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SYNTHESIS OF SUBSTITUTED HEXAHYDROINDAZOLES

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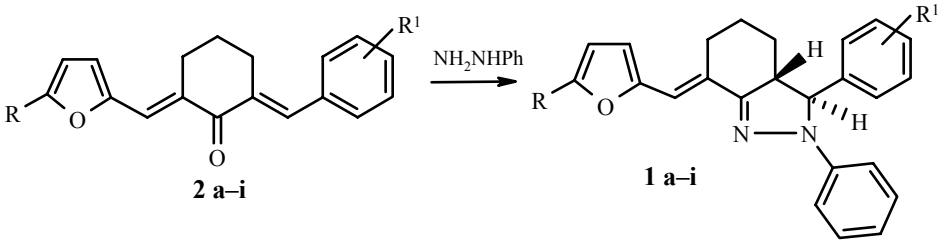
Substituted hexahydroindazoles were obtained by the reaction of 6-arylidene-2-furfurylidene-cyclohexanones with phenylhydrazine. It was concluded by means of the NMR spectra that azacyclization takes place regioselectively with participation of the arylidenecyclohexanone fragment.

Keywords: 6-arylidene-2-furfurylidenecyclohexanones, hydrazines, indazoles, α,β-unsaturated ketones, heterocyclization.

Compounds containing the hexahydroindazole fragment are biologically active and can be used as depressants of the central nervous system [1, 2] and antiinflammatory [3-5] and antimicrobial [6] agents. α,β-Unsaturated ketones are widely used in organic synthesis for the production of heterocyclic compounds. There are data on the synthesis of hexahydroindazoles by the reaction of alicyclic α,β-unsaturated ketones and their hetero analogs (2,6-diarylidene- and 2,6-difurfurylidenecyclanones [7-11], 3,5-diarylidenethiopyran-4-ones [12], 3,5-diarylidenepiperid-4-ones [3]) with hydrazines. The reactions of unsymmetrical arylidene-hetarylidenecyclanones with hydrazines have not been studied before.

In the present work we describe the synthesis and discuss the structure of the previously unknown 3-aryl-7-(5-R-furfurylidene)-2-phenyl-3,3a,4,5,6,7-hexahydroindazoles **1a-i**. Compounds **1a-i** were obtained by the reaction of our previously described [13] 6-arylidene-2-furfurylidenecyclohexanones **2a-i** with phenylhydrazine by boiling in alcohol solution with a ketone–phenylhydrazine ratio of 1:8. Here it was found that the nature of the substituent R^1 had a significant effect on the activity of the ketones **2** in the reaction and, consequently, on the yields of the products **1** (55-89%).

The hexahydroindazoles **1a**,**b**,**g**,**i** were obtained with the highest yields (82-89%). The yields of the products **1e**,**f** were significantly lower (55-62%) on account, probably, of the steric effect of the *ortho* substituent on the azacyclization process.



2 a–i **1 a–i**

a R = R^1 = H; **b** R = H, R^1= 3-NO_2; **c** R = H, R^1 = 4-OMe; **d** R = H, R^1 = 4-Br; **e** R = H, R^1 = 2-Cl; **f** R = H, R^1 = 2-F; **g** R = Me, R^1 = 3-NO_2; **h** R = Me, R^1 = H; **i** R = NO_2, R^1 = H

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TABLE 1. The Characteristics of Hexahydroindazoles **1a-i**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1a	$C_{24}H_{22}N_2O$	81.30 / 81.36	6.39 / 6.21	8.28 / 7.91	135-136	82
1b	$C_{24}H_{21}N_3O_3$	71.89 / 72.18	5.67 / 5.26	10.48 / 10.52	218-220	89
1c	$C_{25}H_{24}N_2O_2$	78.16 / 78.13	6.63 / 6.25	7.12 / 7.29	131-132	74
1d*	$C_{24}H_{21}BrN_2O$	66.47 / 66.51	4.86 / 4.85	6.84 / 6.47	166-167	62
1e*[2]	$C_{24}H_{21}ClN_2O$	74.43 / 74.13	5.77 / 5.40	7.50 / 7.21	123-124	61
1f	$C_{24}H_{21}FN_2O$	77.00 / 77.42	5.85 / 5.65	7.58 / 7.53	119-120	55
1g	$C_{25}H_{23}N_3O_3$	72.73 / 72.63	5.86 / 5.55	10.54 / 10.16	226-227	82
1h	$C_{25}H_{24}N_2O$	81.52 / 81.36	6.46 / 6.80	7.60 / 7.88	155-157	74
1i	$C_{24}H_{21}N_3O_3$	72.41 / 72.18	5.52 / 5.26	10.08 / 10.52	162-164	86

* Found %: Br 18.65. Calculated %: Br 18.48.

*[2] Found %: Cl 9.39. Calculated %: Cl 9.14.

The composition and structure of compounds **1a-i** (Table 1) were confirmed by the results from elemental analysis and also by data from the ^1H and ^{13}C NMR spectra.

The IR spectra of the synthesized compounds contain the vibrations of the C–H bonds of the aromatic and aliphatic fragments at 3072-3100 and 2864-2980 cm^{-1} respectively, a wide group of unresolved bands for the vibrations of the conjugated system of bonds C=C–C=N and the aromatic fragments of the molecules at 1595-1610 cm^{-1}, and also bands for the vibrations of the =C–O–C= bonds of the furan ring at 1032-1028 and 1245-1252 cm^{-1}.

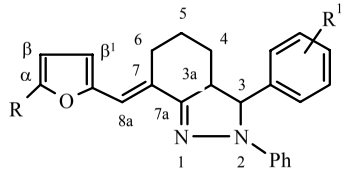
It was established by means of the ^1H NMR spectra that azacyclization takes place regioselectively with the participation of the conjugated system of bonds C=C–C=O of the arylidenecyclohexanone fragment. In the ^1H NMR spectra of the indazoles (Table 2) the signal of the methine proton at the C(3) atom is in the region of 4.52-5.20 ppm in the form of a doublet. The strong effect of the nature and position of the substituent R^1 in the aryl radical on the position of this signal is noted: In the presence of an electron-donating group (4-OMe) this signal lies at 4.52 ppm (compound **4c**), and electron-withdrawing substituents at the *meta* (NO_2, compounds **1b**,**g**) and particularly at the *ortho* position (F, Cl, compounds **1e**,**f**) shift the signal downfield (4.87 and 5.20 ppm respectively).

Such a strong effect on the chemical shift of the C(3)–H proton can be explained by its proximity to the aryl substituent only in the case of the formation of 3-aryl-7-furfurylidene-2-phenyl-3,3a,4,5,6,7-hexahydroindazoles **1**.

The position of the furfurylidene proton (=CH) is determined by the type of substituent R at position 5 of the furan ring. Thus, if R = H or Me this proton is at 6.39-6.50 ppm (compounds **1a-h**), and if R = NO_2 (compound **1i**) it is shifted downfield (6.98 ppm). However, substituents in the furan ring do not have any effect on the position of the methine proton at the C(3) atom.

The signals of the vicinal protons at the C(3) and C(3a) atoms with spin–spin coupling constants of 13-15 Hz indicate their *trans*-diaxial arrangement, which corresponds to data in [14] on the structure of the similarly constructed hexahydrothiopyranopyrazole.

TABLE 2. The ^{1}H NMR Spectra of Hexahydroindazoles **1a-i**



Com-pound	Chemical shifts, δ, ppm (SSCC, *J*, Hz)								
	H-3 (1H, d)	H-3a (1H, m)	=CH–Het (1H, s)	H-4 (2H, m)	H-5 (2H, m)	H-6 (2H, m)	H_{Ar}	H_{Fur}: β (1H, m); β^1 (1H, m); α (1H, m)	Other signals
1a	4.62 (*J* = 15)	3.20	6.50	2.00-2.20	1.50-1.70	2.90	7.00-7.40 (10H, m)	6.45, 6.72, 7.50	—
1b	4.85 (*J* = 15)	3.22	6.50	2.00-2.20	1.50-1.80	3.05	7.00, 7.65-8.30 (9H, m)	6.50, 6.80, 7.50	—
1c	4.52 (*J* = 15)	3.24	6.50	2.00-2.20	1.53-1.74	2.92	6.90-7.30 (9H, m)	6.45, 6.72, 7.50	3.80 (3H, s, OCH_3)
1d	4.60 (*J* = 15)	3.22	6.50	2.00-2.15	1.50-1.82	2.85	6.92-7.35 (9H, m)	6.45, 6.75, 7.50	—
1e	5.20 (*J* = 15)	3.22	6.50	2.00-2.40	1.52-1.84	3.05	6.84-7.45 (9H, m)	6.42, 6.74, 7.50	—
1f	4.87 (*J* = 15)	3.18	6.42	2.08-2.32	1.51-1.60	2.94	7.00 (9H, m)	6.36, 7.00*, 7.40	—
1g	4.63 (*J* = 13)	3.25	6.39	2.07-2.18	1.50-1.73	2.80	6.79-8.24 (9H, m)	6.02, 6.28	2.30 (3H, s, CH_3)
1h	4.54 (*J* = 13)	3.22	6.43	1.80-2.20	1.42-1.73	2.94	6.77-7.36 (10H, m)	6.04, 6.27	2.32 (3H, s, CH_3)
1i	4.76 (*J* = 13)	3.19	6.98	1.98-2.64	1.50-1.82	3.00	6.89, 7.09-7.25 (10H, m)	7.64, 6.78	—

* The signal overlaps with the signals of the aromatic protons.

Thus, of the two possible alternatives azacyclization in the reaction of arylidenefurfurylidene-cyclohexanones with phenylhydrazine takes place with participation of the arylidene fragment of the molecule, leading to the formation of 3-aryl-7-furfurylidene-2-phenyl-3,3a,4,5,6,7-hexahydroindazoles.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer (300 and 75 MHz respectively) in DMSO-d_6 with TMS as internal standard. The IR spectra were recorded on an FSM-1201 infrared Fourier spectrometer. The reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates with 3:1:1 hexane–diisopropyl ether–chloroform as eluant, iodine vapor as developer, and UV radiation.

7-Furfurylidene-2,3-diphenyl-3,3a,4,5,6,7-hexahydroindazole (1a). To a solution of 6-benzylidene-2-furfurylidenecyclohexanone (**2a**) (3 g, 0.01 mol) in isopropyl alcohol (20 ml) we added a solution of phenylhydrazine (4 g, 0.08 mol) in isopropyl alcohol (10 ml), and we refluxed the mixture for 1 h. The reaction mass was cooled and kept for 24 h. The crystals that separated were washed with isopropyl alcohol and recrystallized from isopropyl alcohol. ^{13}C NMR spectrum, δ, ppm: 72.72 (C(3)), 56.31 (C(3a)), 27.97 (C(4)), 22.98 (C(5)), 27.79 (C(6)), 119.72 (C(7)), 143.27 (C(7a)), 125.96 (C(8)).

Hexahydroindazoles (1b-i). These compounds were obtained similarly.

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