C-SUBSTITUTION OF NITROGEN HETEROCYCLES

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Abstract - An attempt has been made to summarize, evaluate and compare the available methods for the introduction of C-substituents into aromatic nitrogen heterocycles. However due to the large number of publications on this topic this review is necessarily limited to the most important publications.

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*) Dedicated to Professor T. Kametani on the occasion of his 70th birthday

+) Deceased on October 22, 1985

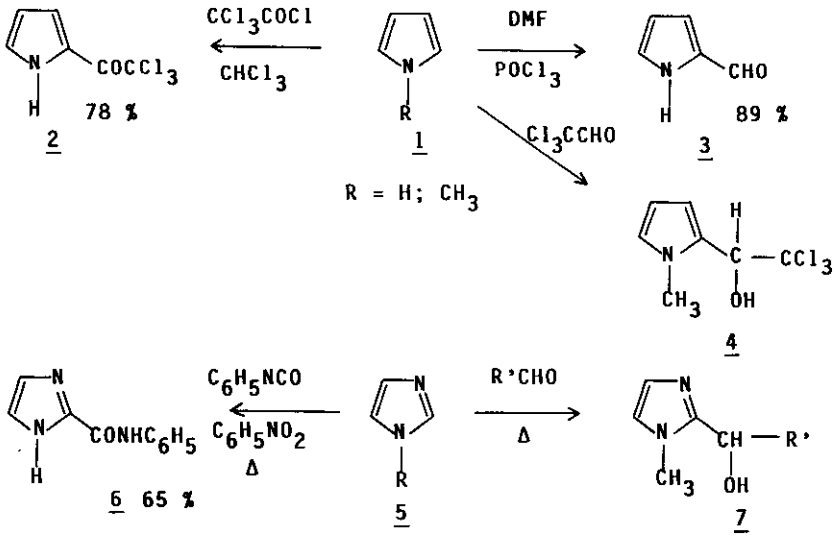
1.0. PREFACE

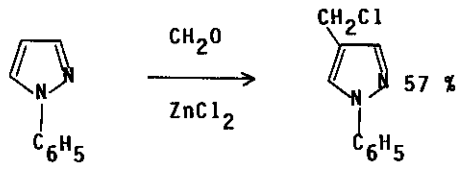
Many natural products, drugs, herbicides and pesticides are C-substituted N-heterocycles, which can be prepared by various methods. Since these methods have not as yet been reviewed, we attempt to survey in this article the different reactions which permit a C-substitution of nitrogen heterocycles. Due to the vast amount of literature on this topic, no attempt has been made to give a complete review. Instead, typical reactions of the different types of C-substitutions in the most common nitrogen heterocyclic systems, preferably from the most recent literature, have been selected. We hope that this permits a comparison of the available methods by providing access to the literature and complementing the standard textbooks and review literature e.g. A. Weissberger, The Chemistry of Heterocyclic Compounds, Elderfield, as well as Advances in Heterocyclic Chemistry.

2.0. DIRECT INTRODUCTION OF C-SUBSTITUENTS

2.1. Electrophilic Substitutions

An electrophilic substitution of nitrogen heterocycles under mild conditions is only possible with weakly basic systems like pyrroles (1) which can either be trichloroacetylated to 2 [1], formylated to 3 [2] or add chloral to 4 [3]. Imidazoles (5) react on heating with phenylisocyanate to 6 [4] and with aldehydes to 7 [5]. Furthermore N-phenylpyrazole (8) is readily chloromethylated to 9 [6]. Isoxazoles [7] and isothiazoles [8] react analogously.

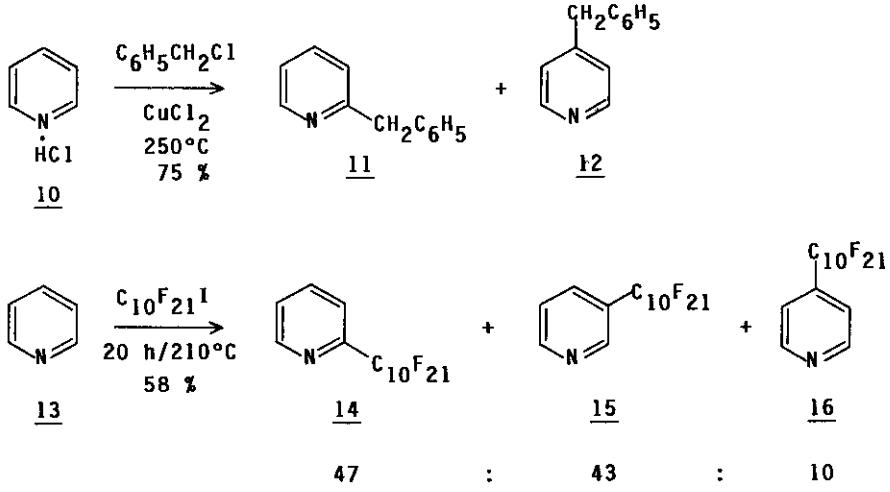




8 9

Most of the other electrophilic substitutions demand rather drastic conditions.

The Ladenburg reaction of pyridine hydrochloride (10) affords a mixture of 2- and 4-benzylpyridines (11 and 12) in 75 % yield [9,10]. However, the mechanism of this reaction has not as yet been determined. Pyridine (13) is alkylated by perfluoroalkyl iodides to afford the monoalkylated products (14, 15 and 16) in the ratios given [11].



10 11 12

13 14 15 16

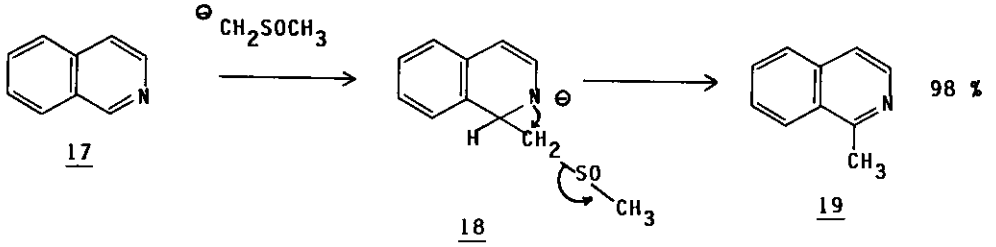
47 : 43 : 10

2.2. Ionic Nucleophilic Additions

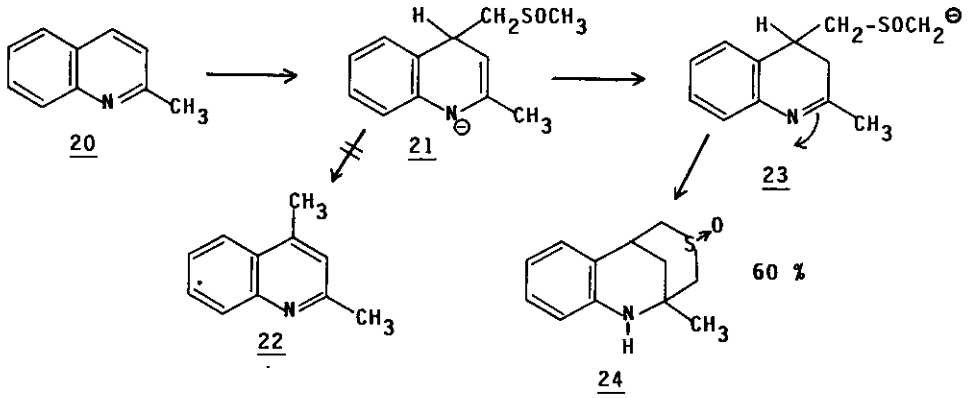
2.2.1. Addition of Dimsylsodium

Methylsulfinyl carbanion sodium salt (dimsylsodium) adds to more reactive heterocycles like quinoline [12], isoquinoline (17) [12] acridine [12], phenanthridine [12], 4,6-phenanthroline [13], 1,5- and 1,6-naphthyridine [14] or benzoquinoline [15] via intermediates like 18 which eliminate methanesulfinic acid to afford the corresponding methylated heterocycles like 1-methylisoquinoline (19) in high

yields.

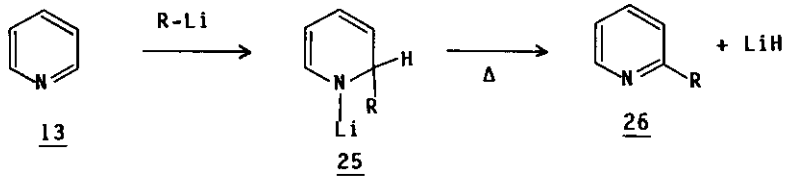


Quinaldine (20) apparently affords the anticipated intermediate addition product 21 which, however, does not eliminate methanesulfinic acid to 2,4-dimethylquinoline (22) but instead cyclises via 23 in 60 % yield to 24 [16].

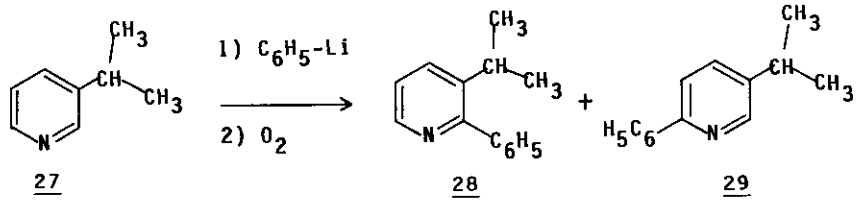


2.2.2. Addition of Alkyl- or Aryllithium and Grignard Reagents

N-Heterocycles like pyridine (13), quinolines, and acridines [17,18,19] react with alkyllithiums to adducts such as 25 which eliminate lithium hydride on heating to form C-substituted heterocycles such as 26 in high yields.

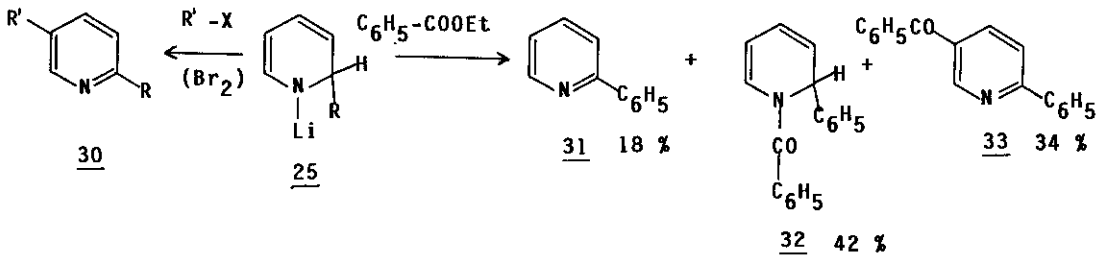


Under more vigorous conditions, further alkyllithiums can be added to pyridines to furnish 2,6-dialkylpyridines, for example 2,6-di-tert-butylpyridines, in high yields [20,21]. Under even more drastic conditions, pyridine reacts with excess tert-butyllithium to give 2,4,6-tri-tert-butylpyridine in 55 % yield [22]. Reaction intermediates like 25, which were investigated by NMR [23-24], can be trapped by methanol at -78°C to afford 1,2- and 2,5-dihydropyridines [25]. 3-Isopropylpyridine (27) reacts with phenyllithium to give, after subsequent oxidation, a 7 : 3 mixture of the 1,2- (28) and the 1,6-addition product (29) [26].



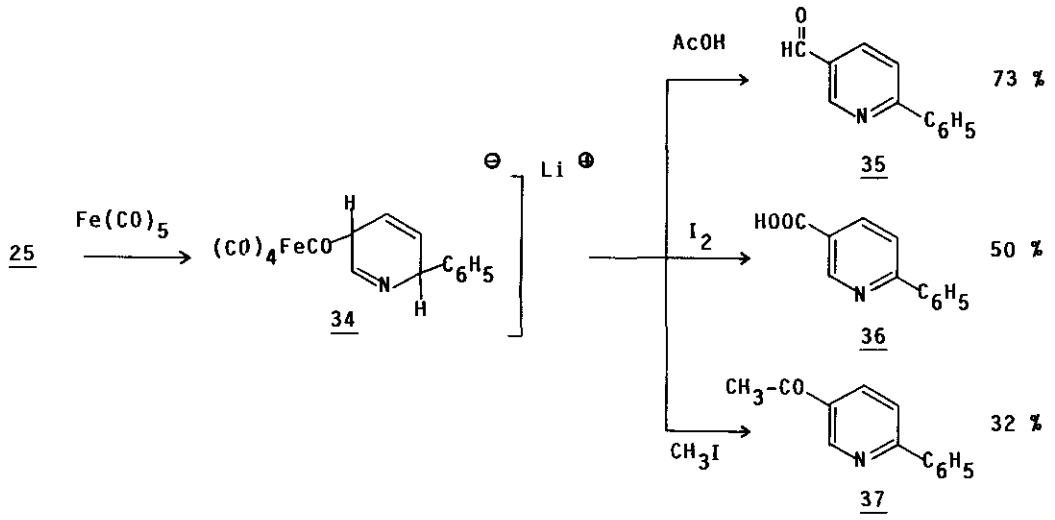
27 28 29

Of special importance are the reactions of intermediate adducts (25) with electrophiles. Thus, 25 (R = CH_3, n-butyl or C_6H_5) reacts as an N-metallated enamine with soft electrophiles such as alkyl halides to afford, after dehydrogenation, the corresponding 2,5-dialkylated pyridines (30) in moderate yields [27]. Addition of lithiumaluminium hydride to pyridines gives intermediates (25) (R = H) which furnish readily 3-alkylated or brominated pyridines (30) (R = H; R' = alkyl or Br) [28]. However, reaction of 25 (R = C_6H_5) with harder electrophiles such as ethyl benzoate gives also N-substituted products, e.g. a mixture of 31 (18 %), 32 (42 %) and 33 (34 %) [29].

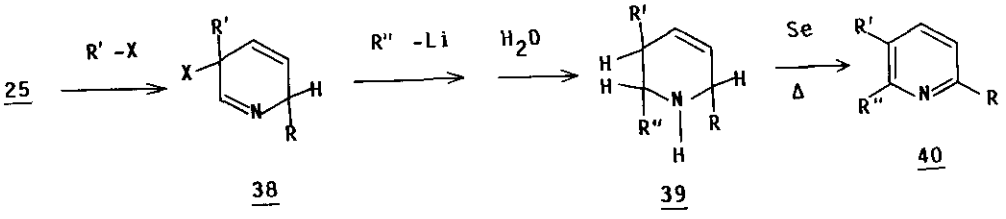


30 25 31 18 % 32 42 % 33 34 %

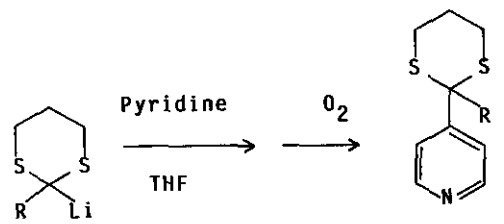
Formylation of intermediate 25 (R = C_6H_5) with ironpentacarbonyl furnishes 34 which is cleaved by acetic acid to 2-phenyl-5-formylpyridine (35). Oxidation of 34 with iodine gives 2-phenyl-5-pyridinecarboxylic acid (36), whereas alkylation with methyl iodide yields 2-phenyl-5-acetylpyridine (37) [30].



Intermediates 25 (R = n-butyl) react furthermore with aliphatic or aromatic isocyanates to give complex mixtures [31], whereas 25 (R = t-butyl) is dimerized by bromine to give 6,6'-di-tert-butyl-3,3'-bipyridyl [32,33]. When intermediates 25 are alkylated to 38 and again treated with lithium reagents to 39, the resulting trisubstituted tetrahydropyridines can be dehydrogenated with selenium to the trisubstituted pyridines (40) [34]. The dehydrogenation of dihydropyridines is also discussed by Giam [35].

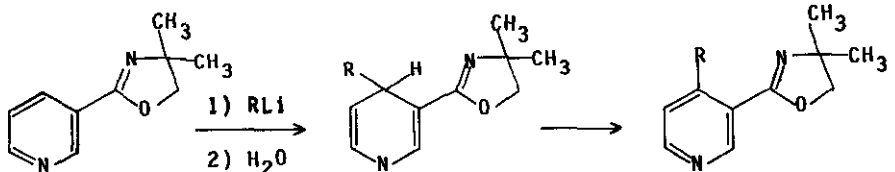


Reactions of pyridine with 2-lithio-1,3-dithianes (41) in THF gives, after oxidation with air or p-quinone, the corresponding 4-substituted pyridines (42) in up to 69 % yield [36].



41 42

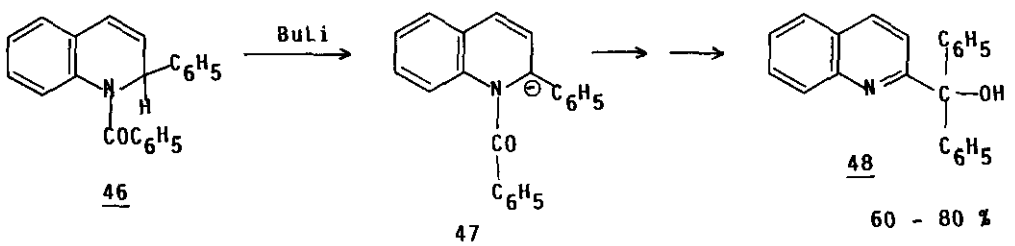
R = H; CH_3; $CH_2C_6H_5$



43 44 45

3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)pyridine (43) adds alkyllithiums to 44 which is readily oxidized to 45 [37-40].

Additions of alkyl- and arylmagnesium halides as well as lithium reagents to pyrimidines [41-43], pyridazines [42,44], and pyrazines [42] have been described recently. Addition of phenyllithium to quinoline followed by N-acylation with benzoyl chloride gives more than 75 % of 46 which is transformed by butyllithium in boiling ether via a Reissert-type anion and rearrangements in 60 - 80 % yield to 48 [45].

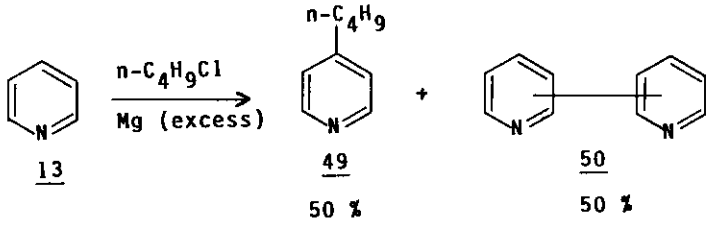


46 47 48

60 - 80 %

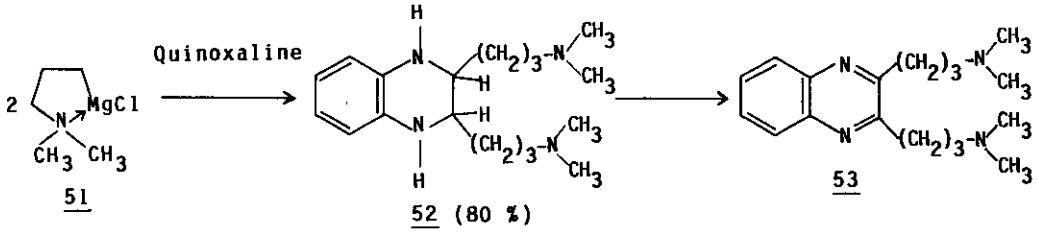
Addition of Grignard reagents instead of alkyl lithiums to pyridine and other N-heterocycles is usually more complex. Thus, benzylmagnesium chloride reacts with pyridine to give in 10 % yield a 8 : 2 mixture of 4-benzylpyridine and 2-benzylpyridine [46]. However, allylmagnesium halides add "normally" to quinoline, isoquinoline, quinoxaline, and acridine in good yields [47].

Reaction of Grignard reagents generated in situ from butyl chloride in the presence of excess magnesium metal with pyridine (13) furnishes 50 % of 4-butylpyridine (49) as well as 50 % of a mixture of bipyridyls (50) (mainly of 4,4-bipyridyl [48]), the formation of which indicates intermediate radical reactions caused by electron transfer from the magnesium metal.

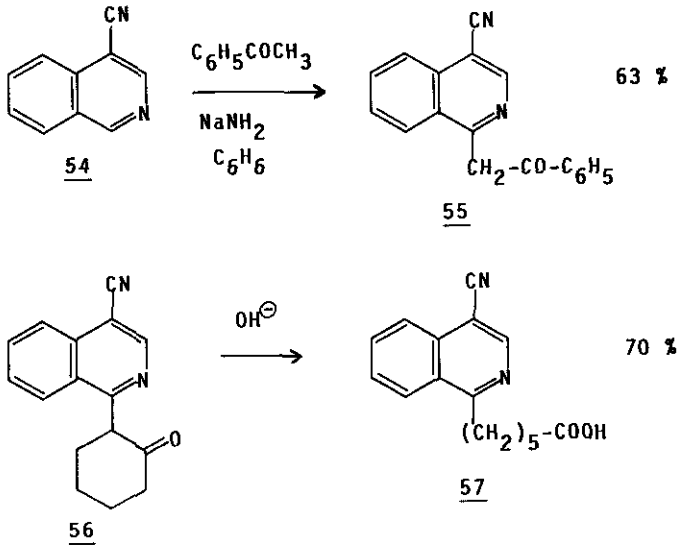


3-Dimethylaminopropylmagnesium chloride (51), which is intramolecularly stabilized by complexation with the dimethylamino group, adds readily to quinoxalines to form the mono- or bis-adduct (52) which can be oxidized to the mono- or bis-substituted quinoxalines (53) [49]. Analogous reactions have been described with phthalazines, phthalazones [50,51], quinazolines [52], and quinoxalines [53].

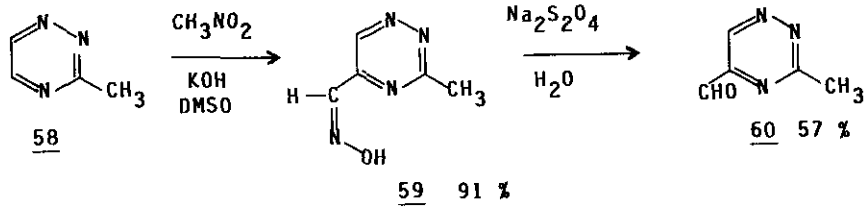
Recently, Grignard reagents have been added to purines [54], triazolo[4,5-d]-pyrimidines [55], and 1,8-naphthyridines [56] as well as to acridine [57].



Due to its electron-attracting nitrile group, 4-cyanoisoquinoline (54) reacts readily with sodium enolates of ketones like acetophenone with concomitant oxidation to afford the corresponding 1-substituted isoquinolines such as 55 which can undergo further reactions. Thus, the cyclohexanone product (56) is hydrolyzed by alkali in 71 % yield to the acid (57) [58].



Finally, vicarious nucleophilic substitutions proceed also with heterocycles. Thus, 3-methyl-1,2,4-triazine (58) reacts readily with nitromethane and base to form the oxime (59) in 91 % yield which is readily converted in 57 % yield into the aldehyde (60) [59].



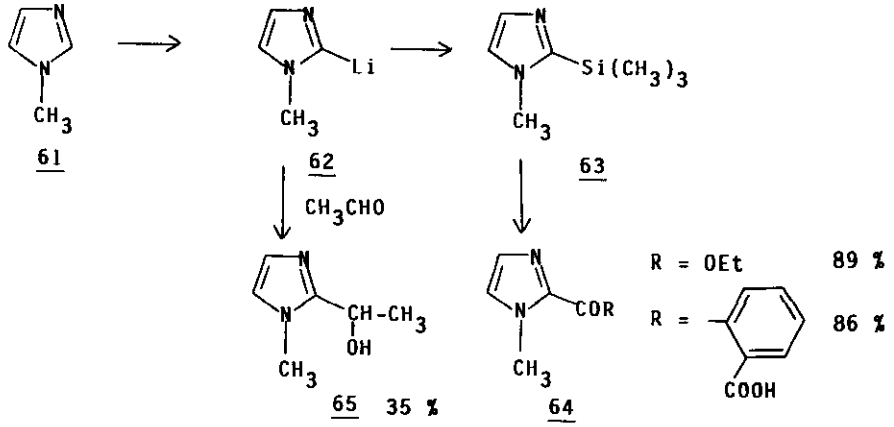
2.2.3. Hydrogen-Metal Exchange and Subsequent Reactions

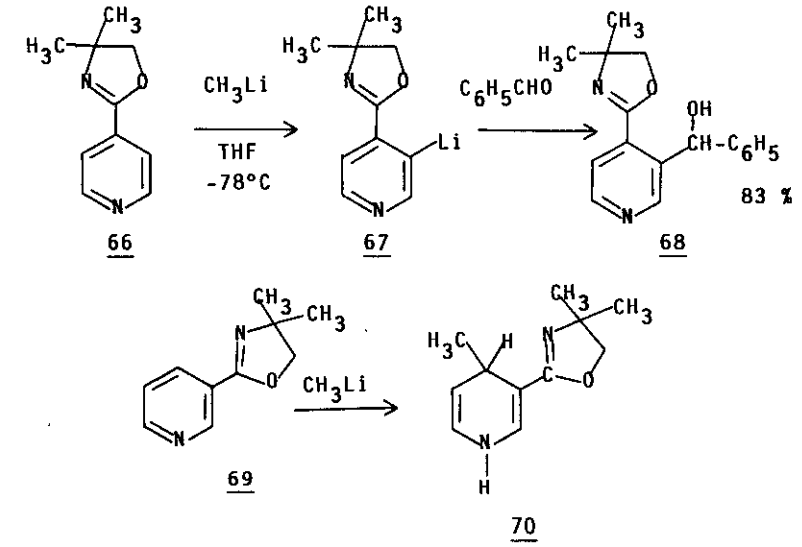
The more acidic hydrogen atoms between two hetero atoms in 5-membered heterocycles are exchanged most readily by metal atoms. Thus, N-methylimidazole (61) is rapidly metallated by n-butyllithium to 62, which can easily be trimethylsilylated to 63 and then reacted with electrophiles like ethyl chloroformate or phthalic anhydride to 64 [60]. Reaction of 62 with acetaldehyde affords 65 in 35 % yield [61]. N-Benzenesulfonylimidazole behaves analogously [62]. For further reactions of imidazole derivatives, compare a recent review article [63]. Thiazole

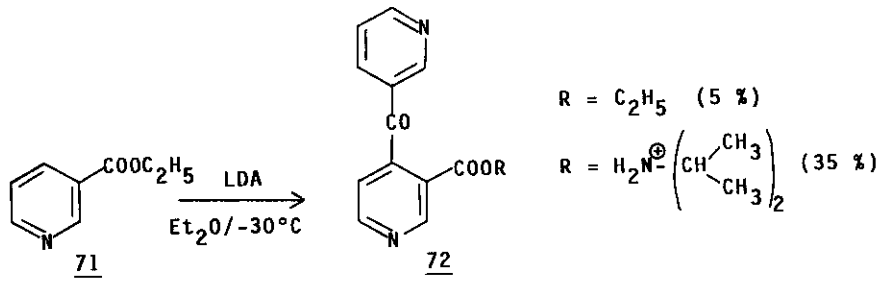
derivatives are also lithiated in the 2-position to react with various electrophiles [64,65]. When the 2-position in thiazoles or oxazoles is blocked by a methyl group, metallation and subsequent reaction with electrophiles occurs in the 5-position [66]. Isothiazoles give analogously 5-substituted derivatives [67,68]. Finally, it should be mentioned that N-methylpyrrole can also be metallated by butyllithium into a mono- and dianion, which react with CO_2 [69]. Recently, Meyers succeeded in metallating the 2-(4-pyridyl)-4,4-dimethyloxazoline (66) with methyllithium to 67 which was treated with a variety of electrophiles e.g. with benzaldehyde to 68 [70]. However, the oxazoline of nicotinic acid (69) reacts with methyllithium to give the 1,4-dihydropyridine (70) (cf. 2.2.2.). Ethyl nicotinate (71) can be metallated by lithium diisopropylamide (LDA) to give the 4-lithium salt, which reacts *in situ* with ethyl nicotinate to afford 4-nicotinoylnicotinic acid (72) and derivatives [71]. 3-Cyanopyridine can be metallated and alkylated in the 4-position if 12-crown-6 is added [72]. On addition of N,N,N',N'-tetramethylethylenediamine (TMEDA), 3-chloropyridine [72] as well as 3-alkoxypyridine [73] are primarily metallated in the 2-position.

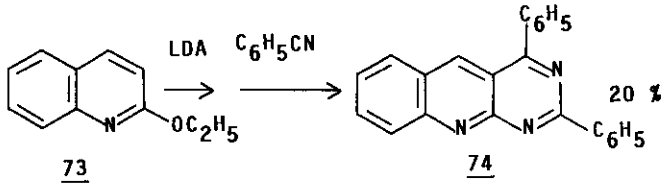
When 2-ethoxyquinoline (73) is lithiated by LDA and reacted subsequently with excess benzonitrile the tricyclic system (74) is obtained in 20 % yield [74].

2',3'-O-Isopropylidene-5'-methoxymethyluridine can be converted by excess LDA into the N^3,C^6-dilithio derivative, which reacts with various electrophiles like benz- or propionaldehyde, ketones, and ethyl formate to give 6-substituted uridines in moderate yields [75,76]. 6-Substituted 9-(2',3'-O-isopropylidene-ß-D-ribofuranosyl)purines give analogously mono- or dilithium salts which react with electrophiles to furnish 8-substituted purine nucleosides [77,78].



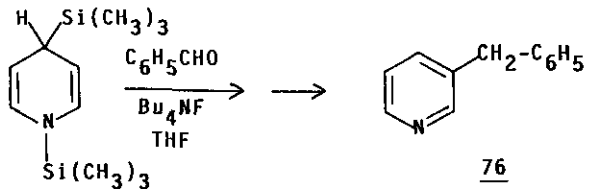






2.2.4. Miscellaneous Reactions

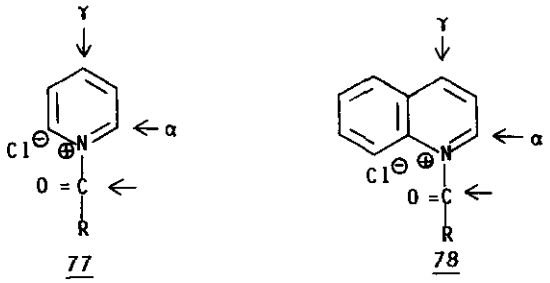
Recently, Tsuge [79] utilized the 1,4-bis(trimethylsilyl)-1,4-dihydropyridine (75), which is readily available from the reduction of pyridine with lithium and trimethylsilyl chloride, for the fluoride catalyzed reaction with aldehydes e.g. benzaldehyde to obtain 3-benzylpyridine (76) in 72 % yield.



75 76

2.3. Reissert-Type Reactions

Electrophilic agents like acid chlorides, acid anhydrides, sulfonyl chlorides, thionyl chloride, and sulfuryl chloride as well as halogens like bromine and Lewis acids combine with pyridines, quinolines, and all the other basic N-heterocyclic compounds to σ-complexes. Typically, acid chlorides furnish complexes like 77 and 78.



77 78

These σ-complexes, which are formed in an equilibrium depending mainly on the electrophilic agent (or Lewis acid) and the basicity and polarizability of the heterocyclic base [80], behave like typical ambident electrophiles which can react

1) with "hard" nucleophiles, such as alcohols, phenols or amines, at the *electrophilic carbon attached to the heterocyclic nitrogen* to furnish either esters or amides (Einhorn-acylation)

2) with alkali at the α-carbon of the heterocycle to yield the so-called *"pseudo bases" which often undergo ring-opening* (Zincke-König reaction [80,81])

3) with cyanides especially in the pyridine, quinoline, and isoquinoline series to form the Reissert compounds (cf. 2.4.)

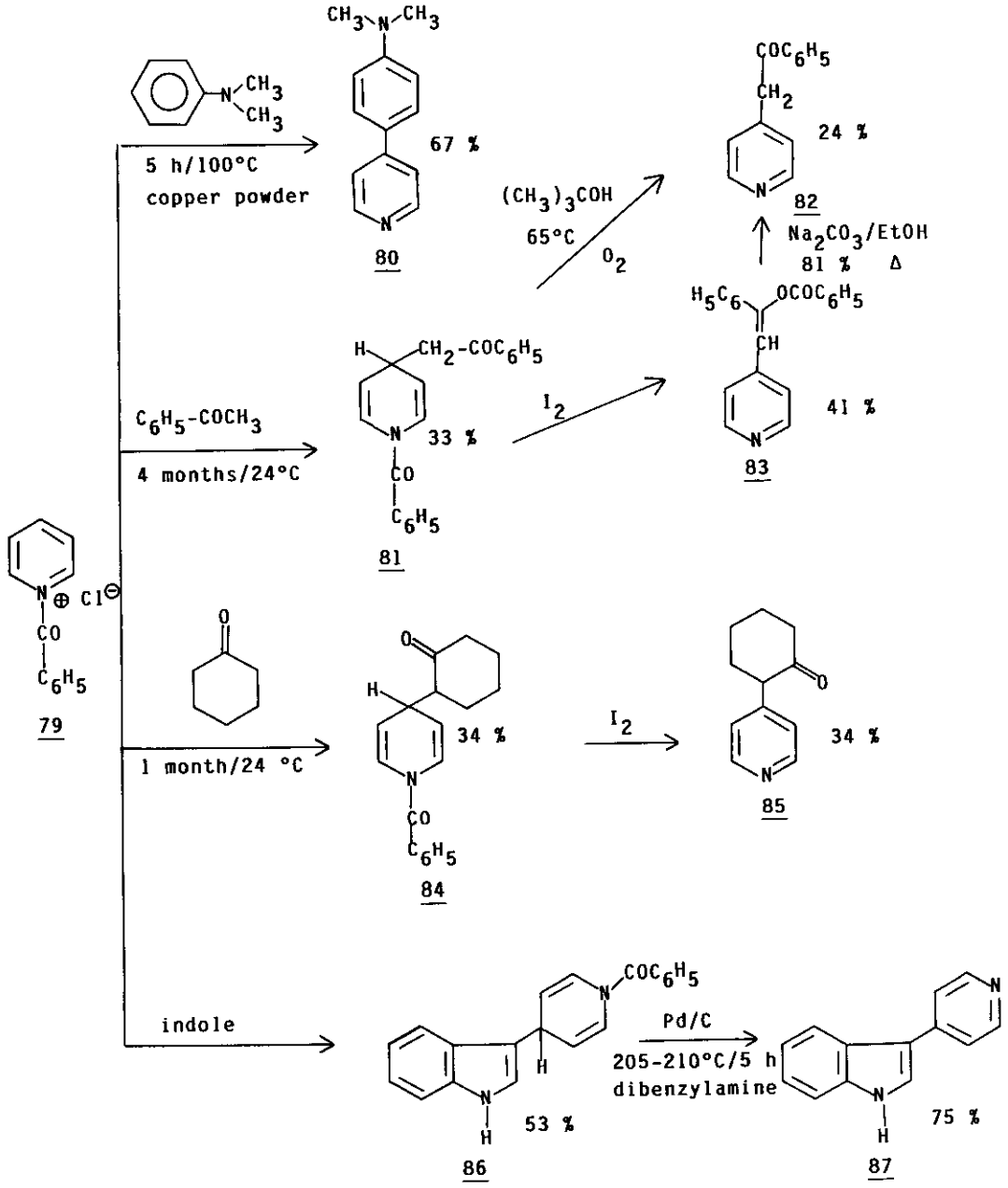
4) with "soft" nucleophiles, e.g. N,N-dimethylaniline, Grignard reagent indoles or ketone enolates, in the α- or γ-positon (for details see below)

5) with pyridine in the presence of zinc-dust in acetic anhydride to generate radicals which subsequently dimerize (Dimroth-reduction, details are discussed below)

The orientation of the attack of nucleophilic agents is determined by steric factors as well as by the relative "softness" or "hardness" of individual positions of the ring or the acyl carbon atom.

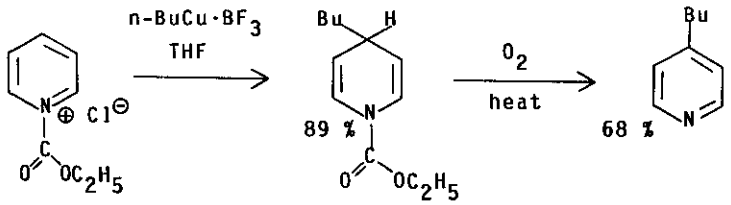
In the pyridine series, electrophiles like thionyl chloride [82] or bromine [83] form very reactive δ-complexes. These complexes, which are only stable at low temperatures, are attacked by chlorine or bromine or free pyridine in the γ-position to afford eventually 4-pyridylpyridinium chloride hydrochloride or 4-pyridylpyridinium bromide hydrobromide in high yields which are interesting starting materials for the C-substitution of pyridines in the 4-position (cf. 4.0.).

The δ-complex between pyridine (79) and benzoyl chloride affords on heating with N,N-dimethylaniline a 67 % yield of 4-(4-dimethylaminophenyl) pyridine (80) (compare also ref. 84). Reaction of 79 with acetophenone for 4 months at 24°C leads to formation of 81, which can be oxidized by oxygen directly to 4-phenacylpyridine (82). The latter is also available via 83 [85]. Comparable treatment of the cyclohexanone derivative (84) with iodine gives 85 [85]. Addition of indole to 79 furnishes the adduct (86) [86,87] which can be efficiently dehydrogenated to 87 [88] The analogous reaction of indole with 4-cyanopyridine affords in 73 % yield the 2-(3-indolyl-4-cyanopyridine [89].


5 h/100°C
copper powder
67 %
80
(CH3)3COH
65°C
O2
24 %
82
Na2CO3/EtOH
81 %
Δ
C6H5-COCH3
4 months/24°C
33 %
81
I2
41 %
83
79
1 month/24 °C
34 %
84
I2
34 %
85
indole
53 %
86
Pd/C
205-210°C/5 h
dibenzylamine
75 %
87

Further reactions of indole with σ-complexes of pyridine with acetyl chloride [90], ethyl chloroformate or cyanogen bromide [91] afford similar yields of compounds analogous to 86. The σ-complexes between benzoyl chloride [92-102], acetic anhydride [103,104,106], or sulfonyl chlorides [101,105,107] and pyridine [93,103,107], quinoline [93,97,99,107], isoquinoline [93,96,104-106], 1,6-naphthyridine [106], 1,8-naphthyridine [92], phenanthridine [93,98] as well as quinoxaline [94] react analogously with N,N-dimethylaniline [97,98,100], indolizine [95], acenaphthenone [103], acetophenone [93,99], cyclopentanone [93], steroid-3-ketones [96,108], ethyl benzoylacetate [99] as well as indoles [92,105,107], or other nucleophiles [99-102,105,109]. Acridine derivatives rearomatize during their reactions [93,100].

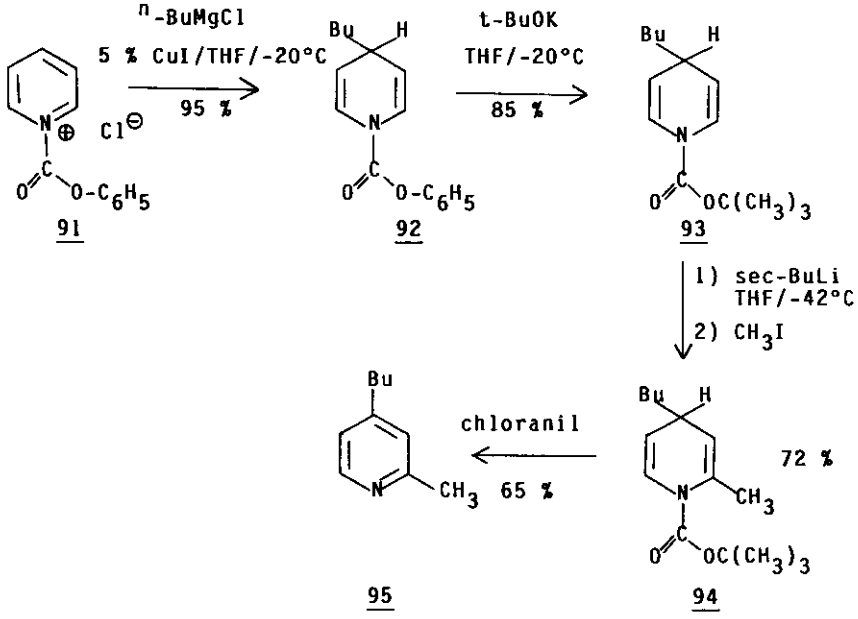
Remarkable are the recently described 1,2- and especially 1,4-additions to Reissert complexes of pyridines. Whereas the regioselectivity in the case of unsubstituted pyridinium salts [110,111] as well as of quaternary salts of nicotinates [112] depends on the structures of the Grignard reagents and the 1-acyl group (compare 2.2.2.), the alkylcopper [111,113] or alkylcopper-boron trifluoride complexes [114-116], titanium-enolates [117], or organoaluminium compounds [118] show very high or exclusive 4-selectivity. Thus, 89 can be prepared from 88 in a nearly regiospecific manner with only 0.5 % of 1,2-adduct as byproduct using the n-BuCu·BF_3-complex [114]. Compound 89 is readily oxidized to 90.



88 89 90

Butylmagnesium chloride adds selectively to the 4-position of 91 in the presence of catalytic amounts of CuI to give a nearly quantitative yield of 92. Transesterification with potassium tert-butoxide to 93 followed by α-metallation permits the subsequent reaction with methyl iodide to give 94 [113]. Dehydrogenation leads finally to the 2,4-substituted pyridine (95).

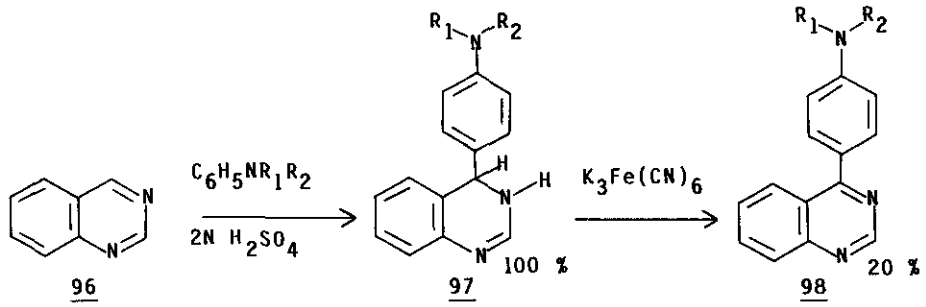
Quaternization of pyridine with bulky tert-butyldimethylsilyl triflate followed by addition of Grignard reagents gives nearly exclusively 4-alkylated products [113,119] (compare also ref. 120).



For further methods to introduce alkyl groups selectively into the 4-position of quinoline, see ref. [121] and into the 1-position of isoquinoline [122].

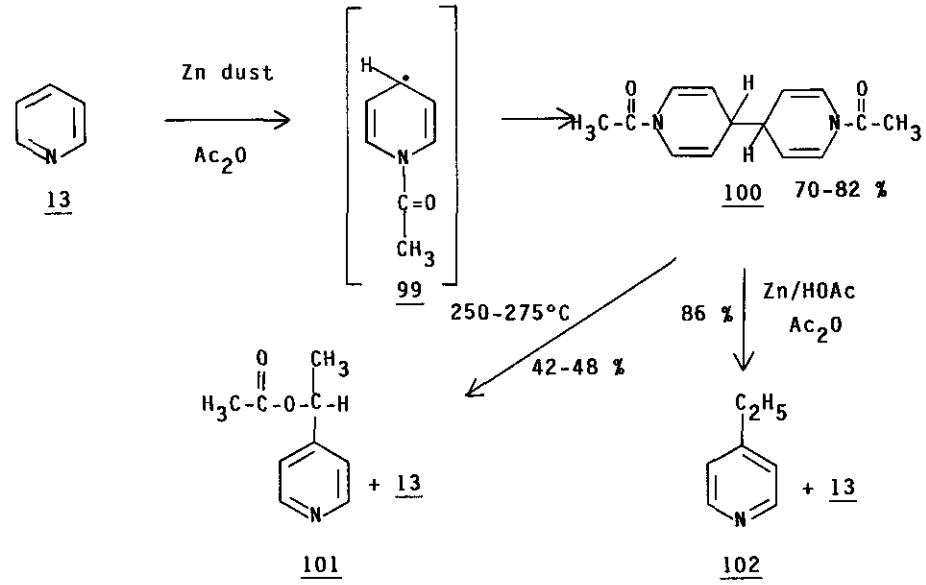
Analogous reactions of Reissert compounds of quinoline [123] and isoquinoline with enol silyl ethers [124,125] or boron enolates [126] give high yields of the corresponding 2- and 4-substituted 1,4-dihydroquinolines and 1-substituted 1,2-dihydroisoquinolines. Enol silyl ethers react also with pyrimidinium salts as has been shown recently [127]. The intermediate 1,4-adducts such as 92 can be acylated by acyl chlorides/$SnCl_4$ in the 3-position [128]. The Reissert-type complexes between pyridine-benzaldehyde and benzoyl chloride are rearranged by strong bases to 2-acylpyridines [129].

In formic, acetic or propionic acid, isoquinoline, phthalazine, and 1,6-naphthyridine add diketene or acetic anhydride to adducts which can be used for subsequent reactions [130-132]. In trifluoroacetic acid or dilute sulfuric acid, pyrimidine [133], quinazoline [109,133] add readily resorcinol, aniline, N-methylaniline, and N,N-dimethylaniline in high yields to give compounds such as 97, which can be oxidized by potassium ferricyanide to 98. Analogous additions of phenol, anisol, indole, and 2-methylfuran to 96 afford the corresponding 3,4-dihydro adducts in nearly 100 % yield [109].



$R_1 = R_2 = H; CH_3$

The σ-complex between pyridine (13) and acetic anhydride dimerizes with zinc-dust via the corresponding radical (99) [134] to the dimer (100) [135] which can be pyrolized to 101 [136] or reduced to 4-ethylpyridine (102) [137,138].

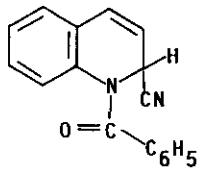


Replacement of acetic anhydride by ethyl chloroformate opens an entry to ethyl isonicotinate [139]. Higher 4-alkyl homologues can be prepared, albeit in lower yields [138]. Coupling of pyridine with indole by the help of zinc-dust has already been discussed (cf. reaction 79→86). [140].

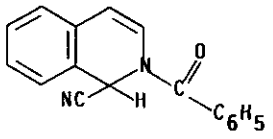
Since all these reactions of σ-complexes with nucleophiles lead initially to 1,2-, 3,4- or 1,4-dihydro derivatives, the overall yields of C-substituted aromatic heterocycles depend very much on the efficiency of the dehydrogenation step (compare the examples given above).

2.4. Reissert Reactions

The Reissert reaction has been the subject of a number of excellent reviews covering the chemical literature up to September 1982 [141-144]. We shall therefore discuss primarily some typical reactions of the two classical "Reissert-compounds", 1-benzoyl-1,2-dihydroquinaldonitrile (103) and 2-benzoyl-1,2-dihydroisoquinaldonitrile (104).

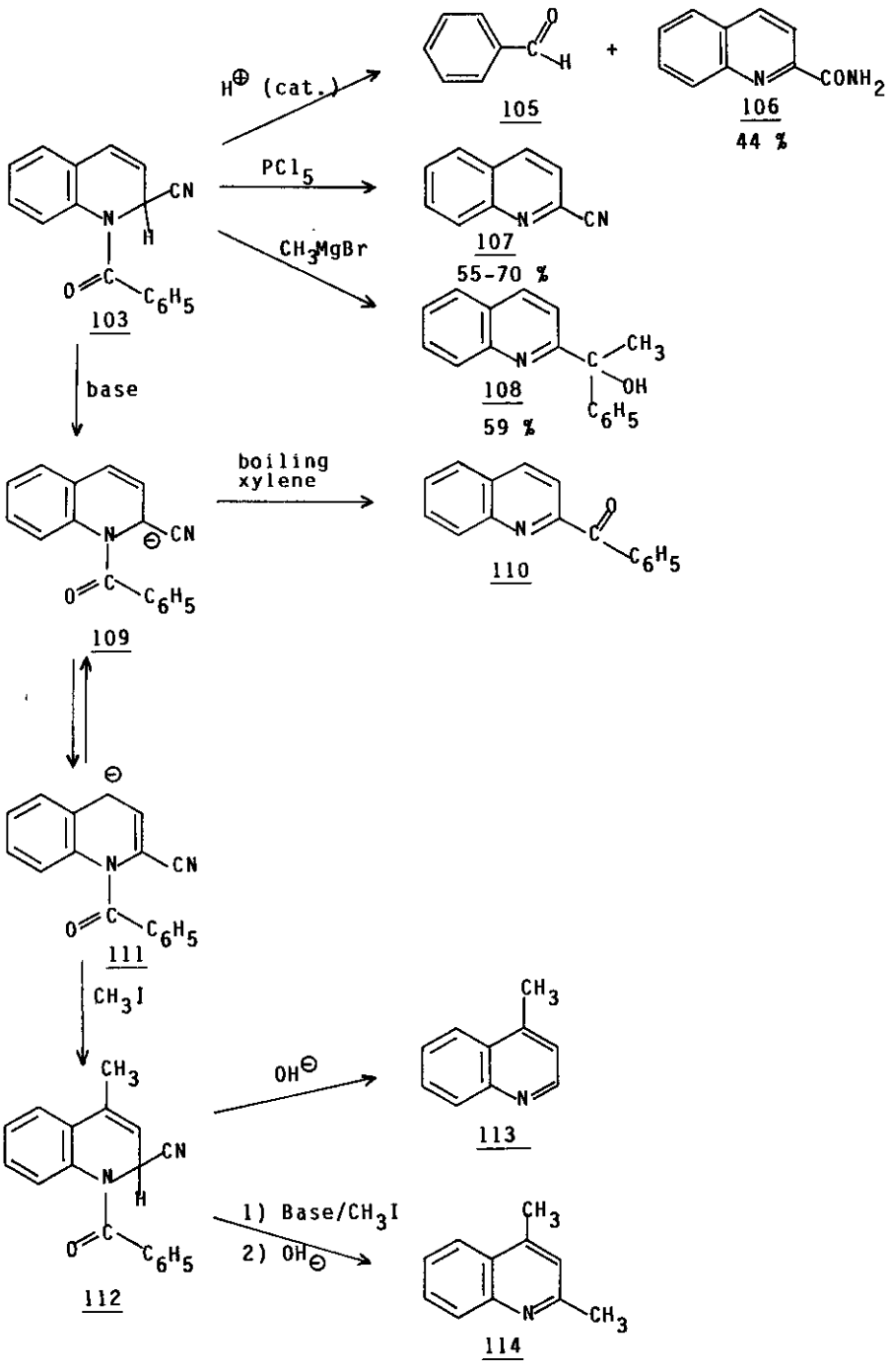


103

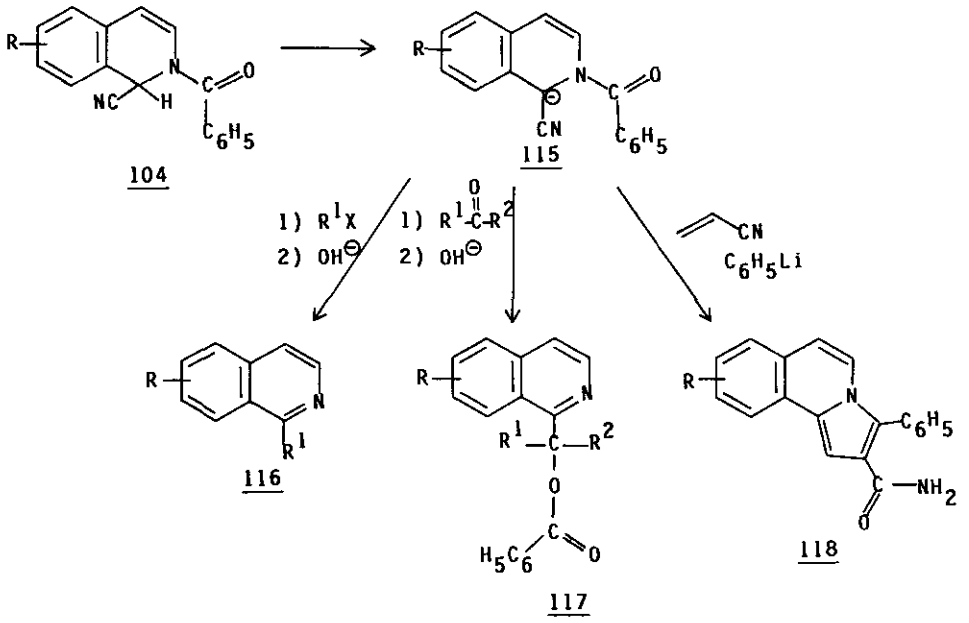


104

They can be prepared under phase-transfer catalysis [145] by adding KCN in heterogenous phase [146], anhydrous HCN [142], or $(CH_3)_3SiCN$ [147,148] in homogenous phase to the σ-complexes between an acyl chloride and quinoline and isoquinoline, resp. (cf. chapter 2.3.). Originally, Reissert compounds such as 103 were hydrolyzed with aqueous mineral acid to give benzaldehyde (105) [149] and quinoline derivatives of structure 106. Whereas treatment of 103 with PCl_5 furnishes 2-cyanoquinoline (107) [150], the addition of methyl Grignard reagent to 103 followed by subsequent rearrangement affords the tertiary alcohol (108) [141]. Heating of the Reissert-anion (109) (prepared from 103 with a base such as phenyllithium or sodium hydride) in refluxing xylene affords the ketone (110) [142], whereas alkylation with methyl iodide gives 112 via 111. Subsequent treatment of 112 with base furnishes 4-methylquinoline (113) [141]. Repeated base treatment of 112 and alkylation with methyl iodide followed by treatment with alkali gives finally 2,4-dimethylquinoline (114) [141].

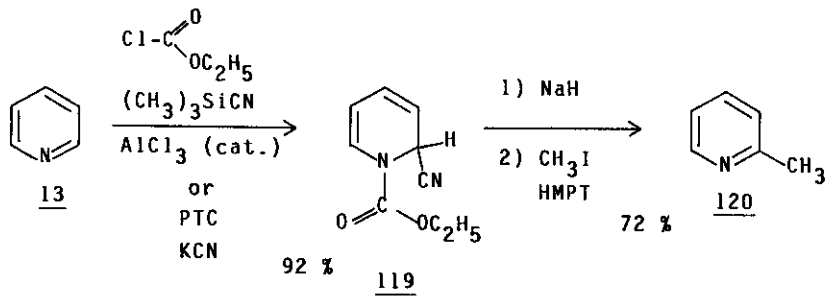

H⊕ (cat.)
105
106
44 %
PCl5
107
55-70 %
CH3MgBr
108
59 %
103
base
boiling
xylene
110
109
111
CH3I
OH⊖
113
112
1) Base/CH3I
2) OH⊖
114

Synthetically even more important are Reissert-compounds derived from isoquinolines. Using phenyllithium [141,143], sodium hydride or alkali and phase-transfer reagents [143,151-154], 104 can be easily deprotonated to 115, which can be readily alkylated to 116 [153-162], reacted with aldehydes [152,155,156,162] or reactive ketones [144,163] to give 117. Addition of Michael acceptors such as ethyl acrylate [164], 2-vinylpyridine [164], or acrylonitrile [164,165] affords cyclic products of structure 118. Intramolecular alkylation or acylation reactions of Reissert-compounds of isoquinoline with halides and aldehydes have also been described [166,167].



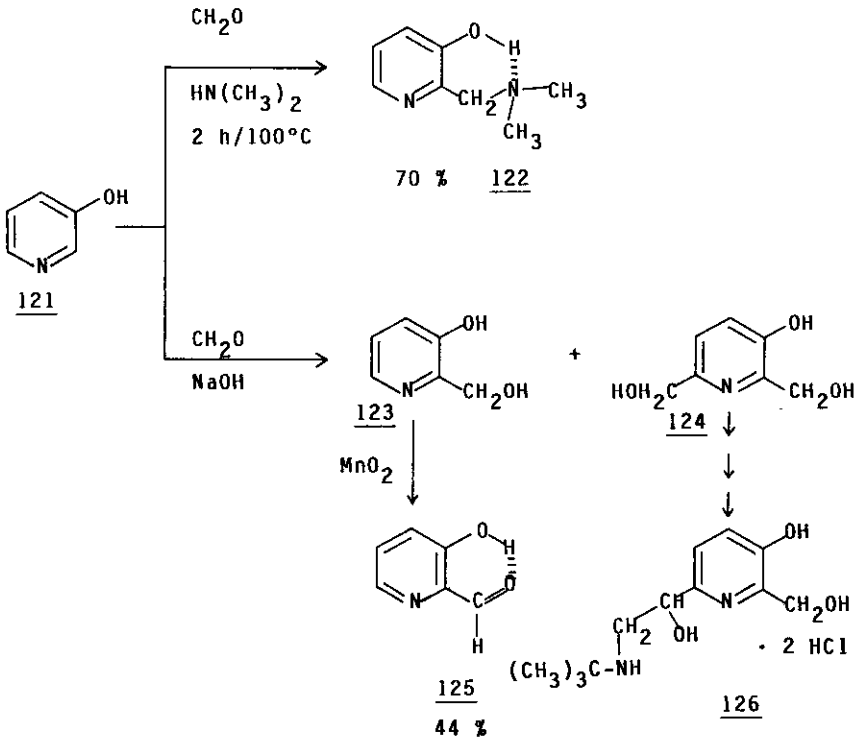
Besides quinolines and isoquinolines, phthalazines [168,169], 1,6- [168], 1,7- [143,168], and 1,8-naphthyridines [168,170] as well as 4,6- [168,171] and 1,7-phenanthroline [168] do form Reissert-compounds. Depending upon the reaction conditions, 4,7-phenanthroline [168] from "mono-Reissert"-compounds, whereas quinazoline [170] and 4,7-phenanthroline [168] yield "bis-Reissert"-compounds using benzoyl chloride/trimethylsilyl cyanide. Reissert-compounds of benzoxazoles and benzothiazoles have also been described [172]. Acridine gives only rise to 9-cyanoacridine [173].

In a very interesting recent development, Popp et al. as well as Cooney et al. have succeeded in preparing the Reissert-compound (119) from pyridine (13) in 92 % yield, whose anion can be converted to the corresponding 2-substituted pyridines - e.g. 120 - in good yields [174]. Compare also reactions under chapters 4.2. and 4.3.



2.5. Reactions of Hydroxy-N-Heterocycles

Hydroxy-N-heterocycles like 3-hydroxypyridine (121) behave in many ways like phenols. However, due to protonation in neutral and acidic medium, 3-hydroxypyridine (121) [175] is most readily aminomethylated under basic conditions to form 2-substituted Mannich bases like 122 [176].

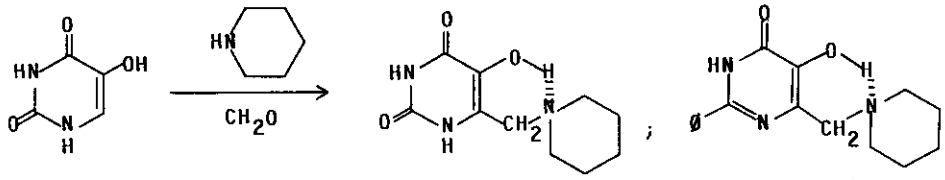


The reaction of 121 with formaldehyde and alkali affords the bis-adduct (124) and the desired mono-adduct (123), which can be oxidized by MnO_2 in boiling ethanol to give the aldehyde (125) [177]. The bis-adduct (124) has been converted in several steps to pirbuterol (126), a potent bronchodilator [178,179].

Analogous reactions with 6-methyl-3-hydroxypyridine and formaldehyde have been described [180].

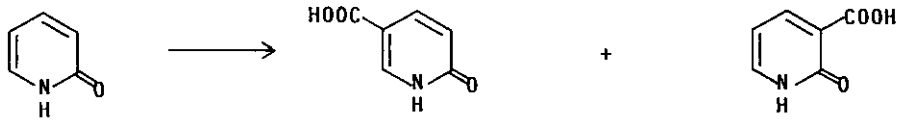
Apparently, 125 cannot be obtained by Reimer-Tiemann reaction [181] of 3-hydroxypyridine (121), whereas hydroxyquinolines afford the corresponding aldehydes [181,182] e.g. 7-hydroxyquinoline the 7-hydroxy-8-formylquinoline [183].

4-Hydroxyquinolines undergo the Mannich reaction and condense with formaldehyde [184]. 5-Hydroxyuracil (127) affords the Mannich-product (128) and 4,5-hydroxy-2-phenyl-pyrimidine-4-one the corresponding Mannich-product (129) [185,186].

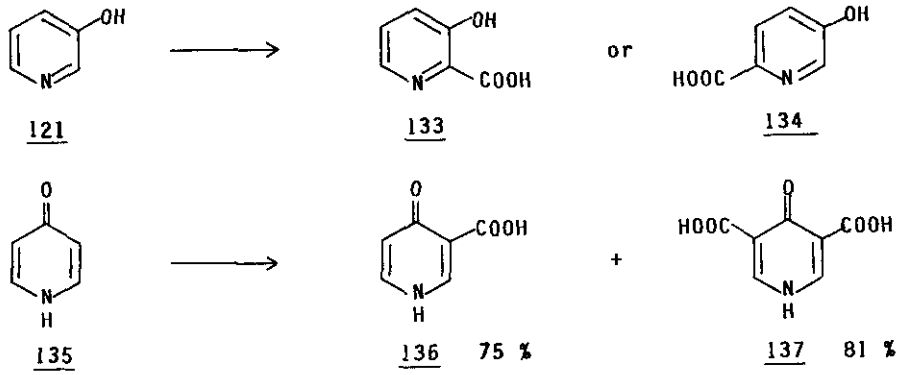


127 128 57 % ; 129 70 %

Hydroxy-N-heterocycles such as 2-, 3- and 4-hydroxypyridines react like phenols and are transformed by the Kolbe-Schmidt reaction [187] to the corresponding hydroxypyridinecarboxylic acids. Thus, 2-pyridone (130) affords under Matasse conditions the corresponding 2-hydroxy-5-pyridinecarboxylic acid (131) and under Kolbe conditions also 2-hydroxy-3-pyridinecarboxylic acid (132) [188], whereas 3-hydroxypyridine (121) gives, depending on the reaction conditions, either 3-hydroxy-2-pyridinecarboxylic acid (133) or 3-hydroxy-6-pyridinecarboxylic acid (134) [189]. Finally, 4-pyridone (135) gives rise to 3-carboxy-4-pyridone (136) and some 3,5-dicarboxy-4-pyridone (137) [190].

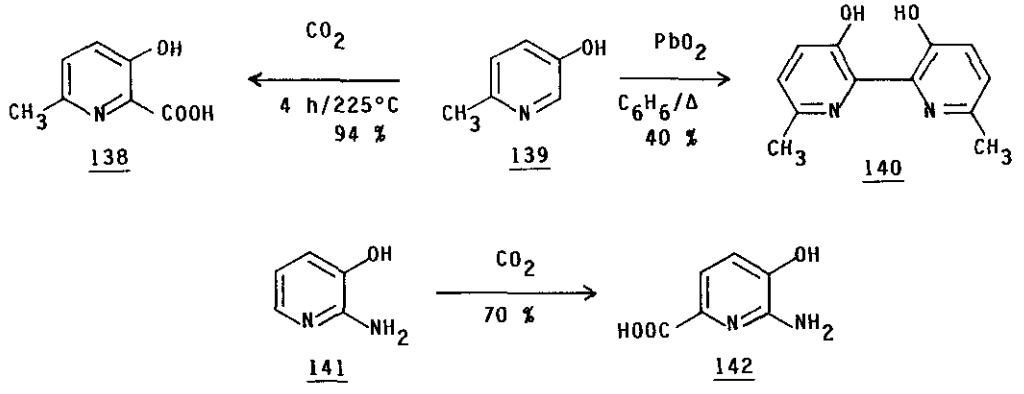


130 131 132

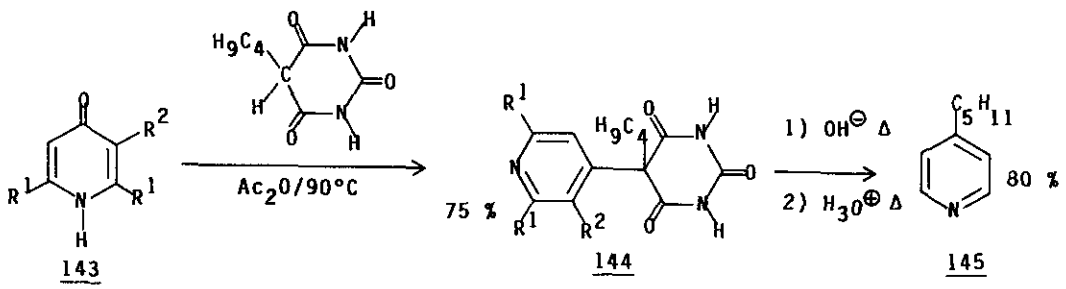


Methyl- and amino-substituted hydroxypyridines lead to the expected Kolbe-products [191-195], e.g. 2-methyl-5-hydroxypyridine (139) affords a nearly quantitative yield of 3-hydroxy-6-methyl-2-pyridinecarboxylic acid (138), whereas 2-amino-3-hydroxypyridine (141) furnishes 2-amino-3-hydroxy-6-pyridinecarboxylic acid (142) [194].

In analogy to phenol oxidations, 139 can be dimerized by lead dioxide to 140 [196].



4-Pyridone (143) (R^1,R^2 = H) and its 3-methyl (R^1 = H; R^2 = CH_3) and 2,6-dimethyl derivatives (R^1 = CH_3; R^2 = H) react readily with various 5-substituted barbituric acids to give, for example, 144, which can be converted to 4-n-pentylpyridine (145) [197].

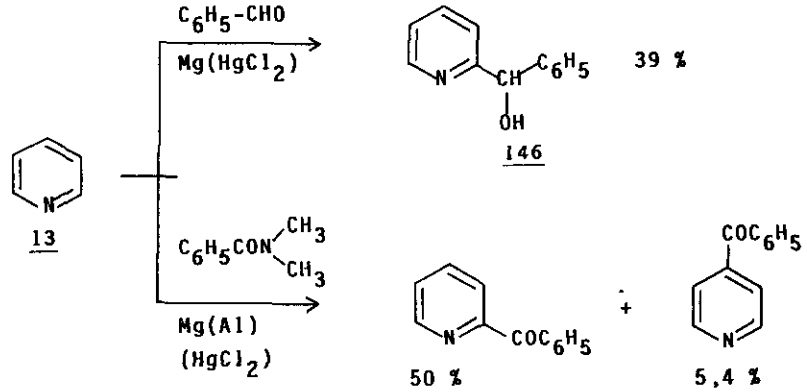


143 144 145

2.6. Emmert Reaction

The Emmert reaction [198] of pyridine, quinoline [199-202], isoquinoline [199] or acridine [203] with carbonyl compounds in the presence of activated magnesium or aluminium metal affords up to 70 % of mainly the α-substituted and some γ-substituted heterocyclic carbinols or ketones.

Thus pyridine 13 reacts with acetophenone [204,207], acetone [198,202], cyclopentanone [200,205], cyclohexanone [200,205], ethyl benzoate [201], benzaldehyde [204], and N,N-dimethylbenzamide [206,207] to the corresponding 2- and some 4-substituted pyridines 146 or 147 and 148 as shown in the following scheme.

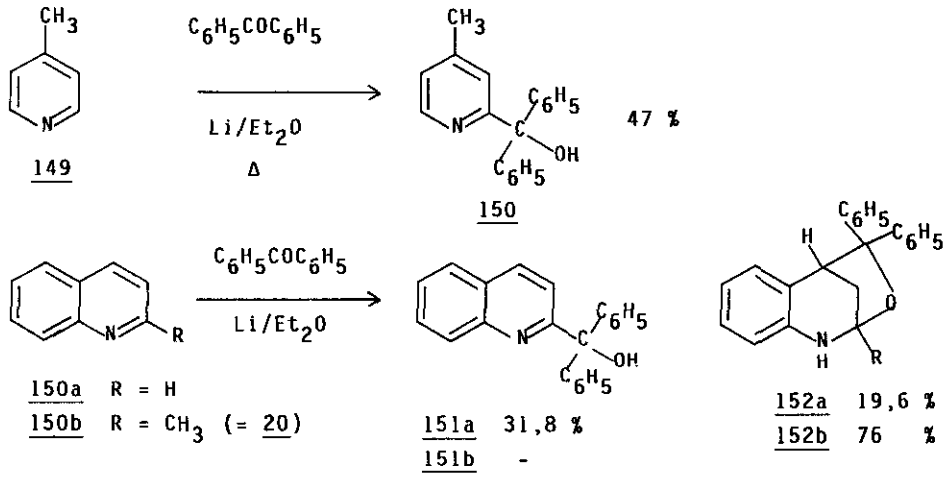


13 146 147 148

As side products, pinacols, benzoin, and benzil can be isolated as neutral products of these reactions [201,204]. The mechanism of the Emmert reaction was investigated by Bachman [207] and Abramovitch [208].

Russell et al. [209] have described the use of lithium metal in the Emmert reaction with benzophenone. Thus, 4-methylpyridine (149) affords the corresponding

2-substituted product (150), whereas quinoline (150a) gives rise to the expected 2-substituted carbinol (151a) as well as the cyclized 4-substituted product (152a). Compound 152b is obtained exclusively in the case of 2-methylquinoline (150b = 20), where the 2-position is blocked.



2.7. Radical Reactions

Although quite a number of reactions like the Emmert reaction (c.f. 2.6.) or some of the $S_{RN}1$ reactions discussed under 3.1.1. - 3.1.3. are also radical reactions, in these Chapters 2.7.1. and 2.7.2., only such reactions will be dealt with, in which the N-heterocycles will be attacked by chemically and photochemically *generated "classical" free radicals.*

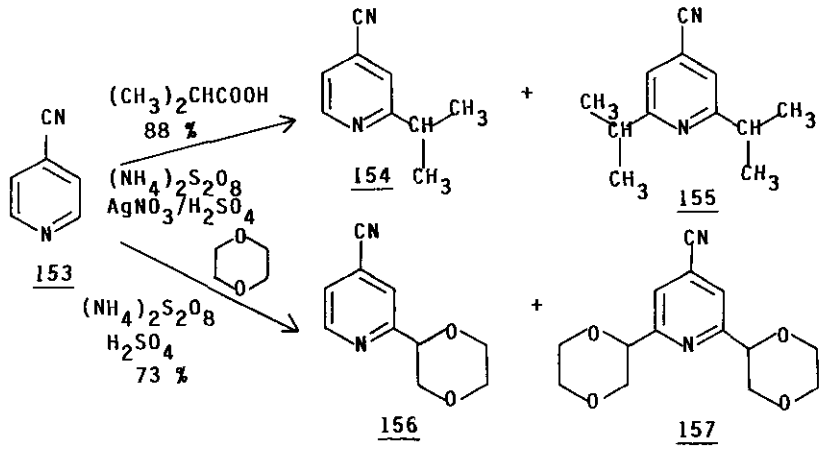
2.7.1. Reactions with Chemically Generated Alkyl Radicals

Minisci as well as Tieco have recently reviewed their pioneering and interesting work in this field [210-216] and have described numerous applications to many different heterocyclic systems. Thus, it should only be emphasized here that protonation of N-heterocycles bases increases their reactivity towards nucleophilic radicals, which attack the heterocyclic rings nearly exclusively at the α- or γ-position to the protonated heterocyclic nitrogen atom. Furthermore electron withdrawing substitutents, such as cyano or ester groups, in the heterocyclic

system vastly increase the reactivity towards these nucleophilic radicals.

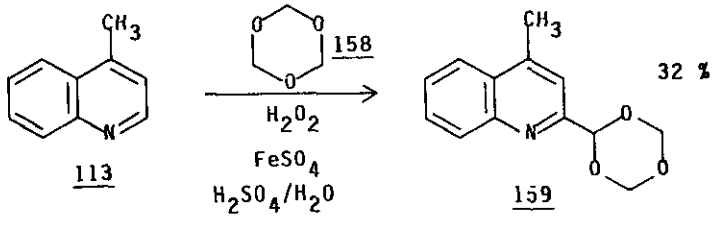
2.7.1.1. Reactions with Alkyl Radicals

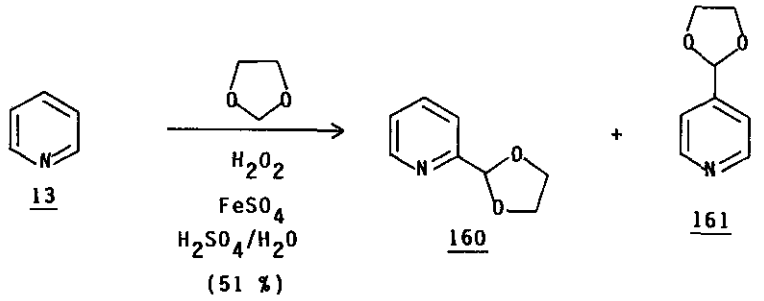
4-Cyanopyridine (153) reacts with a threefold excess of isobutyric acid, $AgNO_3$, and $(NH_4)_2S_2O_8$ in dilute H_2SO_4 to afford a 7 : 3 mixture of 154 and 155 in 88 % yield [211,215], whereas alkylation with dioxane furnishes a 9 : 1 mixture of 156 and 157 [210].



4-Methylquinoline (113) with trioxane (158) gives the derivative (159) in 32 % yield, which can easily be hydrolyzed to the corresponding aldehyde. 2-Methylquinoline, benzothiazole, quinoxaline as well as pyrazine react analogously [210].

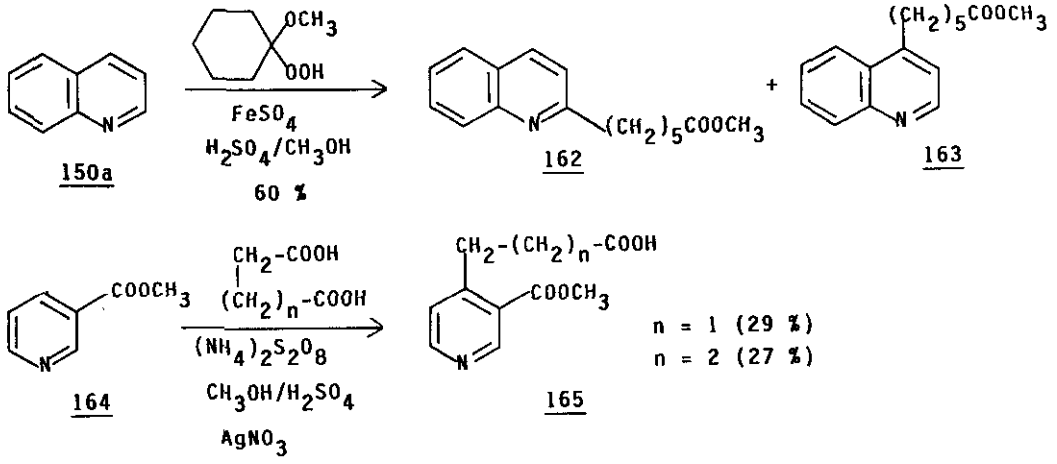
Pyridine (13) and dioxolane afford a mixture of the protected 2- and 4-pyridine aldehydes (160 and 161) in 51 % yield [210,217].



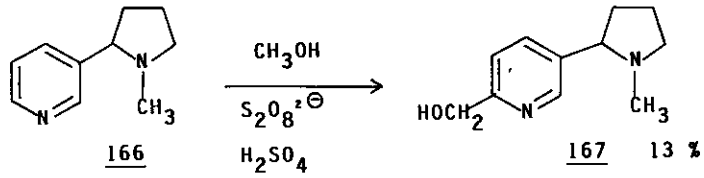


Reacting quinoline (150a) with the methanol-hydrogen peroxide-adduct of cyclohexanone gives a ca. 1 : 1 mixture of 162 and 163 in 50 % yield [210].

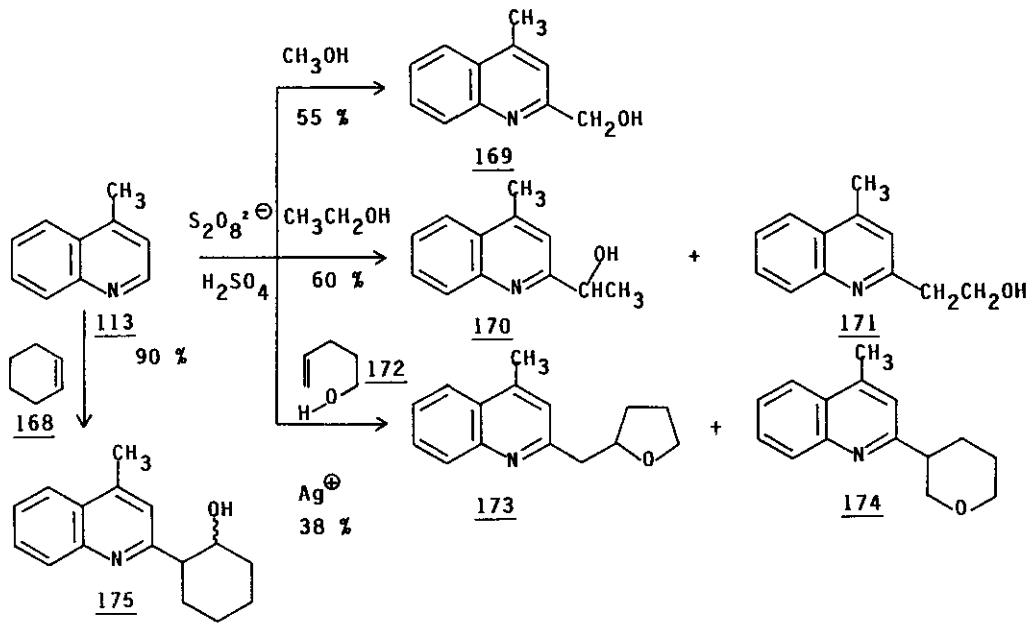
Methyl nicotinate (164), on reaction with succinic or glutaric acid, affords the corresponding 4-substituted acids (165) [218].



Reaction of nicotine (166) with hydrogen peroxide and Fe^{++} in methanol gives in 13 % yield the product (167), whereas quinine affords in 18 % yield the 2-hydroxymethylquinine [219]. Lepidine (113) reacts with methanol or ethanol to furnish the corresponding derivatives (169 or 170 and 171) [210]. In the presence of peroxydisulfate and silver ions, the initially formed alkoxy radical derived from an olefinic alcohol (172) reacts with the double bond to yield two intermediate C-radicals which attack 4-cyanopyridine [220] or lepidine (113) to form the two products (173 and 174) in a 9 : 1 ratio in 38 % yield [221]. The analogous reaction of 113 with cyclohexene (168) affords the products (175) in 90 % yield [216].



166 167 13 %

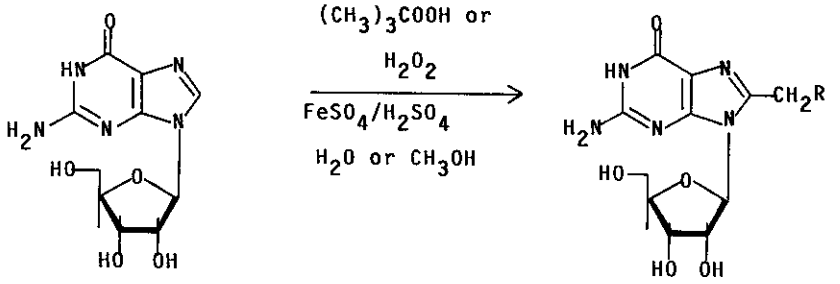


169 170 171 173 174 175

Alkylation of quinoline and isoquinoline with the benzyl-type radical derived from p-methoxytoluene gives the corresponding products in the α- and γ-position of the heterocyclic nitrogen in a combined yield of 33 % and 15 % [222].

In connection with theories on chemical carcinogenesis, radical reactions with purines and purine-nucleosides are important. Thus, guanosine 176 furnishes with aqueous tert-butyl hydroperoxide 8-methylguanosine (177a) in 68 % yield, whereas in methanol with hydrogen peroxyde, only 177b is obtained [223]. Adenosine gives a complicated mixture of 2- and 2,8-methylated products [224]. Thus, 8-methyladenosine is prepared via 8-methylation of 2-methylmercaptoinosine [225]. For further studies with purines, compare the references 226-229.

Finally, some recent radical alkylations of pyrimidines [230,231] and pyridazines [232-234] should be mentioned.



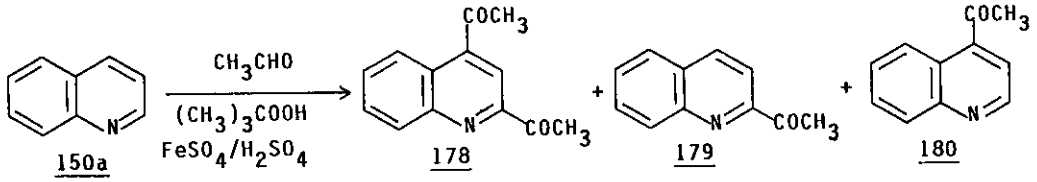
176

177a R = H 68 %
177b R = OH 70 %

In addition to the "Minisci"-type alkylations, the classical Gomberg-Bachmann arylation [235] can be applied to pyridines and quinolines. Thus, pyridine can be arylated by 3,4-dimethoxybenzenediazonium chloride to give 3,4-dimethoxyphenylpyridines in a ratio of 2 : 3 : 4 substitution = 3 : 1 : 1 [236].

2.7.1.2. Reactions with Chemically Generated Acyl Radicals

Protonated heterocyclic bases are readily acylated by nucleophilic acyl radicals generated from aldehydes or α-keto acids to afford mono- or poly-acyl derivatives. Thus, quinoline (150a) affords 80 % of the 2,4-diacetyl derivative (178) and 20 % of the 2- or 4-acetylquinolines (179 and 180) [210]. 2-Methyl-4-phenylpyrimidine (181) affords with acetaldehyde the corresponding 4-acetyl derivative 182 in 75 % yield [237,238]. 4,4'-Bipyridyl is acetylated by acetaldehyde to give 65 % of a 1 : 9 mixture of 2,6,2',6'-tetraacetyl bipyridyl and of 2,6,2',5'-tetraacetyl bipyridyl [239]. Pyrazine (183) is diacetylated by veratraldehyde (184) to 185 [240,241].

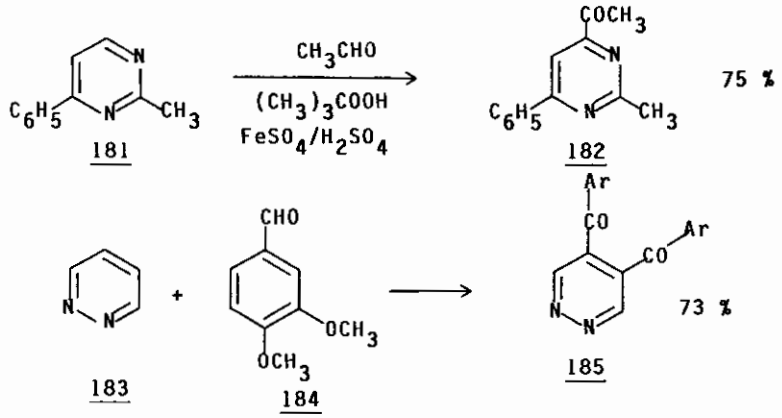


150a

178
80 %

179

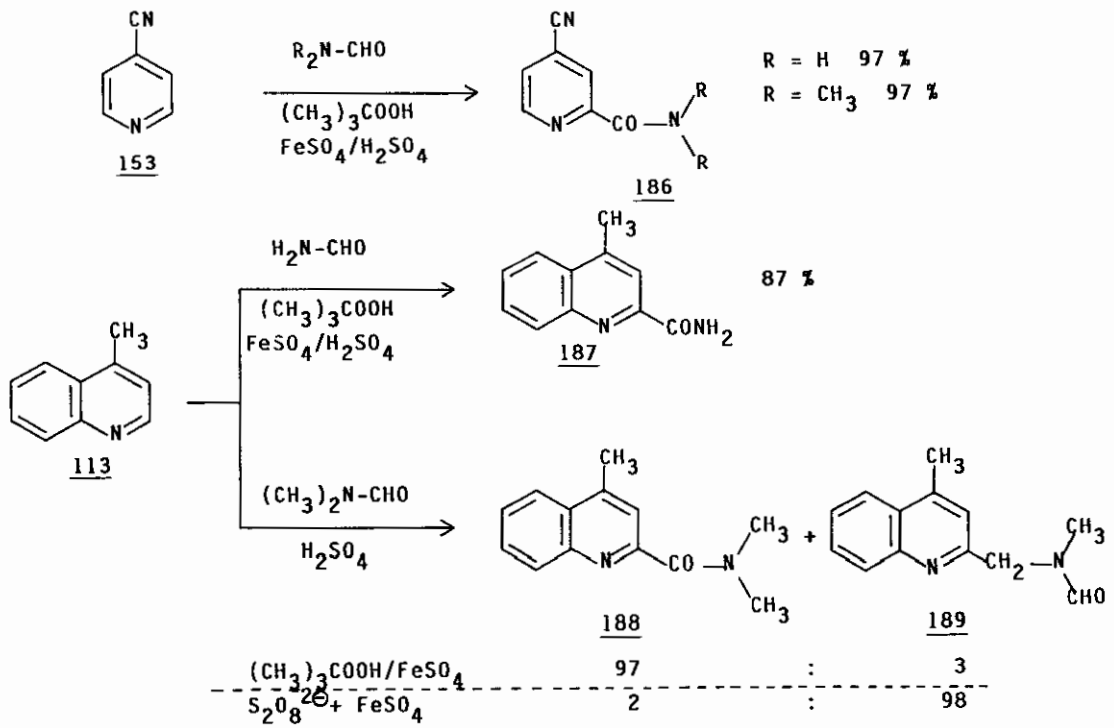
180
20 %



181 182 183 184 185

2.7.1.3. Reactions with Chemically Generated Amide Radicals

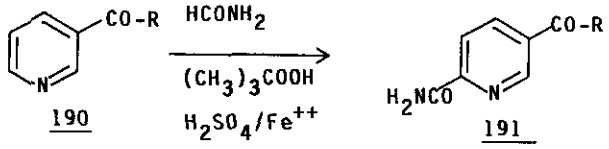
Using hydroxy or alkoxy radicals, hydrogen is abstracted from formamides to give amide radicals $R_2N\text{-}CO^{\bullet}$, which react readily with protonated heterocycles e.g. 4-cyanopyridine (153) or lepidine (113) to give the corresponding amides (186 and 187) in high yields [211]. On reaction of amides with peroxydisulfate, the initially formed amide radicals are transformed by electron transfer into amidomethyl radicals. Thus, lepidine (113) gives with N,N-dimethylformamide completely different ratios of 188 and 189 depending on whether $(CH_3)_3COOH$ or $S_2O_8^{2\ominus}$ are employed.



153 186 113 187 188 189

	188	:	189
$(CH_3)_3COOH/FeSO_4$	97	:	3
$S_2O_8^{2\ominus} + FeSO_4$	2	:	98

These amidations or α-N-amidoalkylations have been applied to many protonated N-heterocycles. Thus, 3-propionyl pyridine (190a) affords in 31 % yield 191a, which can be readily converted into fusaric acid [242] whereas 190b gives 191b in 91 % yield [243].



190 191

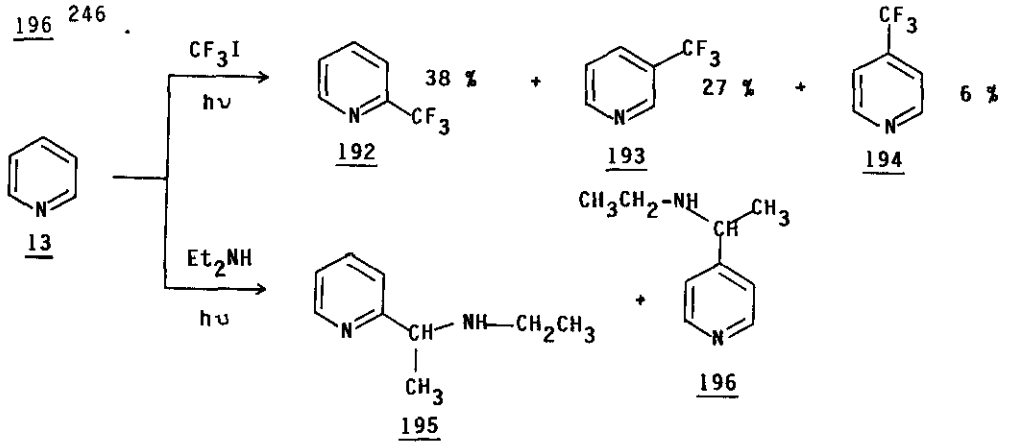
a) R = nC_3H_7; b) R = CH_2CH_2CN
31 % 91 %

2.7.2. Reactions with Photochemically Generated Radicals

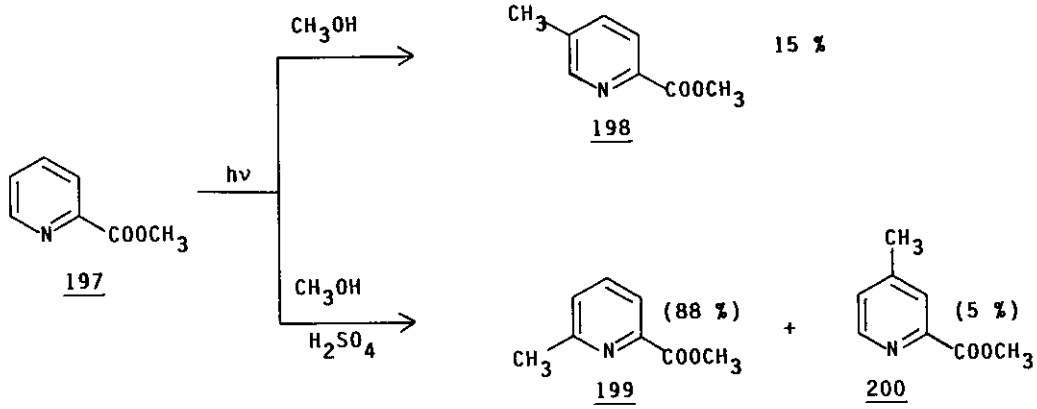
This part of the review covers only the typical photochemical reactions, not those which can be initiated by photochemical induction like the $S_{RN}2$-reactions (compare 3.1.) of heterocyclic halogens. Since photoaddition reactions have been covered by a review until 1976 [244], references are primarily given of recent work.

Substitutents can be introduced directly by irradiating N-heterocycles with reactive halogen compounds, acids, alcohols or amines. Thus, pyridine (13) is readily trifluoromethylated on irradiation with trifluoromethyl iodide to afford the products (192, 193 and 194) [245]. Pyrrole gives analogously 33 % of α-trifluoromethylpyrrole.

Irradiation of pyridine (13) with diethylamine produces a 1 : 1 mixture of 195 and 196 [246].



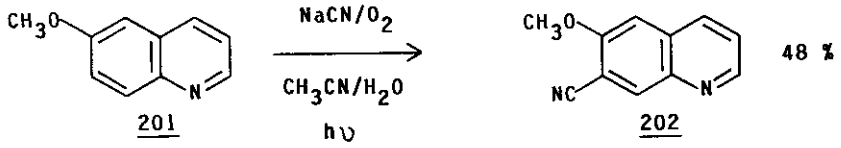
Irradiation of methyl picolinate (197) in acidic methanol gives in neutral solution only the 5-substituted product (198), whereas in acidic solution, the nucleophilic CH_2OH radicals attack the protonated pyridine ring only in the α- or γ-position (200) to the heterocyclic nitrogens [247] (cf. 2.7.1.1.).



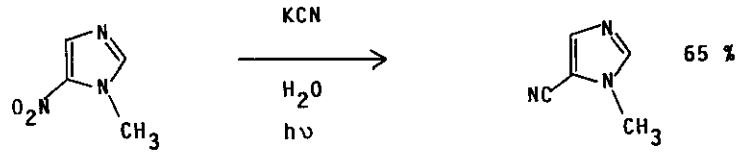
197 198 199 200

Analogous additions of methanol or ethanol to pyrimidines [248], pyridazines [249], quinolines [250,251], isoquinolines [250], and phenanthridine [252] have been described.

Cyano groups can be introduced directly by irradiation with $NaCN/O_2$ in aqueous CH_3CN-solution. Thus, 6-methoxyquinoline (201) affords 202 in 48 % yield, whereas 7-methoxyquinoline or 6,7-dimethoxyquinoline gives the corresponding 8-cyano derivatives in 30 - 40 % yield [253]. The cyano groups can furthermore be introduced photochemically by replacing nitro groups. Thus 1-methyl-5-nitroimidazole (203) furnishes the corresponding 5-cyano-1-methylimidazole (204) in 65 % yield [254].

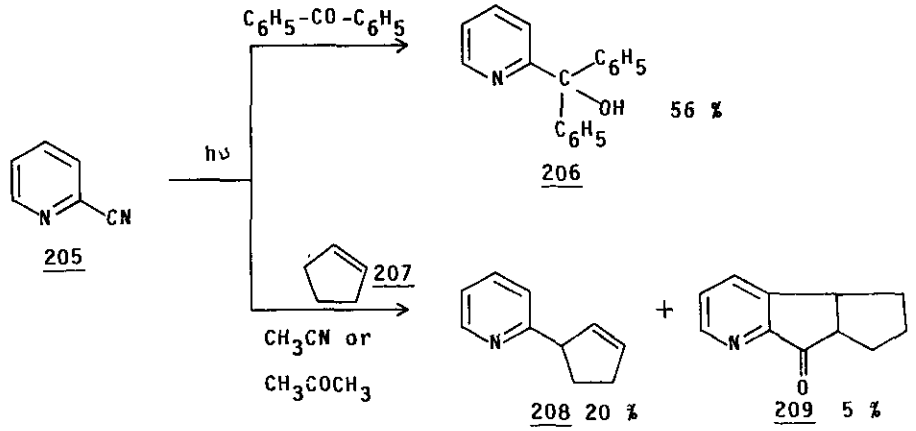


201 202

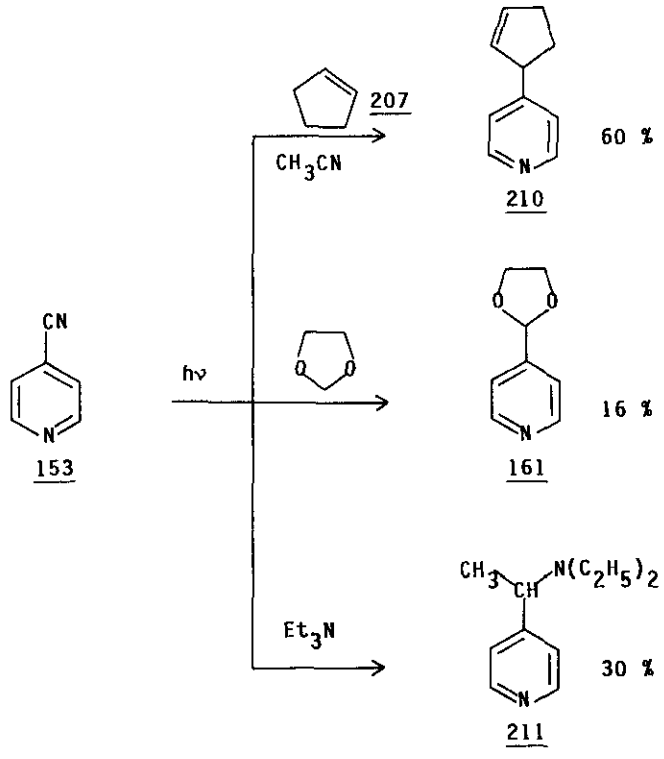


203 204

Recently, the photochemical replacement of the α- or γ-cyano groups in N-heterocycles by alcohols, ketones, ketals, and olefins was described. Thus, 1-cyanoisoquinoline gives, on irradiation in ethanol, 1-(1-hydroxyethyl)isoquinoline in 60 % yield [255] and 2-cyanopyridine (205) affords with benzophenone diphenyl(2-pyridyl)carbinol (206) in 64 % yield [256], whereas 205 reacts with cyclopentene (207) to furnish 2-(2-cyclopentenyl)pyridine (208) in 20 % as well as 209 in 5 % yield [257].



4-Cyanopyridine (153) furnishes with cyclopentene (207) the product (210) in 60 % yield [257], and with 1,3-dioxolane the product (161) in 16 % yield [258].



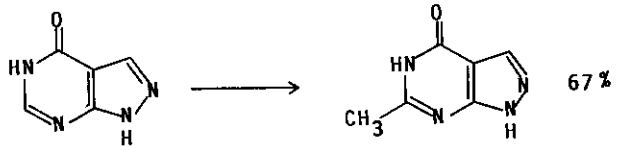
Irradiation of 4-cyanopyridine (153) with triethylamine gives 211 in 30 % yield [259].

Irradiation of chloro-, bromo-, or iodopyridines in benzene, anisole [260], furan, thiophene, pyrrole, or N-methylimidazole [261] affords the corresponding aryl-substituted pyridines in up to 42 % yield. In the case of 2-iodopyridine and N-methylimidazole, a ca. 1 : 1 : 2 mixture of the 2-, 4- and 5-(2-pyridyl)-N-methylimidazole [261] was obtained.

Biochemically significant are the photochemical additions of 5-bromouridines to tryptophane, tryptophan peptides [262], pyrene, or phenanthrene [263].

2- or 6-Iodo- or chloropurine-nucleosides react readily on irradiation with benzene, furan or pyrroles [264,265], whereas nebularine adds methanol photochemically to give a high yield of a mixture of 6-hydroxymethyl-1,6-dihydronebularines [266].

On irradiation in methanolic HCl, allopurinol (212) is converted in 67 % yield into the 6-methyl derivative (213) [267].



212 213

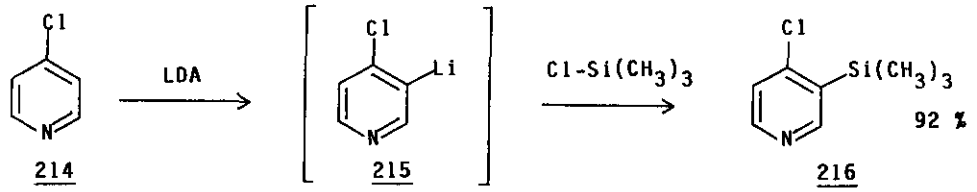
3.0. REACTIONS OR MODIFICATIONS OF REACTIVE SUBSTITUENTS AT THE HETEROCYCLE

3.1. Reactions of Halogens

3.1.1. Reactions of Heteroaryllithium and Magnesium Compounds

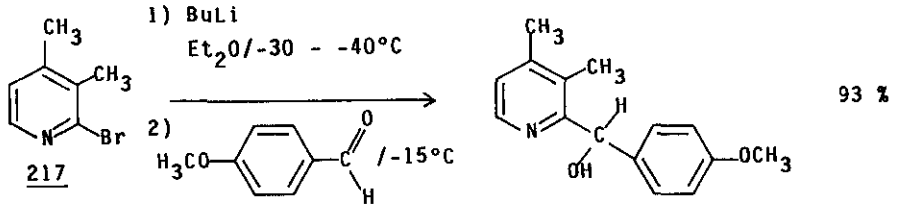
Direct metallation of unsubstituted N-heterocycles is generally not feasible. Thus, pyridine is not metallated, since the organolithium is added to pyridine to give 2-substituted lithium salts [268] as discussed under 2.2.2.

However, halopyridines can be metallated at the hydrogen atoms adjacent to a halogen in 2-, 3-, or 4-position. Thus, 4-chloropyridine (214) gives with LDA in THF at -78°C compound 215, which can be quenched by a reactive electrophile like trimethylchlorosilane to give 216 in 92 % yield [269].



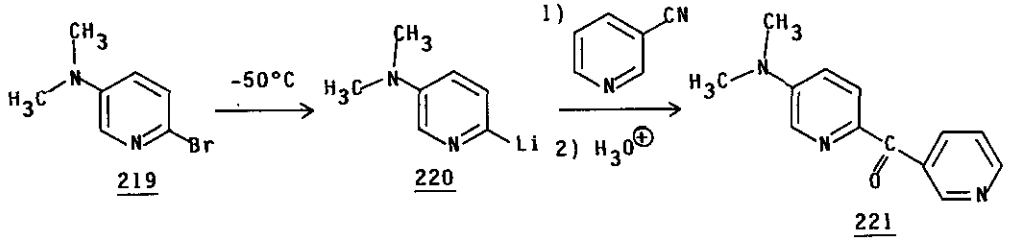
214 215 216

Furthermore, the halogen-metal exchange occurs readily with lithium or Grignard reagents, and 2-, 3-, and 4-pyridyl derivatives can be prepared from the corresponding halopyridines. Thus, 2-bromo-3,4-dimethylpyridine (217) gives, after lithiation and treatment with anisaldehyde, the carbinol (218) in 93 % yield. [270,271]



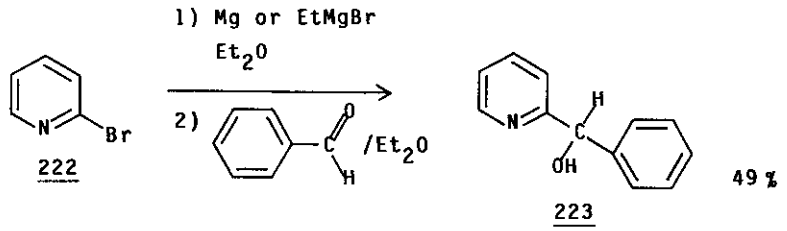
217 218

The lithium derivative (220) of 2-bromo-5-dimethylaminopyridine (219) adds 3-cyanopyridine to yield, after acid hydrolysis, the ketone (221) [272].



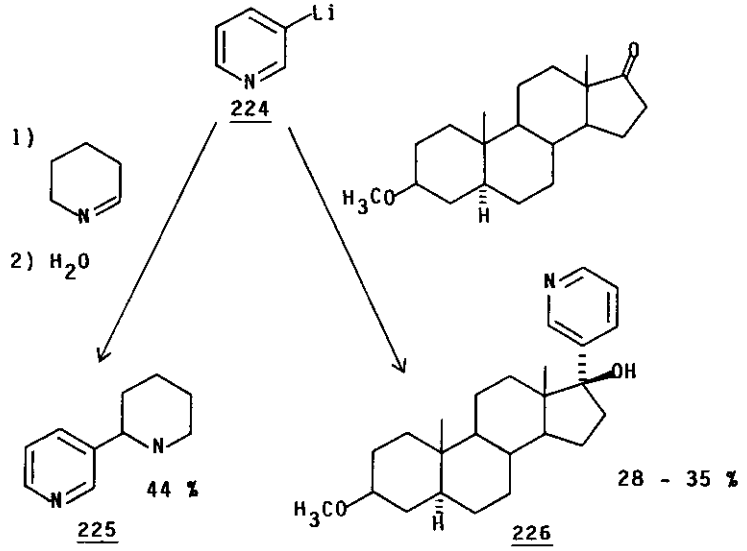
219 220 221

2-Bromopyridine (222) reacts analogously with magnesium or Grignard-reagents [273-275]. Thus, 222 affords with benzaldehyde the product 223 in 49 % yield [273], which is also readily available by the Hammick reaction between picolinic acid and benzaldehyde (cf. 3.6.).



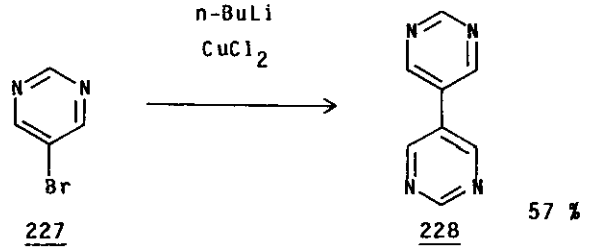
222 223

3-Pyridyllithium (224) derived from 3-bromopyridine was used for the synthesis of dl-anabasine (225) [276] and the preparation of the 17-α-(3-pyridyl) androstane derivative (226) [277].



224 225 226

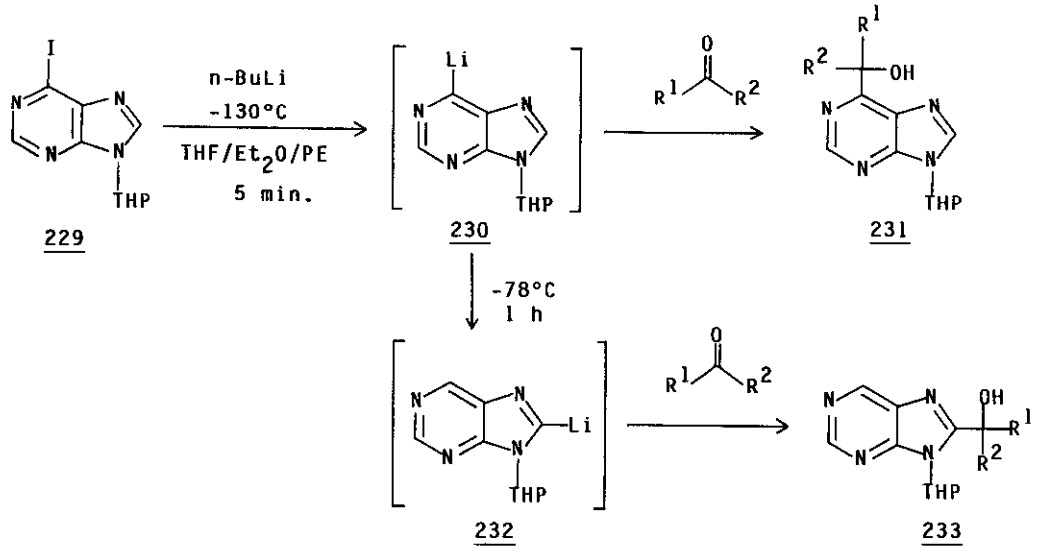
In contrast to the reaction of 4-chloropyridine (214) with LDA to 215, 4-bromopyridine undergoes halogen-metal exchange with butyllithium to give 4-pyridyllithium [278]. Kauffmann et al. [279] reported the preparation of 5,5'-bipyrimidine (228) from 5-bromopyrimidine (227) by a $BuLi/CuCl_2$ coupling reaction in 57 % yield (cf. 3.1.5.).



227 228

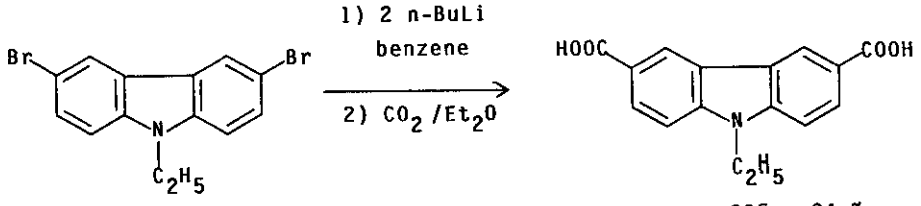
However, in all these metallations complications can arise from the intermediate formation of hetarines [280-282]. For the coupling of a 5-lithiopyrimidine with 2-methoxypyrimidine compare ref. [283]. The reaction of a 5-lithiated protected 2'-desoxyuridine has been described [284].

6-Iodo-9-(tetrahydropyran-2-yl)purine (229) undergoes time and temperature dependent transmetallation reactions with n-butyllithium [285]. A short reaction time and low temperatures favor the formation of the 6-lithio derivative (230), while longer reaction times and higher operating temperatures lead to the 8-lithio isomer(232) as was shown by quenching with various electrophiles to give 231 or 233.



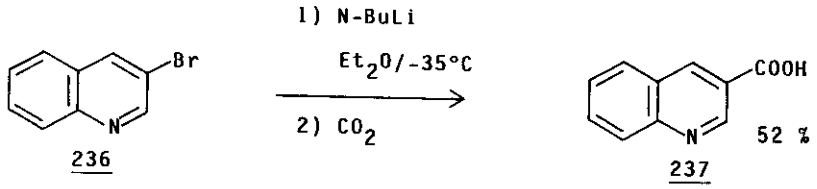
229 230 231 232 233

5-Ethyl-2,8-dibromocarbazole(234) can be converted into the dilithium intermediate which reacts with CO_2 to give the dicarboxylic acid(235) in 84 % yield [286].



234 235 84 %

3-Bromoquinoline (236) gives analogously quinoline-3-carboxylic acid (237) in 52 % yield [286].



236 237

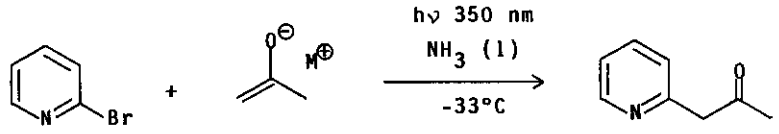
3.1.2. Reactions with Enolates and Activated CH-Active Compounds

In 1970, Bunnett et al. [287,288] introduced the designation "$S_{RN}1$" for radical nucleophilic substitution, which was recently reviewed [289]. $S_{RN}1$ nucleophilic substitutions, which occur with a great number of halogen-containing, non activated, electron-deficient N-heterocycles by the general scheme depicted below [290], were especially investigated by Wolfe and his coworkers [290-292].

$$\text{Het-X} + N^{\ominus} \longrightarrow [\text{Het-X}]\cdot^{\ominus} + N\cdot$$
$$[\text{Het-X}]\cdot^{\ominus} \longrightarrow \text{Het}\cdot + X^{\ominus}$$
$$\text{Het}\cdot + N^{\ominus} \longrightarrow [\text{Het-N}]\cdot^{\ominus}$$
$$[\text{Het-N}]\cdot^{\ominus} + \text{Het-X} \longrightarrow \text{Het-N} + [\text{Het-X}]\cdot^{\ominus}$$

Het means heterocycle; Het-X is an appropriate heteroaromatic substrate; N^- represents a generalized nucleophile capable of initiating the chain process by electron transfer.

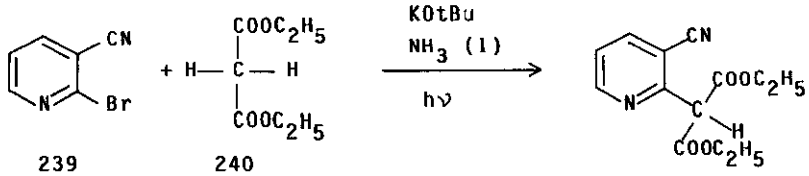
Komin and Wolfe studied the photostimulated reactions of 2-bromopyridine (222) in liquid ammonia with the potassium enolates of several ketones [291]. They clearly established the radical course of the reactions and found reactivity for different enolates of acetone towards 222 to give 238 to be $K^+ > Na^+ > Li^+$ (M^+ means alkali cation) as well as the order of reactivity with potassioacetone to be 2-bromopyridine > 3-bromopyridine > 4-bromopyridine and 2-bromopyridine > 2-chloropyridine > 2-fluoropyridine. For analogous reactions with the potassium enolate of pinacolone compare the references 291-292 and of acetone or cyclohexanone the reference 293.



222 238

$M^{\oplus} = K^{\oplus}$: 95 % 238
$M^{\oplus} = Na^{\oplus}$: 74 % 238
$M^{\oplus} = Li^{\oplus}$: 0 % 238, 58 % 222

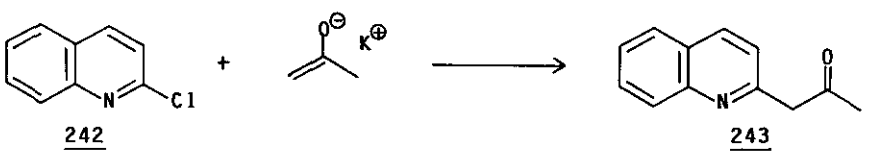
ß-Dicarbonyl compounds like 240 react readily e.g. with 2-bromo-3-cyanopyridine 239 to give nucleophilic displacement products like 241 in high yields [295].



239 240 241 78 %

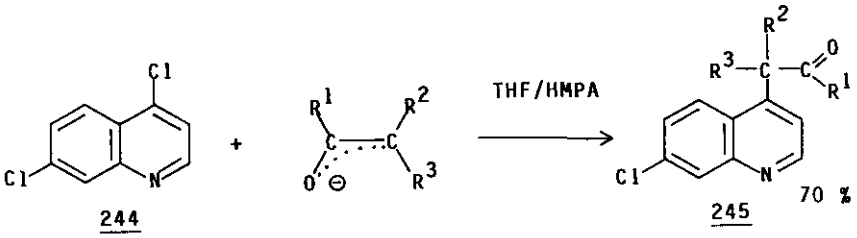
Nucleophilic substitution of the 2-, 3-, and 4-halogen in pyridines with stabilized carbanions derived from 5-butylbarbituric acid [296], benzyl cyanide [297], dibenzyl malonate [298], diethyl methylmalonate [299], diethyl ethylmalonate [300], diethyl acetamidomalonate [301], ethylaceto acetate [302,303], acetylacetonate [302,303] as well as methyl sulfinyl methyl sulfide [304] have been described without investigation of the mechanism of the reaction. Activated halopyridines like 2-chloro-5-nitropyridine [299,301,305], 2-chloro-3-nitropyridine [298], 4-chloro-3-nitropyridine [298,302,303] or diethyl 4-chloro-2,6-pyridinedicarboxylate [300] give the highest yields.

Wolfe and coworkers [306] have analyzed the influence of solvents, light of different wavelength, the presence of radical scavengers, and time on the reaction of 2-chloroquinoline (242) with potassioacetone to give 2-acetonylquinoline (243) and found clearly evidence for an $S_{RN}1$ character. With mixtures of primary and tertiary potassium enolates, 242 shows appreciably preference for combination with tertiary enolates [307]. For further reactions of 242 with enolates compare references 308-310.



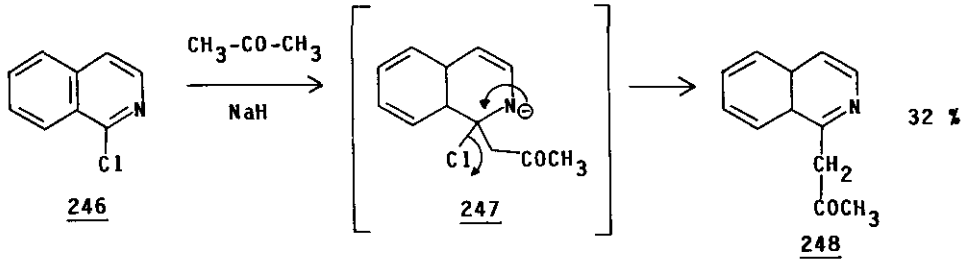
242 243

4,7-Dichloroquinoline (244) reacts with enolizable ketones exclusively in the 4-position [310]. The authors assume a S_NAr type mechanism. Other authors find for the reaction of 244 with potassiopinacolone to give 245 (R^1 = t-Bu; R^2, R^3 = H) clear evidence for an $S_{RN}1$ character [292].



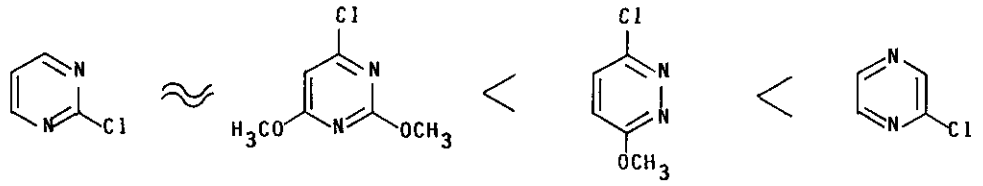
244 245

The reaction of 1-chloroisoquinoline (246) with several enolizable ketones (e.g. acetone) is believed to occur by addition-elimination mechanism via 247 due to the high activation of the 1-position to give 248 [311]; compare also references 312-314.



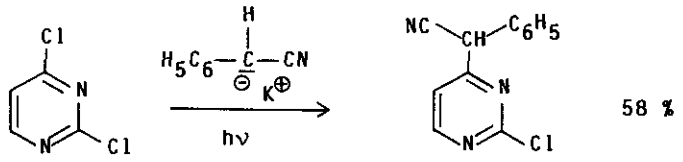
246 247 248

Wolfe's group [315] investigated the reactions of 2-chloropyrimidine (249), 4-chloro-2,6-dimethoxypyrimidine (250), 3-chloro-6-methoxypyridazine (251), and 2-chloropyrazine (252) with representative enolates and found their order of $S_{RN}1$ reactivity to be 252 > 251 > 250 > 249.



249 250 251 252

The 4-position of 2,4-dichloropyrimidine (253) is more reactive than the 2-position as shown below [292].

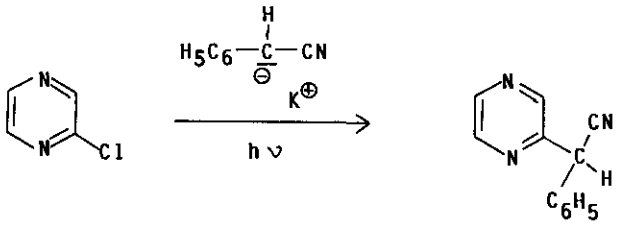


253 254 58 %

For reactions of 5-halogenpyrimidines with enolates compare reference 316, for reaction of a 4-chloropyrimidine with active methylene compounds compare reference 317.

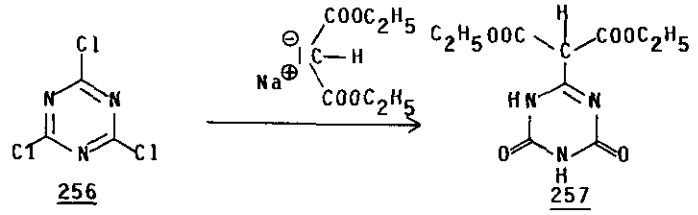
3-Chloropyridazines undergo reactions with enolates [292,315] as well as with the anions of phenylacetonitriles [318].

While reaction of 253 with potassiophenylacetonitrile to yield 254 seems to occur by a dual mechanistic pathway involving both radical-chain and AE reaction [292], the reactions of 2-chloropyrazine (252) with the potassium salts of different enolizable ketones and nitriles give in typical thermal $S_{RN}1$ reaction products like 255. However, the reactions of 2,6-dichloropyrazine and of 2,3-dichloropyrazine with potassiopinakolone to monosubstitution products are classified as mainly addition-elimination (S_nAr) processes [292].



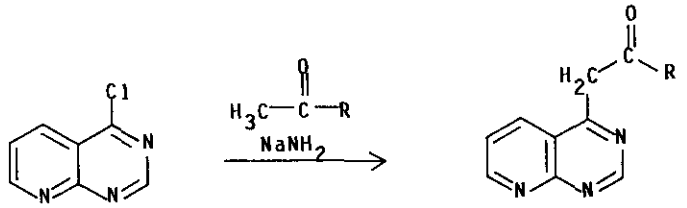
252 255 78 %

Several alkylations of chlorotriazines have been described [319-321]. Typical is the reaction of cyanuric chloride (256) with the sodium salt of diethyl malonate (Kolb 1894) [319] to give the presumable product (257).



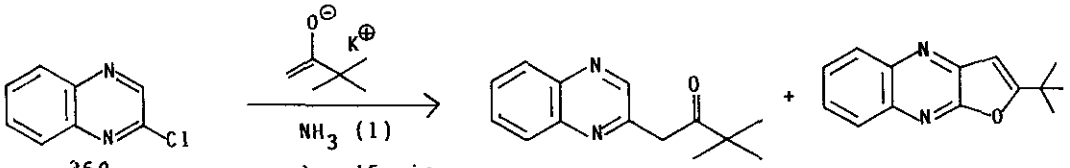
256 257

4-Chloroquinazoline reacts smoothly with active methylene compounds [314] and with enolates [290,322,323] probably via an S_NAr mechanism. 2-Chloroquinazoline shows somewhat lower reactivity towards active methylene compounds than the 4-isomer [314]. As expected, 4-chloropyrido[2,3-d]pyrimidine (258) reacts like 4-chloroquinazoline when treated with the sodium enolates of acetophenone and acetone to afford 259 (R = C_6H_5, 45 %; R = CH_3, 21 %) [324].



258 259

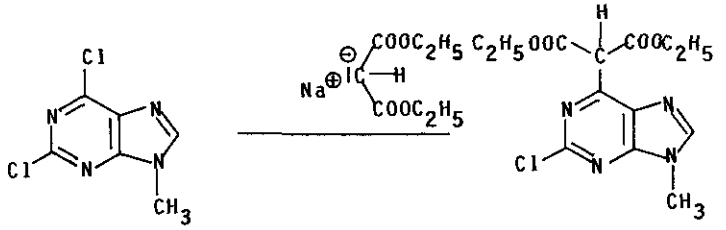
2-Chloroquinoxaline (260) reacts with potassiopinacolone in a dual mechanistic way to give 261 (thermal $S_{RN}1$ product) and 262 as the product of competing addition-substitution processes [290].



260 261 70 % 262 15 %

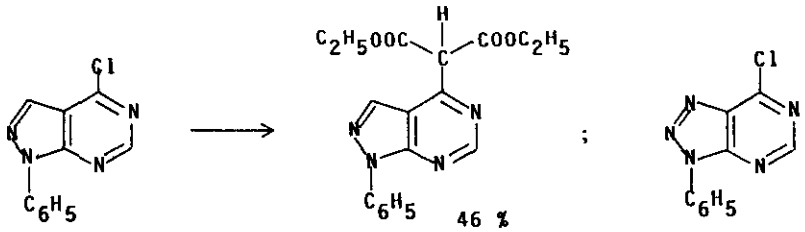
Furthermore, reactions of 2-chloro-3-methylquinoxaline and 4-chloroacridines [325] with active methylene compounds have been described [314].

6-Chloropurines undergo reaction with active methylene compounds [326-330]. 2,6-Dichloro-9-methylpurine (263) reacts with diethyl sodiomalonate exclusively in 6-position to give 264 [331].



263 → 264 76 %

The N-protected 4-chloropyrazolo[3,4-d]pyrimidine (265) reacts comparably [332-334] to afford 266 as does 7-chloro-3-phenyl-3H-1,2,3-triazolo[4,5-d]pyrimidine (267) [335,336].



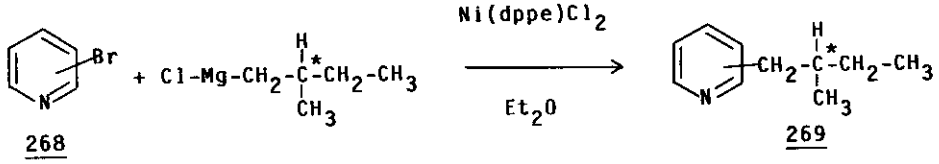
265 → 266 46 % ; 267

Furthermore, the reactions of active methylene compounds with 4-chlorocinnoline, 1-chlorophthalazine, 2-chlorobenzothiazole, 2-bromothiazole, and 2-chlorobenzolepidine have been investigated [314].

3.1.3. Reactions with Grignard Reagents in the Presence of Nickel-Complexes

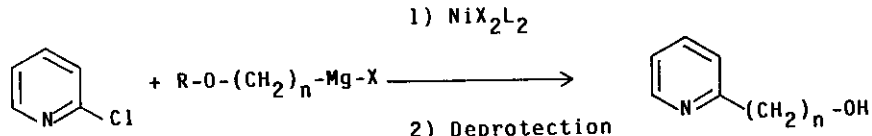
Based on the pioneering work of Kumada [337-339] and Corriu [340], who discovered that olefinic and aromatic halogen compounds react readily with Grignard reagents in the presence of Nickel catalysts, aromatic heterocyclic halogen molecules have been converted in high yields to the corresponding C-substituted heterocycles by reaction with Grignard reagents.

Thus, starting from 2- ,3- or 4-bromopyridine (268), the introduction of a chiral alkyl Grignard reagent into each desired position of the pyridine ring to 269 is achieved in 67 %, 72 % and 53 % yield respectively [341] [$Ni(dppe)Cl_2$ = $Ni(Ph_2$-P-CH_2-CH_2-$PPh_2)Cl_2$].



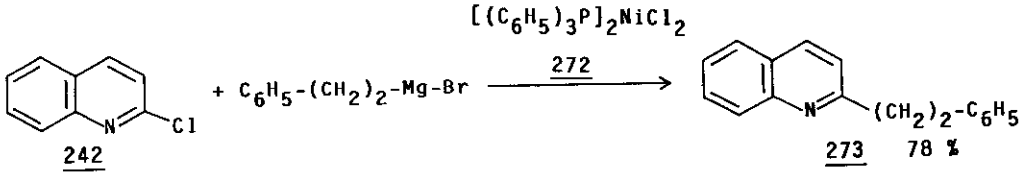
268 269

Starting from 2-chloropyridine (270), Piccolo and Martinengo [342] synthesized a series of (2-pyridyl)alkyl alcohols (271).

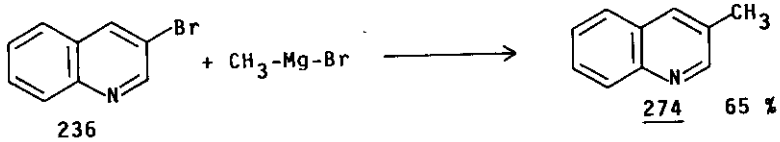


270 271

Analogously, 2-chloroquinoline (242) reacts with different Grignard reagents such as phenylethylmagnesium bromide and dichlorobis(triphenylphosphine)nickel (272) to give the desired product (273) in 78 % yield, whereas 3-bromoquinoline (236) affords with methylmagnesium bromide 3-methylquinoline (274) in 65 % yield [343].

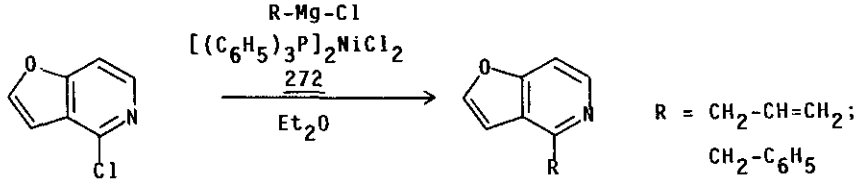


242 273 78 %



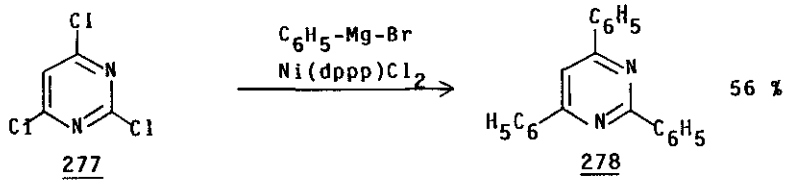
236 274 65 %

4-Chlorofuro[3,2-c]pyridine (275) gives with allylmagnesium chloride or benzylmagnesium chloride [344] in the presence of dichlorobis(triphenylphosphine)nickel (272) the corresponding derivative (276) in 80 % yield.



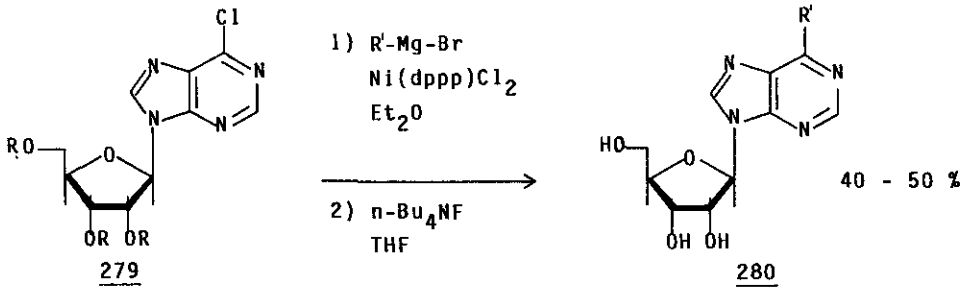
275 276 80 %

2,4,6-Trichloropyrimidine (277) reacts with an excess of phenylmagnesium bromide in the presence of $Ni(dppp)Cl_2$ to give the trisubstituted pyrimidine (278) as the sole product in 56 % yield, whereas methyl or ethyl Grignard reagents furnished the corresponding methyl- or ethylpyrimidines [345,346], compare also reference 347.



277 278

6-Aryl and alkyl substituted purine nucleosides (280) are readily available from 6-chloropurine nucleoside (279) in 40 - 50 % overall yield, after deprotection by this cross- coupling reaction [348].



279 280

R = t-butyldimethylsilyl

2-Halogenbenzothiazoles undergo also efficient C-C cross-coupling with Grignard reagents in the presence of nickel(II)phosphine complexes [349].

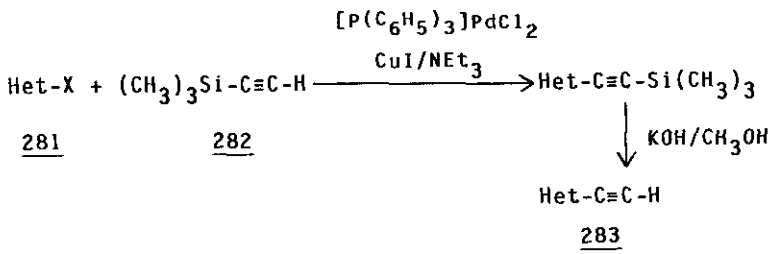
Heteroaromatic thiols and methyl sulfides react analogous to halogens. Examples are described for 2-benzothiazole-, 2-pyridine-, and 2-pyrimidine systems [350].

Instead of Grignard reagents, benzylic zinc reagents have recently been added to 3-bromopyridine in the presence of nickel catalysts [351].

3.1.4. Reactions with Olefins and Acetylenes in the Presence of Palladium Complexes

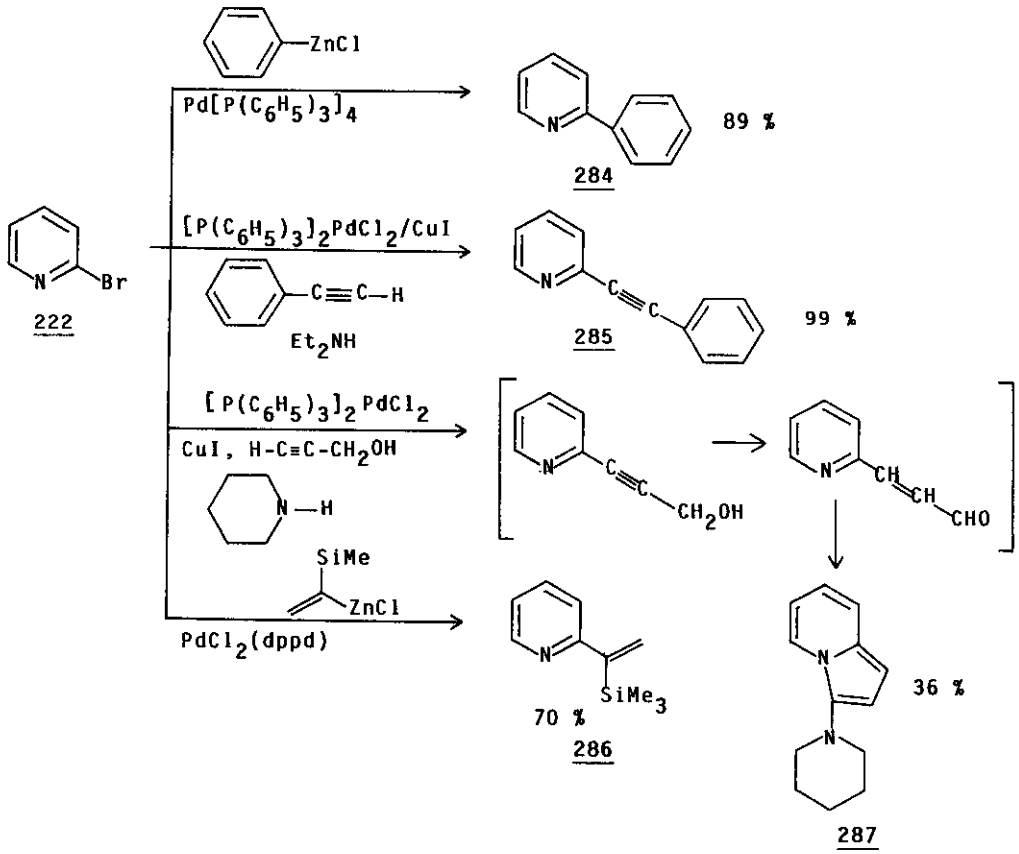
Tsuji [352] and Heck have discovered C-C formation of vinylic- [353] and arylic isocyclic chloromercury [354-355] or halogen [356,357] compounds with unsaturated systems in *presence of stoichiometric amounts* of palladium complexes and reviewed the results of Pd-catalyzed vinylations of organic halides until 1979 [358]. For other general reviews compare references 339,359,360, describing *palladium-catalyzed* synthesis of conjugated systems. Mizoroki et al. discovered that catalytical amounts of palladium compounds are sufficient [361,362].

This methodology has been applied to a variety of nitrogen-heterocycles to afford high yields of substituted heterocyclic compounds. Thus, Yamanaka [363] described a facile synthesis of ethinyl-substituted six-membered N-heteroaromatic compounds (281) like pyridines, quinolines, isoquinolines, pyrazines, pyridazines, and pyrimidines *to their corresponding acetylene* derivatives (283) using the silylated acetylene moiety (282).

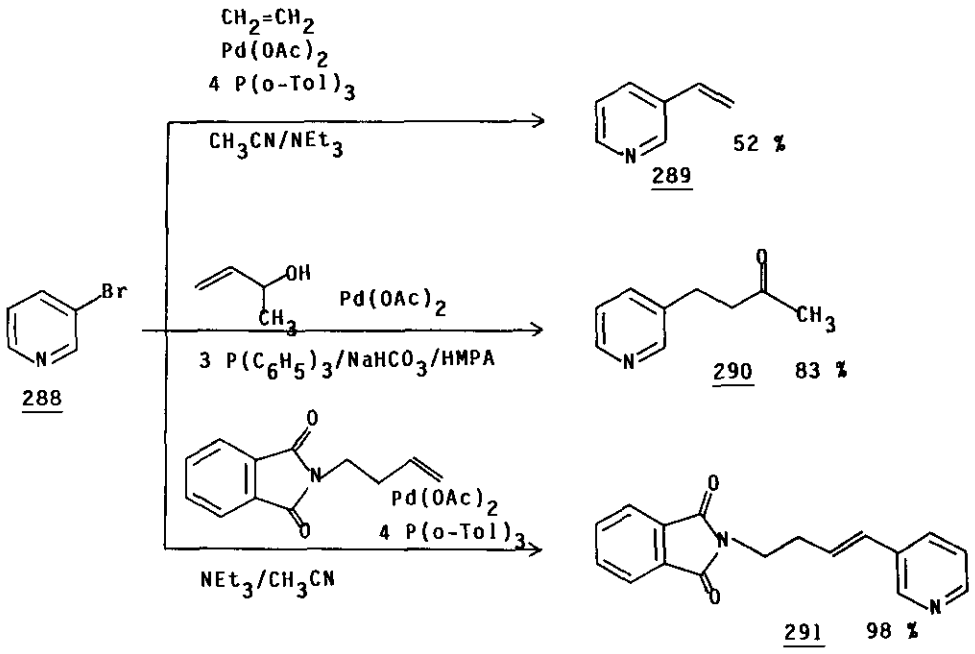


281 282 283

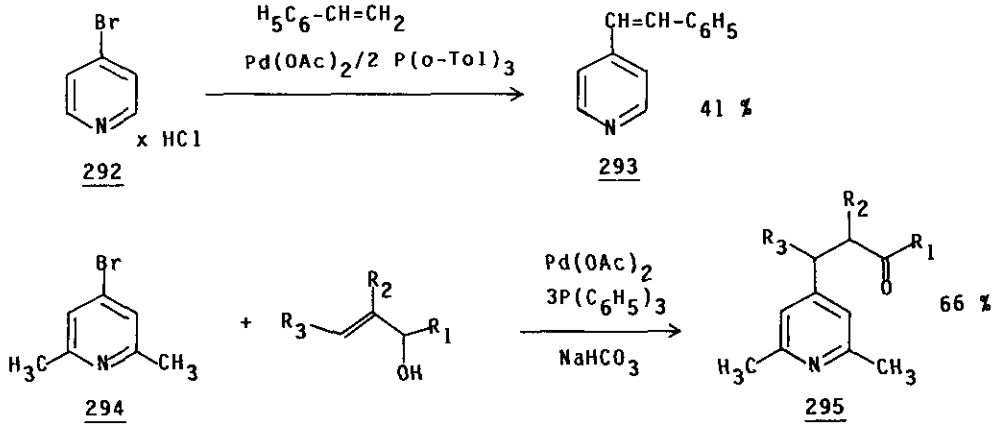
Particularly, the pyridine system has been investigated thoroughly. Using the Pd-complex catalyzed cross-coupling, 2-bromopyridine (222) *is converted into* 2-phenylpyridine (284) [364], 2-phenylethinylpyridine (285) [365], and 2-(α-trimethylsilyl)vinylpyridine (286) [366]. Coupling with propargyl alcohol in the presence of piperidine affords the amino indolizine (287) [367].



3-Bromopyridine (288) gives with ethylene the 3-vinylpyridine (289) [368], with allylic alcohols, for example α-methallyl alcohol compound (290) [369], and with N-3-butenylphthalimide, the corresponding nornicotine precursor (291) [370]. 3-Iodopyridine has reacted with N-allylphthalimide [371].

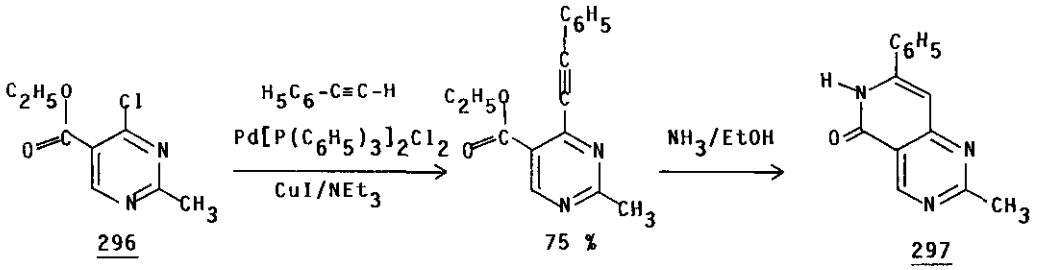


Starting from 4-bromopyridine hydrochloride (292) and styrene the 4-styrylpyridine (293) is obtained [370]. Analogously, 4-bromo-2,6-lutidine (294) reacts with a series of allylic alcohols to give 4-substituted lutidines (295) [372].

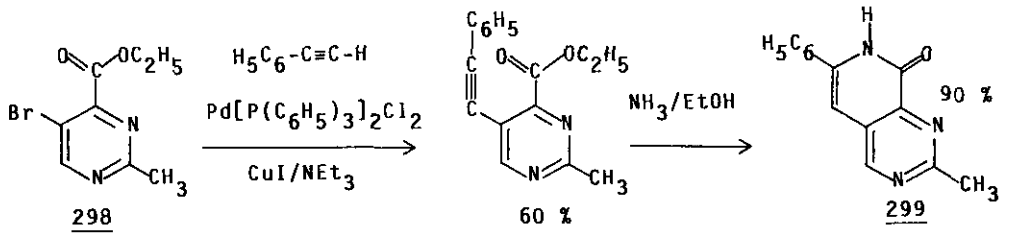


For the preparation of 2,6-diethinylpyridine from 2,6-dibromopyridine in 75 % yield and of 2,5-disubstituted pyridines starting from 2,5-dibromopyridine compare references 373 and 374. The Heck reaction with acetylenes and olefines has been applied to each position of the pyridine moiety in quinoline [375], isoquinoline [375-377], and acridine [375] usually in high yields.

The cross-coupling reaction of halopyrimidines with vinylic esters and acetylenes affords the corresponding 2-, 4-, or 5-substituted pyrimidines [378-383]. Reaction of phenylacetylene with the 4-chloropyrimidine (296) gives an elegant entry to the pyrido[4,3-d]pyrimidine derivative (297), whereas the 5-bromopyrimidine (298) leads to the pyrido[3,4-d]pyrimidine (299) [381].



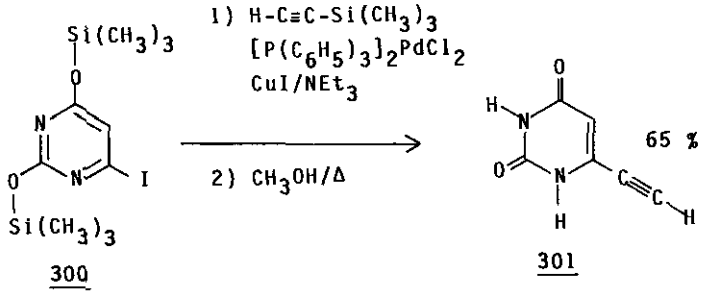
296 → 75 % → 297



298 → 60 % → 299

4-Iodopyrimidines give often as side reaction homocoupling of the starting material [383-385].

Silylated 6-iodouracil (300) affords, after desilylation, the 6-ethinyluracil (301) in 65 % yield [386].



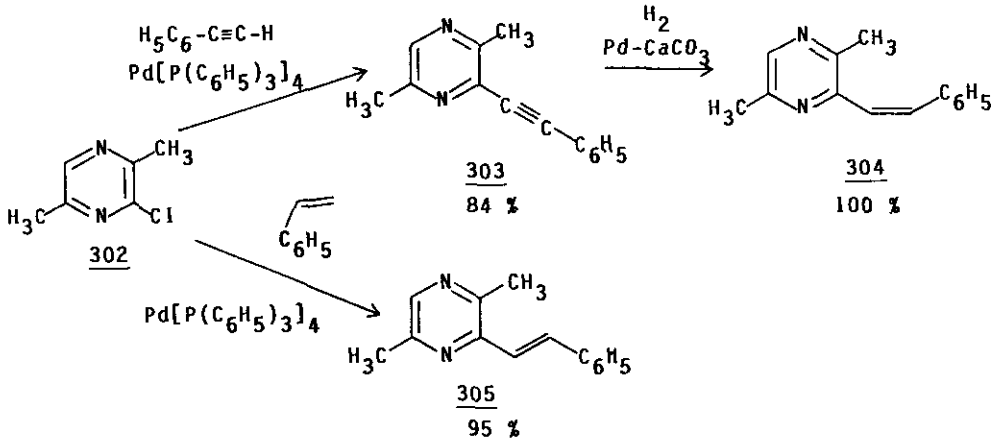
300 → 301

However, silylation may not always be necessary as demonstrated with O- as well as N-methylated 5-iodouracil [387] and 5-iodo pyrimidine nucleosides [388-390].

5-Mercury-substituted uridines react readily with olefines [391-394], styrenes and iodobenzenes [395-397] in the presence of palladium salts.

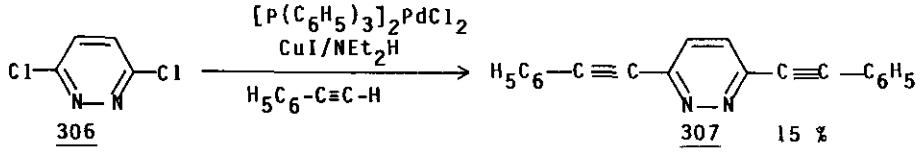
Analogously, alkinylation of 6- and 8-halopurine nucleosides gives the corresponding 6- or 8-substituted nucleosides in high yields [398,399]. For an application to 5-mercuri tubercidin compare reference 400.

A facile synthesis of the natural products Z- and E-2,5-dimethyl-3-styrylpyrazine (304 and 305) can be achieved starting from 302 [401] via 303.

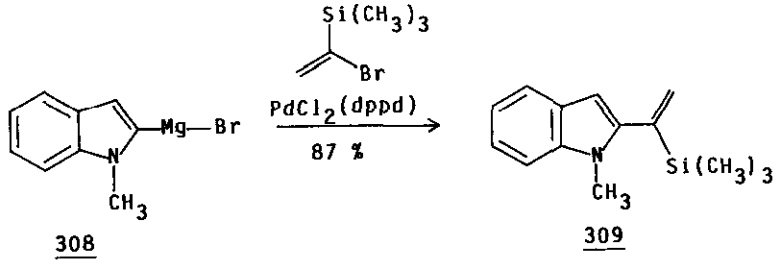


The same authors have introduced cyano groups with KCN in DMF into chloropyrazines using the above described catalyst [402].

Alkinylation of a 5-chloropyrazine as well as a 6-chloropyridazine [403] and 3- and 3,6-halopyrazines [404-405] cf. 306→307 have been described.



Alkenylation of the indole-Grignard-derivative (308) gives readily 309 [366].

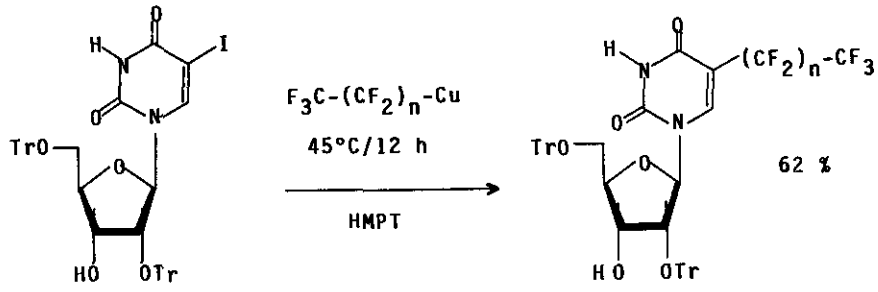


Alkinylation of 5-ring heterocycles, like iodopyrazoles, occurs in high yields [406,407]. 3,5-Disubstituted 4-iodoisoxazoles react both with olefins and acetylenes in the presence of palladium catalysts in good yields, as does 3-phenyl-5-*bromoisoxazole with acetylenes* [406].

However, even in the presence of olefins, homocoupling of the heterocyclic aryl halides can become the predominant reaction as seen in the case of 3-methyl-bromoisothiazole [406]. Homocoupling seems to be general at positions where the π-electron density is reduced by the ring nitrogen (*compare also references* 383, 384).

3.1.5. Reactions with Copper Metal (Ullmann-Type)

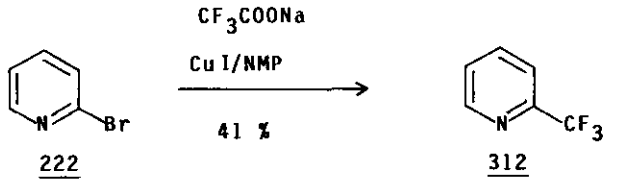
Several authors have developed convenient methods for the introduction of trifluoromethyl groups into heteroaromatic halides. Thus, Kobayashi and coworkers [408] modified their original method of trifluormethylation using a filtered CF_3-Cu solution in HMPT. Thus, 5-iodouridine (310) gives the corresponding trifluormethyl derivative (311) (n = 0) in 62 % yield. Acetylated 6- or 8-halopurine nucleosides furnish the corresponding trifluormethyl analogues.



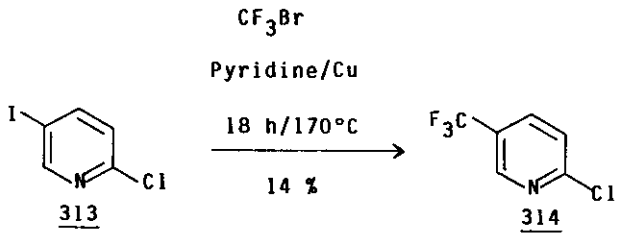
310 311

Perfluorated alkyl iodides (n = 2,4) furnish analogously the higher substituted homologues [409].

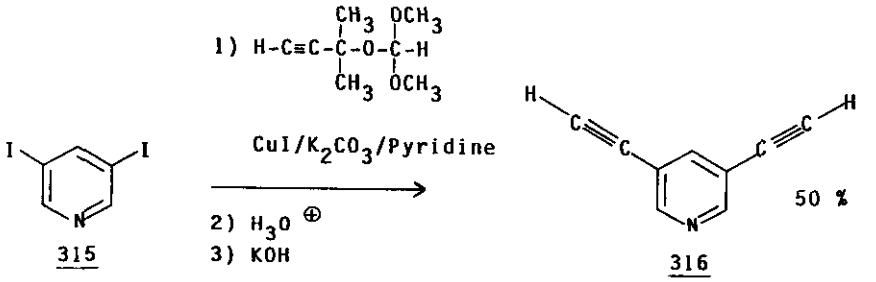
On heating of 2-bromopyridine (222) with sodium trifluoroacetate and copper(I) iodide in N-methylpyrrolidone (NMP), 2-trifluoromethylpyridine (312) is obtained in 41 % yield [410].



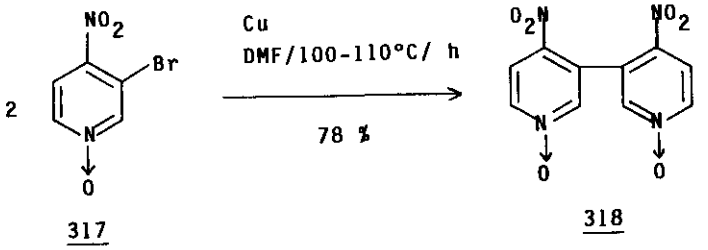
Analogously, 2-chloro-5-iodopyridine (313) affords 2-chloro-5-trifluoromethylpyridine 314 [411].



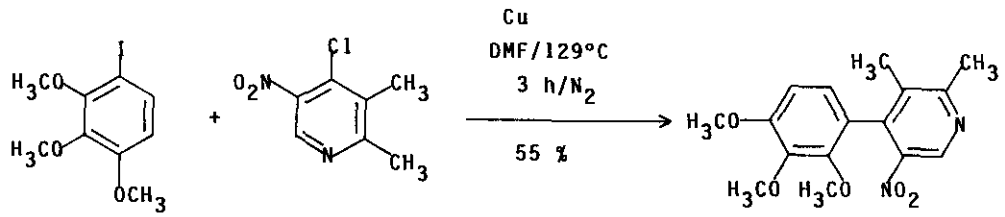
CuI-catalyzed ethinylation of ∝- or ß-iodopyridine results in ∝- or ß-ethinylation. ß,ß-Diiodopyridine (315) afforded compound 316 in 50 % overall yield [412].



However, more reactive halides like 3-bromo-4-nitropyridine N-oxide (317) undergo an Ullmann reaction to the corresponding dimer (318) in high yield [413].



Coupling of 4-iodo-1,2,3-trimethoxybenzene (319) as the active aryl halide with the pyridine (320) furnishes 321 in 55 % yield [414].

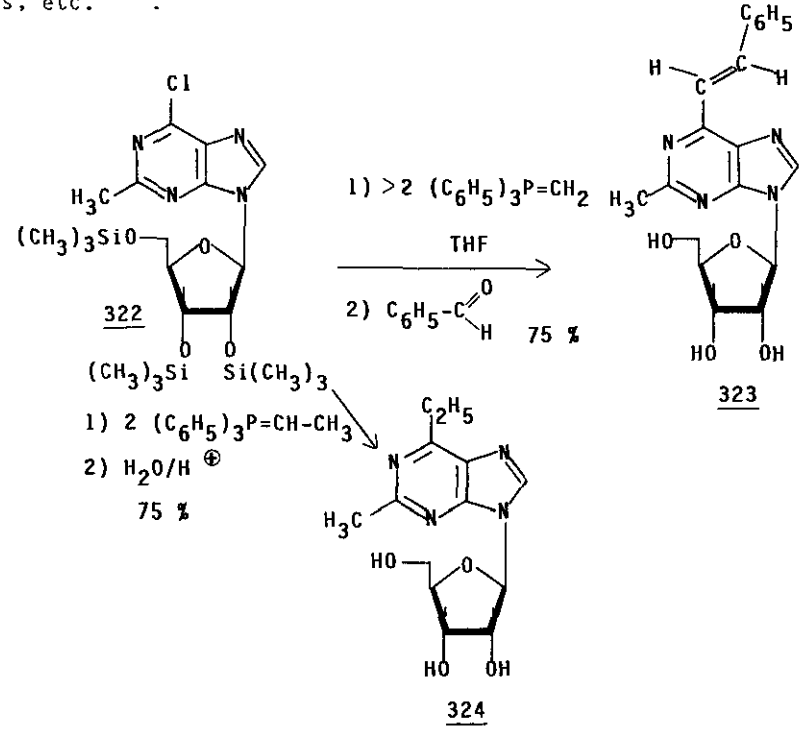


319 320 321

The copper-catalyzed displacement of an iodo group by acetylenic groups has also been described for N-methylimidazoles [415].

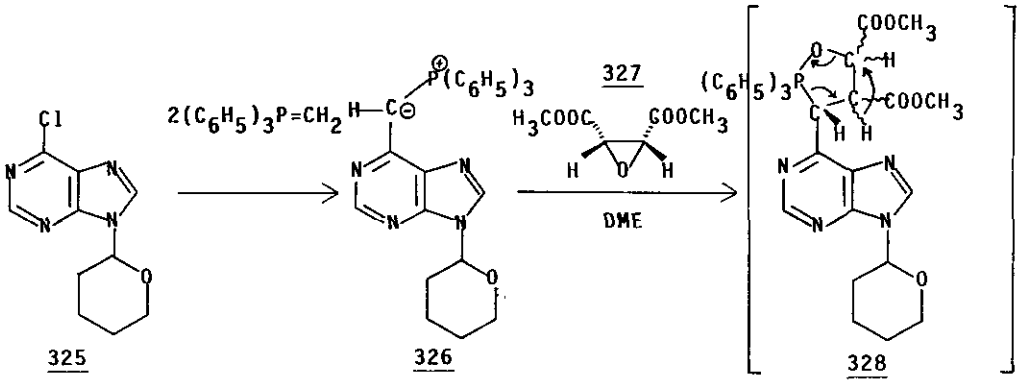
3.1.6. Reactions with Wittig Reagents

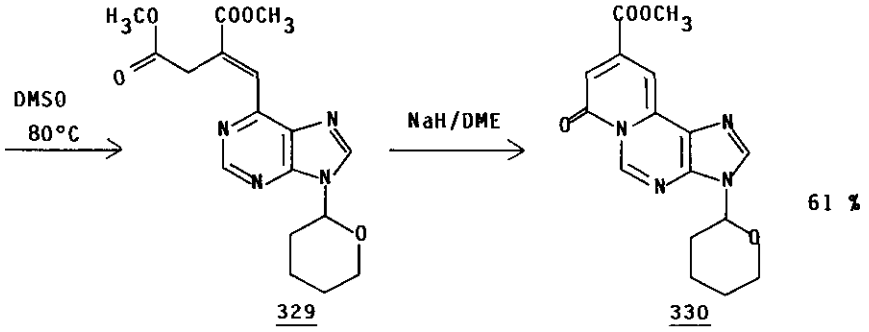
Taylor and Martin [416-418] described a new procedure and gave several examples for the direct displacement of suitable leaving groups (Cl, Br, SO_2CH_3 etc.) by an alkylidenephosphorane (Wittig reagent). The resulting intermediate is converted either by reaction with a carbonyl compound into an alkenyl derivative of the heterocycle or by hydrolysis into an alkyl derivative of the heterocycle. The silylated purine nucleoside (322) gives thus the olefin (323) or the ethyl compound (324) [419]. The method works for halo-pyridines, -pyrazines, -quinolines, or isoquinolines, etc. [418].



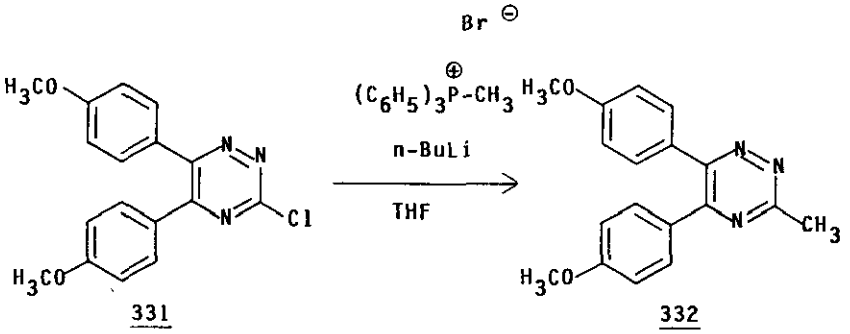
322 323 324

Treatment of the N-protected 6-chloropurine (325) with two equivalents of methylenetriphenylphosphorane at -30°C affords the corresponding purinyl ylid (326) which reacts with cis-dimethyl epoxysuccinate (327) to give via the oxaphospholane derivative (328) and, after ring opening, 329. Treatment of 329 with base furnishes the tricyclus (330) [420].





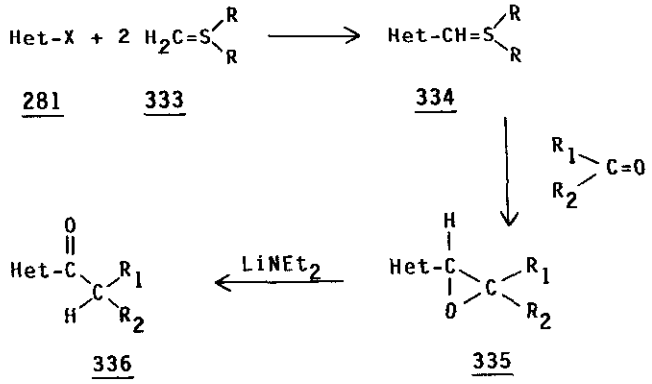
Analogously, the chlorotriazine (331) reacts with methyltriphenylphosphonium bromide and n-BuLi in THF to give the methylated triazine derivative (332) [421].



The transilylation reaction of methyl(triphenylphosphoranylidine)acetate with a 2-chlorocyclohepta[b]pyrrole derivative is described [422].

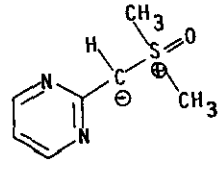
3.1.7. Reactions with Sulfur Ylides

A general procedure for the synthesis of epoxy substituted heterocycles (335) was introduced by Taylor and coworkers [423]. Treatment of a heterocycle (281) possessing an appropiate leaving group with two equivalents of a sulfonium ylide (333) generates a new ylid (334) which, when treated in situ with a carbonyl compound R_1COR_2, affords an epoxide (335) in yields ranging from 17 to 70 %. Rearrangement with lithium diethylamide furnishes the acylated heterocycles (336).



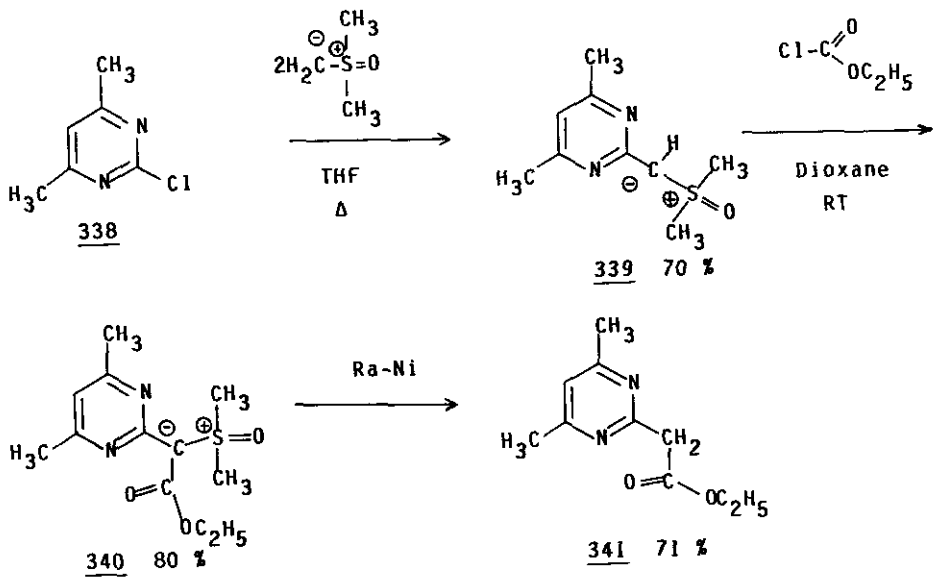
281 333 334 335 336

Oxosulfonium ylides are often considerably more stable than the corresponding sulfonium ylides. Thus, dimethyloxosulfonium pyrimidine-2-yl methylide (337) is a crystalline, at room temperature air-stable compound [424].



337

Yet oxosulfonium ylides retain still a high degree of nucleophilic character. Thus, the 2- respectively 4-chloro compounds (338 and 342) react with two equivalents of the ylid in boiling THF to give 339 resp. 343, which afford, on acylation at room temperature, the products 340 and 344. Desulfurization of these products is accomplished with deactivated Raney nickel to furnish the desired compounds 341 and 345 in high yields [425,426].



338

339 70 %

340 80 %

341 71 %

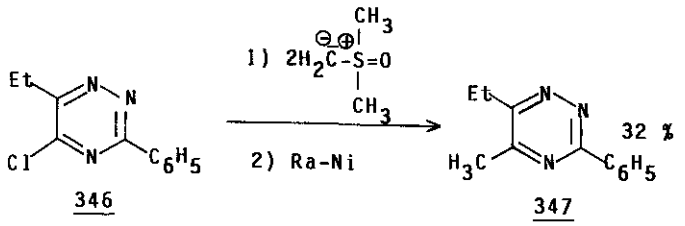
342

343 97 %

344 88 %

345 88 %

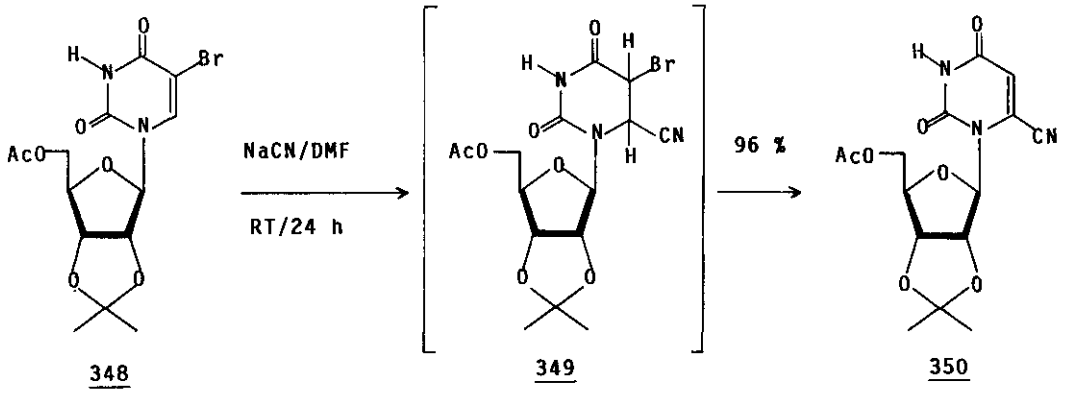
The 5-chloro-1,2,4-triazine(346) can be methylated to 347 in overall yield of 32 % [427].



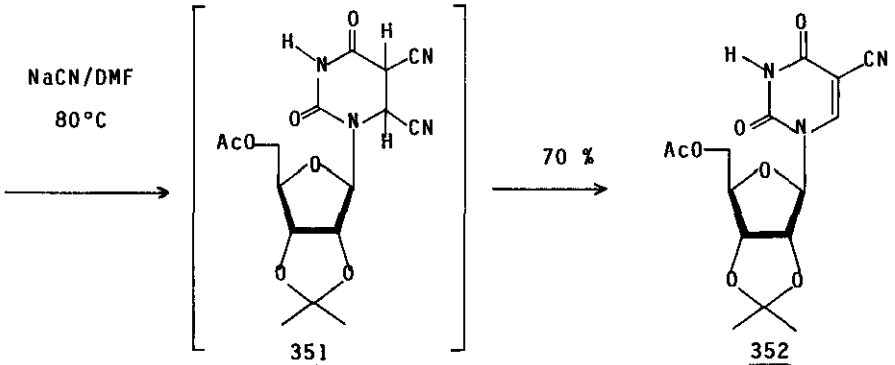
346 347

3.1.8. Reactions with Cyanides

Treatment of the 5-bromouridine derivative (348) with sodium cyanide in dimethylformamide at room temperature for 24 h leads via 349 to the 6-cyanouridine (350) in 96 % yield. Heating 350 in the same solvent at 80°C for 6 h with one equivalent of NaCN results in the formation of 5-cyanouridine (352) in 70 % yield. This apparent migration of the cyano group can be rationalized by the addition-elimination mechanism through the 5,6-dicyano-5,6-dihydro intermediate (351) [428,429] (compare also reference 430).

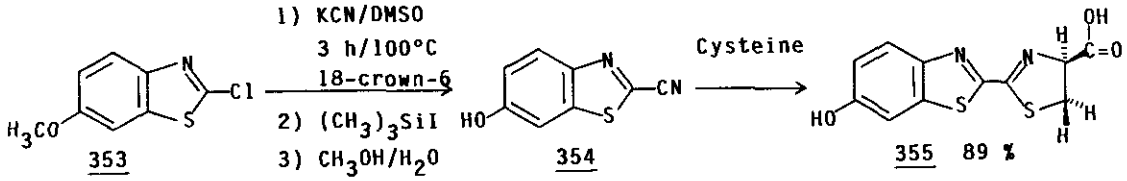


348 349 350

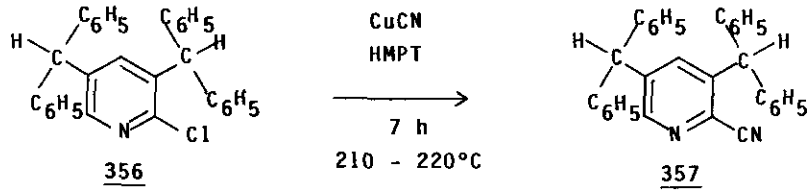


351 352

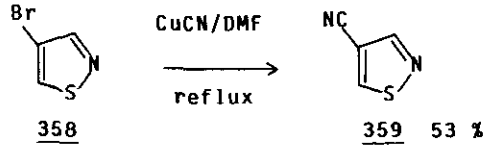
This substitution of the 5-bromouracil moiety to give the 6-cyano derivative proceeds under such mild conditions to be carried out with nucleotides without effecting the 3,5-phosphoester linkage [431]. The 2-chloro-6-methoxybenzothiazole (353) gives readily 354, which is converted by cysteine into luciferine (355) [432].



2-Chloropyridines like 356 reacts with CuCN in hot HMPT to afford 357 [433].



After treating 4-bromoisothiazole (358) with CuCN in refluxing dimethylformamide, 53 % of 4-cyanoisothiazole (359) can be isolated [434]. For further examples in the isothiazole series compare reference 435.

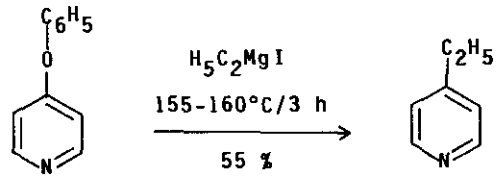


1-Benzyl-4-cyanopyrazole can be prepared from 1-benzyl-4-bromopyrazole (60 - 76 %) [436].

3.2. Replacement of O-Alkyl, O-Aryl, O-Acetyl and O-Sulfonate Groups

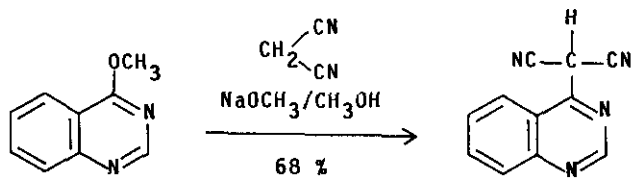
Mixing ether solutions of 4-alkoxy- or 4-phenoxypyridine with ethyl- or phenylmagnesium bromide at room temperature gives an insoluble amorphous precipitate of the formula $(4\text{-RO-Py})_2MgBr_2$, for which a tetrahedral structure is proposed based on its IR and ^{1}H-NMR data [437]. Heating of 4-phenoxypyridine (360) with ethylmagnesium iodide at 155-160°C for 3 h furnishes 4-ethylpyridine (102) in

55 % yield [438].



360 102

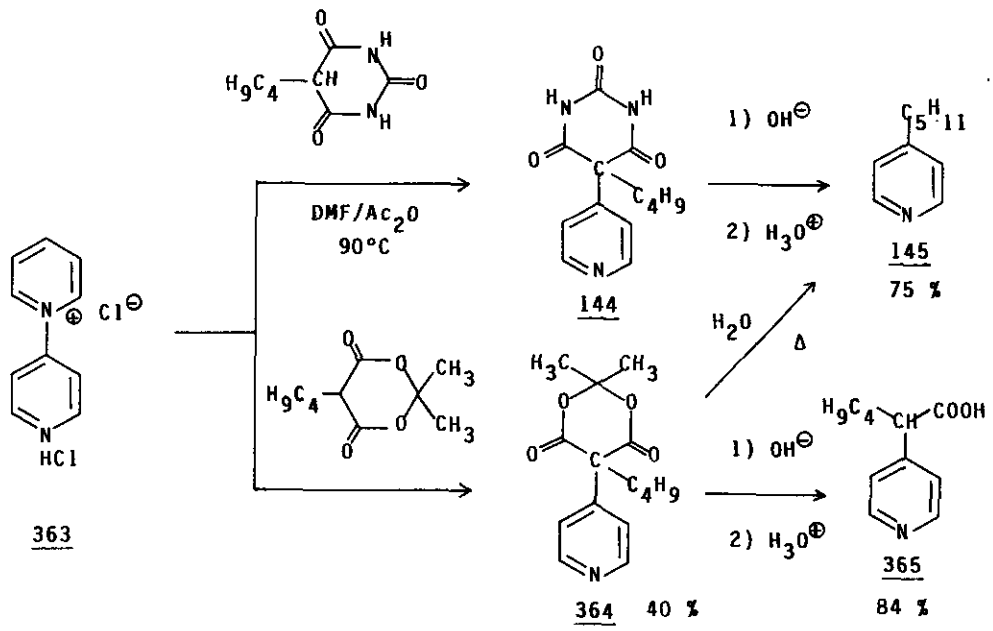
Various γ-alkyl and γ-cycloalkyl substituted pyridines can be obtained under analogous conditions. The alkylmagnesium iodides are prefered, since the bromides and especially the chlorides give considerable amounts of N-containing resins [438]. The nucleophilic displacement of the 4-methoxyl group of the quinazoline (361) by C-H acid compounds as malononitrile, for example to 362, proceeds in the presence of sodium methoxide as a base [439].



361 362

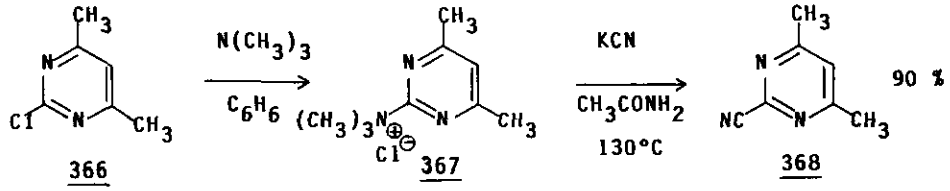
3.3. Replacement of Quaternary Ammonium Groups

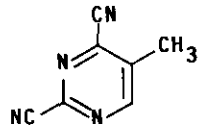
4-Pyridylpyridinium chloride (363), which is readily accessable from pyridine and $SOCl_2$ [440], reacts like 4-pyridone (135 bzw. 143) (cf. chapter 2.5.) with 5-butylbarbituric acid or isopropylidene-butyl malonate in acetic anhydride-N,N-dimethylformamide to give the corresponding 5-butyl-5-(4-pyridyl)barbituric acid (144) or the 4-(isopropylidene-butyl-malonyl)pyridine (364) in 40 - 84 % yield [441]. Both 144 and 364 can be readily saponified in 40 - 85 % yield to the corresponding pure 4-n-pentylpyridine (145) or to the corresponding carboxylic acids (365).



Since this reaction proceeds probably via an addition-elimination reaction at the 4-position of 363, 4-chloro- or 4-bromopyridine react analogously [441] to give, after saponification and decarboxylation, the corresponding 4-alkylpyridine (cf. also chapter 3.1.2.).

Since chloropyrimidines do not react with KCN in ethanol or CuCN in quinoline, 2-chloro-4,6-dimethylpyrimidine (366) can be converted by trimethylamine in benzene to 4,6-dimethylpyrimidine-2-yl-trimethylammonium chloride (367), which reacts smoothly with KCN in acetamide to 2-cyano-4,6-dimethylpyridine (368) [442]. 2,4-Dichloro-5-methylpyrimidine (369) reacts analogously via the bis quaternary salt to 2,4-dicyano-5-methylpyrimidine (369) [443]. Quaternary ammonium salts of quinazolines and quinoxalines can be converted into the corresponding cyano compounds using tetraethylammonium cyanide in methylene chloride [444].



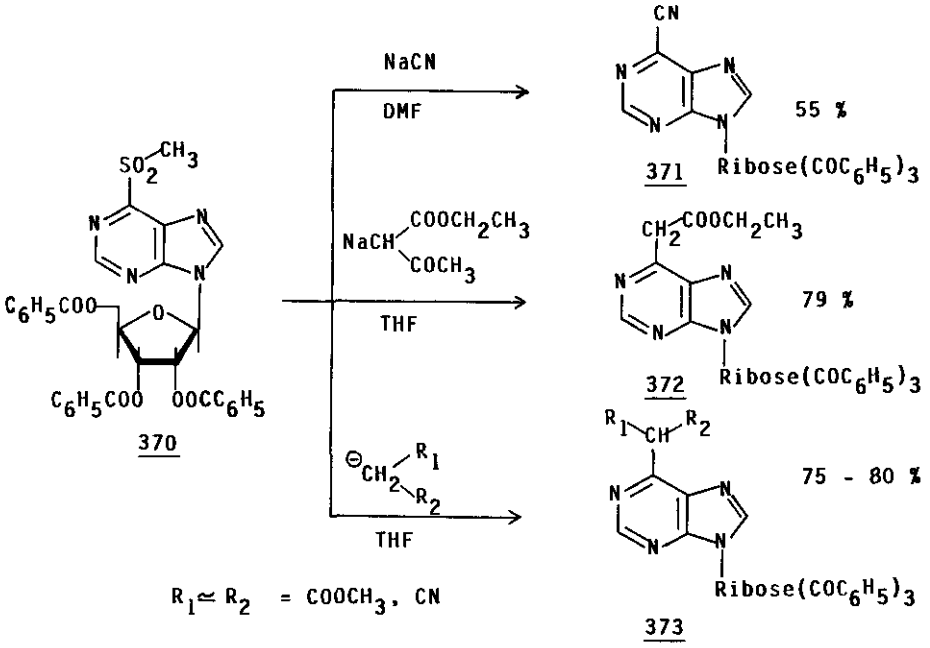


369 33 %

3.4. Replacement of Sulfones

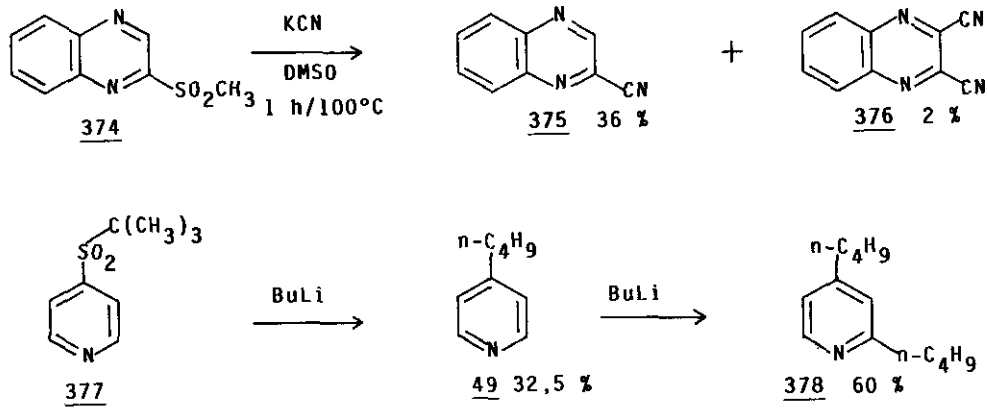
Heterocyclic methylmercapto groups are readily oxidized to the corresponding methylsulfonyl groups which can be displaced by nucleophiles.

Thus, the 2-, 6- as well as 8-methylsulfonyl groups in 9-substituted purines or protected purine-nucleosides can be reacted with sodium cyanide in DMF to afford the corresponding cyano compounds in 55 - 100 % yield [445,446,447]. The protected 6-methylsulfonylnebularine (370) affords with various nucleophiles like sodium cyanide ethyl sodioacetoacetate, ethyl sodiomalonate and sodiomalonitrile in THF the corresponding derivatives (371, 372 and 373) in good yields. The acetic ester side chain in 372 can be alkylated and subsequently decarboxylated to give the corresponding 6-alkylnebularines [445,446]. For additional reactions of 6-methylsulfonylpurines compare references 416-418.



Protected pyrrolo- or pyrazolopyrimidine nucleosides with a methylsulfonyl group permit analogously the introduction of cyanide groups [448].

Furthermore, 2-methylsulfonylquinoxaline (374) reacts with potassium cyanide in DMSO to give, besides the 2-cyano derivative (375), also the 2,3-dicyano compound (376) [449].



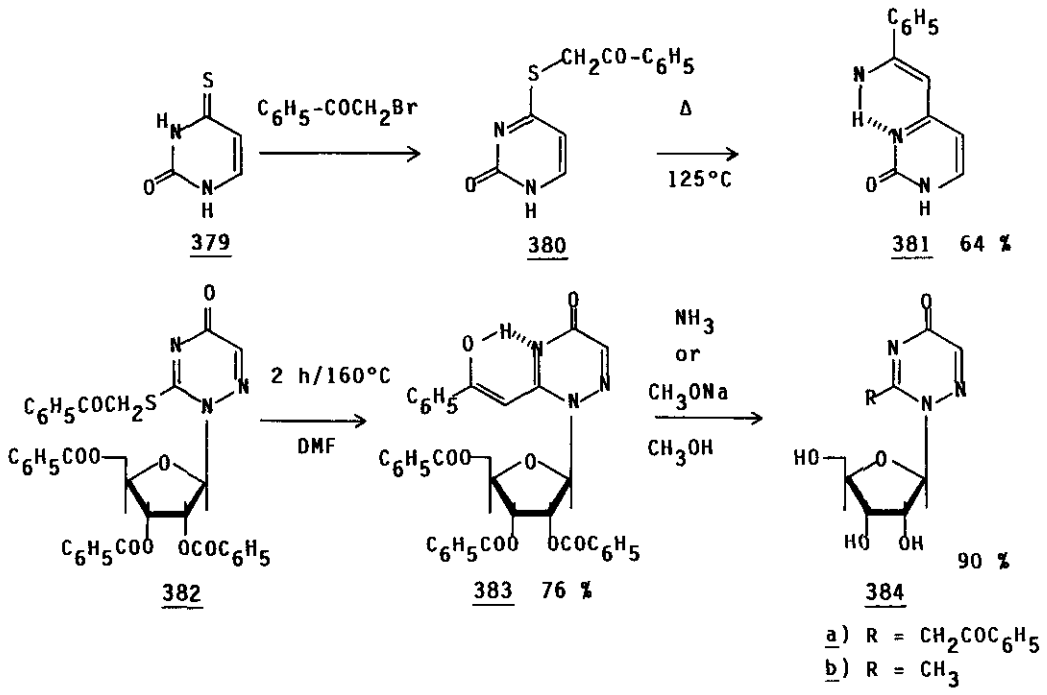
4-t-Butylsulfonylpyridine (377) is converted by equimolar amounts of butyllithium to 4-butylpyridine (49). Excess butyllithium however furnishes in ca. 60 % yield the bis-adduct (378) [450] (cf. chapter 2.2.2.).

Similar replacements by cyanide or active methylene groups of methylsulfonyl or tosyl groups in pyrazines [451] and 1,2,4-triazines [452] have been reported. It should be mentioned here that 2-chloropyridines can be converted into 2-cyanopyridines in 35 - 60 % yields via the corresponding sodium 2-pyridinesulfonates, obtained by heating with Na_2SO_3 in H_2O in an autoclave to 150-210°C [453].

3.5. Sulfide Contractions of S-Alkylated Groups

Since heterocycles containing thiocarbonyl groups or mercapto groups in α- or γ-position to the heterocyclic nitrogen atoms are often easily accessable, the replacement of such sulfur-functions by C-substituents is an interesting preparative pathway.This can be achieved by sulfide contractions of mercapto-N-heterocycles, a reaction whose general applicability was recognized by Eschenmoser [454].

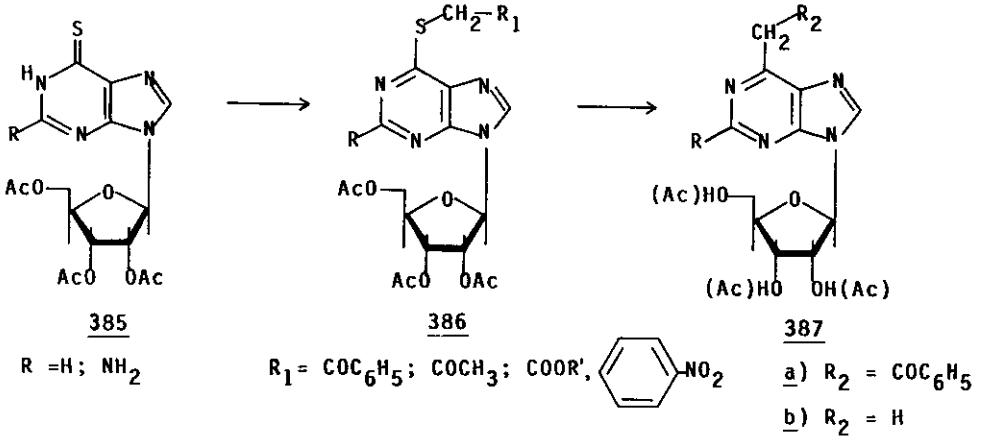
Especially interesting is an early experiment by Roth [455]. Recrystallization from methylglycol of the S-phenacyl derivative (380), which is readily accessable from 4-thiouracil (379) and phenacyl bromide, leads via an episulfide intermediate and sulfur-extrusion to the 4-phenacylpyrimidin-2-one (381) in 64 % yield.



The sulfide contraction turned out to be especially useful for the conversion of protected S-phenacyl-2-thio-6-azauridine (382) into the corresponding 2-phenacyl derivative (383). Saponification with methanolic ammonia affords the free nucleoside (384) in 90 % yield. However, heating of 383 with sodium methylate or DBU in methanol causes retro-aldol cleavage to give the interesting 2-methyl derivative (384b), a compound difficult to prepare by other routes [456].

Protected 4-thiouridine affords analogously the S-phenacyl derivative which extrudes sulfur to give the corresponding 4-phenacyl nucleoside, which can be converted to the 4-methyl derivatives by retro-aldol cleavage.

6-Thiopurines or 6-thiopurine nucleosides (385) can be readily S-alkylated by α-haloketones, α-halo esters as well as p-nitrobenzyl chloride to the corresponding S-alkylated derivatives (386), which undergo the sulfide contraction in the presence of base and triphenylphosphine (as sulfur acceptor) to furnish the corresponding 6-phenacyl-, 6-acetonyl-, 6-ester-, and 6-p-nitrobenzyl derivatives in high yields. Heating of the 6-phenacyl derivative like 387a with sodium methoxide or DBU in abs. methanol causes again retro-aldol cleavage to the corresponding 6-methylpurines or purine nucleosides (387b) (R_2 = H) [456,457].



385

R =H; NH_2

386

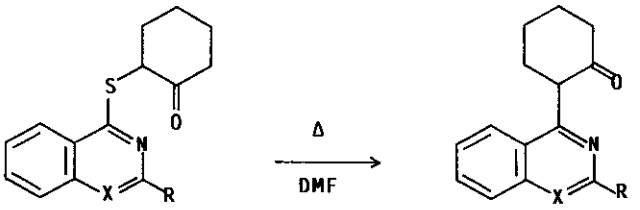
R_1= COC_6H_5; $COCH_3$; COOR',

387

a) R_2 = COC_6H_5

b) R_2 = H

1-Mercaptoisoquinoline as well as 4-mercaptoquinazoline are easily alkylated by 2-chlorocyclohexanone to 388a and 388b, which eliminate sulfur on heating in DMF to the corresponding cyclohexanone derivatives (389a and 389b) [458]. Other S-alkylated derivatives of 4-mercaptoquinazoline react analogously on heating especially in the presence of base [459,460]. The sulfide contraction of compounds like 388b can also be effected by treatment with sulfuric acid [461,462].



388 389

a) X = CH

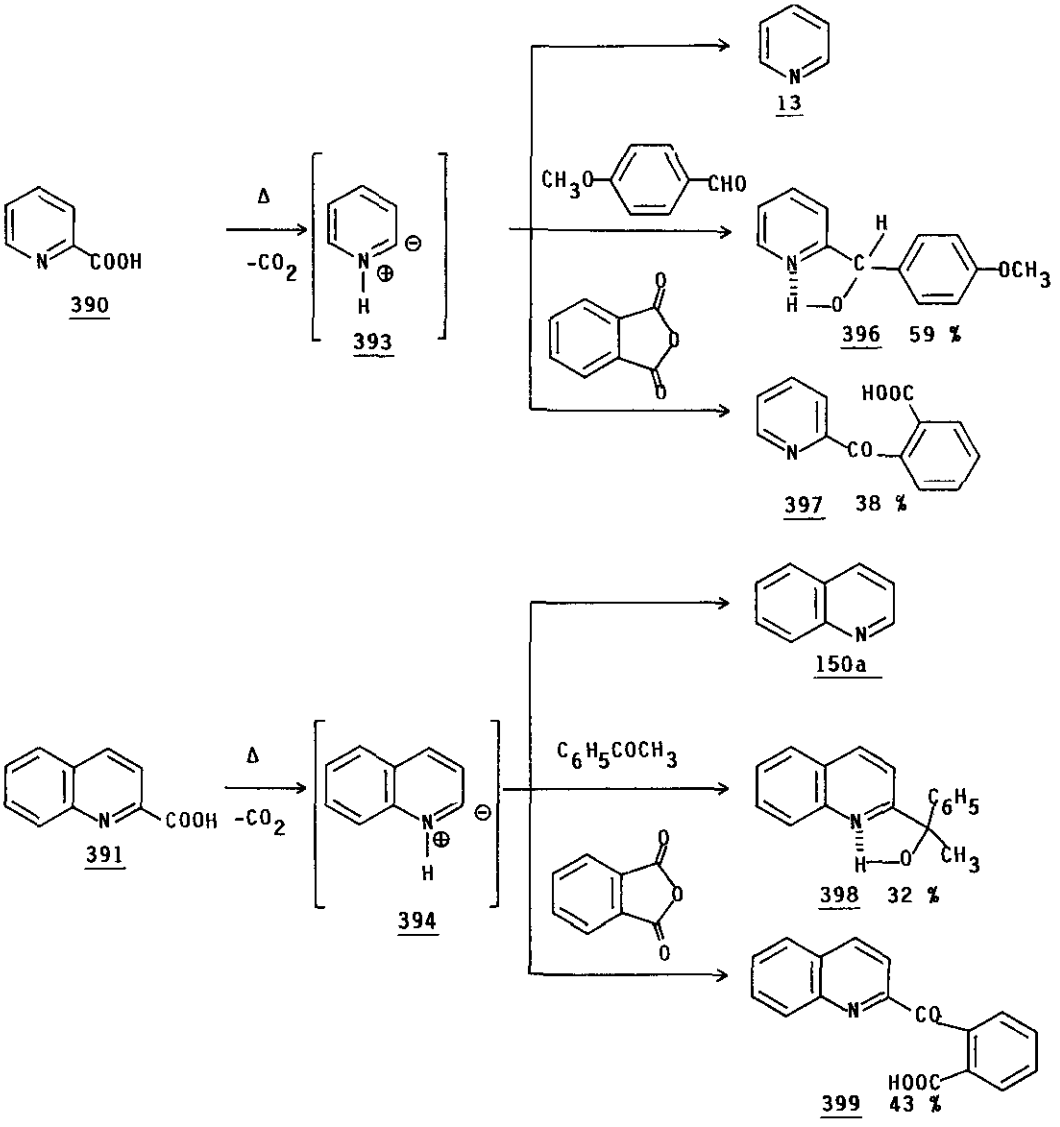
b) X = N

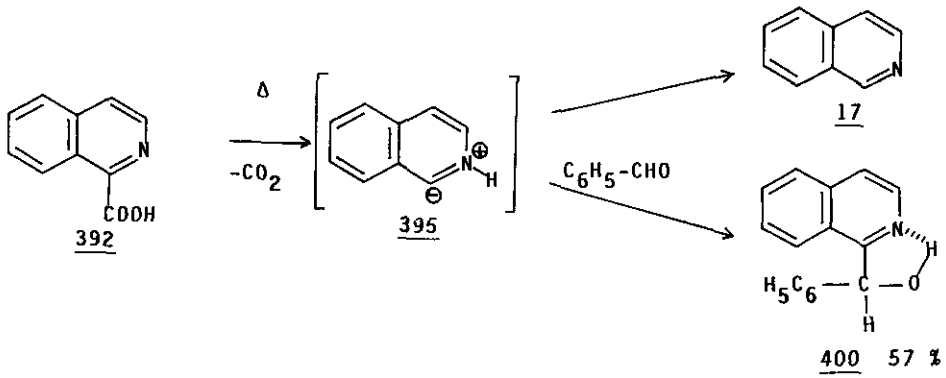
R = H; C_6H_5

Reaction of 3-aminoquinoxaline-2-thione with phenacyl halides results in sulfidecontraction to give 3-amino-2-phenacylquinoxalines [463].

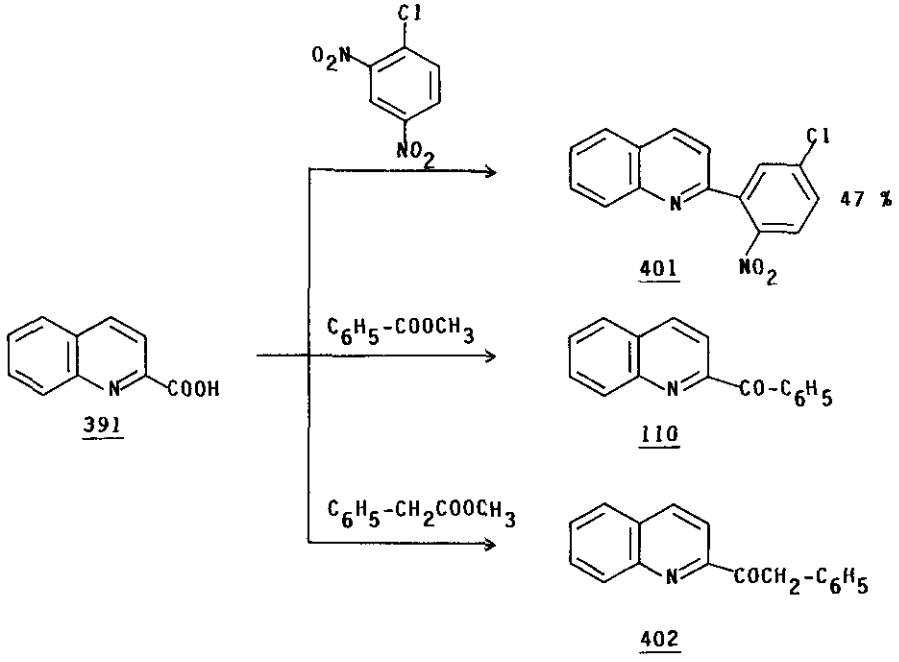
3.6. Replacement of Carboxyl Groups (Hammick-Reaction)

On heating heterocyclic bases containing carboxyl groups α to the heterocyclic nitrogen as picolinic acid (390), quinaldinic acid (391), or isoquinaldinic acid (392) with aldehydes [464-470], ketones [465,467-469,472], esters [472] or acid anhydrides [473] to temperatures between 140-180°C, the carboxylic acids are decarboxylated via their zwitter ions [466,474] to the postulated intermediates (393, 394 and 395), which can either rearrange to the parent heterocycles pyridine (13), quinoline (150a), or isoquinoline (17) or add to the carbonyl groups of the aliphatic or aromatic aldehydes, ketones, or acid anhydrides to furnish adducts like (396 - 400) in ca. 30 - 60 % yield based on the heterocyclic carboxylic acid.





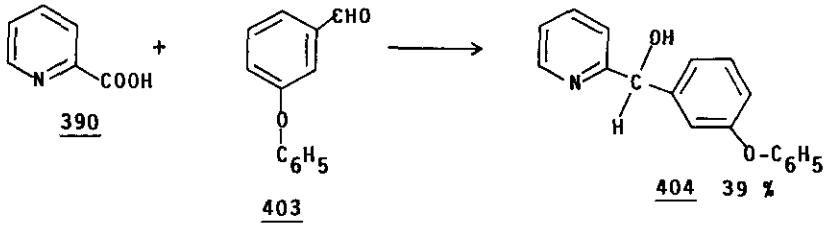
The addition of nonpolar solvents like p-cymene [469] has been claimed to increase the yields in the reaction between picolinic acid (390) and aromatic aldehydes or ketones up to 58 %. The influence of methyl and methoxyl substituents in picolinic acid on the yield of the reaction with benzaldehyde [470], *anisaldehyde* [471], or methyl 7-formylheptanoate [475] was studied in detail. p-Nitrobenzaldehyde, p-dimethylaminobenzaldehyde as well as cinnamaldehyde did not give any addition product with picolinic acid (390) [469]. *Quinaldinic acid* (391) reacts in low yield with 2,4-dinitrochlorobenzene to afford 401 and with methyl benzoate and methyl phenylacetate to give traces of 110 and 402 [472].



Whereas carboxylic acids like pyrimidine-4-carboxylic acid or thiazole-2-carbocylic acids did not give any adduct [469], nor harmanecarboxylic acid reacted, on heating with o-tolualdehyde to afford the corresponding adduct in 26 % yield [476]. α,α-Dicarboxyclic acids like dipicolinic acid (pyridine-2,6-dicarboxylic acid) react like picolinic acid with aldehydes to ketones to form the monoadduct accompanied by only traces of bisadduct [477].

γ-Carboxylic acids like isonicotinic acid [478] or cinchoninic acid [479] afford on heating with benzophenone the corresponding carbinols in only 7 - 10 % yield.

Heating of picolinic acid (390) with equimolecular amounts of 3-phenoxybenzaldehyde (403) without solvent to 170°C furnishes the corresponding carbinol (404) in 39 % yield [480], which can be used for the synthesis of pyrethroids.



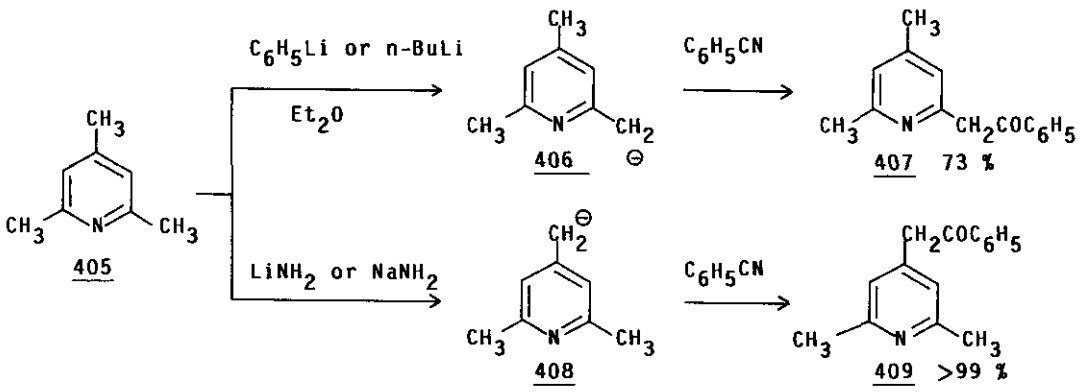
3.7. Modification of Alkyl Groups

N-Heterocycles containing methyl or alkyl groups are easily available by total synthesis as well as modification (compare chapters 2.2.2., 3.6.) of the unsubstituted heterocycle. Compared to alkyl groups in carbocyclic aromatic systems, alkyl groups in N-heteroaromatic systems are usually more acidic and therefore more reactive. Thus, alkyl and especially methyl groups have been alkylated or condensed with a large variety of electrophiles.

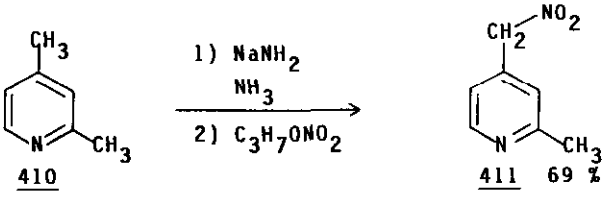
3.7.1. Nucleophilic Reactions

Due to the electron-attracting ring nitrogen atoms, the 2- and 4-methyl groups in pyridines and quinolines are more reactive than the 3-methyl groups [481]. Substitution of the methyl or alkyl group in the 2-postion is often kinetically favored over the 4-position due to metal complexation of strong bases with the neighbouring nitrogen atom [482-487]. Thus s-collidine (405) is metallated with

phenyl- or butyllithium in diethyl ether in a kinetically controlled reaction selectively at one of 2-methyl groups to give the anion (406) which can be trapped by benzonitrile to afford the benzoylated s-collidine (407) in 73 % yield. In contrast, metallation by lithium amide or sodium amide in liquid ammonia gives predominantly or exclusively the thermodynamically controlled anion (408), which affords with benzonitrile the benzoylated product (409) [488].

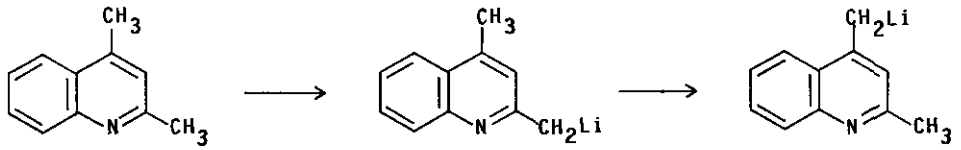


Reaction of 2,4-lutidine (410) with sodium amide in liquid ammonia and subsequent addition of n-propyl nitrate gives selectively the 4-substituted product (411) in 69 % yield [489]. Analogous nitrosations have been described and the reactivities of 2-, 3- or 4-methyl groups in pyridines, pyrimidines, quinolines, and quinazolines estimated using CNDO/2 as well as PPP-calculations [490,491].



2,3-Lutidine can be aminoalkylated (sodium amide, liquid ammonia) selectively at the 2-methyl group [492,493].

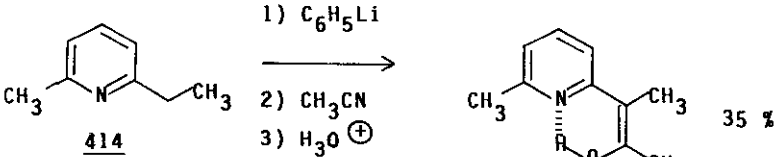
In 2,4-dimethylquinoline (22), the 2-methyl group is metallated initially by butyllithium in ether-THF to give 412 which is gradually converted to the 4-methylated intermediate (413). In analogy to the isomerization of ketone-enolates, the isomerization of 412 to 413 is catalyzed by excess 2,4-dimethylquinoline (22) [494].



22 412 413

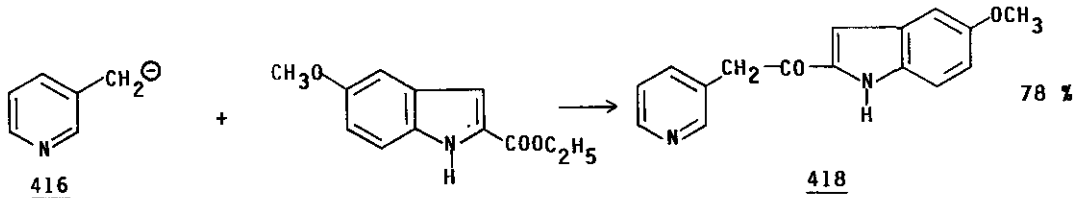
The picolyl (or 2,6-lutidyl) anion has been trapped by benzyl halides [484,496], alkyl halides [497-502], diethyl carbonate [503], aldehydes [504,505], ketones [506,507], esters [508], nitriles [509,510], epoxides like hexene-oxide [511], N,N-dimethylcarboxamides [512], and styrene [513] to give the corresponding products in up to 90 % yields.

Alkylations of 2-picolyl anion with aromatic halides like chlorobenzene or 2-bromostyrene occur by $S_{RN}1$-mechanism [514] (compare chapter 3.1.2.).



414 415

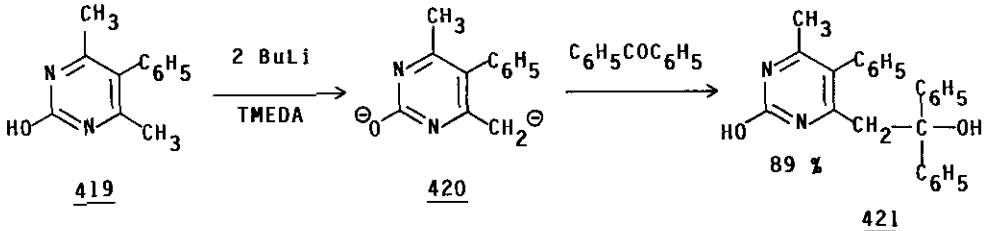
Interestingly, 2-ethyl-6-methylpyridine (414) can be selectively acylated at the methylene group to give 415 in 35 % yield [515], whereas 2-ethylpyridine affords the analogous product in 38 % yield [516]. Like the 2-picolyl anion, the 4-picolyl anion reacts readily with alkyl halides [495,499,500,517,518,519], ethylene oxide [520], aldehydes [523], carbon dioxide [519], diethyl carbonate [521], and esters [522]. The less reactive 3-picolyl anion (416), which can be generated by LDA in THF [482,525], sodium amide [495] or potassium amide in liquid ammonia [524], can be reacted with ethyl 5-methoxyindole-2-carboxylate (417) to afford 418 in high yield [525].



416 417 418

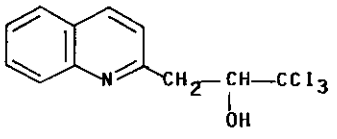
Methylpyridazines are converted by potassium tert-butoxide or LDA into the corresponding anions which react with esters [526,527] and ketones [528]. The 4-methyl group in 2,4-dimethylpyrimidine reacts preferentially, after base treatment, with electrophiles like esters [529] and alkyl nitriles [530-532].

Hydroxypyrimidines e.g. 419 can be metallated to the dianion (420) which reacts in high yields with alkyl halides, ketones, or esters to afford the corresponding substitution products like 421 [533].



419 420 421

Methylpyrazines can be mono- or diacylated [534,535]. 3-Methyl-2-pyrazinone can be acetylated via the corresponding dianion [536]. 2-Methylquinoline (20) reacts, on heating, with chloral in pyridine to afford 422 [537,538]. The 2-methyl group of 2,3-dimethylpyridine reacts analogously under similar conditions [539]. The 2- and 4-methyl groups in quinolines can form Mannich bases [537,540,541] as well as the anions, which react with esters [542,543]. The 1-methyl group in isoquinoline is more reactive than the 3-methyl group to form the corresponding anion which reacts readily with a large variety of electrophiles to products like 423 in high yields [544-546]. Methylated quinoxalines [542,547,548], pteridines [549], and purines [550,551] can be condensed with esters and aldehydes. Methyl groups on 5-membered ring heterocycles as in imidazoles [552], benzimidazoles [553], isoxazoles [554], oxadiazoles [554], and thiadiazoles [554] can be condensed with electrophiles.



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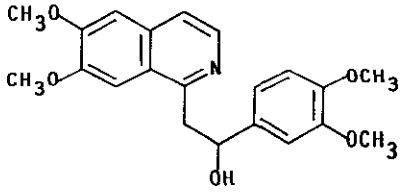
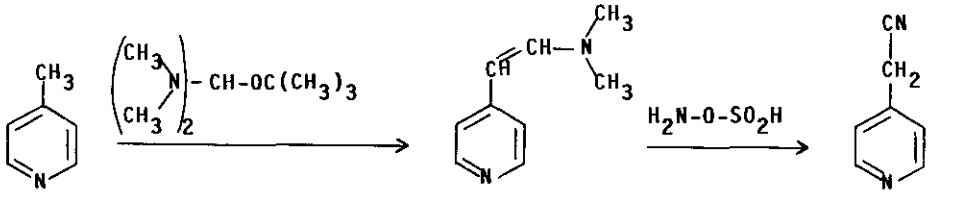


423

Generally, methyl groups in nitrogen heterocycles can react with amide acetals or aminals to afford the corresponding enamines [555-557] which are valuable intermediates e.g. for the conversion of 4-picoline (149) via the corresponding enamine (424) into the corresponding nitrile (425) [557].

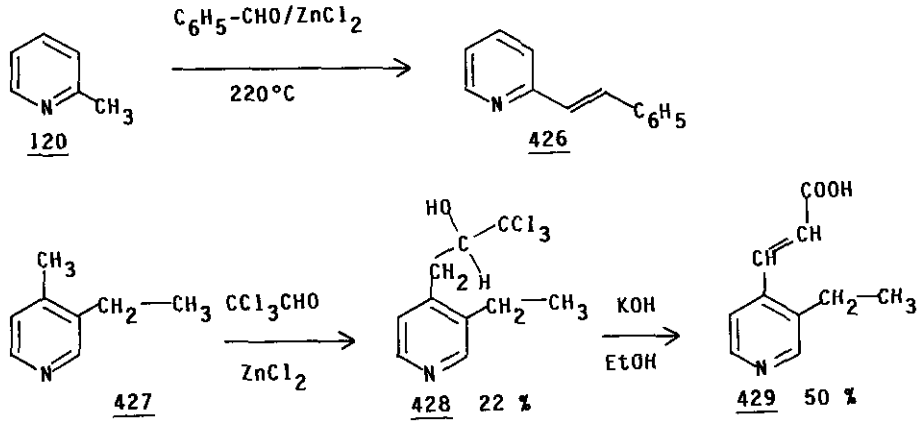


149 424 30 % 425 68 %

As was expected, methylene groups containing anion-stabilizing groups like the cyano [558,559], trimethylsilyl [560-563] or diethoxyphosphonate [564] groups combine readily with electrophiles in the presence of base. Furthermore, alkyl groups in heterocyclic N-oxides are even more reactive (cf. chapter 4.1.1.).

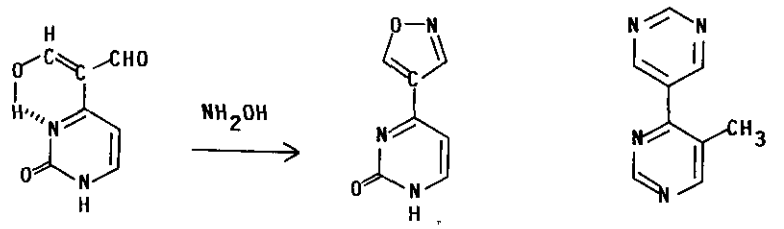
3.7.2. Electrophilic Reactions

Acid or Lewis acid catalyzed reactions of heterocyclic methyl groups have been known for a long time. Thus, 2-picoline (120) condenses with benzaldehyde in the presence of $ZnCl_2$ to afford α-styrylpyridine (426) [565,566], whereas the 4-methyl group in 3-ethyl-4-methylpyridine (427) reacts with chloral and $ZnCl_2$ to afford the adduct (428) in 22 % yield [567,568], which can be dehydrated and saponified in 50 % yield to the acid (429).



Analogous condensations e.g. of methylpyrazines [569], methylpyridazines [570], 1-methylisoquinolines [571], methylquinoxalines [572], 2-methylbenzothiazoles [573], 2-methylbenzoxazole [573], and methylisothiazoles [574] have been described.

Heterocyclic methyl groups e.g. of pyrimidines [575] and purines [576] react also with Vilsmeier reagents to afford the corresponding diformyl derivatives e.g. 430 which reacts with hydroxylamine to afford the substituted isoxazole (431) [575]. 4,5-Dimethylpyrimidine reacts with formamide-$POCl_3$ to give the substituted pyrimidine (432) in 12 % yield [577].

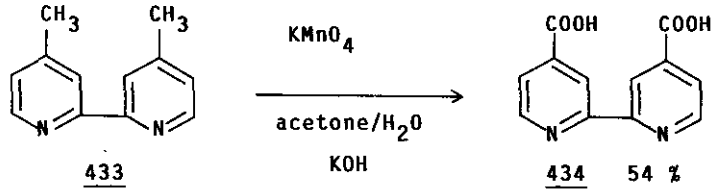


430 431 432 12 %

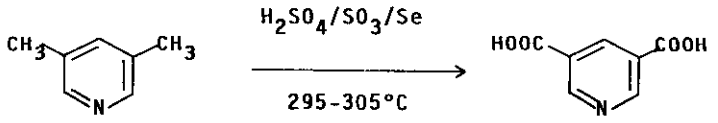
3.7.3. Oxidation and Halogenation of Alkyl Groups

Methyl or alkyl groups in N-heterocycles can be oxidized by $KMnO_4$ [578,579], SeO_2 [580-582], or oleum in the presence of selenium metal [583] and dichromate-sulfuric acid [584].

Thus, 4,4-dimethyl-2,2-bipyridine (433) affords with $KMnO_4$ the dicarboxylic acid (434) in 54 % yield [579], and 3,5-dimethylpyridine (435) with oleum/selenium metal pyridine-3,5-dicarboxylic acid (436) in 76 % yield [583].



433 434 54 %



435 436 76 %

Methyl groups can be monohalogenated e.g. by NBS [585,586] or perhalogenated by Br_2 [587,588] or SO_2Cl_2 in CF_3COOH [589].

3.8. Modification of Cyano Groups

Cyano groups can be introduced in N-heterocycles by displacement of leaving groups with cyanide ion (cf. chapters 3.1.8. and 3.3.) or by reaction of heterocyclic N-oxides with $(CH_3)_3SiCN$ (cf. chapter 4.1.2.) and classically by conver-

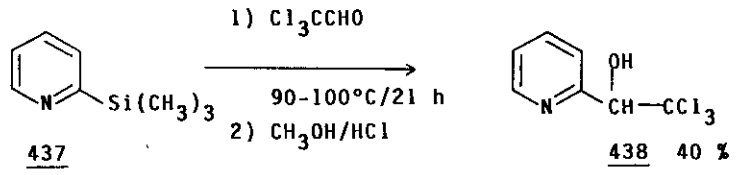
sion of carboxyl or amide groups.

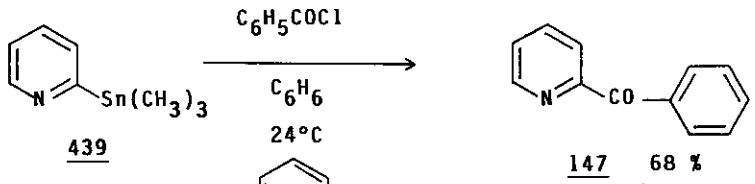
Cyano moieties in N-heterocycles like 4-cyanopyridine react with Grignard reagents to form ketones [590,591] but can also be replaced by sodium malonates or sodium cyanoacetates as in 1-phthalazine carbonitrile [592] or photochemically by alcohols in 2-cyanopyridine [593] (cf. chapter 2.7.2.).

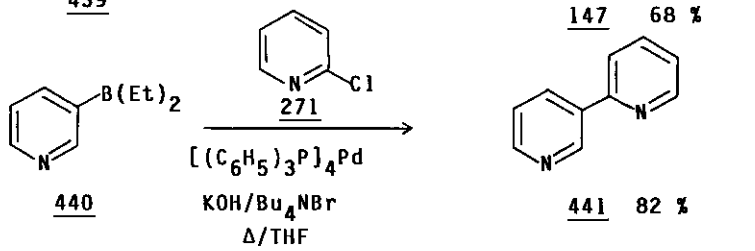
These typical reactions may suffice as examples.

3.9. Reactions of Miscellaneous Organometallic Substituents

Heating of 2-trimethylsilylpyridine(437) with chloral gave, after transsilylation with methanolic hydrogen chloride(438) in 40 % yield [594]. 2-Trimethylstannylpyridine(439) reacted with benzoylchloride at r.t. to give 2-benzoylpyridine(147) in 77 % yield. The 2-trimethylstannylquinoline or 1-trimethylstannylisoquinoline behave analogously, whereas 3- or 4-trimethylstannylpyridine or -quinoline react only in the presence of palladium catalysts [595].







Analogously, diethyl(3-pyridyl)borane (440) can be arylated by aryl halides like 2-chloropyridine to form arylated pyridines like 441 in high yields [596].

4.0. REACTIONS OF N-QUATERNARY-TYPE BASES

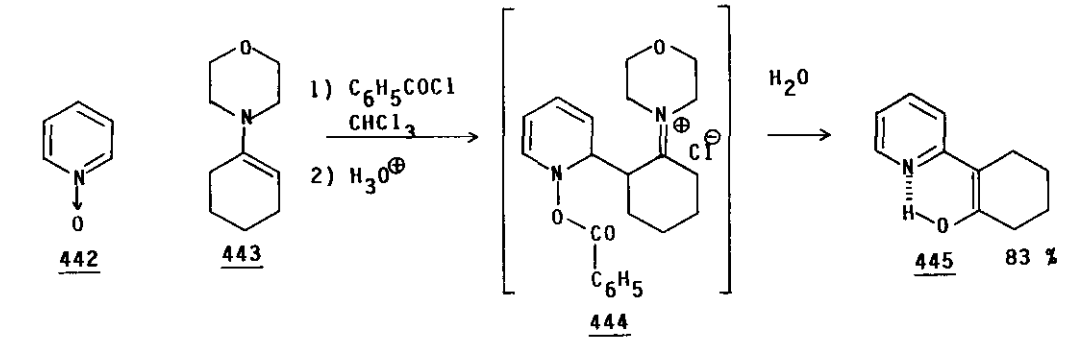
4.1. Reactions of Aromatic N-Oxides and N-Amino Compounds

Since this chemistry has been repeatedly reviewed during the last years [597-600] only a few pertinent examples are given to illustrate the basic principles of C-substitution via aromatic N-oxides as well as some recent advances.

Amine oxides like pyridine, quinoline, isoquinoline or pyrimidine N-oxides react readily with soft nucleophiles at the "soft" α- or γ-positions if the hard oxygen is converted by acylation, mesylation, tosylation, alkylation or silylation into a better leaving group. The success of these reactions depends on the proper balance between the "softness" of the nucleophile and the "hardness" of the leaving groups at the N-oxide oxygen.

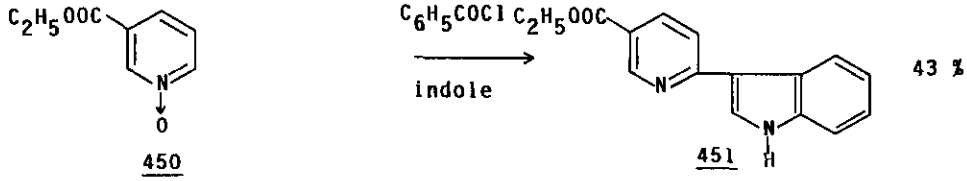
4.1.1. Activation via O-Acylation or O-Sulfonylation and Rearrangements

Thus, pyridine N-oxide (442) is converted by benzoyl chloride and the enamine (443) via the intermediate (444) and subsequent hydrolysis in 83 % yield into 2-(2-pyridyl)cyclohexanone (445) [598]. Lepidine N-oxide (446) reacts analogously with 443 in the presence of tosyl chloride to afford the 2-(2-lepidyl)cyclohexanone (447) [598]. For additional reactions of N-oxides with enamines compare references 601-609. Likewise quinoline N-oxide (448), acetylacetone and acetic anhydride furnish the 2-acetonylquinoline (449) in 68 % yields [623].



Other soft nucleophiles like malonic ester [598], cyanacetic ester [610,611], cyanacetamide [612], cyanacetic acid [613], malonitrile [614], acrylamide [615], propiolic esters [616,617], ß-dicarbonyl compounds [618-623], enaminones [619,624,625], O-acylated cyanhydrins [626-628], 2-buten-4-olide [629], rhodanines [630], 2-phenyl-2-thiazolin-4-one [631], 2-oxazolin-5-ones [632], barbituric acid [633], indole [634], indole-copper reagents [635], oxindole [636], and 2-alkoxyindoles [637] react analogously with heterocyclic N-oxides.

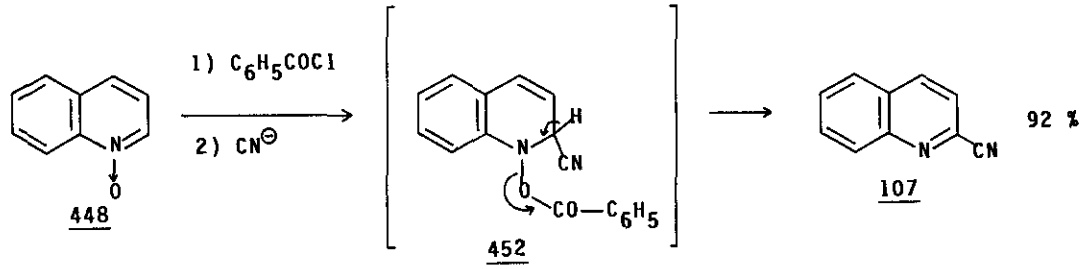
Thus, ethylnicotinate N-oxide (450) combines readily with indole in the presence of benzoyl chloride to afford ethyl 6-(3-indoyl)nicotinate (451) in 43 % yield [634].



450 451

Sulfonium ylides [638-640] as well as diketene [641-642] react with N-oxides to furnish new 5- and 6-membered ring systems.

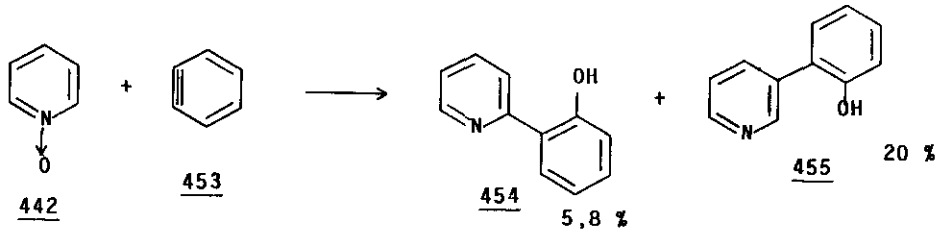
Acylation of quinoline N-oxide (448) with benzoyl chloride followed by treatment with aqueous KCN leads via the probable intermediate (452) with elimination of benzoic acid to 2-cyanoquinoline (107) in ca. 92 % yield [643]. Although this type of procedure is successful with many heterocyclic systems [644], in the pyridine-series, only 4-chloropyridine N-oxide has been reported to give the corresponding 2-cyano-4-chloropyridine in 63 % yield (cf. chapter 4.1.2.) [644].

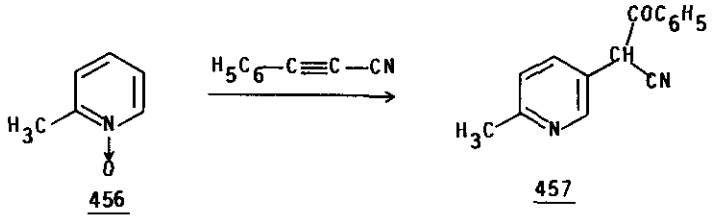


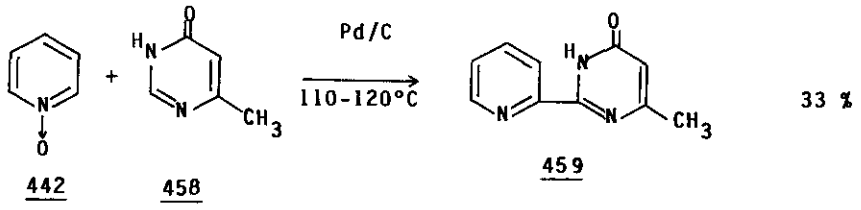
448 452 107

O-Acylation of pyridine and quinoline N-oxides, however, with dimethylcarbamoyl chloride using trimethylsilyl cyanide at the cyanide source furnishes the corresponding 2-cyanopyridines and -quinolines in good yields [645].

In related reactions of C≡C bond systems with the 1,3-dipol-system of N-oxides, pyridine N-oxide (442) reacts with benzyne (453) to give mixtures of products (454 and 455) via symmetry allowed rearrangements [599,600,646].







Similar rearrangements are postulated for the reaction of 2-picoline N-oxide (456) with phenylpropionitrile to furnish the 5-alkylated 2-picoline (457).

Heating of pyridine N-oxide (442) with 6-methyl-4(3H)-pyrimidinone (458) in the presence of palladium-charcoal leads probably to a radical reaction with the soft 2-pyrimidyl radical to afford the adduct (459) as well as the 2,2'-dimer of 458 [647].

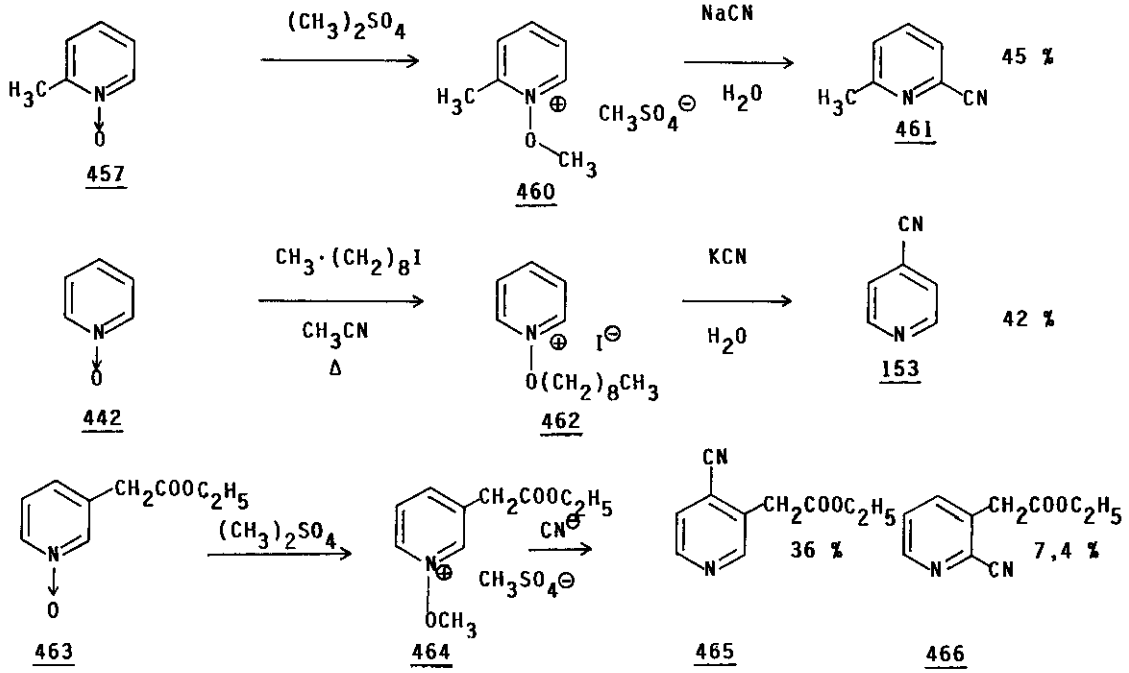
In this connection, it should be noted that the N-oxidation of N-heterocycles leads to a considerable increase in the reactivity of nuclear hydrogen atoms [648], nuclear methyl groups [649] as well as nuclear halogen groups [650], which can be used for substitution reactions.

4.1.2. Activation via O-Alkylation and O-Silylation

Since O-alkylated heteroaromatic N-oxides, which can be readily prepared by O-alkylation, are much more stable towards hydrolysis than the corresponding O-benzoates or O-tosylates, they give, on reaction with alkali cyanides, generally higher yields of the corresponding cyano compounds [651-653]. Thus α-picoline N-oxide (457) affords on methylation with dimethyl sulfate, in nearly quantitative yield the O-methyl derivative (460) which reacts with aqueous KCN solution in ca. 45 % yield to 6-methylpicolinonitrile (461) [653,654].

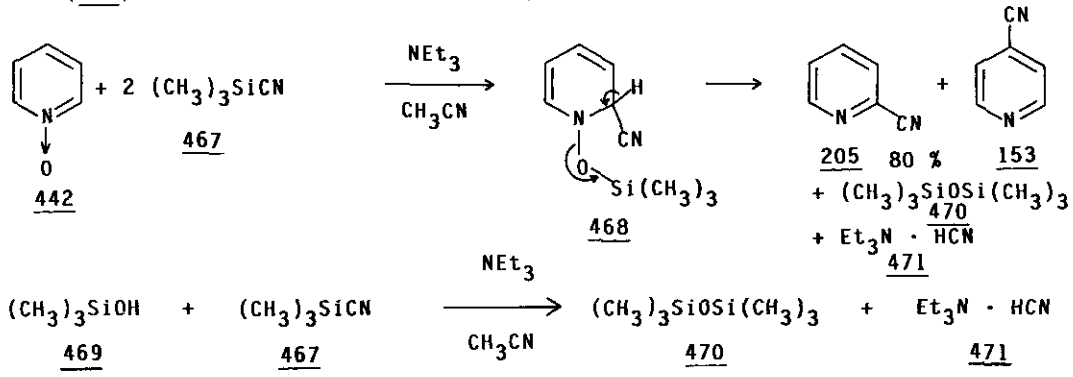
Pyridine N-oxide (442) gives, on alkylation and subsequent treatment with cyanide, 2-cyanopyridine (205) and small amounts of 4-cyanopyridine (153) [651-653]. The amount of 4-cyanopyridine formed is dependent on the sterical bulk of the alkoxyl group as well as on the substituents in the pyridine ring [653,655]. Thus, the O-nonyl derivative (462) obtained from pyridine N-oxide (442) gives, with cyanide, a 42 % yield of 4-cyanopyridine (153) [653]. The N-oxide of ethyl pyridine-3-acetate (463) furnishes, on methylation 464 and cyanide treatment, a mixture of mainly 465 and 466 [656].

For some recent applications of O-alkylation and subsequent cyanation to pyridine N-oxides [657-661], quinoline N-oxides [662], α-carboline N-oxides [663], and γ-carboline N-oxide [664] compare the references.



Since O-alkyl and O-silyl groups behave very similarly as leaving groups [665] and since furthermore O-silyl groups are readily formed due to the high affinity of silicon to oxygen, both steps, the addition of cyanide ion to the N-oxide system and the activation of the N-oxide oxygen atom, by silylation, can be combined by using trimethylsilyl cyanide (467) as a reagent.

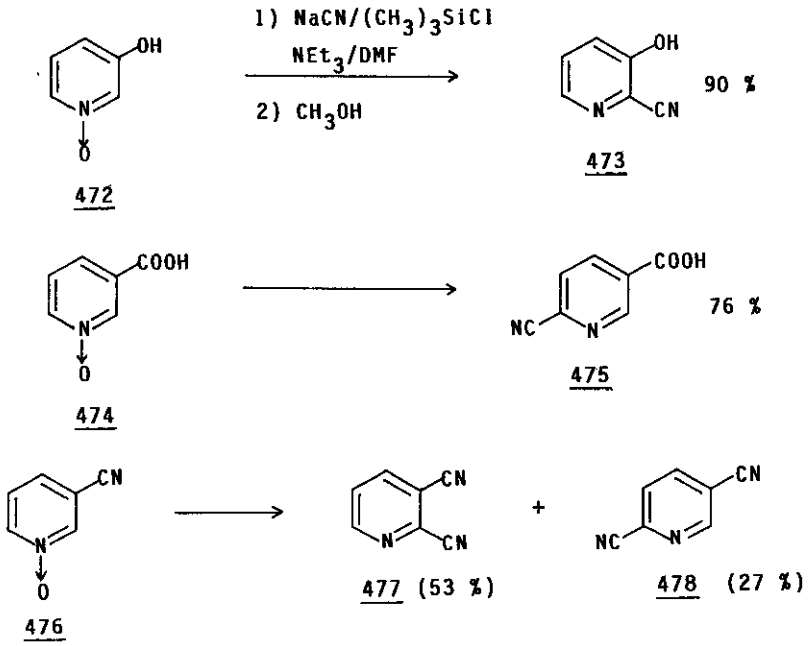
Heating heterocyclic N-oxides like pyridine N-oxide (442) with trimethylsilyl cyanide (467) in an organic solvent like acetonitrile leads to an intermediate like 468, which aromatizes with formation of trimethylsilanol (469) to afford 2-cyanopyridine (205) in 80 % yield and traces of 4-cyanopyridine (153). Trimethylsilanol (469) is subsequently silylated by a second equivalent of trimethylsilyl cyanide (467) to hexamethyldisiloxane (470). The HCN, which is liberated, has to be *neutralized by a tertiary base* like triethylamine to triethylammonium cyanide (471) to drive the reaction to completion [666].



$$(CH_3)_3SiOH \;(469) + (CH_3)_3SiCN \;(467) \xrightarrow[CH_3CN]{NEt_3} (CH_3)_3SiOSi(CH_3)_3 \;(470) + Et_3N \cdot HCN \;(471)$$

The reaction can be simplified by generating trimethylsilyl cyanide *in situ* from NaCN and trimethylsilyl chloride in DMF and simultaneously silylating reactive groups like hydroxy or carboxy groups by excess trimethylsilyl chloride-triethylamine.

Thus, 3-hydroxypyridine N-oxide (472) is converted smoothly into 2-cyano-3-hydroxypyridine (473) in 90 % yield. 3-Carboxypyridine N-oxide (474) gives 2-cyano-5-carboxypyridine (475) in 76 % yield, whereas 3-cyanopyridine N-oxide (476) affords a mixture of the 2,3- (411) and 2,5-dicyanopyridine (478) [666].



472 → 473 (90 %)

474 → 475 (76 %)

476 → 477 (53 %) + 478 (27 %)

As demonstrated for the reaction of 3-cyanopyridine N-oxide (476), the reaction with trimethylsilyl cyanide can be catalysed by tetrabutylammonium fluoride (TBAF) in THF to proceed already at +5°C to give a 48 : 18 mixture of 477 and 478 [666].

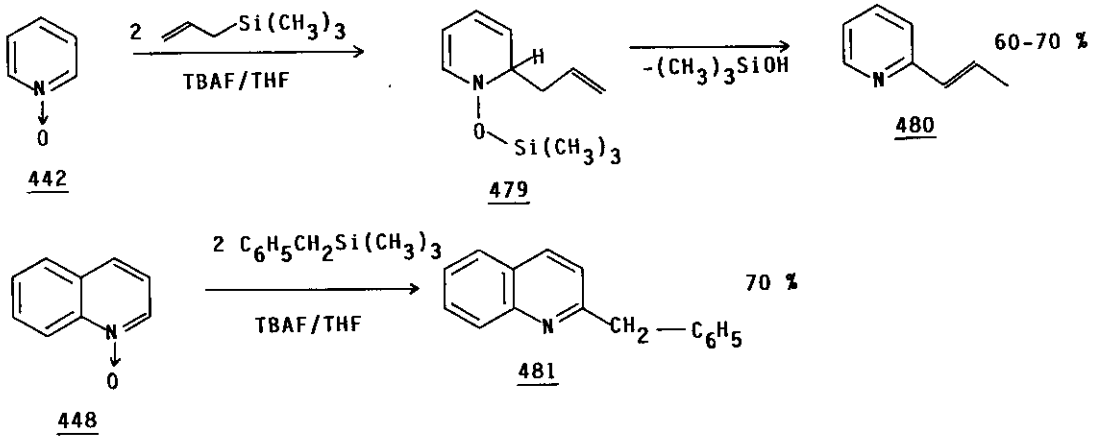
The more reactive quinoline and isoquinoline N-oxides are cyanated under much milder conditions [666] as are the pyrimidine N-oxides [667]. The different procedures of reacting heterocyclic N-oxides with trimethylsilyl cyanide have recently been reviewed [668] and furthermore experimentally compared [669].

It should be mentioned here that quinolines and isoquinolines can be cyanated directly in good yields using tosyl chloride and KCN in CH_2Cl_2/H_2O via a Reissert intermediate (cf. chapter 2.3.) from which the sulfinic acid is eliminated using DBU [670,671].

As already discussed in the introduction of chapter 4.1., the aforementioned smooth reactions of heterocyclic N-oxides with trimethylsilyl cyanide can be rationalized as the favored reaction of the "soft" cyanide ion with the "soft" α-position of the N-oxide system and the "hard" potential trimethylsilyl cation with the "hard" N-oxide oxygen atom.

Analogously, the "soft" allylic of "benzylic" anions which are readily generated from allyl- or benzyltrimethylsilane and fluoride ion add to the "soft" α-position of pyridine or quinoline N-oxides to give, after elimination of trimethylsilanol, the α-propenyl or α-benzyl heterocycle [672].

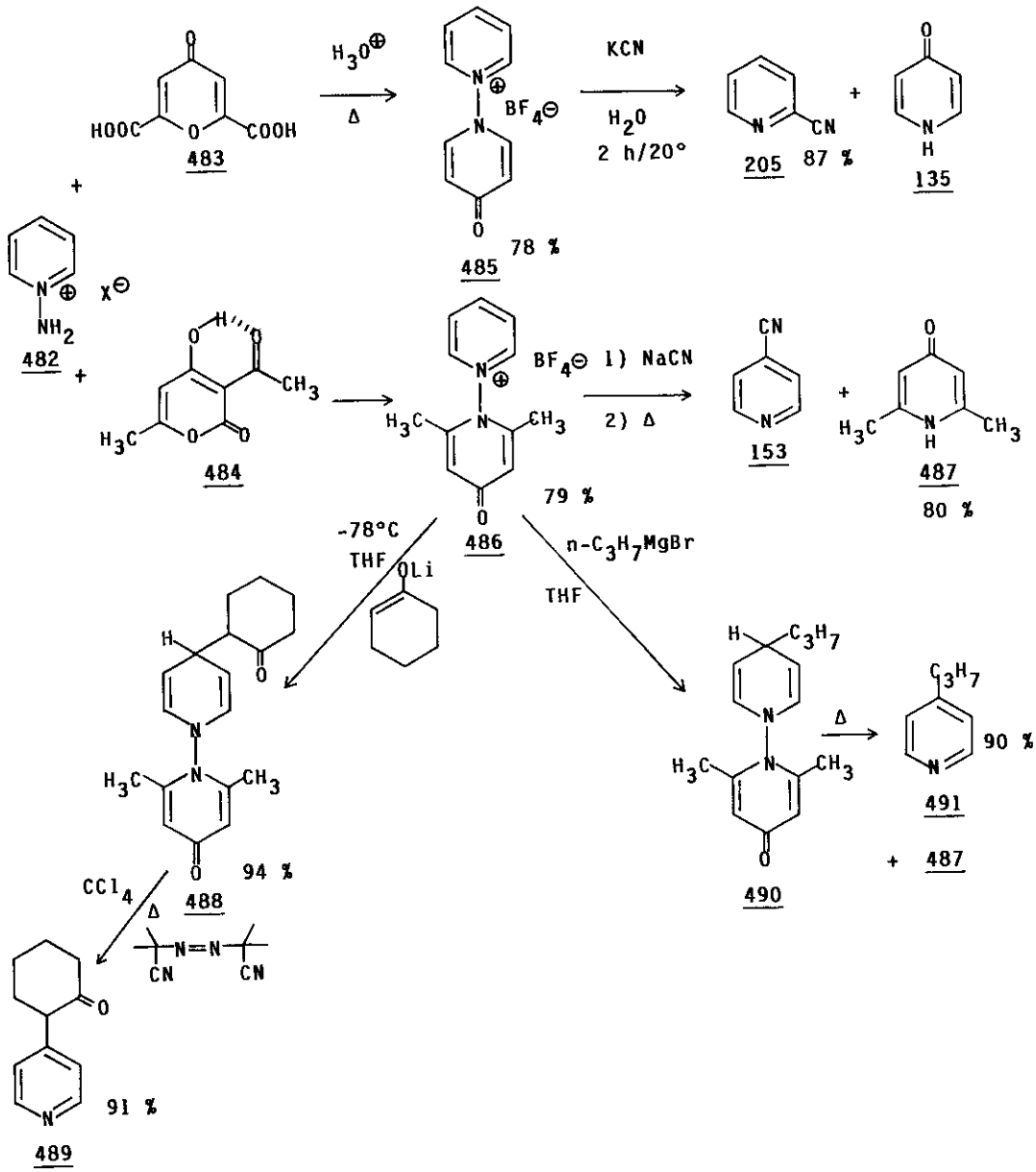
Thus, pyridine N-oxide (442) reacts with 2 equivalents of allyltrimethylsilane to give, via the probable intermediate (479), the 2-propenylpyridine (480) as the sole product in ca. 60 - 70 % yield. Quinoline N-oxide (448) affords with benzyltrimethylsilane analogously 2-benzylquinoline (481) [672].



It can be anticipated that further useful reactions of heterocyclic N-oxides with silicon reagents will be discovered.

4.2. Reactions of N-Amino Heterocycles

Reaction of N-aminopyridinium salts (482) [673] with 4- or 2-pyrones like 483 and 484 gives rise to 1-pyridinio-4-pyridones (485 or 486). Compound 485 is transformed by aqueous KCN to afford 2-cyanopyridine (205) and probably 4-pyridone (135), which is not isolated [674].


HOOC
COOH
483
$H_3O^{\oplus}$
Δ
$BF_4^{\ominus}$
485
78 %
KCN
H_2O
2 h/20°
205
87 %
135
482
$X^{\ominus}$
NH_2
484
CH_3
H_3C
$BF_4^{\ominus}$
1) NaCN
2) Δ
153
487
80 %
79 %
486
-78°C
THF
OLi
$n\text{-}C_3H_7MgBr$
THF
94 %
488
CCl_4
Δ
CN
CN
91 %
489
C_3H_7
490
Δ
90 %
491
+ 487

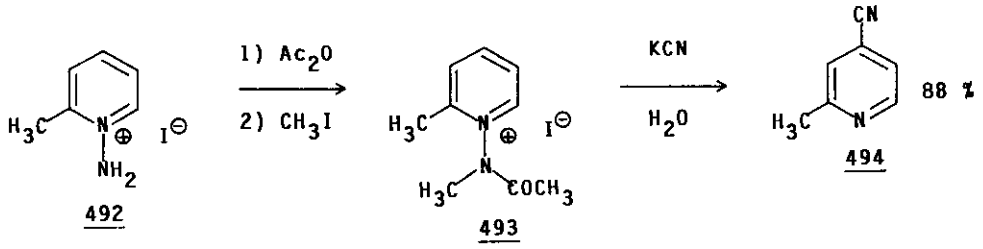
Due to the steric shielding of the α-position of 486 by the two methyl groups, nucleophiles attack exclusively the γ-position. Thus, 486 reacts with cyanide ion to give, after pyrolysis of the intermediate, 4-cyanopyridine (153) in ca. 80 % yield as well as 487 [675].

Lithium enolates of ketones like cyclohexanone add to 486 to afford intermediates like 488, which are decomposed by a free radical mechanism in high yields to 4-(α-acylalkyl)pyridines such as 489 [676], which can be usually prepared by acylation of 4-alkylpyridines (cf. chapter 3.7.) or alternatively by sulfide contraction (cf. chapter 3.5.).

Excess aliphatic or aromatic Grignard reagents like propylmagnesium halide react with the intermediate (486) to the 1,4-addition product (490), which give on heating 4-n-propylpyridine (491) in 90 % yield [677]. Whereas anions derived from nitroalkanes add readily to 486 to afford the 4-(nitroalkyl)pyridines in high yields [678], the anions derived from esters, nitriles, malonitriles, or ethyl cyanoacetates give only poor yields of the desired 4-alkylated pyridine due to competing ring-opening reactions [679].

These reactions work also very well with 2- or 3-substituted N-aminopyridines, which can then be transformed into a series of 4-substituted analogues.

Similar results are obtained on employing N-acyl-N-alkyl derivatives like 493, which are obtained from N-amino-2-methylpyridinium salts like 492 by acylation and subsequent alkylation [680]. Thus, compound 493 reacts with aqueous KCN to give 2-methyl-4-cyanopyridine (494) in 88 % yield [681].

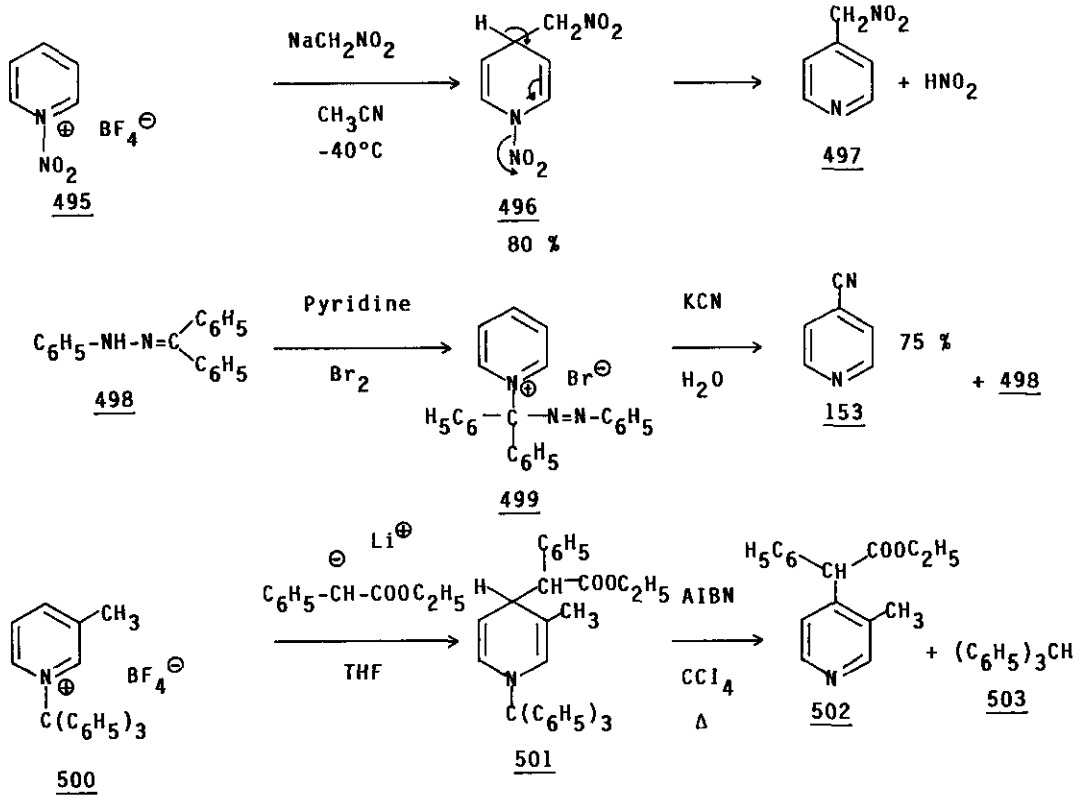


492 493 494

4.3. Reactions of Other N-Substituted Heterocycles

Pyridine is transformed by nitronium tetrafluorborate in anhydrous acetonitrile into 495, which reacts with the sodium salt of nitromethane to give, in 80 % yield, the crystalline 496. However, no attempts have been reported to effect the cleavage of 496 to 497 [682,683].

Pyridine is alkylated by benzophenone phenylhydrazone (498) in the presence of bromine to afford in 97 % yield the phenylazodiphenylmethylpyridinium bromide (499), which reacts with aqueous KCN to give 4-cyanopyridine (153) in 75 % yield [684]. Alkylation of pyridine or 2- or 3-methylpyridine with triphenylmethyl fluorborate affords the corresponding N-triphenylmethylpyridinium tetrafluorborates, which are transformed by the lithium salts of esters and nitrile into the corresponding 1,4-adduct. Radical decomposition with azaisobutyronitrile (AIBN) furnishes the substituted pyridines. Thus, N-triphenylmethyl-3-methylpyridinium tetrafluoroborate (500) reacts with the lithium salt ethyl phenylacetate to give via the adduct (501) the final product (502) in 60 % yield as well as triphenylmethane (503) [685] (compare also the Reissert type reactions under chapter 2.3.).

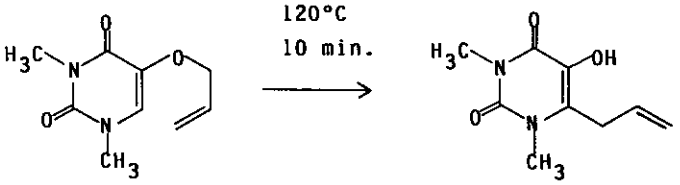


For analogous additions of trichloro- or tribromomethyl groups to N-benzylpyridinium or quinolinium salts compare reference 686.

5.0. C-SUBSTITUTION BY REARRANGEMENTS

5.1. Claisen Rearrangements

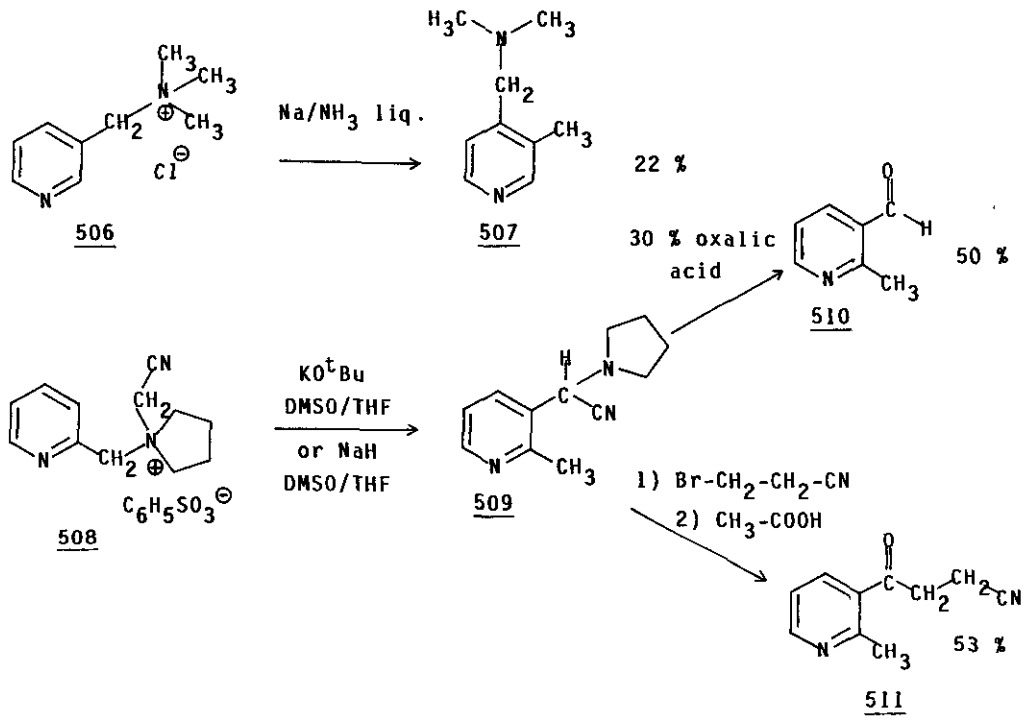
Since the Claisen rearrangement of aromatic and heteroaromatic compounds was recently reviewed [687]; only a few examples are presented. 5-Allyloxy-1,3-dimethyluracil (504) rearranges at 120°C quantitatively to 505 [688]. The analogous rearrangement of 6-allyloxy-1,3-dimethyluracil gives 6-hydroxy-5-allyl-1,3-dimethyluracil in 64 % yield [689]. The uncatalysed [690] as well as the Lewis acid catalysed [691] ortho-Claisen rearrangements of 2-allyloxypyridine have been described as have been Claisen rearrangements of allyl, methallyl and crotyl esters of 4-hydroxyquinoline [692]. For interesting Claisen rearrangements of purine-O^6-allylic ether and 4-ß-carboline ethers compare references 693,694.



504 505 96 %

5.2. Sommelet-Hauser[2,3]Sigmatropic Rearrangements

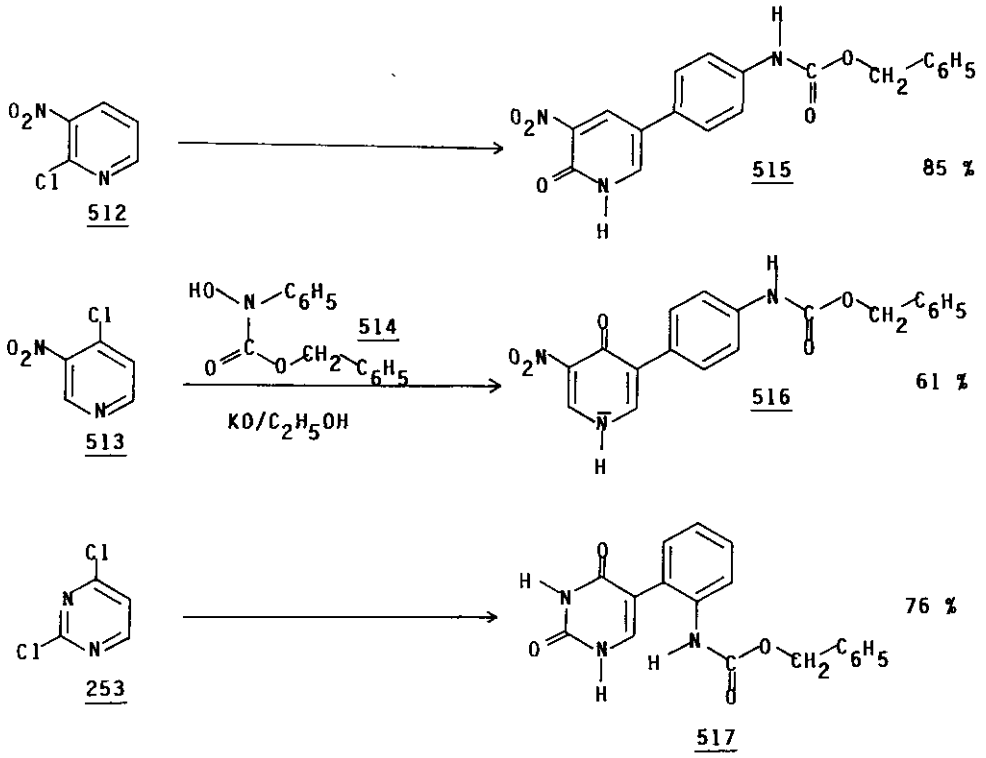
Typically, compounds like 506 rearranges to 507 in the presence of sodamide in 22 % yield [695]. Pyrrol derivatives are found to rearrange analogously [695]. The quaternary salt (508) is converted by potassium t-butoxide or sodium hydride in THF/DMSO at -10°C to 509, which can be hydrolysed *in situ* in ca. 50 % to yield the aldehyde (510), or alkylated with base and alkyl halides to 2-methyl-3-acylpyridines such as 511 [696].



5.3. *Benzidine-Type Rearrangements*

Heterocycles with an activated chlorine atom like 3-nitro-2-chloropyridine (512) or 3-nitro-4-chloropyridine (513) react with benzyl N-hydroxy-N-phenylcarbamate (514) under alkaline conditions to give, via an oxygen-benzidine-type rearrangement, the corresponding pyridones (515 and 516) in good yields [697,698].

Analogously, 2,4-dichloropyrimidine (253) affords, via displacement of the more reactive 4-chlorine atom, rearrangement, and hydrolysis of the 2-chloro group, the 5-substituted uracil (517) [698]. Since 2-chloropyrimidines or 2-chloropyrazines can be transformed analogously [697], this type of rearrangement seems to be of general interest.



SUPPLEMENT

Due to several unfortunate circumstances, the writing of the final version of this manuscript took longer than anticipated. Thus, a few important publications, which have appeared, since finishing the main draft of this review, are added as a supplement.

2.3. Reissert-Type Reactions

Benzyltin reagents [698] as well as silyl enol ethers [699,700] have been added to the 4-position of pyridinium and pyrimidinium [700] compounds, whereas alkinyl and alkenyl Grignard reagents attack primarily the 2-position of pyridinium salts [701]. α-Additions in pyridinium salts occur also exclusively, when the 4-position is substituted by a halogen [702], methoxyl [703], or trimethylstannyl group [704].

2.7. Radical Reactions

The recent advances in preparative radical chemistry have just been reviewed in a concise monography by Giese [705]. The Minisci-homolytic alkoxycarbonylation of pyridines and pyrazines can also be achieved in a two phase system [706]. On UV-irridation, 5-iodouracils and uridine undergo substitution by alkylsilanes in high yields [707].

3.1. Reactions of Halogens

Reaction of the lithium enolates of ketals of glycoxylic esters with 2-chloro-s-triazines, -quinoxalines, -benzoxazoles, and benzothiazoles and subsequent acidic hydrolysis furnish the α-ketoesters [708].

Chloro- and bromopyridines and -quinolines can be efficiently homo-coupled in *the presence of nickel-complexes to afford* e.g. 3,3-dipyridyl in 78 % yield [709]. Silylated 5-bromouracil couples with 2-thienylzinc chloride [710] and 6-methyl-mercaptopurine nucleoside with Grignard reagents [711] in the presence of nickel-complexes.

Halopyridines [712,713], -pyrimidines [714], -pyrimidine nucleosides [715], -pyrazines [716] and -purines [717] have been cross-coupled with acetylene derivatives in the presence of palladium-complexes.

8-Methylsulfonylpurine nucleosides react readily with the sodium salt of ethyl acetoacetate to give the ethyl ester of the corresponding 8-acetic acid [718].

3.2. Replacement of O-Sulfonate Groups

Reaction of the easily accessable triflates of 2- or 8-hydroxyquinolines with trimethylstannylbenzenes in the presence of tetrakis(triphenylphosphin)palladium(0) affords the corresponding phenylated quinolines in high yields [719]. This type of C-C coupling should be applicable to a wide variety of corresponding triflates of hydroxy N-heterocycles.

3.7. *Modification of Alkyl Groups*

The lithium salt of a substituted 4-methylpyridine adds to 2-cyclopenten-1-one in high yield [720]. The competition between nucleophilic addition and metallation in 4- and 2-methylpyridine by different lithium reagents has been studied [720].

4.1. Reactions of Aromatic N-Oxides and N-Amino Compounds

A further comprehensive review on the reaction of aromatic N-oxides was published by Hamana [722].

Several 3- and 4-substituted pyridine N-oxides has recently been reacted with trimethylsilyl cyanide to give the corresponding 2-cyanopyridines in 70 - 88 % yield [723,724].

Finally, C-alkylations of γ-chloro heterocycles or heterocyclic N-oxides by phase transfer catalysis has been recently reviewed [725].

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