Acta Chemica Scandinavica B 36 (1982) 381 – 388

Potential Acyl-transfer Agents. Reactions of *N*-Acyl-2-pyridinecarboxamides with Nucleophiles

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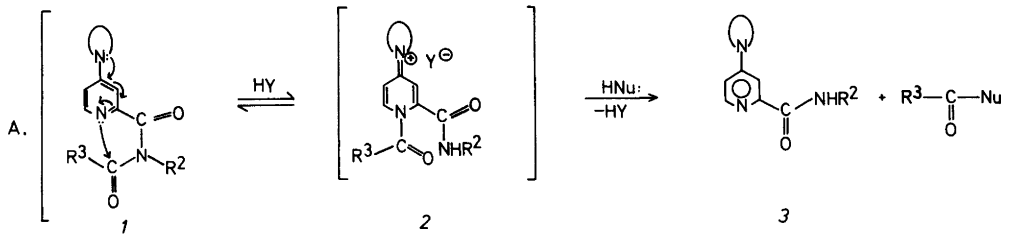
A fast reaction is observed between a series of *N*-acyl-2-pyridinecarboxamides and cyclopentylamine or pyrrolidine. Most of the acylamides react exclusively at the pyridine-2-carbonyl group. The selectivity of these reactions is explained by the reaction of the pyridine – nitrogen as a base towards the external nucleophile in a five-ring transition state. The acylamides undergo slow reactions with 4-methylaniline, methanol or water. Several reaction paths are observed with these less reactive nucleophiles. An intramolecular acyl group transfer prior to the reaction with an external nucleophile is indicated for three of the *N*-acylamides which have an *N*,*N*-dialkylamino substituent in the pyridine-4 position. Nucleophilic attack occurs predominantly at the *N*-acyl group of these three compounds which are moderately active acyl-transfer agents.

Several years ago imidazole was shown to enhance the solvolysis of esters and amides through an intramolecular nucleophilic reaction.[1] The present studies are based on those observations and the *N*-acyl-2-pyridinecarboxamides *1* with an *N*,*N*-dialkylamino group as R^1, see Schemes 1 and 2, were visualized as potential acyl-transfer agents. Thus, in protic, weakly basic solutions a resonance stabilized *N*-acylpyridinium salt *2* might be formed by an intramolecular nucleophilic attack on the acyl group $R^3C(O)$ by the pyridine nitrogen of *1*. The intermediate *2* would be an active acyl-transfer agent in the presence of an appropriate nucleophile. The expected transformations are shown as reactions (A) in Scheme 1. The related compounds 4-(*N*,*N*-dialkylamino)pyridines are presently subject to much interest as catalysts in acyl-transfer reactions[2] and the reactive intermediates in these reactions certainly are *N*-acylpyridinium salts.[3] Recent studies of compounds *1* also have shown[4] that *1* with an *N*,*N*-dialkylamino substituent in the 4-position of the pyridine ring react as nucleophiles towards acyl chlorides. Therefore, the nucleophilicity of the pyridine nitrogen of *1* would suffice for an intramolecular acyl-transfer as shown in (A), Scheme 1. Presently reactions of *1* with nucleophiles are reported.

RESULTS

The potential acyl-transfer agents *1* can be prepared by reactions of 2-pyridinecarboximidoyl



Scheme 1.

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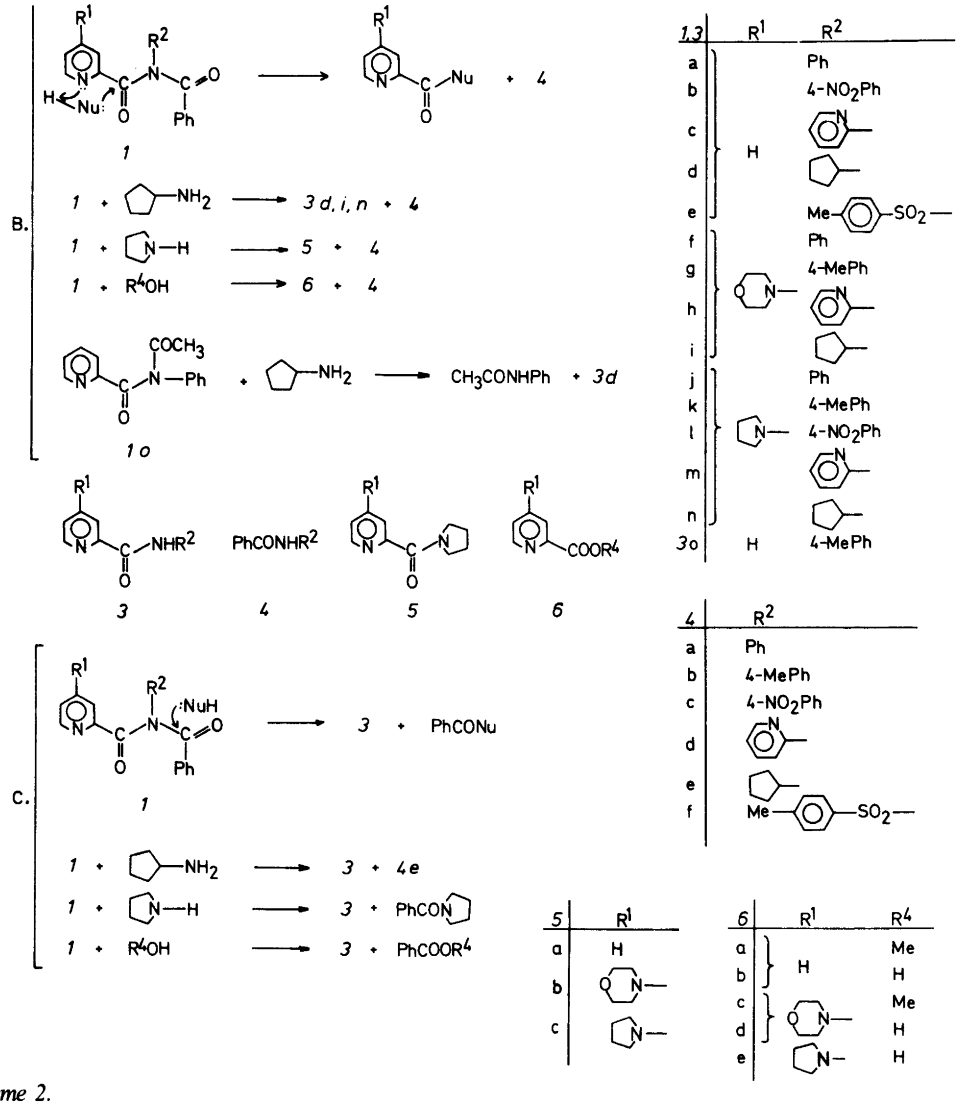
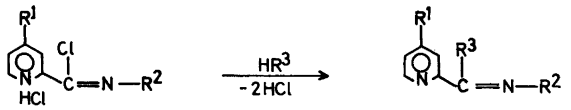
chlorides with salts of carboxylic acids.[5,6] This reaction sequence must be used if the objective is activation and subsequent transfer of the acyl group $R^3C(O)$ which presently is either PhC(O) or MeC(O), see Scheme 2. However, *1* also have been obtained by alternative reaction sequences.[6,7]

The imidoyl chloride hydrochlorides 7 are rather slow reacting towards carboxylate ions.[6] Presently *7a* was reacted with sodium benzoate for 18 h at ambient temperature; cyclopentylamine then was added to the reaction mixture which after another 30 min yielded *1b* (20%), *3b* (16%) and *8a* (58%). Thus, after 18 h about equal amounts of *7a* had reacted with benzoate ions to give *1b* or had hydrolyzed to *3b*. Unreacted *7a* then underwent a rapid reaction with cyclopentylamine to yield *8a*.

Attempts were made to enhance the reactivity of 7 by reacting these compounds with silver tosylate. The intermediate tosyl imidates thus formed are expected to be more reactive than 7 towards carboxylate ions due to the tosylate ion as a leaving group. However, whereas a reaction of *7a* with silver tosylate and cyclopentylamine yields the expected amidine *8a* as the major product, a similar reaction



Scheme 2.



7 8

7	R^1	R^2
a	H	4-NO_2Ph
b	2-pyridyl	4-MePh
c	2-pyridyl	4-NO_2Ph
d	2-pyridyl	Ph
e	3-pyridyl	4-MePh
f	3-pyridyl	4-NO_2Ph

8	R^1	R^2	R^3
a	H	4-NO_2Ph	2-imidazolyl
b	H	4-NO_2Ph	4-morpholinyl
c	2-pyridyl	4-MePh	PhNH
d	2-pyridyl	4-NO_2Ph	PhNH
e	2-pyridyl	Ph	PhNH
f	3-pyridyl	4-MePh	PhNH
g	3-pyridyl	4-NO_2Ph	PhNH

Scheme 3.

of *7f* yields 4-nitroaniline and *N*-cyclopentyl-*p*-toluenesulfonamide instead of the expected product *8g*. Silver tosylate obviously is involved in the formation of 4-nitroaniline from *7f* since a mixture of *7f* and a fourfold molar excess of triethylamine in acetonitrile only produces small amounts of 4-nitroaniline. However, addition of silver tosylate to this reaction mixture produces substantial amounts of 4-nitroaniline and several unidentified compounds.

It will be noted that silver tosylate does not cleave the imidoyl chloride as was observed for *7f* if other reaction conditions are used. The formation of an *N*-acylamide derived from *3l* apparently is enhanced by silver tosylate. Thus, the products isolated from a reaction of *7f-HCl* with triethylammonium acetate, silver tosylate and aniline were *3l* (87%) and acetanilide (56%). These products indicate both the formation of at least 56% of the *N*-acetyl derivative of *3l* and that aniline preferentially reacts at the acetyl – carbonyl of the *N*-acetylamide.

Compounds *7* react with carboxylate ions or aniline at comparable rates; the latter reactions yield amidines *8*. Morpholine and cyclopentylamine, however, undergo rapid reactions with *7* to give *8*. The formation of *8* is shown in Scheme 3.

Reactions of the *N*-acyl-2-pyridinecarboxamides *1* with nucleophiles are summarized in Table 1. The striking feature of these reactions is the predominant attack by the strong nucleophiles cyclopentylamine or pyrrolidine on the pyridine-2-carbonyl group of *1*. Therefore, instead of reaction path (A), Scheme 1, these reactions are best explained by path (B), Scheme 2. The reactions will have a five-ring T.S. where the pyridine – nitrogen reacts as a base by removing a proton from the attacking nucleophile. A similar behavior has been observed[8] for the pyridine – nitrogen of *N*-(2-pyridyl)benzamides; an enhancement of the rate of basic methanolysis was explained by the reaction of the pyridine – nitrogen as an intramolecular base in a six-ring T.S.

The third mode of reaction which has been considered for compounds *1* is shown as path (C) in Scheme 2. *N*-Acylamides are generally not very effective acylating agents,[9] and, therefore, these reactions are expected to proceed at a slow rate. A product analysis will not distinguish between reaction paths (A) and (C). Reactions of *1* with 4-methylaniline, methanol or water are quite slow. For instance, the reaction of *1c* with 4-methylaniline was not yet completed after 72 h. Also, during the long reaction periods of about 200 h compounds *1* might both hydrolyze and react with the added nucleophile as was observed for the reaction of *1i* with 4-methylaniline. However, a change from aprotic to protic solvents has no effect on the product composition from the fast reactions of *1c* or *1g* with cyclopentylamine. A comparison of the reactions of *1a* and *1o* with cyclopentylamine also shows that a change of the *N*-acyl group from benzoyl in *1a* to acetyl in *1o* has no influence on the

Table 1. Reactions of *N*-acyl-2-pyridinecarboxamides *1* with nucleophiles.

Compound	Nucleophile[a]	Solvent	Reaction time, h[b]	Expected products Path (B)	Path (A) or (C)	Observed[c] % Reaction by path (B)
1a	CPA	Benzene[d]	1	*3d*, *4a*	*3a*, *4e*	97
1a	P	EtOH	1	*5a*, *4a*	*3a*, $PhCON(CH_2)_4$	93[e,f]
1b	CPA	Benzene	1	*3d*, *4c*	*3b*, *4e*	99
1c	CPA	MeCN[d]	1	*3d*, *4d*	*3c*, *4e*	95
1c	M	MeCN	72	*3o*, *4d*	*3c*, *4b*	74[g]
1d	P	EtOH	10	*5a*, *4e*	*3d*, $PhCON(CH_2)_4$	65[e,h]
1d	P	MeCN	10	*5a*, *4e*	*3d*, $PhCON(CH_2)_4$	58[e,h]
1d	M	MeCN	200	*3o*, *4e*	*3d*, *4b*	88
1d	MeOH	MeOH	200	*6a*, *4e*	*3d*, PhCOOMe	80
1d	H_2O	Acetone	200	*6b*, *4e*	*3d*, PhCOOH	99
1e	M	MeCN	3	*3o*, *4f*	*3e*, *4b*	42
1f	CPA	MeCN	1	*3i*, *4a*	*3f*, *4e*	95
1f	MeOH	Benzene	240	*6c*, *4a*	*3f*, PhCOOMe	45
1g	CPA	$MeCN/CH_2Cl_2$[i]	1	*3i*, *4b*	*3g*, *4e*	99
1g	P	$MeOH/CH_2Cl_2$	1	*5b*, *4b*	*3g*, $PhCON(CH_2)_4$	86
1g	MeOH	CH_2Cl_2	240	*6c*, *4b*	*3g*, PhCOOMe	60
1h	CPA	MeCN	1	*3i*, *4d*	*3h*, *4e*	97
1i	P	EtOH	10	*5b*, *4e*	*3i*, $PhCON(CH_2)_4$	46[j,k]
1i	P	MeCN	10	*5b*, *4e*	*3i*, $PhCON(CH_2)_4$	47[j,k]
1i	MeOH	MeOH	240	*6c*, *4e*	*3i*, PhCOOMe	30
1i	M	MeCN	240	*3g*, *4e*	*3i*, *4b*	50[l]
1i	H_2O	Acetone	200	*6d*, *4e*	*3i*, PhCOOH	50
1j	CPA	MeOH	1	*3n*, *4a*	*3j*, *4e*	95
1k	CPA	EtOH	1	*3n*, *4b*	*3k*, *4e*	92
1l[m]	CPA	MeCN	1	*3n*, *4c*	*3l*, *4e*	40
1m	CPA	MeCN	1	*3n*, *4d*	*3m*, *4e*	96
1m	M	MeCN	48	*3k*, *4d*	*3m*, *4b*	89[g]
1n	P	EtOH	10	*5c*, *4e*	*3n*, $PhCON(CH_2)_4$	36[j,n]
1n	P	MeCN	10	*5c*, *4e*	*3n*, $PhCON(CH_2)_4$	46[j,n]
1o	CPA	Benzene	1	*3d*, MeCONHPh	*3a*, $MeCONHC_5H_9$	99

[a] Abbreviations used: CPA = cyclopentylamine; P = pyrrolidine and M = 4-methylaniline. [b] All reactions at ambient temperature. [c] Product analysis by GLC at 140 – 300 °C, instrumentation, see Ref. 4. % Reaction by path (B) is calculated from the observed product mixture. Mixed reaction paths, (B) and (A) or (C) give the four products of columns 5 and 6 whereas reactions by path (B) give equimolar amounts of the two products of column 5. % Reactions by paths (A) or (C) are found as the difference between 100 and the number of column 7. [d] Or in methanol and acetone. [e] Glass column for GLC: 3% OV – 225 (213 cm, 2.2 mm i.d.) on Chromosorb W/AW – DMCS 80 – 100 mesh. *5a* and $PhCON(CH_2)_4$ could not be separated. [f] % Reaction by path (B) calculated from the ratio between *4a* and *4a* + *3a*. [g] Incomplete reaction. [h] % Reaction by path (B) calculated from the ratio between *4e* and *4e* + *3d*. [i] Or in methanol and dichloromethane. [j] % Reaction by path (B) calculated from the ratio between *4e* and *4e* + $PhCON(CH_2)_4$. [k] *5b* and *3i* could not be separated even on an SE-30 (35 m, 0.5 mm i.d.) SCOT column. [l] Some *6d* and several unidentified products also present in the reaction mixture. [m] *1l* decomposed on attempted purification; crude *1l* was used. [n] *5c* and *3n* could not be separated.

amount of nucleophilic attack at the pyridine-2-carbonyl group of *1*. Compound *1e* undergoes a fast reaction with 4-methylaniline whereas the other *N*-acylamides give slow reactions with this amine. Nearly 60% of the nucleophilic attack on *1e* occurs at the benzoyl carbonyl group. These observations indicate comparable reaction rates for *1e* by paths (B) and (C). The electron withdrawing arylsulfonyl group probably enhances the reaction by path (C).

The products from the reaction of *1l* with cyclopentylamine also show that 60% of the nucleophilic attack occurs at the benzoyl group. It is

interesting to compare this reaction with that of *1b* with the same nucleophile where no attack at the benzoyl group is observed. Therefore, since the 4-nitrophenyl group of *1b* does not enhance path (C) for the reaction of that compound, path (C) also must be excluded for the reaction of *1l*. Consequently, these results indicate that *1l* reacts with cyclopentylamine by both paths (A) and (B). This also is in accord with the mentioned reactions of *7f-HCl* with nucleophiles where a predominant attack on the acetyl group is observed.

Reactions of *1d*, *1i* and *1n* with cyclopentylamine would give the same reaction products from either path (A), (B) or (C) due to the *N*-cyclopentyl substituent of these compounds. However, since quite similar reaction patterns have been established for *1a* and *1g* with both cyclopentylamine and pyrrolidine, the latter base is used as a substitute for cyclopentylamine in reactions of *1d*, *1i* and *1n*. Only 36 – 65 % of the reactions of these three compounds with pyrrolidine occur by path (B). This is in contrast to the reactions of compounds *1* which have an *N*-aryl substituent. All of those compounds, except *1l*, react with a strong base only by path (B). Compounds *1i* and *1n* with enhanced pyridine-*N* nucleophilicity compared to *1d* show less reaction by path (B) than *1d*. Also, the least amount of reaction by path (B) is observed for *1n* in a protic solvent. These observations indicate that *1n* reacts with pyrrolidine in ethanol mostly by path (A) and that *1i* reacts somewhat less by path (A) under the same reaction conditions.

DISCUSSION

There are two limitations to the use of compounds *1* as acyl-transfer agents. Firstly, the reactivity of the imidoyl chloride hydrochlorides *7* towards carboxylate ions needs to be improved. Attempts to use silver tosylate for this purpose led to erratic results; a reaction of *7f-HCl* with acetate ions was enhanced by silver tosylate as shown by the products isolated after the addition of aniline to this reaction mixture. However, a reaction of *7f* with triethylamine and silver tosylate was shown by GLC to produce substantial amounts of 4-nitroaniline which had been produced through cleavage of the imide bond of *7f*.

The second limitation is the favorable competition in most instances of path (B) with the planned path (A). However, there are some exceptions to this pattern. Compound *1l* reacts predominantly by path (A), and this may be explained by both the electron-withdrawing 4-nitrophenyl group and the enhanced pyridine-*N* nucleophilicity of *1l*. Compound *1n* also reacts mostly by path (A) and *1i* reacts substantially by path (A). Compounds *1i* and *1n* have a pyridine-4 substituent which is expected to promote path (A) but the apparent effect of the cyclopentyl group of these compounds is less obvious. Thus, further studies of compounds related to *1f* – *1n* but with a variety of amide-*N* substituents are indicated.

EXPERIMENTAL

General. The instrumentation has been described.[4] Cyclopentylamine, pyrrolidine, 4-methylaniline, benzanilide and 2-pyridinecarboxylic acid, all *purum*, were obtained from Fluka. Acetanilide and *p*-toluenesulfonamide were obtained from Schuchardt, methyl benzoate from Riedel-de-Haën, hippuric acid and *p*-toluenesulfonic acid from Merck.

Silver tosylate[10] and *N*-cyclopentylacetamide, liq., lit.[11] b.p. 146 – 149 °C/22 mmHg were prepared.

2-Pyridinecarboxamides, 3a – o *and* 5a – c. Compounds *3a*, *3b*, *3o*, *3f*, *3g* and *3j* – *l* have been described,[5] *3c*[4,12] and compounds *3d*, *3h* – *i*, *3m* – *n* also have been described.[4] Compound *3e* was prepared from equimolar amounts of 2-pyridinecarbonyl chloride, *p*-toluenesulfonamide and triethylamine in tetrahydrofuran at ambient temperature. *3e* (60 %) m.p. 134 – 136 °C. IR (nujol): 3300 (s), 1710 (s) cm^{-1}. ^1H NMR (CD_3NO_2): δ 2.47 (3H, s), 7.46 – 8.71 (8H, m). MS [*m/e* (% rel. int.)]: 212 (39, M – SO_2).

Compound *5a* was prepared,[13] and *5b* was obtained from a reaction of *6d*,[5] first with thionyl chloride and thereafter with an excess of pyrrolidine in benzene. Chromatography on silica gel yielded *5b* (70 %), m.p. 84 – 85 °C. IR (nujol): 1630 (s), 1595 (s) cm^{-1}. ^1H NMR (CD_3NO_2): δ 1.90 (4H, m), 3.29 – 3.84 (12H, m), 6.80 (1H, dd, *J* 2.9 Hz), 7.05 (1H, d, *J* 2.9 Hz), 8.20 (1H, d, *J* 5.7 Hz). MS [*m/e* (% rel. int.)]: 261 (18, M). Mol. wt., obs. 261.1476, calc. for $C_{14}H_{19}N_3O_2$ 261.1477.

Compound *5c* was prepared by heating methyl 4-chloropyridine-2-carboxylate with pyrrolidine (3 mol eq.) at 90 °C for 24 h.[5] The reaction mixture was extracted with benzene. The benzene extract was washed with water, chromatographed on silica gel and *5c* was eluted with chloroform and acetone, 1:1. The liquid product was crystallized from diethyl ether and *5c* (62 %) m.p. 87 – 88 °C was obtained. IR (nujol): 1625 (s), 1600 (s) cm^{-1}. ^1H NMR (CD_3NO_2): δ 2.0 (4H, m), 3.5 (4H, m), 6.54 (1H, dd, *J* 2.9 Hz), 6.77

(1H, d, *J* 2.9 Hz), 8.14 (1H, d, *J* 5.7 Hz). MS [*m/s* (% rel. int.)]: 245 (21.7, M). Mol. wt. obs., 245.1521, calc. for $C_{14}H_{19}N_3O$ 245.1528.

Methyl 2-pyridinecarboxylates. Compound *6a* was prepared [14] and was purified by chromatography on silica gel. Compound *6c* was prepared by heating 4-(4-morpholinyl)-2-pyridinecarbonyl chloride hydrochloride with an excess of dry methanol at 60 °C for 30 min. Excess methanol was removed under reduced pressure and the liquid residue was extracted with benzene and triethylamine. Triethylammonium chloride was removed by filtration and the filtrate yielded *6c* (88 %), m.p. 108 – 109 °C (diethyl ether). IR (nujol): 1750 (s), 1600 (s) cm^{-1}. ^1H NMR (CD_3CN): δ 3.3 (4H, m), 3.75 (7H, m), 6.88 (1H, dd, *J* 2.9 Hz), 7.50 (1H, d, *J* 2.9 Hz), 8.30 (d, *J*, 5.7 Hz). MS [*m/e* (% rel. int.)]: 222 (41.7, M). Mol. wt., obs. 222.1003, calc. for $C_{11}H_{14}N_2O_3$ 222.1004.

Benzamides, 4b – f. These compounds were prepared from benzoyl chloride and an amine.

4b, M.p. 157 – 158 °C, lit.[15] m.p. 158 °C.

4c, M.p. 198 – 201 °C, lit.[16] m.p. 199 °C.

4d, M.p. 81 – 82 °C, lit.[17] m.p. 82 – 83 °C.

4e, M.p. 159 – 161 °C, lit.[18] m.p. 157.5 – 158.5 °C.

4f, M.p. 146 – 149 °C, lit.[19] m.p. 147 – 150 °C.

N-Benzoylpyrrolidine, m.p. 51 – 53 °C, lit.[20] m.p. 46 – 47 °C.

p-*Toluenesulfonamides*. *N*-Cyclopentyl-*p*-toluenesulfonamide, m.p. 75 – 76 °C was prepared from cyclopentylamine and *p*-toluenesulfonyl chloride, lit.[21] m.p. 84 °C. *N*-(4-Nitrophenyl)-*p*-toluenesulfonamide, m.p. 188 – 190 °C, lit.[22] m.p. 189 – 190 °C.

N-*Acyl-2-pyridinecarboxamides*, 1a – o. Compounds *1a*, *1f* and *1j* have been described,[7] *1b* and *1o*,[6] *1c – d*, *1h – i* and *1m – n* also are known compounds.[4]

1e (75 %), m.p. 124 – 126 °C was obtained from a reaction of *3e* with equimolar amounts of benzoyl chloride and triethylamine. IR (nujol): 1725 (s), 1710 (s), 1700 (s) cm^{-1}. ^1H NMR (CD_3NO_2): δ 2.50 (3H, s), 7.4 – 8.3 (13H, m). MS [*m/e* (% rel. int.)]: 316 (3.1, $M-SO_2$). Anal. $C_{20}H_{16}N_2O_4S$: C, H, S.

1g (63 %), m.p. 203 – 207 °C dec. was obtained[4] from equimolar amounts of *N*-(4-methylphenyl)-benzimidoyl chloride,[23] *6d* and triethylamine. IR (nujol): 1695 (s), 1685 (s), 1600 (s) cm^{-1}. ^1H NMR (CD_3NO_2): δ 2.35 (3H, s), 3.35 (4H, m), 3.78 (4H, m), 6.77 (1H, dd, *J* 2.9 Hz), 7.2 – 8.1 (11H, m). MS [*m/e* (% rel. int.)]: 401 (38.2, M). Mol. wt., obs. 401.1746, calc. for $C_{24}H_{23}N_3O_3$ 401.1739.

1k (50 %), m.p. 192 – 196 °C dec. was obtained[4] from *N*-(4-methylphenyl)benzimidoyl chloride,[23] *6e* and triethylamine. IR (nujol): 1695 (s), 1690 (s), 1610 (s) cm^{-1}. ^1H NMR (CD_3NO_2); δ 2.0 (4H, m), 2.30 (3H, s), 3.25 (4H, m), 6.47 (1H, dd, *J* 2.9 Hz), 6.95 – 8.2 (11H, m). MS [*m/e* (% rel. int.)]: 385 (30.9, M). Mol. wt., obs. 385.1790, calc. for $C_{24}H_{23}N_3O_2$ 385.1790.

1l was prepared[4] from equimolar amounts of *N*-(4-nitrophenyl)benzimidoyl chloride,[24] triethylamine and *6e*. The benzene soluble product, which was a liquid, was reacted with cyclopentylamine without further purification. IR (film): 1715 – 1690 (s), 1675 (s), 1600 (s) cm^{-1}.

Amidines, 8. These compounds were prepared by the following procedure. Three molar equivalents of cyclopentylamine or morpholine, or 1.1 molar equivalent of aniline plus two molar equivalents of triethylamine were added to a suspension of the imidoyl chloride hydrochloride[5] *7* in acetonitrile. The reaction mixture was stirred at ambient temperature for 24 h. The solvent was removed under reduced pressure and the residue was extracted with diethyl ether. The diethyl ether soluble amidine was recrystallized from a mixture of hexane and diethyl ether or chromatographed on silica gel.

8a (70 %), m.p. 91 – 93 °C. IR (nujol): 3380 (s), 1610 (s) cm^{-1}. ^1H NMR (CD_3NO_2): δ 1.5 – 2.1 (9H, m), 4.1 (1H, broad s), 6.8 – 8.1 (7H, m), 8.7 (1H, d, *J*, 5.7 Hz). MS [*m/e* (% rel. int.)]: 310 (76.4, M). Mol. wt., obs. 310.1427, calc. for $C_{17}H_{18}N_4O_2$ 310.1430.

8b (69 %), m.p. 120 – 122 °C. IR (nujol): 1605 (sh), 1600 (s) cm^{-1}. ^1H NMR (CD_3NO_2): δ 3.4 – 3.7 (8H, m), 6.7 – 7.9 (7H, m), 8.55 (1H, m). MS [*m/e* (% rel. int.)]: 312 (100, M). Mol. wt., obs. 312.1220, calc. for $C_{16}H_{16}N_4O_3$ 312.1222.

8c (69 %), m.p. 135 – 136 °C. IR (nujol): 3280 (m), 1640 (s) cm^{-1}. ^1H NMR (CD_3NO_2): δ 2.26 (3H, s), 3.05 (4H, m), 3.65 (4H, m), 6.7 – 7.2 (11H, m), 8.23 (1H, d, *J* 5.7 Hz). MS [*m/e* (% rel. int.)]: 372 (94.2, M). Mol. wt., obs. 372.1950, calc. for $C_{23}H_{24}N_4O$ 372.1950.

8d (50 %), m.p. 117 – 120 °C dec. IR (nujol): 3300 (m), 1640 (m), 1610 (m) cm^{-1}. ^1H NMR (CD_3CN): δ 2.5 (1H, broad s), 3.1 (4H, m), 3.7 (4H, m), 6.6 – 7.2 (10H, m), 8.03 (1H, d, *J* 8.6 Hz), 8.23 (1H, d, *J* 5.7 Hz). MS [*m/e* (% rel. int.)]: 403 (69.5, M). Mol. wt., obs. 403.1634, calc. for $C_{22}H_{21}N_5O_3$ 403.1644.

8e (50 %), m.p. 129 – 132 °C. IR (nujol): 3340 (s), 1640 (s), 1615 (s), 1595 (s) cm^{-1}. ^1H NMR (CD_3NO_2 and CD_3CN): δ 1.95 (4H + CD_3CN, m), 3.0 (4H, m), 6.4 – 7.2 (12H, m), 8.13 (1H, d, *J* 5.7 Hz). MS [*m/e* (% rel. int.)]: 342 (66.2, M). Mol. wt., obs. 342.1843, calc. for $C_{22}H_{22}N_4$ 342.1844.

8f (60 %), m.p. 96 – 98 °C. IR (nujol): 3350 (s), 1635 (s), 1610 (s), 1590 (s) cm^{-1}. ^1H NMR (CD_3NO_2): δ 1.95 (4H, m), 2.27 (3H, s), 3.1 (4H, m), 6.5 – 7.3 (11H, m), 8.12 (1H, d, *J* 5.7 Hz). MS [*m/e* (% rel. int.)]: 356 (79.9, M). Mol. wt., obs. 356.2003, calc. for $C_{23}H_{24}N_4$ 356.2003.

8g (46 %), m.p. 137 – 138 °C. IR (nujol): 3350 (m), 3320 (sh), 1650 (s), 1605 (s) cm^{-1}. ^1H NMR (CD_3CN): δ 1.5 – 2.0 (12H + CD_3CN, m), 3.1 (4H, m), 3.4 (1H, m), 4.14 (1H, broad s), 6.4 – 6.8 (4H, m), 7.9 – 8.2 (3H, m). MS [*m/e* (% rel. int.)]: 379 (63.6, M).

Mol. wt., obs. 379.2011, calc. for $C_{21}H_{25}N_5O_2$ 379.2008.

Reactions of 7a *with nucleophiles.* Silver tosylate (140 mg, 0.5 mmol) was added to a mixture of *7a* (150 mg, 0.5 mmol) and triethylamine (50 mg, 0.5 mmol) in 10 ml of acetonitrile. The reaction mixture was stirred at ambient temperature for 45 min. Cyclopentylamine (85 mg, 1 mmol) was added and stirring was continued for 30 min. Silver chloride was removed by filtration. The filtrate was analyzed by GLC at 300 °C, four compounds were found and were identified as *8a* (0.62 mol eq.), *3d* (0.28 mol eq.), *3b* (0.06 mol eq.) and *N*-cyclopentyl-*p*-toluenesulfonamide (0.04 mol eq.).

A mixture of *7a* (150 mg, 0.5 mmol), triethylamine (100 mg, 1 mmol) and sodium benzoate (72 mg, 0.5 mmol) in 10 ml of dichloromethane and 1 ml of acetonitrile was stirred at ambient temperature for 18 h. The solvents were removed under reduced pressure, 8 ml of benzene were added, the mixture was filtered and cyclopentylamine (45 mg, 0.5 mmol) was added to the filtrate. The reaction mixture was filtered after 30 min at ambient temperature. The benzene insoluble material was treated with water and yielded 20 mg (16%) of *3b*, m.p. 232 – 235 °C. The benzene was removed from the filtrate and diethyl ether (10 ml) was added to the residue. The mixture was filtered and 40 mg (20%) of *1b*, m.p. 160 – 170 °C was removed as insoluble material. The filtrate was concentrated and gave 90 mg (58%) of *8a*, m.p. 91 – 95 °C.

Hippuric acid (90 mg, 0.5 mmol) was added to a mixture of *7a* (150 mg, 0.5 mmol) and triethylamine (120 mg, 1.2 mmol) in 10 ml of dichloromethane. The reaction mixture was stirred at ambient temperature for 18 h. Cyclopentylamine (45 mg, 0.5 mmol) was added and the reaction mixture was analyzed by GLC after 1 h at ambient temperature. The two compounds *3b* and *8a* were present in a molar ratio of 1:5. The solvent was removed from the reaction mixture and 100 mg (64%) of *8a* m.p. 90 – 95 °C was isolated as diethyl ether soluble material, 15 mg (12%) of *3b*, m.p. 235 °C as diethyl ether insoluble material.

Reaction of 7e *with triethylammonium benzoate.* A mixture of *7e* (340 mg, 1 mmol), benzoic acid (122 mg, 1 mmol) and triethylamine (300 mg, 3 mmol) in 10 ml of acetonitrile was stirred at ambient temperature for 40 h. The solvent was removed under reduced pressure, and the benzene soluble fraction of the residue was chromatographed on silica gel. Compound *1k*, 190 mg (49%) m.p. 192 – 196 °C decl. was eluted from the column with acetone.

Reaction of 7f *with nucleophiles.* Silver tosylate (31 mg, 0.11 mmol) was added to a mixture of *7f* (40 mg, 0.11 mmol) and triethylamine (15 mg, 0.15 mmol) in 4 ml of acetonitrile. The reaction mixture was stirred for 10 min at ambient temperature. Cyclopentylamine (26 mg, 0.3 mmol) was added and stirring was continued for 30 min. The suspension was filtered and the filtrate was analyzed by GLC. Three compounds were identified, 4-nitroaniline (0.65 mol eq.), *N*-cyclopentyl-*p*-toluenesulfonamide (0.27 mol eq.) and *3n* (0.08 mol eq.).

In another experiment a mixture of *7f* and a fourfold molar excess of triethylamine in acetonitrile was analyzed by GLC. Only minute amounts of 4-nitroaniline were present in the solution. Silver tosylate (1 mol eq.) was added, the reaction mixture was filtered after 15 min and was analyzed by GLC. Substantial amounts of 4-nitroaniline were found in addition to other unidentified products.

In another experiment a solution of triethylammonium acetate (161 mg, 1 mmol) in 5 ml of tetrahydrofuran was added to a solution of *7f* – *HCl*[5] (331 mg, 1 mmol) in 10 ml of tetrahydrofuran. To this solution was added silver tosylate (279 mg, 1 mmol) in 10 ml of acetonitrile. The reaction mixture was stirred, protected from light and moisture, at ambient temperature for 1 h. Aniline (93 mg, 1 mmol) was added and the reaction mixture was stirred for 23 h. The solvents were removed under reduced pressure and the residue was extracted with 30 ml of benzene and 10 ml of a saturated aqueous sodium hydrogencarbonate solution. Some undissolved material was removed by filtration, and the chloroform soluble part of this solid gave 120 mg (38%) of *3l*, m.p. 219 – 222 °C. The benzene solution was extracted with 10 ml of 5% aqueous hydrogen chloride and the hydrochloric acid extract yielded 153 mg (49%) of *3l* m.p. 205 – 220 °C upon neutralization. The benzene solution was washed with water, dried over magnesium sulfate and yielded 76 mg (56%) of acetanilide, m.p. 105 – 112 °C (benzene and heptane).

Reactions of 1 *with nucleophiles.* Compound *1* was dissolved in a specified solvent (Table 1) and a fourfold molar excess of cyclopentylamine or pyrrolidine, or 1.1 molar equivalent of 4-methylaniline, was added. The solutions were left at ambient temperature before analysis by GLC. Compounds *1* also were reacted with methanol or water (Table 1) and these were used in a large molar excess. Response factors and retention times were found for the expected reaction products by GLC analysis of authentic samples under the same conditions which were used for the product analyses.

Acknowledgements. Financial support from *Norges Tekniske Høgskoles Fond* and from the U.S. Public Health Service General Medicine Division is gratefully acknowledged.

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Received December 8, 1981.