INTRAMOLECULAR CYCLOADDITION OF 2-(2-ALLYLPHENOXY)PYRIMIDINES

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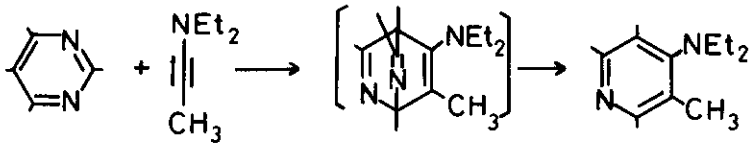
Abstract — Novel ring fused heterocycles, 3, 10a-(11-azaetheno)-3,4,4a,10a-tetrahydro-[1]benzopyrano[2,3-b]pyridines were synthesized by the reaction of 2-chloropyrimidines with 2-allylphenols in the presence of a base. These compounds were formed by the intramolecular cycloaddition of initially formed 2-(2-allylphenoxy)pyrimidines.

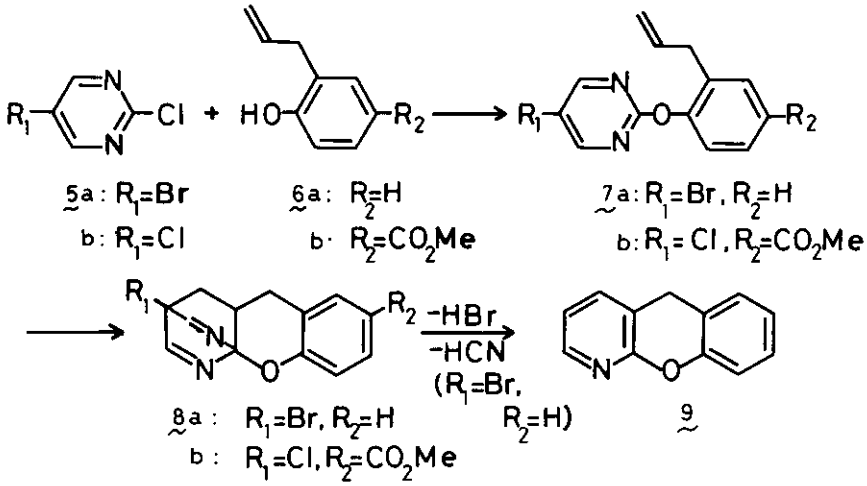
Few papers have been published on Diels-Alder reactions of pyrimidine derivatives. Recently, Neunhoeffer and Werner[1] obtained pyridines by the reaction of 1-diethylaminopropyne with pyrimidines having a methoxycarbonyl group as substituents. They proposed 3 as plausible intermediates, but failed to isolate these compounds. In the course of studies on the synthesis and chemistry of phenoxypyrimidines as potential fungicides and herbicides[2], we noticed that the adducts similar to 3 can really be obtained as stable compounds under appropriate conditions.



1 2 3 4

Thus, an equimolar mixture of 5-bromo-2-chloropyrimidine (5a), 2-allylphenol (6a) and K_2CO_3 was heated at 150° for 2 hr. Extraction of the reaction mixture with ether and column chromatography of the extracts over silica gel gave [1]benzopyrano[2,3-b]pyridine; 9, mp 83-84° (87-88°)[3] in 27 % yield. Refluxing 5a and 6a

in benzene in the presence of sodium gave rise to 2-(2-allylphenoxy)-5-bromopyrimidine (7a) in 71 % yield. When 7a was refluxed in diethylaniline for 1 hr, 9 was produced in 8 % yield. From these results, the intermediacy of the adduct 8a was evident, but it could not be isolated.

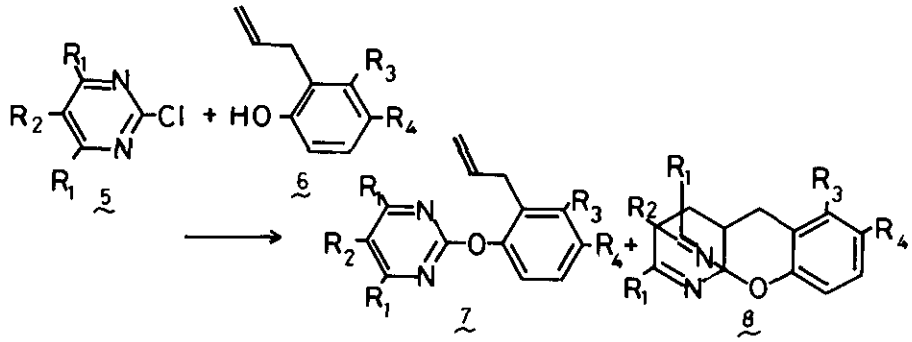


On the other hand, a mixture of 2,5-dichloropyrimidine (5b), methyl 3-allyl-4-hydroxybenzoate (6b) and sodium was allowed to reacte in refluxing xylene for 27 hr. The xylene was evaporated in vacuo, the residue was treated with benzene, and the insoluble solid was collected by filtration to give the adduct, 3-chloro-7-methoxycarbonyl-3,10a-(11-azaetheno)-3,4,4a,10a-tetrahydro-[1]benzopyrano[2,3-b]-pyridine; 8b, 24 %, mp 178-181° (dec), ν_{max}^{nujol} cm^{-1}: 1710, δ (DMSO-d_6): ca 1.5 (1H, m, 4a-H), 2.0-2.6 (4H, m, 4,5-H), 3.82 (3H, s, OCH_3), 7.17 (1H, d, J=8 Hz, 9-H), 7.74 (1H, d, J=2.5 Hz, 6-H), 7.84 (1H, dd, J=2.5 and 8 Hz, 8-H), 8.19 (2H, s, 2,12-H). The benzene solution was evaporated in vacuo and the residue was purified by column chromatography over silica gel to give 2-(2-allyl-4-methoxycarbonylphenoxy)-5-chloropyrimidine; 7b, 30 %, mp 75-76.5° (hexane), ν_{max}^{nujol} cm^{-1}: 1710 (COOMe). The NMR spectrum of 8b showed aliphatic proton signals ascribable to $-CH_2CHCH_2-$ in rather high field and did not exhibit any allylic proton signals. The formation of stable Diels-Alder adduct such as 8b is in sharp contrast with our previous findings in the pyridazine series. Namely, no adducts of these types have ever been isolated in the intramolecular cycloaddition of 3-(2-allylphenoxy)-pyridazines[4].

In order to clarify the scope and limitation of this novel intramolecular cycloaddition, the reaction of various pyrimidines with 2-allylphenols[5] were carried

out under similar conditions (Table I). Generally speaking, the yields of adducts were better with pyrimidines having halogen atom on the 5-position. An attempt to isolate the adduct (8a) from 5a and 6a by method A failed. On the other hand, the pyrimidine (5, R_1=CH_3, R_2=Br) gave the adduct (8c) in 25 and 9 % yields by method A and B, respectively, and did not produce the benzopyranopyridine like 9 under the conditions of both methods. These results will be attributed to the difference in stability between the two adducts. The HCN moiety in the former should be more readily eliminated than the CH_3CN in the latter.

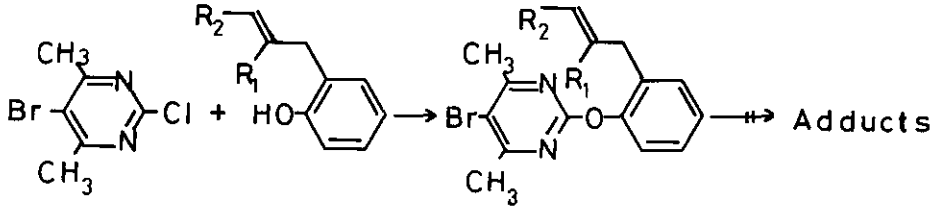
Table I. Reaction of 2-chloropyrimidines (5) with 2-allylphenols (6)



Run	R_1	R_2	R_3	R_4	Condition[a]	7 Yield (%)	7 Mp or bp (°C)	8 Yield (%)	8 Mp (°C)
a	H	Br	H	H	A	14	150-155(0.15 mm)	-	
c	CH_3	Br	H	H	A	39	150-158(0.02 mm)	25	166-167[b]
					B	37		7	
d	CH_3	Br	H	CH_3	A	40	170(0.3 mm)	19	171-172[b]
e	CH_3	Br	H	CH_3O	A	67	81[c]	9	166[b]
f	CH_3	Br	H	NO_2	B	17	77.5[c]	24	201-204[d]
g	CH_3	Br	H	COOEt	B	27	106-107[c]	27	182[b]
h	CH_3	Br			A	16	112[c]	43	193-195[b]
i	CH_3	H	H	H	A	78	132-136(0.2 mm)	5	201[b]
j	CH_3	CH_3	H	H	A	56	e)	7	190-193[b]

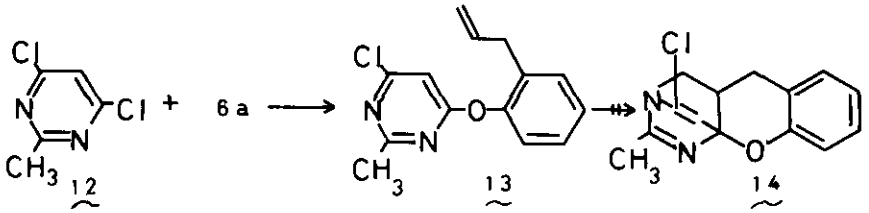
a) A: Refluxing in xylene in the presence of Na for 7-13 hr. B: Heating with K_2CO_3 at 150° for 1-7 hr. b) Recrystd from hexane-AcOEt. c) Recrystd from hexane. d) Recrystd from AcOEt. e) n_D^{24} 1.5588.

In the case of 2-(3-methylallyl)phenol (10a) and 2-(2-methylallyl)phenol (10b), only the ethers (11a and 11b) were obtained and the formation of adducts were not observed even after prolonged heating (7 hr, Method B). This may be attributed to a steric hyndrance of the methyl group in the transition state.



10a: R_1=H, R_2=Me 11a: R_1=H, R_2=Me
b: R_1=Me, R_2=H b: R_1=Me, R_2=H

Finally, heating 4,6-dichloro-2-methylpyrimidine (12) with 6a in the presence of K_2CO_3 at 160° for 7 hr afforded the ether (13) as sole product, and the possible adduct (14) could not be obtained.



Thus, the present experiments show that novel ring fused heterocycles can be obtained by the intramolecular cycloaddition of 2-(2-allylphenoxy)pyrimidines which are obtainable by the reaction of 2-chloropyrimidines with 2-allylphenols in the presence of a base.

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