The Reaction of 2-Substituted-4,5-dichloro-3(2*H*)-pyridazinones with Alkoxides and Alkylthiolates

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The reaction of 2-substituted-4,5-dichloro-3(2*H*)-pyridazinones **1a-b** with alkoxides and alkylthiolates was investigated. Regiospecific displacement of either the 4 or 5 chlorine atom could be achieved in most cases by appropriate selection of the reaction solvent.

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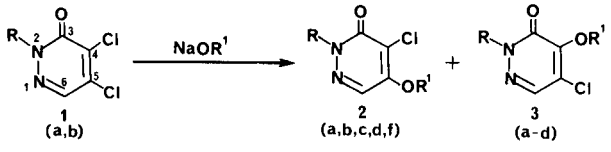
Introduction.

There have been many investigations into the reactivity of 4,5-dihalo-2-substituted-3(2*H*)-pyridazinones toward nucleophiles [1-5]. It had been generally accepted, up until the late 1970's, that the halogen at position 5 was preferentially substituted [3,4]. This preference had been explained either by considering the 5-chloro to be an activated vinylogous acid chloride [4a] or that the reaction at position 4 was suppressed due to steric reasons [4b]. Recently, both the 4- and 5-substituted compounds were obtained as a mixture when using ammonia or amines in polar aprotic solvents [5a] or solvents with a low dielectric constant ($\epsilon < 10$) [5b] and when using alkoxides in toluene or xylene [5c]. This latter work prompted us to report on our findings on the effect of solvent on product distribution using alkoxides and alkylthiolates.

Results and Discussion.

When 4,5-dichloro-2-phenyl-3(2*H*)-pyridazinone (**1a**) (see Scheme I and Table I) was treated with sodium ethoxide in ethanol or aqueous 1,4-dioxane, the 5-substituted isomer **2a** was obtained as expected [3,4,6]. When **1a** was treated with sodium ethoxide in dry 1,4-dioxane, however, the 4-substituted isomer **3a** was obtained exclusively [7]. The same results were observed with the 2-methylpyridazinone **1b** and when 2-propanol, or phenol was used in place of ethanol.

Scheme I



Due to the unexpected regiospecificity, we decided to examine the effect of a variety of solvents on product distribution (see Table II). When nonpolar solvents like carbon tetrachloride or 1,4-dioxane were used, only the 4-substituted isomer was obtained. The moderately polar solvents, 2-propanol and acetone, gave mixtures of 4- and 5-substituted products. Polar solvents like dimethylformamide and dimethyl sulfoxide afforded only the 5-substituted isomer. The only exception being acetonitrile which gave a 3:2 mixture of the 4- and 5-substituted compounds,

Table I

Compound	R	X	Z
1a	C_6H_5	Cl	Cl
1b	CH_3	Cl	Cl
2a	C_6H_5	Cl	OC_2H_5
2b	CH_3	Cl	OC_2H_5
2c	C_6H_5	Cl	$OCH(CH_3)_2$
2d	C_6H_5	Cl	OC_6H_5
2e	C_6H_5	Cl	SC_2H_5
2f	C_6H_5	Cl	OCH_3
2g	C_6H_5	Cl	$SCH_2CO_2C_2H_5$
2h	C_6H_5	Cl	SC_6H_5
3a	C_6H_5	OC_2H_5	Cl
3b	CH_3	OC_2H_5	Cl
3c	C_6H_5	$OCH(CH_3)_2$	Cl
3d	C_6H_5	OC_6H_5	Cl
3e	C_6H_5	SC_2H_5	Cl
3f	CH_3	SC_2H_5	Cl
3g	C_6H_5	$SCH_2CO_2C_2H_5$	Cl
4a	C_6H_5	$SCH_2CO_2C_2H_5$	$SCH_2CO_2C_2H_5$
4b	C_6H_5	SC_6H_5	SC_6H_5

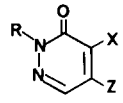


Table II (R = C_6H_5)
(see Scheme I)

Solvent	Dielectric Constant (ϵ) [a]	R'	%2 [b]	%3 [b]
CCl_4	2.23	ethyl	0	89
THF	7.32	ethyl	0	87
t-butyl alcohol	10.9	ethyl	0	81
pyridine	12.3	ethyl	0	81
2-propanol	18.3	2-propyl	45	34
acetone	20.7	ethyl	57	36
ethanol	24.3	ethyl	89	0
methanol	32.6	methyl	86	0
CH_3CN	36.2	ethyl	36	53
DMF	36.7	ethyl	88	0
DMSO	49	ethyl	75	0

[a] Source: CRC Handbook of Chemistry and Physics. [b] Isolated yield.

respectively.

We next looked at the reaction of thiols with 4,5-dichloropyridazinones (Scheme II, Table III). Treatment of **1a**

Scheme II

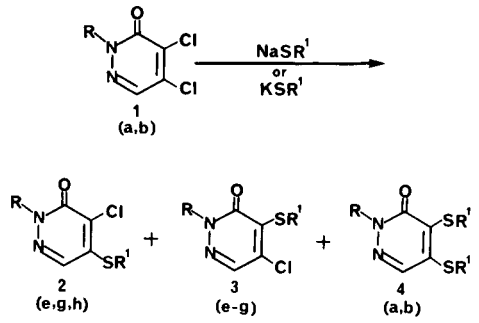


Table III (R = C_6H_5)
(see Scheme II)

Solvent [a]	R'	%2 [b]	%3 [b]	%4 [b]
A	ethyl	84	0	0
B	ethyl	0	78	0
A	$CH_2CO_2C_2H_5$	51	0	17
B	$CH_2CO_2C_2H_5$	0	39	22
A	C_6H_5	73	0	16
B	C_6H_5	0	0	45

[a] A: 1,4-dioxane/water, 8:2; B: 1,4-dioxane. [b] Isolated yield.

with ethanethiol and potassium hydroxide in aqueous 1,4-dioxane gave the 5-substituted isomer **2e** in good yield. Reaction of **1a** or **1b** with sodium ethanethiolate, generated from ethanethiol and sodium hydride, in dry 1,4-dioxane cleanly provided the 4-substituted isomer, **3e** or **3f**. The reaction of **1a** with other thiols, however, gave a slightly different result.

Treatment of **1a** in aqueous dioxane with ethyl 2-mercaptoacetate and aqueous potassium hydroxide afforded the 5-substituted isomer **2h** as the major product and the 4,5-bis-substituted adduct **4a** as a minor product along with unreacted **1a**. The same result was observed with thiophenol. Under anhydrous conditions, less regiospecificity was observed. Reaction of **1a** in anhydrous 1,4-dioxane with sodium phenylthiolate gave only the 4,5-bis material **4b** with 50% recovery of **1a**. Under the same conditions, the sodium salt of ethyl 2-mercaptoacetate gave the 4-substituted compound **3g**, and the 4,5-bis compound **4a**. In general, however, mono-substitution reactions occur at the 4-position in solvents of low dielectric constant and at the 5-position in solvents of high dielectric constant.

Konecny *et al.* have suggested that substitution at position 4, when using toluene, was favored due to the electron-withdrawing effect of the chlorine atoms and of the carbonyl group at C-4 [5c]. MNDO calculations [10], however, indicate that C-4 bears a slightly negative charge and C-5 a slightly positive charge. An alternative explanation may be that in the absence of overriding solvent effects, the driving force for the reaction at the 4-position may be due to the relief of unfavorable electrostatic interactions between the adjacent chlorine atoms and carbonyl group [11]. In solvents of high dielectric constant, polarization of the enone favors the 1,4-addition-elimination mechanism to give the 5-substituted isomer.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 735B spectrophotometer. Proton nmr spectra were recorded on a Varian T60-A (60 MHz), EM 360-L (60 MHz), Nicolet NT300 (300 MHz) or a General Electric QE300 (300 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Solvents were purchased from Baker and used directly. All other chemicals were purchased from Aldrich. Flash chromatography was performed according to the procedure of Still [8]. Elemental analyses were performed at FMC Corporation, Analytical Services Department. See Table IV for physical and analytical data.

4-Chloro-5-ethoxy-2-phenyl-3(2*H*)-pyridazinone (**2a**).

A suspension of 0.80 g (3.32 mmoles) of **1a** [3] in 20 ml of ethanol (95%) was treated with 1.3 ml of 21% sodium ethoxide in ethanol (3.32 mmoles) at room temperature. The mixture was heated at reflux for 30 minutes then poured into water and extracted with ethyl acetate. After drying over magnesium sulfate, the solvent was removed at reduced pressure to afford 0.79 g (95%) of a white solid.

Compound **2b** was prepared simularly from **1b**.

4-Chloro-5-(2-propoxy)-2-phenyl-3(2*H*)-pyridazinone (**2c**) and 5-chloro-4-(2-propoxy)-2-phenyl-3(2*H*)-pyridazinone (**3c**).

A solution of 1.0 g (4.15 mmoles) of **1a** in 25 ml of 2-propanol was stirred at room temperature as 0.166 g (4.15 mmoles) of sodium hydride (60% dispersion) was added portionwise over several minutes. After stirring for 30 minutes, the mixture was poured into water, extracted with ethyl acetate, dried over magnesium sulfate and concentrated at reduced pressure. The resulting solid was flash chromatographed (2:1, heptane/ethyl acetate) to afford 0.37 g (38%) of **2c** and 0.49 g (50%) of **3c**.

4-Chloro-5-phenoxy-2-phenyl-3(2*H*)-pyridazinone (**2d**).

A solution of 1.0 g (4.15 mmoles) of **1a** and 0.39 g (4.15 mmoles) of phenol in 40 ml of dimethylformamide and 5 ml of water was treated with 0.18 g (4.5 mmoles) of sodium hydroxide and stirred at room temperature for 1 hour. Work-up as in **2a** afforded 1.0 g (82%) of a white solid.

4-Chloro-5-ethylthio-2-phenyl-3(2*H*)-pyridazinone (**2e**).

A mixture of 1.0 g (4.14 mmoles) of **1a** in 25 ml of 1,4-dioxane and 5 ml of water was treated with 0.31 ml (0.26 g, 4.15 mmoles) of ethanethiol followed by 0.27 g (4.15 mmoles) of potassium hydroxide (85%) in 1 ml of water. The solution was stirred at 25° for 15 minutes then poured onto

Table IV

Physical and Analytical Data

Compound	Yield %	mp/bp (°C)	Molecular formula	Lit mp (°C) or Analysis (%) Calcd./Found C	H	N	IR (C=O) ν (cm^{-1})	^1H NMR (deuteriochloroform) δ (ppm)
2a	95	135-136	$C_{12}H_{11}ClN_2O_2$	140-141 [a]			1660 (KBr)	1.50 (t, CH_3, 3H), 4.40 (q, CH_2, 2H), 7.50 (m, Ar, 5H), 7.90 (s, H-6, 1H)
2b	83	100-101	$C_7H_9ClN_2O_2$	105-107 [a]			1640 (KBr)	1.47 (t, CH_3, 3H), 3.80 (s, NCH_3, 3H), 4.30 (q, CH_2, 2H), 7.73 (s, H-6, 1H)
2c	38	118-118	$C_{13}H_{13}ClN_2O_2$	119-121 [a]			1655 (KBr)	1.45 (d, CH_3, 6H), 4.83 (m, CH, 1H), 7.33-7.60 (m, Ar, 5H), 7.87 (s, H-6, 1H)
2d	82	99-100	$C_{16}H_{11}ClN_2O_2$	64.33 64.30	3.71 3.52	9.38 9.21	1660 (KBr)	7.1-7.5 (m, Ar, 10H), 7.6 (s, H-6, 1H)
2e	84	101-102	$C_{12}H_{11}ClN_2OS$	92-93 [b]			1665 (KBr)	1.47 (t, CH_3, 3H), 3.13 (q, CH_2, 2H), 7.57 (m, Ar, 5H), 7.80 (s, H-6, 1H)
2f	91	149-150	$C_{11}H_9ClN_2O_2$	154-156 [a]			1645 (KBr)	4.10 (s, CH_3, 3H), 7.40-7.60 (m, Ar, 5H), 7.90 (s, H-6, 1H)
2g	51	111-112	$C_{14}H_{13}ClN_2O_3S$	51.77 51.50	4.03 3.78	8.63 8.53	1640, 1730 (KBr)	1.27 (t, CH_3, 3H), 3.80 (s, CH_2, 2H), 4.21 (q, CH_2, 2H), 7.33-7.57 (m, Ar, 5H), 7.85 (s, H-6, 1H)
2h	73	114-116	$C_{16}H_{11}ClN_2OS$	61.05 61.27	3.52 3.66	8.90 8.64	1660 (KBr)	7.10 (s, H-6, 1H), 7.20-7.66 (m, Ar, 10H)
3a	78	85-86	$C_{12}H_{11}ClN_2O_2$	74-76 [a]			1645 (KBr)	1.43 (t, CH_3, 3H), 4.70 (q, CH_2, 2H), 7.50 (m, Ar, 5H), 7.90 (s, H-6, 1H)
3b	75	33-34	$C_7H_9ClN_2O_2$	30-32 [a]			1660 (KBr)	1.40 (t, CH_3, 3H), 3.37 (s, NCH_3, 3H), 4.46 (q, CH_2, 2H), 7.70 (s, H-6, 1H)
3c	50	bp 165 (1.4 mm Hg)	$C_{13}H_{13}ClN_2O_2$	58.99 59.09	4.95 4.73	10.58 10.54	1660 (neat)	1.37 (d, CH_3, 6H), 5.45 (m, CH, 1H), 7.36-7.57 (m, Ar, 5H), 7.84 (s, H-6, 1H)
3d	96	101-102	$C_{16}H_{11}ClN_2O_2$	64.33 64.11	3.71 3.65	9.38 9.20	1670 (KBr)	7.0-7.5 (m, Ar, 10H), 7.95 (s, H-6, 1H)
3e	78	64-65	$C_{12}H_{11}ClN_2OS$	54.03 53.75	4.16 3.98	10.30 10.32	1660 (KBr)	1.78 (t, CH_3, 3H), 3.40 (q, CH_2, 2H), 7.50 (m, Ar, 5H), 7.80 (s, H-6, 1H)
3f	79	oil	$C_7H_9ClN_2OS$	41.08 41.50	4.43 4.45	13.69 13.61	1640 (neat)	1.30 (t, CH_3, 3H), 3.42 (q, CH_2, 2H), 3.77 (s, NCH_3, 3H), 7.70 (s, H-6, 1H)
3g	39	89-90	$C_{14}H_{13}ClN_2O_3S$	51.77 51.52	4.03 3.91	8.63 8.83	1650 1750 (KBr)	1.22 (t, CH_3, 3H), 4.14 (q, CH_2, 2H), 4.20 (s, CH_2, 2H), 7.38-7.59 (m, Ar, 5H), 7.86 (s, H-6, 1H)
4a	17	oil	$C_{18}H_{20}N_2O_5S_2$	52.93 52.63	4.94 4.78	6.86 7.36	1650 1735 (neat)	1.16 (t, CH_3, 3H), 1.25 (t, CH_3, 3H), 3.75 (s, CH_2, 2H), 4.04 (s, CH_2, 2H), 4.09 (m, CH_2, 2H), 4.20 (m, CH_2, 2H), 7.50-7.96 (m, Ar, 5H), 7.84 (s, H-6, 1H)
4b	45	168-170	$C_{22}H_{16}N_2OS_2$	68.01 67.81	4.15 4.13	7.21 7.29	1660 (KBr)	7.18 (s, H-6, 1H), 7.22-7.64 (m, Ar, 10H)

[a] See reference [5c]. [b] See reference [9].

water/ethyl acetate. The organic layer was dried over magnesium sulfate, concentrated to a solid and recrystallized from ethyl acetate/heptane to afford 0.92 g (84%) of a tan solid.

4-Chloro-5-methoxy-2-phenyl-3(2*H*)-pyridazinone (**2f**).

A solution of 1.0 g (4.15 mmoles) of **1a** in 25 ml of methanol was stirred at room temperature as 0.166 g (4.15 mmoles) of sodium hydride was added portionwise over several minutes. The mixture was stirred for 1 hour then poured into water and the solid was filtered and dried to give 0.89 g (91%) of a white fluffy solid.

Reaction of **1a** with Ethyl Mercaptoacetate.

A solution of 1.0 g (4.15 mmoles) of **1a** in 25 ml of 20% aqueous 1,4-dioxane and 0.46 ml (4.15 mmoles) of ethyl mercaptoacetate was treated with 0.28 g (4.15 mmoles) of 85% potassium hydroxide in 5 ml of water. After 1 hour at room temperature the mixture was poured into water and the solid was filtered then flash chromatographed using 3:7 ethyl acetate-heptane to afford 0.69 g (51%) of **2g** and 0.23 g (17%) of **4a**.

Treatment of **1a** and ethyl mercaptoacetate as above in anhydrous dioxane with sodium hydride gave, after work-up, 0.50 g (39%) of **3g** and 0.31 g (22%) of **4a**,

Reaction of **1a** with Thiophenol.

A solution of 1 g (4.15 mmoles) of **1a** and 0.43 ml (4.15 mmoles) of thiophenol in 25 ml of 20% aqueous 1,4-dioxane was treated with 0.28 g of potassium hydroxide in 5 ml of water as above to give 0.95 g (73%) of **2h** after recrystallization from heptane-ethyl acetate. The mother liquor was concentrated then recrystallized from heptane to give 0.21 g of **4b**.

Treatment of **1a** and thiophenol as above in anhydrous 1,4-dioxane with sodium hydride gave, after work-up, 0.72 g (45%) of **4b**.

5-Chloro-4-ethoxy-2-phenyl-3(2*H*)-pyridazinone (**3a**).

A solution of 2.2 g (9.1 mmoles) of **1a** in 50 ml of 1,4-dioxane was treated either with 0.36 g (9.1 mmoles) of sodium hydride (60% dispersion) followed by 0.53 ml (0.42 g, 9.1 mmoles) of ethanol or 3.4 ml (9.1 mmoles) of 21% ethanolic sodium ethoxide and left to stir at room temperature for 16 hours. The mixture was poured into water and the solid was collected and dried to give 1.8 g (78%) of a white solid.

Compound **3d** was prepared simularly.

5-Chloro-4-ethoxy-2-methyl-3(2*H*)-pyridazinone (**3b**).

A solution of 0.8 g (4.47 mmoles) of **1b** in 20 ml of 1,4-dioxane was treated with 1.6 ml of 21% ethanolic sodium ethoxide at room temperature. After 30 minutes, the mixture was poured onto water/ethyl acetate and the organic layer was dried over magnesium sulfate and concentrated to an oil which solidified to yield 0.63 g (75%) of a tan solid.

5-Chloro-4-ethylthio-2-phenyl-3(2*H*)-pyridazinone (**3e**).

A suspension of 0.32 g (8 mmoles) of sodium hydride (60% dispersion) in 10 ml of 1,4-dioxane was treated with 0.5 ml (0.42 g, 6.7 mmoles) of ethanethiol. After the hydrogen evolution ceased, 1.6 g (6.6 mmoles) of **1a** in 25 ml of 1,4-dioxane was added. After 1 hour at 25°, the mixture was poured into water/ethyl acetate and the organic phase was dried over magnesium sulfate and concentrated to a solid which was recrystallized from heptane to yield 1.4 g (78%) of white needles.

Compound **3f** was prepared simularly from **1b**.

Solvent Effects in the Reaction of **1a** with Alkoxides. General procedure (see Table II).

A solution of 1 g (4.15 mmoles) of **1a** in 25 ml of solvent and 4.15 mmoles of the appropriate alcohol was stirred at room temperature as 0.166 g (4.15 mmoles) of sodium hydride (60% dispersion) was added in several portions. After 1 hour, the mixture was poured into water and the solid filtered, dried, and chromatographed as necessary.

Acknowledgement.

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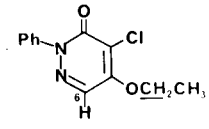
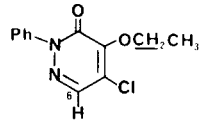
[7] Both **2a** and **3a** were subjected to an nOe experiment for structure verification. Irradiation of the methylene protons of **2a** resulted in an 8.9% enhancement of the H-6 nmr signal, whereas, irradiation of **3a** resulted in no enhancement at H-6, consistent with the structural assignment.



2a



3a

(Figure i)

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