Chemistry of Heterocyclic Compounds, Vol. 46, No. 11, February, 2011 (Russian Original Vol. 46, No. 11, November, 2010)

POLYFLUOROALKYLATION AND ALKENYLATION OF 1-BENZYL-1H-INDAZOL-3-OL

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The polyfluoroalkylation and alkenylation of 1-benzyl-1H-indazol-3-ol by halopolyfluoroalkanes and fluorinated olefins has been studied. It was shown that only reactions proceeding with the participation of difluorocarbene lead to a mixture of N- and O-alkylation products. In all other cases, interaction with halopolyfluoroethanes and polyfluoroalkenes forms O-polyfluoroalkyl and alkenyl derivatives of indazolol.

Keywords: dibromodifluoromethane, 1,2-dibromotetrafluoroethane, 1,2-dichlorodifluoroethylene, chlorodifluoromethane, 1,1-difluoroethylene, indazol-3-ol, tetrafluoroethylene, 1,1,2-trichlorotrifluoroethane, chlorotrifluoroethylene, polyfluoroalkylation, fluoroalkenylation.

Five-membered heterocyclic compounds with alkoxyfluorinated substituents have been little studied in spite of the fact that α,α,α-trifluoroanisole was synthesized for the first time in 1955 [1], and α-fluoroalkylphenyl ethers of the benzene series have been well investigated in more recent times and have wide practical application [2]. Among this class of compounds only the trifluoromethoxy derivatives of indole and benzofuran may be mentioned, synthesized by adding trifluoromethyl hypofluorite and subsequent fission of dehydrofluorination [3], and difluoromethoxy derivatives of pyrazole (including the herbicide Pyraflufenethyl [2]), obtained by the action of difluorocarbene, generated from chlorodifluoromethane [4, 5].

In the present work we have studied the alkylation and alkenylation of 1-benzyl-1H-indazol-3-ol (**1a**) with halopolyfluoroalkanes and polyfluoroalkenes. The selection of such a subject for investigation was caused by the fact that indazole derivatives possess a broad spectrum of biological activity (anti-inflammatory and antibacterial [6-8], antitumor, and cytostatic [9, 10]), and most of all, the preparation Benzydamine hydrochloride is used in clinical practice as a nonsteroidal anti-inflammatory agent [11]. It is known that 1-substituted indazol-3-ols with alkyl sulfates, alkyl halides, or diazomethane give a mixture of products of O-and N-alkylation, with 3-dimethylaminopropylbenzene sulfonate only the product of O-alkylation, and with acrylonitrile and ethyl acrylate the product of addition at the nitrogen atom [12].

We have found that the reaction of 1-benzylindazol-3-ol (**1a**) with difluorocarbene, generated from chlorodifluoromethane, proceeds unselectively, although in high overall yield (~80%), and a mixture is formed of the products of O- and N-alkylation **2** and **3** in a ratio of 5:4 (Scheme 1). Compounds **2** and **3** differ substantially in physical properties and may be separated by column chromatography.

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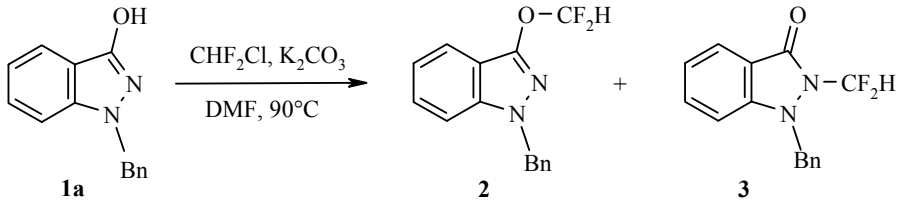
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1649-1658, November, 2010. Original article submitted February 1, 2010.

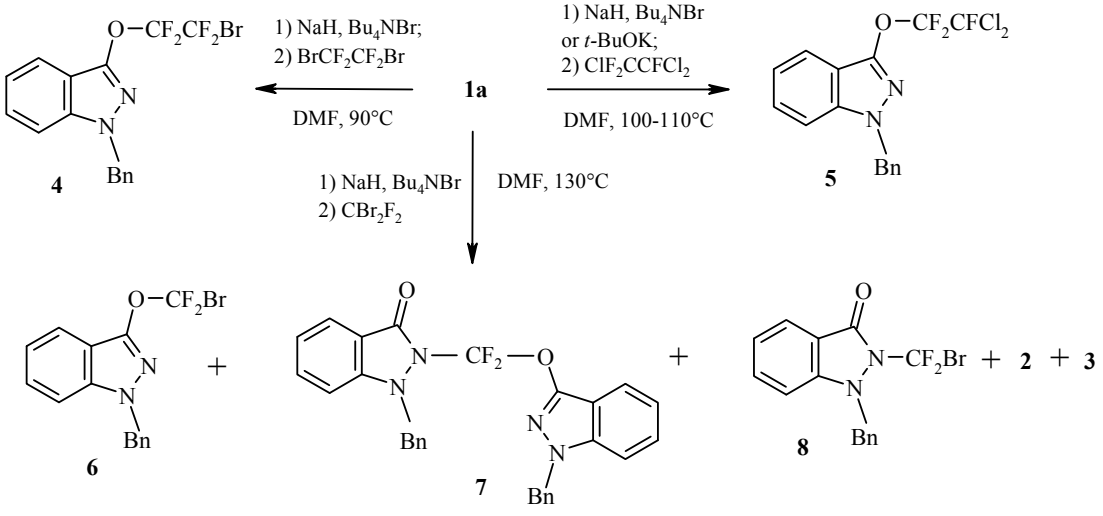
Scheme 1



The addition of polyfluorohaloalkyl groups to various heteroatoms was made possible by the halophilic polyfluoroalkylation reaction [13]. In [14] it was shown that the use of tetrabutylammonium salts as catalyst enabled such reactions to be carried out in high yield and selectivity. We established that the interaction of the sodium salt of indazolol **1a** with 1,2-dibromotetrafluoroethane or 1,1,2-trichlorotrifluoroethane leads to the formation of the products of O-alkylation **4** and **5** (Scheme 2). The nucleophilicity of the indazolol is less, consequently the reaction occurs under rigorous conditions, in which it is accompanied by partial resinification of the substrate. 1,1,2-Trichloro-trifluoroethane and the potassium salt of indazolol **1a** react practically in the same way.

On interacting the sodium salt of indazolol **1a** with dibromodifluoromethane a more complex picture was observed (Scheme 2). The reaction was prolonged at a much higher temperature, and was characterized by a lower overall yield (32%) and lower selectivity. The main fluorine-containing products were the O-bromodifluoromethyl **6** and the O-difluoromethyl **2** derivatives, and also compound **7**, in which the difluoromethylene group is combined with the oxygen atom of one and the nitrogen atom of another indazole ring. The formation of small quantities of N-bromodifluoromethyl (**8**) and N-difluoromethyl derivatives **3** was also observed. The selectivity of this reaction is low in comparison with the interaction given above with halo-fluoroethanes, probably due to the fact that according to a halophilic mechanism, in the first case a fluoroethylene, and in the latter a far more reactive difluorocarbene is formed [15].

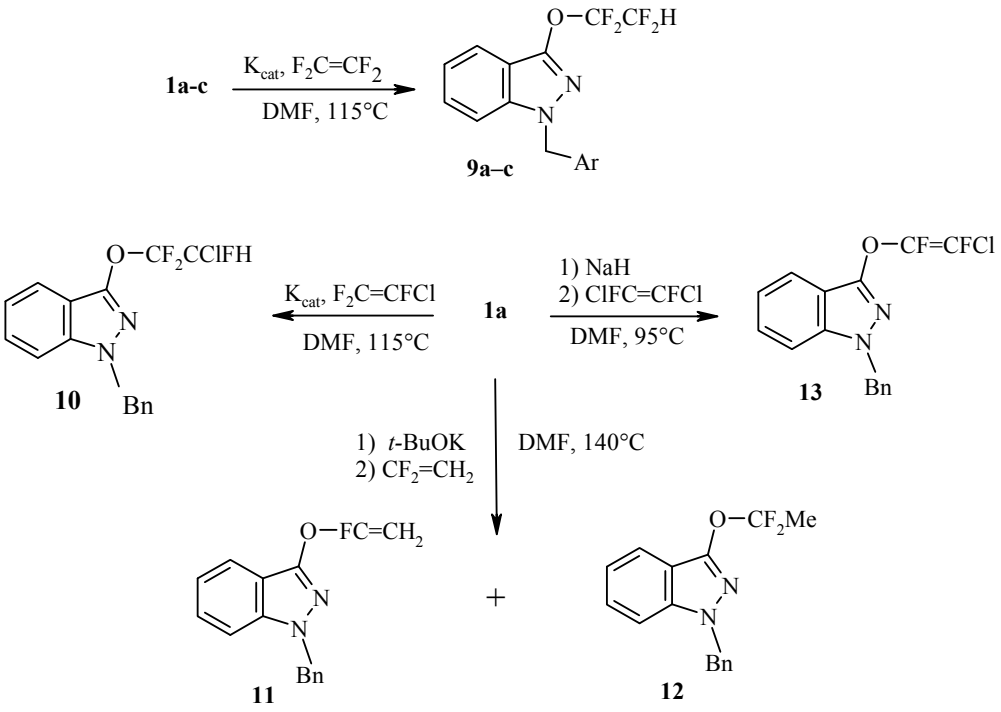
Scheme 2



A convenient method of introducing polyfluoroalkyl groups at the heteroatom (oxygen, nitrogen, sulfur) is the addition of fluorinated olefins catalyzed by bases [16]. Interaction of indazolols **1a-c** (in the presence of catalytic quantities of their potassium derivatives K_{cat}) with tetrafluoroethylene or chlorotrifluoroethylene leads

to the corresponding O-fluoroalkyl derivatives **9a-c** and **10** (Scheme 3). When carrying out the analogous process with catalytic amounts of base, 1,1-difluoroethylene was fairly reactive but its reaction with the potassium salt of indazolol **1a** was accompanied by dehydrofluorination and led to the formation of olefin **11** as the main product, together with insignificant contamination by addition product **12**. The sodium salt of indazolol **1a** reacts analogously with 1,2-dichlorodifluoroethane, but hydrogen chloride is eliminated more effectively and leads in high yield to olefin **13** (Scheme 3). A mixture of *cis* and *trans* olefins in a 1:1 ratio was used in the reaction. The product was a mixture of olefins in the same ratio, the separation of which by distillation or chromatographically was unsuccessful.

Scheme 3



1, 9 a Ar = Ph, **b** Ar = 4-$MeOC_6H_4$, **c** Ar = 2-pyridyl

We have attempted to debenzylate indazoles **9a-c**. It turned out that compounds **9a**,**c** were stable towards catalytic hydrogenation (10% Pd on carbon) at atmospheric pressure. They were also stable towards alkaline (boiling in 10% K_2CO_3 aqueous solution) and acidic hydrolysis (boiling in trifluoroacetic acid or in 10% aqueous HCl solution). Indazole **14** could to be obtained by the action of trifluoroacetic acid on N-*p*-methoxybenzyl derivative **9b** (Scheme 4).

Scheme 4

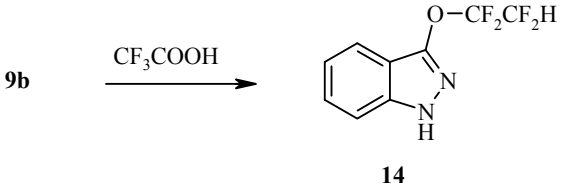


TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				Bp, °C (0.1 mm Hg) [Mp, °C]	Yield, %
		C	H	Br (Cl)	N		
2	$C_{15}H_{12}F_2N_2O$	65.78 / 65.69	4.36 / 4.42		10.13 / 10.22	117	45 (9*)
3	$C_{15}H_{12}F_2N_2O$	65.80 / 65.69	4.25 / 4.42		10.27 / 10.22	[52-53]	36 (2*)
4	$C_{16}H_{11}BrF_4N_2O$	47.55 / 47.66	2.52 / 2.76	19.96 / 19.82	6.95 / 6.95	133 [29-30]	60
5	$C_{16}H_{11}Cl_2F_3N_2O$	51.28 / 51.21	2.95 / 2.96	(18.50) / (18.90)	7.49 / 7.47	140 [37-38]	—*[2]
6	$C_{15}H_{11}BrF_2N_2O$	50.81 / 51.01	3.39 / 3.15	22.39 / 22.62	8.12 / 7.93	[28-9]	12
7	$C_{29}H_{22}F_2N_4O_2$	69.91 / 70.14	4.42 / 4.47		11.30 / 11.29		7
8	$C_{15}H_{11}BrF_2N_2O$			22.32 / 22.62		[54-55]	2
9a	$C_{16}H_{12}F_4N_2O$	58.91 / 59.25	3.50 / 3.74		8.54 / 8.65	125	85
9b	$C_{17}H_{14}F_4N_2O_2$	57.94 / 57.62	4.10 / 3.99		7.82 / 7.91	130	85
9c	$C_{15}H_{11}F_4N_3O$	55.55 / 55.38	3.55 / 3.42		12.81 / 12.92	107	82
10	$C_{16}H_{12}ClF_3N_2O$	56.51 / 56.39	3.50 / 3.56	(10.67) / (10.40)	8.20 / 8.22	133	95
11	$C_{16}H_{13}FN_2O$	71.67 / 71.62	5.12 / 4.89		10.40 / 10.44	115	38
12	$C_{16}H_{14}F_2N_2O$				10.01 / 9.72		5
13	$C_{16}H_{11}ClF_2N_2O$	59.67 / 59.91	3.38 / 3.46	(11.38) / (11.05)	8.61 / 8.74	125	89
14	$C_9H_6F_4N_2O$	46.07 / 46.16	2.53 / 2.58		11.74 / 11.96	[97–98]	97

*Yield of product in the reaction with CBr_2F_2.

*[2]Yield of product using **1a** sodium salt was 70%, using **1a** potassium salt 74%.

The compositions and structures of the obtained compounds were confirmed by the elemental analysis data, chromato-mass spectroscopy, and by ^1H and ^{19}F NMR spectra (Tables 1-3).

In the IR spectra of carbonyl-containing compounds **3, 7**, and **8** an intense $\nu_{C=O}$ absorption band was observed at 1720-1730 cm^{-1}, and this was missing for the remaining compounds.

It is extremely remarkable that in the ^1H NMR spectra the singlet signal of the methylene group of the arylmethylene fragment was observed for the carbonyl-containing compounds **3, 7**, and **8** in the 4.77-4.92 ppm range, and in the alkoxy- and alkenoxy derivatives at lower field (5.36-5.76 ppm). In the spectrum of compound **2**, the signal of the difluoromethyl group has a F–H coupling constant characteristic to difluoromethyl ethers [17], However in the spectrum of its isomer **3,** it was characteristic to N-difluoromethyl derivatives [18]. In addition, one of the aromatic protons of the synthesized compounds was displayed as a doublet signal at more lower field (7.60-7.81 ppm) than the remaining (if the signals of the pyridyl fragment of compound **9c** are discounted). Evidently, this proton is in the position 4 of the indazole ring, since precisely it may test the deshielding influence of the sterically close carbonyl oxygen atom, and also of the fluoroalkoxy or fluoroalkenoxy groups.

The interaction of 1-arylmethyl-1H-indazol-3-ols with halopolyfluoroethanes and polyfluoroalkenes is therefore directed on the oxygen atom. However, the reaction involving difluorocarbene has a low selectivity

and leads to a mixture of N- and O-alkylation products. The investigated reactions are a convenient and general method for the synthesis of previously unknown indazoles with various polyfluoroalkoxy and fluoroalkenoxy substituents.

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds*

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
2	5.38 (2H, s, CH_2); 7.04 (1H, t, $^2J_{H,F}$ = 73.2, $OCHF_2$); 7.08-7.30 (8H, m, H Ar); 7.62 (1H, d, $^3J_{H,H}$ = 8.4, H-4)
3	4.86 (2H, s, CH_2); 7.07-7.17 (7H, m, H Ar); 7.21 (1H, t, $^2J_{H,F}$ = 58.2, $NCHF_2$); 7.51 (1H, t, $^3J_{H,H}$ = 7.8, H Ar); 7.68 (1H, d, $^3J_{H,H}$ = 7.8, H-4)
4	5.65 (2H, s, CH_2); 7.25-7.33 (6H, m, H Ar); 7.51 (1H, t, $^3J_{H,H}$ = 8.4, H Ar); 7.64 (1H, d, $^3J_{H,H}$ = 8.4, H-7); 7.81 (1H, d, $^3J_{H,H}$ = 8.4, H-4)
5	5.65 (2H, s, CH_2); 7.25-7.33 (6H, m, H Ar); 7.51 (1H, t, $^3J_{H,H}$ = 8.4, H Ar); 7.65 (1H, d, $^3J_{H,H}$ = 8.4, H-7); 7.81 (1H, d, $^3J_{H,H}$ = 8.4, H-4)
6	5.48 (2H, s, CH_2); 7.09-7.33 (8H, m, H Ar); 7.52 (1H, d, $^3J_{H,H}$ = 8.4, H-4)
7	4.77 (2H, s, CH_2); 5.38 (2H, s, CH_2); 7.00-7.30 (15H, m, H Ar); 7.48 (1H, t, $^3J_{H,H}$ = 7.8, H Ar); 7.68 (1H, d, $^3J_{H,H}$ = 7.8, H-4); 7.81 (1H, d, $^3J_{H,H}$ = 8.4, H-4')
8	4.92 (2H, s, CH_2); 7.03-7.17 (7H, m, H Ar); 7.50 (1H, t, $^3J_{H,H}$ = 7.8, H Ar); 7.68 (1H, d, $^3J_{H,H}$ = 7.8, H-4)
9a	5.62 (2H, s, CH_2); 6.97 (1H, tt, $^2J_{H,F}$ = 52.8, $^3J_{H,F}$ = 2.7, CHF_2); 7.22-7.32 (6H, m, H Ar); 7.49 (1H, t, $^3J_{H,H}$ = 8.4, H Ar); 7.65 (1H, d, $^3J_{H,H}$ = 7.8, H-7); 7.78 (1H, d, $^3J_{H,H}$ = 8.4, H-4)
9b	3.76 (3H, s, OCH_3); 5.36 (2H, s, CH_2); 6.05 (1H, tt, $^2J_{H,F}$ = 52.8, $^3J_{H,F}$ = 2.7, CHF_2); 6.75 (2H, d, $^3J_{H,H}$ = 8.4, H Ar); 7.01-7.31 (5H, m, H Ar); 7.60 (1H, d, $^3J_{H,H}$ = 8.4, H-4)
9c	5.59 (2H, s, CH_2); 6.08 (1H, tt, $^2J_{H,F}$ = 52.8, $^3J_{H,F}$ = 2.7, CHF_2); 6.84 (1H, d, $^3J_{H,H}$ = 8.4, H-7); 7.10-7.21 (2H, m, H Ar); 7.32-7.34 (2H, m, H Ar); 7.52 (1H, t, $^3J_{H,H}$ = 4.2, H Ar); 7.64 (1H, d, $^3J_{H,H}$ = 8.4, H-4); 8.52 (1H, d, $^3J_{H,H}$ = 3.4, H Ar)
10	5.63 (2H, s, CH_2); 7.24-7.32 (6H, m, H Ar); 7.48 (1H, dt, $^2J_{H,F}$ = 45.9, $^3J_{H,F}$ = 4.8, CHClF); 7.49 (1H, t, $^3J_{H,H}$ = 8.4, H Ar); 7.65 (1H, d, $^3J_{H,H}$ = 8.4, H-7); 7.78 (1H, d, $^3J_{H,H}$ = 8.4, H-4)
11	4.14 (1H, dd, $^3J_{H,F}$ = 39.8, $^2J_{H,H}$ = 4.8, CF=CH *trans*); 4.28 (1H, dd, $^3J_{H,F}$ = 4.7, $^2J_{H,H}$ = 4.8, CF=CH *cis*); 5.58 (2H, s, CH_2); 7.18-7.33 (6H, m, H Ar); 7.49 (1H, t, $^3J_{H,H}$ = 8.4, H Ar); 7.68-7.77 (2H, m, H Ar)
12	2.04 (3H, t, $^3J_{H,F}$ = 13.5, CH_3); 5.76 (2H, s, CH_2); 7.09-7.30 (8H, m, H Ar); 7.90 (1H, d, $^3J_{H,H}$ = 8.4, H-4)
13	5.58 (2H, s, CH_2); 7.00-7.28 (8H, m, H Ar); 7.61 (1H, d, $^3J_{H,H}$ = 8.4, H-4)
14	6.09 (1H, tt, $^2J_{H,F}$ = 52.8, $^3J_{H,F}$ = 2.7, CHF_2); 7.16-7.19 (1H, m, H-5); 7.39-7.40 (2H, m, H-6,7); 7.66 (1H, d, $^3J_{H,H}$ = 8.4, H-4); 10.23 (1H, br. s, NH)

*^{1}H NMR spectra were taken in DMSO-d_6 (compounds **2-5**, **9a**, **10-12**) and $CDCl_3$ (compounds **6-8**, **9b,c**, **13**, **14**).

EXPERIMENTAL

The IR spectra were obtained on a UR-20 instrument in KBr disks (crystalline compounds **3** and **8**) and in a thin film on a KBr disk (compound **7**). ^{1}H NMR spectra were recorded on a Varian VXR-300 (300 MHz) instrument, internal standard was TMS. The ^{19}F NMR spectra were obtained on a Varian Gemini 200 (188 MHz) instrument, internal standard was trichlorofluoromethane. The chromato-mass spectra (GC/MS) were described on a Hewlett-Packard HP GC/MS 5890/5972 spectrometer (EI 70 eV) with a HP-5MS column, HP part number 19091S-102. Melting points were determined on a Stuart Scientific SMP3 instrument. A check on the progress of reactions was effected by TLC on Silufol UV-254 plates. Silica gel MN-Kieselgel-60 was used for column chromatography, and TLC plates precoated with SI F 10×20 cm (Riedel-de Haën), layer thickness 0.25 mm, were used for preparative TLC.

DMF was distilled over CaH_2 directly before use.

TABLE 3. ^{19}F NMR Spectra of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm (*J*, Hz)*
2	-84.77 (2F, d, $^2J_{F,H}$ = 73.2, $OCHF_2$)
3	-103.37 (2F, d, $^2J_{F,H}$ = 58.2, $NCHF_2$)
4	-69.08 (2F, s, $CBrF_2$); -87.01 (2F, s, OCF_2)
5	-75.41 (1F, s, CCl_2F); -84.57 (2F, s, OCF_2)
6	-18.14 (2F, s, $OCBrF_2$)
7	-60.57 (2F, s, OCF_2N)
8	-18.30 (2F, s, $NCBrF_2$)
9a	-89.59 (2F, s, OCF_2); -138.00 (2F, d, $^2J_{F,H}$ = 52.8, CHF_2)
9b	-89.79 (2F, s, OCF_2); -137.20 (2F, d, $^2J_{F,H}$ = 52.8, CHF_2)
9c	-89.20 (2F, s, OCF_2); -137.55 (d, $^2J_{F,H}$ = 52.8, CHF_2)
10	-83.18 (2F, s, OCF_2); -154.69 (1F, d, $^2J_{F,H}$ = 45.9, CHClF)
11	-82.35 (1F, dd, $^3J_{F,H\ trans}$ = 39.8, $^3J_{F,H\ cis}$ = 4.7, $OCF{=}CH_2$)
12	-61.77 (2F, quin., $^3J_{F,H}$ = 13.5, OCF_2CH_3)
13	-120.29 (1F, d, $^2J_{F,F}$ = 38.7, =CClF, *cis*), -118.30 (1F, d, $^2J_{F,F}$ = 119.3, =CClF, *trans*), -128.25 (1F, d, $^2J_{F,F}$ = 38.7, OCF=, *cis*), -133.45 (1F, d, $^2J_{F,F}$ = 119.3, OCF=, *trans*)
14	-88.92 (2F, s, OCF_2); -137.30 (2F, d, $^2J_{F,H}$ = 52.8, CHF_2)

*^{19}F NMR spectra were taken in DMSO-d_6 (compounds **2-5**, **9a**, **10-12**) and in $CDCl_3$ (compounds **6-8**, **9b**,**c**, **13**, **14**).

Alkylation of Indazol-3-one with Benzyl Chlorides. Indazol-3-one (4 g, 30 mmol) was added to a solution obtained from NaOH (1.2 g, 30 mmol) (in the case of compound **1c** (2.4 g, 60 mmol)) and water (30 ml) and the mixture heated at 35°C until solution occurred. The appropriate benzyl chloride (30 mmol) was added (in the case of **1c** 2-chloromethylpyridine hydrochloride was used), and the mixture heated at 70°C for 2-3 h. The reaction mixture was cooled. The solid was filtered off, washed with water, and air dried. The product was crystallized from a heptane–benzene, 3:1, mixture.

1-Benzyl-1H-indazol-3-ol (1a). Yield was 5.23 g (78%); mp 167-168°C [19].

1-(*p*-Methoxybenzyl)-1H-indazol-3-ol (1b). Yield was 3.12 g (41%); mp 159-160°C [6].

1-(2-Pyridylmethyl)-1H-indazol-3-ol (1c). Yield was 4.52 g (67%). Pale-yellow crystalline substance; mp 156-157°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 5.41 (2H, s, CH_2); 6.90-7.33 (5H, m, H Ar); 7.47 (1H, t, $^3J_{H,H}$ = 7.8, H Ar); 7.68 (1H, d, $^3J_{H,H}$ = 7.8, H-4); 8.50 (1H, d, $^3J_{H,H}$ = 3.4, H Ar); 10.20 (1H, br. s, OH). Found, %: C 69.28; H 5.00; N 18.50. $C_{13}H_{11}N_3O$. Calculated, %: C 69.32; H 4.92; N 18.65.

Interaction of Indazolol 1a with Chlorodifluoromethane. Anhydrous K_2CO_3 (3.7 g, 26.8 mmol) was added to a solution of indazolol **1a** (2.0 g, 8.9 mmol) in anhydrous DMF (25 ml) and chlorodifluoromethane was bubbled through for 6 h with vigorous stirring and heating at 90°C. The reaction mixture was cooled, poured into water (100 ml), and extracted with CH_2Cl_2 (3×50 ml). The extract was washed with water (5×25 ml), dried over $MgSO_4$, the solvent distilled off in vacuum (15 mm Hg), and the residue chromatographed on a column of SiO_2 (eluent CH_2Cl_2).

1-Benzyl-3-difluoromethoxy-1H-indazole (2). Yield was 1.10 g, colorless oily substance, R_f 0.8. Mass spectrum, *m/z* (I_{rel}, %): 274 $[M]^+$ (25), 91 $[PhCH_2]^+$ (100).

1-Benzyl-2-difluoromethyl-1,2-dihydro-3H-indazol-3-one (3). Yield was 0.88 g, white crystalline substance, R_f 0.5. IR spectrum, ν, cm^{-1}: 1720 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 274 $[M]^+$ (100), 223 $[M\text{-}CF_2H]^+$ (18).

Interaction of Indazolol 1a with 1,2-Dibromotetrafluoroethane and 1,1,2-Trichlorotrifluoroethane. A. NaH (60% in vaseline oil) (0.2 g, 5 mmol) was added to a solution of indazolol **1a** (1.12 g, 5 mmol) in anhydrous DMF (50 ml) and the mixture was stirred at room temperature until the end of hydrogen

evolution (2 h). Tetrabutylammonium bromide (0.02 g, 0.05 mmol) and dibromotetrafluoroethane (3.9 g, 15 mmol), or 1,1,2-trichlorotrifluoroethane (2.8 g, 15 mmol) were added and the mixture was heated for 30 h at 90°C (in the case of indazole **4**) or 48 h at 110°C (in the case of indazole **5**). The reaction mixture was cooled, poured into water (150 ml), extracted with CH_2Cl_2 (4 x 50 ml), the extract was washed with water (5×40 ml), dried with $MgSO_4$, the solvent was distilled off in vacuum (15 mm Hg), and the residue chromatographed on a column of SiO_2 (eluent CH_2Cl_2).

B. Potassium *tert*-butylate (0.34 g, 3 mmol) was added to a solution of indazolol **1a** (0.67 g, 3 mmol) in anhydrous *tert*-butanol (15 ml) and the mixture stirred at room temperature for 2 h. The solvent was distilled at reduced pressure (15 mm Hg), the residue of solvent was removed in vacuum (6 h, 40°C, 0.05 mm Hg). To the **1a** potassium salt obtained in this way was added anhydrous DMF (25 ml), 1,1,2-trichloro-trifluoroethane (1.69 g, 9 mmol) and the mixture was heated at 100°C for 48 h. The reaction mixture was then processed as in procedure A.

1-Benzyl-3-(2-bromo-1,1,2,2-tetrafluoroethoxy)-1H-indazole (4). Yield 1.21 g (method A). White crystalline or colorless oily substance. R_f 0.8. Mass spectrum, *m/z* (I_{rel}, %): 403 $[M]^+$ (100), 223 $[M\text{-}CF_2CF_2Br]^+$ (25), 91 $[PhCH_2]^+$ (82).

1-Benzyl-3-(2,2-dichloro-1,1,2-trifluoroethoxy)-1H-indazole (5). Yield 1.31 g (method A) and 0.83 g (method B), white crystalline substance, R_f 0.8. Mass spectrum, *m/z* (I_{rel}, %): 376 $[M(^{37}Cl)^+$ (8), 374 $[M]^+$ (21), 223 $[M\text{-}CF_2CFCl_2]^+$ (10), 91 $[PhCH_2]^+$ (100).

Interaction of Indazolol 1a and Dibromodifluoromethane. Sodium hydride (60% in vaseline oil) (0.2 g, 5 mmol) was added to a solution of indazolol **1a** (1.12 g, 5 mmol) in anhydrous DMF (50 ml) and the mixture was stirred at room temperature until the end of hydrogen evolution (2 h). Tetrabutylammonium bromide (0.02 g, 0.05 mmol) and dibromodifluoromethane (5.25 g, 25 mmol) were added and the mixture was heated for 80 h at 130°C. The reaction mixture was cooled, poured into water (150 ml), extracted with CH_2Cl_2 (4×50 ml), the extract washed with water (5×40 ml), dried over $MgSO_4$, the solvent was distilled in vacuum (15 mm Hg), and the residue chromatographed on a column of SiO_2 (eluent CH_2Cl_2–hexane, 10:15).

1-Benzyl-3-bromodifluoromethoxy-1H-indazole (6). Additionally purified by preparative TLC (eluent CH_2Cl_2–hexane, 10:15). Yield 0.21 g. Colorless oily substance. R_f 0.6. Mass spectrum, *m/z* (I_{rel}, %): 353 $[M]^+$ (26), 223 $[M\text{-}CF_2Br]^+$ (19), 91 $[PhCH_2]^+$ (100).

1-Benzyl-2-[(1-benzyl-1H-indazol-3-yloxy)difluoromethyl]-1,2-dihydroindazol-3-one (7). Yield 0.09 g, colorless oily substance. R_f 0.2. IR spectrum, ν, cm^{-1}: 1730 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 496 $[M]^+$ (40), 91 $[PhCH_2]^+$ (100).

1-Benzyl-2-bromodifluoromethyl-3H-indazol-3-one (8). Additionally purified by preparative TLC (eluent CH_2Cl_2–hexane, 10:15). Yield 0.03 g. White crystalline substance, R_f 0.4. IR spectrum, ν, cm^{-1}: 1720 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 353 $[M]^+$ (100), 223 $[M\text{-}CF_2Br]^+$ (25).

Also isolated were compounds **2** (yield 0.12 g, R_f 0.5) and **3** (yield 0.03 g, R_f 0.35), which, according to ^1H, ^{19}F NMR data and chromato-mass spectra, were identical to samples obtained in the reaction with chlorodifluoromethane.

Interaction of Indazolols 1a-c with Tetrafluoroethylene and of Indazolol 1a with Chlorotrifluoroethylene. Metallic potassium (0.2 g, 0.5 mmol) was added to a solution of the appropriate indazolol **1a-c** (5 mmol) in DMF (50 ml) and the mixture stirred for 4 h at room temperature (until complete solution of K). Tetrafluoroethylene, or chlorotrifluoroethylene in the case of compound **10**, was then bubbled through the obtained solution under vigorous stirring and heating at 115°C during 4-6 h. The reaction mixture was cooled, poured into water (150 ml), extracted with CH_2Cl_2 (4×50 ml), the extract was washed with water (5×40 ml), dried over $MgSO_4$, the solvent was removed in vacuum (15 mm Hg), and the residue chromatographed on a column of SiO_2 (eluent CH_2Cl_2).

1-Benzyl-3-(1,1,2,2-tetrafluoroethoxy)-1H-indazole (9a). Yield 1.38 g, colorless oily substance, R_f 0.6. Mass spectrum, *m/z* (I_{rel}, %): 324 $[M]^+$ (22), 91 $[PhCH_2]^+$ (100).

1-(*p*-Methoxybenzyl)-3-(1,1,2,2-tetrafluoroethoxy)-1H-indazole (9b). Yield 1.51 g, colorless oily substance, R_f 0.6. Mass spectrum, *m/z* (I_{rel}, %): 354 $[M]^+$ (27), 121 $[CH_3OPhCH_2]^+$ (100).

1-(2-Pyridylmethyl)-3-(1,1,2,2-tetrafluoroethoxy)-1H-indazole (9c). Yield 1.33 g, yellow oily substance, R_f 0.6. Mass spectrum, *m/z* (I_{rel}, %): 325 $[M]^+$ (100), 246 $[M\text{-}C_5H_4N+H]^+$ (87), 208 $[M\text{-}OCF_2CF_2H]^+$ (29), 93 $[C_5H_4NCH_2+H]^+$ (27).

1-Benzyl-3-(2-chloro-1,1,2-trifluoroethoxy)-1H-indazole (10). Yield 1.62 g, colorless oily substance, R_f 0.7. Mass spectrum, *m/z* (I_{rel}, %): 342 $[M(^{37}Cl)]^+$ (19), 340 $[M]^+$ (56), 223 $[M\text{-}CF_2CFClH]^+$ (18), 91 $[PhCH_2]^+$ (100).

Interaction of Indazolol 1a with 1,1-difluoroethylene. Potassium *tert*-butylate (0.54 g, 4.5 mmol) was added to a solution of indazolol **1a** (1 g, 4.5 mmol) in anhydrous *tert*-butanol (15 ml) and the mixture stirred at room temperature for 2 h. The solvent was distilled under reduced pressure (15 mm Hg), and the residue of the solvent was removed under vacuum (6 h, 40°C, 0.05 mm Hg). Anhydrous DMF (40 ml) was added to the obtained potassium salt of **1a**. 1,1-Difluoroethylene was bubbled through the obtained solution during 16 h under vigorous stirring and heating at 140°C. The reaction mixture was cooled, poured into water (150 ml), extracted with CH_2Cl_2 (4×50 ml), the extract was washed with water (5×40 ml), dried over $MgSO_4$, the solvent was removed in vacuum (15 mm Hg), and the residue chromatographed on a column of SiO_2 (eluent CH_2Cl_2–hexane, 10:3).

1-Benzyl-3-(1-fluorovinyloxy)-1H-indazole (11). Yield 0.46 g, colorless oily substance, R_f 0.5. Mass spectrum, *m/z* (I_{rel}, %): 268 $[M]^+$ (31), 91 $[PhCH_2]^+$ (100).

1-Benzyl-3-(1,1-difluoroethoxy)-1H-indazole (12). Yield 0.07 g, colorless oily substance, R_f 0.4. Mass spectrum, *m/z* (I_{rel}, %): 288 $[M]^+$ (20), 91 $[PhCH_2]^+$ (100).

1-Benzyl-3-(1,2-difluoro-2-chlorovinyloxy)-1H-indazole (13). Sodium hydride (60% in vaseline oil) (0.2 g, 5 mmol) was added with stirring at room temperature to a solution of indazolol **1a** (1.12 g, 5 mmol) in anhydrous DMF (50 ml) until the end of hydrogen evolution (2 h). A solution of 1,2-dichlorodifluoroethylene (1.33 g, 10 mmol) in DMF (5 ml) was added and the mixture heated for 8 h at 95°C. The reaction mixture was cooled, poured into water (150 ml), extracted with CH_2Cl_2 (4×50 ml), the extract washed with water (5×40 ml), dried over $MgSO_4$, the solvent distilled in vacuum (15 mm Hg), and the residue chromatographed on a column of SiO_2 (eluent CH_2Cl_2). Yield was 1.43 g, colorless oily substance, R_f 0.6. Mass spectrum, *m/z* (I_{rel}, %): 322 $[M(^{37}Cl)]^+$ (7), 320 $[M]^+$ (16), 91 $[PhCH_2]^+$ (100).

3-(1,1,2,2-Tetrafluoroethoxy)indazole (14). A solution of indazole **9b** (0.4 g, 1.1 mmol) in trifluoroacetic acid (5 ml) was heated at 72°C for 4 h. The acid was distilled off in vacuum (15 mm Hg) and the solid residue purified by sublimation at 70°C in vacuum (0.05 mm Hg). Yield was 0.25 g, colorless crystalline substance. Mass spectrum, *m/z* (I_{rel}, %): 234 $[M]^+$ (100), 133 $[M\text{-}OCF_2CF_2H]^+$ (68).

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