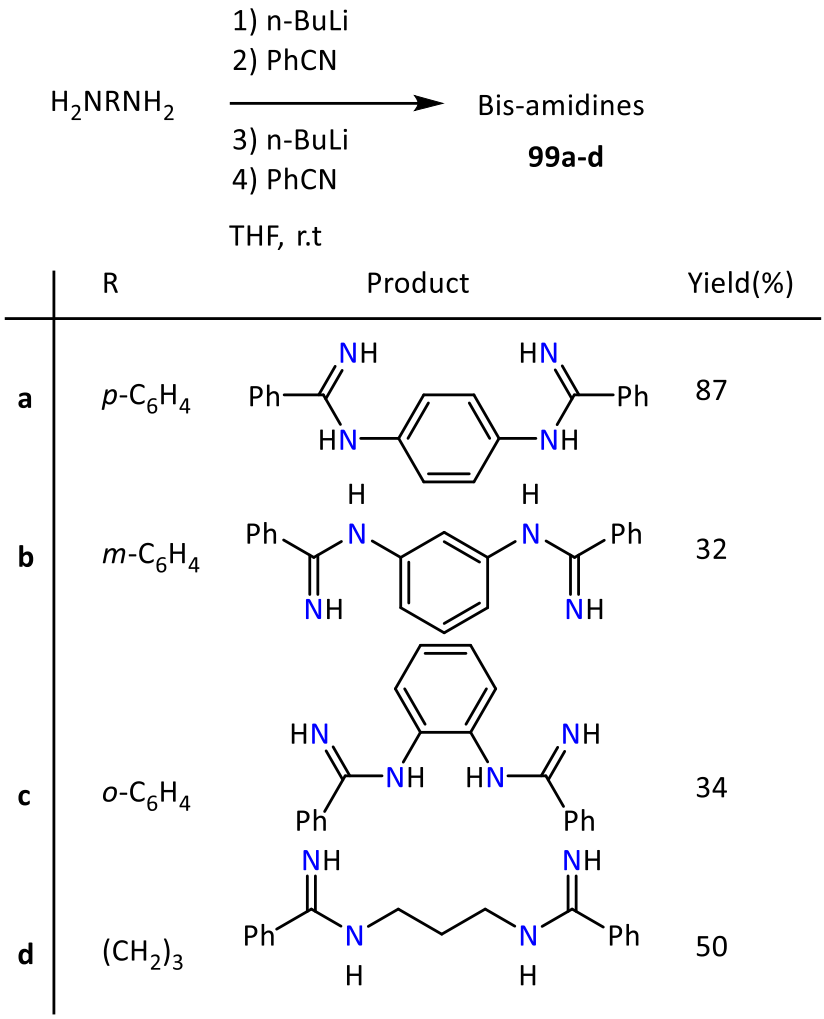
	Nitrile	Aluminum Reagent	Product	Yield (%)
a	CH_3CN	$(CH_3)_2AlH(Cl)$—N(OMe)Me	ClH.HN(OCH3)N(CH3)CH3	94
b	CN	**96**	NH.HCl, N—OCH3, H3C	98
c	H3CO, CN	**96**	H3CO, NH.HCl, N—OCH3, H3C	50
e	Cl, CN	**96**	Cl, NH.HCl, N—OCH3, H3C	96
d	H3C, CN, H3C	**96**	ClH.HN(OCH3)N(CH3), H3C, CH3	67

Scheme 46. Synthesis of *N*-alkoxy amidine salts **98**.

Addition of trimethylaluminum (**96**) to alkoxyamine hydrochlorides gave (*N*-alkyl-*N*-alkoxyamine)-dimethylaluminum chlorides **97** as intermediates, which on addition to nitriles provided a good yield of the *N*-alkoxy amidine salts **98** (Scheme 46).[76]

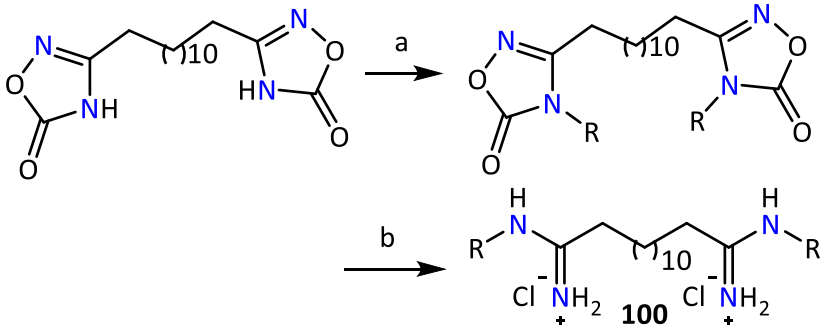
4.12. Synthesis of bisamidines

Using successive double addition of primary diamines to the same equivalents of benzonitrile afforded bisamidines **99** as shown in Scheme 47.[77] The latter were utilized in the synthesis of RNA with amidine linkage.[77]



Scheme 47. Synthesis of bis amidines **99**.

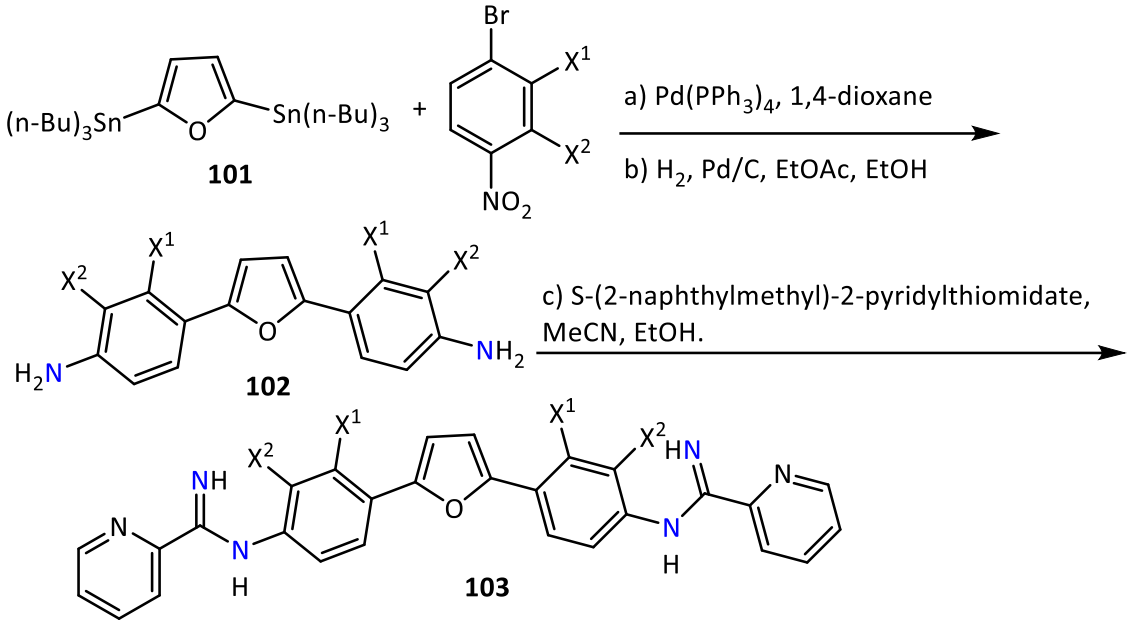
The strategy for the synthesis of *N*-substituted bisalkylamidines **100** is shown in Scheme 48.[78,79]



Scheme 48. Synthesis of bis amidines **100.** Reagent and Condition: i) RX/DMF, MeONa, 25 °C, Overnight. ii) H_2/Pd, 10% MeOH, HCl 3N, r.t, 4 hr or Zn, MeOH / AcOH, 60 °C, 3 h.

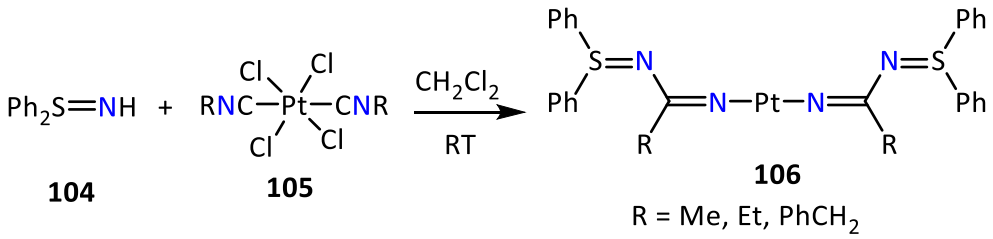
The syntheses of dicationic molecules containing either diguanidino or reversed amidine cationic groups were achieved starting with 2,5 bis(tri-*n*-butylstannyl)furan **101** with arylbromides.[80] Thus 2,5-bis(4-

aminophenyl)furan analogues **102** were obtained in good yields. The reaction of **102** with *S*-(2-naphthyl-methyl)thioimidates gave the reversed amidines **103** (Scheme 49).[81]



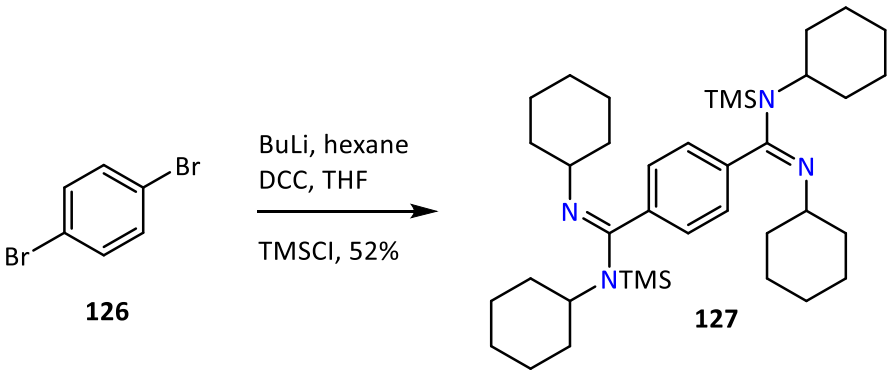
Scheme 49. Synthesis of bisamidines **103**.

Diphenylsulfimide (Ph_2S=NH, **104**) reacts with nitrile-coordinated platinum complexes **105** to give platinum bisamidine complexes **106** (Scheme 50).[82]



Scheme 50. Synthesis of bisamidines **106**.

When 1,4-dibromobenzene reacted with two equivalents of butyllithium, a double metal halogen exchange reaction occurred, and subsequent reaction with two molecules of dicyclohexylcarbodiimide (DDC) followed by silylation (i.e. TMSCl) produced the bis-silylated amidine **107** (Scheme 51).[83,84]

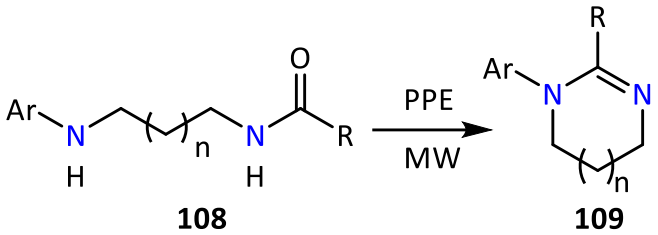


Scheme 51. Synthesis of bisamidines **107**.

4.13. Synthesis of cyclic amidines

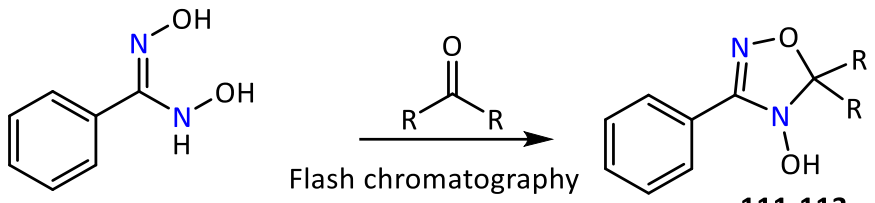
4.13.1. Synthesis of monocyclic amidines. A simple and efficient microwave-based protocol for the synthesis of heterocyclic amidine started with ethyl polyphosphate ester (PPE) promoted cyclodehydration of *N*-aryl-*N*′-acylalkylenediamines **109** (Scheme 52). That method has been considered general for five- to eight-membered heterocycles and affords high yields of the desired products in remarkably short reaction time (Scheme 52).[85]

N,*N*′-Dihydroxybenzimidamide (**110**) was prepared using a literature procedure.[85] The condensation between *p*-unsubstituted **110** and ketones led to three new cyclic *N,N*′-dihydroxybenzamidine derivatives, the 1,2,4-oxadiazolines **111**-**113** (Scheme 53). These decomposed after few hours on storage as the concentrated crude product mixtures. However, immediate flash chromatography led to pure substances of **111-113** (Scheme 53).[85]



109	Ar	R	n	**109**	Ar	R	n
a	4-ClC_6H_4	Et	1	**h**	2-$O_2NC_6H_4$	*t*-Bu	0
b	4-ClC_6H_4	Et	1	**i**	1-naphthyl	C_6H_5	0
c	4-$O_2NC_6H_4$	Et	1	**j**	2-$O_2NC_6H_4$	Et	2
d	4-$O_2NC_6H_4$	*t*-Bu	1	**k**	4-BrC_6H_4	C_6H_5	2
e	2,4,6-$Me_3C_6H_2$	Et	1	**l**	1-naphthyl	*t*-Bu	2
f	C_6H_5	$C_6H_5C_2H_4$	1	**m**	C_6H_5	C_6H_5	3
g	2-$O_2NC_6H_4$	C_6H_5	0	**n**	4-$CH_3C_6H_4$	C_6H_5	3

Scheme 52. Synthesis of monocyclic amidines **109**.

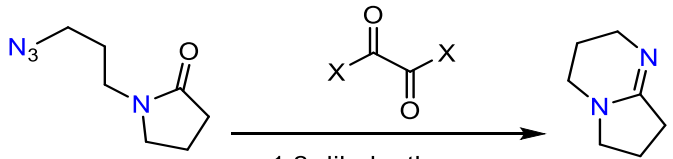


110 **111-113**

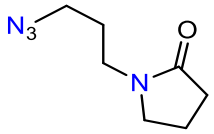
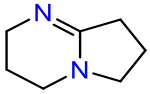
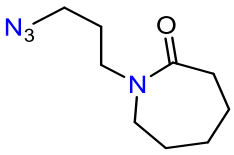
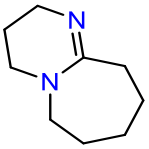
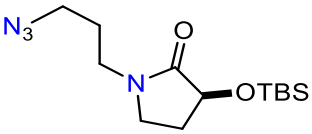
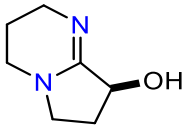
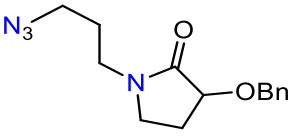
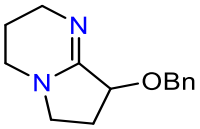
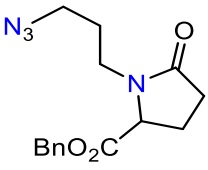
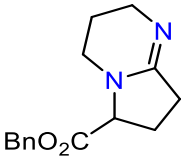
111: R,R = Me; **112**: R,R = -$(CH_2)_4$-; **113**: R,R = -$(CH_2)_5$-

Scheme 53. Synthesis of monocyclic amidines **111-113**.

4.13.2. Synthesis of bicyclic amidines. In amides **114** the azido group serves as a nucleophile or a 1,3-dipole that undergoes cyclization with an activated amide moiety, followed by the extrusion of molecular nitrogen to afford the bicyclic amidine. Thus, bicyclic amidines **115** were obtained during the reaction of **114a-k** with oxalyl halides (Scheme 54).[86]



114a-k **115a-k**

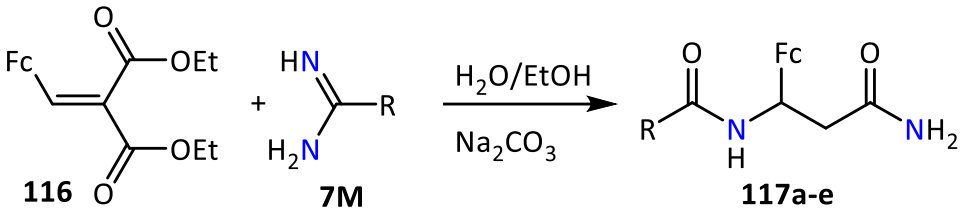
	Substrate	Product	Reagent	T (°C)	T (h)	Yield (%)
a			Cl Br	RT RT	24 4	81 92
b			Br	RT	6	87
c			Br	50	4	84
d			Cl Br	RT RT	24 6	78 88
e			Cl	RT	24	86

Scheme 54. Synthesis of bicyclic amidines **115.**

5. Chemical Reactions of Amidines

5.1. Addition of amidines to electrophiles

Amidines can serve as reactive nitrogen nucleophiles and react with Michael acceptor to build a carbon-nitrogen bond. Depending on the substrates and the reaction conditions, either *N*-alkylamidines are formed, or hydrolysis led to the formation of amides. An example of the latter is the reaction of diethyl 2-(ferrocenylmethylidene)malonate **116** with excess of amidines **7M** in aqueous ethanol in the presence of Na_2CO_3 at 80-85 °C to afford products **117a-e** (Scheme 55).[87]



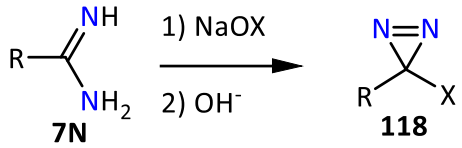
117: a, R=Me; b, R= Ph; c, R= NH_2; d, R= NMe_2; e, R= OMe. Fc= $C_5H_5FeC_5H_4$

Scheme 55. Addition of amidines to electrophiles.

5.2. Synthesis of heterocyclic derivatives

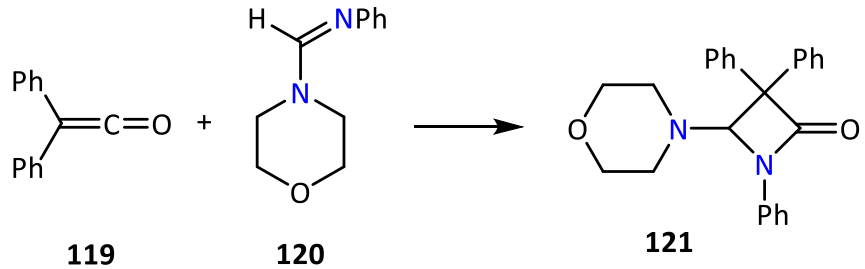
Cyclization is the most important reactions of functionalized and unfunctionalized amidines; thereby different heterocyclic compounds containing the -N=C-N= group are obtained. In the next paragraphs, ordered by ring sizes, some examples are highlighted.

5.2.1. Synthesis of three-membered rings. Reaction of alkyl- or aryl-amidines 7N with sodium hypochlorite in dimethyl sulfoxide (DMSO) solution afforded the corresponding 3-halodiazirenes 118 (Scheme 56).[88]



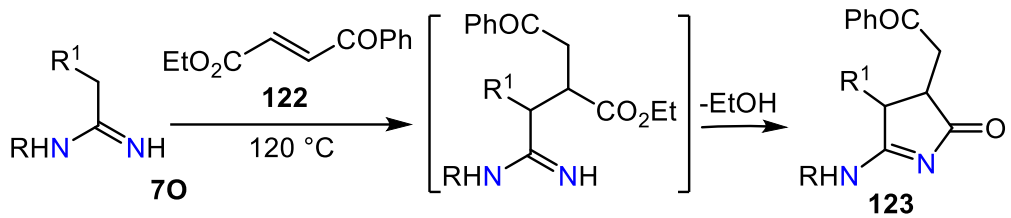
Scheme 56. Synthesis of diazirenes **118**.

5.2.2. Synthesis of four-membered rings. Reaction of diphenylketene (**119**) with 4-(*N*-phenylformimidinoyl)-morpholine (**120**) gave 1,3,3-triphenyl-4-morpholinoazetidinone (**121**) (Scheme 57).[89]



Scheme 57. Synthesis of azetidinone **121**.

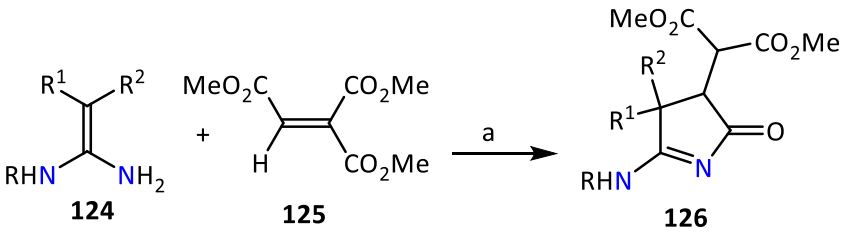
5.2.3. Synthesis of five-membered rings. 5.2.3.1. Pyrroles. When a diglyme solution of the amidines **7O** and ethyl-3-benzoylacrylate (**122**) was heated at 120 °C, 3,4-dihydropyrrol-2-one derivatives **123** were obtained (Scheme 58).[90]



123	a	b	c	d	e
R^1	Ph	4-Me-C_6H_4	4-MeO-C_6H_4	4-Cl-C_6H_4	4-Br-C_6H_4

Scheme 58. Synthesis of pyrrolinones **123**

Reaction of amidine-ylidines **124** with trimethyl ethylenetricarboxylate (**125**) afforded the 3,4-dihydro-pyrrol-2-ones **126** (Scheme 59).[91]

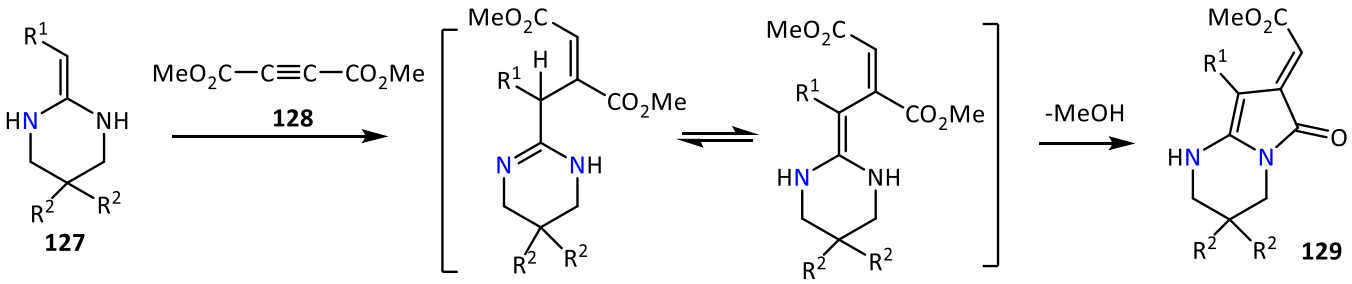


126	a	b	c	d	e	f	g	h
R^1	Ph	4-Cl-C_6H_4	4-Br-C_6H_4	4-MeO-C_6H_4	4-Me-C_6H_4	Ph-CH_2	H	Me
R^2	H	H	H	H	H	H	H	Me
Yield (%)	87	71	72	88	56	51	50	50

Scheme 59. Synthesis of dihydropyrrolinones **126**.

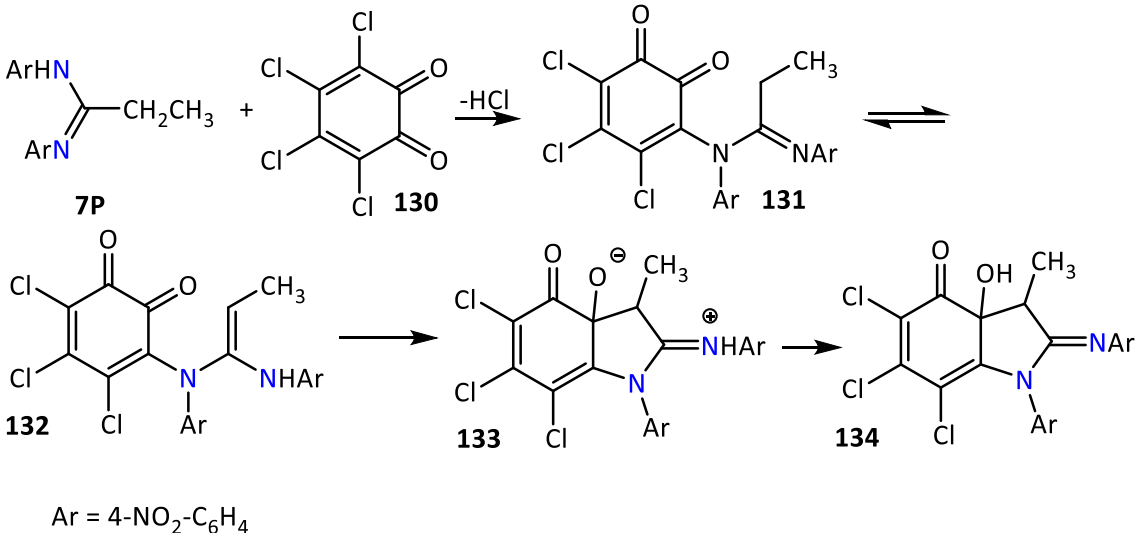
Methyl 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrimidine-7-ylideneacetates **129** were prepared by the reaction of **127** with dimethyl acetylenedicarboxylate (**128**) in methanol at room temperature (Scheme 60).[87] The proposed mechanism for the formation of **129** is as shown in Scheme 60.[92]

A new synthesis of 5,6,7-trichloro-3α-hydroxy-3-methyl-1-(4-nitrophenyl)-2-[(4-nitrophenyl)imino]-1,2,3,3α-tetrahydro-4*H*-indol-4-one (**134**) was discovered in the reaction of nitro-substituted *N,N*′-diarylamidine **7P** with 3,4,5,6-tetrachloro-1,2-benzoquinone (**130**) (Scheme 61).[93] The proposed mechanism to explain the formation of **134** is as follows. Nucleophilic attack on C-3 of **130** by the imino nitrogen atom N^2 of **7P** is followed by liberation of hydrogen chloride to give **131**. Tautomerism of **131** to **132** followed by amidine-ene addition to form salt **133** (Scheme 61). Hydrogen transfer in **133** led ultimately to the formation of **134** (Scheme 61).[93]



129	a	b	c	d	e	f
R^1	Ph	Ph	4-MeC_6H_4	4-MeC_6H_4	4-$MeOC_6H_4$	4-$MeOC_6H_4$
R^2	H	Me	H	Me	H	Me
Yield (%)	43	55	44	60	37	41

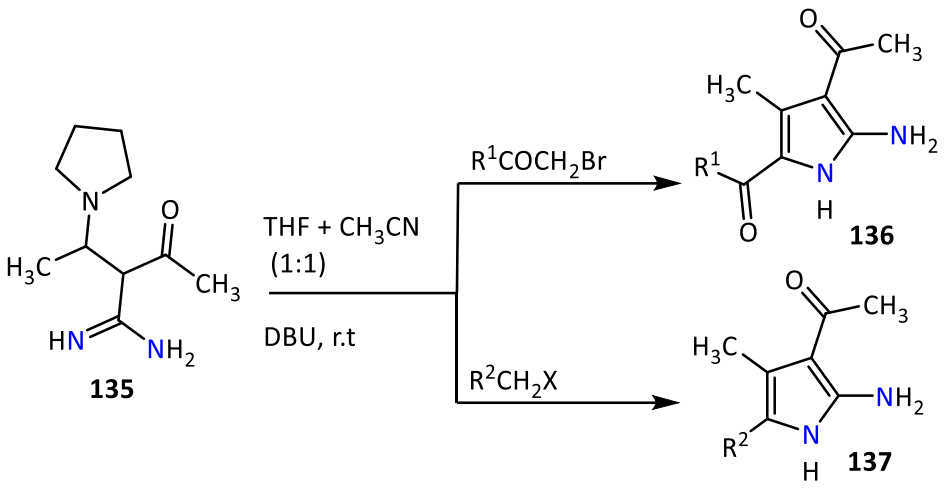
Scheme 60. Synthesis of fused pyrrolidinones **129**.



Ar = 4-NO_2-C_6H_4

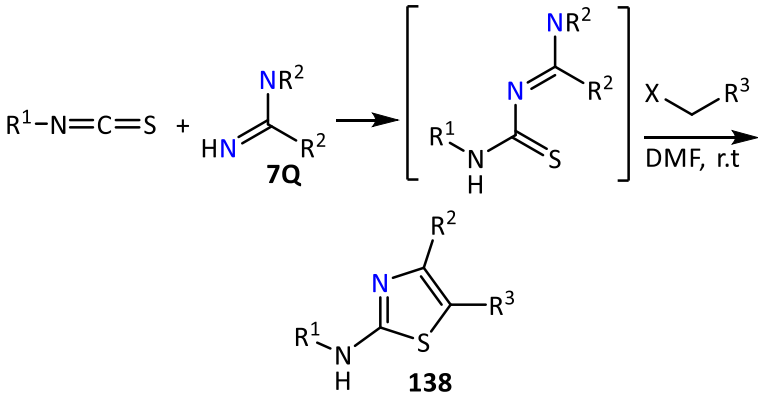
Scheme 61. Synthesis of hydroindoles **134**.

The reaction of amidines **135** with various phenacyl, benzyl, or heteroalkyl halides in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) produced 2-aminopyrroles **136** and **137** in good to excellent yields (Scheme 62).[94]



Scheme 62. Synthesis of pyrroles **136** and **137**.

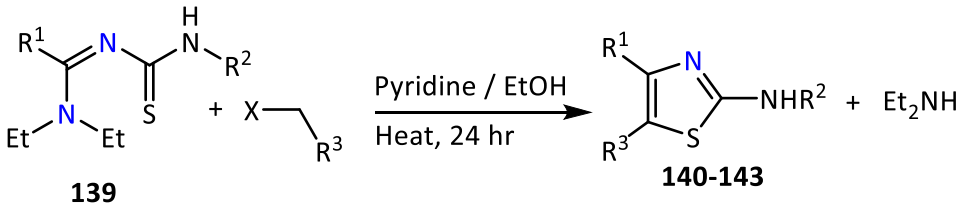
5.2.3.2. Thiazoles. An efficient one-pot method for the synthesis of 2-aminothiazoles **138** using isothiocyanates, amidines **7Q** and various halomethylenes is reported. The synthesis of 2-aminothiazoles **138** involves reaction such as nucleophilic addition-alkylation and intramolecular nucleophilic substitution in which amines departs as the leaving group (Scheme 63).[95]



Scheme 63. Synthesis of thiazoles **138.**

The preparation of 4,5-disubstituted 2-alkylaminothiazoles **140-143** involves the cyclocondensation of *N*-thioamidoamidines **139** with 2-haloalkyl derivatives in refluxing ethanol in the presence of one equiv. of pyridine (Scheme 64).[96]

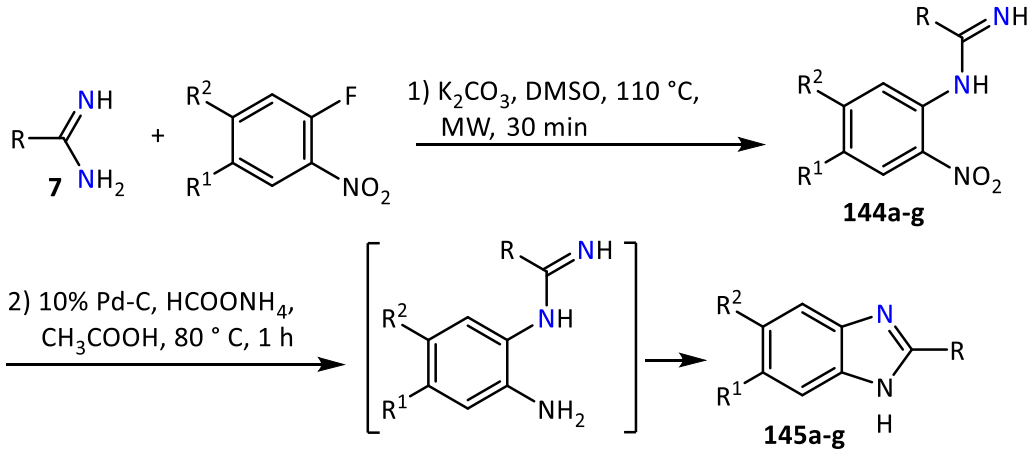
5.2.3.3. Imidazoles. Treating amidines with 2-fluoronitrobenzenes led within 30 min under microwave irradiation to the formation of *N*-(2-nitroaryl)-carboximidamides **144a-g** (Scheme 65).[97] Reduction of **144a-g** using Pd-C gave an aminoamidine intermediate which cyclized to give imidazoles **145a-g** (Scheme 65).[97]



139 **140-143**

	X	R^1	R^2	R^3
140a	Br	Ph	Ph	CO_2Et
140b	Br	Ph	Bn	CO_2Et
140c	Br	Ph	CH_3CH_2	CO_2Et
140d	Br	CH_2-Ph	Ph	CO_2Et
141a	Br	Ph	Ph	C(O)-Ph-p-NO_2
141b	Br	CH_2-Ph	CH_2-Ph	C(O)-Ph-p-NO_2
142a	Cl	Ph	Ph	CN
142b	Cl	CH_2-Ph	CH_2-Ph	CN
143a	Cl	Ph	Ph	C(O)-CH_3
143b	Cl	CH_2-Ph	CH_2-Ph	C(O)-CH_3

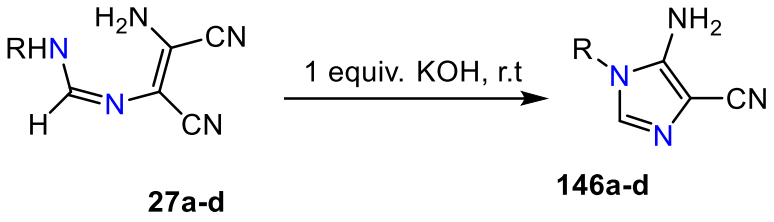
Scheme 64. Synthesis of thiazoles **140-143**.



145	R	R^1	R^2	Yield (%)
a	C_6H_5	H	H	96
b	C_6H_5	H	CH_3	97
c	C_6H_5	CF_3	H	91
d	4-(OCH_3)-C_6H_4	H	H	95
e	4-(OCH_3)-C_6H_4	H	CH_3	93
f	4-(OCH_3)-C_6H_4	CF_3	H	94
g	4-(CH_3)-C_6H_4	H	H	97

Scheme 65. Synthesis of fused imidazoles **145a-g**.

5-Amino-1-aryl-4-cyanoimidazoles **146a-d** were prepared from the reaction functionalized amidines **27a-d** in the presence of aqueous potassium hydroxide (1M) at room temperature (Scheme 66).[98] One equivalent of cyanide is released during the reaction for the bisnitrile.

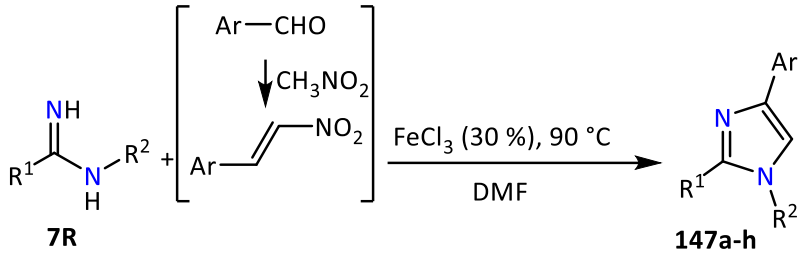


27a-d **146a-d**

27 and **146**	**a**	**b**	**c**	**d**
R	2-$ClC_6H_4CH_2$	3,4-$(CH_3O)_2C_6H_3CH_2$	3,4-$(CH3O)_2C_6H_3$	4-$CH_3OC_6H_4$
Yield (%)of **146a-d**	85	90	89	93

Scheme 66. Synthesis of imidazoles **146a-d**.

Under the conditions shown in Scheme 67, benzaldehydes reacted with *N*-phenylbenzamidines **7R** to provide the corresponding 1,2,4-trisubstituted imidazole derivatives **147** (Scheme 67).[99]

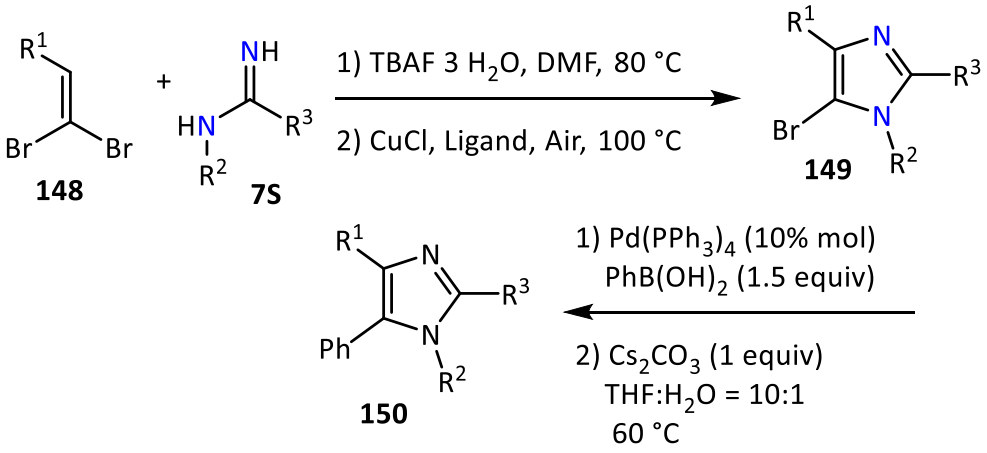


7R **147a-h**

147	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
R^1	C_6H_5	C_6H_5	4-CH_3-C_6H_4	C_6H_5	C_6H_5	C_6H_5	C_6H_5	C_6H_5
R^2	C_6H_5	4-CH_3-C_6H_4	C_6H_5	3-CH_3-C_6H_4	4-$CH_3OC_6H_4$	2 -$C_2H_5C_6H_4$	4-ClC_6H_4	3-ClC_6H_4
Yield (%)	62	72	71	62	75	61	58	54

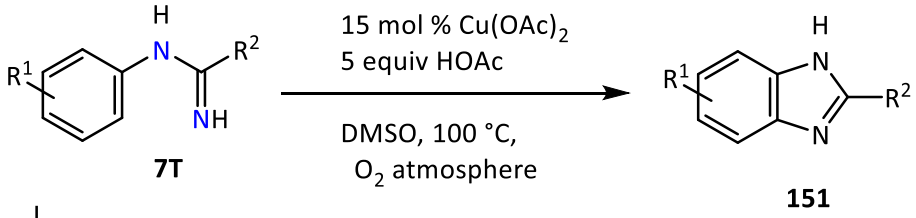
Scheme 67. Synthesis of imidazoles **147a-h.**

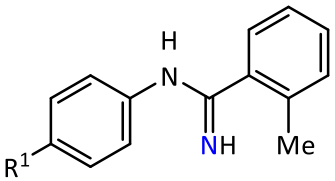
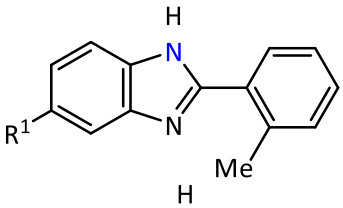
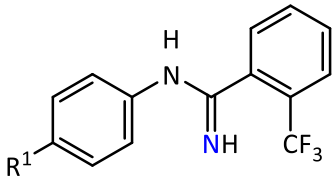
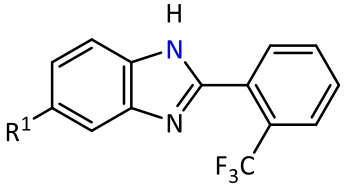
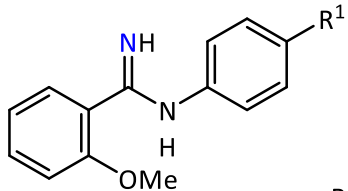
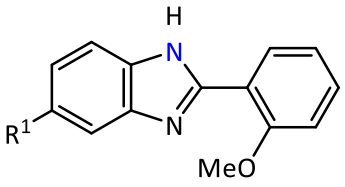
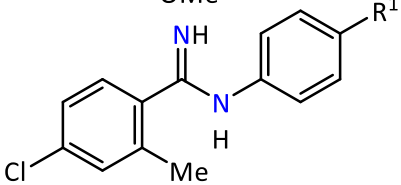
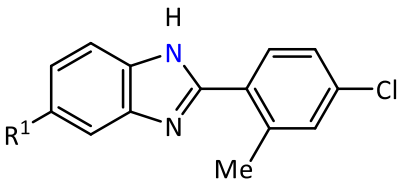
Copper and palladium-catalyzed cycloamination reaction of 1,1-dibromoalkenes **148** with mono-functionalized amidines **7S** in the presence of tetrabutylammonium fluoride solution (TBAF) to afford polysubstituted bromoimidazole derivatives **149** (Scheme 68).[100] The bromo group from **149** was selectively replaced by a phenyl group under the conditions shown in Scheme 68 to give polysubstituted imidazoles **150** (Scheme 68).[101]



Scheme 68. Synthesis of imidazoles **150**.

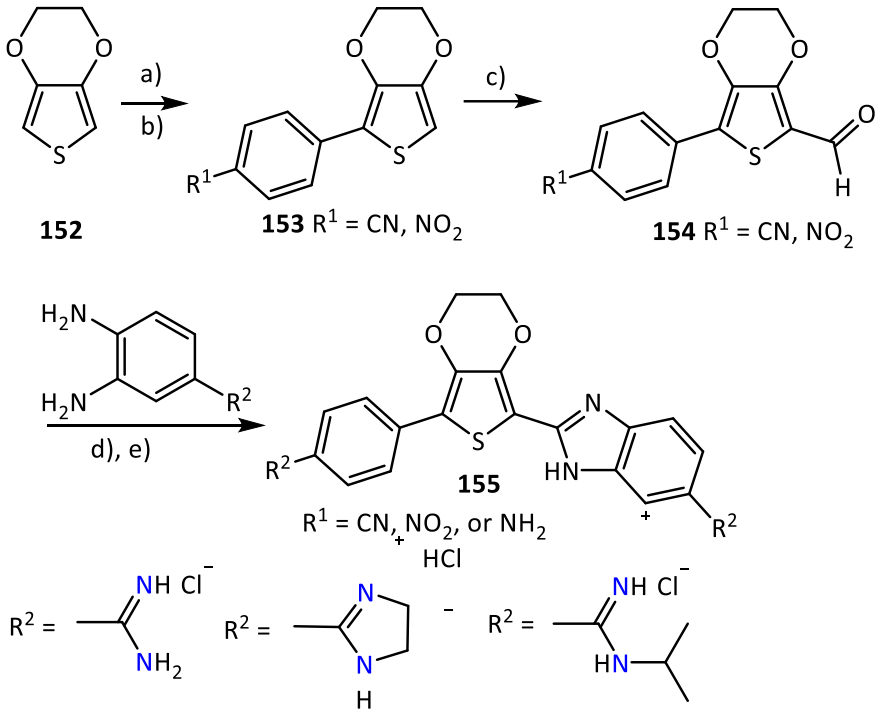
Benzimidazoles **151a-d** can easily be prepared by the reaction of *N*-arylamidines **7T** with 15% mol $Cu(OAc_2)$ in DMSO at 100 °C and under an oxygen atmosphere together with 5 equiv. of acetic acid (Scheme 69).[102]



	Substrate	Product	R^1	Yield (%)
a			H OMe F Cl Br	89 70 86 89 89
b			H OMe CO_2tBu I	87 74 88 89
c			H Cl	68 75
d			H Br	85 88

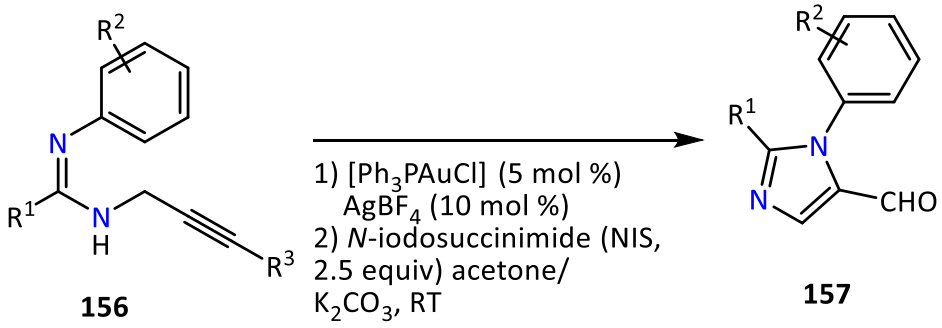
Scheme 69. Synthesis of fused imidazoles **151a-d**.

Starting with 2,3-dihydrothieno[3,4-*b*][1,4]dioxin (**152**), functionalized benzimidazoles **155** were prepared *via* oxidative coupling of thiophencarbaldehydes **153** or **154** with the appropriate 3,4-diaminobenzamidines in 60-70% yields (Scheme 70).[103]



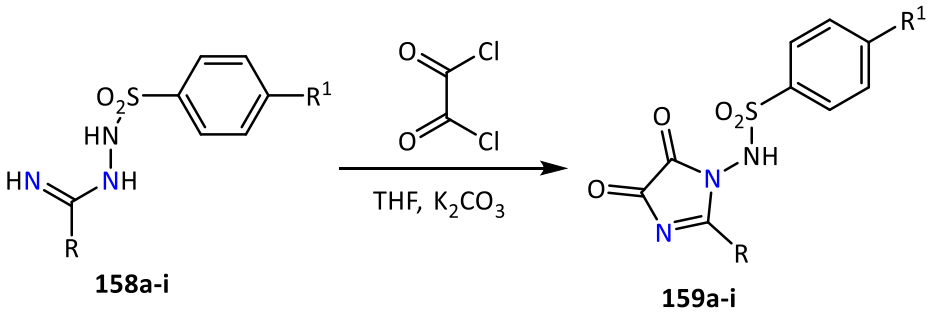
Scheme 70. Synthesis of imidazoles **155.** Reagents and Conditions: (i) 1. n-BuLi, THF; 2. Bu_3SnCl; (ii) $Pd(PPh_3)_4$, 4-bromobenzonitrile or 1-bromo-4-nitrobenzene, THF; (iii) $POCl_3$, DMF; (iv) 3,4-diaminobenzimidamide hydrochloride, 3,4-diamino-*N*-isopropylbenzimidamide hydrochloride, 4-(4,5-dihydro-1*H*-imidazol-2-yl)benzene-1,2-diaminehydrochloride, 1,4-benzoquinone, C_2H_5OH; v) H_2, 10% Pd/C, CH_3OH.

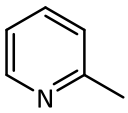
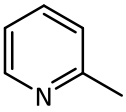
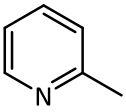
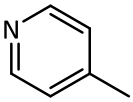
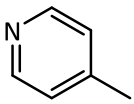
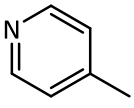
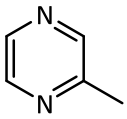
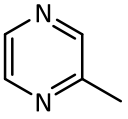
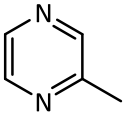
Gold(I)-catalyzed synthesis of imidazole-5-carbaldehydes **157** from *N*-propargyl amidines **156** is as shown in Scheme 71.[104]



Scheme 71. Synthesis of imidazoles **157**.

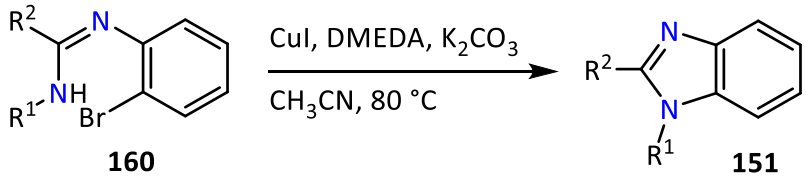
Five-membered condensed dihydroimidazolylbenzenesulfonamide derivatives **159a-i** were obtained by the reaction of amidine derivatives **158a-i** [105] with acylating agent oxalyl chloride (Scheme 72).[106]



161	a	b	c	d	e	f	g	h	i
R									
R^1	CH_3	OCH_3	H	H	CH_3	OCH_3	H	CH_3	OCH_3
Yield (%)	48	42	58	41	49	64	81	38	55

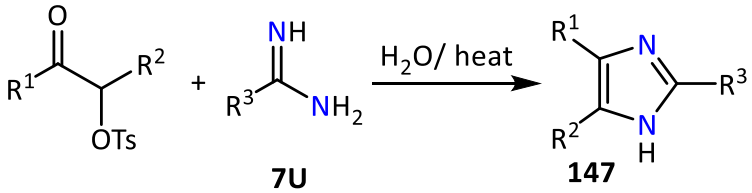
Scheme 72. Synthesis of imidazole-4,5-diones **159a-i**.

It was found that the CuI-promoted cyclocondensation of **160** proceeded in refluxing acetonitrile in the presence of potassium carbonate and 10% mol of *N*,*N*′-dimethylethylenediamine (DMEDA) as the base to give benzimidazoles **151** (Scheme 73).[107]



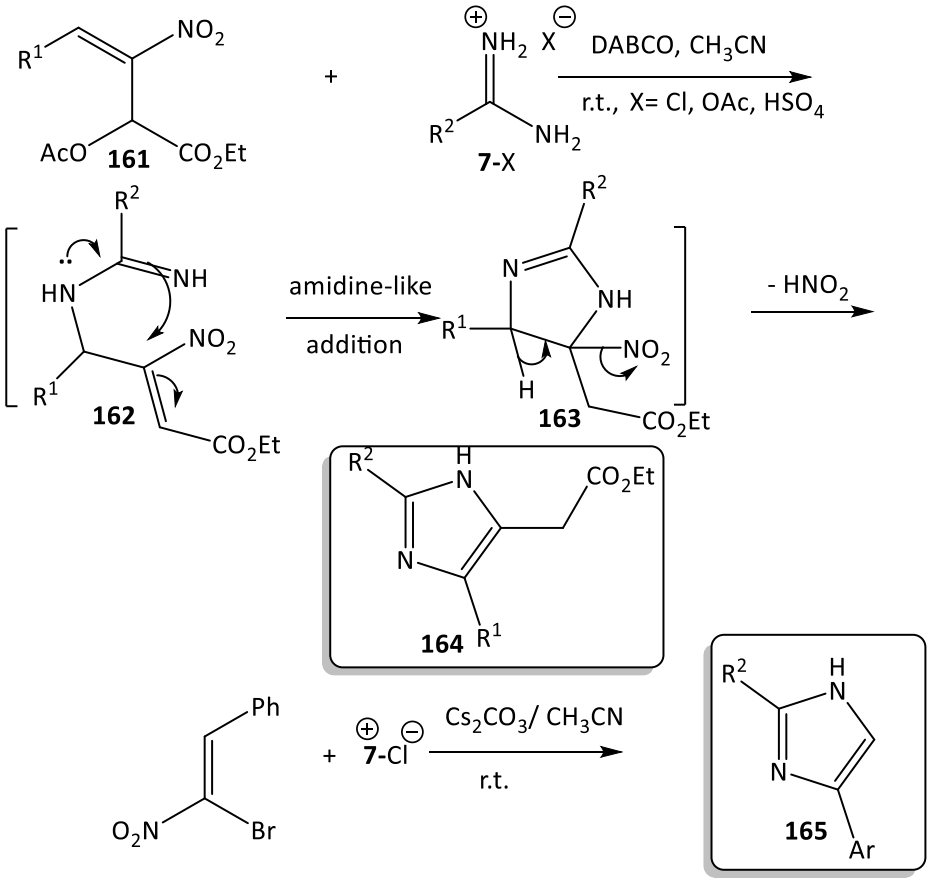
Scheme 73. Synthesis of benzimidazoles **151.**

The formation of diarylimidazoles **147** was established by reacting α-tosyloxyketones with amidines **7U** in water as a solvent (Scheme 74).[108]



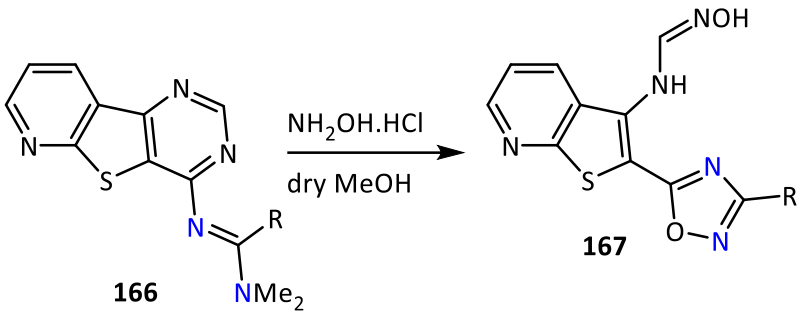
Scheme 74. Synthesis of imidazoles **147**.

It was reported on the synthesis of imidazole esters **164** from nitroallylic acetates **161** and amidine salts through a one-pot cascade intermolecular aza-SN2' reaction–intramolecular aza-Michael addition (Scheme 75).[109] The reaction was described as due to addition of **161** to the positively nitrogen to form intermediate **162** (Scheme 74). Amidine-like addition accompanied by cylization process gave intermediate **163** (Scheme 74). Elimination of HNO_2 from **163** produced **164** (Scheme 75). The same group used $CsCO_3$ and at room temperature to synthesize imidazoles **165** *via* reaction (*Z*)-(2-bromo-2-nitrovinyl)benzene, as an example, with amidine chlorides in CH_3CN (Scheme 75).[110]



Scheme 75

5.2.3.4. Oxadiazoles. The reaction of **166** with 4 equivalents of hydroxylamine hydrochloride in methanol at room temperature led to complete consumption of **166** and gave 1,2,4-oxadiazoles **167** in 14-73% yields (Scheme 76).[111]

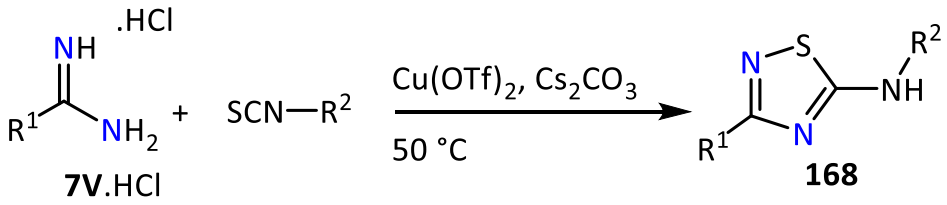


166 **167**

167	R	Yield %	**167**	R	Yield %
a	Me	73	**f**	4-$MeOC_6H_4$	Crude
b	Et	14	**g**	4-FC_6H_4	46
c	Ph	42	**h**	4-ClC_6H_4	46
d	4-MeC_6H_4	72	**I**	4-$O_2NC_6H_4$	55
e	3,4-$Me_2C_6H_3$	60	**j**	3-pyridyl	*45*

Scheme 76. Synthesis of 1,2,4-oxadiazoles **167**.

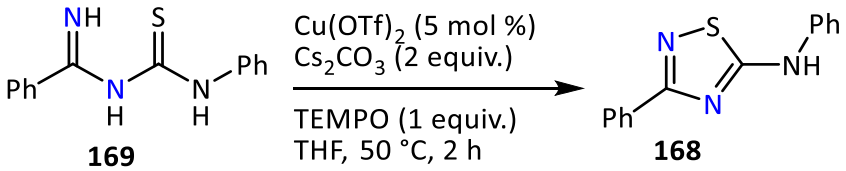
5.2.3.5. Thiadiazoles. A one-pot synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles **168** from amidine hydrochlorides **7**.HCl and isothiocyanates was reported by Wu and Zhang (Scheme 77).[112]



7V.HCl **168**

Scheme 77. Synthesis of thiadiazoles **168 .** Reaction conditions: isothiocyanate (0.5 mmol), 7.HCl (0.5 mmol), Cs_2CO_3 (3 equiv), $Cu(OTf)_2$) 5% mol), and solvent (10 mL) under air at 50 °C.

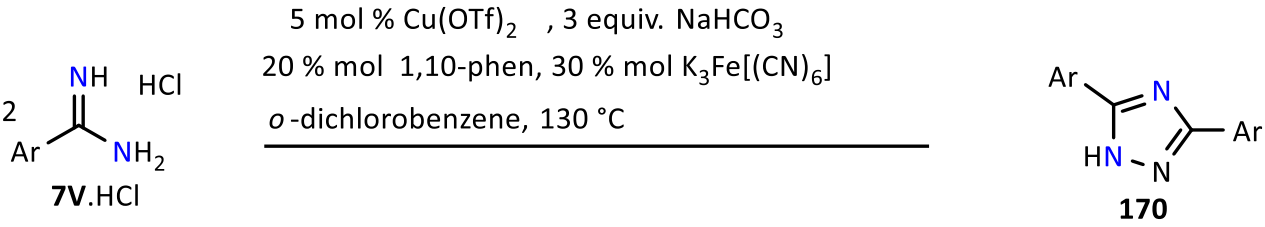
N-Thiocarbamoylamidine **169** is involved in N-S bond formation in the presence of (2,2,6,6-tetramethyl-piperidin-1-yl)oxidanyl (TEMPO), which is known to be a good oxidizing agent, as shown in Scheme 78 to give 1,2,4-thiadiazole derivatives **168**.[113]



169 **168**

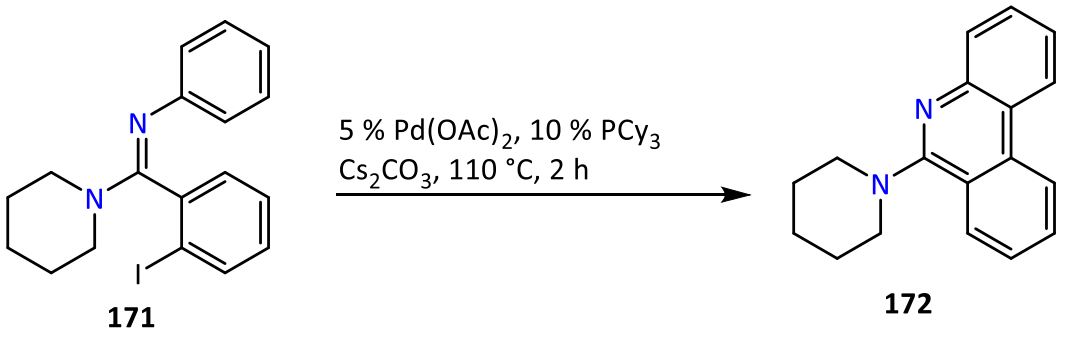
Scheme 78. Synthesis of thiadiazoles **168**.

5.2.3.6. Triazoles. Synthesis of 3,5-diaryl-1,2,4-triazoles **170** can be achieved from amidines **7V** by a $Cu(OTf)_2$-catalyzed reaction using $NaHCO_3$ as a base, with 1,10-phenanthroline as an additive and $K_3[Fe(CN)_6]$ under atmospheric oxygen (Scheme 79).[114-116]



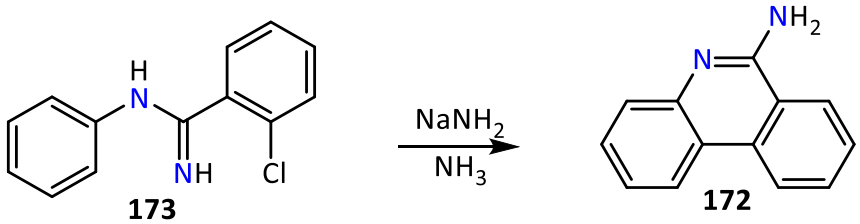
Scheme 79. Synthesis of triazoles **170**.

5.2.4. Synthesis of six-membered rings. 5.2.4.1. Pyridines. *N*-Arylamidine **171** was converted into the 6-aminophenanthridine **172** in excellent yield through a Pd-catalyzed intramolecular coupling reaction (Scheme 80).[117]



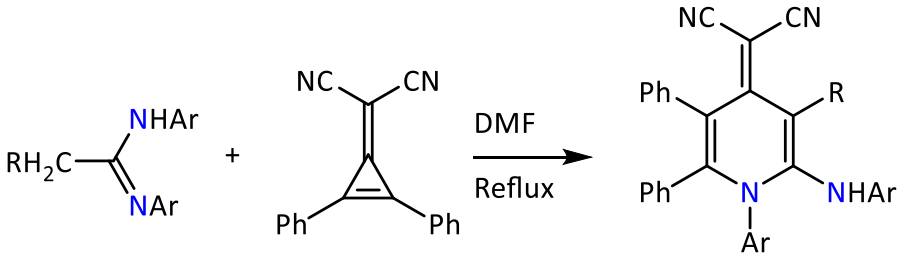
Scheme 80. Synthesis of phenanthridine **172**.

Addition of *N*-phenyl-2-chlorobenzamidine (**173**) to a sodium amide suspension in liquid ammonia led to the formation of 6-aminophenanthridine (**172**) (Scheme 81).[118]



Scheme 81. Synthesis of 6-aminophenanthridine.

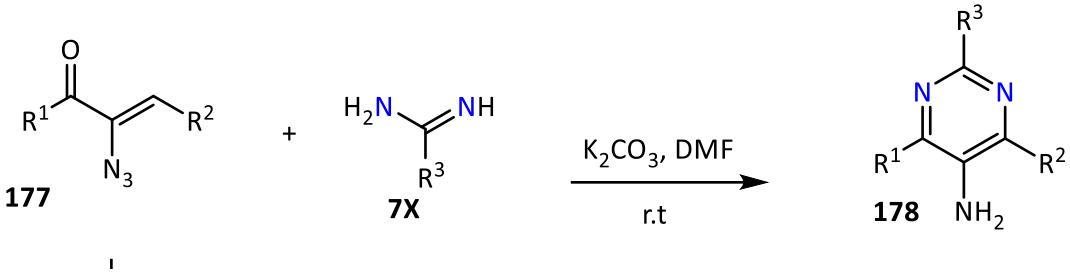
Gomaa and Döpp *et al*. prepared 1,4-dihydropyridines **176** from the reaction of N^1,N^2-diarylamidines **7W** and (2,3-diphenylcyclopropen-1-ylidene)propanedinitrile (**175**, Scheme 82).[119]



7W **175** **176**

Scheme 82. Reaction of acetamidines with (2,3-diphenylcyclopropen-1-ylidene)propanedinitrile (**175**).

5.2.4.2. Pyrimidines. A simple and direct synthesis of polysubstituted 5-aminopyrimidines **178** from α-azidovinyl ketones **177** and amidines **7X** in the presence of base was developed. The reaction was performed in anhydrous DMF with 1.2 equivalent of amidines and 2.4 equivalent of K_2CO_3 under N_2 atmosphere and at room temperature (Scheme 83).[120]

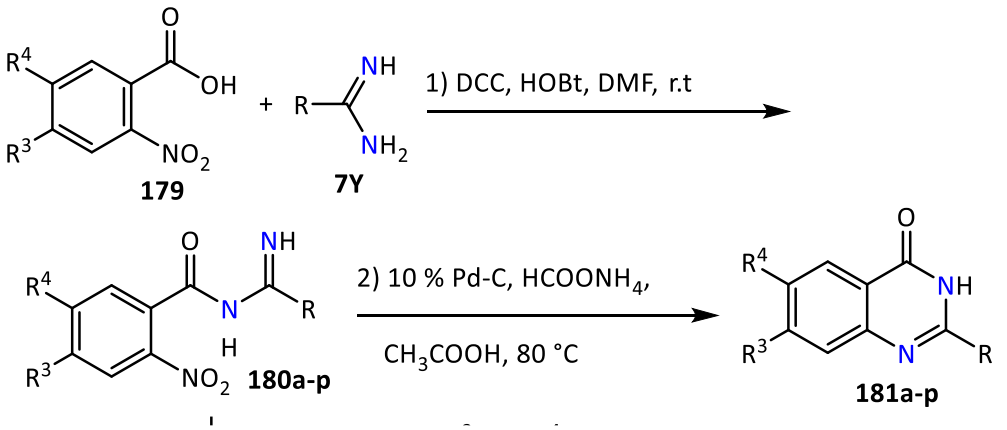


178	R^1	R^2	R^3	Yield %
a	Ph-	4-BrC_6H_4-	H	95
b	4-MeC_6H_4	4-BrC_6H_4-	CH_3	81
c	4-ClC_6H_4	4-BrC_6H_4-	Ph	81
d	4-O_2NC_6H_4	4-MeOC_6H_4-	CH_3	77
e	4-MeOC_6H_4	2-BrC_6H_4-	H	70
f	2-thienyl	4-FC_6H_4-	CH_3	82

Scheme 83. Synthesis of 5-aminopyrimidines **178**.

When *N*-[imino(phenyl)methyl]-2-nitrobenzamides **179** reacted with amidines **7Y** with 2-nitrobenzoic acid derivatives, various **181a-o** were obtained by the sequences shown in Scheme 84.[98] It is important to show that the hydroxybenzotriazole (HOBt) was used as a catalyst to suppress peptide linkage. In addition to *N,N'*-dicyclohexylcarbodiimide (DDC) was also used in the former reaction to couple amino acids during artificial peptide synthesis.

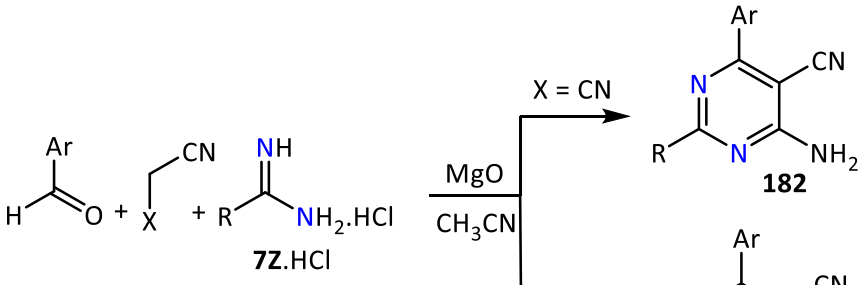
Magnesium oxide (MgO) effectively catalyzed the three-component reaction of aldehydes, amidine salts **7Y**.HCl, and malononitrile or ethyl cyanoacetate to form 4-amino-5-pyrimidine-carbonitriles **182** and pyrimidinone derivatives **183**, respectively (Scheme 85).[121]



179 **7Y** **180a-p** **181a-p**

181	R	R^3	R^4	Yield %
a	Ph	H	H	96
b	Ph	H	Me	91
c	Ph	OMe	H	95
d	4-$MeOC_6H_4$	H	H	97
e	4-$MeOC_6H_4$	H	Me	92
f	4-$MeOC_6H_4$	OMe	H	96
g	4-MeC_6H_4	H	H	91
h	4-MeC_6H_4	H	Me	95
i	4-MeC_6H_4	OMe	H	93
k	3-MeC_6H_4	H	H	94
l	3-MeC_6H_4	H	Me	91
m	3-MeC_6H_4	OMe	H	94
n	CH_3	H	H	93
o	CH_3	H	Me	95
p	CH_3	OMe	H	96

Scheme 84. Synthesis of fused pyrimidines **181a-p**.

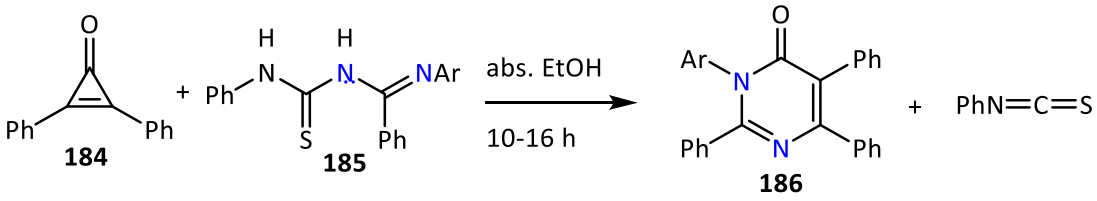


7Z.HCl **182** **183**

182 or **183**	Ar	R	Time (min)	Yield **182** (%)
a	C_6H_5	C_6H_5	18	90
b	C_6H_5	NH_2	13	92
c	C_6H_5	C_6H_5	26	97
d	4-ClC_6H_4	C_6H_5	13	96
e	4-ClC_6H_4	NH_2	11	97
f	4-ClC_6H_4	C_6H_5	32	95

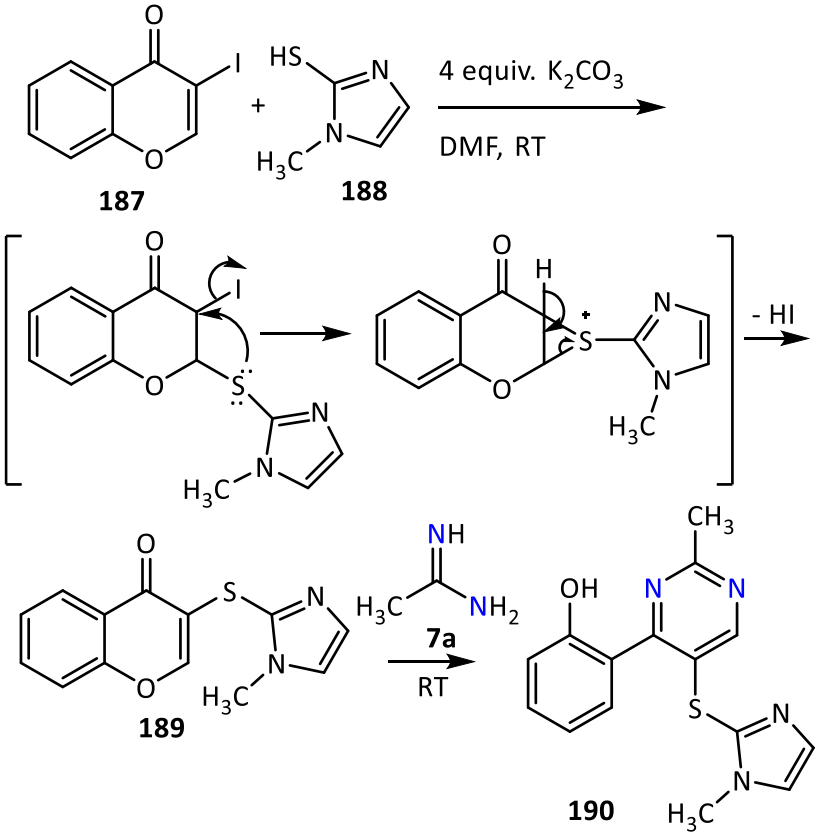
Scheme 85. Synthesis of pyrimidines **182** and **183**.

Aly *et al.*[122] demonstrated that 2,3-diphenylcyclopropenone (**184**) reacted with substituted thiocarbamoyl-amidines **185** to form the pyrimidin-4(*3H*)-ones **186** (Scheme 86).[122]



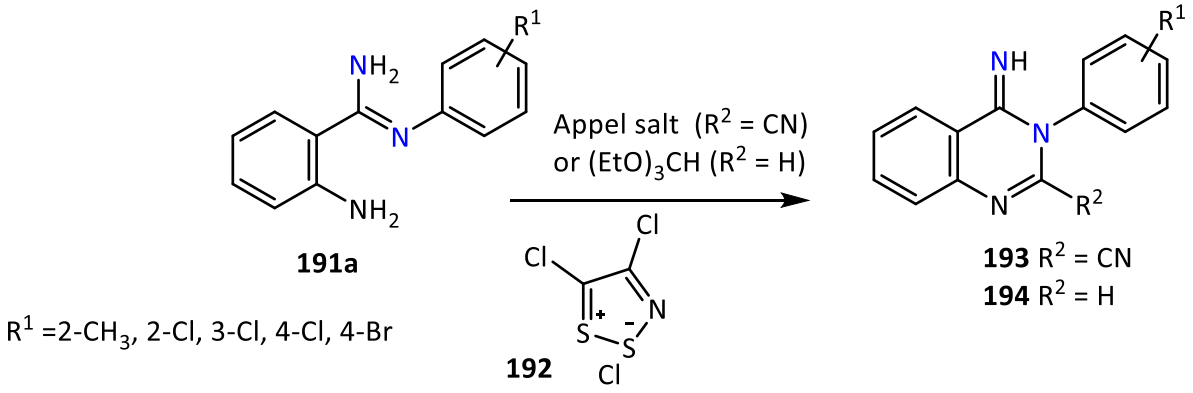
Scheme 86. Synthesis of pyrimidinones **186.**

The synthesis of 2,4-substituted 5-azolythiopyrimidines **190** was achieved by sequential Michael-addition of 3-iodochromone (**187**) with 1-methyl-1*H*-imidazole-2-thiol (**188**) and then condensation with amidine **7a** (Scheme 87).[123] It was believed that the reaction pathway involved the formation of intermediate **189** as shown in Scheme 87.



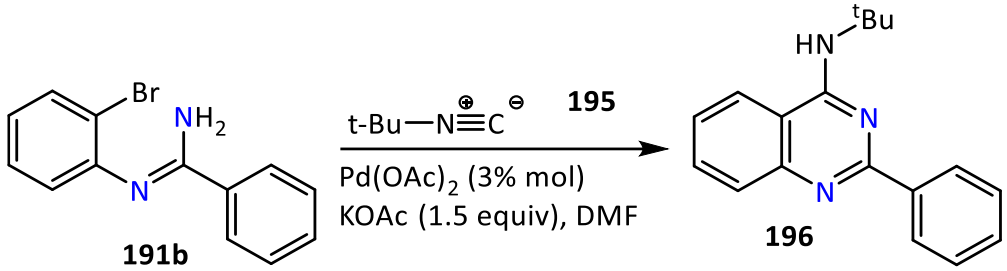
Scheme 87. Synthesis of pyrimidines **190**.

It was previously known that the reaction of 2-amino-N^1-(2-aminoaryl)benzamidines **191a** with 4,5-dichloro-1,2,3-dithiazolium chloride **192** (Appel salt) produce 3-aryl-4-imino-3,4-dihydroquinazoline-2-carbonitriles **193**.[124] Szczepankiewicz *et al.*[125,126] developed a solvent free synthesis of 3-arylquinazolin-4(3*H*)-imines **194** from **191a** and triethyl orthoformate (Scheme 88).



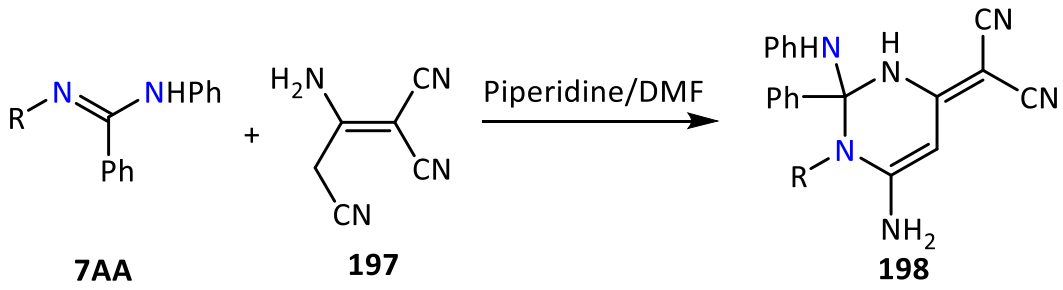
Scheme 88. Synthesis of fused pyrimidines **193** and **194** with the aid of Appel salts.

The synthesis of 4-aminoquinazolines **196** was made possible by palladium-catalyzed intramolecular imidoylation of *N*-(2-bromoaryl)amidines **191b** with *tert*-butylisocyanide (**195**) in the presence of KOAc and DMF mixture (Scheme 89).[127,128]



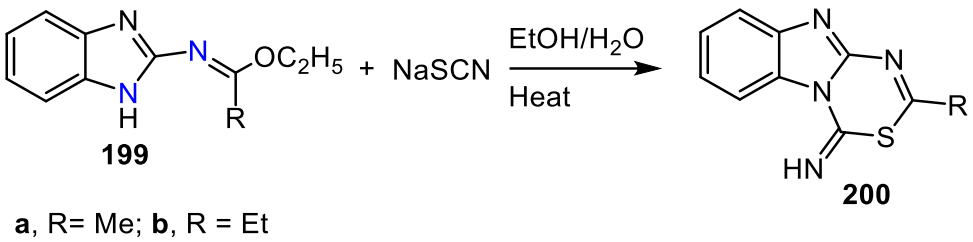
Scheme 89. Synthesis of 4-aminoquinazolines **196.**

Aly *et al.* have recently reported that amidines **7AA** react with malononitrile dimer **197** in DMF catalyzed with a few drops of piperidine to give hydropyrimidines **198** in 70-89% yield (Scheme 90).[129]



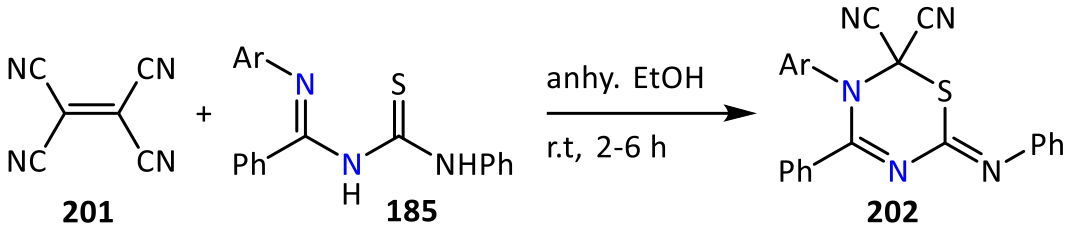
Scheme 90. Synthesis of pyrimidines **198**.

5.2.4.3. Thiadiazines. It has been shown that treatment of [1,2-*a*]benzimidazol-2-yl as iminoesters derivatives **199** with NaSCN in dioxane/H_2O under reflux gave only the fused thiadiazine products **200** (Scheme 91).[130]



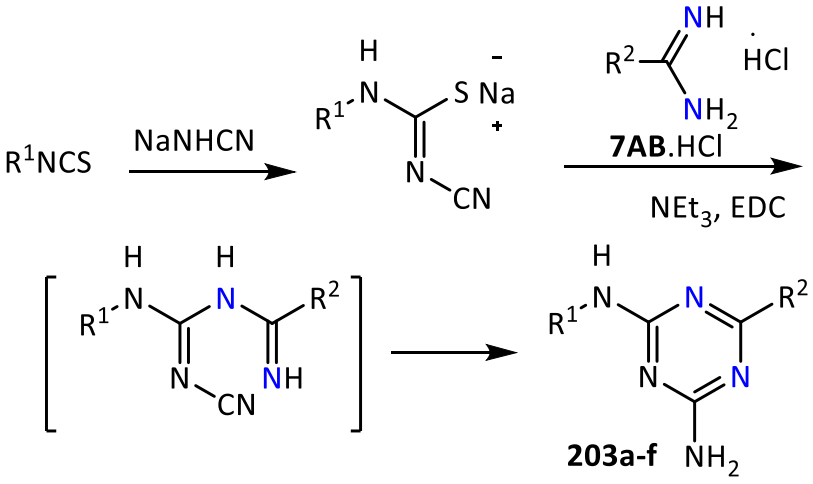
Scheme 91. Synthesis of fused imidazothiadiazines **200.**

Aly and co-workers reported the reaction of thiamidoamidines **185** with 1,1,2,2-tetracyanoethylene (**201**) affording thiadiazines **202** in 85-68% yields (Scheme 92).[131]



Scheme 92. Synthesis of thiadiazines **202**.

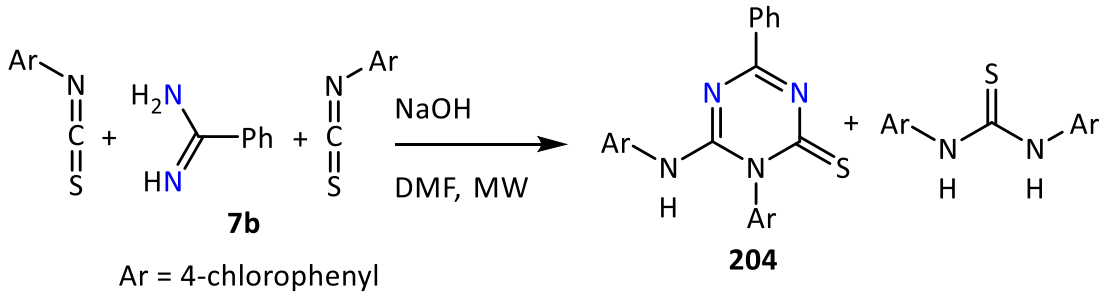
5.2.4.4. Triazines. A reaction sequence furnishing triazines **203** starts with 3,4,5-trimethylphenyl isothiocyanate which was added to the sodium salt of cyanamide in DMF. In turn, benzamidine hydrochloride **7**.HCl reacts smoothly with this intermediate at room temperature in the presence of triethylamine and EDC to yield 1,3,5-triazine-2,4-diamines **203** in good yields (Scheme 93).[132]



203	R^1	R^2	Yield %	**203**	R^1	R^2	Yield %
a	3,4,5-$Me_3C_6H_2$	Ph	71	**d**	Ph	4-$H_2NCOC_6H_4$	65
b	2,4-$Cl_2C_6H_3$	Ph	54	**e**	Ph	Ph	72
c	cyclohexyl	Ph	50	**f**	$PhCH_2$	Ph	44

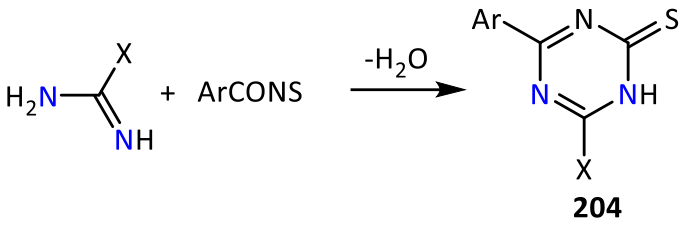
Scheme 93. Synthesis of triazines **203a-f**.

Benzamidine (**7b**) reacted with (4-chlorophenyl)isothiocyanate in DMF at 80 °C using NaOH as a base under microwave heating to provide polysubstituted 1,3,5-triazines **204** in moderate yields (Scheme 94).[133]



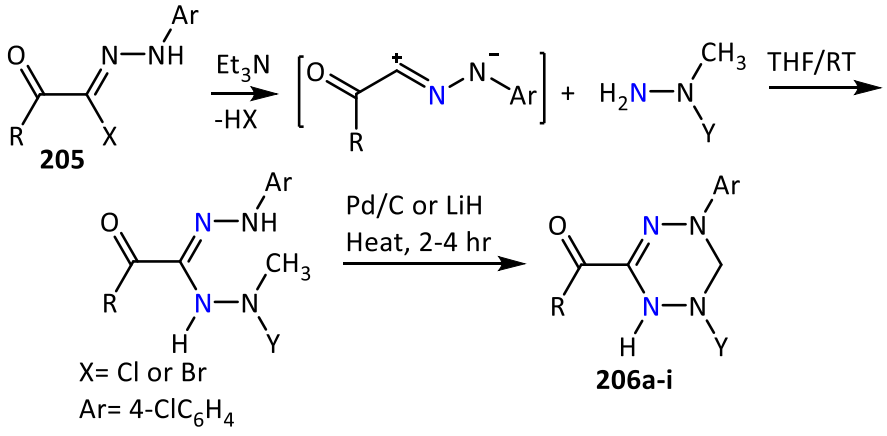
Scheme 94. Synthesis of triazines **204.**

It has been reported that amidines, isoureas, isothioureas and guanidines react with aroyl isothiocyanates to give 1,3,5-triazine thione derivatives **204** (Scheme 95).[134-136]



Scheme 95. Synthesis of 1,3,5-triazines **204**.

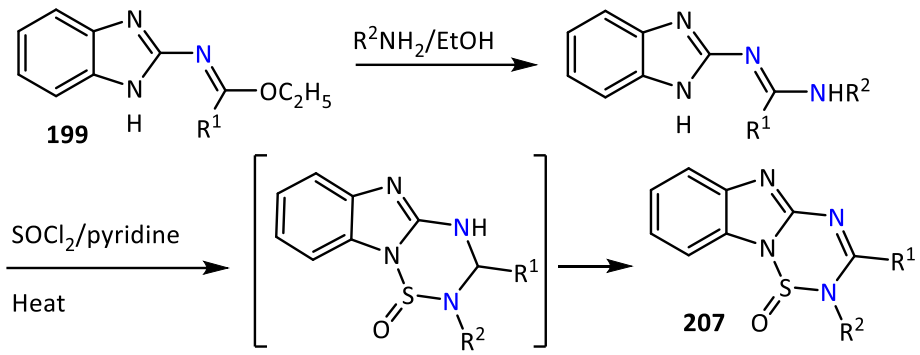
5.2.4.5. Tetrazines. The reaction of *C*-aroyl-*N*-arylnitrilimines **205** with 1,1-dimethylhydrazine or 1-methyl-1-phenylhydrazine led to the formation of the acyclic electrophilic addition products, which underwent thermal oxidative cyclization at CH_3 to 1,2,3,4-tetrahydro-*s*-tetrazines **206** as shown in Scheme 96.[137,138]



R/Y: a, Me/Me; b, Me/Ph; c, Ph/Ph; e, PhNH/Me; f, PhNH/Ph; g, 2-Furyl/Me; h, 2-Furyl/Ph; i, 2-Thienyl/Me; j, 2-Thienyl/Ph; k, 2-Naphthyl/Me; l, 2-Naphthyl/Ph

Scheme 96. Synthesis of 1,2,4,5-tetrazines **206a-i.**

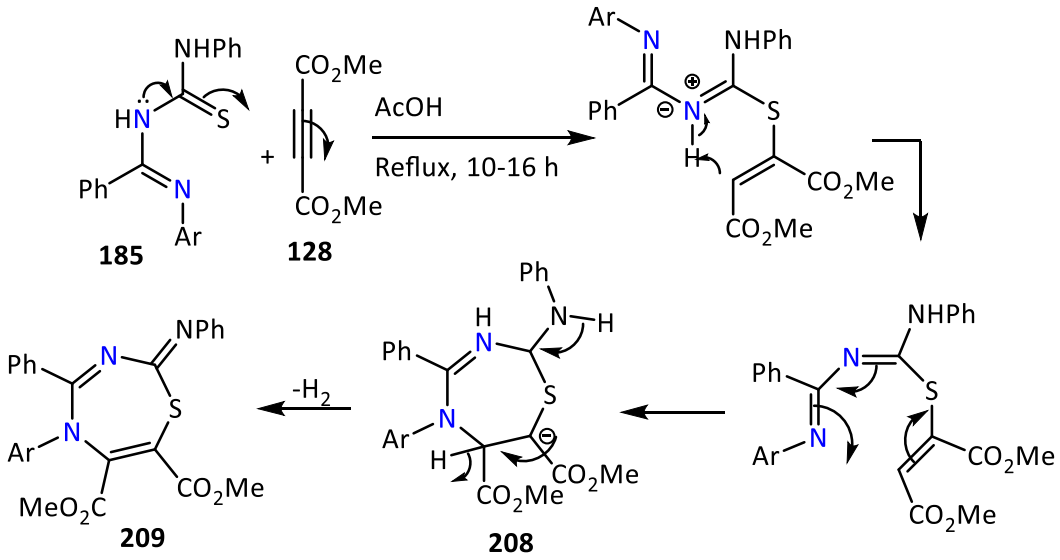
5.2.4.6. Thiatriazines. Reaction of primary aliphatic amines with benzimidazole **199** in the presence of two equivalent of thionyl chloride pyridine under reflux yielded [1,2,4,6]thiatriazino[2,3-*a*][1,3]benzimidazol-1(*2H*)-one **207** in good yields (Scheme 97).[139]



207	a	b	c	d	e	f
R^1	Me	Et	Me	Et	Me	Et
R^2	Et	Et	Pr	Pr	Ph-CH_2	Ph-CH_2

Scheme 97. Synthesis of imidazothiatriazines **207.**

5.2.5. Synthesis of seven-membered rings. 5.2.5.1. Thiadiazepines. In a different manner, the reactions between **185** and **128** in acetic acid at reflux temperature afforded the 1,3,5-thiadiazepines **209** in 65-84% yield (Scheme 98).[140]



Scheme 98. Synthesis of 1,3,5-thiadiazepines **209.**

The reaction mechanism was explained by a conjugate addition of thione lone pair to the acetylenic bond followed by hydrogen transfer and cyclization to form salt **208**). Finally, elimination of hydrogen molecule from **208** would form **209**.[140]

Abbreviations

TEA – triethylamine; Bt – benzotriazolyl; HOBt – 1-hydroxybenzotriazole; MW – microwave; EDC – 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; NCS – *N*-chlorosuccinimide; SFRC* – solvent free reaction conditions; NaHMDS – sodium hexamethyldisilazide; phen – phenanthroline; TEMPO – tetramethylpiperidinyl *N*-oxide

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