SELECTIVITY OF NUCLEOPHILIC SUBSTITUTION ON 3-SUBSTITUTED 2,6-DICHLOROPYRIDINES WITH ALKOXIDE. PYRIDINOPHANE PREPARATION

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Abstract—— Electron withdrawing groups at the 3-position of 2,6-dichloropyridines were found to assist nucleophilic displacement of the 2-chloro group with alkoxide. Pyridinophanes were prepared via stepwise substitution.

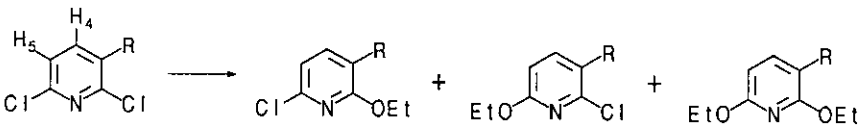
In view of the synthetic and mechanistic interests concerning pyridine-linked nucleotide models,[2] we have prepared numerous 2- and/or 6-substituted nicotinic acid derivatives.[3] During the course of these studies, nucleophilic displacement of the 2-chloro substituent on nicotinamide derivatives was noted to be more facile than for the related 6-isomer. We herein report the application of this selective nucleophilic attack on 2,6-dichloropyridine derivatives to generate pyridinophanes.

Treatment of 3-substituted 2,6-dichloropyridine (1) with 1 equiv. of sodium ethoxide afforded a mixture of 2- and 6-ethoxypyridines. The positions of attachment of ethoxy and chloride groups were defined by means of nmr experiments, and the key observation concerning the unambiguous structure of 2-ethoxy-6-chloro-N,N-dimethylnicotinamide (2a) came via reductive dehalogenation to give 2-ethoxy-N,N-dimethylnicotinamide.[3f] The 4- and 5-H chemical shifts for all starting materials and reaction products were characterized by an AB spectral pattern with the 5-H appearing at a higher magnetic field; chemical shift differences are shown in Table 1.

Table 1. Differences in Chemical Shifts between 5-Pyr-H and 4-Pyr-H

Substituents	2,6-H	2,6-Cl	2-OEt 6-Cl	2-Cl 6-OEt	2,6-OEt	2,6-O(CH_2CH_2O)$_{4-6}$
3-H	0.38	0.39[a]	0.62[a]	0.89[a]	-	1.15 - 1.18[b]
3-$CONMe_2$	0.43[a]	0.30[c]	0.63[c]	0.84[c]	1.24[c]	1.19 - 1.20[c]
3-CH_2NMe_2	-	0.57	0.71	1.02	1.23[c]	1.18 - 1.19[c]
3-CN	0.56[a]	0.53[c]	0.85	1.08	1.39	1.32 - 1.34[c]

[a]Values derived from Sadtler spectra. [b]Ref 4. [c]Ref 3.



1a R:$CONMe_2$
b R:CN
c R:CH_2NMe_2
d R:CO_2Me
e R:CHO

2a R:$CONMe_2$
b R:CN
c R:CH_2NMe_2
d R:CO_2Me

3a R:$CONMe_2$
b R:CN
c R:CH_2NMe_2
d R:CO_2Me

4a R:$CONMe_2$
b R:CN
c R:CH_2NMe_2
d R:CO_2Me

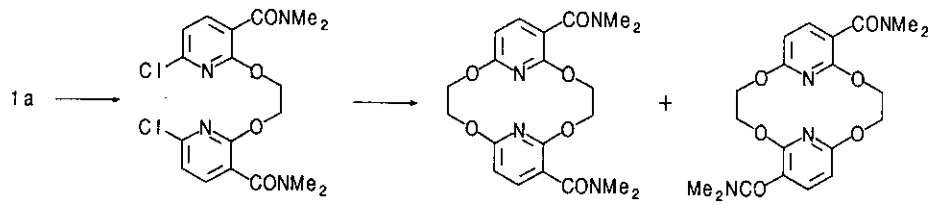
The relative propensities for ethoxide attack at the 2-position compared with the 6-position of the nicotinic acid derivatives are given in Table 2. The reactions of 1a, 1b, and 1d were found to proceed smoothly, as expected, methyl 2,6-dichloronicotinate, upon treatment with sodium ethoxide, underwent a facile transesterification as well as the anticipated substitution reactions. The simultaneous transesterification and substitution of heteroaryl halides have been used to prepare nicotinate Crown ethers.[3g,3i]

Although 2,6-dichloronicotinamide 1a was previously shown[3c] to form an isomeric

Table 2. Product Ratios of Substitution of Chloride for Ethoxide

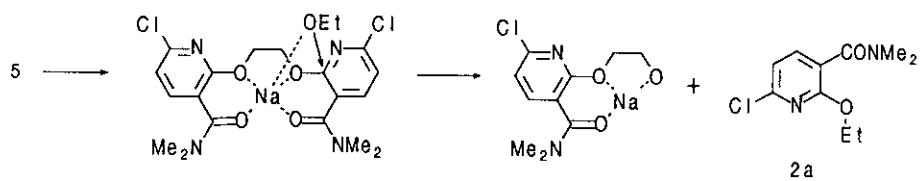
Substituents	Product Ratios 2-OEt-6-Cl	2-Cl-6-OEt
3-$CONMe_2$	96	4
3-CN	80	20
3-CH_2NMe_2	50	50

mixture of ethereal metacyclophanes, the significantly higher reactivity of the 2-position of nicotinamide 1a was applied toward the specific synthesis of the Crown ether cyclophane 6. Treatment of 1a with a half equiv. of disodium ethylene glycolate smoothly gave (65%) the 2:1 adduct 5. However, the reaction of an equimolar amount of 5 and disodium ethylene glycolate failed to give exclusively the desired cyclophane 6, but rather a mixture of 6 and 7 was obtained along with other products.[3c]



5 6 7

In general, chloride is a much better leaving group than alkoxide;[5] however, the 2-alkoxy moiety of 5 was displaced by nucleophilic attack due in part by metal ion chelation. When 5 was treated with 1 equiv. of sodium ethoxide, amide 2a was the major product, thus supporting the initial chelation of the sodium ion by the carbonyl and ethyl oxygen moiety.[6,7] A reasonable mechanism for the reaction is outlined in the following scheme.



2a

It is noteworthy that the dimethylaminomethyl function did not exert neighboring group assistance in support of the ortho-ethoxylation process. Benzylamines have been shown to undergo smooth lithiation and subsequent electrophilic substitution selectively at the ortho position;[8] similar reactions for the N,N-dimethyl derivatives have been reported.[9] Although evaluation of the relative contributions of the structural and electronic factors can be difficult, the combination of alkali metal ion coordination and the adjacent electron withdrawing functionality should facilitate this directed nucleophilic substitution; whereas with electron

releasing substituents(e.g., 1c), the substitution should be less favorable.

EXPERIMENTAL

All melting points were taken in capillary tubes and were uncorrected. The nmr spectra were obtained in $CDCl_3$ with Me_4Si, as the internal standard (δ=0 ppm), and recorded on either a Varian Associates A-60A or HA-100 Spectrophotometer. Mass spectral (ms) data were obtained with Hewlett-Packard HP 5992A GC/MS Spectrometer. Infrared (ir) spectra were recorded on a Perkin Elmer 621 Grating-Infrared Spectrophotometer. Recorded R_f values were ascertained via a standardized thin-layer chromatography (tlc) procedure: 0.25 mm Brinkmann SiO_2 60HF-254-366 plates eluting with ethyl acetate. For the preparative (2 mm) thick-layer chromatography (thlc), SiO_2 PF-254-366 plates were used, eluting with ethyl acetate. Sodium hydride (50 % oil dispersion) was washed with dry petroleum ether (bp 30-60 °C), then dried under nitrogen prior to use. All solvents were dried over sodium and distilled, prior to use. Dichloropyridines 1a[3f] and 1b[3d] were prepared by standard methods.

2,6-Dichloro-3-(N,N-dimethylaminomethyl)pyridine (1c)

A solution of 1a (1.5 g, 6.8 mmol) in benzene (50 ml) was added dropwise to a solution of "Red-Al" [2.9 g, 20 mmol, sodium bis(2-methoxyethoxy)aluminum hydride in toluene] in benzene (50 ml) at 30 °C with stirring under nitrogen. The mixture was refluxed for 30 min, cooled, and 5 N aqueous HCl (15 ml) was added slowly with external cooling. Extraction with benzene and subsequent concentration gave 2,6-dichloronicotinaldehyde [1e; 50 mg, 4 %; ^1H nmr δ 7.53 (d, J=8.1 Hz, 1H, 5-PyH), 8.25 (d, J=8.1 Hz, 1H, 4-PyH), 10.45 (s, 1H, CHO)]. Solid NaOH (7.5 g) was added to the aqueous solution, which was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated in vacuo to give amine 1c (1.25 g, 89 %) as a colorless oil: bp 96-97 °C (1.2 mm); ^1H nmr δ 2.27 (s, 6H, NCH_3), 3.50 (s, 2H, NCH_2), 7.26 (d, J=8.1 Hz, 1H, 5-PyH), 7.83 (d, J=8.1 Hz, 1H, 4-PyH); ir (neat) 2823 (NCH_3), 2775 (NCH_3), 2725 (NCH_3) cm^{-1}. Anal. Calcd for $C_8H_{10}N_2Cl_2$: C, 46.85; H, 4.91; N, 13.66. Found: C, 46.82; H, 4.99; N, 13.68.

Methyl 2,6-Dichloronicotinate (1d)

A solution of 2,6-dichloronicotinoyl chloride[10] (5 g, 23.8 mmol) in methanol (20 ml) was refluxed for 3 h. After concentration in vacuo, recrystallization of the residue from methanol gave 1d (4.55 g, 93 %), as colorless crystals: mp 56.0-

56.5°C; ^{1}H nmr δ 3.99 (s, 3H, OC$\underline{H}_3$), 7.41 (d, $\underline{J}$=8.0 Hz, 1H, 5-Py$\underline{H}$), 8.22 (d, $\underline{J}$=8.0 Hz, 1H, 4-Py$\underline{H}$); ir (KBr) 1730 (C=O) cm^{-1}. Anal. Calcd for $C_7H_5NO_2Cl_2$: C, 40.81; H, 2.45; N, 6.80. Found: C, 40.82; H, 2.44; N, 6.96.

2-Ethoxy-6-chloronicotinonitrile (2b) and 2-Chloro-6-ethoxynicotinonitrile (3b)

To a suspension of NaH (0.17 g, 7.1 mmol) in xylene (30 ml), ethanol (0.295 g, 6.4 mmol) in xylene (10 ml) was added dropwise under nitrogen. The mixture was stirred for 20 min, then nitrile 1b (1.1 g, 6.4 mmol) in xylene (30 ml) was added. The mixture was refluxed for 24 h, cooled, then water (5 ml) was carefully added. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to give the mono-ethoxy isomeric mixture (2b and 3b; 1.0 g, 86 %), as pale yellow crystals. From nmr analyses, the product ratio 2b : 3b was 80 : 20. Both isomers exhibited the same R_f values on tlc with common solvent combinations and were isolated by fractional recrystallization (C_6H_{12}-$CHCl_3$).

Isomer 2b: colorless needles; mp 53-55°C; 0.37 g (32 %); R_f 0.47; ^{1}H nmr δ 1.46 (t, $\underline{J}$=7.3 Hz, 3H, $CH_2C\underline{H}_3$), 4.55 (q, $\underline{J}$=7.3 Hz, 2H, $C\underline{H}_2CH_3$), 7.05 (d, $\underline{J}$=8.1 Hz, 1H, 5-Py$\underline{H}$), 7.90 (d, $\underline{J}$=8.1 Hz, 1H, 4-Py$\underline{H}$); ir (KBr) 2235 (C≡N) cm^{-1}. Anal. Calcd for $C_8H_7N_2OCl$: C, 52.62; H, 3.86; N, 15.34. Found: C, 52.28; H, 3.79; N, 15.30.

Isomer 3b: colorless brick crystals; mp 110-111°C; 0.14 g (12 %); R_f 0.47; ^{1}H nmr δ 1.42 (t, $\underline{J}$=7.4 Hz, 3H, $CH_2C\underline{H}_3$), 4.48 (q, $\underline{J}$=7.4 Hz, 2H, $C\underline{H}_2CH_3$); 6.79 (d, $\underline{J}$=8.7 Hz, 1H, 5-Py$\underline{H}$), 7.87 (d, $\underline{J}$=8.7 Hz, 1H, 4-Py$\underline{H}$); ir (KBr) 2235 (C≡N) cm^{-1}. Anal. Calcd for $C_8H_7N_2OCl$: C, 52.62; H, 3.86; N, 15.34. Found: C, 52.49; H, 3.76; N, 15.26.

2,6-Diethoxynicotinonitrile (4b)

To a suspension of NaH (0.1 g, 4.2 mmol) in xylene (20 ml), ethanol (0.2 g, 4.3 mmol) was added slowly under nitrogen. A mixture of nicotinonitriles 2b and 3b (0.7 g, 3.8 mmol) in xylene (20 ml) was added, then the solution was refluxed for 24 h and worked up as described above to give 4b (0.66 g, 90 %), as white crystals: mp 44-45°C (hexane); ^{1}H nmr δ 1.40 (t, $\underline{J}$=7.2 Hz, 3H, 6-PyOCH$_2$C$\underline{H}_3$), 1.44 (t, $\underline{J}$=7.2 Hz, 3H, 2-PyOCH$_2$C$\underline{H}_3$), 4.44 (q, $\underline{J}$=7.2 Hz, 2H, 6-PyOC$\underline{H}_2$CH$_3$), 4.52 (q, $\underline{J}$=7.2 Hz, 2H, 2-PyOC$\underline{H}_2$CH$_3$), 6.38 (d, $\underline{J}$=8.4 Hz, 1H, 5-Py$\underline{H}$), 7.77 (d, $\underline{J}$=8.4 Hz, 1H, 4-Py$\underline{H}$); ir (KBr) 2220 (C≡N) cm^{-1}. Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.45; H, 6.33; N, 14.63.

Reaction of 1c with Sodium Ethoxide

To a stirred suspension of NaH (35 mg, 1.5 mmol) in xylene (30 ml), ethanol (60

mg, 1.3 mmol) was added under nitrogen. After 30 min, a solution of 1c (260 mg, 1.3 mmol) in xylene (20 ml) was added, then the mixture was refluxed for 50 h. After working-up in a usual way, 210 mg of oil was obtained and characterized to be an equal mixture (26 % each) of 2-ethoxy-3-(N,N-dimethylaminomethyl)-6-chloropyridine (2c) 2-chloro-6-ethoxy isomer (3c), and unchanged 1c by comparison of the spectral data with those of authentic samples. Amine 3c could not be purified via distillation and/or thlc chromatography; however, the ^{1}H nmr spectrum was consistent with the assigned structure: ^{1}H nmr δ 1.38 (t, J=7.1 Hz, 3H, CH_2CH_3), 2.27 (s, 6H, NCH_3), 3.47 (s, 2H, NCH_2), 4.38 (q, J=7.1 Hz, 2H, CH_2CH_3), 6.67 (d, J=8.3 Hz, 1H, 5-PyH), 7.69 (d, J=8.3 Hz, 1H, 4-PyH).

2-Ethoxy-3-(N,N-dimethylaminomethyl)-6-chloropyridine (2c)

A solution of 2a (2.84 g, 12.4 mmol) in benzene (50 ml) was added dropwise to a stirred solution of "Red-Al" (4 g, 13.8 mmol) in benzene (30 ml) at 40 °C under nitrogen. The mixture was refluxed for 1 h, cooled, and then water (10 ml) was added slowly with external cooling. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2. The combined organic solution was dried (Na_2SO_4) and concentrated in vacuo to give amine 2c (2.56 g, 96 %): bp 86-87 °C (1.2 mm); ^{1}H nmr δ 1.38 (t, J=7.1 Hz, 3H, CH_2CH_3), 2.27 (s, 6H, NCH_3), 3.41 (s, 2H, NCH_2), 4.42 (q, J=7.1 Hz, 2H, CH_2CH_3), 6.90 (d, J=7.9 Hz, 1H, 5-PyH), 7.61 (d, J=7.9 Hz, 1H, 4-PyH); ir (neat) 2815 (NCH_3), 2765 (NCH_3), 2720 (NCH_3) cm^{-1}. Anal. Calcd for $C_{10}H_{15}N_2OCl$: C, 55.94; H, 7.04; N, 13.05. Found: C, 55.69; H, 7.09; N, 13.01.

Reaction of 1a with Sodium Ethoxide

Reaction of an equimolar amount of 1a and sodium ethoxide in the above manner gave a mixture of 2a and 3a;[3f] the product ratio was (^{1}H nmr) 96 : 4, respectively.

2,2'-(Ethylenedioxy)bis(N,N-dimethyl-6-chloronicotinamide) (5)

Ethylene glycol (310 mg, 5 mmol) was added slowly to a stirred suspension of NaH (500 mg, 10 mmol) in xylene (80 ml) under nitrogen. After 10 min, 1a (2.19 g, 10 mmol) in xylene (50 ml) was added, then the mixture was refluxed for 10 h. After acidic aqueous work-up and recrystallization (ethanol-ether), the desired 2:1 amide 5 (1.40 g, 65.5%) was isolated as white crystals: mp 100-103 °C; R_f 0.082; ^{1}H nmr δ 2.85, 3.05 (2s, 6H each, NCH_3), 4.76 (br s, 4H, OCH_2), 7.01 (d, J=7.9 Hz, 2H, 5-PyH), 7.62 (d, J=7.9 Hz, 2H, 4-PyH); ir (KBr) 1630 (C=O), 1280 (C-O), 1030 (C-O) cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_4O_4Cl_2$: C, 50.60; H, 4.72; N, 13.11. Found:

C, 50.43; H, 4.64; N, 12.95.

2:2 Macrocycle Preparation. Reaction of 5 with Disodium Ethylene Glycolate

To a stirred suspension of NaH (270 mg, 11 mmol) in xylene (100 ml), ethylene glycol (310 mg, 5 mmol) was added slowly under nitrogen. After 30 min, 5 (2.1 g, 5 mmol) in xylene (50 ml) was added, then the suspension was refluxed for 40 h. Upon cooling, water was carefully added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic fraction was dried (Na_2SO_4). The solvent was removed in vacuo and the resultant oil was chromatographed (thlc) to give the 2:2 macrocycles along with unchanged 5 (1.14 g), uncyclized oligomers (total 230 mg), and other slow moving fractions.

7,18-Bis(N,N-dimethylaminocarbonyl)-2,5,11,14-tetraoxa-19,20-diazatricyclo-[13,3,1,$1^{6,10}$]eicosa-1(19),6,8,10(20),15,17-hexene (6): decomp 270°C; 40 mg (1.9 %); R_f 0.13; ^1H nmr (40°C) δ 2.93, 3.11 (2s, 6H each, NCH_3), 4.72 (bs, 8H, OCH_2), 6.42 (d, J=8.0 Hz, 2H, 5-PyH), 7.62 (d, J=8.0 Hz, 2H, 4-PyH); ir (KBr) 1635 (C=O), 1270 (C-O), 1020 (C-O) cm^{-1}; ms (70 eV) m/z 416 (M^+, 5.6 %). Anal. Calcd for $C_{20}H_{24}N_4O_6$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.14; H, 6.04; N,13.26.

7,16-Bis(N,N-dimethylaminocarbonyl)-2,5,11,14-tetraoxa-19,20-diazatricyclo-[13,3,1,$1^{6,10}$]eicosa-1(19),6,8,10(20),15,17-hexene (7): 32 mg (1.5 %); R_f 0.08; ms m/z 416 (M^+, 7.6 %); ^1H nmr and ir data were closely similar to those of 6. Similar R_f values of 7 and 5 on tlc with common solvent systems gave possible structure assignment of 7.

Reaction of 5 with Sodium Ethoxide. N,N-Dimethyl-2-ethoxy-6-chloronicotinamide (2a)

To a stirred suspension of NaH (30 mg, 1.2 mmol) in xylene (30 ml), ethanol (55 mg, 1.2 mmol) was added under nitrogen. After 30 min, 5 (240 mg, 0.56 mmol) in xylene (20 ml) was added, then the mixture was refluxed for 24 h and worked up as noted above to give N,N-dimethyl-2-ethoxy-6-chloronicotinamide (2a), as white needles: 120 mg (47 %); mp 65°C (lit.[3f]: mp 65.0-65.5°C). The similarity of the R_f values and solvent properties for mono- and diethoxylation products of 5 prevented further purification: 15 mg (total); R_f 0.08; ^1H nmr δ 1.36, 1.37 (2t, J=7 Hz, CH_2CH_3), 2.83, 2.92 (2s, NCH_3), 3.04, 3.08 (2s, NCH_3), 4.34, 4.41 (2q, J=7 Hz, CH_2CH_3), 4.67 (br s, OCH_2), 4.70 (s, OCH_2), 6.36 (m, 5-PyH), 6.98 (d, J=8 Hz, 5-PyH), 7.58 (m, 4-PyH).

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