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A large scale synthesis of 3-chloro-5-methoxypyridazine was developed (18 moles) that relies on the protection of the pyridazinone nitrogen of 4,5-dichloro-3(2H)-pyridazinone as the tetrahydropyranyl derivative 2. The 5-chloro position of the protected pyridazinone was selectively displaced with methoxide to give 3 followed by catalytic hydrogenation of the 4-chloro group to give 4. Removal of the protecting group with acid followed by phosphorous oxychloride treatment gave the target compound 6 in good yield. This route is superior to the previously described synthesis of this compound.

We sought to develop a large scale synthesis (18 moles) of 3-chloro-5-methoxypyridazine since this material was found to be an important intermediate in the synthesis of a number of highly active pyridazine herbicides [1-4]. A previously published report of the synthesis of 3-chloro-5-methoxypyridazine by Wagner [5] *et. al.* could not be repeated in our hands. The Wagner procedure reported that treatment of 4,5-dichloro-3(2H)-pyridazinone with sodium methoxide in methanol at reflux for several days gave 4-chloro-5-methoxy-3(2H)-pyridazinone in 90% yield. We found that this procedure resulted in precipitation of the pyridazinone salt which for the most part prevented further reaction with methoxide. A small amount of the desired material was obtained which was not sufficient for further transformations.

We found that it was necessary to protect the pyridazinone nitrogen as the tetrahydropyranyl derivative in order to displace the 5-position effectively. The procedure for

the preparation of 3-chloro-5-methoxypyridazine is outlined in Scheme I. The pyridazinone nitrogen of 4,5-dichloro-3(2H)-pyridazinone was protected by treatment with excess dihydropyran and p-toluenesulfonic acid in refluxing tetrahydrofuran to give crude 2 which was a dark oily mass and was used without further purification. Compound 2 was then reacted with potassium hydroxide in methanol which after workup and trituration with 12 l of 2:1 hexanes/ether gave a 77% yield over the two steps of the 5-methoxypyridazinone 3. An alternative procedure was also used for the preparation of 3 which prevented the extensive polymerization of the dihydropyran. Combining compound 1 with excess dihydropyran in refluxing tetrahydrofuran with pyridinium p-toluenesulfonate resulted in a cleaner reaction to give 2 which was followed by methoxide displacement to produce 3 in 73% yield over the two steps. The only advantage to the second procedure for the preparation of 3 is that the dihydropyran does not polymerize as extensively when the weaker acid pyridinium p-toluenesulfonate is utilized. 5-Methoxy-4-chloropyridazinone 3 was then hydrogenated using triethylamine, hydrogen, and palladium on carbon to give compound 4. Compound 4 was refluxed with 6 N hydrochloric acid and after workup the 5-methoxypyridazinone 5 was obtained as a white solid in 65% yield from compound 3. The target compound was prepared from 3 by careful treatment with phosphorous oxychloride to give 3-chloro-5-methoxypyridazine in 78% yield from 3.

Initially there was some question as to whether the tetrahydropyranyl group was attached to the nitrogen of the pyridazinone as shown in compounds 2, 3, and 4 or the oxygen of the tautomeric form giving a 3-tetrahydropyranyloxypyridazine. In an effort to answer this question we independently synthesized both methoxy-substituted isomers for comparison of their nmr spectra, Scheme II. Combination of 5-methoxypyridazinone 5 with potassium carbonate and methyl iodide produced the N-methylpyridazinone 7. Treatment of 3-chloro-5-methoxypyridazine with potassium hydroxide and methanol can only give the 3, 5-dimethoxypyridazine 8. Comparison of the nmr spectra of

Scheme I
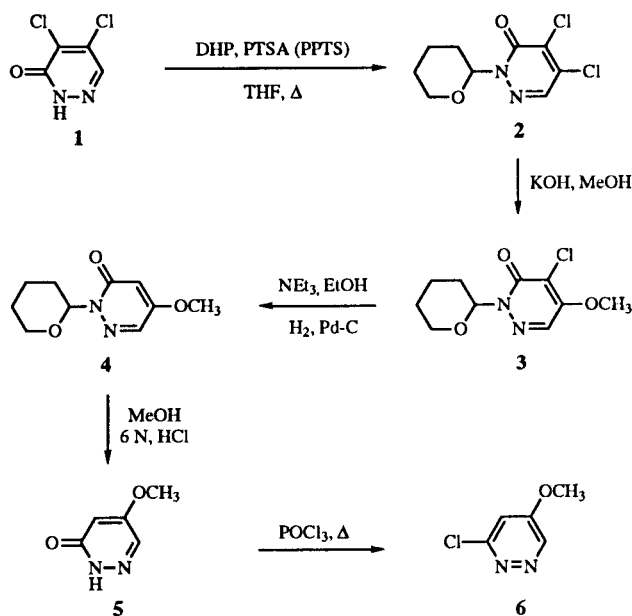
Scheme II
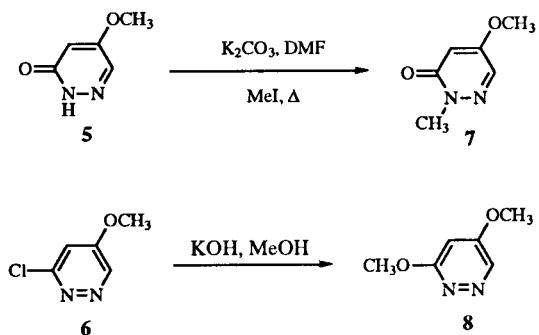
the two prepared isomers 7 and 8 with the tetrahydropyranyl derivative 4 provided conclusive evidence as to whether the pyranyl group was substituted on nitrogen or oxygen of the heterocycle, Table 1. Note that in the 400 MHz ^{1}H nmr

Table 1

| Compound | 400 MHz ^{1}H NMR PPM | | Analysis Calcd./Found | | |
	H_a	H_b	C	H	N
7	6.11	7.50	51.42 51.26	5.75 5.76	19.91 20.00
8	6.25	8.52	51.42 51.46	5.75 5.75	19.99 20.06
4	5.94	7.45	57.13 56.86	6.71 6.61	13.32 13.21
6	6.83	8.67	41.54 41.62	3.49 3.51	19.38 19.34

spectrum of compound 7 that the proton in the 6-position (labeled H_b) gave a resonance at 7.50 ppm and the proton in the 4-position (labeled H_a) gave a resonance at 6.11 ppm. This corresponds to the resonances found for compound 4 where the proton in the 6-position appears at 7.45 ppm and the proton in the 4-position appears at 5.94 ppm. For the 3,5-dimethoxy-substituted pyridazine 8 the resonance for the proton at the 6-position appears at 8.52 and the 4-position appears at 6.25 ppm [6]. The resonance for the proton at the 6-position of compound 8 is 1 ppm downfield relative to the proton at the 6-position of compounds 7 and 4. 3-Chloro-5-methoxypyridazine also follows this general trend of having the proton at the 6-position in the 8.5-8.6

ppm range. Therefore, one can definitively assign the tetrahydropyranyl group of compounds 2, 3, and 4 to be substituted on the pyridazinone nitrogen as shown.

EXPERIMENTAL

General.

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded using a Varian XL-400 spectrometer. Thin layer chromatography was performed on E. Merck TLC plates, 60F-254, 0.25 mm. Radial preparative thin layer chromatography was performed on a chromatotron (Harrison Research) and was conducted under a nitrogen atmosphere on glass coated with up to 4 mm of E. Merck "silica gel 60" PF-254 containing a gypsum binder. Elemental analyses were performed by Atlantic Microlabs, Inc., Atlanta, GA. Dry solvents and commercial compounds were obtained from Aldrich Chemical Co.

4,5-Dichloro-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (2).

4,5-Dichloro-3(2*H*)-pyridazinone 1 (3000 g, 18.18 moles), dihydropyran (1943 g, 23.08 moles), *p*-toluenesulfonic acid monohydrate (283 g, 1.49 moles), and 16 l of tetrahydrofuran were added to a 50 l round bottomed flask equipped with a heating mantle, reflux condenser, and a mechanical stirrer. The mixture was stirred at reflux for 29 hours. Additional dihydropyran was added at 6 hours (1328 g, 15.79 moles) and at 21 hours (780 g, 9.25 moles). The reaction mixture was allowed to cool to room temperature overnight. The mixture was concentrated *in vacuo* to an oily residue. The residue was taken up in 16 l of ethyl acetate and washed with 2 *N* sodium hydroxide (2 x 6 l). The organic solution was dried (magnesium sulfate) and concentrated *in vacuo* to give 4,5-dichloro-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone 2 which was a black oily solid which was used without further purification in the next step. The product could be purified by filtration through silica gel with ethyl acetate followed by evaporation and recrystallization from ethyl acetate/cyclohexane to give a white solid, mp 74-76°; ^{1}H nmr (400 MHz, deuteriochloroform): δ 7.71 (s, 1-H), 5.87 (dd, J = 10.4, 2.4 Hz, 1-H), 3.98 (d, J = 11.6 Hz, 1-H), 3.60 (apparent t, J = 11.6 Hz, 1-H), 2.06-1.87 (m, 2-H), 1.65-1.40 (m, 4-H); ^{13}C nmr (100 MHz, deuteriochloroform): δ 155.3, 135.8, 135.1, 133.7, 83.5, 68.1, 28.1, 24.1, 22.0.

Anal. Calcd. for $C_9H_{10}N_2O_2Cl_2 \cdot 0.1C_6H_{12}$: C, 44.78; H, 4.38; N, 10.89. Found: C, 44.63; H, 4.22; N, 10.94

4-Chloro-5-methoxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (3).

4,5-Dichloro-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone 2 from the previous step and 17 l of methanol were added to a 50 l round bottomed flask equipped with a glycol cooling jacket and a mechanical stirrer. The resulting solution was cooled to 0° and 87% potassium hydroxide (1172 g 18.17 moles) was added in portions over approximately 1 hour. The mixture exothermed to 40°. Following the addition the mixture was allowed to stir an additional 3 hours at ambient temperature. The reaction mixture was partitioned with 12 l of ethyl acetate and

12 l of water. The aqueous layer was extracted with ethyl acetate (2 x 4 l). The combined organic layers were washed with brine (2 x 10 l) and dried (magnesium sulfate). The organic solution was clarified by filtration and concentrated to give a dark semi-solid. The crude material was equally divided and added to two 22 l flasks. The material was suspended and stirred in 12 l hexanes/ethyl ether (2:1 ratio). The washed material was vacuum filtered on a Buchner funnel and air dried overnight to give 3,406 g (77% over 2 steps) of 4-chloro-5-methoxy-2-(tetrahydro-2H-pyran-2-yl)-3(2H)-pyridazinone 3 as a dark tan solid suitable for further transformations. The product could be purified by recrystallization from ethyl acetate/cyclohexane to give a white solid, mp 118-120°; ^{1}H nmr (400 MHz, deuteriochloroform): δ 7.76 (s, 1-H), 5.91 (d, J = 9.2 Hz, 1-H), 3.95-3.70 (m, 1-H), 3.93 (s, 3-H), 3.59 (apparent t, J = 11.2 Hz, 1-H), 2.05-1.85 (m, 2-H), 1.65-1.38 (m, 4-H); ^{13}C nmr (100 MHz, deuteriochloroform): δ 157.4, 154.0, 126.1, 115.7, 83.0, 68.1, 57.0, 28.2, 24.2, 22.1.

Anal. Calcd. for $C_{10}H_{13}N_2O_3Cl$: C, 49.09; H, 5.36; N, 11.45. Found: C, 49.04; H, 5.38; N, 11.43

Alternative Procedure for the Preparation of 4-Chloro-5-methoxy-2-(tetrahydro-2H-pyran-2-yl)-3(2H)-pyridazinone 3.

4,5-dichloro-3(2H)-pyridazinone 1 (165 g, 1.0 mole), dihydropyran (127.7 g, 1.52 moles), pyridinium p-toluenesulfonate (PPTS, 51.8 g, 0.21 mole), and 1 l of tetrahydrofuran were added to a 2 l round bottomed flask equipped with a heating mantle, reflux condenser, and a mechanical stirrer. The mixture was stirred at reflux under nitrogen for 7 hours. Additional dihydropyran was added after 7 hours (88 g, 1.05 moles). The mixture was then refluxed under nitrogen for 18 additional hours. The mixture was then cooled and 650 ml of tetrahydrofuran were removed by rotary evaporation. The mixture was cooled in an ice water bath and the precipitated pyridinium p-toluenesulfonate was removed by vacuum filtration. The filtrate was diluted with 300 ml of methanol and cooled to 5°. A solution of 25% w/w sodium methoxide in methanol (1.5 moles) was added in a rapid dropwise fashion. The mixture was allowed to warm to 20° during the addition and then stirred an additional 30 minutes. The reaction mixture was then vacuum filtered through a bed of celite. The filtrate was concentrated, and the residue was partitioned with 1 l of brine and 1 l of ethyl acetate. The brine layer was extracted with ethyl acetate (2 x 300 ml). The combined organics were dried (magnesium sulfate), filtered, and the solvent was removed by rotary evaporation. The crude material was slurried in 1 l of hexanes and filtered which gave 179.4 g (73% yield) of 4-chloro-5-methoxy-2-(tetrahydro-2H-pyran-2-yl)-3(2H)-pyridazinone 3 as a clay colored solid that was identical in all respects to the sample obtained above.

5-Methoxy-2-(tetrahydro-2H-pyran-2-yl)-3(2H)-pyridazinone (4).

4-Chloro-5-methoxy-2-(tetrahydro-2H-pyran-2-yl)-3(2H)-pyridazinone 3 (2486 g, 10.16 moles), ethanol (8 l), triethylamine (2 l, 14.23 moles), and 5% palladium on carbon (100 g of 50% water-wet Pd-C) were added to a 5 gallon autoclave. The mixture was hydrogenated at 50-60 psi of hydrogen and heated to a maximum temperature of 43°. After 24 hours, the reaction was complete. The reaction mixture was diluted with a small amount of water and vacuum filtered through celite. The filtrate was concentrated and partitioned with 10 l of ethyl acetate and 8 l of water. The aqueous phase was extracted with ethyl acetate (2

x 2 l). The combined organics were washed with 5 l brine, dried (magnesium sulfate), and vacuum filtered. The solution was concentrated *in vacuo* to give 2,133 g (100 % yield) of 5-methoxy-2-(tetrahydro-2H-pyran-2-yl)-3(2H)-pyridazinone 4 as a dark oil which later crystallized to give a tan product suitable for further transformations. The product could be purified by recrystallization from ethyl acetate/cyclohexane to give a white solid, mp 76-78°; ^{1}H nmr (400 MHz, deuteriochloroform): δ 7.45 (s, 1-H), 5.94 (s, 1-H), 5.83 (d, J = 10.4 Hz, 1-H), 3.94 (d, J = 10.8 Hz, 1-H), 3.63 (s, 3-H), 3.56 (apparent t, J = 10.8 Hz, 1-H), 2.05-1.80 (m, 2-H), 1.60-1.30 (m, 4-H); ^{13}C nmr (100 MHz, deuteriochloroform): δ 160.6, 159.5, 132.2, 102.2, 81.6, 68.0, 55.0, 28.2, 24.2, 22.3.

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.32. Found: C, 56.86; H, 6.61; N, 13.21

5-Methoxy-3(2H)-pyridazinone (5).

5-Methoxy-2-(tetrahydro-2H-pyran-2-yl)-3(2H)-pyridazinone 4 (2035 g, 9.69 moles) and 2 l of methanol were added to a 22 l round bottomed flask equipped with a heating mantle, reflux condenser, and mechanical stirrer. The mixture was warmed to 35° and 8 l of 6 N hydrochloric acid was added and then the mixture was heated to reflux for 2 hours. The reaction mixture was then cooled slightly and transferred to a glycol cooled 22 l flask where the mixture was cooled further to 30°. The mixture was made basic (pH 13-14) by cautious addition of 50% sodium hydroxide in portions. The basic mixture was extracted with methylene chloride (4 x 3 l). The aqueous phase was then acidified with concentrated hydrochloric acid (pH 1-2) to precipitate the product. The product was collected by vacuum filtration on a Buchner funnel. The product was dried to constant weight on a fluid bed dryer at 70°. This afforded 798 g (65% yield) of 5-methoxy-3(2H)-pyridazinone 5 as a white solid which could be recrystallized from methanol, mp 253-255°; ^{1}H nmr (400 MHz, deuteriochloroform): δ 7.72 (d, J = 2.8 Hz, 1-H), 6.27 (d, J = 2.8 Hz, 1-H), 4.05 (s, 3-H), the NH proton was not observed; ^{13}C nmr (100 MHz, dimethyl sulfoxide-d$_6$): δ 162.8, 161.0, 132.9, 103.5, 56.1.

Anal. Calcd. for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.60; H, 4.83; N, 22.18.

3-Chloro-5-methoxypyridazine 6.

5-Methoxy-3(2H)-pyridazinone 5 (629.6 g, 4.99 moles) and phosphorous oxychloride (2.5 l, 27 moles) were added to a 5 l round bottomed flask equipped with a heating mantle and a mechanical stirrer. The resulting stirred slurry was rapidly heated (less than 30 minutes) to 75°. At this temperature the heating mantle was removed. The reaction mixture continued to exotherm to a final temperature of 82.3°. After the solids had dissolved in the darkening reaction mixture, stirring was continued an additional 2 minutes. The homogeneous reaction mixture was then rapidly cooled to room temperature with an ice/water bath. The reaction mixture was concentrated *via* rotary evaporator using pump vacuum and a water bath temperature of 45°. The residue was taken up in 2 l of methylene chloride and slowly poured into a stirring mixture of 2 l methylene chloride and 6 l of water chilled to 10°. The layers were separated and enough 50% sodium hydroxide was added to the aqueous phase to give a pH of 2-4. The aqueous phase was extracted with additional methylene chloride (2 x 2 l). The combined organic layers were washed with 4 l of water and dried (magnesium sulfate).

The solution was vacuum filtered through 1 kg of silica gel. The silica gel was washed with 4 l of ethyl acetate/hexanes (1:1). The filtrate was concentrated *in-vacuo* to afford 564 g (78% yield) of 3-chloro-5-methoxypyridazine **6** as a pale yellow solid. The product was stored in a freezer to prevent gradual decomposition. The product could be recrystallized from ethyl acetate/cyclohexane to give a white solid, mp 98-100°; ^{1}H nmr (400 MHz, deuteriochloroform): δ 8.67 (d, J = 2.4 Hz, 1-H), 6.83 (d, J = 2.4 Hz, 1-H), 3.81 (s, 3-H); ^{13}C nmr (100 MHz, deuteriochloroform): δ 158.3, 156.0, 142.8, 108.8, 55.3.

Anal. Calcd. for $C_5H_5N_2OCl$: C, 41.54; H, 3.49; N, 19.38. Found: C, 41.62; H, 3.51; N, 19.34.

5-Methoxy-2-methyl-3(2*H*)-pyridazinone (**7**).

5-Methoxy-3(2*H*)-pyridazinone **5** (2.5 g, 19.8 mmoles), potassium carbonate (4.1 g, 29.8 mmoles), and methyl iodide (2.0 ml) were stirred in anhydrous *N,N*-dimethylformamide (30 ml) at 50° under nitrogen for 15 hours. The mixture was then quenched with water and extracted with ethyl acetate (3 x 50 ml). The organic layers were dried (magnesium sulfate), filtered, and evaporated. The residue was purified on a chromatotron (1:1 ethyl acetate/methylene chloride) to give 500 mg (18% yield) of 5-methoxy-2-methyl-3(2*H*)-pyridazinone **7** as a white solid, mp 107-108°; ^{1}H nmr (400 MHz, deuteriochloroform): δ 7.50 (s, 1-H), 6.11 (s, 1-H), 3.76 (s, 3-H), 3.68 (s, 3-H); ^{13}C nmr (100 MHz, deuteriochloroform): δ 161.6, 160.1, 131.6, 102.5, 55.2, 38.8; ir (chloroform): 2225, 1645, 1600 cm^{-1}.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.26; H, 5.76; N, 20.00.

3, 5-Dimethyoxypyridazine (**8**).

3-Chloro-5-methoxypyridazine **6** (0.95 g, 6.6 mmoles) and potassium hydroxide (0.4 g, mmoles) were stirred in methanol (20 ml) under nitrogen at room temperature for 20 hours. The solvent was removed by rotary evaporation and the residue was treated with water and extracted with methylene chloride (3 x 50 ml). The organic layers were dried (magnesium sulfate), filtered and evaporated. The crude product was recrystallized (methylene chloride/hexanes) to give 900 mg (98% yield) of 3,5-dimethoxypyridazine **8** as a white solid, mp 70-71°; ^{1}H nmr (400 MHz, deuteriochloroform): δ 8.52 (d, J = 2.40 Hz, 1-H), 6.25 (d, J = 2.40 Hz, 1-H), 4.06 (s, 3-H), 3.81 (s, 3-H); ^{13}C nmr (100 MHz, deuteriochloroform): δ 165.8, 159.4 140.8, 96.1, 54.9, 54.4; ir (chloroform): 2250, 1600 cm^{-1}.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.46; H, 5.75; N, 20.06.

REFERENCES AND NOTES

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