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Cyanoacetophenone as a Synthon for 1,4,5-Substituted Pyrazoles

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Summary. An improved synthesis of cyanoacetophenone is described. Cyanoacetophenone was reacted with dimethylformamide-dimethylacetal and diphenylformamidine to give 1-dimethylamino-3-oxo-3-phenyl-1-propene-2-carbonitrile and 1-anilinomethylene-3-oxo-3-phenyl-1-propene-2-carbonitrile. Reaction of 1-dimethylamino-3-oxo-3-phenyl-1-propene-2-carbonitrile with hydrazines gave either 1-substituted 5-amino-4-benzoylpyrazoles or (1-substituted) 4-cyano-5-phenylpyrazoles. Treatment of 1-anilinomethylene-3-oxo-3-phenyl-1-propene-2-carbonitrile with phenylhydrazine also yielded 5-amino-4-benzoyl-1-phenylpyrazole, whereas reaction with unsubstituted hydrazine afforded 4-cyano-5-phenylpyrazole.

Keywords. Cyanoacetophenone; 1-, 4-, 5-Substituted pyrazoles; Ring closure reaction.

Cyanacetophenon, ein Synthon für 1,4,5-substituierte Pyrazole

Zusammenfassung. Eine verbesserte Darstellung von Cyanacetophenon wird beschrieben. Cyanacetophenon reagierte mit Dimethylformamid-dimethylacetal bzw. Diphenylformamidin zu 1-Dimethylamino-3-oxo-3-phenyl-1-propen-2-carbonitril und 1-Anilinomethylen-3-oxo-3-phenyl-1-propen-2-carbonitril. Durch Umsetzung von 1-Dimethylamino-3-oxo-3-phenyl-1-propen-2-carbonitril mit Hydrazinen wurden entweder 1-substituierte 5-Amino-4-benzoylpyrazole oder (1-substituierte) 4-Cyano-5-phenylpyrazole erhalten. Reaktion von 1-Anilinomethylen-3-oxo-3-phenyl-1-propen-2-carbonitril mit Phenylhydrazin ergab ebenfalls 5-Amino-4-benzoyl-1-phenylpyrazol, während unsubstituiertes Hydrazin zu 4-Cyan-5-phenylpyrazol reagierte.

Introduction

Introduction of substituents into the pyrazole system is easy in position 4. Other ring positions are less accessible for electrophilic substitutions. Thus, in many cases substituted pyrazoles have been obtained by ring closure reactions of already substituted starting materials. In classical syntheses, 1,3-dioxo compounds were cyclized with monosubstituted hydrazines to yield 3,5-di- or 1,3,5-trisubstituted pyrazoles. Hydrazines and substituted hydrazines were cyclized with 1,3-dipoles like *e.g.* ethoxymethylene-malononitrile [1–4] or 2-cyano-3-dimethylaminopropenal [5]. In some cases, also rearrangements of substituents have been observed

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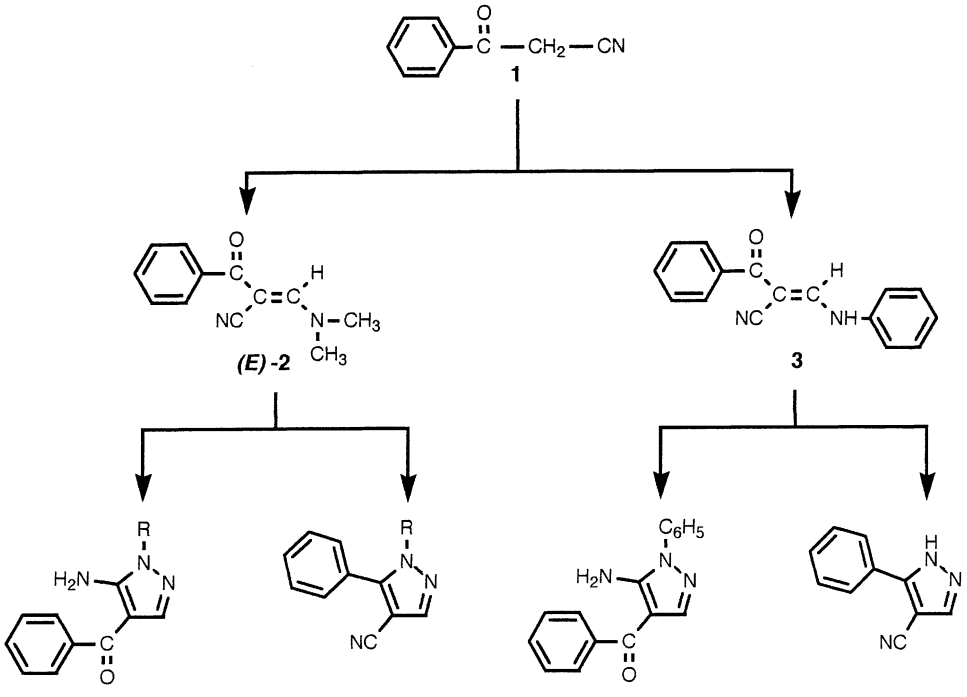
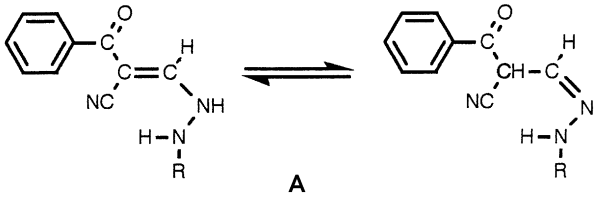
[6]. In this paper we report on a two step procedure for the synthesis of substituted pyrazoles from easily accessible starting materials. The synthesis of cyanoacetophenone **1** has been reported earlier [7–9], however, with poor yields; therefore, we developed an alternative synthesis which gave 70–74% of products.

Results and Discussion

Cyanoacetophenone (**1**) was reacted with dimethylformamide-dimethylacetal (*DMFDMA*) at room temperature to yield the (*E*)- and (*Z*)-isomers of the aminomethylene derivative **2** (Scheme 1). Typically, 80 to 100% of the product had (*E*)-configuration. The ratio of (*E*)- and (*Z*)-isomers had no influence on the following condensations of **2** with different hydrazines which were performed either in ethanol or in mixtures of ethanol and hydrochloric acid. In the first step of the reaction, the dimethylamino group was substituted by hydrazines to give intermediate **A** (Scheme 2). The imino form gave compounds **4a**, **b** and **5a–f** by ring closure to the carbon atoms of the carbonyl and nitrile groups. Structures of **4a**, **b** and **5a–f** were confirmed by spectroscopical data (see Experimental).

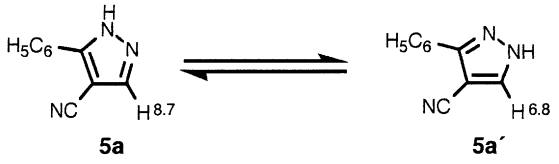


Scheme 1



A

Scheme 2



5a **5a´**

Scheme 3

5-Amino-4-benzoyl-1-phenylpyrazole (**4b**) was also obtained by condensation of **3** [10] with phenylhydrazine. This was somewhat surprising as we had expected to obtain 1,5-diphenyl-4-cyano-pyrazole which has been described earlier [10]. Other pathways to obtain **5a** were either to condensate **2** with hydrazinoformic methylester or to react **3** with hydrazine hydrate.

^{1}H NMR spectroscopic data showed that **5a** was the only structure present at room temperature (singulet of the CH-proton at 8.7 ppm). At lower temperatures, *e.g.* at 235 K, also **5a′** [10, 11] (Scheme 3) could be observed (additional singulet at 6.8 ppm). According to the experiments described above, **1** proved to be a valuable synthon on the way to 1,4,5-substituted pyrazoles.

Experimental

All melting points are uncorrected (Büchi 500). Spectroscopic data were recorded with the following instruments: IR spectra: Perkin-Elmer-Spectrophotometer 500 (KBr), ^{1}H NMR spectra: Gemini 200 (referenced to internal *TMS*). Elemental analyses were performed on a C,H,N-Automat Carlo Erba 1106; the results were in accordance with the calculated values.

Cyanoacetophenone (**1**; C_9H_7NO)

In an improved synthesis, 45.50 g (300 mmol) ω-chloroacetophenone were dissolved in 240 ml ethanol and stirred together with a solution of 29.41 g (600 mmol) NaCN in 120 ml H_2O at room temperature for 1 h. The brownish solution was filtered and the solvent evaporated *in vacuo* to give a precipitate. The residue was poured into 1000 ml ice/water and stirred for 3 h at room temperature. The mixture was filtered, and the filtrate was acidified with conc. HCl to give **1**.

Colourless platelets; 32.00 g (74%); m.p.: 79–80°C (H_2O; Refs. [7–9]: 80–81°C); IR (KBr): $\nu = 1690, 2220, 2920\,cm^{-1}$; ^{1}H NMR (200 MHz, δ, *DMSO*-d_6): 4.78 (s, 2H, CH_2), 7.55–7.78 (m, 3H, *m*-, *p*-aromatic protons), 7.94–8.00 (d, 2H, *o*-aromatic protons) ppm.

1-Dimethylamino-3-oxo-3-phenyl-1-propene-2-carbonitrile (**2**; $C_{12}H_{12}N_2O$)

4.35 g (30 mmol) **1** and 7.14 g (60 mmol) N,N-dimethylformamide-dimethylacetal were stirred at room temperature. Compound **2** precipitated immediately. After 1 h, petroleum ether was added, and the mixture was filtered giving yellowish crystals.

4.50 g (67%); m.p.: 106–108°C (ethanol); IR (KBr): $\nu = 2200$, 1650, 1600 cm^{-1}; ^1H NMR (200 MHz, δ, *DMSO*-d_6): 3.40 (s, 6H, N-CH_3), 7.45–7.69 (m, 5H, aromatic protons, 7.93 (s, 1H, CH) ppm.

5-Amino-4-benzoylpyrazole (**4a**; $C_{10}H_9N_3O$)

A mixture of 5.00 g (25 mmol) **2**, 1.00 g (20 mmol) hydrazine hydrate, and 105 ml ethanol was refluxed for 2 h. After evaporation of the yellow reaction mixture, yellow crystals were filtered and washed with cold methanol and petroleum ether.

Colourless crystals; 1.14 g (30%); m.p.: 160–162°C (acetonitrile); IR (KBr): $\nu = 3380$, 3150, 2960, 1610, 1580 cm^{-1}; ^1H NMR (200 MHz, δ, *DMSO*-d_6): 6.79 (s, 2H, NH_2), 7.47–7.57 (m, 3H, *p*-aromatic protons), 7.60 (s, 1H, CH), 7.71–7.73 (m, 2H, *o*-aromatic protons), 12.05 (s, 1H, NH) ppm.

5-Amino-4-benzoyl-1-phenylpyrazole (**4b**; $C_{16}H_{13}N_3O$)

Method A: A mixture of 2.00 g (10 mmol) **2**, 15 ml ethanol, 1.2 ml conc. HCl, and 1.08 g (10 mmol) phenylhydrazine was refluxed for 1 h. After cooling to room temperature, the precipitate was filtered and washed with ethanol to afford 1.96 g (74%) colourless crystals.

Method B: 1.48 g (10 mmol) **3** and 7.56 g (70 mmol) phenylhydrazine were refluxed in 50 ml ethanol for 2 h. The precipitate was filtered after cooling to room temperature and washed with ethanol.

Colourless crystals; 0.65 g (27%); m.p.: 183°C; IR (KBr): $\nu = 3370$, 3260, 3180, 1760, 1620 cm^{-1}; ^1H NMR (200 MHz, δ, *DMSO*-d_6): 7.19 (s, 2H, NH_2), 7.43–7.62 (m, 8H, aromatic protons), 7.77–7.80 (m, 2H, *o*-aromatic protons), 7.82 (s, 1H, CH) ppm.

4-Cyano-5-phenylpyrazole (**5a**; $C_{10}H_7N_3$)

Method A: A mixture of 2.00 g (10 mmol) **2**, 0.50 g (10 mmol) hydrazine hydrate, 20 ml ethanol, and 0.2 ml conc. HCl was refluxed for 3 h. After evaporation of the solvent, the residue was diluted with water and evaporated again. The precipitate was filtered to give 1.50 g (89%) of yellowish needles.

Method B: 2.00 g (10 mmol) **2**, 0.90 g (10 mmol) hydrazinoformic acid methylester, 15 ml ethanol, and 0.2 ml conc. HCl were refluxed for 6 h. After cooling to room temperature, the solution was evaporated *in vacuo*. The residue was diluted with water and evaporated again. Yellowish crystals were filtered off by suction and washed with a small amount of methanol to afford 1.36 g (80%) of **5a**.

Method C: 2.48 g (10 mmol) **3** and 0.40 g (10 mmol) hydrazine hydrate were refluxed in 50 ml ethanol for 2 h. The solution was evaporated and the precipitate diluted with petroleum ether and filtered to give colourless platelets.

Yield: 1.11 g (82%); m.p.: 130°C (methanol/H_2O); IR (KBr): $\nu = 3320$, 3120, 2960, 2230, 1660 cm^{-1}; ^1H NMR (200 MHz, δ, *DMSO*-d_6): 7.30–7.60 (m, 3H, aromatic protons), 7.82–7.97 (m, 2H, aromatic protons), 8.70 (s, 1H, CH), 13.90 (br s, 1H, NH) ppm.

4-Cyano-1,5-diphenylpyrazole (**5b**; $C_{16}H_{11}N_3$)

2.00 g (10 mmol) **2**, 1.00 g (10 mmol) phenylhydrazine, and 15 ml ethanol were refluxed for 3 h. After cooling to room temperature, **5b** was filtered and washed with ethanol.

Colourless needles; 0.93 g (38%); m.p.: 100°C (ethanol); IR (KBr): $\nu = 2220$, 1595 cm^{-1}; ^1H NMR (200 MHz, δ, *DMSO*-d_6): 7.30–7.50 (m, 10H, aromatic protons), 8.45 (s, 1H, CH) ppm.

4-Cyano-5-phenyl-1-p-tolylpyrazole (**5c**; $C_{17}H_{13}N_3$)

A mixture of 2.00 g (10 mmol) **2**, 1.60 g (10 mmol) 4-tolylhydrazine, 1.2 ml conc. HCl, and 15 ml ethanol was refluxed for 1 h. The solvent was evaporated, the residue diluted with water and evaporated again. The precipitate was filtered after addition of a small amount of methanol.

Yellow platelets; 0.37 g (14%); m.p.: 127–129°C (methanol); IR (KBr): $\nu = 2220$, 1620 cm^{-1}; ^1H NMR (200 MHz, δ, *DMSO*-d_6): 2.31 (s, 3H, CH_3), 7.11–7.55 (m, 9H, aromatic protons), 8.40 (s, 1H, CH) ppm.

1-(4-Chlorophenyl)-4-cyano-5-phenylpyrazole (**5d**; $C_{16}H_{10}N_3Cl$)

3.00 g (15 mmol) **2**, 2.70 g (15 mmol) 4-chlorophenylhydrazine, 0.3 ml conc. HCl, and 50 ml ethanol were refluxed for 3 h. After cooling to room temperature, the solid was filtered giving yellow needles.

Yield: 1.97 g (47%); m.p.: 149°C (ethanol); IR (KBr): $\nu = 2240$, 1540, 1505 cm^{-1}; ^1H NMR (200 MHz, δ, *DMSO*-d_6): 7.32–7.41 (m, 4H, aromatic protons), 7.47–7.55 (m, 5H, aromatic protons), 8.45 (s, 1H, CH) ppm.

4-Cyano-1-(4-nitrophenyl)-5-phenylpyrazole (**5e**; $C_{16}H_{10}N_4O_2$)

3.00 g (15 mmol) **2**, 2.30 g (15 mmol) 4-nitrophenylhydrazine, 0.3 ml conc. HCl, and 50 ml ethanol were refluxed for 3.5 h. **5e** precipitated from the boiling red solution; it was filtered after cooling to room temperature and washed with ethanol to give yellow crystals.

Yield: 2.92 g (67%); m.p.: 171–172°C (ethanol); IR (KBr): $\nu = 3080$, 2240, 1600 cm^{-1}; ^1H NMR (200 MHz, δ, *DMSO*-d_6): 7.40–7.55 (m, 5H, aromatic protons), 7.55–7.64 (m, 2H, aromatic protons of the nitrophenyl group), 8.25–8.34 (m, 2H, aromatic protons of the nitrophenyl group), 8.54 (s, 1H, CH) ppm.

4-Cyano-1-(4-methoxyphenyl)-5-phenylpyrazole (**5f**; $C_{17}H_{13}N_3O$)

A mixture of 2.00 g (10 mmol) **2**, 1.38 g (10 mmol) 4-methoxyphenylhydrazine, 0.3 ml conc. HCl, and 15 ml ethanol was refluxed for 1 h. The solution was evaporated and the precipitate was filtered.

Yield: 2.06 g (75%); m.p.: 125°C (ethanol); IR (KBr): $\nu = 2228$, 1510 cm^{-1}; ^1H NMR (200 MHz, δ, *DMSO*-d_6): 3.75 (s, 3H, OCH_3), 6.90–7.55 (m, 9H, aromatic protons), 8.37 (s, 1H, CH) ppm.

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