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Vilsmeier Formylation of Hydrazones and Semicarbazones Derived from Alkyl, Benzyl, and Cycloalkyl Methyl Ketones

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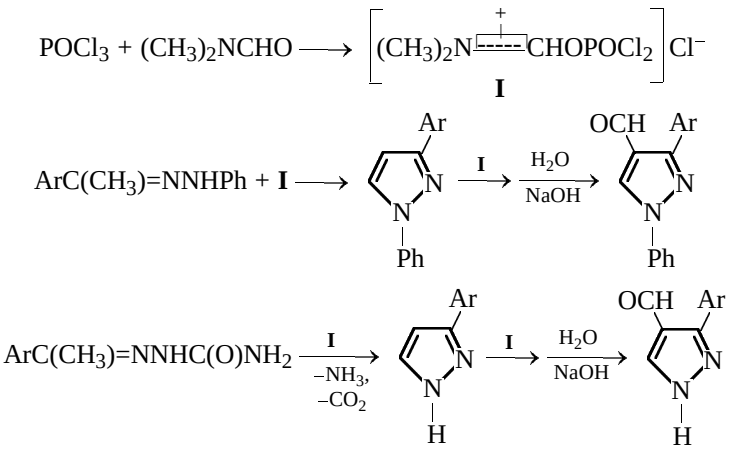
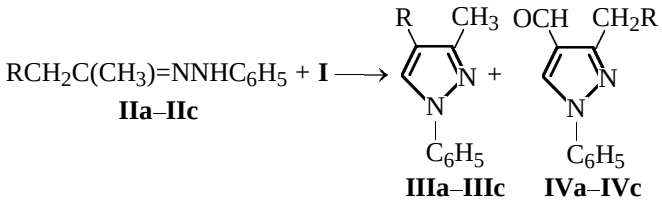
Abstract — Formylation of ten accessible phenylhydrazones and semicarbazones derived from alkyl, benzyl, and cycloalkyl methyl ketones with the complex of $POCl_3$ with dimethylformamide was studied. Depending on the electronic and steric structure of the substrates, the reaction yields 1-phenyl- or 1-unsubstituted 3,4-dialkyl-, 3-alkyl-4-aryl-, or 3-alkyl-4-formylpyrazoles. These compounds can be readily oxidized into the corresponding carboxylic acids.

It is known [1–4] that phenylhydrazones and semicarbazones derived from aryl methyl ketones enter into the Vilsmeier reaction with the complex $POCl_3$–$HC(O)N(CH_3)_2$ (**I**) to give 3-arylpyrazol-4-carboxaldehydes via the sequence of two attacks by complex **I**: first at the CH_3 group of the substrate with the subsequent cyclization into 3-arylpyrazoles and then at the C^4 atom of the resulting heterocycles:



In view of considerable interest in functional derivatives of pyrazole, we studied the similar reaction of complex **I** with phenylhydrazones and semicarbazones of alkyl, benzyl, and cycloalkyl methyl ketones. We found that phenylhydrazones of linear alkyl methyl ketones **IIa**–**IIc** react with **I** in 1 : 2 molar ratio in excess dimethylformamide (DMF) to give as major products the corresponding 1-phenyl-3-methyl-4-alkylpyrazoles **IIIa**–**IIIc**.



R = CH_3 (**a**), C_2H_5 (**b**), *n*-C_3H_7 (**c**).

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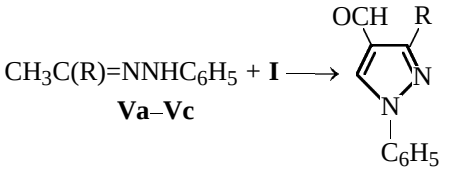
The product ratio **III** : **IV** varies from 50 : 1 for compounds **a** to 10 : 1 for compounds **b** and **c**. These data indicate that the electrophilic attack of **I** is mainly directed at the more electronegative carbon atom of the methylene group of hydrazones **IIa**–**IIc**. Formylation of **IIIa**–**IIIc** at the C^5 atom does not occur.

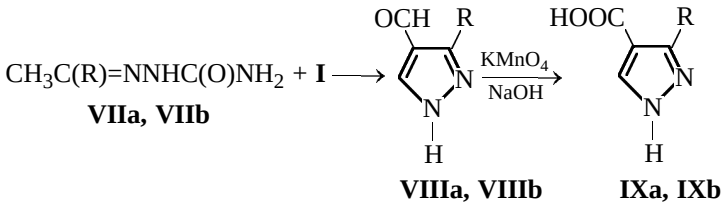
Phenylhydrazones **Va**–**Vc**, in which the methylene group at the C=N bond is either absent or shielded by a branched alkyl group, react differently. The major products are the corresponding 1-phenyl-3-alkylpyrazole-2-carbaldehydes **VIa**–**VIc**; thus, complex **I** mainly attacks the methyl group at the C=N bond.



R = $CH_2CH(CH_3)_2$ (**a**), $CH(CH_3)_2$ (**b**), 1-adamantyl (**c**).

The yield of pyrazolecarbaldehydes **VIa**–**VIc** was 72, 60, and 58%, respectively. Also detected were unchanged starting hydrazones and unidentified compounds with the structure differing from that of **III**.

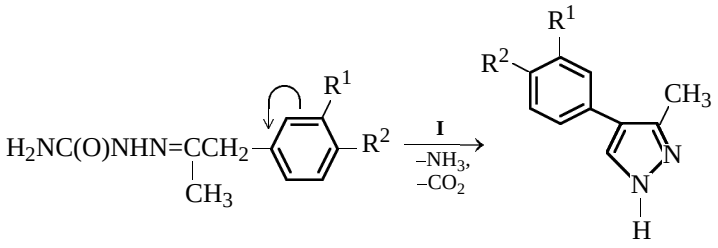
Proceeding from the relationships revealed, we prepared pyrazolecarbaldehydes **VIIIa** and **VIIIb** containing no substituent at the N atom by the reaction of complex **I** with semicarbazones derived from carbocyclic and aliphatic methyl ketones in which the methylene group at the C=N bond is either absent (**VIIa**) or sterically shielded (**VIIb**) compared to the methyl group.



R = cyclohexyl (**a**), $CH_2CH(CH_3)_2$ (**b**).

Pyrazolecarbaldehydes **VIIIa** and **VIIIb**, which are readily soluble in alkalis, are readily oxidized into the corresponding pyrazole-4-carboxylic acids **IXa** and **IXb**.

As expected, under the conditions similar to those of preparation of **VIIIa** and **VIIIb**, semicarbazones **Xa** and **Xb** derived from benzyl methyl ketones form the corresponding 3-methyl-4-arylpyrazoles **XIa** and **XIb**, which is due to the higher electron density on the methylene component in **Xa** and **Xb**, compared to the that on the methyl group, owing to the conjugation of the C=N bond with the benzene ring.



$R^1 = R^2 = H$ (**a**), $R^1 + R^2 = OCH_2O$ (**b**).

The structures of pyrazoles **IIIa**–**IIIc**, **IVa**–**IVc**, **VIa**–**VIc**, **VIIIa**, **VIIIb**, **IXa**, **IXb**, **XIa**, and **XIb** were confirmed by elemental analysis, mass spectrometry, and ^{1}H NMR spectroscopy. It should be noted that the tautomerism of 3(5)-substituents in the diazole ring, typical of 1-unsubstituted pyrazoles and promoted by intermolecular N–H hydrogen bonding, is manifested only in **XIa** as characteristic splitting of the ^{1}H NMR signals of the CH_3, CH, and NH groups of the diazole ring. The ratio of the 3- and 5-CH_3 isomers is 1.8 : 1.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AM-360 spectrometer (360.14 MHz, solvent DMSO-d_6). The mass spectra were taken on a QP-5000 spectrometer (electron impact, 70 eV).

Phenylhydrazones IIa–IIc and Va–Vc. 2-Butanone, 2-pentanone, 2-hexanone, 4-methyl-2-pentanone, or 3-methyl-2-butanone was carefully mixed with an equimolar amount of freshly distilled phenylhydrazine. After the completion of the exothermic reaction, the mixture was cooled to 45°C, five drops of glacial acetic acid were added, and the mixture was stirred for 1 h on a boiling water bath. Then the mixture was cooled, a small amount of aqueous ethanol was added, the aqueous layer was separated, and the residue was distilled at a reduced pressure in a nitrogen flow to obtain compounds **IIa**–**IIc**, **Va**, and **Vb**. Below are the compound nos., bp [°C (*p*, mm Hg)], n_D^{20}, and yield (%): **IIa**, 115–116 (3), 1.5742, 90; **IIb**, 130–133 (3), 1.5637, 80; **IIc**, 141–144 (3), 1.5530, 83; **Va**, 140–142 (3), 1.5494, 95; **Vb**, 102–104 (2), 1.5600, 93.

Compound **Vc** was obtained in 85% yield by dropwise addition of phenylhydrazine to an alcoholic solution of 1-adamantyl methyl ketone in the presence of several drops of glacial acetic acid, followed by refluxing for 2 h, cooling, filtration, washing with ethanol, and drying in a vacuum (decomposition point 198–200°C).

Semicarbazones VIIa, VIIb, Xa, and Xb. A mixture of 100 g of semicarbazide hydrochloride and 100 g of anhydrous sodium acetate was thoroughly ground in a porcelain mortar, suspended in 1 l of isopropyl alcohol, refluxed for 30 min, and filtered while hot. A 0.8-mol portion of methyl cyclohexyl ketone, 4-methyl-2-pentanone, methyl benzyl ketone, or piperonyl methyl ketone was added to the refluxing mother liquor. The mixture was refluxed for 1 h, cooled to room temperature, allowed to stand for 10 h, and filtered. The precipitate on the filter was washed with cold isopropyl alcohol and dried at 100°C. Semicarbazones **VIIa**, **VIIb**, **Xa**, and **Xb** were obtained in 90% yield.

Reactions of phenylhydrazones IIa–IIc with I. A 153.5-g portion of freshly distilled $POCl_3$ was added dropwise at 0°C to 220 g of anhydrous DMF; the mixture was left for 20 min. Under external cooling, 0.5 mol of freshly distilled phenylhydrazone **IIa**–**IIc** was slowly added dropwise, avoiding warming-up of the mixture above 50°C. After adding the whole amount of **IIa**–**IIc**, the mixture was stirred for 2 h at 80°C and poured onto 0.5 kg of ice. The resulting mixture was alkalized with 30% NaOH to pH 8–9, left for 20 min, and neutralized with 20% HCl to pH 6–7. The mixture was extracted with chloroform (3 × 180 ml). After removing the solvent, the mixture was analyzed by ^{1}H NMR spectroscopy and distilled in a vacuum with a long Vigreux column. Yields: **IIIa** 43 g (50%); **IIIb** 56 g (61%) + **IVb** 4.9 g (6%); **IIIc** 65 g (65%) + **IVc** 6.1 g (6.4%).

1-Phenyl-3,4-dimethylpyrazole IIIa: bp 116–118°C (3 mm Hg), n_D^{20} 1.5860. Mass spectrum, *m/z*: 172 $[M]^{+\cdot}$. ^{1}H NMR spectrum, δ, ppm: 2.02 s (3H, CH_3), 2.17 s (3H, CH_3), 7.20 t (1H, CH), 7.43 t (2H, 2CH), 7.73 d (2H, 2CH), 8.13 s (1H, CHN). Found, %: C 76.59; H 7.04. $C_{11}H_{12}N_2$. Calculated, %: C 76.71; H 7.02.

1-Phenyl-3-methyl-4-ethylpyrazole IIIb: bp 140–142°C (4 mm Hg), n_D^{20} 1.5750. Mass spectrum, *m/z*: 186 $[M]^{+\cdot}$. ^{1}H NMR spectrum, δ, ppm: 1.17 t (3H, CH_3), 2.18 s (3H, CH_3), 2.42 q (2H, CH_2), 7.21 t (1H, CH), 7.43 t (2H, 2CH), 7.75 d (2H, 2CH), 8.16 s (1H, CHN). Found, %: C 77.30; H 7.60. $C_{12}H_{14}N_2$. Calculated, %: C 77.38; H 7.58.

1-Phenyl-3-methyl-4-propylpyrazole IIIc: bp 148–150°C (3 mm Hg), n_D^{20} 1.5664. Mass spectrum, *m/z*: 200 $[M]^{+\cdot}$. ^{1}H NMR spectrum, δ, ppm: 1.08 t (3H, CH_3), 1.30–1.58 m (2H, CH_2), 2.19 s (3H, CH_3), 2.38 q (2H, CH_2), 7.20 t (1H, CH), 7.44 t (2H, 2CH), 7.78 d (2H, 2CH), 8.15 s (1H, CHN). Found, %: C 78.02; H 8.02. $C_{13}H_{16}N_2$. Calculated, %: C 77.96; H 8.05.

1-Phenyl-3-ethylpyrazole-4-carbaldehyde IVa. Yield according to ^{1}H NMR spectrum 1%. ^{1}H NMR spectrum, δ, ppm: 1.28 t (3H, CH_3), 2.90 q (2H, CH_2), 7.06 t (1H, CH), 7.52 t (2H, 2CH), 7.87 d (2H, 2CH), 9.14 s (1H, CHN), 9.95 s (1H, CHO).

1-Phenyl-3-propylpyrazole-4-carbaldehyde IVb: bp 151–153°C (4 mm Hg), n_D^{20} 1.5840. Mass spectrum, *m/z*: 214 $[M]^{+\cdot}$. ^{1}H NMR spectrum, δ, ppm: 0.96 t (3H, CH_3), 1.69 m (2H, CH_2), 2.85 t (2H, CH_2), 7.30 t (1H, CH), 7.52 t (2H, 2CH), 7.86 d (2H, 2CH), 9.14 s (1H, CHN), 9.93 s (1H, CHO). Found, %: C 72.82; H 6.60. $C_{13}H_{14}N_2O$. Calculated, %: C 72.87; H 6.59.

1-Phenyl-3-butylpyrazole-4-carbaldehyde IVc: bp 160–162°C (3 mm Hg), n_D^{20} 1.5790. Mass spectrum, *m/z*: 228 $[M]^{+\cdot}$. ^{1}H NMR spectrum, δ, ppm: 0.94 t (3H, CH_3), 1.25–1.40 m (2H, CH_2), 1.60–1.80 m (2H, CH_2), 2.83 t (2H, CH_2), 7.36 t (1H, CH), 7.49 t (2H, 2CH), 7.87 d (2H, 2CH), 9.15 s (1H, CHN), 9.94 s (1H, CHO). Found, %: C 73.51; H 7.14. $C_{14}H_{16}N_2O$. Calculated, %: C 73.66; H 7.06.

Reactions of phenylhydrazones Va–Vc with I. A 153.5-g portion of freshly distilled $POCl_3$ was added dropwise at 0°C to 220 g of anhydrous DMF; the mixture was left for 20 min. Under external cooling, 0.5 mol of freshly distilled phenylhydrazone was slowly added dropwise (for **Va**, **Vb**) or in portions (for **Vc**), avoiding warming-up of the mixture above 55°C. After adding the whole amount of **Va**–**Vc**, the mixture was stirred for 2 h at 80°C and poured while hot onto 0.5 kg of ice. The resulting mixture was alkalized with 30% NaOH to pH 8–9, left for 20 min, and neutralized with 20% HCl to pH 7. The mixture was extracted with chloroform (3 × 180 ml). After removing the solvent, the mixture was analyzed by ^{1}H NMR spectroscopy and distilled in a vacuum with a Vigreux column (for **VIa**, **VIb**). Compound **VIb** slowly crystallized, after which it was recrystallized from hexane. Pyrazole **VIa** was purified by additional vacuum distillation. Crude pyrazole **VIc** was dissolved in pure chloroform and treated with a solution of sodium bisulfite at 50°C. The resulting precipitate of the bisulfite derivative was filtered off, washed with hot chloroform, dried, treated with 20% H_2SO_4, and extracted with chloroform (2 × 150 ml). After removing the solvent, pyrazole **VIc** was recrystallized from isopropyl alcohol. Yields: **VIa** 82.1 g (72%), **VIb** 64.2 g (60%), and **VIc** 88.7 g (58%).

1-Phenyl-3-isobutylpyrazole-4-carbaldehyde VIa: bp 173–174°C (4 mm Hg, n_D^{20} 1.5815. Mass spectrum, *m/z*: 228 $[M]^{+\cdot}$. ^{1}H NMR spectrum, δ, ppm: 0.92 d (6H, $2CH_3$), 1.97–2.09 m (1H, CH), 2.77 d (2H, CH_2), 7.39 t (1H, CH), 7.53 t (2H, 2CH), 7.90 d (2H, 2CH), 9.16 s (1H, CHN), 9.95 s (1H, CHO). Found, %: C 73.63; H 7.05. $C_{14}H_{16}N_2O$. Calculated, %: C 73.66; H 7.06.

1-Phenyl-3-isopropylpyrazole-4-carbaldehyde VIb: bp 140–150°C (2 mm Hg), mp 58–59°C. Mass spectrum, *m/z*: 214 $[M]^{+\cdot}$. ^{1}H NMR spectrum, δ, ppm: 1.28 d (6H, $2CH_3$), 3.37–3.49 m (1H, CH), 7.37 t (1H, CH), 7.52 t (2H, 2CH), 7.84 d (2H, 2CH), 9.14 s (1H, CHN), 9.95 s (1H, CHO). Found, %: C 72.83; H 6.57. $C_{13}H_{14}N_2O$. Calculated, %: C 72.87; H 6.59.

1-Phenyl-3-(1′-adamantyl)pyrazole-4-carbaldehyde VIc: mp 116–118°C. Mass spectrum, *m/z*: 306 $[M]^{+\cdot}$. ^{1}H NMR spectrum, δ, ppm: 1.75–2.20 m (15H, $C_{10}H_{15}$), 7.30 t (1H, CH), 7.43 t (2H, 2CH), 7.68 d (2H, 2CH), 8.40 s (1H, CHN), 10.18 s (1H, CHO). Found, %: C 78.35; H 7.28. $C_{20}H_{22}N_2O$. Calculated, %: C 78.40; H 7.24.

Reactions of semicarbazones VIIa, VIIb, Xa, and Xb with I. A 153.5-g portion of freshly distilled $POCl_3$ was added dropwise at 0°C to 220 g of anhydrous DMF; the mixture was left for 20 min. Under external cooling, 0.5 mol of freshly distilled **VIIa**, **VIIb**, **Xa**, or **Xb** was slowly added dropwise in portions, avoiding warming-up of the mixture above 50°C. After adding the whole amount of semicarbazones, the mixture was stirred for 1 h at 80°C and poured while hot onto 0.5 kg of ice. The resulting mixture was alkalized with 30% NaOH to pH 8–9, left for 20 min, and neutralized with 20% HCl to pH 7. In the case of **VIIa** and **VIIb**, the mixture was extracted with chloroform (3 × 250 ml). After removing the solvent, the residue was analyzed by ^{1}H NMR spectroscopy and recrystallized from hexane (for **VIIa**) or immediately subjected to oxidation (for **VIIb**). In formylation of **Xa** and **Xb**, the precipitates formed upon neutralization were filtered off and recrystallized from water. Yields: **VIIIa** 59.7 g (70%), **VIIIb** ~45 g (62%), **XIa** 26.55 g (35%), and **XIb** 38.8 g (40%).

3-Cyclohexylpyrazole-4-carbaldehyde VIIIa: mp 111–112°C. Mass spectrum, *m/z*: 178 $[M]^{+\cdot}$. ^{1}H NMR spectrum, δ, ppm: 1.15–1.40 m (3H, C_6H_{11}), 1.45–1.58 q (2H, C_6H_{11}), 1.66–1.74 d (1H, C_6H_{11}), 1.74–1.86 t (4H, C_6H_{11}), 3.12 t (1H, C_6H_{11}), 8.05 br (1H, CHN), 9.86 s (1H, CHO), 13.15 br (1H, NH). Found, %: C 67.30; H 7.96. $C_{10}H_{14}N_2O$. Calculated, %: C 67.39; H 7.92.

3-Isobutylpyrazole-4-carbaldehyde VIIIb. ^{1}H NMR spectrum, δ, ppm: 0.85 d (6H, $2CH_3$), 1.95 m (1H, CH), 2.73 d (2H, CH_2), 7.95 s (1H, CHN), 9.83 s (1H, CHO), 13.25 br (1H, NH).

3-Methyl-4-phenylpyrazole XIa: mp 144–145°C. Mass spectrum, *m/z*: 158 $[M]^{+\cdot}$. ^{1}H NMR spectrum, δ, ppm: 2.32 and 2.38 d (3H, CH_3), 7.22 t (1H, CH), 7.38 t (2H, 2CH), 7.43 d (2H, 2CH), 7.67 and 7.91 d (1H, CHN), 12.65 d (1H, NH). Found, %: C 75.90; H 6.36. $C_{10}H_{10}N_2$. Calculated, %: C 75.92; H 6.37.

3-Methyl-4-(3′,4′-methylenedioxyphenyl)pyrazole XIb: mp 97–99°C. Mass spectrum, *m/z*: 202 $[M]^{+\cdot}$. ^{1}H NMR spectrum, δ, ppm: 2.31 s (3H, CH_3), 6.00 s (2H, OCH_2O), 6.90 q (2H, 2CH), 7.00 s (1H, CH), 7.67 s (1H, CHN). Found, %: C 65.24; H 4.92. $C_{11}H_{10}N_2O_2$. Calculated, %: C 65.34; H 4.98.

Oxidation of aldehydes VIIIa and VIIIb. Aldehyde **VIIIa** (23.32 g) or a reaction mixture from synthesis of **VIIIb** (70% main substance, 26.55 g,

0.131 mol of **VIIIb**) was dissolved in 500 ml of water containing 25 g of NaOH. The mixture was cooled to 15°C, and a solution of 17 g of $KMnO_4$ in 500 ml of water was quickly added. The mixture was stirred for 30 min and then heated to 96–98°C to complete decolorization of the solution. The solution after cooling was filtered to remove MnO_2 and acidified with HCl to pH 3 (for **IXa**) or 6 (for **IXb**). The precipitate that formed was filtered off, washed with water (as far as possible), and dried at 110°C, after which it was washed and dried again. Yields: **IXa** 23.3 g (92%) and **IXb** 22.1 g (90%); colorless crystalline substances.

3-Cyclohexylpyrazole-4-carboxylic acid IXa: mp > 270°C. Mass spectrum, *m/z*: 194 $[M]^{+\cdot}$. ^{1}H NMR spectrum, δ, ppm: 1.15–1.33 m (3H, C_6H_{11}), 1.35–1.55 q (2H, C_6H_{11}), 1.65–1.75 d (1H, C_6H_{11}), 1.75–1.85 t (4H, C_6H_{11}), 3.25 t (1H, C_6H_{11}), 7.82 s (1H, CHN), 12.5 br (2H, NH and COOH). Found, %: C 61.80; H 7.24. $C_{10}H_{14}N_2O_2$. Calculated, %: C 61.84; H 7.26.

3-Isobutylpyrazole-4-carboxylic acid IXb: mp > 270°C. Mass spectrum, *m/z*: 168 $[M]^{+\cdot}$. ^{1}H NMR spectrum, δ, ppm: 0.85 d (6H, $2CH_3$), 1.90–2.04 m (1H, CH), 2.72 d (2H, CH_2), 7.80 s (1H, CHN), 12.50 br (2H, NH and COOH). Found, %: C 57.10; H 7.15. $C_8H_{12}N_2O_2$. Calculated, %: C 57.13; H 7.19.

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