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Reactions of 4-(1-Pyrrolidinyl)pyridine-2-carboxanilides with Acyl Halides to Give Acyl Imidate Hydrohalides

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Some acyl imidate hydrohalides are obtained from reactions of acyl halides with 4-(1-pyrrolidinyl)pyridine-2-carboxanilides. These compounds are thought to be formed through an intramolecular *O*-acylation of the amide function subsequent to the acylation of the pyridine-nitrogen. The usual $O \rightarrow N$ acyl migration within the amide function is suppressed because of certain stabilizing features of these acyl imidate hydrohalides.

Acyl imidates are well established as the initial acylation products of amides,[1] but a rapid intramolecular $O \rightarrow N$ acyl migration usually occurs and the thermodynamically more stable *N*-acyl amides, or imides, are isolated. Such $O \rightarrow N$ acyl migration may be suppressed provided the secondary amide which is to be acylated has a sufficiently electron-withdrawing *N*-substituent.[2] Similarly the $O \rightarrow N$ acyl migration may be suppressed by large steric requirements of one substituent as recently shown by the isolation of an *O*-acylisourea.[3]

The picolinanilides *1*, *cf.* Scheme 1, provide two possible sites for reaction with an acyl halide, the pyridine nitrogen or the amide function. Addition compounds of pyridine and acyl chlorides are known as better acylating agents than acyl chlorides [4] and recently 4-(1-pyrrolidinyl)pyridine [5] has been used as an even more effective catalyst for acyl transfer reactions.[6] Thus, reactions between the amides *1* and acyl halides are expected to occur through an initial attack of the pyridine nitrogen on the acyl halides. The acyl-group of this intermediate which is shown in Scheme 1, might be transferred intramolecularly to the amide function. In accord with the accepted mechanism of amide acylations [1] an initial *O*-acylation is expected; it would occur through a five-ring transition state to form the acyl imidate hydrohalides *2*.

Compared to other acyl imidates the structure of *2* shows two stabilizing features; these are an extended conjugated system from the pyridine moiety to the imide-aryl group, and an intramolecular hydrogen bond between the acyloxy group and the pyridinium hydrogen. Thus compounds *2* might not undergo the usual intramolecular acyl migration to the imide-nitrogen.

Presently a series of acyl imidate hydrohalides *2* is prepared from reactions of the picolinanilides *1* with acyl halides.

RESULTS

Reactions of the picolinanilides *1a—d* with acyl halides give the acyl imidate hydrohalides *2a—m* (Table 1). However, when acyl chlorides are used, substantial amounts of the hydrochlorides of *1* which are practically insoluble in benzene and acetonitrile, precipitate during the reactions and remain unchanged. Since the hydroiodides of *1* are somewhat more soluble than the hydrochlorides, improved yields of *2* are obtained from reactions of *1* with acyl iodides, the latter being prepared *in situ* from acyl chlorides and sodium iodide. It will be noted that *2* is obtained in an amount corresponding to (1—*1*.HX) from the experiments where acyl chloride and *1* are used in a 1:1 molar ratio (Table 1).

The acyl imidate hydrohalide structure of compounds *2* is consistent with the observed

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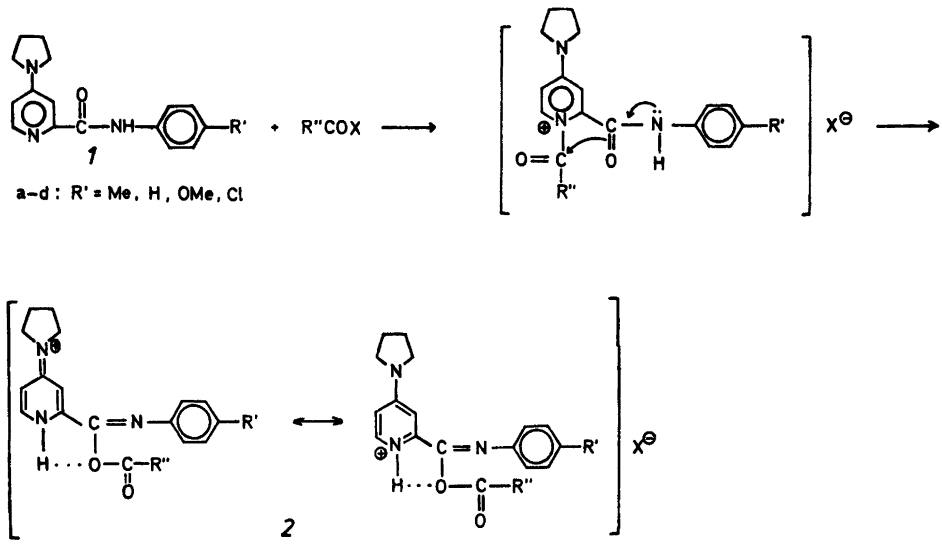

	R'	R"	X		R'	R"	X
a :	Me	4-Ph-Ph	I	j :	OMe	4-Ph-Ph	I
b–c:	Me	Ph; Me	Cl	k :	OMe	Me	Cl
d–e:	H	4-Ph-Ph	Cl; I	l :	Cl	4-Ph-Ph	I
f :	H	Ph	I	m :	Cl	Me	Cl
g– i :	H	Me	Cl; Br; I				

Scheme 1.

properties of these compounds. The highest molecular ion observed in mass spectra of *2* is that of an acyl group added to *1*. This does not exclude that *2* adopts the acylpyridinium structure since a fairly strong covalent bond is expected between an acyl group and the pyridine nitrogen.[7] However, 1-acetyl-4-(1-pyrrolidinyl)-pyridinium chloride *3a* was prepared and was found to be hydrolyzed rapidly in air whereas compounds *2* are quite stable. The spectral properties of *3a* are in good agreement with those of 1-acetyl-4-(*N*,*N*-dimethylamino)pyridinium chloride.[7] Thus, the IR spectrum of *3a* shows a carbonyl absorption at 1760 cm^{-1} and a C=N absorption at 1660 cm^{-1} and the ^1H NMR absorption signal for the methyl protons is found at δ 3.0. Compounds *2* on the other hand show carbonyl absorptions at 1740–1730 cm^{-1} consistent with an acyl imidate structure.[2] Compounds *2c*, *2g*, *2h*, *2i*, *2k* and *2m* also show ^1H NMR absorption signals at δ 1.9–2.1, characteristic of acetoxy methyl protons, whereas the methyl protons of *N*-acetyl-*N*-benzoylaniline resonate[8] at δ 2.41; these data clearly indicate an acyl imidate structure of compounds *2*. Titrations of compounds *2d* and *2e* with sodium hydroxide also confirm the assigned structures.

EXPERIMENTAL

General. The instrumentation was the same as previously described.[9] Solvents for the preparations of compounds *2* and *3* were dried over molecular sieves, 3 Å from Merck. The acyl chlorides were commercial samples, Merck reagent grade, except 4-biphenylcarbonyl chloride m.p. 112 °C, lit.[10] m.p. 113 °C.

4-(1-Pyrrolidinyl)pyridine 1-oxide. A solution of 3 g (23 mmol) of 4-chloropyridine 1-oxide[11] in 5 ml of pyrrolidine and 3.5 ml of water was heated at 120 °C in a Lieboff tube for

Table 1. Reactions of picolinanilides with acyl halides.

Anilide	Acyl halide [a] R″	X	Reaction conditions Solvent	Time/h	Temp./°C	Products *2*/%	*1*·HX/%
1a	4-Ph-Ph	I	MeCN	0.5	80	*a*, 64	[b]
1a	Ph	Cl	PhH	1	80	*b*, 59	35
1a	Me	Cl	THF	1	20	*c*, 27	70
1a	Me	Cl	MeCN	0.2	80	*c*, 61	20
1b	4-Ph-Ph	Cl	MeCN	1.5	80	*d*, 44	54
1b	4-Ph-Ph	I	MeCN	3	50	*e*, 70	[b]
1b	Ph	I	MeCN/PhH	0.25	80	*f*, 50	[b]
1b	Me	Cl	MeCOCl	0.5	20	*g*, 30	68
1b	Me	Cl	Me_2CO/PhH	0.3	70	*g*, 28	65
1b	Me	Br	MeCN/PhH	0.5	70	*h*, 46	50
1b	Me [c]	I	MeCN/PhH	0.75	75	*i*, 34	[b]
1c	4-Ph-Ph	I	MeCN	0.5	80	*j*, 57	[b]
1c	Me	Cl	MeCN	0.2	60	*k*, 43	35
1d	4-Ph-Ph	I	MeCN	0.5	70	*l*, 55	[b]
1d	Me	Cl	MeCN/PhH	0.3	80	*m*, 32	47

[a] The acyl iodides were prepared *in situ* from equimolar amounts of acyl chloride and sodium iodide. A 5–10 % molar excess of the acyl halide was used for R″ = 4-Ph-Ph and Ph, whereas two molar equivalents were used for R″ = Me. [b] The amide hydroiodide was not separated from sodium chloride. [c] The acylating agents were acetic anhydride and sodium iodide.

5 h. A saturated solution of sodium hydrogencarbonate (10 ml) was added and the reaction mixture was extracted with 3 × 20 ml of chloroform. The residue from the dried chloroform extract gave, upon addition of acetone, 2.05 g (54 %) m.p. 217–219 °C dec. of the title compound. An additional amount of this compound, 1.16 g (30 %) m.p. 195–205 °C dec. was obtained by evaporating the aqueous layer, extraction with chloroform and crystallization from acetone. The combined products were eluted with chloroform when chromatographed on silica gel and gave 4-(1-pyrrolidinyl)-pyridine 1-oxide, m.p. 222–224 °C. MS [*m/e* (% rel. int.)]: 164 (100, M), 148 (10.5, M–O). Mol. wt., obs. 164.0955, calc. for $C_9H_{12}N_2O$ 164.0950. IR (nujol): 1220 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.02 (4H, m), 3.26 (4H, m), 6.34 (2H, d, J 8.6 Hz), 7.94 (2H, d, J 8.5 Hz).

1-Acetyl 4-(1-pyrrolidinyl)pyridinium chloride, 3a. To a benzene solution of 4-(1-pyrrolidinyl)pyridine,[5] which was prepared by reduction of the corresponding 1-oxide by phosphorus trichloride in chloroform,[12] was added an equimolar amount of acetyl chloride. Compound *3a* separated as a white solid and was filtered immediately. IR (nujol): 1760 (s), 1660 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.14 (4H, m), 3.0 (3H, s), 3.49 (2H, m), 3.79 (2H, m), 6.63 (1H, d, J 7.14 Hz), 7.06 (1H, d, J 7.14 Hz), 7.23 (1H, m), 8.06 (1H, d, J 7.14 Hz), 9.07 (1H, d, J 7.14 Hz). M.p. 190 °C gas ev., 305 °C gas ev.

Picolinanilides 1a–d. Compounds *1a–b* have been reported.[9] 4-(1-Pyrrolidinyl)-*N*-(4-methoxyphenyl)picolinamide, *1c*, was prepared in 70 % yield, m.p. 196–197 °C. MS [*m/e* (% rel. int.)]: 297 (73.3, M). Mol. wt., obs. 297.1475, calc. for $C_{17}H_{19}N_3O_2$ 297.1477. IR (nujol): 3340 (m), 3320 (m), 1675 (s) cm^{-1}. 4-(1-Pyrrolidinyl)*N*-(4-chlorophenyl)picolinamide *1d* was prepared in 68 % yield, m.p. 219–221 °C. MS [*m/e* (% rel. int.)]: 301 (35.6, M). Mol. wt., obs. 301.0982, calc. for $C_{16}H_{16}ClN_3O$ 301.0983. IR (nujol): 3300 (m), 1690 (s) cm^{-1}.

Picolinanilide hydrochlorides. Dry hydrogen chloride gas was led into a benzene solution of the picolinanilide. The precipitate was filtered off, washed with benzene and dried over phosphorus(V) oxide. *1a.HCl*, m.p. 272–275 °C dec. IR (nujol): 1680 (m), 1640 (s), 1615 (w) cm^{-1}. *1b.HCl*, m.p. 306–309 °C dec. IR (nujol): 1680 (m), 1635 (s) cm^{-1}. *1c.HCl*, m.p. 284–286 °C dec. IR (nujol): 1675 (w), 1640 (s) cm^{-1}. *1d.HCl*, m.p. 268–270 °C dec. IR (nujol): 1685 (m), 1635 (s), 1605 (w) cm^{-1}.

Acyl imidate hydrohalides, 2a–m. To a solution (Table 1) of the picolinanilide was added the acyl chloride or acyl bromide and, in some instances, sodium iodide. At the end of the reaction period the picolinanilide hydrohalide was removed by filtration. The filtrate was evaporated to dryness under reduced pressure and the residue was crystallized either from a mixture of acetone and diethyl ether or from diethyl ether.

2a, m.p. 163–165 °C dec. MS [*m/e* (% rel. int.)]: 461 (8.3, M–HI). Mol. wt., obs. 461.2105, calc. for $C_{30}H_{27}N_3O_2$ 461.2103. IR (nujol): 1740 (s), 1660 (s) cm^{-1}.

2b, m.p. 80–100 °C g.ev.; solidified; 210 °C dec. MS [*m/e* (% rel. int.)]: 385 (2.5, M–HCl). Mol. wt., obs. 385.1794, calc. for $C_{24}H_{23}N_3O_2$ 385.1790. IR (nujol): 1730 (s), 1655 (s) cm^{-1}.

2c, m.p. 70 °C g.ev.; solidified; 230 °C dec. MS [*m/e* (% rel. int.)]: 323 (21.7, M–HCl). Mol. wt., obs. 323.1636, calc. for $C_{19}H_{21}N_3O_2$ 323.1634. IR (nujol): 1730 (s), 1660 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.0 (3H, s), 2.14 (4H, s), 2.38 (3H, s), 3.54 (4H, s), 7.0–7.54 (6H, m), 9.0 (1H, d, *J* 7.14 Hz).

2d, m.p. 142–145 °C; solidified; 230 °C dec. IR (nujol): 1740 (s), 1665 (s) cm^{-1}. A solution of *2d* (24.8 mg, 0.051 mmol) in 3 ml of acetone was titrated with 0.2 M sodium hydroxide with phenolphthalein as indicator. The amount of sodium hydroxide used, 0.26 ml, gives an equivalent weight of 477 compared to 483.6 for *2d*.

2e, m.p. 176–178 °C dec. MS [*m/e* (% rel. int.)]: 447 (2.0, M–HI). Mol. wt., obs. 447.1948, calc. for $C_{29}H_{25}N_3O_2$ 447.1947. IR (nujol): 1740 (s), 1665 (s) cm^{-1}. A similar titration as for *2d* gave an equivalent weight of 562 compared to 575 for *2e*.

2f, m.p. 152–154 °C dec. MS [*m/e* (% rel. int.)]: 371 (0.9, M–HI). Mol. wt., obs. 371.1634, calc. for $C_{23}H_{21}N_3O_2$ 371.1634. IR (nujol): 1740 (s), 1660 (s) cm^{-1}.

2g, m.p. 65 °C g.ev.; solidifed; 165 °C dec. MS [*m/e* (% rel. int.)]: 309 (8.6, M–HCl). Mol. wt., obs. 309.1481, calc. for $C_{18}H_{19}N_3O_2$ 309.1477. IR (nujol): 1730 (s), 1660 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.0–2.11 (7H, m), 3.51 (4H, s), 7.0–7.66 (7H, m), 9.0 (1H, d, *J* 8.5 Hz).

2h, m.p. 157–160 °C dec. MS [*m/e* (% rel. int.)]: 309 (7.0, M–HBr). Mol. wt., obs. 309.1476, calc. for $C_{18}H_{19}N_3O_2$ 309.1477. IR (nujol): 1725 (s), 1710 (w), 1665 (s) cm^{-1}. ^1H NMR ($CDCl_3/CD_3OD$): δ 1.90 (3H, s), 2.17 (4H, s), 3.60 (4H, s), 7.14 (2H, m), 7.46 (5H, s), 8.60 (1H, d, *J* 7.14 Hz).

2i, m.p. 130–133 °C dec. MS [*m/e* (% rel. int.)]: 309 (0.3, M–HI). Mol. wt., obs. 309.1484, calc. for $C_{18}H_{19}N_3O_2$ 309.1477. IR (nujol): 1750 (s), 1715 (w), 1675 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.14–2.23 (7H, 2s), 3.66 (4H, s), 7.13–7.54 (7H, m), 9.47 (1H, d, *J* 7.14 Hz).

2j, m.p. 160–163 °C dec. MS [*m/e* (% rel. int.)]: 477 (3.7, M–HI). Mol. wt., obs. 477.2051, calc. for $C_{30}H_{27}N_3O_3$ 477.2052. IR (nujol). 1740 (s), 1665 (s) cm^{-1}.

2k, m.p. 155 °C; solidified; 263–265 °C dec. MS [*m/e* (% rel. int.)]: 339 (7.2, M–HCl). Mol. wt., obs. 339.1583, calc. for $C_{19}H_{21}N_3O_3$ 339.1582. IR (nujol): 1730 (s), 1660 (s) cm^{-1}. ^1H NMR ($CDCl_3/CD_3OD$): δ 1.9 (3H, s), 2.2 (4H, s), 3.66 (4H, s), 3.83 (3H, s), 7–7.5 (aromatic H), 8.57 (1H, d, *J* 8.5 Hz).

2l, m.p. 165–167 °C dec. MS [*m/e* (% rel. int.)]: 481 (3.6, M–HI). Mol. wt., obs. 481.1557 calc. for $C_{29}H_{24}ClN_3O_2$ 481.1558. IR (nujol): 1740 (s), 1665 (s) cm^{-1}.

2m, m.p. 149 °C; solidified; 220–225 °C dec. MS [*m/e* (% rel. int.)]: 343 (8.9, M–HCl). Mol. wt., obs. 343.1089, calc. for $C_{18}H_{18}ClN_3O_2$ 343.1088. IR (nujol): 1730 (s), 1665 (s) cm^{-1}. ^1H NMR ($CDCl_3/CD_3CN$): δ 1.91 (3H, s), 2.23 (4H, s), 3.71 (4H, s), 7.11 (1H, dd, *J* 2.86 Hz), 7.34 (1H, d, *J* 2.86 Hz), 7.57 (4H, s), 8.6 (1H, d, *J* 7.14 Hz).

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