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**SHORT COMMUNICATIONS**

# Synthesis of 6,7,8,9-Tetrahydropyrazolo[1,5-*a*]quinazolines Containing a 5-Phenylamine Fragment

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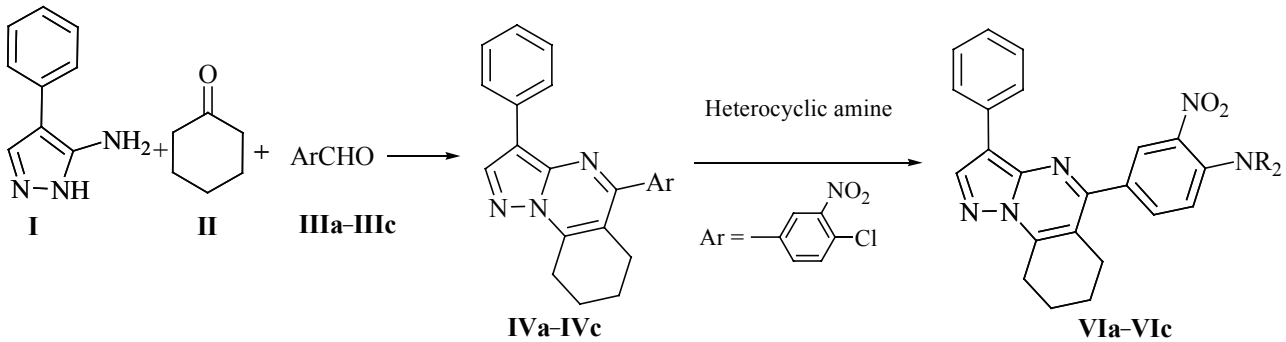
3(5)-Aminoazoles are key reagents in the synthesis of nitrogen bi-and polycyclic compounds possessing a wide range of biological activity [1–5]. At the multicomponent heterocyclization of 3(5)-aminopyrazoles the reaction may proceed by several alternative routes and lead to the formation of isomeric products owing to the presence of two nonequivalent nucleophilic sites ($NH_2$ and NH).

Three-component reaction of 3(5)-amino-4-phenylpyrazole (**I**) with aromatic aldehydes **IIIa–IIIc** and cyclohexanone in acetic acid within 5 h led to the formation of 5-aryl-3-phenyl-6,7,8,9-tetra-hydropyrazolo[1,5-*a*] quinazolines **IVa–IVc** in 75–80% yields. The reaction proceeds regioselectively (see the scheme).

The most probable sequence of the reactions between the reagents in the three-component process may be presumed: In the first stage the aminopyrazole reacts with the aldehyde forming the Schiff base which adds the cyclohexanone to the polarized C=N bond giving an aminoketone that either first undergoes cyclization into octahydropyrazolo[1,5-*a*]quinazolin-9a-ol with subsequent dehydration and dehydrogenation, or suffers the dehydrogenation affording enaminoketone followed by the cyclization and water elimination. The intermediate 3,5-diphenyl-4,6,7,8,9,9a-hexahydro-pyrazolo[1,5-*a*] quinazoline was detected at monitoring the reaction by $^1$H NMR spectroscopy and mass spectrometry ([*M* + H]$^+$ 328.1817) and was isolated as an impurity when the reaction was carried out less than 5 h. The similar bicyclic 4,7-dihydropyrazolo[1,5-*a*]pyrimidines form in reactions of aminopyrazoles with chalcones and benzylideneacetones [6, 7].

In compound **IVc** the chlorine atom is activated by the adjacent nitro group and it is capable of an easy nucleophilic substitution ($S_N$Ar). In order to functionalize

**Scheme.**




**I** **II** **IIIa–IIIc** **IVa–IVc** **VIa–VIc**

**III, IV**, Ar = H (a), 4-Cl (b), 4-Cl-3-$NO_2$ (c); **VI**, $NR_2$ = N (**a**), N (**b**), N O (**c**).

the pyrimidine ring in the position *5* of the aromatic ring we introduced cyclic secondary amines.

At boiling compound **IVc** in toluene with 3-fold excess of heterocyclic amines **Va–Vc** (pyrrolidine, piperidine, morpholine) over 5 h we obtained substituted tetrahydropyrazolo-[1,5-*a*]quinazolines, containing pharmacophore pyrazole, pyrimidine fragments and a phenyl ring substituted with hydrophilic cyclic amines. The composition and structure of compounds **IVa–IVc, VIa–VIc** were established by $^1$H and $^{13}$C NMR spectra and high resolution mass spectra.

**Compounds IVa–IVc.** General procedure. A mixture of 1 mmol of aminopyrazole, 1.1 mmol of cyclohexanone, and 1 mmol of aromatic aldehyde was boiled in 3 ml of acetic acid for 5 h. The solvent was removed at a reduced pressure, the residue was washed with water, filtered off, dried, and.

**3,5-Diphenyl-6,7,8,9-tetrahydropyrazolo[1,5-*a*] quinazoline (IVa)**. Yield 78%, yellow crystals, mp 176–177°C (butanol). $^1$H NMR spectrum, δ, ppm: 1.83 m (2H, 7-$CH_2$), 2.07 m (2H, 8-$CH_2$), 2.78 t.t (2H, 6-$CH_2$, *J* 6.5, 1.5 Hz), 3.27 t.t (2H, 9-$CH_2$, *J* 6.5, 1.5 Hz), 7.24 t (1H, H$^p$, 3-Ph, *J* 7.4 Hz), 7.44 t (2H, H$^m$, 3-Ph, *J* 7.8 Hz), 7.50 m (2H, H$^o$, 5-Ph), 7.70 m (3H, H$^{m,p}$, 5-Ph), 8.16 d (2H, H$^o$, 3-Ph, *J* 7.8 Hz), 8.45 s (1H, H$^2$). $^{13}$C NMR spectrum, δ, ppm: 21.13, 22.54, 24.71, 26.74 (C$^{6–9}$), 110.32 (C$^3$), 115.44 (C$^{5a}$), 125.52 (C$^p$, 3-Ph), 126.06, 128.11, 128.58, 129.00 ($CH_{arom}$), 128.81 (C$^p$, 5-Ph), 132.57 (C$^i$, 3-Ph), 139.05 (C$^i$, 5-Ph), 141.43 (C$^2$), 143.25 (C$^{3a}$), 144.39 (C$^{9a}$), 158.68 (C$^5$). Found $[M + H]^+$ 326.1657. $C_{22}H_{20}N_3$. Calculated 326.1652.

**3-Phenyl-5-(4-chlorophenyl)-6,7,8,9-tetrahydropyrazolo[1,5-*a*]quinazoline (IVb)**. Yield 80%, yellow crystals, mp 195–196°C (butanol). $^1$H NMR spectrum, δ, ppm: 1.81 m (2H, 7-$CH_2$), 2.04 m (2H, 8-$CH_2$), 2.72 t.t (2H, 6-$CH_2$, *J* 6.5, *J* 1.5 Hz), 3.24 t.t (2H, 9-$CH_2$, *J* 6.5, *J* 1.5 Hz), 7.23 t (1H, H$^p$, 3-Ph, *J* 7.5 Hz), 7.42 t (2H, H$^m$, 3-Ph, *J* 7.6 Hz), 7.47 d (2H, H$^m$, 5-Ar, *J* 8.0 Hz), 7.61 d (2H, H$^o$, 5-Ar, *J* 8.0 Hz), 8.12 d (2H, H$^o$, 3-Ph, *J* 7.6 Hz), 8.44 s (1H, H$^2$). $^{13}$C NMR spectrum, δ, ppm: 21.02, 22.46, 24.68, 26.68 (C$^{6–9}$), 110.35 (C$^3$), 115.44 (C$^{5a}$), 125.80 (C$^p$, 3-Ph), 125.96, 128.33, 128.56, 130.40 ($CH_{arom}$), 132.38 (C$^i$, 3-Ph), 134.99 (C$^p$, 5-Ar), 137.35 (C$^i$, 5-Ar), 141.49 (C$^2$), 143.08 (C$^{3a}$), 144.59 (C$^{9a}$), 157.27 (C$^5$). Found $[M + H]^+$ 360.1260. $C_{22}H_{19}ClN_3$. Calculated 360.1263.

**5-(3-Nitro-4-chlorophenyl)-3-phenyl-6,7,8,9-tetrahydropyrazolo[1,5-*a*]quinazoline (IVc)**. Yield 75%, light brown crystals, mp 216–217єC. $^1$H NMR spectrum, δ, ppm: 1.88 m (2H, 7-$CH_2$), 2.10 m (2H, 8-$CH_2$), 2.79 t.t (2H, 6-$CH_2$, *J* 6.5, *J* 1.5 Hz), 3.29 t.t (2H, 9-$CH_2$, *J* 6.5, *J* 1.5 Hz), 7.27 t (1H, H$^p$, 3-Ph, *J* 7.4 Hz), 7.45 t (2H, H$^m$, 3-Ph, *J* 7.8 Hz), 7.71 d (1H, 5-Ar, *J* 8.2 Hz), 7.88 d.d (1H, 5-Ar, *J* 8.2, *J* 1.9 Hz), 8.09 d (2H, H$^o$, 3-Ph, *J* 7.8 Hz), 8.22 s (1H, 5-Ar, *J* 1.9 Hz), 8.47 c (1H, C$^2$H). $^{13}$C NMR spectrum, δ, ppm: 21.89, 22.39, 24.74, 26.54 (C$^{6–9}$), 110.96 (C$^3$), 115.03 (C$^{5a}$), 126.05 (CH, 3-Ph), 126.09, 126.18 (CH$^p$, 3-Ph, CH$^o$, 5-Ar), 127.54 (C$^p$, 5-Ar), 128.71 (CH, 3-Ph), 131.78 (CH$^m$, 5-Ar), 132.03 (C$^i$, 3-Ph), 133.66 (CH$^o$, 5-Ar), 138.78 (C$^i$, 5-Ar), 141.92 (C$^2$), 142.91 (C$^{3a}$), 145.40 (C$^{9a}$), 147.54 (C$^m$, 5-Ar), 154.48 (C$^5$). Found $[M + H]^+$ 405.1096. $C_{22}H_{18}ClN_4O_2$. Calculated 405.1113.

**Compounds VIa–VIc**. **General procedure**. 1 mmol of compound **IVc** and 3 mmol of amine **Va–Vc** were boiled in 5 ml of toluene for 5 h. The solvent was removed at a reduced pressure, the residue was recrystallized from butanol.

**5-[3-Nitro-4-(pyrrolidin-1-yl)phenyl]-3-phenyl-6,7,8,9-tetrahydropyrazolo[1,5-*a*]quinazoline (VIa)**. Yield 88%, light brown crystals, mp 214–216єC. $^1$H NMR spectrum, δ, ppm: 1.87 m (2H, 7-$CH_2$), 2.06 m (6H, 8-$CH_2$ + 4H$_{pyrrolidine}$), 2.88 t.t (2H, 6-$CH_2$, *J* 6.5, *J* 1.5 Hz), 3.29 t.t (2H, 9-$CH_2$, *J* 6.5, *J* 1.5 Hz), 3.33 m (4H$_{pyrrolidine}$), 7.05 d ( 1H, H$^m$, 5-Ph, *J* 8.9 Hz), 7.25 t (1H, H$^p$, 3-Ph, *J* 7.5 Hz), 7.44 t (2H, H$^m$, 3-Ph, *J* 7.8 Hz), 7.88 d.d (1H, H$^o$, 5-Ph, *J* 8.9, *J* 2.0 Hz), 8.12 d (2H, H$^o$, 3-Ph, *J* 7.8 Hz), 8.17 d (1H, H$^o$, 5-Ph, *J* 2.0 Hz), 8.47 s (1H, C$^2$H). $^{13}$C NMR spectrum, δ, ppm: 21.15, 22.72, 24.87, 27.07 (C$^{6–9}$), 25.74, 50.58 (4$CH_{2\ pyrrolidine}$), 110.25 (C$^3$), 115.48 (C$^{5a}$), 115.80 (CH$^m$, 5-Ph), 125.82 (C$^p$, 3-Ph), 126.08 (CH, 3-Ph), 127.66 (CH$^o$, 5-Ph), 128.68 (CH, 3-Ph), 132.62 (C$^i$, 3-Ph), 133.93 (CH$^o$, 5-Ph), 136.21 (C, 5-Ph), 141.60 (C$^2$, 5-Ph), 142.94, 143.26 (C$^m$, 5-Ph, C$^{3a}$), 144.68 (C$^{9a}$), 156.28 (C$^5$). Found $[M + H]^+$ 440.2069. $C_{26}H_{26}N_5O_2$. Calculated $[M + H]$ 440.2082.

**5-[3-Nitro-4-(piperidine-1-yl)phenyl]-3-phenyl-6,7,8,9-tetrahydropyrazolo[1,5-*a*]quinazoline (VIb)**. Yield 82%, light brown crystals, mp 197–199єC. $^1$H NMR spectrum, δ, ppm: 1.67 m (2H, $CH_{2\ piperidine}$), 1.78 m (4H, $CH_{2\ piperidine}$), 1.86 m (2H, 7-$CH_2$), 2.09 m (2H, 8-$CH_2$ ), 2.85 t.t (2H, 6-$CH_2$, *J* 6.5, 1.5 Hz), 3.16 m (4H$_{piperidine}$), 3.29 t.t (2H, 9-$CH_2$, *J* 6.5, 1.5 Hz), 7.24 t (1H, H$^p$, 3-Ph, *J* 7.5 Hz), 7.27 m (1H, H$^m$, 5-Ar), 7.45 t (2H, H$^m$, 3-Ph, *J* 7.8 Hz), 7.87 d.d (1H, H$^o$, 5-Ar, *J* 8.7, 2.0 Hz), 8.12 d (2H, H$^o$, 3-Ph, *J* 7.8 Hz), 8.16 d (1H, H$^o$, 5-Ar, *J* 2.0 Hz), 8.44 s (1H,

$C^2H$). $^{13}C$ NMR spectrum, δ, ppm: 21.03, 22.57, 24.77, 26.85 ($C^{6–9}$), 23.94, 25.79, 50.47 (5 $CH_{2\ piperidine}$), 110.38 ($C^3$), 115.39 ($C^{5a}$), 120.21 ($CH^o$, 5-Ar), 125.88 ($C^p$, 3-Ph), 126.02, 128.67 (CH, 3-Ph), 127.24 ($CH^o$, 5-Ar), 130.24 ($C^i$, 5-Ar), 132.42 ($C^i$, 3-Ph), 134.27 ($CH^o$, 5-Ar), 140.55 ($C^p$, 5-Ar), 141.62 ($C^2$), 143.12 ($C^{3a}$), 144.79 ($C^{9a}$), 147.06 ($C^m$, 5-Ar), 155.94 ($C^5$). Found $[M + H]^+$ 454.2240. $C_{27}H_{28}N_5O_2$. Calculated 454.2238.

**5-[4-(Morpholine-1-yl)-3-nitrophenyl]-3-phenyl-6,7,8,9-tetrahydropyrazolo[1,5-*a*]quinazoline (VIc)**. Yield 85%, yellow crystals, mp 172–173єC. $^1H$ NMR spectrum, δ, ppm: 1.87 m (2H, 7-$CH_2$), 2.10 m (2H, 8-$CH_2$), 2.84 t.t (2H, 6-$CH_2$, *J* 6.5, *J* 1.5 Hz), 3.19 m ($4H_{morpholine}$), 3.28 t.t (2H, 9-$CH_2$, *J* 6.5, 1.5 Hz), 3.91 m ($4H_{morpholine}$), 7.27 m ( 2H, $H^p$, 3-Ph , $H^m$, 5-Ar), 7.45 t (2H, $H^m$, 3-Ph, *J* 7.8 Hz), 7.90 d.d (1H, $H^o$, 5-Ar, *J* 8.7, 2.0 Hz), 8.11 d (2H, $H^o$, 3-Ph, *J* 7.8 Hz), 8.19 d (1H, $H^o$, 5-Ar, *J* 2.0 Hz), 8.45 s (1H, $C^2H$). $^{13}C$ NMR spectrum, δ, ppm: 20.95, 22.50, 24.73, 27.20 ($C^{6–9}$), 51.66, 66.66 ($4CH_{2\ morpholine}$), 110.50 ($C^3$), 115.28 ($C^{5a}$), 120.22 ($CH^m$, 5-Ar), 125.94 ($C^p$, 3-Ph), 126.00, 128.66 (CH, 3-Ph), 126.99 ($CH^o$, 5-Ar), 132.21, 132.30 ($CH^i$, 3-Ar, $CH^i$, 5-Ar), 134.41 ($CH^o$, 5-Ar), 141.67 ($C^2$), 141.80 ($C^p$, 5-Ar), 143.04 ($C^{3a}$), 144.94 ($C^{9a}$), 145.98 ($C^m$, 5-Ar), 155.56 ($C^5$). Found $[M + H]^+$ 456.2035. $C_{27}H_{28}N_5O_2$. Calculated 456.2031.

$^1H$ and $^{13}C$ NMR spectra were registered on a spectrometer Bruker DPX-300 (300.13 and 75.47 MHz) in $CDCl_3$ at 22°C. Chemical shifts were measured from the signals of residual protons of the deuterated solvent $CDCl_3$ (7.28, 77.00 ppm). Elemental composition was determined with the help of the high resolution mas spectrometry on an instrument Bruker Daltonics microTOF at the positive electrospray ionization. The synthesis of 3(5)-amino-4-phenyl-1*H*-pyrazole was described in [8].

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