DISPLACEMENT REACTIONS OF 2-ALKYLSULFONYL-4-CHLOROPYRIMIDINE DERIVATIVES WITH NUCLEOPHILES

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The displacement reactions of 4-chloro-2-ethylsulfonyl-6-phenyl-, 4-chloro-2-ethylsulfonyl- and 4-chloro-6-methyl-2-methylsulfonyl-pyrimidine with ammonia gave the corresponding 4-alkylsulfonyl-2-aminopyrimidine derivatives in which the alkylsulfonyl groups migrated from the 2-position to the 4-position. In addition, it was found that the relative ease of displacement of sulfonyl group versus chloro group in the nucleophilic substitution of 2- and 6-alkylsulfonyl-4-chloro-pyrimidine derivatives depended on nucleophiles.

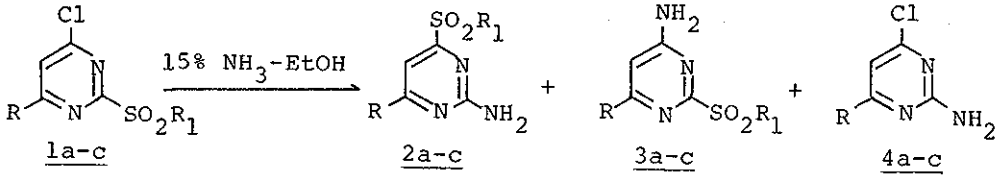
In the course of a research on pyrimidine derivatives possessing antihypertensive activities, the investigation on the displacement reactions of 4-chloro-2-ethylsulfonyl-6-phenylpyrimidine (1a) with some nitrogen nucleophiles became necessary. Sprague[1] and Chi[2] previously reported that the ammonolyses of the analogous 5-alkyl-4-chloro-2-ethylsulfonylpyrimidines gave the corresponding 5-alkyl-4-amino-2-ethylsulfonylpyrimidines in which ethylsulfonyl group remained intact, while the ammonolysis of 1a gave 2-amino-4-ethylsulfonyl-6-phenylpyrimidine (2a) as a major product against expectation. This communication deals with migrations of the alkyl-

sufonyl groups and the relative ease of displacement of sulfonyl group versus chloro group in 2- and 6-alkylsulfonyl-4-chloropyrimidine derivatives.

Treatment of 1a with 15% NH_3-EtOH in a sealed tube at 110° for 1.5 hr, gave two amino-ethylsulfonyl-6-phenylpyrimidines (2a and 3a) and 4-chloro-2-ethoxy-6-phenylpyrimidine [11, mp 58.5-59° (n-hexane), 9% yield†]. The structures of 2a [mp 177-8° (EtOH), 54% yield†, mass spectrum(m/e): 263(M^+), 128(base peak), nmr(DMSO-d_6) : 7.56 ppm(s, 1H: C_5-H)] and 3a [mp 195-6°(iso-propanol), 9% yield†, mass spectrum(m/e): 263(M^+), 128(base peak), nmr(DMSO-d_6): 7.06 ppm (s, 1H: C_5-H)] were speculated to be 2-amino-4-ethylsulfonyl-6-phenylpyrimidine and 4-amino-2-ethylsulfonyl-6-phenylpyrimidine, respectively. Their structures were confirmed by means of the unequivocal syntheses of 2a and 3a by oxidations of 2-amino-4-ethylthio-6-phenyl- and 4-amino-2-ethylthio-6-phenyl-pyrimidine with m-chloroperbenzoic acid, respectively. Such a migration of an alkylsulfonyl group from the 2-position to the 4-position in a pyrimidine ring was also observed in each ammonolysis of 1b and 1c. The ammonolyses of 1a-c at room temperature, however, gave mainly the corresponding 2-amino-4-chloropyrimidine derivatives (4a, 4b and 4c) which were considered to be the precursors of 2a, 2b and 2c, respectively (Table 1). Actually, the reaction of the mixture of 1b and 4a with 15% NH_3-EtOH in a sealed tube at 120° for 2 hr gave 2a in 39% yield† (Scheme 1). Therefore, the migration of the sulfonyl groups mentioned above proved to be due to the intermolecular rearrangement.

Our finding described above is contrary to that of Sprague[1] and

Table 1

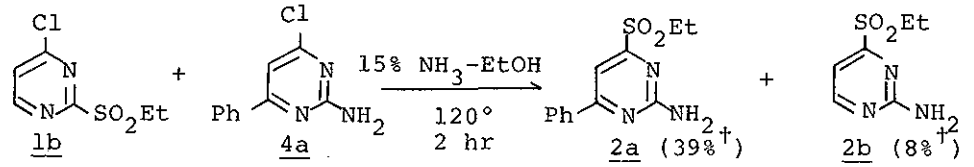


1a-c 2a-c 3a-c 4a-c

1			2 (%†)	3 (%†)	4 (%†)
a	R=Ph R_1=Et	110°	54	9	0
		r.t.[a]	12	10	37
b	R=H R_1=Et	100°	35	4	5
		r.t.[a]	0	2	61
c	R=R_1=Me	r.t.[a]	4	trace	51

a) Chloroform was added to dissolve the substrate.

Scheme 1



1b + 4a → 2a (39%†) + 2b (8%†)

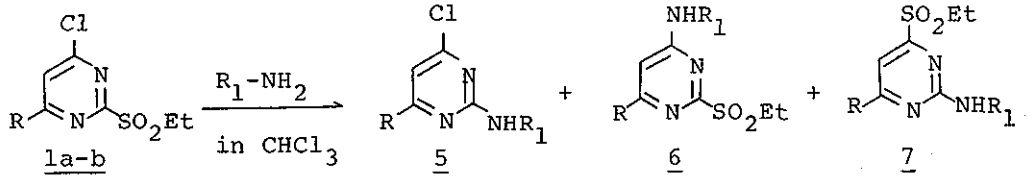
Chi^2 in respect of the preferred leaving group. This might be explained in terms of the influence of the presence of an alkyl-substituent at the 5-position in 2-alkylsulfonyl-4-chloro-pyrimidine system.

In the displacement reactions of 1a-b with primary amines at room temperature, the sulfonyl groups were a little more liable to be displaced by the corresponding amino groups than the chloro groups without migrations of the sulfonyl groups. On treatment of 1a with benzylamine under heating, the similar migration of the sulfonyl group was observed. In the case of aniline, however, the

displacement of the chloro group occured exclusively (Table 2).

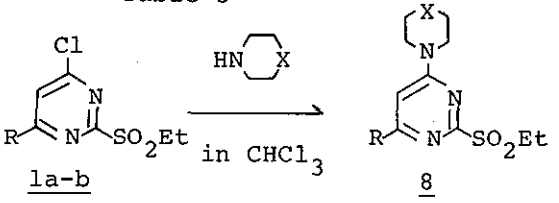
In addition, treatment of 1a-b with secondary amines gave 8 selectively (Table 3).

Table 2



1	R_1-NH_2		5 (%†)	6 (%†)	7 (%†)
R=Ph	$PhCH_2NH_2$	r.t.	46	28	0
		115°	16	32	19
	CH_3NH_2-EtOH	r.t.	45	10	0
R=H		r.t.	50	32	0
R=Ph	Ph-NH_2	reflux	0	82	0

Table 3



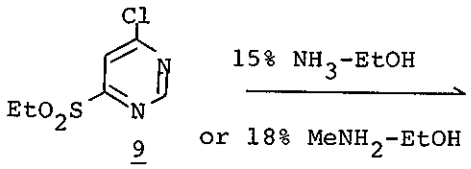
R	X	%†
Ph	-O-	88
	$-CH_2-$	93
	>NMe	73
	$>NCH_2CH_2OH$	97
H	-O-	67

The result described above showed that the selectivity of these two leaving groups in the displacement reaction of 1a-c with a nitrogen nucleophile was affected to a great extent by the bulkiness rather than the basicity of the nucleophile because of

the considerable bulkiness of the sulfonyl group.

On the other hand, Cheng[3] showed that in the reactions of 4-chloro-6-methylsulfonylpyrimidine with secondary and aromatic amines, the chloro groups were selectively displaced by the amino groups. In confirmation of our above-mentioned conception concerning selectivity, the ammonolysis and the methylaminolysis of 4-chloro-6-ethylsulfonylpyrimidine (9) were investigated. Treatment of 9 with 15% NH_3-EtOH and 18% CH_3NH_2-EtOH at room temperature, gave exclusively 4-amino-6-chloro- and 4-chloro-6-methylamino-pyrimidine, respectively, as expected (Table 4).

Table 4



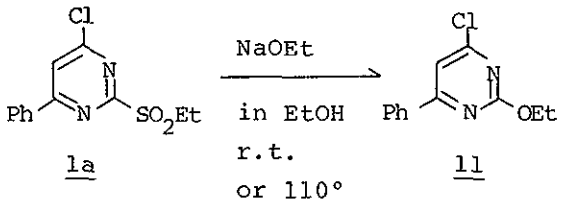
9 10

R	% †
H	48 a)
CH_3	81

a) This low yield is due to that the product is easily soluble in water.

As to an oxygen nucleophile, reaction of 1a with sodium ethoxide in ethanol at room temperature afforded exclusively 4-chloro-2-ethoxy-6-phenylpyrimidine (11) (Scheme 2). The migration of the ethylsulfonyl group, however, did not take place even at a higher temperature at 110° in contrast with results in ammonolyses of 1. The above-mentioned result provides an interesting aspect on

Scheme 2



1a 11

behavior of an alkylsulfonyl group as a leaving group.

On the other hand, a carbon nucleophile such as sodium cyanide in dimethyl sulfoxide in a series of 5-halo-2-methylsulfonylpyrimidines was reported[4] to attack the 2-position to afford 2-cyano-5-halopyrimidine and, at elevated temperature above 100°, to afford 2-cyano-5-methylsulfonylpyrimidine.

Thus, the further investigation on the displacement reaction of the alkylsulfonyl-chloropyrimidine system with other nucleophiles such as sulfur and carbon nucleophiles is of much interest.

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REFERENCES AND NOTES

† Yields in all reactions were isolating yields.

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