ACTA CHEMICA SCANDINAVICA 24 (1970) 751–754

Addition of Grignard Reagents to Pyridazines

X. 3-Chloro-6-dimethylaminopyridazine

INGOLF CROSSLAND and HANS KOFOD

Department of Organic Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark

The reaction of 3-chloro-6-dimethylaminopyridazine with ethylmagnesium bromide and phenylmagnesium bromide gives, after protonation, 5-substituted-3-chloro-4,5-dihydro-6-dimethylaminopyridazines, whereas the corresponding reactions with *t*-butylmagnesium chloride afford the 4-alkylated-4,5-dihydropyridazines. Isopropylmagnesium bromide gives about equal amounts of the two isomers. The dihydropyridazines are identified by oxidation to the corresponding 4- or 5-substituted 3-chloro-6-dimethylaminopyridazines, which are subsequently dehalogenated and subjected to NMR analyses. The results may be rationalized in terms of electronic and steric effects.

The addition of *t*-butylmagnesium chloride to unsymmetrically 3,6-disubstituted pyridazines has been shown to give 4- or 5-*t*-butyldihydropyridazines.[1–3] These investigations have now been extended to include the reaction of 3-chloro-6-dimethylaminopyridazine (I) with ethyl-, isopropyl-, *t*-butyl-, and phenyl-magnesium bromide (see Chart).

Identification of products. The NMR spectra of the crude products (II and III) revealed their nature as 4,5-dihydropyridazines displaying ABC systems of the ring protons at δ=*ca.* 2.2—3.3.[4] Vinylic protons were absent, thus excluding the alternative 1,4-dihydropyridazine tautomers.[3] The position of the alkyl group introduced was determined by bromination of the crude dihydropyridazines (II and III) and subsequent dehydrobromination. Halogen exchange took place and the 3-bromopyridazines (IV and V) were obtained. These were hydrogenolytically dehalogenated [5] to give the disubstituted pyridazines (VI and VII), NMR analysis of which indicated *ortho* coupling (J=4.8—5.0 cps) [5] in (VI) and *meta* coupling (J=1.0—2.0 cps) in (VII).

Further evidence may be obtained from the chemical shift data (presented in Table 1). Introduction of a substituent *ortho* to the dimethylamino group gives rise to a small upfield shift of the latter (*ca.* 0.2 ppm) probably due to steric inhibition of resonance. The difference between the chemical shifts of

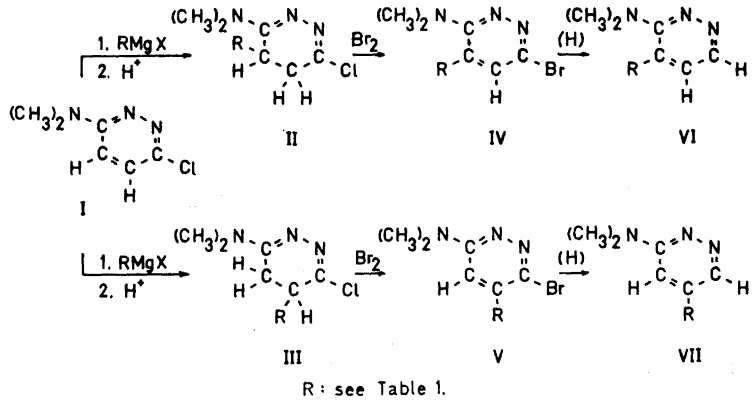

Table 1. Relative yields and NMR data of compounds (IV) and (V).

Compound	R	Rel. yields (IV):(V)	δ of 6-$(CH_3)_2N$ (IV)	(V)	δ of H^4 and H^5 (IV)	(V)
a	Ethyl	9	3.0	3.15	7.3	6.6
b	Isopropyl	1	2.95	3.15	7.3	6.6
c	*t*-Butyl	0	—	3.2	—	6.8
d	Phenyl	∞	2.9	—	7.25	—

the 4- and 5-protons is also characteristic. Both effects are in accordance with data given for the analogous 3-chloro-4- or 5-methyl-6-dimethylaminopyridazines.[5]

The ratio between the isomers formed (II and III) could not be determined directly from the NMR spectra of the crude reaction mixture. It was therefore assumed that the ratio between the aromatized products (IV and V) given in Table 1 reflects the ratio between the dihydropyridazines formed by the Grignard reaction. Apparently, the dimethylamino group tends to direct the attack of the nucleophilic Grignard reagent to the *ortho* position (compounds II) except in the case of the *t*-butylmagnesium chloride and, to a lesser degree, isopropylmagnesium bromide, where steric factors probably are operative. This directive influence of the dimethylamino group also applies to the selective hydrogenolytic dehalogenation of di- and trichlorodimethylaminopyridazines [5] and to the substitution of the 3-chlorine of 3,6-dichloro-4-dimethylaminopyridazine by methoxide anion to give 6-chloro-3-methoxy-4-dimethylaminopyridazine;[6] the postulated structure of the latter compound [6] has been substantiated, see *Experimental*. These examples illustrate *ortho* and *para* indirect deactivations as discussed in a recent review.[7]

EXPERIMENTAL

3-Bromo-5-(and 4-)-ethyl-6-dimethylaminopyridazine (IVa and Va). 3-Chloro-6-dimethylaminopyridazine (I) [5] (1.57 g) was dissolved in ethylmagnesium bromide (8.5 ml, 2.4 M in ether) and kept at reflux temperature for 5 min. The adduct was decomposed by pouring onto ice and adding conc. hydrochloric acid (10 ml). Ice and aqueous ammonia were added until pH = *ca.* 9, the reaction products extracted with chloroform (three times), and the extracts concentrated *in vacuo*. The residue was brominated by dissolving in acetic acid (17 ml, containing hydrogen bromide, *ca.* 2 M) and adding bromine (0.52 ml). The solution was refluxed for 5 min and excess acids removed *in vacuo*. Ice and ammonia (excess) were added. Extraction with chloroform and evaporation gave a dark oil (1.95 g) from which (IVa) (1.19 g, 52 %) could be isolated by chromatography (eluent benzene—ether 1:1). Elution with ether gave the isomer (Va) (0.13 g, 5 %) contaminated with *ca.* 25 % of the starting material (I). (IVa) was characterized as the picrate, m.p. 140—141°. (Found: C 36.98; H 3.40; N 18.39; Br 17.37. Calc. for $C_{14}H_{15}N_6O_7Br$: C 36.65; H 3.34; N 18.30; Br 17.40). (IVa) was hydrogenated [5] to give 5-ethyl-6-dimethylaminopyridazine (VIa), identified by its NMR spectrum (H^3 and H^4, $\delta = 8.79$ and 7.21 ppm, respectively, doublets, $J = 5.0$ cps) and picrate, m.p. 103—104° (Found: C 44.63; H 4.34; N 22.16. Calc. for $C_{14}H_{16}N_4O_7$: C 44.25; H 4.24; N 22.08). Crude (Va) was hydrogenated [5] to give (VIIa), identified by the NMR spectrum (H^3 and H^5 $\delta = 8.3$ and 6.5 ppm, respectively, doublets, $J = 1.0$ cps), and by the methylpyridazinium iodide formed by reaction with methyl iodide, m.p. 172—173° (Found: C 36.79; H 5.52. Calc. for $C_9H_{16}IN_3$: C 36.90; H 5.51).

3-Bromo-5-(and 4-)-isopropyl-6-dimethylaminopyridazine (IVb and Vb) could be prepared by essentially the same procedure as for the corresponding ethyl compounds above. The total yield of the chromatographed products was 46 %, the ratio about 1:1. (IVb) was characterized as the quaternization product with methyl iodide; halogen exchange took place and the product was recrystallized from aqueous ethanol, m.p. 169—170° (Found: C 27.61; H 3.94; N 9.58. Calc. for $C_{10}H_{17}I_2N_3$: C 27.74; H 3.96; N 9.71). Hydrogenolysis of (IVb) gave (VIb), b.p. 90—92°/1 mm. (Found: C 64.80; H 9.20; N 25.09. Calc. for $C_9H_{15}N_3$: C 65.43; H 9.15; N 25.43). NMR: H^3 and H^4 $\delta = 8.75$ and 7.2 ppm, respectively, both doublets, $J = 5.0$. The isomer (Vb) was recrystallized from aqueous ethanol, m.p. 60—61° (Found: C 44.37; H 5.86; Br 32.82; N 17.07. Calc. for $C_9H_{14}BrN_3$: C 44.27; H 5.78; Br 32.73; N 17.21). Hydrogenolyses gave (VIIb), NMR: H^3 and H_5 $\delta = 8.45$ and 6.6 ppm, respectively, both doublets, $J = 1.5$. Quaternization of (VIIb) with methyl iodide gave crystals precipitated from chloroform on adding ether, m.p. 139—140°. (Found: C 39.00; H 5.87; N 13.63. Calc. for $C_{10}H_{18}IN_3$: C 39.09; H 5.91; N 13.68).

3-Bromo-4-t-butyl-6-dimethylaminopyridazine (Vc). 3-Chloro-6-dimethylaminopyridazine (I; 4.0 g in 50 ml of benzene) was added at once to *t*-butylmagnesium chloride (40 ml 2.2 M) and decomposed after 15 sec to give 4.85 g of crude dihydropyridazine. Addition of ether induced crystallization. Recrystallization from aqueous ethanol or ligroin gave (IIIc), colorless crystals, m.p. 126—127°. (Found: C 55.53; H 8.50; Cl 16.38; N 19.47. Calc. for $C_{10}H_{18}ClN_3$: C 55.75; H 8.42; Cl 16.42; N 19.40). Bromination of the crude dihydropyridazine (above) with bromine (2.3 ml, excess) in acetic acid (45 ml containing HBr, 2 M), keeping at reflux temperature for 15 min, and cooling to room temperature gave orange yellow crystals (8.6 g after washing with acetic acid and ether), probably a perbromide of (Vc). The crude product liberates iodine from a solution of potassium iodide and contains bromine (55.4 %. Calc. for $C_{10}H_{16}Br_3N_3$: 57.5 %). Thorough stirring of the bromide with cold aqueous ammonia and chloroform and extraction with chloroform gave, after removal of the solvent *in vacuo*, a spontaneously crystallizing oil (3.93 g). One recrystallization from ligroin (80/110°; 50 ml) and decantation from a little dark oil gave colorless crystals of (Vc) (2.95 g, 45 %), m.p. 77—78°. Recrystallization from aqueous ethanol did not alter the m.p. However, analysis gave too high values (about 3 %), consistent with an admixture with the chloro compound. (Found: C 47.65; H 6.46; N 16.71. Calc. for $C_{10}H_{16}BrN_3$: C 46.50; H 6.27; N 16.25). If the bromination was carried out in acetic acid at 100° for 10 min and worked up as above, the product was 5-bromo-4-*t*-butyl-3-chloro-4,5-dihydro-6-dimethylaminopyridazine, m.p. 115° from toluene-ligroin. (Found: C 40.59; H 5.87; N 14.11. Calc. for $C_{10}H_{17}ClBrN_3$: C 40.76; H 5.82; N 14.28). NMR: H^4 and H^5 $\delta = 2.73$ and 4.71, respectively, doublets, $J = 1.3$ cps. Reflux

in methanolic sodium methoxide gave 4-*t*-butyl-3-chloro-6-dimethylaminopyridazine, the chloro analogue of (Vc), m.p. 47—48° or 86—87° from aqueous ethanol. (Found: C 55.78; H 7.70; Cl 16.24; N 19.49. Calc. for $C_{10}H_{16}ClN_3$: C 56.20; H 7.55; Cl 16.59; N 19.67). Hydrogenolysis gave (VIIc), NMR: H^3 and H^5 $\delta=8.7$ and 6.7, respectively, doublets, $J=2.0$ cps. The hydrogenated product was also characterized by the methylpyridazinium iodide, m.p. 223°d. (Found: C 41.41; H 6.35; N 12.80. Calc. for $C_{11}H_{20}IN_3$: C 41.12; H 6.26; N 13.11).

3-Chloro-4,5-dihydro-6-dimethylamino-5-phenylpyridazine (IId) was prepared as above (reflux for 30 min in a 5 M excess of phenylmagnesium bromide). The crude dihydropyridazine was crystallized from ethanol (yield 18 %, m.p. 177—179°). Recrystallization from ethanol gave colorless crystals m.p. up to 184° (depending on the rate of heating). (Found: C 60.71; H 5.88; N 17.58. Calc. for $C_{12}H_{14}ClN_3$: C 61.15; H 5.98; N 17.82). 3-Phenyl-6-dimethylaminopyridazine [8] was isolated from the residue by chromatography (benzene-ether 1:3). The NMR spectra of the two products are characteristic and allowed NMR analysis of the crude product. Apparently, the two products (above) were the only species formed.

3-Bromo-6-dimethylamino-5-phenylpyridazine (IVd) was obtained by bromination of the dihydropyridazine (IId, above, 2.3 g recrystallized product) with bromine (2 ml; 15 min. reflux) as above. Recrystallization from ethanol (5 ml) gave light brown crystals (m.p. 90—92°, 1.40 g). Recrystallization gave colorless crystals, m.p. 92—93°. (Found: C 51.95; H 4.39; N 14.92. Calc. for $C_{12}H_{12}BrN_3$: C 51.80; H 4.36; N 15.12). Hydrogenolysis of (IVd) gave the dehalogenated product (VId), NMR: H^3 and H^4 $\delta=8.74$ and 7.14, respectively, doublets, $J=5.0$ cps. The hydrogenated product was characterized by the methylpyridazinium iodide, m.p. 138—139° (Found: C 45.50; H 4.76; N 12.08. Calc. for $C_{13}H_{16}IN_3$: C 45.79; H 4.72; N 12.33).

3-Methoxy-4-dimethylaminopyridazine. 3-Methoxy-4-dimethylamino-6-chloropyridazine [6] (12.4 g, m.p. 88—90, *cf.* 82—85° [6]) was hydrogenated (2 atm; 0.5 g Pd on C; 5.0 g KOH in 200 ml of methanol) with stirring for 48 h at room temperature. Filtration, evaporation of solvents *in vacuo*, addition of water, extraction with chloroform, and distillation gave 3-methoxy-4-dimethylaminopyridazine, b.p. 105°/0.3 mm, 7.4 g colorless oil. (Found: C 54.90; H 7.36; N 27.60. Calc. for $C_7H_{11}N_3O$: C 54.85; N 7.22; N 27.40). NMR: H^5 and H^6 $\delta=6.5$ and 8.4, respectively, both doublets, $J=5.5$ cps.

Melting points are uncorrected. Chromatography was carried out on silica gel (Merck, 0.05—0.20 mm). Analyses were performed by Mr. Preben Hansen, Chemical Laboratory of the University of Copenhagen. NMR spectra were recorded on a Varian A-60 spectrometer; the solvent was deuteriochloroform and TMS served as an internal standard. The experimental participation of Mr. Henning Petersen is acknowledged.

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Received September 2, 1969.