AN IMPROVED SYNTHESIS OF 2-CARBAMOYLOXYMETHYL-1,4-DIHYDROPYRIDINE

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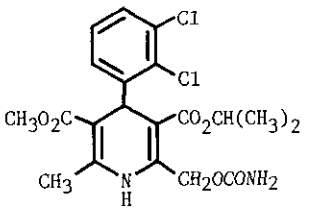
Abstract —— A new synthesis of 3-amino-4-carbamoyloxybutenoic esters by conjugate addition of ammonia to 4-carbamoyloxy-2-butynoic esters is reported. Numerous dihydropyridines were prepared from the resulting 3-aminobutenoates by condensation with benzylideneacetoacetates.

Aryldihydropyridines have occupied an important position as therapeutic agents among various types of calcium entry blockers[1]. The clinical usefulness of nifedipine[2], a prototype of aryldihydropyridines, in the management of cardiovascular diseases stimulated extensive research in this area, leading to the discovery of nicardipine[3], a cerebrovasodilating agent. Cerebrovasodilating activity has been a subject of great interest since improvement of cerebral circulation was reported to be effective for sequelae of various cerebrovascular diseases[4] in recent years.

During the course of our modifications in search of new aryldihydropyridines, 2-carbamoyloxymethyl-4-(2,3-dichlorophenyl)-3-isopropoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine, NB-818, was found to show selective and long-lasting action on cerebrovascular systems[5a]. In connection with our ongoing program with this compound, the lack of synthetic access to the requisite O-functionalized 3-amino-4-hydroxy-2-butenoates prompted us to develop the synthetic method. The authors describe a new synthetic method of 3-amino-4-carbamoyloxy-2-butenoates, and an improved synthesis of 2-carbamoyloxymethyldihydropyridines including NB-818 by the reaction of the aminobutenoates with substituted benzylideneacetoacetates.

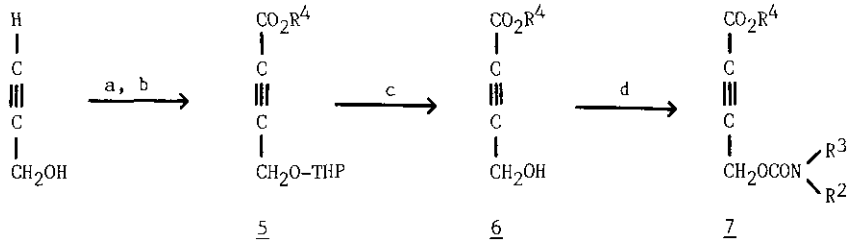


1 NB-818

The carbamoyloxymethylaryldihydropyridines[5b] were prepared by acylation of 2-hydroxymethylaryldihydropyridines[6] with appropriate isocyanates, its equivalents or carbamoyl chlorides in the beginning. However, the method gave no satisfactory results in the preparation of diverse carbamoyloxymethyl derivatives in that the yields were contingent on the acylating agents used. In particular, some N,N-disubstituted carbamoyloxymethyl derivatives were obtained in extremely poor yields or not at all, when N,N-disubstituted carbamoyl chlorides were used as the acylating agent. Aryldihydropyridines, in general, are prepared by the Hantzsch method[7] comprising the reaction of an arylaldehyde with 2 moles of a β-ketoester and ammonia, or more frequently by its modification[8] comprising the reaction between α-aralkylideneacetoacetate and 3-amino-2-butenoate which is readily prepared from acetoacetate by the action of ammonia. However, attempts to prepare the requisite 3-amino-4-carbamoyloxy-2-butenoates from 4-hydroxyacetoacetate were not successful due to the instability of the γ-hydroxy-β-ketoester. We reasoned that conjugate addition of ammonia to the 3-position of 2-butynoates could give 3-amino-2-butenoates. Then our effort was directed toward the preparation of 3-amino-4-carbamoyloxy-2-butenoates 3 from 4-carbamoyloxy-2-butynoic esters 7.

The 4-hydroxy-2-butynoates 6[9] were prepared from propargyl alcohol according to Scheme 1. Protection of the hydroxy group with a tetrahydropyranyl (THP) group, followed by the action of n-butyllithium and chloroformate gave the protected 4-hydroxybutynoate 5, which was deprotected to furnish 6. Acylation of 6 with chlorosulfonyl isocyanate (CSI), and subsequent hydrolysis provided the unsubstituted carbamoyloxybutynoates 7 (Method A). N,N-Disubstituted carbamoyloxybutynoates 7 were prepared by the action of phosgene followed by treatment with N,N-disubstituted amines (Method B). Reaction of 6 with isocyanates gave the N-monosubstituted carbamoyloxybutynoates 7 (Method C).

Scheme 1. Preparation of 7

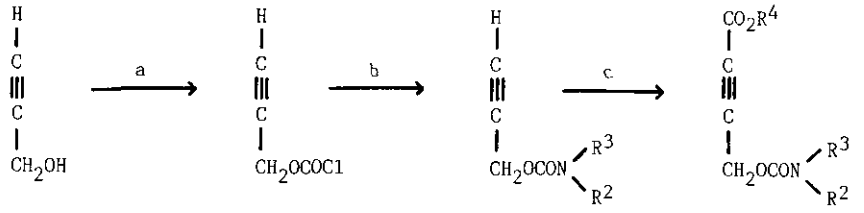


a) THP, TsOH b) i n-BuLi, ii $ClCO_2R^4$ c) H^+.

d) Method A i CSI, ii H_2O; Method B i $COCl_2$, ii R^2R^3NH; Method C R^2NCO.

As an alternative route to 7, the introduction of carbamoyl group on propargyl alcohol was performed first as described in Scheme 2 (Method D). Propargyl alcohol was transformed to the chloroformate by the action of phosgene or phosgene generated *in situ* from trichloromethyl chloroformate with a base. Reaction of the chloroformate 9 with secondary amines afforded the N,N-disubstituted carbamates 10. Carbonylation of the acetylenic group was performed with n-butyllithium and chloroformate to give 7. Compounds 7a-s, thus prepared, are listed in Table 1.

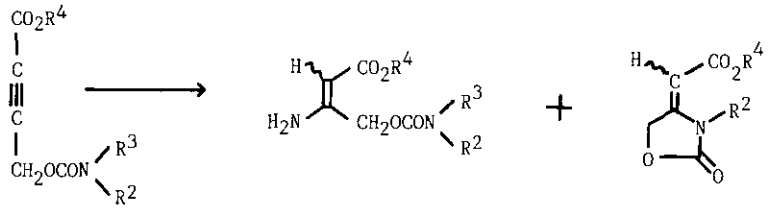
Scheme 2. Alternative route to 7 (Method D)



9 10 7

a) $COCl_2$ b) $\begin{matrix} R^3 \\ R^2 \end{matrix}\!\!>\!NH$ c) i n-BuLi, ii $ClCO_2R^4$.

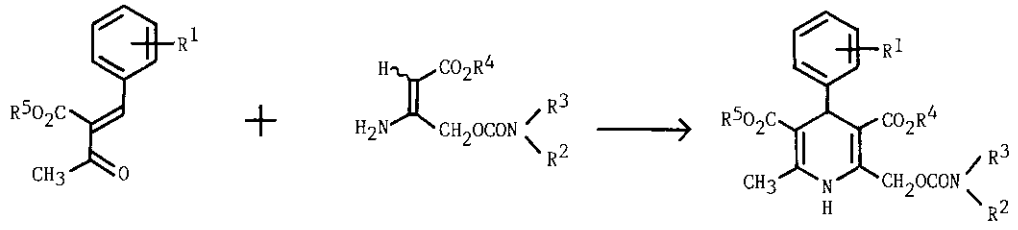
Scheme 3



7 3 8

Method A $AcONH_4$; Method B NH_4HCO_3; Method C $C_6H_5CO_2NH_4$; Method D NH_4OH.

Scheme 4



2 3 1

Although conjugate addition of secondary amines to propiolates is well documented[10], there is no instance in which ammonia or its equivalents were used as a nucleophile. In an attempt to obtain 3-amino-4-carbamoyloxy-2-butenoates 3a, we examined conjugate addition of ammonia (Method D) to 4-carbamoyloxy-2-butynoates 7. Unfortunately, the intramolecular conjugate addition predominated to give the cyclic carbamates 8 as inseparable mixture of E- and Z-isomers even at low temperature(0 - 5°C). However, the problem was overcomed with the use of ammonium salt such as ammonium acetate (Method A), ammonium bicarbonate (Method B) or ammonium benzoate (Method C) to afford the desired aminobutenoates 3 in an acceptable yield (Table 2)[11] together with the cyclic carbamates 8 as a side-product. In a similar fashion N-monosubstituted carbamoyloxybutynoates 7 gave the corresponding aminobutenoates 3 along with the cyclic carbamates 8; with an exception of ethyl 4-(N-phenylcarbamoyloxy)butynoate 7j, in which case a mixture of the E- and Z-cyclic carbamate 8; was exclusively obtained, and the mixture was separated into each isomer by preparative HPLC. Upon treatment with either ammonia or ammonium acetate, N,N-disubstituted carbamoyloxybutynoates 7 gave the aminobutenoates 3 with no side-products.

Condensation of the aminobutenoates 3 with the benzylideneacetoacetates 2 proceeded smoothly in a usual manner, giving the end products in good yields (Tables 3 and 4). This methodology which was shown to be general allowed the preparation of a variety of 2-carbamoyloxymethyldihydropyridine derivatives 1.

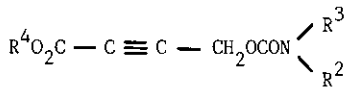


Table 1. Preparation and physico-chemical data of compounds 7a-s[b]

Compound	$N<^{R^3}_{R^2}$	R^4	Method[a]	Yield (%)	mp (°C)	^{1}H nmr Solvent	C4-CH_2 (s)	$CONHR^2$ (br)	ir (cm^{-1})
7 a	NH_2	CH_3	A	80	113-114	DMSO-d_6	4.82	6.80	1750, 1700
b	NH_2	C_2H_5	A	83	86-87	DMSO-d_6	4.82	6.80	1755, 1720
c	NH_2	$CH_2CH_2OC_3H_7$(n)	A	85	oil	$CDCl_3$	4.82	5.15	1720, 1650
d	$NHCH_3$	CH_3	B	80	oil	$CDCl_3$	4.82	5.15	1720
e	$NHCH_3$	C_2H_5	B	80	oil	$CDCl_3$	4.88	5.00	1720, 1710
f	$NHCH_3$	$CH_2CH_2OC_3H_7$(n)	B	75	oil	$CDCl_3$	4.85	5.10	1720
g	NHC_2H_5	C_2H_5	B	77	oil	$CDCl_3$	4.84	4.95	1720
h	NHC_4H_9(t)	C_2H_5	B	60	oil	$CDCl_3$	4.79	4.94	1780, 1720
i	NHC_6H_{11}	C_2H_5	B	74	67-68	$CDCl_3$	4.83	4.90	1715, 1695
j	NHC_6H_5	C_2H_5	C	85	oil	$CDCl_3$	4.93	7.05	1720
k	$N(C_2H_5)_2$	$CH_2CH_2OC_3H_7$(n)	D	46	oil	$CDCl_3$	4.86	-	1700
l	$N(CH_2CH_2Cl)_2$	C_2H_5	B(D)	90(31)	oil	$CDCl_3$	4.90	-	1710
m	$N(CH3)CH_2C_6H_5$	C_2H_5	B(D)	28(49)	oil	$CDCl_3$	4.87	-	1720
n	$N(C_6H_{11})_2$	C_2H_5	B(D)	33(41)	oil	$CDCl_3$	4.83	-	1785, 1705
o	$N(C_6H_5)_2$	C_2H_5	B(D)	41(55)	oil	$CDCl_3$	4.90	-	1720
p	1-pyrrolidinyl	C_2H_5	B(D)	29(46)	oil	$CDCl_3$	4.79	-	1710
q	piperidino	C_2H_5	B(D)	46(76)	oil	$CDCl_3$	4.77	-	1705
r	morpholino	C_2H_5	B(D)	39(58)	oil	$CDCl_3$	4.88	-	1710
s	4-Me-piperazinyl	C_2H_5	B(D)	54(85)	oil	$CDCl_3$	4.86	-	1710

[a] A; i CSI, ii H_2O (from 6) B; i $COCl_2$, ii $R^3_{R^2}>NH$ (from 6) C; R^3NCO (from 6) D; i n-BuLi, ii $ClCO_2R^4$ (from 10).

[b] All these compounds are new, and were judged to be pure from TLC, HPLC, and spectral data.

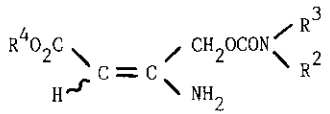


Table 2. Preparation and physico-chemical data of compounds 3a-s[d]

Compound[a]	Method[b]	Yield (%)	mp (°C)	^{1}H nmr(in $CDCl_3$[c]) C2-H (s)	C4-CH_2 (s)	$CONHR^2$ (br)	NH_2 (br)	ir (cm^{-1})
3 a	A	54	90-92	4.63	4.58	5.90	6.70	1730
b	A	52	42-44	4.52	4.5	6.76	7.20	1730
c	A	45	oil	4.60	4.6	5.30	6.50	1720, 1660
d	A	48	146-147	4.54	4.54	7.25	7.25	1710, 1680
e	A(B,C)	44(40,55)	60-61	4.66	4.60	4.92	6.45	1720, 1660
g	B	47	oil	4.66	4.60	5.08	6.40	1720, 1665
h	B	37	oil	4.65	4.53	4.89	6.46	1720, 1660
i	B	25	oil	4.66	4.58	4.85	6.55	1715, 1665
j	B	34	oil	4.65	4.60	6.70	6.20	1710, 1640
k	D	65	oil	4.71	4.62	-	6.50	1695
l	D	46	oil	4.73	4.68	-	6.45	1710, 1670
m	D	36	oil	4.67	4.67	-	6.50	1710, 1670
n	D	33	87.5	4.68	4.16	-	6.55	1690, 1660
o	D	40	115-117	4.60	4.68	-	6.25	1670
p	D	51	oil	4.67	4.62	-	6.50	1700, 1670
q	D	52	oil	4.69	4.64	-	6.50	1700, 1670
r	D	43	oil	4.70	4.65	-	6.50	1700, 1670
s	D	56	oil	4.67	4.62	-	6.50	1700, 1675

[a] R^2, R^3 and R^4 correspond with those of 7a-s.

[b] A; NH_4OAc B; NH_4HCO_3 C; $C_6H_5CO_2NH_4$ D; NH_4OH.

[c] Nmr was taken in DMSO-d_6.

[d] All these are new compounds[11].

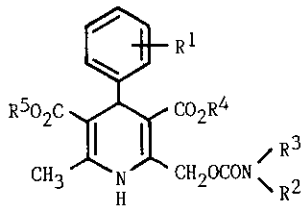


Table 3. Dihydropyridines la-u

Compound	R^1	$N\langle^{R^3}_{R^2}$	R^4	R^5
la	3-NO_2	NH_2	CH_3	CH_3
b	3-NO_2	NH_2	CH_3	CH_2CH_2N⬡
c	2,3-Cl_2	NH_2	CH_3	CH_3
d	3-NO_2	NH_2	CH_3	$CH_2CH_2OCH_2CH{=}CH_2$
e	3-NO_2	NH_2	$CH_2CH_2OC_3H_7$(n)	$CH_2CH_2OC_3H_7$(n)
f	3-NO_2	$NHCH_3$	CH_3	$CH_2CH_2N(CH_3)CH_2C_6H_5$
g	2-NO_2	$NHCH_3$	C_2H_5	C_2H_5
h	3-NO_2	$NHCH_3$	$CH_2CH_2OC_3H_7$(n)	C_2H_5
i	3-NO_2	NHC_2H_5	C_2H_5	C_3H_7(i)
j	2,3-Cl_2	NHC_4H_9(t)	C_2H_5	C_2H_5
k	3-NO_2	NHC_6H_{11}	C_2H_5	C_3H_7(i)
l	3-NO_2	NHC_6H_5	C_2H_5	$CH_2CH_2OC_2H_5$
m	3-NO_2	$N(C_2H_5)_2$	$CH_2CH_2OC_3H_7$(n)	$CH_2CH_2OC_3H_7$(n)
n	3-NO_2	$N(CH_2CH_2Cl)_2$	C_2H_5	C_2H_5
o	2,3-Cl_2	$N(CH_3)CH_2C_6H_5$	C_2H_5	C_2H_5
p	3-NO_2	$N(C_6H_{11})_2$	C_2H_5	C_2H_5
q	3-NO_2	$N(C_6H_5)_2$	C_2H_5	C_2H_5
r	3-NO_2	1-pyrrolidinyl	C_2H_5	C_2H_5
s	3-NO_2	piperidino	C_2H_5	C_2H_5
t	3-NO_2	morpholino	C_2H_5	C_2H_5
u	3-NO_2	4-Me-piperazinyl	C_2H_5	C_2H_5

Table 4. Preparation and physico-chemical data of compounds 1a-u[a]

Compound	Yield (%)	mp (°C)	^{1}H nmr					
			Solvent	C6-CH_3 (s)	C4-H (s)	C2-CH_2	CONHR[2]	N1-H (br s)
1 a	60	110-114	$CDCl_3$	2.38	5.20	5.39(s)	5.35(br s)	8.20
b	40	75-80	$CDCl_3$	2.48	5.12	4.79(s)	4.73(br s)	8.77
c	20	176	DMSO-d_6	2.30	5.30	4.87 & 5.10(ABq,J=12Hz)	6.67(br s)	8.93
d	48	135-139	DMSO-d_6	2.38	5.09	5.12(s)	6.70(br s)	9.12
e	62	91-99	DMSO-d_6	2.40	5.12	4.85 & 5.18(ABq,J=12Hz)	6.73(br s)	9.13
f	30	77-82	DMSO-d_6	2.35	5.11	5.13(s)	7.17(m)	9.16
g	43	165-169	$CDCl_3$	2.38	5.98	5.38(s)	5.15(m)	7.29
h	51	152-155.5	DMSO-d_6	2.40	5.14	5.14(s)	7.20(m)	9.12
i	48	153-154.5	DMSO-d_6	2.34	5.06	5.06(s)	7.28(t,J=7Hz)	9.05
j	43	111	$CDCl_3$	2.30	5.40	4.88 & 5.06(ABq,J=13Hz)	6.97(br s)	8.70
k	42	157-159.5	DMSO-d_6	2.37	5.09	5.09(s)	7.26(d,J=8Hz)	9.07
l	49	138-142	DMSO-d_6	2.40	5.15	5.05 & 5.20(ABq,J=12Hz)	9.86(br s)	9.27
m	45	83-84	DMSO-d_6	2.33	5.08	4.98 & 5.18(ABq,J=13Hz)	-	9.26
n	3	88.5-90	DMSO-d_6	2.33	5.04	5.06 & 5.25(ABq,J=12Hz)	-	9.17
o	8	92-96	DMSO-d_6	2.27	5.40	5.08(s)	-	9.02
p	59	oil	DMSO-d_6	2.35	5.03	4.96 & 5.13(ABq,J=12Hz)	-	9.23
q	47	187-189	DMSO-d_6	2.30	5.00	5.07 & 5.28(ABq,J=12Hz)	-	9.03
r	32	128.5	DMSO-d_6	2.35	5.10	5.03 & 5.16(ABq,J=9Hz)	-	9.12
s	44	148.8	DMSO-d_6	2.35	5.06	4.98 & 5.20(ABq,J=11Hz)	-	9.18
t	13	119-121	DMSO-d_6	2.35	5.06	5.06 & 5.23(ABq,J=12Hz)	-	9.15
u	24	148-150	DMSO-d_6	2.33	5.05	5.03 & 5.18(ABq,J=12Hz)	-	9.20

[a] All these compounds are new, and were judged to be pure from TLC, HPLC, and spectral data.

EXPERIMENTAL

Melting points and boiling points are uncorrected. Proton nmr spectra were recorded at 90 MHz on a Hitachi R-40 spectrometer (chemical shifts are given as δ values in ppm from internal TMS in $CDCl_3$ or DMSO-d_6), uv spectra on a Shimadzu UV-200 spectrophotometer, ir spectra on a JASCO A-102 infrared spectrophotometer using KBr disks or as liquid films. Purifications were performed by column chromatography using Wakogel C-200 (100-200 mesh), and by preparative HPLC using a Waters Associates Prep LC System 500A equipped with a PrepPAK 500/silica column. Thin-layer chromatography was performed on E. Merk silica gel F_{254}. Concentration and evaporation of solvent were carried out under reduced pressure or in vacuo using a rotary evaporater.

PROCEDURE FOR THE PREPARATION OF COMPOUNDS 7a-s :

Methyl 4-carbamoyloxy-2-butynoate (7a)

Method A: To a stirred solution of methyl 4-hydroxy-2-butynoate (22.8 g, 0.2 M) in CH_2Cl_2 (200 ml) was added portionwise chlorosulfonyl isocyanate (17.5 ml, 0.2 M) under cooling at -20°C. After stirring for 20 min at -10°C to -20°C, the mixture was treated with H_2O (20 ml) and stirred for 20 min at about 0°C. The resulting crystalline precipitates were collected by filtration to give crude 7a (18 g). The filtrate was extracted with CH_2Cl_2. The combined extract was washed with H_2O, dried (Na_2SO_4), and then concentrated to give a second crop of crude 7a (10 g). The combined crude crystals were recrystallized from EtOAc to afford 7a (25.1 g, 80%), mp 113-114° C; ir (KBr) cm^{-1} 3410, 3350, 3300, 3220, 2250, 1750, 1700, 1620, 1440, 1320, 1295, 1090, 1050, 930, 750; nmr (DMSO-d_6) 3.77(3H, s), 4.82(2H, s), 6.8(2H, br s).

Ethyl 4-(N-methylcarbamoyloxy)-2-butynoate (7e)

Method B: To a stirred solution of phosgene (6.2 g, 62.5 mM) in benzene (40 ml) was added ethyl 4-hydroxy-2-butynoate (6.4 g, 50 mM) all at once under ice-cooling. After stirring at the same temperature for 30 min the reaction mixture was allowed to rise to room temperature, and then stood overnight. The mixture was evaporated below 50°C to give ethyl 4-chlorocarbonyloxy-2-butynoate (8.1 g, 85%) as an oily residue, which was used without further purification in the next step, ir (liquid film) cm^{-1} 2250, 1785, 1720; nmr ($CDCl_3$) 1.34(3H, t, J=7.5 Hz), 4.28(2H, q, J=7.5 Hz), 5.02 (2H, s).

A solution of the above chloroformate (2.85 g, 15 mM) in benzene (30 ml) was added dropwise to a stirred 2.25 M solution (12 ml) of methylamine (0.84 g, 27 mM) in benzene under ice-cooling. After stirring at the same temperature for 30 min, the mixture was poured into ice-H_2O, adjusted to pH 2 with dil HCl and extracted with EtOAc (100 ml). The extract was dried (Na_2SO_4) and evaporated to give 7d (6.9 g, 80%) as an oily residue, ir (liquid film) cm^{-1} 2970, 2250, 1720,

1535, 1435, 1250, 1130, 1070, 990, 940, 770, 750; nmr ($CDCl_3$) 2.82(3H, d, J=6 Hz), 3.80(3H, s), 4.82(2H, s), 5.13(1H, br).

Ethyl 4-(N-phenylcarbamoyloxy)-2-butynoate (7j)

Method C: To a stirred solution of ethyl 4-hydroxy-2-butynoate (6.4 g, 50 mM) in CH_2Cl_2 (100 ml) was added consecutively phenyl isocyanate (6 ml, 55 mM) under cooling at -20°C and then triethylamine (0.5 ml, 3.6 mM). After stirring at the same temperature for 1 h, the reaction mixture was washed with 1N HCl (10 ml) and H_2O successively. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by preparative HPLC eluting with AcOEt-hexane (1:3). The fraction containing the desired compound was evaporated to give 7j (10.6 g, 85.8%) as a colorless oil, ir (liquid film) cm^{-1} 3350, 2250, 1720, 1540, 1255, 1210, 1050, 750; nmr ($CDCl_3$) 1.33(3H, t, J=8.5 Hz), 4.30(2H, q, J=8.5 Hz), 4.92(2H, s), 7.05(1H, br s), 7.30-7.60(5H, br s).

2-Propoxyethyl 4-(N,N-diethylcarbamoyloxy)-2-butynoate (7k)

Method D: To an ice-cooled solution of phosgene (248 g, 2.5 M) in diethyl ether (800 ml) was added propargyl alcohol (112.1 g, 2 M) all at once under stirring. After 2 h of stirring under ice-cooling, the reaction mixture was allowed to rise to room temperature and then stood overnight. The mixture was concentrated and then purified by vacuum distillation to give propargyl chloroformate (194 g, 81.8%), bp 44°C/33 mmHg-47°C/40 mmHg; nmr ($CDCl_3$) 2.68(1H, t, J=3 Hz), 4.88(2H, d, J=3 Hz).

The above chloroformate (11.8 g, 99.6 mM) was added portionwise to a stirred solution of diethylamine (26 ml, 249 mM) in benzene (200 ml) under ice-cooling, and then stirred under ice-cooling for 30 min. The reaction mixture was poured into ice-H_2O and extracted with benzene. The extract was dried (Na_2SO_4), and then concentrated. The oily residue was purified by vacuum distillation to give propargyl N,N-diethylcarbamate (14.7 g, 95%) as a colorless oil, ir (liquid film) cm^{-1} 3320, 3270, 3000, 2140, 1700; nmr ($CDCl_3$) 1.16(6H, t, J=7.5 Hz), 2.48(1H, t, J=3 Hz), 3.33 (4H, q, J=7.5 Hz), 4.73(2H, d, J=3 Hz).

To a solution of propargyl N,N-diethylcarbamate (14.7 g, 94.7 mM) in THF (60 ml) was added dropwise consecutively n-butyllithium (57.4 ml of 1.65 M solution in hexane, 94.7 mM) and 2-propoxyethyl chloroformate (16.6 g, 99.5 mM) at -65°C to -75°C in a dry ice-acetone bath. After stirring for 30 min at -60°C to -70°C, the cooling bath was removed. The reaction mixture was allowed to rise to room temperature, poured into ice-H_2O and extracted with EtOAc. The extract was dried (Na_2SO_4) and concentrated. The oily residue was chromatographed on a silica gel (150 g) column with benzene as an eluant. The fraction containing the desired com-

pound was evaporated to give 7j(12.65 g, 46.8%) as a colorless oil, ir (liquid film) cm^{-1} 2250, 1750, 1710, 1430, 1255, 1165; nmr ($CDCl_3$) 0.93(3H, t, J=7 Hz), 1.16(6H, t, J=7.5 Hz), 1.62(2H, m), 3.33(4H, q, J=7.5 Hz), 3.45 (2H, m), 3.67(2H, t, J=7.5 Hz), 4.33(2H, t, J=7.5 Hz), 4.86(2H, s).

PREPARATION OF COMPOUNDS 3a-s :

Ethyl 3-amino-4-(N-methylcarbamoyloxy)-2-butenoate (3e)

Method A: A mixture of ethyl 4-(N-methylcarbamoyloxy)-2-butynoate (7e, 1.85 g, 10 mM) and ammonium acetate (3.84 g, 50 mM) in MeOH (20 ml) was warmed at 60°C for 4 h under stirring and then concentrated. The residue was partitioned between EtOAc (50 ml) and 20% aq NaCl (10 ml). The organic layer was separated and dried ($MgSO_4$). After removing the organic solvent, the residue was purified by preparative HPLC eluting with hexane-EtOAc (5:4) to give 3e (0.88 g, 44%) as crystals, mp 60-61°C; uv $\overset{MeOH}{Max}$ nm(ε) 274 (14,000); ir (KBr) cm^{-1} 3450, 3350, 3000, 2950, 1720, 1660, 1620, 1590, 1540, 1445, 1370, 1280, 1190, 1170, 1055, 1040, 955, 790; nmr ($CDCl_3$) 1.27(3H, t, J=7.5 Hz), 2.83(d, 3H, J=6 Hz), 4.60(2H, s), 4.66(1H, s), 4.92(1H, br), 6.45(2H br).

Method B: A mixture of 7e (1.85 g, 10 mM) and ammonium bicarbonate (3.95 g, 50 mM) in methyl cellosolve (20 ml) was warmed at 60°C for 4 h under stirring. Work-up described in Method A gave 3e (0.8 g, 40%), which was identical with the product 3e obtained by Method A.

Method C: A mixture of 7e (1.85 g, 10 mM) and ammonium benzoate (1.73 g, 12.5 mM) in DMF (20 ml) was warmed at 60°C for 1 h under stirring. Work-up described in Method A gave 3e (1.1 g, 55%), which was identical with the product obtained by Method A or B.

2-Propoxyethyl 3-amino-4-(N,N-diethylcarbamoyloxy)-2-butenoate (3k)

Method D: A mixture of 2-propoxyethyl 4-(N,N-diethylcarbamoyloxy)-2-butynoate (7k, 12.5 g, 43.8 mM) and 28% NH_4OH (11 ml) in i-PrOH (180 ml) was warmed 60°C for 1 h with stirring and then concentrated. The residue was extracted with EtOAc and the extract was dried (Na_2SO_4) and then evaporated. The crude oily product was purified by preparative HPLC eluting with hexane-EtOAc (2:1) to give 3k (8.6 g, 65%) as a colorless oil, uv $\overset{MeOH}{Max}$ nm(ε) 275 (13,500); ir (liquid film) cm^{-1} 3450, 3350, 2980, 1695, 1625, 1575, 1480, 1430, 1380, 1365, 1275, 1160, 1120, 1095, 1070, 1005, 790, 765; nmr ($CDCl_3$) 0.92(3H, t, J=8 Hz), 1.15(6H, t, J=7.5 Hz), 1.62(2H, m), 3.32(4H, q, J=7.5 Hz), 3,45(2H, t, J=8 Hz), 3.65(2H, t, J=4.5 Hz), 4.25(2H, t, J=4.5 Hz), 4.62(2H, s), 4.71(1H, s), 6.50(2H, br s).

FORMATION OF CYCLIC CARBAMATES 8 FROM 4-CARBAMOYLOXY-2-BUTYNOATE DERIVATIVES 7 :

Methyl (2-oxo-4-oxazolidinylidene)acetate (8a)

A mixture of methyl 4-carbamoyloxy-2-butynoate (7a, 24 g, 152 mM) and ammonium acetate (50 g, 65

mM) in MeOH (200 ml) was warmed with stirring at 60-70°C for 5 h and then concentrated. The residue was partitioned between EtOAc and H_2O. The organic layer was separated, washed with H_2O, and evaporated. The crude product was purified by preparative HPLC eluting with EtOAc-hexane (3:2) to give an inseparable mixture (1:1)[12] of Z- and E-isomers of the cyclic carbamate 8a (3.3 g, 13.7%), and 3a (4.9 g, 18.8%). 8a: mp 128-129°C, ir(KBr) cm^{-1} 3260, 1790, 1690, 1640, 1460, 1355; nmr (DMSO-d_6) 3.62 and 3.65(3H, s), 4.90-5.40(3H, m). 3a: mp 90-92°C; ir (KBr) cm^{-1} 3370, 1730, 1650, 1620, 1570, 1335, 1280, 1170; nmr ($CDCl_3$) 3.64(3H, s), 4.58(2H, s), 4.63(1H, s), 5.90(2H, br s), 6.70(1H, br s).

Ethyl (3-methyl-2-oxo-4-oxazolidinylidene)acetate (8e)

Into a stirred solution of ethyl 4-(N-methylcarbamoyloxy)-2-butynoate (7e, 1.8 g, 9.7 mM) in EtOH (30 ml) was introduced NH_3 gas under ice-cooling at 0°C for 30 min. The reaction mixture was evaporated. The crystalline residue was suspended with diisopropyl ether, collected by filtration and then washed with diisopropyl ether to give cyclic carbamate 8e (0.5 g, 27.8%; a mixture of Z- and E-isomers in the ratio of 1:1)[12] as crystals. The filtrate and the washing were combined and concentrated. The residue was subjected to preparative HPLC eluting with EtOAc-hexane (1:1) to give ethyl 3-amino-4-(N-methylcarbamoyloxy)-2-butenoate 3e (147 mg, 7.5%) as a colorless oil, which was identical with the product obtained by Method A for preparation of 3-amino-2-butenoate derivatives 3. 8e: ir (KBr) cm^{-1} 1785, 1640, 1630, 1190; nmr ($CDCl_3$) 1.33(3H, t, J=7.5 Hz), 3.14 and 3.56(3H, s), 4.2 (2H, m), 4.80-5.20(2H, m), 5.37 and 5.40(1H, s)

Ethyl (2-oxo-3-phenyl-4-oxazolidinylidene)acetate (8j and j')

A mixture of ethyl 4-(N-phenylcarbamoyloxy)-2-butynoate (7j, 10.6 g, 42.8 mM) and ammonium acetate (15.6 g, 20 mM) in EtOH (100 ml) was heated under stirring at 60-70°C for 3 h, and then concentrated. The residue was partitioned between EtOAc and H_2O. The organic layer was separated, washed with H_2O and dried (Na_2SO_4). The crude products were purified by preparative HPLC eluting with EtOAc-hexane (1:2), to give E-isomer 8j (3.3 g, 31.1%) and then Z-isomer 8j' (4.1 g, 38.7%). 8j: mp 118-120°C; ir (KBr) cm^{-1} 1790, 1700, 1640, 1185, 1170, 1155; nmr (DMSO-d_6) 1.20(3H, t, J=7.5 Hz), 4.10(2H, d, J=7.5 Hz), 4.80(1H, t, J=1.5 Hz), 5.55(1H, d, J=1.5 Hz), 7.30-7.80(5H, m). 8j': mp 98-100°C; ir (KBr) cm^{-1} 1790, 1700, 1660, 1180, 1150; nmr (DMSO-d_6) 0.87(3H, t, J=7.5 Hz), 3.53(2H, q, J=7.5 Hz), 5.15(1H, s), 5.20(2H, s), 7.20-7.70(5H, m).

PREPARATION OF DIHYDROPYRIDINES 1a :

2-Carbamoyloxymethyl-3,5-di(methoxycarbonyl)-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine (1a)

A mixture of methyl 3-amino-4-carbamoyloxy-2-butenoate (3a, 8.7 g, 50 mM) and methyl 2-(3-

nitrobenzylidene)acetoacetate (12.2 g, 50 mM) in EtOH (200 ml) was warmed at 60-70°C for 16 h with stirring, and then concentrated. The residual solid was recrystallized from EtOAc-hexane to give 1a (12.2 g, 60%), mp 110-114°C; uv λ_{Max}^{MeOH} nm 235, 355; ir (KBr) cm^{-1} 1715, 1690, 1495, 1210; nmr ($CDCl_3$) 2.38(3H, s), 3.72(6H, s), 5.20(1H, s), 5.35(2H, s), 5.40(2H, s), 7.30-8.25(5H, m).

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11. All the aminobutenoates 3a-s formed as a major product by the conjugate addition were isolated by preparative liquid chromatography. TLC, HPLC and ^1H nmr data indicated that all these compounds were in a high state of purity as a single geometric isomer, respectively. The stereochemistry has not been determined. Minor products in the reaction were not isolated.
12. The ratio of E to Z was determined from the peak intensities of the vinyl proton of each isomer in the ^1H nmr spectrum.

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