Reaction of Pyrimidin-2(1H)-ones and -thiones with Organometallic Compounds. Regioselective Preparation of Dihydropyrimidin-2(1H)-ones and -thiones

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4,6-Dimethyl-1-phenylpyrimidin-2(1*H*)-one (1) reacted with methylmagnesium iodide to afford 4,6,6-trimethyl-1-phenyl-3,6-dihydropyrimidin-2(1*H*)-one (8a) selectively; compound (1) reacted with methyl-lithium to give mainly 4,4,6-trimethyl-1-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (8b). The reactions of various pyrimidin-2(1*H*)-ones and -thiones with organometallic compounds, and the influence of bulkiness of alkyl groups upon the product ratio, are also discussed.

VARIOUS dihydropyrimidin-2(1H)-ones and -thiones have been prepared from the reaction of 1,1-dimethyl-3oxobutyl isocyanate ¹ and 2-methyl-2-thiocyanopentan-4-one ² with anilines, $\alpha\beta$ -unsaturated enones ³⁻⁵ and 3ethoxy-2-methoxymethylenepropionitrile with ureas,^{6,7} and the condensation of mesityl oxide, ammonium thiocyanate, and amines.⁸ On the other hand, few papers concerning the preparation of dihydropyrimidin-2(1H)-ones and thiones by the reaction of pyrimidin-2(1H)-ones and -thiones with nucleophiles have been reported.⁹

The 2-, 4-, and 6-position atoms in the pyrimidine ring are electron deficient by virtue of the electron-withdrawing effect of the ring-nitrogen atoms.¹⁰ Nucleophilic attack, therefore, could be expected to take place on these carbon atoms. While Hauser and co-workers reported that organolithium reagents reacted with benzalacetophenone to yield predominantly 1,2-addition product, the Grignard reagents gave exclusively the 1,4addition product.¹¹

In this paper, we discuss the regioselective preparation of dihydropyrimidin-2(1H)-ones and -thiones by the reaction of pyrimidin-2(1H)-ones and thiones with organometallic compounds such as Grignard and organolithium reagents.

RESULTS AND DISCUSSION

The reaction of 4,6-dimethyl-1-phenylpyrimidin-2(1H)one (1) with methylmagnesium iodide (MeMgI) yielded two products, m.p. 191-192 °C (compound A) and m.p. 163 °C (compound B). Both compounds had the same formula, C₁₃H₁₆N₂O, from elemental analysis. Compound A shows the following spectral data; i.r., v_{max} 3 200 (N-H) and 1 660 cm⁻¹ (C=O), ¹H n.m.r., 8 1.18 (6 H, s) and 1.70 (3 H, d, J = 0.6 Hz), attributed to the allylic coupling of methyl protons with the olefinic proton at 5-position of the pyrimidine ring. Compound B; i.r. $\nu_{\rm max}$ 3 220 (N–H) and 1 660 cm $^{-1}$ (C=O); and $^{1}{\rm H}$ n.m.r., δ 1.30 (6 H, s) and 1.53 (3 H, d, J = 0.6 Hz). From these spectral data, compounds A and B were assumed to be structurally isomeric with each other, and compound B was found to be 4,4,6-trimethyl-1-phenyl-3,4-dihydropyrimidin-2(1H)-one (8b) by comparison with an authentic sample (m.p. 162-164 °C) obtained from the reaction

of 1,1-dimethyl-3-oxobutyl isocyanate with aniline.¹ It appears that compound (8a) is formed by the attack of the methyl Grignard at the 4-position of the pyrimidine ring. Therefore, compound A was assigned the structure 4,6,6-trimethyl-1-phenyl-3,6-dihydropyrimidin-2(1H)-

one (8a) which was formed by the attack of the methyl Grignard at the 6-position. The total yield of (8a) and



(8b) was 29%, in the ratio of 95:5. Pyrimidin-2(1*H*)-one (1) also reacted with methyl-lithium (MeLi) to give two products (8a) and (8b) in 65% yield, but the ratio was 15:85 (see Table).

4,6-dimethyl-1-phenylpyrimidin-2(1H)-thione When (2) was treated with MeMgI and MeLi to afford a mixture of two products, (12a) and (12b), in 62 and 43% yield, respectively. The structures of (12a) and (12b) were determined from the fact that the chemical shifts of the geminal dimethyl and allylic methyl protons were very similar to those of compounds (8a) and (8b), respectively. Further, (12b) was found to be identical with an authentic sample of 4,4,6-trimethyl-1-phenyl-3,4-dihydropyrimidine-2(1H)-thione (12b) obtained from the reaction of 2-methyl-2-thiocyanatopentan-4-one with aniline.8 Similarly, the reaction of pyrimidin-2(1H)-one (1) and -thione (2) with various alkyl Grignards and alkyllithium reagents was examined and the results are summarized in the Table.

These results suggest that the bulkiness of the alkyl group of the Grignard reagent has a large influence on the ratio of the 3,6-dihydropyrimidin-2(1H)-ones (8a), (9a), (11a) to the 3,4-dihydropyrimidin-2(1H)-ones (8b)—(11b), but not on the ratio of the 2-thioxo-derivatives (12a)—(15a) to the corresponding derivatives (12b)—(15b).

6-Methyl-1,4-diphenylpyrimidin-2(1H)-one (5) reacted

with MeMgI to give only 6,6-dimethyl-1,4-diphenyl-3,6dihydropyrimidin-2(1H)-one (18a) in 67% yield, while 1,6-diphenyl-4-methylpyrimidin-2(1H)-thione (6) with MeMgI gave only 4,4-dimethyl-1,6-diphenyl-3,4-dihydropyrimidin-2(1H)-thione (19b) in 82% yield (see Table).

Finally, we examined the reaction of MeMgI or MeLi with 1-phenylpyrimidin-2(1H)-one (7), which has no substituent at the 4- and 6-positions of the pyrimidine ring. Pyrimidin-2(1H)-one (7) reacted with MeMgI to yield only 6-methyl-1-phenyl-3,6-dihydropyrimidin-

added and the mixture was stirred for 5 h at room temperature. Excess of alkyl-lithium was destroyed by the dropwise addition of water. The reaction mixture was extracted with dichloromethane and dried over anhydrous magnesium sulphate. The crude product was chromatographed on silica gel with chloroform-acetone-ethanol (100:10:2) in the case of pyrimidin-2(1H)-one, and with chloroform-benzene-ethyl acetate (4:4:1) in the case of pyrimidine-2(1H)-thione. In this way the following compounds were prepared: 4,6-dimethyl-4-ethyl-1-phenyl-3,4dihydropyrimidine-2(1H)-thione (13b), m.p. 194--195 °C



^o t-Butylmagnesium chloride. ^b Phenylethynylmagnesium bromide.

2(1H)-one (20a) in 59% yield. On the other hand, compound (7) also reacted with MeLi to give exclusively 4-methyl-1-phenyl-3,4-dihydropyrimidin-2(1H)-one (20b) in 88% yield (see Table).

It is thus possible to prepare regioselectively 3,6- and 3,4-dihydropyrimidines by the reaction of pyrimidin-2(1H)-one and -thiones with the appropriate organometallic compounds. Further, it is concluded that alkyl Grignards attack the 6-position in preference to the 4position of the pyrimidine ring, while alkyl-lithium reagents predominantly attack the 4-position.

EXPERIMENTAL

Materials.—Pyrimidin-2(1H)-ones (1) and (3) and the thione (2) were prepared by the method of Hutchins.¹² 6-Methyl-1,4-diphenylpyrimidin-2(1H)-one (5) and 4-methyl-1,6-diphenylpyrimidine-2(1H)-thione (6) were prepared from the reaction of benzolyacetone with N-phenylurea and N-phenylthiourea, respectively.¹³ 1-Methylpyrimidin-2(1H)-one (4) ¹⁴ and 1-phenylpyrimidin-2(1H)-one (7) ¹⁵ were prepared by literature methods.

Reaction of Pyrimidin-2(1H)-ones and -thiones with Organometallic Compounds.—Reaction with alkyl-lithium reagents. Alkyl-lithium (10 mmol) was prepared from alkyl iodide (10 mmol) and lithium wire (25 mmol) in anhydrous ether (20 ml) uder an argon atmosphere in an ice-bath. To this solution, pyrimidin-2(1H)-one or -thione (3 mmol) was

(decomp.) (from ethyl acetate); $v_{max.}$ (KBr) 3 180, 2 960, 1 685, 1 230, 760, and 700 cm⁻¹; 8 (CDCl₃) 1.02 (3 H, d, J 6.0 Hz), 1.33 (3 H, s), 1.52 (3 H, s), 4.70 (1 H, br s), and 7.2-7.5 (5 H, m) (Found: C, 68.55; H, 7.4; N, 11.4. C14H18N2S requires C, 68.25; H, 7.36; N, 11.37%): 4isopropyl-4,6-dimethyl-1-phenyl-3,4-dihydropyrimidine-2(1H)-thione (14b), m.p. 181-182 °C (decomp.) (from ethyl acetate-hexane); ν_{max} (KBr) 3 180, 2 960, 1 685, 760, and 700 cm⁻¹; δ (CDCl₃) 0.92 (3 H, d, J 6.0 Hz), 1.05 (3 H, d, J 6.0 Hz), 1.32 (3 H, s), 1.52 (3 H, s), 4.73 (1 H, br s), and 7.2-7.5 (5 H, m) (Found: C, 69.2; H, 7.8; N, 10.7. C₁₅H₂₀N₂S requires C, 69.18; H, 7.74; N, 10.75%): 4methyl-1-phenyl-3,4-dihydropyrimidin-2(1H)-one (20b), m.p. 123—124 °C (from benzene–hexane); ν_{max} (KBr) 3 200, 2 960, 1 690, 1 660, 760, and 690 cm⁻¹; δ (CDCl₃) 1.25 (3 H, d, / 6.0 Hz), 4.1-4.4 (1 H, m), 4.6-5.0 (1 H, m), 5.92 (1 H, br s), 6.1-6.3 (1 H, dd, J 8.0 and 1.0 Hz), and 7.2-7.4 (5 H, m) (Found: C, 70.5; H, 6.3; N, 14.9. C₁₁H₁₂N₂O requires C, 70.19; H, 6.42; N, 14.88%).

Reaction with alkyl Grignards. Pyrimidin-2(1H)-one or -thione (1 mmol) was added to the solution of methylmagnesium iodide (10 mmol) in anhydrous ether (20 ml) and the mixture was stirred for 6 h. The reaction mixture was washed with cold water, extracted with dichloromethane was washed with cold water, extracted with dichloromethane, and dried over anhydrous magnesium sulphate. The crude product was chromatographed on silica gel with chloroform-acetone-ethanol (100:20:4) [(100:10:2) in

the case of pyrimidin-2(1H)-ones], and with chloroformbenzene-ethyl acetate (4:4:1) [(4:10:1) in the case of pyrimidin-2(1H)-thiones]. In this way the following compounds were prepared: 4,6,6-trimethyl-1-phenyl-3,6-dihydropyrimidin-2(1H)-one (8a), m.p. 191-192 °C (from benzene-hexane); ν_{max} (KBr) 3 200, 2 960, 1 660, and 760 cm⁻¹; λ_{max} (EtOH) 233 nm (ε 4.52 × 10³); δ (CDCl₃) 1.18 (6 H, s), 170 (3 H, d, J 0.6 Hz), 4.45 (1 H, br s), and 7.2--7.5 (5 H, m) (Found: C, 72.2; H, 7.4; N, 13.0. $C_{13}H_{16}N_2O$ requires C, 72.19; H, 7.45; N, 12.95%): 4,4,6-trimethyl-1phenyl-3,4-dihydropyrimidin-2(1H)-one (8b), m.p. 163 °C (lit.,¹ 162—164 °C) (from ethyl acetate-hexane); ν_{max} (KBr) 3 220, 2 960, 1 660, 1 395, 1 380, 760, and 695 cm⁻¹; λ_{max} (EtOH) 229 nm (ϵ 6.77 \times 10³); δ (CDCl₃) 1.30 (6 H, s), 1.53 (3 H, d, J 0.6 Hz), 4.62 (1 H, br s), 5.02 (1 H, br s), and 7.1---7.4 (5 H, m) (Found: C, 72.0; H, 7.4; N, 13.1. C₁₃H₁₆N₂O requires C, 72.19; H, 7.45; N, 12.95%): 6-ethyl-4,6 dimethyl-1-phenyl-3,6-dihydropyrimidin-2(1H)-one (9a), m.p. 143—144 °C (from benzene-hexane); ν_{max} (KBr) 3 220, 2 960, 1 660, and 755 cm⁻¹; δ (CDCl₃) 1.08 (3 H, t, $\int 6.0$ Hz), 1.33 (3 H, s), 1.73 (3 H, s), 4.25 (1 H, br s), and 7.0-7.2 (5 H, m) (Found: C, 72.9; H, 7.7; N, 12.2. C14H18N2O requires C, 73.01; H, 7.87; N, 12.16%): 4-ethyl-4,6dimethyl-1-phenyl-3,4-dihydropyrimidin-2(1H)-one (9b), m.p. 168 °C (from benzene-hexane); v_{max} (KBr) 3 230, 2 960, 1 660, and 755 cm⁻¹; δ (CDCl₃) 1.00 (3 H, t, J 6.0 Hz), 1.28 (3 H, s), 1.53 (3 H, s), 4.48 (1 H, br s), 4.76 (1 H, br s), and 7.0-7.2 (5 H, m) (Found: C, 72.5; H, 7.9; N, 12.0. C14H18N2O requires C, 73.01; H, 7.87; N, 12.16%): 4isopropyl-4,6-dimethyl-1-phenyl-3,4-dihydropyrimidin-2(1H)one (10b), m.p. 202 °C (from benzene--hexane); ν_{max} (KBr) 3 200, 2 960, 1 690, 1 660, 760, and 690 cm⁻¹; δ (CDCl₃) 0.97 (6 H, d, f 6.0 Hz), 1.27 (3 H, s), 1.52 (3 H, s), 4.50 (1 H, br s), 4.83 (1 H, br s), and 7.0-7.2 (5 H, m) (Found: C, 73.55; H, 8.3; N, 11.5. $C_{15}H_{20}N_2O$ requires C, 73.73; H, 8.25; N, 11.46%): 6-t-butyl-4,6-dimethyl-1-phenyl-3,6-dihydropyrimidin-1(1H)-one (11a), m.p. 191 °C (from benzene-hexane); ν_{max} (KBr) 3 200, 2 960, 1 700, 1 650, 1 380, and 760 cm⁻¹; δ (CDCl₃) 0.98 (9 H, s), 1.17 (3 H, s), 1.72 (3 H, s), 4.37 (1 H, br s), and 6.9-7.3 (5 H, m) (Found: C, 74.2; H, 8.6; N, 10.7. C₁₆H₂₂N₂O requires C, 74.38; H, 8.58; N, 10.84%): $\label{eq:constraint} \textbf{4-t-butyl-4,6-dimethyl-1-phenyl-1,2,3,4-tetrahydropyrimidine}$ (11b), m.p. 139 °C (from hexane); $\nu_{max.}$ (KBr) 3 240, 2 960, 1 690, 1 660, 760, and 680 cm^-1; δ (CDCl₃) 0.96 (9 H, s), 1.23 (3 H, s), 1.52 (3 H, s), 4.60 (1 H, br s), 5.07 (1 H, br s), and 7.0-7.3 (5 H, m) (Found: C, 74.6; H, 8.65; N, 10.95. C₁₆H₂₂N₂O requires C, 74.38; H, 8.58; N, 10.84%): 4,6,6trimethyl-1-phenyl-3,6-dihydropyrimidine-2(1H)-thione (12a),* m.p. 215-223 °C (from ethyl acetate); δ (CDCl₃) 1.22 (6 H, s), 1.78 (3 H, d, J 0.6 Hz), 4.50 (1 H, br s), and 7.1-7.5 (5 H, m) {Found [for a mixture of (12a) and (12b)]: C, 67.15; H, 6.95; N, 11.95. C₁₃H₁₆N₂S requires C, 67.20; H, 6.94; N, 12.05% : 6-ethyl-4,6-dimethyl-1-phenyl-3,6dihydropyrimidine-2(1H)-thione (13a),* m.p. 170-179 °C (decomp.) (from ethyl acetate); δ (CDCl₃) 1.02 (3 H, t, J 6.0 Hz), 1.13 (3 H, s), 1.85 (3 H, d, J 0.6 Hz), 4.50 (1 H, br s), and 7.2-7.5 (5 H, m) {Found [for a mixture of (13a) and (13b)]: C, 63.25; H, 7.35; N, 11.3. C₁₄H₁₈N₂S requires C, 68.25; H, 7.36; N, 11.37% : 6-isopropyl-4,6-dimethyl-1phenyl-3,6-dihydropyrimidine-2(1H)-thione (14a),* m.p. 197-203 °C (decomp.) (from benzene-hexane); δ (CDCl₃) 0.80 (6 H, d, J 6.0 Hz), 1.15 (3 H, s), 1.83 (3 H, s), 4.48 (1 H,

br s), 7.2-7.5 (5 H, m), and 8.27 (1 H, br s) {Found [for a * Attempts to separate the mixture by column chromatography or fractional recrystallization was unsuccessful.

mixture of (14a) and (14b)]: C, 69.25; H, 7.8; N, 10.7. C15H20N2O requires C, 69.18; H, 7.74; N, 10.75%}: 6-tbutyl-4,6-dimethyl-1-phenyl-3,6-dihydropyrimidine-2(1H)thione (15a), m.p. 167-168 °C (decomp.) (from ethyl acetatehexane); ν_{max} (KBr) 3 240, 2 960, 1 710, 1 240, and 710 cm⁻¹; δ (CDCl₃) 1.03 (9 H, s), 1.18 (3 H, s), 1.85 (3 H, s), 4.60 (1 H, br s), 7.1-7.5 (5 H, m), and 8.43 (1 H, br s) (Found: C, 69.8; H, 7.9; N, 10.1. C₁₆H₂₂N₂S requires C, 70.02; H, 8.08; N, 10.20%): 4-t-butyl-4,6-dimethyl-1phenyl-3,4-dihydropyrimidine-2(1H)-thione (15b), m.p. 180 °C (decomp.) (from benzene-hexane); ν_{max} (KBr) 3 180, 2 960, 1 680, 1 600, and 760 cm⁻¹; δ (CDCl₃) 1.01 (9 H, s), 1.28 (3 H, s), 1.53 (3 H, s), 4.75 (1 H, br s), and 7.1-7.4 (5 H, m) (Found: C, 70.0; H, 8.0; N, 10.2. $C_{16}H_{22}N_2S$ requires C, 70.02; H, 8.08; N, 10.20%): 4,6,6-trimethyl-1-ptolyl-3,6-dihydropyrimidine-2(1H)-one (16a), m.p. 211-212 °C (from ethyl acetate-hexane); ν_{max} (KBr) 3 200, 2 960, 1 710, 1 660, 1 400, 810, and 740 cm⁻¹; δ (CDCl₃) 1.20 (6 H, s), 1.75 (3 H, d, $\int 0.6$ Hz), 2.36 (3 H, s), 4.47 (1 H, br s), and 7.1-7.2 (4 H, m) (Found: C, 73.6; H, 7.95; N, 12.15. C14H18N2O requires C, 73.01; H, 7.87; N, 12.16%): 4,4,6trimethyl-1-p-tolyl-3,4-dihydropyrimidin-2(1H)-one (16b), m.p. 193 °C (from ethyl acetate-hexane); v_{max} (KBr) 3 220, 2 960, 1 700, 1 670, 1 510, 805, and 750 cm⁻¹; 8 (CDCl₃) 1.32 (6 H, s), 1.51 (3 H, d, J 0.6 Hz), 2.35 (3 H, s), 4.64 (1 H, br s), 5.04 (1 H, br s), and 7.1-7.2 (4 H, m) (Found: C, 73.3; H, 7.9; N, 12.5. C₁₄H₁₈N₂O requires C, 73.01; H, 7.87; N, 12.16%): 1-methyl-6-phenylethynyl-3,6-dihydropyrimidin-2(1H)-one (17a), m.p. 134-135 °C (from ethyl acetatehexane); $\nu_{max.}$ (KBr) 3 220, 2 940, 1 680, and 750 cm⁻¹; δ (CDCl₃) 3.04 (3 H, s), 4.6–5.0 (2 H, m), 6.0–6.3 (1 H, dd, J 7.0 and 4.8 Hz), 7.2-7.5 (5 H, m), and 8.50 (1 H, br s) (Found: C, 73.7; H, 5.65; N, 13.2. C₁₃H₁₂N₂O requires C, 73.56; H, 5.69; N, 13.19%): 6,6-dimethyl-1,4-diphenyl-3,6-dihydropyrimidin-2(1H)-one (18a), m.p. 196-197 °C (from ethyl acetate); $\nu_{max.}$ (KBr) 3 220, 2 980, 1 640, 1 410, 760, and 740 cm⁻¹; δ (CDCl₃) 1.33 (6 H, s), 4.93 (1 H, br s), and 7.0-7.5 (10 H, m) (Found: C, 77.7; H, 6.45; N, 10.05. C₁₈H₁₈N₂O requires C, 77.66; H, 6.51; N, 10.06%): 4,4dimethyl-1,6-diphenyl-3,4-dihydropyrimidine-2(1H)-thione (19b), m.p. 206-207 °C (decomp.) (from benzene-hexane); $\nu_{max.}~({\rm KBr})$ 3 200, 2 980, 1 680, 1 540, 1 340, 1 200, and 700 cm⁻¹; $\delta~({\rm CDCl}_3)$ 1.48 (6 H, s), 5.10 (1 H, br s), and 7.0–7.3 (10 H, m) (Found: C, 73.5; H, 6.10; N, 9.55. C₁₈H₁₈N₂S requires C, 73.43; H, 6.16; N, 9.51%): 6-methyl-1-phenyl-3,6-dihydropyrimidin-2(1H)-one (20a), m.p. 140.5 °C (decomp.) (from ethyl acetate-hexane); $\nu_{max.}~({\rm KBr})$ 3 220, 2 960, 1 650, 1 190, and 760 cm⁻¹; 8 (CDCl₃) 1.17 (3 H, d, J 6.0 Hz), 4.2-4.9 (2 H, m), 5.9-6.2 (1 H, dd, J 8.0 and 5.6 Hz), 7.2-7.5 (5 H, m), and 8.35 (1 H, br s) (Found: C, 69.95; H, 6.4; N, 14.8. C₁₁H₁₂N₂O requires C, 70.19; H, 6.42; N, 14.88%)

[0/787 Received, 23rd May, 1980]

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