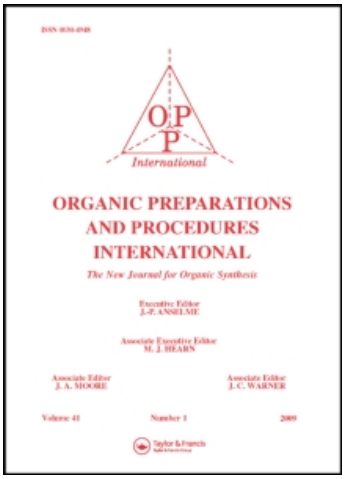

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HOMOLYTIC ALKYLATIONS OF 3, 6-DICHLOROPYRIDAZINE

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HOMOLYTIC ALKYLATIONS OF 3,6-DICHLOROPYRIDAZINE

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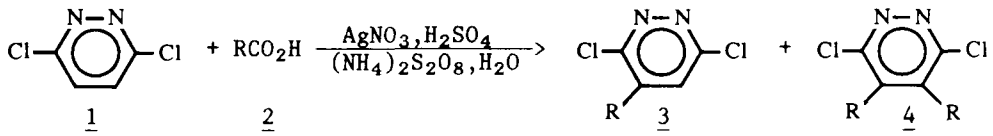
During the course of a research program aimed at evaluating the chemistry of the pyridazine ring, it became necessary to prepare several alkylated 3,6-dichloropyridazines, most of which whose syntheses are not described in the chemical literature.

Crossland and co-workers,[1,2] Letsinger and Lasco,[3] and Ohsawa and co-workers[4] have alkylated several substituted pyridazines using Grignard and organolithium reagents. More recently, Minisci's method of alkylating protonated heteroaromatic bases using free radicals[5] has successfully been applied to pyridazine by Heinisch and co-workers.[6] Although 3,6-dichloropyridazine itself had not been utilized as a substrate, the method appeared quite attractive owing to the ease and convenience of generating the alkyl free radicals by the silver-catalyzed oxidative decarboxylation of carboxylic acids.[7]



a) t-Bu b) i-C_3H_7 c) C_2H_5 d) cyclohexyl e) 1-adamantyl f) $CH_3CH_2CH_2C(CH_3)_2$ g) $PhOCH_2$ h) 1-methylcycloprop-1-yl i) $CH_3CH_2CHCH_3$ j) $CH_3CH_2C(CH_3)_2$

Treatment of 3,6-dichloropyridazine (1) in aqueous sulfuric acid at 65-75° with the redox couple silver (I)/peroxydisulfate in the presence of

a carboxylic acid (2) affords a mixture of monoalkylated (3) and dialkylated (4) dichloropyridazines[8] (Table 1). It has been observed in some cases that the yield of 4 can be increased at the expense of 3 by employing a larger quantity of the redox system ($RCO_2H/Ag^+/S_2O_8^=$). For example, by increasing the number of equivalents with respect to 1 from 2.25/0.10/1.5 to 3.5/0.25/2.5, the isolated yield of 4c is increased from 9% to 61%.

TABLE 1. Alkylated Pyridazines 3 and 4

	Isolated Yield (%)	mp. (°C)
3a	87	37-40[a]
3b	84	oil
4b	12	138-141.5
3c	28	oil
4c	9	108-109.5
3d	50	72-73.5
3e	21	172-174
3f	74	oil
3g	55	139-142
3h	59	73-80
4h	12	177-185
3i	69	oil
4i	2	97.5-100.5
3j	64	oil

a) lit.[1] mp. 39-41°C.

The result that alkylation occurs at the unsubstituted positions is similar to that obtained by Minisci and co-workers[9] and Clerici and co-workers[10] who observed no ipso-substitution[11] in 3-chloro and 4-chloropyridines.

Investigations involving unsymmetrically 3,6-disubstituted pyridazines are currently underway. Preliminary findings reveal a highly regioselective alkylation.

EXPERIMENTAL SECTION

Melting points are uncorrected. NMR spectra were obtained on Bruker WM 250 FT, IBM NR-80 FT, and Varian T-60 spectrometers. All chemical shifts are reported in ppm (δ) downfield from tetramethylsilane in $CDCl_3$ solutions. Mass spectra were obtained with the Hewlett-Packard HP-5985B GC-MS system. 3,6-Dichloropyridazine was purchased from Aldrich Chemical Company and was used without further purification.

General Procedure - To a mixture of 3,6-dichloropyridazine (1, 10.0 mMol), carboxylic acid (2, 22.5 mMol), sulfuric acid (15.0 mMol), and silver nitrate (1.00 mMol) in 30 mL of distilled water at 65-75° was added dropwise a solution of ammonium peroxydisulfate (15.0 mMol) in 10 mL of distilled water over a 10-15 minute period. The mixture was held at 70-75° for an additional 30 minutes and poured onto ice. The pH was adjusted to 9-10 with concentrated ammonium hydroxide and the contents were extracted twice with dichloromethane. The combined extracts were then washed once with 1.0 N sodium hydroxide and dried ($MgSO_4$). Concentration in vacuo afforded mixtures which were purified by recrystallization or by chromatography on silica gel, using hexane/ethyl acetate mixtures as eluants.

TABLE 2. NMR and Mass Spectral Data of 4

	^{1}H-NMR δ(ppm)	MS(70 eV) m/e(%)
4b	1.44(d, 12H, J=7.4 Hz, $2CH(C\underline{H}_3)_2$) 3.69(br.m, 2H, $2C\underline{H}(CH_3)_2$)	234(12), 232(M+,17) 41(100)
4c	1.25(t, 6H, J=7.7 Hz, $2CH_2C\underline{H}_3$) 2.84(q, 4H, $2C\underline{H}_2CH_3$)	206(34), 204(M+,52) 77(100)
4h	0.76-1.42(m, 8H, 2 cyclopropyl) 1.37(s, 6H, $2C\underline{H}_3$)	258(53), 256(M+,78) 213(100)
4i	0.91(t, 6H, J=7.5 Hz, $2CH_2C\underline{H}_3$) 1.39(d, 6H, J=6.9 Hz, $2CHC\underline{H}_3$) 1.67-3.26(m, 4H, $2C\underline{H}_2CH_3$) 3.16-3.77(m, 2H, $2C\underline{H}CH_3$)	262(66) 260(M+,100)

TABLE 3. NMR and Mass Spectral Data of 3

	^{1}H-NMR δ(ppm)	MS(70 eV) m/e(%)
3a	1.50(s, 9H, t-C_4H_9) 7.42(s, 1H, H-pyr.)	206(64), 204(M+,97) 189(100)
3b	1.32(d, 6H, J=8.0 Hz, $CH(CH_3)_2$) 3.28(m, 1H, $CH(CH_3)_2$) 7.40(s, 1H, H-pyr.)	192(37) 190(M+,57) 91(100)
3c	1.33(t, 3H, J=7.4 Hz, CH_3) 2.79(q, 2H, CH_2) 7.41(s, 1H, H-pyr.)	178(10) 176(M+,14) 77(100)
3d	1.17-1.59(m, 5H,CHC_5H_{10}) 1.71-2.06(m, 5H, CHC_5H_{10}) 2.89(br.t, 1H, pyr.CHC_5H_{10} 7.36(s, 1H, H-pyr.)	232(66) 230(M+,100)
3e	1.78(br.s, 6H, adamantyl) 2.12(br.s, 9H, adamantyl) 7.28(s, 1H, H-pyr.)	284(65) 282(M+,100)
3f	0.73-1.12(m, 5H, CH_2CH_3) 1.48(s, 6H, n-PrC$(CH_3)_2$) 1.80-2.03(m, 2H, $CH_3CH_2CH_2$) 7.44(s, 1H, H-pyr.)	234(15) 232(M+,23) 41(100)
3g	5.10(d, 2H, J=1.5 Hz, CH_2O) 6.99-7.40(m, 5H, OC_6H_5) 7.82(t, 1H, J=1.5 Hz, H-pyr.)	256(63) 254(M+,100)
3h	ca. 0.88(d, 2H, CH_ACH_A') ca. 0.95(d, 2H, CH_BCH_B') 1.41(s, 3H, CH_3) 7.44(s, 1H, H-pyr.)	204(66) 202(M+,98) 103(100)
3i	0.94(t, 3H, J=7.3 Hz, CH_2CH_3) 1.29(d, 3H, J=7.3 Hz, CH_2CHCH_3) 1.67(m, 2H, CH_3CH_2CH) 3.09(m, 1H, $CH_3CH_2CHCH_3$) 7.37(s, 1H, H-pyr.)	206(28) 204(M+,38) 32(100)
3j	0.69(t, 3H, J=7.8 Hz, CH_2CH_3) 1.44(s, 6H, $CH_2C(CH_3)_2$) 2.01(q, 2H, CH_2CH_3) 7.44(s, 1H, H-pyr.)	220(32) 218(M+,50) 189(100)

TABLE 4. Elemental Analyses of 3 and 4 (Theory)

	C	H	N	Cl
3a	46.73(46.85)	5.02(4.91)	13.38(13.66)	34.55(34.57)
3b	44.02(44.01)	4.07(4.22)	14.36(14.66)	37.39(37.11)
4b	51.29(51.52)	5.88(6.05)	11.90(12.02)	30.59(30.41)
3c	41.00(40.71)	3.48(3.42)	15.98(15.82)	
4c	46.64(46.85)	4.81(4.91)	13.74(13.66)	34.72(34.57)
3d	52.24(51.97)	5.08(5.23)	12.24(12.12)	30.53(30.68)
3e	59.14(59.38)	5.58(5.69)	9.88(9.89)	24.82(25.04)
3f	51.75(51.52)	6.07(6.05)	12.02(12.02)	30.19(30.41)
3g	51.93(51.79)	2.95(3.16)	10.99(10.98)	
3h	47.28(47.32)	3.88(3.97)	13.81(13.79)	
4h	56.29(56.05)	5.42(5.49)	11.07(10.89)	
3i	47.15(46.85)	4.96(4.91)	13.69(13.66)	
4i	55.48(55.18)	7.01(6.95)	10.50(10.73)	
3j	49.63(49.33)	5.33(5.52)	13.05(12.78)	

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