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Advances in the synthesis of 4-aryl- and 4-hetarylpyridines

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Abstract. Information on the methods of synthesis of 4-aryl- or 4-hetaryl-substituted pyridines developed in the recent years is discussed and generalised. Examples of the practical use of 4-(het)arylpyridine derivatives are given. The bibliography includes 166 references.

I. Introduction

4-Aryl- and 4-hetarylpyridines possess various properties valuable for practice. This class of pyridine derivatives is used in the synthesis of cyanine dyes,[1] liquid-crystalline materials, coordination compounds,[2–17] organic luminophores,[18] laser dyes, and also as the precursors or components in the preparation of light-emitting polymers.[19–25] Moreover, 4-(het)arylpyridine derivatives are promising biologically active substances. For example, they exhibit high activity with respect to certain types of nerve cells, particularly, dophaminergic neurons.[26,27] They can also modulate functioning of the mitochondrial respiratory chain[28] by affecting the permeability of the transport system, first of all, the temporarily permeable mitochondrial pores.[29] Thus, these compounds can be used in curing different neurodegenerative diseases.[30] Among 4-(het)arylpyridine derivatives, compounds with sedative and analgetic,[31–33] antimicrobial,[34] antitumour and hypoglycemic action[35–37] were revealed, while 4,4′-bipyridyls exhibited pronounced herbicidal activity.[38–40]

To date, 4-(het)arylpyridines are less accessible compounds as compared with 2-(het)arylpyridines. The known methods of synthesis make it possible to obtain 4-arylpyridines as a result of 'construction' of a pyridine ring, by free-radical arylation, regioselective addition of Grignard reagents or organolithium compounds to the pyridine ring and also by cross-coupling reactions. Different versions of the Michael reaction were used as the main approach to the synthesis of 4-aryl substituted 2,2′-bipyridyls.[19,41,42] However, in many cases, the methods mentioned rely on the starting compounds that are very expensive. In addition, they are toxic and hardly available.

Several reviews[19,41,42] and papers[43,44] were devoted to the synthesis of 2,4,6-triarylpyridines and oligopyridines. The present-day data on the methods of synthesis of pyridines and their derivatives can be found in such publications as '*Comprehensive Heterocyclic Chemistry*',[45] '*Handbook of Heterocyclic Chemistry*';[46] however, the available information on the methods of synthesis of 4-(het)arylpyridine is limited to few examples. Thus to date, there is no comprehensive survey of the methods of synthesis of 4-(het)arylpyridines; furthermore, the development of new methods is still a topical problem.

In this review, we consider the methods of synthesis of pyridine derivatives containing an aryl or a hetaryl substituent in position 4. We excluded 4-arylpyridones and their thio-analogues from our discussion as well as the derivatives annulated to the pyridine ring. Moreover, high-molecular-weight compounds containing fragments of 4-arylpyridines are also beyond the scope of this review. Data on the syntheses of 4-aryl- and 4-hetarylpyridines published in the past decade are systematised.

II. Methods of synthesis involving pyridine ring formation

The methods of pyridine ring formation differ in the type of reactions used. The main methods include pyrylium ring conversions, condensation of carbonyl compounds with ammonia and dehydrogenation of dihydro- and tetrahydropyridines.

1. Ring transformation of pyrylium salts

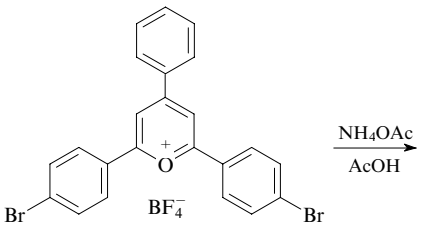
In reactions with ammonia or its derivatives, pyrylium salts were easily converted to pyridine derivatives.[47–49] The

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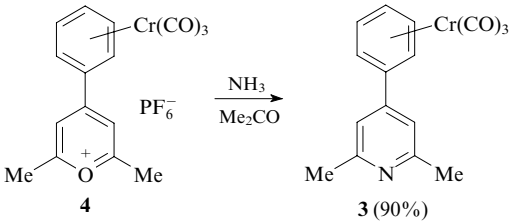
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reagent employed is usually aqueous (ethanolic) ammonia or ammonium acetate in glacial acetic acid. This method is suitable for the synthesis of 2,4,6-trisubstituted pyridines; it was used rarely for the synthesis of other derivatives due to inaccessibility of precursors.

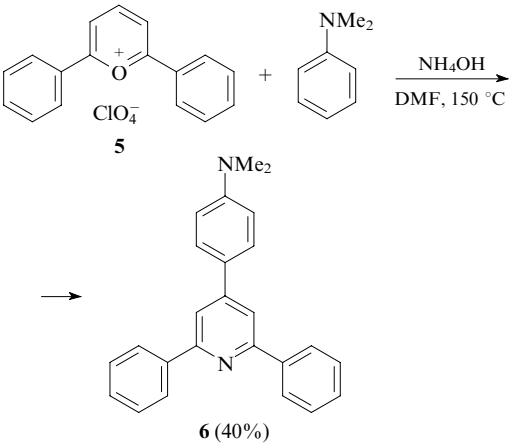
For instance, this approach was applied in the synthesis of 2,4,6-triarylpyridine **1**, which is used in the production of light-emitting polymers and photodiodes on their basis.[20] This conversion occurred on heating of pyrylium salt **2** with ammonium acetate in acetic acid.



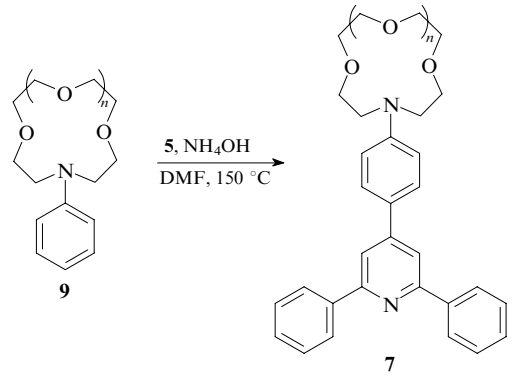
The ability of a pyrylium ring to undergo a conversion into a pyridine ring on treatment with ammonia was used in the preparation of metal complex **3** from salt **4**.[50]



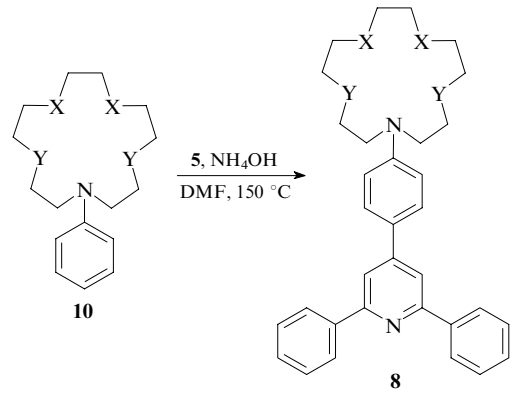
Heating of 2,6-diphenylpyrylium perchlorate (**5**) with *N,N*-dimethylaniline in aqueous ammonia afforded 4-(4-dimethylaminophenyl)-2,6-diphenylpyridine (**6**). Substitution of a nitrogen atom for an oxygen atom to yield a pyridine ring was accompanied by hetarylation of a benzene derivative containing an electron-donating group.



Crown-containing triarylpyridines **7**, **8**, which were proposed to use as fluorescent chemosensors, were synthesised under analogous conditions from phenylazacrown ethers **9**, **10**. Compounds **7**, **8** contain two complexation centres, namely, the monodentate residue of 2,6-diphenylpyridine and a crown-ether macrocycle. Coordination of a dye molecule to the pyridine nitrogen or to the crown-ether fragment gave rise to different spectral responses of the chromophore.[51]



n = 1 (37%), 2 (43%), 3 (42%).



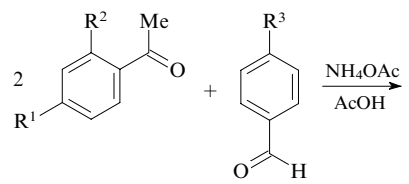
X = O, Y = S (45%); X = S, Y = O (40%).

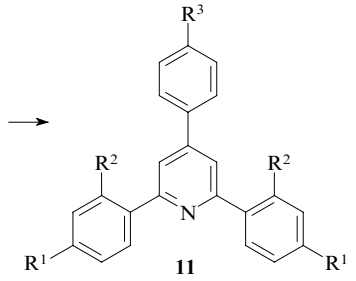
2. Addition reactions

a. Condensation of aldehydes or ketones with ammonia or its derivatives

This approach is based on condensation of aromatic compounds, namely, of two ketone and one aldehyde molecules, with ammonia or its derivatives. Dihydropyridines were the primary cyclisation products and were oxidised to the corresponding pyridines by chalcone also formed in this reaction.

This method was used for synthesising 2,4,6-triarylpyridines **11**, which are applied as sensitising dyes in colour photography [52, 53] and as the precursors in the synthesis of heterocyclic polymers.[54]

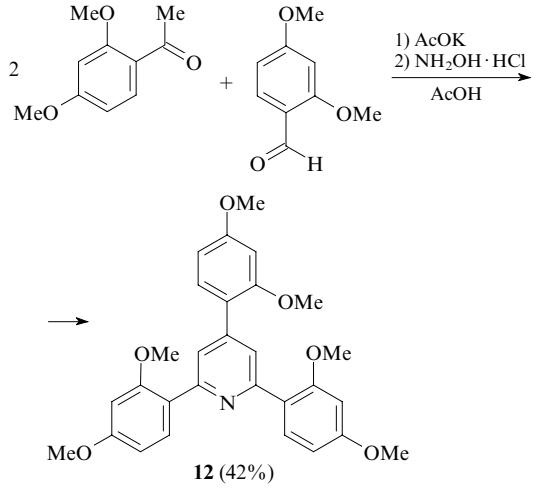




11

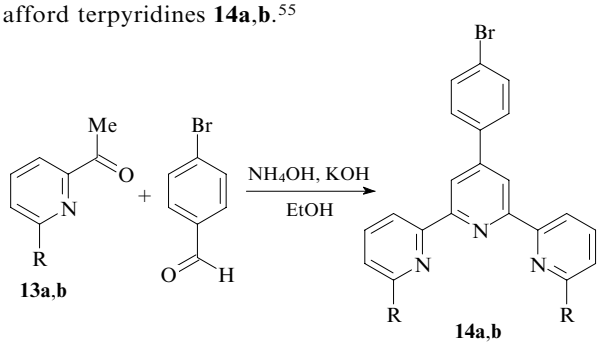
R^1	R^2	R^3	Yield (%)
MeO	H	MeO	30
AcNH	O_2N	H	40
AcNH	O_2N	F_3C	52

Sensitising dye **12**, which pertains to the family of 2,4,6-triarylpyridines, was synthesised by an analogous method, but hydroxylamine hydrochloride or non-symmetrical dimethylhydrazine were used in place of ammonium acetate.[52,53] In this case, *N*-hydroxydihydropyridine or *N*,*N*-dimethylaminodihydropyridine were formed as intermediates to undergo subsequent elimination and aromatisation without recourse to any special oxidant.



12 (42%)

Yet another example of this type of reactions is the condensation of 4-bromobenzaldehyde and 2-acetylpyridines **13a**,**b** under the action of a base on reflux in ethanol to afford terpyridines **14a**,**b**.[55]

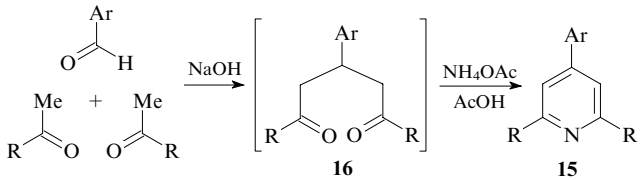


13a,**b** **14a**,**b**

R = H (**a**, 64%), Br (**b**, 72%).

b. Condensation of 1,5-dicarbonyl compounds with ammonia

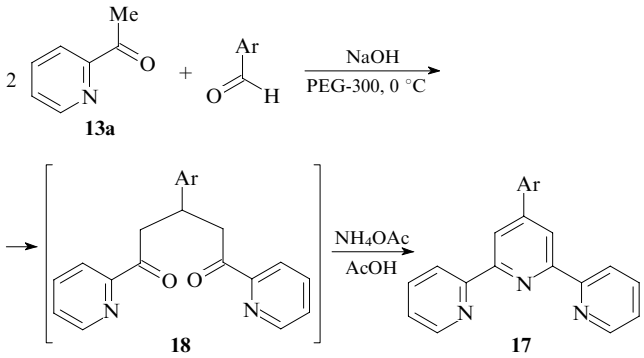
In certain cases, the condensation of aldehydes and ketones to pyridines (see Section II.2.a) was carried out in two steps. In the first step, the condensation of aldehyde with 2 equivalents of ketone under the action of a base afforded a 1,5-dicarbonyl compound, which then reacted with ammonia or its salts. In the reaction of 1,5-dicarbonyl compounds with ammonia, two molecules of water were abstracted to afford 1,4-dihydropyridines, which were oxidised to the corresponding pyridines. This synthesis was very often carried out without isolation of the intermediate 1,5-dicarbonyl compound. Thus the derivatives of 4-arylpyridine **15** were synthesised by one-pot condensation of a methyl ketone and aldehyde taken in the molar ratio of 2 : 1, under the action of sodium hydroxide in the absence of a solvent and subsequent treatment of intermediate 1,5-diketone **16** with ammonium acetate in acetic acid.[56]



16 **15**

R = 4-pyridyl (4-Py), Ar = 4-Bu^{t}OC$_6$H$_4$ (76%);
R = 4-IC$_6$H$_4$, Ar = Ph (85%).

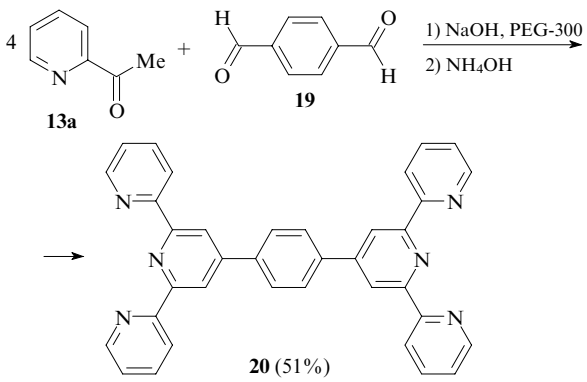
Terpyridines **17** were synthesised by condensation of aromatic aldehydes with 2 equivalents of 2-acetylpyridine (**13a**) under the action of a base in polyethylene glycol (PEG-300) at 0 °C. The reaction was also conducted in a one-pot manner. After the formation of 1,5-diketone **18**, the reaction mixture was treated with a concentrated aqueous ammonia solution.[57] The yields of compounds **17** were 13%–63%. This approach conformed to the principles laid in the basis of 'green chemistry', namely, intermediates are not isolated and the solvent, polyethylene glycol, can be recovered and reused.



13a **18** **17**

Ar = X$_n$C$_6$H$_{4-n}$ (X = H, 4-MeO, 4-Cl, 4-MeS, 4-BnO, 4-HOCH$_2$, 4-HO(CH$_2$)$_2$O, 4-MeO$_2$C, 2,4,6-(MeO)$_3$), 9-anthryl.

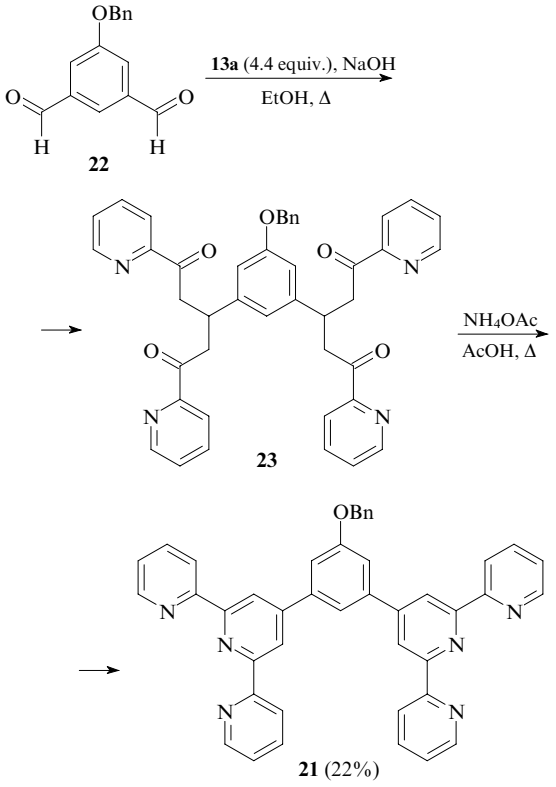
Carried out by the same procedure, the reaction of terephthalaldehyde (**19**) with a fourfold excess of 2-acetylpyridine (**13a**) afforded 1,4-bis(terpyridino)benzene (**20**).[57]



13a **19**

20 (51%)

In the synthesis of bis(terpyridine) **21** from dialdehyde **22** and 4.4 equivalents of 2-acetylpyridine (**13a**) under the action of sodium hydroxide in ethanol with heating, tetraketone **23** was formed initially.[58] Being treated with ammonium acetate in acetic acid, the latter cyclised to bis(terpyridine) **21**.

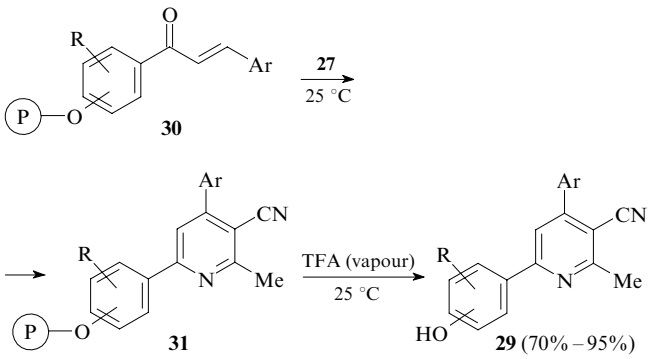


c. Syntheses using the Michael reaction

One of the most popular approaches to the synthesis of 4-arylpyridines consists of the addition of a nucleophile to an activated double bond (the Michael reaction).

Using this method, the solid-phase synthesis of a 4,6-diarylpyridine-3-carbonitrile derivative **24** (Scheme 1) was carried out.[59] In this synthesis, immobilised aldehyde **25** formed upon acylation of the amino group in modified polystyrene with 4-formylbenzoic acid was used as the precursor. The reaction was carried out in *N*,*N*-dimethylacetamide (DMA) in the presence of *N*,*N*′-diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) at room temperature. Condensation of aldehyde **25** with acetophenone under the action of a base yielded chalcone **26**, which added 3-aminocrotononitrile (**27**) by the Michael mechanism. The latter reactant (**27**) formed *in situ* from acetonitrile under the action of potassium *tert*-butoxide. This stage was carried out at room temperature with sonication. After the treatment of immobilised pyridine **28** with trifluoroacetic acid (TFA), 4,6-diarylpyridine **24** was isolated.

An analogous solid-phase synthesis produced a large number of 4,6-diarylpyridines **29** that may attract interest as the fluorescent dyes for biological studies. Compounds **29** formed by the reaction of chalcone (**30**) immobilised on cellulose (chromatographic paper) with 3-aminocrotononitrile (**27**).

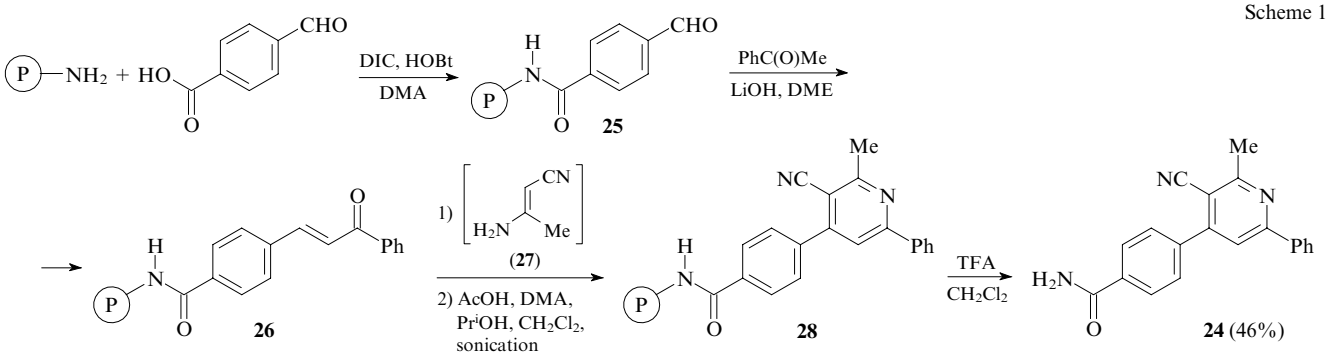


Ar = $X_nC_6H_{4-n}$ [X = H, 2-F, 4-F, 4-Br, 4-MeO, 3-MeO, 4-Me_2N, 3,4-$(MeO)_2$]; R = 4-HO, 3-MeO, 4-MeO, 3-HO, 3,4-$(MeO)_2$.

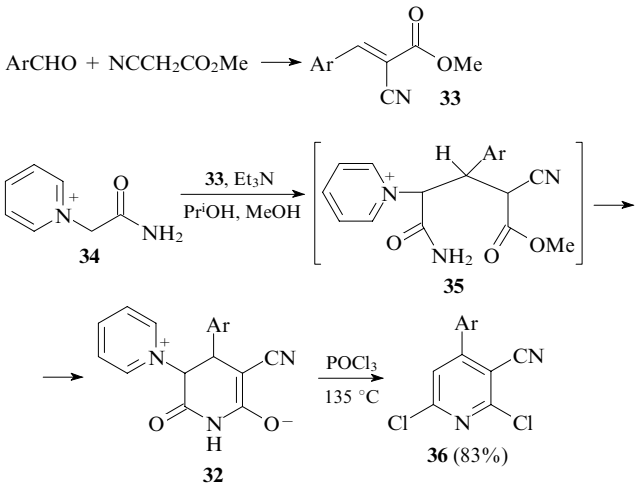
In the first stage, chalcone **30** easily transformed into 4,6-diarylpyridine-3-carbonitrile **31** as a result of addition of nitrile **27**. In the final step, product **29** was isolated under the action of vapour of trifluoroacetic acid.[60]

A method of constructing a pyridine ring based on a one-pot synthesis of pyridinium inner salt **32** was described.[61] Condensation of an aromatic aldehyde ArCHO (Ar = 2-MeC_6H_4, 4-F-2-MeC_6H_3) with methyl cyanoacetate yielded unsaturated ester **33**. The latter reacted with pyridinium salt **34** (the Michael reaction) to form adduct **35** that cyclised to afford inner salt **32**. 4-Arylpyridines **36** were formed as a result of treating salts **32** with phosphorus(V) oxychloride.

Scheme 1

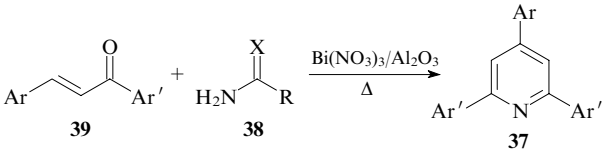


(P) is a polymeric carrier, DME is 1,2-dimethoxyethane.



Ar = 2-MeC_6H_4, 4-F-2-MeC_6H_3.

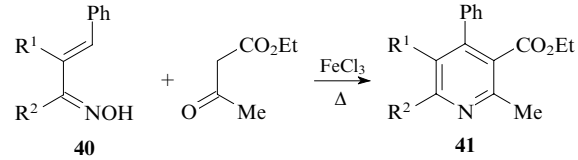
2,4,6-Triarylpyridines **37** were synthesised by a solid-phase reaction of (thio)amides **38** with chalcones **39** prepared beforehand from the corresponding benzaldehyde and acetophenone derivatives.[62] Condensation of chalcones **39** and (thio)amides **38** taken in the ratio of 2 : 1 was carried out on heating in the absence of solvent with $Bi(NO_3)_3/Al_2O_3$ as the solid phase and the catalyst. After complection of the reaction, the catalyst could be recovered and reused. The yields of products were 50% – 82%.



Ar = $Y_nC_6H_{4-n}$ (Y = H, 4-Me, 4-F, 4-Cl, 4-Br, 4-I, 4-HO, 3,4-$(CH_2O)_2$, 3,4-Cl_2); Ar′ = Ph, 4-ClC_6H_4, 4-BrC_6H_4; R = Me, Ph, H_2N, NH_2NH, $NH_2C(O)NH$; X = O, S.

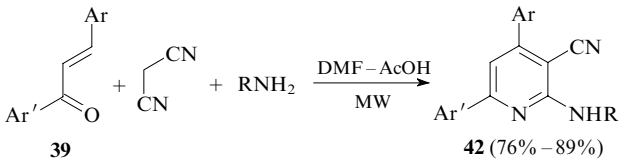
Presumably, the reaction followed the mechanism shown in Scheme 2.

Yet another method of synthesis of 4-arylpyridines was based on the reaction of α,β-unsaturated oximes and β-dicarbonyl compounds in the presence of iron(III) chloride. As a rule, the Michael reaction was catalysed by a base; however, the use of iron(III) chloride in this case turned out to be more efficient because it became possible to carry out this process under milder conditions.[63, 64] Thus the reaction of oximes **40** with ethyl acetoacetate in the presence of iron(III) chloride produced ethyl 4-phenylnicotinate derivatives **41**.



R^1 = H: R^2 = Ph (41%), Me (81%); R^1 = Et, R^2 = Ph (45%).

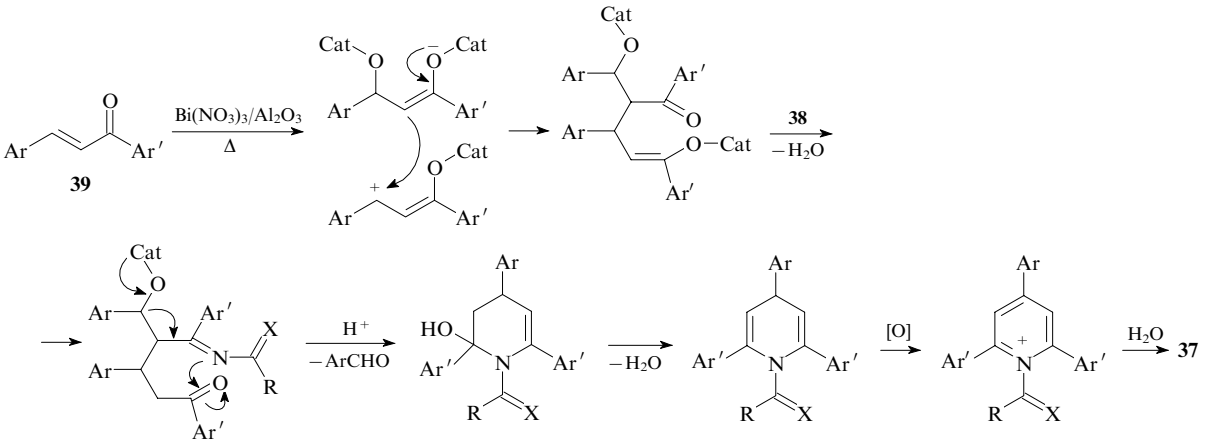
The reaction of chalcone **39** with malononitrile and a primary amine in a 1 : 4 mixture of DMF and acetic acid under the action of microwave radiation (100 – 200 W) produced 2-amino-4,6-diarylpyridine-3-carbonitriles **42**.[65]



Ar = 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 2-thienyl; Ar′ = 2-Py, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$; R = n-C_6H_{13}, Ph, 4-MeC_6H_4, (*S*)-PhMeCH, (*R*)-PhMeCH; MW is microwave radiation.

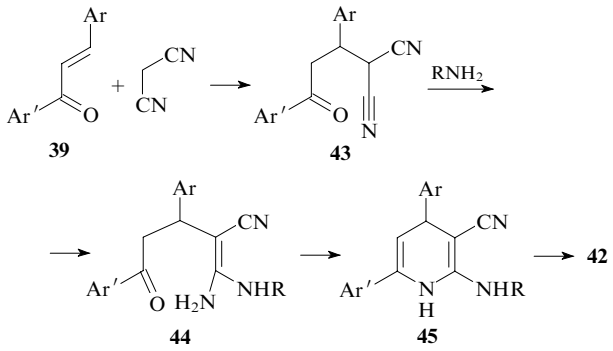
It turned out that the basicity of the reaction medium played a significant role in the formation of pyridines **42.** (In the absence of an acid, amines played the role of a base catalysing the side process, namely, the Knövenagel condensation of malononitrile with adduct **43**.) The following reaction mechanism was proposed (Scheme 3): in the first stage, the nucleophilic β-carbon atom of malononitrile adds to chalcone **39** (the Michael addition); then, the adduct **43** formed adds a primary amine that acts as a nucleophile. Cyclisation of the intermediate compound **44** followed by aromatisation of dihydropyridine **45** yielded 4-arylpyridine **42**.

Scheme 2



Cat is the catalyst surface.

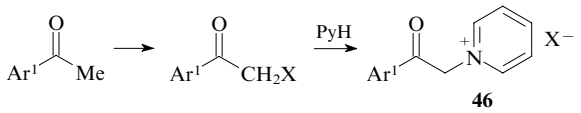
Scheme 3



d. The Kröhnke method

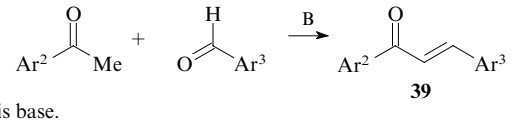
Yet another approach to the synthesis of 4-aryl- and 4-hetarylpyridines is based on the addition of an active methylene group of an *N*-acylmethylpyridinium salt to the chalcone double bond and includes several stages (the Kröhnke method [41]).[66–68]

Pyridinium salt **46** (the Kröhnke salt) was obtained by halogenation of a methyl ketone at the α-position followed by treatment of the resulting halogen derivative with pyridine.



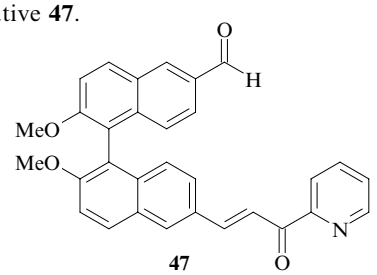
X = Br, I.

Chalcone **39** was synthesised by the aldol-crotonic condensation of another methyl ketone with an aromatic aldehyde in the presence of a base (sodium or potassium hydroxide, sodium methoxide, sodium *tert*-butoxide, potassium carbonate, potassium hydrogencarbonate).

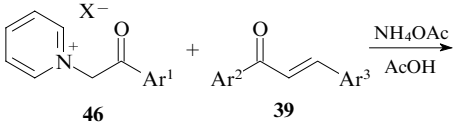


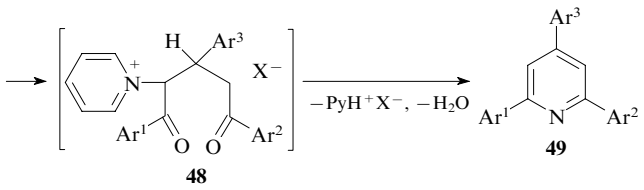
B is base.

Note that in addition to substituted benzaldehydes, this reaction was also carried out with binaphthaldehyde derivative **47**.



In the last stage, the Michael reaction of the Kröhnke salt **46** with unsaturated ketone **39** was carried out. The *in situ* produced 1,5-diketone **48** was cyclised to pyridine **49** upon treatment with ammonium acetate in glacial acetic acid (sometimes, methanol or water were used).





X = Br, I.

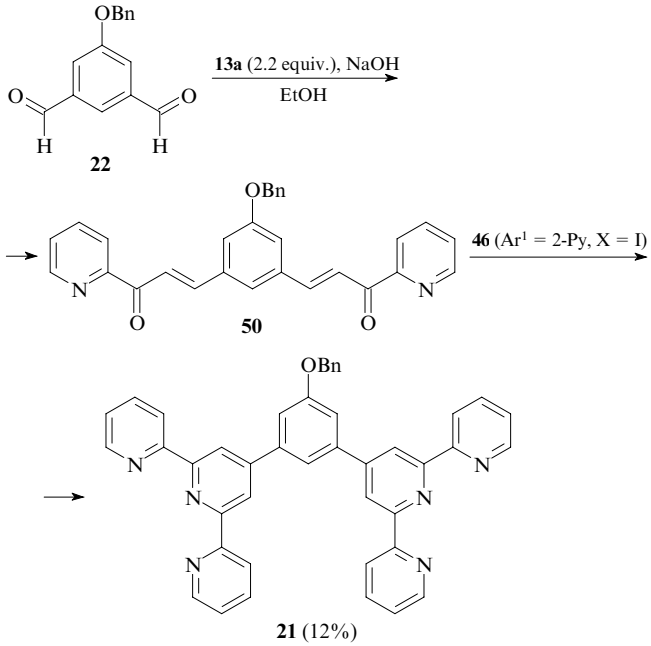
Several triaryl- and terpyridines **49** were obtained by this method (Table. 1).

Table 1. 4-(Het)arylpyridines **49** synthesised using the Kröhnke method.

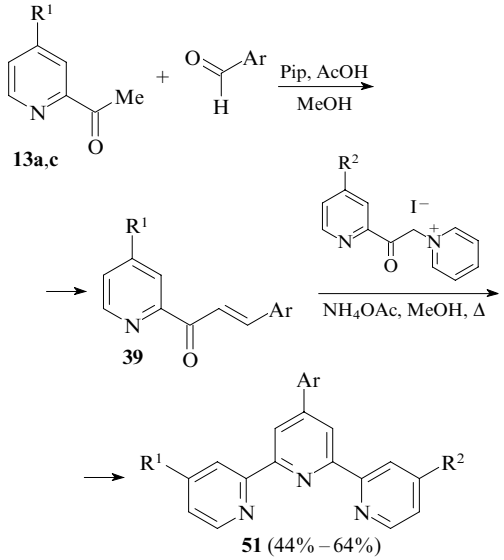
Ar^1	Ar^2	Ar^3	Yield (%)	Ref.
Ph	Ph	$HO_2CC_6H_4$	–	66
	$HO_2CC_6H_4$	MeC_6H_4	–	66
2-Py	2-Py	ãü. ô	42	67
	2-Py	$4\text{-}BrC_6H_4$	73	68
4-Me-2-Py	2-Py	$4\text{-}BrC_6H_4$	72	68
	4-Me-2-Py	$4\text{-}BrC_6H_4$	33	68
$4\text{-}MeO_2C\text{-}2\text{-}Py$	2-Py	$4\text{-}BrC_6H_4$	37	68
	4-Me-2-Py	$4\text{-}BrC_6H_4$	39	68
	$4\text{-}MeO_2C\text{-}2\text{-}Py$	$4\text{-}BrC_6H_4$	51	68
	4-NC-2-Py	$4\text{-}BrC_6H_4$	38	68
4-NC-2-Py	2-Py	$4\text{-}BrC_6H_4$	58	68
	4-Me-2-Py	$4\text{-}BrC_6H_4$	41	68
	4-NC-2-Py	$4\text{-}BrC_6H_4$	48	68

[a] Aldehyde **47** was used.

In the base-induced condensation of dialdehyde **22**, the introduction of 2.2 equivalents of 2-acetylpyridine (**13a**) (in place of 4.4 equivalents, as described above) resulted in dienone **50**. The latter compound without any additional purification was introduced into the reaction with the Kröhnke salt **46** (Ar^1 = 2-Py, X = I) to yield bis(terpyridine) **21**.[58] However, the use of the Kröhnke method for the synthesis of this compound was less effective (the product yield was 12%) as compared with the procedure described in Section II.2.b (yield 22%).



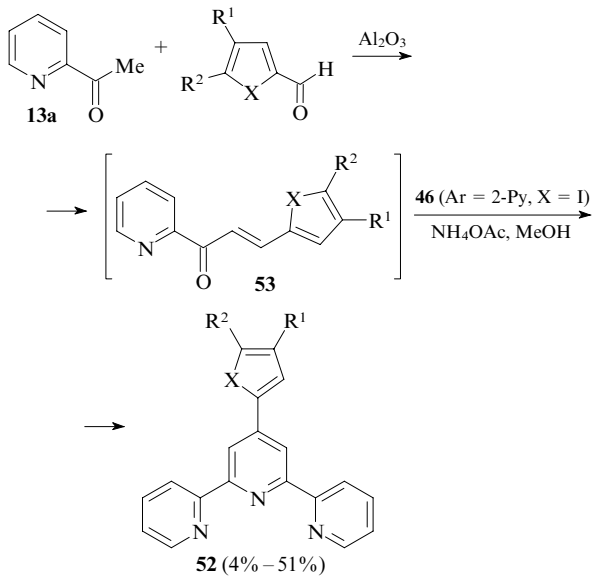
Unsaturated ketones **39**, which were prepared by the condensation of 2-acetylpyridine (**13a**) or its 4-methoxycarbonyl derivative **13c** with aromatic aldehydes, reacted with the Kröhnke salt under the action of piperidinium acetate in the presence of ammonium acetate to form terpyridines **51**.[69]



Ar = 4-MeC_6H_4, 4-BrC_6H_4, 4-$MeO_2CC_6H_4$; R^1, R^2 = H, MeO_2C; Pip is piperidine.

Terpyridines **51** were used as the ligands in the synthesis of luminescent ruthenium complexes.[69]

The Kröhnke method was also used in the synthesis of hetaryl-substituted terpyridines **52**. The original unsaturated ketones **53** were prepared by the solvent-free aldol–crotonic condensation of 2-acetylpyridine (**13a**) with hetarenes containing an aldehyde group in the α-position. Sodium hydroxide, barium hydroxide or alumina were used as the catalysts. The highest yields of compounds **53** were obtained with alumina,[70] which was the weakest base and, apparently, prevented the side formation of a diketone. In the second step, ammonium acetate was used as the source of a nitrogen atom in the formation of a pyridine ring.



X = O, S, NH; R^1 = H, Br; R^2 = H, Br, O_2N, $O(CH_2CH_2)_2N$.

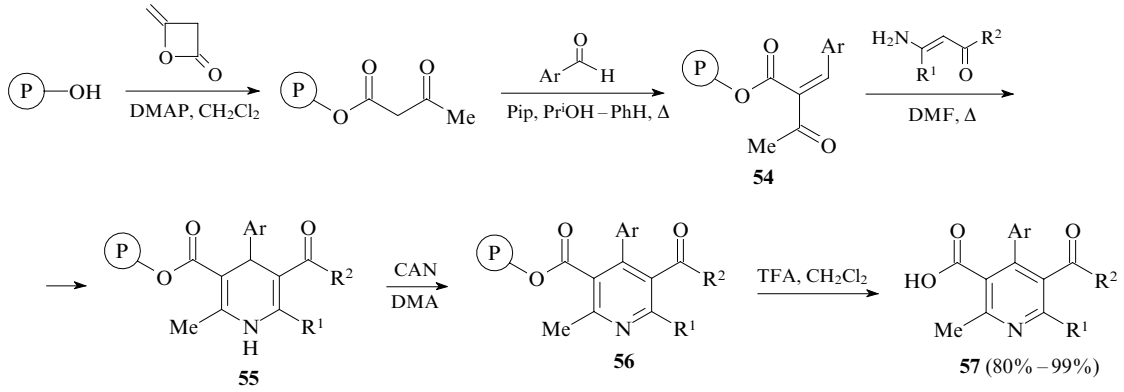
e. Miscellaneous condensation reactions

A large group of methods of the synthesis of 4-arylpyridines is based on the formation of the target products in one or several condensation reactions, as a rule, base-catalysed.

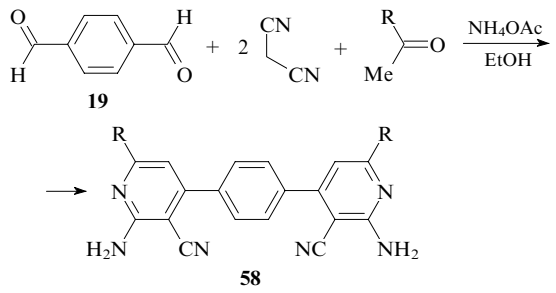
A method of solid-phase synthesis of 4-arylpyridines on the basis of the Knövenagel–Hantzsch condensation was developed.[71,72] Immobilised β-keto esters[71] (β-keto amides or β-diketones[72]) were synthesised by treating a polymer with diketene[71] (butyl acetoacetate or lithium acetoacetate[72]). 4-Dimethylaminopyridine (DMAP) was used as the catalyst. Condensation of the β-keto ester with an aldehyde under the action of a base produced adduct **54** that reacted with an enamine to form 1,4-dihydropyridine **55** (Scheme 4). Oxidation of the latter with ammonium hexanitratocerate(IV) (CAN) led to pyridine **56**. The use of different aldehydes and enamines made it possible to obtain a large series of 4-arylpyridines **57**. After the completion of the synthesis, the immobilised product was treated with trifluoroacetic acid to recover the active groups of the polymeric support and to liberate the target compounds.

A reaction of terephthalaldehyde (**19**) with two equivalents of malononotrile and acetylhetarenes in the presence of ammonium acetate afforded 1,4-bis(4-pyridyl)benzenes **58** in the yields of 68%–76%.[73]

Scheme 4

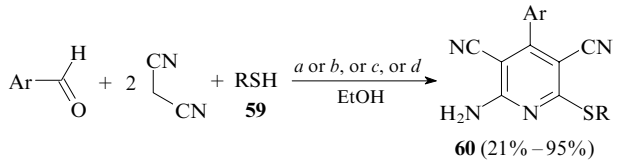


Ar = Ph, 4-$MeOC_6H_4$, 2-FC_6H_4, 4-$HO_2CC_6H_4$, 3-$O_2NC_6H_4$, 4-Py, 2-naphthyl; R^1 = Me, PhC(O)NH; R^2 = MeO, Pr^iO.



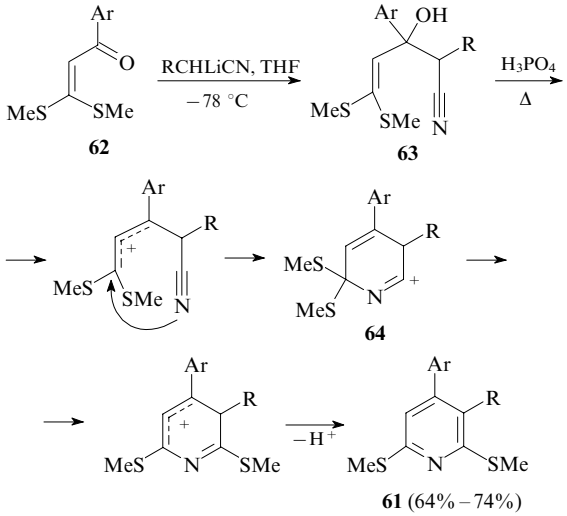
R = 2- and 3-Py, 2-thienyl, 2-furyl, 5-Me-2-furyl.

Recent studies aimed at the development of new pharmaceutical agents have shown that 2-amino-6-aryl(alkyl)thio-3,5-dicyanopyridine derivatives are the promising selective modulators of adenosine receptors and can be used in treatment of epilepsy, asthma and malignant tumours. Condensation of aromatic aldehydes with malononitrile and thiols **59** under the action of a base (a tertiary amine or *o*-phenylenediamine) on boiling in ethanol produced a large series of these derivatives with 4-hetaryl substituents, namely, compounds **60**.[74, 75] However, the formation of comparable amounts of a side product, namely, enaminonitrile, decreased the target product yield. The use a basic ionic liquid, namely, 1-butyl-3-methylimidazolium hydroxide ([bmIm]OH) in place of amines suppressed the side reaction, which in certain cases favoured the formation of 4-arylpyridines **60** in higher yields and under milder conditions. Moreover, the advantages of this method include the possibility of recovering and recycling the ionic liquid.[76]



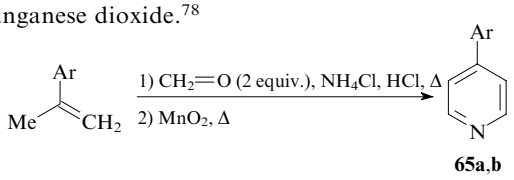
(*a*) Et_3N; (*b*) 1,2-$(H_2N)_2C_6H_4$; (*c*) 1,4-diazabicyclo[2.2.2]octane (DABCO); (*d*) [bmIm]OH; Ar = $X_nC_6H_{4-n}$ [X = H, 4-Me, 4-MeO, 4-BnO, 4-HO, 4-O_2N, 4-Et_2N, 4-HO_2C, 4-Cl, 4-F, 3-Br, 2-Br, 4-MeS, 3,4-$(MeO)_2$, 2,5-$(MeO)_2$, 2,3-$(MeO)_2$, 2,4-$(MeO)_2$, 3,4,5-$(MeO)_3$, 3-HO-4-MeO, 3-Br-4-Me_2N, 2,6-Cl_2, 3,4-OCH_2O], 1-MeO-2-naphthyl, 3- and 4-Py, 3- and 2-thienyl, 2-furyl; R = Ph, 4-ClC_6H_4, 2-$H_2NC_6H_4$, 2-HOC_6H_4, 2,4,6-$Me_3C_6H_2$ (Mes), cyclo-C_6H_{11}, Bn, $HO(CH_2)_2$, 2-furfuryl.

4-Arylpyridines **61** were synthesised from vinyl ketones **62** as a result of the 1,2-addition of the lithium derivatives of acetonitrile or propionitrile. On treatment with phosphoric acid, alcohol **63** underwent cyclisation to form intermediate **64**; under these conditions, the latter was aromatised with the 1,3-migration of the methylthio group.[77]



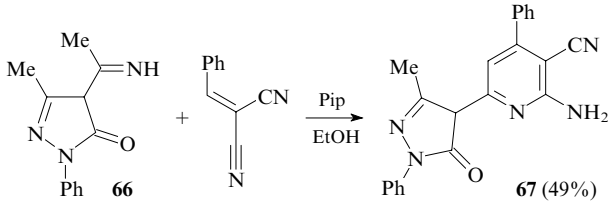
Ar = Ph, 3-Py, 2-naphthyl, 2-thienyl, 2-furyl; R = H, Me.

4-Arylpyridines **65a**,**b** could be synthesised in yields reaching 32% by the modified Prince reaction, namely, by the condensation of arylpropenes with formaldehyde and ammonium chloride in an acidic medium in the presence of manganese dioxide.[78]



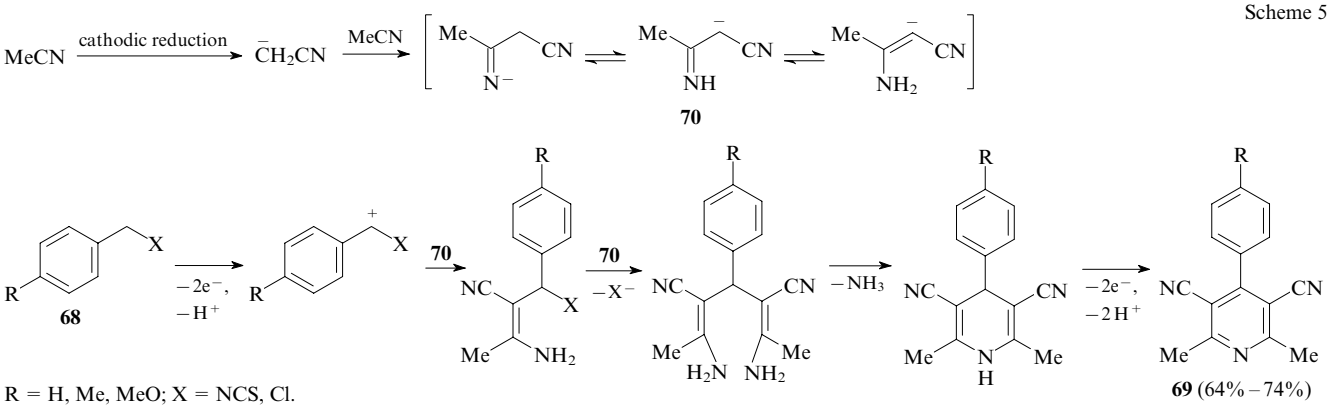
Ar = Ph (**a**), 4-MeC_6H_4 (**b**).

The reaction of imine **66** with benzylidenemalononitrile under the action of piperidine in ethanol produced a pyrazoline derivative of 4-phenylpyridine (**67**).[79]



An unusual synthesis of 4-arylpyridines was described.[80] Electrolysis of benzyl derivatives **68** in anhydrous acetonitrile on a platinum electrode in a cell with two compartments separated by a porous glass membrane yielded 4-arylpyridines **69** (Scheme 5).

Scheme 5

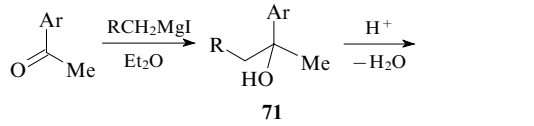


R = H, Me, MeO; X = NCS, Cl.

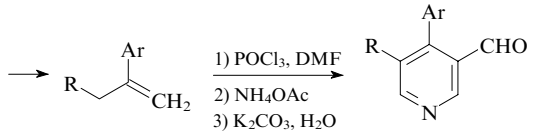
The authors of the latter study discussed several versions of the reaction mechanism but noted that under the given conditions all substrates could be oxidised to benzyl cations that react with anions of dimerised acetonitrile **70**. Scheme 5 shows this reaction.

f. The Vilsmeier – Haack reaction

Based on tertiary alcohols **71**, it is possible to synthesise 4-arylpyridine-3-carbaldehydes **72** by the Vilsmeier – Haack reaction. The original alcohols were synthesised in the reaction of aromatic ketones with the Grignard reagents. In the presence of acid, alcohol **71** underwent dehydration to form the corresponding alkene, which was successively treated with the Vilsmeier reagent ($POCl_3 + DMF$), ammonium acetate and a saturated aqueous solution of potassium carbonate.[81]



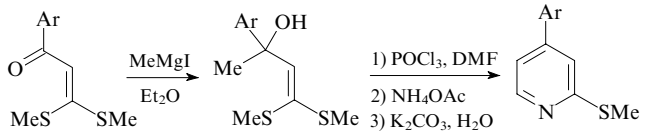
71



72 (43% – 66%)

Ar = 4-XC_6H_4 (X = H, Me, Cl, Br, MeO), 2-naphthyl; R = H, Me.

The same method allowed a series of 4-aryl-2-methylthiopyridines **74** to be synthesised from allylic alcohols **73**.[82]

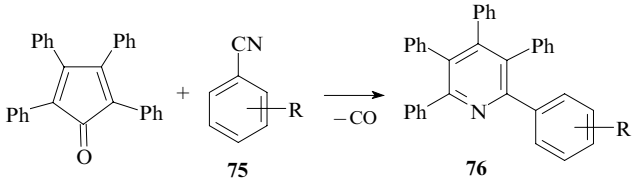


62 **73** **74** (41% – 56%)

Ar = 4-XC_6H_4 (X = H, Cl, Br, Me, MeO), 2-naphthyl.

g. Synthesis on the basis of cyclopentadiene derivatives

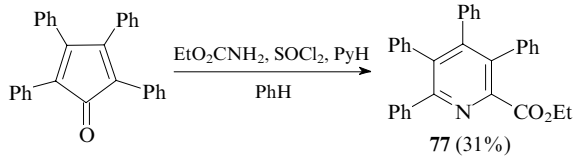
The addition of tetraphenylcyclopentadienone (tetracyclone) to benzonitriles **75** yielded pentaphenylpyridines **76** (see Ref. 46, p. 547); unfortunately, the yields of products were not reported.



75 **76**

R = 2-Br, 4-Br, 4-Me, 4-MeO.

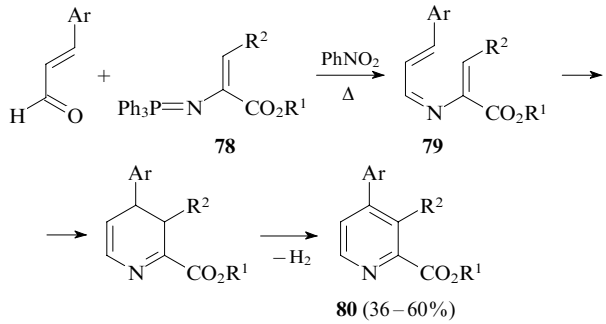
Tetraphenylpyridine derivatives, *e.g.*, compound **77**,[83] were obtained on boiling tetracyclone in benzene with the Katz reagent formed *in situ* from urethane, thionyl chloride and pyridine.



77 (31%)

h. Synthesis using iminophosphoranes

This approach to the synthesis of 4-arylpyridines is based on the Wittig reaction of iminophosphoranes **78** with α,β-unsaturated aldehydes. Initially, this reaction affords 3-aza-1,3,5-trienes **79**, which undergo aromatisation to 4-arylpyridine-2-carboxylates (**80**).[84,85]



78 **79**

80 (36 – 60%)

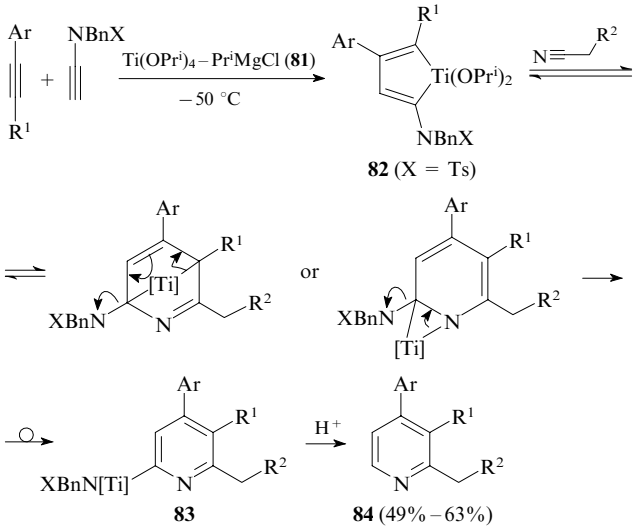
Ar = XC_6H_4 (X = H, 4-Cl, 2-MeO, 4-MeO, 2-Me, 2-O_2N), 2-thienyl; R^1 = Me, Et; R^2 = H, Me, EtO_2C.

i. Synthesis based on acetylene derivatives and nitriles

The basis of this method is a four-component coupling reaction of two different acetylene derivatives with a nitrile and reagent **81**, which contains a Ti alkoxide, *i.e.*, a mixture of $Ti(OPr^i)_4$ and Pr^iMgCl in the molar ratio of 1 : 2. By varying the reactants one can synthesise different 4-arylpyridine derivatives.[86]

The following reaction mechanism was proposed[86] (Scheme 6). The reaction of acetylene and *N*-benzyl-*N*-tosylaminoacetylene with reagent **81** yielded titanacyclopentadiene **82**, which then reacts with chloro- or methoxyacetonitrile. The reaction proceeded *via* metallated pyridine derivative **83**; in the final stage, hydrolysis, pyridine **84** was obtained in high yields. The driving force of this process was the elimination of the *N*-benzyl-*N*-tosylamide group.

Scheme 6

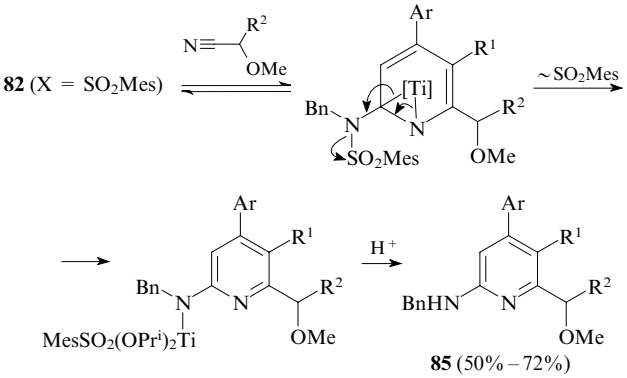


82 (X = Ts)

83 **84** (49% – 63%)

[Ti] = $Ti(OPr^i)_2$; Ar = Ph, 4-$MeOC_6H_4$, *N*-methylpyrrol-2-yl; R^1 = Ph, 4-$MeOC_6H_4$, $SiMe_3$; R^2 = Cl, MeO; X = Ts.

The replacement of the tosyl group in acetylene by a bulkier mesitylenesulfonyl group by the analogous reaction with a symmetrical diarylacetylene resulted in the formation of aminopyridine derivatives **85**.

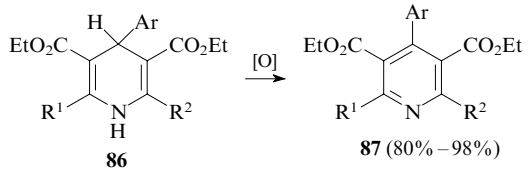


[Ti] = $Ti(OPr^i)_2$; Ar = R^1 = XC_6H_4 (X = H, 4-Me, 3-Me, 4-MeO, 4-Cl); R^2 = H, Ph.

3. Oxidation of 4-aryldihydropyridine and -tetrahydropyridine derivatives

One of the most widely used methods of the synthesis of 4-arylpyridines is the oxidation or dehydrogenation of the 4-aryl-1,4-dihydropyridine and 4-aryltetrahydropyridine derivatives.

4-Aryl-1,4-dihydropyridines **86** synthesised by the Hantzsch method are easily oxidised because they contain two double bonds in the ring. Classical methods of 1,4-dihydropyridine dehydrogenation are based on the use of nitric or nitrous acids. This transformation proceeded smoothly with other oxidants such as H_2O_2, MnO_2, $KMnO_4$, CrO_3, nicotinium dichromate, manganese(III) acetate, zirconium(IV) nitrate, ammonium hexanitratocerate(IV), copper(II) acetate, copper(II) chloride, pyridinium chlorochromate (PCC).[87–93] Recently, attention was drawn to an effective, mild and selective oxidant, namely, 2-iodoxybenzoic acid.[91] The merits of this reagent include the reduction of the reaction time to 2–4 h, while its drawbacks include poor solubility in many organic solvents.



(1)

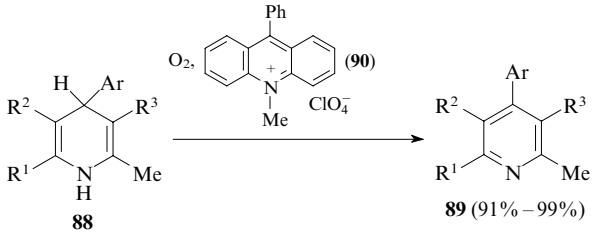
R^1 = H, Me; R^2 = Me, Et; Ar = XC_6H_4 (X = H, 4-Me, 4-HO, 4-MeO, 4-O_2N, 3-O_2N, 2-O_2N, 4-Cl, 2-Cl), 2-naphthyl, 3-Py, 2-furyl, 2-thienyl.

Oxidation of the Hantzsch 1,4-dihydropyridines **86** (R^1 = Me, R^2 = Et: Ar = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 2-furyl, 2-thienyl) to the corresponding pyridines **87** [reaction (1)] was conducted in dichloromethane under the action of PCC adsorbed on alumina, silica gel, or aluminium hydrosilicate; the product yields were above 90%.[92] The aromatisation time depended on the nature of substituents in position 4 in the original dihydropyridine. Oxidation of derivatives with electron-withdrawing substituents required substantially longer time. It was shown that the reaction time can be shortened as a result of a several-fold decrease in the size of solid support particles.

The oxidation of 4-aryl-1,4-dihydropyridines **86** (R^1 = Me; R^2 = Me, Et; Ar = Ph, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$) under the action of atmospheric oxygen dried by passage through anhydrous calcium chloride was described.[93] This reaction was carried out in DMSO at 70 °C, the product yields were 89% – 94%.

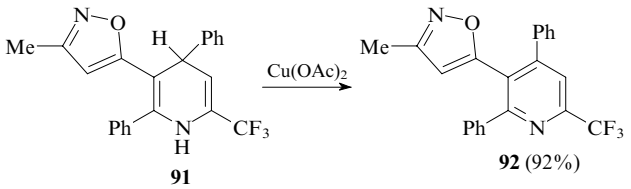
Dehydrogenation of the corresponding 1,4-dihydropyridines in the presence of a palladium catalyst in acetic acid at 80 °C produced 4-arylpyridines **87** (R^1 = Me, R^2 = Et: Ar = Ph, 4-HOC_6H_4, 4-$O_2NC_6H_4$) in yields of 91% – 97%. The advantage of this method lies in the reduction of the reaction time.[94]

The Hantzsch dihydropyridines were efficiently oxidised under mild conditions in the presence of a photocatalyst. Thus aromatisation of 1,4-dihydropyridines **88** to 4-arylpyridines **89** proceeded at room temperature in air-saturated acetonitrile under the mercury lamp radiation (150 W, $\lambda < 310$ nm) in the presence of 5% *N*-methyl-9-phenylacridinium perchlorate (**90**). Compound **90** acted as the catalyst and could be recovered and reused.[95]

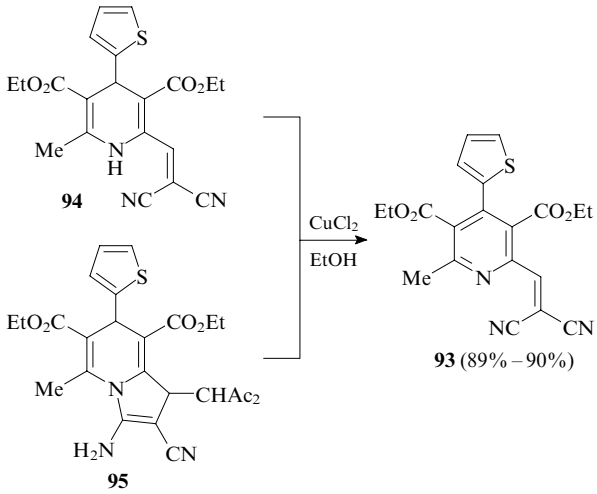


Ar = Ph, 2-BrC_6H_4, 3-$O_2NC_6H_4$, 4-$MeOC_6H_4$; R^1 = Me, Ph; R^2, R^3 = EtO_2C, Ac, N≡C.

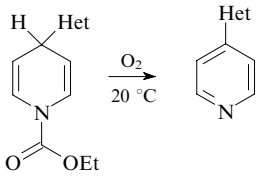
Oxidation of dihydropyridine **91** with copper(II) acetate yielded isoxazole-substituted 4-phenylpyridine **92**.[96]



4-Thienylpyridine **93** was prepared in high yields by the oxidation of 1,4-dihydropyridine **94** and dihydroindolizine **95**.[97] In both cases, copper(II) chloride was used as the oxidant and the reaction was carried out at room temperature.



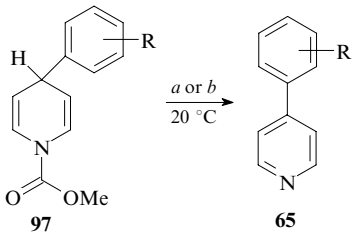
The addition of organometallic compounds to pyridinium salts also produced 1,4-dihydropyridines that could easily be oxidised to the corresponding pyridines. Thus oxidation of 4-hetaryl-1,4-dihydropyridines **96** in the oxygen flow at room temperature afforded a large number of 4-hetarylpyridines.[98,99]



96

Het	Yield (%)	Ref.
6-MeO-2-Py	58	98
6-BnO-2-Py	62	98
N-Methylpyrrol-2-yl	45	99
2-Furyl	49	99
5-Methyl-2-furyl	44	99
5-Ethyl-2-furyl	41	99
3-Bromo-2-furyl	40	99
3-Bromo-2-thienyl	51	99

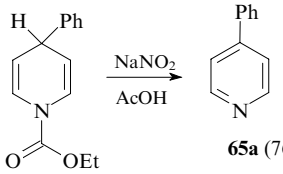
A series of 4-arylpyridines **65** with different substituents in the benzene ring were synthesised by oxidation of the corresponding *N*-methoxycarbonyldihydropyridines **97** on silica gel in oxygen flow at room temperature. The product yields were 35% – 69%.[100] However, this method proved to be ineffective for the derivatives that contained strong electron-withdrawing substituents in the benzene ring. In the latter cases, a mixture of acetic acid and 30% hydrogen peroxide was used as the oxidant and the reaction was carried out in DMF at room temperature; the yields were 44% – 66%.



97 **65**

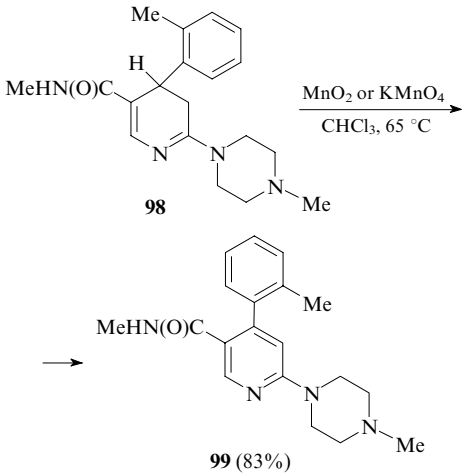
(*a*) O_2, SiO_2: R = 4-Me, 4-Pr^i, 2-MeO, 3-MeO, 4-MeO, 3,4-OCH_2CH_2O, 4-EtO_2C, 3-EtO_2C, 4-Ac, 3-Ac, 4-NC;
(*b*) H_2O_2, AcOH, DMF: R = 4-F_3C, 3-F_3C, 4-F, 3-Cl.

4-Phenylpyridine (**65a**) was synthesised by the oxidation of *N*-ethoxycarbonyl-4-phenyl-1,4-dihydropyridine with sodium nitrite in acetic acid.[101]

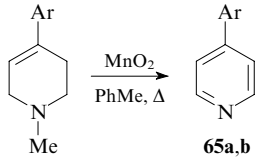


65a (76%)

Oxidation of 3,4-dihydropyridine derivative **98** to 4-(2-tolyl)nicotinamide **99** proceeded under sufficiently mild conditions under the action of manganese dioxide or potassium permanganate.[102]



4-Aryltetrahydropyridines **100a**,**b** were oxidised under more drastic conditions, namely, on boiling in toluene with tenfold excess of MnO_2.[103,104]

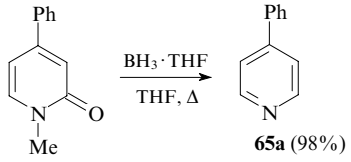


100a,**b** **65a**,**b**

Ar = Ph (**a**, 45%), 4-MeC_6H_4 (**b**, 42%).

4. Reduction of pyridones

An unusual reduction of *N*-methyl-4-phenylpyridin-2-one (**101**) to 4-phenylpyridine (**65a**) with borane was described.[105] The reaction was carried out on heating in anhydrous tetrahydrofuran.



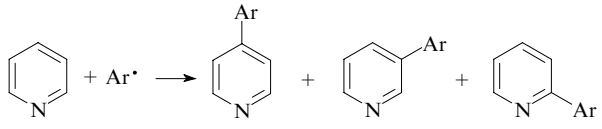
101 **65a** (98%)

III. Arylation of pyridine and its derivatives

Yet another approach to the synthesis of 4-arylpyridines consists of arylation of the pyridine ring with different reagents. This method includes the free-radial arylation and also different coupling and cross-coupling reactions.

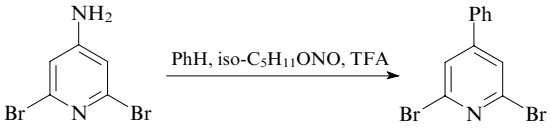
1. Radical arylation of pyridine

The free-radical arylation of pyridine produces a mixture of isomeric α-, β- and γ-arylpyridines. The ratio of reaction products is almost independent of the source of aryl radicals. (Aryl radicals are usually generated from diazo compounds.)



Although under the free-radical arylation conditions, the directing effect of nitrogen atom was weaker as compared with nucleophilic substitution, the increase in the radical nucleophilicity accelerated its reaction with pyridine and increased the degree of substitution into positions 2 and 4.

The displacement of a hydrogen atom in benzene in the reaction with 4-amino-2,6-dibromopyridine apparently proceeded *via* the pyridyl radical. The benzene solution of 4-amino-2,6-dibromopyridine was first treated with isopentyl nitrite in trifluoroacetic acid and then the diazonium salt formed was refluxed. The yield of 2,6-dibromo-4-phenylpyridine (**102**) was 49%.[5]



102 (49%)

Based on 2,6-dibromo-4-phenylpyridine (**102**), the ligand ({*N*,*N*,*N*′,*N*′-[2,6-bis(3-aminomethylpyrazol-1-yl)-4-phenylpyridine]tetrakis(acetic acid)} was synthesised its complex with Tb^{3+} was used as the fluorescent marker in biological and medicinal studies.[5]

4-Arylpyridines were also prepared by the homolytic substitution of a 4-pyridyl radical for a hydrogen atom in benzene or its derivatives. Thus the arylation of benzene by a 4-pyridyl radical, which was produced from 4-bromopyridine on heating in the presence of tris(trimethylsilyl)silane (TTMSS) and azobisisobutyronitryl (AIBN), led to 4-phenylpyridine (**65a**).[106]



65a (55%)

Pyridyl radicals were also generated in the electrochemically induced reaction of 4-chloropyridine with nitrogen-containing heterocycles (pyrrole, 2,5-dimethylpyrrole and indole).[107] The reaction produced a complex mixture of mono- and disubstituted products, both 4- and 3-pyridyl derivatives. In the cited study, the yields were presented only for selected reaction products.

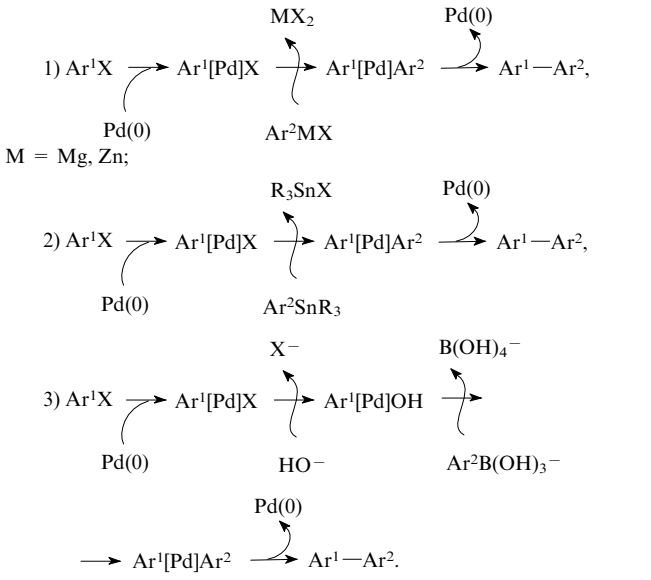
At present, the synthetic significance of reactions of free-radical substitution has dramatically reduced due to their low selectivity and small yields.

2. Coupling and cross-coupling reactions

The popular approach to the synthesis of 4-arylpyridines is the catalytic cross-coupling reactions, such as the Kharash, Negishi, Stille and Suzuki reactions. This type of reactions were used in the synthesis of biaryls, arylhetarenes and bihetarenes; palladium and nickel complexes usually served as the catalysts.

All the listed reactions are characterised by the presence of three common stages, as illustrated below by the example of palladium complexes (Scheme 7). The first stage is the oxidative addition of a catalyst to an aryl halide to form the $Ar^1[Pd]X$ intermediate, the second stage, remetallation, yields diarylpalladium compounds$Ar^1[Pd]Ar^2$ and the final stage, reductive elimination of the diarylated palladium compound, affords a biaryl (or another cross-coupling product) and the Pd(0) catalyst.[19]

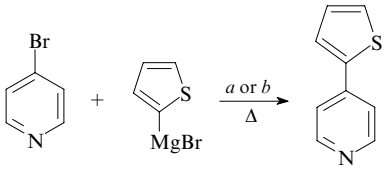
Scheme 7



a. Kharash reaction

The synthesis of 4-arylpyridines by the Kharash reaction is, as a rule based on the reaction of a pyridyl halide with a Grignard reagent (arylmagnesium bromide or arylmagnesium chloride) in the presence of a nickel or palladium catalyst. The high reactivity of the Grignard reagent prevents the use of compounds containing the keto, nitro, aldehyde, or ester groups in this reaction.

Thus the reaction of 4-bromopyridine with 2-thienylmagnesium bromide in the presence of a nickel or palladium catalyst produced 4-(2-thienyl)pyridine (**103**) in the yield of 70%–84%. The nickel complex activity was lower as compared with the palladium complex; hence, in the former case, the reaction was carried out in a solvent with a higher boiling point, namely, tetrahydrofuran.[108, 109]

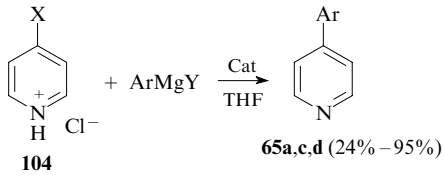


103

(*a*) $NiCl_2$(dppp), THF; (*b*) $PdCl_2$(dppf), Et_2O; dppp is 1,3-bis(diphenylphosphino)propane, dppf is 1,1′-bis(diphenylphosphino)ferrocene.

4-(2-Thienyl)pyridine (**103**) was used in the synthesis of solvatochromic compounds and materials for non-linear optics.[109]

In certain cases, pyridyl halides are introduced in the form of hydrochlorides which activates the C–Hal bond. For example, the reaction of 4-chloro(bromo)pyridinium hydrochloride with Grignard reagents produced derivatives of 4-arylpyridine **65a**,**c**,**d**.[110, 111]

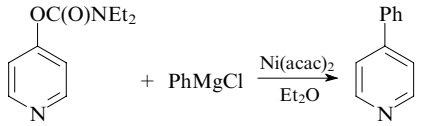


104 **65a**,**c**,**d** (24%–95%)

X, Y = Cl, Br; Ar = Ph (**a**), 4-ClC_6H_4 (**c**), 4-(4-$MeOC_6H_4$)C_6H_4 (**d**); Cat = $PdCl_2$(dppb) [dppb is 1,4-bis(diphenylphosphino)butane], $Pd(dba)_2$(dppf) (dba is dibenzylideneacetone).

In addition to halides, other aromatic derivatives, namely, triflates, mesylates, sulfides, sulfones, carbamates can serve as the Kharash cross-coupling reaction substrates.[19]

The synthesis of 4-phenylpyridine (**65a**) by cross-coupling of *N*,*N*-diethyl-4-pyridylcarbamate with phenylmagnesium chloride in the presence of a nickel catalyst was described.[112] Apparently, the process followed the mechanism of nucleophilic *ipso*-substitution.



65a (81%)

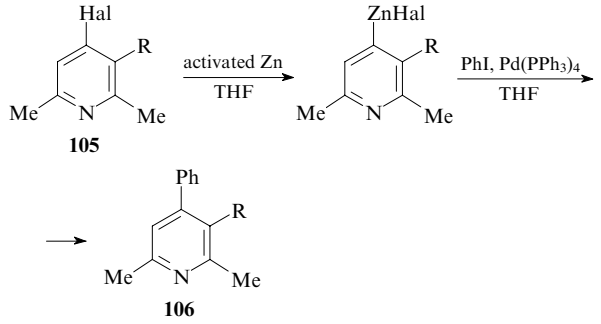
acac is acetylacetonate.

4-Phenylpyridine (**65a**) was also formed upon arylation of 4-cyanopyridine with phenylmagnesium chloride in the presence of the catalytic system $NiCl_2(PMe_3)_2$ – lithium 2,6-di-*tert*-butyl-4-methylphenoxide (LiOBHT) or LiSPh; the product yield was 75% or 86%.[113,114]

b. The Negishi reaction

In the synthesis of 4-arylpyridines by the Negishi reaction, pyridylzinc halide and aryl iodide are commonly used as the starting reagents; the reaction is carried out in the presence of a palladium or nickel catalyst.[115–118]

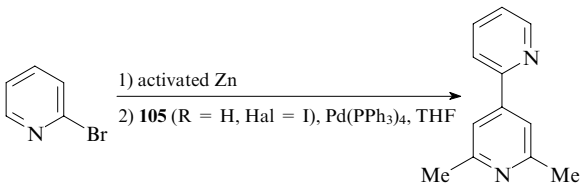
Pyridylzinc halide was prepared by treating 4-iodo-2,6-dimethylpyridine (**105**; R = H, Hal = I) with zinc in tetrahydrofuran. The subsequent reaction with iodobenzene in the presence of a palladium catalyst produced 2,6-dimethyl-4-phenylpyridine **106** (R = H) in the yield of 65%. In the case of 4-bromopyridine **105** (R = H, Hal = Br), the yield of product **106** (R = H) dropped to 31%.[115]



105 **106**

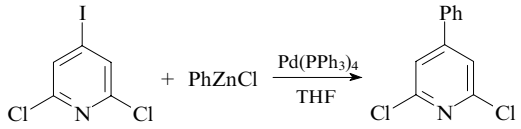
In a similar way, ethyl 2,6-dimethyl-4-phenylnicotinate **41** (R^1 = H, R^2 = Me) was synthesised from ethyl 4-iodo-2,6-dimethylnicotinate (**105**; R = EtO_2C, Hal = I) (yield 80%).

Synthesis of 2,6-dimethyl-2′,4-bipyridyl (**107**) was carried out using 2-pyridylzinc bromide and 4-iodo-2,6-dimethylpyridine (**105**; R = H, Hal = I) as the reactants.[117]



107 (72%)

Using the Negishi reaction, 4-phenyl-2,6-dichloropyridine (**108**) was synthesised from 4-iodo-2,6-dichloropyridine and phenylzinc chloride.[118]



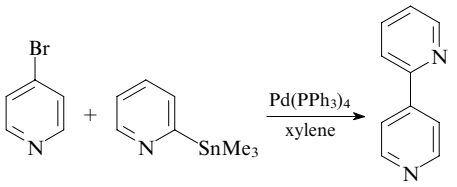
108 (98%)

c. The Stille reaction

4-Arylpyridines can be obtained by the Stille reaction, namely, the reaction of (het)arylstannane with (het)aryl halide in the presence of a palladium catalyst.

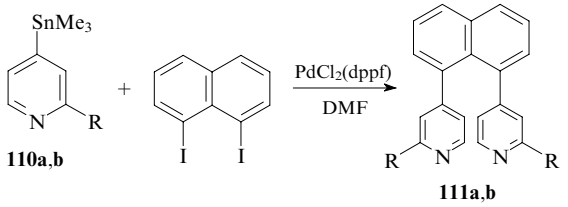
The Stille reaction is versatile, both components can contain a wide diversity of functional groups, which is not allowed for the Kharash reaction. The main drawback of this process is the toxicity of organotin compounds and side products.

Cross-coupling of 4-bromopyridine with trimethyl(2-pyridyl)stannane in the presence of a palladium catalyst produced 2,4′-bipyridyl (**109**) in the yield of 70%.[119]



109

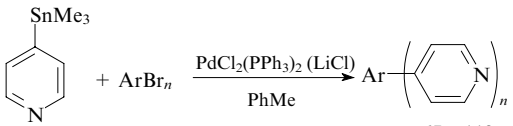
The Stille reaction of trimethyl(4-pyridyl)stannanes **110a**,**b** with 1,8-diiodonaphthalene afforded bipyridylnaphthalenes **111a**,**b**.[120]



110a,**b** **111a**,**b**

R = H (**a**, 61%), Me (**b**, 70%).

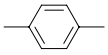
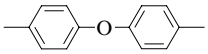
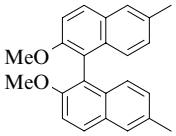
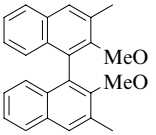
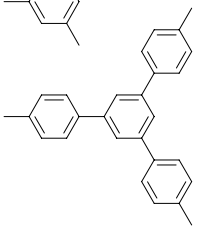
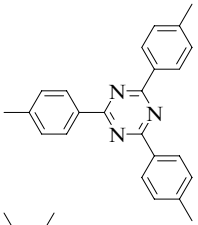
In certain cases, lithium chloride was added to increase the efficiency of the Stille reaction involving pyridylstannanes. For example, poly(4-pyridyl)-substituted compounds **112** were synthesised in good yields (up to 99%) from trimethyl(4-pyridyl)stannane (**110a**) and polybromoarenes on palladium catalysts in the presence of lithium chloride (Table 2).[121]



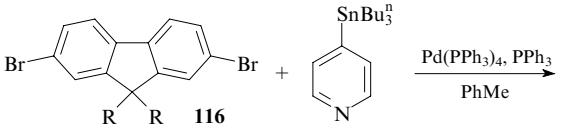
(2)

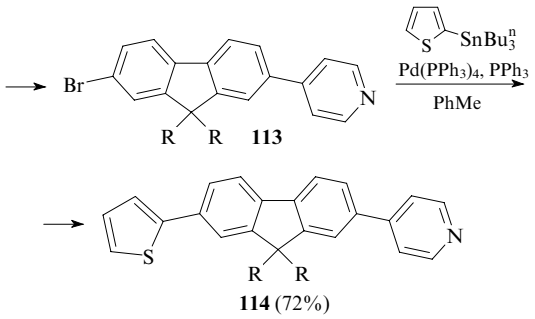
110a **65a**, **112**

Table 2. Mono- (**65a**) and poly(pyridyl)arenes (**112**) synthesised according to reaction (2).

n	Ar	Yield (%)	
		in the presence of LiCl	in the absence of LiCl
1		79	34
2		50	–
		99	18
		51	–
		96	–
		51	17
		98	33
3		90	7
		79	–
		66	–
4		58	–

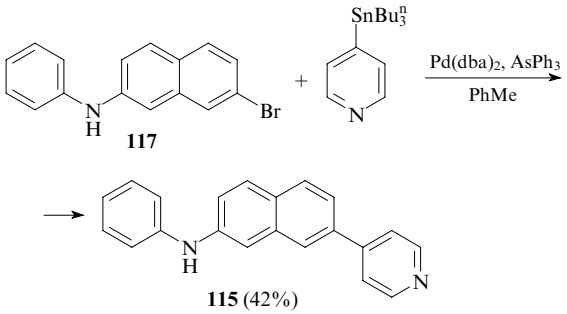
In the synthesis of laser dyes **113**–**115**, dibromo fluorenes **116** or bromonaphthylphenylamine **117** and tri-n-butyl-(4-pyridyl)stannane were used as the precursors. The reaction proceeded in the presence of a palladium complex and triphenylphosphine(arsine).[122]





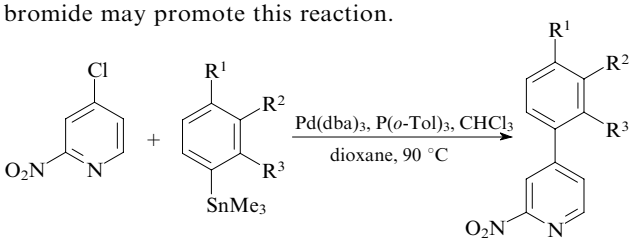
114 (72%)

R = n-$C_{10}H_{21}$.



115 (42%)

In certain cases, it proved more reasonable to introduce a trialkylstannyl group into the electron-excessive benzene ring and a halogen into the electron-deficient pyridine ring. Thus, quite a number of derivatives **118** were obtained [123] that are the intermediate products in the synthesis of streptonigrine.† It was shown that the addition of copper(I) bromide may promote this reaction.



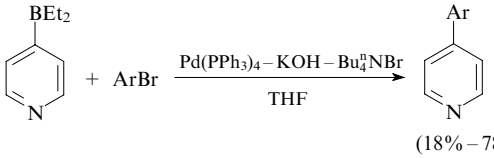
118 (45%–84%)

R^1, R^2 = H, MeO; R^3 = H, MeO, $MeOCH_2O$; *o*-Tol is *o*-tolyl.

d. The Suzuki reaction

The Suzuki reaction is based on the reaction of aryl halides with arylboron derivatives in the presence of a palladium catalyst and a base (sodium carbonate, potassium hydrogencarbonate, potassium phosphate, potassium hydroxide, *etc.*).[19, 126] Below, the examples of syntheses of 4-arylpyridines by the Suzuki reaction are shown.

The reaction of 4-pyridyldiethylborane with aryl bromides in the presence of a catalytic system $Pd(PPh_3)_4$–KOH–Bu^n_4NBr produced a large series of 4-(het)arylpyridines in the yields from 18% to 78%.[127]

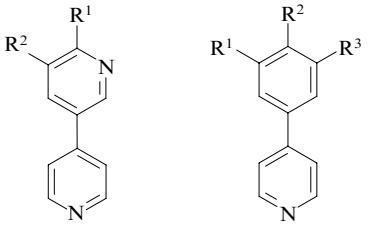


(18%–78%)

Ar = $X_nC_6H_{4-n}$ (X = H, 2-Me, 4-Me, 2-MeO, 4-MeO, 2-Cl, 4-Cl, 2-H_2N, 3-H_2N, 4-H_2N, 2-O_2N, 4-O_2N, 2-MeO_2C, 4-MeO_2C, 2-PhNHC(O), 2-$PhCH_2O$), 2- and 3-Py, 3(5,6)-Me-2-Py, 3-MeO-2-Py, 3-O_2N-2-Py, 2- and 3-quinolyl, 2- and 3-thienyl, 3-furyl.

† Streptonigrinoids are natural alkaloids that belong to the class of antitumour antibiotics.[124, 125]

A similar method was used for the synthesis of terpyridines **119** (yields 47%–66%)[127] and 4-arylpyridines **120** (yields 57%–74%).[128]

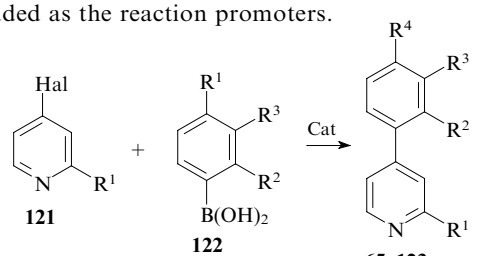


119 **120**

119: R^1 = H: R^2 = 3-Py, 4-Py; R^2 = H: R^1 = 3-Py, 4-Py;
120: R^2 = HO, R^3 = H: R^1 = $HOCH_2$, HC(O); R^1–R^2 = OCHMeO, R^3 = H; R^1 = HC(O), R^2 = HO, R^3 = Bu^t.

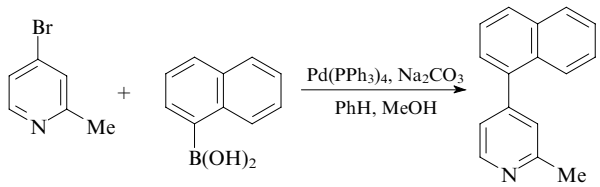
This method was used for the production of hemicyanine dyes that contain a 4-arylpyridine fragment. These dyes are effective potential-sensitive probes in biomembranes.[129]

The reaction of pyridyl halides **121** with arylboronic acids **122** in the presence of a palladium catalyst produced a large series of 4-arylpyridines **65** (R^1 = H) and **123** ($R^1 \neq$ H) in the yields approaching 100% (Table 3).[130–136] The reaction efficiency depended on the nature of the phosphine ligand in the palladium complex, which affected the catalyst stability, and also on the composition of the catalytic system and the nature of reactants. Aromatic hydrocarbons (benzene, toluene, xylene), DMF or dimethoxyethane were used as the solvents. In certain cases, CuI or CsF were added as the reaction promoters.



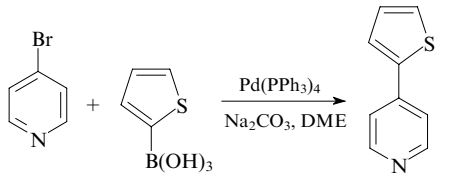
121 **122** **65**, **123**

Naphthylpyridine **124** was formed in the reaction of 4-bromo-2-methylpyridine with 1-naphthylboronic acid.[120]



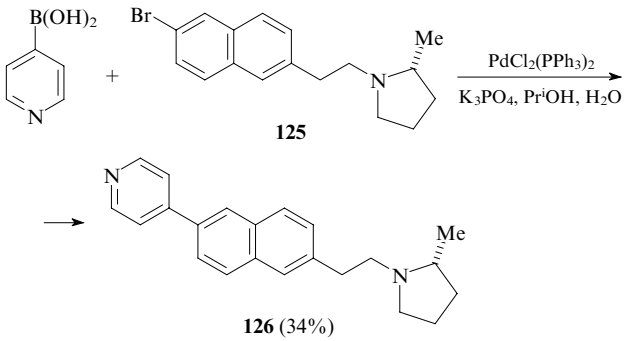
124 (90%)

The reaction of 4-bromopyridine with 2-thienylboronic acid in the presence of sodium carbonate and a palladium catalyst led to 4-(2-thienyl)pyridine (**103**).[136]



103 (90%)

Cross-coupling of 4-pyridylboronic acid with naphthalene derivative **125** produced compound **126**. It was found[137] that the latter exhibits affinity to histamine H3-receptors and is therefore considered as a promising drug for curing memory disorders and improving cognitive functions.



125

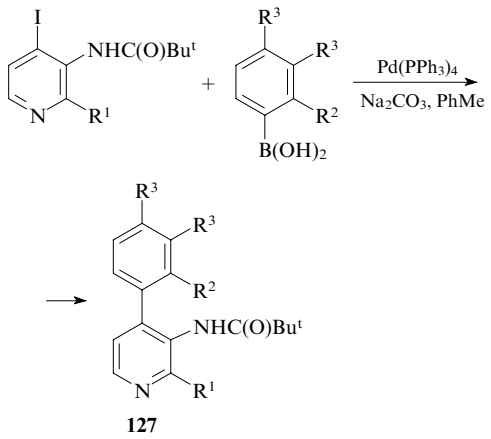
126 (34%)

Using the Suzuki reactions, a series of 4-aryl-3-pivaloylaminopyridines **127** that serve as the precursors of a natural alkaloid streptonigrine were synthesised in the yields of 68%–95%.[138, 139]

Table 3. Conditions of synthesis and yields of 4-arylpyridines **65** and **123**.

Hal	R^1	R^2	R^3	R^4	Catalyst	Yield (%)	Ref.
Br	H	H	H	H	$Pd(PPh_3)_4$, Na_2CO_3	95	131
					$Pd(PPh_3)_4$, K_2CO_3	63	132
					$Pd(Tedicyp)_4$, K_2CO_3	81	133
					$Pd(Tedicyp)_4$, K_2CO_3	100	134
					Pd/C, Na_2CO_3, TBAB	95	135
					Pd/C, Na_2CO_3, PPh_3	60	135
Br	H	H	H	Me	$Pd[PPh_2(m\text{-}C_6H_4SO_3Na)]_4$	98	130
Br	H	Me	H	H	$Pd(Tedicyp)_4$, K_2CO_3	59	133
Br	H	H	H	F	$Pd(Tedicyp)_4$, K_2CO_3	85	133
Cl	MeNHC(O)	H	H	H	$Pd(OAc)_2$, P(*o*-Tol)$_3$, CuI	63	134
Cl	H	MeO	H	H	$Pd(PPh_3)_4$, Na_2CO_3	75	134
Cl	H	H	MeO	MeO	$Pd(PPh_3)_4$, Na_2CO_3	65	134
Cl	H	H	H	F_3C	$Pd(PPh_3)_4$, Na_2CO_3	57	134
Cl	MeO_2C	H	H	H	$Pd(OAc)_2$, P(*o*-Tol)$_3$, CsF	50	134
Cl	Bu^tO_2C	H	H	H	$Pd(OAc)_2$, P(*o*-Tol)$_3$, K_2CO_3	81	134

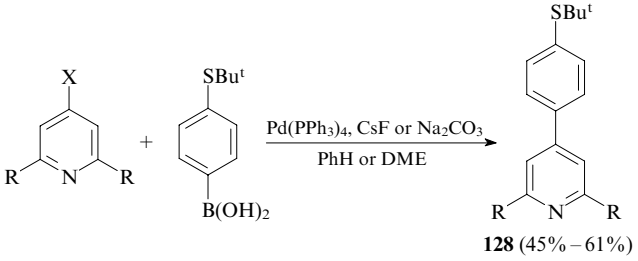
Note. The following designations were taken: TBAB is tetrabutylammonium bromide; Tedicyp is *cis*,*cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane.



127

R^1 = H, Cl, MeO, Bu^{t}C(O)NH; R^2 = H, MeO, $Pr^i_2NC(O)$, Et_2NCO_2; R^3 = H, MeO.

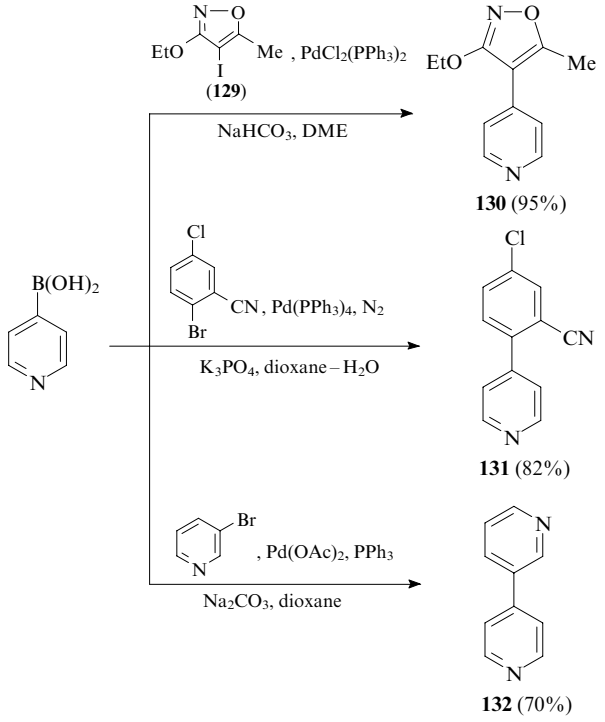
The Suzuki reaction was used [140] for the preparation of dendrimers based on 4-phenylpyridine thio derivatives (**128**). The latter were formed in good yields from 4-halopyridines and 4-(*tert*-butylthio)phenylboronic acid.



128 (45% – 61%)

X = I, Cl; R = MeO_2C, $HOCH_2$.

The reaction of 4-pyridylboronic with 4-iodoisoxazole **129**, 2-bromo-5-chlorobenzonitrile and 3-bromopyridine yielded isoxazol-4-ylpyridine **130**,[141] reactions of this acid with 4-arylpyridine **131**[142] and 3,4′-bipyridyl (**132**),[143] respectively.

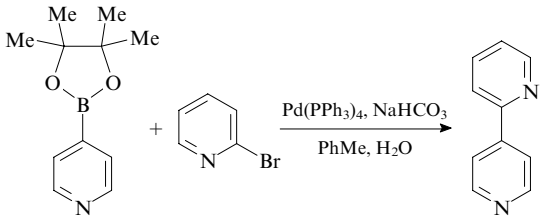


130 (95%)

131 (82%)

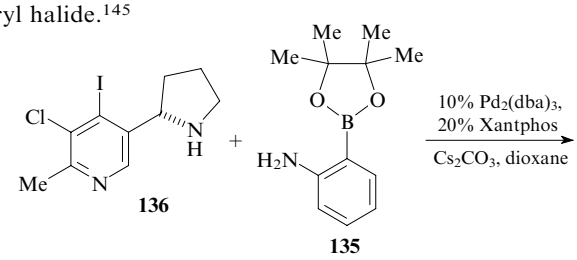
132 (70%)

2,4′-Bipyridyl (**109**) was synthesised from boronate **133** and 2-bromopyridine in the presence of a palladium complex with triphenylphosphine.[144]

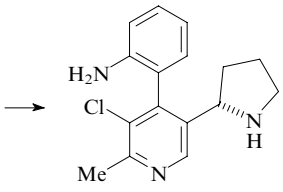


133 **109** (57%)

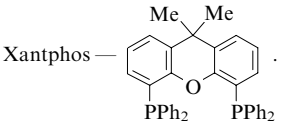
The synthesis of a precursor of a natural alkaloid (*S*)-brevicolin (**134**), involved the use of boronate **135**; (*S*)-nicotine halogen derivative **136** was used as the starting aryl halide.[145]



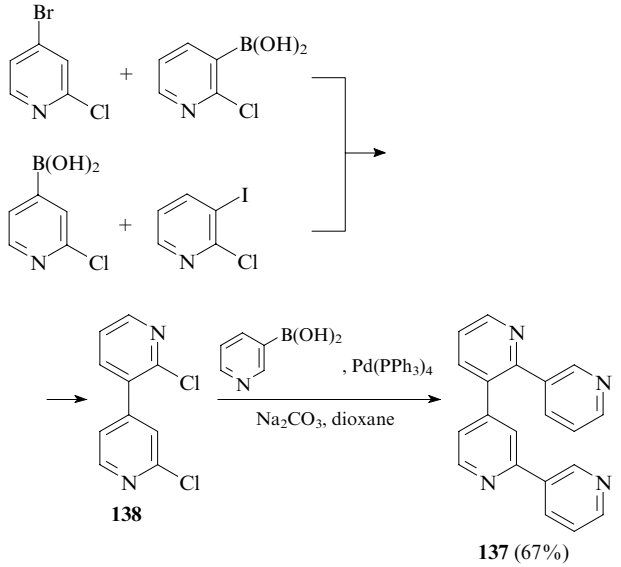
136 **135**



134 (77%)



The synthesis of nemertelline (**137**), a neurotoxic compound isolated from a marine worm also involved the use of the Suzuki reaction.[146] First, 2,2′-dichloro-3,4′-bipyridyl (**138**) was synthesised to be introduced later in the cross-coupling reaction with 3-pyridylboronic acid. Bipyridyl **138** was synthesised by two ways. In the first method, the



138

137 (67%)

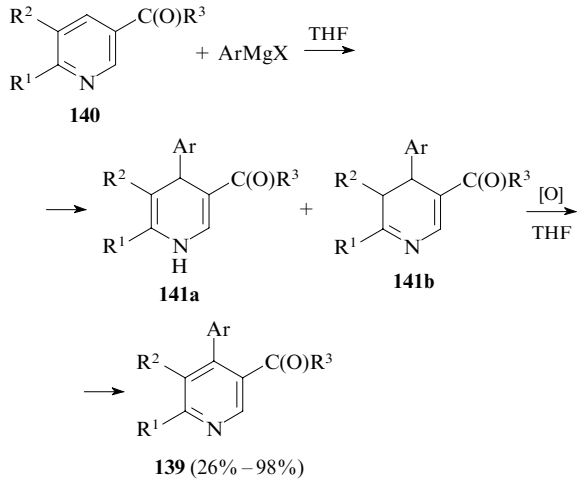
starting compounds were 4-bromo-2-chloropyridine and 2-chloro-3-pyridylboronic acid (the yield of bipyridyl **138** was 63%); in the second, 3-iodo-2-chloropyridine and 2-chloro-4-pyridylboronic acid were the starting compounds (the yield was 66%).

In all these reactions, a palladium complex with triphenylphosphine was used as the catalyst and the reaction was carried out in dioxane in the presence of sodium carbonate.

A specific feature of this type of reactions is their exclusive regioselectivity. For example, in bromochlorobenzene, only the bromine atom was substituted, while in bromoiodobenzene, it was only the iodine atom, *i.e.*, in the series Cl – Br – I, the iodine atom was replaced most easily.

e. Cross-coupling reactions of pyridine derivatives with organomagnesium and -lithium compounds

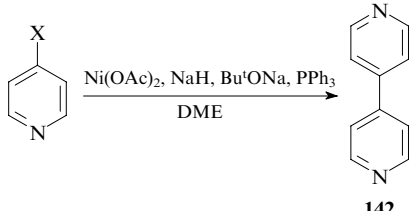
Aimed at the synthesis of new effective antagonists of the neurokinin-1 (NK_1) receptor, an attempt was undertaken to synthesise 4-aryl derivatives of nicotinamide **139** by the Suzuki reaction. However, it proved to be more effective (as regards both the cost and the yields) to use Grignard reagents as the arylating agents. The regioselective addition of organomagnesium compounds to substituted nicotinamides **140** yielded isomeric dihydropyridines **141a** and **141b**. These unstable derivatives were easily oxidised to pyridines **139** by such oxidants as $KMnO_4$, manganese(III) acetate, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), I_2, *o*-chloranil.[147]



Ar = 2-MeC_6H_4, 4-FC_6H_4, 4-F-2-MeC_6H_3; R^1 = Cl, Me, $O(CH_2CH_2)_2N$; R^2 = H, Cl; R^3 = HONH, Et_2N, BnNH, Bu^tNH; X = Cl, Br.

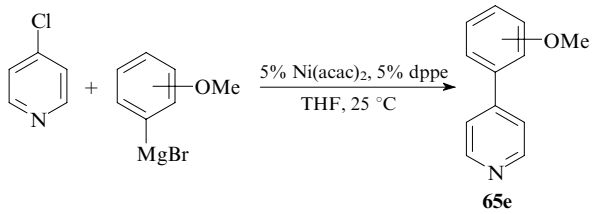
f. Coupling reactions catalysed by nickel complexes

The reaction of symmetrical coupling of 4-iodo(bromo)pyridines proceeded in the presence of a nickel catalyst prepared *in situ* from nickel acetate, sodium hydride, sodium *tert*-butoxide and triphenylphosphine. In both cases, the yields of 4,4′-bipyridyl (**142**) were sufficiently high.[148]



X = I (86%), Br (78%).

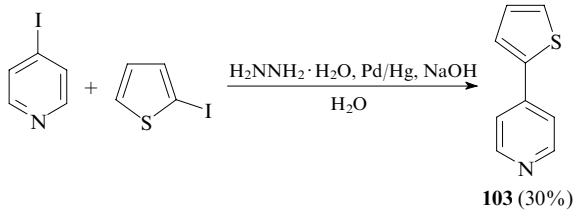
Isomeric 4-anisylpyridines **65e** were synthesised in good yields by the Kumada – Tamao – Corriu reactions, *i.e.*, the reaction of 4-chloropyridine with anisylmagnesium bromide in the presence of a nickel catalyst.[149]



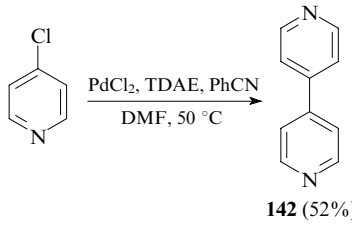
Isomers: 2-OMe (65%), 3-OMe (55%), 4-OMe (45%); dppe is bis(diphenylphosphino)ethane.

g. Miscellaneous coupling reactions catalysed by palladium and its complexes

The reaction of 4-iodopyridine with 2-iodothiophene under the action of hydrazine hydrate in an alkaline media was promoted by palladium amalgam to yield 4-(2-thienyl)pyridine (**103**).[150]

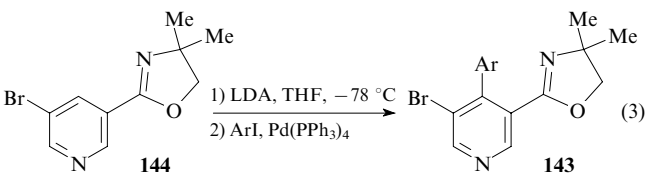


In the presence of palladium(II) chloride in combination with tetrakis(dimethylamino)ethylene (TDAE), 4-chloropyridine was converted into 4,4′-bipyridyl (**142**) under rather mild conditions (50 °C).[151]



If in this reaction, 4-bromopyridine hydrochloride was substituted for 4-chloropyridine, the product yield increased to 92%.[152]

Niacin (vitamin PP) derivatives **143** attracted interest as the potential antagonists of the neurokinin-1 receptor. These compounds were synthesised by direct metallation of 3-bromonicotinic acid **144** at position 4 of pyridine ring. The reaction was carried out in tetrahydrofuran at low temperature using lithium diisopropylamine (LDA) as the metallating agent.[153] The 4-pyridyllithium derivative formed was treated with aryl iodide in the presence of a palladium catalyst.

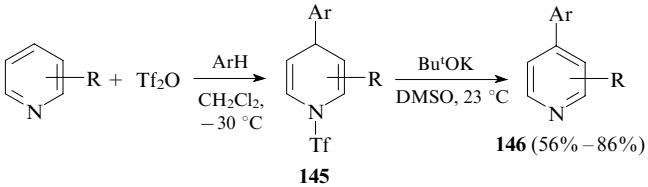


Ar = Ph (90%), 4-$MeOC_6H_4$ (65%), 4-NCC_6H_4 (70%).

Metallation of pyridine derivatives that contain a directing dimethyloxazoline group is usually carried out with lithium 2,2,6,6-tetramethylpiperidide (LTMP). However, it was noted [153] that the use of this sterically hindered agent in reaction (3) led to lithiation at position 2 of pyridine; hence, LDA was used.

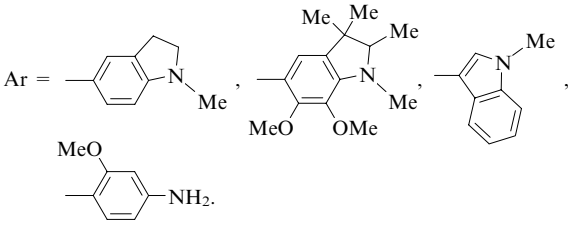
h. Miscellaneous arylation reactions

An approach to the synthesis of 4-arylpyridines by direct regioselective addition of (het)arenes with π-donating substituents to pyridine was described.[154] To direct the attack of a nucleophilic (het)arene at position 4, the pyridine ring was activated by the addition of a triflate group (Tf = CF_3SO_2), which exhibits a strong electron-withdrawing effect, to the nitrogen atom. The addition of a nucleophilic (het)arene to the thus activated pyridines led to 4-(het)aryl-1,4-dihydropyridines **145** in high yields. The corresponding 4-arylpyridines **146** were synthesised by treating dihydropyridines **145** with potassium *tert*-butoxide in DMSO at room temperature.

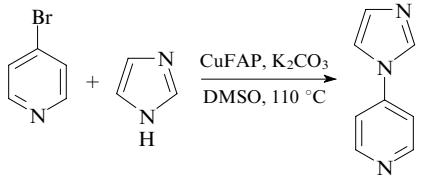


145 **146** (56% – 86%)

R = H, 2-Me, 3-Me, 2-OMe, 2-CN, 2-Br, 3-CO_2Me;



The arylation of imidazole with 4-bromopyridine was catalysed with copper(II) fluoroapatite (CuFAP). The process proceeded under the action of a base on heating; this method was used for the synthesis of 4-imidazolylpyridine **147**.[155]



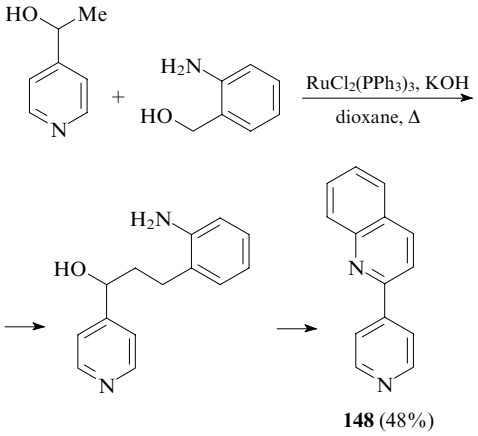
147 (92%)

IV. Formation of 4-hetaryl substituents in the pyridine ring

1. Condensation and cyclisation reactions

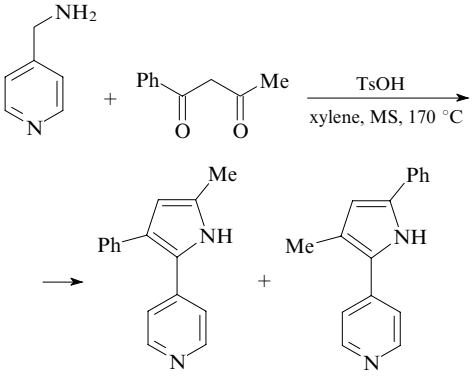
Reactions of condensation, cyclisation and oxidation as a result of which an aromatic substituent is formed in position 4 of a pyridine ring are not very popular and were largely used in the synthesis of 4-hetarylpyridines.

For example, 4-(2-quinolyl)pyridine (**148**) was formed in the ruthenium complex-catalysed coupling and cyclisation of 1-(4-pyridyl)ethanol with 2-aminobenzyl alcohol on heating in dioxane.[156]



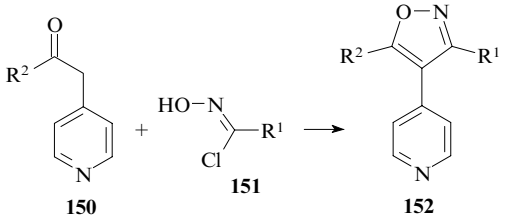
148 (48%)

The pyrrolle ring in pyridine derivatives **149a**,**b** was formed as a result of condensation of 4-aminomethylpyridine with benzoylacetone. The reaction proceeded on heating of the starting compounds in xylene in the presence of *p*-toluenesulfonic acid and molecular sieves (MS). The authors did not report the yields of reaction products but mentioned its regioselective nature, namely, the ratio of 4-pyrrolylpyridine derivatives **149a** and **149b** was 94 : 6.[157]



149a **149b**

The condensation of ketones **150** and hydroximoyl chlorides **151** under the action of a base produced isoxazolylpyridines **152**. This reaction was carried out under different conditions, the yields of reaction products were moderate.[158]



150 **151** **152**

R^1	R^2	Conditions	Yield (%)
4-FC_6H_4	Pr^i	Et_3N, EtOH	45
Pr^i	4-FC_6H_4	LDA, THF, −78 °C	40
Ph	4-FC_6H_4	1) AcONa – $H_2NOH \cdot HCl$, EtOH, 78 °C 2) Et_3N, CH_2Cl_2, 0 °C	17

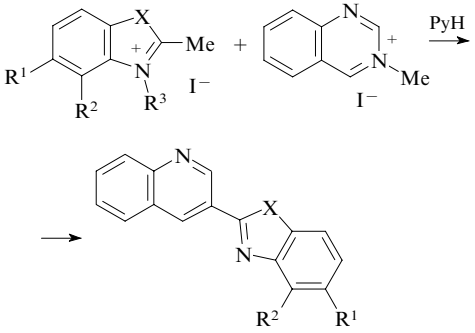
Studies of the recent years have shown that protein kinases play an important role in the transmission of stress signals. In connection with this, is seems interesting to search for substances that would regulate the activity of

these enzymes. It was shown that isoxazolylpyridines **152** exhibit inhibiting activity with respect to stress-kinase p38α.

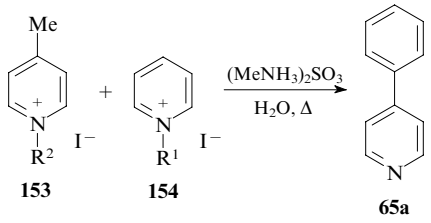
2. Pyridine ring transformation

Recently, a new concept of the synthesis of aryl and hetaryl derivatives of heterocyclic compounds has been put forward based on the intermolecular transformation of the ring, which involves the use of a heterocyclic salt containing a methyl group in position 2 or 4.

It was shown earlier [159, 160] that the reaction of quaternary salts of certain 2(4)-methyl-substituted heterocyclic bases with 3-methylquinazolinium iodide in pyridine leads to the transformation of the quinazoline ring to form 3-hetarylquinolines in yields reaching 63%.



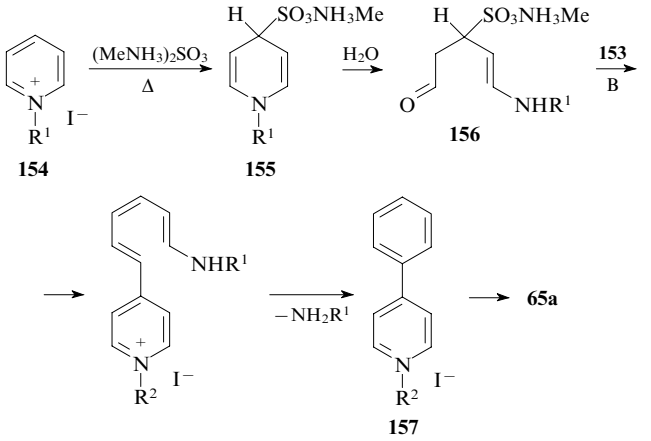
It was shown that this approach can also be used in the synthesis of 4-arylpyridines. Thus 4-methylpyridinium salts **153** reacted with pyridinium salts **154** under the action of an aqueous solution of methylammonium sulfite on heating. The transformation of the pyridine ring of salt **154** afforded 4-phenylpyridine (**65a**) in yields approaching 57%.[161–163]



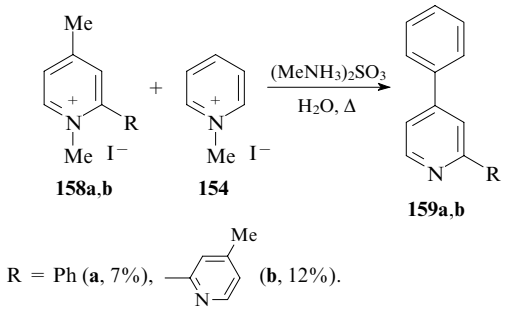
R^1	R^2	Yield of **65a** (%)
Me	Me	42
	Et	49
	Pr^i	57
Et	Me	35
Pr^i	Me	29

Presumably, the reaction proceeded by the following mechanism (Scheme 8). Being a 'softer' nucleophile, sulfite ion preferentially added into position 4 of pyridinium salt **154**, *i.e.*, the primary reaction products were 1,4-dihydropyridines **155**. The violation of the pyridine ring aromaticity made easier its hydrolytic opening. The thus formed derivative of glutaconic dialdehyde **156** underwent condensation with the active methyl group of 4-methylpyridinium salt **153** under the action of a base. The subsequent closure led to the formation of a benzene ring and the generation of the corresponding quaternary salt of 4-phenylpyridinium **157**. In the last step, as a result of *N*-deactivation of compound **157**, 4-phenylpyridine (**65a**) was obtained.

Scheme 8



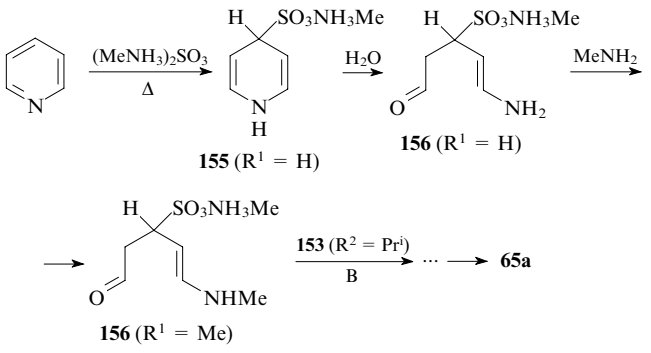
Starting from 1,4-dimethyl-2-phenylpyridinium iodide (**158a**) or 1,4,4′-trimethyl-2,2′-bipyridylium iodide (**158b**) and 1-methylpyridinium iodide **154** (R^1 = Me), 2,4-diphenylpyridine (**159a**) or 4-phenylbipyridyl (**159b**) were obtained by this method in small yields.[164]



The low yields of reaction products were apparently associated with the presence of a bulky substituent in position 2 of salts **158a**,**b**, which favoured the competitive reaction of *N*-demethylation of the starting compounds.

This method allows one to transform rings of not only 1-alkylpyridinium salts **154**, but also of pyridine itself (Scheme 9). Thus the long-term heating of pyridine and 4-methylpyridinium salt **153** ($R^2 = Pr^i$) with an aqueous solution of methylammonium sulfite made it possible to obtain 4-phenylpyridine (**65a**) in yields approaching 20%.[162]

Scheme 9

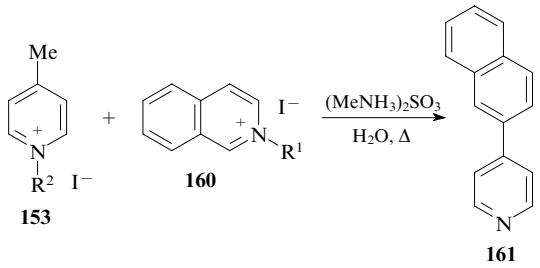


Bearing in mind that a considerable part of pyridine remained unchanged in this reaction, the yield of 4-phenyl-

pyridine (**65a**) recalculated to the consumed pyridine should be substantially higher.

The driving force of this pyridine ring transformation was the substitution of the methylamine group (R^1 = Me) for the amine residue (R^1 = H) in intermediate acyclic structure **156** as a result of its treatment with methylamine (see Scheme 9). Apparently, under the action of the base, intermediate **156** (R^1 = Me) underwent condensation with 4-methylpyridinium salt **153** (R^2 = Pr^i), followed by the formation of 4-phenylpyridine (**65a**).

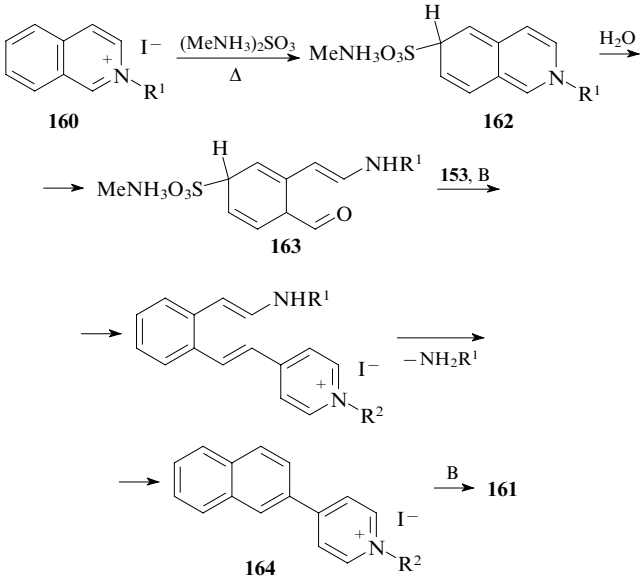
The reaction of 4-methylpyridinium salts **153** with isoquinolinium salts **160** included the regiospecific addition of a 2-naphthyl residue into position 4 of the pyridine ring. The intermolecular transformation of the isoquinoline ring, which involved the methyl group of salt **153**, produced 4-naphthylpyridine (**161**) in the yield reaching 62%. This reaction occurred under the action of methylammonium sulfite on heating.[165, 166]



R^1	R^2	Yield **161** (%)
Me	Me	62
	Et	57
	Pr^i	52
Et	Me	54
Pr^i	Me	52
	Pr^i	45

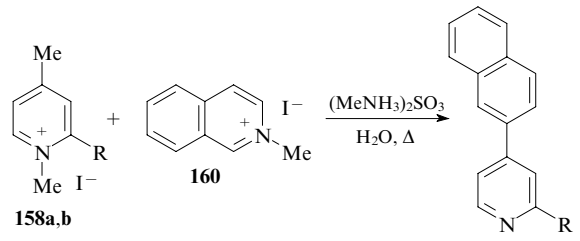
Apparently, the sulfite ion added to isoquinolinium salt **160** in position 6, which led to the transient 2,6-dihydroisoquinoline **162** (Scheme 10). The violation of aromaticity of the isoquinoline ring made its opening easier. Under the action of a base, acyclic intermediate **163** formed underwent

Scheme 10



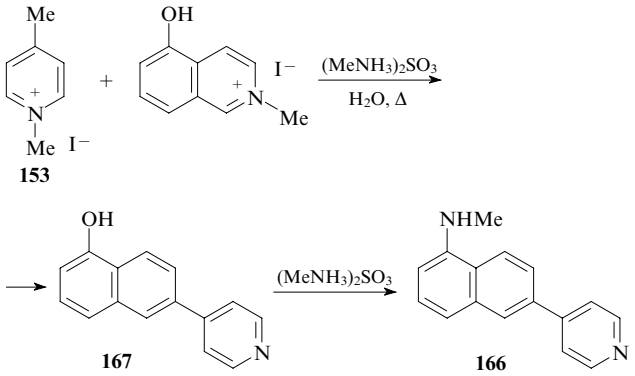
condensation with the active methyl group of 4-methylpyridinium salt **153**. The subsequent electrocyclic closure led to the formation of a naphthalene residue and the corresponding quaternary salt of 4-naphthylpyridinium **164**. In the final stage, as a result of *N*-dealkylation, 4-naphthylpyridine formed (**161**).

Heating of a mixture of 1,4-dimethyl-2-phenylpyridinium iodide (**158a**) or 1,4,4′-trimethyl-2,2′-bipyridylium iodide (**158b**) with 2-methylisoquinolinium **160** iodide (R^1 = Me) and methylammonium sulfite produced 4-naphthylpyridine (**165a**) or 4-naphthylbipyridyl (**165b**).[164]



R = Ph (**a**, 39%),  (**b**, 41%).

The introduction of a donor group into the benzene ring of isoquinoline hindered or even totally prevented the addition of the sulfite ion, so that the target product is formed in a considerably smaller yield or is not formed at all. Thus the yield of naphthylpyridinium **166** formed in the reaction of 1,4-dimethylpyridinium iodide **153** (R = Me) with 5-hydroxy-2-methylisoquinolinium iodide was only 22%.[166]



Apparently, the reaction included the following two stages: in the first stage, hydroxynaphthalinopyridine **167** was formed; in the second stage, the methylamino group substituted the hydroxyl group according to the Bucherer reaction, which is known to proceed especially easily in the naphthalene series.

The found method enabled transformation of not only the 1-alkylisoquinolinium ring of salt **160**, but also the ring in free isoquinoline.[166] For example, long-term heating of isoquinoline and 4-methylpyridinium salt **153** (R^2 = Me) with an aqueous solution of methylammonium sulfite made it possible to synthesise 4-(2-naphthyl)pyridine (**161**) in yields reaching 48%. The driving force of this reaction could be the replacement of the NH_2 group by NHMe in the transient acyclic structure of the type **163**, by analogy with Scheme 9.

Heating of isoquinoline and salts **158a**,**b** with an aqueous methylammonium sulfite solution afforded 4-naphthylpyridine (**165a**) in 3% yield and 4-naphthylbipyridyl (**165b**) in 22% yield.[164]

It was found that the nature of the counter-ion in quaternary salts of heterocyclic bases does not affect the efficiency of pyridine ring transformations.

Thus, by the example of the simplest derivatives of pyridine, isoquinoline and quinazoline, the prospects of using a new reaction of regioselective arylation and hetarylation based on the heterocycle transformation in the chemistry of heterocyclic compounds were demonstrated. This reaction serves as a simple and convenient method of synthesising 4-aryl- and 4-naphthylpyridines and makes it possible to obtain target products with high degrees of purity and in good yield from available substances. Pyridines that contain a naphthalene residue can be transformed into different compounds that are of interest as organic luminophores, ligands for the synthesis of fluorescent metal complexes and biologically active substances.

V. Conclusion

In the present review, the literature data are arranged in groups according to synthetic methods and reaction types. Summarising, it is reasonable to briefly systematise the presented material from the viewpoint of the popularity of methods used. Analysing the bibliography of this review, it can be concluded that at present, despite the wide diversity of approaches, the main methods of synthesis of 4-aryl- and 4-hetarylpyridines are the coupling and cross-coupling reactions. This approach is the most versatile despite being highly expensive and operating with highly toxic reactants and catalysts. The rest methods either do not allow one to synthesise monosubstituted 4-arylpyridines or have limitations. All the methods described can be used in the synthesis of pyridine 4-aryl and 4-hetaryl derivatives. The number of studies devoted to the synthesis of 4-arylpyridines is more than 2.5 times larger as compared with that for 4-hetarylpyridines. The highest interest was drawn to studies that describe the procedure of synthesis of 4-arylpyridines that is based on the ring transformation in the pyridinium and isoquinolinium salts and allows one to synthesise monosubstituted pyridines in high yields from accessible substances. In certain cases, this method can be a promising alternative to the conventional approaches to the synthesis of 4-(het)arylpyridines.

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