A Simple Preparation of 4-Oxo-3,4-dihydro-5*H*-pyridazino[4,5-*b*]indoles

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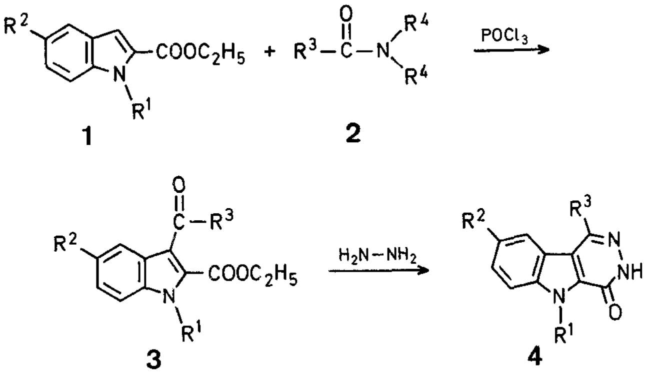
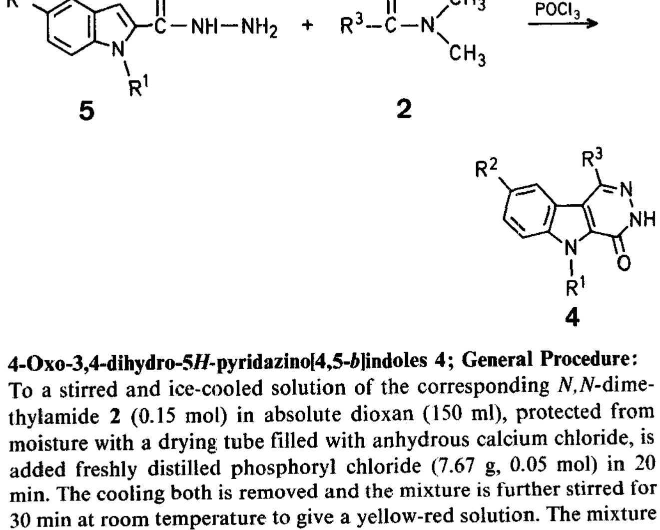
4-Oxo-3,4-dihydro-5*H*-pyridazino[4,5-*b*]indole derivatives **4** are generally prepared by the condensation of 2-alkoxycarbonyl-3-acylindoles **3** with hydrazine[1-7]. The 3-acylindoles **3** are generally obtained by Vilsmeier-Haack acylation[2-9] of 2-alkoxycarbonylindoles **1** with *N*,*N*-disubstituted amides **2** and phosphoryl chloride.



Earlier, we have reported[3] the preparation of **4a** (R^1, R^2, R^3 = H) from 2-indolecarbohydrazide **5a** (R^1, R^2 = H) by direct formylation with dimethylformamide/phosphoryl chloride. When carried out at room temperature, this reaction is known[6] to yield 3-hydroxymethyl-2-indolecarbohydrazide. The latter, however, cyclizes on heating to give the 4-oxo-1,2,3,4-tetrahydro-5*H*-pyridazino[4,5-*b*]indole.

We have now extended our earlier work[3] and report here its generalization using different 2-indolecarbohydrazides **5** and *N*,*N*-dimethylamides **2** to prepare 4-oxo-3,4-dihydro-5*H*-pyridazino[4,5-*b*]indoles **4** (Table). The method utilized for the synthesis of **4** is general and the compounds **4** are obtained in good yield (Table).



4-Oxo-3,4-dihydro-5*H*-pyridazino[4,5-*b*]indoles 4; General Procedure: To a stirred and ice-cooled solution of the corresponding *N*,*N*-dimethylamide **2** (0.15 mol) in absolute dioxan (150 ml), protected from moisture with a drying tube filled with anhydrous calcium chloride, is added freshly distilled phosphoryl chloride (7.67 g, 0.05 mol) in 20 min. The cooling both is removed and the mixture is further stirred for 30 min at room temperature to give a yellow-red solution. The mixture is recooled in an ice-bath and a solution of the corresponding 2-indolecarbohydrazide **5** (0.05 mol) in absolute dioxan (10–15 ml) is added in 30 min while maintaining the reaction temperature at ~8–10°C.

Table. 4-Oxo-3,4-dihydro-5*H*-pyridazino[4,5-*b*]indoles 4 prepared

Product No.	R^1	R^2	R^3	*Yield* [%]	*m.p.* [°C] (solvent)	*Appearance*	*Molecular formula*[a] or Lit. m.p. [°C]
4a	H	H	H	90	326-328° (dioxane)	white needles	326-327°[3]
4b	CH_3	H	H	90	282-283° (dioxane)	white needles	282-283°[2,7]
4c	H	$C_6H_5—CH_2—O$	H	85	273-274° (ethanol/water)	white needles	273-274°[2]
4d	H	H	CH_3	90	211-213° (ethanol/water)	white needles	$C_{11}H_9N_3O$ (199.2)
4e	CH_3	H	CH_3	90	149-150° (ethanol/water)	white needles	$C_{12}H_{11}N_3O$ (213.2)
4f	H	$C_6H_5—CH_2—O$	CH_3	85	287° (ethanol/water)	white needles	$C_{18}H_{15}N_3O_2$ (305.3)
4g	H	H	C_2H_5	90	176-178° (ethanol)	yellow crystals	$C_{12}H_{11}N_3O$ (213.2)
4h	H	H	*n*-C_3H_7	90	185-187° (ethanol)	yellow crystals	$C_{13}H_{13}N_3O$ (227.2)
4i	H	H	4-Cl—C_6H_4	90	275-277° (ethanol/water)	bone-coloured crystals	$C_{16}H_{10}ClN_3O$ (295.7)
4j	CH_3	H	4-Cl—C_6H_4	90	179-180° (ethanol/water)	white needles	$C_{17}H_{12}ClN_3O$ (309.7)

[a] Satisfactory microanalyses obtained: C ±0.30; H ±0.40; N ±0.30. I.R. and ^{1}H-N.M.R. spectra are in agreement with the proposed structure.

The mixture is then heated to 60°C, cooled, and poured onto crushed ice (100 g). The precipitate obtained is collected by suction filtration, washed with water (5 x 30 ml), and purified by recrystallization (Table).

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[1] S. P. Hiremath, S. B. Thakar, M. G. Purohit, *J. Ind. Chem. Soc.* **58**, 782 (1981).

[2] A. Monge Vega, J. A. Palop, M. T. Martínez, E. Fernández-Alvarez, *An. Quim.* **75**, 889 (1979).

[3] A. Monge Vega, I. Aldana, E. Fernández-Alvarez, *Eur. J. Med. Chem.* **13**, 573 (1979).

[4] A. Monge Vega, V. Huarte, J. A. Palop, M. T. Martínez, E. Fernández-Alvarez, *An. Quim.* **73**, 278 (1977).

[5] A. Monge Vega, V. Huarte, J. A. Palop, M. T. Martínez, E. Fernández-Alvarez, *An. Quim.* **72**, 889 (1976).

[6] T. Nogrady, L. Morris, *Can. J. Chem.* **47**, 1999 (1969).

[7] N. V. Suvorov, Z. D. Ovchinnikova, Y. N. Sheinker, *Zh. Obshch. Khim.* **31**, 2333 (1961); *C. A.* **56**, 3478 (1962).

[8] R. H. Sundberg, *The Chemistry of Indoles*, Academic Press Inc., New York, 1970, pp. 36, 401-420.

[9] W. A. Remer in: *Indoles*, Part III, Ed. W. H. Houlihan, Wiley-Inter-