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A NEW EFFECTIVE ROUTE FOR THE SYNTHESIS OF SUBSTITUTED 2H-INDAZOLES

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A two-stage synthesis of 2H-indazoles has been established, based on consecutive reactions of reduction of 2-alkyl-, 2-cyclopropyl-, and 2-arylcarbonylazobenzenes to phenylazo-substituted benzyl alcohols and intramolecular heterocyclization of the reduction products under the influence of organic acids.

Keywords: 2-aminoacylbenzenes, 2-arylazobenzyl alcohols, 2-acylazobenzenes, intramolecular heterocyclizations.

In recent years there has been a considerably strengthened interest in the synthesis and study of the medico-biological properties of derivatives of 2H-indazoles, resulting from the observation in a series of compounds which are seldom encountered in nature, a class of heterocycles with a wide range of biological activity: antiangiogenic [1], anticarcinogenic and anti-inflammatory [2,3], antimicrobial [4], antifungal [5, 6], cytotoxic [7], and antihelminthic [8]. In addition compounds of this class show potential as inhibitors of NO-synthetases [9, 10], protein kinases [11, 12], tubulin [13], modulators of X-receptors of the liver [14], and they also show properties of male contraceptives [15, 16].

The discovery of the biological activity of the 2H-indazoles caused the real problem of the synthesis of new derivatives of this class of heterocycles. It is important to underline that at present a wide range of precursors has been used to synthesize the 2H-indazole ring, in practice including all strategic routes for its synthesis. For example, 2H-indazoles have been synthesized from 2-azidobenzylideneamines [17] or 2-azidobenzoylamines [18,19], oxidative cyclization from N-acylhydrazones of 2-aminoacylbenzenes [20, 21], reaction of carbenes with azobenzene [22, 23], rearrangement of *ortho*-substituted azobenzenes [24, 25], and reductive heterocyclization of *ortho*-nitrobenzylideneamines [26-28], and heterocyclization of *ortho*-nitrobenzylamines [29-33]. A variant of the formation of the 2H-indazole system from compounds containing the pyrazole unit have been described. For example, oxidation of 4,5-tetramethylenepyrazoles with dichlorodicyanobenzoquinone gave substituted 2H-indazoles in high yield [34]. However, despite the abundance of variants for the construction of the 2H-indazole ring, the variation of substituents is practically limited to those in positions 2 and 3, and only in the papers [30, 31, 33] were syntheses of 2H-indazoles containing substituents in the annelated benzene ring reported.

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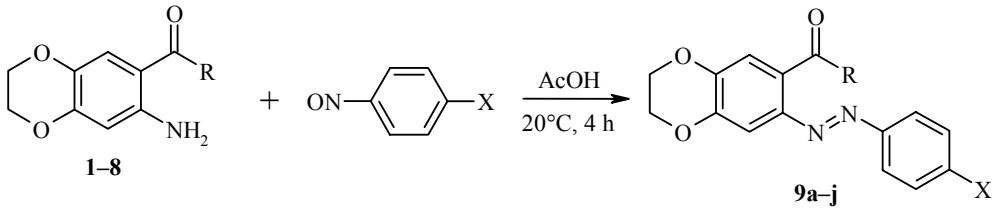
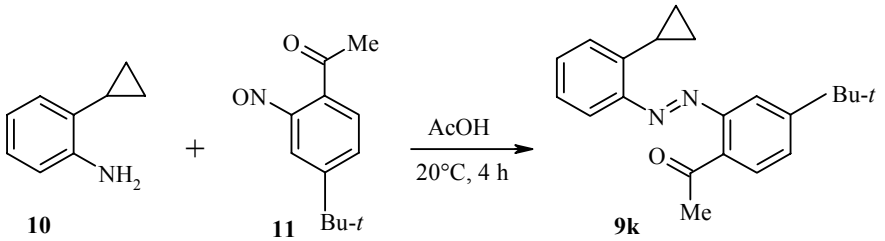
Recently [35] we have shown that 2-benzoyl-4,5-ethylenedioxiazobenzenes are converted in high yield into 2,3-diaryl-5,6-ethylenedioxy-2H-indazoles by a two-step process (reduction to the corresponding phenylazosubstituted benzhydrol and acid-catalyzed heterocyclization of these alcohols). In fact this was the first example of a new variant using a compounds of a series of azobenzenes in the synthesis of 2H-indazoles.

The objective of the present work was to investigate the range of this two-stage transformation of *ortho*-acylazobenzenes into the corresponding 2H-indazoles and the possibility of obtaining of 2H-indazoles with substituents in the annelated benzene ring by this route. With this aim in mind we have synthesized a series of asymmetrically substituted *ortho*-acylazobenzenes by the condensation of *ortho*-amino ketones **1-8** and 2-aminophenylcyclopropane **10** with nitrosobenzenes and have studied their behavior in the conditions of the two-stage transformation.



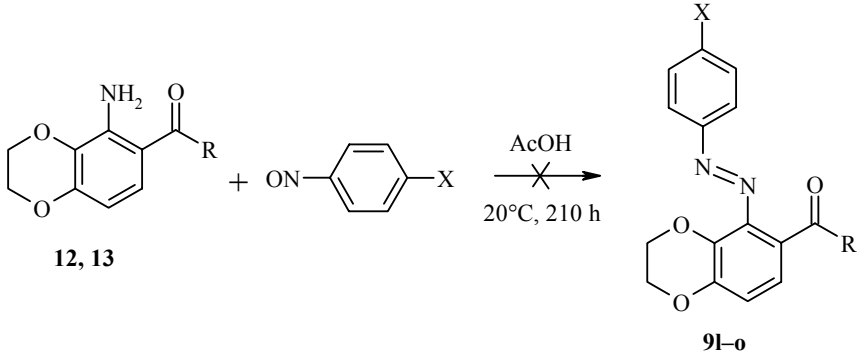
1–8 **9a–j**

1, **9a** R = Me; **2**, **9b**,**c** R = *i*-Pr, **3**, **9d**,**e** R = *c*-Pr; **4**, **9f** R = Ph; **5**, **9g** R = 4-MeC_6H_4; **6**, **9h** R = 4-$MeOC_6H_4$; **7**, **9i** R = 4-ClC_6H_4; **8**, **9j** R = 3-FC_6H_4; **9a**,**b**,**d**,**g**,**i**,**j** X = H, **c**,**e**,**h** X = Cl, **f** X = Ph



10 **11** **9k**

It should be noted that despite the presence of two groups capable of condensation in the nitroso-compound **11**, the reaction occurs with the nitroso group only to give the azobenzene **9k**. It is interesting that the 5-amino-6-acyl-substituted 1,4-benzodioxanes **12** and **13**, unlike their 6-amino-7-acyl-substituted isomers, do not form the corresponding azobenzenes **9l-o.**



12, 13 **9l–o**

12, 9 l,m R = Me, **13**, **9 n,o** R = *i*-Pr; **9 l,n** X = H, **m**,**o** X = Cl

Table 1. Characteristics of 2-Acyl-substituted Azobenzenes **9a-k**, 2-Arylazo-substituted Benzyl Alcohols **14a-k**, and 2H-Indazoles **15a-k**

Compound	Empirical formula	Found, % / Calculated, %			mp*, °C	Yield, %
		C	H	N		
1	2	3	4	5	6	7
9a	$C_{16}H_{14}N_2O_3$	67.92 / 68.07	5.03 / 5.00	9.99 / 9.92	105-106	49
9b	$C_{18}H_{18}N_2O_3$	69.42 / 69.66	5.89 / 5.85	9.11 / 9.03	74-75	52
9c	$C_{18}H_{17}ClN_2O_3$	62.78 / 62.70	4.81 / 4.97	8.16 / 8.12	117-118	48
9d	$C_{18}H_{16}N_2O_3$	69.91 / 70.12	5.31 / 5.23	9.16 / 9.09	128-129	51
9e	$C_{18}H_{15}ClN_2O_3$	62.76 / 63.07	4.46 / 4.41	8.26 / 8.17	120-121	45
9f	$C_{21}H_{16}N_2O_3$	73.01 / 73.24	4.59 / 4.68	8.02 / 8.13	130-131	48
9g	$C_{22}H_{18}N_2O_3$	73.61 / 73.73	5.09 / 5.06	7.93 / 7.82	124-125	54
9h	$C_{22}H_{17}ClN_2O_4$	64.71 / 64.63	4.26 / 4.19	7.01 / 6.85	141-142	46
9i	$C_{21}H_{15}ClN_2O_3$	66.28 / 66.58	3.91 / 3.99	7.45 / 7.40	127-128	52
9j	$C_{21}H_{15}FN_2O_3$	69.37 / 69.61	4.22 / 4.17	7.88 / 7.73	131-132	51
9k	$C_{21}H_{24}N_2O$	78.51 / 78.71	7.31 / 7.55	8.92 / 8.74	Sticky oil	53
14a	$C_{16}H_{16}N_2O_3$	67.41 / 67.59	5.76 / 5.67	9.93 / 9.85	Sticky oil	87
14b	$C_{18}H_{20}N_2O_3$	69.03 / 69.21	6.31 / 6.45	9.14 / 8.97	Sticky oil	81
14c	$C_{18}H_{19}ClN_2O_3$	62.11 / 62.34	5.58 / 5.52	8.21 / 8.08	105-106	86
14d	$C_{18}H_{18}N_2O_3$	69.52 / 69.66	5.94 / 5.85	9.21 / 9.03	90-91	92
14e	$C_{18}H_{17}ClN_2O_3$	62.61 / 62.70	4.88 / 4.97	8.22 / 8.12	115-116	87
14f	$C_{21}H_{18}N_2O_3$	72.64 / 72.82	5.03 / 5.24	7.82 / 8.09	115-116	85
14g	$C_{22}H_{20}N_2O_3$	73.21 / 73.32	5.48 / 5.59	7.56 / 7.77	61-62	86
14h	$C_{22}H_{19}ClN_2O_4$	64.14 / 64.31	4.51 / 4.66	6.62 / 6.82	128-129	82
14i	$C_{21}H_{17}ClN_2O_3$	66.18 / 66.23	4.36 / 4.50	7.02 / 7.36	73-74	95
14j	$C_{21}H_{17}FN_2O_3$	68.98 / 69.22	4.62 / 4.70	7.81 / 7.69	125-126	94
14k	$C_{21}H_{26}N_2O$	78.01 / 78.22	8.24 / 8.13	8.46 / 8.69	Oil	83
15a	$C_{16}H_{14}N_2O_2$	72.01 / 72.16	5.36 / 5.30	10.68 / 10.52	118-119	85
15b	$C_{18}H_{18}N_2O_2$	73.11 / 73.45	6.28 / 6.16	9.71 / 9.52	124-125	79
15c	$C_{18}H_{17}ClN_2O_2$	65.97 / 65.75	5.36 / 5.21	8.44 / 8.52	151-152	79
15d	$C_{18}H_{16}N_2O_2$	73.78 / 73.95	5.41 / 5.52	9.32 / 9.58	78-79	89 (96)*[2]
15e	$C_{18}H_{15}ClN_2O_2$	65.95 / 66.16	4.68 / 4.63	8.48 / 8.57	118-119	94
15f	$C_{21}H_{16}N_2O_2$	76.53 / 76.81	4.80 / 4.91	8.44 / 8.53	199-200	91

* Crystallized from ethanol.

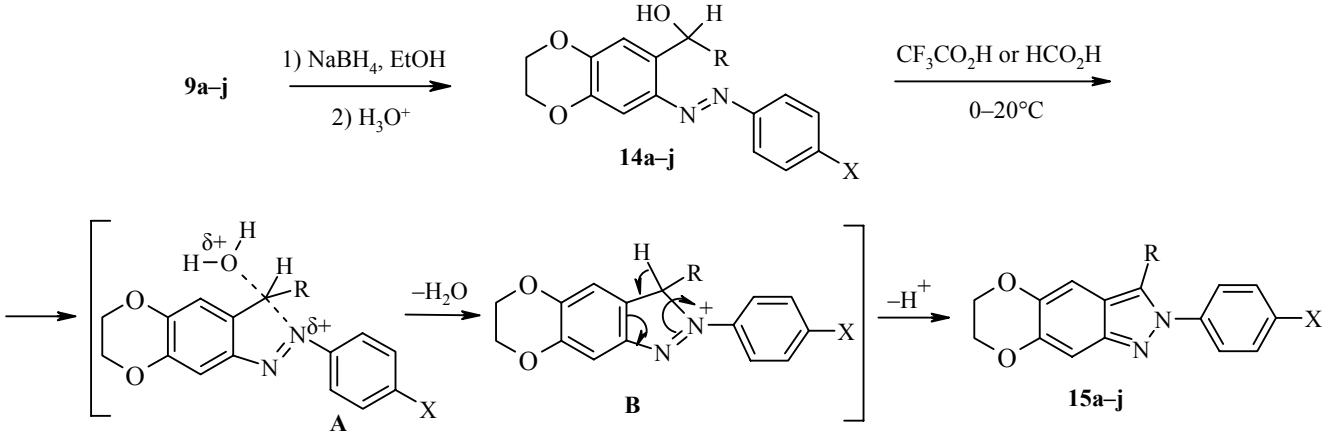
*[2] The yields in brackets refer to the reaction carried out in formic acid.

Table 1 (continued)

1	2	3	4	5	6	7
15g	$C_{22}H_{18}N_2O_2$	76.92 77.17	5.18 5.30	8.03 8.18	184-185	95
15h	$C_{22}H_{17}ClN_2O_3$	67.14 67.26	4.31 4.36	7.28 7.13	208-209	91 (96)
15i	$C_{21}H_{15}ClN_2O_2$	69.31 69.52	3.91 4.17	7.53 7.72	179-180	94
15j	$C_{21}H_{15}FN_2O_2$	73.08 72.82	4.44 4.37	7.88 8.09	201-202	88 (94)
15k	$C_{21}H_{24}N_2$	82.78 82.85	8.07 7.95	9.24 9.20	146-147	87 (93)

Even when the reaction time was increased manifold the amino ketones **12** and **13** reacted with neither nitrosobenzene nor 4-chloronitrosobenzene and were recovered quantitatively unchanged, whereas the nitrosobenzenes were converted into the corresponding azoxybenzenes.

Reduction of the *ortho*-acylazobenzenes **9a-k** to the phenylazo-substituted benzyl alcohols **14a-k**, immediately converted into the 2H-indazoles **15a-k**, was carried out with $NaBH_4$ in ethanol: the reactions occurred in high yield (Table 2) and in no case was the transformation of the azo group observed under the influence of the reducing agent used. This result shows that the azo group can be added to the number of groups which do not react with $NaBH_4$, at least when groups reducible by $NaBH_4$ are present in the substrate.



Heterocyclization of *ortho*-phenylazobenzyl alcohols into the required 2H-indazoles occurred readily in high yield in the presence of trifluoroacetic acid (Table 3). Since this conversion occurs practically with no complications even in the presence of a cyclopropane unit on a benzene carbon (see below), it can be assumed that carbenium ion of benzyl type is not formed as a discrete particle during the heterocyclization*, and it occurs as an intramolecular variant of a nucleophilic substitution of the S_N2 type via the transition state **A**: the intermediate **B** which is then formed is stabilized by the loss of a proton from the benzyl position and is transformed into the 2H-indazole heterocycle.

Of particular interest is the heterocyclization of the alcohol **14k**. This alcohol presents itself as a model in which the reactivity of two groups in *ortho*-position to the azo group, possible sources of carbenium ions of the benzyl type, capable of regioselective formation of the corresponding 2H-indazole.

* A cyclopropane fragment, directly bonded to a carbon atom with a complete positive charge, is easily isomerized [36].

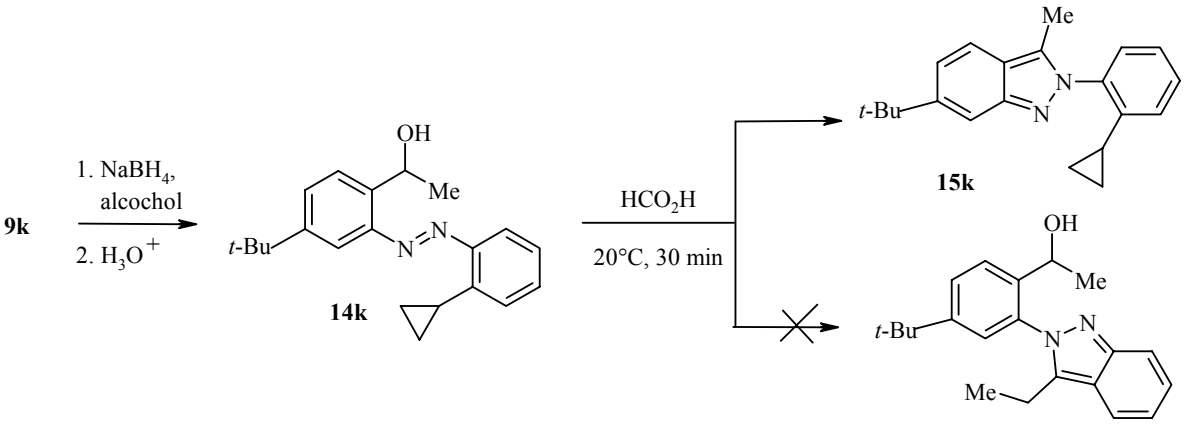


Table 2. ^{1}H NMR Spectra of Compounds **9**, **14**, and **15**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz*)
1	2
9a	2.68 (3H, s, CH_3); 4.34 (4H, s, OCH_2CH_2O); 7.28 (1H, s), 7.34 (1H, s) – H-5,8; 7.52 (3H, m), 7.88 (2H, m) – ArH
9b	1.19 (6H, d, *J* = 6.4, $CH(C\underline{H}_3)_2$); 3.36 (1H, sp, *J* = 6.4, $C\underline{H}(CH_3)_2$); 4.33 (4H, m, OCH_2CH_2O); 7.07 (1H, s), 7.39 (1H, s) – H-5,8; 7.48 (3H, m), 7.85(2H, m) – ArH
9c	1.17 (6H, d, *J* = 6.5, $CH(C\underline{H}_3)_2$); 3.31 (1H, sp, *J* = 6.5, $C\underline{H}(CH_3)_2$); 4.35 (4H, s, OCH_2CH_2O); 7.06 (1H, s), 7.41 (1H, s) – H-5,8; 7.45 (2H, d, *J* = 8.4), 7.78 (2H, d, *J* = 8.4) – ArH
9d	0.99 (2H, m), 1.31 (2H, m), 2.51 (1H, m) – cyclopropane protons; 4.34 (4H, s, OCH_2CH_2O); 7.18 (1H, s), 7.41 (1H, s) – H-5,8; 7.48 (3H, m), 7.91 (2H, d, *J* = 8.0) – ArH
9e	0.99 (2H, m), 1.32 (2H, m), 2.45 (1H, m) – cyclopropane protons; 4.35 (4H, s, OCH_2CH_2O); 7.17 (1H, s), 7.39 (1H, s) – H-5,8; 7.48 (2H, d, *J* = 8.6), 7.84 (2H, d, *J* = 8.6) – ArH
9f	4.42 (4H, m, OCH_2CH_2O); 7.17 (1H, s), 7.42 (1H, s) – H-5, H-8; 7.28 (2H, m), 7.39 (3H, m); 7.46 (2H, m), 7.57 (1H, m); 7.68 (2H, m) – ArH
9g	2.37 (3H, s, CH_3); 4.35 (4H, s, OCH_2CH_2O); 7.13 (1H, s, H-8); 7.19 (2H, d, *J* = 8.0, H-3',5'); 7.33 (3H, m), 7.40 (2H, m) – ArH''; 7.51 (1H, s, H-5); 7.71 (2H, d, *J* = 8.0, H-2',6')
9h	3.83 (3H, s, OCH_3); 4.36 (4H, s, OCH_2CH_2O); 7.10 (1H, s), 7.48 (1H, s) – H-5,8; 6.87 (2H, d, *J* = 8.6), 7.29 (2H, d, *J* = 8.6), 7.38 (2H, d, *J* = 8.4), 7.77 (2H, d, *J* = 8.4) – ArH
9i	4.42 (4H, m, OCH_2CH_2O); 7.19 (1H, s, H-8); 7.32 (2H, d, *J* = 7.6), 7.42 (3H, m) – ArH''; 7.44 (1H, s, H-5); 7.53 (2H, d, *J* = 8.2, H-3',5'); 7.68 (2H, d, *J* = 8.2, H-2',6')
9j	4.43 (4H, m, OCH_2CH_2O); 7.19 (1H, s, H-8); 7.32 (2H, d, *J* = 8.4), 7.39-7.51 (7H, m) – ArH; 7.44 (1H, s, H-5)
9k	0.89 (2H, m), 1.15 (2H, m) – CH_2-cyclopropane protons; 1.40 (9H, s, $C(CH_3)_3$); 2.51 (3H, s, CH_3); 2.93 (1H, m, CH- cyclopropane); 7.01 (1H, m), 7.23 (1H, m), 7.41 (1H, m), 7.75 (1H, dd, J_1 = 7.4, J_2 = 1.6), 7.58-7.68 (2H, m), 7.81 (1H, d, *J* = 7.6) – ArH
14a	1.61 (3H, d, *J* = 6.5, CH_3); 3.90 (1H, br. s, OH); 4.31 (4H, m, OCH_2CH_2O); 5.56 (1H, q, *J* = 6.5, $C\underline{H}OH$); 7.05 (1H, s, H-5); 7.40 (1H, s, H-8); 7.51 (3H, m), 7.85 (2H, d, *J* = 8.2) – ArH
14b	0.82 (3H, d, *J* = 6.6), 1.09 (3H, d, *J* = 6.6) – $CH(C\underline{H}_3)_2$; 2.03 (1H, sp, *J* = 6.6, $C\underline{H}(CH_3)_2$); 3.62 (1H, d, *J* = 6.8, OH); 4.34 (4H, m, OCH_2CH_2O); 4.94 (1H, m, $C\underline{H}OH$); 6.95 (1H, s, H-5); 7.42 (1H, s, H-8); 7.48 (3H, m), 7.83 (2H, d, *J* = 8.3) – ArH
14c	0.82 (3H, d, *J* = 5.9), 1.06 (3H, d, *J* = 5.9) – $CH(C\underline{H}_3)_2$; 1.99 (1H, m, $C\underline{H}(CH_3)_2$); 3.35 (1H, br. s, OH); 4.32 (4H, m, OCH_2CH_2O); 4.96 (1H, m, $C\underline{H}OH$); 6.99 (1H, s, H-5); 7.39 (1H, s, H-8); 7.48 (2H, d, *J* = 8.6), 7.75 (2H, d, *J* = 8.6) – ArH

Table 2 (continued)

1	2
14d	0.34 (1H, m), 0.48 (1H, m), 0.58 (1H, m), 0.71 (1H, m), 1.34 (1H, m) – cyclopropane protons; 3.70 (1H, br. s, OH); 4.32 (4H, m, OCH_2CH_2O); 4.63 (1H, d, *J* = 6.4, C<u>H</u>OH); 7.11 (1H, s), 7.44 (1H, s) – H-5,8; 7.51 (3H, m), 7.83 (2H, d, *J* = 8.3) – ArH
14e	0.31 (1H, m), 0.51 (1H, m), 0.55 (1H, m), 0.68 (1H, m), 1.29 (1H, m) – cyclopropane protons; 3.45 (1H, br. s, OH); 4.31 (4H, m, OCH_2CH_2O); 4.69 (1H, d, *J* = 6.4, C<u>H</u>OH); 7.13 (1H, s), 7.40 (1H, s) – H-5,8; 7.49 (2H, d, *J* = 8.4), 7.78 (2H, d, *J* = 8.4) – ArH
14f	4.27 (2H, m), 4.33 (2H, m) – OCH_2CH_2O; 5.95 (1H, d, *J* = 4.4, OH); 6.58 (1H, d, *J* = 4.4, C<u>H</u>OH); 7.15 (1H, s), 7.19 (1H, s) – H-5,8; 7.13 (1H, t, *J* = 7.3), 7.24 (2H, t, *J* = 7.3), 7.32 (2H, d, *J* = 7.3), 7.53 (1H, t, *J* = 7.4), 7.59 (2H, t, *J* = 7.4), 7.85 (2H, d, *J* = 7.4) – ArH
14g	2.32 (3H, s, CH_3); 3.85 (1H, br. s, OH); 4.31 (4H, m, OCH_2CH_2O); 6.55 (1H, s, C<u>H</u>OH); 6.97 (1H, s, H-5); 7.12 (2H, d, *J* = 8.2, H-3',5'); 7.30 (2H, d, *J* = 8.2, H-2',6'); 7.42 (1H, s, H-8); 7.48 (3H, m), 7.80 (2H, d, *J* = 7.8) – ArH"
14h	3.58 (1H, br. s, OH); 3.77 (3H, s, OCH_3); 4.30 (4H, m, OCH_2CH_2O); 6.53 (1H, s, C<u>H</u>OH); 7.01 (1H, s), 7.40 (1H, s) – H-5,8; 6.84 (2H, d, *J* = 8.4), 7.30 (2H, d, *J* = 8.4), 7.46 (2H, d, *J* = 8.2), 7.71 (2H, d, *J* = 8.2) – ArH
14i	4.27 (2H, m), 4.33 (2H, m) – OCH_2CH_2O; 6.06 (1H, d, *J* = 4.5, OH); 6.77 (1H, d, *J* = 4.5, C<u>H</u>OH); 7.17 (2H, s, H-5,8); 7.31 (2H, d, *J* = 8.8, H-3', 5'); 7.33 (2H, d, *J* = 8.8, H-2',6'); 7.53 (1H, t, *J* = 7.2), 7.59 (2H, t, *J* = 7.2), 7.85 (2H, d, *J* = 7.2) – ArH"
14j	4.27 (2H, m), 4.33 (2H, m) – OCH_2CH_2O; 6.06 (1H, d, *J* = 4.5, OH); 6.77 (1H, d, *J* = 4.5, C<u>H</u>OH); 7.17 (2H, s, H-5,8); 7.31 (2H, d, *J* = 8.8, H-3',5'); 7.33 (2H, d, *J* = 8.8, H-2',6'); 7.53 (1H, t, *J* = 7.2), 7.59 (2H, t, *J* = 7.2), 7.85 (2H, d, *J* = 7.2) – ArH"
14k	0.92 (2H, m), 1.15 (2H, m) – CH_2-cyclopropane protons; 1.37 (9H, s, $C(CH_3)_3$); 1.63 (3H, d, *J* = 6.8, CH_3); 1.73 (1H, br. s, OH); 2.93 (1H, m, CH- cyclopropane); 5.54 (1H, m, C<u>H</u>OH); 7.05 (1H, d, *J* = 7.8), 7.23 (1H, m), 7.41 (1H, m), 7.53 (3H, m), 7.79 (1H, d, *J* = 1.8) – ArH
15a	2.57 (3H, s, CH_3); 4.31 (4H, m, OCH_2CH_2O); 6.98 (1H, s), 7.12 (1H, s) – H-4,7; 7.52 (5H, m, ArH)
15b	1.45 (6H, d, *J* = 6.4, $CH(C\underline{H}_3)_2$); 3.31 (1H, sp, *J* = 6.4, $CH(C\underline{H}_3)_2$); 4.32 (4H, m, OCH_2CH_2O); 7.12 (1H, s), 7.22 (1H, s) – H-4,7; 7.48 (5H, m, ArH)
15c	1.45 (6H, d, *J* = 6.4, $CH(C\underline{H}_3)_2$); 3.26 (1H, sp, *J* = 6.4, $CH(C\underline{H}_3)_2$); 4.32 (4H, s, OCH_2CH_2O); 7.09 (1H, s), 7.19 (1H, s) – H-4,7; 7.42 (2H, d, *J* = 9.1), 7.50 (2H, d, *J* = 9.1) – ArH
15d	0.82 (2H, m), 0.97 (2H, m), 2.09 (1H, m) – cyclopropane protons; 4.31 (4H, m, OCH_2CH_2O); 7.08 (1H, s), 7.11 (1H, s) – H-4,7; 7.43 (1H, t, *J* = 8.0), 7.51 (2H, t, *J* = 8.0), 7.67 (2H, d, *J* = 8.0) – ArH
15e	0.81 (2H, m), 1.01 (2H, m), 2.06 (1H, m) – cyclopropane protons; 4.31 (4H, m, OCH_2CH_2O); 7.06 (1H, s), 7.08 (1H, s) – H-4,7; 7.48 (2H, d, *J* = 8.8), 7.64 (2H, d, *J* = 8.8) – ArH
15f	4.31 (4H, m, OCH_2CH_2O); 7.11 (1H, s), 7.22 (1H, s) – H-4,7; 7.30–7.44 (10H, m, ArH)
15g	2.38 (3H, s, CH_3); 4.33 (4H, m, OCH_2CH_2O); 7.11 (1H, s), 7.19 (1H, s) – H-4,7; 7.18 (2H, d, *J* = 8.3, H-3',5'); 7.22 (2H, d, *J* = 8.3, H-2',6'); 7.38 (3H, m), 7.43 (2H, m) – ArH"
15h	3.85 (3H, s, OCH_3); 4.30 (2H, m), 4.35 (2H, m) – OCH_2CH_2O; 7.07 (1H, s), 7.24 (1H, s) –H-4,7; 6.94 (2H, d, *J* = 8.4), 7.21 (2H, d, *J* = 8.4), 7.36 (4H, m) – ArH
15i	4.32 (4H, m, OCH_2CH_2O); 7.06 (1H, s), 7.19 (1H, s) – H-4,7; 7.24 (2H, d, *J* = 8.2, H-3',5'); 7.35 (2H, d, *J* = 8.2, H-2',6'); 7.41 (5H, m, ArH")
15j	4.33 (4H, m, OCH_2CH_2O); 7.01-7.10 (3H, m, ArH); 7.11 (1H, s), 7.22 (1H, s) – H-4,7; 7.31-7.44 (6H, m, ArH)
15k	0.65-0.85 (4H, m), 1.36 (1H, m) – cyclopropane protons; 1.42 (9H, s, $C(CH_3)_3$); 2.45 (3H, s, CH_3); 6.97 (1H, d, *J* = 7.8), 7.24 (1H, d, *J* = 8.4), 7.28 (2H, m), 7.43 (1H, m), 7.61 (1H, d, *J* = 8.4), 7.66 (1H, m) – ArH

* ^{1}H NMR spectra were recorded in$CDCl_3$ (compounds **9a-e,g,h,k, 14a-e, g,h,k** and **15a-k**) and in DMSO-d_6 (compounds **9f,i,j** and **14f,i**)

Table 3. Mass Spectra of Compounds **9**, **14** and **15**

Compound	*m/z* (I_{rel}, %)
9a	282 $[M]^+$ (56.2), 267 (6.3), 205 (12.2), 177 (25.8), 149 (30.4), 123 (8.8), 105 (17.1), 77 (100.0), 51 (46.5), 43 (42.2)
9d	308 $[M]^+$ (8.2), 280 (10.3), 203 (7.3), 175 (13.5), 163 (9.5), 147 (6.1), 131 (11.2), 119 (8.2), 103 (24.2), 91 (12.6), 77 (100.0), 51 (40.6), 39 (26.6)
9e	342 $[M]^+$ (8.1), 314 (7.2), 203 (8.2), 175 (16.1), 163 (12.4), 131 (13.1), 119 (12.2), 111 (100.0), 103 (30.5), 91 (16.1), 75 (52.1), 69 (13.2), 50 (51.1), 39 (52.6)
9f	344 $[M]^+$ (46.5), 239 (45.2), 183 (16.1), 167 (11.8), 155 (18.2), 139 (34.8), 127 (22.5), 105 (36.1), 77 (100.0), 69 (15.1), 51 (80.1), 39 (11.1)
9g	358 $[M]^+$ (35.4), 253 (14.1), 197 (6.5), 169 (9.1), 153 (13.2), 119 (13.5), 91 (40.6), 77 (100.0), 65 (30.6), 51 (52.5), 39 (18.2)
9i	378 $[M]^+$ (40.4), 273 (10.8), 238 (23.6), 173 (6.5), 154 (9.1), 139 (13.4), 126 (14.8), 111 (21.2), 105 (14.1), 77 (100.0), 69 (11.1), 51 (40.1)
9j	362 $[M]^+$ (72.2), 257 (68.4), 201 (16.4), 185 (15.1), 173 (19.1), 157 (34.2), 145 (14.1), 123 (19.2), 105 (34.2), 95 (48.1), 77 (100.0), 69 (20.8), 51 (51.2)
14d	310 $[M]^+$ (11.3), 293 (9.2), 218 (16.1), 190 (18.2), 178 (11.9), 164 (11.3), 134 (24.2), 107 (12.1), 91 (14.1), 77 (100.0), 65 (19.2), 51 (63.1), 39 (37.1)
14f	346 $[M]^+$ (59.8), 329 (55.1), 254 (94.1), 211 (12.2), 198 (16.4), 182 (12.2), 170 (14.1), 139 (15.1), 128 (15.6), 115 (16.1), 105 (18.2), 77 (100.0), 51 (68.1), 39 (18.1)
14g	360 $[M]^+$ (61.1), 343 (51.1), 268 (100.0), 225 (6.1), 212 (9.1), 184 (12.2), 128 (8.1), 119 (14.2), 91 (28.2), 77 (56.1), 65 (18.1), 51 (36.2), 39 (15.4)
14i	380 $[M]^+$ (66.1), 363 (49.1), 288 (100.0), 253 (41.2), 197 (16.2), 139 (24.4), 111 (17.1), 77 (96.2), 65 (12.5), 51 (58.2), 39 (15.2)
14j	364 $[M]^+$ (62.5), 347 (50.6), 272 (100.0), 229 (16.1), 216 (17.2), 200 (14.3), 188 (14.2), 157 (13.3), 146 (13.4), 133 (14.6), 123 (18.1); 95 (32.3), 77 (86.5), 69 (19.5), 51 (68.3), 39 (17.5)
15f	328 $[M]^+$ (100), 271 (45.7), 255 (7.1), 243 (29.9), 204 (30.1), 150 (8.5), 77 (28.5), 50 (15.7)

It has been shown [24] that 2-cyclopropylazobenzene is capable of rearrangement into 3-ethyl-2-phenyl-2H-indazole under the influence of trifluoroacetic acid, but is unchanged under the influence of formic acid even on heating. With the objective of retaining the three-carbon ring under the conditions of cyclization of the azoalcohol **14k**, we carried out the reaction in formic acid. However the reaction occurred regioselectively at room temperature and only 6-*tert*-butyl-2-(2-cyclopropyl)phenyl-3-methyl-2H-indazole (**15k**) was formed.

This result shows that in the process of synthesis of 2H-indazoles by the two-step conversion of *ortho*-acylazobenzenes, the step involving the heterocyclization of *ortho*-arylazo-substituted benzyl alcohols, containing substituents unstable to the influence of strong acids, can be carried out with formic acid which is much weaker than trifluoroacetic acid.

With the examples of the azo alcohols **14d,j,** and **h** we have shown that conversion of precursors of this type into the corresponding 2H-indazoles occurs as readily with trifluoroacetic acid as with formic acid.

Thus this type of conversion of 2-acylazobenzenes can be used to create a library of 2H-indazoles with the objective of testing their biological activity.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian VXR-400 (400 MHz) spectrometer in $CDCl_3$ with residual $CHCl_3$ as internal standard, and on a Bruker DRX-500 (500 MHz) spectrometere in DMSO-d_6 with TMS as internal standard. Mass spectra were recorded on a Finnigan MAT Incos-50 machine with electron impact ionization, 70eV. Preparative separation of the reaction mixture and monitoring of the purity of the compounds obtained was carried by TLC with Al_2O_3 (activity II) with 1:1:3 ether-CH_2Cl_2-petroleum ether as eluant.

Physicochemical and spectral characteristics of compounds **9**, **14**, and **15** are given in Tables 1-3.

7-Acetyl-6-Amino-1,4-benzodioxane (1). Reduced iron (17 g) was added to a solution of 6-acetyl-7-nitro-1,4-benzodioxane (2.23 g, 10 mmol) in benzene (100 ml) heated to 75°C and stirred at this temperature for 30 min, then water (7 ml) was added in portions over 2 h. The reaction mixture was stirred for 1 h at 80°C, the hot benzene solution was decanted, the solvent was evaporated, and the residue was recrystallized from ethanol. Yield 79%; mp 126-127°C [37].

Amines **2-8**, **12**, and **13** were made analogously by reduction of the corresponding nitro-compound.

6-Amino-7-isobutyroyl-1,4-benzodioxane, (2), yield 69%; mp 114°C [38].

6-Amino-7-cyclopropylcarbonyl-1,4-benzodioxane (3), yield 68%; mp 93-95°C [38].

6-Amino-7-benzoyl-1,4-benzodioxane (4), yield 84%; mp 134-135°C [37].

6-Amino-7-(4-methylbenzoyl)-1,4-benzodioxane (5), yield 79%; mp 136-137°C [38].

6-Amino-7-(4-methoxybenzoyl)-1,4-benzodioxane (6), yield 78%; mp 160-161°C [38].

6-Amino-7-(4-chlorobenzoyl)-1,4-benzodioxane (7), yield 82%; mp 123-124°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.12 (2H, m); 4.23 (2H, m) –OCH_2CH_2O; 6.32 (1H, s, H-5); 6.68 (1H, s, H-8); 6.85 (2H, br. s, NH_2); 7.52 (4H, m ArH'). Found, %: C 61.92; H 3.91; N 4.63. $C_{15}H_{12}ClNO_3$. Calculated, %: C 62.19; H 4.17; N 4.83.

6-Amino-7-(3-fluorobenzoyl)-1,4-benzodioxane (8), yield 82%; mp 124-125°C [38].

6-Acetyl-5-amino-1,4-benzodioxane (12), yield 74%; mp 115-116°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.55 (3H, s, CH_3); 4.27 (4H, m, OCH_2CH_2O); 6.22 (1H, d, *J* = 9.2, H-8); 6.52 (2H, br. s, NH_2); 7.24 (1H, d, *J* = 9.2, H-7). Found, %: C 61.93; H 5.68; N 7.29. $C_{10}H_{11}NO_3$. Calculated, %: C 62.17; H 5.74; N 7.25,

5-Amino-6-isobutyroyl-1,4-benzodioxane (13), yield 69%; mp 67-68°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.19 (6H, d, *J* = 6.5, $CH(C\underline{H}_3)_2$)); 3.51 (1H, sp, $C\underline{H}(CH_3)_2$)); 4.29 (4H, m, OCH_2CH_2O); 6.22 (1H, d, *J* = 9.3, H-8); 6.61 (2H, br. s, NH_2); 7.35 (1H, d, *J* = 9.3, H-7). Found, %: C 64.88; H 6.91; N 6.47. $C_{12}H_{15}NO_3$. Calculated, %: C 65.14; H 6.83;N 6.33.

2-Aminophenylcyclopropane was prepared as in [39]. Yield 72%; bp 103-104°C (9 mmHg), n_D^{20} 1.5810.

2-Acetyl-5-*tert*-butylnitrosobenzene (11) was synthesized as described in [40]. Yield 87%; mp 140-143°C (ethanol).

2-Arylazoacylbenzenes 9a-k (General Method). The corresponding nitrosobenzene (10 mmol) was added to a solution of the amino ketone **1-8**, **10** (10 mmol) in glacial acetic acid (30 ml) over 3 min. The uniform solution was kept for 8 h at 20°C and then poured into water (250 ml), the product was extracted with $CHCl_3$, the extract was dried with $CaCl_2$, the solvent was evaporated, and the residue was chromatographed on a strip on Al_2O_3.

2-Arylazobenzyl Alcohols 14a-k (General Method). A 2-arylazoacylbenzene **9a-k** (10 mmol) was added in portions to a suspension of $NaBH_4$ (0.38 g, 10 mmol) in ethanol (30 ml), the mixture was stirred for 6-8 h at 40-50°C, the reaction mass was carefully decomposed with10% HCl solution (~2-3 ml), and the ethanolic solution was poured into water (200 ml). The reduction products were extracted with $CHCl_3$, the extract was dried with $MgSO_4$, the solvent was evaporated, and the residue was either recrystallized or chromatographed on strips with Al_2O_3.

Cyclization of 2-Arylazobenzyl Alcohols 14a-k into 2H-Indazoles 15a-k under the Influence of Trifluoroacetic Acid (General Method). An azo alcohol **14a-k** (1 mmol) was added CF_3COOH at 0-5°C, the temperature was increased to 20°C, the mixture was stirred for 30 min, poured into ice water (100 ml), neutralized with Na_2CO_3, extracted with $CHCl_3$ (2×30 ml), dried over $MgSO_4$, the solvent was evaporated, and the residue was recrystallized from ethanol.

Cyclization of 2-Arylazobenzyl Alcohols 14d, j, h, and k into 2H-Indazoles 15d, j, h, and k under the Influence of Formic Acid (General Method). An azo alcohol **14d,j,h,k** (1 mmol) was added to HCO_2H (10 ml) at 20°C, stirred for 2 h, the reaction mixture was poured into cold water (150 ml), neutralized with Na_2CO_3, the residue was filtered off , washed with water and crystallized from ethanol.

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