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Possible Rearrangements During the Syntheses of Di- and Trisubstituted Pyrazoles

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Summary. The reaction of ethoxymethylene malononitrile and ethoxymethylene cyanoacetic acid ethylester with substituted hydrazines to substituted 5-aminopyrazoles is described. The influence of different substituents on possible migrations during the ring closure was studied.

Keywords. Ethoxymethylene malononitrile; Ethoxymethylene cyanoacetic acid ethylester; 1,4,5-Trisubstituted pyrazoles; 4,5-Disubstituted pyrazoles; Acyl migration; Rearrangement.

Mögliche Umlagerungen während der Synthese von zwei- und dreifach substituierten Pyrazolen

Zusammenfassung. Die Reaktion von Ethoxymethylenmalodinitril und Ethoxymethylencyanessigsäureethylester mit substituierten Hydrazinen zu substituierten 5-Aminopyrazolen wird beschrieben. Der Einfluß unterschiedlicher Substituenten auf mögliche Wanderungen während des Ringschlusses wurde untersucht.

Introduction

Recently we have reported on the syntheses of di- and trisubstituted pyrazoles from aminomethylene- and anilinomethylene derivatives of cyanoacetophenone and various hydrazines [1]. No rearrangements have been observed during the ring closure reactions. Reactions of ethoxymethylene malononitrile with semicarbazides and thiosemicarbazides have been performed earlier and have afforded 1-acyl-5-aminopyrazoles [2]. However, no ^{13}C NMR data have been given, making it hard to decide, if acyl migrations towards 1-acyl-3-aminopyrazoles have occured. Rearrangements have been observed in N-carbamoyl pyrazoles, resulting in three products: compounds **A** and **B** and substituted urea **C** arising from migration of the carbamoyl residue to the amino group (Scheme 1, $R^1 =$ carbamoyl, $R^2 = H$) [3, 4].

In our experiments, N-substituted pyrazoles have been obtained directly by condensation reactions of substituted hydrazines with ethoxymethylene malononi-

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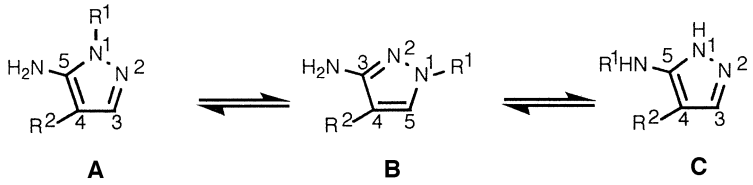


Scheme 1

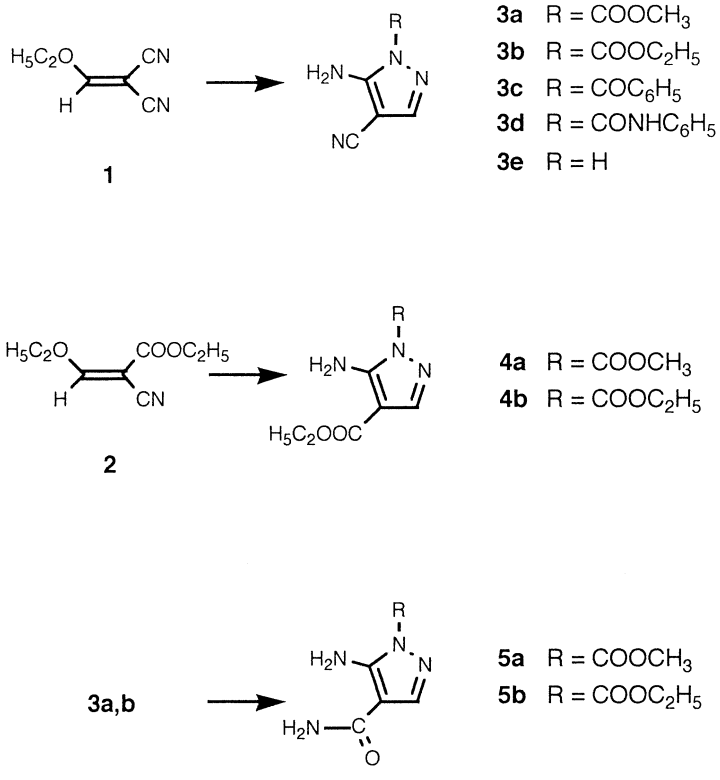
trile (**1**) and ethoxymethylene cyanoacetic acid ethylester (**2**). Thus, we tried to find out if migrations of acyl or carbamoyl groups are possible also during the ring closure reaction itself.

Results and Discussion

Reactions of **1** [5–8] and **2** generally gave the 1-substituted 5-amino-4-cyano-pyrazoles **3a–e** and 5-amino-4-ethoxycarbonyl pyrazoles **4a**, **b**, (Scheme 2).

Condensations of **1** with hydrazinoformic acid methylester were performed in ethanol or xylol at different temperatures. All syntheses gave **3a** as the sole product.

Hydrolysis of the nitrile groups of **3a**, **b** under mild conditions gave carbamoyl compounds **5a**, **b** as expected [9]. However, migrations of the ester groups were not observed.



Scheme 2

Table 1. Selected ^{13}C NMR data of compounds **3a–e**, **4a**, **b**, and **5a**, **b**; for the numbering of the carbon atoms, see isomer **A** in Scheme 1; ^{13}C NMR spectra were recorded with a Varian CFT-20 NMR spectrometer in *DMSO*-d_6 (ppm relative to internal *TMS*)

	C-3	C-4	C-5
3a	144	72	150
b	143	71	154
c	144	73	156
d	142	73	154
	157[a]	84[a]	129[a]
e	140	72	154
4a	143	93	151
b	143	93	153
5a	142	95	152
b	142	95	151

[a] Signals of isomer **B** (Scheme 1)

Selected ^{13}C NMR data of compounds **3a–e**, **4a**, **b**, and **5a**, **b** are given in Table 1. All 1-substituted 5-aminopyrazoles (isomer **A** in Scheme 1) showed the signal of C-3 at 140 to 144 ppm. Atoms C-5 (those bearing the amino groups) displayed signals at 150 to 156 ppm. The signals of C-4 were strongly substituents dependent. **4a**, **b** with a 4-alkoxy-carbonyl group and **5a**, **b** with a 4-carbamoyl group showed the signals of C-4 at 95 or 93 ppm, respectively. A nitrile group at C-4 resulted in an upfield shift of the signal of C-4 to 73 to 71 ppm.

Interestingly, **3d** was the only compound to show migration of R^1: The reaction of **1** and 4-phenylsemicarbazide gave two isomers (**A** and **B**, R^1 = N-phenyl-carbamoyl, R^2 = nitrile in Scheme 1). The ^{13}C NMR spectra of **A** and **B** were significantly different. Whereas the signal of C-3 resonated at 142 ppm in **A**, C-5 gave a signal at 129 ppm in isomer **B**, the upfield shift being caused by the carbamoyl group at N-1. Signals of C-4 occured at 73 (isomer **A**) or at 84 (isomer **B**) ppm. No distinct difference was found for the signal of the carbon atom bearing the amino group (C-5 in isomer **A**, 154 ppm; C-3 in isomer **B**, 157 ppm).

The first ^{13}C NMR spectrum of product **3d** pointed at a mixture of 3.7 parts **A** and 1 part **B**. Heating the sample to 100°C for approximately one minute changed this ratio to 2 parts **A** and 1 part **B**, indicating a thermal isomerization. However, if **3d** was heated for prolonged time intervals or to higher temperatures (150°C), the signals of isomer **A** as well as of isomer **B** disappeared due to sample decomposition.

Conclusion

Ring closure reactions of **1** and **2** with substituted hydrazines generally resulted in the formation of 1-substituted 5-amino-pyrazoles with electron withdrawing substituents in position 4. In only one case (**3d**), a second isomer was found; due to a thermal equilibrium reaction, it could not be obtained in pure form. Thus it may

be derived that electron withdrawing groups in position 4 of 5-aminopyrazoles lower their tendency for rearrangements of the substituents at N-1.

Experimental

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

Ethoxymethylene cyanoacetic acid ethylester (**2**; $C_8H_{11}NO_3$)

A mixture of 28.25 g (0.25 mol) cyanoacetic acid ethylester, 36.00 g (0.24 mol) triethylorthoformate, and 51.00 g (0.50 mol) acetic acid anhydride was refluxed for 5.5 h. The solvent was removed under reduced pressure, and the precipitate was allowed to crystallize in the refrigerator overnight. Colourless needles were filtered and washed with a small amount of cold ethanol.

Yield: 15.08 g (37%); m.p.: 50°C; IR (KBr): ν = 3020, 2990, 2940, 2230, 1710, 1620 cm^{-1}; ^{1}H NMR (200 MHz, δ, *DMSO*-d_6): 1.22–1.32 (t, 3H, CH_3), 1.32–1.38 (t, 3H, CH_3), 4.17–4.28(q, 2H, CH_2), 4.43–4.53 (q, 2H, CH_2), 8.42 (s, 1H, CH) ppm.

5-Amino-4-cyano-1-methoxycarbonylpyrazole (**3a**; $C_6H_6N_4O_2$)

3.66 g (30 mmol) **1** were refluxed with 2.70 g (30 mmol) hydrazinoformic acid methylester in 20 ml ethanol for 6 h. Compound **3a** precipitated from the hot solution. After cooling to room temperature, the product was filtered by suction and washed with ethanol, giving 1.10 g yellowish platelets (22%).

M.p.: 180–182°C (acetonitrile); IR (KBr): ν = 3460, 3380, 3205, 3115, 2210, 1750, 1630 cm^{-1}; ^{1}H NMR (200 MHz, δ, *DMSO*-d_6): 3.95 (s, 3H, OCH_3), 7.78 (s, 2H, NH_2), 7.85 (s, 1H, CH) ppm.

5-Amino-4-cyano-1-ethoxycarbonylpyrazole (**3b**; $C_7H_8N_4O_2$)

A mixture of 3.66 g (30 mmol) **1**, 3.12 g (30 mmol) hydrazinoformic acid ethylester, and 20 ml ethanol was refluxed for 5 h. The precipitate was filtered after cooling to room temperature and washed with cold ethanol to give 3.20 g yellow platelets (60%).

M.p.: 164–168°C (acetonitrile); IR (KBr): ν = 3500, 3280, 3220, 3160–3120, 2220, 1770, 1630 cm^{-1}; ^{1}H NMR (200 MHz, δ, *DMSO*-d_6): 1.28–1.36 (t, 3H, CH_3), 4.35–4.45 (q, 2H, CH_2), 7.72 (s, 2H, NH_2), 7.82 (s, 1H, CH) ppm.

5-Amino-1-benzoyl-4-cyanopyrazole (**3c**; $C_{11}H_8N_4O$)

A mixture of 2.24 g (18 mmol) **1**, 2.52 g (18 mmol) benzoylhydrazine, and 20 ml ethanol was refluxed for 1 h. Compound **3c** precipitated from the hot solution. After cooling to room temperature, the mixture was filtered to yield 2.76 g colourless needles (72%).

M.p.: 176°C (acetonitrile); IR (KBr): ν = 3430, 3300, 3240, 2230, 1690, 1650 cm^{-1}; ^{1}H NMR (200 MHz, δ, *DMSO*-d_6): 7.50–7.58 (t, 2H, aromatic protons (*m*)), 7.65–7.73 (t, 1H, aromatic protons (*p*)), 7.91–7.95 (d, 3H, aromatic protons *(o*), CH), 8.07–8.11 (s, 2H, NH_2) ppm.

5-Amino-4-cyano-N-phenyl-1-pyrazole-carboxamide (**3d**; $C_{11}H_9N_5O$)

4.24 g (35 mmol) **1** and 5.00 g (33 mmol) 4-phenylsemicarbazide were stirred in 90 ml ethanol at room temperature for 20 h. The precipitate was filtered and washed with ethanol to yield 1.60 g colourless needles (21%).

M.p.: 172°C (ethanol) Ref. [2]: 171–173°C; IR (KBr): $\nu = 3440$, 3360, 3300, 2240, 1730, 1630 cm^{-1}; ^1H NMR (200 MHz, δ, *DMSO*-d_6): 7.11–7.20 (t, 1H, aromatic protons (*p*)), 7.31–7.40 (t, 2H, aromatic protons (*m*)), 7.63–7.70 (d, 2H, aromatic protons (*o*)), 7.78–7.81 (s, 2H, NH_2), 7.96 (s, 1H, CH), 10.25 (s, 1H, NH) ppm.

5-Amino-4-cyanopyrazole (**3e**; $C_4H_4N_4$)

2.44 g (20 mmol) **1**, 1.00 g (20 mmol) hydrazine hydrate, and 50 ml ethanol were refluxed for 6 h. The mixture was filtered, and the filtrate was evaporated to yield 0.77 g **3e** (36%).

M.p.: 173°C (acetonitrile) (Ref. [10]: 172–173°C); IR (KBr): $\nu = 1645$, 2240, 2830, 2950, 3140, 3340, 3420 cm^{-1}; ^1H NMR (200 MHz, δ, *DMSO*-d_6): 6.15 (s, 2H, NH_2), 7.70 (s, 1H, CH), 12.08 (s, 1H, NH) ppm.

5-Amino-4-ethoxycarbonyl-1-methoxycarbonyl-pyrazole (**4a**; $C_8H_{11}N_3O_4$)

3.38 g (20 mmol) **2** were refluxed with 1.80 g (20 mmol) hydrazinoformic acid methylester in 20 ml ethanol for 22 h. After cooling to room temperature, the solid was filtered and washed with ice cold ethanol to yield 2.10 g colourless crystals (49%).

M.p.: 134–136°C; IR (KBr): $\nu = 3460$, 3280, 3210, 2980, 1750, 1680, 1620 cm^{-1}; ^1H NMR (200 MHz, δ, *DMSO*-d_6): 1.28–1.32 (t, 3H, CH_3), 3.98 (s, 3H, OCH_3), 4.18–4.28 (q, 2H, CH_2), 7.21 (s, 2H, NH_2), 7.75 (s, 1H, CH) ppm.

5-Amino-1,4-diethoxycarbonylpyrazole (**4b**; $C_9H_{13}N_3O_4$)

5.07 g (30 mmol) **2**, 3.12 g (30 mmol) hydrazinoformic acid ethylester, and 25 ml ethanol were refluxed for 22 h. From the clear solution the product crystallized upon cooling to room temperature. The precipitate was filtered and washed with cold ethanol to give 3.82 g colourless crystals (84%).

M.p.: 86°C; IR (KBr): ν = 3480, 3280, 3120, 2980, 1750, 1690, 1620 cm^{-1}; ^1H NMR (200 MHz, δ, *DMSO*-d_6): 1.22–1.29 (t, 3H, CH_3), 1.30–1.38 (t, 3H, CH_3), 4.13–4.25 (q, 2H, CH_2), 4.35–4.45 (q, 2H, CH_2), 7.15 (s, 2H, NH_2), 7.72 (s, 1H, CH) ppm.

5-Amino-1-methoxycarbonylpyrazole-4-carboxamide (**5a**; $C_6H_8N_4O_3$)

To 0.80 g (5 mmol) **3a**, 10 ml of cold conc. H_2SO_4 were added, and the mixture was stirred in an ice bath for 10 min. The ice bath was removed, and stirring was continued at room temperature for 20 h. Upon pouring carefully onto ice chips, 0.35 g (38%) yellow needles were obtained.

M.p.: 182°C; IR (KBr): ν = 3440, 3340, 3170, 1725, 1670, 1600 cm^{-1}; ^1H NMR (200 MHz, δ, *DMSO*-d_6): 3.95 (s, 3H, OCH_3), 6.90–7.50 (m, 4H, NH_2), 7.92 (s, 1H, CH) ppm.

5-Amino-1-ethoxycarbonylpyrazole-4-carboxamide (**5b**; $C_7H_{10}N_4O_3$)

To 30 ml conc. H_2SO_4, 6.80 g (38 mmol) **3b** were added at 0°C and stirred at room temperature for 22 h. The solution was carefully poured onto ice chips, and the precipitate was filtered and washed with cold ethanol.

Yield: 3.72 g yellow crystals (51%); m.p.: 200°C; IR (KBr): ν = 3460, 3360, 3160, 2990, 1750, 1670, 1630 cm^{-1}; ^1H NMR (200 MHz, δ, *DMSO*-d_6): 1.29–1.38 (t, 3H, CH_3), 4.35–4.45 (q, 2H, CH_2), 6.90–7.45 (m, 4H, NH_2), 7.93 (s, 1H, CH) ppm.

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