Tetrahedron Letters,Vol.29,No.42, pp 5405-5408,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

REGIOSELECTIVE SYNTHESIS OF N-SUBSTITUTED DIHYDROPYRIMIDIN-2(1H) OR (3H)-ONE

Hidetsura Cho*, Yumi Takeuchi, Masaru Ueda, and Akira Mizuno
Suntory Institute for Biomedical Research, 1-1-1, Wakayamadai, Shimamoto-cho, Mishimagun, Osaka, JAPAN

Summary: Alkoxycarbonylation of dihydropyrimidin-2-one 1 with alkyl chloroformate in the presence of NaH occurred regioselectively at position-3 to provide N-substituted dihydropyrimidin-2(1H)-one 2, but the reaction of 1 with trichloromethyl chloroformate (phosgene dimer) and aminoalcohol in the presence of NaH and Et_3N afforded regioselectively N-substituted dihydropyrimidin-2(3H)-one 3 or compound 2. In this case, regioselectivity was dependent upon the substitution pattern of the phenyl ring. The reaction of 1 with phosgene dimer and ordinary alcohol in the base gave regioselectively compound 3 in contrast to the result of alkyl chloroformate method.

A survey of the literature revealed only a few papers concerned with regioselective single N-acylations of uracil, thymine, and their derivatives[1a,1b] and one example of acetylation of the N-1 alkylated dihydropyrimidin-2-one.[1c] Alkoxycarbonylation of dihydropyrimidin-2-one 1 has not been reported in the literature except for the patents to date.[2]

Recently, we discovered a very potent calcium antagonist, namely the novel N-substituted 3,4-dihydropyrimidine, an aza analog of dihydropyridine.

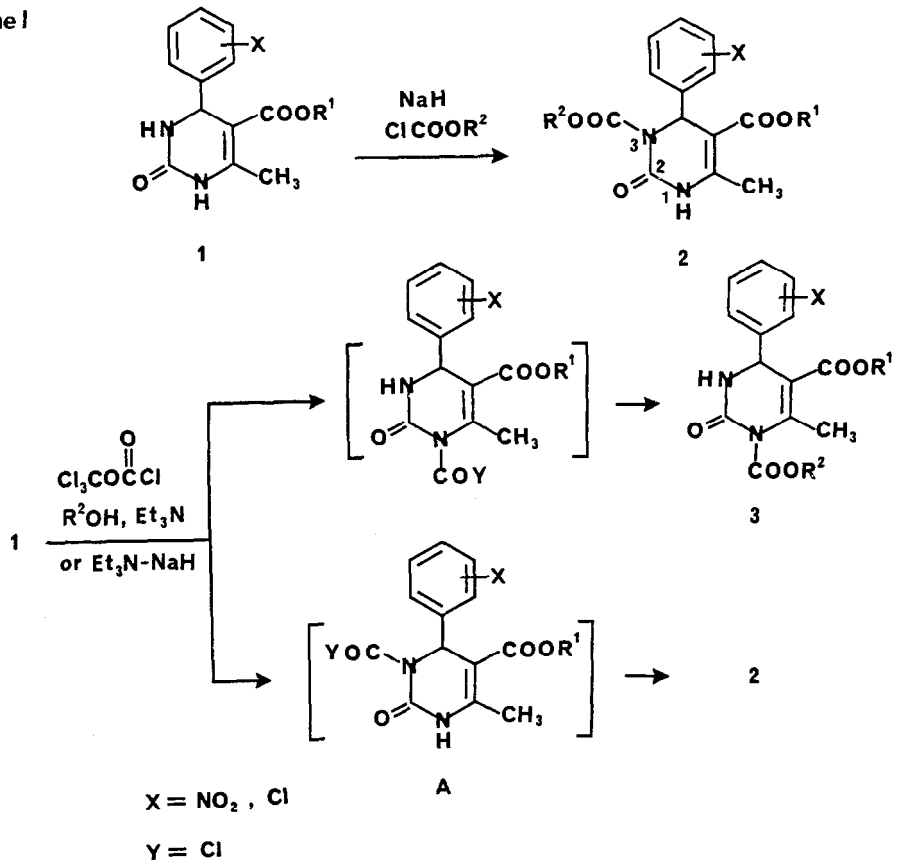
Continuing our investigations into the synthesis of new dihydropyrimidine derivatives, we became interested in the reaction of compound 1 with A) alkyl chloroformate or B) phosgene dimer and alcohol in the presence of NaH and Et_3N, and succeeded in the regioselective synthesis of the novel compounds, N-substituted dihydropyrimidine-2(1H)-ones 2 and dihydropyrimidin-2(3H)-one 3 from compound 1. (See scheme I).

Compound 1 was prepared according to the literature procedure.[3]

Treatment of 1a (X=m-NO_2, R^1=Et) with 0.9 equiv of ethyl chloroformate in the presence of 1.5 equiv of NaH in THF afforded regioselectively 2a in 99% yield. The proposed structure for 2a was confirmed by ^{1}H-NMR and C-13 NMR spectra using the long range selective proton decoupling method (LSPD) as reported previously.

Therefore, the reaction occurred regioselectively at position-3 to provide N-substituted 3,4-dihydropyrimidin-2(1H)-one 2a. Similarly, alkoxycarbonylation of the m-NO_2 substituted compounds 1 with $ClCOOC_7H_{15}$ afforded 2b or 2d as the sole compound in 80% or 25% yield, respectively. (Table I) However, the reaction of the o-nitro compounds 1 with $ClCOOC_7H_{15}$ gave 2c or 2e in low yields with the recovered starting materials (77-85%). Apart from the yields, this regioselectivity corresponds with that of a previous paper which reports regioselective reaction of 5-alkoxycarbonyl-4-

Scheme I



Scheme II

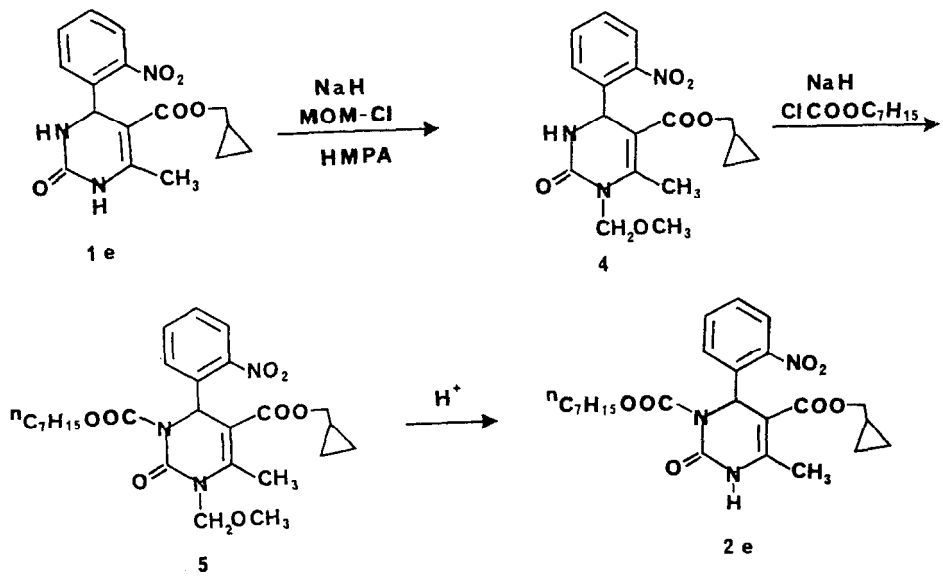


Table I Product 2 from the regioselective reaction of compound 1 with $ClCOOR^2$ in the presence of NaH

Compound	X	R^1	R^2	Yield %	mp°C (solvent)
2a	m-NO_2	Et	Et	99	107-108 (AcOEt-C_6H_{14})
2b	m-NO_2	Et	n-C_7H_{15}	80	107-108 (AcOEt-C_6H_{14})
2c	o-NO_2	Et	n-C_7H_{15}	10*1	88-90 (AcOEt-C_6H_{14})
2d	m-NO_2	CH_2-cyclopropyl	n-C_7H_{15}	25	70-72 (AcOEt-C_6H_{14})
2e	o-NO_2	CH_2-cyclopropyl	n-C_7H_{15}	6*1,2	101-104 (AcOEt-C_6H_{14})

*1 The rest of percentage is compound 1. *2 40% overall yield from 1e via 5.

Table II Regioselective synthesis of 2 and/or 3 in the presence of NaH-Et_3N

Compound	X	R^1	R^2	Product 2	Product 3	Recovery 1
f	m-NO_2	Et	$CH_2CH_2NMe(CH_2C_6H_5)$	26	4	39
g	m-NO_2	CH_2-cyclopropyl	$CH_2CH_2NMe(CH_2C_6H_5)$	13	7	29
h	m-NO_2	Et	Et	4(2a)	35	18
i	o-NO_2	CH_2-cyclopropyl	C_7H_{15}	0(2e)	63	0
j	o-NO_2	CH_2-cyclopropyl	$CH_2CH_2NMe(CH_2C_6H_5)$	0	73	0
k	o-NO_2	Et	$CH_2CH_2NMe(CH_2C_6H_5)$	0	55	10
l	o-NO_2	CH_2-cyclopropyl	CH_2CH_2-N(piperazine)-$NCH(C_6H_5)_2$	0	40	10

aryl-2,6-dimethyl-1,4(3,4)-dihydropyrimidines with NaH-ClCOOR.[4] When excess of Et_3N was employed as a base instead of NaH, only a small amount of product 2a was obtained from 1a.

In order to obtain compounds bearing various ester groups on the nitrogen atom of position-3, we studied the reaction of compound 1 with trichloromethyl chloroformate (phosgene dimer) and alcohol.[5] However, N-substituted aminoalkyl chloroformate could not be prepared by treating phosgene dimer with aminoalcohol, even at low temperature (-23°C-0°C). Therefore, we chose the unstable intermediate A in order to obtain the desired product 2. Using this method, we have already reported to get regioselectively an N-substituted 2,6-dimethyl-dihydropyrimidine which had an alkyl group R^2 containing a nitrogen atom.[5] However, in the case of ortho nitro compound, successive treatment of 1e (X=o-NO_2, CH_2-cyclopropyl) with 0.9 equiv of NaH, 0.5 equiv of phosgene dimer and 6 equiv of 2-(N-benzyl-N-methylamino)-ethanol or 2-(4-benzhydrylpiperazinyl)ethanol in Et_3N-THF did not give compound 2 but 3. Thus, the sodium salt of 1e in 6 equiv of Et_3N and THF was added to a solution of 0.5 mol equiv of phosgene dimer (1 equiv of free phosgene) in THF at -23°C, and after 30 min a solution of 6 equiv of aminoalcohol in THF was added at 0°C. After purification on SiO_2, the N-1 substituted compound 3j or 3l were obtained in 73% or 40% yield, respectively. The compound 3j was also obtained with Et_3N as the base in 80%

yield in a similar manner. The chemical structure of 3j was determined by ^{1}H-NMR. The C-4 methine proton appeared at δ 5.84 (J=3 Hz) as a doublet, which changed to a sharp singlet on the addition of D_2O to the sample.

But, in the case of meta nitro compound N-alkoxycarbonylation at the N-3 position occurred somewhat predominantly than at the N-1 position.

On the other hand, in the case of alkyl chloroformate the reaction seems to yield always alkoxycarbonylation products at the N-3 position in the presence of NaH. A reason for the low yield of 2c and 2e is unclear but might be due to the steric hindrance by the ortho nitro group. When Et_3N was as a base, the same regioselectivity was observed as described above.

In order to compare the result of the phosgene dimer method with that of the alkyl chloroformate method, we treated the sodium salt of 1a or 1e with phosgene dimer and EtOH or $C_7H_{15}OH$ according to the synthetic method of compounds 2f and 3f. In these cases, the different selectivity was observed. Thus, compounds 3h or 3i were selectively obtained as listed in table II.

Alternatively, in order to improve the yield of compound 2e, the transformation of 1e via dihydropyrimidin-2-one 4 and 5 into 2e was undertaken. (See scheme II) Alkylation of 1e with 1.0 equiv of NaH and 1.5 equiv of methoxymethyl chloride in HMPA (0.66 M solution) gave the compound 4 in 52% yield. The chemical structure was determined by ^{1}H-NMR-experiment; namely, NOE (3%) was observed at the methylene protons of the MOM group by irradiation of the methyl group at position-6. The subsequent alkoxycarbonylation of 4 with 1.2 equiv of NaH and 1.0 equiv of n-heptyl chloroformate occurred at position-3 to afford 5 in 77% yield, which was quantitatively hydrolyzed (reflux, 2h) with a mixture of conc HCl and $CHCl_3$ (1:1) to provide 2e in 40% overall yield from 1e.

REFERENCES

1) a) M. Botta, F. D. Angelis, G. Finizia, R. Nicoletti, Tetrahedron Lett., 1985, 26, 3345.
b) K. A. Cruickshank, J. Jiricny, C. B. Reese, Tetrahedron Lett., 1984, 25, 681.
c) V. P. Kadysh, Y. P. Stradyn, E. L. Khanina, G. Y. Duber, D. K. Mutsenietse, Khim. Geterotsiklich Soedin, 1985, 117.
2) a) H. Cho, Y. Miyazaki, Japan Patent Kokai, 1987, 87574.
b) K. S. Atwal, Japan Patent Kokai, 1987, 221674.
c) J. J. Baldwin, S. M. Pitzenberger, D. E. McClure, US Patent, 1987, 4675321.
3) a) T. Chiba, H. Sato, T. Kato, Heterocycles, 1984, 22, 493.
b) A. Ehsan, Karimullah, Pakistan J. Sci. Ind. Res., 1967, 10, 83.
4) H. Cho, K. Shima, M. Hayashimatsu, Y. Ohnaka, A. Mizuno, Y. Takeuchi, J. Org. Chem., 1985, 50, 4227.
5) H. Cho, A. Mizuno, K. Shima, M. Ueda, Y. Takeuchi, M. Hamaguchi, N. Taniguchi, Heterocycles, 1988, 27, 769.

(Received in Japan 12 July 1988)