SYNTHESIS OF VICINALLY SUBSTITUTED NITROPYRIDINE DERIVATIVES AND THEIR N-OXIDES

Ryszard Gawinecki and Danuta Rasała
Institute of Chemistry, Pedagogical University, 25-020 Kielce, Poland

Abstract - The synthetic methods leading to 4- and 2-substituted 3-nitropyridines and 3-substituted 4- and 2-nitropyridines are reviewed in this paper. Their preparative convenience is discussed.

The synthesis of nitropyridines has been reviewed in the Klingsberg-Abramovitch monograph[1,2] and, recently, by the Russian workers[3]. Only some syntheses of nitropyridines carrying another substituent in the ortho position to the nitro group are mentioned there.

Nitropyridines, including those mentioned above, can be obtained by nitration of substituted pyridines, substitution in the nitropyridine derivative or transformation of that substituent. Every one of these reactions must be followed by reduction of the oxide function when N-oxide of pyridine derivative was the starting material. Besides, such compounds can be formed during oxidation of the proper aminopyridine derivatives and pulling out the redundant substituents in poly-substituted nitropyridine derivatives.

The title compounds, as well as corresponding aminopyridines, are useful intermediates for medicinals[4,5] and dyes[6], and starting materials in the synthesis of heterocyclic compounds such as naphthyridines[7], pyrrolopyridines[8] and pyridodiazines[9,10]. Some of them are active as inhibitors in enzymatic reactions[11].

1. Nitropyridines by nitration of substituted pyridines

The nitration of pyridine itself and some of its alkyl derivatives such as 2-methylpyridine requires extremely vigorous conditions and the yields of formed nitroderivatives are very low[12-16]. However, numerous pyridine derivatives react very easily with nitric acid /see Tables 1 and 2/.

1.1. Aminopyridines

The nitration of aminopyridines by a sulfuric acid - nitric acid mixture gives, at first, nitramine derivatives[17]. In hot acid 2- and 4-nitraminopyridines undergo a rearrangement to 2-amino-3- and -5-nitropyridines and 4-amino-3-nitropyridine, respectively[17-24]. Instead, under the same conditions 3-nitraminopyridine gives 3-hydroxypyridine[25,26]. However, 3-/N-methylnitramino/pyridine in an acidic medium is rearranged to 2-nitro-3-/N-methylamino/pyridine[27]. 2-Acetylaminopyridine is deacetylated during nitration[28], but pyridylcarbamates give products carrying the nitro group in the ring /see Table 1/.

1.2. Hydroxypyridines

Hydroxypyridines and pyridones undergo nitration without difficulties /see Table 1/. The products of the reaction are very useful starting materials in the preparation of many other nitropyridine derivatives /see Section 2/. The convenient nitration of 4-hydroxypyridine[29] is worthy of recommendation.

1.3. Other pyridine derivatives

Also 3-alkoxypyridines and polymethyl substituted pyridines can be nitrated /see Table 1/. The pulling out of redundant substituents in the products of nitration of the mentioned polymethyl pyridines /see the following Sections/ is a good method for preparing some nitropicolines.

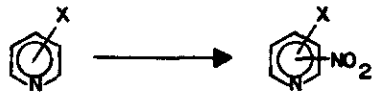
The nitration of pyridine N-oxides gives mainly 4-nitroderivatives[30]. However, 3-hydroxy- and 3-t-butylpyridine N-oxides are nitrated in the positions 2 and 2 and 6, respectively[31-34]. Deoxygenation of obtained nitropyridine N-oxides leads to 4-nitropyridines or to the corresponding aminopyridines /see Table 2/. These amino compounds can be easily oxidized to proper nitropyridines /see Section 3/. It is possible to obtain 4-nitropyridine from pyridine N-oxide in the mixture of sulfuric and nitric acid in 56.6% yield[35].

The nitration of 4-hydroxypyridine N-oxide by nitric acid in acetic anhydride leads to 4-acetoxy-3-nitropyridine N-oxide /90%/[36].

2. Ring substitution in other nitropyridines

One can expect an easy nucleophilic subetitution in nitropyridine derivatives. It is the way to prepare many new nitropyridines. The nitro group itself also can be subetituted in such reactions: during deoxygenation of 4-nitro-3-methylpyridine N-oxide by phosphorus trichloride in chloroform 4-chloro-3-methyl de-

Table 1. Mononitration[a] of pyridines



1

X	Substituents in 1	References /yield, %/
2-OH	3-NO_2-2-OH + 5-NO_2-2-OH	37/85+0/, 38, 39
3-OH	2-NO_2-3-OH	31/42/,33/70/,32
4-OH	3-NO_2-4-OH	40-42,29/70/,43/88/,44/61/ 45/38/,46/87/,47/70/
3-OMe	2-NO_2-3-OMe	48,31/43/
3-OEt	2-NO_2-3-OEt[b]	49/75-80/
4-OMe	3-NO_2-4-OMe	45/48/,50/34/
4-OEt	3-NO_2-4-OEt	51/65-70/,50/41/
2-NH_2	3-NO_2-2-NH_2[c] + 5-NO_2-2-NH_2[c]	20/20+63.1/,21-23,52-55
4-NH_2	4-NH_2-3-NO_2[c]	17[d] and 56[d]
2-NHMe	3-NO_2-2-NHMe[c] + 5-NO_2-2-NHMe[c]	18
3-NHMe	2-NO_2-3-NHMe[c]	27
4-NHMe	3-NO_2-4-NHMe[c]	19
2-NMe_2	3-NO_2-2-NMe_2 + 5-NO_2-2-NMe_2	57/11+51/,58
3-NMe_2	2-NO_2-3-NMe_2 + 2-NO_2-3-N/NO/Me	57/8+14/
4-NMe_2	3-NO_2-4-NMe_2	57/81/
3-$NHCO_2Et$	2-NO_2-3-$NHCO_2Et$	59/90/,60/60/,61
4-$NHCO_2Et$	3-NO_2-4-$NHCO_2Et$	62/60/
2-OH-4-Me	3-NO_2-2-OH-4-Me + 5-NO_2-2-OH-4-Me	37
2-NH_2-4-Me	3-NO_2-2-NH_2-4-Me[c] + 5-NO_2-2-NH_2-4-Me[c]	20/24.2+46.4/,63/25+56/,64, 65
2-NH_2-6-Me	3-NO_2-2-NH_2-6-Me[c] + 3-NO_2-6-NH_2-2-Me[c]	66/33+54/,67,68/25.3+58.4/
2,4-Me_2	3-NO_2-2,4-Me_2 + 5-NO_2-2,4-Me_2	69
2,6-Me_2	3-NO_2-2,6-Me_2	70/85/,71/81/,16/66/,72
2,4,6-Me_3	3-NO_2-2,4,6-Me_3	71/93/,16/90/

a/ Nitrating agents: concentrated or fuming nitric acid or potassium nitrate in concentrated sulfuric acid or oleum.

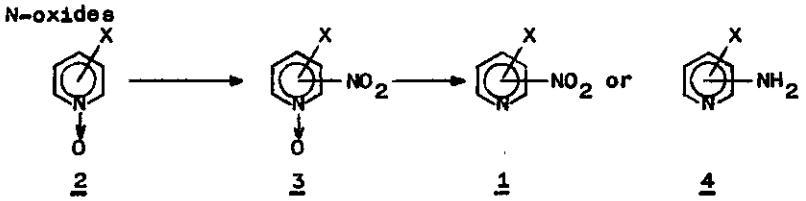
b/ According to ref.[73] the nitration of 3-ethoxypyridine affords 2-nitro-5-ethoxypyridine.

Table 1. /contd./

c/ Products formed in a two-step /sometimes one-pot/ synthesis /see the text/.

d/ The respective steps of the synthesis /compare note c/ are described in those two papers.

Table 2. Nitration[a] of pyridine N-oxides and deoxygenation[b] of nitropyridine



2 3 1 4

X	2 → 3[a]		3 → 1 or 4		
	Substituents in 3	References /yield, %/	Deoxidizer	Substituents in 1 or 4	References /yield, %/
H	4-NO_2	74/72/,75,76/63/, 77/72/	PCl_3	4-NO_2	77/79/,35/71/
H	4-NO_2	78/82-85/,79/85-90/	Fe,AcOH	4-NH_2	79
3-Me	4-NO_2-3-Me	80/76/,81/64/,82,83	Fe,AcOH	4-NH_2-3-Me	80/63/,81/60-70/
3-Me	4-NO_2-3-Me	84/70-73/,85	H_2/Pd	4-NH_2-3-Me	82/78.5/
3-Me	4-NO_2-3-Me		PCl_3	4-NO_2-3-Me	82/65/,86
3-Et	4-NO_2-3-Et	34	PCl_3	4-NO_2-3-Et	34
3-i-Pr	4-NO_2-3-i-Pr	34/60/	PCl_3	4-NO_2-3-i-Pr	34/79/
3-OH	2-NO_2-3-OH	87/60.5/	Fe,AcOH	2-NH_2-3-OH	87
3-OMe	4-NO_2-3-OMe	88/70-75/	Fe,AcOH	4-NH_2-3-OMe	88/95-100/
3-OEt	4-NO_2-3-OEt	89/70-80/	Fe,AcOH	4-NH_2-3-OEt	89
3-F	4-NO_2-3-F	90,91	$FeSO_4$	4-NH_2-3-F	90/84.7/
3-Cl	4-NO_2-3-Cl	76/84.5/	Fe/OH/$_2$	4-NH_2-3-Cl	92
3-Br	4-NO_2-3-Br	79/40/,93/57.5/ 62/84/	Fe,AcOH	4-NH_2-3-Br	79/80/
3-Br	4-NO_2-3-Br	34,76/84.2/,94	$FeSO_4$	4-NH_2-3-Br	95
3-J	4-NO_2-3-J	73/56.4/	PBr_3	4-NO_2-3-J	96/85.1/
4-NMe_2	3-NO_2-4-NMe_2	54/27/			

a/ See note e in Table 1.

b/ See also Table 4.

rivative is also formed[97,98] besides 4-nitro-3-methylpyridine. The data concerning the syntheses of nitropyridines and their N-oxides by ring substitution reactions are given in Tables 3 and 4. Numerous 4-aminopyridines can be easily oxidized to nitropyridines.

2.1. Hydroxypyridines

Although the equilibrium favours the pyridone forms of hydroxy-3-nitropyridines[99,100], the substitution of the hydroxy groups in those compounds by halogen is very easy /see Table 3/.

2.2. Halopyridines

4-Chloro-3-nitropyridine cannot be stored in a pure state for a long time, but its reactivity[101] makes that compound the good starting material in the syntheses of 4-substituted 3-nitropyridines /see Table 3/.

It should be mentioned that 3-chloro-, 3-bromo- and 3-iodo-4-nitropyridines and their N-oxides exchange the nitro group in the reaction with amines, potassium hydroxide and sodium alcoholates[102].

Tables 3 and 4 show the possibilities of the transformation of halonitropyridines to other nitropyridine derivatives.

2.3. Other pyridines

As it can be seen from Table 3 nitroamino and alkoxy groups in nitroamino and alkoxy-nitropyridines, respectively, can also be substituted by nucleophiles.

3. Nitropyridines by side-chain reactions

As it is known, the pyridone and thiopyridone forms of 2- and 4-XH substituted 3-nitropyridines /X = O, S/ are the favoured ones[99,100,113]. The absorption spectra show that equilibrium is much shifted towards the amino form of 2- and 4-amino-3-nitropyridines[162]. All those compounds, however, can be alkylated by alkyl halides at oxygen, sulfur and amino nitrogen atoms, respectively /see Table 5/.

The amino groups of aminonitropyridines are readily acylated by acetic anhydride /see Table 5/. However, in the reaction of 2-/N-methylamino/-3-nitropyridine and that anhydride the starting material was recovered[18].

The reactions of aminonitropyridines in which the amino group is transformed to the other ones *via* diazonium salts are also discussed in the present Section

Table 3. Ring substitution[a] in nitropyridines

X	Y	Position of nitro group	Notes	References /yield, %/
2-OH	2-NHR	3	R = H, Me	18,103
2-OH	2-Cl	3		104/91/,104/89/
2-OH	2-Br	3		105
3-OH	3-F	4	b	102/81.1/
4-OH	4-NH_2	3		56
2-OMe	2-Cl	3		106/65/,107
3-OMe	3-F	4	b	102/79.5/
4-OMe	4-Cl	3		47,62,108,109
3-OEt	3-F	4	b	102/89.3/
4-OEt	4-Cl	3	c	40,41,51/75-80/,62
2-OPh	2-Cl	3	d	110,111
4-OPh	4-Cl	3		43/89/
2-SH	2-Br	3		112/47/
2-SH	2-Cl	3		103,113
4-SH	4-Cl	3		43/70/
2-SMe	2-Cl	3		114/87.6/
4-SEt	4-Cl	3		115/100/
2-SBu-t	2-Cl	3		116/28/,117/32/,118/58/
4-SBu-t	4-Cl	3		119/44/
2-SPh	2-Cl	3		120
4-SPh	4-Cl	3		43
2-NH_2	2-F	3		98
3-NH_2	3-F	2		121
3-NH_2	3-Cl	2	e	121/15/
3-NH_2	3-Br	2	e	121/15/
3-NH_2	3-J	2	e	121/15/
3-NH_2	3-OEt	2		122

Table 3. /contd./

3-NH_2	3-F	4	b	102/76.6/
4-NH_2	4-Cl	3		40
4-NH_2	4-OEt	3		62/98/
2-NHMe	2-Cl	3		123/95/,124
3-NHMe	3-OMe	2		125
4-NHMe	4-Cl	3		126/93/,98,124
4-NHMe	4-OEt	3		62/98/
3-NHEt	3-F	4	b	102/86/
4-NHEt	4-Cl	3		126/89/
4-NHPr-n	4-OMe	3		127/100/
4-NHBu-n	4-Cl	3		126
3-NH/CH_2/$_2$OH	3-F	4	b	102
4-NH/CH_2/$_2$OH	4-Cl	3		126
4-NH/CH_2/$_2$$NH_2$	4-Cl	3		126
4-NH/CH_2/$_2$Ph	4-Cl	3		127/78/
3-$NHCH_2Ph$	3-F	2		121
3-$NHCH_2Ph$	3-J	2		121/15/
4-$NHCH_2Ph$	4-Cl	3		126,128/70/
2-$NHCH_2CO_2Et$	2-Cl	3		129
4-$NHCH_2CO_2Et$	4-Cl	3		44
2-NHC_6H_{11}-c	2-Cl	3		130/47/
4-NHC_6H_{11}-c	4-Cl	3		130/60.5/,128/90/
2-NHPh	2-Cl	3		131
2-NHAr	2-Cl	3	f	106,131
3-NHPh	3-F	2		121/55/
3-NHPh	3-F	4	b	102/79.2/
4-NHPh	4-Cl	3		132/50/
4-NHAr	4-Cl	3	f	131-133
4-NHAr	4-OMe	3	f	106
4-NHC_5H_4N-α	4-Cl	3		132/31/
2-$NHC_{10}H_7$-α	2-Cl	3		130/37/
4-$NHC_{10}H_7$-α	4-Cl	3		130/41/
2-$NHNH_2$	2-Cl	3		134/81/,135/100/

Table 3. /contd./

2-$NHNH_2$	2-$NHNO_2$	3		136/64.3/
3-$NHNH_2$	3-F	2	g	137/70-75/
4-$NHNH_2$	4-Cl	3		40,135/96/
4-$NHNH_2$	4-$NHNO_2$	3		136/68.3/
2-NMe_2	2-Cl	3		114/50/,57,124
4-NMe_2	4-Cl	3		98,124
2-N/Me/Ph	2-Cl	3		138
2-N/Me/NH_2	2-Cl	3		134/84/,116/43/
3-N/Me/NH_2	3-F	2		137/65-70/
2-$N/CH_2/_n$	2-Cl	3	n=2,4,5,6	124,139
4-$N/CH_2/_n$	4-Cl	3	n=4,5,6	124,139
3-$N/CH_2/_4O$	3-F	2		121
3-$N/CH_2/_4O$	3-Cl	2	h	121
3-$N/CH_2/_4O$	3-Br	2	h	121
3-$N/CH_2/_4O$	3-J	2		121/40/
2-$N/CH_2/_4O$	2-Cl	3		139
4-$N/CH_2/_4O$	4-Cl	3		139
2-F	2-Cl	3		140/76/
2-Cl	2-OH	3		103-105,131,141/97/, 107/100/
2-Cl	2-$NHNO_2$	3		142/17.4/,142/57.9/
4-Cl	4-OH	3		43/82/,133/70-80/,41,44 47,108,109,131,143,144
4-Cl	4-$NHNO_2$	3		142/58/
2-Br	2-OH	3		114/51.7/,145/54/,104,105
2-Br	2-$NHNO_2$	3	i	142/13.6/
2-Br	2-$NHNO_2$	3		142/58.9/
4-Br	4-OH	3		119/51/
4-Br	4-$NHNO_2$	3		142/20.2/,142/36.4/
2-CN	2-Br	3		105
2-SCN	2-Cl	3		146,147
4-SCN	4-Cl	3		144
2-$CH/CO_2Et/_2$	2-Cl	3		148
4-$CH/CO_2Et/_2$	4-Cl	3		149/37/,149/97/,119

Table 3. /contd./

4-CH/CO_2Et/$_2$	4-OMe	3		47
4-CH/CO_2Et/$_2$	4-OEt	3	j	41
2-CH/CN/CO_2Me	2-Cl	3		150/82/
2-CH/CN/CO_2Et	2-Cl	3		150/87/
4-CH/CN/CO_2Et	4-Cl	3		150/52/
4-CH/Ac/CO_2Et	4-Cl	3		149/96/
4-CH/Ac/$_2$	4-Cl	3		149/66/
4-NHC/NH_2/=NH	4-Cl	3		151/22/
2-NHC$_m$H$_n$$CO_2$H	2-F	3	k	152
2-Cl-4-Me	2-OH-4-Me	3		153/80/,154/76.6/,64
6-Cl-4-Me	6-OH-4-Me	3		64
2-Cl-4-Me + + 6-Cl-4-Me	2-OH-4-Me + + 6-OH-4-Me	3		65/60/
6-Cl-2-Me	6-OH-2-Me	3		66/87/
6-NHNH_2-2-Me	6-Cl-2-Me	3		66/88/
6-NHNH_2-2-Me	6-NHNO_2-2-Me	3		136/53.5/

a/ To substitute the group Y by X, sodium, potassium and barium hydroxides, hydrogen potassium sulfide, alcohols and thioalcohols, alcoholates and thioalcoholates, halides of phosphorus, potassium fluoride and thiocyanate, cuprous cyanide, ammonia derivatives and sodium salts of ethyl and methyl malonate, cyanoacetate and acetoacetate and some other reagents were used.

b/ Other 3-halogeno-4-nitropyridines exchange the nitro group in similar conditions.

c/ The product described erroneously as 4-chloro-3-nitropyridine[62].

d/ Also the reaction with substituted phenols.

e/ Respective 2-amino-3-halogenopyridines /50-60%/ are also formed.

f/ Ar = substituted phenyls.

g/ Triazolopyridine derivative /15-20%/ is also formed in the reaction.

h/ 2-Morpholino-3-halogenopyridine is also formed in the reaction.

i/ 2-Amino-3-nitropyridine /46.4%/ is also formed in the reaction.

j/ Ethoxynitropyridine was the starting material /see note c/.

k/ The reaction of 2-fluoro-3-nitropyridine with amino acids.

Table 4. Ring substitution[a] in nitropyridine N-oxides and deoxygenation[b] of pyridine N-oxides

5 3 1 4

Y	X	5 → 3[a] Position of nitro group	Notes	References /yield, %/	3 → 1 or 4 Deoxidizer	Substituents in 3	Substituents in 1 or 4	References /yield, %/
H	H	2		-	PCl_3	$2\text{-}NO_2$	$2\text{-}NO_2$	155
H	H	3		-	PCl_3	$3\text{-}NO_3$	$3\text{-}NO_2$	156/43/
		4			$HOSO_3NO$	$4\text{-}NO_2$	$4\text{-}NO_2$	35/93/
					NO	$4\text{-}NO_2$	$4\text{-}NO_2$	35/91.5/
					H_2SO_4,HNO_3	$4\text{-}NO_2$	$4\text{-}NO_2$	157/93-95/, 35/91/
3-Me	3-Me	2		-	PCl_3	$2\text{-}NO_2\text{-}3\text{-}Me$	$2\text{-}NO_2\text{-}3\text{-}Me$	155
3-Me	3-Me	4		-	PCl_3	$4\text{-}NO_2\text{-}3\text{-}Me$	$4\text{-}NO_2\text{-}3\text{-}Me$[c]	97
					NO,H_2SO_4	$4\text{-}NO_2\text{-}3\text{-}Me$	$4\text{-}NO_2\text{-}3\text{-}Me$	35/81/
3-F	3-OH	4	d	90/50.8/,				
			d	90/91.1/,				
			d	90/81.2/				
3-F	3-OH	4		90/88.8/				
3-F	3-OMe	4	d	90/100/				

Table 4. /contd./

3-F	3-OEt	4	d	90/100/				
3-F	3-OPh	4		158/40.8/				
3-F	3-$OC_6H_4NO_2$-p	4		90/72.2/				
3-F	3-SPh	4		158/76.4/				
3-F	3-SCN	4		158/55.1/				
3-Br	3-NH_2	4	d	159/28.8/				
3-F	3-NH_2	4	d	90/100/	PCl_3	4-NO_2-3-NH_2	4-NO_2-3-NH_2	90/89.2/
3-Br	3-NHMe	4		62/90/	H_2/Ni	4-NO_2-3-NHMe	4-NH_2-3-NHMe	62/87/
3-F	3-NHEt	4	d	158/98.4/				
3-Br	3-$NHCH_2Ph$	4		159/81.3/				
3-Br	3-NHC_6H_{11}-c	4		159/75.6/	Fe,AcOH	4-NO_2-3-NHC_6H_{11}-c	4-NH_2-3-NHC_6H_{11}-c	159/71.8/
3-Br	3-NHPh	4	d	159/47.4/	Fe,AcOH	4-NO_2-3-NHPh	4-NH_2-3-NHPh	159/87.4/
3-Cl	3-NHPh	4	d	76				
3-F	3-NHPh	4	d	90/89/				
3-J	3-NHPh	4	d	76				
3-F	3-NHAr	4	e	158/90.3-96.7/				
3-Br	3-$NH/CH_2/_2OH$	4	d	159/73.4/				
3-F	3-$NH/CH_2/_2OH$	4	d	158/82.6/				
3-F	3-$NHC_mH_nCO_2H$	4	f	160/46.6-99/				
3-F	3-$NHNH_2$	4		158/98.5/				
3-Br	3-$NHNH_2$	4		159/68.7/				

Table 4. /contd./

3-F	3-NHNHC$_6$H$_4$Me-p	4		158/60.8/				
3-Br	3-NMe$_2$	4		159/83.3/	Fe,AcOH	4-NO$_2$-3-NMe$_2$	4-NH$_2$-3-NMe$_2$	159/75.6/
3-F	3-NEt$_2$	4		158/95.5/				
3-Br	3-NEt$_2$	4		159/57.1/				
3-F	3-N/CH$_2$/$_5$	4		91				
4-OH	4-Cl	3		141/82/				
4-OAc	4-Cl	3		36				
3-Br	3-Br	4		-	NO,H$_2$SO$_4$	4-NO$_2$-3-Br	4-NO$_2$-3-Br	35/75/
3-CO$_2$H	3-CO$_2$H	4		-	H$_2$/Pd	4-NO$_2$-3-CO$_2$H	4-NH$_2$-3-CO$_2$H	97,161
3-Br	3-CH/CO$_2$Et/$_2$	4		93/91.9/				
3-Br	3-CH/CN/CO$_2$Et	4		93/80.3/				
3-Br	3-CH/Ac/CO$_2$Et	4		93/65.4/				

a/ See note e in Table 3.

b/ See also Table 2.

c/ 4-Chloro-3-methylpyridine is also formed in the reaction.

d/ It was found[102] that 3-chloro-, 3-bromo- and 3-iodo-4-nitropyridine N-oxides exchange the nitro group in such reactions.

e/ Ar = o-, m- and p-methylphenyls.

f/ Reaction of 3-fluoro-4-nitropyridine N-oxides with amino acids.

Table 5. Side-chain reactions in nitropyridines

X	Y	Position of nitro group	Reagent	Notes	References /yield, %/
2-Me	2-CH/CO_2Et/$_2$	3	HClaq		148
4-Me	4-CH/CO_2Et/$_2$	3	HClaq		149/86/,41, 47,119
2-OH	2-OMe	3	HClaq		106
2-OMe	2-OH	3	1/$AgNO_3$,2/MeJ	a	106/18/
3-OMe	3-OH	2	Me_2SO_4		125/77-99/
3-OAc	3-OH	2	AcCl		33/74/
4-SH	4-SEt	3	NaOHaq		115
4-SH	4-SCN	3	EtONa		163
2-SMe	2-SH	3	1/NaOHaq,2/MeJ		113
4-SMe	4-SH	3	1/NaOHaq,2/MeJ		113
4-SR	4-SH	3	1/KOHaq,2/RHal	b	163
4-SEt	4-SH	3	EtJ		115
4-SO_2R	4-SR	3	$KMnO_4$	c	163/30-80/
2-SO_2NH_2	2-SH	3	1/HClaq,Cl_2, 2/NH_4OH		164/<1/
2-SCl	2-SH	3	Cl_2		165/100/
2-SBr	2-SH	3	Br_2		165
2-SOMe	2-SCl	3	MeOH,Et_3N		165/78/, 166/78/
2-SOR	2-SCl	3	ROH[d]	f	166
2-SNRR'	2-SCl	3	R'RNH[e]	f	165
3-N_3	3-NH_2	2	1/HNO_2,2/NaN_3		167/78-80/
3-NH_2	3-NHCO_2Et	2	NaOHaq		60/86/,61/57/
2-NHMe	2-NH_2	3	MeJ		18
3-NHMe	3-N/Me/CO_2Et	2	KOHaq		60/64/
4-NHMe	4-N/Me/CO_2Et	3	KOHaq	g	62
2-NHAc	2-NH_2	3	Ac_2O		168

Table 5. /contd./

3-NHAc	3-NH_2	2	Ac_2O		169/70/
4-NHAc	4-NH_2	3			144
4-$NHSO_2C_6H_4Me$-p	4-NH_2	3	p-$MeC_6H_4SO_2Cl$		62/98/
2-$NHNO_2$	2-NH_2	3	H_2SO_4,HNO_3		136/90.4/, 170
3-$NHNO_2$	3-NH_2	4	H_2SO_4,HNO_3		136/52.9/
4-$NHNO_2$	4-NH_2	3	H_2SO_4,HNO_3		136/75.5/,56
2-NHNHAc	2-$NHNH_2$	3	Ac_2O		134/65/
4-NHNHAc	4-$NHNH_2$	3	Ac_2O		151/78/
4-$NHCO_2Me$	4-NHCSOMe	3	KOHaq,H_2O_2		171
4-$NHCO_2Et$	4-NHCSOEt	3	KOHaq,H_2O_2		171
4-$NHCO_2Et$	4-NH_2	3	$ClCO_2Et$		171
2-N/Me/NHAc	2-N/Me/NH_2	3	Ac_2O		134/70/
2-N/Me/NO_2	2-NHMe	3	H_2SO_4,HNO_3		18
4-N/Me/NO_2	4-NHMe	3	H_2SO_4,HNO_3		172/26/
3-N/Me/CO_2Et	3-$NHCO_2Et$	2	Me_2SO_4		60/93/
4-N/Me/CO_2Et	4-$NHCO_2Et$	3	Me_2SO_4	g	62
2-NH/CH_2/$_2$Cl	2-N/CH_2/$_2$	3	HClaq		124
3-F	3-NH_2	2	1/HBF_4,EtONO, 2/140°		121/25/
3-Cl	3-NH_2	2	1/HNO_2,2/Cu_2Cl_2		169/60/, 121/55/
3-Br	3-NH_2	2	1/HNO_2,2/Cu_2Br_2		169/60/, 121/65/
3-J	3-NH_2	2	1/HNO_2,2/KJ		169/40/, 121/70/
2-CHO	2-Me	3	SeO_2		173
2-CHO	2-CH_2OH	3	SeO_2		173
3-CHO	3-$CHBr_2$	2	$AgNO_3$aq		174/80/
4-CHO	4-Me	3	SeO_2		175/<74/
2-CO_2H	2-Me	3	$KMnO_4$		71/12/, 153/45/
3-CO_2H	3-Me	2	$KMnO_4$ or H_2O_2		153/42/,176

Table 5. /contd./

3-CO_2H	3-Me	4	$KMnO_4$		153/45/,97
4-CO_2H	4-Me	3	$KMnO_4$		153/35/
2-CO_2Me	2-CO_2H	3	CH_2N_2		116/50/
3-CO_2Me	3-CO_2H	2	MeOH,PPA[h]		176
3-CO_2Me	3-CO_2H	2	CH_2N_2	i	169/56/
3-CO_2Me	3-CO_2H	4	CH_2N_2	j	169/28/
4-CO_2Me	4-CO_2H	3	CH_2N_2		119/84/
2-$CONH_2$	2-CO_2Me	3	NH_4OH		98
3-$CONH_2$	3-CO_2Me	2	NH_4OH		169/85/
3-$CONH_2$	3-CO_2Me	4	NH_4OH		169/90/
4-$CONH_2$	4-CO_2Me	3	NH_4OH		119/50/
3-CN	3-NH_2	2	1/HNO_2, 2/$Cu_2/CN/_2$		169/12/
4-CN	4-$CONH_2$	3	P_2O_5		119/60/
2-CH_2Br	2-Me	3	Br_2		148/31/
2-$CHBr_2$	2-Me	3	Br_2		148/39/
4-CH_2Ac	4-$CHAc_2$	3	HCl,EtOH		149/96.4/
4-CH_2CO_2Et	4-$CH/Ac/CO_2Et$	3	HCl,EtOH		149/86/
2-CH_2NHPh	2-CH_2Br	3	$PhNH_2$		148/82/
2-CH_2NHAr	2-CH_2Br	3	$ArNH_2$	k	148
3-$CHBr_2$	3-Me	2	NBS[l]		174
3-$CH=C/CO_2Et/_2$	3-CHO	2	$CH_2/CO_2Et/_2$		174/90/
2-CH=CHPh	2-Me	3	PhCHO		177
4-CH=CHAr	4-Me	3	ArCHO		177,47
2-OH-4-Me	2-NH_2-4-Me	3	HNO_2		178/100/, 154/77/
2-OH-4-Me + + 6-OH-4-Me	2-NH_2-4-Me + + 6-NH_2-4-Me	3	HNO_2		65/66/,64
6-OH-2-Me + + 6-Cl-2-Me	6-NH_2-2-Me	3	HCl aq,$NaNO_2$		66/98+0/, 68/49+29/
6-NHNHSO_2Ph-2-Me	6-$NHNH_2$-2-Me	3	$PhSO_2Cl$		65/57/
2-CH_2OAc-4-Me + + 6-CH_2OAc-4-Me	2,4-Me_2 + + 4,6-Me_2	3	1/AcOH,H_2O_2, 2/Ac_2O		173

Table 5. /contd./

2-CH_2OH-4-Me + + 6-CH_2OH-4-Me	2-CH_2OAc-4-Me + + 6-CH_2OAc-4-Me	3	HCl aq		173
2-CO_2H-4-Me + + 6-CO_2H-4-Me	2-CH_2OH-4-Me + + 6-CH_2OH-4-Me	3	$KMnO_4$		173
2-CO_2H-4-Me + + 4-CO_2H-2-Me	2,4-Me_2	3	$KMnO_4$		71
6-CO_2H-2-Me	2,6-Me_2	3	$KMnO_4$		71
6-CO_2H-2-Me	2,6-Me_2	3	1/SeO_2, 2/$KMnO_4$ or HNO_3		70/31/, 72/30/
6-CO_2H-2,4-Me_2 + + 4-CO_2H-2,6-Me_2	2,4,6-Me_3	3	$KMnO_4$		71

a/ N-Methyl-3-nitro-2-pyridone is the main product /59%/ in the reaction.

b/ R = Me, Et, n-Pr, i-Pr and other groups.

c/ R = Me, Et and n-Pr.

d/ Various C- and N-hydroxy compounds.

e/ Secondary amines.

f/ Substituents R and R' are those occuring in the reagent.

g/ Overall yield of the reaction -$NHCO_2Et$ ⟶ -/Me/CO_2Et ⟶ -NHMe amounts to 65%.

h/ PPA = polyphosphoric acid.

i/ The product of the reaction has mp 46.5-47.0°C and proper ir, nmr and mass spectra and correct C, H and N analyses. According to ref.[164] ester melts at 125°C.

j/ Methyl 4-hydroxynicotinate /56%/ is also formed in the reaction.

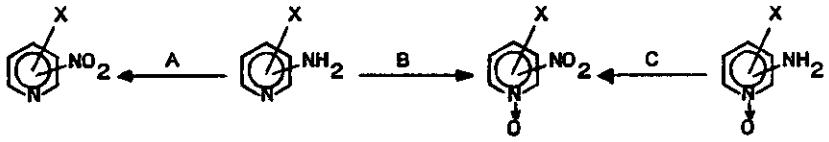
k/ Ar = substituted phenyls.

l/ NBS = N-bromosuccinimide.

considering the step -NH_2 ⟶ -$N_2^{\oplus}$. How useful is that reaction in the preparation of nitropyridines one can see from Table 5.

The amino groups in the positions 2 and 4 of the ring of pyridine derivatives can be easily oxidized to the nitro groups /see Table 6/. Caro acid is a good oxidizer for 3-chloro- and 3-bromo-4-aminopyridines but not for the respective iodo derivative[92]. Similar reactions of the 3-amino group are known[57,179]. How-

Table 6. Transformation of amino to nitro group in aminopyridines and their N-oxides



X	Position of amino or nitro group	Reaction	Reagent	References /yield, %/
H	2	A	oleum, H_2O_2	182
H	2	A	/NH_4/$_2S_2O_8$, H_2O_2, H_2SO_4	183/30/
H	3	A	oleum, H_2O_2	179/37.9/, 184/10/
H	3	A	1/H_2SO_4, KNO_2, 2/Chevreul salt, KNO_2	179/20/
H	3	A	1/HNO_2, 2/$NaBF_4$, 3/Cu, $NaNO_2$	185
H	4	A	oleum, H_2O_2	182/80/
2-Me	3	A	1/H_2SO_4, KNO_2, 2/Chevreul salt, $NaNO_2$	66/15/
3-Me	2	A	oleum, H_2O_2	186/60-68/, 176
3-Me	4	A	oleum, H_2O_2	153/82/
3-Me	4	A + B	oleum, H_2O_2	97
3-F	4	A	oleum, H_2O_2	102/89/
3-Cl	4	A	oleum, H_2O_2	92/71.2/
3-Br	4	A	oleum, H_2O_2	92/85.2/
3-SO_2NH_2	2	A	oleum, H_2O_2	164/31/
3-SO_2NH_2	4	A	oleum, H_2O_2	164/7/
H	2	C	oleum, H_2O_2	155/50/
H	3	A + B	/CF_3CO/$_2O$, H_2O_2	156/21.2+22.4/
H	3	C	/CF_3CO/$_2O$, H_2O_2	156/34/
3-Me	2	C	oleum, H_2O_2	155/55/

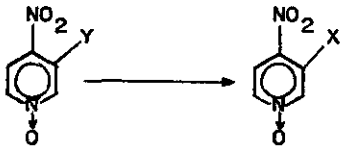
ever, the repeating of the synthesis of 3-nitropyridine from 3-aminopyridine using Caro acid was unsuccesseful[98]. The required 3-nitropyridines can also be obtained in the reaction of 3-pyridyldiazonium salts with sodium or potassium nitrite in the presence of cuprous ions supplied by the Chevreul salt /"cupro-cupri sulfite"/[66,179]. The synthesis of that catalyst is well described[180,181].

4-Cyano-3-nitropyridine can be obtained from 3-nitroisonicotinamide[119]. Dehydration of 3-nitroisonicotinaldehyde oxime also gives the respective nitrile[98]. The conditions of that reaction are the same as described for the transformation of 2,4-dinitrobenzaldehyde to 2,4-dinitrobenzonitrile /dehydration of oxime by acetic anhydride[187].

The transformation of 3-nitro-4-chloropyridine to 3-nitro-4-methylpyridine via diethyl 4-/3-nitropyridyl/malonate /see Tables 3 and 5/ is worthy of recommendation. The overall yield of the synthesis amounts to 90%[119]. The skin irritating properties of staring 4-chloro-3-nitropyridine are the serious problem in the reaction.

Table 7 contains the information concerning the synthesis of some important 3-substituted 4-nitropyridine N-oxides which are the potential source of 3-substituted 4-nitropyridines

Table 7. Side-chain reactions in 3-substituted 4-nitropyridine N-oxides

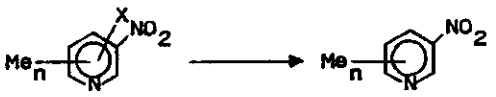


X	Y	Reagent	References /yield, %/
CO_2H	Me	H_2SO_4, $Na_2Cr_2O_7$	122/75/, 188/56/, 97
CO_2Me	CO_2H	1/$AgNO_3$, 2/MeJ	97
$CONH_2$	CO_2H	1/Et_3N, $ClCO_2Et$, 2/NH_4OH	189/65/
CH_2CO_2H	$CH/CO_2Et/_2$	H_2SO_4	93/81/
$NHNO_2$	NH_2	H_2SO_4, HNO_3	136/92.3/

4. Pulling out the redundant substituents in poly-substituted nitropyridine derivatives

The exchange of some substituents, e.g. -Cl, $-NHNH_2$, $-CO_2H$, in some poly-substituted nitropyridine derivatives /for their syntheses see Tables 1, 3 and 5/ by hydrogen affords some 3-nitropicolines /see Table 8/. Eepecially the decarboxylation of proper 3-nitropicolinecarboxylic acids is worthy of recommendation. 3-Nitropyridine can be obtained by the oxidation of the hydrazine groups in 2-, 4- and 6-hydrazino- or 4,6-dihydrazino-3-nitropyridines by silver acetate[136] or silver oxide[135]. The reaction of 2-hydrazino-5-nitropyridine with copper sulfa-

Table 8. Synthesis of nitropicolinee by pulling out the redundant substituents in poly-substituted nitropyridines



n	Position of methyl groups	X	Reaction conditions	References /yield. %/
1	4	2-Cl	$PhCO_2H$,Cu	153/70/
1	4	2-Cl + 6-Cl[a]	$PhCO_2H$,Cu	65/44/
1	2	6-Cl	$PhCO_2H$,Cu	65/33/
1	2	6-$NHNH_2$	$CuSO_4$	66/15-20/
1	2	6-$NHNHSO_2Ph$	$OH^{\ominus}$	65/21/
1	2	4-CO_2H	280°	71
1	2	6-CO_2H	205-255°	71/97.6/,72,173/85/
1	4	2-CO_2H	145°	71
1	4	2-CO_2H + 6-CO_2H[b]	130°	173
2	2,4	6-CO_2H	180-220°	71/86/

a/ The starting material was a mixture of 2- and 6-chloro-4-methyl-3-nitropyridines.

b/ The starting material was a mixture of 4-methyl-3-nitro-2- and -6-pyridinecarboxylic acids.

te also gives 3-nitropyridine[190].

5. Other methods

2-Nitro-3-aminopyridine was obtained by the hydrolysis of N,N'-di/2-nitro-3-pyridyl/urea[191].

3-Nitropyridine N-oxide obtained from 3-aminopyridine /see Table 6/ can be transformed to a mixture of 2-chloro-3- and -5-nitropyridines /30 and 8.4%, respectively/ in the reaction with phosphorus oxychloride[156]. The mentioned N-oxide can react with acetic anhydride[156] giving 2-hydroxy-3-nitropyridine /50%/.

4-Amino-3-nitropyridine is formed in the reaction of 4-chloro-3-nitropyridine with potassium thiocyanate in acetic buffer[144].

The mixture of 3-nitro-4-aminopyridine and proper alkyl 4-/3-nitropyridyl/thiocarbamate is formed in the reaction of 4-/3-nitropyridyl/thiocyanate with ethyl,

n- and iso-propyl and n-butyl alcohols[115].

2- and 4- hyroxymethyl-3-nitropyridine acetates were obtained in the reaction of 2- and 4-methyl-3-nitropyridine N-oxides with acetic anhydride[173]. The former product was hydrolysed in diluted hydrochloric acid to 2-hydroxymethyl-3-nitropyridine[173].

Peroxyacetic acid oxidation of 2- and 4-methyl-3-nitropyridine gives proper pyridine N-oxides in 66 and 57% yield, respectively[173]. These compounds can also be obtained from 3-nitrolutidine N-oxides by decarboxylation of their oxidation products[173]. Similar treatment of 2-methyl-3-nitropyridine N-oxide affords 3-nitropyridine N-oxide[192].

6. Complementary remarks

The information presented in this Section is based mainly on our results not published yet. The elementary analyses /C, H and N/ and ir, nmr and mass spectra of the compounds are in agreement with the assigned structures.

As it can be seen from Table 3, tert-butyl thiolate reacts with 2- and 4-chloro-3-nitropyridine giving the respective 3-nitropyridyl-tert-thioethers. Such substitution of a chlorine atom by tert-butoxy group does not proceed /starting material is being recovered/[193]. The above mentioned chloronitropyridines also react with tert-butylamine. Thus, refluxing /2h/ the mixture of 2-chloro-3-nitropyridine and tert-butylamine /molar ratio 1 : 30/ leads to 2-/N-tert-butylamino/-3-nitropyridine /97.5%/, mp 29-31°C /purified by steam followed by vacuum distillations/. Similarly, 4-chloro-3-nitropyridine refluxed /0.5h/ together with the same amine /ratio 1 : 20/ in THF is transformed to 4-/N-tert-butylamino/-3-nitropyridine /72%/, mp 99.5-101.5°C /tert-butylamine hydrochloride was removed from the reaction mixture by filtration, THF evaporated and the residue recrystallized from 50% aqueous acetone/.

Some important information concerning the reaction of O-, S- and NH-tert-butyl nucleophiles with halonitroarenes has been published[193].

Acetylaminonitropyridines can be easily obtained from respective aminonitropyridines. 4-Acetylamino-3-nitropyridine was synthetized in the conditions given for the other isomers[98] /see Table 5/. The residual starting material is removed by extraction with benzene.

2- and 4-/N-benzoylamino/-3-nitropyridines are not formed in the reaction of proper aminonitropyridines with benzoyl chloride in an aqueous solution of so-

dium hydroxide or in anhydrous pyridine.

Amides were not obtained either in the reactions of 2- and 4-amino-3-nitropyridines with trifluoroacetic anhydride.

2-/N-Tosylamino/-3-nitropyridine was obtained in the manner given for its isomer /see Table 5/ during 5h reflux. After crystallization from ethanol it melts at 153-154.5°C.

2-/N-2-Pyridylamino/-3-nitropyridine was obtained by heating the mixture of 2-chloro-3-nitropyridine and 2-aminopyridine /molar ratio 1 : 2/ at 150°C till it got black. The product has mp 119-121°C /from water/. 4-Chloro-3-nitropyridine refluxed in an excess of concentrated aqueous solution of ammonia affords 4-amino-3-nitropyridine. 2-Hydrazino-3-nitropyridine was obtained in 50% yield when hydrazine hydrate was added to the methanolic solution of 2-bromo-3-nitropyridine.

The substitution of chlorine by iodine in 2- and 4-chloro-3-nitropyridines /the same conditions as in the reaction 2,4-dinitrochlorobenzene ⟶ 2,4-dinitroiodobenzene[194]/ was unsuccessful: the starting materials have been recovered. Unlike the reaction of 2-bromo-3-nitropyridine and cuprous cyanide /see Table 3/, the respective 4-bromo derivative is not a good starting material in the synthesis of 3-nitroisonicotinenitrile in DMF or without solvent. Perhaps, it is difficult to decompose the formed adduct of the products of the reaction[195,196]. It should be said that the position of the bromine atom and the presence and position of the nitro group should not be the explanation of the failure of the reaction because the respective nitriles are formed in similar conditions from 2-ethyl-4-bromopyridine[196] and 2,4-dinitrobromobenzene[195].

2- and 4-aminopyridines exist mainly in the amino form[197]. It is necessary to use the more concentrated acid during diazotization because some protons react with the ring nitrogen atom[198]. As it can be seen from Table 5 the amino group in aminonitropyridines can be transformed in the discussed way to any halogen. The 2-amino group in some methyl substituted amino-3-nitropyridines reacts with hydrofluoric acid and sodium nitrite giving, after a decomposition of the formed diazonium salt, respective 2-fluoro derivatives[199]. Unfortunately, it was not possible to obtain 2-iodo-3-nitropyridine from 2-amino-3-nitropyridine[98] /conditions of the reaction were taken from the synthesis of 2-iodo-5-nitropyridine from 2-amino-5-nitropyridine[200]/ and 4-cyano-3-nitropyridine[98] and 4-fluoro-3-nitropyridine[201] from 4-amino-3-nitropyridine. The expected exceptionally

high reactivity of 4-fluoro-3-nitropyridine is, perhaps, responsible for the difficulties in its obtaining.

Unlike 4-nitro-3-methylpyridine N-oxide /see Section 2/ 4-chloro-3-ethylpyridine is not formed during the deoxygenation of 4-nitro-3-ethylpyridine N-oxide by phosphorus trichloride.

The syntheses of 3-substituted 4-nitropyridines mentioned in the previous Sections are more complicated than it was stated in the original papers. The corrected procedures for some of them will be published in the near future.

The reactions of nitroamino-3-nitropicolines with silver acetate and copper sulfate /see Table 8/ afford proper nitropicolines in a very low yield. Instead, the decarboxylation of the respective methylnitropyridinecarboxylic acids /see Table 8/ is worthy of recommendation.

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Received, 29th January, 1987