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ACYLATION OF AMINES AND PYRAZOLE WITH [2-ISOPROPYL-4-(*o*-METHOXYPHENYL)-TETRAHYDROPYRAN-4-YL]ACETYL CHLORIDE

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[2-Isopropyl-4-(o-methoxyphenyl)tetrahydropyran-4-yl]acetic acid has been obtained by the hydrolysis of previously synthesized [2-isopropyl-4-(o-methoxyphenyl)tetrahydropyran-4-yl]acetonitrile. The acyl chloride prepared from this acid gave new amides and 1-acylpyrazole upon interaction with various amines and with pyrazole.

Keywords: [2-isopropyl-4-(*o*-methoxyphenyl)tetrahydropyran-4-yl]acetic acid, *N*-substituted amides, acylation, hydrolysis.

There are data in the literature on the antimicrobial, analgesic, anxiolytic, antioxidant, and antiarrythmic activity of amides; certain amides display fairly high antimicrobial activity against strains of staphylococci, *Escherichia coli*, aerobic bacilli, and yeast fungi [1-4].

In a continuation of our investigations devoted to the search for new biologically active compounds among the derivatives of (4-aryl-2-isopropyltetrahydropyran-4-yl)acetonitrile [5], we have engaged in the synthesis of amides in this series.

[2-Isopropyl-4-(*o*-methoxyphenyl)tetrahydropyran-4-yl]acetic acid (**2**) was obtained by the hydrolysis of *o*-methoxyphenyl derivative **1**. Treatment of the acid **2** with thionyl chloride led to the acyl chloride **3**, which upon interaction with various primary and secondary amines (including cyclic amines) gave *N*-substituted amides of [2-isopropyl-4-(*o*-methoxyphenyl)tetrahydropyran-4-yl]acetic acid **4a-i** and the 1-acylpyrazole **4k**.

The composition and structures of the synthesized compounds were confirmed by data of elemental analysis (Table 1) and ^{1}H NMR spectra (Table 2).

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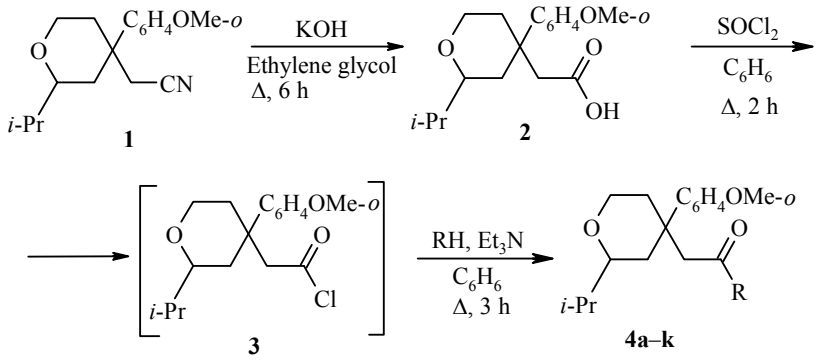

4 a R = NEt_2, **b** R = NHC_6H_4OMe-*n*, **c** R = 2-furylmethylamino, **d** R = $NH(CH_2)_3NMe_2$, **e** R = $NH(CH_2)_3NEt_2$, **f** R = $NH(CH_2)_3OMe$, **g** R = 1-pyrrolidinyl, **h** R = 2-thiazolylamino, **i** R = 1-piperidinyl, **j** R = 1-morpholino, **k** R =1-pyrazolyl

A simple synthesis has therefore been developed for the synthesis of new amides of 4-tetrahydropyranylacetic acid.

EXPERIMENTAL

The IR spectra were recorded on a Nicolet Avatar 330 FT-IR spectrometer in nujol. The ^1H NMR spectra were recorded on a Varian Mercury 300 instrument (300 MHz) in DMSO-d_6, internal standard was TMS. Melting points were determined on Boetius hot stage apparatus.

[2-Isopropyl-4-(*o*-methoxyphenyl)tetrahydropyran-4-yl]acetonitrile (1) was obtained as described previously [5].

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds **4a-k**

Compound	Empirical formula	Found, % / Calculated, %			Bp, °C (mm Hg) or mp, °C	Yield, %
		C	H	N		
4a	$C_{21}H_{33}NO_3$	72.63 / 72.58	9.59 / 9.57	4.00 / 4.03	175-178 (1)	64
4b	$C_{24}H_{31}NO_4$	72.58 / 72.52	7.79 / 7.86	3.55 / 3.52	125-126	72
4c	$C_{22}H_{29}NO_4$	71.08 / 71.13	7.91 / 7.87	3.70 / 3.77	208-210 (1)	65
4d	$C_{22}H_{36}N_2O_3$	70.25 / 70.18	9.69 / 9.64	7.41 / 7.44	200-204 (2)	68
4e	$C_{24}H_{40}N_2O_3$	71.31 / 71.25	9.92 / 9.97	6.89 / 6.92	205-208 (2)	70
4f	$C_{21}H_{33}NO_4$	69.45 / 69.39	9.18 / 9.15	3.81 / 3.85	190-195 (1.5)	71
4g	$C_{21}H_{31}NO_3$	72.97 / 73.01	9.09 / 9.04	4.12 / 4.05	205-210 (1)	67
4h	$C_{20}H_{26}N_2O_3S$	64.06 / 64.14	7.08 / 7.00	7.52 / 7.48	112-114	70
4i	$C_{22}H_{33}NO_3$	73.46 / 73.50	9.30 / 9.25	3.94 / 3.90	220-223 (1)	65
4j	$C_{21}H_{31}NO_4$	69.71 / 69.78	8.58 / 8.64	3.81 / 3.87	225-230 (2)	63
4k	$C_{20}H_{26}N_2O_3$	70.10 / 70.15	7.71 / 7.65	8.20 / 8.18	98-100	58

TABLE 2. ^{1}H NMR Spectra of Compounds **4a-k**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
4a	0.70 (3H, t, ^3J =7.0) and 0.94 (3H, t, ^3J =7.0, N($CH_2C\underline{H}_3$)$_2$); 0.93 (3H, d, ^3J = 6.8) and 0.94 (3H, d, ^3J = 6.8, ($C\underline{H}_3$)$_2$CH); 1.30 (1H, dd, ^2J = 12.9, ^3J =11.5, 3-C$\underline{H}_A$H$_B$); 1.56-1.68 (2H, m, (CH_3)$_2$C$\underline{H}$, 5-C$\underline{H}_A$H$_B$); 2.58-2.72 (2H, m, 3-CH$_A\underline{H}_B$, 5-CH$_A\underline{H}_B$); 2.93-3.05 (4H, m, N(CH_2)$_2$); 2.95 (2H, s, CH_2CO); 3.34 (1H, ddd, ^3J = 11.5, ^3J = 5.6, ^3J = 1.7, 2-CH); 3.66-3.87 (2H, m, 6-CH_2); 3.83 (3H, s, OCH_3); 6.80-6.86 (2H, m, H Ar); 7.08-7.16 (2H, m, H Ar)
4b	0.93 (6H, d, ^3J = 6.8, ($C\underline{H}_3$)$_2$CH); 1.38 (1H, dd, ^2J = 12.8, ^3J = 11.6, 3-C$\underline{H}_A$H$_B$); 1.55-1.70 (1H, m, (CH_3)$_2$C$\underline{H}$); 1.70 (1H, ddd, ^2J = 13.6, ^3J = 11.2, ^3J = 6.7, 5-C$\underline{H}_A$H$_B$); 2.47 (2H, m, 3-CH$_A\underline{H}_B$, 5-CH$_A\underline{H}_B$); 3.03 (2H, s, CH_2CO); 3.41 (1H, ddd, ^3J = 11.6, ^3J = 5.9, ^3J = 1.2, 2-CH); 3.70 (3H, s, *p*-C$\underline{H}_3$OC$_6$H$_4$NH); 3.75-3.88 (2H, m, 6-CH_2); 3.85 (3H, s, *o*-OCH_3); 6.61-6.67 (2H, m, H Ar); 7.09-7.14(2H, m HAr); 6.81-6.88 (2H, m, H Ar); 7.09-7.17 (4H, m, H Ar); 8.55 (1H, s, NH)
4c	0.92 (6H, d, ^3J = 6.8, ($C\underline{H}_3$)$_2$CH); 1.33 (1H, dd, ^2J =12.9, ^3J = 11.6, 3-C$\underline{H}_A$H$_B$); 1.53-1.69 (2H, m, (CH_3)$_2$C$\underline{H}$, 5-C$\underline{H}_A$H$_B$); 2.36-2.48 (2H, m, 3-CH$_A\underline{H}_B$, 5-CH$_A\underline{H}_B$); 2.90 (2H, s, CH_2CO); 3.35 (1H, ddd, ^3J = 11.6, ^3J = 5.8, ^3J = 1.6, 2-CH); 3.72-3.85 (2H, m, 6-CH_2); 3.82 (3H, s, OCH_3); 3.99 (2H, d, ^3J = 5.7, C$\underline{H}_2$NH); 5.73 (1H, d, ^3J = 3.3, H-3 furan); 6.18 (1H, dd, ^3J = 3.3, ^3J = 1.9, H-4 furan); 6.79-6.85 (2H, m, H Ar); 7.01 (1H, t, ^3J = 5.7, NH); 7.07-7.15 (2H, m, H Ar); 7.27 (1H, d, ^3J = 1.9, H-5 furan)
4d	0.93 (3H, d, ^3J = 6.7) and 0.94 (3H, d, ^3J = 6.7, ($C\underline{H}_3$)$_2$CH); 1.15 (2H, quin., ^3J = 6.9, NHC$H_2\underline{CH}_2$); 1.33 (1H, dd, ^2J = 12.9, ^3J = 11.4, 3-C$\underline{H}_A$H$_B$); 1.53-1.70 (2H, m, (CH_3)$_2$C$\underline{H}$, 5-C$\underline{H}_A$H$_B$); 1.96 (2H, t, ^3J = 6.9, C$\underline{H}_2$N(CH_3)$_2$); 2.07 (6H, s, N(CH_3)$_2$); 2.38-2.49 (2H, m, 3-CH$_A\underline{H}_B$, 5-CH$_A\underline{H}_B$); 2.80 (2H, td, ^3J = 6.9, ^3J = 5.7, NHC$\underline{H}_2$); 2.81 (2H, s, CH_2CO); 3.35 (1H, ddd, ^3J = 11.4, ^3J = 5.7, ^3J = 1.7, 2-CH); 3.71-3.87 (2H, m, 6-CH_2); 3.85 (3H, s, OCH_3); 6.38 (1H, t, ^3J = 5.7, NH); 6.81-6.89 (2H, m, H Ar); 7.10-7.16 (2H, m, H Ar)
4e	0.93 (6H, d, ^3J = 6.8, ($C\underline{H}_3$)$_2$CH); 0.94 (6H, t, ^3J = 7.1, N($CH_2C\underline{H}_3$)$_2$); 1.15 (2H, quin., ^3J = 6.9, NHC$H_2\underline{CH}_2$); 1.32 (1H, dd, ^2J = 12.9, ^3J = 11.5, 3-C$\underline{H}_A$H$_B$); 1.52-1.64 (1H, m, (CH_3)$_2$C$\underline{H}$); 1.64 (1H, td, ^2J = ^3J = 13.1, ^3J = 5.7, 5-C$\underline{H}_A$H$_B$); 2.15 (2H, t, ^3J = 6.9, CH_2NEt_2); 2.38 (4H, q, ^3J = 7.1, N($C\underline{H}_2CH_3$)$_2$); 2.38-2.48 (2H, m, 3-CH$_A\underline{H}_B$, 5-CH$_A\underline{H}_B$); 2.79 (2H, td, ^3J = 6.9, ^3J = 5.8, NHCH_2); 2.81 (2H, s, CH_2CO); 3.35 (1H, ddd, ^3J = 11.5, ^3J = 5.8, ^3J = 1.6, 2-CH); 3.71-3.85 (2H, m, 6-CH_2); 3.84 (3H, s, OCH_3); 6.34 (1H, t, ^3J = 5.8, NH); 6.81-6.88 (2H, m, H Ar); 7.09-7.15 (2H, m, H Ar)
4f	0.92 (3H, d, ^3J = 6.7) and 0.93 (3H, d, ^3J = 6.7, ($C\underline{H}_3$)$_2$CH); 1.23 (2H, tt, ^3J = 6.7, ^3J = 6.1, NHC$H_2\underline{CH}_2$); 1.32 (1H, dd, ^2J = 12.9, ^3J = 11.4, 3-C$\underline{H}_A$H$_B$); 1.52-1.66 (1H, m, (CH_3)$_2$C$\underline{H}$); 1.64 (1H, td, ^2J = ^3J = 12.9, ^3J = 5.6, 5-C$\underline{H}_A$H$_B$); 2.38-2.50 (2H, m, 3-CH$_A\underline{H}_B$, 5-CH$_A\underline{H}_B$); 2.80 (2H, s, CH_2CO); 2.82 (2H, td, ^3J = 6.7, ^3J = 5.8, NHC$\underline{H}_2$); 3.02 (2H, t, ^3J = 6.1, C$\underline{H}_2$OCH_3); 3.17 (3H, s, $CH_2OC\underline{H}_3$); 3.34 (1H, ddd, ^3J = 11.4, ^3J = 5.7, ^3J = 1.5, 2-CH); 3.70-3.84 (2H, m, 6-CH_2); 3.85 (3H, s, OCH_3); 6.37 (1H, t, ^3J = 5.8, NH); 6.80-6.88 (2H, m, H Ar); 7.08-7.15 (2H, m, H Ar)
4g	0.94 (3H, d, ^3J = 6.8) and 0.95 (3H, d, ^3J = 6.8, ($C\underline{H}_3$)$_2$CH); 1.31 (1H, dd, ^2J = 13.0, ^3J = 11.4, 3-C$\underline{H}_A$H$_B$); 1.56-1.69 (6H, m, 5-C$\underline{H}_A$H$_B$, (CH_3)$_2$C$\underline{H}$, N($CH_2C\underline{H}_2$)$_2$); 2.57-2.70 (2H, m, 3-CH$_A\underline{H}_B$, 5-CH$_A\underline{H}_B$); 2.94 (2H, s, CH_2CO); 2.96-3.08 (4H, m, N(CH_2)$_2$); 3.34 (1H, ddd, ^3J = 11.4, ^3J = 5.7, ^3J = 1.7, 2-CH); 3.66-3.87 (2H, m, 6-CH_2); 3.83 (3H, s, OCH_3); 6.82-6.88 (2H, m, H Ar); 7.09-7.18 (2H, m, H Ar)
4h	0.92 (6H, d, ^3J = 6.8, ($C\underline{H}_3$)$_2$CH); 1.40 (1H, dd, ^2J = 13.4, ^3J = 11.5, 3-C$\underline{H}_A$H$_B$); 1.54-1.69 (1H, m, (CH_3)$_2$C$\underline{H}$); 1.69 (1H, ddd, ^2J = 13.7, ^3J = 10.5, ^3J = 7.4, 5-C$\underline{H}_A$H$_B$); 2.39-2.49 (2H, m, 3-CH$_A\underline{H}_B$, 5-CH$_A\underline{H}_B$); 3.23 (2H, s, CH_2CO); 3.41 (1H, ddd, ^3J = 11.5, ^3J = 5.7, ^3J = 1.7, 2-CH); 3.80-3.85 (2H, m, 6-CH_2); 3.83 (3H, s, OCH_3); 6.81 (1H, d, ^3J = 3.6, H-5 thiazole); 6.81-6.86 (2H, m, H Ar); 7.08-7.18 (2H, m, H Ar); 7.26 (1H, d, ^3J = 3.6, H-4 thiazole); 11.49 (1H, s, NH)
4i	0.93 (3H, d, ^3J = 6.7) and 0.94 (3H, d, ^3J = 6.7, ($C\underline{H}_3$)$_2$CH); 0.94 (1H, m) and 1.12-1.43 (5H, m, NCH_2($C\underline{H}_2$)$_3$); 1.29 (1H, dd, ^2J = 12.9, ^3J = 11.4, 3-C$\underline{H}_A$H$_B$); 1.55-1.67 (2H, m, (CH_3)$_2$C$\underline{H}$, 5-C$\underline{H}_A$H$_B$); 2.53-2.66 (2H, m, 3-CH$_A\underline{H}_B$, 5-CH$_A\underline{H}_B$); 2.99 (2H, s, CH_2CO); 2.99-3.03 (2H, m) and 3.15-3.22 (2H, m, N(CH_2)$_2$); 3.37 (1H, ddd, ^3J = 11.4, ^3J = 5.7, ^3J = 1.5, 2-CH); 3.72-3.86 (2H, m, 6-CH_2); 3.84 (3H, s, OCH_3); 6.83-6.88 (2H, m, H Ar); 7.10-7.16 (2H, m, H Ar)
4j	0.93 (3H, d, ^3J = 6.8) and 0.94 (3H, d, ^3J = 6.8, ($C\underline{H}_3$)$_2$CH); 1.30 (1H, dd, ^2J = 12.9, ^3J = 11.4, 3-C$\underline{H}_A$H$_B$); 1.54-1.68 (2H, m, (CH_3)$_2$C$\underline{H}$, 5-C$\underline{H}_A$H$_B$); 2.52-2.65 (2H, m, 3-CH$_A\underline{H}_B$, 5-CH$_A\underline{H}_B$); 2.77-3.03 (4H, m, N(CH_2)$_2$); 2.98 (2H, s, CH_2CO); 3.15-3.28 (4H, m, O(CH_2)$_2$); 3.38 (1H, ddd, ^3J = 11.4, ^3J = 5.7, ^3J = 1.7, 2-CH); 3.73-3.87 (2H, m, 6-CH_2); 3.84 (3H, s, OCH_3); 6.86-6.92 (2H, m, H Ar); 7.13-7.20 (2H, m, H Ar)
4k	0.92 (6H, d, ^3J = 6.7, ($C\underline{H}_3$)$_2$CH); 1.45 (1H, dd, ^2J = 13.4, ^3J = 11.5, 3-C$\underline{H}_A$H$_B$); 1.54-1.68 (1H, m, (CH_3)$_2$C$\underline{H}$); 1.78 (1H, ddd, ^2J = 13.8, ^3J = 11.9, ^3J = 5.7, 5-C$\underline{H}_A$H$_B$); 2.40-2.52 (2H, m, 3-CH$_A\underline{H}_B$, 5-CH$_A\underline{H}_B$); 3.41 (1H, ddd, ^3J = 11.5, ^3J = 5.6, ^3J = 1.5, 2-CH); 3.75 (3H, s, OCH_3); 3.78-3.92 (2H, m, 6-CH_2); 3.97 (2H, s, CH_2CO); 6.36 (1H, dd, ^3J = 2.8, ^3J = 1.5, H-4 pyrazolyl); 6.77-6.85 (2H, m, H Ar); 7.06-7.19 (2H, m, H Ar); 7.58 (1H, d, ^3J = 1.5, H-3 pyrazolyl); 8.01 (1H, d, ^3J = 2.8, H-5 pyrazolyl)

[2-Isopropyl-4-(*o*-methoxyphenyl)tetrahydropyran-4-yl]acetic Acid (2). KOH (33.6 g, 0.60 mol) was dissolved with heating in ethylene glycol (120 ml). The obtained solution was added to nitrile **1** (41.0 g, 0.15 mol). The mixture was refluxed for 6 h, cooled, water (120 ml) was added, and the obtained suspension was extracted with diethyl ether. The aqueous layer was acidified with concentrated HCl solution (60 ml) and extracted with benzene (3×100 ml). The benzene extract was washed with water, dried, and after distilling off the benzene, the residue was distilled in vacuum. Yield 26.3 g (60%). Bp 205-208°C (1.5 mm Hg). IR spectrum, ν, cm^{-1}: 3400-3200 (OH), 1710 (C=O), 1610, 1590 (C=C arom.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.94 (6H, d, ^3J = 6.8, $(C\underline{H}_3)_2CH$); 1.39 (1H, dd, ^2J = 13.0, ^3J = 11.6, $(3\text{-}C\underline{H}_AH_B)$; 1.54-1.68 (1H, m, $(CH_3)_2C\underline{H}$); 1.73 (1H, td, $^2J = {}^3J$ = 12.9, ^3J = 5.1, $5\text{-}C\underline{H}_AH_B$); 2.39-2.53 (2H, m, $3\text{-}CH_A\underline{H}_B$, $5\text{-}CH_A\underline{H}_B$); 3.00 (2H, s, CH_2CO); 3.32 (1H, ddd, ^3J = 11.6, ^3J = 5.8, ^3J = 1.5, 2-CH); 3.69-3.89 (2H, m, $6\text{-}CH_2$); 3.85 (3H, s, OCH_3); 6.83-6.90 (2H, m, H Ar); 7.11-7.18 (2H, m, H Ar); 11.21 (1H, br. s, COOH). Found, %: C 69.75; H 8.33. $C_{17}H_{24}O_4$. Calculated, %: C 69.84; H 8.27.

[2-Isopropyl-4-(*o*-methoxyphenyl)tetrahydropyran-4-yl]acetyl Chloride (3). A mixture of acid **2** (29.2 g, 0.1 mol) and $SOCl_2$ (13.1 g, 0.11 mol) in dry benzene (30-35 ml) was boiled at reflux for 2 h, the benzene was removed by distillation, and the residual viscous mass, 27.7 g (yield of crude product **3** ~90%), was used for acylation without isolation.

***N*-Substituted Amides of [2-Isopropyl-4-(*o*-methoxyphenyl)tetrahydropyran-4-yl]acetic Acid 4a-k.** Acyl chloride **3** (3.1 g, 0.01 mol) was added dropwise with stirring to a solution of the corresponding amine or pyrazole (0.01 mol) and Et_3N (1.0 g, 0.01 mol) in dry benzene (20 ml). The reaction mixture was refluxed for 3 h, then cooled, acidified with concentrated HCl solution to a weakly acidic reaction, and extracted with benzene. The extract was washed with water, dried, and benzene was distilled off. Compounds **4a-k** were isolated from the residue by distillation in vacuum, or by recrystallization from ethanol.

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