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ACYLATION OF 1-ARYLPYRAZOLIDIN-3-ONES

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Acylation of 1-arylpyrazolidin-3-ones using aromatic acid anhydrides and chlorides in the presence of base occurs principally at the oxygen atom to give 1-aryl-3-acyloxy-2-pyrazolines, subsequent heating or microwave irradiation of which leads to the corresponding N-acylpyrazolidin-3-ones. The action of aliphatic acid anhydrides and chlorides on 1-arylpyrazolidin-3-ones gives predominantly the N-acylpyrazolidin-3-ones.

Keywords: acylarylpyrazolid-5-ones, acylation, 3-acyloxypyrazolines, pyrazolidone.

The presence of two nucleophilic centers in the molecule of 1-arylpyrazolidin-3-ones leads to the proposal that attack of acylating agents can take place by two routes thus leading to 3-acyloxy-2-pyrazolines (O-acylation) or to 2-acylpyrazolidin-3-ones (N-acylation). Hence, for example, it is known that 1-phenylpyrazolidin-3-one reacts with ketene to give 3-acetyloxy-1-phenyl-2-pyrazoline [1] but it yields 1-phenyl-2-acylpyrazolidin-3-one with acetic anhydride in the presence of sulfuric acid [2].

We have investigated in detail the acylation of 1-arylpyrazolidin-3-ones with aromatic and aliphatic acid chlorides and anhydrides.

Reaction of 1-phenylpyrazolidin-3-one (**1a**) with benzoyl chloride in the presence of NaH gives a mixture of 3-benzoyloxy-1-phenyl-2-pyrazoline (**2a**) and 2-benzoyl-1-phenylpyrazolidin-3-one (**3a**) which can be readily separated chromatographically.

The acylation route was identified on the basis of a combination of spectroscopic data (Table 1). In the IR spectrum of the starting compound **1a** there is present an absorption band for the carbonyl group at 1710 cm^{-1}. In the spectrum of compound **3a** two such absorption bands are seen at 1710 and 1790 cm^{-1} which are characteristic of cyclic imides and in the spectrum of compound **2a** two absorption bands at 1640 (C=N) and 1750 cm^{-1} (COOR).

The ^{1}H NMR spectrum of compound **2a** shows a downfield shift of the signal for the 4-CH$_2$ protons when compared with the signals for this group in the spectrum of the starting pyrazolidinone **1a** and the prepared compound **3a**. The mass spectra of compounds **2a** and **3a** have similar fragmentations but the presence in the mass spectrum of compound **2a** of a peak for the ion M$^+$-2, typical of the class of pyrazolines [3], confirms the formation of this pyrazoline structure via acylation of the starting compound **1a** at the oxygen atom. In the mass spectrum of compound **3a**, this ion peak is not observed. When triethylamine is used as the base in this reaction the acylation occurs only at the oxygen atom. A similar result is obtained in the reaction of benzoic anhydride with 1-phenylpyrazolidin-3-one **1a** at 50°C. The yield of compound **2a** is 30%. The 3-aroyloxy-2-pyrazolines obtained are relatively stable compounds. Heating compound **2a** at 180°C causes its conversion to 2-benzoyloxy-1-phenylpyrazolidin-3-one **3a**. When compound **2a** is treated with microwave radiation, its rearrangement to isomer **3a** is also observed but the process is less complete.

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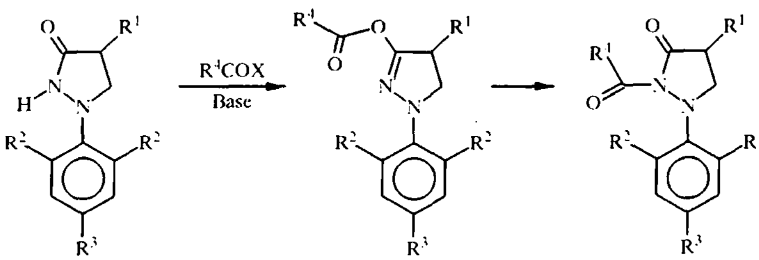

1a–d **2a–i** **3a–o**

$X = Cl, OCOR^4$

1a $R^1 = R^2 = R^3 = H$, **1b** $R^1 = CH_3$, $R^2 = R^3 = H$, **1c** $R^1 = R^2 = H$, $R^3 = Cl$, **1d** $R^1 = H$, $R^2 = R^3 = CH_3$

	2a, 3a	**2b, 3b**	**2c**	**2d**	**2e, 3e**	**2f, 3f**	**2g, 3g**	**2h**
R^1	H	CH_3	H	H	H	H	H	H
R^2	H	H	H	CH_3	H	H	H	H
R^3	H	H	Cl	CH_3	H	H	H	H
R^4	C_6H_5	C_6H_5	C_6H_5	C_6H_5	p-$H_3COC_6H_4$	p-$O_2NC_6H_4$	$C_6H_5CH_2$	p-$H_3CC_6H_4$

	2i	**3j**	**3k**	**3l**	**3m**	**3n**	**3o**
R^1	H	H	H	CH_3	H	H	CH_3
R^2	H	H	H	H	CH_3	H	H
R^3	H	H	H	H	CH_3	H	H
R^4	p-BrC_6H_4	CH_3	C_2H_5	C_2H_5	C_2H_5	C_3H_7	C_3H_7

Reaction of 1-phenylpyrazolidin-3-one with p-nitrobenzoyl chloride and p-methoxybenzoyl chloride in the presence of triethylamine gives the basic 2-pyrazoline reaction products **2e** and **2f** but also gives rise to the N-acylated 1-phenylpyrazolidin-3-ones **3e** and **3f** in the same (3 : 1) ratio. The mass spectra of the 2-pyrazoline **2e** and pyrazolidin-3-one **3e** isomers show the presence of a molecular ion peak at 311, subsequent breakdown of which in compound **2e** occurs via a known scheme for functional derivatives of 2-pyrazolines [3] (M^+-2) and also with fission of p-nitrobenzoic acid (M^+-143), whereas for compound **3e** such a breakdown does not occur. In the reaction with p-tolyl chloride and p-bromobenzoyl chloride the basic reaction products are the acyloxypyrazolines **2h, i**, formation of N-acylated products being established by TLC.

The reaction of acetyl chloride with arylpyrazolidin-3-one proceeds similarly to the process described for the acylation by the aromatic acid chlorides (O-acyloxylation identified by TLC) but the acyloxypyrazoline series derivative is unstable and, in the course of the process, there occurs a rearrangement to the thermally more stable N-acyl derivative. Acylation with other aliphatic acid chlorides gives the same results. An exception is the stable 3-phenacyloxy derivative **2g**, prepared by the action of phenylacetic anhydride. Irradiation in a microwave oven for 45 min leads to the formation of the isomeric 1-phenyl-2-phenylacylpyrazolidin-3-one **3g**. Under these conditions the rearrangement (as in the case of the aroyl derivatives) does not take place to completion and there are present in the reaction mixture both compounds **2g** and **3g** in the ratio 2 : 1.

TABLE 1. Spectroscopic Data for Compounds of Type **2** and **3**

	2a	3-Anilino-1-phenyl-2-pyrazoline [3]	**3a**	**1a**
4-H Signals (^1H NMR spectrum), ppm	3.28	3.10	2.78	2.66
$\nu_{C=O, C=N}$ (IR spectrum), cm^{-1}	1640, 1750	1640	1710, 1790	1710

TABLE 2. Mass Spectral Breakdown for Certain Isomers

Compound	m/z (I_{rel},%)
2a	266 (M^+, 11.59), 264 (4.07), 162 (5.53), 161 (5.87), 160 (12.87), 145 (2.33), 144 (3.15), 122 (14.39), 119 (4.42), 118 (2.18), 117 (3.15), 107 (3.49), 106 (34.53), 105 (100), 104 (11.32), 78 (14.48), 77 (85.26)
3a	266 (M^+, 7.17), 162 (1.26), 161 (3.09), 160 (5.31), 122 (4.39), 119 (2.60), 106 (16.13), 105 (100), 104 (6.45), 78 (6.43), 77 (57.92)
2f	311 (M^+, 32.55), 310 (1.73), 309 (9.22), 169 (2.90), 168 (19.50), 167 (4.86), 162 (16.18), 161(93.24), 160 (12.74), 151 (8.78), 150 (100), 121 (3.50), 120 (8.30), 119 (39.03), 105 (11.77), 104 (32.56), 92 (9.08), 91 (14.88), 78 (6.98), 77 (64.48), 76 (16.52)
3f	311 (M^+, 48.57), 16 (12.19), 161 (100), 151 (4.96), 150 (56.98), 120 (3.88), 119 (15.46), 105 (8.43), 104 (22.56), 92 (4.64), 9 (6.54), 78 (4.75), 77 (52.94), 76 (10.51)

Heating the 1-arylpyrazolidin-3-ones **1a-d** with aliphatic acid anhydrides at 130-150°C gives only the 2-acyl-1-arylpyrazolidin-3-ones **3j-o**. Lowering the reaction temperature to 50-60°C produces a mixture of the N-acylated derivative and the unreacted starting material.

TABLE 3. Spectroscopic Characteristics for Compounds Synthesized

Compound	^{1}H NMR spectrum, ppm				IR spectrum, cm^{-1}
	4-H	5-H	Ar	other signals	
2a	3.28, t (2H)	4.12, t (2H)	7.00-8.21 (10H)		1640, 1750
2b	3.79, m (1H)	3.52, t (1H), 4.15, t (1H)	6.83-7.67 (10H)	1.23, d (4-CH_3)	1640, 1750
2c	3.29, t (2H)	4.90, t (2H)	6.91-7.67 (9H)		1645, 1750
2d	3.18, t (2H)	3.80 t (2H)	6.82-8.18 (7H)	2.24, s (*p*-CH_3), 2.31, s (*o*-CH_3)	1630, 1740
2e	3.31, t (2H)	4.05, t (2H)	7.12-8.15 (9H)	4.12, s (*p*-CH_3O)	1625, 1750
2f	3.22, t (2H)	4.01, t (2H)	6.83-8.30 (9H)		1640, 1760
2g	3.12, t (2H)	3.90, t (2H)	6.81-7.36 (10H)	3.82, s (CH_2)	1640, 1760
2h	3.24, t (2H)	3.87, t (2H)	7.00-8.01 (9H)	2.42, s (*p*-CH_3)	1645, 1760
2i	3.25, t (2H)	3.95, t (2H)	6.80-8.03 (9H)		1640, 1750
3a	2.78, t (2H)	4.06, t, (2H)	7.15-8.05 (10H)		1710, 1790
3b	2.99, m (1H)	3.65, t (1H), 4.15, t (1H)	6.83-7.67 (10H)	1.20, d (4-CH_3)	1700, 1760
3e	2.71, t (2H)	4.05, t (2H)	7.12-8.15 (9H)	4.09, s (*p*-CH_3O)	1705, 1780
3f	2.70, t (2H)	4.05, t (2H)	7.05-8.15 (9H)		1690, 1770
3g	2.66, t (2H)	3.98, t (2H)	6.81-7.36 (10H)	3.86, s (CH_2)	1690, 1770
3j	2.70, t (2H)	3.95, t (2H)	6.80-7.39 (5H)	2.45, s (CH_3)	1700, 1760
3k	2.65, t (2H)	3.97, t (2H)	6.90-7.35 (5H)	1.15, t (CH_3), 2.89, q (CH_2)	1720, 1760
3l	2.85, m (1H)	3.59, t (1H), 3.96, t (1H)	6.92-7.33 (5H)	1.09, t (CH_3), 1.17, d (4-CH_3), 2.99, q (CH_2)	1725, 1760
3m	2.89, t (2H)	3.59, t (2H)	6.80, s (2H)	1.07, t (CH_3), 2.22, s (*p*-CH_3), 2.27, s (*o*-CH_3), 2.79, q (CH_2)	1710, 1760
3n	2.66, t (2H)	3.90, t (2H)	6.94-7.31 (5H)	0.96, t (CH_3), 1.73, q (CH_2), 2.86, m (CH_2)	1720, 1760
3o	2.79, m (1H)	3.55, t (1H) 3.91, t (1H)	6.90-7.31 (5H)	0.98, t (CH_3), 1.13, d (4-CH_3), 1.72, q (CH_2), 2.94, m (CH_2)	1720, 1760

TABLE 4. Characteristics for Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, % C	H	N	mp, °C	R_f	Yield, %
2a	$C_{16}H_{14}N_2O_2$	72.47 72.18	5.36 5.26	9.78 10.53	72-74	1.0	64
2b	$C_{17}H_{16}N_2O_2$	71.37 71.86	5.54 5.71	 10.00	Oil	1.0	53
2c	$C_{16}H_{13}N_2O_2Cl$	64.77 64.00	4.25 4.33	8.47 9.33	97-99	1.0	68
2d	$C_{19}H_{20}N_2O_2$	75.19 75.02	6.44 6.49	 9.09	50-51	1.0	48
2e	$C_{17}H_{16}N_2O_3$	68.12 68.92	4.97 5.40	8.69 9.46	127-129	1.0	67
2f	$C_{15}H_{13}N_3O_4$	61.73 61.74	4.30 4.18	13.50 13.50	162-163	1.0	75
2g	$C_{17}H_{16}N_2O_2$	72.87 72.85	5.80 5.71	9.80 10.00	95-97	1.0	73
2h	$C_{17}H_{16}N_2O_2$	72.66 72.85	5.84 5.71	9.00 10.00	96-98	1.0	60
2i	$C_{16}H_{13}N_2O_2Br$	55.42 55.49	3.75 3.76	8.25 8.09	112-115	1.0	61
3a	$C_{16}H_{14}N_2O_2$	72.26 72.18	5.33 5.26	9.82 10.53	110-112	0.58	21 35*
3b	$C_{17}H_{16}N_2O_2$	71.91 72.86	5.63 5.71	9.78 10.00	124-126	0.56	19
3e	$C_{17}H_{16}N_2O_3$	68.72 68.92	5.05 5.40	8.63 9.46	153-156	0.52	23
3f	$C_{16}H_{13}N_3O_4$	61.76 61.74	4.13 4.18	12.61 13.50	186-188	0.62	25
3g	$C_{17}H_{16}N_2O_2$	72.87 72.85	5.80 5.71	9.78 10.00	107-109	0.58	37*
3j	$C_{11}H_{12}N_2O_2$	64.37 64.70	6.09 5.88	13.90 13.72	70-71	0.51	55
3k	$C_{12}H_{14}N_2O_2$	65.76 66.05	6.76 6.42	12.41 12.84	74-76	0.48	63
3l	$C_{13}H_{16}N_2O_2$	67.20 67.24	6.85 6.89	12.12 12.06	55-59	0.49	76
3m	$C_{15}H_{20}N_2O_2$	69.35 69.23	7.28 7.64	 10.77	Oil	0.51	48
3n	$C_{13}H_{16}N_2O_2$	66.84 67.24	7.19 6.89	12.18 12.06	83-84	0.51	59
3o	$C_{14}H_{18}N_2O_2$	67.77 68.29	7.15 7.32	 11.38	75-78	0.51	62

* With rearrangement of the O-acylation product.

EXPERIMENTAL

IR spectra were measured on a UR-20 instrument in CCl_4 and CH_2Cl_2 solution and ^1H NMR spectra on a Varian VXR-400 using $CDCl_3$ solution and TMS as internal standard. Mass spectra were taken on a Kratos MS-890 with direct introduction of the sample into the ion source and an ionization energy of 70 eV. For the microwave irradiation a Funai MO785VT oven (850 watts) was used. Monitoring of the reaction course and the purity of the compounds prepared was carried out by TLC on Silufol UV-254 plates in the system benzene-petroleum ether (2 : 1) and revealed with iodine vapor and an alcohol solution of $FeCl_3$. Purification of the compounds obtained was performed chromatographically on a dry column with L 5/40 grade silica gel. The spectral data, characteristics, and yields for the compounds obtained are given in Tables 2-4.

Acylation Using Acid Chlorides (General Method). A solution of the acid chloride (4 mmol) in absolute THF was added dropwise with stirring to a solution of pyrazolidin-3-one (4 mmol) **1** and NaH or NEt_3 (4 mmol) in absolute THF. After 12 h the precipitate was filtered off, solvent evaporated in vacuo, the product washed with water, extracted with benzene, dried over magnesium sulfate, and chromatographed on a dry column using the system benzene–petroleum ether.

Acylation Using Acid Anhydrides (General Method). A solution of the pyrazolidin-3-one (4 mmol) **1** in the anhydride (5 mmol) was heated at 130-150°C (for benzoic anhydride in a melt at 50°C) until the disappearance of the 1-arylpyrazolidin-3-one (monitored by TLC). Excess anhydride was decomposed by a solution of sodium carbonate and the product was extracted with benzene and dried over magnesium sulfate. Chromatography was carried out on a dry column using the system benzene-petroleum ether.

Rearrangement of Compound 2 to 3. 2-Acyloxy-1-phenyl-2-pyrazoline **2** (4 mmol) was heated for 30 min on an oil bath at 180°C or irradiated for 1 h in a microwave oven (510 watts). The reaction mixture was chromatographed on a dry column using the system benzene–petroleum ether.

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