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6-Phenyl-2-(*p*-toluenesulfonyl)-3(2*H*)pyridazinone (I) reacted with Grignard reagents to give 5-substituted 4,5-dihydro-3(2*H*)pyridazinones II and two types of dihydropyridazines, III and IV. The ratio of II, III, and IV was sensitively dependent on the reaction conditions. Further, by quenching the reaction mixture with alcohol, the ring-opened product VII was mainly isolated.

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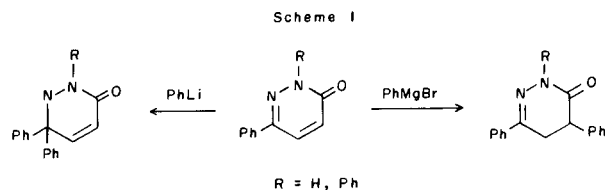
We have investigated the regioselective reaction and the synthetic utility of heterocyclic compounds. For example, 3,5-dimethylisoxazole reacted with alkyl halides in the presence of strong bases to give regioselectively 5-alkylated isoxazoles, which were easily converted into various α,β -unsaturated ketones [1]. 1-Substituted 2(1*H*)-pyrimidines were also converted into not only other heterocyclic compounds [2-4], but also chain compounds [5,6]. As a positional isomer of 2(1*H*)-pyrimidinones, 3(2*H*)-pyridazinones could similarly be expected to occur the regioselective reactions by nucleophilic attack on the conjugated system of α,β -unsaturated carbonyl and imine moieties. Recently the regioselective behaviour of 2-unsubstituted and 2-phenyl-3(2*H*)-pyridazinones in the reactions with organometallic compounds was reported by Fateen and co-workers (Scheme 1) [7]. However, these pyridazinones are less reactive and the reaction with the organometallic compounds requires forced conditions. By increasing the reactivity, the reaction of pyridazinones should be applicable as synthons. Therefore, the introduction of an electron-withdrawing group such as an acyl and a *p*-toluenesulfonyl group on the N-2 position should be favourable for the extension of the usefulness of the regioselective reaction of 3(2*H*)-pyridazinones with the organometallic compounds.

The *p*-toluenesulfonyl group is easily removed by the hydrolysis. Especially in the case of *p*-toluenesulfonyl hydrazones, the removal of *p*-toluenesulfonyl group under basic conditions causes the elimination of nitrogen to afford olefins [8].

Under these situations, 2-(*p*-toluenesulfonyl)-3(2*H*)-pyridazinone is seemed to be useful synthetic intermediate for olefins. Here, we describe on the Grignard reaction and the ring-opening reaction of 6-phenyl-2-(*p*-toluenesulfonyl)-3(2*H*)-pyridazinone.

Results and Discussion.

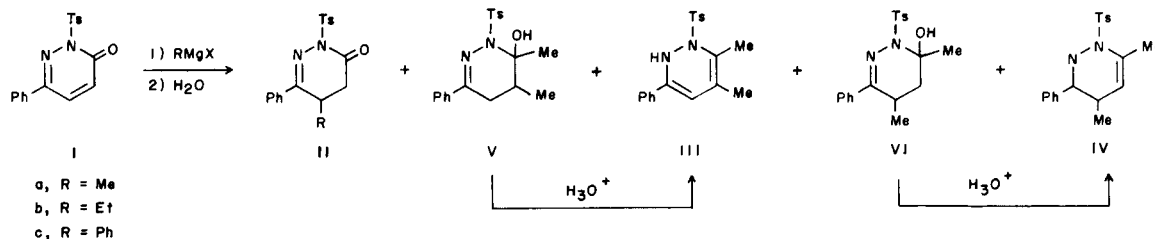
When 6-phenyl-2-(*p*-toluenesulfonyl)-3(2*H*)-pyridazinone (I) reacted with 10 equimolar amounts of methylmagnesium iodide at room temperature, and then the reaction mixture was quenched with cold water, compound A (mp



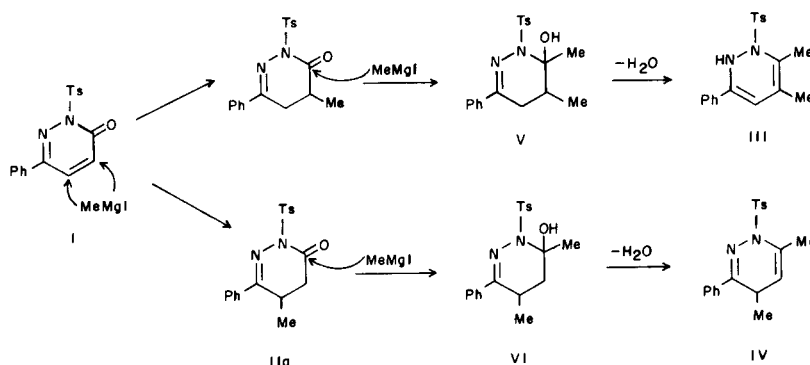
167°), compound B (mp 154°), compound C (mp 117°), and a mixture of D and E were isolated. A mixture of D and E, which showed an OH absorption band at 3500 cm^{-1} in the ir spectrum, was easily converted into B and C by dehydration with dilute hydrochloric acid. From these facts, the compounds D and E were deduced to be 3,4- (V) and 3,5-dimethyl-3-hydroxy-6-phenyl-2-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydropyridazine (VI). The elemental analysis indicated that A was a one molar adduct of methylmagnesium iodide. The ir absorption band at 1710 cm^{-1} due to the C=O stretching was observed. The ^1H -nmr spectrum exhibited a doublet at δ 1.20 ppm (3H, $J = 7.3$ Hz) attributable to the C-5 methyl protons. Furthermore, the ^{13}C -nmr spectrum showed two singlet peaks at δ 157.0 and 165.2 ppm due to the C=N and C=O carbon of the pyridazine ring, respectively. From these data, compound A was determined to be 4,5-dihydro-5-methyl-6-phenyl-2-(*p*-toluenesulfonyl)-3(2*H*)-pyridazinone (IIa). Compounds B and C had the same formula $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$, and showed no absorption band due to the C=O stretching. Compound B displayed a strong ir band at 3310 cm^{-1} due to the NH stretching. The ^1H -nmr spectrum of B showed two singlets at δ 1.90 (3H) and 2.31 ppm (3H) attributable to C-3 and C-4 methyl protons respectively, while that of C showed a doublet at δ 0.99 ppm (3H) and a singlet at δ 2.22 ppm (3H) assignable to C-5 and C-3 methyl protons. From these data, compounds B and C were determined to be 1,2-dihydro-3,4-dimethyl- (III) and 2,5-dihydro-3,5-dimethyl-6-phenyl-2-(*p*-toluenesulfonyl)pyridazine (IV), respectively.

The ratio of IIa, III, and IV was sensitive to change in the reaction conditions. In the reaction of I with other Grignard reagents, only 5-substituted 4,5-dihydro-3(2*H*)-pyridazinones IIb,c could be isolated.

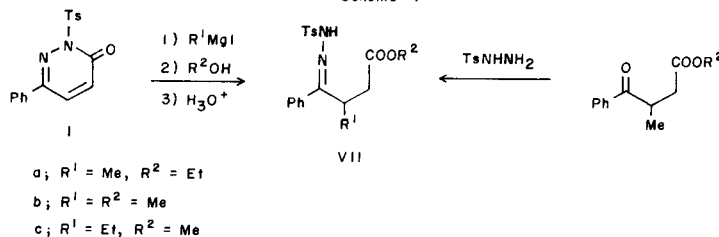
Scheme 2



Scheme 3



Scheme 4



The mechanism is explained by the competitive reaction between path a and b, outlined in Scheme 3. In both paths, the nucleophilic attack of the second methylmagnesium iodide occurred at the C-3 carbonyl carbon in the pyridazine ring. Therefore, the C-3 carbonyl carbon of II was expected to be attacked by other nucleophiles such as alcohols to afford the ring opening product, especially *p*-toluenesulfonyl hydrazones. On this speculation, compound I was treated with 5 equimolar amounts of methylmagnesium iodide, and the reaction mixture was quenched with methanol under acidic conditions. As the results, the ring-opened product, methyl 3-methyl-4-phenyl-4-[*N'*-(*p*-toluenesulfonyl)]hydrazonobutanoate (VIIa), was obtained in 33% yield. The quenching with ethanol also gave the ring-opened product VIIb. The structures of VIIa and VIIb were determined by comparison of the samples which were independently prepared by the method as shown in Scheme 4.

In conclusion, the reactivity of 6-phenyl-2-(*p*-toluenesulfonyl)-3(2*H*)-pyridazinone toward Grignard reagents is different from *N*-unsubstituted and *N*-phenyl derivatives, re-

ported by Fateen and coworkers [7,9]. Furthermore, the ring-opened products were mainly obtained by quenching the reaction mixture with alcohols.

EXPERIMENTAL

Melting points were measured on a Yanagimoto Micro Melting Point Apparatus, and were uncorrected. The ir spectra were recorded as potassium bromide discs on a Jasco IRA-1 Infrared Spectrometer. The ¹H-nmr and ¹³C-nmr spectra were taken on JEOL-100 Spectrometer, in deuteriochloroform solution using TMS as an internal standard. The uv spectra were measured in ethanol on a Shimadzu UV 365 UV-VIS-NIR Spectrophotometer. All new compounds were recrystallized from benzene-hexane mixture, except for compound I.

Preparation of 6-Phenyl-2-(*p*-toluenesulfonyl)-3(2*H*)-pyridazinone (I).

6-Phenyl-3(2*H*)-pyridazinone (10 mmoles) [9] was added to the suspension of sodium hydride (30 mmoles) in anhydrous THF. After stirring for 1 hour at 0°, *p*-toluenesulfonyl chloride (10 mmoles) was added to the mixture and further stirred for 1.5 hours at room temperature. After that, cold water was added to the reaction mixture, and extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and evaporated. The residue was recrystallized from ethanol, yield 70%, mp 180-181°; ir: 1680, 1380, 1170; uv: 312 (4100), 245 (29400);

¹H-nmr: δ 8.07 (d, 2H, J = 8.8 Hz), 7.9-7.8 (m, 3H), 7.68 (d, 1H, J = 9.8 Hz), 7.5-7.3 (m, 4H), 6.88 (d, 1H, J = 9.8 Hz), 2.43 (s, 3H); ¹³C-nmr: δ 157.4 (s), 146.3 (s), 144.5 (s), 133.6 (s), 133.3 (s), 132.4 (d), 131.9 (d), 130.2 (d), 129.8 (d), 129.6 (d), 128.9 (d), 126.3 (d), 21.8 (q).

Anal. Calcd. for C₁₈H₁₄N₂O₃S: C, 62.56; H, 4.32; N, 8.58. Found: C, 62.45; H, 4.30; N, 8.52.

Reaction of Compound I with Methylmagnesium Iodide. Method A.

The hot solution of 6-phenyl-2-(*p*-toluenesulfonyl)-3(2*H*)-pyridazinone (I, 2 mmoles) in anhydrous THF (20 ml) was added to the solution of methylmagnesium iodide (20 mmoles) in anhydrous ether (15 ml) and the mixture was stirred for 14 hours at room temperature. The reaction mixture was quenched with cold water, extracted with dichloromethane, dried over anhydrous magnesium sulfate, and evaporated. The crude product was chromatographed on silica gel with benzene-ethyl acetate (20:1).

Method B.

Compound I reacted with methylmagnesium iodide as Method A. After the reaction mixture was quenched with cold water, diluted hydrochloric acid was added, and extracted with dichloromethane. The crude product was chromatographed on silica gel with benzene-ethyl acetate (20:1).

Method C.

The reaction of compound I with methylmagnesium iodide was carried out similar to Method A at 0°.

4,5-Dihydro-5-methyl-6-phenyl-2-(*p*-toluenesulfonyl)-3(2*H*)-pyridazinone (IIa).

Compound IIa was obtained by method A, B and C in 14, 16 and 7% yield, respectively, mp 167°; ir: 1710, 1600, 1380, 1180; uv: 275 (11800), 269 (11900), 244 (9840); ¹H-nmr: δ 8.06 (d, 2H, J = 8.3 Hz), 7.9-7.8 (m, 2H), 7.5-7.2 (m, 5H), 3.4-3.2 (m, 1H), 2.6-2.5 (m, 2H), 2.42 (s, 3H), 1.20 (d, 3H, J = 7.3 Hz); ¹³C-nmr: δ 165.2 (s), 157.0 (s), 145.2 (s), 134.8 (s), 133.5 (s), 130.7 (d), 129.5 (d), 128.8 (d × 2), 126.5 (d), 36.3 (t), 28.5 (d), 21.7 (q), 16.1 (q).

Anal. Calcd. for C₁₈H₁₈N₂O₃S: C, 63.13; H, 5.29; N, 8.18. Found: C, 63.31; H, 5.33; N, 8.15.

1,2-Dihydro-3,4-dimethyl-6-phenyl-2-(*p*-toluenesulfonyl)-pyridazine (III).

Compound III was obtained by method A, B and C in 30, 31 and 10% yield, respectively, mp 154°; ir: 3310, 1340, 1160; uv: 286 (7700), 234 (9190); ¹H-nmr: δ 8.00 (s, 1H), 7.18 (d, 2H, J = 8.3 Hz), 7.1-7.0 (m, 2H), 6.85 (d, 2H, J = 8.3 Hz), 6.8-6.7 (m, 3H), 5.80 (s, 1H), 2.36 (s, 3H), 2.31 (s, 3H), 1.90 (s, 3H); ¹³C-nmr: δ 143.8 (s), 134.0 (s), 130.9 (d), 129.2 (d), 128.7 (d), 127.7 (d × 2), 125.6 (d), 116.1 (s), 107.9 (d), 21.5 (q), 12.0 (q), 11.8 (q).

Anal. Calcd. for C₁₉H₂₀N₂O₃S: C, 67.03; H, 5.92; N, 8.22. Found: C, 67.15; H, 6.02; N, 8.18.

2,5-Dihydro-3,5-dimethyl-6-phenyl-2-(*p*-toluenesulfonyl)-pyridazine (IV).

Compound IV was obtained by method A, B and C in trace amount, 10 and 23% yield, respectively, mp 117°; ir: 1660, 1595, 1350, 1160; uv: 290 (7330), 223 (20600); ¹H-nmr: δ 7.91 (d, 2H, J = 8.8 Hz), 7.8-7.7 (m, 3H), 7.5-7.3 (m, 4H), 4.91 (dq, 1H, J = 1.5, 6.3 Hz), 3.46 (quint, 1H, J = 6.8 Hz), 2.36 (s, 3H), 2.22 (s, 3H), 0.99 (d, 3H, J = 6.8 Hz); ¹³C-nmr: δ 152.3 (s), 144.0 (s), 135.9 (s), 134.5 (s), 133.9 (s), 129.7 (d), 129.1 (d), 128.5 (d), 128.0 (d), 126.4 (d), 100.8 (d), 28.1 (d), 21.5 (q), 19.7 (q), 19.3 (q).

Anal. Calcd. for C₁₉H₂₀N₂O₃S: C, 67.03; H, 5.92; N, 8.22. Found: C, 66.89; H, 5.99; N, 8.06.

Mixture of 3,4-Dimethyl- (V) and 3,5-Dimethyl-3-hydroxy-6-phenyl-2-(*p*-toluenesulfonyl)-2,3,4,5-tetrahydropyridazine (VI).

The mixture of V and VI could not be separated and the yield of the mixture was 30% in method A; ir: 3500, 1680, 1600, 1340, 1160; ¹H-nmr: δ 7.86 (d, J = 8.3 Hz), 7.5-6.9 (m), 4.63 (s), 4.20 (s), 3.1-2.7 (m), 2.33 (s), 2.0-1.9 (m), 1.77 (s), 1.13 (d, J = 7.0 Hz), 1.10 (d, J = 7.0 Hz).

4,5-Dihydro-5-ethyl-6-phenyl-2-(*p*-toluenesulfonyl)-3(2*H*)-pyridazinone (IIb).

The reaction of compound I with ethylmagnesium iodide was accomplished by method C. The crude product was chromatographed on silica gel with chloroform-benzene-ethyl acetate (4:10:1), mp 134-135°; ir: 1700, 1360, 1160; ¹H-nmr: δ 8.00 (d, 2H, J = 8.3 Hz), 7.9-7.8 (m, 2H), 7.5-7.3 (m, 5H), 3.3-3.1 (m, 1H), 2.7-2.6 (m, 2H), 2.42 (s, 3H), 1.8-1.4 (m, 2H), 0.88 (t, 3H, J = 7.3 Hz); ¹³C-nmr: δ 165.5 (s), 156.7 (s), 145.2 (s), 134.9 (s), 134.1 (s), 130.7 (d), 129.5 (d), 128.8 (d × 2), 126.7 (d), 34.9 (d), 33.6 (t), 23.1 (t), 21.7 (q), 11.2 (q).

Anal. Calcd. for C₁₉H₂₀N₂O₃S: C, 64.02; H, 5.65; N, 7.85. Found: C, 63.97; H, 5.69; N, 7.80.

4,5-Dihydro-5,6-diphenyl-2-(*p*-toluenesulfonyl)-3(2*H*)-pyridazinone (IIc).

The reaction of compound I with phenylmagnesium bromide was carried out by method C, and the crude product was chromatographed on silica gel with benzene to remove biphenyl. The subsequent elute was again chromatographed on silica gel with chloroform-benzene-ethyl acetate (2:4:1), mp 103°; ir: 1710, 1600, 1380, 1170; ¹H-nmr: δ 7.99 (d, 2H, J = 8.3 Hz), 7.8-7.7 (m, 2H), 7.4-6.9 (m, 12H), 4.6-4.5 (m, 1H), 2.9-2.8 (m, 2H), 2.40 (s, 3H); ¹³C-nmr: δ 164.1 (s), 154.1 (s), 145.3 (s), 136.2 (s), 134.7 (s), 134.2 (s), 130.6 (d), 129.5 (d), 128.6 (d × 2), 127.9 (d), 126.7 (d × 2), 40.2 (d), 37.6 (t), 21.7 (q).

Anal. Calcd. for C₂₂H₂₀N₂O₃S: C, 68.29; H, 4.98; N, 6.92. Found: C, 68.47; H, 5.39; N, 6.68.

Quenching of Grignard Reaction with Alcohols.

The reactions of compound I with alkyl Grignard reagents were carried out similar to Method C. The reaction mixture was quenched with alcohol, extracted with dichloromethane, dried and evaporated. The crude product was chromatographed on silica gel with chloroform-benzene-ethyl acetate (4:10:1) or (2:4:1).

Ethyl 3-Methyl-4-phenyl-4-[*N'*-(*p*-toluenesulfonyl)hydrazono]butanoate (VIIa).

Compound VIIa was obtained in 25% yield, mp 97°; ir: 3200, 1720, 1620, 1340, 1160; ¹H-nmr: δ 7.76 (d, 2H, J = 8.3 Hz), 7.5-7.1 (m, 7H), 4.00 (q, 2H, J = 6.8 Hz), 3.06 (dd, 1H, J = 7.3, 14.3 Hz), 2.75 (dd, 1H, J = 7.8, 16.1 Hz), 2.43 (s, 3H), 2.30 (q, 1H, J = 6.8 Hz), 1.21 (t, 3H, J = 7.3 Hz), 1.03 (d, 3H, J = 6.8 Hz); ¹³C-nmr: δ 172.1 (s), 159.8 (s), 143.8 (s), 135.4 (s), 132.2 (s), 129.9 (d), 129.5 (d), 129.4 (d), 127.9 (d), 127.2 (d), 60.4 (t), 38.1 (t), 38.0 (q), 21.6 (d), 18.0 (q), 14.1 (q).

Anal. Calcd. for C₂₀H₂₄N₂O₄S: C, 61.83; H, 6.22; N, 7.21. Found: C, 61.79; H, 6.25; N, 7.19.

Methyl 3-Methyl-4-phenyl-4-[*N'*-(*p*-toluenesulfonyl)hydrazono]butanoate (VIIb).

Compound VIIb was obtained in 33% yield, mp 82-83°; ir: 3150, 1720, 1320, 1180; ¹H-nmr: δ 7.74 (d, 2H, J = 8.3 Hz), 7.5-7.1 (m, 7H), 3.54 (s, 3H), 3.2-2.7 (m, 3H), 2.43 (s, 3H), 1.03 (d, 3H, J = 6.8 Hz); ¹³C-nmr: δ 172.5 (s), 159.8 (s), 143.8 (s), 135.3 (s), 132.2 (s), 129.9 (d), 129.5 (d × 2), 127.8 (d), 127.1 (d), 51.5 (q), 38.0 (t), 37.8 (d), 21.6 (q), 18.1 (q).

Anal. Calcd. for C₁₉H₂₂N₂O₄S: C, 60.94; H, 5.92; N, 7.48. Found: C, 60.64; H, 5.88; N, 7.27.

Methyl 3-Ethyl-4-phenyl-4-[*N'*-(*p*-toluenesulfonyl)hydrazono]butanoate (VIIc).

Compound VIIc was obtained in 41% yield, mp 120-121°; ir: 1700, 1340, 1160; ¹H-nmr: δ 9.30 (broad s, 1H), 7.87 (d, 2H, J = 8.3 Hz), 7.5-7.2 (m, 7H), 3.53 (s, 3H), 2.8-2.7 (m, 2H), 2.69 (d, 2H, J = 7.3 Hz), 2.36 (s, 3H), 1.7-1.4 (m, 2H), 0.83 (t, 3H, J = 7.3 Hz); ¹³C-nmr: δ 174.0 (s), 158.3 (s), 143.5 (s), 136.0 (s), 135.3 (s), 129.1 (d), 128.8 (d), 128.2 (d), 127.5 (d), 52.2 (t), 37.1 (d), 36.9 (q), 25.6 (t), 21.5 (q), 12.0 (q).

Anal. Calcd. for C₂₀H₂₄N₂O₄S: C, 61.83; H, 6.22; N, 7.21. Found: C, 61.69; H, 6.25; N, 7.17.

Alternative Preparation of Alkyl 3-Methyl-4-phenyl-4-[*N'*-(*p*-toluenesulfonyl)hydrazono]butanoates (VIIa) and (VIIb).

A mixture of 3-benzoylbutanonitrile (1.2 mmoles) [10] and concentrated sulfuric acid (3.6 ml) in methanol (20 ml) was refluxed for 8 hours.

Methyl 3-benzoylbutanoate was obtained in 74% yield (bp 140-141°/3 mm Hg). A mixture of methyl 3-benzoylbutanoate (2.8 mmoles), *p*-toluenesulfonyl hydrazide (3 mmoles), and *p*-toluenesulfonic acid (0.3 mmoles) in dry benzene (30 ml) was refluxed for 4 hours with Dean-Stark apparatus. The benzene solution was washed successively with aqueous sodium bicarbonate and water, and then dried over anhydrous magnesium sulfate. Compound VIIb was obtained in 55% yield. Similarly compound VIIa was obtained in 39% overall yield.

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