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SOLVENT AND TEMPERATURE DEPENDENT REGIOSELECTIVE REACTIONS BETWEEN 2-CHLORO-6-CYANOPYRIDINE AND ALIPHATIC ALCOHOLS

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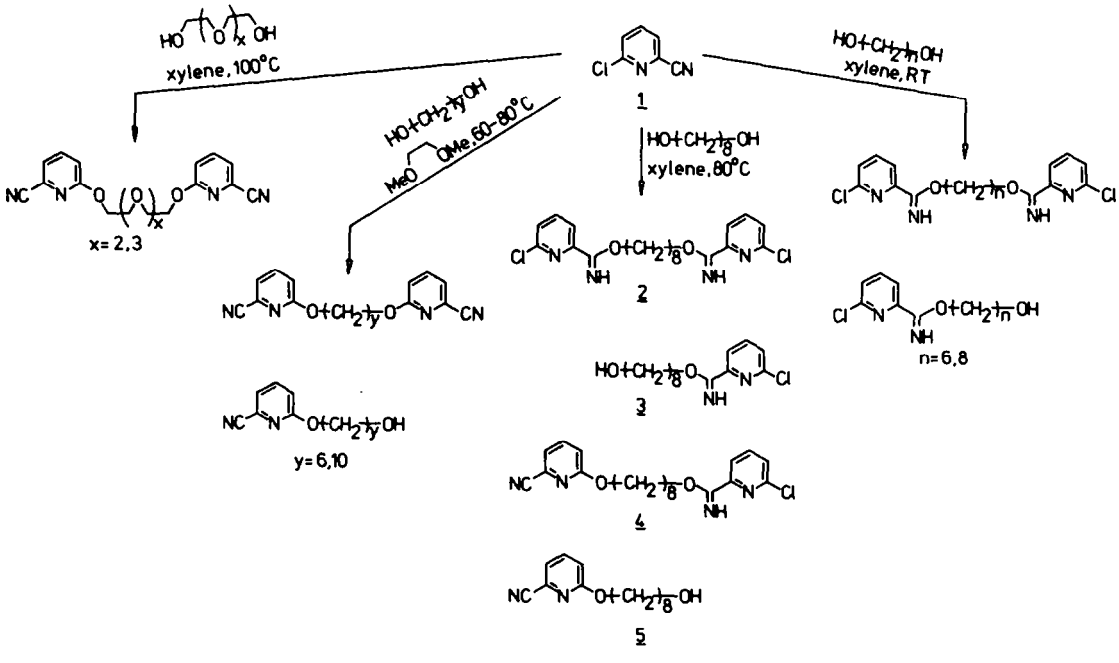
ABSTRACT: Reaction of 2-chloro-6-cyanopyridine with aliphatic mono- and di-alcohols or ethylene glycols affords, depending on the reaction conditions, alkoxypyridines or imino ester pyridines or a mixture of both types of compounds. It is suggested that the product distribution is determined by the stability of an imidate anion formed as an intermediate. An improved synthesis of 2-chloro-6-cyanopyridine is also described.

In connection with studies of reagents for liquid-liquid extraction of metal ions we synthesized various substituted pyridine-2-carboxylic acids. Attempts to alkoxylate 2-chloro-6-cyanopyridine according to Newkome's procedure[1], but exchanging ethylene glycols for linear carbon chain diols, did not give the desired dipyridyloxyalkanes. Instead, imino ester pyridines[2], mixed imino ester alkoxypyridines and mono pyridyloxyalkanes were formed. It is known[3-9] that a regiochemical choice of a nucleophile, attacking a substrate with two or more reactive sites, can be determined by either type of solvent, reaction time or reaction temperature, or by taking all three variables into account simultaneously. We now report that, by a proper choice of reaction conditions, the reactions could be directed towards formation of either dipyridyloxyalkanes or diimidates.

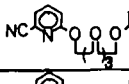
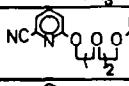
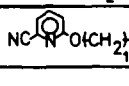
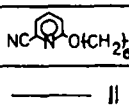
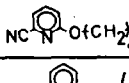
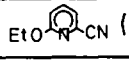
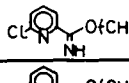
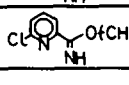
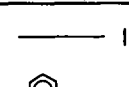
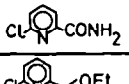
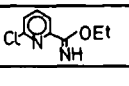
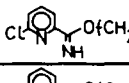
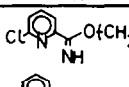
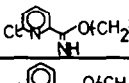
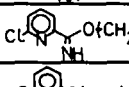
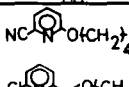
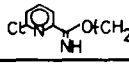
RESULTS

Reaction of 2-chloro-6-cyanopyridine[10] with various alcoholates (results are summarized in table 1) in coordinating solvents such as tetrahydrofuran (THF), monoglyme or a mixture of ethylene glycol and xylene at elevated temperatures (60-100°C) gave products resulting from substitution of the chlorine atom, whereas products resulting from alcoholate attack at the nitrile function were obtained when xylene was used at room temperature. A mixture of both types of products, alkoxy- and imino ester pyridines, were formed in xylene at 80-100°C or at room temperature under prolonged reaction times. Representative reactions are shown in scheme 1.



Scheme 1

TABLE 1. REACTIONS BETWEEN 2-CHLORO-6-CYANOPYRIDINE AND DIFFERENT ALCOHOLS WITH SODIUM HYDRIDE AS A BASE.

EXP.	TYPE OF ALCOHOL	EQ. OF REACT. 1 :ALC:BASE	SOLVENT	REACTION TIME(h)	REACTION TEMP.(C)	ISOLATED PRODUCTS AND YIELDS[a](%)
1	tetra-ethylene glycol	2:1:2	xylene	2	100	 (68)
2	tri-ethylene glycol	2:1.2:2.4	xylene	2	100	 (>22)[c]
3	1,10-decane-diol	1:2:2	mono-glyme	2.6	80	 (16), (30)
4	1,10-decane-diol	2:1:2	mono-glyme	3.25	80	——— II ——— (51), ——— II ——— (40)
5	1,10-decane-diol	2:1:4	mono-glyme	3.25	80	——— II ——— (78), ——— II ——— (0)
6	1,6-hexane-diol	1:1:1	mono-glyme	4.5	70	 (14), (34)
7	1,6-hexane-diol	1:1:1	THF	6.5	70	——— II ——— (6), ——— II ——— (23), 1 (10) + mixture of crystalline compounds[b]
8	1,4-butane-diol	1:1:1	THF	32	66	 (46), 1 (20)
9	ethanol	1:1:1	THF	3	66	 (38), (4), 1 (25)
10	1,8-octane-diol	2:1:2	xylene	69	RT	 (24), 1 (76)
11	1,6-hexane-diol	1:1:1	xylene	120	RT	 (13), 1 (40)
12	1,6-hexane-diol	1:1:1	xylene/t-butan-ol 4:1	2	RT	——— II ——— (11),  (8),  (22), 1 (23)
13	ethanol	1:1:1	ethanol	0.08	RT	 (76)
14	1,10-decane-diol	2:1:2	xylene	4	100	 (13) + other products[c]
15	1,8-octane-diol	1:1:2	xylene	21	80	 (5), (11), 1 (26),  (4), (7)
16	1,6-hexane-diol	2:1:4	xylene	137	RT	 (32), (8), 1 (9)
17	1,4-butane-diol	1:1.2:1.2	THF	90	RT	 (3), (30),  (3), 1 (10)

a) Calculations based on the amount of alcohol.
b) Spectra (IR and NMR) show that these compounds are alkoxylated 2-picolinic amides and/or acids.
c) Destroyed in a fire.

To obtain alkoxypyridines from alkanediols and 1 it was necessary to use THF or monoglyme as the solvent (exp. 3-9, tab. 1) while ethylene glycols and 1 gave alkoxypyridine even though the solvent was xylene (exp. 1-2). When sodium ethoxide in ethanol at room temperature reacted with 1, ethyl 6-chloropyridine-2-imidate was formed in high yield in less than 5 min. (exp. 13). Repeating this experiment in refluxing THF (exp. 9) yielded 2-cyano-6-ethoxypyridine[11] and 6-chloro-2-picolinamide.[12] Following exp. 9 on a tlc plate revealed (by comparison with an authentic sample) that initially the ethyl imidate was also formed, but at the end of the reaction the ethyl imidate spot had disappeared. When ethyl 6-chloropyridine-2-imidate was added to a refluxing THF suspension of sodium hydride (exp. 18 at the end of the experimental section) the imidate was transformed into 2-cyano-6-ethoxypyridine (together with some 6-chloro-2-picolinamide and 1). From tlc one could see that after 5 min a considerable amount of 1 had been formed. Since the reaction between 1 and ethoxide in ethanol, leading to an imino ester product, was a comparably fast reaction, t-butanol (dry) was used as a co-solvent with xylene when 1,6-hexanediol was reacted with 1 (exp. 12). The formation of the diiminoester compound was at least 50 times faster in xylene/t-butanol 4:1 than in xylene alone (see exp. 12 and 11). Unfortunately, an unwanted transformation[13] of the starting material to 6-chloro-2-picolinamide took place when t-butanol was present (eg. exp. 9). No imino ester product from the reaction of t-butoxide and the cyanopyridine was detected. This behaviour of t-butanol under similar conditions has been pointed out by Serio Duggan *et al*.[14]

Following experiment 10 by HPLC showed that after 24 hours reaction time only the monoimidate from 1,8-octanediol had been formed. Then the monoimidate was continously transformed into the diimidate without any new monoimidate beeing formed. After 69 hours all the monoimidate had been consumed. The yields obtained show that 1 was exclusively transformed into the diimidate. This suggests that the diol is probably degrading to some other compound/compounds. Similar conclusions can be drawn from many of the other experiments (eg. exp. 16). No attempt to overcome this problem with the diols was carried out.

When experiment 15 (see table 1 and scheme 1) was followed by HPLC one could see that after 1.5 hours only 2 and 3 had been formed, 4 and 5 were then formed later. The reaction of 1 and 1,4-butanediol in THF at room temperature yielded, except for the alkoxypyridine compounds, a mixed compound analogous to 4 (exp. 17). If the reaction was carried out in refluxing THF the mixed compound was not formed (exp. 8).

Both the imino ester pyridines and the alkoxypyridines had in most cases significant peaks in their mass and NMR spectra. The imino esters showed typical mass ion fragments of m/z 138, 140 ($ClC_5H_3NCN^+$) (sometimes at m/z 139, 141) and characteristic ABX-coupling patterns in the aromatic region of the 200 MHz ^{1}H-NMR spectra. The alkoxypyridines showed typical mass ion fragments at m/z 120 ($OC_5H_4NCN^{+\cdot}$) and 121 ($HOC_5H_3NHCN^+$) and in the aromatic region of the 200 MHz ^{1}H-NMR characteristic AMX-coupling patterns were found.

DISCUSSION

When comparing experiments 1 and 14, which are run under identical conditions, one can see that the product distribution is greatly influenced by the type of alcohol used. Tetraethylene glycol results in the clean formation of a dipyridyloxy compound whereas 1,10-decanediol gives a mixture of products. The reaction of 1,10-decanediol in monoglyme, however, also affords a dipyridyloxy compound (exp. 5). These results suggest that the product distribution is determined by the coordinating ability of the alcohol or the solvent. A possible explanation to this may be that when monoglyme or xylene with a polyethylene glycol are used as solvents the alcoholate and the cation are fully dissociated. Even though this leads to a naked and reactive alcoholate, subsequently formed imidate anion will be poorly stabilized since the counter ion is already well solvated,

see exp. 1-5. Others[14] have also demonstrated that alkoxycyanopyridine formation takes place when a naked alkoxide ion reacts with a chlorocyanopyridine.

The rate of formation of the imidate anion depends of the degree of association (alcoholate-counter ion) and complexation (nitrile-counter ion). Comparing exp. 9 and exp. 13 it appears that the reversibility of the imidate anion formation is highly dependent on to what extent the imidate anion is forming an intimate ion pair with the counter ion. From exp. 18 it is apparent that once the imidate anion has been formed it dissociates into the cyanopyridine and ethoxide because of the low stability of the imidate - sodium ion pair in THF. In xylene a strongly associated (tight) ion pair is obtained between the alcoholate and the counter ion. Thus the reactivity of the alcoholate is diminished (longer reaction times), but when the imidate anion is formed it becomes strongly associated with the counter ion. Considerable amounts of imidate product are formed. This is confirmed by exp. 10, 11 and 16.

It has been shown[2] that methoxide in methanol reacts with cyanopyridine under catalytic conditions. This means that the imidate anion formed abstracts a proton from the solvent, thus driving the equilibrium towards the product side. In ethanol the imidate anion is obviously stabilized by the solvent and not by the counter ion, since this is also well solvated (c.f. exp. 13). The results of experiment 12 (when compared to exp. 11) show a large rate increase when t-butanol is used as a co-solvent. The reaction in exp. 13 is also a comparatively fast reaction. From these results one can assume that complexation (nitrile - protic solvent) takes place to a considerable degree.

In THF a loose ion pair between the alcoholate and the counter ion is formed and consequently some complexation could be expected. This is confirmed by the initially formed ethyl imidate in exp. 9 and the "mixed" compound in exp. 17.

Lefour and Loupy[15] (1978) discussed the cause of regioselectivity according to solvents, temperature and type of counter ion when a nucleophile reacts with α-enones. The α-enones and 2-chloro-6-cyanopyridine react analogously from a regiochemical point of view. In solvents that permit a high degree of complexation (cation - carbonyl or nitrile) this leads to the formation of 1,2-adducts in the α-enone case and imidate adducts in the chlorocyanopyridine case, while in solvents where a low degree of complexation exist 1,4- and alkoxypyridine-adducts are formed. When using a solvent that can give both types of products in both cases the same trend is seen according to reaction temperature, low temperatures: 1,2- and imidate-adducts, high temperatures: 1,4- and alkoxy-adducts.

When using a solvent with high solvating power alkoxypyridnes are produced at lower temperatures than when a solvent of lower solvating power is used. This is shown by the following example; in xylene higher temperatures are required to form some alkoxypyridines (exp. 15) while in THF room temperature is sufficient (exp. 17). A prolonged reaction time may also lead to the formation of some alkoxypyridine products where a shorter reaction time only gives the imino ester pyridine (exp. 16 compared to exp. 10). These facts show that imino ester- and alkoxy-pyridines can be produced under kinetic and thermodynamic control, respectively. Table 1 is organized so that exp. 1-9 are reactions carried out under thermodynamic control and exp. 10-13 are reactions carried out under kinetic control. In exp. 14-17 the reactions are carried out under intermediate conditions. Kinetic and thermodynamic control in connection with solvent effects have been demonstrated by Wartski et al. (1979)[16]. Finally we conclude that the degree of solvation of the cation is determining the relative reaction rates of alkoxy- and imino ester pyridine formation and that the alkoxypyridines are, thermodynamically, the more stable compounds.

EXPERIMENTAL SECTION

Melting points were determined on a Büchi melting point apparatus and are uncorreced. Mass spectra were run on an LKB 9000 spectrometer. NMR spectra were recorded in $CDCl_3$ on a Jeol JNM-PMX spectrometer at 60 MHz or on a Bruker WP 200 spectrometer at 200 MHz. IR spectra were recorded on a Perkin Elmer 421 spectrophotometer. Most of the isolated compounds were purified by flash chromatography on silica gel (Merck 0.040-0.063 mm). Xylene and monoglyme were dried over molecular sieves (4 Å) and THF was distilled from benzophenone ketyl under nitrogen. All experiments were carried out using oven dried glassware and in a dry nitrogen atmosphere.

General procedure (unless otherwise stated)

A suspension of sodium hydride (80% dispersion in mineral oil, MERCK) in monoglyme, THF or xylene was allowed to react with the appropriate alcohol for 15 min. A solution of 2-chloro-6-cyanopyridine was added, using a syringe or a dropping funnel, and the mixture reacted at the temperature indicated in table 1. All experiments were terminated by the addition of a saturated ammonium chloride solution. When monoglyme or THF were used as solvents, after extraction with ammonium chloride, the organic phase was evaporated and the resulting material dissolved in CH_2Cl_2 and then dried ($MgSO_4$).

1,10-Decanediyl di(6-chloropyridine-2-carboximidate) (exp. 14) Chromatography eluent: CH_2Cl_2-EtOAc (85:15), R_f = 0.37, yield 13%, recryst. from EtOH, m.p. 98-100°C. IR(KBr): 3310 (N-H), 1750, 1650 (C=N imidate) cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.1-1.9 (16H, m, $-CH_2-$), 4.3 (4H, t, J=6 Hz, $O-CH_2-$), 7.25-7.5 (2H, m, X-pyridyl), 7.6-7.85 (4H, m, AB-pyridyl) and 9.0 (2H, s, NH). MS (70 eV) m/z (rel. int. %): 159(4), 157(15), 141(6), 140(29), 139(17), 138(74), 121(19), 113(16), 103(100), 76(42), 55(22), 51(21), 41(20). Calcd. for $C_{22}H_{28}N_4O_2Cl_2$: C 58.5, H 6.2, N 12.4. Found: C 58.5, H 6.6, N 12.3%.

1,8-Octanediyl di(6-chloropyridine-2-carboximidate) (exp. 10 and 15) Chromatography eluent: CH_2Cl_2-EtOAc (85:15), R_f = 0.20, yield 24 or 5%, m.p. 102-103°C. IR(KBr): 3310 (N-H), 1745, 1645 (C=N imidate) cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.1-1.9 (12H, m, $-CH_2-$), 4.4 (4H, t, J=6 Hz, $O-CH_2-$), 7.3-7.5 (2H, m, X-pyridyl), 7.7-8 (4H, m, AB-pyridyl) and 9.0 (2H, s, NH). MS (20 eV), m/z (rel. int. %): 159(19), 157(56), 140(60), 138(79), 113(37), 103(100), 82(24), 76(34), 67(29), 55(32), 44(29), 41(24).

1,6-Hexanediyl di(6-chloropyridine-2-carboximidate) (exp. 11 and 12) Chromatography eluent: CH_2Cl_2-EtOH (95:5), R_f = 0.28, yield 13%, recryst. from CH_3CN, m.p. 106.5-107.5°C. IR (KBr): 3310 (N-H), 1720, 1650 (C=N imidate) cm^{-1}. ^{1}H-NMR (200 MHz): δ 1.57-1.60 (4H, m, $O(CH_2)_2-CH_2-$), 1.83-1.9 (4H, m, OCH_2-CH_2-), 4.38 (4H, t, J = 6.5 Hz, $O-CH_2-$), 7.37, 7.40, 7.42, 7.44 (2H, m, X-pyridyl), 7.74, 7.76 (4H, two peaks, AB-pyridyl) and 9.09 (2H, s, NH). MS (20 eV), m/z (rel. int. %): 159(8), 157(23), 140(39), 138(100), 113(13), 103(100), 76(24), 67(13), 55(64), 51(13), 43(16), 42(17), 31(12).

1,10-Di(2-cyano-6-pyridyloxy)decane (exp. 3, 4 and 5) Chromatography eluent: $CHCl_3$, R_f = 0.68, yield 78%, recryst. from cyclohexane, m.p. 110-111.5°C. IR (KBr): 2230 (CN), 1610, 1590, 1560 (C=C and C=N conjugated) cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.1-1.9 (16H, m, $-CH_2-$), 4.25 (4H, t, J =7 Hz, $-CH_2OAr$), 7.0 (2H, dd, J = 8 and 2 Hz, 5-pyridyl), 7.4 (2H, dd, J = 8 and 2 Hz, 3-pyridyl) and 7.8 (2H, dd, J = 8 and 6 Hz, 4-pyridyl). ^{13}C-NMR (50.29 MHz) δ: 164.41 (C_1), 138.87 (C_4), 130.68 (C_6), 121.89 (C_3), 117.37 (C_2), 116.13 (C_5), 67.03 (C_7), 29.49 (C_8), 29.34 (C_9), 28.81 (C_{10}) and 26.05 (C_{11}). MS (70 eV) m/z (rel. int. %): 378(5), 122(20), 121(100), 103(49), 83(20), 69(28), 67(21), 55(30), 43(24), 41(30), 39(35), 29(43), 27(26). Calcd. for $C_{22}H_{26}N_4O_2$: C 69.8, H 6.9, N 14.8. Found: C 69.2, H 6.9, N 14.6 %.

1,6-Di(2-cyano-6-pyridyloxy)hexane (exp. 6 and 7) Chromatography eluent: CH_2Cl_2-EtOAc (9:1), R_f = 0.64, yield 14%, recryst. from cyclohexane, m.p. 124-125°C. IR(KBr): 2230 (CN), 1610, 1590, 1560 (C=C, C=N conjugated) cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.3-2.1 (8H, m, $-CH_2-$), 4.4 (4H, t, J = 6 Hz, $O-CH_2-$), 7.0 (2H, d, J = 8 Hz, 5-pyridyl), 7.3 (2H, d, J = 8 Hz, 3-pyridyl) and 7.7 (2H,dd, J = 8 and 6 Hz, 4-pyridyl). MS (70 eV), m/z (rel. int. %): 322(1), 203(33), 121(100), 120(28), 103(32), 92(14), 82(24), 67(26), 55(42), 41(37), 39(15).

1,4-Di(2-cyano-6-pyridyloxy)butane (exp. 17) Chromatography eluent: 1) EtOAc-petroleum ether (1:1) separating other compounds from the mixture, then taking the material gained from the first fractions on a new column. 2) CH_2Cl_2-petroleum ether (93:7), R_f = 0.16, yield 3%, recryst. from cyclohexane, m.p. 127-128°C. IR (KBr): 2230 (CN), 1590, 1560 (C=C, C=N conjugated) cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.5-2.3 (4H, m, $-OCH_2-CH_2-$), 4.4 (4H, m, $O-CH_2-$), 7.0 (2H, d, J = 8 Hz, 5-pyridyl), 7.3 (2H, d, J = 8 Hz, 3-pyridyl) and 7.8 (2H, t, J = 8 Hz, 4-pyridyl). MS (70 eV), m/z (rel. int. %): 175(29), 174(100), 147(36), 146(38), 145(43), 121(84), 120(57), 103(71), 55(74), 28(34).

8-Hydroxyoctyl 6-chloropyridine-2-carboximidate (exp. 15) Chromatography: The crude reaction mixture from exp. 15, 0.58 g, was separated on a column with a diameter of 3 cm. The five compounds were gradually eluted by 1) 250 ml CH_2Cl_2-EtOAc (85:15) 2) 250 ml CH_2Cl_2-EtOAc (70:30) and 3) 140 ml CH_2Cl_2-EtOAc (1:1). Fractions of 20-25 ml size were collected. 8-Hydroxyoctyl 6-chloropyridine-2-carboximidate was obtained from fractions 21-24. R_f = 0.07 (85:15), yield 11%, m.p. 78-80°C. IR (KBr): 3400-3100 (OH and NH broad), 1640 (C=N imidate) cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.1-2.1 (12H, m, $-CH_2-$), 3.6 (2H, t, J = 6 Hz, $-CH_2-OH$), 4.4 (2H, t, J = 6 Hz, $-C(NH)-O-CH_2-$), 7.3-7.6 (1H, m, X-pyridyl) and 7.8-7.9 (2H, m, AB-pyridyl) (no NH or OH peak/peaks, probably due to exchange reactions). MS (20 eV), m/z (rel. int. %): 185(2), 183(4), 159(37), 157(100), 142(15), 140(52), 138(47), 115(25), 113(81), 103(49), 82(43), 78(34), 68(44), 67(51), 55(54), 31(13).

6-Hydroxyhexyl 6-chloropyridine-2-carboximidate (exp. 12) Chromatography eluent: CH_2Cl_2-EtOH (95:5), R_f = 0.13, yield 8%, recryst. from CH_2CN, m.p. 99-101°C. IR(KBr): 3320 (NH), 1750, 1650 (C=N imidate), 1580, 1565 (C=C and C=N conjugated) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.1-2.1 (8H, m, $-CH_2-$), 3.6 (2H, t, J = 6 Hz, $-CH_2-OH$), 4.4 (2H, t, J = 6 Hz, $-C(NH)-O-CH_2-$), 7.3-7.6 (1H, m, X-pyridyl) and 7.8-7.9 (2H, m, AB-pyridyl). MS (70 eV), m/z (rel. int. %): 159(71), 157(20), 140(30), 138(45), 113(16), 103(58), 100(73), 76(19), 69(14), 50(45), 31(82), 28(100).

2-Cyano-6-(10-hydroxydecyloxy)pyridine (exp. 3 and 4) Chromatography eluent: CH_2Cl_2-EtOH (9:1), R_f = 0.28, yield 40%, m.p. 52-55°C. IR(KBr): 3400 (OH broad), 2230 (CN), 1610, 1590, 1560 (C=C and C=N conjugated) cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.1-2.0 (16H, m, $-CH_2-$), 3.5 (2H, t, J = 6 Hz, $-CH_2-OH$), 4.3 (2H, t, J = 6 Hz, $ArO-CH_2-$), 6.8 (1H, d, J = 8 Hz, 5-pyridyl), 7.2 (1H, d, J = 8 Hz, 3-pyridyl) and 7.6 (1H, dd, J = 8 and 6 Hz, 4-pyridyl). MS (70 eV), m/z (rel. int. %): 276(3), 246(4), 121(100), 120(39), 103(10), 69(14), 67(12), 55(35), 43(13), 41(33). 29(11), 28(10).

2-Cyano-6-(8-hydroxyoctyloxy)pyridine (exp. 15) Chromatographic procedure: see 8-hydroxyoctyl 6-chloropyridine-2-carboximidate. 2-Cyano-6(8-hydroxyoctyloxy)pyridine was obtained from fractions 10-14. R_f = 0.28 (CH_2Cl_2-EtOAc (85:15)), yield 7%, m.p. 40-49°C. IR (film): 3350 (O-H broad), 2230 (CN), 1590, 1560 (C=C and C=N conjugated) cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.2-2.0 (12H, m, $-CH_2-$), 3.6 (2H, t, J = 6 Hz, $-CH_2OH$), 4.3 (2H, t, J = 6 Hz, $ArO-CH_2-$), 6.9 (1H, d, J = 8 Hz, 5-pyridyl), 7.3 (1H, d, J = 8 Hz, 3-pyridyl) and 7.7 (1H, dd, J = 8 and 6 Hz, 4-pyridyl). MS (20 eV), m/z (rel. int. %): 248(3), 230(1), 122(15), 121(100), 120(55), 82(11), 81(11), 69(26), 68(13), 67(16), 55(27), 41(17).

2-Cyano-6-(6-hydroxyhexyloxy)pyridine (exp. 6 and 7) Chromatography eluent: CH_2Cl_2-EtOAc (9:1), R_f = 0.21, yield 34%, m.p. 37-40%. IR(KBr): 3210 (OH broad), 2240 (CN), 1590, 1565 (C=C and C=N conjugated) cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.1-1.9 (8H, m, $-CH_2-$), 3.6 (2H, t, J = 6 Hz, $-CH_2-OH$), 4.3 (2H, t, J = 6 Hz, $ArO-CH_2-$), 6.9 (1H, d, J = 8 Hz, 5-pyridyl), 7.2 (1H, d, J = 8 Hz, 3-pyridyl) and 7.6 (1H, dd, J = 8 and 6 Hz, 4-pyridyl). MS (20 eV), m/z (rel. int. %): 220(2), 202(2), 121(100), 120(40), 92(12), 83(11), 82(16), 67(19), 55(33), 44(10), 43(10), 41(18).

2-Cyano-6-(4-hydroxybutoxy)pyridine (exp. 8 and 17) Chromatography eluent: petroleum ether - EtOAc (1:1), R_f = 0.25, yield 46%, slowly crystallizing oil. IR(KBr): 3400 (OH broad), 2240 (CN), 1590 (C=C and C=N conjugated) cm^{-1}. ^{1}H-NMR (60 MHz): δ 1.5-1.9 (4H, m, $-CH_2-$), 3.7 (2H, t, J = 6 Hz, $-CH_2-OH$), 4.4 (2H, t, J = 6 Hz, $ArO-CH_2-$), 6.9 (1H, d, J = 8 Hz, 5-pyridyl), 7.3 (1H, d, J = 8 Hz, 3-pyridyl) and 7.7 (1H, dd, J = 8 and 6 Hz, 4-pyridyl). MS (70 eV), m/z (rel. int. %): 192(8), 174(2), 133(19), 121(95), 120(100), 103(27), 92(47), 55(34), 43(22), 41(23), 39(19), 31(26).

8-(2-Cyano-6-pyridyloxy)octyl 6-chloropyridine-2-carboximidate (exp. 15) Chromatographic procedure: see 8-hydroxyoctyl 6-chloropyridine-2-carboximidate. 8-(2-Cyano-6-pyridyloxy)octyl 6-chloropyridine-2-carboxyimidate was obtained from fractions 4-6. R_f = 0.52 (CH_2Cl_2-EtOAc (85:15)), yield 4%, slowly crystallizing oil. IR(KBr): 3280 (NH), 2230 (CN), 1640 (C=N imidate), 1590, 1560 (C=C and C=N conjugated) cm^{-1}. ^{1}H-NMR (200 MHz): δ 1.42 (8H, m, $-CH_2-$), 1.78-1.82 (4H, m, $-CH_2-$), 4.31 (2H, t, J = 6.7 Hz, $O-CH_2-$), 4.36 (2H, t, J = 6.6 Hz, $O-CH_2-$), 6.94 (1H, d, J = 8.5 Hz, 5-pyridyl), 7.28 (1H, d, 3-pyridyl), 7.38-7.45 (1H, m, X-pyridyl), 7.65 (1H, dd, J = 8.5 and 7.3 Hz, 4-pyridyl), 7.76-7.79 (2H, m, AB-pyridyl) and 9.09 (1H, s, NH). MS (20 eV), m/z (rel. int. %): 386 (<1), 140(16), 138(50), 122(9), 121(100), 120(38), 104(10), 103(65), 76(18), 69(17), 67(10), 55(26), 43(10), 41(21).

6-(2-Cyano-6-pyridyloxy)hexyl 6-chloropyridine-2-carboximidate (exp. 16) Chromatography eluent: CH_2Cl_2-EtOAc (7:3), R_f = 0.76 yield 8%, slowly crystallizing oil. IR(KBr): 3280 (NH), 2230 (CN), 1640 (C=N imidate), 1590, 1560 (C=C and C=N conjugated) cm^{-1}. ^{1}H-NMR (200 MHz): δ 1.52-1.58 (4H, m, $-CH_2-$), 1.78-1.85 (4H, m, $-CH_2-$), 4.33 (2H, t, J = 6.6 Hz, $-O-CH_2-$), 4.38 (2H, t, J = 6.5 Hz, $-O-CH_2-$), 6.93 (1H, dd, J = 8.5 and 0.8 Hz, 5-pyridyl), 7.28 (1H, dd, J = 7.2 and 0.8 Hz, 3-pyridyl), 7.38-7.43 (1H, m, X-pyridyl), 7.65 (1H, dd, J = 8.5 and 7.2 Hz, 4-pyridyl), 7.76-7.78 (2H, m, AB-pyridyl) and 9.10 (1H, s, NH). MS (70 eV), m/z (rel. int. %): 360(<1), 358(<1), 140(24), 138(64), 121(93), 120(42), 103(100), 92(18), 82(17), 76(34), 67(21), 55(38), 41(32).

4-(2-Cyano-6-pyridyloxy)butyl 6-chloropyridine-2-carboximidate (exp. 17) Chromatography eluent: CH_2Cl_2-EtOAc (93-7), R_f = 0.13, yield 3%, slowly crystallizing oil. IR(film): 3290 (N-H), 2240 (CN), 1650 (C=N imidate), 1595, 1565 (C=C and C=N conjugated) cm^{-1}. ^{1}H-NMR (200 MHz): δ 1.99 (4H,m, $-CH_2-$), 4.42-4.45 (4H, m, $-O-CH_2-$), 6.96 (1H, d, J = 8.2 Hz, 5-pyridyl), 7.29 (1H, d, J = 7.2 Hz, 3-pyridyl), 7.39-7.43 (1H, m, X-pyridyl), 7.66 (1H, dd, J = 8.4 and 7.3 Hz, 4-pyridyl), 7.79-7.82 (2H, m, AB-pyridyl) and 9.13 (1H, s, NH). MS (20 eV), m/z (rel. int. %): 174(22), 145(24), 140(37), 138(47), 121(100), 120(89), 140(20), 113(20), 103(93), 92(34), 76(27), 71(20), 55(35). Calcd. for $C_{16}H_{15}N_4O_2Cl$: C 58.09, H 4.57, N 16.94. Found: C 58.4, H 4.7, N 16.8 %.

1,11-Di(2-cyano-6-pyridyloxy)-3,6,9-trioxaundecane (exp. 1) Chromatography eluent: petroleum ether - EtOAc (1:4), R_f = 0.38, yield 68%, recryst. from CCl_4, m.p. 67-70°C. IR(KBr): 2990-2860 (CH_2), 2230 (CN), 1615, 1600, 1570 (C=C and C=N conjugated) cm^{-1}. ^{1}H-NMR (60 MHz, $(CD_3)_2CO$): δ 3.5-4.0 (12H, m, $O-CH_2-CH_2-O$), 4.35-4.6 (4H, m, $ArO-CH_2$), 7.1 (2H, dd, J = 10 and 2 Hz, 5-pyridyl), 7.6 (2H, dd, J = 8 and 2 Hz, 3-pyridyl) and 7.9 (2H, dd, J = 8 and 6 Hz, 4-pyridyl). MS (70 eV), m/z (rel. int. %): 398(<1), 148(10), 147(100), 121(13), 113(13), 103(23), 78(9), 76(10), 45(9).

1,8-Di(2-cyano-6-pyridyloxy)-3,6-dioxaoctane (exp. 2) Chromatography eluent: CH_2Cl_2-EtOAc (9:1), R_f = 0.38, yield: 22%, m.p. 142-144°C. IR(KBr): 2980-2840 (CH_2), 2240 (CN), 1620, 1605, 1570 (C=C and C=N conjugated) cm^{-1}. ^{1}H-NMR (200 MHz): δ 3.73 (4H, s, $O-(CH_2)_2-O$), 3.84-3.88 (4H, m, $ArO-CH_2-CH_2-$)$_2$, 4.47-4.52 (4H, m, $ArO-CH_2-$), 7.02 (2H, d, J = 8 Hz, 5-pyridyl), 7.30 (2H, d, J = 7.2 Hz, 3-pyridyl) and 7.67 (2H, t, J = 7.3 Hz, 4-pyridyl). MS (70 eV) m/z (rel. int. %): 354(<<1), 234(3), 205(4), 190(6), 177(6), 148(10), 147(100), 121(14), 103(23), 76(6), 70(9), 43(5), 28(5).

Ethyl 6-chloropyridine-2-carboximidate (exp. 13) Sodium ethoxide was prepared by reacting sodium (3.6 mmol, 0.083 g) with ethanol (10 ml). To this solution 6-chloro-2-cyanopyridine (3.6 mmol, 0.5 g) was added. After 5 min the reaction was terminated by the addition of a few drops of a saturated aqueous NH_4Cl solution. The solvents were evaporated and the crude product was distilled in a bulb to bulb apparatus, b.p. 50°C/0.05 mmHg. Ethyl 6-chloropyridine-2-carboximidate was obtained in 76% yield (0.50 g), m.p. 32-34°C. IR(KBr): 3300 (NH), 1650 (C=N imidate), 1580, 1565 (C=C and C=N conjugated) cm^{-1}. ^1H-NMR (60 MHz) δ: 1.4 (3H, t, J = 7 Hz, CH_3), 4.5 (2H, q, J = 7 Hz, CH_2), 7.3-7.6 (1H, m, X-pyridyl), 7.7-7.9 (2H, m, AB-pyridyl) and 9.1 (1H, s, NH). MS (20 eV), m/z (rel. int. %): 186(<1), 185(<1), 184(2), 183(2), 158(6), 156(17), 142(8), 141(8), 140(24), 139(14), 115(30), 113(100), 112(17), 103(16), 78(26), 76(16), 71(15), 57(18), 44(21).

2-Cyano-6-ethoxypyridine (exp. 9)[11] Chromatography eluent: petroleum ether - EtOAc (7:3), R_f = 0.48, yield 38%, recryst. from petroleum ether, m.p. 68-69%.

6-Chloropicolinamide[12] IR(KBr): 3440, 3260, 3160 (NH), 1700 (C=O) cm^{-1}. MS (70 eV), m/z (rel. int. %): 158(12), 156(36), 115(30), 114(14), 113(100), 112(22), 78(48), 77(6), 76(17), 51(10), 50(4), 44(13), 28(5).

Preparation of 2-cyano-6-ethoxypyridine from ethyl 6-chloropyridine-2-carboximidate (exp. 18)

To a refluxing suspension of sodium hydride (32 mg, 1.32 mmol) in THF ethyl 6-chloropyridine-2-carboximidate (0.24 g, 1.32 mmol) was added. After 2.5 h the reaction was terminated by the addition of 1 ml of a saturated aqueous NH_4Cl solution. The crude product obtained after separation of the organic phase was separated by flash cromatography (column diameter = 1 cm). Eluent: 1) 70 ml petroleum ether - EtOAc (7:3) and 2) 50 ml EtOAc. Fractions of 4-5 ml volume were collected. From fractions 3-5 48 mg (26%) of 1, from fractions 6-12 138 mg (70%) of 2-cyano-6-ethoxypyridine and from fractions 17-19 9 mg (4%) of 6-chloro-2-picolinamide were obtained.

Preparation of 2-chloro-6-cyanopyridine (1)

2-Chloropyridine-N-oxide[17] (8.47 g, 65.4 mmol) was added in small portions with stirring to 6.2 ml dimethyl sulphate (65.4 mmol) keeping the temperature below 40°C. It is very important that the N-oxide is added to the DMS since a reversed order of addition always led to a vigourous and uncontrolled evolution of gas. After 1.5 h the reaction mixture began to crystallize. When fully crystallized the crystal cake was crushed and washed with ether. The methylated N-oxide was dissolved in 70 ml of water and transferred to a dropping funnel that was connected to a reaction vessel containing sodium cyanide (12.8 g, 261 mmol) in 70 ml H_2O. Air was thoroughly excluded and replaced by N_2. The stirred cyanide solution was cooled to -10°C followed by dropwise addition of the methylated-N-oxide. White crystals formed immediately when the two solutions mixed. When the addition was complete the product was immediately filtered off and washed with water. After drying and sublimation (90°C/0.02 mmHg) 6.55 g (72.3%) of 1 was obtained, m.p. 85-87°C. Spectral data were in agreement with the structure of 1.

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REFERENCES AND NOTES

1. G. Newkome, T. Kawato, J. Org. Chem., 44, 2693 (1979).

2. F. Schaefer, G. Peters, J. Org. Chem., 26, 412 (1961).

3. N. Ono, H. Miyakee, Y. Tanabe, K. Tanaka, A. Kaji, Chem. Lett., 11, 1365 (1980).

4. K. Sato, S. Inoue, M. Ohasi, S. Kuranami, Chem. Lett., 5, 405 (1975).

5. G.D. Melnikov, S.P. Melnikova, A.A. Petrov, Zh. Org. Khim., 17, 2620 (1981). CA 96:84997.

6. F. Benedetti, S. Fabrissin, A. Risoliti, Tetrahedron, 40, 977 (1984).

7. M.F. Schlecht, J.C.S. Chem. Commun., 23, 1331 (1982).

8. E.M. Kaiser, W.R. Thomas, T.E. Synos, J.R. Mclure, T.S. Mansour, J.R. Garlich, J.E. Chastain, J. Organometal. Chem., 213, 405 (1981).

9. Y. Besace, J. Berlan, G. Pourcelot, M. Huche, J. Organometal. Chem., 247, C11 (1983).

10. To our knowledge a laboratory scale preparation of 6-chloro-2-cyanopyridine has only been described once, by H. Tani, Yakugaku Zasshi, 80, 1418-24 (1960). We have modified the reaction conditions of that procedure and as a result of that increased the yield from 46.7 to 72.3% (see the last part of the experimental section).

11. A. Sugimori, T. Furihata, S. Mikayama, M. Yoshida, Y. Nakanishi, Bull. Chem. Soc. Japan, 55, 2906 (1982).

12. Only mentioned once in the litterature. U.S. 4, 148, 902. CA 91:P 20340t.

13. J.H. Hall, M. Gisler, J. Org. Chem., 41, 3769 (1976).

14. A.J. Serio Duggan, E.J.J. Grabowski, W.K. Russ, Synthesis, 573 (1980).

15. J. Lefour, A. Loupy, Tetrahedron, 34, 2597 (1978).

16. L. Wartski, M. El-Bouz, J. Seyden-Penne, J. Organometal. Chem., 177, 17 (1979).

17. Prepared quantitatively from m-chloroperbenzoic acid and 2-chloropyridine in CH_2Cl_2 at room temperature for 20 h. Workup by bubbling NH_3 (g) through the reaction mixture for a few minutes and then filtering off the formed ammonium salts.