SYNTHESIS OF 3-SUBSTITUTED 3,4-DIHYDROPYRIMIDINES: N-ALKOXY-CARBONYLATION WITH TRICHLOROMETHYL CHLOROFORMATE AND ALCOHOLS

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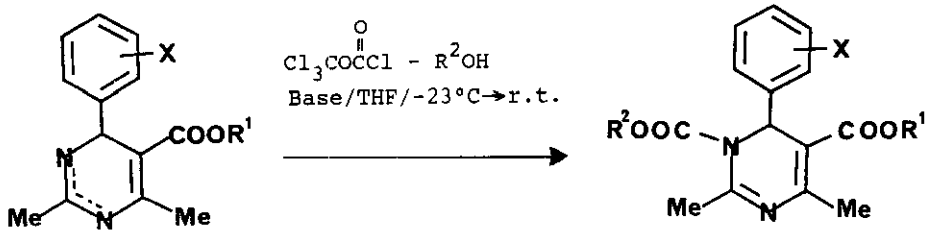
Abstract——N-Alkoxycarbonylation reactions of dihydropyrimidines with trichloromethyl chloroformate (phosgene dimer) and an alcohol were carried out in order to obtain the dihydropyrimidines with a complicated alkyl group or an alkyl group containing a nitrogen atom. Especially, the synthetically difficult problem of the unstable N-substituted dihydropyrimidines containing a nitrogen atom in an ester group was overcome by the method II: 0.5-1.2 mol equiv. of phosgene dimer, 1.0-6.0 equiv. of tertiary aminoalcohol, and 6 equiv. of Et_3N in THF at -23°C-r.t.

Recently, we discovered that dihydropyrimidine derivatives have very potent calcium antagonistic activity. For the purpose of obtaining dihydropyrimidine derivatives of more potent activity and longer duration which seem to be pharmaceutically important, the introduction of a variety of ester groups to position-3 of the dihydropyrimidine skeleton was investigated. Thus, in a previous paper[1], we reported that regioselective alkoxycarbonylation with commercially available alkyl chloroformate ($ClCOOR^2$) occurred on the nitrogen



atom at position-3 of 1,4(3,4)-dihydropyrimidines. In the present work, the introduction of the $COOR^2$ group was achieved using a reagent which is not commercially available. Especially, a new mild procedure of alkoxycarbonylation was developed for the synthesis of N-substituted dihydropyrimidines which contain an N-substituted group possessing a complicated alkyl group or an alkyl group containing a nitrogen atom.

First, we prepared the new alkyl chloroformates by treating trichloromethyl chloroformate (phosgene dimer) with an alcohol in the presence of a suitable base (NaH, Et_3N or diethylaniline).

In some cases, the alkyl chloroformates were isolated, but usually it was used in situ for the subsequent reaction with the dihydropyrimidine. Three methods were employed for the synthesis of dihydropyrimidine derivatives.

[Method Ia] Phosgene dimer (5 mol equiv.) was added to a sodium alkoxide generated by the reaction of an alcohol (10 equiv.) with NaH (10 equiv.) or Et_3N (10 equiv.) in THF at 0°C. The alkyl chloroformate preparated was added to a suspension of a sodium salt of the appropriate dihydropyrimidine (1.0 equiv.) in THF at 0°C.

[Method Ib] Phosgene dimer (2 mol equiv.) and an alcohol (4.4 equiv.) in the presence of N,N-diethylaniline (4.4 equiv.) afforded an alkyl chloroformate which was added to a solution of a dihydropyrimidine (1.0 equiv.) in Et_3N (10 equiv.) at 0°C.

Thus, a variety of dihydropyrimidine derivatives (a-e) were obtained as shown in Table I.

However, these methods were unsuccessful with 2-(N-methyl-N-cinnamylamino)ethanol and the other tertiary aminoalcohols. This can be explained by assuming that the alkyl chloroformate is decomposed by addition of the nitrogen atom of the aminoalcohol to the carbonyl carbon of the chloroformate generated. Then, tertiary aminoalcohol hydrochloride was employed without base to phosgene dimer in order to depress the nucleophilicity of the lone pair of the nitrogen atom of the aminoalcohol, but the reaction was not successful.

This problem was overcome by employing a different strategy and by use of the following mild reaction conditions.

[Method II] A solution of a dihydropyrimidine and Et_3N (6 equiv.) in THF was added to phosgene dimer (0.5-1.2 mol equiv.) in THF at -23°C, and the resulting solution was stirred for 1 h. A solution of a tertiary aminoalcohol (1.0-6.0

Table I Products synthesized from the reaction of phosgene dimer and alcohol [Method Ia and Ib]

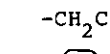
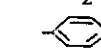
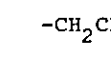
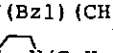
	X	R^1	R^2	Method	Yield%
a	m-NO_2		$-(CH_2)_6-Cl$	Ia	36
b	m-NO_2		$-(CH_2)_5-C_6H_5$	Ia	47
c	o-NO_2	i-Pr		Ib	42
d	o-NO_2	i-Pr		Ib	36
e	o-NO_2	i-Pr		Ib	55

Table II Products synthesized from the reaction of phosgene dimer and aminoalcohol [Method II]

	X	R^1	R^2	Equivalent to dihydropyrimidine; Phosgene dimer	Amino alcohol	Yield%
f	o-NO_2		$CH_2CH_2N(Bzl)(CH_2)_3Ph$	1.2	6.0	69
g	o-NO_2		$CH_2CH_2N(Bzl)(CH_2)_3Ph$	0.6	1.2	56
h	2,3-diCl	i-Pr	$CH_2CH_2N(Bzl)(CH_2CH=CH-Ph)$	1.2	6.0	66
i	2,3-diCl	i-Pr	$CH_2CH_2N(Bzl)(CH_2CH=CH-Ph)$	0.5	1.0	59
j	o-NO_2		CH_2CH_2N 	1.0	6.0	81
k	o-NO_2	i-Pr	CH_2CH_2-2-Pyridyl	1.0	6.0	64

equiv.) in THF at 0°C was added to the mixture, and stirring was continued at r.t. for 2 h.

Thus, a series of the compounds (f-k) listed in Table II were synthesized. Normally, 0.5 equiv. of phosgene dimer and 1.2 equiv. of an aminoalcohol were employed in the reaction, but use of larger amounts of both reagents afforded the corresponding compounds in better yields.

This strategy is somewhat similar to the reported procedure,[2] in which the drastic conditions (phosgene, 110-115°C in toluene) to the stable substrate were employed. In the unstable dihydropyrimidine synthesis, the reaction conditions were not suitable, but the milder and less hazardous reaction conditions were required as described above. We expect that this milder method II can be applied to other unstable substrates to give suitable alkoxycarbonylated compounds.

EXPERIMENTAL

General Methods. ^1H Nmr spectra were recorded with a JEOL GX-270 (270 MHz) spectrometer in $CDCl_3$ solution with tetramethylsilane (Me_4Si) as an internal standard, unless otherwise noted. Ir spectra were taken on a Hitachi 260-10 infrared spectrometer in $CHCl_3$, and uv spectra on a Beckman DU-8 spectrophotometer. High-resolution mass spectra were obtained with a JEOL JMS-01SG-2 spectrometer at an ionizing voltage of 70 ev. TLC was carried out on Merck silica gel plates 60F-254. Column chromatography was performed on Merck silica gel (70-230 mesh).

Typical Procedure for the Preparation of 3-Substituted 3,4-Dihydropyrimidines

3-(6-Chlorohexyl) 5-Cyclopropylmethyl 3,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyrimidinedicarboxylate (a) (Method Ia)

To a stirred slurry of 162 mg of 50% NaH-mineral oil in 1 ml of THF was added a solution of 433 mg of 6-chloro-1-hexanol in 3 ml of THF at r.t. After 5 min, 189 µl of trichloromethyl chloroformate was added at 0°C. Stirring was continued at 0°C for 5 min and then at r.t. for 25 min. To this was added a suspension of a sodium salt prepared from 104 mg of a dihydropyrimidine and 17 mg of 50% NaH-mineral oil in 4 ml of THF at 0°C. The mixture was stirred at r.t. for 1 h, quenched with H_2O, and extracted with $CHCl_3$. The organic layer was dried and evaporated to leave the residue, which was purified by SiO_2 preparative TLC (development: $CHCl_3$; elution: $CHCl_3$/MeOH=5/1) to give 56 mg (36%) of compound a.

Ir 1725, 1710 cm^{-1}. Nmr (δ) 0.15-1.20 (5H, m), 1.35-1.90 (8H, m), 2.42 (3H, s), 2.46 (3H, s), 3.50-3.60 (2H, m), 3.90-4.08 (2H, m), 4.29 (2H, t, J=7 Hz), 6.28 (1H, s), 7.48 (1H, t, J=8 Hz), 7.60 (1H, d, J=8 Hz), 8.16 (1H, d, J=8 Hz), 8.17 (1H, s). High ms, calcd for $C_{24}H_{30}ClN_3O_6$, m/z 491.1820, found m/z 491.1805. Anal. calcd. for $C_{24}H_{30}ClN_3O_6$:C, 58.59;H, 6.15;N, 8.54. Found C, 58.61;H, 6.17;N, 8.51.

3-(2-Cyclopentylethyl) 5-Isopropyl 3,4-Dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyrimidinedicarboxylate (c) (Method Ib)

To a stirred solution of 96 µl of trichloromethyl chloroformate in 3 ml of THF was added a solution of 201 mg of 2-cyclopentylethanol and 262 mg of N,N-diethylaniline in 3 ml of THF at 0°C. After 5 min, the resulting reagent was added to a stirred solution of 126 mg of 5-isopropyl 1,4(3,4)-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-5-pyrimidinecarboxylate and 556 µl of Et_3N in 5 ml of THF. The reaction mixture was stirred at r.t. for 1 h, quenched with water, and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated to leave 690 mg of the residue, which was purified by preparative TLC (SiO_2, Merck, 2mm, development $CHCl_3$, elution 5%MeOH-$CHCl_3$) to yield 76 mg (42%) of the compound c.

Ir: 1730, 1700 cm^{-1}. Nmr (δ) 1.07 (3H, d, J=6 Hz), 1.29 (3H, d, J=6 Hz), 1.45-1.90 (11H, m), 2.32 (3H, s), 2.46 (3H, brs), 4.10-4.35 (2H, m), 5.05 (1H, m), 6.86 (1H, s), 7.35-7.82 (4H, m). High ms, calcd for $C_{24}H_{31}N_3O_6$, m/z 457.5290, found m/z 457.5299. *Anal. calcd. for* $C_{24}H_{31}N_3O_6$*:C, 63.01;* H, 6.83;N, 9.18. Found C, 63.03;H, 6.86;N, 9.17.

3-{2-[N-Benzyl-N-(3-phenylpropyl)amino]ethyl} 5-Cyclopropylmethyl 3,4-Dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyrimidinedicarboxylate (f) (Method II)

To a stirred solution of 719 µl of trichloromethyl chloroformate in 40 ml of THF was added a solution of 1.65 g of 5-cyclopropylmethyl 1,4(3,4)-dihydro-2,6-dimethyl-4-(2-nitrophenyl)pyrimidinecarboxylate and 3.04 g of triethylamine in 80 ml of THF at -23°C. After 1 h, a solution of 6.73 g of 2-[N-benzyl-N-(3-phenylpropyl)amino]ethan-1-ol in 40 ml of THF was added at 0°C, and stirring was continued at r.t. for 2 h. The reaction mixture was quenched with brine and extracted with $CHCl_3$. The organic layer was dried and evaporated to leave 12 g of the residue, which was chromatographed by SiO_2 (AcOEt:n-hexane=1:1) to give 2.14 g (69%) of the compound f.

Ir: 1720, 1695 cm^{-1}. Nmr (δ) 0.06-0.23 (2H, m), 0.32-0.51 (2H, m), 0.98-1.17 (1H, m), 1.68-1.88 (2H, m), 2.30 (3H, s), 2.45 (3H, s), 2.45-2.65 (4H, m), 2.78 (2H, t, J=7 Hz), 3.61 (2H, s), 3.81-3.97 (2H, m), 4.11-4.24 (1H, m), 4.26-4.40 (1H, m), 6.87 (1H, s), 7.06-7.83 (14H, m). Uv λ_{Max}^{MeOH}305 nm (ε: 4900). Anal. calcd for $C_{36}H_{40}N_4O_6$:C, 69.21;H, 6.45; N; 8.97. Found C, 69.25;H, 6.55;N, 8.81.

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