Homolytic Alkylations of Substituted Pyridazines [1]

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The unsymmetrically substituted pyridazines **1** (X = Ph, CH_3) have been found to undergo homolytic heteroaromatic alkylation in moderate to good yields with high regioselectivity. The site of substitution was established by conversion to **5** and measurement of the pyridazine proton coupling constant. In addition, homolytic alkylations of **1** (X = CH_3) afforded the *N*-alkylated products **6** and **7**.

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Introduction.

It was previously reported [2] that 3,6-dichloropyridazine undergoes homolytic substitution with alkyl radicals at C4 of the ring. Pyridazines unsymmetrically substituted at C3 and C6 offer two nonequivalent sites for approaching radicals to attack. Such is the case with 3-chloro-6-phenylpyridazine (**1**, X = Ph) and 3-chloro-6-methylpyridazine (**1**, X = CH_3) which are readily prepared from beta-benzoylpropionic acid [3] and levulinic acid [4], respectively. Homolytic alkylation of unsymmetrically substituted pyridazines has received some attention mainly by Heinisch [5], however the behavior of **1** has not been investigated and appeared quite interesting since both unsubstituted positions are available for alkylation in view of the proposed mechanism for homolytic substitution of protonated heteroaromatic bases [6].

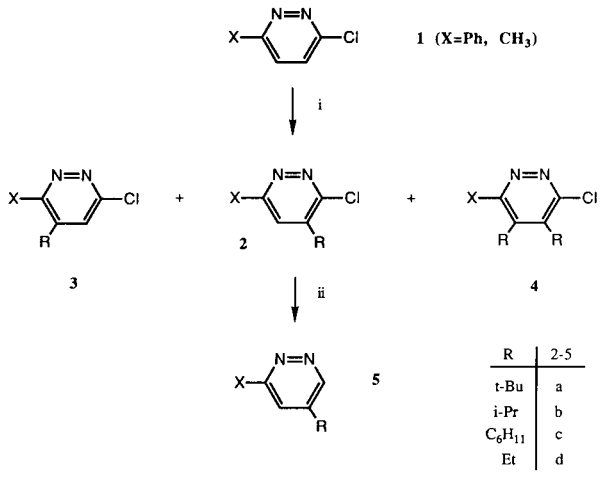
Results and Discussion.

The alkylations of **1** were performed using the silver-catalyzed oxidative decarboxylation of carboxylic acids [7] as the method of generating alkyl radicals. All alkylations of **1** afforded one monoalkylated regioisomer as the major product as evidenced by nmr and gas chromatographic analysis. The site of substitution was determined by subsequent hydrogenolysis of the chloropyridazine (Scheme 1) and measurement of the pyridazine proton coupling constant.

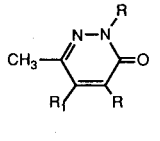
Alkylation of **1** (X = Ph) with *t*-butyl radicals afforded **2a** (X = Ph) in 69% yield (Scheme 1). The structure of **2a** (X = Ph) was established through conversion to **5a** (X = Ph) using hydrogen and palladium on carbon. The observed pyridazine proton coupling constant of 2.25 Hz is diagnostic for meta coupling in pyridazine derivatives [8]. Compound **3a** (X = Ph) was not observed to be present in any fraction of the chromatographed reaction mixture.

Homolytic alkylations of **1** (X = Ph) were also carried out with isopropyl and ethyl radicals. Again the major products in both cases were found to be the 4-monoalkylated isomers **2b** and **2d** (X = Ph). Only from the isopropylation of **1** (X = Ph) was a 5-monoalkylated product isolated and characterized (**3b**, X = Ph). The observed ratio **2b**/**3b** (X = Ph) was 94/6 based upon materials isolated. The appearance of the phenyl proton pattern in the nmr spectrum of **3b** (X = Ph) is indicative of the hindrance to phenyl group rotation imposed by the adjacent isopropyl group. A broadened singlet similar to that of toluene is observed for the phenyl protons suggesting that resonance interaction between phenyl and pyridazine rings is not operative. In **2b** (X = Ph) coplanarity results in differential downfield shifting of the ortho, meta, and para protons.

Scheme 1



i. RCO_2H, $AgNO_3$, H_2SO_4, $(NH_4)_2S_2O_8$, H_2O/CH_3CN ii. H_2, Pd(C), NH_4OH, EtOH



6a R=i-Pr R_1=H
6b R=C_6H_{11} R_1=H

7a R=R_1=i-Pr
7b R=R_1=C_6H_{11}

To more accurately probe the influence of electronic effects on the homolytic alkylation, differences in the steric requirements of the substituents at C3 and C6 must be minimized since the potential sites of alkylation lie ortho to each substituent. 3-Chloro-6-methylpyridazine (**1**, X = CH_3) appeared to be suited quite well for this purpose

since the van der Waal's radii of the chlorine atom and the methyl group are within 0.2 Ångstroms of each other [9].

Homolytic alkylations of **1** (X = CH_3) were carried out with radicals generated from pivalic, isobutyric, cyclohexanecarboxylic, and propionic acids. In each case both isomers (2 and 3, X = CH_3) were observed by mass spectrmetry/gas chromatography and were isolated and characterized. Alkylations were found to be highly regioselective affording product ratios of greater that 95/5 in favor of **2** (X = CH_3). Again hydrogenolysis of the major monoalkylated isomer and measurement of the pyridazine proton coupling constant of **5** (X = CH_3) established the site of substitution.

Interestingly no change in the ratio **2/3** (X = CH_3) is observed in proceeding from *t*-butyl to ethyl. Also under the conditions employed of mineral acid and excess persulfate small amounts of dialkylated material were formed (**4b-d**, X = CH_3). Since the reactivities of **2** and **3** to give **4** would most likely differ, a true measure of regioselectivity can only be made by quenching the alkylation prior to formation of **4** (X = CH_3). Accordingly aliquots from the ethylation and isopropylation were removed and worked up after 0.4-0.5 equivalents of persulfate had been added. Gas chromatographic analysis indicated that no dialkylated material had been formed and the only components present were **2** and **3** along with unreacted **1** (X = CH_3). The observed ratio **2/3** was found to be 90/10 in both cases.

It was also observed that the pyridazinones **6** and **7** were formed in significant quantities but only when the two secondary radicals (isopropyl and cyclohexyl) were used. These products were detected by gas chromatographic analysis and were subsequently isolated and characterized. Analogous products were not formed during the *t*-butylation or ethylation of **1** (X = CH_3). The *N*-alkylation also appears to be substrate dependent as neither *N*-isopropyl nor *N*-cyclohexyl pyridazinones are observed in reactions with either **1** (X = Ph) or 3,6-dichloropyridazine [1].

The ^{13}C nmr of **6a** is offered as proof of an *N*-alkylated pyridazinone. In the proton coupled ^{13}C nmr spectrum of **6a**, a doublet ($^1J_{CH}$ = 139.7 Hz) was observed at 48.77 ppm assignable to NC*H of the *N*-isopropyl group. The corresponding values for an *O*-alkylated product would have been *ca.* 145 Hz for the one-bond coupling constant [10] and *ca.* 69 ppm for the chemical shift [11]. The predicted values for the *N*-alkylated product are in good agreement with the observed values, *viz.* 134 Hz and 49 ppm respectively for the $^1J_{CH}$ [10] and the chemical shift [11].

Carbon-13 nmr also provides proof that the other iospropyl group in **6a** is at C-4 and not C-5. Values of 27.5 ppm for C4-C*H and 159.1 Hz for the C5-H5 one-bond coupling are in excellent agreement with estimated values of 26 ppm [11] and 161.7 Hz [12]. The value of the one-bond coupling constant is quite diagnostic. If the isopropyl group were bonded to C-5, the corresponding C4-H4 one-bond coupling constant would be expected to be greater than 10 Hz larger [12].

Nuclear Overhauser effect (nOe) difference spectroscopy corroborates the regiochemistry assigned from ^{13}C nmr for **6a** and, by analogy, **6b**. Thus in both cases selective irradiation of 6-Me in an nOe difference experiment resulted in enhancement of the pyridazinone protons at 6.84 and 6.74 ppm, respectively.

Conclusions.

Pyridazines **1** (X = Ph, CH_3) are suitable substrates for homolytic heteroaromatic alkylation. The alkylations proceed with high regioselectivity and in the case of **1** (X = CH_3) the regioselectivity observed, particularly in the ethylation, cannot be explained on steric grounds alone. Certainly polar effects play a significant role in the outcome of these alkylations and investigations designed to probe the influence of these polar effects are underway.

EXPERIMENTAL

Melting points were obtained in glass capillaries using a Laboratory Devices Mel-Temp apparatus and are uncorrected. The proton nmr spectra were measured on either a Bruker WM-250 spectrometer or an IBM NR-80 spectrometer. Carbon-13 nmr spectra were measured on the WM-250 spectrometer as were the nOe difference spectra. Samples were dissolved in chloroform-d_1 (Merck) containing internal tetramethylsilane as reference. Values of coupling constants are ±0.1 Hz. Mass spectra were obtained by electron impact (EI, 70eV) or fast atom bombardment (FAB) using dithiothreitol/dithioerythritol (5/1, Sigma) as matrix on a Hewlett-Packard 5985A GC/MS system. Gas chromatographic analyses were performed on either a Hewlett-Packard 5720A gas chromatograph or on the 5985A GC/MS system using a 10 ft. x 2 mm id 3% SP 2250 column. Preparative Dry Column Chromatography was performed using silica woelm (63-200 microns, 70-230 mesh, Universal Scientific) in Michel-Miller columns (Ace Glass).

Starting materials **1** (X = Ph, CH_3) were prepared according to established procedures [3,4]. 3-Chloro-6-methylpyridazine was purified by sublimation (80-85°/0.1 mm) prior to subjection to the alkylation conditions [13]. 3-Chloro-6-phenylpyridazine was used without further purification. Carboxylic acids, ammonium persulfate [14], and silver nitrate were obtained from the Aldrich Chemical Company and were used without further purification.

General Procedure for the alkylation of **1** (X = Ph, CH_3).

To a mixture of **1** (0.010 mole), carboxylic acid (0.0225 mole), sulfuric acid (0.015 mole), and silver nitrate (0.0010 mole) in 30 ml of water (when X = Me) or 30 ml of 50% aqueous acetonitrile (when X = Ph) at 60-75° was added dropwise over a 10-15 minute period a solution of ammonium peroxydisulfate (0.015 mole) in 10 ml of water. The mixture was held at 75° for 30

minutes, and was allowed to cool and was poured onto ice. The mixture was adjusted to *p*H 9-10 with concentrated ammonium hydroxide and was extracted once with dichloromethane. The extract was washed twice with 1.0 *N* sodium hydroxide and was dried (magnesium sulfate). Concentration afforded product mixtures which were dry column chromatographed on silica woelm.

3-Chloro-4-*t*-butyl-6-phenylpyridazine (**2a**, X = Ph).

Dry column chromatography on silica woelm using 99/1 dichloromethane/ethyl ether afforded a 69% yield of **2a** (X = Ph); ^{1}H nmr (deuteriochloroform): 1.56 (s, 9, *t*-butyl), 7.53 (m, 3, ArH), 7.77 (s, 1 pyrH), 8.02 (m, 2, ArH); ms: (EI, 70 eV) m/e (%), 248 (19), 246 (M^+, 57), 231 (100).

A small portion was recrystallized from petroleum ether at -20° for microanalysis, mp 60-61°.

Anal. Calcd. for $C_{14}H_{15}ClN_2$: C, 68.15; H, 6.13; N, 11.35. Found: C, 68.30; H, 6.07; N, 11.18.

3-Chloro-4-isopropyl-6-phenylpyridazine (**2b**, X = Ph) and 3-Chloro-5-isopropyl-6-phenylpyridazine (**3b**, X = Ph).

Dry chromatography on silica woelm using 98/2 and 97/3 heptane/ethyl acetate afforded a 61% yield of **2b** (X = Ph), mp 71-74.5°; ^{1}H nmr (deuteriochloroform): 1.36 (d, 6, $CH(CH_3)_2$, J = 6.9 Hz), 3.34 (m, 1, $CH(CH_3)_2$, J = 6.8 Hz), 7.46-7.60 (m, 3, ArH), 7.69 (s, 1, pyrH), 7.96-8.08 (m, 2, ArH); ms: (FAB) m/e (%), 235 (33), 233 ($M+1^+$, 100).

Anal. Calcd. for $C_{13}H_{13}ClN_2$: C, 67.10; H, 5.63; N, 12.04. Found: C, 66.95; H, 5.65; N, 11.96.

The remaining fractions of lower R_f were rechromatographed using 70/30 and 60/40 dichloromethane/heptane to give a 4% yield of **3b** (X = Ph), mp 65-68.5; ^{1}H nmr (deuteriochloroform): 1.19 (d, 6, $CH(CH_3)_2$, J = 6.8 Hz), 3.11 (m, 1, $CH(CH_3)_2$), 7.48 (br. s., 6, ArH and pyrH); ms: (FAB) m/e (%), 235 (34), 233 ($M+1^+$, 100).

Anal. Calcd. for $C_{13}H_{13}ClN_2$: C, 67.10; H, 5.63; N, 12.04. Found: C, 66.86; H, 5.60; N, 11.93.

Starting material **1** (X = Ph) was also recovered (12%).

3-Chloro-4-ethyl-6-phenylpyridazine (**2d**, X = Ph).

Dry chromatography on silica using 97/3 hexane/ethyl acetate afforded a 17% yield of **2d** (X = Ph), mp 61-63.5°; ^{1}H nmr (deuteriochloroform): 1.34 (t, 3, CH_2CH_3, J = 7.5 Hz), 2.81 (q, 2, CH_2CH_3), 7.45-7.53 (m, 3, ArH), 7.67 (s, 1, pyrH), 7.96-8.09 (m, 2, ArH); ms: (EI, 70 eV): m/e (%), 220 (32), 218 (M^+, 100).

Anal. Calcd. for $C_{12}H_{11}ClN_2$: C, 65.91; H, 5.07; N, 12.81. Found: C, 65.90; H, 5.39; N, 12.83.

3-Chloro-4-*t*-butyl-6-methylpyridazine (**2a**, X = CH_3) and 3-Chloro-5-*t*-butyl-6-methylpyridazine (**3a**, X = CH_3).

Gas chromatography (130°) of the crude reaction mixture indicated a ratio of greater than 95:5 for **2a**:**3a**. Chromatography on silica gel using 80/20 hexane/ethyl acetate gave a 71% yield of **2a** (X = CH_3), mp 59-62°; ^{1}H nmr (deuteriochloroform): 1.47 (s, 9, *t*-butyl), 2.67 (s, 3, CH_3), 7.28 (s, 1, pyrH); ms: (EI, 70 eV), m/e (%), 186 (36), 184 (M^+, 100).

Anal. Calcd. for $C_9H_{13}ClN_2$: C, 58.54; H, 7.10; N, 15.17. Found: C, 58.43; H, 7.19; N, 15.28.

Compound **3a** (X = CH_3) was also eluted and was obtained in 0.7% yield; ^{1}H nmr (deuteriochloroform): 1.42 (s, 9, *t*-butyl), 2.89 (s, 3, CH_3), 7.36 (s, 1, pyrH); ms: (EI, 70 eV) m/e (%), 186 (25), 184 (M^+, 77), 57 (100).

3-Chloro-4-isopropyl-6-methylpyridazine (**2b**, X = CH_3), 3-Chloro-5-isopropyl-6-methylpyridazine (**3b**, X = CH_3), 3-Chloro-4,5-diisopropyl-6-methylpyridazine (**4b**, X = CH_3), 2,4-Diisopropyl-6-methyl-3(2*H*)pyridazinone (**6a**, X = CH_3), and 2,4,5-Triisopropyl-6-methyl-3(2*H*)pyridazinone (**7a**, X = CH_3).

Gas chromatography (130°) of the crude reaction mixture indicated a ratio of greater than 95:5 for **2b**:**3b**. Chromatography on silica gel using gradient elution with 97/3 hexane/ethyl acetate and increasing the polarity to 70/30 afforded the following compounds; **2b** in 54% yield as a colorless oil; ^{1}H nmr (deuteriochloroform): 1.29 (d, 6, $CH(CH_3)_2$, J = 6.8 Hz), 2.67 (s, 3, CH_3), 3.26 (m, 1, $CH(CH_3)_2$), 7.21 (s, 1, pyrH); ms: (EI, 70 eV) m/e (%), 172 (12), 170 (M^+, 35), 91 (100).

Anal. Calcd. for $C_8H_{11}ClN_2$: C, 56.31; H, 6.50; N, 16.42. Found: C, 56.38; H, 6.32; N, 16.49.

Compound **3b** was obtained in 0.9% yield as an oil; ^{1}H nmr (deuteriochloroform): 1.27 (d, 6, $CH(CH_3)_2$, J = 6.8 Hz), 2.70 (s, 3, CH_3), 3.05 (m, 1, $CH(CH_3)_2$), J = 6.8 Hz), 7.28 (s, 1, pyrH); ms: (FAB) m/e (%), 173 (32), 171 ($M+1^+$, 100).

Compound **4b** in 7.5% yield, mp 103-107°; ^{1}H nmr (deuteriochloroform); 1.38 (d, 6, $CH(CH_3)_2$, J = 7.2 Hz), 1.43 (d, 6, $CH(CH_3)_2$), J = 7.2 Hz), 2.72 (s, 3, CH_3), 3.55 (m, 2, $2CH(CH_3)_2$); ms: (EI, 70 eV) m/e (%), 214 (20), 212 (M^+, 59), 41 (100).

Anal. Calcd. for $C_{11}H_{17}ClN_2$: C, 62.11; H, 8.06; N, 13.17. Found: C, 62.27; H, 8.11; N, 13.24.

Compound **7a** was obtained in 5% yield, mp 97-98°; ^{1}H nmr (deuteriochloroform): 1.31 (d, 6, $CH(CH_3)_2$, J = 6.5 Hz), 1.32 (d, 6, $CH(CH_3)_2$, J = 7.3 Hz), 1.37 (d, 6, $CH(CH_3)_2$, J = 6.9 Hz), 2.34 (s, 3, $pyrCH_3$), 3.29 (br m, 2, $2CH(CH_3)_2$), 5.27 (m, 1, $NCH(CH_3)_2$, J = 6.6 Hz), ^{13}C nmr (deuteriochloroform): 28.72 ($pyrCH_3$), 47.82 ($NCH(CH_3)_2$), 159.53 (C=O); ms: (EI, 70 eV), m/e (%), 236 (M^+, 37), 41 (100).

Anal. Calcd. for $C_{14}H_{24}N_2O$: C, 71.14; H, 10.23; N, 11.85. Found: C, 71.33; H, 10.08; N, 11.69.

Compound **6a** was obtained in 7% yield as an oil; ^{1}H nmr (deuteriochloroform): 1.18 (d, 6, $CH(CH_3)_2$, J = 6.8 Hz), 1.33 (d, 6, $NCH(CH_3)_2$, J = 6.7 Hz), 2.30 (s, 3, $pyrCH_3$), 3.23 (m, 1, $CH(CH_3)_2$, J = 6.8 Hz), 5.31 (m, 1, $NCH(CH_3)_2$, J = 6.7 Hz), 6.83 (d, 1, pyrH, J = 1.0 Hz); ^{13}C nmr (deuteriochloroform): 27.50 ($pyrCH_3$), 48.77 ($NCH(CH_3)_2$), 159.47 (C=O); ms: (FAB) m/e (%) 195 ($M+1^+$, 100).

Anal. Calcd. for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34; N, 14.42. Found: C, 68.03; H, 9.24; N, 14.50.

3-Chloro-4-cyclohexyl-6-methylpyridazine (**2c**, X = CH_3), 3-Chloro-5-cyclohexyl-6-methylpyridazine (**3c**, X = CH_3), 3-Chloro-4,5-dicyclohexyl-6-methylpyridazine (**4c**, X = CH_3), 2,4-Dicyclohexyl-6-methyl-3(2*H*)pyridazinone (**6b**), and 2,4,5-Tricyclohexyl-6-methyl-3(2*H*)-pyridazinone (**7b**).

Gas chromatography (130°) of the crude reaction mixture indicated a ratio of greater than 95:5 for **2c**:**3c**. Silica gel chromatography of the crude reaction mixture using hexane/ethyl acetate eluants afforded, **2c** in 61% yield, mp 79-80.5°; ^{1}H nmr (deuteriochloroform): 0.97-1.10 (m, 10, cyclohexyl), 2.66 (s, 3, CH_3), 2.52-3.07 (m, 1, cyclohexyl), 7.16 (s, 1, pyrH); ms: (EI, 70 eV) m/e (%), 212 (26), 210 (M^+, 78) 41 (100).

Anal. Calcd. for $C_{11}H_{15}ClN_2$: C, 62.70; H, 7.18; N, 13.29. Found: C, 62.87; H, 7.01; N, 13.12.

Compound **3c** was obtained in 2% yield as an oil; ^{1}H nmr (deuteriochloroform): 1.02-2.12 (m, 10, cyclohexyl), 2.38-2.84 (m, 1, cyclohexyl), 2.68 (s, 3, CH_3), 7.24 (s, 1, pyrH); ms: (EI, 70 eV) m/e (%), 212 (12), 210 (M^+, 36), 41 (100).

Compound **4c** was obtained in 5% yield, mp 154-159; ^{1}H nmr (deuteriochloroform): 1.03-3.77 (m, 22, 2cyclohexyl), 2.71 (s, 3, CH_3); ms: (EI, 70 eV) m/e (%), 294 (33), 292 (M^+, 100).

Anal. Calcd. for $C_{17}H_{25}ClN_2$: C, 69.72; H, 8.60; N, 9.57. Found: C, 69.47; H, 8.30; N, 9.65.

Compound **6b** was obtained in 4% yield as an oil; ^{1}H nmr (deuteriochloroform): 1.00-2.07 (m, 20, 2cyclohexyl), 2.28 (s, 3, CH_3), 2.52-3.17 (m, 1, C-cyclohexyl), 4.65-5.07 (m, 1, *N*-cyclohexyl), 6.77 (s, 1, pyrH); ^{13}C nmr (deuteriochloroform): 56.5 (*N*-cyclohexyl), 159.3 (C=O); ms: (EI, 70 eV), m/e (%), 274 (M^+, 17), 193 (100).

Anal. Calcd. for $C_{17}H_{26}N_2O$: C, 74.41; H, 9.55; N, 10.21. Found: C, 74.54; H, 10.01; N, 9.96.

Compound **7b** was obtained in 0.4% yield, mp 135-136°; ^{1}H nmr (deuteriochloroform): 1.00-3.22 (m, 32, 3cyclohexyl), 2.32 (s, 3, CH_3), 4.59-5.05 (br m, 1, *N*-cyclohexyl); ^{13}C nmr (deuteriochloroform): 56.0 (*N*-cyclohexyl), 160.1 (C=O); ms: (EI, 70 eV) m/e (%), 356 (M^+, 30), 275 (100).

Anal. Calcd. for $C_{23}H_{36}N_2O$: C, 77.47; H, 10.20; N, 7.86. Found: C, 77.52; H, 10.01; N, 7.82.

3-Chloro-4-ethyl-6-methylpyridazine (**2d**, X = CH_3), 3-Chloro-5-ethyl-6-methylpyridazine (**3d**, X = CH_3), and 3-Chloro-4,5-diethyl-6-methylpyridazine (**4d**, X = CH_3).

Gas chromatography (130°) of the crude reaction mixture indicated a ratio of greater than 95:5 for **2d**:**3d**. Chromatography on silica gel using hexane/ethyl acetate afforded **4d** (X = CH_3), mp 66-71°; ^{1}H nmr (dideuteriomethylene chloride): 1.16 and 1.19 (2t, 6, $2CH_2CH_3$), 2.63 (s, 3, pyrCH_3), 2.68 (q, 2, CH_2CH_3), 2.78 (q, CH_2CH_3); ms: (EI, 70 eV) m/e (%), 186 (21), 184 (M^+, 64), 39 (100) and **2d** (X = CH_3) as an oil; ^{1}H nmr (dideuteriomethylene chloride): 1.26 (t, 3, CH_2CH_3), 2.65 (s, 3, pyrCH_3), 2.72 (q, 2, CH_3CH_3), 7.21 (s, 1, pyrH); ms: (EI, 70 eV) m/e (%), 158 (7), 156 (M^+, 21), 43 (100). Compound **3d** was not isolated in pure form. Gas chromatographic/mass spectral analysis of the product mixture gave the following mass spectral data for **3d** (X = CH_3); ms: (EI, 70 eV) m/e (%), 158 (33), 156 (M^+, 100).

General Procedure for the Hydrogenolysis of **2** (X = Ph, CH_3).

A solution of **2** (0.0050 mole), 5% or 10% palladium on carbon catalyst (200 mg), and 1 g of concentrated ammonium hydroxide in 100 ml of 95% ethanol was placed on a Parr shaker at room temperature at an initial pressure of 50 lbs of hydrogen for approximately 30 minutes and was then filtered and the filtrate was concentrated to a residue which was partitioned between dichloromethane and water. The layers were separated and the organic phase was dried (magnesium sulfate) and was concentrated to a residue which was either recrystallized or chromatographed on dry pack silica woelm.

3-Phenyl-5-*t*-butylpyridazine (**5a**, X = Ph).

This compound was obtained in 69% yield, mp 97-97.5 (hexane); ^{1}H nmr (deuteriochloroform): 1.41 (s, 9, *t*-butyl), 7.46-7.55 (m, 3, phenyl), 7.75 (d, 1, pyrC4-H, J = 2.3 Hz), 8.01-8.13 (m, 2 phenyl), 9.22 (d, 1, pyrC6-H, J = 2.2 Hz); ms: (EI, 70 eV) m/e (%), 212 (M^+, 79), 197 (100).

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.43; H, 7.36; N, 13.41.

3-Phenyl-5-isopropylpyridazine (**5b**, X = Ph).

This compound was obtained in 72% yield, mp 62-64° (hexane): ^{1}H nmr (deuteriochloroform): 1.22 (d, 6, $CH(CH_3)_2$, J = 7.5 Hz), 3.02 (m, 1, $CH(CH_3)_2$, J = 7.5 Hz), 7.48-7.62 (m, 3, phenyl), 7.67 (d, 1 pyrC4-H, 2.2 Hz), 8.03-8.17 (m, 2, phenyl), 9.03 (d, 1, pyrC6-H, J = 2.1 Hz); ms: (FAB) m/e (%), 199 ($M+1^+$, 100).

Anal. Calcd. for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.53; H, 7.22; N, 13.94.

3-Phenyl-5-ethylpyridazine (**5d**, X = Ph).

This compound was obtained in 94% yield, mp 56-58.5° (hexane); ^{1}H nmr (deuteriochloroform): 1.33 (t, 3, CH_2CH_3, J = 7 Hz), 2.74 (q, 2, CH_2CH_3, J = 7 Hz), 7.45-7.52 (m, 3, phenyl), 7.64 (dd, 1, pyrC4-H), 8.00-8.14 (m, 2, phenyl), 9.00 (d, 1, pyrC6-H, J = 1.9 Hz); ms: (EI, 70 eV) m/e (%), 184 (M^+, 100).

Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.20. Found: C, 77.90; H, 6.57; N, 14.95.

3-Methyl-5-*t*-butylpyridazine (**5a**, X = CH_3).

This compound was obtained in 94% yield, mp 68-71° (hexane); ^{1}H nmr (deuteriochloroform): 1.35 (s, 9, *t*-butyl), 2.70 (s, 3, CH_3), 7.23 (d, 1, pyrC4-H, J = 2.35 Hz), 9.09 (d, 1, pyrC6-H, J = 2.35 Hz); ms: (EI, 70 eV) m/e (%), 150 (M^+, 58), 39 (100).

Anal. Calcd. for $C_9H_{14}N_2$: C, 71.96; H, 9.39; N, 18.65. Found: C, 71.95; H, 9.31; N, 18.83.

3-Methyl-5-isopropylpyridazine (**5b**, X = CH_3).

This compound was obtained as an oil in 97% yield; ^{1}H nmr (deuteriochloroform): 1.29 (d, 6, $CH(CH_3)_2$, J = 6.9 Hz), 2.69 (s, 3, CH_3), 2.90 (m, 1, $CH(CH_3)_2$, J = 6.9 Hz), 7.15 (d, 1, pyrC4-H, J = 2.1 Hz), 8.93 (d, 1, pyrC6-H, J = 2.1 Hz); ms: (EI, 70 eV) m/e (%), 136 (M^+, 79), 77 (100).

Anal. Calcd. for $C_8H_{12}N_2$: C, 70.55; H, 8.88; N, 20.57. Found: C, 71.50; H, 8.90; N, 21.23.

Chromatography (silica woelm) of the crude product gave **5b** (X = CH_3) as an oil which resulted in no impovement of the elemental analysis. Gas chromatographic analysis indicated a purity of greater than 98%.

3-Methyl-5-cyclohexylpyridazine (**5c**, X = CH_3).

This compound was obtained in 96% yield, mp 57-59° (hexane); ^{1}H nmr (deuteriochloroform): 1.29-2.81 (m, 11, cyclohexyl), 2.67 (s, 3, CH_3), 7.12 (d, 1, pyrC4-H, J = 2.0 Hz), 8.89 (d, 1, pyrC6-H, J = 2.0 Hz); ms: (EI, 70 eV) m/e (%), 176 (M^+, 100).

Anal. Calcd. for $C_{11}H_{16}N_2$: C, 74.96; H, 9.15; N, 15.89. Found: C, 75.11; H, 9.18; N, 15.87.

3-Methyl-5-ethylpyridazine (**5d**, X = CH_3).

This compound was obtained as an oil, bp 78-79.5° (0.2 mm); ^{1}H nmr (deuteriochloroform): 1.28 (t, 3, CH_2CH_3), 2.65 (q, 2, CH_2CH_3), 2.68 (s, 3, CH_3), 7.14 (d, 1, pyrC4-H, J = 1.8 Hz), 8.89 (d, 1, pyrC6-H, J = 1.8 Hz); ms: (EI, 70 eV) m/e (%), 122 (M^+, 100).

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[13] Purified material (**1**, X = CH_3) was found to be superior for alkylation. In some cases with crude **1** (X = CH_3) no alkylation was observed.

[14] Use of ammonium persulfate which had been stored at room temperature for eight months resulted in poor yields. The reagent was subsequently stored at 0°.