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Short Note

(2-Chlorophenyl)-3-methylchromeno[2,3-*c*]pyrazol-4(1*H*)-one

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Abstract: The title compound was prepared by treatment of 1-(2-chlorophenyl)-3-methyl-2-pyrazolin-5-one with 2-chlorobenzoyl chloride / $Ca(OH)_2$ in 1,4-dioxane and subsequent cyclization of the thus obtained 4-aroyl-5-hydroxypyrazole with sodium hydride in dry DMF. Detailed spectroscopic data (^{1}H NMR, ^{13}C NMR, ^{15}N NMR, IR, MS) are presented.

Keywords: 2-pyrazolin-5-one; chromeno[2,3-*c*]pyrazol-4(1*H*)-one; acylation; cyclization

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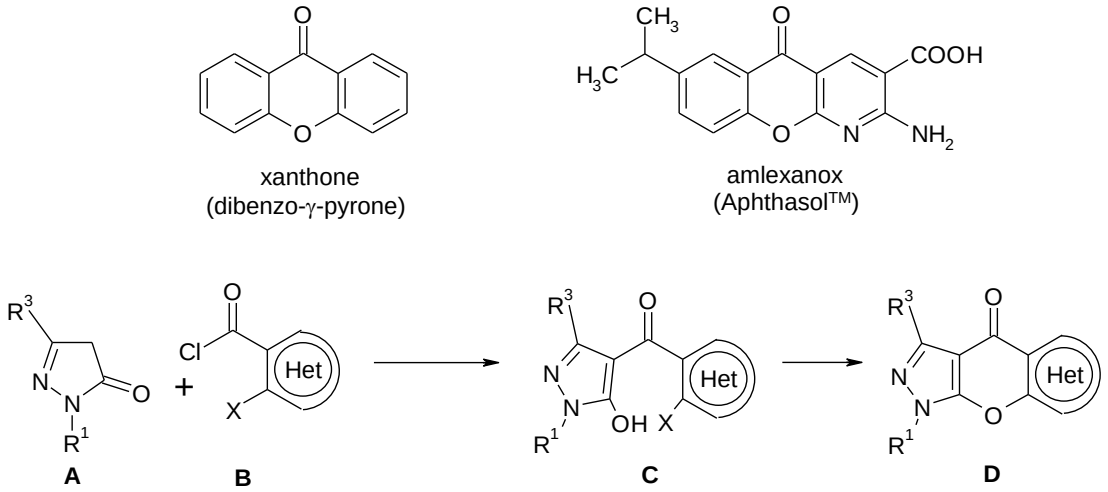
The xanthone system is a partial structure of several biologically active compounds (Figure 1) [1]. Also heterocyclic analogues, in which one or both benzene rings of the parent tricyclic system is/are replaced by heteroaromatic moieties, are of considerable interest for medicinal chemists−as an example the anti-ulcer drug amlexanox (Aphthasol™, Figure 1) may serve [2]. In this respect, we recently presented a simple and generally applicable synthetic approach to various fused pyrano [2,3-*c*]pyrazol-4(1*H*)-ones of type **D** (Figure 1), which can be considered as heterocyclic analogues of xanthone (Figure 1) [3–9]. In these compounds, one benzene ring of the parent xanthone is replaced by a pyrazole ring and the other one by a variable heteroaromatic moiety. However, we also prepared congeners carrying a benzene ring at the 'east' end of the tricyclic system **D** ('Het' = benzene) [4], some related compounds have been previously reported by Russian authors [10].

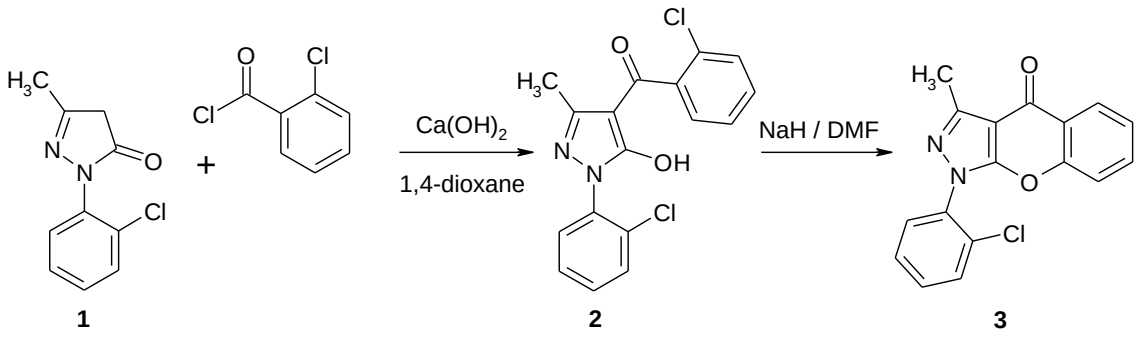
The synthesis of type **D** compounds is based on the reaction of 1-substituted or 1,3-disubstituted 2-pyrazolin-5-ones (**A**) with *O*-halo(hetero)arenecarbonyl chlorides **B** under the conditions described by *Jensen* for the C-4 acylation of pyrazolones (calcium hydroxide, dioxane, reflux) [11]. The so formed 4-aroylpyrazol-5-ols **C** can be smoothly cyclized into the target systems **D** in alkaline (NaH/DMF) or –occasionally – acidic (HCl/EtOH) [9] medium.

Figure 1.



Here, we report the synthesis of the new chromeno[2,3-*c*]pyrazol-4(1*H*)-one **3**, characterized by a 2-chlorophenyl substituent attached to N-1 (Scheme 1). According to the above mentioned synthetic approach, 1-(2-chlorophenyl)-3-methyl-2-pyrazolin-5-one (**1**) was reacted with 2-chlorobenzoyl chloride (**2**) under *Jensen*-conditions. In contrast to the typical cases within the the synthesis of type **C** compounds [3–9], here the aroylation product **2** did not precipitate from the reaction mixture upon addition of water. Instead, a sticky mass was obtained after extraction of the reaction mixture with ethyl acetate, which was coarsly purified by flash chromatography. Treatment of the thus obtained crude **2** with NaH in DMF finally afforded the target product **3**. Although the overall yield (25%) is only moderate, the presented procedure permits a rapid and simple access to the tricycle **3** starting from cheap, commercially available compounds.

Scheme 1. Synthesis of the title compound **3**.



A detailed characterization of **3** including IR, MS and NMR (^{1}H, ^{13}C, ^{15}N) spectral data as well as microanalytical data is given in the Experimental. Full and unambiguous assignment of all ^{1}H, ^{13}C and ^{15}N NMR resonances was achieved by combined application of standard NMR spectroscopic techniques such as ^{1}H-coupled ^{13}C-NMR (gated decoupling), APT, COSY, TOCSY, NOESY, gs-HSQC and gs-HMBC [12].

Experimental

The melting point was determined on a Kofler hot-stage microscope and is uncorrected. Mass spectrum: Shimadzu QP 1000 instrument (EI, 70 eV). IR spectrum: Perkin-Elmer FTIR 1605 spectrophotometer (KBr-disc). The elemental analysis was performed at the Microanalytical Laboratory, University of Vienna. All NMR spectra were recorded from $CDCl_3$ solutions on a Bruker Avance 500 instrument with a 'directly' detecting broadband observe probe (BBFO) at 298 K (500.13 MHz for ^{1}H, 125.76 MHz for ^{13}C, 50.68 MHz for ^{15}N). The centre of the solvent signal was used as an internal standard which was related to TMS with δ = 7.26 ppm (^{1}H in $CDCl_3$) and δ = 77.0 ppm (^{13}C in $CDCl_3$). The digital resolutions were 0.2 Hz/data point in the ^{1}H and 0.4 Hz/data point in the ^{1}H-coupled ^{13}C-NMR spectra (gated decoupling). The ^{15}N NMR spectrum (gradient-selected ^{15}N,^{1}H-HMBC) was referenced against external nitromethane. Pyrazolone **1** and acid chloride **2** are commercially available (TCI Europe).

*1-(2-Chlorophenyl)-3-methylchromeno[2,3-*c*]pyrazol-4(1*H*)-one* (**3**)

Under anhydrous conditions, to a suspension of 1-(4-chlorophenyl)-3-methyl-2-pyrazolin-5-one (**1**) (2.086 g, 10 mmol) and $Ca(OH)_2$ (1.482 g, 20 mmol) in dry 1,4-dioxane (30 mL) a solution of 2-chlorobenzoyl chloride (1.750 g, 10 mmol) in 20 mL of 1,4-dioxane was added dropwise. Then the reaction mixture was heated at reflux for 2 h under stirring. After cooling to room temperature, the mixture was treated with 40 mL of 2 N HCl, stirred for 15 min, and poured into 200 mL of H_2O. After 30 min, the aqueous reaction mixture was extracted with ethyl acetate (3 × 50 mL), the combined organic layers were subsequently washed with $NaHCO_3$ solution and water, dried (Na_2SO_4) and evaporated under reduced pressure. The sticky residue was purified by flash chromatography (silica gel, eluent: ethyl acetate). The obtained aroylation product **2** (1.70 g, 4.97 mmol) was dissolved in dry DMF (25 mL), 215 mg (5.38 mmol) NaH (60% dispersion in mineral oil) was added portionwise and the mixture was heated to reflux for 12 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was taken up in H_2O. The resulting mixture was stirred for 1 h and then filtered with suction. The residue was washed with H_2O and light petroleum and recrystallized from ethanol to afford 778 mg (25% overall yield) of a colorless solid with mp 209–212 °C.

IR (KBr) ν (cm^{-1}): 1667 (C=O).

MS (EI, 70 eV): (*m/z*, %) 310/312 (M^+, 2.5/0.8), 138 (21), 111 (30), 96 (37), 95 (22), 85 (26), 83 (40), 81 (29), 69 (56), 42 (100).

^{1}H NMR ($CDCl_3$): δ (ppm) 2.71 (s, 3H, 3-Me), 7.41 (m, 1H, H-8), 7.44 (m, 1H, H-6), 7.49 (m, 1H, NPh H-5), 7.50 (m, 1H, NPh H-4), 7.56 (m, 1H, NPh H-6), 7.61 (m, 1H, NPh H-3), 7.66 (m, 1H, H-7), 8.36 (m, 1H, H-5).

^{13}C NMR ($CDCl_3$): δ (ppm) 14.2 (3-Me, ^{1}J = 129.3 Hz), 104.0 (C-3a, ^{3}J(C3a,3-Me) = 2.7 Hz), 117.6 (C-8), 123.4 (C-4a), 125.1 (C-6), 126.9 (C-5), 127.8 (NPh C-5), 129.4 (NPh C-6), 130.6 (NPh C-3), 131.0 (NPh C-4), 131.8 (NPh C-2), 133.7 (C-7), 133.8 (NPh C-1), 148.8 (C-3, ^{2}J(C3,3-Me) = 7.1 Hz), 154.4 (C-9a), 154.6 (C-8a), 173.7 (C-4).

^{15}N NMR ($CDCl_3$): δ (ppm) –200.1 (N-1), –91.6 (N-2).

Anal. Calcd for $C_{17}H_{11}ClN_2O_2$ • 0.4 H_2O: C, 64.22%; H, 3.74%; N, 8.81%. Found: C, 64.31%; H, 3.40%; N 8.99%.

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