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SYNTHESIS OF NOVEL 1,4-, 3,4-, AND 4,5-DIHYDROPYRIMIDINES: FIRST SUCCESSFUL $POCl_3$ CHLORINATION AND REGIOSELECTIVE ALKOXYCARBONYLATION

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Summary: Chlorination of 5,6-dihydropyrimidine-4-(3H)-one derivatives (1) with $POCl_3$ gave 1,4(3,4)-dihydropyrimidines (3), whose alkoxycarbonylation ($ClCOOR^3$-Et_3N or NaH) afforded regioselectively novel compounds (4). A new Pummerer type rearrangement of compound (1, X=p-$S(O)CH_3$) with $POCl_3$ gave compound (5h).

The chemistry of dihydropyrimidine derivatives has not been sufficiently investigated, because of the instability by air oxidation and the possibility of ambiguous chemical structures by isomerization or tautomerism.[1)]

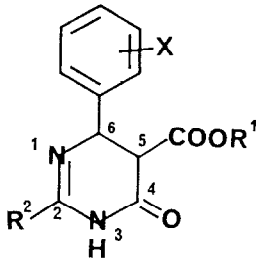
In this communication, we wish to disclose the synthesis of the novel various dihydropyrimidine derivatives (2), (3), and (4) from compound (1),[2)] specifically using first successful $POCl_3$ chlorination and regioselective alkoxycarbonylation.

Treatment of 5,6-dihydropyrimidin-4(3H)-one (1a)(X=H, R^1=Et, R^2=Me) with Meerwein reagent (1.0 eq of Et_3OBF_4/CH_2Cl_2, r.t. 17 hr) or of compound (1b)(X=m-Br, R^1=R^2=Me) with 1.0-1.3 eq of dimethyl sulfate-10 eq of K_2CO_3 at r.t. in MeOH afforded 4,5-dihydropyrimidines (2a) or (2b), respectively.[3)] The chemical structure of (2) was confirmed by the NMR spectrum. (See Table)

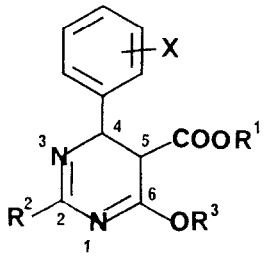
A survey of the literature reveals no example of synthesis (isolation) of a chloro-dihydroheterocycle from an amide using $POCl_3$. Folkers et al. tried to obtain 5-carbethoxy-2-chloro-6-methyl-4-phenyl-1,4-dihydropyrimidine by the reaction of 5-carbethoxy-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine with $POCl_3$. However, they could not isolate the unstable compound. Interestingly, chlorination of compound (1) with excess $POCl_3$ under reflux for 20-30 min gave a series of compounds (3a)-(3g) as the tautomer of 1,4- and 3,4-dihydropyrimidines in good yield. The possibility of 4,5-dihydropyrimidine was ruled out, because the NMR spectra indicated a methine proton α to the phenyl ring between δ 5.5 and 6.2 as a broad singlet in the case of (3a)-(3g).

The generality of these reactions is illustrated by the fact that they can be applied to 5-alkoxycarbonyl-5,6-dihydropyrimidin-4(3H)-one derivatives (1) which have thienyl, pyridyl, or furyl group instead of the substituted phenyl group. Thus, compounds (2i-k) and (3j)(3k) were obtained in a similar manner.

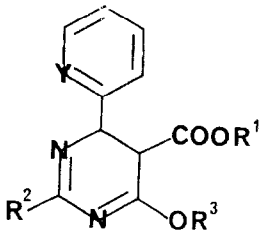
Next, alkoxycarbonylation of dihydropyrimidine (3) with alkyl chloroformate was investigated. Treating dihydropyrimidine (3) with 4.5 eq of $ClCOOR^3$(R^3=Me, Et) and 5 eq of Et_3N in $CHCl_3$ at r.t. for 15 hr yielded regio-



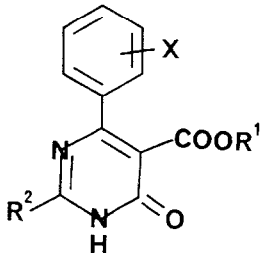
1



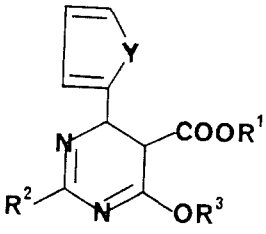
2 a , b



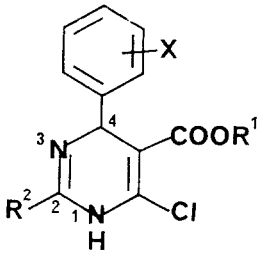
2 i , Y = N

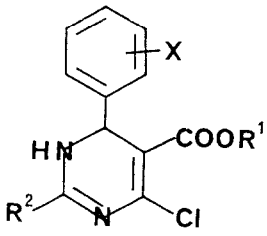


6 e

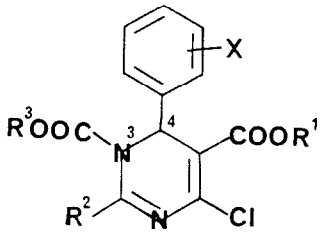


2 j , Y = S
k , Y = O

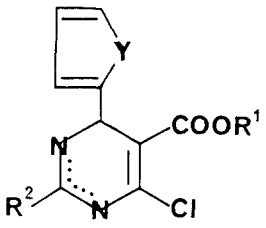




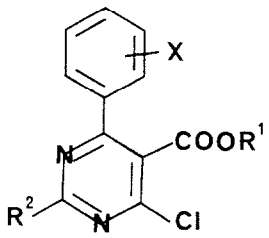
3 a - g



4 a , b , l , m



3 j , Y = S
k , Y = O



5 e - h

Table

#	R^1	R^2	R^3	X or Y	Yield(%)	mp °C(solv)	Typical Signal of NMR*1	UV λ_{max}^{MeOH} (nm)
2a	Et	Me	Et	H	42	oil	δ 3.49 (1H, d, J=12 Hz)	
							4.92 (1H, brd*2)	
2b	Me	Me	Me	m-Br	44	oil	3.43 (1H, d, J=12 Hz)	
							4.84 (1H, brd)	
2i	Et	Me	Me	N	39	oil	3.94 (1H, d, J=10 Hz)	
							5.05 (1H, brd)	260 (ε 2600)
2j	Et	Me	Et	S	23	oil	3.54 (1H, d, J=10 Hz)	
							5.21 (1H, brd)	
2k	Et	Me	Et	O	21	oil	3.66 (1H, d, J=10 Hz)	
							5.07 (1H, brd)	
3a	Et	Me	--	H	60	155-156 (Et_2O-acetone)	5.50 (1H, s)	
3b	Et	Me	--	o-Cl	77	126-127 (AcOEt-Et_2O-C_6H_{14})	6.20 (1H, s)	
3c	Et	Me	--	o-NO_2	87	oil	5.93 (1H, s)	313 (ε 4100)
3d	Et	Me	--	m-NO_2	64	199-201 (HCl salts, Et_2O-MeOH)	6.03 (1H, s)	
3e	Et	Me	--	p-SMe	27	182-187 (Et_2O-MeOH)	5.76 (1H, s)	
3f	Et	NMe_2	--	m-NO_2	66	135-137 (Et_2O-acetone)	5.62 (1H, s)	
3g	Et	C_6H_5	--	p-SMe	81	146-149 (HCl salts, Et_2O-MeOH)	5.60 (1H, s)	
3j	Et	Me	--	S	74	oil	5.83 (1H, s)	330 (ε 5500)
3k	Et	Me	--	O	54	oil	5.65 (1H, s)	
4a	Et	Me	Et	m-NO_2	76	97-98 (acetone-C_6H_{14})	6.39 (1H, s)	
4b	Me	Me	Me	m-NO_2	63	128-129 (AcOEt-C_6H_{14})	6.40 (1H, s)	314 (ε 6400)
4l	Et	Me	C_6H_{13}	p-SMe	93	oil	6.25 (1H, s)	
4m	Et	Me	C_6H_{13}	m-NO_2	68	oil	6.39 (1H, s)	
5e	Et	Me	--	p-SMe	43	oil		
5f	Et	NMe_2	--	m-NO_2	38	oil		
5g	Et	C_6H_5	--	p-SMe	88	92-93 ---		
5h	Et	Me	--	p-SCH_2Cl	99	oil		
6e	Et	Me	--	p-SMe	20	oil		

*1 All NMR spectra (60 MHz) were recorded in $CDCl_3$ solution with tetramethylsilane as an internal standard using free form dihydropyrimidines.

*2 All brd signals---The long range coupling between this proton and the methyl protons at position-2 was also observed.

selectively a sole compound, 4-aryl-6-chloro-3,5-dialkoxycarbonyl-2-methyl-3,4-dihydropyrimidine (4a) or (4b) in good yield, whose structure was proved by proton NMR and carbon 13 NMR (long range selective proton decoupling (LSPD) experiment). Namely, C-4 methine proton and 2-methyl group of (4a) appeared at δ 6.39 and 2.48, respectively, as sharp singlets. Moreover, by LSPD experiment the carbonyl carbon(152.41 ppm) in the 3-ester group coupled with the methine proton (3 bond coupling) and the coupling constant (J=2.9 Hz) was exactly same as that of the carbonyl carbon (163.23 ppm) in the 5-ester group and the methine proton. Similarly, by treating (3) with 1.1 eq of NaH and 2.5

eq of $ClCOOC_6H_{13}$ in THF or dioxane at 80 °C for 1-2 hr, alkoxycarbonylation occurred to give (4l) or (4m).

This interesting regioselectivity can be rationalized in two ways. Since the dihydropyrimidine ring bears almost perpendicularly the phenyl ring at the 4-position, the nitrogen atom between the 2-methyl and the 4-phenyl group in the molecule (3) should be less hindered than that between the 2-methyl and the 6-chloro group. Therefore, the reagent should approach more easily to the 3-position. Moreover, considering the possible resonance structures of (3), nitrogen at the 3-position should have a greater electron density than the N-1 position.

In the reaction of compound (1) (X=p-$S(O)CH_3$, R^1=Et, R^2=Me) with $POCl_3$ a novel Pummerer type rearrangement (usually, of sulfoxides with acyclic anhydrides) occurred with air oxidation of the dihydropyrimidine ring to afford quantitatively the pyrimidine derivative (5h) (X=p-SCH_2Cl). NMR ($CDCl_3$) δ 4.95 (-SCH_2Cl)(High resolution Mass; Calcd, 356.0150; Found, 356.0140).

On the contrary, in the case of compound (1)(X=p-SMe, R^1=Et, R^2=Me), usual chlorination reaction proceeded without oxidation to give the dihydropyrimidine (3e) or (3g).

Finally, dichlorodicyanoquinone oxidation (1.2 eq of DDQ in benzene, reflux, 1 hr) of 5,6-dihydropyrimidin-4-one (1) or dihydropyrimidine (3e)-(3g) afforded 4-pyrimidone (6) or pyrimidine derivative (5e)-(5g), but 4,5-dihydropyrimidine (2) could not be oxidized with DDQ.

According to our experiences, no isomerization of C-5 and C-6 double bond of (3) and (4) or C-1 and C-6 double bond of (2) was observed in these dihydropyrimidines. Moreover, they are fairly stable against air oxidation and sunlight.

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