Chemistry of Heterocyclic Compounds, Vol.35, No. 12, 1999

CHLOROTROPIC REARRANGEMENT OF 3,5-DICHLORO-3-CYANO-4-METHYLPYRIDINE-2,6(1H)-DIONE IN THE MEDIUM OF POLAR SOLVENTS. SYNTHESIS OF 5-CHLORO-3-CYANO-6-HYDROXY-4-METHYLPYRIDIN-2-ONE

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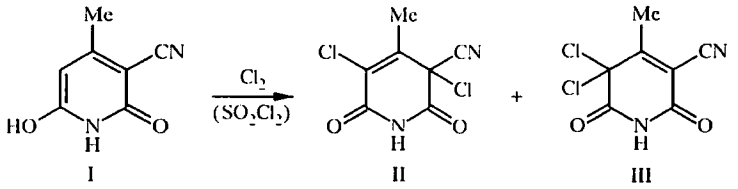
Isomeric conversion of 3,5-dichloro-3-cyano-4-methylpyridine-2,6(1H)-dione to 5,5-dichloro-3-cyano-4-methylpyridine-2,6(1H)-dione in polar solvents was shown. A new method for the synthesis of 5-chloro-3-cyano-6-hydroxy-4-methylpyridin-2-one was proposed.

Derivatives of pyridine, particularly hydroxypyridones and pyridinediones, present interest as synthons in fine organic synthesis and as potential bioactive compounds [1]. With the purpose of investigating intermediates for the synthesis of new biologically active compounds in the series of pyridine derivatives, we studied chlorination at the position 5 of 3-cyano-6-hydroxy-4-methylpyrid-2-one (I). The chlorination agent usually utilized for this is sulfuryl chloride or chlorine [2-4]. When hydroxypyridone I is chlorinated with excess of sulfuryl chloride at 30 to 80°C or chlorine at -10 to 80°C, the disubstituted product is formed exclusively, independently of the temperature regime. The disubstituted product is obtained as the mixture with the initial compound I, even at the equimolar ratio of the reacting substances. The chlorination of pyridone I with sulfuryl chloride in the dark (cf. [3]) also does not lead to the monochloro derivative.

The composition of the synthesized chlorination products was confirmed by results of the elemental analysis, and the structure was confirmed by the methods of ^{1}H and ^{13}C NMR and mass spectrometry. The data obtained allow it to conclude that the reaction product represents the mixture of the two isomeric compounds II and III.



The character of the change in the NMR spectra with time favors the conclusion that the chlorotropic rearrangement of 3,5-dichloro-3-cyano-4-methylpyridine-2,6(1H)-dione (II) to 5,5-dichloro-3-cyano-4-methylpyridine-2,6(1H)-dione (III) proceeds in polar solvents, whereby its rate increases with the increase in the dielectric constant of the solvent.

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0009-3122/99/3512-1437$22.00©1999 KluwerAcademic/Plenum Publishers

The isomer III is obtained in the discrete form, even by the brief heating of the mixture of the compounds II and III in alcohol or acetone with the subsequent removal of the solvent. The attempt to isolate the isomer II did not lead to the desired result in spite of wide variation of the conditions. The quantitative composition of the mixture of substituted pyridinediones II and III does not change on storage. Both isomers are stable in the crystalline state.

The mass spectra of the isomer III and its mixture with the isomer II are identical. They do not contain peaks of the molecular ions, and characteristic fragments are $[M\text{-}NC\text{-}OH]^+$ and $[M\text{-}HCl]^+$ with the corresponding masses 175 (100%) and 183 (15-20%).

The parameters of the ^1H NMR spectra of the chlorination products, measured directly after the solution of the sample and after 24 h, are presented in Table 1. The assignment of the signals was performed taking into account the spectral data of the isomer III obtained in the same time intervals. From Table 1 follows that the isomerization II → III does not proceed in the medium of nonpolar solvents (benzene, dioxane); and the isomer III is present exclusively in the medium of polar solvents acetone and methanol already after 24 h.

The question of the structure of the products II and III was resolved using the ^{13}C NMR spectra. For this purpose, the spectra of the isomer III and the mixture of isomers were recorded under conditions of the complete suppression of the spin–spin coupling and with partial uncoupling from the protons. The set of signals corresponding to the each isomeric form was determined by comparative analysis of the given spectra. The assignment of the signals was performed taking into account known structural criteria [5]. The character of the multiplets in the monoresonance spectra and the SSCCs of the ^{13}C–^1H nuclei were also considered (Table 2). It can

TABLE 1. ^1H NMR Spectral Parameters (δ, ppm) of Chlorination Products of Compound I Recorded Directly after the Dissolution of their Mixture (A) and after 24 h (B)

Solvent	Spectrum A				Spectrum B			
	Compound	Content in the mixture, %*	CH_3, 3H, s	NH, 1H, s	Compound	Content in the mixture, %	CH_3, 3H, s	NH, 1H, s
Benzene-d_6	II	48	1.66		II	48	1.66	
	III	52	1.77	—	III	52	1.77	—
Dioxane-d_8	II	48	2.43	—	II	48	2.43	—
	III	52	2.62	—	III	52	2.62	—
Chloroform-d	II	48	2.48	8.76	II	26	2.48	8.77
	III	52	2.69	8.80	III	74	2.69	8.81
Acetone-d_6	II	40	2.46	11.30	II	0	—	—
	III	60	2.67	11.34	III	100	2.68	11.31
Methanol-d_4	II	37	2.47	—	II	0	—	—
	III	63	2.68	—	III	100	2.68	—

* The determination error is ±3%.

TABLE 2. ^{13}C NMR Spectral Characteristics of Compounds II and III (Acetone-d_6)

Isomer	Chemical shifts, ppm (multiplicity, SSCC in the monoresonance spectrum, Hz						
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	CN	CH_3
II	157.92 (d, 5.6)	55.18 (q, 3.7)	141.51 (q, 5.5)	128.40 (d, 5.5)	161.95 (d, 5.6)	113.41 (s)	17.92 (q, 130)
III	158.34 (d, 5.6)	109.11 (q, 5.5)	162.54 (q, 7.4)	76.46 (q, 4.0)	163.22 (d, 5.6)	112.58 (s)	19.12 (q, 130)

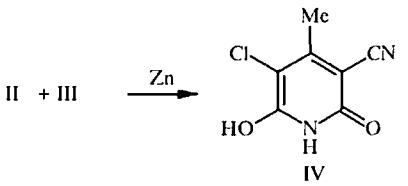
TABLE 3. Calculated and Experimental Values of the Difference in Chemical Shifts of $C_{(3)}$, $C_{(4)}$, and $C_{(5)}$ Atoms of the Isomers II and III (ppm)

Δ of the chemical shifts	$C_{(3)}$ (II) $C_{(4)}$ (III)	$C_{(5)}$ (II) $C_{(3)}$ (III)	$C_{(3)}$ (II) $C_{(5)}$ (III)
Calculated	-21	19	-25
Experimental	-21.03	19.29	-21.28

be seen from Table 2 that the isomers investigated are most strongly distinguished by the signals of the $C_{(3)}$, $C_{(4)}$, and $C_{(5)}$ atoms. The last appear in the monoresonance spectra as quadruplets due to the spin–spin coupling of the ^{13}C nuclei and the protons of the CH_3 group. That also favored the structures of the compounds II and III presented above.

The application of the known additive scheme [5] to calculate the signals of the $C_{(3)}$, $C_{(4)}$, and $C_{(5)}$ atoms of the isomers II and III for the purpose of confirming the proposed structure is complicated due to the absence of tabular data for the increments of some groups. These difficulties were overcome by the determination of the difference in the chemical shifts of the indicated carbon atoms of the individual structures II and III, which allowed the simplification of the equations of additive contributions. In the end, this difference was expressed by the difference of the increments, the values of which are known [5]. The results of the calculations (Table 3) indicate the adequate reliability of such an approach for the confirmation of the structure of the isomers.

The increased mobility of the chlorine atom allowed the development of a convenient method for the synthesis of the requisite 5-chloro-3-cyano-6-hydroxy-4-methylpyrid-2-one (IV), including the reduction of the mixture of isomers II and III using zinc powder in a protonic solvent with a good yield (77%) [6].



IV

Therefore, the chlorotropic rearrangement of 3-cyano-3,5-dichloro-4-methylpyridine-2,6(1H)-dione (II) to the corresponding 5,5-*gem*-dichloride III was found to occur under the action of polar solvents; this reveals new possibilities for the synthesis of reactive intermediates in organic synthesis.

EXPERIMENTAL

The mass spectra were registered on the model LKB-2091 chromato-mass spectrometer with the direct input of the sample at the source; the energy of the ionizing electrons was 20 eV. The ^1H NMR spectra were obtained on the Varian FT-80A (80 MHz) and Bruker WM-250 (250 MHz) spectrometers. The ^{13}C NMR spectra were taken on the Bruker WM-250 instrument (62.86 MHz) under conditions of the complete and partial suppression of the spin–spin coupling of the protons with the carbon atoms. The internal standard was TMS. The solvents utilized are shown in Tables 1 and 2.

3,5-Dichloro-3-cyano-4-methylpyridine-2,6(1H)-dione (II) and 5,5-Dichloro-3-cyano-4-methylpyridine-2,6(1H)-dione (III). Into suspension of pyridone I (1.5 g, 0.01 mol) in absolute carbon tetrachloride (20 ml) at 20-25°C chlorine is passed until the ceasing of the release of hydrogen chloride. The residue is filtered off, washed with CCl_4 until neutral reaction is obtained, and dried. Yield of the 48:52 mixture of the compounds II and III is 2.15 g (98%); mp 147-150°C (white crystals). Found, %: C 38.25; H 1.62; N 12.62; Cl 32.23. $C_7H_4Cl_2N_2O_2$. Calculated, %: C 38.38; H 1.84; N 12.79; Cl 32.37.

5,5-Dichloro-3-cyano-4-methylpyridine-2,6(1H)-dione (III). The mixture of the compounds II and III (1.0 g) is heated to boiling in ethanol (15 ml), and the solvent is removed. Yield of compound III is 1 g; mp 163-164°C (yellow crystals). Found, %: C 38.14; H 1.58; N 12.61; Cl 32.28. $C_7H_4Cl_2N_2O_2$. Calculated, %: C 38.38; H 1.84; N 12.79; Cl 32.37.

5-Chloro-3-cyano-6-hydroxy-4-methylpyrid-2-one (IV). To solution of mixture of compounds II and III (2.0 g, 0.0091 mol) in ethanol (30 ml) Zn powder (1.17 g, 0.0179 mol) is added with stirring in small portions, not allowing the temperature to increase above 30°C. The reaction mixture is maintained at this temperature for 5-10 min more. The resulting residue is separated and dissolved in boiling water (50 ml), and the solution is cooled and acidified with concentrated HCl to pH >1. The residue of the product, which separated out, is filtered off and dried in vacuo at 110°C prior to the isolation of 1.3 g (77%) of compound IV; mp 248-249°C. Mass spectrum, *m/z* (I_{rel}, %): M^+ 184 (200), $[M - H_2O]^+$ 164 (6), $[M - CO]^+$ 156 (20), $[M - Cl]^+$ 149 (13), $[156 - CH_3]^+$ 141 (7), $[156 - Cl]^+$ 121 (5). Found, %: C 45.19; H 2.64; N 15.38; Cl 19.54. $C_7H_5ClN_2O_2$. Calculated, %: C 45.45; H 2.74; N 15.18; Cl 19.20.

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