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SYNTHESIS OF NOVEL POLYCYCLIC RING SYSTEMS CONTAINING TWO PYRANO[2,3-*c*]PYRAZOL-4(1H)-ONE MOIETIES

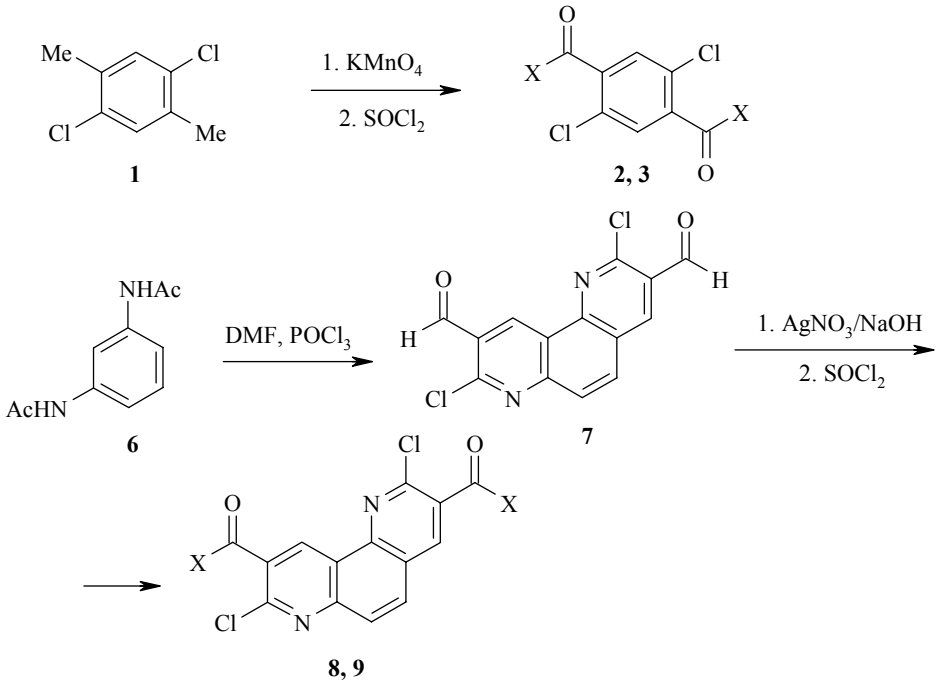
Novel penta- or heptacyclic ring systems containing two pyrano[2,3-*c*]pyrazol-4(1H)-one units are prepared in one or two steps from the reaction of 3-methyl-1-phenyl-2-pyrazolin-5-one and bis(*o*-chlorocarbonyl chlorides) derived from benzene- or 1,10-phenanthroline.

Keywords: pyrazolones fused ring systems, acylations.

Recently, we presented a short and efficient synthesis of novel azaxanthones containing a pyrano[2,3-*c*]pyrazol-4(1H)-one moiety by the reaction of 1-substituted 2-pyrazolin-5-ones with *o*-halo(hetero)arenecarbonyl chlorides [1–4]. In continuation of these investigations we here report on the related preparation of hitherto unknown polyheterocycles, which contain two units of the above-mentioned substructure.

Hence, as the acid chloride reactants we have chosen the dicarbonyl dichlorides **3** and **9**, which were synthesized as outlined in Scheme 1, applying slight modifications of the procedures described in the literature.

Scheme 1

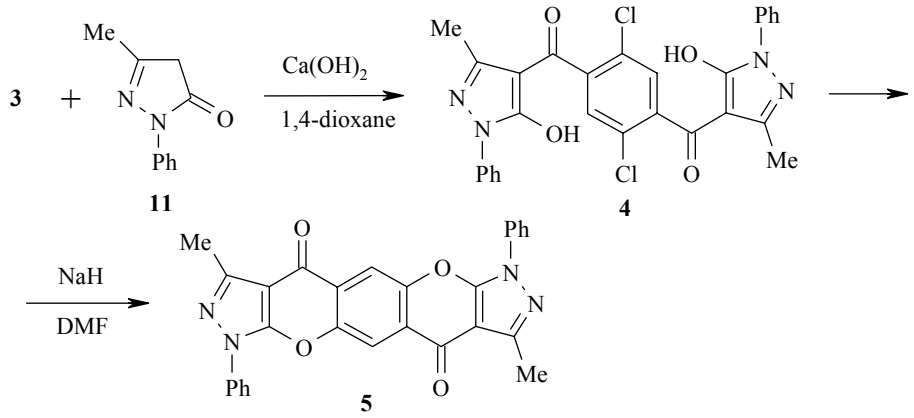


2, **8** X = OH; **3**, **9** X = Cl

When the terephthaloyl dichloride **3** reacted with pyrazolone **11** under the

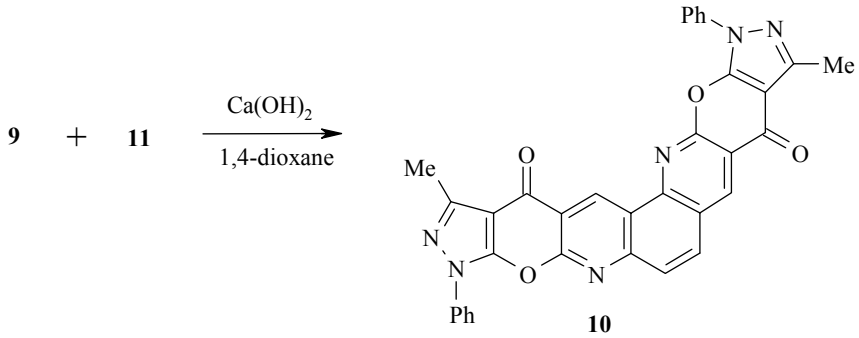
typical conditions reported by Jensen [5] ($Ca(OH)_2$, refluxing 1,4-dioxane), (Scheme 2) we isolated the expected 4-aroylpyrazol-5-ol **4**. The latter was subsequently converted into the pentacycle **5** by treatment with NaH in refluxing DMF. The total yield over two steps (starting from the dicarbonyl dichloride **3**) was 23%.

Scheme 2



The reaction of pyrazolone **11** with the phenanthrolinedicarbonyl dichloride **9** under Jensen-type reaction conditions directly led to the target heptacycle **10** in 11% yield (Scheme 3). Such type of spontaneous intramolecular cyclization of the intermediate 4-aroylpyrazol-5-ols has been previously observed with some related pyridinecarbonyl chlorides [1, 3, 4].

Scheme 3



EXPERIMENTAL

Melting points were determined on a Reichert–Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV). IR spectra were recorded on a Perkin–Elmer FTIR 1605 spectrophotometer in KBr. Elemental analyses were performed at the Microanalytical Laboratory, University of Vienna. The ^1H and ^{13}C NMR spectra were recorded on a Varian UnityPlus 300 spectrometer at 28°C or on a Bruker Avance 500 spectrometer at 293 K. The center of the solvent signal (DMSO-d_6) was used as an internal standard which was related to TMS. The digital resolutions were 0.2 Hz/data point in the ^1H NMR spectra and 0.4 Hz/data point in the ^{13}C NMR spectra (^1H broadband decoupling or gated decoupling). ^{15}N NMR spectra were obtained on a Bruker Avance 500 instrument with a directly detecting broadband observe probe and were referenced against external nitromethane (coaxial capillary). It is important to note that owing to the very low solubility or the even

practical insolubility of compounds **3**–**5**,**7**,**9** and **10** in common NMR solvents such as DMSO-d_6 or $CDCl_3$ only limited NMR spectroscopic investigations were possible. Systematic names were generated with ACD/Name [6] according to the IUPAC recommendations and were also checked manually to ensure the correct use of nomenclature within this publication [7]. The alternative name for compound **4** is according to phane nomenclature [8, 9]. Product yields were not optimized.

1,4-Dichloro-2,5-dimethylbenzene (**1**). This product is commercially available (Aldrich). ^{1}H NMR spectrum (300 MHz), δ, ppm: 7.38 (2H, s, H-3,6); 2.25 (6H, s, CH_3). ^{13}C NMR spectrum (75 MHz), δ, ppm (*J*, Hz): 134.7, 131.5, 130.8 (C-3,6; ^1J = 165.5), 18.7 (CH_3, ^1J = 128.4).

2,5-Dichloroterephthalic acid (**2**). To a well stirred suspension of 1 g Aliquat© 336 (trioctylmethylammonium chloride), 4.74 g (30 mmol) of $KMnO_4$, and 5.25 g (30 mmol) of xylene **1** in 50 ml H_2O was added dropwise a solution of $KMnO_4$ (14.2 g, 90 mmol) in 150 ml of H_2O. Then the reaction mixture was heated to 80°C for 72 h. After cooling the mixture to room temperature, it was filtered off and the remaining filter cake was extracted twice with 30 ml of Et_2O. The combined organic layers were washed with H_2O (10 ml), dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to afford 1.10 g (21%) of unreacted starting material **1**. The filtrate was treated with small amounts of $NaHSO_3$ and brought to pH 1 by dropwise addition of 2N HCl. Upon cooling in the refrigerator overnight colorless crystals of **2** separated, which were filtered off and dried. Yield 4.52 g (64%; 81% based upon not recovered educt). Alternatively, this product can be obtained from TCI Europe Organic Chemicals. ^{1}H NMR spectrum (300 MHz), δ, ppm: 13.71 (2H, br. s, OH); 7.89 (2H, s, H-3,6). ^{13}C NMR spectrum (75 MHz), δ, ppm (*J*, Hz): 164.9 (CO), 134.8, 132.1 (C-3,6; ^1J = 171.3), 130.0. MS, *m/z* (I_{rel}, %): 238 $[M]^+$ (10), 236 $[M]^+$ (75), 234 $[M]^+$ (100), 221 (11), 219 (62), 217 (90), 135 (23), 133 (32), 109 (21), 74 (51), 73 (27), 45 (26).

2,5-Dichloroterephthaloyl dichloride (**3**). A suspension of terephthalic acid **2** (2.35 g, 10 mmol), cyclohexane (5 ml), DMF (1 drop), and $SOCl_2$ (15 ml) was heated at reflux for 4 h. Excess $SOCl_2$ was removed under reduced pressure, the reaction mixture was refrigerated over night and then filtered off to afford the acid chloride **3**. Yield 2.20 g (81%). Mp 77.5–79°C (mp 80.5–81°C [10]). MS, *m/z* (I_{rel}, %): 276 $[M]^+$ (1), 274 $[M]^+$ (5), 272 $[M]^+$ (11), 270 $[M]^+$ (8), 239 (28), 237 (100), 235 (91), 209 (39), 207 (37), 109 (28), 74 (43), 73 (24).

(**2,5-Dichloro-1,4-phenylene)bis[(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methanone]** (**4**). To a suspension of pyrazolone **11** (697 mg, 4 mmol) and $Ca(OH)_2$ (593 mg, 8 mmol) in 1,4-dioxane (6 ml) was added the acid chloride **3** (544 mg, 2 mmol), suspended in 1,4-dioxane (2 ml), and the reaction mixture was heated at reflux for 3 h. After cooling to room temperature, the mixture was treated with 2N HCl (16 ml) and then stirred for 1 h before it was poured onto H_2O (40 ml). After 30 min, the mixture was filtered off and the remaining solid was repeatedly washed with H_2O to give crude compound **4** (510 mg, 47%). For analytical purposes 100 mg were recrystallized from EtOH–DMF. Mp 262–268°C. IR spectrum, ν, cm^{-1}: 1622 (C=O). ^{1}H NMR spectrum (500 MHz), δ, ppm: 7.63 (4H, m, NPh H-2,6); 7.51 (2H, s, Ph H-3,5); 7.46 (4H, m, NPh H-3,5); 7.29 (2H, m, NPh H-4); 2.28 (6H, s, CH_3). ^{13}C NMR spectrum (125 MHz), δ, ppm: 185.1 (CO), 141.9 (C_q), 136.8 (NPh C-1), 129.0 (NPh C-3,5), 128.6 (Ph C-3,6), 128.1 (C_q), 126.2 (NPh C-4), 121.0 (NPh C-2,6), 104.0 (pyrazole C-4), 14.2 (CH_3). MS, *m/z* (I_{rel}, %): 550 $[M]^+$ (5), 548 $[M]^+$ (30), 546 $[M]^+$ (30), 513 (26), 511 (54), 475 (45), 355 (36), 327 (32), 325 (77), 311 (40), 238 (26), 201 (32), 92 (29), 91 (76), 88 (64), 77 (100), 67 (69), 58 (35), 43 (40). Found, %: C 60.95; H 3.58; N 10.25. $C_{28}H_{20}Cl_2N_4O_4 \cdot 0.2H_2O$. Calculated, %: C 60.94; H 3.74; N 10.15.

3-9-Dimethyl-1,7-diphenylbenzo[1'',2'':5',6';4'',5'':5'6']dipyrano[2,3:*d*;2',3':*d*']dipyrazole-4,10(1H,7H)-dione (**5**). Under anhydrous conditions, a suspension of compound **4** (274 mg, 0.5 mmol) and NaH (50% in mineral oil, 44 mg, 1 mmol) in DMF (3 ml) was heated at reflux over night. Then the solvent was removed under reduced pressure and H_2O (5 ml) was added to the residue. The mixture was stirred for 1 h and the formed precipitate was filtered off, washed with H_2O and petroleum ether and recrystallized from DMF to afford the pure pentacycle **5**. Yield 94 mg (49%); mp > 340°C. IR spectrum, ν, cm^{-1}: 1668 (C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm: 8.51 (2H, s, H-5,11); 8.03 (4H, m, NPh H-2,6); 7.65 (4H, m, NPh H-3,5); 7.48 (2H, m, NPh H-4); 2.62 (6H, s, CH_3). MS, *m/z* (I_{rel}, %): 475 $[M]^+$ (26), 474 (79), 473 (23), 121 (100), 77 (35). Found, %: C 70.58; H 3.72; N 11.78. $C_{28}H_{18}N_4O_4$. Calculated, %: C 70.88; H 3.82; N 11.81.

N,N'-(1,3-Phenylene)diacetamide (**6**). Similarly to the known procedure [11], to molten 1,3-benzenediamine (54.1 g, 0.5 mol) was added dropwise Ac_2O (76.6 g, 0.75 mol) under stirring.

The solution was heated to reflux for 2 h, then further Ac_2O (25.5 g, 0.25 mol) was added, and the reaction mixture was again refluxed for 2 h. The solution was cooled to room temperature and then poured into H_2O (ca. 300 ml) under stirring. Upon standing in the refrigerator for 1 h, diacetamide **6** separated as almost colorless crystals, which were dried at 90°C for 1 h. Yield 89.5 g (93%); mp 186–189°C (mp 191°C [12]). ^{1}H NMR spectrum (300 MHz), δ, ppm: 9.89 (2H, s, NH); 7.87 (1H, br. s, H-2); 7.25 (2H, m, H-4,6); 7.16 (1H, m, H-5); 2.02 (6H, s, CH_3). ^{13}C NMR (75 MHz): δ 168.2 (CO), 139.5 (C-1,3), 128.7 (C-5), 113.8 (C-4,6), 109.8 (C-2), 24.0 (CH_3). MS, *m/z* (I_{rel}, %): 192 $[M]^+$ (21), 150 (32), 108 (100), 80 (31), 43 (100).

2,8-Dichloro-1,7-phenanthroline-3,9-dicarbaldehyde (**7**). Similarly to the known procedure [13], $POCl_3$ (107 g, 0.7 mol) was added dropwise to DMF (21.9 g, 0.3 mol) at 0°C under stirring. To this solution was added the diacetamide **6** (9.61 g, 0.05 mol) and the resulting mixture was refluxed for 4 h. The deeply colored solution was cooled to room temperature and added dropwise to ice water (ca. 500 ml) with stirring. Then the pH was adjusted to 2–3 by addition of 2 N NaOH to precipitate phenanthroline **7**, which was filtered off and washed with H_2O and light petroleum to afford a yellowish powder. Yield 10.9 g (71%). IR spectrum, ν, cm^{-1}: 1685–1695 (2×C=O). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 10.47 (1H, s, 9-CHO); 10.45 (1H, s, 3-CHO); 9.68 (1H, d, $^5J_{10,6}$ = 0.7, H-10); 9.15 (1H, s, H-4); 8.62 (1H, d, $^3J_{5,6}$ = 9.1, H-5); 8.17 (1H, dd, $^3J_{6,5}$ = 9.1, $^5J_{6,10}$ = 0.7, H-6). MS, *m/z* (I_{rel}, %): 308 $[M]^+$ (4), 307 (19), 306 $[M]^+$ (59), 305 (56), 304 $[M]^+$ (100), 303 (65), 275 (36), 240 (43), 211 (39), 177 (59), 176 (85), 151 (78), 150 (56), 124 (47), 123 (44), 100 (33), 99 (39), 75 (36), 74 (35).

2,8-Dichloro-1,7-phenanthroline-3,9-dicarboxylic acid (**8**). Similarly to the known procedure [13], to dialdehyde **7** (6.10 g, 20 mmol), suspended in EtOH (96%, 3200 ml), was added $AgNO_3$ (13.6 g, 80 mmol), dissolved in aqueous EtOH (80%, 200 ml). To the clear solution was added in small portions NaOH (10.0 g, 250 mmol), dissolved in aqueous EtOH (80%, 200 ml), and the dark reaction mixture was stirred at room temperature for 4 h. Then Ag_2O was filtered off and the filtrate was concentrated to almost dryness under reduced pressure. H_2O (ca. 50 ml) was added and the solution was filtered again. Upon acidification of the solution by dropwise addition of conc. HCl a precipitate formed, which was filtered off, washed with H_2O, and dried to give the yellow acid **8**, which was used without further purification in the next reaction step. Yield 2.97 g (44%); mp >320°C. ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 9.50 (1H, s, H-10); 9.01 (1H, s, H-4); 8.36 (1H, d, $^3J_{5,6}$ = 9.1, H-5); 7.98 (1H, d, $^3J_{6,5}$ = 9.1, H-6). ^{13}C NMR spectrum (75 MHz), δ, ppm: 165.3 (3-COOH), 165.1 (9-COOH), 149.9 (C-6a), 149.7 (C-8), 147.9 (C-2), 144.9 (C-10b), 141.4 (C-4), 137.2 (C-10), 132.4 (C-5), 127.8 (C-6), 127.1* (C-3), 125.9* (C-9), 124.6* (C-4a), 122.9* (C-10a); ^{15}N NMR spectrum (50 MHz), δ, ppm: −77.2 (N-7), −86.0 (N-1).

2,8-Dichloro-1,7-phenanthroline-3,9-dicarbonyl dichloride (**9**). A suspension of diacid **8** (1.69 g, 5 mmol), cyclohexane (5 ml), DMF (1 drop), and $SOCl_2$ (10 ml) was heated at reflux for 6 h. Then excess $SOCl_2$ was removed under reduced pressure and the reaction mixture was stored in the refrigerator over night. The precipitated crystals were filtered off to afford the pure acid chloride **10**. Yield 1.56 g (84%). IR spectrum, ν, cm^{-1}: 1748–1761 (2×C=O). MS, *m/z* (I_{rel}, %): 376 $[M]^+$ (3), 374 $[M]^+$ (7), 372 $[M]^+$ (6), 341 (36), 339 (97), 337 (100), 151 (25), 123 (37), 105 (25). Found, %: C 45.07; H 1.29; N 7.59. $C_{14}H_4Cl_4N_2O_4$. Calculated, %: C 44.96; H 1.08; N 7.49.

3,12-Dimethyl-1,10-diphenylbis(pyrazolo[4',3':5,6]pyrano)[2,3-*b*:2',3'-*j*][1,7]phenanthroline-4,13(1H,10H)-dione (**10**). To a suspension of pyrazolone **11** (348 mg, 2 mmol) and $Ca(OH)_2$ (296 mg, 4 mmol) in 1,4-dioxane (3 ml) was added acid chloride **9** (374 mg, 1 mmol), suspended in 1,4-dioxane (2 ml), and the reaction mixture was heated at reflux for 3 h. After cooling to room temperature, the mixture was treated with 2N HCl (8 ml) and then stirred for 1 h before it was poured onto H_2O (20 ml). After 30 min, the mixture was filtered and the remaining solid was repeatedly washed with H_2O. Recrystallization from DMF afforded the pure heptacycle **10**. Yield 64 mg (11%); mp >340°C. IR spectrum, ν, cm^{-1}: 1669–1683 (2×C=O). MS, *m/z* (I_{rel}, %): 577 $[M + 1]^+$ (12), 576 $[M]^+$ (14), 91 (45), 77 (73), 44 (100), 41 (37). Found, %: C 69.60; H 3.26; N 14.50. $C_{34}H_{20}N_6O_4 \cdot \frac{1}{3}H_2O$. Calculated, %: C 69.74; H 3.61; N 14.35.

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* Differentiation between C-3/C-9 and between C-4a/C-10a was not unambiguously possible.

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