

# Studies of *N*-Acyl-2-pyridinecarboxanilides. Preparation by Various Reaction Sequences and Reaction with Hydrogen Chloride to give Acyl Imidate Hydrochlorides through an Intramolecular *N*→*O* Acyl Migration

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The preparation of *N*-acyl-2-pyridinecarboxanilides from imidoyl chlorides and salts of carboxylic acids is reported. Only small amounts of the same *N*-acylamides are obtained from acylations of 2-pyridinecarboxanilides with acyl chlorides and a base. Treatment of the *N*-acyl-2-pyridinecarboxanilides with hydrogen chloride induces an intramolecular *N*→*O* acyl migration and the corresponding acyl imidate hydrochlorides are obtained.

In order to improve our understanding of various intramolecular acyl-transfer reactions of *N*-acyl-4-dialkylamino-2-pyridinecarboxanilides the *N*-acylamides **3** have been chosen as reference compounds. These *N*-acylamides are easily prepared by reactions of imidoyl chlorides with carboxylate ions, *i.e.* by methods (A) and (B), in Scheme 1. Attempts to prepare **3** by direct acylation of amides either result in low yields of **3** or fail completely.

An interesting intramolecular *N*→*O* acyl migration is observed upon treating **3** with hydrogen chloride, the products being the acyl imidate hydrochlorides **4**; *cf.* Scheme 1.

Reactions of the 2-pyridinecarboxanilides **1** with acyl chlorides in the absence of an external base were expected<sup>1</sup> to yield **4** but only the hydrochlorides of **1** are obtained from such reactions.

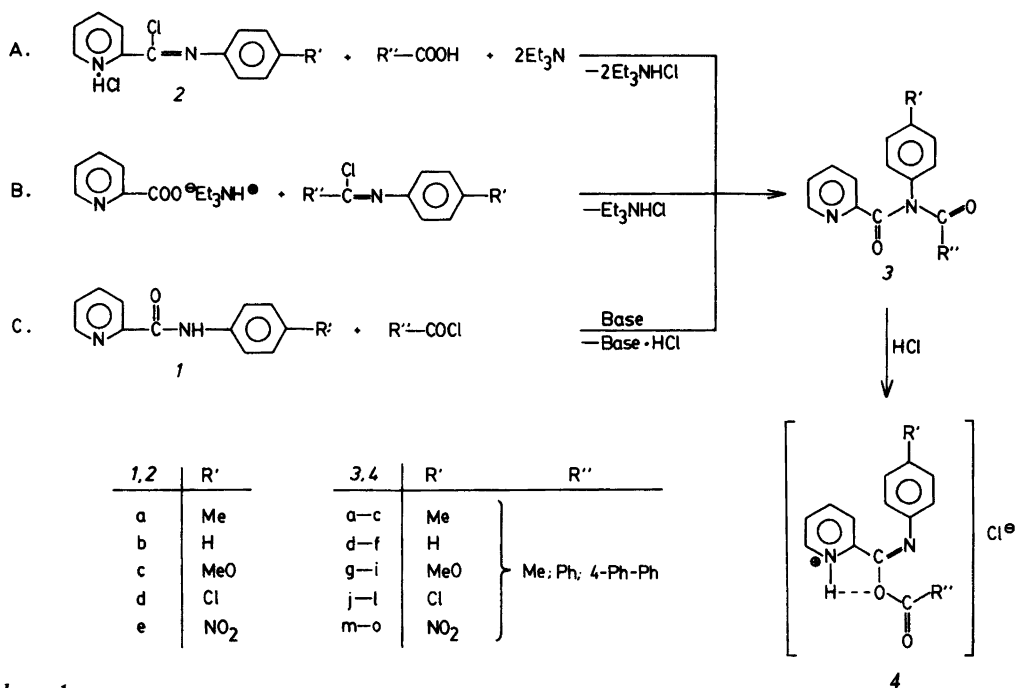
## RESULTS

The *N*-acyl-2-pyridinecarboxanilides **3a–o** are prepared either by reactions of carboxylate ions

with the 2-pyridinecarboximidoyl chloride hydrochlorides **2** and triethylamine, method (A), or by reactions of triethylammonium 2-pyridinecarboxylate with imidoyl chlorides, method (B), in Scheme 1 and Table 1. Several of the *N*-acylamides **3** were prepared by both methods thus confirming the structure of these compounds; for each set of R' and R'' substituents two different acyl imidates would initially be formed, one by method (A) and another by (B). These compounds subsequently rearrange through the expected<sup>2</sup> *O*→*N* acyl migrations to give the same *N*-acylamide **3**.

Reactions of the 2-pyridinecarboxanilides **1** with acyl chlorides and an external base, method (C), were expected to yield **3**, particularly since the somewhat related isoquinoline-1-carboxanilide easily was benzoylated in a pyridine solution.<sup>3</sup> However, various attempts to acylate **1** were generally unsuccessful; for instance, low yields of **3b** were obtained from reactions of **1a** with benzoyl chloride in the presence of either triethylamine or sodium hydride. Extensive decomposition of the pyridine ring was apparent<sup>4</sup> during reactions in polar solvents of **1d** with acyl chlorides and various bases, or of 2-pyridinecarbonyl chloride with acetanilide and triethylamine.

Reactions of **1b** with one molar equivalent of sodium hydride in tetrahydrofuran and with a molar excess of either acetyl chloride or benzoyl chloride gave low yields of two products which showed the presence of halide. These compounds had IR spectra similar to those of the acyl imidate



Scheme 1.

Table 1. *N*-Acyl-2-pyridinecarboxanilides.

Compound	Yield/% Method		M.p./°C	Mol.wt.		IR/cm <sup>-1</sup> <sup>a</sup> HCB <sup>b</sup>	<sup>1</sup> H NMR/ $\delta$ CDCl <sub>3</sub>
	A	B		Obs.	Calc.		
3a	67		97–98	254.1057	254.1055	1370 (s)	2.26
3b	70		122–123	316.1213	316.1212		
3c	68		129–131	392.1521	392.1525		
3d	66		75–77	240.0899	240.0899	1370 (s)	2.26
3e <sup>c</sup>	83	97	125–126	302.1053	302.1055		
3f	54	45	123–125	378.1366	378.1368		
3g	67		84–86	270.1000	270.1004	1370 (s)	2.24
3h	80		145–146	332.1161	332.1161		
3i	64		132–134	408.1474	408.1474		
3j	36	29	89–91	274.0511	274.0509	1372 (s)	2.31
3k	66	89	125–126	336.0663	336.0665		
3l	48		110–112	412.0983	412.0979		
3m	45		137–139	285.0752	285.0750	<sup>d</sup>	2.46
3n	61	85	160–161	347.0901	347.0906		
3o		76	150–151	423.1222	423.1219		

<sup>a</sup>IR (nujol): Compounds 3 show two carbonyl absorptions in the region 1710–1660 cm<sup>-1</sup>. <sup>b</sup>Hexachlorobutadiene. <sup>c</sup>Previously reported, cf. Ref. 3. <sup>d</sup>Nitro groups absorb in this region.

Table 2. Acyl imidate hydrochlorides.

Compound	M.p./°C	IR/cm <sup>-1</sup>		<sup>1</sup> H NMR/δ <sup>b</sup>
		Nujol	HCB <sup>a</sup>	
4a	165–167 dec.	1730(s), 1635(m)	1395(s)	2.13
4b	170–172 dec.	1740(s), 1630(s)		
4d	162–163 dec.	1740(s), 1640(m)	1390(s)	2.11
4e	155–157 dec.	1745(s), 1630(m)		
4g	164–165 dec.	1735(sh), 1725(s), 1635(w)	1390(s)	2.12
4j	152–154 dec.	1745(s), 1640(m)	1390(s)	2.10
4m	229–232 dec.	1750(s), 1640(w)	<sup>c</sup>	2.20

<sup>a</sup> Hexachlorobutadiene. <sup>b</sup> In a mixture of deuteriochloroform and methanol-*d*<sub>4</sub> except 4j which was dissolved in deuteriochloroform and acetonitrile-*d*<sub>3</sub>. <sup>c</sup> Nitro groups absorb in this region.

hydrochlorides which previously had been obtained<sup>1</sup> from 4-(1-pyrrolidinyl)-2-pyridinecarboxanilides and acyl chlorides. The structures 4d and 4e were tentatively assigned to these compounds in agreement with the observed molecular weights. Attempts to acylate the amides 1 with either benzoyl chloride or acetyl chloride only yielded the hydrochlorides of 1. However, when the *N*-acylamides 3d and 3e were treated with hydrogen chloride the products which were obtained were identical to 4d and 4e, respectively. The implication of these results is that upon treatment of 3 with hydrogen chloride, an intramolecular *N*→*O* acyl migration occurs. Even if *N,N*-diacylamines usually are more stable than acyl imidates, *i.e.* *N*-acyl groups are more stable than *O*-acyl groups, examples are known to the contrary. For instance, 2-acetoxypyridine is found to be far more stable than *N*-acetyl-2(1*H*)-pyridone.<sup>5</sup> The possibility of a conversion of *N*-acylamides to acyl imidates also has been considered for *N*-formylamides.<sup>6</sup>

The *N*-acylamides 3a, 3d, 3g, 3j and 3m which have an *N*-acetyl group were treated with hydrogen chloride and <sup>1</sup>H NMR and IR absorptions of the products are shown in Table 2. A comparison of the IR absorptions of 3, Table 1, with those of the above products shows a marked shift of the double carbonyl absorption at 1710–1660 cm<sup>-1</sup> for 3 to one strong absorption at 1750–1730 cm<sup>-1</sup> for the hydrogen chloride treated *N*-acylamides. This shift towards higher frequencies in addition to the appearance of a new absorption at 1640–1635 cm<sup>-1</sup>, the latter being interpreted as a C=N absorption, is in accord with an acyl imidate structure.<sup>5a,7</sup> It may be noted that a similar change in the carbonyl absorption is not observed upon treating

the 2-pyridinecarboxanilides 1 with hydrogen chloride. IR spectra of 3 and the hydrogen chloride treated *N*-acylamides also were recorded using the mulling agent hexachlorobutadiene which is transparent in the 1400–1300 cm<sup>-1</sup> region. The absorption of 3 at 1370 cm<sup>-1</sup> is shifted to 1390 cm<sup>-1</sup> after treatment with hydrogen chloride and this shift is interpreted as a change from an acetyl group to an acetoxy group.<sup>8</sup>

The <sup>1</sup>H NMR signals of the acetyl protons of these *N*-acylamides are shifted towards lower δ-values upon treatment with hydrogen chloride and this increase in shielding of the methyl protons is in the right direction for a change from the acetyl group of 3 to the acetoxy group of 4. The changes in δ-values are small, Δδ 0.12–0.26, and it might be argued that these changes are insignificant. However, these observations are in good agreement with Δδ 0.28 which was found<sup>9</sup> for some pyrrole derivatives; the methyl protons of an *N*-acetyl group were recorded at δ 2.40 and those of a corresponding acetoxy group at δ 2.12. Also, it may be argued that the hydrochlorides of 3 are expected to show methyl absorptions at higher δ than the *N*-acetyl amides. Thus, the conformation of 3 which is shown in Scheme 1 apparently is the preferred one<sup>6</sup> and a protonation of the pyridine-nitrogen would have a deshielding effect on the methyl protons of the acetyl group of 3.

In addition to the *N*-acylamides 3 with R'' = Me, 3b with R'' = Ph was treated with hydrogen chloride. This product also shows an IR carbonyl absorption at a higher frequency than the *N*-acylamide 3b, see Tables 1 and 2.

In conclusion, the various data presented above point in the same direction and are interpreted as

convincing evidence for an intramolecular  $N \rightarrow O$  acyl migration, *i.e.* the acyl imidates **4** are formed upon treatment of **3** with hydrogen chloride. Further analyses of these and related compounds by  $^{13}\text{C}$  NMR have been initiated.\*

## EXPERIMENTAL

**General.** The instrumentation, the solvents and reagents have been described.<sup>1,3,10</sup> Sodium hydride 55–60% in oil, practical grade, *N*-(4-chlorophenyl)-acetamide, reagent grade, and Florisil, 60–100 mesh, were obtained from Fluka.

**2-Pyridinecarboxanilides, 1.** These are known compounds and the preparation of **1a**, **1b** and **1e** has been described.<sup>10</sup> The same method was used to prepare **1c**, m.p. 92–94 °C, IR (nujol): 3360 (m), 1685 (s)  $\text{cm}^{-1}$ , lit.<sup>11</sup> m.p. 93–94 °C and **1d**, m.p. 135–137 °C, IR (nujol): 3330 (m), 1685 (s)  $\text{cm}^{-1}$ , lit.<sup>11</sup> m.p. 138–139 °C.

**2-Pyridinecarboxanilide hydrochlorides, 1·HCl.** Dry hydrogen chloride gas was led into a benzene solution of the 2-pyridinecarboxanilide. The precipitate was filtered off, washed with benzene and dried over phosphorus(V) oxide. **1a·HCl**, m.p. 195–196 °C, IR (nujol): 1685 (s)  $\text{cm}^{-1}$ . **1b·HCl**, m.p. 178–180 °C, IR (nujol): 1680 (s)  $\text{cm}^{-1}$ . **1c·HCl**, m.p. 190–193 °C dec. IR (nujol): 1670 (s)  $\text{cm}^{-1}$ . **1d·HCl**, m.p. 205–208 °C dec. IR (nujol): 1675 (s)  $\text{cm}^{-1}$ . **1e·HCl**, m.p. 234–236 °C; this compound reverts to **1e** upon melting and also upon attempted recrystallization from nitromethane. IR (nujol): 1680 (s)  $\text{cm}^{-1}$ .

**2-Pyridinecarboximidoyl chloride hydrochlorides, 2.** The preparation of **2a**, **2b** and **2e** has been described.<sup>10</sup> Compound **2c** was obtained in 74% yield from **1c** and phosphorus(V) chloride in thionyl chloride, m.p. 133–135 °C dec. IR (nujol): 1650 (m)  $\text{cm}^{-1}$ . MS [ $m/e$  (% rel.int.)]: 246 (0.4, M–HCl). Mol.wt., 246.0562, calc. for  $\text{C}_{13}\text{H}_{11}\text{ClN}_2\text{O}$ : 246.0559. Compound **2d** was obtained in 93% yield by the same method, m.p. 167–170 °C dec. IR (nujol): 1660 (s)  $\text{cm}^{-1}$ . MS [ $m/e$  (% rel.int.)]: 250 (9.9, M–HCl). Mol.wt. 250.0069, calc. for  $\text{C}_{12}\text{H}_8\text{Cl}_2\text{N}_2$ : 250.0064.

**Diarylamides.** 4-Phenylbenzanilide was prepared from 4-biphenylcarbonyl chloride and aniline, m.p. 228–231 °C. IR (nujol): 3330 (m), 1650 (s)  $\text{cm}^{-1}$ . 4'-Nitro-4-phenylbenzanilide was prepared from 4-biphenylcarbonyl chloride and 4-nitroaniline, m.p. 263–265 °C dec. IR (nujol): 3370 (m), 1665 (s)  $\text{cm}^{-1}$ .

\* An alternative conformation of **4** with a hydrogen bond between the pyridine  $N-H$  and the imidate  $N$  has been considered and cannot be ruled out presently. Work in progress is expected to resolve this problem.

**Diarylimidoyl chlorides.** These compounds were prepared from benzene solutions of the corresponding amides and phosphorus(V) chloride. *N*-(4-Chlorophenyl)benzimidoyl chloride m.p. 61–63 °C, lit.<sup>12</sup> m.p. 62 °C. *N*-(4-Nitrophenyl)benzimidoyl chloride, m.p. 116–118 °C, lit.<sup>13</sup> m.p. 114–116 °C. *N*-Phenyl-4-phenylbenzimidoyl chloride, m.p. 117–118 °C. IR (nujol): 1650 (s)  $\text{cm}^{-1}$ . MS [ $m/e$  (% rel.int.)]: 291 (14.2, M), 256 (100, M–Cl). Mol.wt., obs. 291.0809, calc. for  $\text{C}_{19}\text{H}_{14}\text{ClN}$ : 291.0814. *N*-(4-Nitrophenyl)-4-phenylbenzimidoyl chloride, m.p. 190–191 °C, IR (nujol): 1660 (s)  $\text{cm}^{-1}$ . MS [ $m/e$  (% rel.int.)]: 336 (11.6, M), 301 (100, M–Cl). Mol.wt., obs. 336.0667, calc. for  $\text{C}_{19}\text{H}_{13}\text{ClN}_2\text{O}_2$ : 336.0665.

*N*-(4-Chlorophenyl)acetimidoyl chloride was prepared from the corresponding amide and phosphorus(V) chloride and was obtained as a yellow oil which was used immediately. IR (film): 1700 (s)  $\text{cm}^{-1}$ .

***N*-Acyl-2-pyridinecarboxanilides, 3. Method A.** To a suspension of **2** in acetonitrile was added either sodium acetate (1 mol eq.) and triethylamine (1 mol eq.), or benzoic acid (1 mol eq.) and triethylamine (2 mol eq.), or 4-biphenylcarboxylic acid (1 mol eq.) and triethylamine (2 mol eq.). The reaction mixture was stirred at ambient temperature for 20–30 h. The solvent was removed under reduced pressure and the solid residue was extracted with benzene. The benzene extract was chromatographed on silica gel with chloroform as eluent.

**Method B.** To an acetonitrile solution of equimolar amounts of picolinic acid and triethylamine was added the diaryl- or alkyl-arylimidoyl chloride (1 mol eq.). The reaction mixture was treated as described for method A.

**Acyl imidate hydrochlorides, 4.** The imide **3** was dissolved in benzene and dry hydrogen chloride gas was led through the solution. The yellow, oily precipitate which formed, crystallized upon addition of a small amount of acetone. Compound **4** was filtered and washed with diethyl ether.

**Reaction of 1a with acylating agents and a base.** A benzene solution of **1a** (212 mg, 1 mmol), triethylamine (110 mg, 1.1 mmol) and benzoyl chloride (140 mg, 1 mmol) was heated at 80 °C for 144 h. The reaction mixture was filtered and chromatography on silica gel of the filtrate yielded 90 mg (42%) of **1a**, m.p. 100–102 °C and 55 mg (17%) of **3b**, m.p. 122–123 °C.

To a solution of **1a** (212 mg, 1 mmol) in acetonitrile was added sodium hydride (70 mg, 1.5 mmol). The suspension was stirred at ambient temperature for 5 min, benzoyl chloride (155 mg, 1.1 mmol) was added and stirring was continued for 1 h. Chromatography on silica gel of the benzene soluble part of the reaction products yielded 75 mg (36%) of **1a**, m.p. 101–103 °C and 60 mg (20%) of **3b**, m.p.

120–123 °C.

To a solution of *1a* (212 mg, 1 mmol) in 4 ml of pyridine was added acetic anhydride (150 mg, 1.5 mmol) and the solution was heated at 100–110 °C for 39 h. Benzene was added and the solvents were removed under reduced pressure. The residue was chromatographed on Florisil with chloroform as eluent and yielded 210 mg (95 %) of *1a*, m.p. 97–99 °C.

*Reactions of 1b with sodium hydride and acyl chlorides.* A solution of *1b* (200 mg, 1 mmol) in 25 ml of tetrahydrofuran was treated with sodium hydride (45 mg, 1.1 mmol) for 40 min at 20 °C. Acetyl chloride (160 mg, 2 mmol) was added and the reaction mixture was stirred for 2 h. Insoluble material was removed by filtration and the filtrate gave upon concentration and addition of diethyl ether 30 mg (11 %) of *4d*, m.p. 162–163 °C dec. MS [*m/e* (% rel. int.)]: 240 (1.2, M–HCl). Mol. wt., obs. 240.0897, calc. for C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> 240.0899. This product gave a positive Beilstein test for halogen. IR (nujol): 1740 (s), 1640 (m) cm<sup>-1</sup>.

A solution of *1b* (200 mg, 1 mmol) in 15 ml of tetrahydrofuran was treated with sodium hydride (45 mg, 1.1 mmol) for 5 min at 20 °C. Benzoyl chloride (140 mg, 1 mmol) was added and the reaction mixture was stirred at 20 °C for 40 min. The solvent was removed under reduced pressure and the residue was extracted with chloroform and water. The dried chloroform extract yielded 35 mg (10 %) of *4e*, 155–157 °C des. MS [*m/e* (% rel. int.)]: 302 (20.6, M–HCl). Mol. wt., obs. 302.1059, calc. for C<sub>19</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> 302.1055. This product gave a positive test for halogen. IR (nujol): 1745 (s), 1630 (m) cm<sup>-1</sup>.

*Reaction of 1c with acetyl chloride.* To a solution of *1c* (230 mg, 1 mmol) in 10 ml of acetonitrile was added acetyl chloride (160 mg, 2 mmol). The reaction mixture was heated at 70 °C for 0.5 h. The precipitate was filtered, washed with acetonitrile and yielded 230 mg (87 %) of *1c*·HCl, m.p. 190–193 °C dec. IR (nujol): 1670 (s) cm<sup>-1</sup>.

Similar reactions of *1a–1e* with acetyl chloride or benzoyl chloride yielded the hydrochlorides of the 2-pyridinecarboxanilides in 90–95 % yields.

*Reactions of 1d with base and acyl chlorides.* To a solution of *1d* (350 mg, 1.5 mmol) in 4 ml of pyridine was added benzoyl chloride (210 mg, 1.5 mmol) and the solution which turned purple was stirred at 20 °C for 3.5 h. Benzene was added and the solvents were removed under reduced pressure. The residue yielded 400 mg of hygroscopic crystals upon addition of diethyl ether. This product was not further identified.

To a solution of *1d* (280 mg, 1.2 mmol) in 10 ml of benzene was added 2,4,6-trimethylpyridine (240 mg, 2 mmol) and benzoyl chloride (170 mg, 1.2 mmol). The reaction mixture was stirred at ambient tem-

perature for 90 h and the benzene-soluble part of the reaction mixture gave 200 mg (71 %) of *1d*, m.p. 131–135 °C and 140 mg, m.p. 190–250 °C subl. which was not further identified.

A benzene solution of *1d* (150 mg, 0.7 mmol), 2,4,6-trimethylpyridine (85 mg, 0.7 mmol) and 4-biphenylcarbonyl chloride (150 mg, 0.7 mmol) was heated at 60 °C for 4 h. The solid residue after removal of the benzene yielded 140 mg (93 %) of *1d*, m.p. 135–137 °C upon addition of acetonitrile.

A solution of *1d* (230 mg, 1 mmol), 2,4,6-trimethylpyridine (120 mg, 1 mmol) and benzoyl chloride (140 mg, 1 mmol) in 5 ml of nitromethane was heated at 80 °C for 2 h. The benzene soluble part of the reaction mixture yielded 190 mg (82 %) of *1d*, m.p. 130–135 °C.

A solution of equimolar amounts of *1d*, *N,N*-dimethylaniline and benzoyl chloride in acetonitrile became dark blue after heating for 5 min at 80 °C. The reaction products were not isolated.

*Reactions of 2-pyridinecarbonyl chloride hydrochloride with triethylamine and acetanilide.* To a suspension of 2-pyridinecarbonyl chloride hydrochloride (356 mg, 2 mmol) in 10 ml of nitromethane was added triethylamine (400 mg, 4 mmol) and acetanilide (270 mg, 2 mmol). The black reaction mixture was stirred at 20 °C for 100 h. Chromatography on silica gel of the benzene soluble material yielded 100 mg (37 %) of acetanilide, m.p. 107–111 °C which was eluted with chloroform. No additional material was eluted with acetone from the column.

To a solution of acetanilide (270 mg, 2 mmol) in 10 ml of benzene was added triethylamine (400 mg, 4 mmol) and 2-pyridinecarbonyl chloride hydrochloride (356 mg, 2 mmol). The black solution was stirred for 21 h at 20 °C. The benzene soluble material yielded upon addition of diethyl ether 90 mg (33 %) of acetanilide, m.p. 90–100 °C which also was identified by TLC.

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