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Addition of Grignard Reagents to Pyridazines

VII. *tert*-Butylmagnesium Chloride and 3,4,6-Trichloropyridazine

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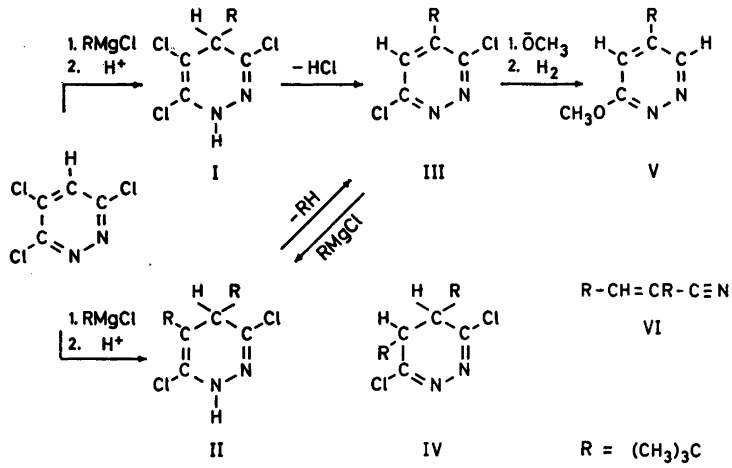
The reaction between 3,4,6-trichloropyridazine and *tert*-butylmagnesium chloride gives 4-*tert*-butyl-3,5,6-trichloro-1,4-dihydropyridazine and 4,5-di-*tert*-butyl-3,6-dichloro-1,4-dihydropyridazine. Both products afford 4-*tert*-butyl-3,6-dichloropyridazine by elimination reactions. Small amounts of 4,5-di-*tert*-butyl-3,6-dichloro-4,5-dihydropyridazine and of 4,4-dimethyl-2-*tert*-butyl-2-pentenonitrile are isolated.

The reaction between Grignard reagents and pyridazines gives 4- (or 5-) substituted dihydropyridazines.[1] This is shown to apply also to the reaction between *tert*-butylmagnesium chloride and 3,4,6-trichloropyridazine, which mainly gives 4-*tert*-butyl-3,5,6-trichloro-1,4-dihydropyridazine (I, see chart). The presence of the chlorine at position 4 in the starting material renders the pyridazine highly reactive and the reaction also gives



small amounts of the di-*tert*-butyldihydropyridazine II, the di-*tert*-butylacrylonitrile VI, and unidentified products.

The formation of the dihydropyridazine II probably involves addition of the Grignard reagent to the intermediary *tert*-butylpyridazine III, which may in turn be formed either *via* I or by direct substitution of the 4-chlorine in 3,4,6-trichloropyridazine.

The formation of the nitrile VI may tentatively be accounted for by assuming a synchronous shift of three pairs of electrons in the nucleus of the dihydropyridazine II and subsequent elimination of hydrogen chloride.

Elimination of hydrogen chloride or isobutane from the dihydropyridazines I and II, respectively, gives 4-*tert*-butyl-3,6-dichloropyridazine III, the structure of which is confirmed by methoxylation and subsequent dehalogenation to give V. The preparation of compounds of type III carrying two reactive chlorine atoms is not feasible by the procedure given earlier.[2] The procedure given here may therefore be of synthetic value, even though the yield is only *ca.* 30 %. The crude product III is contaminated by the dihydropyridazine IV, formed by isomerization of II.

The positions of the protons in the two 1,4-dihydropyridazines I and II is based on NMR and is in accordance with recent work on chloro-, alkyl- and aryl-substituted dihydropyridazines,[3] *cf.* the corresponding methoxydihydropyridazines.[1] The structure of the dihydropyridazine IV is proposed to be the *trans* form on basis of the magnetic equivalence of the protons of the two *tert*-butyl groups as well as that of the two ring protons (NMR data, see Experimental); other structures, *e.g.* the corresponding *cis* configuration, would probably involve non-identity of the two *tert*-butyl groups and also of the two ring protons.

EXPERIMENTAL

The melting points are uncorrected. NMR spectra are taken on a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as an internal reference. Merck silica gel 0.05—0.2 mm is used for chromatography. Microanalyses are by Preben Hansen.

4-tert-Butyl-3,6-dichloropyridazine III. To a solution of 3,4,6-trichloropyridazine [4] (9.2 g, 0.05 mole) in ether (100 ml) is added with efficient stirring *tert*-butylmagnesium chloride (0.075 mole, titrated according to Vlismas [5]) in 5 min. After stirring for further 2 min the products are decomposed with methanol (5 ml in 50 ml of ether) in 2 min with stirring; both additions are exothermic. The magnesium complexes are removed by filtration, washed several times with ether, and the filtrates concentrated *in vacuo*. The resulting oil, containing the dihydropyridazines I and II, is dissolved in chloroform, saturated with hydrogen chloride and allowed to stand for 30 min. The chloroform is removed *in vacuo* and the products distilled to give a yellow oil (6.65 g, b.p. 70—135°/1 mm). Fractionation through an 8 cm Vigreux column gives 0.5 g forerun and 5.0 g oil (114—117°/1 mm). The latter fraction dissolved in petroleum ether (20 ml), filtered, crystallized at −80° and washed with a small amount of cold petroleum ether gives colorless crystals (3.0 g, 29 %, m.p. 37—40°). Recrystallization from petroleum ether gives m.p. 39—41°. (Found: C 46.27; H 4.87; N 13.52. Calc. for $C_8H_{10}Cl_2N_2$: C 46.85; H 4.92; N 13.65). NMR: δ=7.47 and 1.52 (singlets; nine protons of the *tert*-butyl group and one aromatic proton, respectively).

5-tert-Butyl-3-methoxypyridazine V. 4-*tert*-Butyl-3,6-dichloropyridazine (III, above) is allowed to react over night at room temperature with a methanolic solution of sodium methoxide in excess. Water is added and the product is extracted with chloroform,

distilled at *ca.* 160°/8 mm and recrystallized twice from petroleum ether at −80° to give colorless crystals of 4-*tert*-butyl-3-chloro-6-methoxypyridazine, m.p. 40−41°. (Found: C 53.75; H 6.47; N 14.14. Calc. for $C_9H_{13}ClN_2O$: C 53.86; H 6.52; N 13.94). Hydrogenation at atmospheric pressure and room temperature for 24 h (Raney nickel catalyst in *ca.* 0.5 N methanolic potassium hydroxide) and chromatographic purification gives an oil, V, which is characterized by its picrate (from ethanol; m.p., fast heating, 136−137°. Found: C 45.61; H 4.33; N 17.34. Calc. for $C_{15}H_{17}N_5O_8$: C 45.55; H 4.35; N 17.70), and by its NMR spectrum: $\delta = 8.82$ and 6.79 (two doublets, $J = 2.0$ cps, indicating two aromatic protons in *meta* positions [6]); 4.13 (singlet, 3 protons of the methoxy group); 1.32 (singlet, 9 protons of the *tert*-butyl group).

4,4-Dimethyl-2-tert-*butyl-2-pentenonitrile VI* crystallizes in the condenser as a forerun by the distillation of the pyridazine III. Recrystallisation from petroleum ether at −80° gives colorless crystals, m.p. 57−58°. (Found, mean of four determinations: C 80.18; H 11.73; N 8.99. Calc. for $C_{11}H_{19}N$: C 79.90; H 11.62; N 8.47). NMR: $\delta = 6.10$, 1.25 and 1.17 for one vinylic proton and two *tert*-butyl groups, respectively. Infrared spectroscopy shows absorption at 2220 cm^{-1} (conjugated nitrile). Mass spectrometry shows a molecular peak at 165 and base peak at 150.

4-tert-*Butyl-3,5,6-trichloro-1,4-dihydropyridazine I* and *4,5-di*-tert-*butyl-3,6-dichloro-1,4-dihydropyridazine II* are isolated from the crude dihydropyridazine mixture (above; after removal of ether) by chromatography on silicagel (1 mm layer, eluent: benzene-petroleum ether 1:1). The R_F values are both near 0.5, I above II. Recrystallization of I from petroleum ether gives colorless crystals, destr. 63−64° (evolution of gas; fast heating: 86°). The sample must be kept cold and analyzed as fast as possible. (Found: C 39.87; H 4.51; N 11.54. Calc. for $C_8H_{11}Cl_3N_2$: C 39.80; H 4.60; N 11.60). NMR: $\delta = 7.37$ (broad, one proton); 3.32 (singlet, one proton) and 1.05 (singlet, nine protons). Upon standing the deuteriochloroform solution gives off hydrogen chloride and the spectrum of 4-*tert*-butyl-3,6-dichloropyridazine III may be obtained.

Recrystallization of the fraction containing II from petroleum ether at −80° (slow crystallization) gives colorless crystals, m.p. 91−93°. NMR: $\delta = 7.32$ (broad, one proton); 3.40 (singlet, one proton); 1.30 and 1.00 (both singlets and both nine protons). The same product is obtained by adding *tert*-butylmagnesium chloride (10 ml, *ca.* 1 M) to a solution of 4-*tert*-butyl-3,6-dichloropyridazine (III, 2 mmoles) in ether (10 ml), decomposing the product with methanol (1 ml in 10 ml of ether), filtering off the magnesium salts and removing the ether *in vacuo*. Crystallization from petroleum ether gives the pure product. (Found: C 54.30; H 7.59; N 10.53. Calc. for $C_{12}H_{20}Cl_2N_2$: C 54.75; H 7.54; N 10.63).

trans-*4,5-Di*-tert-*butyl-3,6-dichloro-4,5-dihydropyridazine IV* may be isolated by chromatography (eluent: benzene + 5 % ether) of the residue from the crystallization of 4-*tert*-butyl-3,6-dichloropyridazine (III, see above). Recrystallization from aqueous ethanol gives colorless crystals, m.p. 102−103°. (Found: C 54.45; H 7.59; N 10.52. Calc. for $C_{12}H_{20}Cl_2N_2$: C 54.75; H 7.64; N 10.63). NMR: $\delta = 2.50$ and 1.05 (both singlets; ratio 1:9).

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