Novel Pyrazole Analogues of Flavanone, Flavone and Flavane

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The synthesis of the new pyrano[2,3-*c*]pyrazole derivatives **4**, **5**, and **7** starting from (*E*)-1-(1,3-dimethyl-5-hydroxy-4-pyrazolyl)-3-phenyl-2-propen-1-one (**2**) is reported.

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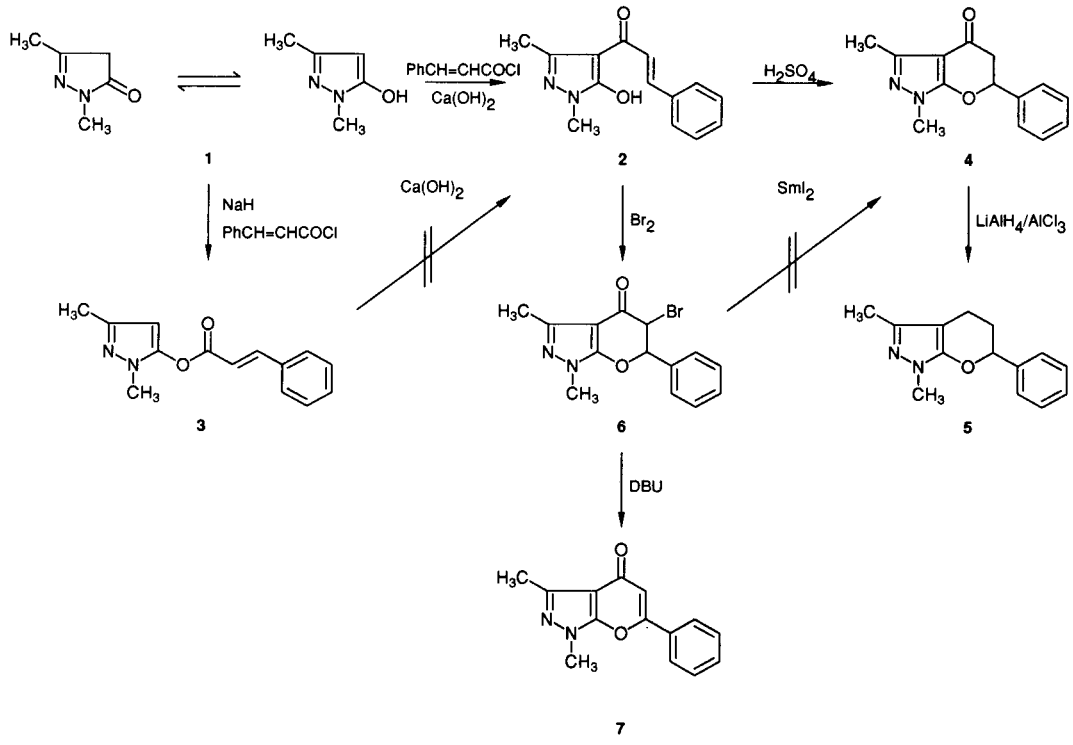
Flavanes, flavones and flavanones represent important substructures of a wide variety of natural products exhibiting various interesting biological activities [3]. Accordingly, there is interest also in related compounds in which the benzo-moiety is replaced by a heteroaromatic system. Thus, for instance, pyridine- and thiophene-derived congeners have been prepared [4-6].

Our continuing interest in the synthesis of diaza-heteroaromatic compounds as potential bio-isosters of bio-active agents [7-9] now prompted us to prepare a series of pyrano[2,3-*c*]pyrazoles of type **4**, **5** and **7**, in which the 1,2-diazole system bears methyl substituents at N-1 and C-3. For recent reports on 1-aryl-3-substituted pyrano[2,3-*c*]-pyrazoles compare references [10,11].

An access to the flavanone analogue **4** could be found by employing the well established strategy for annelation of a dihydro-γ-pyrone system to an aromatic ring (*i.e.* isomerisation of an *o*-hydroxychalcone [12,13]). An initial attempt to prepare the required intermediate **2** *via* generation of a C-4 carbanion in the conveniently available pyrazolone **1** [14] and subsequent reaction with cinnamoyl chloride led to the formation of the *O*-acylated compound **3** exclusively. Treatment of the latter with calcium hydroxide, as described for O-5 → C-4 acyl group migration in related 5-acyloxypyrazoles [15], was found to yield only traces of **2**. However, a one-step procedure consisting of treatment of **1** with cinnamoyl chloride/calcium hydroxide in dioxane solution according to reference [15] afforded the required *o*-hydroxychalcone analogue **2** in satisfactory yield. Cyclisation of **2** to the desired flavanone analogue **4** then was achieved by treatment with concentrated sulfuric acid at room temperature [16].

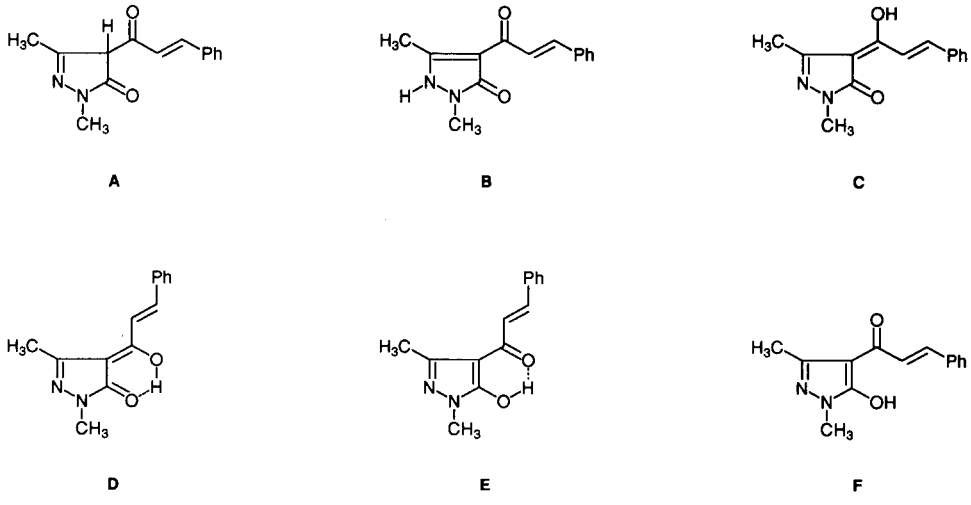
The target flavane analogue **5** could be prepared in satisfactory yield by reduction of **4** using lithiumalumin-

Scheme 1



1 2 3 4 5 6 7

Scheme 2



ium hydride/aluminium chloride [18].

Addition of bromine to the double bond of the chalcone **2** unexpectedly led directly to the condensed system **6**; other than in the benzene or the thiophene series [19,6,20], the 2,3-dibromoketone, in this case, could not be isolated. Whereas an attempt to debrominate the α-halogeno ketone **6** using samarium iodide [21] failed, **6** could be converted into the desired heteroaromatic flavone analogue **7** by heating with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [22].

The structures of all new compounds prepared rest on elemental analyses and spectroscopic data. For the (*E*)-*o*-hydroxychalcone analogue **2** several tautomeric forms have to be taken into consideration. Both theoretically possible dioxo-structures (**A**, **B**) simply can be excluded on basis of the nmr spectra (deuteriochloroform, hexadeuterioacetone): structure **A** would require a one-proton singlet in the aliphatic region of the ^{1}H-nmr spectrum; comparison of the ^{13}C chemical shifts (pyrazole C-3, C-5, N-CH_3, 3-CH_3) of **2** with those observed for related 4-acyl-1,3-dimethyl-5-pyrazolones [23] permits to exclude form **B**. Moreover, the pyrazolone forms **C** and **D** have to be excluded taking into account the ^{1}H-coupled ^{13}C-nmr spectrum of compound **2** (deuteriochloroform): for these forms, quartet-multiplicity has to be anticipated for the signal of the most deshielded carbon atom (C=O; δ 180.68 ppm). Instead, we observed a pseudo-triplet multiplicity (J = 6.5 Hz) which may be interpreted in terms of coupling of the carbonyl-C with the two olefinic protons in the 5-hydroxy structures **E** and **F** [24]. In accordance, a signal with the quartet-multiplicity required for pyrazole C-5 in forms of type **E**, **F** ($^3J_{C\text{-}5,1\text{-}Me}$ = 2.4 Hz) appears at 162.93 ppm. Dilution experiments with deuteriochloroform or hexadeuterioacetone solutions of **2** (200 mg/ml → 10 mg/ml) revealed a marked upfield shift and broadening of the OH-resonance indicating intermolecular hydrogen bonding. Thus, we conclude form **F** to be the far predominant species. Also in hexadeuteriodimethyl sulfoxide solution, the equilibrium is in favour of a non-chelated structure as can be concluded from the chemical shift of the OH-proton (10.7 ppm). For a study of the tautomeric and conformational behaviour of related 4-acyl-5-pyrazolones compare reference [23].

EXPERIMENTAL

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. The ir spectra were recorded for potassium bromide pellets on a Jasco IRA-1 spectrophotometer. The mass spectra were obtained on a Varian MAT 311A instrument (70 eV). The nmr spectra were recorded either on a Bruker AC 80 (80.13 MHz for ^{1}H, 20.15 MHz for ^{13}C) or on a Bruker AM 400 WB (400.13 MHz for ^{1}H, 100.61 MHz for ^{13}C) spectrometer, both equipped with an Aspect 3000 computer and standard software. Chemical shifts are given in δ-units downfield from TMS. Acquisition of ^{1}H-decoupled ^{13}C-nmr spectra was carried out using the J-modulated spin-echo technique [25] in order to obtain multiplicity selection (decoupler switch-off delay: 7 ms); coupled ^{13}C-nmr spectra were obtained with the gated decoupling mode. For tlc, Merck aluminium sheets pre-coated with Kieselgel 60 F_{254} were used; column chromatography was carried out on Merck Kieselgel 60 (70-230 mesh). 1,4-Dioxane was dried by passing through a column of aluminia (activity I, basic); light petroleum refers to the fraction of bp 50-70°.

1,3-Dimethyl-2-pyrazolin-5-one (1,3-Dimethyl-5-hydroxypyrazole) (**1**).

The preparation of compound **1** was carried out following the procedure given in reference [14]; ^{1}H-nmr (deuteriochloroform): δ

3.27 (s, 3 H, N-CH_3), 3.17 (s, 2 H, pyrazoline H-4), 2.09 (s, 3 H, C3-CH_3); ^{1}H-nmr (deuteriodimethyl sulfoxide-d_6): δ 10.70 (s, broad, 1 H, OH), 5.09 (s, 1 H, pyrazole H-4), 3.36 (s, 3 H, N-CH_3), 1.98 (s, 3 H, C3-CH_3); ^{13}C-nmr (deuteriodimethyl sulfoxide-d_6): δ 155.14 (s, C-5), 145.43 (s, C-3), 86.88 (d, C-4), 32.02 (q, NCH_3), 13.60 (q, C3-CH_3).

(*E*)-1-(1,3-Dimethyl-5-hydroxy-4-pyrazolyl)-3-phenyl-2-propen-1-one (**2**).

To a stirred suspension of 1.00 g (8.92 mmoles) of **1** [14] and 1.32 g (17.82 mmoles) of dry calcium hydroxide in 20 ml of dry 1,4-dioxane a solution of 1.57 g (8.92 mmoles) of (*E*)-ethyl cinnamate in 3 ml of dry dioxane was added dropwise and the resulting mixture was heated to reflux for 1.5 hours. After cooling, the suspension was treated with 20 ml of 2 *N* hydrochloric acid and stirring was continued for further 30 minutes. The mixture was poured onto water (50 ml), the yellow precipitate was filtered off, washed with cold diethyl ether and recrystallized from light petroleum to yield 1.10 g (51%) of orange crystals, mp 132-133° [26]; ^{1}H-nmr (deuteriochloroform, c = 20 mg/ml): δ 10.20 (s, broad, 1 H, OH), 7.87 (A-part of an AB-system, J = 15.6 Hz, 1 H, PhC*H*=), 7.68-7.25 (m, 5 H, Ph-H), 7.14 (B-part of an AB-system, J = 15.6 Hz, 1 H, COCH=), 3.56 (s, 3 H, N-CH_3), 2.50 (s, 3 H, 3-CH_3); ^{1}H-nmr (deuteriodimethyl sulfoxide-d_6): δ 10.70 (s, 1 H, OH). 7.95 (A-part of an AB-system, J = 15.8 Hz, 1 H, PhCH=), 7.55 (B-part of an AB-system, J = 15.8 Hz, 1 H, COCH=), 7.70-7.35 (m, 5 H, Ph-H), 3.37 (s, 3 H, N-CH_3), 2.38 (s, 3 H, 3-CH_3); ^{13}C-nmr (deuteriochloroform): δ 180.68 (C=O, ^{2}J = 6.5 Hz, ^{3}J = 6.5 Hz), 162.93 (pyrazole C-5, $^3J_{5,Me}$ = 2.4 Hz), 145.57 (pyrazole C-3, $^2J_{3,Me}$ = 6.9 Hz), 142.98 (Ph*C*H=, ^{1}J = 159.5 Hz), 134.27 (Ph C-1), 130.40 (Ph C-4), 128.70 (Ph C-3,5), 128.13 (Ph C-2,6), 120.30 (CO*C*H=, ^{1}J = 160.5 Hz, ^{2}J = 5.9 Hz), 103.09 (pyrazole C-4, $^3J_{4,Me}$ = 2.5 Hz), 31.56 (NCH_3, ^{1}J = 140.4 Hz), 15.74 (3-CH_3, ^{1}J = 128.1 Hz); ir: cm^{-1} 3400 (OH), 1625 (C=O); ms: m/z (%) 242 (M^+, 31), 139 (20), 138 (100), 131 (16), 115 (13), 104 (13), 103 (29), 102 (11), 77 (32), 70 (12), 67 (23), 51 (17), 43 (75), 39 (29).

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.58; H, 5.99; N, 11.65.

(*E*)-(1,3-Dimethyl-5-pyrazolyl) 3-Phenyl-2-propenoate (**3**).

To a solution of 1.00 g (8.92 mmoles) of **1** [14] in 18 ml of dry 1,4-dioxane 268 mg (8.92 mmoles) of sodium hydride (80% suspension in paraffine oil) were added with stirring. To the resulting suspension a solution of 1.57 g (8.92 mmoles) of (*E*)-ethyl cinnamate in 3 ml of dioxane was added dropwise, then the mixture was heated to reflux for 45 minutes. After cooling, the mixture was acidified to *p*H 4 by adding 2 *N* hydrochloric acid and diluted with a tenfold volume of water. The precipitated solid was filtered off and recrystallized from light petroleum to give 1.32 g (61%) of colorless crystals, mp 70.5-71.5°; ^{1}H-nmr (deuteriodimethyl sulfoxide-d_6): δ 7.94 (A-part of an AB-system, J = 16.0 Hz, 1 H, PhC*H*=), 7.88-7.76 (m, 2 H, Ph H-2,6), 7.50-7.42 (m, 3 H, Ph H-3,4,5), 6.88 (B-part of an AB-system, J = 16.0 Hz, 1 H, COCH=), 5.92 (s, 1 H, pyrazole H-4), 3.58 (s, 3 H, NCH_3), 2.12 (s, 3 H, pyrazole 3-CH_3); ^{13}C-nmr (deuteriochloroform): δ 161.77 (CO, ^{2}J = 2.7 Hz, ^{3}J = 7.2 Hz), 147.89 (PhCH=, ^{1}J = 154.5 Hz), 146.69 (pyrazole C-3, $^2J_{3,4}$ = 4.3 Hz, $^2J_{3,Me}$ = 6.7 Hz), 144.72 (pyrazole C-5, $^2J_{5,4}$ = 2.0 Hz, $^3J_{5,Me}$ = 2.0 Hz), 133.39 (Ph C-1), 130.88 (Ph C-4), 128.74 (Ph C-3,5), 128.15 (Ph C-2,6), 115.11 (CO*C*H=, ^{1}J = 162.0 Hz), 93.37 (pyrazole C-4, ^{1}J = 180.6 Hz, $^3J_{4,Me}$ = 3.6 Hz), 33.93 (NCH_3, ^{1}J = 140.2 Hz), 14.02 (pyrazole 3-CH_3, ^{1}J = 127.5 Hz); ir: cm^{-1} 1735 (C=O), 1620 (C=C); ms: m/z (%) 242 (M^+, 1), 132 (11), 131 (100), 103 (38), 77 (24), 51 (11).

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.61; H, 5.92; N, 11.55.

5,6-Dihydro-1,3-dimethyl-6-phenylpyrano[2,3-*c*]pyrazol-4(1*H*)-one (**4**).

A solution of 1.00 g (8.92 mmoles) of **2** in 35 ml of concentrated sulfuric acid was left to stand for 16 hours at room temperature before it was poured onto ice/water (80 ml). The mixture was extracted with dichloromethane (3 x 50 ml), the combined organic layers were shaken with sodium carbonate solution until the yellow color disappeared, dried, and evaporated *in vacuo*. The residue was recrystallized from ethanol to give 20 mg (2%) of **4** as colorless crystals, mp 154-155°. The combined sodium carbonate phases were acidified with 2 *N* hydrochloric acid and exhaustively extracted with dichloromethane. These organic phases were dried and evaporated *in vacuo* to afford 950 mg (95%) of unchanged starting material **2**. Compound **4** had ^{1}H-nmr (deuteriochloroform): δ 7.44 ("s", 5 H, Ph-H), 5.63 (X-part of an ABX-system, J_{AX} = 12.7 Hz, J_{BX} = 3.2 Hz, 1 H, H-6), 3.61 (s, 3 H, N-CH_3), 2.93 (A-part of an ABX-system, J_{AB} = -17.0 Hz, J_{AX} = 12.7 Hz, 1 H, H-5), 2.66 (B-part of an ABX-system, J_{AB} = -17.0 Hz, J_{BX} = 3.2 Hz, 1 H, H-5'), 2.42 (s, 3 H, C3-CH_3); ^{13}C-nmr (deuteriochloroform): δ 184.76 (CO), 158.44 (pyrazole C-5, $^3J_{5,Me}$ = 2.0 Hz), 146.62 (pyrazole C-3, $^2J_{3,Me}$ = 7.0 Hz), 137.10 (Ph C-1), 128.75 (Ph C-4), 128.48 (Ph C-3,5), 125.92 (Ph C-2,6), 101.37 (pyrazole C-4), 84.06 (C-6, ^{1}J = 149.7 Hz), 43.42 (C-5), 32.78 (NCH_3, ^{1}J = 140.9 Hz), 13.48 (pyrazole 3-CH_3, ^{1}J = 128.7 Hz); ir: cm^{-1} 1660 (C=O); ms: m/z (%) 242 (M^+, 28), 138 (100), 104 (17), 70 (18), 67 (16).

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.66; H, 5.55; N, 11.47.

5,6-Dihydro-1,3-dimethyl-6-phenylpyrano[2,3-*c*]pyrazole (**5**).

To a suspension of 28 mg (0.74 mmole) of lithium aluminium hydride in 2 ml of dry diethyl ether a solution of 195 mg (1.46 mmoles) of anhydrous aluminium chloride in 2 ml of dry diethyl ether was added with stirring at 0°. Then 100 mg (0.41 mmole) of **4** in 2 ml of anhydrous diethyl ether were added dropwise keeping the temperature below 10°. After the addition was complete, the reaction mixture was allowed to come to room temperature, where stirring continued for an additional hour. Wet diethyl ether (20 ml) was added, then the mixture was acidified with diluted hydrochloric acid and subsequently extracted with diethyl ether. The combined ether layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (dichloromethane-ethyl acetate, 3:2) to afford 50 mg (53%) of colorless crystals, mp 67-69°; ^{1}H-nmr (deuteriochloroform): δ 7.39 ("s", 5 H, Ph-H), 5.11 (m, 1 H, H-6), 3.60 (s, 3 H, N-CH_3), 2.65-2.38 (m, 2 H, H-4,4'), 2.15 (s, 3 H, 3-CH_3), 2.15-1.88 (m, 2 H, H-5,5'); ^{13}C-nmr (deuteriochloroform): δ 150.92 (pyrazole C-5), 144.17 (pyrazole C-3), 140.30 (Ph C-1), 128.54 (Ph C-3,5), 128.18 (Ph C-4), 126.01 (Ph C-2,6), 93.98 (pyrazole C-4), 80.96 (C-6), 32.97 (NCH_3), 30.56 (C-4), 17.70 (C-5), 12.48 (3-CH_3); ir: cm^{-1} 2900 (C-$H_{aliph.}$); ms: m/z (%) 228 (M^+, 22), 124 (100), 123 (21), 104 (28), 91 (20), 53 (11), 43 (24).

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.37; H, 7.33; N, 12.07.

5-Bromo-5,6-dihydro-1,3-dimethyl-6-phenylpyrano[2,3-*c*]pyrazol-4(1*H*)-one (**6**).

At 60°, to a solution of 200 mg (0.83 mmole) of **2** in 50 ml of glacial acetic acid 132 mg (0.83 mmole) of bromine in 10 ml of the same solvent were added dropwise within 1 hour and stirring was continued for additional 2 hours. Then the reaction mixture was cooled, treated with water (100 ml), neutralized with sodium bicarbonate solution and extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with 2 *N* sodium hydroxide solution, dried over anhydrous sodium sulfate and evaporated *in vacuo*. Recrystallisation from ethanol afforded 86 mg (32%) of colorless needles, mp 161-162°; ^{1}H-nmr (deuteriochloroform): δ 7.39 ("s", 5 H, Ph-H), 5.77 (part of an AB-system, J = 6.3 Hz, 1 H, H-6), 4.78 (part of an AB-system, J = 6.3 Hz, 1 H, H-5), 3.63 (s, 3 H, N-CH_3), 2.40 (s, 3 H, 3-CH_3); ^{13}C-nmr (deuteriochloroform): δ 178.60 (CO), 156.75 (pyrazole C-5), 148.13 (pyrazole C-3), 135.12 (Ph C-1), 129.62 (Ph C-4), 128.86 (Ph C-3,5), 126.89 (Ph C-2,6), 99.62 (pyrazole C-4), 87.86 (C-6, ^{1}J = 153.7 Hz), 50.23 (C-5, ^{1}J = 149.4 Hz), 33.26 (NCH_3, ^{1}J = 141.2 Hz), 13.71 (3-CH_3, ^{1}J = 129.1 Hz); ir: cm^{-1} 1670 (C=O); ms: m/z (%) 322, 320 (M^+, 2), 182, 184 (4), 139 (10), 138 (100), 103 (14), 77 (11), 70 (10).

Anal. Calcd. for $C_{14}H_{13}BrN_2O_2$: C, 52.36; H, 4.08; N, 8.72. Found: C, 52.23; H, 3.90; N, 8.65.

1,3-Dimethyl-6-phenylpyrano[2,3-*c*]pyrazol-4(1*H*)-one (**7**).

To a solution of 200 mg (0.62 mmole) of **6** in 10 ml of 1,4-dioxane 100 mg (0.66 mmole) of DBU (1,8-diazabicyclo[5.4.0]-undec-7-ene) were added and the resulting mixture was stirred for 1 hour at 90°. After cooling, 20 ml of water was added and stirring was continued for 0.5 hours. The precipitated solid was filtered off and purified by column chromatography (dichloromethane-ethyl acetate, 3:2) to give 81 mg (54%) of colorless crystals, mp 197-198°; ^{1}H-nmr (deuteriochloroform): δ 7.75-7.65 (m, 2 H, Ph H-2,6), 7.50-7.35 (m, 3 H, Ph H-3,4,5), 6.50 (s, 1 H, H-5), 3.82 (s, 3 H, N-CH_3), 2.45 (s, 3 H, 3-CH_3); ^{1}H-nmr (deuteriodimethyl sulfoxide-d_6): δ 8.10-7.97 (m, 2 H, Ph H-2,6), 7.60-7.50 (m, 3 H, Ph H-3,4,5), 6.79 (s, 1 H, H-5), 3.87 (s, 3 H, N-CH_3), 2.39 (s, 3 H, 3-CH_3); ^{13}C-nmr (deuteriochloroform): δ 175.05 (CO), 159.16 (pyrazole C-5), 153.66 (C-6), 144.91 (pyrazole C-3), 130.83 (Ph C-4), 130.45 (Ph C-1), 128.61, 125.45 (Ph C-3,5,2,6), 109.10 (C-5), 105.02 (pyrazole C-4), 33.33 (NCH_3), 13.30 (3-CH_3); ir: cm^{-1} 1630 (C=O); ms: m/z (%) 240 (M^+, 90), 139 (13), 138 (100), 137 (12), 102 (16), 71 (42), 70 (12), 67 (26), 42 (12).

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.80; H, 4.98; N, 11.58.

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[16] Owing to an unfavourable equilibrium **2** ⇌ **4** the yield of **4** in this reaction is very low, thus multiple repetition of the process is required. It should be noted that various other cyclisation methods reported in the literature [17] gave even poorer results.

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[26] Upon attempted recrystallisation of **2** from 96% ethanol a light yellow product was obtained, which was found to be rapidly converted into the orange product described above upon attempted mp-determination or storage in a vacuum-desiccator.