Heterocyclization of *o*-(arylethynyl)arylhydrazines as a new procedure for the synthesis of substituted 1*H*- and 2*H*-indazoles and indoles

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Procedures for the preparation of 3-substituted 1*H*- and 2*H*-indazoles and 2-substituted indoles were developed based on cross-coupling of *o*-iodoarylhydrazines with copper acetylenides in pyridine or dimethylformamide. An alternative procedure for the synthesis of 3-substituted 1*H*-indazoles involves cyclocondensation of (2-chloroaryl)acetylenes with hydrazine hydrate in butanol.

Key words: indazoles, isoindazoles, indoles, cross-coupling, *o*-iodoarylhydrazines, *o*-chloroarylacetylenes, heterocyclization.

One of procedures for the synthesis of fused heterocyclic compounds involves cyclization of *ortho*-functionalized aryl- and hetarylacetylenes.[1—3] Previously, we have reported cyclocondensation of activated (2-chloroaryl)acetylenes with hydrazine giving rise to substituted 1*H*-indazoles[4] and cross-coupling of (2-iodoaryl)hydrazines with terminal acetylenes or their copper salts as a new procedure for the preparation of 2-substituted indoles.[5]

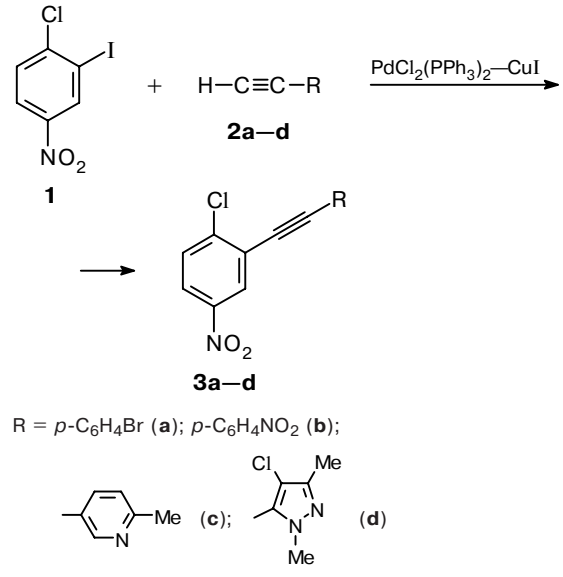
In the present study, we report the detailed experimental conditions, characteristics of the compounds synthesized, and some generalizations concerning these cyclization reactions.

Investigation into heterocyclization of (2-ethynylaryl- and -hetaryl)hydrazines is very promising because these compounds contain two nucleophilic centers in the hydrazino group and the C≡C bond, which can be subject to the attack by the N atoms. The target (2-ethynylaryl- and -hetaryl)hydrazines can be prepared by the reactions of (2-halogenoaryl- and -hetaryl)hydrazines with terminal alkynes as well as by cross-coupling of the corresponding (2-chloroaryl- and -hetaryl)acetylenes with hydrazine. We examined both these possibilities. It should be noted that the first type of reactions has not been studied previously. The second alternative procedure has been mentioned only in the study[6] concerned with the reactions of 4-chlorophenylethynylcinnolines with substituted hydrazines. In the latter case, the expected ethynylarylhydrazines underwent cyclization to form pyrazole or pyrrole derivatives in 20—39% yields. No explanation for the fact that the reactions followed different paths was provided. It is needless to say that the use of highly reactive 4-chlorocinnoline did not allow one to make conclusions about the scope and limitations of this cyclization reaction.

We performed systematic study of hydrazinolysis of (2-chloroaryl)alkynes. It appeared that *o*-chlorotolan remained unconsumed even upon prolonged (34 h) refluxing in *n*-bytanol. An attempt to carry out the reaction of hydrazine hydrate with 2-chloro-5-nitrotolan (60 h) was also unsuccessful.

In this connection, we examined cross-coupling of 4-chloro-3-iodonitrobenzene (**1**) with aryl- and hetarylacetylenes (**2a—d**) in the presence of the $PdCl_2(PPh_3)_2$—CuI system in Et_3N (Scheme 1). The reactions gave rise to (2-chloro-5-nitrophenyl)arylacetylenes (**3a—d**) in 65—84% yields. Their physicochemical characteristics and spectral characteristics are given in Tables 1 and 2, respectively.

Scheme 1



The reactions of compounds **3a—d** with hydrazine involved the replacement of the Cl atom and cyclization

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Table 1. Principal physicochemical characteristics of acetylenes **3a—d**

Compound	Yield (%)	M.p./°C (solvent)	Found / Calculated (%) C	H	Cl	Molecular formula
3a*	65	112—113 (C_6H_6)	50.02 / 49.96	2.08 / 2.10	10.33 / 10.53	$C_{14}H_7BrClNO_2$
3b	77	164—165 (C_6H_6)	55.73 / 55.56	2.29 / 2.23	11.44 / 11.71	$C_{14}H_7ClN_2O_4$
3c	84	140—141 (EtOH)	66.67 / 61.66	3.21 / 3.33	12.80 / 13.00	$C_{14}H_9ClN_2O_2$
3d	78	188.5—189.5 (C_6H_6)	50.19 / 50.35	3.05 / 2.93	22.70 / 22.86	$C_{13}H_9Cl_2N_3O_2$

* Found (%): Br, 23.80. Calculated (%): Br, 23.74.

Table 2. Spectral characteristics of acetylenes **3a—d**

Compound	IR,* ν/cm^{-1}	^1H NMR,** δ (J/Hz)
3a	1350, 1525 (NO_2); 2210 (C≡C)	7.48 (d, 2 H, H(3′), H(5′), $J_{3',2'(5',6')}$ = 7.0); 7.52 (d, 2 H, H(2′), H(6′); 7.61 (d, 1 H, H(3), $J_{3,4}$ = 7.1); 8.14 (dd, 1 H, H(3), $J_{3,6}$ = 1.6); 8.43 (d, 1 H, H(6))
3b	1350, 1540 (NO_2); 2215 (C≡C)	7.60—8.40 (m, 6 H, H arom.); 8.47 (d, 1 H, H(6), $J_{3,6}$ = 1.5)
3c	1350, 1540 (NO_2); 2225 (C≡C)	2.60 (s, 3 H, CH_3); 7.20—7.80 (m, 3 H, H(5), H (5′), H(6′)); 8.10 (dd, 1 H, H(3), $J_{3,4}$ = 7.0); 8.40 (d, 1 H, H(6), $J_{3,6}$ = 1.5); 8.70 (d, 1 H, H(2′), $J_{2',5'}$ = 1.6)
3d	1350, 1545 (NO_2); 2235 (C≡C)	2.25 (s, 3 H, C—CH_3); 3.95 (s, 3 H, N—CH_3); 7.60 (d, 1 H, H(3), $J_{3,4}$ = 7.2, $J_{3,6}$ = 1.7); 8.15 (d, 1 H, H(4)); 8.42 (d, 1 H, H(6))

* Solutions in $CHCl_3$; in the case of compound **3a**, KBr pellets.
** In $CDCl_3$.

giving rise to 3,5-disubstituted 1*H*-indazoles (**4a—d**) (Scheme 2). Their physicochemical and spectral characteristics are listed in Tables 3 and 4, respectively.

Scheme 2

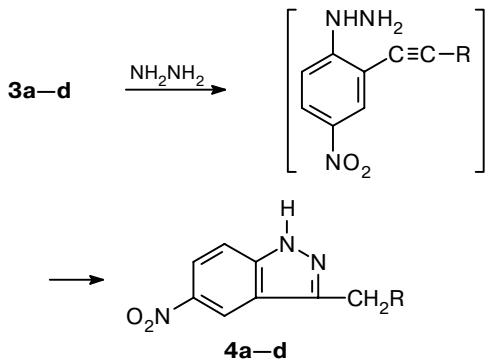


Table 3. Principal physicochemical characteristics of 1*H*-indazoles **4a—d**

Compound	Yield (%)	M.p./°C (solvent)	Found / Calculated (%) C	H	N	Molecular formula
4a*	75	187—188 (C_6H_6)	50.49 / 50.62	3.06 / 3.03	—	$C_{14}H_{10}BrN_4O_2$
4b	88	213—214 (Me_2CO)	56.10 / 56.38	3.33 / 3.38	19.04 / 18.78	$C_{14}H_{10}N_4O_4$
4c	65	218—219 (EtOH)	62.84 / 62.68	4.70 / 4.51	21.04 / 20.88	$C_{14}H_{12}N_4O_2$
4d	66	243—244 (EtOH)	50.66 / 51.07	4.17 / 3.96	11.91 / 11.60	$C_{13}H_{12}ClN_5O_2$

* Found (%): Br, 23.90. Calculated (%): Br, 24.06.

Table 4. Spectral characteristics of 1*H*-indazoles **4a—d**

Compound	IR,* ν/cm^{-1}	^1H NMR,** δ (J/Hz)
4a	1330, 1480 (NO_2); 3260 (br., NH)	4.39 (s, 2 H, CH_2); 7.28 (d, 2 H, H(2′), H(6′), $J_{2',3'(6',5')}$ = 7.1); 7.48 (d, 1 H, H(3′), H(5′)); 7.55 (d, 1 H, H(6), $J_{6,7}$ = 7.2); 8.31 (dd, 1 H, H(7), $J_{7,4}$ = 1.5); 8.58 (d, 1 H, H(4)); 12.60 (br.s, 1 H, NH)
4b	1370, 1400, 1530, 1570 (NO_2); 3450 (br., NH)	4.64 (s, 2 H, CH_2); 7.70—8.30 (m, 6 H, $C_6H_4NO_2$, H(6), H(7)); 8.72 (d, 1 H, H(4), $J_{4,7}$ = 1.6); 12.60 (br.s, 1 H, NH)
4c	1370, 1510 (NO_2); 3450 (br., NH)	2.43 (s, 3 H, CH_3); 4.45 (s, 2 H, CH_2); 7.16 (d, 1 H, H(5′), $J_{5',6'}$ = 7.0); 7.65 (d, 1 H, H(6′)); 7.72 (d, 1 H, H(6), $J_{6,7}$ = 7.2); 8.21 (dd, 1 H, H(7), $J_{7,4}$ = 1.6); 8.55 (s, 1 H, H(2′)); 8.70 (d, 1 H, H(4)); 12.70 (br.s, 1 H, NH)
4d	1330, 1510 (NO_2); 3400 (br., NH)	2.75 (s, 3 H, C—CH_3); 3.70 (s, 3 H, N—CH_3); 4.45 (s, 2 H, CH_2); 7.65 (d, 1 H, H(6), $J_{6,7}$ = 9.0); 8.15 (dd, 1 H, H(7), $J_{7,4}$ = 2.2); 8.70 (d, 1 H, H(4)); 12.50 (br.s, 1 H, NH)

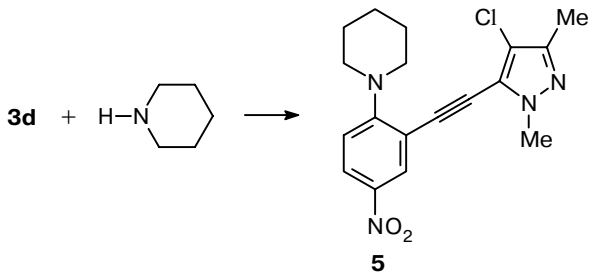
* KBr pellets.
** In $(CD_3)_2CO$; in the case of **4a**, in $CDCl_3$.

We attribute the formation of the pyrazole ring instead of the pyrrole ring to the higher nucleophilicity of the terminal N atom of the hydrazino group and polarization of the C≡C bond. The latter is caused by the combined effect of the electron-withdrawing group of the acetylenic fragment and the electron-donating $NHNH_2$ group as a result of which the α-carbon atom of the C≡C bond acquires a partial positive charge.

Examination of the reaction of compound **3d** with piperidine as an example demonstrated that it began with the replacement of the halogen atom to give exclu-

sively 4-chloro-1,3-dimethyl-5-(5-nitro-2-piperidinophenylethynyl)pyrazole (**5**) (the yield was 94.3%) (Scheme 3).

Scheme 3



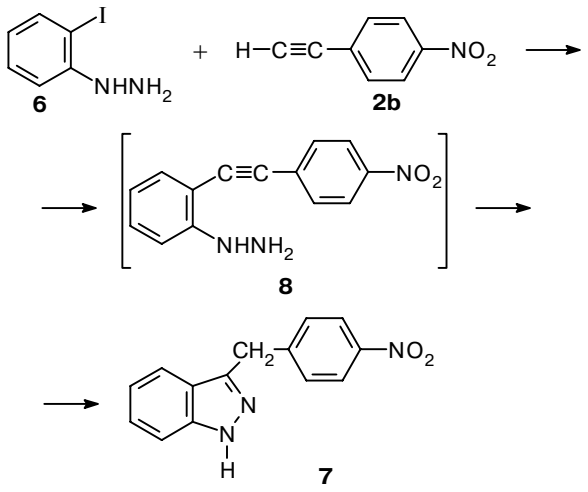
Therefore, cyclocondensation of activated (2-chloroaryl)acetylenes with hydrazine hydrate affords 3-substituted 1*H*-indazoles and provides a new procedure for the synthesis of these compounds. However, this procedure has essential limitations associated with the necessity of using both aryl halides and acetylenic components containing only electron-withdrawing substituents. In addition, attempts to isolate intermediates, *viz.*, (2-ethynylaryl)hydrazines, formed in cyclocondensation of *o*-chloro-substituted arylacetylenes with NH_2NH_2 failed. Hence, there is no way of studying cyclization of these intermediates as such depending on the reaction conditions. However, it is known that the direction of cyclization of (2-ethynylaryl)carbohydrazides, which also bear two N atoms exhibiting different nucleophilicity, can be controlled by the reaction conditions.[7]

We suggested that an alternative procedure for the synthesis of (2-ethynylaryl)hydrazines by the reactions of (2-iodoaryl)hydrazines with terminal acetylenes or their copper salts would make it possible not only to isolate intermediates in the free form, but also to examine the direction of cyclization of (ethynylaryl)hydrazines in the absence of electron-withdrawing substituents or even in the presence of electron-donating substituents. This could also help in gaing a better insight into the influence of the internal (the nature of the substituents) and external (cyclization conditions) factors on the direction of heterocyclization, its scope, and limitations and in performing the directed synthesis of not only 1*H*-indazoles but also other fused heterocyclic systems.

However, the reaction of (2-iodophenyl)hydrazine (**6**) with *p*-nitrophenylacetylene (**2b**) under the standard conditions of cross-coupling ($PdCl_2(PPh_3)_2$—CuI, Et_3N, 80 °C) afforded 3-substituted 1*H*-indazole (**7**) in 38% yield (Scheme 4). We failed to isolate the expected intermediate **8**.

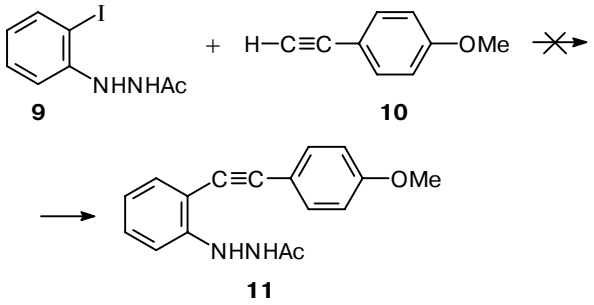
We hypothesized that the introduction of an acyl protective group into the hydrazine fragment would lead to a decrease in its nucleophilicity and make it possible to obtain the target intermediate. However, catalytic cross-coupling of 2′-(2-iodophenyl)acetohydrazide (**9**) with *p*-methoxyphenylacetylene (**10**) did not give rise

Scheme 4



to compound **11** due to substantial resinification (Scheme 5).

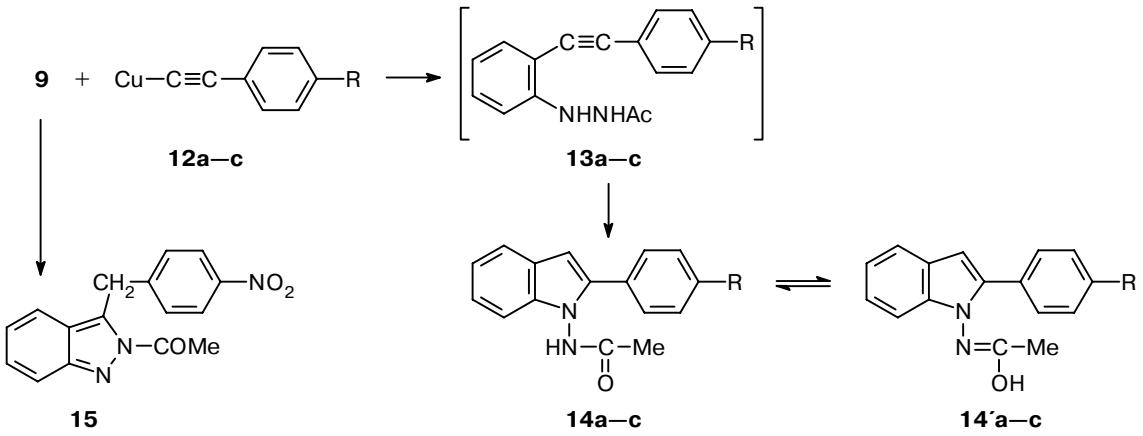
Scheme 5



This result can be assigned to lability of the starting compound **9**, the low reactivity of the halogen atom due to the +M effect of the hydrazino group, and the lower acidity of alkyne **10** compared to alkyne **2b** (for **10**, $pK = 29.7$; for **2b**, $pK \approx 26.9$).[8] Analogous results were observed in the reactions of *vic*-iodoaminopyrazoles with arylacetylenes whose pK's are lower than 29. Complications were circumvented with the use of acyl protection of the amino group and by performing the synthesis accoding to the acetylenide procedure instead of catalytic cross-coupling.[9] We also used this approach in the present study. Cross-coupling of iodide **9** with copper phenyl- (**12a**), *p*-nitrophenyl- (**12b**), or *p*-methoxyphenylacetylenide (**12c**) in DMF at 155 °C afforded 2-substituted indoles **14a—s**, respectively, (in 30—73% yields) instead of the expected intermediates **13a—c**. According to the data from ^1H NMR spectroscopy, indoles **14a—c** existed in the tautomeric equilibrium with **14′a—c** (Scheme 6). The reaction involving substrate **12b** proceeded most smoothly.

The fact that heterocyclization afforded the pyrrole rather than the pyrazole ring is apparently associated

Scheme 6



R = H (**a**); *p*-NO_2 (**b**); *p*-OMe (**c**)

with the higher nucleophilicity of the amine N atom compared to the amide N atom.

A different direction of cyclocondensation was observed in the reaction of iodide **9** with acetylenide **12b** in pyridine giving rise to 2*H*-indazole (**15**) (30%), which is apparently associated with the generation of a stronger nucleophile, *viz.*, of the N-anion, from the acidic MeCONH group in the presence of the base (Py). An attempt to perform condensation of iodohydrazine **9** with acetylenide **12c** under analogous conditions was unsuccessful due apparently to the opposite polarization of the C≡C bond in intermediate **13c** compared to **13b** and to the fact that no aromatic system can be formed.

Hydrazine **13b** was synthesized from compounds **9** and **2b** using catalytic cross-coupling at the temperature below 80 °C (the yield was 68%).

We failed to prepare monosubstituted hydrazine by removing acyl protection of **13b** with the use of refluxing in *n*-butanol in the presence of K_2CO_3 due to cyclization of the target product to 1*H*-indazole **7** (48%).

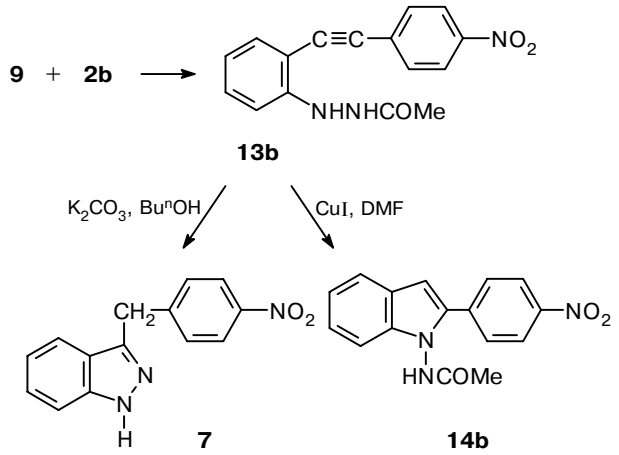
In the absence of a base, no deacetylation of compound **13b** occurred and heterocyclization afforded indole **14b** in 75% yield (Scheme 7).

Thus, cyclocondensation of 2′-(2-iodophenyl)acetohydrazide with *p*-nitrophenylacetylene in pyridine gave rise to 2*H*-indazoles, whereas cyclocondensation in DMF afforded 2-substituted indoles regardless of the character of the substituents in copper arylacetylenides. The above reactions provide a new procedure for the synthesis of these compounds. Cross-coupling of (2-iodophenyl)hydrazine or 2′-(2-iodophenyl)acetohydrazide with *p*-nitrophenylacetylene was accompanied by heterocyclization to form 3-substituted 1*H*-indazoles.

Experimental

The IR spectra were recorded on UR-20 and Specord-IR instruments. The ^{1}H NMR spectra were measured on a JEOL

Scheme 7



FX-90Q spectrometer in $CDCl_3$ and $(CD_3)_2CO$. TLC was carried out on Silufol UV-254 plates.

Pyridine, DMF, and triethylamine, which were purchased from Lancaster, as well as benzene and chloroform (both of analytical grade) were used without additional purification. 4-Chloro-3-iodonitrobenzene (**1**),[10] terminal acetylenes **2a—d**,[11—14] and copper arylacetylenides **12a—c** [15] were prepared according to known procedures.

Aryl(2-chloro-5-nitrophenyl)acetylenes (3a—d) (general procedure). A solution of 4-chloro-3-iodonitrobenzene[10] (**1**) (10 mmol), terminal acetylene **2a—d** (10—15 mmol), $Pd(PPh_3)_2Cl_2$ (40 mg), and CuI (20 mg) in a 1 : 3 mixture of Et_2NH (or Et_3N) and benzene was stirred under in an atmosphere of Ar at 25—80 °C for 4—11 h until the starting iodide **1** disappeared (TLC control). After completion of the reaction, the mixture was diluted with ether and filtered through a small layer of Al_2O_3. The filtrate was concentrated *in vacuo*. The residue was chromatographed on a 4×5-cm column with SiO_2 using benzene as the eluent. The yields and physicochemical characteristics of compounds **3a—d** are given in Table 1. The ^{1}H NMR spectral data are listed in Table 2.

3-Substituted 5-nitro-1*H*-indazoles (4a—d) (general procedure). Compound **3a—d** (2—5 mmol) was refluxed with a

2—5-fold excess of $NH_2NH_2 \cdot H_2O$ in Bu^nOH (5—10 mL) for 1—6 h until the starting chloride disappeared (TLC control). The solvent was evaporated and the residue was passed through a small layer of Al_2O_3 using ether and $CHCl_3$ as the eluents. The yields and physicochemical characteristics of compounds **4a—d** are given in Table 3. The ^1H NMR spectral data are listed in Table 4.

4-Chloro-1,3-dimethyl-5-(5-nitro-2-piperidinophenylethynyl)pyrazole (5). A solution of chloride **3d** (0.3 g, 0.001 mmol) and piperidine (0.9 g, 0.001 mol) in Bu^nOH (10 mL) was heated at 90—100 °C for 5 h (TLC control). Then the reaction mixture was cooled and the precipitate of compound **5** (0.15 g) that formed was filtered off. The mother liquor was concentrated, the residue was washed with ether, and an additional amount of compound **5** was obtained (0.18 g); the total yield was 0.33 g (94.3%). After recrystallization from EtOH, the yield was 0.22 g (62.9%), m.p. 113—114 °C. ^1H NMR, ($CDCl_3$), δ: 1.75 (m, 6 H, $C(CH_2)_3C$); 2.35 (s, 3 H, CCH_3); 3.45 (m, 4 H, CH_2NCH_2); 3.95 (s, 3 H, NCH_3); 6.95 (dd, 1 H, H(3), $J_{3,4}$ = 8.0 Hz, $J_{3,6}$ = 1.5 Hz); 8.15 (d, 1 H, H(4)); 8.40 (d, 1 H, H(6)). Found (%): C, 60.05; H, 5.44; Cl, 9.64. $C_{18}H_{19}ClN_4O_2$. Calculated (%): C, 60.25; H, 5.34; Cl, 9.88. IR (KBr), ν/cm^{-1}: 1330, 1540 (NO_2); 2220 (C≡C).

(2-Iodophenyl)hydrazine (6) was prepared from *o*-iodoaniline in 68% yield according to procedures reported previously.[16,17] Hydrazine **6** was subjected to acylation without purification.

2′-(2-Iodophenyl)acetohydrazide (9). Ac_2O (11 mL, 0.1165 mol) was added portionwise to a solution of hydrazine **6** (12.15 g, 0.052 mol) in dry benzene (80 mL). The crystals that precipitated were filtered off and washed with hexane. Compound **9** was obtained in a yield of 12.78 g (89.2%), m.p. 179—180.5 °C (from benzene). ^1H NMR ($CDCl_3$), δ: 2.10 (s, 3 H, CH_3); 6.10—7.75 (m, 4 H, C_6H_4). Found (%): C, 35.30; H, 3.45; I, 45.11. $C_8H_9IN_2O$. Calculated (%): C, 34.80; H, 3.29; I, 45.97. IR ($CHCl_3$), ν/cm^{-1}: 1695 (C=O); 3300 (br.), 3435 (NH).

Reactions of hydrazide 9 with copper phenyl- (12a), *p*-nitrophenyl- (12b), and *p*-methoxyphenylacetylenides (12c). ***A.*** A mixture of iodide **9** (2.76 g, 0.01 mol), copper phenylacetylenide (1.7 g, 0.01 mol) (**12a**), and DMF (20 mL) was refluxed under a stream of Ar for 5 h. After completion of the reaction, the mixture was poured into water (50 mL) and extracted with $CHCl_3$ (6×50 mL). The extract was washed with an aqueous solution of NH_3 and water, dried with Na_2SO_4, and filtered through a layer of Al_2O_3 (4×4 cm, $CHCl_3$ as the eluent). The solvent was distilled off. The residue was twice chromatographed on SiO_2 (4×7 cm, $PhCH_3$ as the eluent) and crystallized from $PhCH_3$ with activated carbon. 1-Acetamido-2-phenylindole (**14a**) was obtained in a yield of 0.43 g (17.2%), m.p. 216—217 °C (from EtOAc). ^1H NMR ($CDCl_3$), δ: 1.55 and 2.10 (s, 3 H, =C(OH)Me and $COCH_3$); 6.65 and 6.75 (both s, 1 H, H(3) and H(3′)); 7.10—8.25 (m, 9 H, C_6H_4 and C_6H_5). Found (%): C, 76.28; H, 5.57; N, 11.39. $C_{16}H_{14}N_2O$. Calculated (%): C, 76.78; H, 5.64; N, 11.19. IR ($CHCl_3$), ν/cm^{-1}: 1710 (C=O); 3230, 3400 (br., NH, OH).

B. A mixture of iodide **9** (2.8 g, 0.01 mol), acetylenide **12c** (2.2 g, 0.0112 mol), and DMF (25 mL) was refluxed under a stream of Ar for 7 h. After completion of the reaction, the mixture was filtered through a layer of SiO_2 (2×5 cm, $CHCl_3$ as the eluent), the solution was concentrated to dryness, and the residue was chromatographed on SiO_2 (3.5×22 cm, benzene and $CHCl_3$ as the eluents). 1-Acetamido-2-(*p*-methoxyphenyl)indole (**14c**) was obtained in a yield of 1.15 g (41.07%), m.p. 193—194 °C (from EtOAc). ^1H NMR ($CDCl_3$), δ: 1.53 and 2.12 (both s, 3 H, =C(OH)Me and $COCH_3$); 3.83 and 3.85 (both s, 3 H, OCH_3 and $OCH_3′$); 6.55 and 6.65 (both s, 1 H, H(3) and H(3′)); 6.9—8.1 (m, 8 H, H arom.). Found (%): C, 72.85; H, 5.62; N, 10.22. $C_{17}H_{16}N_2O_2$. Calculated (%): C, 72.84; H, 5.75; N, 9.99. IR ($CHCl_3$), ν/cm^{-1}: 1040 (OCH_3); 1705 (C=O); 3250, 3390 (br., NH, OH).

C. A mixture of iodide **9** (2.8 g, 0.01 mol), acetylenide **12b** (2.3 g, 0.0112 mol), and Py (50 mL) was refluxed under a stream of Ar for 1.5—2 h. After completion of the reaction (TLC control), the solvent was blown off with air and a solution of the residue in $CHCl_3$ was filtered through a layer of Al_2O_3 (4×5 cm, $CHCl_3$ as the eluent). The filtrate was washed with an aqueous solution of NH_3 (until the blue color disappeared) and water and then dried with Na_2SO_4. The solution was chromatographed on SiO_2 (5×6 cm, benzene as the eluent) three times and 2-acetyl-3-(*p*-nitrobenzyl)-1*H*-indazole (**15**) was isolated in a yield of 0.47 g (15.2%), m.p. 123—125 °C (from EtOAc). ^1H NMR ($CDCl_3$), δ: 2.75 (s, 3 H, CH_3); 4.41 (s, 2 H, CH_2); 7.3—7.6 (m, 5 H, H(3′), H(5′), H(4), H(5), H(6)); 8.17 (d, 2 H, H(2′), H(6′), $J_{2′,6′}$ = 11.25 Hz); 8.46 (d, 1 H, H(7), $J_{7,6}$ = 8.4 Hz). Found (%): C, 64.92; H, 4.32; N, 14.11. $C_{16}H_{13}N_3O_3$. Calculated (%): C, 65.08; H, 4.44; N, 14.23. IR ($CHCl_3$), ν/cm^{-1}: 1350, 1330 (sh), 1530 (NO_2); 1720, 1710 (sh) (C=O).

2′-[2-(Nitrophenylethynyl)phenyl]acetohydrazide (13b). A mixture of iodide **9** (3.0 g, 0.0108 mol), *p*-nitrophenylacetylene **2b** [18] (2.0 g, 0.013 mol), $(Ph_3P)_2PdCl_2$ (80 mg), and CuI (40 mg) was refluxed in a mixture of Et_3N (6 mL) and benzene (40 mL) under an atmosphere of Ar for 12 h. The reaction mixture was filtered through a layer of SiO_2 (3×3 cm, $CHCl_3$ as the eluent), the solvent was distilled off, and the residue was twice chromatographed on SiO_2 (4×7 cm, $PhCH_3$ and $CHCl_3$ as the eluents; 4×12 cm, $CHCl_3$ as the eluent). Compound **13b** was isolated in a yield of 2.1 g (67.7%), m.p. 165—166 °C (from EtOH—C_6H_6). ^1H NMR ($CDCl_3$), δ: 2.15 (s, 3 H, CH_3); 6.8—7.62 (m, 6 H, H(3), H(4), H(5), H(6), H(2′), H(6′)); 8.20 (d, 2 H, H(3′), H(5′), $J_{3′,5′}$ = 8.6 Hz). Found (%): C, 64.61; H, 4.24; N, 14.43. $C_{16}H_{13}N_3O_3$. Calculated (%): C, 65.08; H, 4.44; N, 14.23. IR ($CHCl_3$), ν/cm^{-1}: 1350 and 1530 (NO_2); 1710 (C=O); 2220 (C≡C); 3450 (br., NH).

1-Acetamido-2-(4-nitrophenyl)indole (14b). ***A.*** A mixture of compound **13b** (0.88 g, 0.003 mol), CuI (200 mg), and DMF (40 mL) was heated under a stream of Ar at 120 °C for 8 h. The reaction mixture was filtered through a layer of Al_2O_3 (2.5×4 cm, $CHCl_3$ as the eluent), the solvent was distilled off, and the residue was chromatographed on SiO_2 (2.5×4 cm, $CHCl_3$ as the eluent). Compound **14b** was obtained in a yield of 0.39 g. Preparative chromatography on SiO_2 afforded an additional amount of product **14b** (0.25 g); the total yield was 72.7%, m.p. 287.5—288.5 °C (from EtOH). ^1H NMR ($CDCl_3$, 50 °C), δ: 1.52 and 2.22 (both s, 3 H, =C(OH)CH_3 and $COCH_3$); 6.83 and 6.95 (both s, 1 H, H(3) and H(3′)); 7.2—8.45 (m, 8 H, H arom.). Found (%): C, 65.13; H, 4.51; N, 14.05. $C_{16}H_{13}N_3O_3$. Calculated (%): C, 65.08; H, 4.44; N, 14.23. IR ($CHCl_3$), ν/cm^{-1}: 1340, 1510 (NO_2); 1680 (C=O); 3200, 3380 (br., NH, OH).

B. A mixture of iodide **9** (0.7 g, 0.0025 mol), acetylenide **12b** (0.6 g, 0.0029 mol), and DMF (20 mL) was refluxed under a stream of Ar for 3 h. The reaction mixture was diluted with water (50 mL) and extracted with $CHCl_3$. The extract was washed with an aqueous solution of NH_3 and water and then dried with Na_2SO_4. After removal of the solvent, the residue was passed through a layer of SiO_2 (2×4 cm, $CHCl_3$ as the eluent), the solvent was distilled off, and the residue was recrystallized from EtOH. Compound **14b** was obtained in a yield of 0.56 g (74.7%), m.p. 280—283 °C. Its ^1H NMR spectrum is identical with that of compound **14b** prepared from **13b**.

3-(4-Nitrobenzyl)indazole (7). ***A.*** A solution of hydrazine **6** (3.29 g, 0.014 mol), phenylacetylene **2b** (2.65 g, 0.018 mol), $(Ph_3P)_2PdCl_2$ (60 mg), and CuI (30 mg) in a mixture of Et_3N (20 mL) and benzene (50 mL) was refluxed under an atmosphere of Ar for 4.5 h. After completion of the reaction, the mixture was diluted with ether and twice filtered through a layer of SiO_2 (3×7 cm, ether as the eluent), the solvent was distilled off, and the residue was chromatographed on SiO_2 (4.5×13 cm, benzene and ether as the eluents) three times. Compound **7** was obtained in a yield of 1.34 g (38.3%), m.p. 117—118 °C (from a benzene—hexane mixture). ^{1}H NMR ($CDCl_3$), δ: 4.45 (s, 2 H, CH_2); 7.0—8.2 (m, 8 H, H arom.); 10.6 (br.s, 1 H, NH). Found (%): C, 66.44; H, 4.49; N, 16.32. $C_{14}H_{11}N_3O_2$. Calculated (%): C, 66.40; H, 4.38; N, 16.59. IR ($CHCl_3$), ν/cm^{-1}: 1350 and 1530 (NO_2); 3480 (br., NH). When the reaction was carried out at 20 °C (8 h), 80.8% of the starting *p*-nitrophenylacetylene remained unconsumed.

B. A mixture of acetylhydrazine **13b** (1.0 g, 0.0034 mol), K_2CO_3 (200 mg), and Bu^{n}OH (20 mL) was refluxed for 2 h, the solvent was distilled off, and the residue was chromatographed on SiO_2 (2.5×3.5 cm, $CHCl_3$ as the eluent). After recrystallization, compound **7** was isolated in a yield of 0.27 g. The mother liquor was chromatographed on SiO_2 (1.5×7 cm, $PhCH_3$ and $CHCl_3$ as the eluents) to obtain an additional amount of product **7** (0.21 g); the total yield was 48.0%, m.p. 113—114 °C (from a benzene—hexane mixture). The ^{1}H NMR spectrum of the resulting compound is identical with that of compound **7** prepared from hydrazine **6** and phenylacetylene **1b**.

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References

1. S. F. Vasilevsky and E. V. Tretyakov, *Lieb. Ann. Chem.*, 1995, 775.
2. M. S. Shvartsberg, I. D. Ivanchikova, and S. F. Vasilevsky, *Tetrahedron Lett.*, 1994, **35**, 2077.
3. E. V. Tretyakov, D. W. Knight, and S. F. Vasilevsky, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3721.
4. S. F. Vasilevsky and T. A. Prikhodko, *Mendeleev Commun.*, 1996, **3**, 98.
5. T. A. Prikhodko and S. F. Vasilevsky, *Mendeleev Commun.*, 1998, **4**, 149.
6. D. E. Ames and D. Bull, *Tetrahedron*, 1982, **38**, 383.
7. S. F. Vasilevskii, A. V. Pozdnyakov, and M. S. Shvartsberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1985, 1367 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1985, **34**, 1250 (Engl. Transl.)].
8. M. I. Terekhova, E. S. Petrov, S. F. Vasilevskii, M. S. Shvartsberg, and V. F. Ivanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 923 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984, **33**, 850 (Engl. Transl.)].
9. E. V. Tretyakov, D. W. Knight, and S. F. Vasilevsky, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3713.
10. *Beilstein Handbuch der Organischen Chemie*, Springer, Berlin, 1930, **5**, 133.
11. L. Brandsma, S. F. Vasilevsky, and H. D. Verkruijsse, *Application of Transition Metal Catalysts in Organic Synthesis*, Springer-Verlag, Heidelberg—Berlin—New York, 1998, 220.
12. N. A. Bumagin, A. B. Ponomaryov, and I. P. Beletskaya, *Synthesis*, 1984, 728.
13. A. N. Kost, P. B. Terent´ev, and T. Zavada, *Dokl. Akad. Nauk SSSR,* 1960, **130**, 326 [*Dokl. Chem.*, 1960 (Engl. Transl.)].
14. A. I. Belov, M. I. Terekhova, E. S. Petrov, S. F. Vasilevsky, and M. S. Shvartsberg, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 507 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 398 (Engl. Transl.)].
15. R. D. Stephens and C. E. Castro, *J. Org. Chem.*, 1963, **28**, 3313.
16. M. Hunsberger, E. R. Shaw, J. Fugger, R. Ketcham, and D. Lednicer, *J. Org. Chem.*, 1956, **21**, 394.
17. E. Votocek, V. Ettel, and M. B. Koppova, *Bull. Soc. Chim. Fr.*, 1926, **39**, 278.
18. N. A. Bumagin, A. B. Ponomaryov, and I. P. Beletskaya, *Synthesis*, 1984, 728.

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