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Dedicated to Full Member of the Russian Academy of Sciences
N.S. Zefirov on occasion of his 75th anniversary

Cross-Coupling of 4,5,6,7-Tetrahydroindole with Functionalized Haloacetylenes on Active Surfaces of Metal Oxides and Salts

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Abstract—Screening was performed of metal oxides (MgO, CaO, ZnO, BaO, Al_2O_3, TiO_2, ZrO_2) and salts ($CaCO_3$, K_2CO_3, $ZrSiO_4$) as active surfaces for the reaction of ethynylation of 4,5,6,7-tetrahydroindole with ethyl bromopropynoate and bromobenzoylacetylene. It was established that Ca, Mg, Zn, and Ba oxides assist the ethynylation of 4,5,6,7-tetrahydroindole, and their activity in the reaction with ethyl bromopropynoate considerably exceeds that of aluminum oxide. The ethynylation is accompanied with the formation of intermediate *E*-2-(1-bromoethenyl)-4,5,6,7-tetrahydroindole and side 1,1-di(4,5,6,7-tetrahydroindol-2-yl)ethenes and 1,1-di(4,5,6,7-tetrahydroindol-2-yl)bromoethanes.

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The regioselective functionalization of pyrroles and indoles remains an urgent task in the chemistry of heterocyclic compounds since these compounds are structural fragments of numerous biologically active natural substances and pharmaceuticals [1, 2]. A special attention among the compounds of the pyrrole and indole series is attracted by their ethynyl derivatives owing to the rich chemistry of the acetylene function [3–7]. In this connection considerable efforts are devoted to the development of new effective procedures for the synthesis of *C*-ethynylpyrroles and -indoles [8–12].

However the majority of the known methods of the ethynylation of pyrrole ring requires the use of functionalized pyrroles and indoles as initial reagents [13].

We recently developed a new method of introduction of an acetylene substituent into the position *2* of the pyrrole ring [14, 15] or the position *3* of the indole ring [16, 17] based on the cross-coupling of pyrroles or indoles with electrophilic haloacetylenes on the surface of aluminum oxide that did not require special catalysts, bases, solvents, inert atmosphere, and which proceeded at room temperature. The most promising for the use in this reaction is the 4,5,6,7-tetrahydroindole that has become the most available indole derivative due to the development of the one-pot technology of its preparation from cyclohexanone oxime and acetylene [18]. Being actually an active pyrrole (namely, 2,3-dialkyl-substituted pyrrole), 4,5,6,7-tetrahydroindole (**I**) unlike indole has the most reactive position *2* thus providing a possibility of its ethynylation just in this position opening the way to the synthesis o f versatile 2-derivatives of 4,5,6,7-tetrahydroindole and by dehydrogenation, to 2-substituted indoles, structural analogs of many important alkaloids [2, 19].

Yet on the surface of the aluminum oxide the reaction of 4,5,6,7-tetrahydroindole with haloacetylenes occurs nonselectively: Along the expected 2-ethynyl-4,5,6,7-tetrahydroindoles form the corresponding 2-(1-haloethenyl)-4,5,6,7-tetrahydroindoles, and also the products of the exchange in the latter of a halogen atom with the molecule of the initial pyrrole, 1,1-di(4,5,6,7-tetrahydroindol-2-yl)ethenes[14, 20].

In this study aiming at the increase in the efficiency and selectivity of the synthesis of 2-ethynyl-4,5,6,7-tetrahydroindoles we investigated in detail the cross-coupling of 4,5,6,7-tetrahydroindole (**Ia**) with ethyl bromopropynoate (**IIa**) and benzoylbromoacetylene (**IIb**) on the surface of metal oxides (zinc, barium, calcium, magnesium, titanium, and zirconium oxides) and salts (potassium and calcium carbonates, zirconium silicate). The reactions were carried out at room temperature by grinding equimolar quantities of reagents with solid metal oxides or salts taken in 10-fold excess in the absence of solvents. Depending on the nature of the active surface compounds **III–VI** were obtained (Scheme 1). The content of compounds **III–VI** in the reaction mixture was determined from the ^{1}H NMR spectra of samples in $CDCl_3$ taken from the reaction mixture after 0.5 h of grinding (see the table).

The screening of the above series of metal oxides and salts as active surfaces for the cross-coupling of pyrroles with haloacetylenes was performed by an example of reaction of 2-phenylpyrrole with benzoylbromoacetylene [21]. It was established that the oxides of calcium, magnesium, zinc, and barium were efficient in the ethynylation of the pyrrole ring whereas the silicon, titanium, and zirconium oxides and salts (zirconium silicate and calcium carbonate) specifically promoted the region- and stereoselective addition of the 2-phenylpyrrole to the triple bond of the benzoylbromoacetylene.

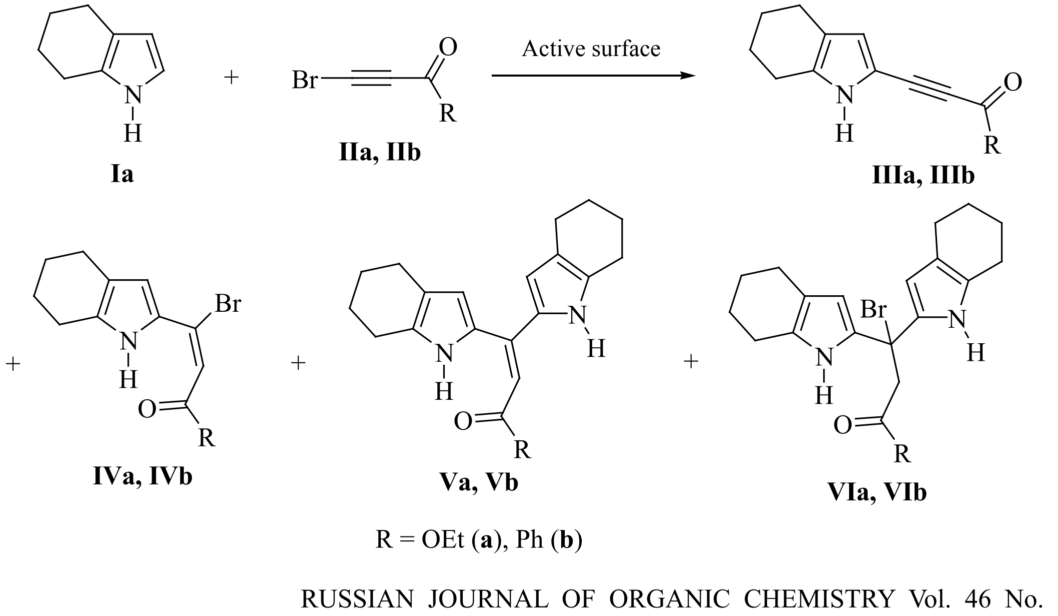
However taking into account the fundamental difference in the reactivity of the 2-phenylpyrrole and the 4,5,6,7-tetrahydroindole in some reactions [22, 23] and also the unlike reactivity of the benzoylbromoacetylene and the ethyl bromopropynoate in the reaction of the ethynylation of the pyrrole [14, 20] and indole [16, 17] rings it was difficult to predict in advance which of the cited active surfaces would be the most suitable for the synthesis of 2-benzoylethynyl- or 2-ethoxycarbonylethynyl-4,5,6,7-tetrahydroindoles.

It actually proved that in contrast to the 2-phenylpyrrole 4,5,6,7-tetrahydroindole (**I**) reacted with ethyl bromopropynoate (**IIa**) on all mentioned active surfaces with the formation of the corresponding ethynyl derivative **IIIa**. Therewith the reaction mixtures obtained on the oxides of calcium, barium, magnesium, and zinc contained several times more 2-ethynyltetrahydroindole **IIIa** than the product mixtures formed on the aluminum oxide. The conversion of tetrahydroindole **Ia** on all studied surfaces was close to 100% (unlike the analogous reactions of the 2-phenylpyrrole whose conversion was 46-100%).

For instance, the reaction mixture obtained with calcium oxide contained 90% of ethynyltetrahydroindole **IIIa** (see the table), whereas the 2-phenylpyrrole under similar conditions reacted to the conversion not exceeding 29%, and the content of 2-ethynyl-5-phenylpyrrole was in this case 19% [21].

Similar to the reaction on aluminum oxide, on the mentioned active surfaces the cross-coupling is accom-

Scheme 1.



R = OEt (**a**), Ph (**b**)

Monitoring by ^{1}H NMR method of reaction between 4,5,6,7-tetrahydroindole (**Ia**) with ethyl bromopropynoate (**IIa**) or benzoylbromoacetylene (**IIb**) (room temperature, 0.5 h)

Oxide or salt (active surface)	Ethyl bromopropynoate (**IIa**)					Benzoylbromoacetylene (**IIb**)				
	Composition of reaction mixture, %									
	Ia	**IIIa**	**IVa**	**Va**	**VIa**	**Ia**	**IIIb**	**IVb**	**Vb**	**VIb**
MgO	0	84	14	2	0	10	62	14	0	14
CaO	0	90	8	2	0	0	80	8	12	0
ZnO	0	61	22	3	14	0	50	43	0	7
BaO	0	87	9	4	0	0	55	24	11	10
Al_2O_3 (pH 9.3)	0	27	54	15	4	0	67	24	9	0
SiO_2	0	16	35	4	45	0	0	100	0	0
TiO_2	0	20	35	6	39	0	5	54	11	30
ZrO_2	0	13	40	10	37	0	21	45	0	34
K_2CO_3	0	100	0	0	0	0	67	30	3	0
$CaCO_3$	0	24	35	7	34	0	25	49	9	17
$ZrSiO_4$	0	17	36	3	44	0	0	58	17	25

panied with the formation of 2-(1-bromoethenyl)-4,5,6,7-tetrahydroindole (**IVa**) and di-(4,5,6,7-tetrahydroindol-2-yl)-ethene (**Va**) (Scheme 1), and the former is an intermediate compound.

The side product of the reaction, 1,1-di(4,5,6,7-tetrahydroindol-2-yl)ethene (**Va**) resulting from the replacement of the bromine atom in intermediate **IV** by the molecule of tetrahydroindole **Ia** (Scheme 2) formed always in negligible amounts.

Scheme 2.

$$\mathbf{IVa,\ IVb} \xrightarrow[-\mathrm{HBr}]{\mathbf{Ia}} \mathbf{Va,\ Vb}$$

As was formerly reported [24] in the presence of the potassium carbonate under the studied reaction conditions 4,5,6,7-tetrahydroindole **Ia** with ethyl bromopropynoate (**IIa**) selectively formed 2-ethynyl-4,5,6,7-tetrahydroindole (**IIIa**).

On the surface of silicon, titanium, zirconium oxides and salts (calcium carbonate and zirconium silicate) the ethynylation occurred to a low yield (13–24%, see the table). The main product of these reactions is unstable di(4,5,6,7-tetrahydroindol-2-yl)bromoethane (**VIa**). This compound was previously shown [20] to form without involvement of the active surface by the nucleophilic addition of tetrahydroindole **Ia** to intermediate 2-(1-bromoethenyl)-4,5,6,7-tetrahydroindole (**IVa**) (Scheme 3). In all cases the content of 2-(1-bromoethenyl)-4,5,6,7-tetrahydroindole (**IVa**) in the reaction mixtures did not exceed 35–40%.

Scheme 3.

$$\mathbf{IVa,\ IVb} \xrightarrow{\mathbf{Ia}} \mathbf{VIa,\ Vib}$$

Tetrahydroindole **Ia** reacted with benzoylbromoacetylene (**IIb**) on the studied metal oxides less actively and less selectively than with ethyl bromopropynoate (**IIa**) (see the table). The only exception is the aluminum oxide: In its presence the content of 2-(benzoylethynyl)-4,5,6,7-tetrahydroindole (**IIIb**) in the reaction mixture is 2.5 times higher than the content of 2-ethynyltetrahydroindole **IIIa** obtained under similar conditions from ethyl bromopropynoate (**IIa**). The only surface exceeding in this respect that of the aluminum oxide is the surface of the calcium oxide. On the titanium and zirconium oxides and on the calcium carbonate tetrahydroindole **Ia** reacted with acetylene derivative **IIb** giving a mixture of 2-(bromoethenyl)- (**IVb**) and 2-ethynyl-4,5,6,7-tetrahydroindoles (**IIIb**). Besides in the reaction products obtained on these active surfaces compound **VIb** was detected.

The only active surface assisting the region- and stereoselective addition of tetrahydroindole **Ia** to the triple bond of benzoylbromoacetylene (**IIb)** was silicon oxide (see the table).

The potassium carbonate, the most selective and efficient in the reaction of tetrahydroindole **Ia** ethynylation with ethyl bromopropynoate (**IIa**), acts nonselectively in the reaction with acetylene **IIb**: Some part of the reaction intermediate bromoethenyltetrahydroindole **IVb** remains in the reaction mixture. Yet the increase in the reaction duration to 1 h or the use of potassium carbonate 2-fold amount made it possible to carry out this reaction materially selectively and to isolate ethynylpyrrole **IIIb** in 66% yield. Analogously from *N*-methyl- and *N*-benzyl-4,5,6,7-tetrahydroindoles we obtained the corresponding ethynyltetrahydroindoles **VII**, **VIII** in 68–71% yield (Scheme 4).

Thus new active surfaces were found (calcium, magnesium, barium, and zinc oxides) permitting the efficient and regioselective introduction of a functional acetylene substituent into the position *2* of the tetrahydroindole skeleton without solvent and specially added transition metal compounds.

The effect of the nature of the active surfaces and the structure of the haloacetylene (ethyl bromopropynoate and benzoylbromoacetylene) was studied on the content in the reaction mixtures of intermediate *E*-2-(1-bromoethenyl)-4,5,6,7-tetrahydroindoles **IVa, IVb** and the side products 1,1-di-(4,5,6,7-tetrahydroindol-2-yl) ethenes **Va, Vb** and 1,1-di-(4,5,6,7-tetrahydroindol-2-yl) bromoethanes **VIa, VIb.**

EXPERIMENTAL

IR spectra of compounds were recorded on a spectrophotometer Bruker IFS-25 in the region 400–4000 CM^{-1} from pellets with KBr. ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker DPX 400 [operating frequencies 400.13 (^{1}H) and 100.6 (^{13}C) MHz], solvent $CDCl_3$, internal reference HMDS.

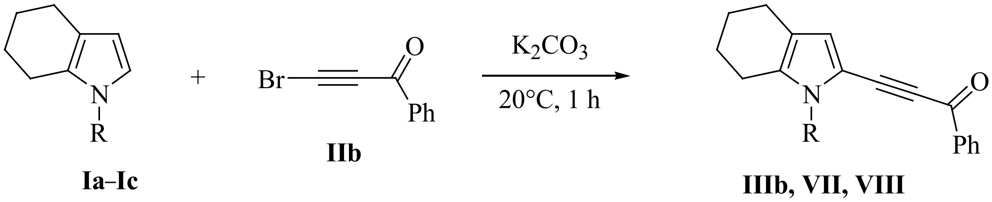
Ethynylation of 4,5,6,7-tetrahydroindole (Ia) with haloacetylenes on active surfaces. Equimolar amounts of 4,5,6,7-tetrahydroindole (**Ia**) and haloacetylene **IIa** or **IIb** were thoroughly ground for 5 min at room temperature in a porcelain mortar with an oxide or a salt taken in 10-fold excess with respect to the overall amount of reagent. The reaction mixture was kept for 25 min more and was analyzed by ^{1}H NMR. To this end a weighed portion (100–120 mg) of the reaction mixture was washed with $CDCl_3$. The ratio of the reaction products was determined by the integral intensity of signals of the H^3 proton of the tetrahydroindole ring of compounds **IIIa** (6.49 ppm) and **IIIb** (6.61 ppm); H^3 and H_a protons of compounds **IVa** (6.66 and 6.05 ppm) and **IVb** (6.84 and 7.10 ppm); H^3, $H^{3'}$, and H_a protons of compounds **Va** (6.29, 6.41, and 5.56 ppm) and **Vb** (6.62, 6.56 and 6.50 ppm); H^3, CH_2COPh, 7-CH_2 of the cyclohexane ring of compounds **VIa** (7.06, 3.90, and 3.20 ppm) and **VIb** (7.15, 4.64, and 3.20 ppm).

Reaction of 4,5,6,7-tetrahydroindole (Ia), 1-methyl- and 1-benzyl-4,5,6,7-tetrahydroindoles (Ib, Ic) with benzoylbromoacetylene (IIb) on K_2CO_3. *General procedure*. A mixture of 1 mmol of tetrahydroindole **Ia–Ic** and 1 mmol of acetylene derivative **IIb** was thoroughly ground for 5 min at room temperature in a porcelain mortar with 10-fold excess of potassium carbonate. The mixture self-heated to 30°C and acquired bright yellow color that further became brown. The reaction mixture was kept for 1 h and then treated with water. The separated crystals were filtered off, dried to the constant weight, and the ethynyltetrahydroindoles **IIIb, VII, VIII** were purified by column chromatography on aluminum oxide (eluent hexane).

Spectral characteristics of 2-benzoylethynyl-4,5,6,7-tetrahydroindole (**IIIb**) were reported in [14].

2-Benzoylethynyl-1-methyl-4,5,6,7-tetrahydroindole (VII). Yield 0.179 g (68%). Orange crystals, mp 116–117°C. IR spectrum, ν, cm^{-1}: 2156 (C≡C), 1608 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.73 m (2H, 5-CH_2),

Scheme 4.



R = H (**Ia, IIIb**), Me (**Ib, VII**), Bn (**Ic, VIII**).

1.83 m (2H, 6-CH_2), 2.49 m (2H, 4-CH_2), 2.55 m (2H, 7-CH_2), 3.63 s (3H, NMe), 6.62 s (1H, H^3), 7.47 m (2H, H^m COPh), 7.57 m (1H, H^p COPh), 8.14 m (2H, H^o COPh). ^{13}C NMR spectrum, δ, ppm: 22.5, 22.7, 22.9, 23.1 (4,5,6,7-CH_2), 31.2 (NMe), 90.0 (C≡), 96.7 (≡C), 110.7 (C^3), 119.4 (C^4), 119.8 (C^2), 128.4 (C^5), 129.0 (C^o COPh), 133.3 (C^m COPh), 136.1 (C^p COPh), 137.3 (C^i COPh), 177.1 (C=O). Found, %: C 81.77; H 6.42; N 5.13. $C_{18}H_{17}NO$. Calculated, %: C 82.10; H 6.51; N 5.32.

2-Benzoylethynyl-1-benzyl-4,5,6,7-tetrahydroindole (VIII). Yield 0.241 g (71%). Light-yellow crystals, mp 106–107°C. IR spectrum, ν, cm^{-1}: 2163 (C≡C), 1622 (C=O). ^1H NMR spectrum, δ, ppm: 1.71 m (2H, 5-CH_2), 1.77 m (2H, 6-CH_2), 2.45 m (2H, 4-CH_2), 2.52 m (2H, 7-CH_2), 5.23 s (2H, NCH_2), 6.70 s (1H, H^3), 7.08 m (2H, H^o CH_2Ph), 7.31–7. 51 m (6H, $H^{m,p}$ CH_2Ph, COPh), 7.97 m (2H, H^o COPh). ^{13}C NMR spectrum, δ, ppm: 22.9, 23.0, 23.2, 23.4 (4,5,6,7-CH_2), 48.5 (NCH_2), 90.0 (C≡), 96.6 (≡C), 111.3 (C^3), 120.3 (C^4), 120.7 (C^2), 126.7 (C^5), 127.8 (C^p CH_2Ph), 128.7 (C^m CH_2Ph), 129.1 (C^o CH_2Ph), 129.3 (C^o COPh), 133.6 (C^p COPh), 136.2 (C^i COPh), 137.6 (C^i CH_2Ph), 177.5 (C=O). Found, %: C 84.57; H 6.42; N 4.03. $C_{24}H_{21}NO$. Calculated, %: C 84.92; H 6.24; N 4.13.

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