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Synthesis and biological activity of vicinal diaryl-substituted 1*H*-imidazoles

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Contents

Keywords: Imidazoles; Synthesis; Selectivity; Bioactivity; Enzyme inhibitors.
Abbreviations: Ac, acetyl; Ar, aryl; Betmip, 1-(benzotriazol-1-yl)-*N*-(triphenylphosphorylidene)-methylamine; Bn, benzyl; Bt, benzotriazol-1-yl; Bz, benzoyl; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; DAD, dimethyl acetylene dicarboxylate; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DIC, *N*,*N*″-dicyclohexylcarbodiimide; DMF, dimethylformamide; DMPA, *N*,*N*-dimethylaminopyridine; DMSO, dimethylsulfoxide; DNA, deoxyribonucleic acid; DOPA, 3,4-dihydroxyphenylalanine; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; FLT3, FMS-related tyrosine kinase 3; GSK-3β, glycogen synthase-3β; Hglur, human glucagon receptor; HIV-1, human immunodeficiency virus type 1; HMG-CoA, hydroxymethylglutaryl-coenzyme A; HMPA, hexamethylphosphoric triamide; KIT, a transmembrane tyrosine kinase receptor; LHMDS, lithium hexamethyldisilazane; LTB_4, leukotriene-B_4; MDR, multidrug resistance; Me, methyl; MW, microwave; NBS, *N*-bromosuccinimide; PDGFR-β, platelet-derived growth factor receptor-β; PKC, protein kinase C; SEM, 2-(trimethylsilyl)-ethoxymethyl; TBAF, tetrabutylammonium fluoride; TBS, *tert*-butyldimethylsilyl; TIPS, triisopropylsilyl; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TosMIC, tosylmethyl isocyanide; Ts, *p*-toluenesulfonyl; VDAs, vascular-disrupting agents; VEGFR, vascular endothelial growth factor receptor; VTAs, vascular targeting agents.

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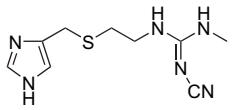
1. Introduction

Imidazoles are common scaffolds in highly significant biomolecules, including biotin, the essential amino acid histidine, histamine, the pilocarpine alkaloids,[1] and other alkaloids, which have been shown to exhibit interesting biological activities such as antimicrobial, anticryptococcal, inhibition of nitric oxide synthase, and cytotoxic activities.[2] Imidazole derivatives have also been found to possess many pharmacological properties and are widely implicated in biochemical processes. Members of this class of diazoles are known to possess NO synthase inhibition,[3] antibiotic,[4] antifungal,[5] and antiulcerative activities[6] and include compounds, which are inhibitors of 5-lipoxygenase[7] and substances with CB_1 receptor,[8] VEGF receptor I and II,[9] and neuropeptide Y antagonistic activities.[10] In addition, these heterocycles include several inhibitors of p38 MAP kinases,[11–14] a subgroup of mitogen-activated protein kinases, which are thought to be involved in a variety of inflammatory and immunological disorders, and some derivatives such as cimetidine (**1**), etomidate (**2**), and ketoconazole (**3**), which have found application in drug therapy.[15,16]



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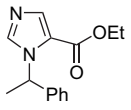

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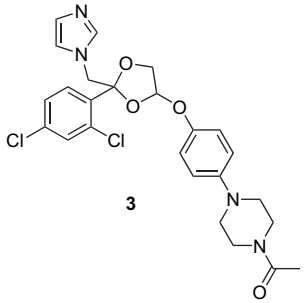


3

Recent advances in organometallic catalysis, coordination chemistry, and green chemistry have extended the boundary of imidazoles to the synthesis and application of imidazole derivatives as ionic liquids[17,18] and stable *N*-heterocyclic carbenes.[19–21] Consequently, it is not surprising that methodologies for the synthesis of imidazoles have attracted much attention from both academia and industry and an ever increasing amount of research has been focused on the preparation and functionalization of the imidazole moiety.[2,22–39] However, to the best of our knowledge, no review on the synthesis of imidazole derivatives with two aryl groups on adjacent positions has been published, even though these diazole derivatives have been found to be able to exhibit a variety of interesting biological properties and, in recent years, much attention has been turned to the synthesis and evaluation of the bioactivity of several classes of vicinal diaryl-substituted five-membered heterocycles.[40]

The purpose of this article is to provide a critical account of the procedures utilized in the literature up to the end of June 2006 for the synthesis of vicinal diaryl-substituted 1*H*-imidazoles. Furthermore, this article, which covers our recent research in this field, aims to summarize and comment on several data concerning the biological properties of these compounds. In fact, many of these heterocycle derivatives are known as inhibitors of p38 MAP kinases,[11–14] JNK3,[41,42] B-Raf kinase,[43–45] transforming growth factor β1 (TGF-β1) type 1 activin receptor-like kinase,[46–49] and acyl-CoA:cholesterol *O*-acyl transferase (ACAT).[50–55] Additionally, some of these diazoles are known as glucagon receptor antagonists,[56,57] anti-inflammatory agents,[58–72] modulators of P-glycoprotein-mediated multidrug resistance,[73–76] antagonists of the cannabinoid CB_1 receptor,[7,78,79] anti-psychotic agents with clozapine-like activities,[80] modulators of the γ-aminobutyric acid (GABA) function,[80,81] cytotoxic agents able to mimic the activity of combretastatin A-4 (CA-4) against the polymerization of tubulin,[82–85] and substances able to abolish the induction of differentiation markers.[86]

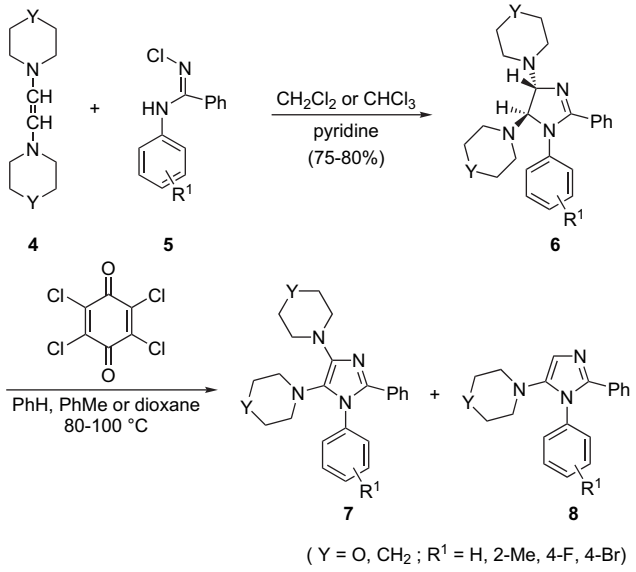
The topics covered in this review include: (i) a critical summary of the methods reported in the scientific literature for the synthesis of 1,2-, 1,5-, and 4,5-diaryl-1*H*-imidazoles; 1,2,4-, 1,2,5-, and 2,4,5-triaryl-1*H*-imidazoles and 1,2,4,5-tetraaryl-1*H*-imidazoles; and (ii) a survey of the literature data on the biological properties of these vicinal diaryl-substituted heterocycles. However, this review does not cover data reported in the patent literature and those concerning the synthesis and biological properties of vicinal diaryl-substituted compounds in which the imidazole ring is fused with another ring.

2. Synthesis of vicinal diaryl-substituted 1*H*-imidazoles

2.1. Synthesis of 1,2-diaryl-1*H*-imidazoles

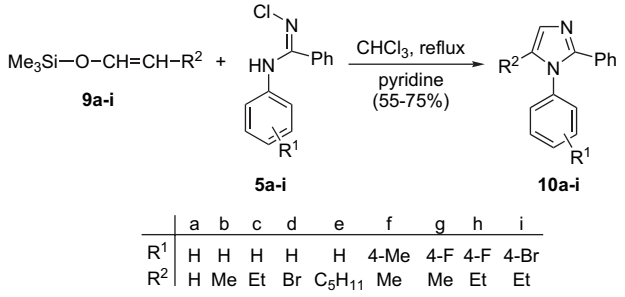
Several methods have been reported in the literature for the synthesis of 1,2-diaryl-1*H*-imidazoles and, as illustrated in this section, some of those recently developed have wide application.

Several years ago, 4,5-diamino-1,2-diaryl-1*H*-imidazoles **7** were synthesized by the reaction of 1,2-diaminoethenes **4** with *N*-aryl-*N*′-chlorobenzamidines **5**[87] in boiling CH_2Cl_2 or $CHCl_3$ in the presence of an equimolar amount of pyridine, followed by oxidation of the resulting *trans*-4,5-diamino-1,2-diaryl-4,5-dihydroimidazoles **6** with chloranil (Scheme 1).[88]



Scheme 1. Synthesis of compounds **7** and **8**.

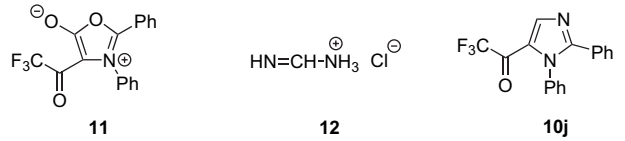
Oxidation of compounds **6** also provided 5-amino-1,2-diaryl-1*H*-imidazoles **8** in variable yields, which, however, could be obtained in excellent yields by reacting **6** with triethylammonium chloride in boiling toluene or 1,1,2-trichloroethane.[88] On the other hand, 1-aryl-2-phenyl-1*H*-imidazoles **10a–i** were synthesized in 55–75% yield by the reaction of silyl enolethers **9a–i** with the required *N*-chloro-*N*′-arylbenzamidines **5** in refluxing $CHCl_3$ in the presence of pyridine (Scheme 2).[89]



	a	b	c	d	e	f	g	h	i
R^1	H	H	H	H	H	4-Me	4-F	4-F	4-Br
R^2	H	Me	Et	Br	C_5H_{11}	Me	Me	Et	Et

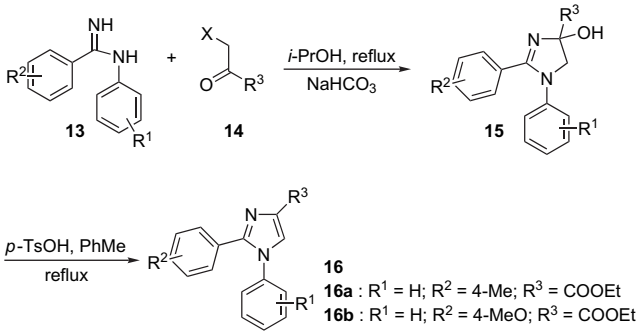
Scheme 2. Synthesis of 1,2-diaryl-1*H*-imidazoles **10a–i**.

In 1994, Kawase reported that treatment of the mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olate **11** with formamidine hydrochloride (**12**) and K_2CO_3 in DMF at 70 °C provides 1,2-diphenyl-5-trifluoroacetyl-1*H*-imidazole (**10j**) in 54% yield.[90]



Other mesoionic compounds, structurally related to **11**, were shown to be able to give a variety of 5-trifluoroacetyl and 5-perfluoroacylated imidazoles in moderate yields by treatment with amidines.[90]

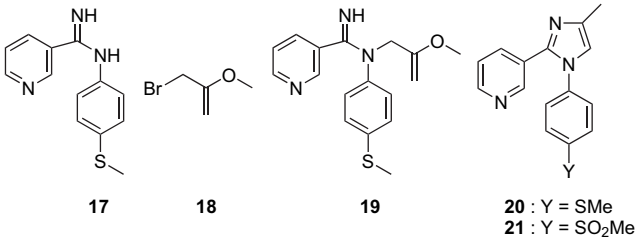
In recent years, a large number of 1,2-diaryl-1*H*-imidazoles of general formula **16**, which include orally active anti-inflammatory agents,[67,68] derivatives with clozapine-like mixed activities at dopamine D_2, serotonin, and $GABA_A$ receptors,[80] potent and selective CB_1 cannabinoid receptor antagonists,[7,91] and compounds that potentiate [^{3}H]-GABA binding to rat brain membranes,[81] have been synthesized by a strategy involving treatment of an amidine derivative **13** with a 2-halomethyl ketone **14**[92] and $NaHCO_3$ in refluxing isopropanol, followed by acid-catalyzed dehydration of the resulting hydroxyimidazoline **15** (Scheme 3).[7,67,68,80,81,91]



Scheme 3. Synthesis of 1,2-diaryl-1*H*-imidazoles **16**.

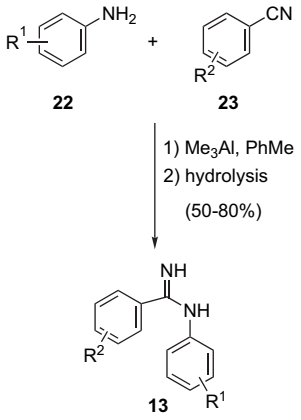
Recently, it has been found that this alkylation–cyclization reaction can furnish carbinols **15** or mixtures of these derivatives and the target imidazoles **16**.[81] However, in the case of compounds **16a** and **16b**, no trace of the corresponding carbinols was detected and the reaction proceeded directly to the required imidazoles.[81] A similar result had previously been obtained for the synthesis of compounds **16** in which R^3 is Ph and R^1 is 4-$MeOC_6H_4$.[67]

Khanna and his group used a modification of the alkylation–cyclization reaction illustrated in Scheme 3 to prepare 3{4-methyl-1-[4-(methylthio)phenyl]-1*H*-imidazol-2-yl}pyridine (**20**).[68] Specifically, amidine **17** was reacted with 1-bromo-2-methoxy-2-propene (**18**) in THF using sodium bis(trimethylsilyl)amide as a base to give regioselectively the *N*-alkylated product **19**, which was then reacted with pyridinium *p*-toluenesulfonate to produce **20** in 78% yield. This imidazole derivative was converted into the corresponding 4-methylsulfonyl derivative **21** in 29% yield by a two-step process involving a reaction with *m*-chloroperbenzoic acid and a subsequent deoxygenation with Pd/C in absolute ethanol and cyclohexene.[68]



The amidine derivatives used to prepare imidazoles **16** were usually synthesized utilizing a methodology (Scheme 4) very similar to that developed by Garigipati.[93] In particular,

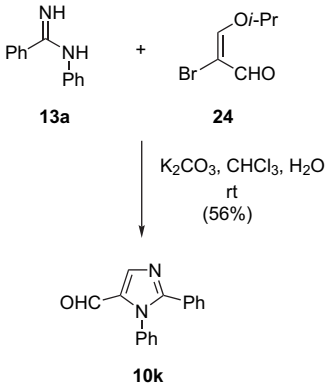
anilines **22** were reacted with trimethylalane in toluene and the resulting aluminum amides were treated with aryl cyanides **23** in toluene at 70–75 °C. Subsequent work up, which involved treatment of the cold reaction mixtures with a slurry of silica gel in $CHCl_3$ and methanol, filtration and concentration of the filtrates, furnished compounds **13** in 50–80% yield.[67,80,81]



Scheme 4. Synthesis of amidines **13**.

However, in certain cases, this protocol gave inconsistent results during the scaleup, since the presence of aluminum salts occasionally led to emulsion formation during the reaction workup. Thus, a base-catalyzed amidine formation was investigated and the best results were obtained when the amidine formation from compounds **22** and **23** was performed in THF with sodium bi(trimethylsilyl)amide as base.[68] This last protocol was used to prepare amidine **17** in 96% yield.[68]

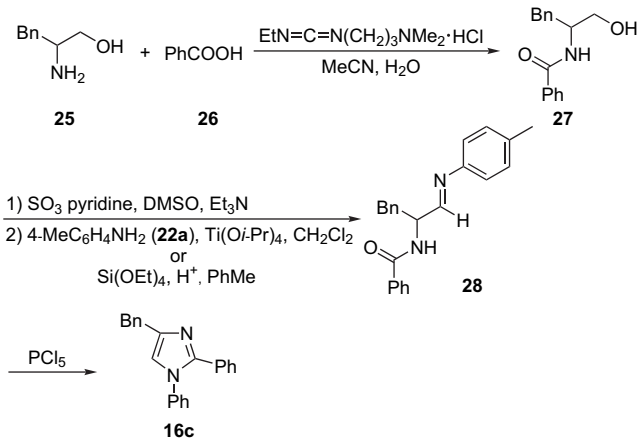
In 1997, an alkylation–cyclization sequence involving the use of amidine **13a** and α-bromoaldehyde **24** was employed to prepare imidazole **10k** highly regioselectively in 56% yield (Scheme 5).[94]



Scheme 5. Synthesis of trisubstituted 1,2-diphenyl-1*H*-imidazole **10k**.

A similar protocol was employed with satisfactory results for the synthesis of other 1,2-disubstituted 1*H*-imidazole-5-carboxyaldehydes.[94]

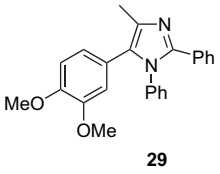
In 2004, the trisubstituted 1,2-diaryl-1*H*-imidazole **16c** was synthesized in 65% overall yield via a four-step procedure involving N-acylation of aminoalcohol **25** with benzoic acid (**26**), oxidation of the resulting compound **27**, formation of imine **28**, and cyclization (Scheme 6).[95]



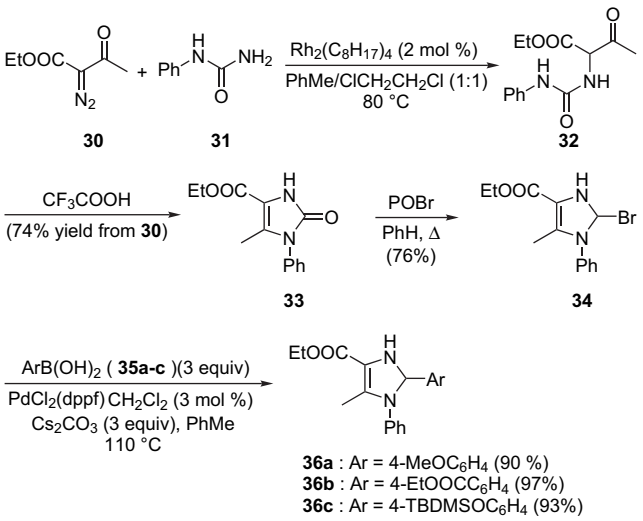
Scheme 6. Synthesis of the trisubstituted 1,2-diphenyl-1*H*-imidazole **16c**.

This methodology was also used for the synthesis of the 1,2,5-triaryl-1*H*-imidazole derivative **29** in 32% overall yield.[95]

Recently, Clapham and co-workers disclosed a four-step reaction sequence for the synthesis of the tetrasubstituted 1,2-diaryl-1*H*-imidazoles **36a–c**.[96]

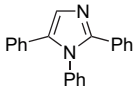


The Rh-catalyzed reaction between the diazocarbonyl compound **30** and *N*-phenylurea (**31**) was used as a key step of this sequence. The resulting compound **32** was cyclized with trifluoroacetic acid to give imidazolone **33**, which was then converted into the 2-bromo-1-phenyl-1*H*-imidazole derivative **34**. Finally, Pd-catalyzed Suzuki-type reactions were employed to prepare compounds **36a–c** from **34** and **35a–c** (Scheme 7).[96]



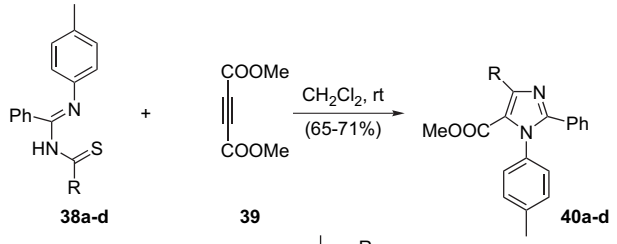
Scheme 7. Synthesis of tetrasubstituted 1,2-diaryl-1*H*-imidazoles **36a–c**.

A similar protocol was used to prepare 1,2,5-triphenyl-1*H*-imidazole (**37a**).[96]



37a

In 2004, 1,2-diaryl-1*H*-imidazoles **40a–d** were concisely synthesized in 65–71% yield by the reaction of thioamides **38a–d** with dimethyl acetylenedicarboxylate (**39**) in CH_2Cl_2 at room temperature (Scheme 8).[97]



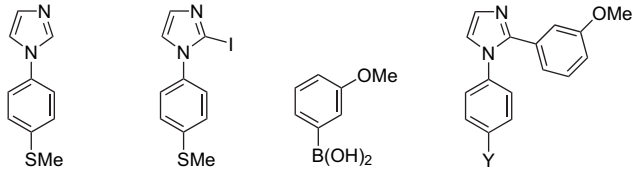
	R
a	NMe_2
b	$N(CH_2)_4O$
c	$N(CH_2)_4$
d	$N(CH_2)_5$

Scheme 8. Synthesis of tetrasubstituted 1,2-diaryl-1*H*-imidazoles **40a–d**.

The Mahajan group had previously shown that a variety of 1-aryl-2-phenyl-4-secondary amino or methyl-1*H*-imidazoles **42a–h** can be prepared in good yields by treatment of 1-aryl-4-secondary amino-4-methylthio or methyl-2-phenyl-1,3-diazabuta-1,3-dienes **41a–h** with the Simmons–Smith reagent generated from diiodomethane and a zinc–copper couple in ether (Scheme 9).[98]

In recent years, several interesting procedures for the synthesis of 1,2-diaryl-1*H*-imidazoles that involve the elaboration of imidazole derivatives instead of the construction of the heteroaromatic ring, have also been reported in the literature. Thus, 2-(3-methoxy)phenyl-1-(4-methylthio)phenyl-1*H*-imidazole (**45a**) has been prepared in 62% overall yield by lithiation of 1-aryl-1*H*-imidazole **43** at position 2 followed by quenching with iodine and Pd-catalyzed cross-coupling of the resulting 2-iodoimidazole **44** with 3-methoxyphenylboronic acid (**35d**).[99] Compound **45a** has then been converted into the corresponding sulfone **45b** by treatment with oxone®.[99]

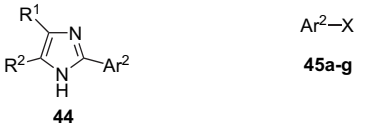
On the other hand, several 1,2-diaryl-1*H*-imidazoles of general formula **47** have conveniently been prepared via



43 **44** **35d**

45a : Y = SMe
45b : Y = SO_2Me

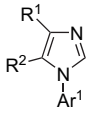
Cu-catalyzed N-arylation of the corresponding 2-aryl-1*H*-imidazoles **44** or highly regioselective transition metal-mediated direct C-2 arylation of the required 1-aryl-1*H*-imidazoles **46** with aryl halides **45**.



44
44a : $R^1 = R^2 = H$; $Ar^2 = Ph$

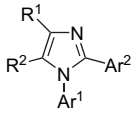
45a-g

	Ar^2	X
a	Ph	I
b	$4\text{-}NO_2C_6H_4$	I
c	$3,4,5\text{-}(MeO)_3C_6H_2$	Br
d	$4\text{-}MeOC_6H_4$	I
e	$4\text{-}MeOC_6H_4$	Br
f	$4\text{-}CF_3C_6H_4$	Br
g	Ph	Br



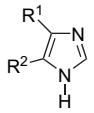
46a-h

	R^1	R^2	Ar^1
a	H	H	Ph
b	H	H	$3,4,5\text{-}(MeO)_3C_6H_2$
c	H	H	$4\text{-}MeOC_6H_4$
d	H	H	$4\text{-}MeSO_2C_6H_4$
e	H	H	2-naphthyl
f	Me	H	$4\text{-}MeSO_2C_6H_4$
g	Cl	Cl	$4\text{-}MeSO_2C_6H_4$
h	H	Me	$4\text{-}MeSO_2C_6H_4$



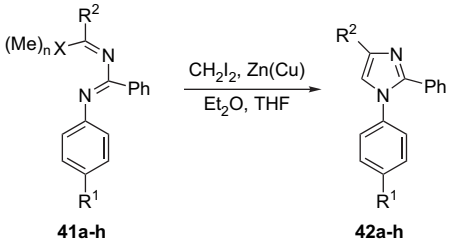
47a-m

	R^1	R^2	Ar^1	Ar^2
a	H	H	Ph	Ph
b	H	H	$3,4,5\text{-}(MeO)_3C_6H_2$	$4\text{-}NO_2C_6H_4$
c	H	H	$3,4,5\text{-}(MeO)_3C_6H_2$	$4\text{-}MeOC_6H_4$
d	H	H	$4\text{-}MeOC_6H_4$	$4\text{-}MeOC_6H_4$
e	H	H	Ph	$4\text{-}CF_3C_6H_4$
f	H	H	Ph	$4\text{-}MeOC_6H_4$
g	H	H	$4\text{-}MeOC_6H_4$	$3,4,5\text{-}(MeO)_3C_6H_2$
h	H	H	$4\text{-}MeSO_2C_6H_4$	$3,4,5\text{-}(MeO)_3C_6H_2$
i	H	H	$4\text{-}MeSO_2C_6H_4$	$4\text{-}MeOC_6H_4$
j	H	H	$3,4,5\text{-}(MeO)_3C_6H_2$	2-naphthyl
k	H	H	2-naphthyl	$3,4,5\text{-}(MeO)_3C_6H_2$
l	Me	H	$4\text{-}MeSO_2C_6H_4$	$4\text{-}ClC_6H_4$
m	Cl	Cl	$4\text{-}MeSO_2C_6H_4$	$4\text{-}MeOC_6H_4$



48a : $R^1 = R^2 = H$

$Ph\text{-}B(OH)_2$
35e



	R^1	R^2	X	n
a	H	NMe_2	S	1
b	Me	NMe_2	S	1
c	H	$N(CH_2)_5$	S	1
d	Me	$N(CH_2)_5$	S	1
e	Me	$N(CH_2)_4O$	S	1
f	Me	$N(CH_2)_4$	S	1
g	H	Me	N	2
h	Me	Me	N	2

41a-h **42a-h**

Scheme 9. Synthesis of 1,2-diaryl-1*H*-imidazoles **42a–h**.

The first of these approaches was used by Sezen and Sames[100] to prepare 1,2-diphenyl-1*H*-imidazole (**47a**) in 82% yield by CuI-catalyzed N-arylation of 2-phenyl-1*H*-imidazole (**44a**) with iodobenzene (**45a**) in dioxane according to the general procedure described by Buchwald and co-workers for N-arylation of nitrogen heterocycles.[101] Compound **47a** was also synthesized in 89% yield by coupling of **44a** with phenylboronic acid (**35e**) in CH_2Cl_2 at room temperature in the presence of a catalytic amount of $[Cu(OH)\cdot TMEDA]_2Cl_2$[100] according to a literature procedure.[102,103]

The second strategy, which involves a regioselective C_{sp2}–C_{sp2} bond-forming reaction by direct arylation of a C–H bond of a 1-aryl-1*H*-imidazole, is a very attractive, practical, and convenient alternative to the approaches in which the imidazolyl–aryl bond is formed by a transition metal-catalyzed cross-coupling reaction of a 2-imidazolyl organometallic with an aryl halide or of an arylmetal with a 2-haloimidazole. In fact, these approaches, which require the pre-activation of both partners of these cross-coupling reactions by installation of stoichiometric amounts of activating agents, are time consuming and economically inefficient and wasteful, since they involve the subsequent disposal of the activating groups. This simplest second strategy was first used by Wang and co-workers[82] for the synthesis of 1,2-diaryl-1*H*-imidazole **47b** in 31% yield via reaction of 1-aryl-1*H*-imidazole **46b** with 2 equiv of aryl iodide **45b** in DMF at 140 °C in the presence of 2 equiv of Cs_2CO_3, 2 equiv of CuI, and 0.67 equiv of PPh_3. Compound **46b** was obtained in 53% yield by the reaction of imidazole (**48a**) with 0.83 equiv of aryl bromide **45c** in DMF at 100 °C in the presence of 0.21 equiv of CuI and 1.08 equiv of K_2CO_3.[82,104–106]

The second strategy was also used by our research group. In fact, we recently reported that 1,2-diaryl-1*H*-imidazoles **47a** and **47c**–**m** can be regioselectively synthesized in moderate-to-high yields by direct coupling of 1-aryl-1*H*-imidazoles **46a**–**h** with the required aryl halides **45** in DMF at 140 °C in the presence of 2 equiv of CuI, 2 equiv of CsF, and 5 mol % $Pd(OAc)_2$ under ligandless conditions.[83] Interestingly, 1,2-diaryl-1*H*-imidazole **47l**, which is a selective COX-2 inhibitor,[67] was prepared through this procedure in 62% yield.[83]

Recently, an improvement of this protocol has been used to prepare 1,2-diaryl-1*H*-imidazoles **47d** and **47e** in 66 and 84% yield, respectively. Specifically, these heterocycles were synthesized by the reaction of **46a** and **46f** with aryl iodide **45d** in DMF at 140 °C in the presence of 5 mol % $Pd(OAc)_2$ and 2 equiv of CuI under base-free and ligandless conditions.[84,107] It should also be noted that this reliable new protocol for the direct and totally regioselective C-2 arylation of 1-aryl-1*H*-imidazoles and other azoles, which does not produce byproducts and thus allows the required imidazole derivatives to be obtained in high purity, has the potential to be of great benefit in the rapid, convenient, and efficient synthesis of substituted imidazoles. Interestingly, this protocol was found to be also suitable for the regioselective arylation of heterocyclic substrates containing base-sensitive groups, such as the NH group of imidazole, benzimidazole or indole, without prior protection.[84,107,108]

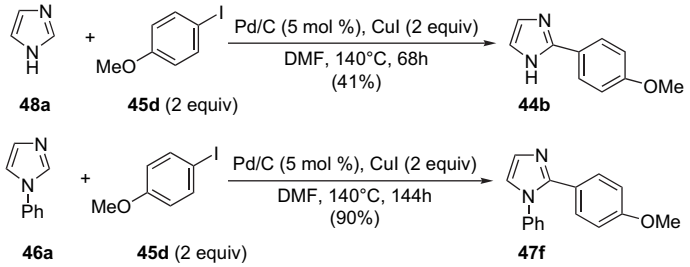
More recently, we also established that the regioselective C-2 arylation of imidazole (**48a**) or 1-aryl-1*H*-imidazoles **46** with aryl iodides can conveniently be performed in DMF at 140 °C in the presence of 2 equiv of CuI under base-free and ligandless conditions using 5 mol % Pd/C in place of 5 mol % $Pd(OAc)_2$ as the catalyst.[107,108] This procedure, in which Pd/C was removed by filtration at the end of the reaction and did not contaminate the reaction product, furnished compound **44b** in 41% yield from **48a** and **45d** and compound **47f** in 90% yield from **46a** and **45d** (Scheme 10).[107,108]

On the other hand, in 2004, 1,2-diaryl-1*H*-imidazoles **51a** and **51b** were synthesized by Revesz and co-workers by a classical nucleophilic substitution reaction.[109] Specifically, the potassium salts, obtained by treatment of 4(5)-substituted 2-aryl-1*H*-imidazoles **49a** and **49b** with potassium bis(trimethylsilyl)amide, were reacted with 4-chloro-2-(methylthio)pyrimidine (**50**) in a 2:1 mixture of DMF and toluene at 80 °C to give compounds **51a** and **51b** in 70–80% yield (Scheme 11).[109]

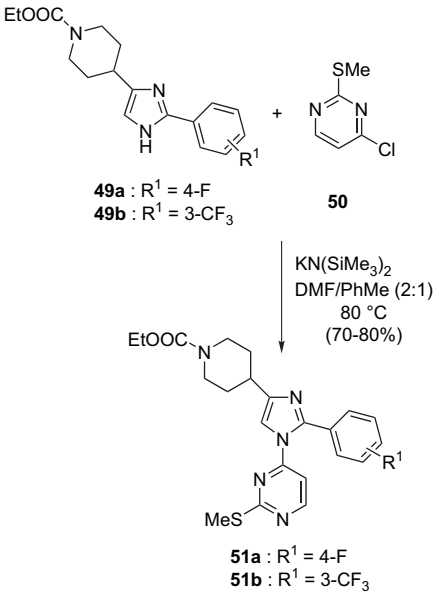
1,2-Diaryl-1*H*-imidazoles have also been reported to be able to undergo structural modification by transition metal-catalyzed C–H bond functionalization. In fact, in 2003, it was claimed that 1,2-diphenyl-1*H*-imidazole (**47a**) can undergo a highly regioselective C-2′ arylation reaction by treatment with 1.2 equiv of an aryl bromide **45** in DMF at 150 °C in the presence of 1.2 equiv of Cs_2CO_3 and 5 mol % $Rh(acac)(CO)_2$ to give compounds **52** in high yield (Scheme 12).[100a]

However, in 2006, one of the authors of this study found that this result could not be reproduced. Thus, the publication was withdrawn.[100b]

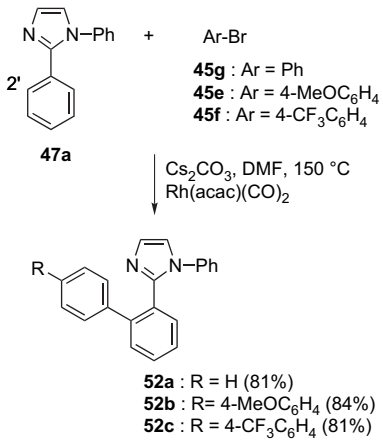
Nevertheless, it is worth mentioning that examples of transition metal-catalyzed arylation reactions of *o*-heteroarylarenes, that involve the activation of an aromatic C–H



Scheme 10. Synthesis of compounds **44b** and **47f** from **48a** and **46a**, respectively.



Scheme 11. Synthesis of 1,2-diaryl-1*H*-imidazoles **51a** and **51b**.

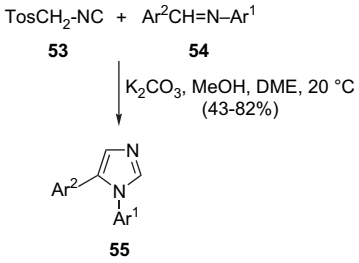


Scheme 12. Synthesis of 1-phenyl-2-aryl-1*H*-imidazoles **52a**–**c**.

bond and in which the heteroarene moiety is an effective directing group for the arylation reaction, have been reported in the literature.[100c,d]

2.2. Synthesis of 1,5-diaryl-1*H*-imidazoles

Few synthetic strategies have been employed in the literature for the synthesis of 1,5-diaryl-1*H*-imidazoles, but one of the most versatile is that developed in 1977 by van Leusen.[110,111] Later, this strategy was employed to prepare a large variety of pharmacologically interesting compounds that include COX-2-selective inhibitors,[70,112] substances with potent antitubulin and cytotoxic activities[82] and derivatives, which display inhibitory activity against COX-2-catalyzed PGE_2 production.[72] In particular, the van Leusen group found that the base-induced [3+2] cycloaddition of *p*-toluenesulfonylmethyl isocyanide (TosMIC) (**53**) to *N*-(arylidene)anilines **54** in a protic medium occurs with concomitant elimination of *p*-toluenesulfinic acid to give 1,5-diaryl-1*H*-imidazoles **55** in satisfactory yields (Scheme 13).[38,110,111,113] TosMIC is a commercially available stable solid, which can be prepared from *p*-toluenesulfonic acid in a two-step process.[114,115]

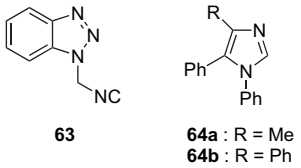


Scheme 13. Synthesis of 1,5-diaryl-1*H*-imidazoles **55** from TosMIC (**53**) and imines **54**.

In 2001, the reaction illustrated in Scheme 13 was used by Almansa and co-workers as a key step of the preparation of UR-8880 (**62**),[112] a COX-2-selective inhibitor, which in a human whole-blood assay was found to be nine times more potent than celecoxib and four times more potent than rofecoxib. Compound **63** was synthesized in 44% yield from arylsulfonyl chloride **56** (Scheme 14).[112] In particular, the reaction of **56** with *tert*-butylamine (**57**) gave sulfonamide **58**, which was transformed into compound **59** by treatment with aqueous KOH in MeOH.

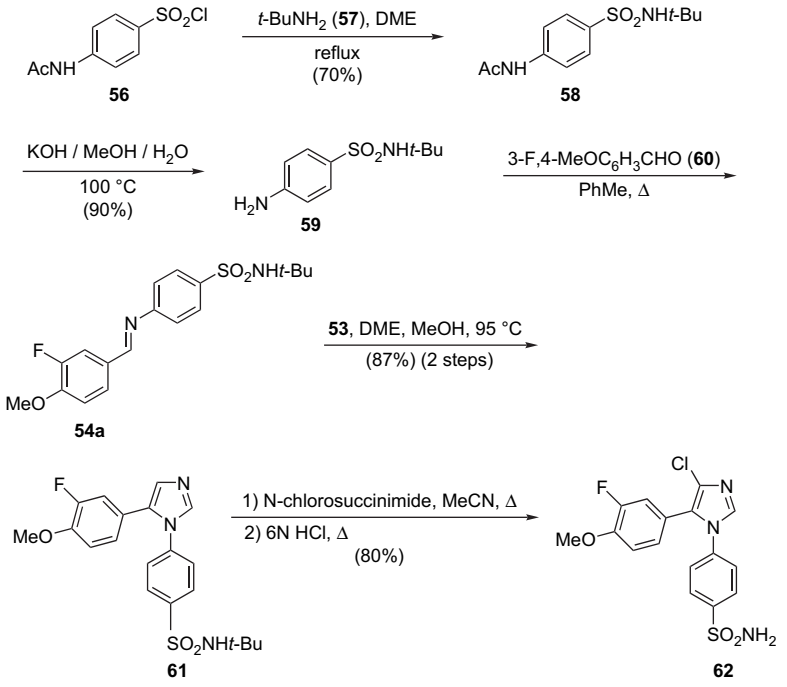
The [3+2] cycloaddition of **53** to aldimine **54a**, obtained from arylamine **59** and aldehyde **60**, followed by elimination of *p*-toluenesulfinic acid gave the imidazole derivative **61**, which was then converted into the required compound **62** by regioselective chlorination with *N*-chlorosuccinimide.

In 1997, Katritzky and co-workers compared TosMIC (**53**) and benzotriazol-1-yl-methyl isocyanide (BetMIC) (**63**) as to their synthetic utilities for the synthesis of 1,5-diaryl- and 1,4,5-triaryl-1*H*-imidazoles and found that these reagents are complementary.[116] In fact, 1,4,5-trisubstituted 1,5-diaryl-1*H*-imidazoles **64a** and **64b**, which could not be obtained from **53**,[110,111] were prepared from **63** in 67 and 23% yield, respectively.[116]

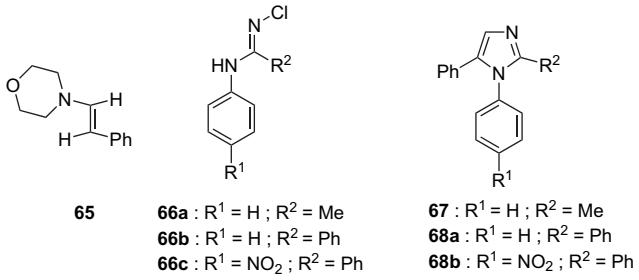


These authors also observed that the best results for the reaction of diarylimines **54** with TosMIC were obtained when an electron-withdrawing group was present on at least one of the aryl substituents.[116]

In 1976, 2-methyl-1,5-diphenyl-1*H*-imidazole (**67**) and 2,4,5-triaryl-1*H*-imidazoles **68a** and **68b** were synthesized in good yields by treatment of β-morpholinostyrene **65** with *N*-chloroamidines **66a**, **66b**, and **66c**, respectively, in boiling $CHCl_3$ in the presence of an equimolar amount of pyridine.[117]

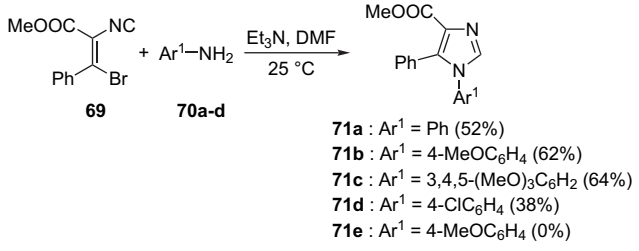


Scheme 14. Synthesis of UR-8880 (**62**).



Compounds **66a–c** were obtained almost quantitatively by the reaction of the corresponding amidines with *N*-chlorosuccinimide in CH_2Cl_2 at room temperature.[117]

A few years later, methyl 1,5-diaryl-1*H*-imidazole-4-carboxylates **71a–d** were synthesized by the reaction of methyl (*Z*)-3-bromo-2-isocyano-3-phenylacrylate (**69**) with 1.2 equiv of arylamines **70a–d** in DMF at 25 °C in the presence of 1 equiv of Et_3N (Scheme 15).[118]



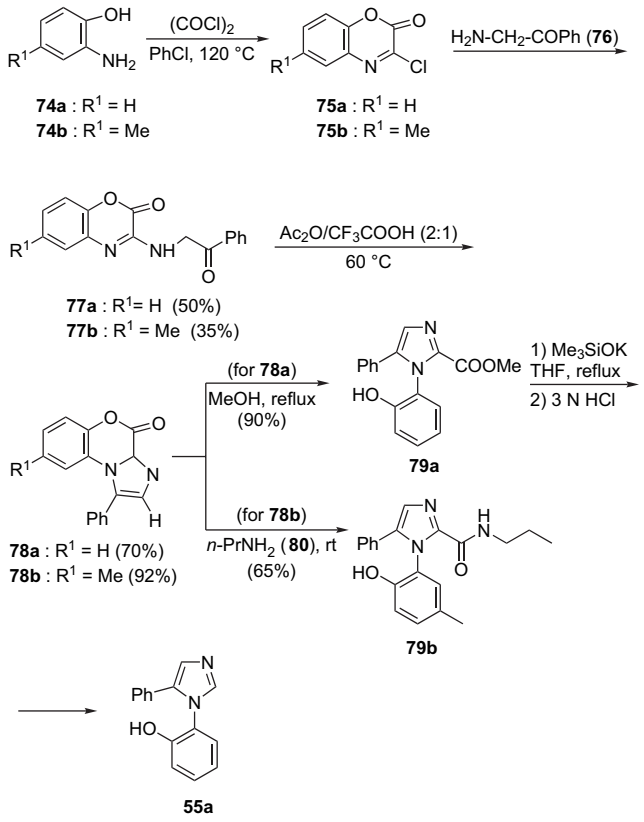
Scheme 15. Synthesis of methyl 1,5-diaryl-1*H*-imidazole-4-carboxylates **71a–d**.

However, the reaction between **69** and amine **70e** that contains an electron-withdrawing group did not proceed to **71e**. Another drawback of this synthetic method was that the preparation of compound **69** involved a three-step sequence in which methyl isocyanoacetate (**72**) and benzaldehyde (**73a**) were the starting materials.[118]

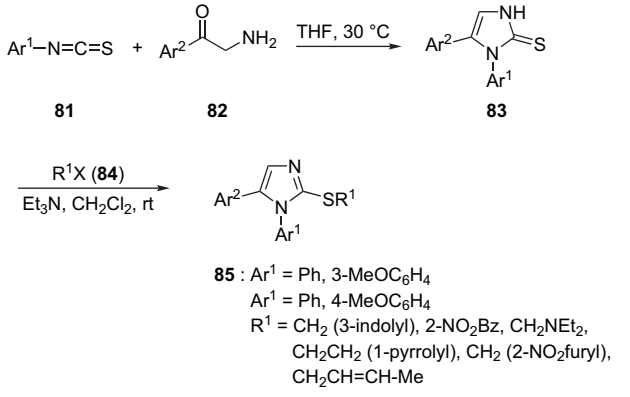
A multi-step reaction sequence was also devised by Medaer and Hoornaert for assembling the imidazole ring of 1,2,5-trisubstituted 1,5-diaryl-1*H*-imidazoles **79a** and **79b** (Scheme 16).[119]

In particular, *o*-aminophenols **74a**,**b** were reacted with oxalyl chloride in chlorobenzene to give 3-chloro-2*H*-1,4-benzoxazin-2-ones **75a**,**b**. Treatment of these compounds with aminoketone **76** furnished 3-(2-phenyl-2-oxoethylamino)-2*H*-1,4-benzoxazin-2-one (**77a**) and 6-methyl-3-(2-phenyl-2-oxoethylamino)-2*H*-1,4-benzoxazin-2-one (**77b**), respectively, which underwent ring closure by treatment with a mixture of acetic anhydride and trifluoroacetic acid to give 1-phenyl-4-imidazo[2,1-*c*][1,4]benzoxazin-4-ones **78a** and **78b**, respectively. Finally, cleavage of the lactone ring of these compounds with methanol and propylamine (**80**) furnished the required imidazoles **79a** and **79b**. On the other hand, treatment of **79a** with the potassium salt of trimethylsilanol in refluxing THF, followed by reaction with 3 N HCl, produced imidazole **55a** in 40% yield.[119]

In 2002, a combinatorial library of substituted 2-thio-1,5-diaryl-1*H*-imidazoles **85** was synthesized by alkylation with **84** of 2,3-dihydroimidazole-2-thiones **83** obtained via reaction of aryl isothiocyanates **81** with β-aminoketones **82** (Scheme 17).[120] Most of the yields were included between 45 and 98% and the synthesized compounds were purified at a purity higher than 85% using a mass-triggered preparative LC/MS apparatus.[120]

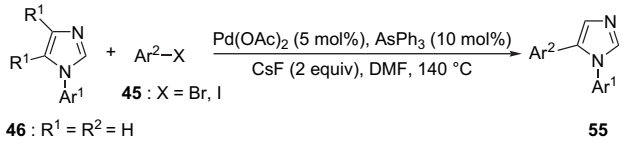


Scheme 16. Synthesis of 1,5-diaryl-1*H*-imidazoles **55a** and **79a**,**b**.



Scheme 17. Synthesis of substituted 2-thio-1,5-diaryl-1*H*-imidazoles **85**.

Recently, the attention of our research group has been directed to the development of an effective procedure to prepare 1,5-diaryl-1*H*-imidazoles **55** by direct arylation of 1-aryl-1*H*-imidazoles **46** (where R^1 and R^2 is H) with aryl halides **45**.[84] After a preliminary study aimed at screening the reaction conditions most suitable for a highly regioselective C-5 arylation of 1-phenyl-1*H*-imidazole (**46a**) with 4-iodoanisole (**45d**), it was found that a variety of imidazoles **55** could be regioselectively synthesized in moderate yields by direct coupling of 1-aryl-1*H*-imidazoles **46** (where R^1 and R^2 is H) with activated, unactivated, and moderately deactivated aryl iodides or bromides **45** in DMF at 140 °C in the presence of 2 equiv of CsF as the base and a catalyst precursor consisting of a mixture of 5 mol % $Pd(OAc)_2$ and 10 mol % $AsPh_3$ (Scheme 18).[84]



[Ar^1 = Ph, 4-$MeOC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, 4-ClC_6H_4;
Ar^2 = Ph, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 3-F, 4-$MeOC_6H_3$, 3,4,5-$(MeO)_3C_6H_2$]

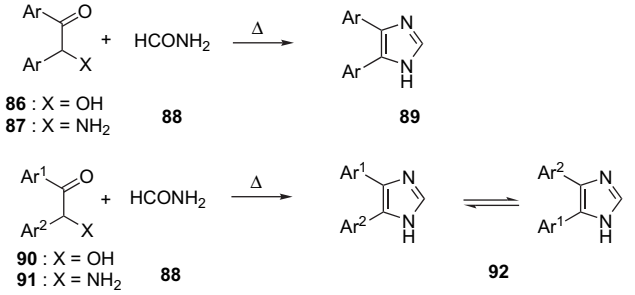
Scheme 18. Synthesis of 1,5-diaryl-1*H*-imidazoles **55** from 1-aryl-1*H*-imidazoles **46**.

This simple and practical preparation method favorably competes with those discussed in this section, which are based on the construction of the imidazole ring. However, it suffers from a limitation due to the fact that the Pd-catalyzed C-5 arylation of 1-aryl-1*H*-imidazoles **46** is hampered by the presence of a sulfur atom in the electrophile or the imidazole substrate.[84]

2.3. Synthesis of 4,5-diaryl-1*H*-imidazoles

The 4,5-diaryl-1*H*-imidazole derivatives include several biologically active compounds. Thus, a variety of synthetic procedures have been devised for the synthesis of this class of heterocycles from the early 1950s.

In 1953, Brodereck and Theilig[121] reported that symmetrical and unsymmetrical 4,5-diaryl-1*H*-imidazoles of general formula **89** and **92**, respectively, can be synthesized by the reaction of a very large molar excess of formamide (**88**) with the appropriate benzoins, **86** or **90**,[122] or 2-amino-1,2-diarylethanones, **87** or **91** (Scheme 19).[123]

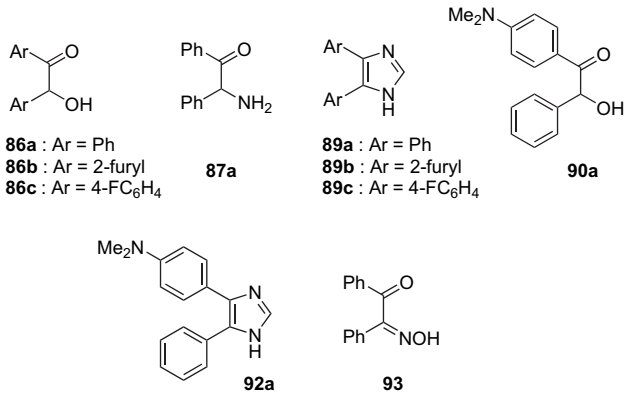


Scheme 19. Synthesis of symmetrical and unsymmetrical 4,5-diaryl-1*H*-imidazoles **89** and **92**, respectively.

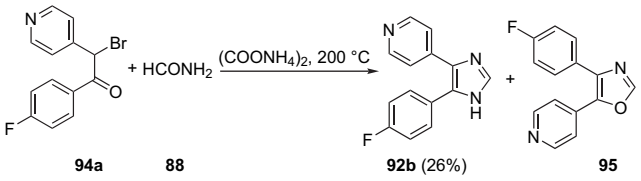
Specifically, 4,5-diphenyl-1*H*-imidazole (**89a**), 4,5-di(2-furyl)-1*H*-imidazole (**89b**), and 4(5)-(4-dimethylaminophenyl)-5(4)-phenyl-1*H*-imidazole (**92a**) were prepared in 91, 89, and 62% yield by treatment of formamide (**88**) with benzoin (**86a**), furoin (**86b**), and 4-dimethylaminobenzoin (**90a**), respectively.[121] Compound **89a** could also be prepared in 90% yield by the reaction of desylamino hydrochloride (**87a**·HCl) with **88** and in 71% yield by treatment of benzyl monoxime (**93**) with **88** at 70 °C in the presence of formic acid and sodium hydrosulfite.[121]

In 1985, the Brodereck protocol was used to prepare 4,5-diaryl-1*H*-imidazole **89c** from **86c** in 63% yield.[124]

In 2000, researchers at Novartis employed a modification of the Brodereck protocol to synthesize 4,5-diaryl-1*H*-imidazole **92b** from α-bromoketone **94a** in 26% yield



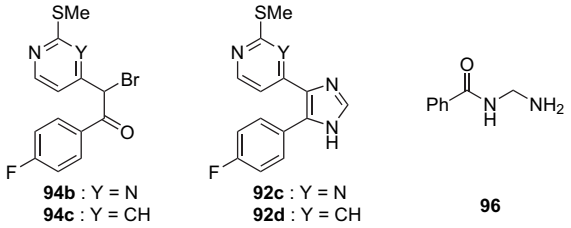
(Scheme 20).[125] This modification involves treatment of an α-bromoketone with ammonium oxalate and formamide (**88**) at 200 °C.



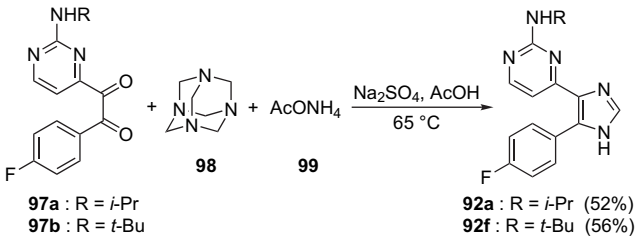
Scheme 20. Synthesis of compound **92b**.

The low yield of this reaction was due to the fact that this imidazole ring-forming process produced a 1:1 mixture of the required heterocycle and 4,5-diaryloxazole **95**.[125]

More recently, modest yields have also been obtained in the preparation of 4,5-diaryl-1*H*-imidazoles **92c** and **92d** by a cyclization reaction of α-bromoketones **94b** and **94c**, respectively, with ammonium formate and formic acid.[109]



A low yield was also obtained in the synthesis of **89a** by another modification of the Brodereck reaction involving treatment of benzoin (**86a**) with *N*-(aminomethyl)benzamide (**96**)[126] in acetic acid at 50 °C.[127] On the contrary, unsymmetrical 4,5-diaryl-1*H*-imidazoles **92e** and **92f**, respectively, were obtained in satisfactory yields when 1,2-diketones **97a** and **97b** were reacted with hexamethylenetetramine (**98**), 5 equiv of ammonium acetate (**99**), and Na_2SO_4 in acetic acid at 65 °C (Scheme 21).[128] Compounds **97a**,**b** were prepared by oxidation of the corresponding alkynes at room temperature with 3.8 equiv of a very finely powdered form of $KMnO_4$ in a solution of water and acetone buffered with $NaHCO_3$ and $MgSO_4$.[128,129]



Scheme 21. Synthesis of compounds **92e** and **92f**.

As regards the synthesis of 1,2-diarylethanediones, it should be mentioned that, besides the oxidation of alkynes, several other methods have been developed to prepare these compounds, which are useful starting materials for the synthesis of a variety of 4,5-diaryl-1*H*-imidazoles. These methods include: (i) the oxidation of precursors such as benzoins,[130–132] hydrobenzoins,[133] stilbenes,[63] methylene ketones,[134–136] and α-benzotriazolyl ketones;[137] (ii) the samarium iodide-mediated reductive coupling of α-ketoamides[138] or *N*-acylbenzotriazoles;[139] (iii) the indium-mediated reductive coupling of α-ketocyanides;[140] (iv) the ytterbium iodide-mediated reductive coupling of α-ketocyanides;[141] and (v) the reaction of 1,1′-oxalyldiimidazole with 2 equiv of aryl Grignard reagents.[142]

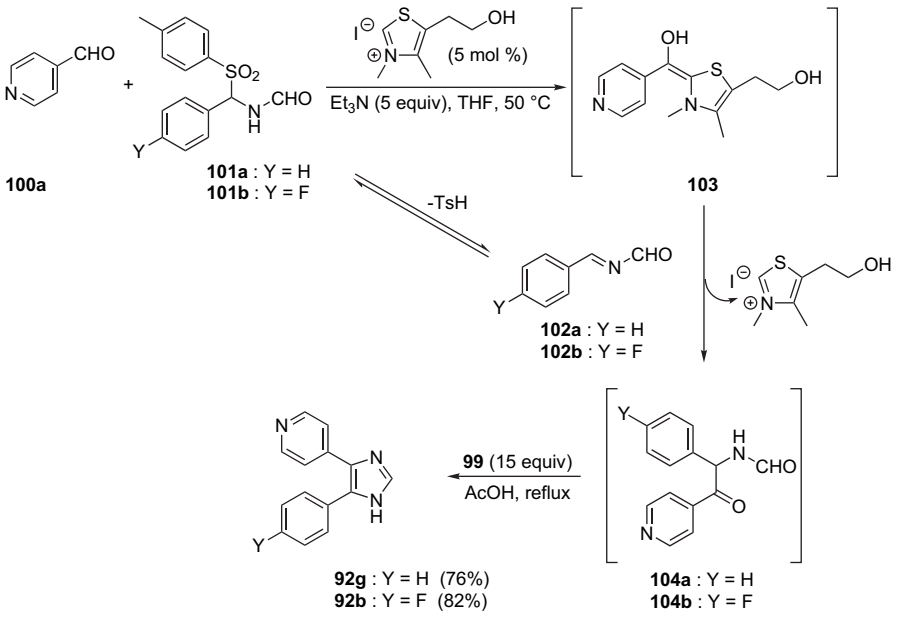
Another useful procedure for producing unsymmetrical 4,5-diaryl-1*H*-imidazoles of general formula **92** involves the cyclization reaction of α-(*N*-acylamino)ketones.[143] This reaction has recently been used as a key step of an elegant one-pot process in which two α-(*N*-acylamino)ketones, compounds **104a** and **104b**, were generated by the thiazolium-catalyzed addition of heteroarylaldehyde **100a** to the *N*-acyl derivatives **102a** and **102b** prepared in situ from the corresponding α-amidosulfones **101a** and **101b**, respectively.[143,144] Scheme 22 illustrates the synthesis of the unsymmetrical 4,5-diaryl-1*H*-imidazoles **92g** and **92b** from aldehyde **100** and α-amidosulfones **101a** and **101b**, respectively, via cyclization of the α-(*N*-acylamino)ketones **104a** and **104b** with ammonium acetate.[143]

This methodology was also applied to the efficient one-pot synthesis of 1-alkyl-4,5-diaryl-1*H*-imidazoles **105a–d**, 2-cycloalkyl-4,5-diaryl-1*H*-imidazole **106a**, 2,4-diphenyl-5-(pyridyn-4-yl)-1*H*-imidazole (**107a**), and 1-alkyl-2,4,6-triaryl-1*H*-imidazoles **108a–c**.[143]

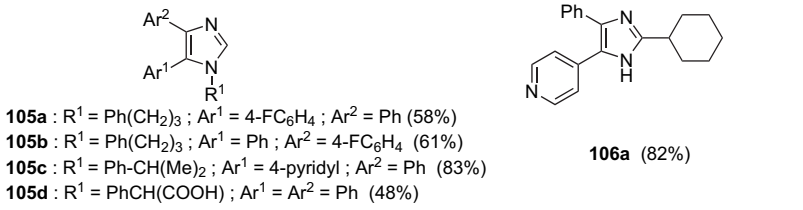
The synthesis of 4,5-diaryl-1*H*-imidazole-2-thiones **109a–h** has also caught the attention of the heterocyclic community over the last few years. In fact, these compounds are direct precursors to several biologically active 2-alkylthio-4,5-diaryl-1*H*-imidazoles.[60,123e,145–149]

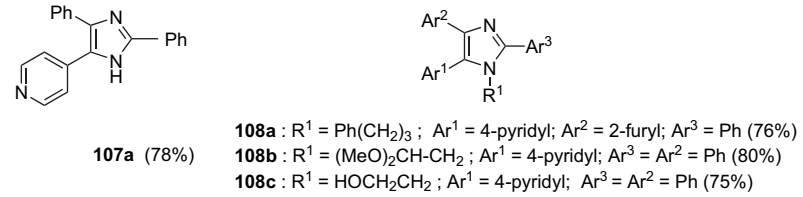
In 1984, Lantos and co-workers synthesized 4-aryl-5-(4-pyridyl)-1*H*-imidazole-2-thiones **109a** and **109b** by the reaction of pyridoins **86d** and **86e**, respectively, with thiourea (**110**) in refluxing DMF (Scheme 23).[145]

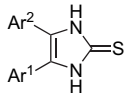
Later, compounds **109c** and **109d** were prepared by classical chemistry[60] by condensation of α-hydroxyketone **86a** with **110** in *n*-hexanol or DMF at 160 °C and by the reaction of α-diketone **97c** with a large molar excess of ammonium thiocyanate (**111**) in *n*-hexanol at 160 °C, respectively.[146]



Scheme 22. Synthesis of unsymmetrical 4,5-diaryl-1*H*-imidazoles **92b** and **92g**.

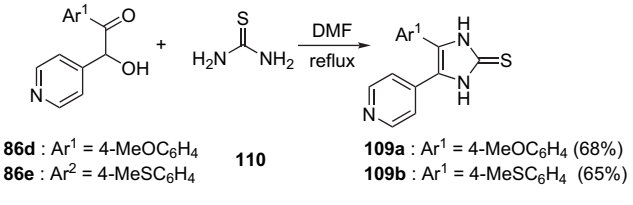




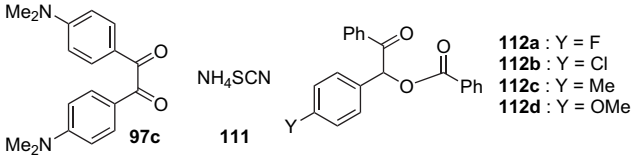


109a-h

109	Ar^1	Ar^2
a	4-$MeOC_6H_4$	4-pyridyl
b	4-$MeSC_6H_4$	4-pyridyl
c	Ph	Ph
d	4-$Me_2NC_6H_4$	4-$Me_2NC_6H_4$
e	4-FC_6H_4	Ph
f	4-ClC_6H_4	Ph
g	4-MeC_6H_4	Ph
h	4-$MeOC_6H_4$	Ph



Scheme 23. Synthesis of compounds **109a**,**b**.



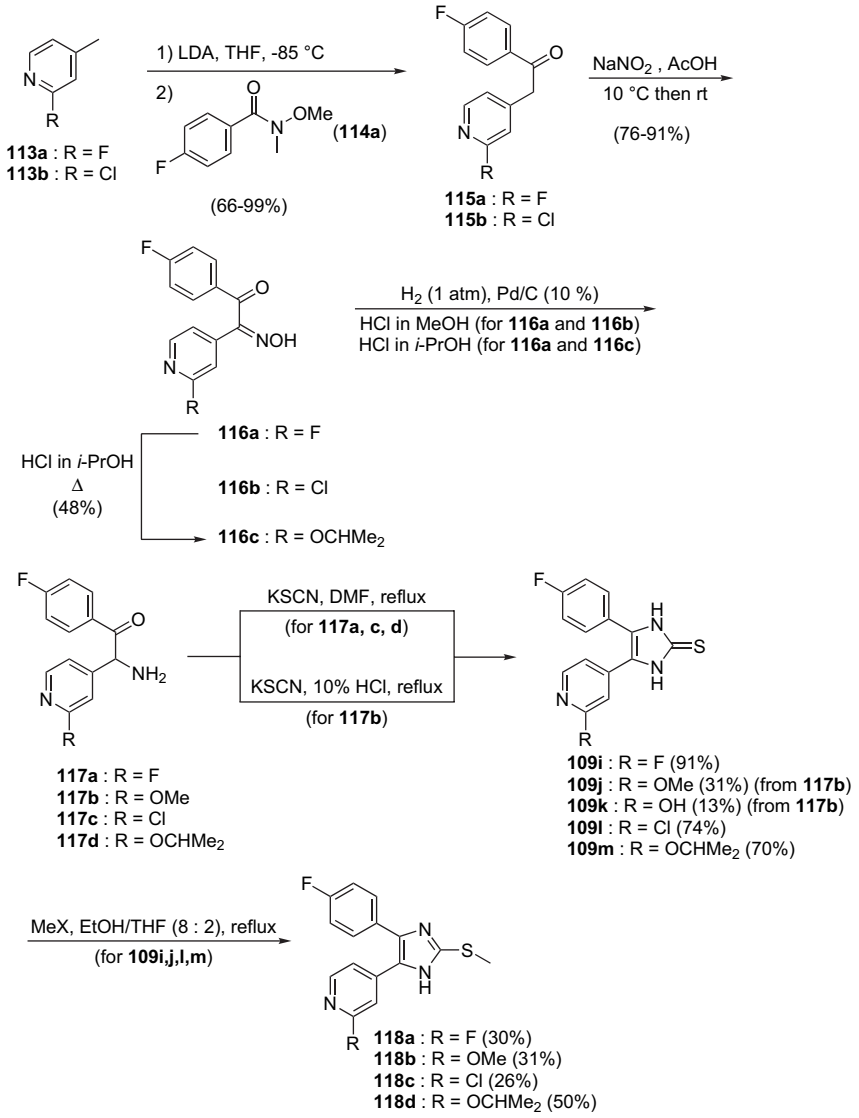
Imidazole-2-thiones **109e**–**h** were alternatively prepared in 80–90% yield by treatment of the corresponding benzoyl

acyloins **112a–d** with an equimolar amount of **111** in refluxing amyl or butyl alcohol.[150]

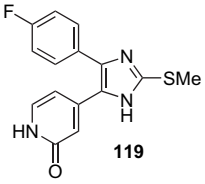
A four-step synthetic protocol, in which the cyclization reaction of α-aminoketones with potassium thiocyanate was a key step, was devised by the Laufer's research group to prepare a variety of 4(5)-(4-fluorophenyl)-5(4)-(3-substituted pyridin-4-yl)-1*H*-imidazole-2-thiones **109**.[123e] Scheme 24 illustrates the nitrosation/reduction/cyclization sequence used to synthesize compounds **109i–m** from 2-halogeno-4-methylpyridines **113a**,**b** and 4-fluoro-*N*-methoxy-*N*-methylbenzamide (**114a**) via formation of ketones **115a**,**b** and their conversion into α-oximinoketones **116a–c**.[123e] Methylation of the exocyclic sulfur atom in **109i**, **109g**, **109l**, and **109m** by treatment with a methyl halide in a refluxing mixture of ethanol and THF furnished the methylsulfanylimidazole derivatives **118a–d**.[123e] Compound **109m** was obtained in 70% yield from **117d** (Scheme 24). Some aspects of this reaction sequence are worth mentioning. Firstly, in the case of the conversion of α-oximinoketones **116a–c** into the corresponding α-aminoketones **117a–c** by Pd-catalyzed hydrogenation in methanolic HCl, the selective reduction of the oximino group was accomplished by acid-catalyzed nucleophilic substitution of the fluorine substituent at the pyridine ring by the solvent alcohol. Secondly, the formation of an alkoxypyridine derivative occurred only as a side reaction when the hydrogenation reaction was performed in 2-propanolic HCl. Thirdly, the synthesis of **109j** from **117b** and KSCN in 10% HCl was accompanied by the formation of its hydrolysis product, **109k**.

However, treatment of **117b** with KSCN in refluxing DMF gave, unexpectedly, 4-[5-(4-fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]-1*H*-pyridin-2-one (**119**) in 45% yield.[123e]

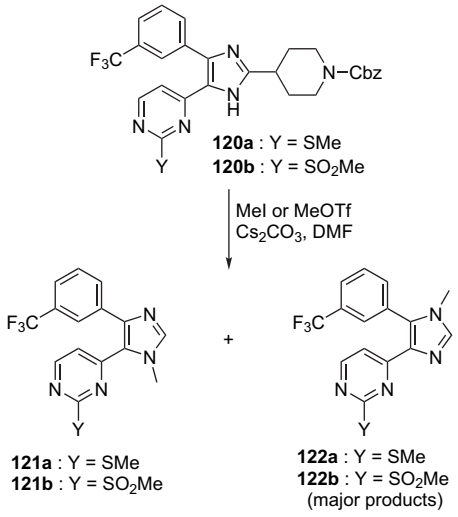
In 1999, Liverton and co-workers attempted the preparation of the tetrasubstituted 4,5-diaryl-1*H*-imidazoles **121a** and **121b** by N-methylation of the 2-substituted 4,5-diaryl-1*H*-imidazoles **120a** and **120b**, respectively.[151]



Scheme 24. Synthesis of compounds **109i–m** and **118a–d**.



However, methylation of **120b** using iodomethane and Cs_2CO_3 in DMF furnished the undesired regioisomer **122b**, together with less than 5% of the required product **121b** (Scheme 25). Sulfide **120a** under the same conditions **122a** and the required isomer **121a** in a 75:25 molar ratio, respectively, and this result was not altered using methyl triflate as electrophile.[151]

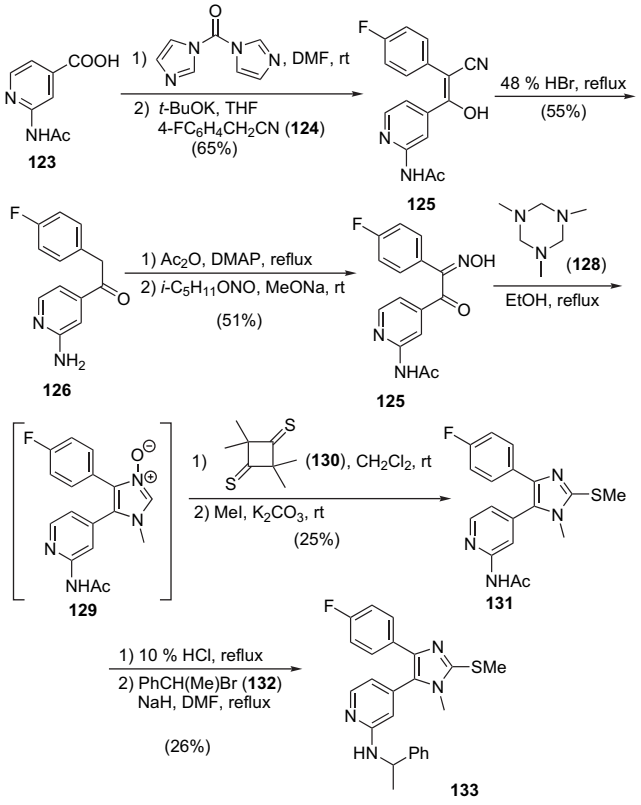


Scheme 25. Synthesis of compounds **121a**,**b** and **122a**,**b**.

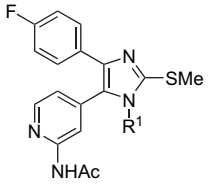
More recently, taking into account these data and the undesired results obtained in the direct N-methylation of 5-(pyridin-4-yl)imidazoles, Laufer and co-workers[123e,152] synthesized the 1-methyl-2-methylsulfanyl-4,5-diaryl-1*H*-imidazole **133** (Scheme 26), using a strategy different from that was followed to prepare compounds **118a**–**d**.

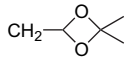
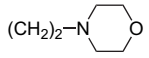
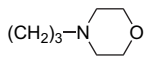
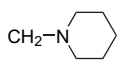
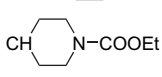
Compound **133** is a potent p38 mitogen-activated protein kinase inhibitor. Specifically, these authors used a multi-step approach in which the cyclization reaction of oximinoketone **127** with 1,3,5-trimethylhexahydro-1,3,5-triazine (**128**) and the conversion of the resulting *N*-oxide **129** into the tetrasubstituted imidazole **131** by treatment with 2,2,4,4-tetramethylcyclobutane-1,3-dithiane (**130**) were the key steps (Scheme 26).[123e,152] Later, an analogous reaction sequence was used for the synthesis of several tetrasubstituted derivatives of general formula **134a**–**g**, which are inhibitors of cytokine release.[149]

A strategy involving the cyclization reaction of 1-(4-fluorophenyl)-2-(pyridin-4-yl)ethane-1,2-dione monoxime (**135**) with aldehydes **136a**,**b** and ammonium acetate (**99**) in refluxing acetic acid, followed by the reaction of the resulting *N*-hydroxyimidazoles **137a**,**b** with triethyl phosphite according to a literature procedure,[153] was used to prepare the 2-substituted 4,5-diaryl-1*H*-imidazoles **138a**,**b** (Scheme 27).[148]

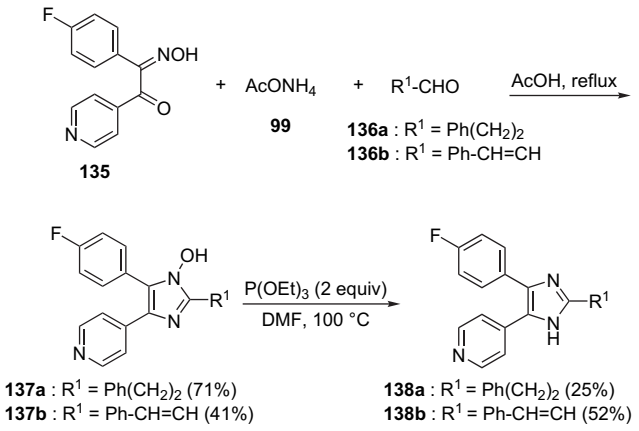


Scheme 26. Synthesis of tetrasubstituted imidazole derivative **133**.

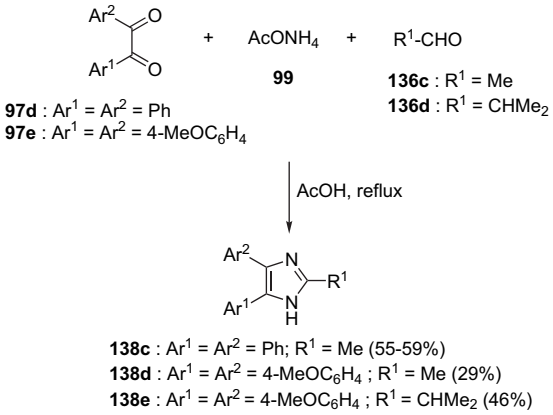


	R^1
a	$(CH_2)_2OH$
b	$(CH_2)_2OMe$
c	$(CH_2)_3OH$
d	$(CH_2)_3OMe$
e	$(CH_2)_3O(CH_2)_2OH$
f	CH_2-CH(Me)OH
g	$(CH_2)_2NHAc$
h	$(CH_2)_2NMe_2$
i	$(CH_2)_2OCH_2$-CH=CH_2
j	$(CH_2)_2OCH_2$-C≡CH
k	$(CH_2)_2SMe$
l	$CH_2CH(OMe)_2$
m	CH_2 
n	$(CH_2)_2$–N 
o	$(CH_2)_3$–N 
p	CH_2–N 
q	CH  N–COOEt

2-Alkyl-4,5-diaryl-1*H*-imidazoles **138c**–**e** were synthesized[58,154] using the Davidson modification[155] of the Radzinszewki imidazole synthesis[156] in which an α-diketone **97** is reacted with an aldehyde **136** and a molar excess of ammonium acetate in refluxing acetic acid. Scheme 28 illustrates the synthesis of the imidazole derivatives **138c**–**e** from α-diketones **97d**,**e** and aldehydes **136c**,**d** according to this procedure.

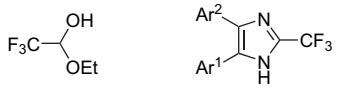


Scheme 27. Synthesis of compounds **138a**,**b**.



Scheme 28. Synthesis of 2-alkyl-4,5-diaryl-1*H*-imidazoles **138c**–**e**.

A similar protocol, which involved treatment of a 1,2-diketone **97** with ammonium acetate and trifluoroacetaldehyde ethyl hemiacetal (**139**) in acetic acid, was used to prepare a large number of 4,5-diaryl-2-trifluoromethyl-1*H*-imidazoles **140** in modest or low yields.[58,63,157] The structures of the so-prepared compounds **140a**–**s** and the yields obtained in their preparation are reported in Table 1.



On the contrary, a good yield (80%) was obtained in the preparation of the 2-formyl-4,5-diaryl-1*H*-imidazole **142a** by treatment of 1,2-diketone **97f** with glyoxal dimethyl acetal (**141**) and ammonium acetate in acetic acid and methyl *tert*-butyl ether at room temperature.

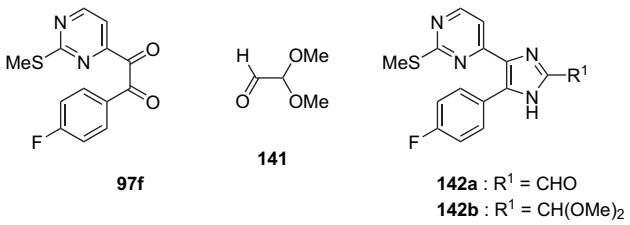
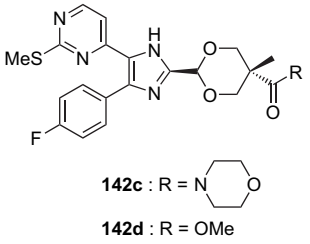


Table 1. Structures and yields of 4,5-diaryl-2-trifluoromethyl-1*H*-imidazoles **140a**–**s** prepared form 1,2-diarylethanediones, ammonium acetate, and trifluoroacetaldehyde ethyl hemiacetal in acetic acid

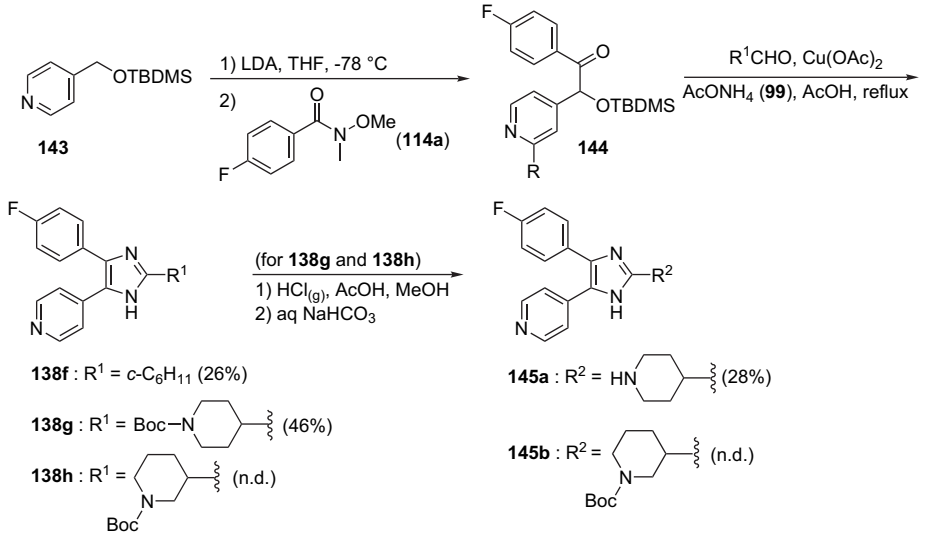
Compound	Ar^1	Ar^2	Yield (%)	Ref.
140a	Ph	Ph	38	56
140b	4-$MeOC_6H_4$	4-$MeOC_6H_4$	47	56
140c	4-BrC_6H_4	Ph	42	56
140d	4-$MeOC_6H_4$	Ph	16	56
140e	4-BrC_6H_4	4-BrC_6H_4	31	56
140f	4-$MeSC_6H_4$	4-$MeSC_6H_4$	11	56
140g	3-$MeOC_6H_4$	3-$MeOC_6H_4$	26	56
140h	2-$MeOC_6H_4$	2-$MeOC_6H_4$	42	56
140i	4-MeC_6H_4	4-MeC_6H_4	31	56
140j	2-$MeOC_6H_4$	2-$MeOC_6H_4$	24	56
140k	2-Pyridyl	2-Pyridyl	28	56
140l	4-$EtOC_6H_4$	4-$EtOC_6H_4$	20	56
140m	4-FC_6H_4	4-FC_6H_4	36	56
140n	4-HOC_6H_4	4-HOC_6H_4	91	56
140o	4-$MeOC_6H_4$	4-HOC_6H_4	9	56
140p	Ph	4-$MeSO_4C_6H_4$	43	61
140q	3-Me_2N-1,2,4-triazin-6-yl	Ph	55	154
140r	3-Me_2N-1,2,4-triazin-6-yl	2-Thienyl	30	154
140s	3-Me_2N-1,2,4-triazin-6-yl	3-Thienyl	25	154

Moreover, dimethyl acetal **142b** was obtained in 86% yield by the reaction of **97f** with **141** and ammonium acetate in methanol and *tert*-butyl ether at room temperature.[134] Compounds **142a**,**b** were afterward used as direct precursors to the 4,5-diaryl-2-(1,3-dioxan-2-yl) derivatives **142c**,**d**.[134,135] Three other 2-substituted 4,5-diaryl-1*H*-imidazoles, compounds **138f**–**h**, were prepared by cyclocondensation of 2-(*tert*-butyldimethylsilyloxy)-1-(4-fluorophenyl)-2-pyridin-4-ylethanone (**144**) with the required aldehydes **136** and 10 equiv of ammonium acetate in refluxing acetic acid in the presence of 2 equiv of copper(II) acetate (Scheme 29).[151] Compound **144** was prepared by the reaction of the anion of 4-[(*tert*-butyldimethylsilyloxy)methyl]pyridine (**143**) with *N*-methoxy-*N*-methyl-4-fluorobenzamide (**114a**) (Scheme 29).[151] On the other hand, the HCl-mediated deprotection of **138g** and **138h** gave the piperidine derivatives **145a** and **145b**, respectively.[151]

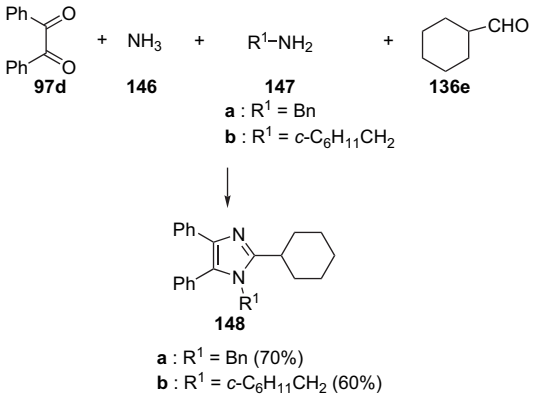


Cyclocondensation reactions involving 1,2-diketones have also been used to prepare tetrasubstituted 4,5-diaryl-1*H*-imidazoles. In fact, compounds **148a** and **148b** were synthesized in satisfactory yields by the reaction of benzil (**97d**) with cyclohexanecarboxyaldehyde (**136e**), ammonia (**146**), and amines **147a** and **147b**, respectively (Scheme 30).[158]

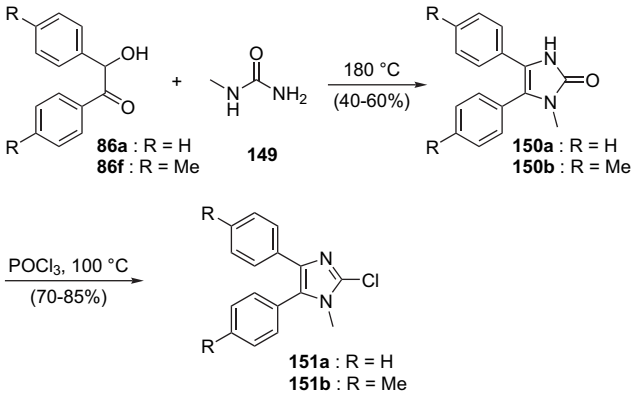
Recently, two other tetrasubstituted 4,5-diaryl-1*H*-imidazoles, compounds **151a**,**b**, have been synthesized by a two-step reaction sequence involving the thermal cyclization of benzoins **86a** and **86f** with *N*-methylurea (**149**), followed by the reaction of $POCl_3$ with the resulting compounds



Scheme 29. Synthesis of compounds **138f–h** and **145a**,**b**.



Scheme 30. Synthesis of 4,5-diaryl-1*H*-imidazoles **148a**,**b**.



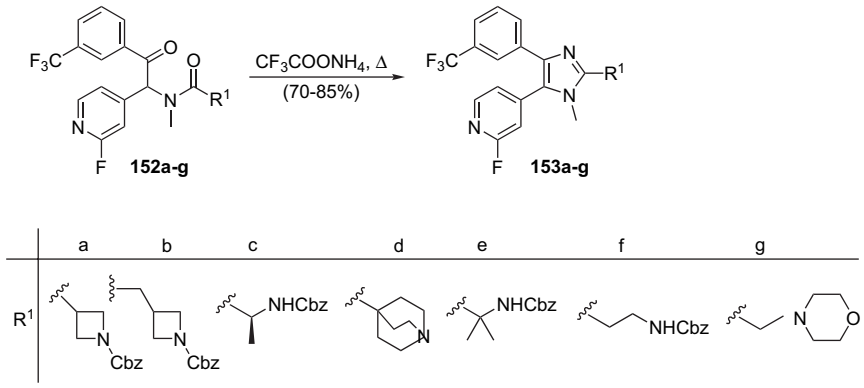
Scheme 31. Synthesis of compounds **151a**,**b**.

150a,**b**.[77] Scheme 31 illustrates the synthesis of these tetrasubstituted imidazole derivatives.

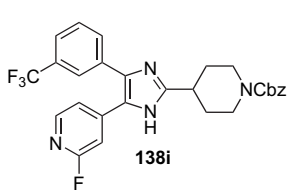
On the other hand, the tetrasubstituted 5-(2-fluoro-4-pyridyl)-4-(3-trifluorophenyl)-1*H*-imidazoles **153a–g** were efficiently prepared by thermal cyclocondensation of the *N*-alkyl-*N*-(β-keto)amides **152a–g** with ammonium trifluoro-acetate (Scheme 32).[159]

This procedure was also used to synthesize the trisubstituted imidazole derivative **138i** and as a key step of the synthesis of compound **154**, which is a p38 MAP kinase inhibitor.[159]

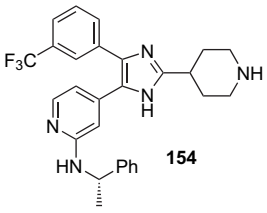
More recently, 4,5-diphenyl-1*H*-imidazole **158** has been prepared by an analogous cyclocondensation of the *N*-butyl-*N*-(β-keto)amide **157** with ammonium acetate in DMF at 90 °C



Scheme 32. Synthesis of tetrasubstituted 4,5-diaryl-1*H*-imidazoles **153a–g**.



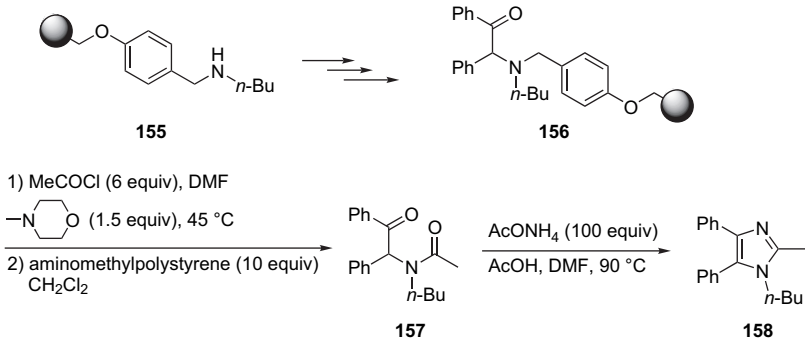
138i



154

in the presence of acetic acid (Scheme 33).[160] Compound **157** was synthesized from the resin-bound secondary amine **155** using a solid-phase approach in which the resin-bound tertiary amine **156** was the direct precursor to **157**.[160]

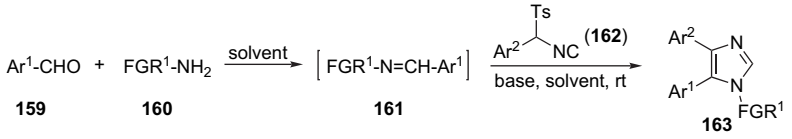
For the preparation of 1-substituted 4,5-diaryl-1*H*-imidazole derivatives, that include several p38 MAP kinase inhibitors, several authors within the space of several years have preferred a methodology, which has relied on the tosylmethyl isocyanide (TosMIC) technology developed by van Leusen and co-workers[110] to that based on the above-described cyclocondensation reactions. This preferred methodology involves the base-induced [3+2] cycloaddition of α-aryl-substituted tosylmethyl isocyanides **162** to aldimines **161** prepared by traditional methods or synthesized in situ from aryl aldehydes **159** and primary amines **160** before the addition of the substituted TosMIC reagents **162**.[80,110,161–169] Table 2 lists an extensive series of



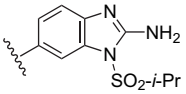
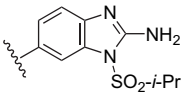
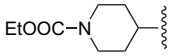
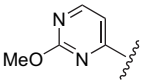
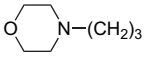
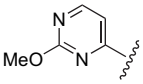
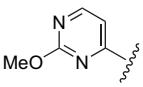
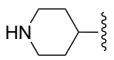
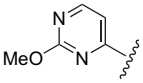
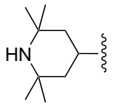
155 156 157 158

Scheme 33. Synthesis of 4,5-diphenyl-1*H*-imidazole **158**.

Table 2. Synthesis of 4,5-diaryl-1*H*-imidazoles **163** from α-aryl-substituted TosMIC reagents

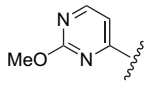
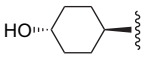
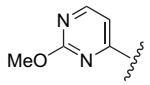
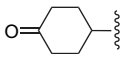
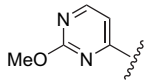
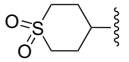
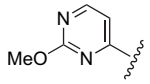
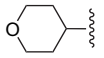
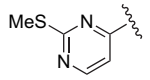
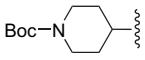
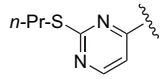
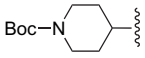
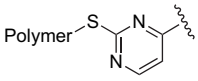
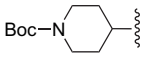
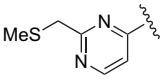
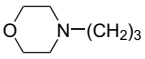
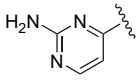
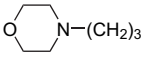
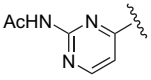
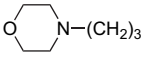
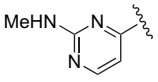
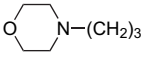
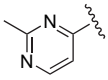
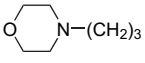
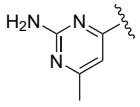
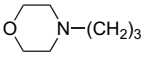
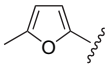
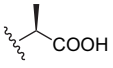
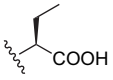
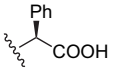
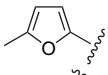
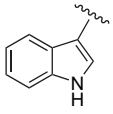
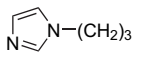


159 160 161 163

Entry	Ar^1	FG-R^1	Ar^2	Base	Solvent[a]	Product	Yield (%)	Ref.
1	Ph	Me	Ph	K_2CO_3	MeOH	**163a**	90	107
2	2-$N_3C_6H_4$	Me-C≡C–CH_2	Ph	K_2CO_3	DMF	**163b**	53	158
3	2-$N_3C_6H_4$	Ph-C≡C–CH_2	Ph	K_2CO_3	DMF	**163c**	60	158
4		Me	4-FC_6H_4	*t*-$BuNH_2$	DMF	**163d**	24	159
5			4-FC_6H_4	*t*-$BuNH_2$	DMF	**163e**	24	159
6			4-FC_6H_4	K_2CO_3	DMF	**163f**	Nd	160
7		*i*-Pr	4-FC_6H_4	K_2CO_3	DMF	**163g**	Nd	160
8			4-FC_6H_4	K_2CO_3	DMF	**163h**	Nd	160
9			4-FC_6H_4	K_2CO_3	DMF	**163i**	Nd	160

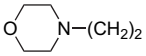
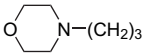
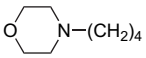
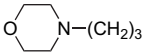
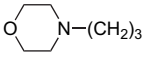
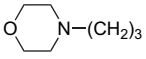
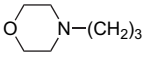
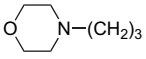
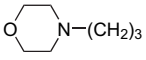
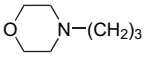
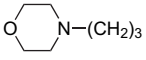
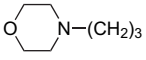
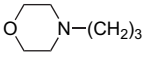
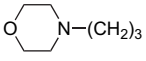
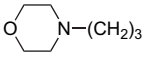
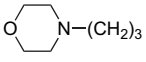
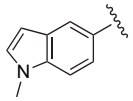
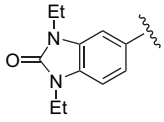
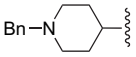
(*continued*)

Table 2. (*continued*)

Entry	Ar^1	$FG\text{-}R^1$	Ar^2	Base	Solvent[a]	Product	Yield (%)	Ref.
10			4-FC_6H_4	K_2CO_3	DMF	**163j**	Nd	160
11			4-FC_6H_4	K_2CO_3	DMF	**163k**	Nd	160
12			4-FC_6H_4	K_2CO_3	DMF	**163l**	Nd	160
13			4-FC_6H_4	K_2CO_3	DMF	**163m**	Nd	160
14			4-FC_6H_4	K_2CO_3	DMF	**163n**	Nd	161
15			4-FC_6H_4	K_2CO_3	DMF	**163o**	Nd	161
16			4-FC_6H_4	K_2CO_3	DMF	**163p**	Nd	161
17			4-FC_6H_4	TBD	DMF	**163q**	Nd	162
18			4-FC_6H_4	TBD	CH_2Cl_2	**163r**	Nd	162
19			4-FC_6H_4	TBD	CH_2Cl_2	**163s**	Nd	162
20			4-FC_6H_4	TBD	CH_2Cl_2	**163t**	Nd	162
21			4-FC_6H_4	TBD	CH_2Cl_2	**163u**	Nd	162
22			4-FC_6H_4	TBD	CH_2Cl_2	**163v**	Nd	162
23			4-FC_6H_4	NaOH and piperazine	MeOH	**163w**	67	163
24			4-FC_6H_4	NaOH and piperazine	MeOH	**163y**	74	163
25	4-MeO,3-HOC_6H_3			NaOH and piperazine	MeOH	**163z**	79	163
26		$(CH_2)_2COOH$	4-FC_6H_4	NaOH and piperazine	MeOH	**163aa**	67	163
27		Et	4-FC_6H_4	Piperazine	MeOH	**163ab**	49	163
28	4-HOC_6H_4	$(CH_2)_3OH$	4-$MeOC_6H_4$	Piperazine	MeOH	**163ac**	67	163
29	4-BrC_6H_4CO		2-Naphthyl	Et_3N and piperazine	DMSO	**163ad**	50	163

(*continued*)

Table 2. (*continued*)

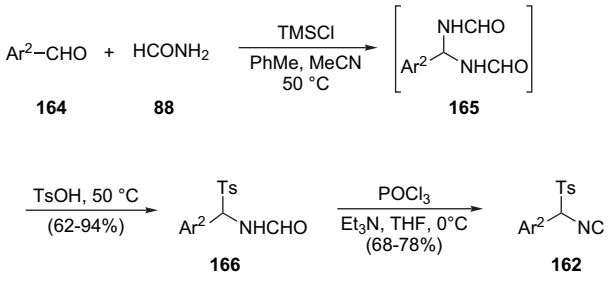
Entry	Ar^1	$FG\text{-}R^1$	Ar^2	Base	Solvent[a]	Product	Yield (%)	Ref.
30[b]	4-Pyridyl		$4\text{-}FC_6H_4$	TBD	CH_2Cl_2	**163ae**	Nd	164
31[b]	4-Pyridyl		$4\text{-}FC_6H_4$	TBD	CH_2Cl_2	**163af**	Nd	164
32[b]	4-Pyridyl		$4\text{-}FC_6H_4$	TBD	CH_2Cl_2	**163ag**	Nd	164
33[b]	4-Pyridyl	$MeOOC\text{-}(CH_2)_3$	$4\text{-}FC_6H_4$	TBD	CH_2Cl_2	**163ah**	Nd	164
34[b]	4-Pyridyl	*i*-Pr	$4\text{-}FC_6H_4$	TBD	CH_2Cl_2	**163ai**	Nd	164
35[b]	4-Pyridyl		$4\text{-}FC_6H_4$	TBD	CH_2Cl_2	**163aj**	Nd	164
36[b]	4-Pyridyl		$4\text{-}FC_6H_4$	TBD	CH_2Cl_2	**163ak**	Nd	164
37[b]	4-Pyridyl	*t*-Bu	$4\text{-}FC_6H_4$	TBD	CH_2Cl_2	**163al**	Nd	164
38[b]	3-Pyridyl		$4\text{-}FC_6H_4$	TBD	CH_2Cl_2	**163am**	Nd	164
39[b]	2-Pyridyl		$4\text{-}FC_6H_4$	TBD	CH_2Cl_2	**163an**	Nd	164
40[b]	2-Me-4-pyridyl		$4\text{-}FC_6H_4$	TBD	CH_2Cl_2	**163ao**	Nd	164
41[b]	$2,6\text{-}Me_2\text{-}4\text{-}pyridyl$		$4\text{-}FC_6H_4$	TBD	CH_2Cl_2	**163ap**	Nd	164
42[b]	4-Quinolyl		$4\text{-}FC_6H_4$	TBD	CH_2Cl_2	**163aq**	Nd	164
43[b]	2-Cl-4-pyridyl		$4\text{-}FC_6H_4$	TBD	CH_2Cl_2	**163ar**	Nd	164
44[b]	$2\text{-}NH_2\text{-}4\text{-}pyridyl$		$4\text{-}FC_6H_4$	TBD	CH_2Cl_2	**163as**	Nd	164
45[b]	4-Pyridyl		$3\text{-}ClC_6H_4$	TBD	CH_2Cl_2	**163at**	Nd	164
46[b]	4-Pyridyl		$3\text{-}MeSC_6H_4$	TBD	CH_2Cl_2	**163au**	Nd	164
47[b]	4-Pyridyl		$3,4\text{-}Cl_2C_6H_3$	TBD	CH_2Cl_2	**163av**	Nd	164
48[b]	4-Pyridyl		$3\text{-}CF_3C_6H_4$	TBD	CH_2Cl_2	**163aw**	Nd	164
49[b]	4-Pyridyl		$3\text{-}MeSO_2C_6H_4$	TBD	CH_2Cl_2	**163ay**	Nd	164
50[b]	4-Pyridyl		$3,5\text{-}(CF_3)_2C_6H_3$	TBD	CH_2Cl_2	**163az**	Nd	164
51[c]	$4\text{-}MeO,3\text{-}(NO_2)C_6H_3$	$PhCH_2$	$3,4,5\text{-}(MeO)_3C_6H_2$	K_2CO_3	EtOH/DME (6:4)	**163ba**	Nd	165
52[c]	$4\text{-}MeO,3\text{-}(BnO_2)C_6H_3$	$PhCH_2$	$3,4,5\text{-}(MeO)_3C_6H_2$	K_2CO_3	EtOH/DME (6:4)	**163bb**	Nd	165
53[c]	$4\text{-}(Me_2N)C_6H_4$	$PhCH_2$	$3,4,5\text{-}(MeO)_3C_6H_2$	K_2CO_3	EtOH/DME (6:4)	**163bc**	Nd	165
54[c]	$4\text{-}MeO,3\text{-}FC_6H_3$	$PhCH_2$	$3,4,5\text{-}(MeO)_3C_6H_2$	K_2CO_3	EtOH/DME (6:4)	**163bd**	Nd	165
55[c]	$4\text{-}MeOC_6H_4$	$PhCH_2$	$3,4,5\text{-}(MeO)_3C_6H_2$	K_2CO_3	EtOH/DME (6:4)	**163be**	Nd	165
56[c]	$4\text{-}MeO,3\text{-}(NO_2)C_6H_3$	Me	$3,4,5\text{-}(MeO)_3C_6H_2$	K_2CO_3	EtOH/DME (6:4)	**163bf**	Nd	165
57[c]		$PhCH_2$	$3,4,5\text{-}(MeO)_3C_6H_2$	K_2CO_3	EtOH/DME (6:4)	**163bg**	Nd	165
58			$4\text{-}FC_6H_4$	Piperazine	THF	**163bh**	20	166
59[d]	4-Pyridyl	$Ph\text{–}(CH_2)_3$	$4\text{-}FC_6H_4$	K_2CO_3	DMF	**163bi**	nd	167

[a] TBD=1,5,7-triazabicyclo[4.4.0]dec-7-ene.
[b] In this entry, imine **161** was prepared by the reaction between the required aldehyde **159** and primary amine **160** in toluene at room temperature in the presence of $MgSO_4$.
[c] In this entry, imine **161**, synthesized before the reaction with **162**, was prepared by treatment of the required aldehyde **159** and primary amine **160** in refluxing ethanol in the presence of a catalytic amount of acetic acid.
[d] In this entry, imine **161** was prepared by the reaction of the required aryl aldehyde **159** and primary amine in methanol solution.

4,5-diaryl-1*H*-imidazoles of general formula **163**, which have been synthesized from α-aryl-substituted TosMIC reagents. Among these imidazole derivatives, compounds **163w–z** and **163aa–ad** were synthesized by Sisko and co-workers using a one-pot protocol in which methanol containing significant amounts of water was the solvent.[166]

The Sisko group also reported an improved procedure for preparing substituted tosylmethyl formamides, which are precursors of the substituted TosMIC reagents.[170] The literature protocols for forming these intermediates had previously been based on heating an acidic aqueous solution of an aldehyde and *p*-toluenesulfinic acid[171] or on condensing thiocresol with an aldehyde and subsequent oxidation with *m*-chloroperbenzoic acid.[172–174]

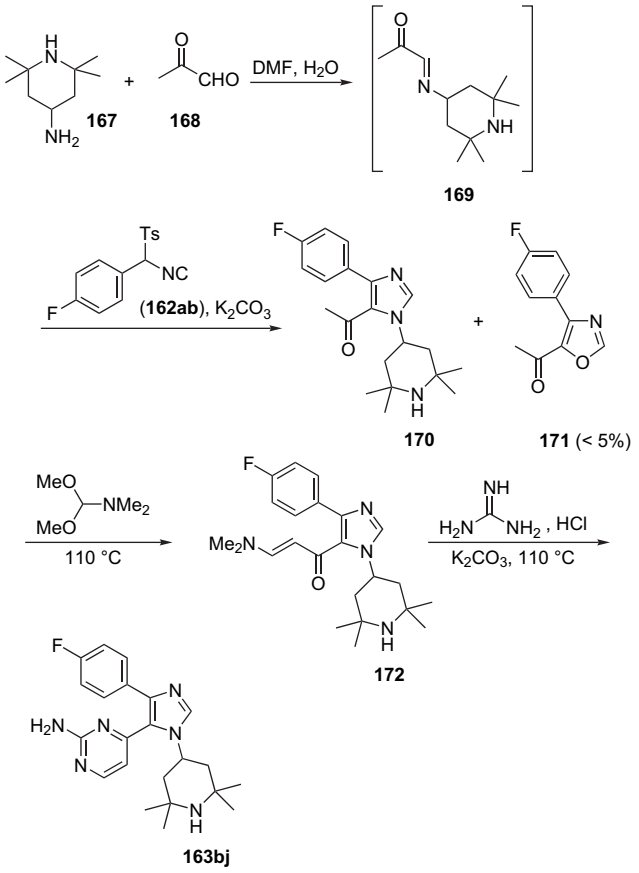
However, electron-poor aldehydes provided poor yields or completely failed these protocols. In the procedure developed by Sisko and co-workers[170] the α-aryl-substituted TosMIC derivatives **162** were obtained by straightforward dehydration of the corresponding α-aryl-substituted tosylmethyl formamides **166** with $POCl_3$ in THF at 0 °C in the presence of Et_3N and compounds **166** were prepared by heating an aryl aldehyde **164**, formamide (**88**), trimethylsilyl chloride (TMSCl), and dry *p*-toluenesulfinic acid in a 1:1 mixture of toluene and acetonitrile at 50 °C to give bis-formamides **165** (Scheme 34).



Scheme 34. Synthesis of α-aryl-substituted TosMIC derivatives **162**.

A drawback of this practical procedure, which allows the preparation of compounds **162** on a large scale, is that dry *p*-toluenesulfinic acid has to be prepared. However, on a large scale, drying of this acid can produce significant amounts of undesired dimeric material.[31]

The van Leusen TosMIC chemistry has also been used for the one-pot synthesis of 1-(2,2,6,6-tetramethyl-4-pyperidinyl)-4-(4-fluorophenyl)-5-(2-amino-4-pyrimidinyl)-1*H*-imidazole (**163bj**), a potent p38 MAP kinase inhibitor.[174] In this flexible route, capable of producing kilogram quantities of **163bj**, the combination of the amine **167** with a 40% aqueous solution of pyruvaldehyde (**168**) in DMF for 10–20 min, followed by addition of isonitrile **163a** and K_2CO_3 to so obtained α-ketoaldimine **169**, produced the imidazole derivative **170** and 5% of oxazole **171**. The synthesis of **163bj** was then completed by heating crude **170** with an excess of *N*,*N*-dimethylformamide dimethyl acetal, followed by direct reaction of the resulting vinylogous amide **172** with guanidine hydrochloride and sodium methoxide at 80 °C (Scheme 35).[174] In this manner, compound **163bj** was obtained in 36% overall yield from **167**.



Scheme 35. Synthesis of compound **163bj**, a p38 MAP kinase inhibitor.

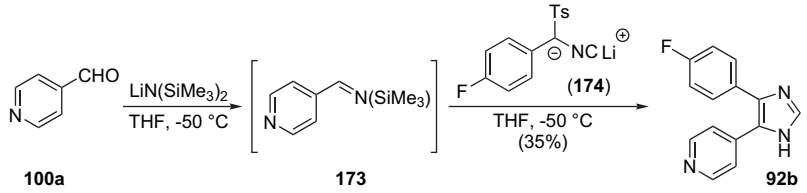
In 1996, a modification of the methodology of van Leusen was applied by Boehm and co-workers toward the synthesis of 4,5-diaryl-1*H*-imidazole **92b**.[167] Specifically, pyridine-4-carboxyaldehyde (**100a**) was treated with lithium bis(trimethylsilyl)amide (LDA) in THF at −50 °C and the solution of the resulting compound **173** was reacted with the lithium derivative **174**, obtained by addition of a THF solution of LDA to isonitrile **163a** (Scheme 36). Compound **92b** was so prepared in 35% overall yield.

Recently, a one-pot procedure involving treatment of THF solutions of aryl aldehydes **100a–c** with an excess of 30% NH_4OH, followed by addition of isonitrile **162b**, has been used by Sisko and co-workers to prepare 4,5-diaryl-1*H*-imidazoles **92b**, **92h**, and **92i** in good yields (Scheme 37).[166]

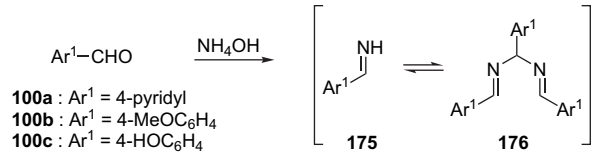
As shown in Scheme 37, the reaction, presumably, involves the formation of arylimines **175** and the corresponding hydrobenzamides **176**.[176]

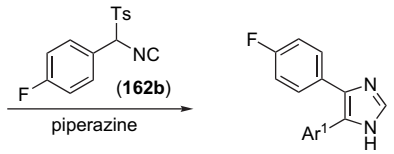
In 2002, 4,5-diaryl-1*H*-imidazoles **92j–o** were prepared by hydrogenolysis of the corresponding 1-benzyl derivatives with ammonium formate and palladium on charcoal.[80] The 1-benzyl-1*H*-imidazoles were synthesized via TosMIC chemistry (Table 2, entries 51–55 and 57).[80]

Soni[177] had previously synthesized 1-methyl-4,5-diaryl-1*H*-imidazoles **178a–e** in satisfactory yields from the corresponding *N*-(substituted benzylidene)methylamine *N*-oxides **177a–e**[178] and cold aqueous ethanolic KCN (Scheme 38)

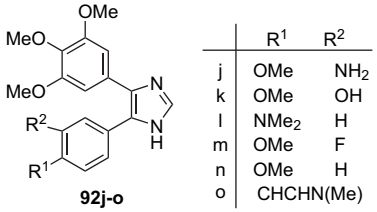


Scheme 36. Synthesis of compound **92b** from aldehyde **100a**.



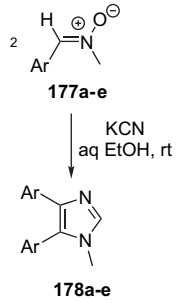


Scheme 37. Synthesis of 4,5-diaryl-1*H*-imidazoles **92b**, **92h**, and **92i**.



	R^1	R^2
j	OMe	NH_2
k	OMe	OH
l	NMe_2	H
m	OMe	F
n	OMe	H
o	CHCHN(Me)	

according to the method developed in 1975 by Clark and Cawkill for the synthesis of 1-alkyl-4,5-diaryl-1*H*-imidazoles from *N*-alkyl-*C*-aryl nitrones.[179]

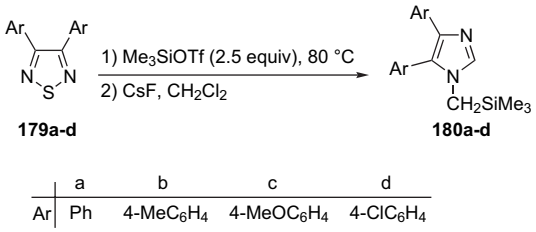


	Ar	Yield (%)
a	Ph	65
b	4-MeC_6H_4	51
c	4-ClC_6H_4	72
d	2-naphthyl	37
e	pyridyn-4-yl	57

Scheme 38. Synthesis of 1-methyl-4,5-diaryl-1*H*-imidazoles **178a**–**e**.

On the contrary, low yields (<30%) were obtained in the synthesis of 4,5-diaryl-1-trimethylsilylmethyl-1*H*-imidazoles **180a**–**d** by treatment of the corresponding 1,2,5-thiadiazoles **179a**–**d**[180] with 2.5 equiv of trimethylsilyl triflate at 80 °C for 12 h, followed by the reaction with CsF in CH_2Cl_2 (Scheme 39).[181]

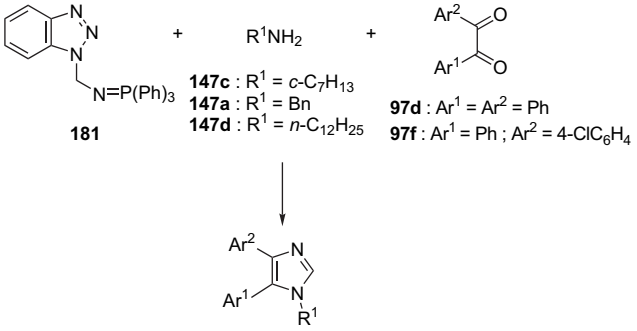
In 1990, Katritzky and co-workers[182] showed that the 1-substituted-4,5-diaryl-1*H*-imidazoles **105e**–**g** could



	a	b	c	d
Ar	Ph	4-MeC_6H_4	4-$MeOC_6H_4$	4-ClC_6H_4

Scheme 39. Synthesis of compounds **180a**–**d**.

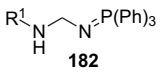
efficiently be synthesized by the reaction of 1-(benzotriazol-1-yl)-*N*-(triphenylphosphorylidene)-methylamine (**181**) (Betmip)[183] with benzils **97d**,**f** and the required primary amines **147** (Scheme 40).



105e : R^1 = *c*-C_7H_{13} ; Ar^1 = Ar^2 = Ph (81%)
105f : R^1 = Bn ; Ar^1 = Ph ; Ar^2 = 4-ClC_6H_4 (55%)
105g : R^1 = *n*-$C_{12}H_{25}$; Ar^1 = Ph ; Ar^2 = 4-ClC_6H_4 (53%)

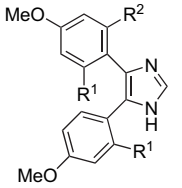
Scheme 40. Synthesis of compounds **105e**–**g**.

Interestingly, the reaction could be performed in one pot without isolation of the intermediate **182**.[182]



Another method for the production of 4,5-diaryl-1*H*-imidazoles is the oxidation of 4,5-diaryl-2-imidazolines[184] with MnO_2 according to the protocol described by Martin and co-workers.[185] This procedure was used by Gust and co-workers to prepare compounds **183a**–**d**.[186]

Some 4,5-diaryl-1*H*-imidazoles have also been synthesized using reaction sequences in which a Pd-catalyzed cross-coupling reaction involving an organometallic reagent is a key step. Thus, the imidazole derivative **92b** was synthesized in 10% overall yield from the known SEM-protected 2,4,5-tribromoimidazole **184**[187] using a four-step sequence

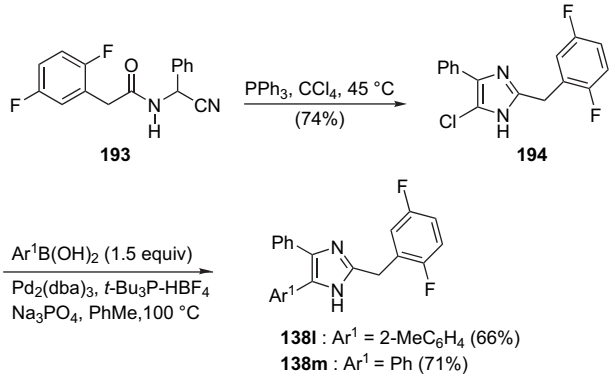


183a : $R^1 = R^2 = H$
183b : $R^1 = F$; $R^2 = H$
183c : $R^1 = Cl$; $R^2 = H$
183d : $R^1 = R^2 = Cl$

in which the 4-pyridyl group at the C-5 position of the intermediate 4-bromo derivative **189** was introduced by a Stille-type reaction between 4-bromopyridine (**188**) and the organotin derivative **187**. This organometallic reagent was regioselectively prepared from **184** via the dibromo derivative **185** and the distannane **186**. On the other hand, the C-4 arylation of **189** was performed by a Suzuki-type reaction with 4-fluorophenylboronic acid (**35f**) (Scheme 41).[188]

A Pd-catalyzed Negishi-type reaction was employed to prepare 1-methyl-4,5-diaryl-1*H*-imidazole **192a** from 2-bromopyridine (**191**) and the organozinc derivative obtained from 4-iodo-1-methyl-5-(4-methoxyphenyl)-1*H*-imidazole (**190**) (Scheme 42).[189] Unfortunately, the yield of this cross-coupling reaction and the procedure used to prepare **190** were not reported.

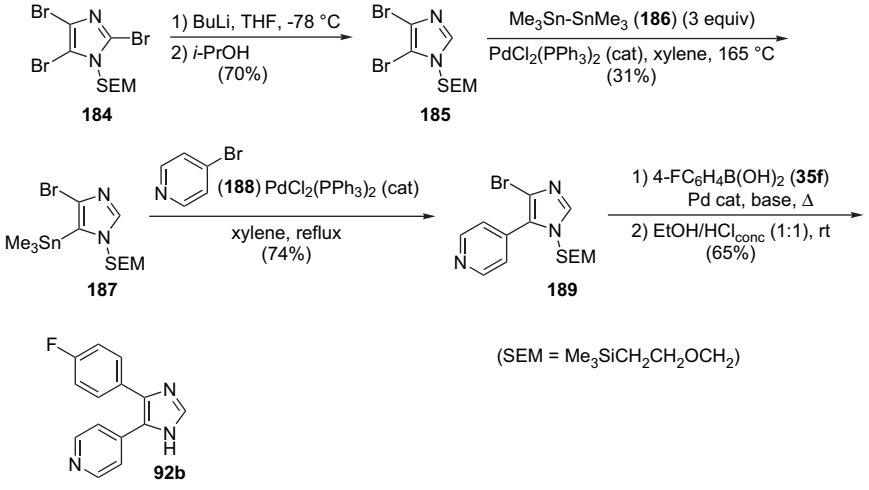
Recently, the syntheses of 2-(2,5-difluorobenzyl)-4,5-diaryl-1*H*-imidazoles **138l** and **138m** by Pd-catalyzed Suzuki coupling reactions involving the use of the unprotected 5-chloroimidazole **194** as the substrate have also been described (Scheme 43).[190] Compound **194** was prepared by treatment of the *N*-acylated α-aminonitrile **193** with PPh_3 and CCl_4.[190]



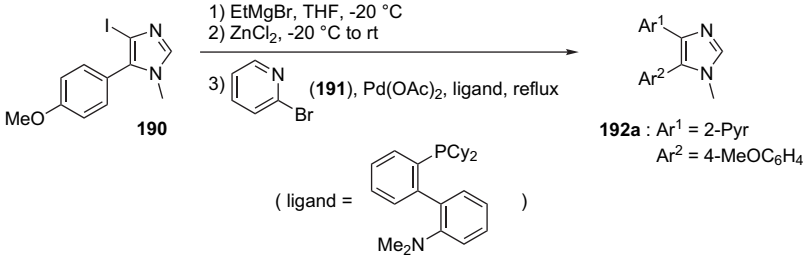
Scheme 43. Synthesis of compounds **138l** and **138m**.

To the best of our knowledge, the Pd-catalyzed reactions reported in Scheme 43 represent the first examples of successful Suzuki reactions performed on an unprotected haloimidazole derivative.

More recently, our research group has explored a new protocol for preparing in three steps 1-methyl-4,5-diaryl-1*H*-imidazoles **192b–d**, which include biologically active derivatives, from 1-methyl-1*H*-imidazole (**195**).



Scheme 41. Synthesis of compound **92b**.



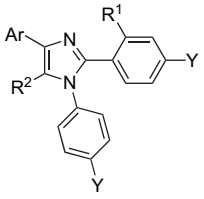
Scheme 42. Synthesis of compound **192a**.

Specifically, we demonstrated[108b,191] that this compound can be regioselectively transformed into 5-aryl-1-methyl-1*H*-imidazoles **196** in satisfactory yields using a modification of the procedure, which we recently developed for the synthesis of 1,5-diaryl-1*H*-imidazoles **55** from the corresponding 1-aryl-1*H*-imidazoles[84] (Scheme 44). This modified procedure for the highly regioselective Pd-catalyzed C-5 arylation of **195** involved the use of tris(2-furyl)phosphine in place of triphenylarsine as the Pd ligand. Toluene was the reaction solvent of choice. Bromination of compounds **196** with *N*-bromosuccinimide (NBS) in acetonitrile at room temperature gave the 4-bromoimidazole derivatives **197**, which proved to be able to undergo Pd-catalyzed Suzuki-type coupling reactions under phase-transfer conditions[192] to provide the required 1-methyl-4,5-diaryl-1*H*-imidazoles **192** in 18–33% overall yield from **195**.[108b,191] Scheme 44 illustrates the synthesis of compounds **192b–d** according to this protocol.

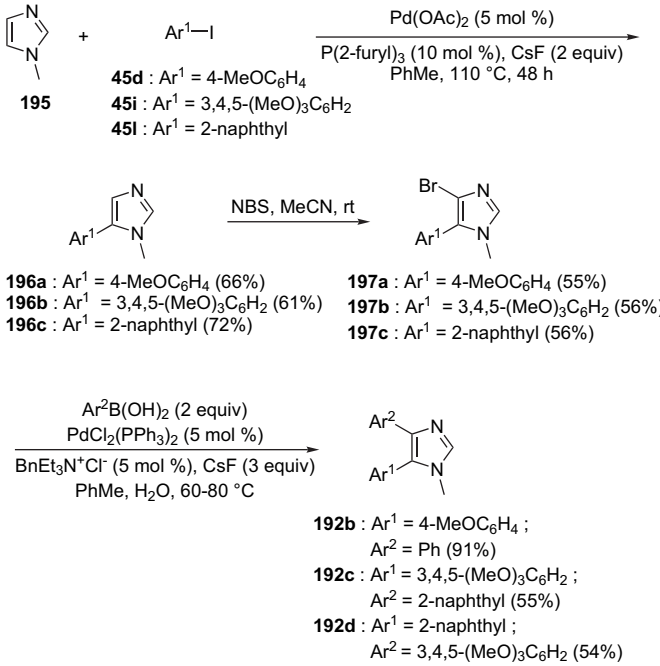
We also developed a new method for the synthesis of 4,5-diaryl-1*H*-imidazoles of general formula **92** starting from *N*-benzylimidazole (**198**) that involves a four-step sequence. The first two steps of this procedure were similar to those employed for the preparation of compounds **192b–d** (Scheme 45).[191] Specifically, the regioselective Pd-catalyzed C-5 arylation of **198** with 2 equiv of aryl iodides gave the 1-benzyl-5-aryl-1*H*-imidazoles **199a–c** in satisfactory yields. These compounds were then converted into their 4-bromo derivatives **200a–c** by treatment with 1.05 equiv of NBS in acetonitrile at room temperature. Attempts to perform the C-4 arylation of these derivatives by a Suzuki-type reaction using the same experimental conditions employed to prepare compounds **192b–d** from the corresponding 4-bromo derivative **197a–c** gave unsatisfactory results. However, when bromides **200a–c** were reacted with 1.5 equiv of an arylboronic acid in a mixture of water and DMF at 100 °C in the presence of 5 mol % $Pd(OAc)_2$, 10 mol % *t*-$Bu_3P\cdot HBF_4$, and 9 equiv of Na_2CO_3, the required 1-benzyl-4,5-diaryl-1*H*-imidazoles **201a–c** were obtained in 24–60% yield. Finally, debenzylation of compounds **201a–c** with a large molar excess of ammonium formate in methanol at 70 °C in the presence of Pd/C provided compounds **92p**,**n**,**q** (Scheme 45).[191] Two aspects of this protocol merit comments. Firstly, the reaction times of the Suzuki-type coupling reactions were significantly higher than those of similar reactions involving 4-bromo-1-methyl-1*H*-imidazole derivatives. Secondly, the crude mixtures, obtained from these cross-coupling reactions, proved to contain significant amounts of compounds **199** that derived from a reductive dehalogenation of bromo imidazoles **200**.

2.4. Synthesis of 1,2,4-triaryl-1*H*-imidazoles

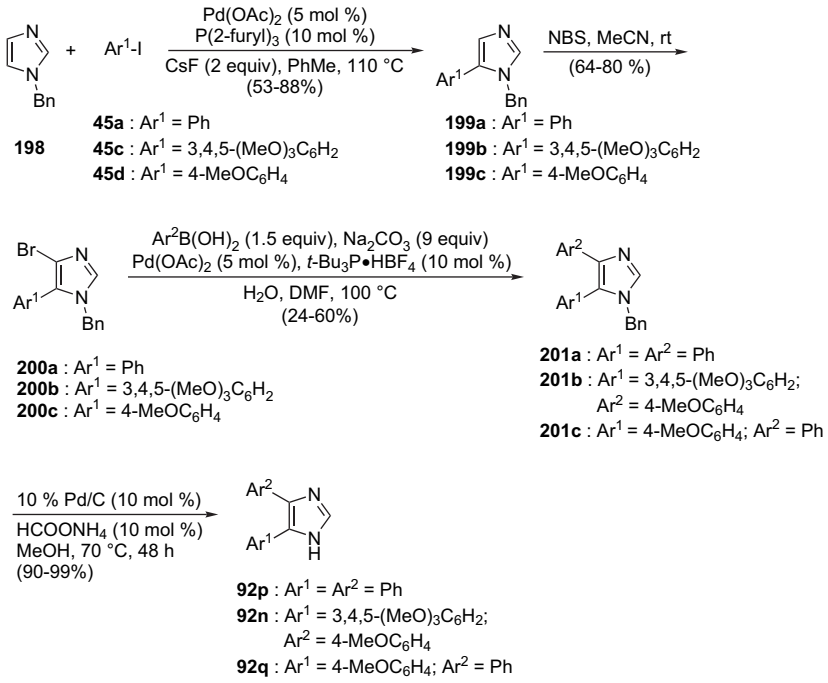
Until a few years ago, it was known that 1,2,4-triaryl-1*H*-imidazoles do not include compounds with significant biological properties. Thus, little attention was directed to the synthesis of this class of imidazole derivatives. However, this state of affairs might change in the near future. In fact, it has recently been reported that 1,2,4-triaryl-1*H*-imidazole **202a** is able to cause hormonal activity in estrogen receptor positive MCF-7-2a cells and that the imidazole derivatives **202b**,**c** are cytotoxic and show strong inhibitory effects on cyclooxygenase enzymes.[193]



202a : Ar = 4-HOC_6H_4; R^1 = H; R^2 = Et; Y = OH
202b : Ar = 2-Cl,4-HOC_6H_3; R^1 = R^2 = H; Y = OH
202c : Ar = 2-Cl,4-HOC_6H_3; R^1 = Cl; R^2 = H; Y = OH



Scheme 44. Synthesis of 1-methyl-4,5-diaryl-1*H*-imidazoles **192b–d**.



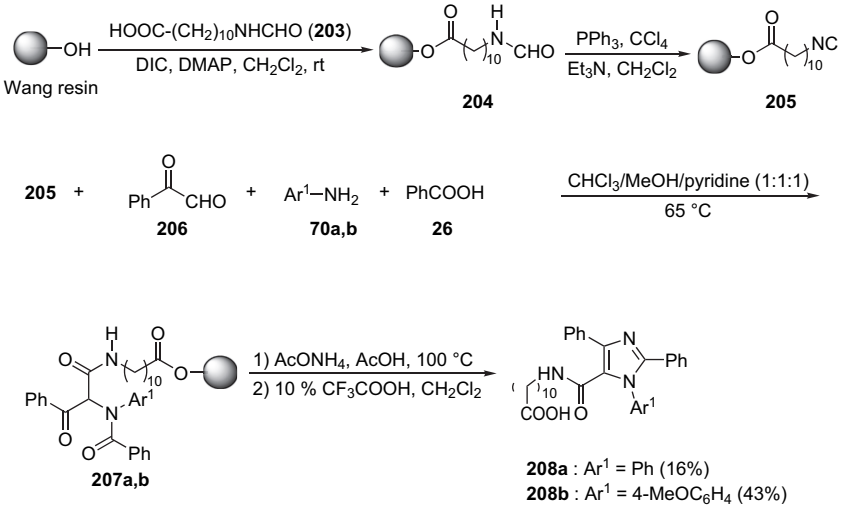
Scheme 45. Synthesis of 4,5-diaryl-1*H*-imidazoles **92** starting from *N*-benzylimidazole (**198**).

In this section, we summarize the few data reported so far in the literature on the synthesis of 1,2,4-triaryl-1*H*-imidazoles.

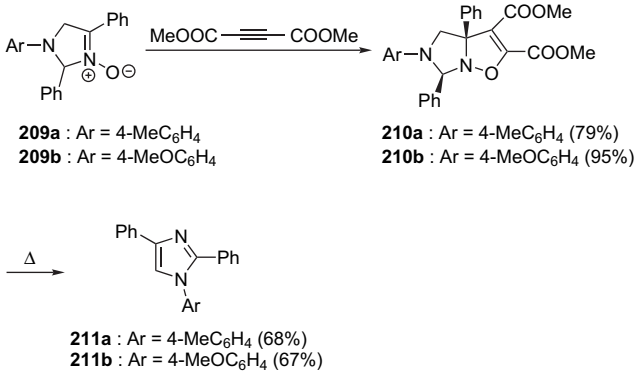
In 1996, the tetrasubstituted 1,2,4-triaryl-1*H*-imidazoles **208a**,**b** were synthesized by cyclization of α-(*N*-acyl-*N*-alkylamino)-β-ketoamides **207a**,**b** with ammonium acetate in acetic acid at 100 °C, followed by treatment of the resulting products with 10% trifluoroacetic acid in CH_2Cl_2 (Scheme 46).[194] Resins **207a**,**b** were obtained via an Ugi four-component condensation (U-4CC)[195] of phenylglyoxal (**206**), the required arylamines **70a**,**b**, benzoic acid (**26**), and isonitrile (**205**) attached on Wang resin.[196] The latter compound was obtained by the reaction of Wang resin with 11-formylaminoundecanoic acid (**203**) in CH_2Cl_2 in the presence of DIC and DMAP, followed by treatment of the resulting resin **204** with PPh_3 and CCl_4 (Scheme 46).[194]

More recently, 1,2,4-triaryl-1*H*-imidazoles **211a**,**b** have been prepared by a thermal ring-opening reaction of 3*a*,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazoles **210a**,**b**, obtained by diastereoselective cycloaddition of dimethyl acetylene dicarboxylate (DAD) with the Δ^3-imidazoline 3-oxides **209a**,**b** (Scheme 47).[197]

Finally, in 2005, the synthesis of 1,2,4-triaryl-1*H*-imidazoles **202a**–**h** has been performed utilizing a procedure very similar to that employed to prepare 1,2-diaryl-1*H*-imidazoles **16a**,**b**[79] (Scheme 48).[193] Specifically, amidines **13b**,**c**, prepared from aryl nitriles **212a**,**b** and anisidine according to Gautier[198] or Daoust[199] using sodium amide as condensing agent, were reacted with the α-bromoketones **213a**–**c** in $CHCl_3$ in the presence of aqueous K_2CO_3 to give the imidazole derivatives **202d**–**g**. Demethylation of these compounds



Scheme 46. Synthesis of 1,2,4-triaryl-1*H*-imidazoles **208a**,**b**.



209a : Ar = 4-MeC$_6$H$_4$
209b : Ar = 4-MeOC$_6$H$_4$

210a : Ar = 4-MeC$_6$H$_4$ (79%)
210b : Ar = 4-MeOC$_6$H$_4$ (95%)

211a : Ar = 4-MeC$_6$H$_4$ (68%)
211b : Ar = 4-MeOC$_6$H$_4$ (67%)

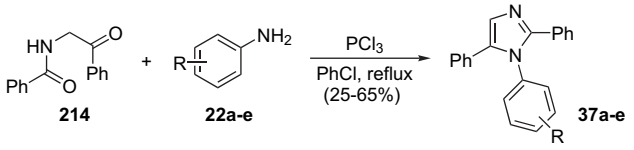
Scheme 47. Synthesis of 1,2,4-triaryl-1*H*-imidazoles **211a**,**b**.

with BBr_3 in CH_2Cl_2 then gave compounds **202h**, **202b**, **202c**, and **202a**, respectively, in high yields (Scheme 48).

2.5. Synthesis of 1,2,5-triaryl-1*H*-imidazoles

Until 1972, 1,2,5-triaryl-1*H*-imidazole derivatives **37** were not described in the literature. However, in that year, Popilin and Tiscenko[200] reported that treatment of ω-benzamidoacetophenone (**214**) with PCl_3 and 6 equiv of arylamines **22a–e** in boiling chlorobenzene gives compounds **37a–e** in 25–60% yield (Scheme 49).

Four years later, van Leusen and co-workers synthesized compounds **37a** and **37f** in 23 and 51% yield, respectively,



214 **22a-e** **37a-e**

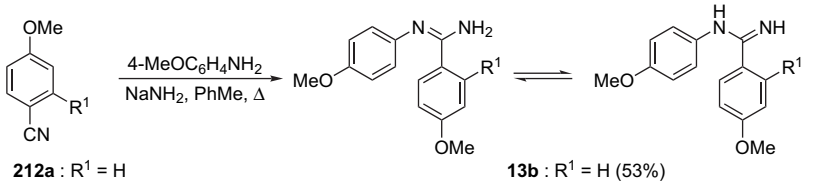
	a	b	c	d	e
R	H	4-MeO	2-MeO	4-Cl	2-Cl
yield (%)	55-60	65	30	50	25

Scheme 49. Synthesis of 1,2,5-triaryl-1*H*-imidazoles **37a–e**.

in a single operation from the *N*-tosylmethylimino compounds **215** and aldimines **216a** and **216b**, respectively (Scheme 50).[201]

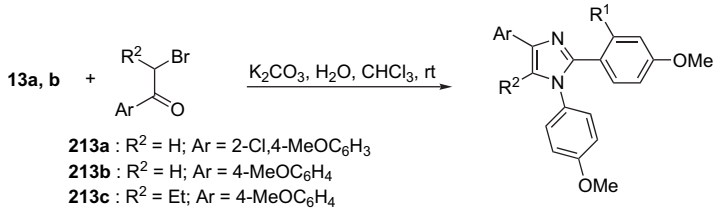
Imidazoles **37** have also been prepared via a multi-step process in which *N*-(benzotriazol-1-ylmethyl)thiobenzamide (**217**) was the starting material.[202] Lithiation of **217** and subsequent reaction with methyl iodide provided *S*-methyl-*N*-(benzotriazol-1-ylmethyl)thioimidate (**218**).

Lithiation of this compound followed by reaction with imines **216** gave 4,5-dihydroimidazoles **219**, which, upon treatment with $ZnBr_2$ or direct refluxing in toluene, yielded the required 1,2,5-triaryl-1*H*-imidazoles **37**.[202] This protocol was used for the preparation of compounds **37a** and **37g** in good yields (Scheme 51).[202]



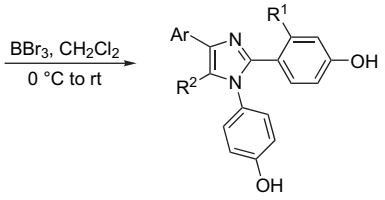
212a : R^1 = H
212b : R^1 = Cl

13b : R^1 = H (53%)
13c : R^1 = Cl (18%)



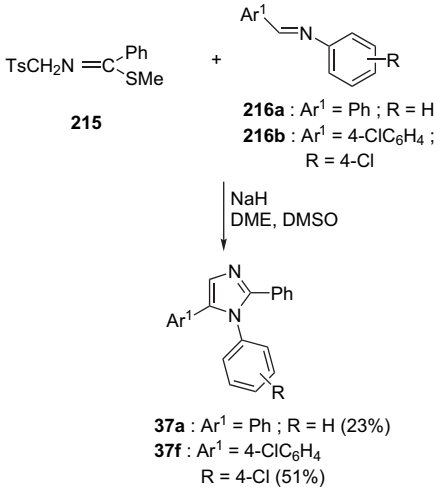
213a : R^2 = H; Ar = 2-Cl,4-MeOC$_6$H$_3$
213b : R^2 = H; Ar = 4-MeOC$_6$H$_4$
213c : R^2 = Et; Ar = 4-MeOC$_6$H$_4$

202d : R^1 = R^2 = H; Ar = 4-MeOC$_6$H$_4$ (63%)
202e : R^1 = R^2 = H; Ar = 2-Cl,4-MeOC$_6$H$_3$ (48%)
202f : R^1 = Cl; R^2 = H; Ar = 2-Cl,4-MeOC$_6$H$_3$ (80%)
202g : R^1 = H; R^2 = Et; Ar = 4-MeOC$_6$H$_4$ (22%)

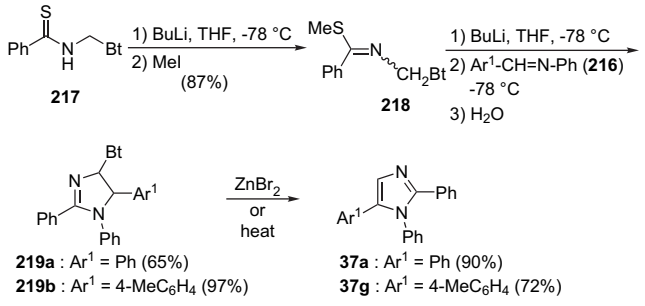


202h : R^1 = R^2 = H; Ar = 4-HOC$_6$H$_4$ (98%)
202b : R^1 = R^2 = H; Ar = 2-Cl,4-HOC$_6$H$_3$ (89%)
202c : R^1 = Cl; R^2 = H; Ar = 2-Cl,4-HOC$_6$H$_3$ (95%)
202a : R^1 = H; R^2 = Et; Ar = 4-HOC$_6$H$_4$ (39%)

Scheme 48. Synthesis of 1,2,4-triaryl-1*H*-imidazoles **202a–h**.



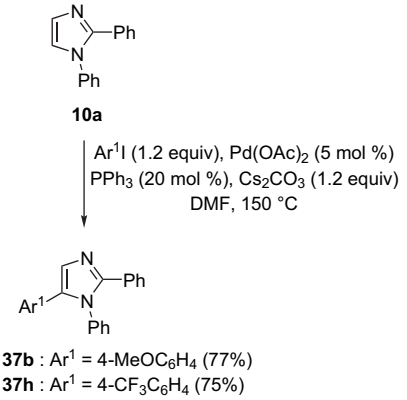
Scheme 50. Synthesis of 1,2,5-triaryl-1*H*-imidazoles **37a** and **37f** from **215** and aldimines **216a** and **216b**, respectively.



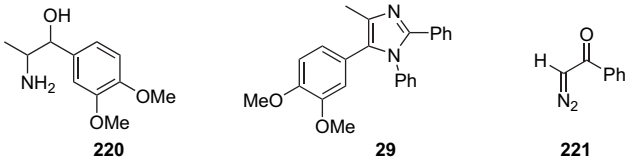
Scheme 51. Synthesis of compounds **37a** and **37g** from *N*-(benzotriazol-1-ylmethyl)thiobenzamide (**217**).

As mentioned in Section 2.1, the methodology developed in 2002 by Capretta and co-workers for the synthesis of 1,2-diaryl-1*H*-imidazole **16c** was also employed for the preparation of 4-methyl-1,2-diphenyl-5-(3,4-dimethoxy)phenyl-1*H* imidazole **29** from aminoalcohol **220** in 32% overall yield.[95]

Recently, compound **37a** has been synthesized from the diazocarbonyl compound **221** using a protocol very similar to that employed to prepare 1,2-diaryl-1*H*-imidazoles **36a–c**.[96]

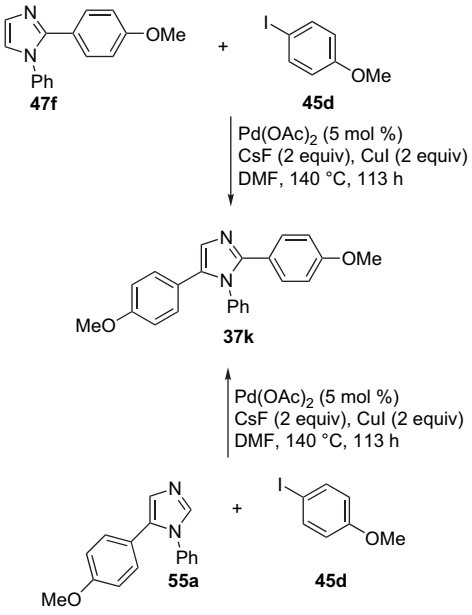


Scheme 52. Synthesis of 1,2,5-triaryl-1*H*-imidazoles **37b** and **37h–j**.

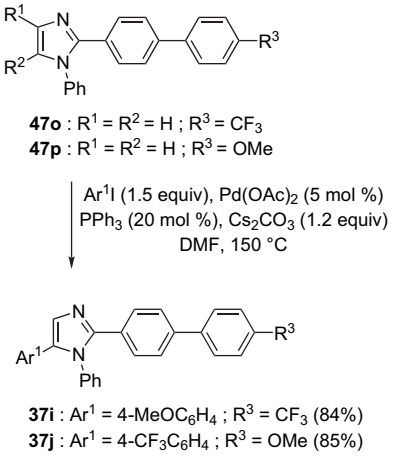


In recent years, the efficient synthesis of 1,2,5-triaryl-1*H*-imidazoles **37** has brilliantly been achieved by regioselective direct transition metal-mediated arylation of 1-aryl-1*H*-imidazoles[84] or 1,2-diaryl-1*H*-imidazoles.[83,100] Thus, Sezen and Sames[100] synthesized compounds **37b** and **37h** by C-5 arylation of 1,2-diphenyl-1*H*-imidazole (**10a**) with the required aryl iodides under the optimized conditions originally reported by Miura[203] for 2-phenyloxazole, 2-methylthiazole, and 1,2-dimethyl-1*H*-imidazole (Scheme 52).

1,2,5-Triaryl-1*H*-imidazoles **37i** and **37j** have analogously been prepared from 1,2-diaryl-1*H*-imidazoles **47o** and **47p**, respectively (Scheme 53).[100]

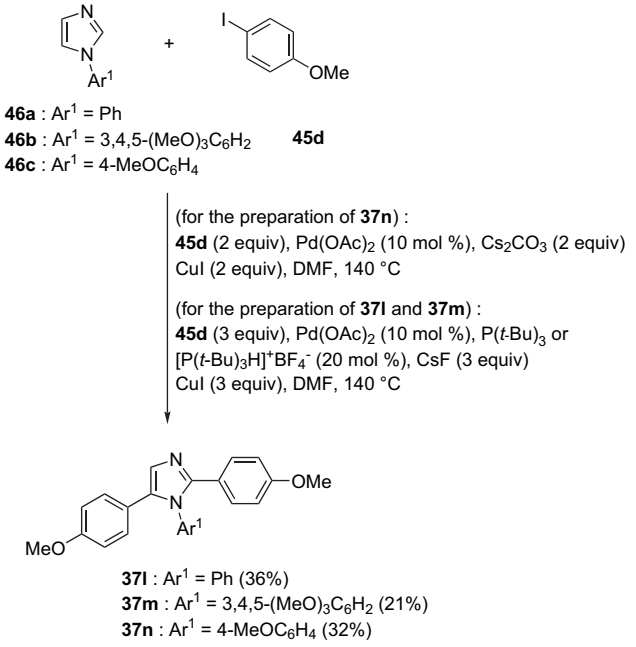


Scheme 53. Synthesis of compound **37k**.



More recently, we found that compound **37k**, which was isolated in 16% yield as a byproduct of the Pd- and Cu-mediated reaction of 1-phenyl-1*H*-imidazole (**46a**) with 4-iodoanisole (**45d**), could be obtained in 57% GLC yield by treatment of the 1,2-diaryl-imidazole derivative **47f** with 2 equiv of **45d** in DMF at 140 °C in the presence of 5 mol % $Pd(OAc)_2$, 2 equiv of CuI, and 2 equiv of CsF. Moreover, we synthesized this same compound in 74% GLC yield by the reaction of 1,5-diaryl-1*H*-imidazole **55a** with 2 equiv of **45d** in DMF at 140 °C in the presence of 5 mol % $Pd(OAc)_2$, 2 equiv of CuI, and 2 equiv of CsF (Scheme 53).[84]

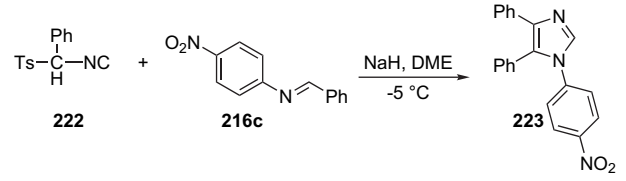
Furthermore, we showed that 1,2,5-triaryl-1*H*-imidazoles **37l–n** can be synthesized via a one-step process involving the direct Pd- and Cu-mediated arylation of 1-aryl-1*H*-imidazoles **46a–c** with iodide **45d** (Scheme 54).[83] Interestingly, this procedure, which allowed us to produce the required heterocycles in modest yields, did not require the necessary use of a phosphine ligand.



Scheme 54. Synthesis of compounds **37l–n** from the corresponding 1-aryl-1*H*-imidazoles **46**.

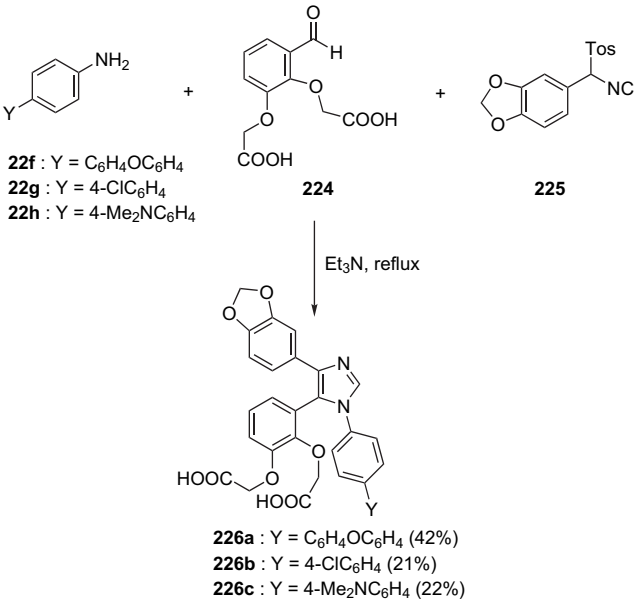
2.6. Synthesis of 1,4,5-triaryl-1*H*-imidazoles

The van Leusen strategy,[110] developed for the synthesis of 1,5-diaryl-1*H*-imidazoles, has also been employed to prepare 4,5-diphenyl-1-(4-chlorophenyl)-1*H*-imidazole (**223**). Specifically, this compound was obtained in 82% yield by the reaction of aldimine **213c** with the sodium salt prepared by treatment of the phenyl-substituted TosMIC derivative **222** with NaH in DME (Scheme 55).[110]



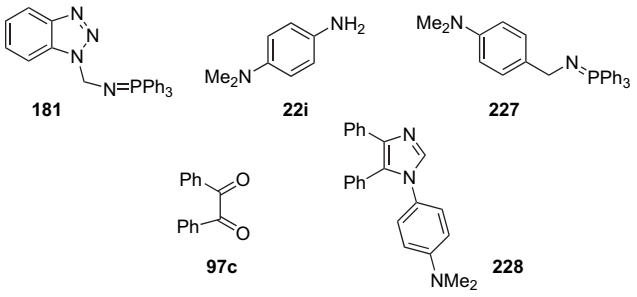
Scheme 55. Synthesis of compound **223**.

More recently, this strategy has been used to build up, in one step, imidazoles **226a–c** starting from aldehyde **224**, arylamines **22f–h**, and the aryl-substituted TosMIC reagent **225** (Scheme 56).[204]



Scheme 56. Synthesis of imidazoles **226a–c** according to the van Leusen strategy.

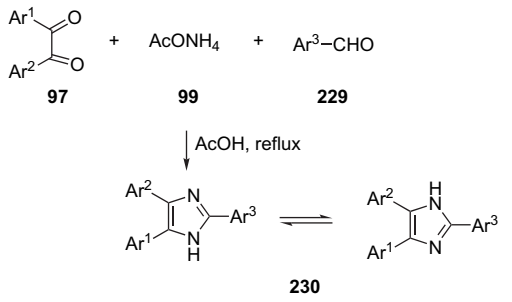
1,4,5-Triaryl-1*H*-imidazole **228** had previously been prepared in 84% yield by treatment of benzil (**97c**) with compound **227** obtained by treatment of Betmip (**181**) with 4-dimethylaminoaniline (**22i**).[182]



2.7. Synthesis of 2,4,5-triaryl-1*H*-imidazoles

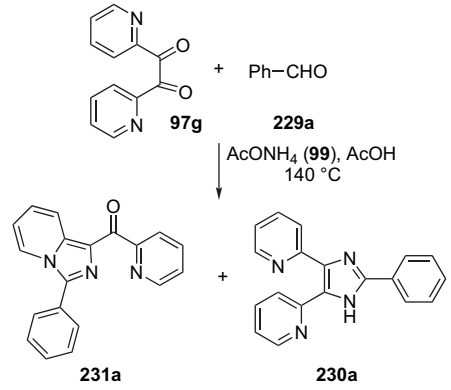
Cyclocondensation of a 1,2-diarylethanedione **97**, an aryl aldehyde **229**, ammonium acetate (**99**) or ammonia in refluxing acetic acid is a well-established procedure for the preparation of 2,4,5-triaryl-1*H*-imidazoles **230** (Scheme 57).[43,57,58,73,74,82,155,205–219]

However, this widely used synthetic protocol suffers from disadvantages such as harsh reaction conditions, prolonged reaction time, laborious work up and purification of the required reaction products, and formation of side products. With regard to this last aspect, it is worth mentioning that it has recently been reported that treatment of benzaldehyde (**229a**) with 2,2′-pyridyl (**97g**) and ammonium acetate in acetic acid at 110 °C gives a mixture of 4,5-bis(2-pyridyl)-



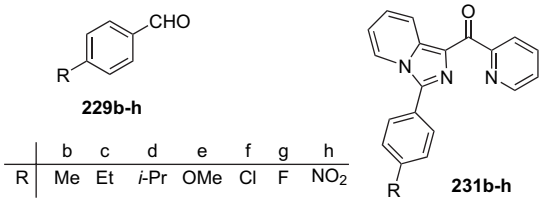
Scheme 57. Synthesis of 2,4,5-triaryl-1*H*-imidazoles **230** from α-diketones **97**, ammonium acetate (**99**), and aldehydes **229**.

2-phenyl-1*H*-imidazole (**230a**) and 1-(2-pyridyl)-3-phenyl-imidazo[1.5-*a*]pyridine (**231a**) (Scheme 58).[220]



Scheme 58. Synthesis of a mixture of compounds **230a** and **231a**.

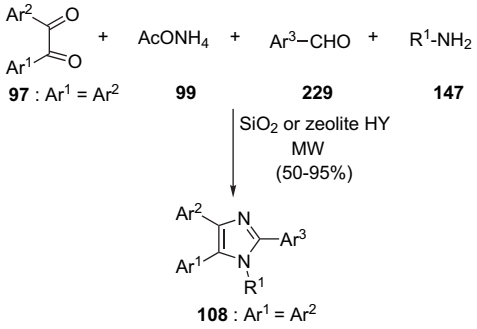
The yield of **231a** was 67.2% when **97f**, **229a**, and **99** were in a 2:1:2 molar ratio, respectively. However, **230a** was obtained in 37.5% yield when these three reagents were in a 1:1:8 molar ratio.[220] Interestingly, imidazo[1.5-*a*]pyridines **231b–h** were obtained in 42–68% yield when **97g**, aryl aldehydes **229b–h**, and ammonium acetate were in a 2:1:2 molar ratio, respectively.[220]



R	b Me	c Et	d *i*-Pr	e OMe	f Cl	g F	h NO_2

Reduction in reaction time, increases in the yield, and suppression of side product formation have recently been reported for several microwave (MW)-assisted syntheses of 2,4,5-triaryl-1*H*-imidazoles from 1,2-diketones **97**, ammonium acetate (**99**), and aryl aldehydes **229**.[221–224]

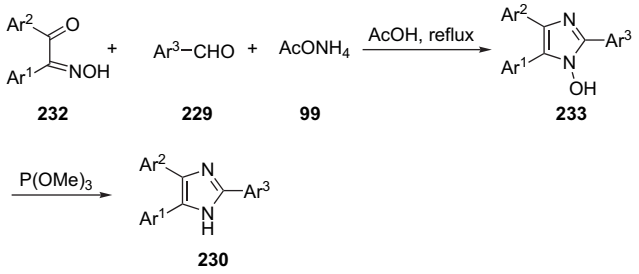
These reactions have sometimes been performed in the presence of silica gel as the solid support[225] and their modifications involving the use of a primary amine **147** and ammonium acetate have been employed in the synthesis of tetrasubstituted 2,4,5-triaryl-1*H*-imidazoles **108** where Ar^1=Ar^2 (Scheme 59).[226–228] The significant shortfall of this methodology is the necessity to use symmetrical benzils, due to a lack of regiocontrol for the 4- and 5-positions in the process.



Scheme 59. Synthesis of tetrasubstituted 2,4,5-triaryl-1*H*-imidazoles **108**.

Recently, a large number of 2,4,5-triaryl-1*H*-imidazoles **230** where Ar^1=Ar^2 have been prepared in excellent yields and short reaction times by the reaction of symmetrical 1,2-diketones **97** with aryl aldehydes **229** and ammonium acetate in 1-butylimidazolium tetrafluoroborate [(Hbim)BF_4], a room temperature ionic liquid,[229] or in 1,1,3,3-*N*,*N*,*N*′,*N*′-tetramethylguanidinium trifluoro-acetate.[230] It should be noted that the methodology involving the use of [(Hbim)BF_4] is characterized by a simple work up procedure and efficient recovery and recycling of the ionic liquid, which acts as a promoter.[229]

On the other hand, Gallagher and co-workers[153] synthesized 2,4,5-triaryl-1*H*-imidazoles **230** by using a strategy that involves the cyclocondensation reaction of keto-oximes **232** with aldehydes **229** and ammonium acetate, followed by reduction of the resulting *N*-hydroxyimidazoles **233** with trimethyl phosphite (Scheme 60).

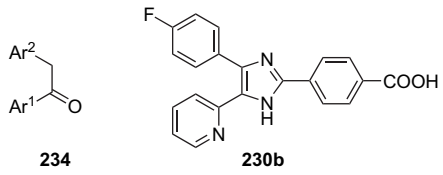


Ar^1 = 4-pyridyl; Ph; 2-Me,4-pyridyl; 4-quinolyl; 4-BnNMeCH$_2$C$_6$H$_4$; 4-MeOOC$_6$H$_4$; 4-CH$_2$-*N*-morpholinoC$_6$H$_4$
Ar^2 = 4-NO_2C$_6$H$_4$; 4-(CN)C$_6$H$_4$; 4-MeSOC$_6$H$_4$; 4-FC$_6$H$_4$; 3-ClC$_6$H$_4$; 2-MeOC$_6$H$_4$; 3-MeOC$_6$H$_4$; 3-NO_2C$_6$H$_4$; 1-naphthyl; 2-naphthyl; 3-NH_2C$_6$H$_4$; 3-$MeSO_2$C$_6$H$_4$
Ar^3 = 4-NO_2C$_6$H$_4$; 4-$MeSO_2$NHC$_6$H$_4$; 4-(CHO)NHCH$_2$C$_6$H$_4$; 4-N_3C$_6$H$_4$; 4-(CN)C$_6$H$_4$; 4-(COOH)C$_6$H$_4$; 4-EtOOCC$_6$H$_4$

Scheme 60. Synthesis of 2,4,5-triaryl-1*H*-imidazoles **230** from keto-oximes **232**.

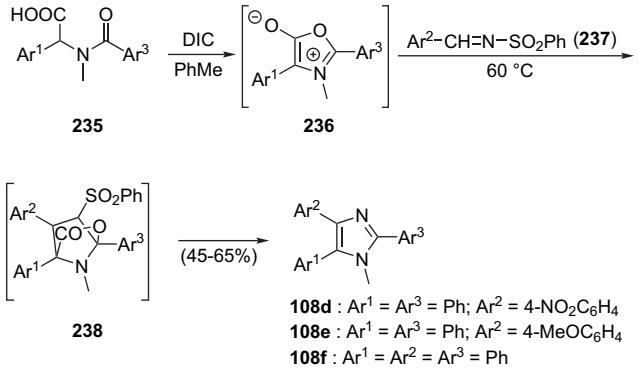
Compounds **232**, which are more readily available compared to the corresponding 1,2-diketones, can be prepared by treatment of ketones **234** with sodium nitrite and HCl.[153]

In 2002, the strategy depicted in Scheme 61 was used to prepare compound **230b**, an imidazole derivative with reduced



234 **230b**

inhibitory activity of ALK5 kinase, which does not inhibit p38 MAP kinase.[48]



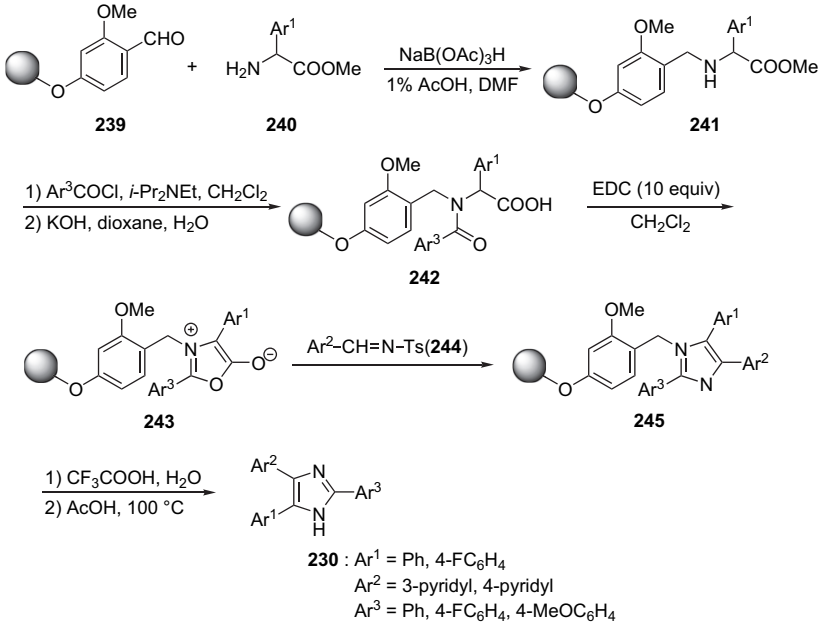
Scheme 61. Synthesis of 1-methyl-2,4,5-triaryl-1*H*-imidazoles **108d–f**.

More recently, compounds **230** where Ar^1 is 4-pyrimidyl or 4-pyridyl have been synthesized in modest yields from the corresponding keto-oximes **232** via cyclization to *N*-hydroxyimidazoles **233** and an unprecedented in situ thermal reduction of the N–O bond upon microwave irradiation at 200 °C for 20 min.[231]

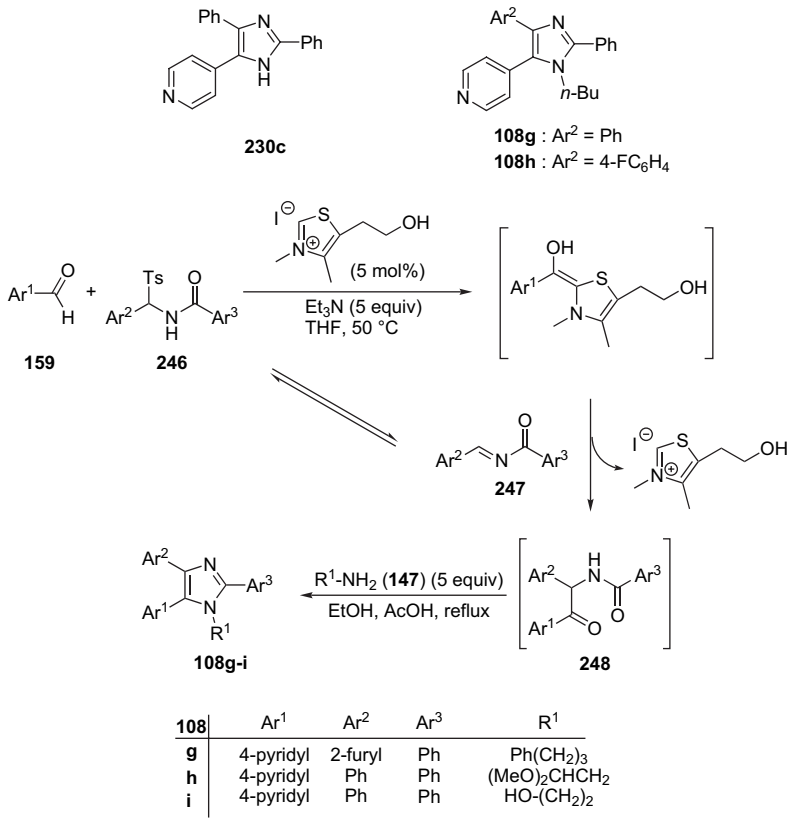
In 1991, a direct approach to 1-methyl-2,4,5-triaryl-1*H*-imidazoles **108** with two different aryl groups at the 4- and 5-positions was achieved by cycloaddition of mesoionic 1,3-oxazolium-5-olates (münchnones) **236** with *N*-(arylmethylene)benzenesulfonamides **237** via formation of unstable primary bicyclic adducts **238** (Scheme 61).[232] Compounds **236** could be prepared in situ from the corresponding *N*-acyl-α-aminoacids **235** and *N*,*N*′-dicyclohexylcarbodiimide (DIC) in toluene. This protocol was used to prepare compounds **108d–f**.

However, the versatility of this methodology proved to be limited to 1-methyl-1*H*-imidazole derivatives. Furthermore, it must be taken into account that münchnones have the potential to selfcondense[232,233] and this can cause low yields. Nevertheless, this side reaction can readily be suppressed in a solid-phase approach. In fact, a library of 12 2,4,5-triaryl-1*H*-imidazoles **230** has been prepared in 53–99% yield and high purity by the reaction of the resin-bound münchnones **243** with tosylimines **244** in CH_2Cl_2 in the presence of 10 equiv of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), followed by release of the imidazoles from the polymer-linked derivatives **245** by acidic treatment (Scheme 62).[234] Münchnones **243** were synthesized via cyclization of compounds **242**, which were obtained by acylation of compounds **241**, prepared from the commercially available polystyrene-poly(ethylene glycol) graft copolymer resin **239** and the amino acid methyl esters **240** (Scheme 62).[234]

Recently, Frantz and co-workers described a methodology that allows the one-pot synthesis of tetrasubstituted 2,4,5-triaryl-1*H*-imidazoles **108** and has no apparent limitation to the amine incorporated in the 1-position of these heterocycles.[143] The cornerstone of this methodology is the thiazolium-catalyzed addition of an aryl aldehyde **159** to an acylimine **247** to generate the corresponding α-ketoamide **248** and the subsequent addition of an appropriate amine **147**, followed by ring closure to the imidizole derivative (Scheme 63). Acylimines **247** were prepared in situ by elimination of *p*-toluenesulfinic acid from compounds **246**.



Scheme 62. Solid-supported synthesis of 2,4,5-triaryl-1*H*-imidazoles **230**.

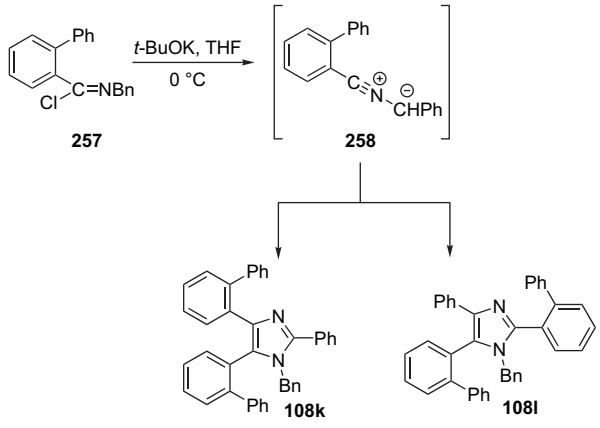


108	Ar1	Ar2	Ar3	R1
g	4-pyridyl	2-furyl	Ph	$Ph(CH_2)_3$
h	4-pyridyl	Ph	Ph	$(MeO)_2CHCH_2$
i	4-pyridyl	Ph	Ph	$HO-(CH_2)_2$

Scheme 63. One-pot synthesis of compounds **108g–i**.

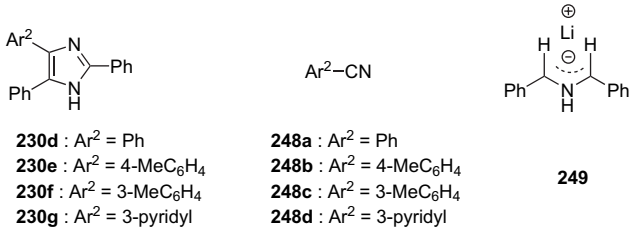
This methodology was used for the one-pot synthesis of compounds **108g**, **108h**, and **108i** in 76, 80, and 75% yield, respectively (Scheme 63) and 2,4,5-triaryl-1*H*-imidazole **230c** in 78% yield.[143]

In 2005, a solid-phase route involving a synthetic approach similar to that shown in Scheme 64 was followed to prepare compounds **108j**, **108k**, and **108l** in 35, 34, and 27% yield, respectively.[235]



Scheme 64. Synthesis of mixture of compounds **108k** and **108l**.

2,4,5-Triaryl-1*H*-imidazoles have also been prepared starting from aryl nitriles. In fact, several years ago, it was reported that compounds **230d** (lophine), **230e**, **230f**, and **230g** can be prepared in 10, 52, 50, and 47% yields, respectively, by the reaction of the required aryl nitriles **248** with the 2-azallyllithium derivative **249**, prepared by treatment of the corresponding azomethine derivative with LDA.[236] More recent work by Hayes and co-workers[237] shows that aryl nitriles **248** are able to react with α,α-dilithioarylnitromethanes **250** to give 2,4,5-triaryl-1*H*-imidazoles **251** in good yields. An unusual cyclization–elimination mechanism has been proposed for this reaction.[237]

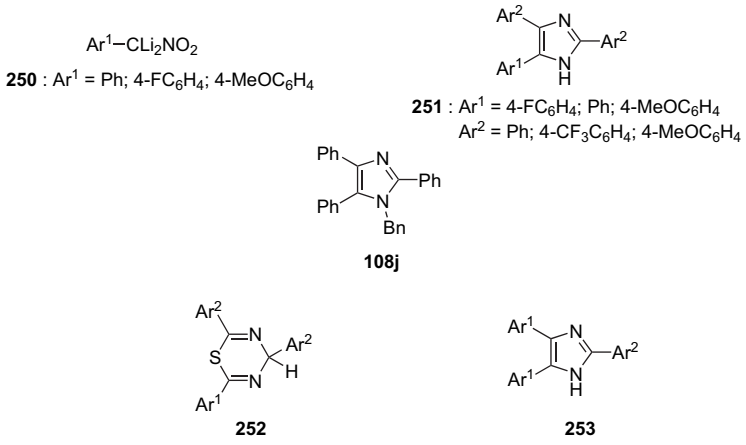


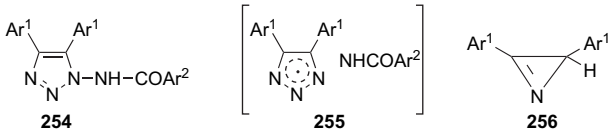
230d : Ar^2 = Ph
230e : Ar^2 = 4-MeC_6H_4
230f : Ar^2 = 3-MeC_6H_4
230g : Ar^2 = 3-pyridyl

248a : Ar^2 = Ph
248b : Ar^2 = 4-MeC_6H_4
248c : Ar^2 = 3-MeC_6H_4
248d : Ar^2 = 3-pyridyl

Lophine (**230d**) and the corresponding 1-benzyl derivative, **108j** had previously been isolated in low yields from the products of the reactions between benzylamine and CCl_4 at 150 °C in an autoclave under CO or nitrogen pressure in the presence of a catalytic quantity of $Co_2(CO)_8$.[238] On the other hand, **230d** and other 2,4,5-triaryl-1*H*-imidazoles of general formula **253** were easily obtained in high yields by reacting 2,4,6-triaryl-4*H*-1,3,5-thiadiazines **252** with aliphatic amines at room temperature.[239]

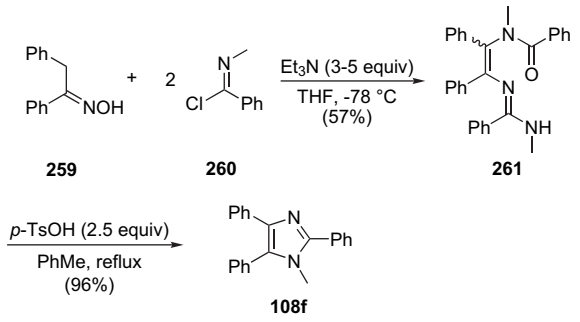
Compounds **253** were also obtained together with the corresponding 2,3-diaryl-2*H*-azirines **256** as the major products of pyrolysis of 1-aroylamino-4,5-diaryl-1,3,3-triazoles **254**, which, presumably, proceeds via the 4,5-diaryl-1,2,3-triazolyl radicals **255**.[240]





On the other hand, a mixture of the tetrasubstituted 2,4,5-triaryl-1*H*-imidazoles **108k** and **108l** was obtained from nitrile ylide **258**, generated via the base-catalyzed 1,3-dehydrochlorination of imidoyl chloride **257** (Scheme 64).[241]

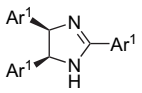
In 1993, a hetero-Cope rearrangement was used as key reaction of a two-step synthesis of imidazole **108f**.[242] Specifically, oxime **259** was reacted with a 2-fold excess of imidoyl chloride **260** in the presence of Et_3N to afford the amidine **261**. This compound readily underwent the hetero-Cope rearrangement in refluxing toluene in the presence of 2.5 equiv of *p*-toluenesulfonic acid to give **108f** (Scheme 65).[242]



Scheme 65. Synthesis of compound **108f** via hetero-Cope rearrangement of amidine **261**.

In 2003, 2,4,5-triaryl-1*H*-imidazoles **263a–f** were synthesized in 40–90% yield by heating the corresponding triaryl-2,4-diazapentadienes **262a–f** with a stoichiometric amount of *t*-BuOK in DMSO in the presence of air or oxygen.[243] Compounds **262** were prepared by the reaction of the corresponding aryl aldehydes with a solution of ammonia in 95% EtOH and ammonium chloride[243] or with liquid ammonia.[244]

More recently, imidazoles **263a**, **263d**, **263g**, and **263h** have been obtained in modest-to-satisfactory yields by thermal cyclization of **262a**, **262d**, **260g**, and **262h**, respectively, at 120 °C and 10^{-2} Torr, followed by further heating at 140–160 °C of the resulting *cis*-imidazolines **264a–d**.[244]

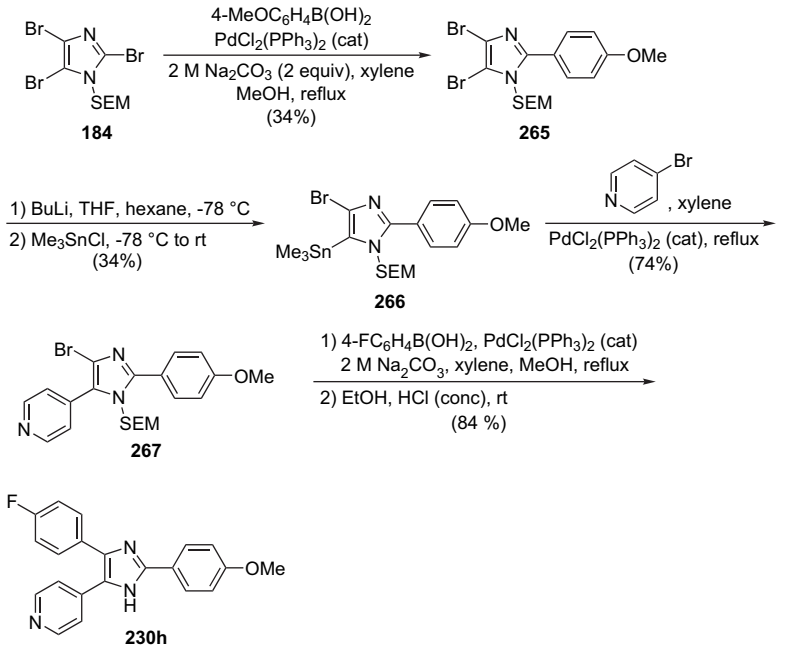


264a : Ar^1 = Ph
264b : Ar^1 = 2-thienyl
264c : Ar^1 = 2-furyl
264d : Ar^1 = 3-thienyl

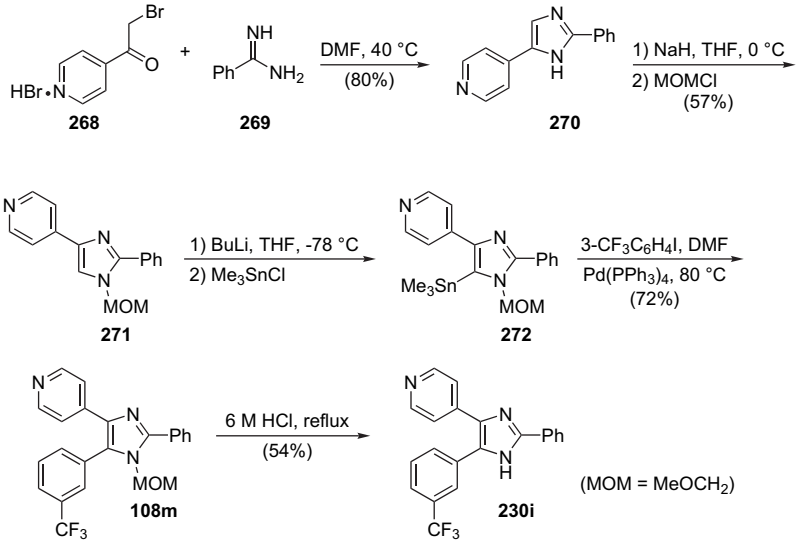
Another strategy followed for the multi-step synthesis of 2,4,5-triaryl-1*H*-imidazoles involves the structural modification of functionalized imidazole derivatives via classical Pd-catalyzed cross-coupling reactions of organometallic reagents. Thus, in 1998, Revesz and co-workers[188] synthesized compound **230h** in 6% overall yield from the known SEM-protected 2,4,5-tribromo-1*H*-imidazole (**184**)[187] using two Suzuki-type reactions involving imidazolyl bromides **184** and **267** and a Stille-type reaction between 4-bromopyridine and the trimethyltin derivative **266** regioselectively prepared from the 4,5-dibromoimidazole derivative **265** (Scheme 66).[188]

A Stille-type coupling was also used as a key step in the synthesis of 2,4,5-triaryl-1*H*-imidazole **230i** from 4-(bromoacetyl)pyridine hydrobromide (**268**) and benzamidine (**269**) (Scheme 67).[151] Thus, imidazole **270**, which was prepared from **268** and a molar excess of **269**, was protected as the

	a	b	c	d	e	f	g	h
Ar^1	Ph	4-BrC_6H_4	4-$MeOC_6H_4$	2-thienyl	3-$NO_2C_6H_4$	4-pyridyl	2-furyl	3-thienyl

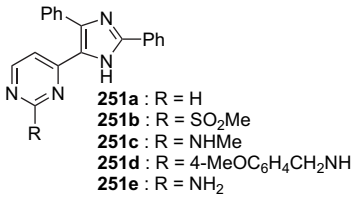


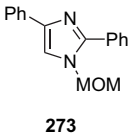
Scheme 66. Multi-step synthesis of 2,4,5-triaryl-1*H*-imidazole **230h**.



Scheme 67. Synthesis of compound **230i**.

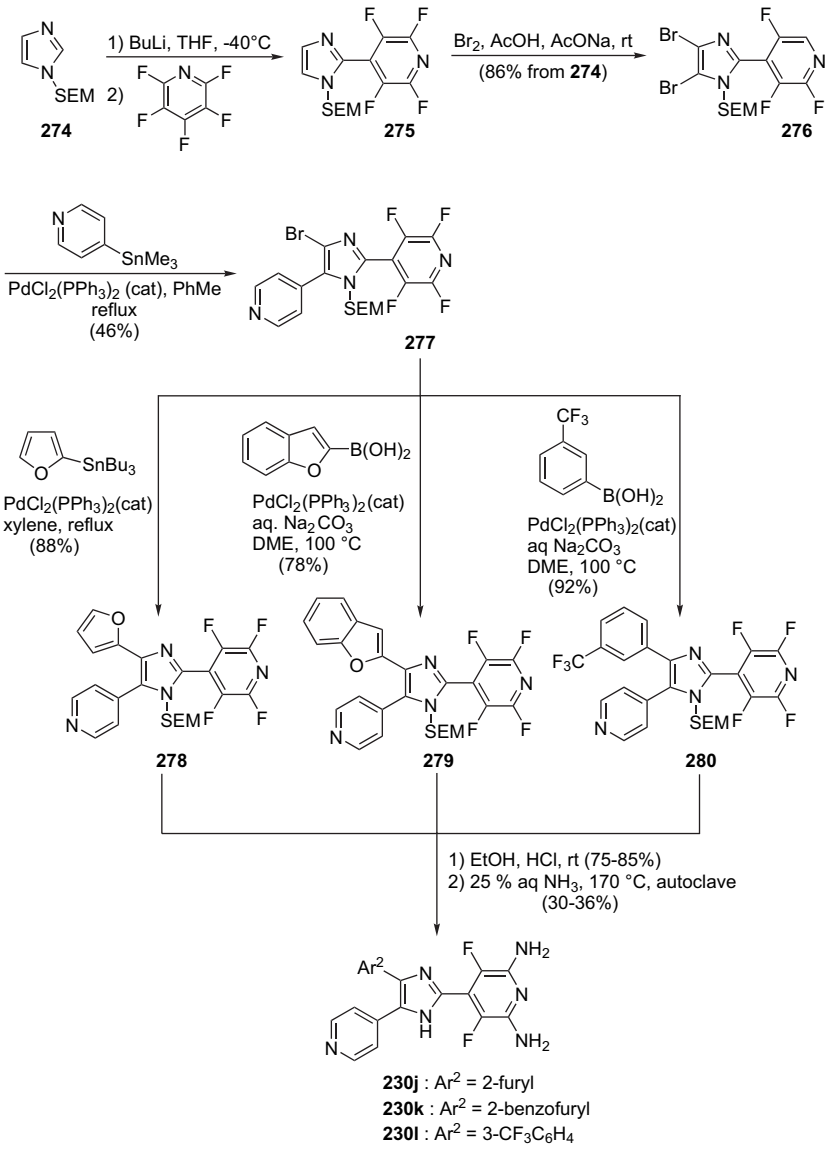
1-methoxymethyl ether to give a 3:1 mixture of regioisomers favoring the less-hindered isomer **271**. This compound was functionalized at the 5-position by treatment with butyllithium and subsequent reaction with chlorotrimethyltin. The resulting organometallic derivative **272** underwent smooth Pd-catalyzed coupling with 3-iodo-(trifluoromethyl)benzene to give the imidazole derivative **108m**. Finally, this compound was deprotected by treatment with aqueous HCl to furnish the required 2,4,5-triaryl-1*H*-imidazole **230i**.





A related stannane coupling-based route was used to prepare the 5-(4-pyrimidinyl)-2-phenyl-1*H*-imidazole derivatives **251a–e** from the MOM-protected imidazole **273**.[151]

In 2002, Novartis Pharma researchers developed a method for preparing the aryl-substituted pyridinylimidazoles **230j–l** (Scheme 68).[245] Specifically, the SEM-protected imidazole **274** was treated with butyllithium and the resulting 2-lithium derivative underwent regioselective arylation with pentafluoropyridine to give compound **275**. Bromination of this compound gave the dibromo derivative **276**, which underwent regioselective Pd-catalyzed reaction with



Scheme 68. Synthesis of compounds **230j–l**.

4-trimethylstannylpyridine to furnish compound **277**. The remaining C–Br bond at C-4 of this compound served to introduce the 2-furyl group of compound **278** via a Stille reaction and the 2-benzofuryl group of compound **279** and the 3-trifluoromethylphenyl group of **280** via Suzuki-type reactions. Removing the SEM-protecting group from **278**, **279**, and **280** under acidic conditions, followed by heating in an autoclave at 170 °C in the presence of 25% aqueous ammonia delivered compounds **230j**, **230k**, and **230l**, respectively, in moderate yields.[245]

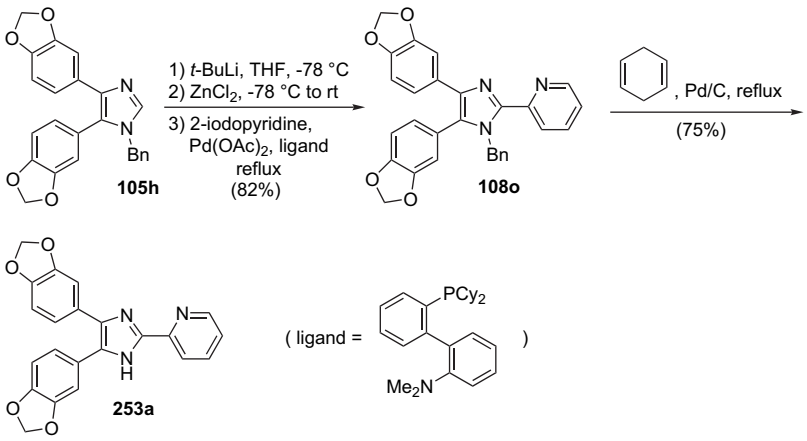
More recently, a Negishi-type cross-coupling reaction has been used to prepare 2,4,5-triaryl-1*H*-imidazole **253a** from 4,5-diaryl-1*H*-imidazole **105h** (Scheme 69).[246] The imidazol-2-ylzinc reagent used in this reaction was generated by treatment of **105h** with *tert*-butyllithium in THF at –78 °C, followed by addition of $ZnCl_2$. The Pd-catalyzed cross-coupling of this organozinc reagent with 2-iodopyridine led to imidazole **108o**, which was then converted into the target compound by Pd-catalyzed hydrogenolysis.[246]

2.8. Synthesis of 1,2,4,5-tetraaryl-1*H*-imidazoles

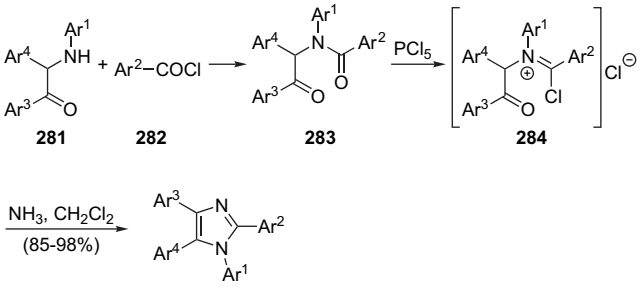
In 1968, Heinze and co-workers developed a three-step procedure for the synthesis of 1,2,4,5-tetraaryl-1*H*-imidazoles **285a–k** from the required desylamines **281** and aroyl chlorides **282**.[247] This procedure involved the formation of *N*-(α-chlorobenzylideneanilino)desoxy-benzoin derivatives **284** from α-amido ketones **283** (Scheme 70).[247] Later, compound **285a** was synthesized by Stradi and co-workers by the reaction of enamine **286** with *N*-chloro-*N*′-phenylbenzamidine (**5a**) and treatment of the resulting compound **287** with sulfuric acid at 130 °C (Scheme 71).[248]

A similar reaction sequence was used to prepare 1,2,4-triaryl-1*H*-imidazoles **288a–c**.[248]

Compound **285a** was alternatively prepared in two steps in 52% overall yield by the reaction of oxime **259** with imidoyl chloride **289** via a hetero-Cope rearrangement of the resulting amidine **290**.[242]

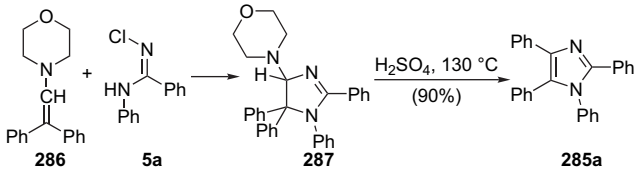


Scheme 69. Synthesis of compound **253a**.

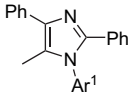


285a : $Ar^1 = Ar^2 = Ar^3 = Ar^4 = Ph$
285b : $Ar^1 = Ar^3 = Ar^4 = Ph$; $Ar^2 = 4\text{-}MeOC_6H_4$
285c : $Ar^1 = Ar^3 = Ar^4 = Ph$; $Ar^2 = 4\text{-}ClC_6H_4$
285d : $Ar^1 = Ar^3 = Ar^4 = Ph$; $Ar^2 = 4\text{-}NO_2C_6H_4$
285e : $Ar^1 = Ar^3 = Ar^4 = Ph$; $Ar^2 = 4\text{-}Me_2NC_6H_4$
285f : $Ar^2 = Ar^3 = Ar^4 = Ph$; $Ar^1 = 4\text{-}MeOC_6H_4$
285g : $Ar^1 = Ar^2 = 4\text{-}MeOC_6H_4$; $Ar^3 = Ar^4 = Ph$
285h : $Ar^1 = Ar^2 = Ph$; $Ar^3 = Ar^4 = 4\text{-}MeOC_6H_4$
285i : $Ar^1 = Ph$; $Ar^2 = Ar^3 = Ar^4 = 4\text{-}MeOC_6H_4$
285j : $Ar^1 = Ar^3 = Ar^4 = 4\text{-}MeOC_6H_4$; $Ar^2 = Ph$
285k : $Ar^1 = Ar^2 = Ar^3 = Ar^4 = 4\text{-}MeOC_6H_4$

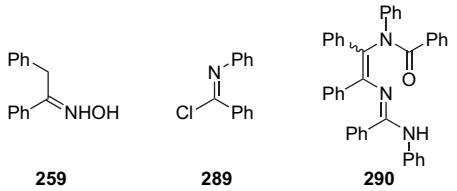
Scheme 70. Synthesis of compounds **285a**–**k**.



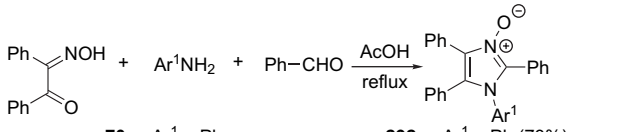
Scheme 71. Synthesis of compound **285a** from **5a** and **286**.

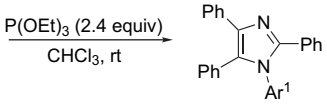


288a : $Ar^1 = Ph$
288b : $Ar^1 = 4\text{-}MeC_6H_4$
288c : $Ar^1 = 4\text{-}FC_6H_4$



Finally, 1,2,4,5-tetraaryl-1*H*-imidazoles **285a** and **285l** were synthesized by condensation of benzil monoxime **291**, benzaldehyde (**73a**), and arylamines **70a** and **70f**, respectively, followed by reduction of the resulting 1-aryl-2,4,5-triphenyl-1*H*-imidazole-*N*-oxides, **291a** and **291b**, with triethyl phosphite (Scheme 72).[249]





285a : $Ar^1 = Ph$ (89%)
285l : $Ar^1 = 4\text{-}MeC_6H_4$ (100%)

Scheme 72. Synthesis of compounds 2**85a** and **285l** via reduction of the corresponding tetraarylimidazole-*N*-oxides.

3. Biological properties of vicinal diaryl-substituted 1*H*-imidazoles

In this section, an overview of the biological properties of imidazole derivatives with two aryl groups on adjacent positions is given. In particular, we dwell upon the compounds included in the following classes: (a) inhibitors of p38 MAP kinase; (b) inhibitors of B-Raf kinase; (c) inhibitors of transforming growth factor β1 (TGF-β1) type 1 activin receptor-like kinase (ALK5); (d) inhibitors of the biosynthesis of interleukin-1 (IL-1); (e) cyclooxygenase-2 (COX-2)

inhibitors; (f) antagonists of the cannabinoid CB_1 receptor; (g) selective acyl-CoA: cholesterol *O*-acyl transferase (ACAT) inhibitors; (h) glucagon receptor antagonists; (i) compounds endowed with a neurochemical profile similar to that of clozapine; (j) combretastatin A-4 (CA-4) analogues with antitumor activities; (k) modulators of P-glycoprotein (P-gp) mediated multidrug resistance (MDR); and (i) antibacterial agents.

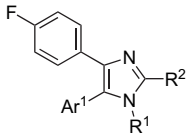
3.1. Inhibitors of p38 MAP kinase

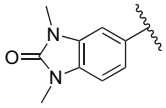
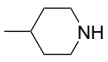
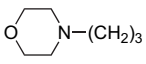
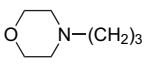
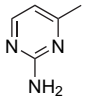
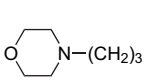
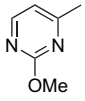
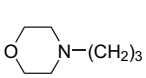
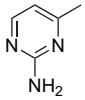
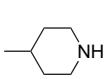
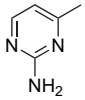
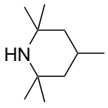
The mitogen-activated protein (MAP) kinases are a family of ubiquitously distributed enzymes, which are able to mediate intracellular signal transduction and participate in a number of physiological as well as pathophysiological cellular processes including cell growth, differentiation, and apoptosis.[13,250,251] The members of the mammalian MAP kinase family that include ERK1, ERK2, ERK3α, ERK3β, JNK1, JNK2, JNK3, p38α, p38β, p38γ, p38δ, and ERK5 share sequence similarity and conserved structural domains.[252,253] The extracellular-signal regulated kinases (ERKs) are activated by growth and mitogen factors via a Ras-dependent pathway.[253,254] In contrast, Jun N-terminal kinases (JNKs) and p38 kinases are activated in response to the pro-inflammatory cytokines interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α) and by environmental stress including toxins, UV light, heat, shock, and cellular injury.[255]

The human p38α MAP kinase was originally identified as the molecular target of the pyridinylimidazole class of compounds that were known to inhibit the biosynthesis of inflammatory cytokines such as IL-1 and TNF in lipopolysaccharide (LPS)-stimulated human monocytes.[256] At the present time, it is known that pyridinylimidazole drugs also inhibit p38β and that the p38 kinases, p38γ and p38δ, are insensitive to these drugs.[256] Nevertheless, during the last 10 years a number of novel chemotypes of p38 kinase inhibitors, which include a variety of 4,5-diaryl- and 2,4,5-triaryl-1*H*-imidazoles, have been discovered via high-throughput screening.[14,257] In particular, 4,5-diaryl-1*H*-imidazoles in which an aryl substituent is a pyrimidine or a pyridine group and the second aryl substituent is a 4-fluorophenyl group form an important class of these inhibitors vigorously pursued by a number of pharmaceutical companies and research institutes as anti-inflammatory drugs.[163,165,167,257–271]

Several examples of 5(4)-aryl-4(5)-(4-fluorophenyl)-1*H*-imidazoles, which are p38 MAP kinase inhibitors and are also known as CSBP, RK or HOG1 inhibitors, are listed in Table 3. Compounds **163af** (SB-210313),[12,151,167] **309**

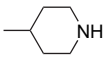
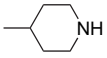
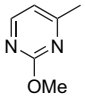
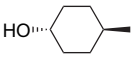
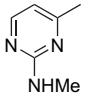
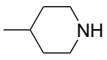
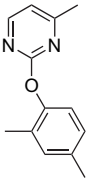
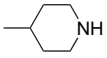
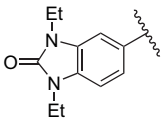
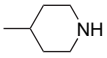
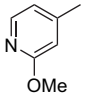
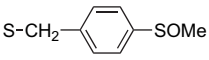
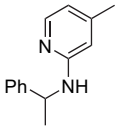
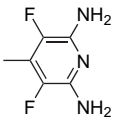
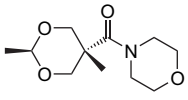
Table 3. 5(4)-Aryl-4(5)-(4-fluorophenyl)-1*H*-imidazole derivatives, which are p38 mitogen-activated protein kinase inhibitors



Compound	Ar^1	R^1	R^2	Ref.
293		H	H	168
294			H	12
295			H	258
163af (SB-210313)			H	167
163r			H	258
296			H	258
297 (SB-220025)			H	259
298			H	256

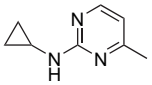
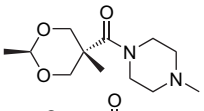
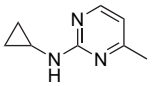
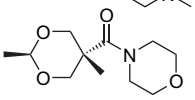
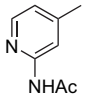
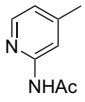
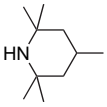
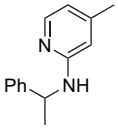
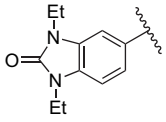
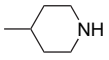
(*continued*)

Table 3. (*continued*)

Compound	Ar^1	R^1	R^2	Ref.
299			H	257
300 (SB-242235)			H	163,260,261
301 (SB-239063)			H	163
302			H	262
303			H	257
304			H	168
305 (ML-3375)		H	SMe	148,151
306		H	SMe	123e
307 (ML-3163)		H		263
308		H	SMe	123e
309 (SB-203580)		H	4-$MeSOC_6H_4$	264–267
310		H	4-ClC_6H_4	268
311		H		125
312 (SB-202190)		H	4-HOC_6H_4	270,267
313		H	*t*-Bu	125
314 (RPR 200765A)		H		258
315		H	$-CMe_2OH$	125

(*continued*)

Table 3. (*continued*)

Compound	Ar^1	R^1	R^2	Ref.
316		H		125
317 (RPR 238677)		H		133
318 (RPR 203494)		H		134
319		CH_2CH_2OMe	SMe	149
320		Me	SMe	270
321			SMe	270
322			SMe	123e
323		Me	SMe	123e
324 (RWJ-67657)		$Ph–(CH_2)_3$	$HO–(CH_2)_2–C\equiv C$	169,271
325		Me		168

(SB-203580),[77,264–267] **312** (SB-202190),[269] **314** (RPR-200765A),[165] and **323** (RWJ-67657)[169,271] are typical examples of pyridinylimidazoles in which the 4-pyridinyl substituent was considered as an essential element in the early p38 inhibitors.[13] Indeed, the strong hydrogen bond established between the p38 amide NH of Met[109] and the pyridine nitrogen is a key determinant of binding affinity common to all pyridinylimidazole p38 MAP kinase inhibitors.[13]

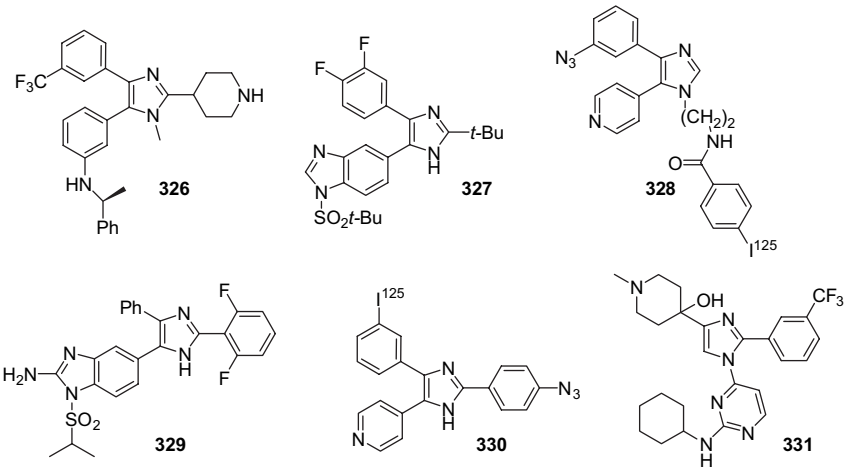
However, these substances also potently inhibit human hepatic cytochrome P-450 enzymes[165,259] and inhibitors of these enzymes are known to potently cause drug–drug interactions or to lead to hepatic changes such as P-450 enzyme induction.[165] The potent in vitro inhibitory activity of these substances for some cytochrome P-450 isoenzymes, due to the fact that both pyridine and imidazole are ligands for the heme iron of cytochrome P-450,[260] and their consequent severe liver toxicity prevented the clinical development of these first-generation p38 inhibitors. Thus, important modifications of their structure were introduced with the successful replacement of the 4-pyridyl moiety by related heterocycles. In particular, replacement of the pyridine ring by a pyrimidine moiety in a number of previous series of pyridinylimidazoles has been an active area in the search for improved p38 inhibitors, which has frequently resulted in analogues, such as RPR-238677 (**317**)[134] and RPR-203494 (**318**),[135] with minimal inhibition of cytochrome P-450. Pyrimidinylimidazole SB-24235 (**300**) has been reported to have entered phase I clinical trials.[13]

It is worth noting that imidazole derivatives, which are p38 MAP kinase inhibitors, but do not contain a 4-fluorophenyl group, have also been described.[109,151,272–275]

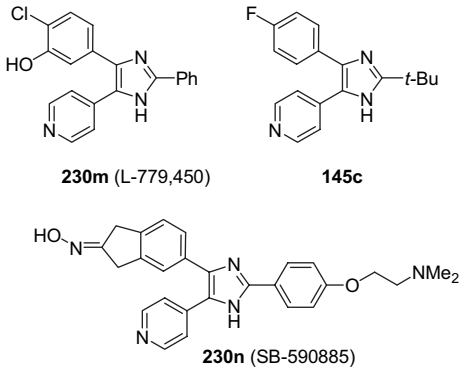
They include compounds **326** (L-790070),[151,272] **327**,[162] **328** (SB-2,27,931),[273] **329**,[274] **330**,[275] and the unusual 1,2-diaryl-substituted imidazole **331**.[109]

3.2. Inhibitors of B-Raf kinase

Ras is a GTP-hydrolyzing protein that once activated binds to and activates the downstream target or effector, the Ser/Thr-specific protein Raf.[276] Raf is a protein kinase that initiates a cascade of other protein kinases by acting on the protein kinases MEK-1 and MEK-2.[277] The phosphorylated active MEK proteins phosphorylate the mitogen-activated protein kinases MAPK, which act on a variety of other proteins.[276] Two MAPK proteins are designed ERK-1 and ERK-2.



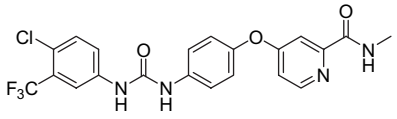
Three isoforms of Raf proteins have been found in mammalian cells: Raf-1 (or C-Raf), A-Raf, and B-Raf. The latter protein, which has higher affinity and stronger stimulation toward MEK than C-Raf and A-Raf, specifically promotes cell survival by activating the mitogen-activated protein kinase pathway.[278] The Ras–Raf–MEK–ERK signaling, which was the first MAP kinase cascade to be characterized,[279] under physiological conditions is activated by mitogens, growth factors and cytokines and regulates cell growth, survival and differentiation.[280,281] Constitutive activation of this signaling pathway is observed in a variety of cancers.[282] Moreover, activating mutations of B-Raf have been reported to be present in 66% of malignant melanomas.[283] Disruption of the Ras–Raf–MEK–ERK signaling cascade could thus offer a novel approach for cancer chemotherapy by development of novel anticancer drugs.[284]



In 1998, Merck researchers reported that 2,4,5-triaryl-1*H*-imidazole **230m** (L-779,450) is a highly potent low nanomolar inhibitor of Raf.[285]

Very recently, screening of the SmithKline Beecham compound bank identified imidazole **145c** as a submicromolar inhibitor of B-Raf (B-Raf IC_{50}=900 nM).[43] Unfortunately, this compound is poorly soluble in aqueous systems, thus precluding its use as an in vivo tool. However, a novel 2,4,5-triaryl-1*H*-imidazole, SB-590885 (**230n**), bearing a 2,3-dihydro-1*H*-inden-1-one oxime substituent, was identified as a potent and extremely selective inhibitor of B-Raf kinase and was shown to be quite soluble (>1 mg/ml) in pH 5 buffer.[43]

Raf inhibitors, which are currently undergoing clinical evaluation show promising signs of anticancer efficacy with a very tolerable safety profile.[286a] On this subject, it should be mentioned that, in December 2005, the U.S. FDA approved the novel oncolytic drug, sorafenib (*Nexavar*®) (**332**), for the treatment of patients with advanced renal cell carcinoma.[286b,c] Compound **332**, which was formerly called BAY-439006, is the first oral multikinase inhibitor that targets Raf kinase, VEGFR-2, VEGFR-3, PDGFR-β, KIT, and FLT3.



On the other hand, the p38 MAP kinase inhibitor, SB-203580 (**309**), has been shown to be able to activate Raf1 in quiescent smooth muscle cells in a dose-dependent fashion.[45] This is particularly interesting in view of the recent reports that compound **309** and related p38 MAP kinase inhibitors can prevent apoptosis in certain cell systems,[45,287–289] because Raf1 has also been suggested to cause anti-apoptotic effects.[290–292]

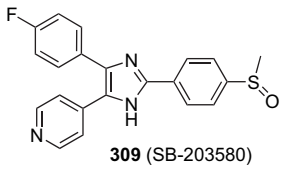
3.3. Inhibitors of transforming growth factor β1 (TGF-β1) type 1 activin receptor-like kinase (ALK5)

The transforming factor-betas (TGF-βs) are members of a large family of cytokines, which also include activins and bone morphogenetic proteins. Members of the TGF-β superfamily regulate a variety of physiological processes such as cell proliferation, differentiation, adhesion, motility, and cell death.[293] Dysregulation of TGF-β signaling contributes to several pathological processes including cancer, fibrosis, and autoimmune disorders.[294–296] Thus, inhibition of this signaling represents a promising and exciting target of therapeutic strategies to control tumor growth and fibrotic diseases.

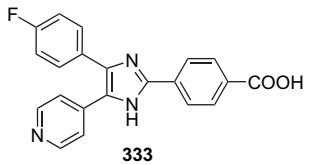
Signaling by the TGF-β superfamily is mediated by two types of transmembrane receptor serine/threonine kinases,

types 1 and 2. The type 2 receptor phosphorylates and activates homodimers of type 1 receptors or activin receptor-like kinases (ALKs). There are seven known mammalian type I receptors (ALK1–7) and five type 2 receptors, and combinations of the type 1 and type 2 receptors confer specificity of ligand signaling.[297]

In 1998, Eyers and co-workers[298] discovered that 2,4,5-triaryl-1*H*-imidazole **309** (SB-203580), which is a potent p38α kinase inhibitor, is also able to inhibit the type 1 TGF-β receptor with an IC_{50} values of 20 μM.



309 (SB-203580)



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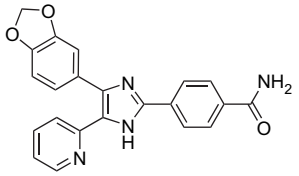


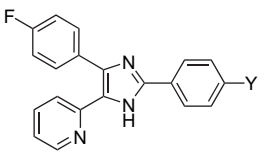
334 (SB-431542)

In 2002, GlaxoSmithKline researchers screened their internal compound collection for inhibitors of the TGF-β1 type 1 receptor (ALK-5) and identified compound **333**.[48] Optimization of this 2,4,5-triaryl-1*H*-imidazole gave the selective inhibitor **334** (SB-431542), which lacks the 4-pyridyl group characteristic of related p38 kinase inhibitors. Compound **334**, which was synthesized using the strategy illustrated in Scheme 61, was shown to be able to inhibit the activity of TGF-β1 activin receptor-like kinases and to be a selective and potent inhibitor of ALK-4, ALK-5, and ALK-7.[46,47] However, it was without effect on ALK-1, -2, -3, and -6. SB-431542 was also shown to inhibit TGF-β1-stimulated proliferation of MG63, a human osteosarcoma cell line ALK-1 that contains another TGF-β type 1 receptor predominantly present in vascular endothelial cells.[299]

3.4. Inhibitors of biosynthesis of interleukin-1 (IL-1)

The pro-inflammatory cytokines TNF-α and IL-1 have been shown to induce the release of prostaglandin E_2 (PGE_2) and collagenase from synovial fibroblasts[300] and upregulate the expression of vascular adhesion molecules, leading to the infiltration of tissues by neutrophils and lymphocytes.[301] p38 MAP kinase regulates the biosynthesis of these cytokines at both the transcriptional and translational level.[302] IL-1, which plays a key role in the body's response to infections, activating lymphocyte products, toxins and inflammatory stimuli,[303,304] consists of two structurally distinct proteins, IL-1α and IL-1β.[305]

Inhibition of IL-1, which is a contributing factor in a host of diseases such as osteoporosis, colitis, arthritis, diabetes, and atherosclerosis,[306] has been a strategy for studying diseases and for new drug development. In 1995, Gallagher and co-workers[307] reported that some 5-(4-pyridinyl)-2,4-diaryl-1*H*-imidazoles were inhibitors of IL-1 biosynthesis and found that compounds SB-203580 (**309**), SB-202190 (**312**), and **335–339** were the most potent among these heterocycles.



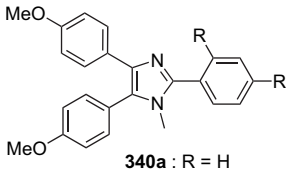
309 : Y = SOMe
312 : Y = OH
335 : Y = NO_2
336 : Y = CH_2NH_2
337 : Y = SO_2NH_2
338 : Y = CN
339 : Y = NH_2

These authors were also able to show that, for this series of compounds, IL-1 inhibition does not correlate with 5-lipoxygenase (5-LO) inhibition and is not a function of nonspecific antioxidant activity.[307]

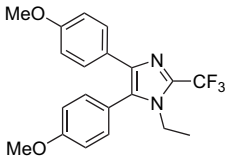
3.5. Cyclooxygenase-2 (COX-2) inhibitors

Classical nonsteroidal anti-inflammatory agents are nonselective COX inhibitors that reduce the formation of physiological prostaglandins produced by COX-1, the isoform of COX, which is expressed constitutively in most tissues, including the gastrointestinal tract and kidneys.[308] These compounds include the 4,5-diaryl-1*H*-imidazole derivatives **340a**,[58] fenflumizole (**340b**),[71] **341**,[58] flumizole (**140t**),[59] and triflumizole (**342**).[71]

By contrast, the COX-2 enzyme is not detected in most normal tissues, but it is induced by pro-inflammatory cytokines IL-1 and TNF-α, which results in enhanced synthesis of prostaglandins in neoplastic and inflamed tissues.[64,309] Thus, selective COX-2 inhibitors have been developed with the hope of producing lesser gastrointestinal side-effects as compared with the conventional nonsteroidal anti-inflammatory drugs.



340a : R = H
340b : R = F



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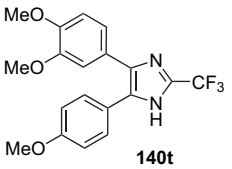
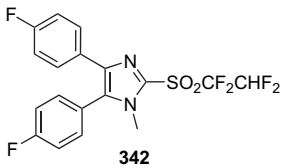
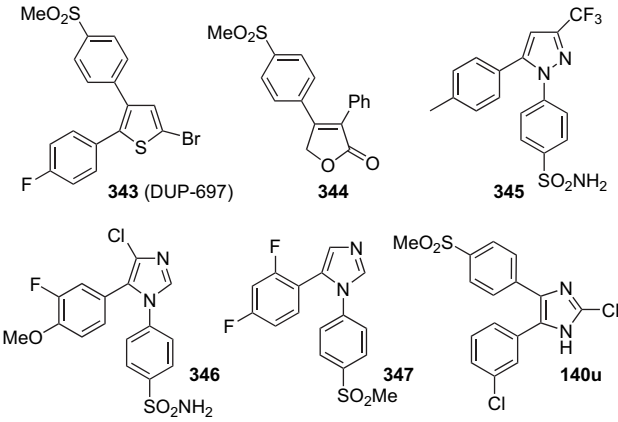


140t



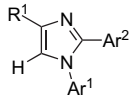
342

The first compound, DUP-697 (**343**),[310] with a clear COX-2 specificity was developed in 1990 and served as template for the development of new COX-2 inhibitors such as rofecoxib (**344**),[311] celecoxib (**345**),[312] and 4-[4-chloro-5-(3-fluoro-4-methoxyphenyl)imidazol-1-yl]benzenesulfonamide (cimicoxib) (**346**).[70]



Compound **346** was identified as a highly selective COX-2 inhibitor showing high potency in all inflammation tests, together with good pharmacokinetics.[70] More recently, another 1,5-diaryl-1*H*-imidazole, compound **347**, has been shown to have strong inhibitory activity on COX-2-catalyzed PGE_2 production.[72] On the other hand, 4,5-diaryl-1*H*-imidazole **140u** was also found to be a COX-2 inhibitor.[63] In fact, it is 6750-fold more selective against COX-1, although it is somewhat less active then celecoxib (**345**) (IC_{50} 690 vs 28 nM).[63]

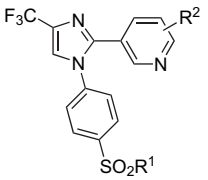
The pharmacological activity of a series of 1,2-diaryl-1*H*-imidazoles developed as potent and selective COX-2 inhibitors has also been described.[67] In 1997, Khanna and co-workers found that some of these heterocycles are very potent (IC_{50} 10–100 nM) and selective (COX-1/COX-2= 10^3–10^4) inhibitors of human COX-2 enzyme and observed that compounds **47p** and **47q** that contained a 4-methylsulfonylphenyl group attached at N-1 were more potent than compounds **47n** and **47o**, in which this group is switched to the C-2 position.[67] Interestingly, compounds **47r** and **47s** and other 1,2-diaryl-1*H*-imidazoles showed excellent inhibition in the adjuvant-induced arthritis model.[67]



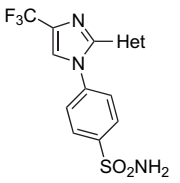
47n : R^1 = Me; Ar^1 = 4-$MeSO_2C_6H_4$; Ar^2 = 4-ClC_6H_4
47o : R^1 = CF_3; Ar^1 = 4-$MeSO_2C_6H_4$; Ar^2 = 4-ClC_6H_4
47p : R^1 = Me; Ar^1 = 4-FC_6H_4; Ar^2 = 4-$MeSO_2C_6H_4$
47q : R^1 = CF_3; Ar^1 = 4-FC_6H_4; Ar^2 = 4-$MeSO_2C_6H_4$
47r : R^1 = CF_3; Ar^1 = 4-$MeSO_2C_6H_4$; Ar^2 = 3-ClC_6H_4
47s : R^1 = CF_3; Ar^1 = 4-$H_2NSO_2C_6H_4$; Ar^2 = 3-ClC_6H_4

In 2002, Khanna and co-workers synthesized a series of heteroaryl-modified 1,2-diaryl-1*H*-imidazoles that included highly selective (1000- to 9000-fold) inhibitors of COX-2.[68] Compound **47t** was found to exhibit excellent activity in acute and chronic models of inflammation and compounds **47u**–**y** demonstrated excellent oral activity in every efficacy model evaluated.[68]

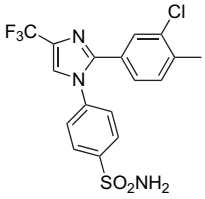
In the same year, Desiraju and Gopalakrishnan[69] performed comparative molecular field analyses and comparative molecular similarity index analyses on 114 1,2-diaryl-1*H*-imidazoles to optimize their COX-2 selective anti-inflammatory activities. Docking studies were also carried out in which these heterocycles were docked into the active sites of COX-1 and COX-2 to analyze the receptor ligand interactions that confer selectivity for COX-2. The most active among these derivatives, compound **47z**, was found to adopt an orientation similar to that of SC-558 (**348**) inside the COX-2 active site.[69]



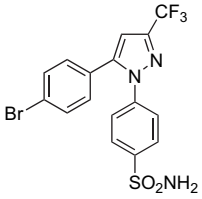
47t : R^1 = Me; R^2 = H
47n : R^1 = NH_2; R^2 = 2-Me
47v : R^1 = NH_2; R^2 = 5-Me



47w : Het = 6-Me-2-pyridyl
47x : Het = 2-Me-4-thiazolyl
47y : Het = 2-Me-5-thiazolyl



47z



348 (SC-558)

In ending this section, we deem it necessary to mention that, recently, it has been reported that the use of some COX-2 inhibitors such as rofecoxib (Vioxx®), celecoxib (Celebrex®), and vadecoxib (Bextra®) causes an increase in the risk of heart attack and stroke. Thus, in 2005, an advisory panel of the US FDA recommended that these drugs carry *black box* warnings, but the panel did not recommend that the drugs should be withdrawn from the market.[313] In fact, these drugs may still remain the best option for treating arthritis in some patients without cardiovascular risk factors who cannot tolerate traditional nonsteroidal anti-inflammatory drugs because of their gastric side effects.

3.6. Antagonists of CB_1 cannabinoid receptor

Cannabinoids are psychotropic constituents of the Indian hemp *Cannabis sativa* L., which, in spite of their potential for abuse, have a number of potential therapeutic uses including antinociception, suppression of chemotherapy-induced nausea, and appetite stimulation in cachexic patients.[314–317]

Mammalian tissues contain at least two types of cannabinoid receptor, CB_1 and CB_2, both coupled to G proteins.[318] CB_1 receptors are expressed mainly in neurones of the peripheral and central nervous system, whereas the CB_2 receptor occurs in non-neuronal tissues, particularly in immune cells.[318] Brain CB_1 receptor antagonists are currently the subject of intensive research, due to their highly promising therapeutic prospects in the treatment of a number of diseases such as neuro-inflammatory disorders, psychosis, anxiety, cognitive disorders, depression, addiction, septic shock, obesity, and

gastrointestinal disorders.[79,319] However, the role of the CB_1 receptors in these psychiatric and neurovegetative disorders is not well understood.

Some vicinal diaryl-substituted imidazole derivatives, structurally related to rimonabant (**349**),[320,321] have been demonstrated to be potent and selective CB_1 cannabinoid receptor antagonists.[8a,77,78] Compound **349**, which was reported to have potent human CB_1 receptor affinity,[322] was later demonstrated with feeding studies in the rat to afford a dose-dependent reduction in both food intake and body weight.[175]

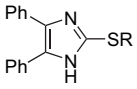
Vicinal diaryl-substituted 1*H*-imidazoles structurally related to **349** include 1,2-diaryl-1*H*-imidazoles **350a–e**[8a] and **350f–j**[78] and 4,5-diaryl-1*H*-imidazoles **351a**,**b**.[77]

Molecular modeling studies have shown a close three-dimensional structural overlap between compound **350g** and rimonabant (**349**).[78] On the other hand, compounds **351a**,**b** demonstrated efficacy in overnight feeding studies in the rat for reduction in both food intake and overall body weight.[77]

3.7. Selective acyl-CoA:cholesterol acyl transferase (ACAT) inhibitors

ACAT, the enzyme principally responsible for the acylation of cholesterol to cholesteryl esters with long-chain fatty acids,[323] plays a key role in the absorption and metabolism of cholesterol. In mammalian species, including humans, it is present in two different forms, ACAT1 and ACAT2.[324,325] These isoforms of the enzyme have different substrate specificity and different potential function.

Some years ago, the implications for inhibiting ACAT for treatment of hyperchloesterolemia and atherosclerosis became clear[326] and a large number of pharmaceutical companies were prompted to pursue ACAT inhibitors as a potential therapeutic target for treatment of both atherosclerosis and hypercholesterolemia.[52–54,146,147,326–335] Thus, a number of 2-(alkylthio)-4,5-diphenyl-1*H*-imidazoles **352** that show potent in vitro and in vivo inhibition of ACAT were discovered and described.[146,147,322–324,326] The lead compound, Dup 128 (**352a**), was an interesting ACAT inhibitor that inhibits ACAT in rat hepatic microsomes with an IC_{50} of 10 nM. The compound is also a potent antihypercholesterolemic agent as evidenced by serum cholesterol lowering in cholesterol-fed hamsters when dosed orally (ED_{50}=3 mg/kg).[336] However, its limited bioavailability and decreased potency against macrophage ACAT suggested that it could not be an effective systemic therapeutic agent.[146]



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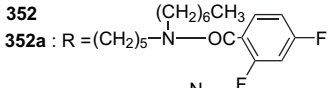
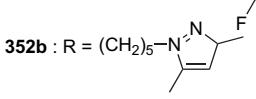
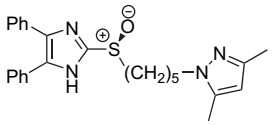


352a : R = $(CH_2)_5$–N(–$(CH_2)_6CH_3$)–OC–(4-F-phenyl)



352b : R = $(CH_2)_5$–N(–2-methylimidazol-1-yl)

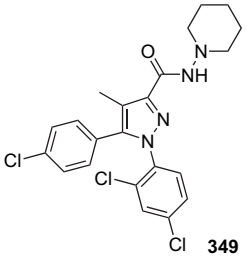


(*S*)-**353** (RP-73163)

Thus, studies directed to the identification and development of bioavailable arterial active ACAT inhibitors, concerning modification of the structure of **352a**, were carried out.[147,321,332,335] These investigations resulted in the development of RP-73163 [(*S*)-**353**], a potent and systemically bioavailable alkylsulfinyl diphenylimidazole ACAT inhibitor.[327] This compound, which is the major metabolite of the ACAT inhibitor RP-76076 (**352b**), was shown to exhibit higher systemic bioavailability than the parent thioether, but it was consistently some 3- to 4-fold less active against ACAT from a variety of tissues and species.[54]

3.8. Glucagon receptor antagonists

Glucagon is a peptide hormone produced in the pancreas and is the major counter-regulating hormone to insulin, stimulating glycogenolysis and gluconeogenesis.[337] In patients with



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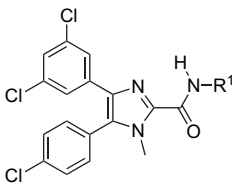
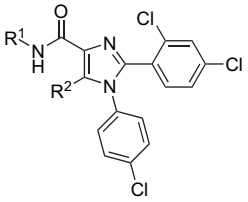


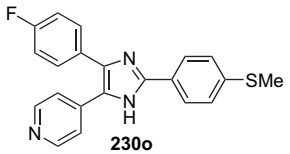
351a : R^1 = 1-piperidinyl
351b : R^1 = *c*-C_6H_{11}



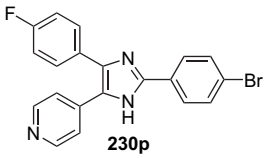
350a : R^1 = 1-piperidinyl; R^2 = H
350b : R^1 = 3-azabicyclo[3.3.0]octan-3-yl; R^2 = H
350c : R^1 = 1-homopiperidinyl; R^2 = H
350d : R^1 = *c*-C_6H_{11}; R^2 = H
350e : R^1 = 3-azabicyclo[3.3.0]octan-3-yl; R^2 = ethynyl
350f : R^1 = 1-piperidinyl; R^2 = Et
350g : R^1 = 1-piperidinyl; R^2 = Me
350h : R^1 = 1-piperidinyl; R^2 = Cl
350i : R^1 = 1-piperidinyl; R^2 = CN
350j : R^1 = 1-piperidinyl; R^2 = CH_2F

diabetes, excess glucagon secretion plays a primary role in the metabolic perturbations associated with diabetes, such as hyperglycemia. The glucagon receptor, which belongs to the superfamily of heptahelical transmembrane G protein-coupled receptors,[338] mediates the effects of glucagon in controlling glucose metabolism by initiating a cascade of events that regulate the amount of glucose released from the liver into the bloodstream.

Glucagon receptor antagonists bind to hepatic glucagon receptors and have the potential to induce a decrease in fasting plasma glucose levels in diabetics.[339,340] Thus, glucagon receptor antagonists have actively been pursued for the treatment of type 2 diabetes, the most common form of diabetes.[339,340] The majority of the initial antagonists were peptide-based substances, whereas more recent efforts have been directed at identification of non-peptide, orally available, low-molecular-weight agents[341–344] that include imidazole derivatives.[56,345] In 1999, screening of the Merck sample collection for compounds with affinity for the cloned human glucagon receptor allowed the identification of 2,4,5-triaryl-1*H*-imidazole **230o**, the precursor to SB-203580 (**309**), an inhibitor of p38 kinase,[265–267] as a weak human glucagon receptor ligand.[56] More recently, another screening programme led to the discovery of the triarylimidazole derivative **230p**, which exhibited an IC_{50} of 0.27 μM in the human glucagon receptor (hGlur) assay, but also registered an IC_{50} of 0.16 μM in a p38 MAP kinase assay.[345]

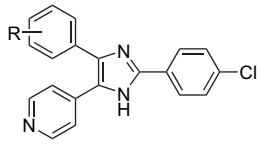


230o



230p

This modestly active, non-selective lead was then optimized for binding affinity with human glucagon receptor (hGlur) and this led to the identification of triarylimidazoles **230q–w** possessing high binding affinity for hGlur.[345]

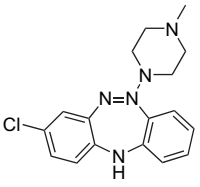


230q : R = 4-*n*-Bu
230r : R = 2-OPh
230s : R = 3-OPh
230t : R = 4-OPh
230u : R = 2-O-*n*-Bu
230v : R = 2,4-(O-*n*-Pr)$_2$
230w : R = 2,4-(O-*n*-Bu)$_2$

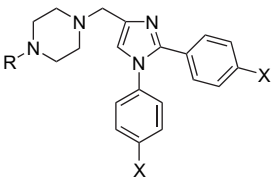
The most significant compound was **230w**, which exhibited an IC_{50} of 0.0053 μM in the hGlur assay and was highly selective over p38 MAP kinase.[345]

3.9. Compounds endowed with a neurochemical profile similar to that of clozapine

Clozapine (**354**) is a benzodiazepine derivative, which is the prototype of a group of atypical anti-psychotic drugs exhibiting clinical efficacy similar to that of the classical antipsychotics, but lacking, or inducing to a lesser extent, most of their motor side effects.[346,347] Unlike typical antipsychotic drugs, clozapine increases GABA turnover in vivo[348] and reversibly inhibits transmission at GABAergic synapses in cultures of tegmental neurons.[349] Although **354** appears to be the most effective anti-psychotic drug for treating resistant schizophrenia and reducing the risk of suicide in schizophrenic or schizoaffective patients judged to belong to a high-risk group with chronic risk for suicidal behavior, its general use is limited because of the risk of hematological disorders (e.g., agranulocytosis), possibly correlated to its oxidizability in vivo.[350] For these reasons, the development of new drugs to replace clozapine has become an active field of research.[349,351,352]

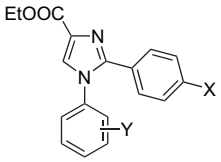


354

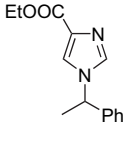


355
355a : X = H; R = 2-MeOC$_6$H$_4$

In this context, a series of 1-[(1,2-diphenyl-1*H*-4-imidazolyl)methyl]-4-piperazine derivatives **355** were designed and synthesized as possible ligands with mixed dopamine D_2/serotonin 5-HT_{1A} affinity.[80] One of these trisubstituted 1,2-diaryl-1*H*-imidazoles, compound **355a**, with a D_2/5-HT_{1A} IC_{50} ratio of ca. 1, was found to inhibit in a concentration-dependent manner GABA-evoked Cl^- currents in *Xenopus laevis* oocytes expressing recombinant human $GABA_A$ receptors composed of α1, β2, and γ2 subunits.[80] This finding suggested that **355a** could represent a prototype of a novel class of drugs endowed with a neurochemical profile similar to that of atypical antipsychotics. In addition, it prompted the Asproni research group to determine whether the 1,2-diaryl-1*H*-imidazole framework of **355a** might serve as the basis for development of more specific modulators of the $GABA_A$ receptor.[81] In 2005, this research group reported that compounds **356a**,**b** and several analogues are effective modulators of human recombinant $GABA_A$ receptor with a molecular mechanism comparable to that of the anesthetic etomidate (**357**).[81]



356a : X = Y = H
356b : X = Cl; Y = 2,4-Cl$_2$



357

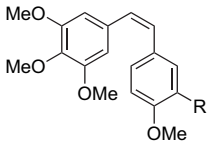
3.10. Combretastatin A-4 (CA-4) analogues with anti-tumor activity

Tubulin is a globular protein, which makes up microtubules and is a major target for anticancer drug discovery.[353] A variety of natural compounds including podophyllotoxin,

colchicine, steganacine, and combretastatins inhibit tubulin polymerization by binding at a common site, the colchicine binding site.[354] Combretastatins are natural antimitotic agents, isolated from the bark of the South African tree *Combretum caffrum*,[355–358] which appear to have antitumor activity as a result of specifically targeting the vasculature of tumors.[359,360] In fact, these substances are able to cause pronounced shutdown in blood flow to solid tumors, resulting in extensive tumor-cell necrosis, while leaving the blood flow in normal tissues relatively intact.[361] Among these natural products, combretastatin A-4 (CA-4) (**358a**) possesses the most potent antitumor activity. In fact, it shows strong cytotoxicity against a variety of cell lines, including multidrug resistant cancer cell lines[362,363] and, most importantly, has demonstrated powerful cancer antivascular properties.[364] However, the low water solubility of CA-4 limits its efficacy in vivo and the water-soluble disodium phosphate prodrug CA-4P (**358b**) has already entered clinical trials.[365] In endothelial cells in culture, CA-4P causes rapid re-organization of the actin cytoskeleton, mediated by disruption of the tubulin cytoskeleton.[361] An increase in vascular permeability is likely to be an important component of the mechanisms that lead to the shutdown of tumor blood flow by this compound and other vascular-disrupting agents (VDAs) structurally related to CA-4P.[361] It should be noted that the VDAs were previously known as vascular-targeting agents (VTAs).

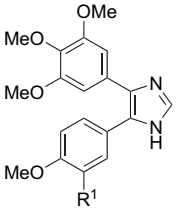
Recently, it has been shown that CA-4P selectively targets endothelial cells, but not smooth muscle cells, and induces regression of unstable nascent tumor neovessels by rapidly disrupting the molecular engagement of the endothelial cell-specific junctional molecular vascular endothelial-cadherin (VE-cadherin) in vitro and in vivo in mice.[366]

Compound **358c** (AVE-8062) (AC-7700), a synthetic analogue of CA-4 bearing a different substitution on ring B, is currently under clinical evaluation as a tumor vascular-targeting agent.[367–369] This compound is the prodrug of AC-7739 (**358d**).

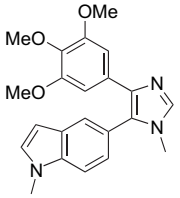


358a (CA-4) : R = OH
358b (CA-4P) : R = OPO_3Na_2
358c (AVE-8062) : R = NHSerHCl
358d (AC-7739) : R = NH_2HCl

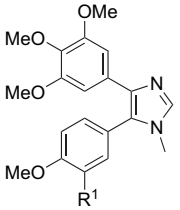
The *Z* configuration of CA-4 and its analogues poses another liability. In fact, the C–C double bond of these substances is prone to isomerize to the *E*-form during their storage and administration and these *E*-configured compounds show a dramatic reduction in both antitubulin activity and cytotoxicity.[370,371] This prompted the synthesis of a number of (*Z*)-restricted analogues of CA-4 in which the C–C double bond of this natural product has been bioisosterically replaced with a 3,4-disubstituted 2(5*H*)-furanone[371–373] or a 3,4-diaryloxazolone ring[374] or disubstituted five-membered heteroaromatic rings including pyrrole,[375] isoxazole,[376–378] pyrazole,[379,380] tetrazole,[380] thiazole,[380] 1,3,4-triazole,[380] indole,[381,382] oxazole,[82] furazan,[383] and imidazole.[83,84,384–387] As far as these last heterocycle derivatives are concerned, it should be noted that, in 2002, Wang and co-workers[384] found that, among a series of 4,5-diaryl-1*H*-imidazoles, compounds **92j** and **92m** had potent antitubulin and cytotoxic activity, but 4,5-diaryl-1-methyl-1*H*-imidazoles **192e** and **192f** had improved pharmacokinetic profiles.



92j : $R^1 = NH_2$
92m : $R^1 = F$

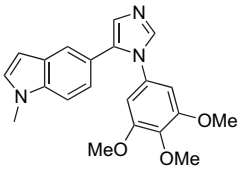


192e



192f

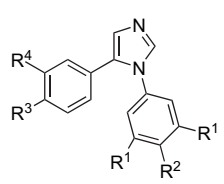
Antitubulin activity was also shown by the 1,5-diaryl-1*H*-imidazole derivative **359**, which possessed antiproliferative properties against NCI-H460 and HCT-15 cancer cell lines.[384]



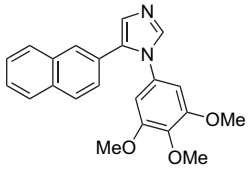
359

In 2005, 1,5-diaryl-1*H*-imidazoles **360a–c** and **361** were also found to be significantly cytotoxic in the NCI's in vitro human disease-oriented tumor cell line screening panel that consists of 60 human cancer cell lines.[385] Among these heterocycles, compound **360c** was the most potent and proved to be able to cause depolymerization of microtubules in endothelial cells.[386,387] Nevertheless, 5-(3-fluoro-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)-1*H*-imidazole (**360d**), which had MG-MID log GI_{50} −7.40, was more recently shown to be more cytotoxic than **360c**.[386] Interestingly, compounds **361** and **360d** proved to be more cytotoxic than CA-4 in cytotoxicity tests involving their evaluation over a 10^{-4}–10^{-8} M range.[385] Recently, it was also found that compounds **360c**, **360d**, and **361** cause profound changes in the morphology of endothelial cells (IC_{50}=6.5, 30.9, and 38.8 μM, respectively) and that in comparable experiments, **360c**, but not **360d** and **361**, induces changes in the shape of endothelial cells at concentrations that did not affect their proliferation.[386] Furthermore, by immunohistochemistry, the ability of **360c** to cause depolymerization of microtubules in endothelial cells has been confirmed.[386] The ability of compounds **360c**, **360d**, and **361** to induce necrosis of experimental tumors in vivo, the hallmark of vascular-disrupting activity, was also analyzed and it was found that, following a single treatment, these substances cause massive central necrosis of tumors.[387]

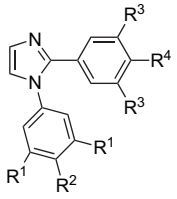
Some 1,2-diaryl-1*H*-imidazoles were also evaluated for cytotoxicity against the 60 human tumor cell lines of the



360a : $R^1 = R^2 = R^4 = H$; $R^3 = CF_3$
360b : $R^1 = R^4 = H$; $R^2 = R^3 = OMe$
360c : $R^1 = R^2 = R^3 = OMe$; $R^4 = H$
360d : $R^1 = R^2 = R^3$ OMe; $R^4 = F$



361



47c : $R^1 = R^2 = R^4 = OMe$; $R^3 = H$
47d : $R^1 = R^3 = H$; $R^2 = R^4 = OMe$
47g : $R^1 = H$; $R^2 = R^3 = R^4 = OMe$

NCI and, among the tested compounds, imidazoles **47c**, **47d**, and **47g** were found to be moderately cytotoxic.[84] Interestingly, compound **47c**, which had cytotoxicity (MG-MID log GI_{50} −5.45) lower than that of the corresponding 1,5-diaryl-1*H*-imidazole, **360c** (MG-MID log GI_{50} −6.33), was, however, significantly active against the COLO-205, HCC-2998, HCT-116, HCT-15, HT-29, KM-12, and SW-620 colon cancer cell lines (MG-MID log GI_{50} −6.33), and the MDA-MB-435 breast cancer line (log GI_{50} −6.95).[84] On the other hand, compound **47d** was very active against the MOLT-4 leukemia cell line (log $GI_{50}<-8.00$) and the human SR leukemia cell line (log GI_{50} −7.88).[84]

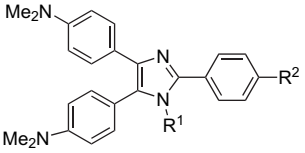
It is also worth mentioning that docking experiments have recently shown a good correlation between the MG-MID log GI_{50} values of compounds **360a–d**, **361**, **47c**, **47d**, and **47g** and their calculated interaction energies with the colchicine binding site of αβ-tubulin.[385]

3.11. Modulators of P-glycoprotein (P-gp)-mediated multidrug resistance (MDR)

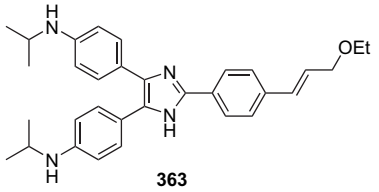
MDR, which is now recognized as one of the most common causes of failure of cancer chemotherapy, is due to overexpression of the plasma membrane P-gp molecule, a protein that functions as an ATP-dependent pump of the efflux of diverse anticancer drugs from MDR cells.[388] The level of expression of P-gp correlates directly with the degree of resistance.[389]

The hope of identifying compounds able to reverse simultaneously the resistance to a number of unrelated drugs has stimulated research in this field and hundreds of compounds have been selected by different approaches, with the properties of inhibiting P-gp.[73] However, the clinical toxicity associated with these agents has limited their use.

In 2000, 2-aryl-4,5-(4-dimethylamino)phenyl-1*H*-imidazoles **362** were identified as a novel class of potent non-toxic modulators of P-gp mediated MDR.[390] These compounds were then optimized via structure–activity relationship studies[74] and the optimized imidazole OC-144-093 (**363**), which was generated via solution-phase combinatorial chemistry, was shown to be able to reverse MDR to doxorubicin, paclitaxel, and vinblastine in human lymphoma, breast, ovarian, uterine, and colorectal carcinoma cell lines expressing P-gp.[391]

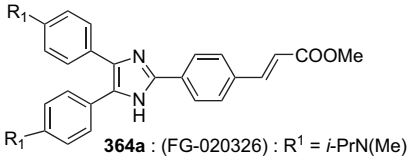


362 : R^1 = H; *n*-C_6H_{13}; $PhCH_2CH_2$
R^2 = COOH; COOMe; CH=CH-COOH; CH=CH-COOMe; OH

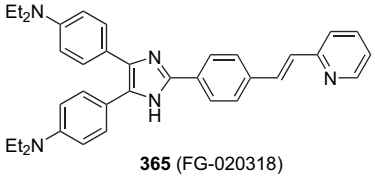


363

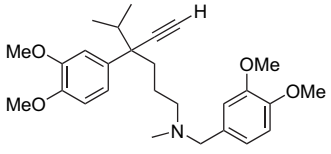
In 2004, Chen and co-workers reported that three imidazole derivatives, compounds **364a**,**b**, and **365**, possess a 3- to



364a : (FG-020326) : R^1 = *i*-PrN(Me)
364b : (FG-020327) : $R^1 = Et_2N$



365 (FG-020318)

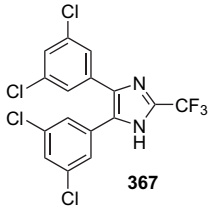


366 (verapamil)

4-fold stronger reversal of MDR activity than verapamil (**366**), a well-known positive MDR modulator.[392] These authors also demonstrated that **365** (FG-020318) is a highly potent, efficacious MDR modulator, not only in vitro, but also in vivo.[393]

3.12. Antibacterial agents

4,5-Diaryl-1*H*-imidazoles have been identified as a class of compounds, which include derivatives showing considerable antimicrobial activity against bacteria, yeast, and fungi.[177,394–396] 4,5-Bis(3,5-dichlorophenyl)-2-trifluoromethyl-1*H*-imidazole (**367**) is the most potent antibacterial agent among a series of 4,5-bis(3,5-dichlorophenyl)-1*H*-imidazole derivatives in which a good electron-withdrawing group, a formyl or an amino group at C-2 are required for good levels of activity against Gram positive bacteria, including methicillin resistant *Staphylococcus aureus*.[396]



367

The minimum inhibitory concentrations (MICs) for **366** against *S. aureus*, *Bacillus subtilis*, *Escherichia coli* permeable mutant, and *E. coli* permeable mutant+polymyxin were found to be 0.25, 4, >32, and 16 μg/ml, respectively.[396]

4. Conclusions and perspectives

The chemistry of imidazoles with two aryl groups on adjacent positions has been investigated from the early 1980s, but the most considerable advances in both the synthetic methodologies and the biological evaluation of these diazole derivatives have been made in the last decade. Although several strategies and methodologies have been applied to achieve conveniently the synthesis of these compounds, further research must, however, be undertaken in order to design and develop efficient, practical, and scalable synthetic routes to some of these compounds and their analogues for biological and preclinical studies. The challenge for prospective research in this area of synthetic organic chemistry involves the optimization of known procedures on the one hand, and the development of new useful synthetic approaches on the other. In particular, future work should be directed to develop effective processes involving multicomponent reactions[397,398] and/or highly selective transition metal-catalyzed reactions, which should be designed to reduce or eliminate the use and generation of hazardous substances,[399,400] which should avoid, whenever possible, the temporary activation of the reaction partners, which should involve the utilization of the atom-economy concept, i.e., the maximization of the incorporation of all materials used in the process in the final product,[401] and which should be conducted at ambient temperature.

Acknowledgements

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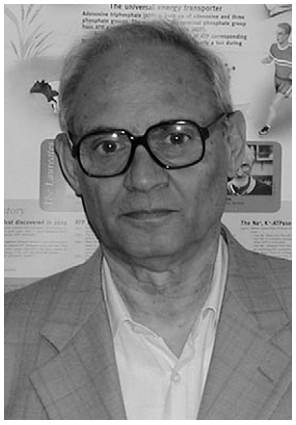
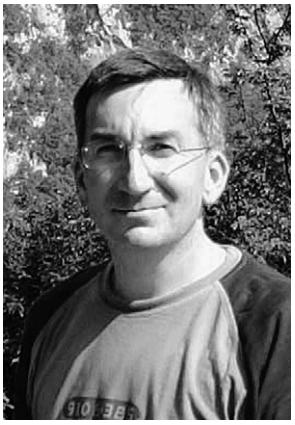
Biographical sketch



Renzo Rossi was born in Pisa (Italy) and graduated in Chemistry with first-class honours at the University of Pisa in 1960 defending a thesis performed under the guidance of Professor Piero Pino. In 1969 he became Assistant Professor and, in 1971, he earned the *libera docenza* in Organic Chemistry. After holding other intermediate positions at the University of Pisa and the Scuola Normale Superiore of Pisa, in 1980 he became Full Professor of Organic Chemistry at the University of Calabria. In 1982, he joined again the University of Pisa where he has held the Chair of Chemistry of Naturally Occurring Compounds. In 1999, the University of Pisa awarded him the *Ordine del Cherubino*. At the beginning of his career, he was interested in stereochemistry, the study of the chemistry and bioactivity of insect pheromones and the synthesis of insecticidal unsaturated carboxyamides, acetylenic and thiophenic phototoxins, structural analogues of naturally occurring fungicidal compounds of agrochemical interest and natural products useful for controlling insects and fungi, which are devasting pests of historical and cultural paper and wooden materials. His current research interests include the total synthesis of naturally occurring compounds of biological and/or pharmacological interest, the study of transition metal-catalyzed carbon–carbon and carbon–heteroatom bond-forming reactions and their applications for the synthesis of pharmacologically active compounds, transition metal-catalyzed direct C- and N-arylation reactions of heteroarene derivatives, and the design and development of new, efficient and selective methods for the synthesis of vicinal diaryl-substituted heterocycles that include potential antineoplastic derivatives. He is a fellow of the Royal Society of Chemistry and the Società Chimica Italiana. In 2006, Tetrahedron awarded Professor Rossi the *Tetrahedron Most Cited Paper 2003–2006 Award*.



Fabio Bellina was born in Catania (Italy) in 1964. He studied Chemistry at the University of Pisa and received his Laurea Degree with first-class honours in 1990 under the supervision of Professor R. Rossi. After his national service (1991–1992) in 1992 he joined the University of Pisa as an Organic Chemistry Researcher at the Dipartimento di Chimica e Chimica Industriale, working under the supervision of Professor R. Rossi. In October 2003, he was appointed by the Faculty of Science of the University of Pisa as an Associate Professor of Organic Chemistry. He is a member of the Drug Development Committee of the PAMM-EORTC group (Pharmacology And Molecular Mechanisms—European Organization for Research and Treatment of Cancer). Most of his research has been devoted to the study of transition metal-catalyzed reactions and their application to the selective synthesis of bioactive natural and synthetic heterocyclic compounds, and particularly of substances, which are cytotoxic against human tumor cell lines or are vascular-disrupting agents.

Silvia Cauteruccio was born in Livorno (Italy) in 1979 and graduated in Chemistry with first-class honours at the University of Pisa in 2005 defending a thesis performed under the guidance of Professor Fabio Bellina and Professor Renzo Rossi. Currently she holds a position as PhD student at the Dipartimento di Chimica e Chimica Industriale of the University of Pisa. She is currently working on the development of novel and efficient protocols for the transition metal-catalyzed selective synthesis of aryl-substituted heterocycles of potential pharmacological interest.