

Short Note

5-Dimethylamino-1-phenylchromeno[2,3-*c*]pyrazol-4(1*H*)-one

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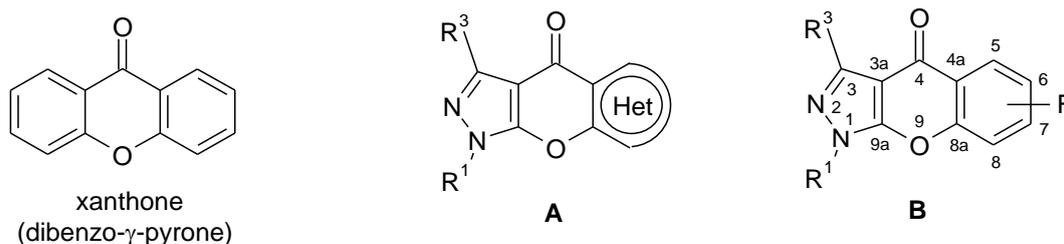
Received: 9 October 2010 / Accepted: 4 November 2010 / Published: 5 November 2010

Abstract: The title compound was prepared by treatment of 5-fluoro-1-phenylchromeno[2,3-*c*]pyrazol-4(1*H*)-one with aqueous dimethylamine. Detailed spectroscopic data (¹H NMR, ¹³C NMR, ¹⁵N NMR, IR, MS) are presented.

Keywords: chromeno[2,3-*c*]pyrazol-4(1*H*)-one; nucleophilic substitution; DMF

In the course of a program devoted to the synthesis of new heterocyclic scaffolds we recently presented the synthesis of various heterocyclic xanthone analogues of type **A** containing a [5,6]pyrano[2,3-*c*]pyrazol-4(1*H*)-one substructure (Figure 1) [1-7]. In these compounds, one benzene ring of the parent xanthone is replaced by a pyrazole system and the other one by a variable heteroaromatic moiety or by a (substituted) benzene ring.

Figure 1.

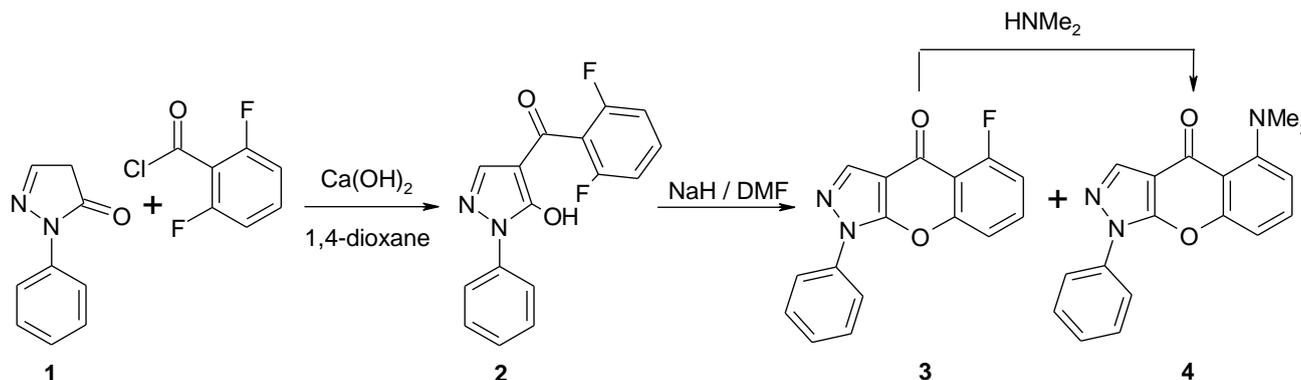


Due to the importance of fluorinated compounds in medicinal chemistry [8-12] we also synthesized appropriate congeners **B** carrying fluoro substituents at different positions of a chromeno[2,3-*c*]pyrazol-4(1*H*)-one scaffold, for instance at positions 5, 6, 7 and 8 (Figure 1) [13]. During the synthesis of 5-fluoro-1-phenylchromeno[2,3-*c*]pyrazol-4(1*H*)-one (**3**, Scheme 1) we observed an

interesting phenomenon. The preparation of **3** was accomplished by cyclization of intermediate **2**, which was obtained upon reaction of 1-phenyl-2-pyrazolin-5-one (**1**) with 2,6-difluorobenzoyl chloride under the conditions described by Jensen for the C-4 acylation of pyrazolones (calcium hydroxide, dioxane, reflux) [14]. When the cyclization of **2** (NaH/DMF) was carried out under forced conditions and prolonged heating, besides the desired fluoro compound **3** also the corresponding dimethylamino congener **4** was obtained in increasing extent (Scheme 1). This finding can be accounted to the known decomposition of DMF (*N,N*-dimethylformamide) at its boiling temperature, leading to the liberation of dimethylamine [15]. This process can also occur at lower temperatures when catalyzed by basic or acidic materials [15]. This special property of DMF has been actually utilized for *N,N*-dimethylaminations of reactive aryl or benzyl halides with DMF, either in the presence or absence of catalysts [16]. Also the conversion of active haloheteroarenes into the corresponding *N,N*-dimethylamino compounds has been described in this way, as an example the synthesis of 6-chloro-3-(dimethylamino)pyridazine from 3,6-dichloropyridazine (95% yield) via 48 hours reflux in DMF solution may serve [16].

For comparison purposes, we prepared amine **4** in an alternative way, *i.e.* by reaction of **3** with excess aqueous dimethylamine. The latter procedure is definitely advantageous compared to the above mentioned one, as here the title compound is smoothly obtained under mild conditions without any by-products, thus superseding a chromatographic separation (Scheme 1).

Scheme 1. Synthesis of compounds **3** and **4**.



A detailed characterization of compound **4** including IR, MS and NMR (^1H , ^{13}C , ^{15}N) spectral data as well as microanalytical data is given in the Experimental. Full and unambiguous assignment of all ^1H , ^{13}C and ^{15}N NMR resonances was achieved by combined application of standard NMR spectroscopic techniques such as ^1H -coupled ^{13}C -NMR (gated decoupling), APT, COSY, NOESY, gs-HSQC and gs-HMBC [17].

Experimental

The melting point was determined on a Kofler hot-stage microscope and is uncorrected. The mass spectrum was obtained on a Shimadzu QP 1000 instrument (EI, 70 eV), the IR spectrum on a 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 ^1H , 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 $\delta = 7.26$ ppm (^1H in CDCl_3) and $\delta = 77.0$ ppm (^{13}C in CDCl_3). The digital resolutions were 0.2 Hz/data point in the ^1H and 0.4 Hz/data point in the ^1H -coupled ^{13}C -NMR spectra (gated decoupling). The ^{15}N NMR spectrum (gradient-selected ^{15}N , ^1H -HMBC) was referenced against external nitromethane.

5-Dimethylamino-1-phenylchromeno[2,3-*c*]pyrazol-4(1*H*)-one (**4**)

In a reaction flask closed with a balloon, to a solution of 5-fluoro-1-phenylchromeno[2,3-*c*]pyrazol-4(1*H*)-one (**3**) (28 mg, 0.1 mmol) in 1,4-dioxane (4 mL) was portionwise added an aqueous solution (40%) of dimethylamine (400 μL) via syringe. Then the mixture was stirred at room temperature for 3 hours. Evaporation of the solvents under reduced pressure produced a light-colored residue which was washed with water and dried to afford 23 mg (75%) of chromatographically pure **4**. For analytical purposes the material was recrystallized from EtOH to give 19 mg (62%) of **4** as yellowish crystals with mp 184–186 $^\circ\text{C}$.

IR (KBr) ν (cm^{-1}): 1651 (C=O).

MS (EI, 70 eV): (m/z , %) 305 (M^+ , 32), 291 (20), 290 (100), 276 (52), 121 (15), 77 (31) 51 (28).

^1H NMR (CDCl_3): δ (ppm) 2.98 (s, 6H, NMe_2), 6.90 (dd, 1H, H-6, $^3J(\text{H6,H7}) = 8.3$ Hz, $^4J(\text{H6,H8}) = 1.0$ Hz), 6.96 (dd, 1H, H-8, $^3J(\text{H8,H7}) = 8.2$ Hz, $^4J(\text{H8,H6}) = 1.0$ Hz), 7.40 (m, 1H, Ph H-4), 7.47 (dd, 1H, H-7, $^3J(\text{H7,H6}) = 8.3$ Hz, $^3J(\text{H7,H8}) = 8.2$ Hz), 7.55 (m, 2H, Ph H-3,5), 7.90 (m, 2H, Ph H-2,6), 8.18 (s, 1H, H-3).

^{13}C NMR (CDCl_3): δ (ppm) 44.8 (NMe_2 , $^1J = 136.3$ Hz, $^3J = 4.1$ Hz), 107.7 (C-3a, $^3J(\text{C3a,H3}) = 9.8$ Hz), 108.1 (C-8), 112.9 (C-6), 113.4 (C-4a), 121.0 (Ph C-2,6), 127.4 (Ph C-4), 129.4 (Ph C-3,5), 133.0 (C-7, $^1J = 160.9$ Hz), 136.8 (C-3, $^1J = 193.6$ Hz), 137.3 (Ph C-1), 151.6 (C-9a, $^3J(\text{C9a,H3}) = 4.8$ Hz), 154.4 (C-5), 157.9 (C-8a), 172.6 (C-4).

^{15}N NMR (CDCl_3): δ (ppm) -325.5 (NMe), -188.8 (N-1), -91.7 (N-2).

Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_2$: C, 70.81%; H, 4.95%; N, 13.76%. Found: C, 70.47%; H, 4.73%; N 13.54%.

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