Chemistry of Heterocyclic Compounds, Vol. 36, No. 10, 2000

NUCLEOPHILIC REARRANGEMENT OF FUNCTIONALLY-SUBSTITUTED 2-ETHYLPYRIDINES*

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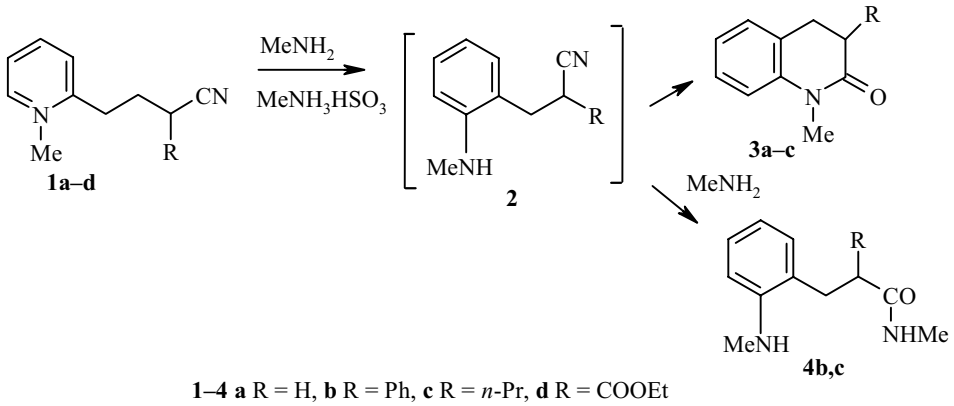
The nucleophilic rearrangement of 2'-substituted 2-ethylpyridines by the action of methylamine was studied. When the side chain has a nitrile group, the rearrangement is accompanied by intra- and intermolecular ammonolysis, leading to cyclic and linear amides, respectively. When the side-chain has an indole substituent, the rearrangement proceeds through the classical scheme.

Keywords: ammonolysis of nitriles, nucleophilic rearrangement of pyridines.

2-Ethylpyridines with functional substituents at $C_{(2')}$, obtained readily by pyridylethylation [1], are interesting compounds for studying nucleophilic rearrangement. In this work, we are the first to report the rearrangement of methyl iodides of several such pyridines, in particular, derivatives containing a nitrile group in the side chain. These compounds hold special interest since the rearrangement in this case may be accompanied by secondary reactions related to the nitrile group and lead not only to N-methylanilines but also to other compound types.

Pyridylethylation was used to synthesize a series of 3'-substituted 2-(3-cyano)propylpyridines. Their salts **1a-d** were obtained by treating the corresponding bases with methyl iodide.



1–4 a R = H, **b** R = Ph, **c** R = *n*-Pr, **d** R = COOEt

We might have expected the rearrangement products would be 2-(2-cyanoethyl)-N-methylanilines **2**, which, however, were not detected. IR and ^{13}C NMR spectroscopy indicated that the only product of the rearrangement of **1a** contains a carbonyl function and lacks a cyano group (Table 1). The mass spectral data given in Table 2 indicate that the molecular mass of this compound $M^+ = 161$. The spectral data suggest that this compound

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1345-1350, October, 2000. Original article submitted July 7, 2000.

TABLE 1. ^{13}C NMR Spectra of 3,4-Dihydro-2-quinolones **3a-c**

Compound	$C_{(4)}$	$C_{(3)}$	N–CH_3	$C_{(8)}$	$C_{(6)}$	$C_{(4a)}$	$C_{(7)}$	$C_{(5)}$	$C_{(8a)}$	CO	Other C
3a	25.27	29.35	31.50	114.40	122.62	126.04	127.26	127.53	140.45	170.29	—
3b	29.93	32.87	46.85	114.54	122.87	125.25	126-128, 7 C atoms		140.18	170.76	138.50 (1'-C), 7C, arom. C
3c	30.34	31.58	40.20	114.13	122.46	125.26	127.13	127.80	140.06	172.55	13.18 (CH_3), 20.03 ($\underline{CH_2}CH_3$), 29.50 ($\underline{CH_2}CH_2CH_3$)

TABLE 2. Physicochemical Characteristics of Products

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Mass spectrum, *m/z* (*I*, %)*
		C	H	N		
3a	$C_{16}H_{14}N_4O_8$*[2]	49.18 / 49.23	3.27 / 3.58	14.53 / 14.36	117	$M^{+\cdot}$ 161 (88), 132 (13), 119 (12), 118 (100), 117 (12), 91 (14)
3b	$C_{16}H_{15}NO$	81.13 / 81.01	6.26 / 6.33	5.74 / 5.91	92	$M^{+\cdot}$ 237 (100), 235 (22), 234 (20), 208 (14), 194 (50), 179 (13), 132 (27), 118 (40), 91 (19)
3c	$C_{13}H_{17}NO$	76.94 / 76.85	7.61 / 6.89	—	Oil	$M^{+\cdot}$ 203 (13), 161 (36), 160 (100), 118 (11)
4b	$C_{19}H_{22}N_2O_2$*[3]	73.88 / 73.55	7.15 / 7.08	8.80 / 9.03	142	$M^{+\cdot}$ 310 (7), 237 (24), 236 (26), 234 (38), 210 (38), 207 (22), 162 (38), 132 (18), 120 (100), 119 (32), 91 (58), 77 (22), 58 (20)
4c	$C_{14}H_{22}N_2O$*[4]	Found: *m/z* 234.1738 Calculated: M^+ 234.1732			Oil	$M^{+\cdot}$ 310(7), 237(24), 236(26), 234(38), 210(38), 207(22), 162(38), 132(18), 120(100), 119(32), 91(58), 77(22), 58(20)
4e	$C_{16}H_{16}N_2$	81.46 / 81.35	7.11 / 6.78	11.41 / 11.86	112	$M^{+\cdot}$ 236 (100), 235 (45), 221 (50), 219 (15), 204 (15), 144 (15), 130 (50), 120 (20), 119 (20), 118 (100), 117 (50), 91 (30), 70 (40)
4f	$C_{22}H_{20}N_2$	84.82 / 84.61	6.39 / 6.41	8.78 / 8.97	155	$M^{+\cdot}$ 312 (74), 297 (24), 235 (13), 206 (30), 205 (12), 204 (33), 194 (28), 193 (100), 120 (38), 119 (47), 118 (51), 91 (32), 77 (32), 51 (25)

* Peaks with intensity less than 10% are not shown.
*[2] Picrate. The mass spectrum of unsubstituted **3a** is given.
*[3] Acetyl derivative.
*[4] High-resolution mass spectrum.

TABLE 3. ^{1}H NMR Spectra of N-Methyl-3,4-dihydro-2-quinolones **3a-c**

Com-pound	3-H	4-H	N-CH_3	8-H	6-H	5-H	7-H	Other protons
3a	2.64 (2H, dd, J_{34a} = 7.0, J_{34b} = 5.4)	2.88 (2H, dd, J_{43a} = 7.9, J_{43b} = 6.9)	3.35 (3H, s)	6.97 (1H, d, J_{87} = 8.4)	7.03 (1H, ddd, J_{67} = 7.4, J_{65} = 8.4, J_{68} = 1.0)	7.16 (1H, dd, J_{56} = 8.4, J_{57} = 1.1)	7.25 (ddd, J_{76} = 7.4, J_{78} = 8.2, J_{75} = 1.0)	
3b	3.84 (1H, t, J_{34} = 7.7)	3.20 (1H, d, J_{43} = 7.6)	3.40 (3H, s)	7.0 (2H, m)	Aromatic protons 7.12-7.30, m			
3c	2.53 (1H, m)	2.67 (1H, dd, J_{34a} = 8.9, J_{4a4b} = 15.3, 4a-H); 2.97 (1H, dd, J_{34b} = 5.2, J_{4a4b} = 15.3, 4b-H)	3.34 (3H, s)	6.94 (1H, d, J_{78} = 7.8)	6.90 (1H, dd, J_{67} = 7.8, J_{65} = 7.5)	7.14 (1H, d, J_{56} = 7.2)	7.23 (1H, dd, J_{78} = 7.8)	0.90 (3H, t, $J_{3'2'}$ = 6.9, CH_3); 1.36 (2H, m, $\underline{CH_2}CH_3$); 1.46 (1H, m, 1a'-H, $CH_3CH_2\underline{CH_2}$); 1.76 (1H, m, 1'b-CH_2)

TABLE 4. ^{1}H NMR Spestra of N-1-Methyl-3-[2-(methylamino)phenyl]propioamides **4b**,**c**

Com-pound	2-H	3-H	CH_3NHCO	CH_3NH_2	3'-H	5'-H	6'-H	4'-H	Other protons
4s	2.3 (1H, m)	2.53 (1H, m, 1a-H); 2.82 (1H, m, 1b-H)	2.62 (3H, d, J_{CH_3NH} = 4.7)	2.80 (s)	6.58 (1H, d, J_{34} = 8.4)	6.63 (1H, ddd, J_{54} = 8.4, J_{56} = 8.4, J_{53} = 1.3)	6.96 (1H, dd, J_{64} = 1.7, J_{65} = 8.4)	7.12 (1H, ddd, J_{43} = 8.4, J_{45} = 8.4, J_{46} = 1.7)	0.90 (3H, m, J = 7.3, CH_3); 1.30 (2H, m, $\underline{CH_2}CH_3$); 1.43 (1H, m, 3a-H, $\underline{CH_2}CH_3CH_3$); 1.70 (m, 3b-H, $\underline{CH_2}CH_2CH_3$)
4b	3.48-3.60 (3H, m)		2.64 (3H, d, J_{CH_3NH} = 5.0)	2.80 (3H, s)	6.56-6.60 (2H, m)		6.87 (1H, dd, J_{65} = 7.5, J_{64} = 1.3)	7.11 (1H, ddd, J_{43} = 8.0, J_{54} = 8.0, J_{46}= 1.4)	7.35 (5H, s)

is N-methyl-3,4-dihydro-2-quinolone (**3a**), whose formation may be explained assuming initial generation of aniline **2**, which then undergoes intramolecular cyclization as the result of attack of the methylamino group on the nitrile group. Subsequent hydrolysis of intermediate 1-methyl-1,2,3,4-tetrahydroquinolinimine leads to dihydroquinolone **3a**.

Analogous dihydroquinolones **3b** and **3c** were obtained in the rearrangement of **1b** and **1c**, respectively. Furthermore, a second reaction product was isolated in each case. The formation of this second product may be explained assuming, as in the former case, that aniline **2** is initially formed but its cyano group does not undergo intermolecular attack. Instead, intermolecular attack by methylamine present in excess in the solution gives an amidine. Hydrolysis of this amidine leads to the N-methylamide of 2-substituted 3-(2-methylaminophenyl)propionic acid **4**. Indeed, the IR and ^{13}C NMR spectra indicate that the second product, similar to the first product, lacks a cyano group but contains a carbonyl group. The spectral data indicate formation of N-methylamide **4** (Tables 3 and 4). N-Methylamides are formed from nitriles by the action of aqueous methylamine at 150°C [2].

We should note that the ^{1}H NMR signal of one of the methyl groups is a doublet due to splitting by the amino group hydrogen atom; the coupling constant is 4.7-5 Hz (Table 4). Since the signal of the aniline methylamino group is a singlet in the spectra of N-methylanilines [3] but a doublet in **4b** and **4c**, this signal is assigned to an amide methyl group.

The product of the pyridylethylation of cyanoacetate ester **1d** has an additional site for nucleophilic attack after the rearrangement, namely, the carbon atom of the ester group. Thus, the secondary processes might be related to intra- and intermolecular attack of the nucleophile at each electron-deficient carbon atom, namely, in the cyano and ester groups. The NMR and mass spectral data indicate that the only product of the rearrangement of **1d** is **3a**. Thus, hydrolysis and decarboxylation of the ester group and intramolecular ammonolysis of the cyano group occur under the reaction conditions.

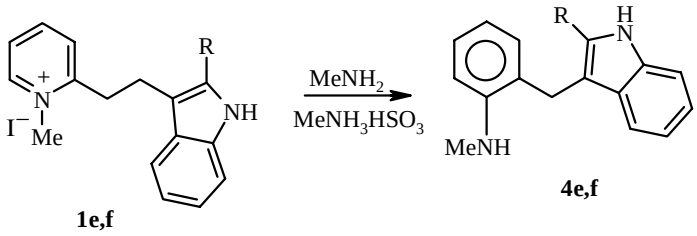
When the temperature is lowered to 100°C, the reaction of nitriles with amines in aqueous media may lead to amides not substituted at the nitrogen atom [2]. Such behavior was not found in our case. The products of the reactions performed at 100 and 160°C proved identical. A difference was found in the product ratio. The total yield of reaction products proved lower at 100°C (Table 5).

An attempt was made to recyclize 2-(2-cyanoethyl)pyridine, which has one methylene group less than 2-(2-cyanoethyl)propylpyridine **1a**. By analogy with the formation of **3a** from salt **1a**, we might have expected formation of 1-methyl-2-indolimine and, after hydrolysis, 1-methyl-2-indolone. However, both these compounds readily oxidize [4] and, thus, would not be stable under the reaction conditions. Indeed, products of the rearrangement of 2-(2-cyanoethyl)pyridine were not isolated.

3-[2-(2-Pyridyl)ethyl]indole and 2-phenyl-3-[2-(2-pyridyl)ethyl]indole and then their methyl iodides **1e** and **1f** were obtained by the pyridine ethylation reaction. The rearrangement of these compounds proceeds according to the classical scheme and leads to 3-substituted indoles **4e** and **4f**. No side-reactions related to the indole substituents occur.

TABLE 5. Reaction Products Yields, %

Compound	160°C				100°C, water	
	water		water + ethanol			
	aniline	dihydroquinolone	aniline	dihydroquinolone	aniline	dihydroquinolone
1a	—	40	—	50	Trace	24
1b	15	20	8	10	14	16
1c	18	39	12	23	24	12
1d	Trace	16	Trace	13	Trace	11
1e	72	—	40	—	—	



1e,f **4e,f**

1e R = H, **1f** R = Ph; **4e** R = H, **4f** R = Ph

EXPERIMENTAL

The NMR spectra of the products were taken on a Varian VXR-400 spectrometer for $CDCl_3$ solutions with TMS as the internal standard. The mass spectra were obtained on a Kratos mass spectrometer. The ionizing electron energy was 70 eV. The high-resolution mass spectrum was taken on a VG ZabSpec spectrometer using perfluorokerosene as the standard. The IR spectra were taken on a UR-20 spectrometer for vaseline mulls.

Nucleophilic Rearrangement of 2'-Substituted 2-Ethylpyridines (General Method). A. A sample of 25% aqueous CH_3NH_2 (5 ml) and the same solution saturated with SO_2 (5 ml) were added to salt **1** (4 mmol) at 0°C.

B. Samples of 38% ethanolic CH_3NH_2 (5 ml) and 25% aqueous CH_3NH_2 saturated with SO_2 (5 ml) were added to **1** (4 mmol) at 0°C. In both variants, the mixtures were heated in a sealed ampule at 160°C for 20 h or at 100°C for 40 h, cooled, and extracted with ether. The extract was dried over Na_2SO_4, evaporated, and separated by gradient elution on a column packed with silica gel 100-160 using ethyl acetate–hexane as the eluent.

The spectra and physicochemical characteristics of the products are given in Tables 1-4 and the yields are given in Table 5.

3-[2-Methylaminophenyl]methyl-1H-indole (4e). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.85 (3H, s, N–CH_3); 4.07 (2H, s, CH_2); 6.77 (2H, m, 3'-H, 2-H); 6.85 (1H, ddd, $J_{5'4'}$ = 7.2, $J_{6'5'}$ = 7.3, $J_{3'5'}$ = 1.0, 5'-H); 7.2-7.4 (5H, m, 4'-, 4-, 5-, 6-, 7-H); 7.7 (1H, dd, $J_{6'5'}$ = 7.5, 6'-H); 7.9 (1H, br. s, NH).

3-[2-Methylaminophenyl]methyl-2-phenyl-1H-indole (4f). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.80 (3H, s, N–CH_3); 3.70 (1H, br. s, NH); 3.96 (2H, s, CH_2); 6.62 (2H, m, 3'-, 5'-H (aniline)); 6.96-7.46 (11H, m, H_{arom}); 8.10 (1H, br. s, NH).

N-Methyl-2-[2-(methylamino)benzyl]pentanamide (4c). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.87 (CH_3), 20.60 ($\underline{CH_2}CH_3$), 25.94 (CH_3-amide), 30.65 (CH_3-aniline), 34.34 (CH_2-benzyl), 35.14 ($\underline{CH_2}CH_2CH_3$), 48.05 (CH), 110.01 (3'-C), 116.80 (5'-C), 124.30 (1'-C), 127.5 (4'-C), 130.04 (6'-C), 147.15 (2'-C), 176.50 (CO). IR spectrum (neat), ν, cm^{-1}: 1660 (CO).

N-Methyl-3-[2-(methylamino)phenyl]-2-phenylpropanamide (4b). IR spectrum (neat), ν, cm^{-1}: 1660 (CO).

N-Methyl-3,4-dihydro-2-quinolone (3a). IR spectrum (neat), ν, cm^{-1}: 1680 (CO).

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