HETEROCYCLES, Vol. 26, No 1, 1987

DEMETHYLATIONS OF METHOXYPYRIDAZINES WITH AMINES

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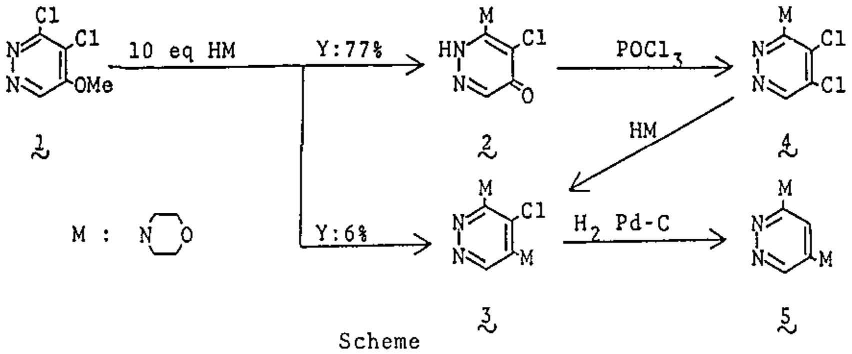
Abstract——When various pyridazines possessing the chlorine and methoxy group at 3, 4 and 5-position were treated with 10 eq. of primary and secondary amines, demethylation was observed. Demethylation of 2-methyl-methoxy-3(2H)-pyridazinones was also investigated.

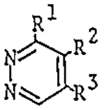
In the course of our studies on the nucleophilic substitution reactions of chloropyridazines, we found the interesting demethylation reaction of chloro-methoxypyridazines with amines. It is well documented that a methoxy group of the methoxypyridazines is replaced by amines.[1,2] However, demethylation of alkoxychloropyridazines with amines was reported only by Landquist and Meek.[3]
This paper described demethylation of chloro-methoxypyridazines and 2-methyl-methoxy-3(2H)-pyridazinones by amines.
When 3,4-dichloro-5-methoxypyridazine (1)[1] was treated with 10 eq. of morpholine, 5-chloro-6-(4-morpholinyl)-4(1H)-pyridazinone (2) and 4-chloro-3,5-di(4-morpholinyl)-pyridazine (3) were obtained in 77% and 6% yields, respectively. 4-Methylmorpholine concurrently formed was isolated in 61% yield by vacuum distilation, after an excess of morpholine was treated with phenylisocyanate and removed as a crystalline urea derivative. Reductive dechlorination of 3 gave 3,5-di(4-morpholinyl)-pyridazine (5), whose spectrum showed a pair of duoblets with a meta coupling constant (j=3 Hz) at δ 6.00 and 8.39 ascribed to 4- and 6-H, respectively. Consequently the structure of the product 3 was confirmed. The compound 3 was also derived from 4-(1H)-pyridazinone 2 by chlorination with phosphorus oxychloride leading to 4,5-dichloro-3-(4-morpholinyl)-pyridazine (4), followed by substitution of 4 with morphline. This transformation also uneqivocally determined the structures of 2 and 4. The present demethylation proceeded more smoothly under milder conditions than that of Landquist et al.[3] (Scheme)
The demethylation of some other chloro-methoxypyridazines with morpholine was futher



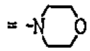
Scheme

investigated. Those results are summerized in Table 1. Among the pyridazines examined, dichloro-methoxypyridazines underwent substitution of a chlorine atom and demethylation of a methoxy group to give chloro-morpholinylpyridazinones (run 1-3). Monochloro-dimethoxypyridazines except 4-chloro-3,5-dimethoxypyridazine (Run 6) were demethylated to give chloro-methoxy-4(1H)-pyridazinones, which did not suffer the subsequent demethylation (Runs 4 and 5). The dihydroxypyridazinone was obtained by demethylation of 4-chloro-3,5-dimethoxypyridazine with morpholine (Run 6). However, 3,5-dimethoxypyridazine was not demethylated by morpholine. The results

Table 1 Reactions of some Dichloromonomethoxy and Monochlorodimethoxypyridazines with Morpholine at 100 °C

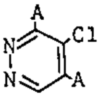
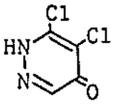


Run	Starting Materials			Reaction Time (h)	Demethylation Products				
	R^1	R^2	R^3		R^1	R^2	R^3	mp(°C)	Yield(%)
1	OMe	Cl	Cl$^{a)}$	2	OH	Cl	M	223-224	49$^{c)}$
2	Cl	OMe	Cl$^{a)}$	2	Cl	OH	M	244-245	80$^{c)}$
3	Cl	Cl	OMe$^{b)}$	2	M	Cl	OH	250(dec)	77
4	Cl	OMe	OMe$^{b)}$	2	Cl	OH	OMe	248-249	46$^{d)}$
5	OMe	OMe	Cl$^{a)}$	0.5	OMe	OH	Cl	240-241	57$^{e)}$
6	OMe	Cl	OMe$^{b)}$	2	OH	Cl	OH	267-268	79$^{f)}$

M =  a):lit.4, b):lit.1. The chloropyridazines prepared by the chlorination of the demethylated products with POCl$_3$ were identified by direct comparison with authentic samples [c):lit.5, d):lit.1, e):lit.4, f):lit.5] obtained from Run 4-6 demonstrated that demethylation of chloro-dimethoxypyridazines depends upon the position of a chlorine and a methoxy group: the methoxy group adjacent to a chlorine can be demethylated by morpholine.

The demethylation reaction of 1 with other amines was examined. Reaction with piperizine caused substitution of 3-chlorine and demethylation of 5-methoxy group to afford 5-chloro-6-(1-piperidinyl)-4(1H)-pyridazinone in 53% yield together with 4-chloro-3,5-di(1-piperidinyl)pyridazine in 10% yield. in contrast, when pyrrolidine was used, both 3-chlorine and 5-methoxy group were substituted by pyrrolidine. Primary and secondary alkyl amines caused the demethylation reaction of 5-methoxy group to give 5,6-dichloro-4(1H)-pyridazinone in moderate yields. Benzylamine and aniline did not react with 1.

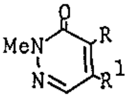
Table 2 Reactions of 3,4-Dichloro-5-methoxypyridazine (1) with Amines at 100°C for 2 h.

							
Run	Amines	mp	Yield	mp	Yield	mp	yield****
NO	(AH)	(°C)	(%)	(°C)	(%)	(°C)	(%)
1	NH	195(dec)	53***	81-83	10***		—
2	NH*	210(dec)	2***	136-137	88***		—
3	$(Et)_2NH$**		—		—	210(dec)	60
4	NH		—		—	210(dec)	49
5	$n\text{-}C_4H_9NH$		—		—	210(dec)	62

* Reflux ** Sealed tube *** The products were identified by same manner as illustrated in scheme. **** The product was proved to be 5,6-dichloro-4(1H)-pyridazinone by the convertion into 3,4,5-trichloropyridazine.[5]

The demethylation of 2-methyl-methoxy-3(2H)-pyridazinones with morpholine was also investigated. The pyridazinones having a chlorine were demethylated in good yields. In the non-chlorinated compounds, 4-methoxy group adjacent to the carbonyl group was demethylated easier than 5-methoxy group.

Table 3 Reaction of 2-Methyl-methoxy-3(2_H_)-pyridazinones with Morpholine at 100 °C for 2 h.



Run	Starting Materials			Reaction Products		mp	Yield(%)	
	R	R^1		R	R^1			
1	Cl	OMe	(lit.7)	Cl	OH	257-258	72	(lit.8)
2	OMe	H	*	OH	H	173-174	38***	(lit.9)
3	OMe	Cl	**	OH	Cl	216	94	(lit.10)
4	OMe	OMe	**	OH	OMe	162	68	(lit.9)

* Starting material was prepared by reductive dechlorination of 5-chloro-4-methoxy-2-methyl-3(2_H_)-pyridazinone. ** Starting materials of Run 3 and 4 were prepared by methoxylation of 4,5-dichloro-2-methyl-3(2_H_)-pyridazinone with NaOMe in benzene and toluene, respectively. *** tarting material was recoverd: 22%.

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Received, 13th June, 1986