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SYNTHESIS AND PROPERTIES OF SOME NEW NICOTINOYL ISOCYANATES AND THEIR FRAGMENTATION UNDER ELECTRON IMPACT

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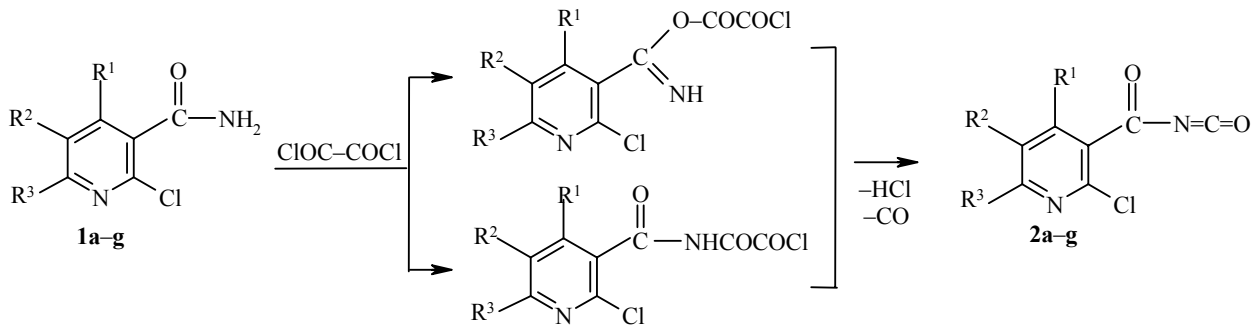
A convenient preparative route for synthesis has been developed and nicotinoyl isocyanates (NIC) have been obtained for the first time by the action of oxalyl chloride on amides of substituted nicotinic acids. A procedure has been found for suppressing the formation of hydrochlorides of nicotinoyl amides by the competing reaction of HCl with the initial amides of nicotinic acids. The special features of the fragmentation of nicotinoyl isocyanates under electron impact have been studied.

Keywords: amides of substituted nicotinic acids, nicotinoyl isocyanates, oxalyl chloride, mass spectra.

The increased interest of investigators in acyl isocyanates is caused by their accessibility and high reactivity, which makes them convenient synthons for the synthesis of substances useful in practice, and in particular for the synthesis of new biologically active compounds [1, 2]. It is known [1, 3] that aromatic acyl isocyanates are obtained by the action of oxalyl chloride on the corresponding acid amides. In spite of the apparent simplicity of such reactions, for amides of pyridinecarboxylic (nicotinic) acids described by us in [4], these reactions, and the isocyanates based on them, remain unstudied up to the present time.

The synthesis of the new nicotinoyl isocyanates **2a-g** from the corresponding amides **1a-g** has been undertaken in the present work according to Scheme 1.

Scheme 1



1, **2 a-d**, **f**, **g** R^1 = Me, **e** R^1 = Cl; **a**, **f** R^2 = H, **b**, **g** R^2 = Cl, **c-e** R^2 = NO_2; **a**, **d**, **e**, **g** R^3 = Cl, **b**, **c**, **f** R^3 = Me

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The formation of the isocyanates probably proceeds through the intermediate stage of forming unstable products of O- and N-acylation, the subsequent thermal decomposition and isomerization of which leads in accordance with [3] to the preparation of the desired nicotinoyl isocyanates.

The reaction of oxalyl chloride with amides **1a-g** was carried out in purified dry dioxane at a molar ratio of starting materials of 2 : 1. We established that, notwithstanding the concepts established [3], nicotinamides **1** react with oxalyl chloride even under mild conditions (20°C) with the formation of intermediate products of O- and N-acylation, soluble in dioxane. However for complete conversion of these intermediates into the desired isocyanates it is necessary to heat at 40°C until the end of gas evolution.

In this reaction the most reactive were nicotinamides containing no strongly withdrawing substituents in the pyridine ring, for example R^2 = H. On adding oxalyl chloride to a solution of 2-chloro-4,6-dimethylnicotinamide (**1f**) the formation was observed of a white solid insoluble in dioxane. The solid is the hydrochloride of the initial amide **1f**, which was demonstrated spectroscopically, and by conversion of the hydrochloride to the initial amide by interaction with aqueous ammonia. Probably the intermediate formed in this case is so reactive that even in the course of the reaction it decomposes spontaneously with elimination of HCl, and the latter reacts with the initial amide **1f** and removes it from the reaction as the hydrochloride, reducing sharply the yield of the desired isocyanate.

In the case of amides **1a,b** this undesirable side reaction also takes place, however it is less marked. Consequently we were obliged specially to develop procedures reducing the side reactions forming hydrochlorides of amides **1** to a minimum. These proved to be to conduct the reaction in dilute (~10 wt.%) solutions of the starting materials, and to add them in the correct order (solution of amide to the solution of oxalyl chloride, and not the reverse).

The nicotinoyl isocyanates, synthesized in good (75-98%) yield, were almost colorless and extremely hygroscopic thick viscous oils, which were decomposed even by the moisture of the air to the initial amides **1**. The physicochemical characteristics of the nicotinoyl isocyanates, their yields, and data of IR and mass spectroscopy are given in Tables 1 and 2.

In the IR spectra of the synthesized isocyanates **2**, in difference to the spectra of the initial amides **1**, the ν_{NH} absorption bands at 3180-3400 cm^{-1} had disappeared. The most important (characteristic) absorptions of the stretching vibrations of the two main N=C=O and C=O groups were displayed as medium intensity absorption bands at 2238-2243 and 1720-1734 cm^{-1} respectively (Table 2). The location of these bands in the spectra was

TABLE 1. Characteristics of Compounds **2a-g**

Compound	Empirical formula	Found, % / Calculated, %				bp, °C/(mm Hg)	Yield, %
		C	H	N	Cl		
2a	$C_8H_4Cl_2N_2O_2$	41.82 / 41.59	1.41 / 1.75	12.34 / 12.16	30.35 / 30.69	118-118.5 (8)	75
2b	$C_9H_6Cl_2N_2O_2$	44.34 / 44.12	2.69 / 2.47	11.51 / 11.44	28.64 / 28.94	131-131.5 (8)	93
2c	$C_9H_6ClN_3O_4$	42.67 / 42.31	2.58 / 2.37	16.31 / 16.45	13.68 / 13.87	182-183 (8)	86
2d	$C_8H_3Cl_2N_3O_4$	34.49 / 34.81	1.04 / 1.10	15.41 / 15.23	25.41 / 25.69	196-197 (8)	79
2e	$C_7Cl_3N_3O_4$	28.16 / 28.35	—	13.67 / 13.88	35.64 / 35.87	209-210	81
2f	$C_9H_7ClN_2O_2$	51.54 / 51.35	3.67 / 3.36	13.42 / 13.30	16.70 / 16.83	112-112.5 (8)	89
2g	$C_8H_3Cl_3N_2O_2$	36.05 / 36.18	1.34 / 1.14	10.69 / 10.55	40.24 / 40.06	159-160 (8)	79

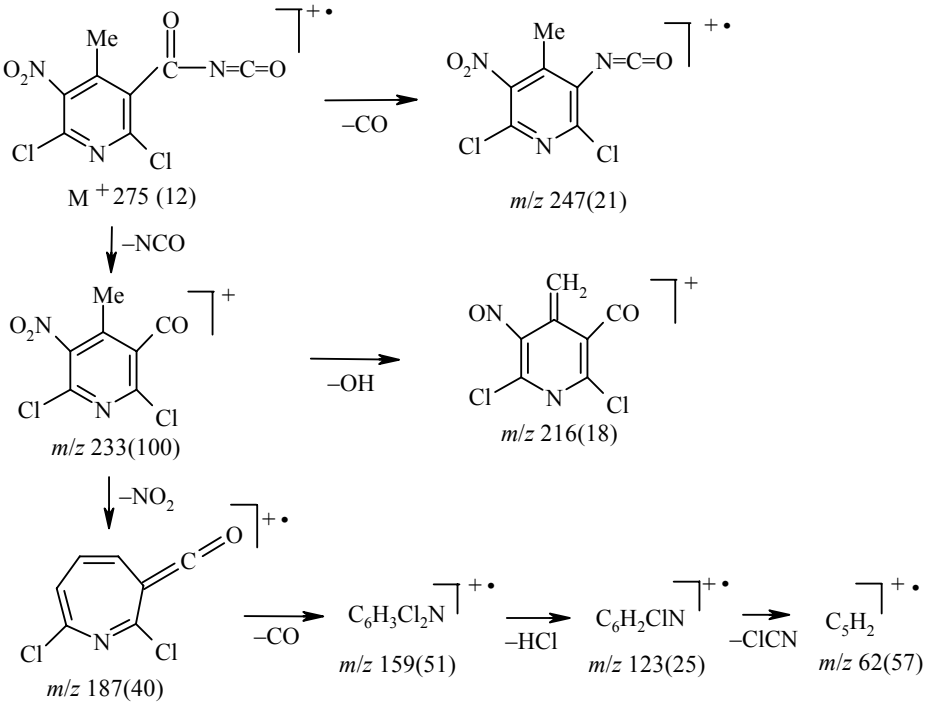
TABLE 2. IR and Mass Spectra of Nicotinoyl Isocyanates **2a-g**

Compound	IR spectrum, ν, cm^{-1}		Mass spectrum*, *m/z* (I_{rel}, % max.)
	NCO	C=O	
2a	2241	1720	230 $[M]^+$ (45); 202 $[M–CO]^+$ (33); 188 $[M–NCO]^+$ (100); 166 (21) $[202–HCl]^+$ (21); 160 $[188–CO]^+$ (21); 124 $[160–HCl]^+$ (24)
2b	2239	1720	244 $[M]^+$ (31); 216 $[M–CO]^+$ (40); 202 $[M–NCO]^+$ (100); 180 $[216–HCl]^+$ (25); 174 $[202–CO]^+$ (38); 138 $[174–HCl]^+$ (44)
2c	2243	1720	255 $[M]^+$ (49); 238 $[M–OH]^+$ (18); 227 $[M–CO]^+$ (11); 213 $[M–NCO]^+$ (100); 167 $[213–NO_2]^+$ (30); 139 $[167–CO]^+$ (51)
2d	2241	1728	275 $[M]^+$ (12); 247 $[M–CO]^+$ (21); 233 $[M–NCO]^+$ (100); 216 $[233–OH]^+$ (18); 187 $[233–NO_2]^+$ (40); 159 $[187–CO]^+$ (51); 123 $[159–HCl]^+$ (25)
2e	2240	1728	295 $[M]^+$ (28); 267 $[M–CO]^+$ (27); 253 $[M–NCO]^+$ (100); 249 $[M–NO_2]^+$ (18); 232 $[267–Cl]^+$ (24); 225 $[253–CO]^+$ (60); 179 $[225–NO_2]^+$ (14)
2f	2239	1734	210 $[M]^+$ (58); 182 $[M–CO]^+$ (31); 168 $[M–NCO]^+$ (100); 146 $[182–HCl]^+$ (52); 140 $[168–CO]^+$ (56); 104 $[140–HCl]^+$ (18)
2g	2238	1727	264 $[M]^+$ (37); 236 $[M–CO]^+$ (30); 222 $[M–NCO]^+$ (100); 200 $[236–HCl]^+$ (22); 194 $[122–CO]^+$ (42); 158 $[194–HCl]^+$ (18); 123 $[158–Cl]^+$ (12)

* Values of *m/z* are shown for ions containing the ^{35}Cl isotope. The molecular and 5-6 of the most characteristic ions are given.

fairly constant and depended little on the structure of the substituents in the environment of the pyridine ring. Absorption bands of medium intensity were also detected at 1500-1603 cm^{-1}, which, according to [5], must belong to $\nu_{C=C}$ and $\nu_{C=N–}$ of the conjugated pyridine ring.

Scheme 2



The sole difference in the ^{1}H NMR spectra of the synthesized nicotinic acid isocyanates **2** compared with the spectra of the known initial amides **1** proved to be the absence from the spectra of the isocyanates of signals for the protons of the amide NH_2 group.

Peaks were detected in the mass spectra of the nicotinoyl isocyanates (Table 2) for molecular ions with intensity 12-58%, but the peak for the $[M\text{-}NCO]^+$ ion had maximum intensity. Analysis of the results of the fragmentation of the isocyanates under electron impact showed that the initial fragmentation was characterized by two main directions, *viz*. ejection from the molecular ion of C=O or N=C=O fragments with the formation of $[M\text{-}NCO]^+$ and $[M\text{-}CO]^+$ ions. From the mass spectral data for nicotinoyl isocyanate **2d** (Scheme 2) possible routes are considered for the further more profound stages of fragmentation in relation to the known data [6]. The routes of fragmentation of the molecular ion in this Scheme and also of the $[M\text{-}NCO]^+$ ion are characteristic for all the group of compounds **2**.

A simple and reliable procedure is proposed for the synthesis of difficultly accessible substituted nicotinoyl isocyanates.

EXPERIMENTAL

The IR spectra were recorded on a Bruker IFS-45 spectrometer with an Aspekt 1000 analyzing computer for thin films of compounds in KBr disks. The mass spectra were recorded on a LKB-2091 chromato-mass spectrometer with direct insertion of samples into the ion source (ionizing energy 70 eV). The ^{1}H NMR spectra were taken in DMSO-d_6 on a Tesla 70 (70 MHz) instrument (external standard was HMDS, δ = 0 ppm) at 30°C. The elemental analysis of the synthesized compounds was carried out on a Carlo-Erba model 1106 analyzer. A check on the course of reactions was effected for the consumption of amides **1** by TLC (Silufol UV 254 in the system acetone–hexane, 1:1, visualizing with iodine vapor). The physicochemical characteristics of the synthesized compounds are given in Table 1, and the spectral characteristics in Table 2. The solvents dioxane and benzene used in the synthesis were purified from contaminants before use and were made absolute by the known procedures of [7, 8]. Oxalyl chloride was obtained from Merck.

2,6-Dichloro-4-methyl-5-nitronicotinoyl Isocyanate (2d). A solution of amide **1d** (12 mmol) in absolute dioxane (50 ml) was slowly added dropwise to a continuously stirred solution of oxalyl chloride (24 mmol) in absolute dioxane (15 ml) at ~20°C. The reaction mixture was stirred for a further 3 h at 50°C. The excess of oxalyl chloride and solvent was distilled off in a water-jet pump vacuum and the residue was maintained in vacuum for 1.5 h at 40-50°C until the end of breakdown of the intermediate and cessation of CO and HCl evolution. The desired nicotinoyl isocyanate **2d** (2.61 g, 79%) was isolated by distillation at 196-197°C/8 mm Hg. The content of main substance was >99%.

Nicotinoyl isocyanates **2a-c,e,g** were obtained analogously.

2-Chloro-4,6-dimethylnicotinoyl Isocyanate (2f). A solution of amide **1f** (2.7 mmol) in absolute dioxane (65 ml) was added dropwise to a solution of oxalyl chloride (5.4 mmol) in absolute dioxane (50 ml) with stirring at ~20°C. Stirring was continued at the same temperature for a further 2 h. After distilling off the oxalyl chloride and dioxane the residue was maintained in vacuum at ~20°C 0.5 h further until the end of gas evolution. The residue was distilled in vacuum, bp 112-112.5°C/8 mm Hg. Yield 0.51 g (89%).

2-Chloro-4,6-dimethylnicotinic Acid Amide (1f) Hydrochloride and 2-Chloro-4,6-dimethylnicotinoyl Isocyanate (2f). A solution of oxalyl chloride (5.4 mmol) in absolute dioxane (10 ml) was added to a solution of 2-chloro-4,6-dimethylnicotinic acid amide (**1f**) (2.7 mmol) in absolute dioxane (20 ml) and the mixture was maintained at 20°C for 1 h. The resulting abundant solid was filtered off, the reaction solution was put into a separate reactor, the residue on the filter was washed with dry EtOH (3 × 10 ml), and the hydrochloride of amide **1f** (0.44 g, 73%) obtained. Found, %: C 43.21; H 4.62; N 12.40; Cl 31.89. $C_8H_{10}N_2OCl_2$. Calculated, %: C 43.46; H 4.57; N 12.67; Cl 32.07. IR spectrum, ν, cm^{-1}: 1650 m (CO); 3308, 3161 br. m (NH).

^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.30 (3H, d, 4-CH_3); 2.45 (3H, d, 6-CH_3); 7.00 (1H, m, $H_{arom)}$; 7.65 (1H, s, CO$\underline{NH_2}$). Mass spectrum, *m/z* (I_{rel}, %): 184 $[M]^+$ (74), 168 $[M\text{-}NH_2]^+$ (100), 140 $[168\text{-}CO]^+$ (31), 105 $[140\text{-}Cl]^+$ (21), 90 $[105\text{-}CH_3]^+$ (7).

The separated reaction solution was stirred for 2 h further at 20°C, the solvent was distilled off, and the residue was maintained in a water-jet pump vacuum for 0.5 h further. Isocyanate **2f** (0.12 g, 21%) was obtained, the physicochemical and spectral characteristics of which are given in Tables 1 and 2.

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