ISSN 1070-4280, Russian Journal of Organic Chemistry, 2017, Vol. 53, No. 1, pp. 62–65. © Pleiades Publishing, Ltd., 2017.
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Synthesis and Properties of Ethyl 1-Aryl-5-methyl-4-[1-(phenylhydrazinylidene)ethyl]-1*H*-pyrazole-3-carboxylates

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Received August 31, 2016

Abstract—Ethyl 1-aryl-4-acetyl-5-methyl-1*H*-pyrazole-3-carboxylates reacted with phenylhydrazine to give the corresponding hydrazones, ethyl 1-aryl-5-methyl-4-[1-(phenylhydrazinylidene)ethyl]-1*H*-pyrazole-3-carboxylates, which were converted to ethyl 1′-aryl-4-formyl-5′-methyl-1-phenyl-1*H*,1′*H*-3,4′-bipyrazole-3′-carboxylates by treatment with the Vilsmeier–Haack reagent. No indole derivatives were formed from the same hydrazones under the Fischer reaction conditions, but cyclization to 2-aryl-3,4-dimethyl-6-phenyl-2,6-dihydro-7*H*-pyrazolo[3,4-*d*]pyridazin-7-ones was observed.

DOI: 10.1134/S1070428017010110

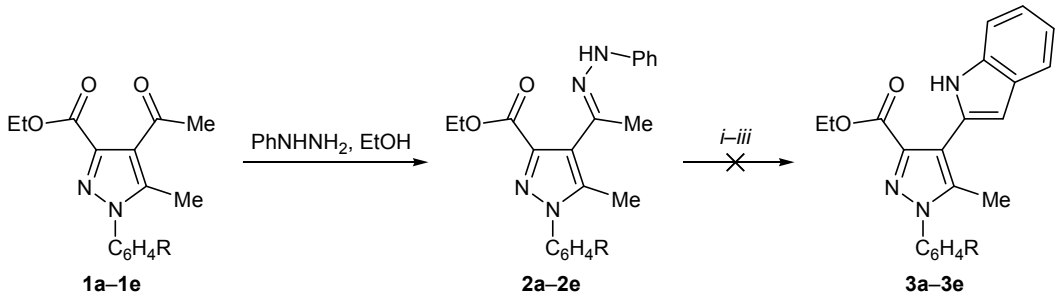
Arylhydrazones derived from aromatic and heteroaromatic ketones are convenient starting compounds for the synthesis of various nitrogen heterocycles. Their treatment with mineral protic or Lewis acids leads to the formation of indole derivatives (Fischer indole synthesis) [1–4]. This reaction also provides the most convenient method for the preparation of 2-aryl (hetaryl)indoles. Pyridinyl- [5], pyrimidinyl- [6], indolyl- [7], and quinazolinyl-substituted indoles [8], as well as other indole derivatives, have been synthesized in this way. Arylhydrazones are known to react with the Vilsmeier–Haack reagent to give 4-formylpyrazoles [9].

We have studied the behavior of ethyl 1-aryl-4-acetyl-5-methyl-4-[1-(phenylhydrazinylidene)ethyl]-1*H*-pyrazole-3-carboxylates **2a**–**2e** in the Fischer and Vilsmeier–Haack reactions. No such reactions have been reported previously for 4-acetylpyrazole phenylhydrazones.

Phenylhydrazones **2a**–**2e** were synthesized by reaction of phenylhydrazine with ethyl 1-aryl-4-acetyl-5-methyl-1*H*-pyrazole-3-carboxylates **1a**–**1e** in ethanol (Scheme 1), and initial ketones **1a**–**1e** were prepared from the corresponding ethyl chloro(arylhydrazinylidene)acetates and acetylacetone [10–12]. No expected indole derivatives **3a**–**3e** were formed when hydrazones **2a**–**2e** were heated in boiling acetic acid (method *a*). By heating compounds **2a**–**2e** in THF in the presence of a mineral acid (HCl) or in dimethylformamide in the presence of a Lewis acid ($ZnCl_2$) (methods *b* and *c*, respectively) we obtained 2-aryl-3,4-dimethyl-6-phenyl-2,6-dihydro-7*H*-pyrazolo[3,4-*d*]-pyridazin-7-ones **4a**–**4e** in 71–82% yields (Scheme 2).

Treatment of hydrazones **2a** and **2b** with the Vilsmeier–Haack reagent ($POCl_3$/DMF) afforded bipyrazoles **5a** and **5b** that are promising as building blocks for organic synthesis. In the ^{1}H NMR spectra of **5a** and **5b**, the aldehyde proton resonated at

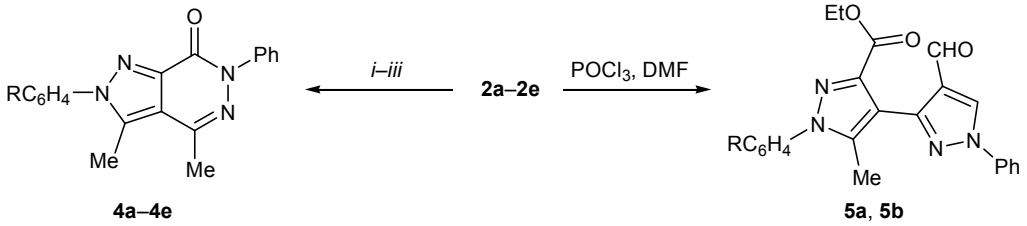
Scheme 1.



1a–1e **2a–2e** **3a–3e**

i: AcOH, reflux; *ii*: HCl, THF, reflux; *iii*: $ZnCl_2$, DMF, 100°C; **1**, **2**, R = H (**a**), 4-Cl (**b**), 3-Cl (**c**), 2-Cl (**d**), 4-Br (**e**).

Scheme 2.



i: AcOH, reflux; *ii*: HCl, THF, reflux; *iii*: $ZnCl_2$, DMF, 100°C;
4, R = H (**a**), 4-Cl (**b**), 3-Cl (**c**), 2-Cl (**d**), 4-Br (**e**); **5**, R = H (**a**), 4-Cl (**b**).

δ 9.82 ppm, and the 5-H proton signal appeared at δ 8.57–8.58 ppm. Pyrazolopyridazines **4a**–**4e** displayed in the ^{1}H NMR spectra signals from methyl groups on the pyrazole and pyridazine rings at δ 2.53–2.58 and 2.62–2.68 ppm, respectively.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer at 200 and 50 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane as internal standard. The elemental analyses were obtained on a Carlo Erba 1106 analyzer. The melting points were measured on a Boetius melting point apparatus.

Compounds 2a–2e (*general procedure*). Phenylhydrazine, 1 mL (10 mmol), was added to a solution of 10 mmol of compound **1a**–**1e** in 20 mL of ethanol, and the mixture was refluxed for 2 h. After cooling, the mixture was poured into 50 mL of water, and the precipitate was filtered off, dried, and recrystallized from ethanol–DMF.

Ethyl 5-methyl-1-phenyl-4-[1-(phenylhydrazinylidene)ethyl]-1*H*-pyrazole-3-carboxylate (2a). Yield 2.6 g (73%), mp 113°C. ^{1}H NMR spectrum, δ, ppm: 1.38 t (3H, CH_3, J = 7.1 Hz), 2.27 s (3H, CH_3), 2.40 s (3H, CH_3), 4.41 q (2H, CH_2, J = 7.1 Hz), 6.86 t (1H, H_{arom}, J = 7.3 Hz), 6.97–7.54 m (10H, NH, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 11.8, 14.3, 17.2, 61.0, 113.0 (2C), 120.0, 123.3, 125.7 (2C), 128.7, 129.09 (2C), 129.13 (2C), 129.3, 137.9, 139.0, 139.5, 145.0, 162.4. Found, %: C 69.41; H 6.27; N 15.24. $C_{21}H_{22}N_4O_2$. Calculated, %: C 69.59; H 6.12; N 15.46.

Ethyl 1-(4-chlorophenyl)-5-methyl-4-[1-(phenylhydrazinylidene)ethyl]-1*H*-pyrazole-3-carboxylate (2b). Yield 3.1 g (77%), mp 119°C. ^{1}H NMR spectrum, δ, ppm: 1.38 t (3H, CH_3, J = 7.1 Hz), 2.25 s (3H, CH_3), 2.40 s (3H, CH_3), 4.41 q (2H, CH_2, J = 7.1 Hz), 6.86 t (1H, H_{arom}, J = 7.0 Hz), 6.96–7.54 m (9H, NH, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 12.1, 14.3, 17.1, 61.1, 112.9 (2C), 120.1, 123.7, 126.4, 126.9 (2C), 129.1 (2C), 129.3 (2C), 129.5, 134.6, 137.2, 139.4, 145.0, 162.2. Found, %: C 63.73; H 5.20; N 13.97. $C_{21}H_{21}ClN_4O_2$. Calculated, %: C 63.55; H 5.33; N 14.12.

Ethyl 1-(3-chlorophenyl)-5-methyl-4-[1-(phenylhydrazinylidene)ethyl]-1*H*-pyrazol-3-carboxylate (2c). Yield 3.4 g (85%), mp 121°C. ^{1}H NMR spectrum, δ, ppm: 1.39 t (3H, CH_3, J = 7.2 Hz), 2.25 s (3H, CH_3), 2.43 s (3H, CH_3), 4.41 q (2H, CH_2, J = 7.2 Hz), 6.80–7.65 m (10H, NH, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 11.8, 14.3, 17.1, 61.2, 113.0 (2C), 120.1, 123.7, 126.0, 128.9, 129.2 (2C), 130.1, 134.9, 137.3, 138.8, 139.5, 140.0, 141.6, 145.0, 162.2. Found, %: C 63.69; H 5.43; N 14.02. $C_{21}H_{21}ClN_4O_2$. Calculated, %: C 63.55; H 5.33; N 14.12.

Ethyl 1-(2-chlorophenyl)-5-methyl-4-[1-(phenylhydrazinylidene)ethyl]-1*H*-pyrazole-3-carboxylate (2d). Yield 3.2 g (82%), mp 123°C. ^{1}H NMR spectrum, δ, ppm: 1.38 t (3H, CH_3, J = 7.2 Hz), 2.27 s (3H, CH_3), 2.29 s (3H, CH_3), 4.41 q (2H, CH_2, J = 7.2 Hz), 6.85 t (1H, H_{arom}, J = 7.2 Hz), 7.10 d (2H, H_{arom}, J = 7.2 Hz), 7.25 t (2H, H_{arom}, J = 7.2 Hz), 7.30 d (2H, H_{arom}, J = 7.2 Hz), 7.37–7.58 m (3H, NH, H_{arom}). Found, %: C 63.32; H 5.41; N 14.27. $C_{21}H_{21}ClN_4O_2$. Calculated, %: C 63.55; H 5.33; N 14.12.

Ethyl 1-(4-bromophenyl)-5-methyl-4-[1-(phenylhydrazinylidene)ethyl]-1*H*-pyrazole-3-carboxylate (2e). Yield 3.3 g (74%), mp 131°C. ^{1}H NMR spectrum, δ, ppm: 1.39 t (3H, CH_3, J = 7.2 Hz), 2.25 s (3H, CH_3), 2.41 s (3H, CH_3), 4.41 q (2H, CH_2, J = 7.2 Hz), 6.78–7.69 m (10H, NH, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 11.8, 14.3, 17.1, 61.2, 112.7, 113.0 (2C), 120.1, 127.2 (2C), 127.4, 129.2 (2C), 132.3 (2C), 132.5, 137.3, 138.0, 139.4, 145.0, 162.2. Found, %: C 57.03; H 4.69; N 12.78. $C_{21}H_{21}BrN_4O_2$. Calculated, %: C 57.15; H 4.80; N 12.69.

Compounds 4a–4e (*general procedures*). *a*. A solution of 2 mmol of compound **2a**–**2e** in 10 mL of acetic

acid was refluxed for 4 h. After cooling, the mixture was poured into 30 mL of water, and the precipitate was filtered off, dried, and recrystallized from ethanol–dimethylformamide.

b. Concentrated aqueous HCl, 1 mL, was added to a solution of 0.72 g (2 mmol) of compound **2a** in 10 mL of THF. The mixture was refluxed for 3 h, cooled, poured into 30 mL of water, and neutralized with 10 mL of a saturated aqueous solution of sodium hydrogen carbonate. The product was extracted with methylene chloride (3×40 mL), the extract was dried over sodium sulfate and concentrated, and the residue was recrystallized from ethanol–DMF.

c. A solution of 0.72 g (2 mmol) of compound **2a** and 0.27 g (2 mmol) of $ZnCl_2$ in 5 mL of DMF was stirred for 5 h at 100°C. The mixture was cooled and poured into 30 mL of water, and the precipitate was filtered off and recrystallized from ethanol–DMF.

3,4-Dimethyl-2,6-diphenyl-2,6-dihydro-7*H*-pyrazolo[3,4-*d*]pyridazin-7-one (4a). Yield 0.51 g (81%, *a*), 0.48 g (76%, *b*), 0.52 g (82%, *c*); mp 239°C. ^{1}H NMR spectrum, δ, ppm: 2.53 s (3H, CH_3), 2.62 s (3H, CH_3), 7.29–7.67 m (10H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 11.5, 19.9, 117.0, 126.1 (2C), 127.4, 127.9, 128.7 (2C), 129.5, 130.3, 131.6, 131.7, 136.0, 138.3, 141.3, 141.7, 142.9, 155.7. Found, %: C 72.35; H 5.19; N 17.53. $C_{19}H_{16}N_4O$. Calculated, %: C 72.14; H 5.10; N 17.71.

2-(4-Chlorophenyl)-3,4-dimethyl-6-phenyl-2,6-dihydro-7*H*-pyrazolo[3,4-*d*]pyridazin-7-one (4b). Yield 0.57g (81%), mp 224°C. ^{1}H NMR spectrum, δ, ppm: 2.58 s (3H, CH_3), 2.66 s (3H, CH_3), 7.29–7.54 m (7H, H_{arom}), 7.65 d.t (2H, H_{arom}, ^3J = 7.2, ^4J = 1.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 12.3, 20.0, 117.7, 125.9 (2C), 127.2 (2C), 127.4, 128.7 (2C), 129.5 (2C), 135.6, 136.6, 136.8, 141.3, 141.6, 142.6, 155.7. Found, %: C 65.30; H 4.16; N 15.79. $C_{19}H_{15}ClN_4O$. Calculated, %: C 65.05; H 4.31; N 15.97.

2-(3-Chlorophenyl)-3,4-dimethyl-6-phenyl-2,6-dihydro-7*H*-pyrazolo[3,4-*d*]pyridazin-7-one (4c). Yield 0.50 g (71%), mp 192°C. ^{1}H NMR spectrum, δ, ppm: 2.58 s (3H, CH_3), 2.68 s (3H, CH_3), 7.29–7.69 m (9H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 12.3, 20.0, 117.7, 124.1, 125.9 (2C), 126.3, 127.4, 128.7 (2C), 129.7, 130.2, 135.0, 136.7, 139.2, 141.3, 141.6, 142.7, 155.7. Found, %: C 65.26; H 4.21; N 15.90. $C_{19}H_{15}ClN_4O$. Calculated, %: C 65.05; H 4.31; N 15.97.

2-(2-Chlorophenyl)-3,4-dimethyl-6-phenyl-2,6-dihydro-7*H*-pyrazolo[3,4-*d*]pyridazin-7-one (4d). Yield 0.51 g (72%), mp 201°C. ^{1}H NMR spectrum, δ, ppm: 2.53 s (3H, CH_3), 2.62 s (3H, CH_3), 7.29–7.67 m (9H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 11.5, 19.9, 117.0, 126.1 (2C), 127.4, 127.9, 128.7 (2C), 129.5, 130.3, 131.6, 131.7, 136.0, 138.3, 141.3, 141.7, 142.9, 155.7. Found, %: C 64.89; H 4.24; N 15.86. $C_{19}H_{15}ClN_4O$. Calculated, %: C 65.05; H 4.31; N 15.97.

2-(4-Bromophenyl)-3,4-dimethyl-6-phenyl-2,6-dihydro-7*H*-pyrazolo[3,4-*d*]pyridazin-7-one (4e). Yield 0.60 g (76%), mp 247°C. ^{1}H NMR spectrum, δ, ppm: 2.53 s (3H, CH_3), 2.62 s (3H, CH_3), 7.29–7.67 m (9H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 11.5, 19.9, 117.0, 126.1 (2C), 127.4, 127.9, 128.7 (2C), 129.5, 130.3, 131.6, 131.7, 136.0, 138.3, 141.3, 141.7, 142.9, 155.7. Found, %: C 57.51; H 3.93; N 14.02. $C_{19}H_{15}BrN_4O$. Calculated, %: C 57.74; H 3.83; N 14.17.

Compounds 5a and 5b (*general procedure*). Phosphoryl chloride, 0.56 mL (6 mmol), was added dropwise with stirring to 5 mL of dimethylformamide cooled to 0°C, maintaining the temperature below 10°C. The mixture was stirred for 30 min, a solution of 2 mmol of compound **2a** or **2b** in 2 mL of DMF was added, and the mixture was stirred for 1 h at a temperature not exceeding 10°C, heated to 65°C, and stirred for 2 h at 65°C. The mixture was cooled, poured onto 30 g of ice, and neutralized with solid potassium carbonate to pH ~8. The precipitate was filtered off, washed with water, and recrystallized from ethanol.

Ethyl 4-formyl-5′-methyl-1,1′-diphenyl-1*H*,1′*H*-3,4′-bipyrazole-3′-carboxylate (5a). Yield 0.61 g (76%). ^{1}H NMR spectrum, δ, ppm: 1.30 t (3H, CH_3, J = 7.1 Hz), 2.39 s (3H, CH_3), 4.34 q (2H, CH_2, J = 7.1 Hz), 7.34–7.58 m (8H, H_{arom}), 7.78 d (2H, H_{arom}, J = 7.9 Hz), 8.58 s (5-H), 9.82 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 11.5, 14.2, 61.2, 113.3, 119.5 (2C), 124.1, 125.7 (2C), 127.8, 129.0, 129.2 (2C), 129.6 (2C), 136.8, 138.8, 139.0, 141.2, 142.1, 146.9, 162.0, 185.1. Found, %: C 69.14; H 4.87; N 13.78. $C_{23}H_{20}N_4O_3$. Calculated, %: C 68.99; H 5.03; N 13.99.

Ethyl 1′-(4-chlorophenyl)-4-formyl-5′-methyl-1-phenyl-1*H*,1′*H*-3,4′-bipyrazole-3′-carboxylate (5b). Yield 0.73 g (84%). ^{1}H NMR spectrum, δ, ppm: 1.29 t (3H, CH_3, J = 7.2 Hz), 2.39 s (3H, CH_3), 4.34 q (2H, CH_2, J = 7.2 Hz), 7.32–7.57 m (7H, H_{arom}), 7.77 d (2H, H_{arom}, J = 8.0 Hz), 8.57 s (5-H), 9.82 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 11.6, 14.1, 61.3, 113.6, 119.5 (2C), 124.1, 126.8 (2C), 127.8, 129.4 (2C),

129.6 (2C), 129.9, 134.9, 137.3, 138.9, 141.2, 142.4, 146.5, 161.9, 184.8. Found, %: C 63.33; H 4.65; N 12.69. $C_{23}H_{19}ClN_4O_3$. Calculated, %: C 63.52; H 4.40; N 12.88.

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