SYNTHESIS OF NOVEL 5-ALKOXYCARBONYL-5,6-DIHYDROPYRIMIDIN-4(3H)-ONES FROM 3-SUBSTITUTED 2-ALKOXYCARBONYL-2-PROPENOATES AND AMIDINES

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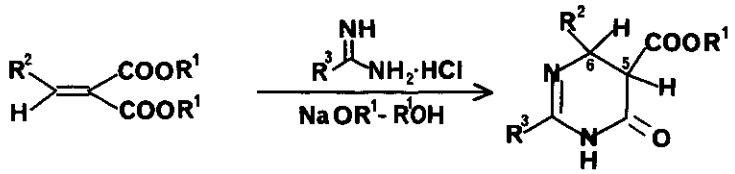
Abstract—— A cyclization of 3-substituted 2-alkoxycarbonyl-2-propenoates with acetamidine, benzamidine, guanidine, or 1,1-dimethylguanidine hydrochloride in the presence of 1-2 eq of metal alkoxide afforded novel 5-alkoxycarbonyl-5,6-dihydropyrimidin-4(3H)-ones in good yield (R^1=Me, Et, ^{i}Pr; R^2=phenyl, furyl, thienyl, pyridyl, alkyl; R^3=Me, C_6H_5, NH_2, NMe_2). Substitution of a functional group on the phenyl ring influenced the trans-cis relationship between the 5-proton and the 6-proton of the dihydropyrimidone skeleton, namely the ratio of trans/cis increased from ortho substitution (3/2-2/1) and meta (9/1) to para (only trans).

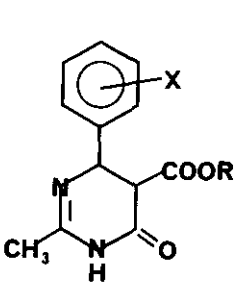
Various cyclizations of α,β-unsaturated carbonyl compounds with amidines were reported to afford pyrimidone or pyrimidine derivatives.[1] In such cases the compound has a good leaving group at a position β to a carbonyl group. However, a survey of the literature reveals only a few papers[2] on cyclizations of amidines with 3-aryl-2-propenals or 2-propenal (acrolein) and no reactions of amidines with 3-aryl-2-propenoates which have no leaving group at the β position. By the latter reactions several types of hydroxytetrahydropyrimidines and dihydropyrimidones can be obtained, respectively.



As a part of investigations on the synthesis of new heterocyclic compounds with potent biological activity, it became necessary to study the preparation of 5-alkoxycarbonyl-5,6-dihydropyrimidin-4(3H)-one derivatives. In this communication, we wish to report briefly a facile synthesis of novel 5-alkoxycarbonyl-6-aryl(or alkyl)-5,6-dihydropyrimidin-4(3H)-ones.

A mixture of 1.0 eq of diethyl benzylidenemalonate and 1.1 eq of acetamidine hydrochloride in the presence of 2.0 eq of NaOEt in EtOH was refluxed for 1 h under Ar. After evaporation of alcohol, the residue was dissolved in $CHCl_3$ and washed with brine, dried and evaporated to leave the compound (1a)[3] in 87% yield. Similarly, several derivatives (1b-1j) were synthesized in good yield (see table). The position of the C=N double bond was determined as shown in the figure, because of the long range coupling (J=1-2 Hz) of the methyl group with the methine proton α to the aromatic ring. Among some bases, metal alkoxide is the most suitable base to afford free amidine from the corresponding hydrochloride. The cyclization appears to be initiated via Michael addition of acetamidine to a double bond and then to complete the cyclization with an ester group. The position of the functional group on the aromatic ring of the compound influenced the ratio of stereoisomers Namely, both the compounds (1b)(X=o-NO_2) and (1d)(X=o-Br) consist of the isomers (trans/cis=2/1)(trans $J_{5,6}$=12.0 Hz, cis $J_{5,6}$=6.5 Hz). Differentiation between trans and cis signals is clear in (1d) and (7d) at the 5-proton and the 6-proton but in other examples trans protons often overlap cis protons. However, the NMR signal at C-5 ethyl or C-2 methyl group and TLC behavior prove them to be stereoisomers. The ratio of stereoisomers increased from ortho substitution (2/1) and meta (9/1) to para. Usually, a para-substituted compound was obtained stereoselectively as the trans isomer. Presumably, this is due to the repulsion between the ester group and ortho nitro or ortho bromo group.

Although the para-substituted dihydropyrimidones (p-CN, p-SMe, p-Br) were easily prepared as described above, an exceptional result was observed in the case of the p-NO_2 derivative (2).[4] The cyclization of 1.0 eq of 2-ethoxycarbonyl-3-p-nitrophenyl-2-propenoate with 1.0 eq of acetamidine hydrochloride in the presence of 2.0 eq of NaOEt gave both dihydropyrimidone (1k) and 4-pyrimidone (2) in 40% and 15 % yield, respectively. Therefore, we examined some reaction conditions in detail. It was interesting to find that the choice of 1.0 eq of NaOEt and 0.5 eq of the ester to 1.0 eq of acetamidine hydrochloride was necessary to obtain exclusively the desired dihydropyrimidone (1k) in 74% yield. This type of reaction can be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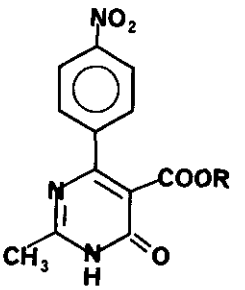
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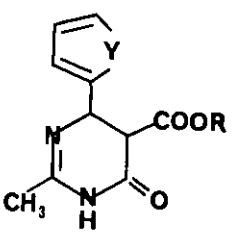
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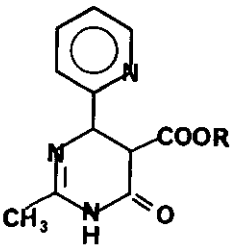
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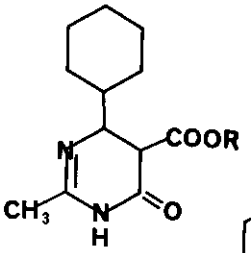
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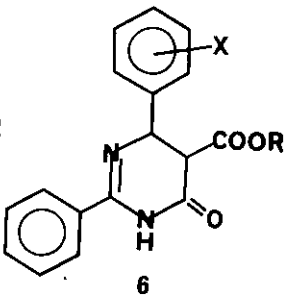
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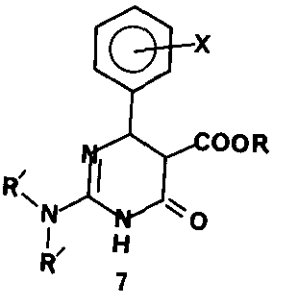
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Table

No	Compound	X or Y	R	Base/ROH	Yield	mp °C (solvent)	NMR(δ) 5&6 protons J=Hz
1	1a	H	Et	NaOEt/EtOH	87%	129-131° (Me_2CO-$n\text{-}C_6H_{14}$)	3.46 (1H, d, J=12), 5.00 (1H, dd, J=12, 2)
2	1b	o-NO_2	Et	NaOEt/EtOH	77%	oil	3.86 (1H, d, J=12), 5.60 (1H, brd, J=12, 1)
3	1c	m-NO_2	Et	NaOEt/EtOH	64%	110-115° (C_6H_6-C_6H_{14})	3.47 (1H, d, J=12), 5.13 (1H, dd, J=12, 2)
4	1d	o-Br	Et	NaOEt/EtOH	70%	oil	trans 3.76 (1H, d, J=10.5), 5.59 (1H, brd, J=10.5, 0.5); cis 3.99 (1H, d, J=6.5), 5.29 (1H, dd, J=6.5, 2)
5	1e	m-Br	Et	NaOEt/EtOH	87%	oil	3.40 (1H, d, J=12), 4.87 (1H, brd, J=12, 1)
6	1f	p-Br	Et	NaOEt/EtOH	55%	oil	3.39 (1H, d, J=12) 4.92 (1H, brd, J=12, 0.5)
7	1g	p-CN	Me	NaOMe/MeOH	56%	178-180° (C_6H_{14}-$CHCl_3$)	3.45 (1H, d, J=12), 5.07 (1H, brd, J=12, 1)
8	1h	p-SMe	^{i}Pr	NaO^{i}Pr/^{i}PrOH	31%	109-110° (Et_2O)	3.40 (1H, d, J=12), 4.97 (1H, brd, J=12, 0.2)
9	1i	2,6-diCl	Et	NaOEt/EtOH	53%	135-136.5° (EtOH-C_6H_{14})	4.28 (1H, d, J=12), 5.89 (1H, dd, J=12, 2.7)
10	1j	3,4,5-triOMe	Et	NaOEt/EtOH	90%	powder	3.50 (1H, d, J=12), 4.94 (1H, d, J=12)
11	1k	p-NO_2	Et	NaOEt/EtOH	74%	oil	3.46 (1H, d, J=12), 5.15 (1H, brd, J=12, 0.5)
12	2	p-NO_2	Et	NaOEt/EtOH	40%	226-229° (MeCOOEt-C_6H_{14})	----
13	3a	O	Et	NaOEt/EtOH	65%	94-95.5° (Et_2O-C_6H_{14})	3.67 (1H, d, J=10), 5.15 (1H, dd, J=10, 1)
14	3b	S	Et	NaOEt/EtOH	64%	76-79° (Et_2O-C_6H_{14})	3.55 (1H, d, J=10), 5.34 (1H, dd, J=10, 1.5)

No	Compound	X	R or R'	Base/ROH	Yield	mp°C	(solvent)	NMR(δ) 5&6 protons J=Hz
15	4	----	Et	NaOEt/EtOH	86%	108-110°	(C_6H_{14}-Et_2O -Me_2CO)	3.95 (1H, d, J=10), 5.15(1H,brd,J=10,0.5)
16	5	----	Et	NaOEt/EtOH	98%	oil		3.33 (1H, d, J=8), 3.80 (1H, m, $W_{\frac{1}{2}}$=12)
17	6a	p-SMe	Et	NaOEt/EtOH	70%	180-181°	(n-C_6H_{14}-Me_2CO)	3.51 (1H, d, J=11), 5.14 (1H, d, J=11)
18	6b	m-NO_2	Et	NaOEt/EtOH	85%	178.5-180°	(C_6H_{14}-EtOAc)	3.58 (1H, d, J=12), 5.37 (1H, d, J=12)
19	7a	m-CF_3	R=Et R'=H	NaOEt/EtOH	62%	200.5-203°	(---)	3.58 (1H, d, J=10.8), 4.94 (1H, d, J=10.8)
20	7b	o-Cl	R=Et R'=H	NaOEt/EtOH	70%	169-172°	($MeOH$-$CHCl_3$ -Me_2CO)	3.51 (1H, d, J=7.2) 5.22 (1H, d, J=7.2)
21	7c	m-NO_2	R=Et R'=Me	NaOEt/EtOH	92%	211-213°	(MeOH)	3.52 (1H, d, J=7.2), 5.12 (1H, d, J=7.2)
22	7d	o-NO_2	R=Me R'=Me	NaOMe/MeOH	90%	213.5-214.5° (---)	trans cis	3.48 (1H, d, J=6.0), 5.42 (1H, d, J=6.0) 3.16 (1H, d, J=5.3), 5.42 (1H, d, J=5.3)

* The NMR spectra were taken in $CDCl_3$ solution except for (7a-d).

(7a), (7b), (7d)---DMSO-d_6, (7c)---$CDCl_3$:CD_3OD=1:1

applied to α-alkoxycarbonyl-2-propenoate with another heterocyclic moiety or an alkyl moiety at the β position. Thus, furyl, thienyl, pyridyl, and cyclohexyl dihydropyrimidinones [(3a), (3b), (4), (5)] were obtained.

Next, the cyclization of dialkyl benzylidenemalonate and benzamidine hydrochloride was carried out under the same reaction condition to yield 5-alkoxycarbonyl-2,6-diphenyl-5,6-dihydropyrimidin-4(3H)-one (6a) or (6b) as a sole compound (trans, J=11 or 12 Hz), respectively.

Finally, we studied the reaction of guanidine or 1,1-dimethylguanidine with α,β-unsaturated esters.[5] In this case, since the product was insoluble in water and most organic solvents except for DMSO, the crystals precipitated as the reaction proceeded. A solution of 1.0 eq of diethyl 3-nitrobenzylidenemalonate in EtOH was added to a stirred mixture of 1,1-dimethylguanidine hydrochloride and 2.0 eq of NaOEt in EtOH. After reflux for 2 h, the solvent was evaporated under reduced pressure to leave the crystals. Then, filtration and washing with water gave the desired compound (7c) in 92% yield. The NMR spectrum of (7d) showed a trans and cis mixture (3:2) but the others (7a-c) only trans isomer.

Consequently, the cyclization of 3-substituted 2-alkoxycarbonyl-2-propenoates with amidine hydrochloride in the presence of 1-2 eq of metal alkoxide provided suitably substituted 5,6-dihydropyrimidin-4(3H)-ones in good yield (R^1=Me, Et, Pr^i; R^2=aryl, alkyl; R^3=Me, C_6H_5, NH_2, NMe_2).

The pharmacological activity of 5,6-dihydropyrimidin-4(3H)-ones will be reported

in due course.

ACKNOWLEDGEMENT

The authors thank Professor Teruhisa Noguchi and Dr. Minoru Morita for their encouragement throughout the investigation and Dr. Fumio Satoh for his kind discussions. We also thank Mr. Keiyuu Shima and Miss Yumi Takeuchi for their helpful experiments.

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Received, 10th May, 1984