

Reaction of 1,5-Diphenyl-1,4-pentadien-3-one and 1,5-Diphenyl-1-penten-4-yn-3-one with Monosubstituted Hydrazines

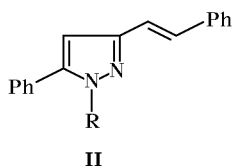
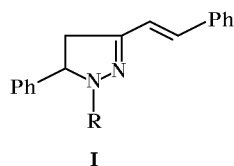
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Abstract—Phenyl- and isopropylhydrazines react with 1,5-diphenyl-1,4-pentadien-3-one to give 4,5,6,7-tetrahydroindazole derivatives instead of the expected 4,5-dihydropyrazoles. The reaction of phenylhydrazine with 1,5-diphenyl-1-penten-4-yn-3-one leads to formation of 1,5-diphenyl-3-phenylethynyl-4,5-dihydropyrazole. 2,4-Dinitrophenylhydrazine reacts with 1,5-diphenyl-1-penten-4-yn-3-one, affording the corresponding unsaturated hydrazone rather than pyrazole derivative.

While studying oxidative addition of *N*-aminoaziridines to compounds having a conjugated double C=C bond [1–3] we turned our attention to 3-styryl-substituted 4,5-dihydropyrazoles and pyrazoles which contain a N=C–C=C fragment. As subjects for study we chose heterocycles of types **I** and **II**, which we planned to obtain by the known [4–8] reaction of monosubstituted hydrazines with readily accessible 1,5-diphenyl-1,4-pentadien-3-one (**III**) and 1,5-diphenyl-1-penten-4-yn-3-one.

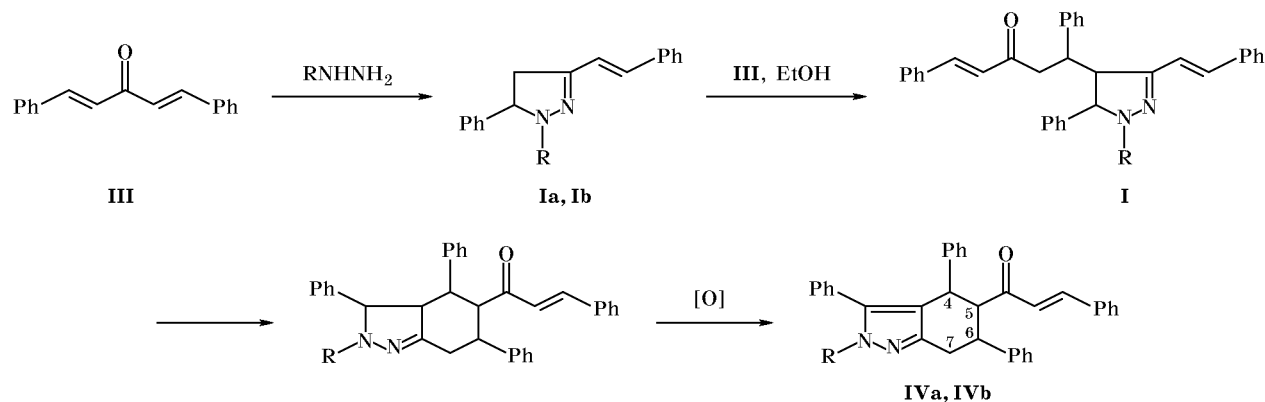


I, R = *i*-Pr (a), Ph (b); **II**, R = Ph (a), 2,4-(NO₂)₂C₆H₃ (b).

However, we found neither published data on dihydropyrazole **Ia** nor general procedure for preparation of *N*-alkyl-substituted 3-styryldihydropyrazoles. Therefore, we made an attempt to synthesize compound **Ia** by analogy with *N*-aryl-substituted derivatives which can be obtained by reaction of **III** with the corresponding arylhydrazines in ethanol, ethyl acetate, or glacial acetic acid [4–7]. We did not use ethyl acetate as solvent, for it is capable of reacting with isopropylhydrazine to give acetohydrazide, and the first experiments were carried out in ethanol. The product obtained by reaction of equimolar amounts of isopropylhydrazine and compound **III** in ethanol,

compound **IV**, was clearly different from the desired styrylpyrazole **Ia**. According to the ¹H and ¹³C NMR spectra (see table), the molecule of **IV** contains four rather than two nonequivalent phenyl groups, tetrasubstituted C=C bond, *trans*-HC=CH bond, carbonyl group, and seven aliphatic carbon atoms, three of which belong to the isopropyl group with diastereotopic methyl substituents. The molecular ion peak in the mass spectrum of **IVa** was observed at *m/z* 522. The elemental composition of the product corresponds to the formula C₃₇H₃₄N₂O which implies addition of two molecules of ketone **III** to one molecule of isopropylhydrazine with loss of water molecule and two hydrogen atoms. The above data led us to assume the following scheme for the reaction of ketone **III** with isopropylhydrazine in ethanol (Scheme 1). The primary addition product, dihydropyrazole **Ia** loses a proton from the methylene group by the action of isopropylhydrazine. The subsequent Michael addition of the second molecule **III**, intramolecular ring closure, and oxidation (probably, with atmospheric oxygen) yield the final product, (*E*)-1-(2-isopropyl-3,4,6-triphenyl-4,5,6,7-tetrahydro-2*H*-indazol-5-yl)-3-phenylpropen-2-one (**IVa**). The proposed structure is well consistent with the aliphatic region of the ¹H NMR spectrum (see table). The doublet at δ 4.64 ppm belongs to the 4-H proton. The 5-H and 6-H protons are coupled both with each other and with 4-H, and their signals merge together into one multiplet at δ 3.50–3.65 ppm. Diastereotopic protons 7-H, each being additionally coupled with 6-H, also give rise to a multiplet at δ 2.97–3.18 ppm. The *m/z* values of

Scheme 1.



I, IV, R = *i*-Pr (a), Ph (b).

most fragment ions in the mass spectrum of **IV** are also consistent with structure **IV**.

Ketone **III** failed to react with isopropylhydrazine in glacial acetic acid both at 20–25°C and on heating. Crystals of isopropylhydrazinium acetate precipitated from the reaction solution on slight cooling.

We tried to synthesize 1,5-diphenyl-3-styryl-4,5-dihydropyrazole (**Ib**) by the known procedure [7], according to which equimolar amounts of phenylhydrazine and ketone **III** should be heated in ethanol. However, the reaction under these conditions gave product **IVb**, whose melting point exceeded by 85°C that given in [7, 9] for **Ib**. The ¹H and ¹³C NMR spectra of **IVb** (see table) were very similar to those obtained for **IVa** (with regard to replacement of the isopropyl group by phenyl). Thus product **IVb** was assigned the structure of 1-(2,3,4,6-tetraphenyl-4,5,6,7-tetrahydro-2*H*-indazol-5-yl)-3-phenyl-2-propen-2-one (**IVb**). The composition of **IVb** was confirmed by elemental analysis.

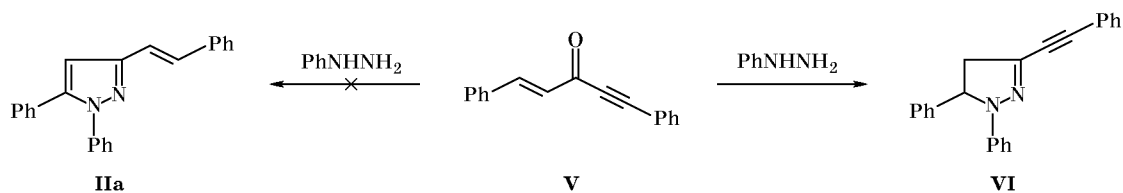
Unfortunately, strong signal overlap did not allow us to determine coupling constants of protons in the six-membered ring of tetrahydroindazoles **IVa** and **IVb**. We clearly observed only the coupling constant ³J_{4,5} which was equal to 8.3 Hz for compound **IVa** and 9.7 Hz for **IVb**. These values indicate pseudo-axial orientation of both 4-H and 5-H and hence *trans*

arrangement of the substituents on C⁴ and C⁵. The orientation of phenyl group on C⁶ was not determined, but we presume that it is located *trans* with respect to the styryl group. In this case the three substituents in the six-membered ring occupy pseudoequatorial positions, so that unfavorable steric interactions are minimized.

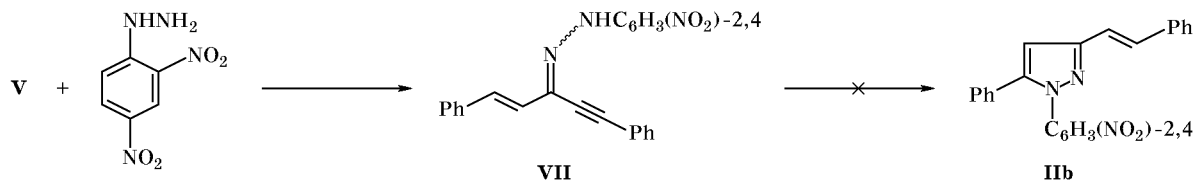
When the reaction of **III** with phenylhydrazine was carried out in glacial acetic acid (by analogy with the procedure given in [5] for *para*-substituted dibenzylideneacetones and various arylhydrazines), we isolated just 1,5-diphenyl-3-[(*E*)-2-phenylethenyl]-4,5-dihydropyrazole (**Ib**) in 71% yield. The structure of **Ib** was confirmed by the ¹H and ¹³C NMR spectra (see table) and analytical data. Its melting point was similar to that reported in [7, 9].

These results lead us to believe that the reaction of ketone **III** with monosubstituted hydrazines is strongly influenced by the acidity of the medium. The reaction with phenylhydrazine in acetic acid leads to formation of the expected product, whereas more basic isopropylhydrazine with acetic acid forms the corresponding acetate which does not react with ketone **III** at all. Ethanol is more basic than acetic acid, and intermediately formed pyrazoles **Ia** and **Ib** are likely to undergo fast deprotonation with the hydrazine present in the reaction mixture, despite

Scheme 2.



Scheme 3.



equimolar amounts of the reactants. As a result, adducts with the second molecule of ketone **III**, tetrahydroindazoles **IVa** and **IVb**, are readily formed.

The reaction of 1,5-diphenyl-1-penten-4-yn-3-one (**V**) with phenylhydrazine was carried out in acidified alcohol, by analogy with the procedure reported in [8]. Contrary to our expectations based on published data [8], the product was 1,5-diphenyl-3-phenylethynyl-4,5-dihydropyrazole (**VI**) (instead of aromatic styrylpyrazole **IIa**; Scheme 2). The structure of **VI** unambiguously follows from its ^1H and ^{13}C NMR spectra. The ^{13}C NMR spectrum contained two signals at δ_{C} 82.7 and 94.3 ppm, typical of *sp*-hybridized carbon atoms, and the ^1H NMR spectrum lacked signals from olefinic protons. The aliphatic region of the proton spectrum (three doublets of doublets) was similar to the corresponding part of the spectrum of **Ib**.

The reaction of 1,5-diphenyl-1-penten-4-yn-3-one (**V**) with 2,4-dinitrophenylhydrazine was performed by the same procedure as with phenylhydrazine, i.e., in ethanol acidified with acetic acid [8]. The melting point of the product coincided with that given in [8], but, contrary to the authors, no cyclization to pyrazole **IIb** occurred. The reaction stopped at the stage of formation of hydrazone **VII** as a mixture of *E* and *Z* isomers at a ratio of $\sim 3:1$ (Scheme 3). Product **VII** showed in the ^1H NMR spectrum two broadened singlets at δ 11.9 and 12.5 ppm with an intensity ratio of $\sim 1:3$. The position and shape of these signals are typical of NH protons in 2,4-dinitrophenylhydrazones derived from aldehydes and ketones with a triple carbon-carbon bond in the α -position to the $\text{C}=\text{N}$ group. The carbon signals at δ_{C} 105.5 and 76.9 ppm (major isomer) indicate that the triple bond is retained.

EXPERIMENTAL

Elemental compositions of the newly synthesized compounds were determined on a Hewlett-Packard HP-185 C,H,N-analyzer. The ^1H (300 MHz) and ^{13}C NMR spectra (75.4 MHz) were recorded on a Bruker DPX-300 instrument from solutions in CDCl_3 containing TMS as internal reference. The mass spectra (70 eV) were obtained on an MKh-1321 mass spec-

trometer. The purity of the products was checked by TLC on Silufol UV-254 plates.

1,5-Diphenyl-1,4-pentadien-3-one (**III**) [10] and isopropylhydrazine [11] were synthesized by known methods.

1,5-Diphenyl-1-penten-4-yn-3-one (V) was synthesized by analogy with the procedure described in [12]. To a suspension of 0.5 g (2.5 mmol) of Cu_2Cl_2 in 30 ml of benzene we added with stirring under nitrogen 5.5 ml (5.1 g, 50 mmol) of phenylacetylene, 10 g (50 mmol) of triethylamine, and 8.3 g (50 mmol) of cinnamoyl chloride in 30 ml of benzene. The mixture was stirred for 3 h at 60°C and cooled, 50 ml of water was added, and the mixture was treated with benzene. The organic layer was repeatedly washed with dilute hydrochloric acid, dried over CaCl_2 , and evaporated. The oily residue was repeatedly treated with hot hexane, and the hexane solution was passed through a layer of silica gel to remove tars. The solvent was removed, and the residue was recrystallized from hexane. Yield 4 g (34.5%), yellow crystals, mp 70°C [8, 13]. ^1H NMR spectrum (cf. [8]), δ , ppm: 7.92 d (1H, 1-H, $J = 15.5$ Hz), 7.35–7.70 m (10H, 2Ph), 6.89 d (1H, 2-H, $J = 15.5$ Hz).

Reaction of 1,5-diphenyl-1,4-pentadien-3-one (III) with isopropylhydrazine in ethanol. To a solution of 2 g (8.5 mmol) of ketone **III** in 40 ml of ethanol we added with stirring 0.76 ml (0.63 g, 8.5 mmol) of isopropylhydrazine. The mixture was stirred for 3 h under reflux and was left overnight. The precipitate, (*E*)-1-(2-isopropyl-3,4,6-triphenyl-4,5,6,7-tetrahydro-2*H*-indazol-5-yl)-3-phenyl-2-propen-1-one (**IVa**) was transferred to a glass filter, washed with alcohol, dried in air, and recrystallized from ethyl acetate. Yield 1.63 g (73%), mp $215\text{--}218^\circ\text{C}$. ^1H NMR spectrum, δ , ppm: 6.82–7.33 m (20H, 4Ph), 6.76 d (1H, $\text{CH}=\text{C}$, $J = 16.2$ Hz), 5.98 d (1H, $\text{COCH}=\text{C}$, $J = 16.2$ Hz), 4.64 d (1H, 4-H, $J = 8.3$ Hz), 4.44 sept [1H, $\text{CH}(\text{Me})_2$, $J = 6.6$ Hz], 3.50–3.65 m (2H, 5-H, 6-H), 2.97–3.18 m (2H, CH_2), 1.59 d (3H, CH_3 , $J = 6.6$ Hz), 1.54 d (3H, CH_3 , $J = 6.6$ Hz). Mass spectrum, m/z (I_{rel} , %): 523 (33) [$M+1$] $^+$, 522 (73) M^+ , 391 (42) [$M-\text{COCH}=\text{CHPh}$] $^+$, 390 (45), 389 (24), 301 (28) [$M-\text{COCH}=\text{CHPh}-\text{CHPh}$] $^+$, 288

^{13}C NMR spectra (δ_{C} , ppm) of condensation products **Ib**, **IVa**, **IVb**, **V**, and **VI**

Comp. no.	Ph			CH	CH ₃ , CH ₂	C≡C, C=C	C=O	CH=CH	C=N
	C ⁱ	C ^o , C ^m	C ^p						
Ib	136.6, 142.5, 143.7	113.0 (N-Ph), 125.8, 126.8, 128.9, 129.0, 129.1	118.8 (N-Ph), 121.3, 127.5 ^a	62.8	42.0	–	–	128.2, ^a 133.3	148.9
IVa	133.9, 134.6, 137.9, 142.2, 142.5 ^b	127.3, 127.7, 127.8, 127.9, 128.0, 128.3, 128.5, 128.6	126.3, 126.4, 127.1 ^c	44.6, 44.9, 50.1, 61.0	22.1, 22.2, 30.6	114.8 ^b	202.5	130.0, 141.8	148.1
IVb	133.5, 134.8, 139.7, 140.5, 142.7, 142.8 ^b	127.9, 128.2, 128.5, 128.7, 129.3, 129.8 ^c	123.3, 126.2, 126.6, 127.2, 127.4	44.6, 44.9, 60.2	32.6	117.7 ^b	201.9	130.8, 142.3	149.7
V	119.9 (5-Ph) 133.7 (1-Ph)	128.3, 128.7, 132.6 ^c	128.2, 130.8 ^a	–	–	86.3, 91.2	177.8	130.3, ^a 147.9	–
VI	119.6, 141.3, 143.3	113.4 (N-Ph), 125.4, 128.1, 128.6, 128.9, 131.3	121.9 (N-Ph), 127.4, 131.0	63.9	46.2	82.7, 94.3	–	–	141.3

^a Alternative assignment is possible.

^b One of these signals belong to carbon atom of the C=C bond.

^c Some signals overlap.

(100) $[\text{M}-\text{COCH}=\text{CHPh}-\text{PhCH}=\text{CH}]^+$, 245 (24)
 $[\text{M}-\text{COCH}=\text{CHPh}-\text{PhCH}=\text{CH}-i\text{-Pr}]^+$, 131 (58)
 $[\text{COCH}=\text{CHPh}]^+$, 115 (15), 103 (48) $[\text{PhCH}=\text{CH}]^+$,
 91 (36) $[\text{PhCH}_2]^+$, 77 (24) $[\text{Ph}]^+$, 43 (12).

Reaction of 1,5-diphenyl-1,4-pentadien-3-one (III) with phenylhydrazine in ethanol. To a solution of 2 g (8.5 mmol) of ketone **III** in 40 ml of ethanol we added with stirring 0.84 ml (0.92 g, 8.5 mmol) of phenylhydrazine. The mixture was stirred for 3 h under reflux and was left overnight. The precipitate of **IVb** was filtered off through a glass filter, washed with ethanol, dried in air, and recrystallized from ethyl acetate. Yield 0.8 g (33%), mp 240°C. ^1H NMR spectrum, δ , ppm: 6.80–7.70 m (26H, 5Ph, CH=), 6.54 d (1H, COCH=, $J = 16.3$ Hz), 4.73 d (1H, 4-H, $J = 9.7$ Hz), 3.71–3.84 m (1H, 5-H), 3.42–3.62 m (2H, CH₂), 2.88–3.04 m (1H, 6-H).

Reaction of 1,5-diphenyl-1,4-pentadien-3-one (III) with phenylhydrazine in acetic acid. To a solution of 1.5 g (6.5 mmol) of ketone **III** in 50 ml of glacial acetic acid we added 0.64 ml (0.702 g, 6.5 mmol) of phenylhydrazine, and the mixture was left overnight. The precipitate of dihydropyrazole **Ib** was filtered off, washed with alcohol, dried in air, and recrystallized from ethyl acetate. Yield 1.5 g (71%), mp 155°C; published data: mp 151–153°C [7], 152–153°C [9] (compound **Ib** was assigned hydrazone

structure in [9]). ^1H NMR spectrum, δ , ppm: 6.69–7.58 m (17H, 3Ph, CH=CH), 5.47 d.d (1H, CH, $J = 5.5, 12.2$ Hz), 3.76 d.d (1H, CH₂, $J = 12.3, 17.1$ Hz), 2.97 d.d (1H, CH₂, $J = 5.5, 17.0$ Hz).

Reaction of 1,5-diphenyl-1-penten-4-yn-3-one (V) with phenylhydrazine. To a solution of 0.696 g (3 mmol) of ketone **V** in 10 ml of acidified alcohol we added 0.3 ml (0.324 g, 3 mmol) of phenylhydrazine, and the mixture was refluxed for 20 min and left overnight. The oily material was separated, 5 ml of glacial acetic acid was added, and the mixture was left to stand for 24 h. The crystals of dihydropyrazole **VI** were filtered off, washed with alcohol, and dried in air. Yield 0.35 g (35%), mp 145°C. ^1H NMR spectrum, δ , ppm: 6.85–7.60 m (15H, 3Ph), 5.31 d.d (1H, CH, $J = 7.2, 9$ Hz), 3.71 d.d (1H, CH₂, $J = 9, 15$ Hz), 3.02 d.d (1H, CH₂, $J = 7.2, 15$ Hz).

1,5-Diphenyl-1-penten-4-yn-3-one 2,4-dinitrophenylhydrazone (VII) [8]. To a solution of 0.696 g (3 mmol) of ketone **V** in 15 ml of alcohol acidified with acetic acid we added 0.6 g (3 mmol) of 2,4-dinitrophenylhydrazine. The precipitate was filtered off, washed with alcohol, and dried in air. Yield 1 g (80%), mp 232°C [8]. ^1H NMR spectrum, δ , ppm: 12.5 br.s (0.75H, NH), 11.9 br.s (0.25H, NH), 9.12 m (1H, 3-H) and 8.00–8.45 m (2H, 5-H, 6-H) (signals from the 2,4-dinitrophenyl group); 7.05–7.85 m (12H,

2Ph, CH=CH). ^{13}C NMR spectrum of the major isomer, δ_{C} , ppm (signals partially overlapped each other or those of the minor isomer): 143.2, 138.3, 134.4, 132.3 (C^{o}); 131.8, 128.6 (C^{m}); 128.5 (C^{m}); 128.3, 127.7, 127.0 (C^{o}); 123.1, 119.8 (C^{i} , 5-Ph); 116.8, 105.5 (C^{s}); 76.9 (C^{4}). For comparison, below is given the ^{13}C NMR spectrum of an authentic sample of 3-phenylpropynal 2,4-dinitrophenylhydrazone, δ_{C} , ppm: 143.7, 138.6, 132.3 (C^{o}); 131.1, 130.5, 129.3 (C^{m}); 126.4, 122.8, 119.8 (C^{i}); 116.8, 104.4 (C^{3}); 79.6 (C^{2}). Mass spectrum of **VII**, m/z (I_{rel} , %): 242 (15) M^+ , 228 (67), 227 (100), 104 (14), 77 (11), 76 (19), 28 (12). Found, %: C 69.70; H 5.65; N 11.68. $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2$. Calculated, %: C 69.41; H 5.82; N 11.56.

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