Chemistry of Heterocyclic Compounds, Vol. 37, No. 7, 2001

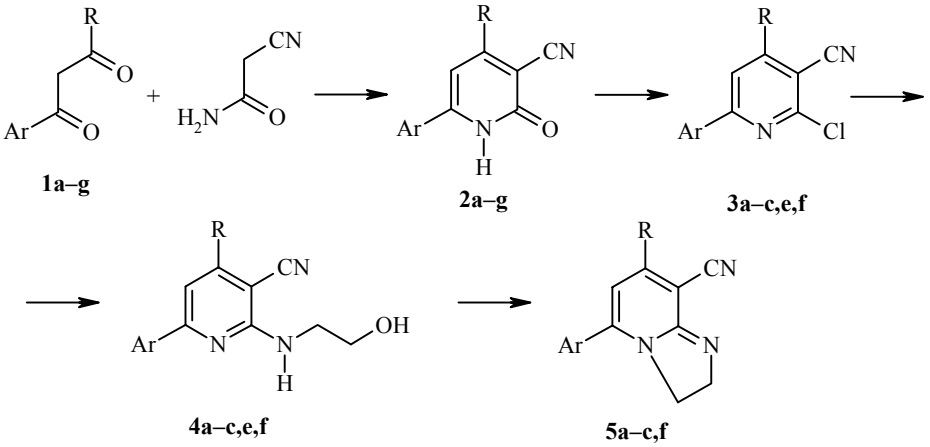
SYNTHESIS OF 2,3-DIHYDROIMIDAZO-[1,2-*a*]PYRIDINES FROM 1,3-DIKETONES

E. Suloeva[1], M. Yure[1], E. Gudriniece[1], M. Petrova[1], and A. Gutcaits[2]

A series of 2-hydroxy-, 2-chloro-, and 2-(2-hydroxyethylamino)-6-aryl-4-polyfluoroalkyl-3-cyanopyridines has been synthesized. The latter react with phosphorus oxychloride to give fluorine containing 2,3-dihydroimidazo[1,2-a]pyridines.

Keywords: 2-(2-hydroxyethylamino)pyridines, 2,3-dihydroimidazo[1,2-*a*]pyridines, pyridin-2-ones, 2-chloropyridines.

In a continuing investigation of the little studied 2,3-dihydroimidazo[1,2-*a*]pyridines [1-3] we have synthesized a series of novel derivatives which contain fluorinated substituents. We have used the fluorine containing 1,3-diketones **1a-g** as starting materials and condensed them with cyanoacetamide in the presence of base [4-6] to get pyridin-2-ones. The reaction was carried out by refluxing the components in ethanol in the presence of ammonium acetate. The pyridin-2-ones **2a-g** are yellowish, crystalline materials which have a light blue fluorescence both in solutions and in the crystalline state. The position of the aryl and polyfluoroalkyl substituent in the pyridin-2-ones **2a-g** has been correlated by us with previous X-ray studies for the series in question [7, 8].



1–5 **a** R = CF_3, Ar = *p*-MeC_6H_4; **b** R = C_3F_7, Ar = Ph; **c** R = C_4F_9, Ar = Ph; **d** R = C_6F_{13}, Ar = Ph; **e** R = $(CF_2)_2H$, Ar = Ph; **f** R = $(CF_2)_4H$, Ar = Ph; **g** R = CF_3, Ar = *p*-BrC_6H_4

[1] Riga Technical University, Riga LV-1048, Latvia; e-mail: mara@ktf.rtu.lv. [2] Latvian Institute of Organic Synthesis, Riga LV-1006; e-mail: guttsait@osi.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 947-951, July, 2001. Original article submitted January 11, 2001.

 0009-3122/01/3707-0872$25.00

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Reaction time, h	Yield, %
		C	H	N			
2a	$C_{14}H_9F_3N_2O$	60.70 / 60.44	3.03 / 3.26	10.00 / 10.07	296-298	3	75
2b	$C_{15}H_7F_7N_2O$	48.66 / 49.47	2.06 / 1.94	8.13 / 7.69	254-255	5	52
2c	$C_{16}H_7F_9N_2O$	46.60 / 46.39	1.73 / 1.70	6.69 / 6.76	242-245	5	57
2d	$C_{18}H_7F_{13}N_2O$	42.69 / 42.04	1.40 / 1.37	5.38 / 5.45	238-240	6	76
2e	$C_{14}H_8F_4N_2O$	56.63 / 56.77	2.52 / 2.74	9.36 / 9.46	251-253 (243-244[4])	4	48
2f	$C_{16}H_8F_8N_2O$	47.97 / 48.50	2.34 / 2.04	7.00 / 7.07	208-210	6	55
2g	$C_{13}H_6BrF_3N_2O$	44.97 / 45.51	1.74 / 1.76	8.12 / 8.16	269-271	5	70
3a	$C_{14}H_8ClF_3N_2$	56.67 / 56.68	2.70 / 2.72	9.43 / 9.44	159-160	8	44
3b	$C_{15}H_6ClF_7N_2$	47.61 / 47.08	1.60 / 1.58	7.24 / 7.32	92-94	8	85
3c	$C_{16}H_6ClF_9N_2$	44.99 / 44.42	1.33 / 1.40	6.35 / 6.47	86-88	8	74
3e	$C_{14}H_7ClF_4N_2$	53.19 / 53.44	2.14 / 2.24	8.79 / 8.90	104-106	8	58
3f	$C_{16}H_7ClF_8N_2$	46.19 / 46.34	1.90 / 1.70	6.60 / 6.76	78-80	8	88
4a	$C_{16}H_{14}F_3N_3O$	59.76 / 59.81	4.42 / 4.39	13.11 / 13.08	157-158	6	92
4b	$C_{17}H_{12}F_7N_3O$	50.20 / 50.13	2.94 / 2.97	10.25 / 10.32	144-145	4	80
4c	$C_{18}H_{12}F_9N_3O$	47.22 / 47.28	2.58 / 2.65	9.11 / 9.19	110-112	3	66
4e	$C_{16}H_{13}F_4N_3O$	55.79 / 56.64	3.66 / 3.86	12.02 / 12.38	110-112	6	70
4f	$C_{18}H_{13}F_8N_3O$	49.01 / 49.21	2.93 / 2.98	9.49 / 9.57	122-123	4	86
5a	$C_{16}H_{12}F_3N_3$	63.21 / 63.36	3.97 / 3.99	13.76 / 13.85	156-158	1	73
5b	$C_{17}H_{10}F_7N_3$	52.45 / 52.45	2.47 / 2.59	10.75 / 10.79	182-184	1	60
5c	$C_{18}H_{10}F_9N_3$	49.16 / 49.22	2.31 / 2.29	9.50 / 9.57	158-160	1	87
5f	$C_{18}H_{11}F_8N_3$	51.32 / 51.32	2.57 / 2.63	9.92 / 9.97	134-136	1	67

Substitution of the hydroxy group for chlorine in the 2-hydroxypyridines (pyridin-2-ones) **2a-c,e,f** has been achieved by refluxing them with an excess of $POCl_3$ in the presence of DMF. The corresponding chloropyridines **3a-c,e,f** were obtained in 44-88% yields.

Thanks to the presence of an electron acceptor substituent at $C_{(3)}$ in the 2-chloropyridines, the atom $C_{(2)}$ becomes an active center in reactions with nucleophiles. Treatment of the 2-chloro-3-cyanopyridines **3a-c,e,f** with aminoethanol under previously reported conditions [1, 9] gave the corresponding 2-(2-hydroxyethylamino)pyridines **4a-c,e,f** in 66-92% yields. Reaction of the latter with phosphorus oxychloride then gave the previously unreported series of 2,3-dihydroimidazo[1,2-*a*]pyridines **5a-c,f** which contained fluorinated substituents. The dark red imidazopyridines melt at 134-138°C. Their IR spectra are characterized by absorption bands for the stretching of the C=N bond in the region 1642-1648 and for the C≡N bond in the region 2219-2243 cm^{-1}. In the ^1H NMR spectra of these compounds in chloroform, the methylene protons of the $N–CH_2–CH_2–N$ fragment are virtually equivalent in chemical shift and are observed as a narrow multiplet signal

TABLE 2. Spectroscopic Characteristics for the Compounds Synthesized

Com-pound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz)
2a*	3200-2600, 2235, 1660, 1625, 1580, 1560	2.38 (3H, s, CH_3); 7.22 (1H, s, =CH–); 7.38 (2H, m, *J* = 7.5, C_6H_4); 7.91 (2H, m, *J* = 7.5, C_6H_4); 13.47 (1H, br. s, NH)
2b*	3200-2650, 2237, 1650, 1630, 1608, 1575, 1553	7.13 (1H, s, =CH–); 7.57 (3H, m, C_6H_5); 7.97 (2H, m, C_6H_5); 12.63 (1H, br. s, NH)
2c*	3200-2600, 2236, 1650, 1605, 1578, 1542, 1524	7.19 (1H, s, =CH–); 7.58 (3H, m, C_6H_5); 7.99 (2H, m, C_6H_5); 13.38(1H, br. s, NH)
2d*	3150-2600, 2227, 1653, 1605, 1577, 1549	7.08 (1H, s, =CH–); 7.53 (3H, m, C_6H_5); 7.94 (2H, m, C_6H_5); 13.30 (1H, br. s, NH)
2e*	3250-2650, 2240, 1670, 1625, 1590, 1565	6.91 (1H, tt, *J* = 52.5, *J* = 3.8, CF_2–H); 7.02 (1H, s, =CH–); 7.58 (3H, m, C_6H_5); 7.94 (2H, m, C_6H_5); 12.33 (1H, br. s, NH)
2f*	3200-2650, 2236, 1648, 1630, 1604, 1576, 1533	7.08 (1H, s, =CH–); 7.22 (1H, tt, *J* = 55, *J* = 5, CF_2–H); 7.58 (3H, m, C_6H_5); 7.99 (2H, m, C_6H_5); 13.55 (1H, br. s, NH)
2g*	3220-2700, 2240, 1658, 1620, 1575, 1540	7.36 (1H, s, =CH–); 7.84 (4H, m, C_6H_4); 11.93 (1H, br. s, NH)
3a	3087, 2231, 1593, 1543	2.38 (3H, s, CH_3); 7.38 (2H, m, *J* = 8, C_6H_4); 8.14 (2H, m, *J* = 8, C_6H_4); 8.45 (1H, s, =CH–)
3b	3079, 2239, 1585, 1537	7.53 (3H, m, C_6H_5); 7.92 (1H, s, =CH–); 8.07 (2H, m, C_6H_5)
3c	2231, 1583, 1543	7.54 (3H, m, C_6H_5); 7.89 (1H, s, =CH–); 8.07 (2H, m, C_6H_5)
3e	2235, 1594, 1542	6.18 (1H, tt, *J* = 54, *J* = 2, CF_2–H); 7.56 (3H, m, C_6H_5); 7.92 (1H, s, =CH–); 8.09 (2H, m, C_6H_5)
3f	3059, 3031, 2239, 1587, 1537	6.09 (1H, tt, *J* = 52, *J* = 5, CF_2–H); 7.52 (3H, m, C_6H_5); 7.89 (1H, s, =CH–); 8.07 (2H, m, C_6H_5)
4a	3391, 2951, 2215, 1585, 1531	2.32 (1H, br. m, OH); 2.38 (3H, s, CH_3); 3.85 (4H, m, $2CH_2$); 5.94 (1H, br. m, NH); 7.27 (1H, s, =CH–); 7.32 (2H, m, *J* = 8, C_6H_4); 7.89 (2H, m, *J* = 8, C_6H_4)
4b	3363, 2939, 2219, 1590, 1576, 1542	2.56 (1H, br. m, OH); 3.89 (4H, m, $2CH_2$); 6.09 (1H, br. s, NH); 7.25 (1H, s, =CH–); 7.59 (3H, m, C_6H_5); 8.04 (2H, m, C_6H_5)
4c	3411, 2943, 2211, 1577, 1529	2.40 (1H, br. s, OH); 3.89 (4H, m, $2CH_2$); 6.05 (1H, br. m, NH); 7.29 (1H, s, =CH–); 7.54 (3H, m, C_6H_5); 8.03 (2H, m, C_6H_5)
4e	3575, 3335, 3011, 2975, 2939, 2891, 2219, 1580, 1532	2.69 (1H, br. m, OH); 3.89 (4H, m, $2CH_2$); 6.12 (2H, tt, *J* = 54, *J* = 3, CF_2–H, br. m, NH); 7.27 (1H, s, =CH–); 7.54 (3H, m, C_6H_5); 8.05 (2H, m, C_6H_5)
4f	3539, 3383, 2223, 1580, 1573, 1537	2.43 (1H, br. t, *J* = 5, OH); 3.87 (4H, m, $2CH_2$); 6.07 (1H, br. m, NH); 6.17 (1H, tt, *J* = 52, *J* = 5, CF_2–H); 7.29 (1H, s, =CH–); 7.59 (3H, m, C_6H_5); 8.05 (2H, m, C_6H_5)
5a	2219, 1645, 1541, 1519	2.41 (3H, s, CH_3); 4.07 (4H, m, $2CH_2$); 5.81 (1H, s, =CH–); 7.34 (4H, m, C_6H_4)
5b	2243, 2648, 1536	4.05 (4H, m, $2CH_2$); 5.69 (1H, s, =CH–); 7.49 (5H, m, C_6H_5)
5c	2223, 1642, 1542	4.09 (4H, m, $2CH_2$); 5.72 (1H, s, =CH–); 7.52 (5H, m, C_6H_5)
5f	2223, 1648, 1536	4.05 (4H, m, $2CH_2$); 5.67 (1H, s, =CH–); 6.12 (1H, tt, *J* = 52, *J* = 5, CF_2–H); 7.52 (5H, m, C_6H_5)

* ^1H NMR spectrum recorded in DMSO-d_6.

in the range 4.03-4.09 ppm. The proton signals for the aryl substituent appear as a multiplet centred in the range 7.34-7.52 ppm. The signal for the pyridine ring hydrogen atom is seen as a singlet in the range 5.67-5.74 ppm, thus showing a characteristic high field shift when compared with the $C_{(5)}$ proton signal in the pyridines **2-4**.

EXPERIMENTAL

IR spectra were taken on a Specord IR-75 spectrometer using vaseline oil (NaCl prism, region 1500-1800 cm^{-1}) or hexachlorobutadiene (LiF prism, region 2000-3600 cm^{-1}). ^1H NMR spectra were recorded on a Bruker WH-90/DS (90 MHz) spectrometer with HMDS as internal standard. Monitoring of the reaction course

and the purity of the compounds obtained was carried out by TLC on Silufol UV-254 plates in the system ethanol–chloroform (1:9).

Characteristics of the synthesized compounds are reported in Tables 1 and 2.

6-Aryl-3-cyano-4-polyfluoroalkylpyridin-2-ones (2a-g). A mixture of the corresponding diketone **1a-g** (15 mmol), cyanoacetamide (1.5 g, 18 mmol), and ammonium acetate (1.4 g, 18 mmol) was refluxed in ethanol (5 ml) for 3-6 h. The reaction mixture was allowed to stand for 8 h at room temperature. The precipitate was recrystallized from a mixture of DMF and water (2:1) to give the yellowish, crystalline materials **2a-g**.

6-Aryl-2-chloro-3-cyano-4-polyfluoroalkylpyridines (3a-c,e,f). DMF (15 mmol) was added slowly to a solution of the pyridone **2a-c,e,f** (6 mmol) and freshly distilled $POCl_3$ (5 ml) at 125-130°C (oil bath) and then heated for 8 h. The product was cooled and gradually poured onto finely crushed ice (200 g). The precipitate was washed on the filter with water and recrystallized from ethanol to give the colorless, needle shaped crystalline pyridines **3a-c,e,f**.

6-Aryl-3-cyano-2-(2-hydroxyethylamino)-4-polyfluoroalkylpyridines (4a-c,e,f). A solution of the chloropyridine **3a-c,e,f** (3.5 mmol) and the corresponding amine (4.2 mmol) in dioxane (5 ml) was refluxed for 3-6 h and poured into water (100 ml). The precipitate was recrystallized from ethanol.

5-Aryl-8-cyano-7-polyfluoroalkyl-2,3-dihydroimidazo[1,2-*a*]pyridines (5a-c,f). A solution of the hydroxyethylaminopyridine **4a-c,f** (0.2 g) in $POCl_3$ (5 ml) was refluxed for 1 h. The reaction mixture was cooled to room temperature and poured onto finely crushed ice (50 g). The solution obtained was basified with an aqueous solution of ammonia to pH 8-9 and left for 1 h at room temperature. The precipitate was recrystallized from ethanol to give the dark red, crystalline imidazopyridines **5a-c,f**.

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