

Chlorination of Substituted 2-Pyridones with Nitril Chloride**M. V. Proštenik, V. Slukan, F. Zorko, Z. Hranilović, and S. Škreb*»PLIVA« *Pharmaceutical and Chemical Works, Zagreb, Croatia, Yugoslavia*

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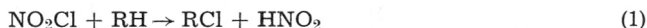
Nitril chloride (NO_2Cl) was used for the first time as a chlorinating agent in the 2-pyridone series. Substituted 2-pyridones were treated with nitril chloride in benzene. 5-Chloro and 3,5-dichloro derivatives were obtained in good yields. Formation of nitro compounds was not observed.

It is already known, that substitution reactions of aromatic hydrocarbons with nitril chloride lead to chloro or nitro derivatives. Thus Price and Sears¹ had reported that benzene in carbon disulfide as a solvent and in the presence of aluminium trichloride was nitrated in 90% yield, whereas toluene gave a mixture of *o*- and *p*- nitro toluene. Without Lewis acids benzene did not react with nitril chloride². On the other hand, phenantrene was nitrated in excellent yield in carbon tetrachloride without using catalyst³. Collis and Goddard⁴ studied the reaction of nitril chloride with various aromatic compounds. The mixtures of chloro and nitro derivatives were obtained with naphthalene, anisole and phenole. With the latter, at low temperature nitration predominated.

Our attempt to prepare 3-cyano-4-methoxymethyl-5-nitro-6-methyl-2-pyridone, an intermediate in pyridoxine production, by nitration of 3-cyano-4-methoxymethyl-6-methyl-2-pyridone (II) with nitril chloride, was unsuccessful. Only 5-chloro derivative XII was obtained in benzene as a solvent. Other solvents (acetic acid, carbon tetrachloride, carbon dichloride and ethyl acetate) were employed and the reaction temperature was varied from -5 to 80°C but changing reaction conditions did not result in the formation of the nitro derivative.

Reactions of nitril chloride with other substituted 2-pyridones (Table I) lead to 5-chloro derivatives (Table II). The yields were similar to those obtained with other used chlorinating agents such as chlorine or sulfuryl chloride^{5,6}.

In the case of 1-amino-2-pyridones VIII, IX and X, deamination occurs at the same time as chlorination. Ried and Meyer⁷ had described deamination of X with sodium nitrite in glacial acetic acid. According to the equation 1² the nitrous acid is formed in reaction of 2-pyridones with nitril chloride, what could be the explanation for deamination of the 1-amino group.



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EXPERIMENTAL

Melting points are uncorrected. Ir spectra were taken on a Perkin-Elmer Model 257 spectrophotometer in KBr pellets.

1,6-Dimethyl-3-cyano-4-methoxymethyl-2-pyridone (IV)

To the solution of 91.2 g K_2CO_3 (anhydrous) and 222 g (2.26 mol) of *N*-methyl cyanoacetamide in 1460 ml of water, 294 g (2.26 mol) of freshly distilled 1-methoxy pentadione-2,4 was added. After stirring for six hours at room temperature, the crude product was collected by filtration; yield 369.6 g, m. p. 83–98 °C. An additional portion (27 g) was obtained by extraction of mother liquor with 3×200 ml of chloroform.

Crude product IV (369 g) was dissolved in 930 ml of hot 96% ethanol. The solution was cooled slowly to room temperature without shaking. The mother liquor was carefully decanted from separated crystals of IV, in order to avoid the crystallization of more soluble isomeric 1,4-dimethyl-3-cyano-6-methoxymethyl-2-pyridone. Thereby, 137.5 g (37.1%) of pure IV, m. p. 100–103 °C, were obtained. Ir spectrum: 2210, 1640, 1590, 1120, 950 and 770 cm^{-1} .

Anal. $C_{10}H_{12}N_2O_2$ (192.21) calc'd: C 62.48; H 6.29; N 14.58%
found: C 62.70; H 6.40; N 14.54%

1-Amino-3-cyano-4-methoxymethyl-6-methyl-2-pyridone (VIII)

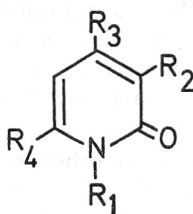
Abs. ethanol (115 ml) and 28.5 g (0.287 mol) of cyanoacetylhydrazine were heated to 60 °C and 37.4 g (0.287 mol) of 1-methoxy pentadione-2,4 and 2.5 ml of diethylamine was added. The mixture was refluxed for six hours. After cooling, the crude product was collected by filtration; yield 38.9 g, m. p. 123–127 °C. Crystallization from 389 ml of water gave 30 g (54.2%) of VIII, m. p. 135–137 °C. Ir spectrum: 3300, 3200, 2220, 1620, 1110, 920 and 760 cm^{-1} .

Anal. $C_9H_{11}N_3O_2$ (193.20) calc'd: C 55.95; H 5.74; N 21.75%
found: C 56.20; H 5.53; N 21.79%

1-Amino-3-cyano-4-carboxyethyl-6-methyl-2-pyridone (IX)

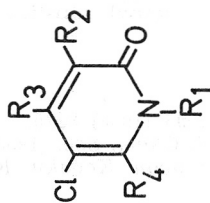
Abs. ethanol (12 ml) and 2.85 g (0.0287 mol) of cyanoacetylhydrazide were heated to 60 °C and 4.55 g (0.0287 mol) of ethylacetyl pyruvate and 0.3 ml of diethylamine were added. The mixture was refluxed for two hours. After cooling the product was

TABLE I



No	R ₁	R ₂	R ₃	R ₄	Ref. No
I	H	CN	CH ₃	CH ₃	9
II	H	CN	CH ₂ OCH ₃	CH ₃	10
III	H	CN	CH ₃	CH ₂ OCH ₃	10
IV	CH ₃	CN	CH ₂ OCH ₃	CH ₃	
V	H	CN	COOEt	CH ₃	
VI	H	H	H	CH ₃	11
VII	H	H	CH ₃	H	12
VIII	NH ₂	CN	CH ₂ OCH ₃	CH ₃	12
IX	NH ₂	CN	COOEt	CH ₃	
X	NH ₂	CN	CH ₃	CH ₃	7

TABLE II



No	From pyridone	R ₁	R ₂	R ₃	R ₄	Yield/%	M. p./°C	Anal.			Calc'd: Found:			Ref. No.
								C	H	N	C	H	N	
XI	I X	H	CN	CH ₃	CH ₃	90.5 85.5	275—8							6
XII	II VIII	H	CN	CH ₂ OCH ₃	CH ₃	86.0 78.1	205 ^a 197			50.83 50.71	4.27 4.00	13.18 13.40		
XIII	III	H	CN	CH ₃	CH ₂ OCH ₃	70.0	220—2 ^b			50.83 50.70	4.27 4.32	13.18 13.00		13
XIV	V IX	H	CN	COOEt	CH ₃	91.0 89.4	180 189							
XV	IV	CH ₃	CN	CH ₂ OCH ₃	CH ₃	71.3	125 ^b			52.99 52.72	4.89 4.62	12.36 12.11		
XVI	VI ^d	H	Cl	H	CH ₃	47.0	219							5
XVII	VII ^c	H	Cl	CH ₃	H	70.0	194 ^c			40.48 40.23	2.83 2.64	7.87 7.76		

t. from 1-propanol. ^b cryst. from ethanol. ^c cryst. from ethylacetate. ^d With 0.045 mol; rature melting points for XI: 279—280 ° and for XVI 219—220 ° are reported

collected by filtration; yield 3.7 g (58.8%) IX, m. p. 166 °C. Sample for analysis was crystalized from abs. ethanol; m. p. 166 °C.

Ir spectrum: 3320, 3240, 3100, 2220, 1740, 1650, 1580, 1260, 1030, 960 and 755 cm⁻¹.

Anal. C₁₀H₁₁N₃O₃ (221.21) calc'd: C 54.29; H 5.01; N 19.00%
found: C 54.03; H 4.79; N 19.17%

Preparation of Nitryl Chloride

It was prepared similarly to the procedure described by Shechter *et al.*⁸

While cooling and stirring by magnetical stirrer 5 ml of fuming sulfuric acid (20% SO₃) was added to 10 ml of fuming nitric acid. Then 15 ml of chlorosulfonic acid (0.18 mol) was dropwise added in during forty minutes at 0–5 °C in a stream of nitrogen. Gaseous nitryl chloride produced during addition of chlorosulfonic acid was introduced into the reaction mixture for chlorination of 2-pyridones. After chlorosulfonic acid was added, the cooling mixture was removed and nitryl chloride was liberated continuously until the temperature of the acid mixture reached 20 °C.

General Procedure for Chlorination of 2-Pyridones

Nitryl chloride was passed through a reaction mixture of 0.09 mol of 2-pyridone in 90 ml of dry benzene without cooling or heating. After all nitryl chloride was passed, the mixture was stirred one hour more, cooled and the product collected by filtration. The crude product was washed with water.

Ir spectra of chlorinated pyridones XI, XII, XIII, XIV, XVI and XVII show broad absorbance at 3100–2600 cm⁻¹ (characteristic for 2-pyridones without substituent in position 1), and at 2220–2210, 1670–1640, 1600–1570 and 770 cm⁻¹. Ir spectrum of XV show absence of broad absorbance at 3100–2600 cm⁻¹ (methyl substituent in position 1).

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SAŽETAK

Kloriranje supstituiranih 2-piridona s nitrilkloridom

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Nitrilklorid je upotrijebljen po prvi put kao sredstvo za kloriranje u nizu 2-piridona. Reakcijom supstituiranih 2-piridona s nitrilkloridom u benzenu dobiveni su s dobrim iskorištenjem 5-klor- i 3,5-diklor-derivati. Nije primijećeno stvaranje nitro spojeva.