

Short Note

5-Methyl-4-oxo-4,6-dihydro-3H-pyridazino[4,5-*b*]carbazole-1-carbonitrile

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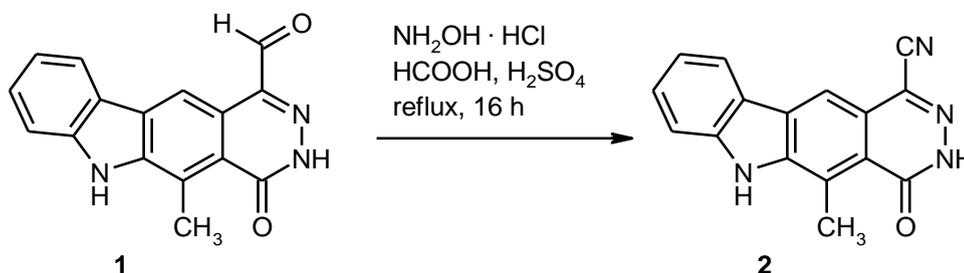
Abstract: The title compound was prepared in excellent yield from 5-methyl-4-oxo-4,6-dihydro-3H-pyridazino[4,5-*b*]carbazole-1-carbaldehyde by treatment with hydroxylamine hydrochloride in formic acid without isolation of the intermediate oxime.

Keywords: pyridazino[4,5-*b*]carbazole; oxime dehydration; nitrile synthesis

In a recent communication [1], we reported the synthesis of 5-methyl-4-oxo-4,6-dihydro-3H-pyridazino[4,5-*b*]carbazole-1-carbaldehyde (**1**) by oxidation of the corresponding hydroxymethyl precursor [2] with a hypervalent iodine reagent. Such functionalised tetracyclic pyridazines are of interest as aza analogues of the pyrido[4,3-*b*]carbazole alkaloids, *ellipticine* and *olivacine* [3–5] and related antitumor agents. The synthesis and anticancer activity of polycyclic nitrogen heterocycles of this and other types has been a major subject in our department's recent research activities [6–11].

In order to extend our library of pyridazino[4,5-*b*]carbazole derivatives, the aldehyde **1** was chosen for further functionalisation at position 1 of the tetracyclic system. Whereas the aldehyde functionality, in principle, offers a wide variety of derivatisation options, the very low solubility of such fused pyridazinones in common organic solvents represents a challenge with respect to compound handling, work-up, and purification. Transformation into a carbonitrile was envisaged, as it would furnish a stable carboxylic acid derivative offering high flexibility with respect to further derivatisation. Initial attempts to effect the desired transformation of the aldehyde into the nitrile *via* the corresponding oxime in two consecutive steps gave unsatisfactory results. However, we found that the target nitrile (**2**) can be prepared very efficiently by treatment of the aldehyde with hydroxylamine hydrochloride in refluxing formic acid in the presence of a catalytic amount of concentrated sulfuric acid, applying a

one-pot protocol previously reported by Bertini *et al.* [12]. The product, in this case, can be isolated very conveniently by dilution of the reaction mixture with water, followed by filtration of the precipitate. The structure of compound **2** thus obtained in 95% yield is clearly evident from its spectral data. The IR spectrum shows a nitrile absorption band at $2,240\text{ cm}^{-1}$. In the ^1H NMR spectrum, the aldehydic proton is no longer detectable and in the ^{13}C NMR spectrum the aldehyde carbon signal (at 191.9 ppm) had disappeared in favour of a resonance at 114.7 ppm, which is typical for the nitrile carbon atom.



Experimental

The melting point was determined on a Kofler hot-stage microscope (Reichert) and is uncorrected. The IR spectrum was recorded on a Perkin-Elmer Spectrum 1000 instrument, ^1H NMR and ^{13}C NMR spectra were recorded on a Varian UnityPlus 300 spectrometer. The low-resolution mass spectrum was obtained on a Shimadzu QP5050A DI 50 instrument, the HR-MS was recorded on a Finnigan MAT 8230 at the Institute of Organic Chemistry, University of Vienna.

5-Methyl-4-oxo-4,6-dihydro-3H-pyridazino[4,5-b]carbazole-1-carbonitrile (**2**)

To a suspension of 5-methyl-4-oxo-4,6-dihydro-3H-pyridazino[4,5-b]carbazole-1-carbaldehyde (**1**) [1] (100 mg, 0.37 mmol) in formic acid (2 mL) was added hydroxylamine hydrochloride (149 mg, 0.55 mmol) and one drop of concentrated sulfuric acid. The mixture was refluxed for 16 h, then it was cooled to room temperature and diluted with water (6 mL). The precipitate was collected by filtration, washed with water, and dried to afford the nitrile **2** as brownish crystals, m.p. $> 300\text{ }^\circ\text{C}$ (decomp.); yield: 97 mg (95%).

IR (KBr): 3362, 3171, 2240, 1648, 1501, 1376, 1265, 1235, 1107, 750 cm^{-1} .

MS (EI, 70 eV): $m/z = 275$ (19%), 274 (M^+ , 100), 218 (18), 217 (12), 216 (11), 191 (21), 82 (11).

^1H NMR (DMSO- d_6 , 300 MHz): $\delta = 3.15$ (3H, s, 5- CH_3), 7.29–7.35 (1H, m, 9-H), 7.57–7.67 (2H, m, 7-H, 8-H), 8.48 (1H, d, $J = 8.1\text{ Hz}$, 10-H), 8.58 (1H, s, 11-H), 12.02 (1H, s, carbazole-NH), 12.99 (1H, s, pyridazinone-NH).

^{13}C NMR (DMSO- d_6 , 75 MHz): $\delta = 15.1$ (5- CH_3), 111.6, 113.9, 114.7 (nitrile-C), 120.0, 120.6, 120.8, 121.4, 121.9, 122.2, 123.9, 126.4, 128.5, 141.6, 141.8, 160.8 (4-C).

HR-MS Calcd. for $\text{C}_{16}\text{H}_{10}\text{N}_4\text{O}$: 274.0855. Found: 274.0851.

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