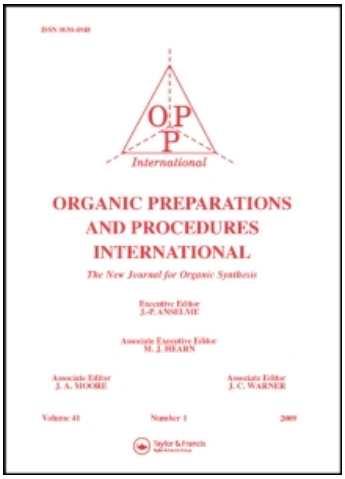

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PREPARATION OF 3-CHLORO-6-(TRIPHENYLMETHYLAZO)PYRIDAZINE

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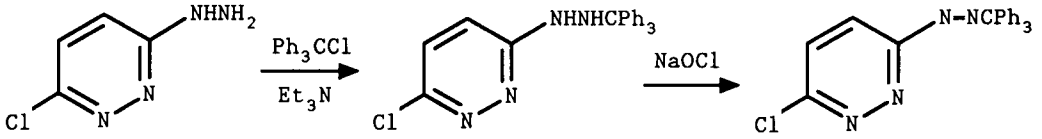
A number of 3-alkylamino or 3-alkoxy-6-hydrazinopyridazines possess interesting pharmacological activity and are currently undergoing clinical evaluation as peripheral vasodilators.[1a-e] They are always prepared from 3,6-dichloropyridazine, which is commercially available or can be prepared from maleic anhydride.[2] While the substitution of the first chlorine atom is facile, the reactivity of the second chlorine atom is greatly diminished when the first group introduced has electron-donating properties.[3] Since 3-chloro-6-hydrazinopyridazine is practically unreactive towards nucleophiles,[4a-b] in order to obtain 3-substituted-6-hydrazinopyridazines it is necessary to introduce the hydrazino group in the amino or alkoxy substituted compound, generally by employing a great excess of hydrazine under forcing conditions.[1a,c] This operation is not suitable for scale up; moreover, due to the high reactivity of hydrazine, by-products are often formed, especially in the case of 3-alkoxy-6-chloropyridazines which give low yields of the desired products along with corresponding amounts of 3-chloro-6-hydrazinopyridazine and 3,6-dihydrazinopyridazine.[1e]

In order to overcome these difficulties, 3,6-dichloropyridazine was converted into 3-chloro-6-(triphenylmethylazo)pyridazine (III),in which the chlorine atom, as expected,[5] is strongly activated toward nucleophilic

substitution, as shown by the fact that reaction with amines or alkoxides occurs smoothly. The hydrazino group is easily regenerated[1b] by reduction of the azo[6] followed by removal of the triphenylmethyl group by acidic treatment.[7]



I II III

This simple and very mild procedure affords high yields (up to 500 g) and eliminates the use of hazardous reagents. Moreover, for the oxidation of II to the azo derivative III, sodium hypochlorite was preferred to other oxidizing agents reported in the literature[9] because it involves fewer problems for waste disposal in view of a scale up.

EXPERIMENTAL SECTION

Mps were taken in capillary tubes using a Büchi apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 197 spectrophotometer. The NMR spectra were run with a Perkin-Elmer R12B spectrometer using TMS as an internal standard. Thin layer chromatography was performed on silica gel plates (Merck 60 FP_{254}), developed with cyclohexane : ethyl acetate 6:4 and visualized by UV light.

3-Chloro-6-hydrazinopyridazine (I).- To a mechanically stirred solution of 25% aqueous hydrazine (425 ml, 2.19 mol) and 30% ammonium hydroxide (750 ml, 19 mol) in water (2.4 l), 3,6-dichloropyridazine (300 g, 2.01 mol) was added, and the mixture was refluxed for 1 hr. The solution obtained was cooled to 0-5° and stirring was continued at this temperature for 3 hrs. The precipitate was collected, washed twice with water (200 ml) and dried in a vacuum oven at 40° over P_2O_5 to yield 249 g (86%) of I, mp. 140-141°, lit.[4a] 138-139°. Nonaqueous solvent titration: 98.6%. IR (nujol mull): 3340-3000, 1630, 1600 and 830 cm^{-1}; NMR

(DMSO-d_6): δ 8.1 (bs, 1H, $NHNH_2$), 7.30 and 7.03 (ABq J=9.3 Hz, 2H, H_4 and H_5), 4.30 (bs, 2H, NH_2).

Anal. Calcd for $C_4H_5ClN_4$: Cl, 24.53; N, 38.77

Found: Cl, 24.89; N, 38.91

3-Chloro-6-[2-(triphenylmethyl)hydrazino]pyridazine (II).- To a mixture of 3-chloro-6-hydrazinopyridazine (249 g, 1.72 mol) and triethylamine (240 ml, 1.72 mol) in dichloromethane (6 l), a solution of chlorotriphenylmethane (480 g, 1.72 mol) in dichloromethane (1.7 l) was added dropwise. The opalescent solution was stirred at room temperature for 1 hr. and then extracted twice with water (1.5 l). The organic phase was dried over anhydrous magnesium sulfate and evaporated under vacuum. The residue was triturated with cyclohexane (1 l) to yield 556 g (84%) of II as a cream colored solid, mp. 165-168°. Nonaqueous solvent titration: 99.7%. IR (nujol mull): 3310, 3300, 1590, 1520, 835, 755 and 695 cm^{-1}; NMR (DMSO-d_6): δ 7.40-7.17 (complex absorption, 17H, PhH, H_4 and H_5), 6.95 6.45 (bs, 2H, NHNH); Rf = 0.38.

Anal. Calcd for $C_{23}H_{19}ClN_4$: Cl, 9.16; N, 14.48

Found: Cl, 9.59; N, 14.12

3-Chloro-6-(triphenylmethylazo)pyridazine (III).- To a solution of 3-chloro-6-[2-(triphenylmethyl)hydrazino]pyridazine (556 g, 1.437 mol) and tetrabutylammonium bromide (17.7 g, 0.055 mol) in dichloromethane (5.6 l), an 8% aqueous solution of sodium hypochlorite (4.8 kg) was slowly added over 30 minutes. Stirring was continued at room temperature for 4 hrs., then a solution of sodium metabisulfite (195 g) in water (1.7 l) was added; stirring was continued for 15 min. and the phases were separated. The aqueous layer was extracted again with dichloromethane (1.5 l), and the combined organic phases were washed with water (1.5 l), dried over anhydrous sodium sulfate and evaporated to a small volume (about 1 kg

residue). Addition of light petroleum (5 l) with vigorous stirring afforded 461 g (83%) of III as a yellow-orange solid, mp. 127-128° (with decomposition). IR (nujol mull): 1590, 1555, 740 and 690 cm^{-1}; NMR ($CDCl_3$): δ 7.70 (s, 2H, H_4 and H_5), 7.30-7.15 (complex absorption, 15H, PhH); Rf = 0.57.

Anal. Calcd for $C_{23}H_{17}ClN_4$: Cl, 9.21; N, 14.55

Found: Cl, 9.62; N, 14.72

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