Regioselective Conversion of 3-Cyano-6-hydroxy-2-pyridones into 3-Cyano-6-amino-2-pyridones

Alan R. Katritzky* and Stanislaw Rachwal

Center for Heterocyclic Chemistry, Department of Chemistry,
University of Florida, Gainesville, FL 32611-7200

Terrance P. Smith

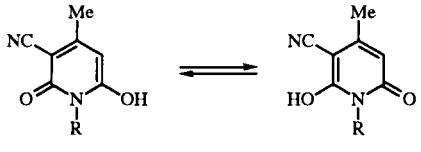
Graphic Research Laboratory, 3M, St. Paul, MN 55144-1000
Received January 20, 1995

The reaction of a tautomeric mixture of 1-butyl-1,2-dihydro-6-hydroxy-4-methyl-2-oxopyridine-3-carbonitrile and its 2-hydroxy-6-oxo analog with phosphorus oxychloride gave 1-butyl-6-chloro-1,2-dihydro-4-methyl-2-oxopyridine-3-carbonitrile (68%) and 1-butyl-2-chloro-1,6-dihydro-4-methyl-6-pyridine-3-carbonitrile (3%). Both chloropyridones were converted to their corresponding aminopyridones by reaction with liquid ammonia. Strong support for the molecular structure of 6-amino-1-butyl-1,2-dihydro-4-methyl-2-oxopyridine-3-carbonitrile was obtained on the basis of nmr techniques.

J. Heterocyclic Chem., **32**, 1007 (1995).

Introduction.

1,2-Dihydro-6-hydroxy-4-methyl-2-oxo-3-pyridinecarbonitrile (**1a**), its 1-methyl **1b** and other 1-substituted derivatives, **1c** and **1d**, have found wide application in the preparation of azo dyes, especially as disperse dyes for polymeric materials. The literature contains hundreds of patents on coupling products of **1a-1d** with various diazotized amines. The simple preparative methods available for **1a-1d**, especially the condensation of methyl acetoacetate with the appropriate amine and methyl cyanoacetate [1], make these compounds inexpensive and therefore attractive starting materials for the dye industry. Many compounds of this type have been recently patented as dyes for thermal transfer recording media [2-10] and as electrophotographic materials [11,12].



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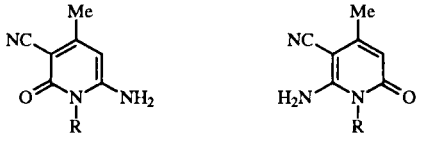


2 **3**

a: R = H
b: R = Me
c: R = alkyl, hydroxyalkyl or alkoxyalkyl
d: R = aryl

Similar or even wider application could be anticipated for the corresponding aminopyridones **2**. However, a literature survey revealed that compounds of type **2** are completely unknown, whereas only one compound of the isomeric class (**3d**, R = Ph) has been reported: it was obtained by condensation of acetoacetanilide with malononitrile [13]. We now demonstrate that aminopyridones of type **2** or **3**, can be readily obtained from the hydroxypyridones **1**. The results are exemplified by the *N*-butyl derivative (**1**, R = Bu) as described below.

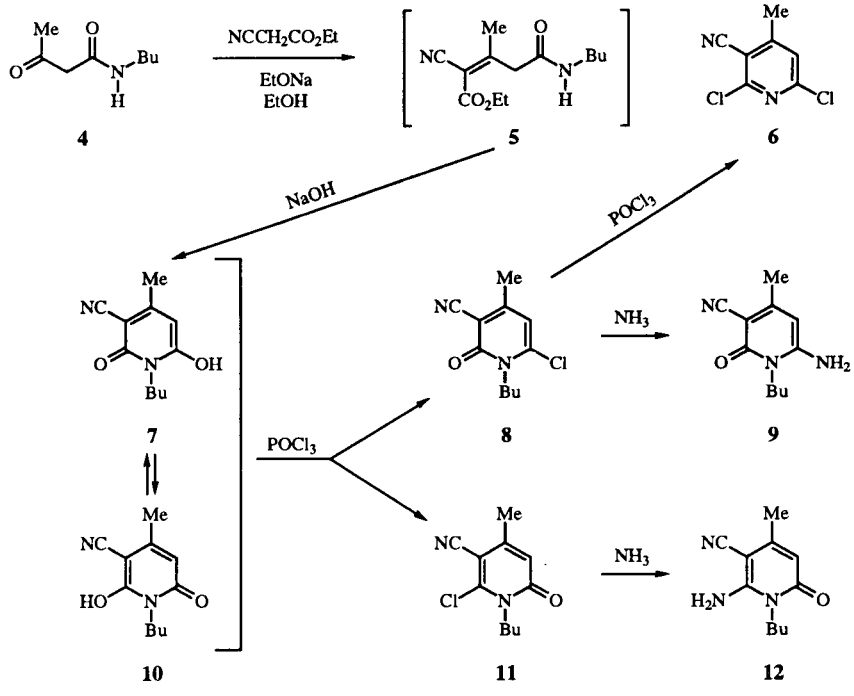
Results and Discussion.

N-Butylacetoacetamide **4** was obtained from the reaction of diketene with butylamine according to a literature method [14]. Upon heating a solution of **4**, ethyl cyanoacetate and sodium ethoxide in ethanol, formation of ester **5** was observed (by nmr). Prolonged heating resulted in slow conversion of **5** to hydroxypyridone **7**. Compound **7** was obtained in a better yield and higher purity, when the initial reaction was carried out in ethanol in the presence of sodium ethoxide, then water was added, followed by evaporation of the solvent, and the obtained mixture was heated to 140°. Nmr spectra of the product indicated, as expected [15], fast equilibration between tautomers **7** and **10**.

Reaction of hydroxypyridone **7** with phosphorus oxychloride gave chloropyridone **8** together with small amounts of isomer **11** and of the *N*-dealkylated dichloropyridine **6**. The bulk of compound **8** was isolated (62% yield) by recrystallization of the crude product from ethanol. Column chromatography of the residue obtained after evaporation of the mother liquor gave compound **6** (1% yield) and a mixture of **8** (additional 4% yield) and **11** (3% yield). Fractional recrystallization of the mixture allowed the separation of a small sample of pure **11** and its full characterization.

The most significant contrast between isomers **8** and **11** can be observed in their ^{1}H nmr spectra. Compound **8** exhibits the methyl and H-5 resonances as singlets,

Scheme



whereas a doublet and a quartet with the coupling constants of 1.1 Hz, are observed in the spectrum of **11**. The long range allylic type coupling between the methyl group on C-4 and the H-5 atom of a pyridone is possible only through a bond of high bond-order [16] proving the structural assignments for **8** and **11**.

The highly selective conversion of the tautomeric pyridones **7** and **10** to isomer **8** can be rationalized on steric grounds. This reaction seems to be the first example of the direct conversion of 1-alkyl-6-hydroxy-2-pyridone into 1-alkyl-6-chloro-2-pyridone. Previous reports on the preparation of 1-alkyl-6-chloro-2-pyridones include: *N*-alkylation reactions of 6-chloro-2-pyridones [17,18], *N*-alkylation reactions of 2,6-dichloropyridines followed by hydrolysis of the resultant pyridinium salts [19] and thermal rearrangement of 2-alkoxy-6-chloropyridines [20]. In general, reactions of 1-alkyl-2-pyridones with phosphorus oxychloride or phosphorus pentachloride were reported to occur with the N-C bond cleavage yielding 2-chloropyridines [21]. Dichloropyridine **6** must be formed in this way.

When chloropyridone **8** was heated under reflux with 27% ammonia in water, it gave back hydroxypyridone **7**. However, reaction with anhydrous ammonia in a pressure reactor converted **8** quantitatively into aminopyridone **9**. In a similar manner, a mixture of chloropyridones **8** and **11** was converted into a mixture of aminopyridones **9** and **12** which were separated by column chromatography.

As with the ^{1}H nmr spectra of the chloropyridones, no coupling ≥0.2 Hz was observed between the methyl group and the atom H-5 in **9**, whereas the ^{1}H nmr spectrum of **12** exhibits the methyl group as a doublet (J = 0.9 Hz) and the H-5 resonance as a quartet (J = 1.0 Hz). Strong support for the structural assignments is derived from the ^{13}C nmr spectra. Thus, the C-3 resonance of **9** is observed at δ 82.9 and that at of **12** at δ 74.1, due to the strong ortho effect [22] of the amino group (*via* a double bond) in **12**. The same effect causes the upfield shift of the C-5 resonance of **9** to δ 91.8 *vs.* the C-5 resonance of **12** at δ 107.0. A two-dimensional nuclear Overhauser effect experiment was performed on the major isomer. A strong correlation was observed between the primary amino group protons and H-5; this correlation is only possible for isomer **9**, confirming the assignment made above.

Further, HMBC (heteronuclear multiple bond correlation) experiment [23,24] revealed correlations between the carbons at δ 160.6 and 154.4 and the NCH_2 protons at δ 3.95. Thus, these two carbons had to be assigned to C-2 and C-6, respectively. A resolution enhanced undecoupled ^{13}C spectrum of **9** was measured in order to aid in the assignment of the carbon resonances. The long range couplings, along with selective assignments for **9**, are listed in the Table. Most of the assignments are unambiguous based on the observed multiplicity patterns and the values of the coupling constants. The C-2 resonance is observed as a triplet due to long range coupling to the N-CH_2 protons. (The lack of coupling to H-5 is also consistent with our assignment of the major isomer as **9**.) The resonance of C-6 is observed as a poorly resolved quartet due to

Table

Selective Assignments, Chemical Shifts, and Longe Range Coupling Constants for **12**

Assignment	Chemical Shift (ppm)	Coupling Constants (Hz)
C-2	160.64	t, 3.4
C-3	82.89	d, 7.6, q, 4.7
C-4	155.11	q, 5.9
C-5	91.81	d, 168.4, q, 4.9
C-6	154.40	q, 3.0
CN	118.61	d, 1.6

coupling to both the N-CH_2 protons and to H-5; in this case, the two coupling constants could not be resolved. Atom C-5 is observed as doublet of quartets, the large coupling constant establishes that it is bond to H-5. Assignments for C-3 and C-4 can not be made on the basis of the coupling information. Not even, a heteronuclear multiple bond correlation experiment was not definitive. Using an algoritm [25], based on substituent effects on the olefinic carbon, values of 96.2 ppm and 165.2 ppm were calculated for C-3 and C-4, respectively. This suggests that C-3 and C-4 should be assigned to 82.89 ppm and 155.1 ppm, respectively. The assignments for C-3 and C-4 are also consistent with values reported for other cyanopyridones [26].

EXPERIMENTAL

The ^1H (300 MHz) and ^{13}C (75 MHz) nmr spectra were obtained on a Varian VXR-300 spectrometer and chemical shifts are reported in ppm relative to tetramethylsilane. The undecoupled nmr ^{13}C spectrum of **9** was obtained on a Varian UNITY 500 nmr in dimethyl sulfoxide-d_6 solutions with an acquisition time of 4.0 sec. The two-dimensional nuclear Overhauser effect (2D-NOE) experiments were performed on a Varian UNITY 500 NMR in dimethyl sulfoxide-d_6 solutions. Mix times of 0.10, 0.15, and 0.20 were employed, in the 2D-NOE experiment, to verify that the correlation was not due to either spurious noise or long range coupling interactions. The 2D-NOE experiment was acquired using a 4125 Hz sweep with a 0.12 acquisition time with 128 increments. The spectrum was zero-filled to 1024 x 1024, weighted using standard Lorentzian/Gaussian values, and symmetrized. The relaxation times were measured using the inversion recovery pulse sequence. The spin-lattice relaxation times (T_1) were determined by dividing the null times by 0.693. The T_1's for the amino protons and the N-CH_2 protons were 0.26 sec and 0.32 sec, respectively. The T_1's for all the other protons exceeded 0.58 sec. The spin-spin lattice relaxation times were found to be within experimental error of the corresponding T_1's. Melting points (°) were determined on Thomas-Hoover melting point apparatus and are uncorrected.

1-Butyl-1,2-dihydro-6-hydroxy-4-methyl-2-oxo-3-pyridinecarbonitrile (**7**).

Ethyl cyanoacetate (25.5 ml, 240 mmoles), followed by *N*-butylacetoacetamide (31.44 g, 200 mmoles) were added to a solution of sodium (5.52 g, 240 mmoles) in ethanol (100 ml). The mixture was stirred at 80° for 16 hours. Water (50 ml) was then added and the mixture was stirred and heated in an open flask (in an oil bath) until all the ethanol and water evaporated. The stirring was continued at 140° for an additional 2 hours. The sticky oil was dissolved in hot water (200 ml), poured onto ice (400 g) and acidified with 10% hydrochloric acid to *p*H 1. The white precipitate was collected, washed with water and dried in a vacuum oven at 70° to give pure **7** (25.80 g, 63%), yellowish prisms, mp 205-207°; ^1H nmr (dimethyl sulfoxide-d_6): δ 0.94 (3H, t, J = 7.3 Hz, Bu), 1.36 (2H, sextet, J = 7.2 Hz, Bu), 1.62 (2H, m, Bu), 2.29 (3H, s, Me), 4.01 (2H, t, J = 7.3 Hz, Bu), 5.70 (1H, s, H-5); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 13.7 (Bu), 20.0 (Bu), 20.9, 29.8 (Me), 41.2 (Bu), 90.4 (C-3), 92.4 (C-5), 117.2 (CN), 158.3, 160.0, 161.0.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.99; H, 6.82; N, 13.52.

Reaction of Hydroxypyridone **7** with Phosphorus Oxychloride. Chloro Derivatives **6**, **8**, and **11**.

A mixture of **7** (24.00 g, 116 mmoles) and phosphorus oxychloride (55.9 ml, 600 mmoles) was stirred at 105° for 3 hours. The mixture was poured onto crushed ice (800 g), neutralized with 10% sodium hydroxide and extracted with chloroform. The extract was washed with water, 5% aqueous sodium bicarbonate and again with water, and then dried over magnesium sulfate. Evaporation of the solvent gave a semicrystalline material. Recrystallization of the crude product from ethanol gave 1-butyl-6-chloro-1,2-dihydro-4-methyl-2-oxo-3-pyridinecarbonitrile (**8**) (16.21 g, 62%) as colorless plates, mp 119°; ^1H nmr (deuteriochloroform): δ 0.97 (3H, t, J = 7.3 Hz, Bu), 1.41 (2H, sextet, J = 7.6 Hz, Bu), 1.70 (2H, m, Bu), 2.42 (3H, s, Me), 4.23 (2H, t, J = 7.6 Hz, Bu), 6.32 (1H, s, H-5); ^{13}C nmr (deuteriochloroform): δ 13.6 (Bu), 20.0 (Bu), 20.9 (Me), 30.0 (Bu), 47.2 (Bu), 102.6 (C-3), 109.3 (C-5), 114.7 (CN), 142.5, 158.2, 160.0.

Anal. Calcd. for $C_{11}H_{13}N_2ClO$: C, 58.80; H, 5.83; N, 12.47. Found: C, 58.93; H, 5.78; N, 12.52.

The filtrate from **8** was evaporated and the residue subjected to column chromatography (toluene:ethyl acetate, 4:1) to give, as the first fraction, 2,6-dichloro-4-methyl-3-pyridinecarbonitrile (**6**) (0.22 g, 1%), as colorless prisms (from ether), mp 109° (lit [27] mp 109-110°); ^1H nmr (deuteriochloroform): δ 2.59 (3H, d, J = 0.8 Hz, Me), 7.29 (1H, q, J = 0.8 Hz, H-5); ^{13}C nmr (deuteriochloroform): δ 20.7 (Me), 110.3, 113.3, 124.2 (H-5), 152.5, 153.6, 156.6.

The second fraction gave a mixture of **8** and **11** (1.95 g, 7%, **8**:**11** = 58:42). A pure sample of 1-butyl-2-chloro-1,6-dihydro-4-methyl-6-oxo-3-pyridinecarbonitrile (**11**) (0.12 g) was obtained after fractional recrystallizations from hexane/toluene and then from methanol, colorless prisms, mp 111°; ^1H nmr (deuteriochloroform): δ 0.97 (3H, t, J = 7.3 Hz, Bu), 1.41 (2H, sextet, J = 7.6 Hz, Bu), 1.69 (2H, m, Bu), 2.33 (3H, d, J = 1.1 Hz, Me), 4.22 (2H, t, J = 7.8 Hz, Bu), 6.36 (1H, q, J = 1.1 Hz, H-5); ^{13}C nmr (deuteriochloroform): δ 13.6 (Bu), 20.0 (Bu), 20.7 (Me), 30.1 (Bu), 47.4 (Bu), 95.2 (C-3), 114.6 (CN), 117.6 (C-5), 145.0, 149.4, 160.6.

Anal. Calcd. for $C_{11}H_{13}N_2ClO$: C, 58.80; H, 5.83; N, 12.47. Found: C, 58.69; H, 5.81; N, 12.39.

6-Amino-1-butyl-1,2-dihydro-4-methyl-2-oxo-3-pyridinecarbonitrile (**9**).

To a 10 ml pressure reactor containing **8** (2.25 g, 10 mmoles)

cooled in dry ice was added liquid ammonia (4 ml), the reactor was sealed and allowed to warm up to 20°. After 16 hours at 20° the reactor was cooled again in dry ice, opened and left to stand until the ammonia had evaporated. The residue was triturated with water (20 ml) to remove ammonium chloride. The precipitate was collected, washed with water and dried in a vacuum oven at 60° to give pure (nmr) aminopyridone **9** (1.95 g, 95%). Recrystallization from ethanol gave an analytically pure sample as yellowish prisms, mp 195-197°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 0.93 (3H, t, J = 7.3 Hz, Bu), 1.38 (2H, sextet, J = 7.9 Hz, Bu), 1.56 (2H, m, Bu), 2.18 (3H, s, Me), 3.95 (2H, t, J = 7.3 Hz, Bu), 5.52 (1H, s, H-5), 7.15 (2H, bs, NH_2); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 13.8 (Bu), 19.7 (Bu), 20.6 (Me), 28.9 (Bu), 40.9 (Bu), 82.9 (C-3), 91.8 (C-5), 118.6 (CN), 154.4, 155.1, 160.6.

Anal. Calcd. for $C_{11}H_{15}N_3O$: C, 64.37; H, 7.37; N, 20.47. Found: C, 64.03; H, 7.36; N, 20.07.

2-Amino-1-butyl-1,6-dihydro-4-methyl-6-oxo-3-pyridinecarbonitrile (**12**).

Reaction of a mixture of **8** and **11** (1.00 g, **8**:**11** = 58:42) with liquid ammonia (2 ml) as above produced a mixture of amines **9** and **12**. A suspension of the mixture in ethyl acetate (25 ml) was heated to reflux and allowed to cool down to 22°. The precipitate was separated, washed with ethyl acetate (5 ml) and dried to give pure **9** (0.26 g). The filtrate was subjected to column chromatography (ethyl acetate) to give, as the first fraction, amine **12** (0.37 g), yellowish prisms, mp 182°; ^{1}H nmr (deuteriochloroform): δ 0.96 (3H, t, J = 7.3 Hz, Bu), 1.41 (2H, sextet, J = 7.6 Hz, Bu), 1.67 (2H, m, Bu), 2.22 (3H, d, J = 0.9 Hz, Me), 4.01 (2H, t, J = 7.8 Hz, Bu), 5.59 (2H, bs, NH_2), 5.80 (1H, q, J = 1.00 Hz, H-5); ^{13}C nmr (deuteriochloroform): δ 13.8 (Bu), 20.2 (Bu), 20.6 (Me), 29.3 (Bu), 41.8 (Bu), 74.1 (C-3), 107.0 (C-5), 117.3 (CN), 150.8, 154.8, 161.2.

Anal. Calcd. for $C_{11}H_{15}N_3O$: C, 64.37; H, 7.37; N, 20.47. Found: C, 64.12; H, 7.34; N, 20.28.

Aknowledgment.

Richard Newmark's assistance in obtaining the two dimensional nmr results is greatly appreciated.

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