Tetrahedron Vol 44, No 17, pp 5343 to 5353, 1988
Printed in Great Britain

0040-4020/88 $3.00 + .00
Pergamon Press plc

SOLID-LIQUID PHASE TRANSFER CATALYTIC SYNTHESIS OF α-AMINO ACID VIA ALKYLATION AND NUCLEOPHILIC ADDITION OF BENZALDEHYDE IMINES

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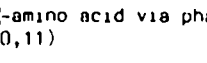
(Received in USA 21 December 1987)

Summary: A short, mild and efficient synthetic route of α-amino acid via alkylation, Michael addition and carbonyl addition as well as cycloaddition of aldimines derived from glycine and alanine esters with benzaldehyde under solid-liquid phase transfer catalytic condition has been studied. The key to solid-liquid phase transfer catalyzed reactions is the selection of a base for the various reactants. The yield is dependent on the base used. The results obtained using KOH, K_2CO_3 and Na_2CO_3 are discussed. The kinetics of solid-liquid PTC benzylation has been investigated and we propose a possible mechanism of solid-liquid PTC as an interface auto-catalytic procedure. The details of some syntheses of α-amino acids are presented.

1. INTRODUCTION

Among the various approaches to the preparation of higher α-amino acids, the alkylation of Schiff bases derived from glycine or alanine esters and aldehydes or ketones is probably the most direct one. The main limitation of this technique is the use of strong bases such as lithium diisipropylamide under anhydrous conditions.[1-6] Nevertheless, a great improvement has been made since the pioneering effort by O'Donnell[7-14] led to a simple synthesis of α-amino acid via phase transfer catalytic (PTC) alkylation of ketimine 1[7,8] and aldimine 2.[10,11]



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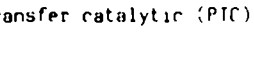

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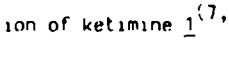

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The practical worth of this methodology is, however, to a large degree determined by the availability of the starting imine. Aldimine 3, which has a less acidic α-hydrogen, would be more suitable than imine 1 and 2 for the large scale preparation of α-amino acids. It is well known[15] that the differences of pKa between 1 (pKa = 18.8) and 2 (pKa = 18.7) or 3 (pKa ≈ 20) led to their different activities in PTC reactions. Aldimine 3 undergoes PTC alkylation or addition and would be more difficult to use than imine 1 or 2, but this problem can be solved by using a stronger base in the PTC reaction. We have tried the variant condition of using different bases. If a suitable base in the PTC reaction is selected, a better yield can be obtained. We report here the investigation of the solid-liquid phase transfer catalytic alkylation, Michael addition and carbonyl addition as well as the "1:3-dipolar" cycloaddition of the readily available benzylidene derivatives of glycine and alanine esters. This obviously provides a particularly simple and practical route to α-amino acids and their derivatives.

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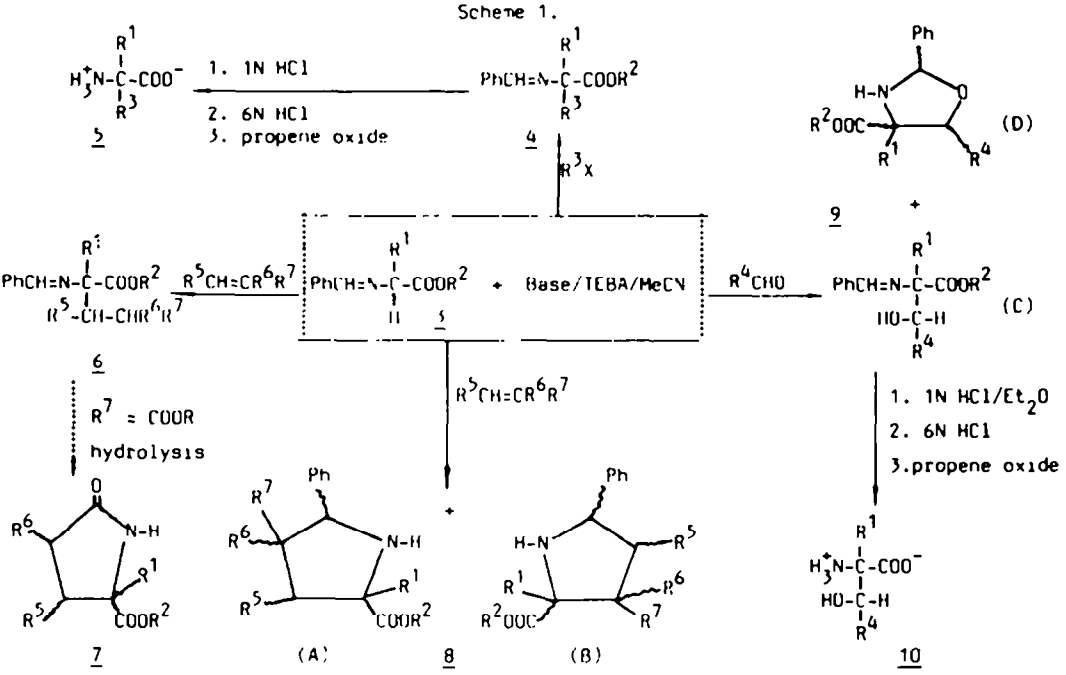
2. SYNTHETIC ROUTE

The general synthetic route to α-amino acids and their derivatives via the alkylation, Michael addition, carbonyl and "1:3-dipolar" addition in solid-liquid PTC is given in Scheme 1.

Scheme 1.



The method reported here is convenient in that it utilizes only readily available reagents. It is also versatile in that each of the three vital stages, i.e., protection, main reaction, and deprotection, is readily accomplished. Benzaldehyde is chosen as the most suitable protecting group due to its ease of introduction and removal.

a. Alkylation[16-21]

Deprotonation of aldimine 3 under solid-liquid PTC conditions using K_2CO_3, Na_2CO_3 and KOH as bases gives a highly active carbanion, whose reaction with alkyl halides gives the alkylated product 4 in good yield. Table 1 shows the factors influencing the yield of the alkylated product 4 are complicated and one of the most important factors may be the selection of the base.

In alkylation of the first α-hydrogen of 3 with an active halide such as benzyl bromide, the weaker mixed base of K_2CO_3 and Na_2CO_3 can be used and only the monoalkylated product 4a is observed. With less active halides, such as isopropyl bromide, the mixed base of KOH and K_2CO_3 must be used. In the case of dialkylation, potassium hydroxide is also necessary. Therefor monoalkylation and dialkylation of aldimine 3 can be controlled by the selection of different bases for the solid-liquid PTC reaction. It is known[15] that the α-hydrogen of methyl N-benzylidene alaninate has the weaker acidity (pKa > 20) and is relatively more stable than ethyl N-benzylidene amino acetate. Therefor a strong base such as potassium hydroxide should be used in the alkylation of methyl N-benzylidene alaninate with a less alkyl halide.

It should also be noted that the velocity of alkylation is dependent on the solid base. If potassium hydroxide is not used in the alkylation of methyl N-benzylidene alaninate, the velocity of the reaction is very slow or no reaction takes place. On the other hand, the velocity and the yield are also obviously influenced by the alkylated reagents. The higher the electrophilic activity of the alkyl halides, the shorter the reaction time, and the better the chemical yield.

Table 1. Alkylation of aldimine 3 and hydrolysis of 4

4	R^1	R^2	R^3	X	Base	Solvent	Temp.	Time hr	yield* %	Yield** of 5, (%)
a	H	Et	$C_6H_5CH_2OCH_2$	Cl	K_2CO_3/KOH	MeCN	r.t	14	80	10***
b	H	Et	4-$MeOC_6H_4CH_2$	Cl	K_2CO_3/KOH	MeCN	r.t	20	75	41
c	H	Et	CH_2=$CHCH_2$	Br	K_2CO_3/KOH	MeCN	r.t	14	89	50
d	H	Et	$EtOOCCH_2$	Br	K_2CO_3	MeCN	50 C	8	50	27****
e	H	Et	$C_6H_5CH_2$	Br	K_2CO_3/Na_2CO_3	MeCN	r.t	10	97	72
f	H	Et	$(CH_3)_2CH$	Br	K_2CO_3/KOH	MeCN	r.t	8	60	48
g	Me	Me	$C_6H_5CH_2OCH_2$	Cl	K_2CO_3/KOH	MeCN	r.t	16	90	44***
h	Me	Me	4-$MeOC_6H_4CH_2$	Cl	K_2CO_3/KOH	MeCN	r.t	14	92	45
i	Me	Me	$Me_2C_6H_3CH_2$	Cl	K_2CO_3/KOH	MeCN	r.t	8	92	47
j	Me	Me	$(MeO)_2C_6H_3CH_2$	Br	K_2CO_3/KOH	MeCN	r.t	14	90	41
k	Me	Me	$C_6H_5CH_2$	Cl	K_2CO_3/KOH	CH_2Cl_2	r.t	6	96	68
l	Me	Me	CH_2=$CHCH_2$	Br	K_2CO_3/KOH	MeCN	r.t	8	85	56
m	Me	Me	$(CH_3)_2CHCH_2$	Br	KOH	MeCN	r.t	10	41	19
n	Me	Me	$(CH_3)_2CH$	Br	KOH	MeCN	r.t	10	78	40
o	$C_6H_5CH_2$	Et	$C_6H_5CH_2$	Cl	KOH	MeCN	r.t	8	73	43

* Yield after chromatographic separation. All reactions were conducted using 10 mmoles of the starting imine (3/R^3X/K_2CO_3/KOH/TEBAC = 1.0/1.2/3.0/1.0/0.1; 3/R^3X/K_2CO_3/TEBAC = 1.0/1.2/4.0/0.1; 3/R^3X/KOH/TEBAC = 1.0/1.2/3.0/0.1). The CH_3CN was distilled from P_2O_5.

** Yield after recrystalization. Based on 4. *** R^3= $HOCH_2$ **** R^3= $HOOCCH_2$

Compound 4 can be hydrolyzed directly to the corresponding α-amino acid 5 by refluxing in 6N hydrochloric acid or by a two step hydrolysis in which 1N hydrochloric acid is used for breaking the C=N bond as well as recovering benzaldehyde and following the hydrolysis of esters in 6N hydrochloric acid. We have obtained 15 α-amino acids via this methodology. (The yield is given in Table 1.)

It is notable that the benzylation of ethyl N-benzylidene amino acetate has been performed on a two mole scale in our laboratory with no reduction in yield. It is clear from the above results that this synthetic operation is suitable for the large scale preparation of α-amino acids.

b. Michael addition[22-24]

An interesting and synthetically useful reaction occurs between aldimine 3 and active methylene compounds (R^5=H, Ar; R^6=H; R^7=CN, COOR, COPh) leading to a Michael adduct 6 in good yield under phase transfer catalytic conditions using solid K_2CO_3 as a base. The reaction is accomplished by simply stirring the solid K_2CO_3, aldimine 3 and electrophilic olefin in acetonitrile in the presence of benzyl triethylammonium chloride (TEBAC) at room temperature for 1-3 hours. The results are shown in Table 2.

The good selectivity of monoaddition has been observed when an equimolar ratio of the substrates is used in the PTC reaction. For the monoaddition using methyl acrylate or acrylonitrile as substrates, an excess of K_2CO_3 must be used. In all other cases the catalytic amount of K_2CO_3 works very well.

We have found that some addition reactions can be carried out in protic solvents such as methanol in the presence of the solid K_2CO_3.[25] The action of methanol on the reaction is considered to increase polarization of substrates via formation of a hydrogen bond. It is noteworthy that the monoaddition of methyl N-benzylidene amino acetate to methyl acrylate as well as the reaction of methyl N-benzylidene alaninate with methyl methacrylate are unsuccessful in protic solvents.

Owing to the apparent instability of the Michael adduct 6 in acid solution, the conversion

Table 2. Michael addition of aldimine 3

6	R^1	R^2	R^5	R^6	R^7	Yield,* % K_2CO_3/TEBAC/MeCN	K_2CO_3/MeOH
a	CH_2CH_2COOMe	Me	H	H	COOMe		82**
b	CH_2CH_2CN	Me	H	H	CN		72**
c	Me	Me	H	H	COOMe	92	85
d	Me	Me	H	H	CN	90	80
e	Me	Me	C_6H_5	H	COOMe	94	
f	H	Me	C_6H_5	H	COOMe		87
g	H	Me	4-Cl-C_6H_4	H	COPh		63
h	H	Et	H	H	COOMe	93***	
i	H	Et	H	H	CN	92***	

* Blank entry represents that no expected product was obtained.

** From methyl N-benzylidene amino acetate; 3/dipolarophile/K_2CO_3 = 1.0(eq.)/2.0(eq.)/0.2(eq.)

*** 3/dipolarophile/K_2CO_3/TEBAC = 1.0(eq.)/1.0(eq.)/3.0(eq.)/0.1(eq.). See the Experimental Section(Method A).

of the compound 6 to glutamic acid derivatives 7 could be easily finished by the procedure detailed by the Ref. 2.

c. Cycloaddition[26]

As a consequence of our interest in aldimine compounds, we initiated a study to examine the possibility of cycloaddition of aldimine 3 under solid-liquid PTC conditions. Table 3 shows that 1:1 adducts are formed in good yield in both method A (MeCN/TEBAC/K_2CO_3) and method B (alkanol/K_2CO_3).

Table 3. Cycloaddition of aldimine 3

8	R^1	R^2	R^5	R^6	R^7	Yield, (%) K_2CO_3/TEBAC/MeCN*	K_2CO_3/R^2OH**
a	Me	Me	4-MeOC$_6H_4$	H	COPh		82
b	Me	Me	C_6H_5	H	COPh	34	85
c	Me	Me	4-Cl- C_6H_4	H	COPh	37	87
d	Me	Me	C_6H_5CH=CH	H	COPh		63
e	H	Et	4-MeO-C_6H_4	H	COPh		85
f	Me	Me	H	Me	COOMe	90	
g	Me	Me	Me	H	CHO	92	

* Method A ; See the experimental Section. ** Method B; See the Experimental Section.

Although the reactions give rise to mixtures of all the possible regio- and stereo- isomeric pyrrolidines 8 (ratio of 8A and 8B not to be determined), we are attracted by the simplicity of the process and its potential synthetic flexibility.[27] In practice, the reactions are finished by simply stirring aldimine 3 and dipolarophile in two phase systems at room temperature for half an hour. The adducts 8a-8e have low solubility in alkanol and can be readily precipitated out of the reaction system.

d. Carbonyl addition[22-23]

Our initial studies of carbonyl addition of the aldimine 3 show that the 1:1 adducts are obtained in high yield in solid-liquid two phase systems. However, these reactions give rise to mixtures of all the possible regio- and stereo-isomeric aldimine 9(C) as well as oxazolidine

9(D). Successful condensation behaviour is illustrated by Table 4, which includes the conversion of the adduct 9 to β-hydroxyl α-amino acid 10. Once again, the reaction in protic solvents affords the advantage of simplicity and efficiency of the manipulation, but it is noteworthy that the reaction of aldimine 3 with low electrophilic aldehydes such as 4-methoxybenzaldehyde is unsuccessful.

Table 4. Carbonyl addition of aldimine 3 and hydrolysis of adduct 9

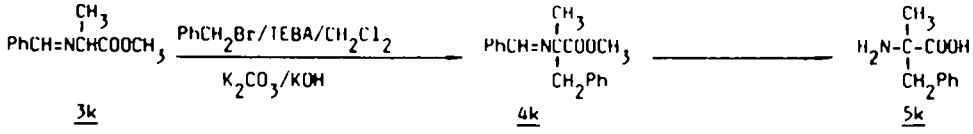
9	R^1	R^2	R^4	Yield, % A*	B*	10	R^1	R^4	Yield, % A*	B*
a	H	Et	4-O_2N-C_6H_4	95	88	a	H	4-O_2N-C_6H_4	64	62
b	H	Et	4-Cl-C_6H_4	75	75	b	H	4-Cl-C_6H_4	43	45
c	H	Et	C_6H_5	64	70	c	H	C_6H_5	10	7
d	Me	Me	H	82	80	d	Me	H	56	54

* A: K_2CO_3/TEBA/MeCN; B: K_2CO_3/R^2OH. In all cases the catalytic quantity of the base is enough.

3. MECHANISM OF ALKYLATION[21]

The influencing factors and kinetics of liquid-liquid PTC alkylation have been widely investigated.[28,29] But few papers[30] deal with the mechanism of solid-liquid PTC reactions. In order to obtain reliable data to evaluate the different factors which govern the kinetic tendency of these useful well known PTC reactions, we are now engaged in the kinetic study of solid-liquid PTC benzylation of methyl N-benzylidene alaninate.

Scheme 2.



3k 4k 5k

The factors affecting solid-liquid PTC benzylation of aldimine 3k are complicated. This paper only deals with the effects of catalyst, quantity and particle size of solid base on the reaction as well as the kinetics of the reaction. The results are summarized in Table 5.

Table 5. The influencing factors of the PTC benzylation of aldimine 3k

Entry	KOH/K_2CO_3 molar ratio	Particle size of base Mo.	TEBAC molar ratio	Reaction yield by HPLC method (%)
1	1.5/3.0	200-220	0.10	99.5
2	1.5/3.0	200-220	0.05	56.5
3	1.5/3.0	200-220	0.00	2.31
4	3.0/3.0	220	0.10	77.0
5	2.0/3.0	220	0.10	85.0
6	1.5/3.0	220	0.10	89.6
7	1.5/2.0	220	0.10	83.8
8	1.5/0.0	220	0.10	0.20
9	1.5/3.0	100-220	0.10	86.9
10	1.5/3.0	50 - 70	0.10	79.2

The benzylation here is a typical PTC reaction. When TEBAC is not added to the reaction system, the product 4k is obtained only in very low yield. However, a catalytic amount of TEBAC induces an almost quantitive benzylation. In certain conditions (Entry 1, 6, 9 and 10) a strong dependence on the base particle size is observed. The velocity of benzylation increases with decreas-

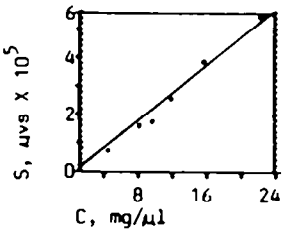
ing base particle size. Thus, a surface procedure could be presented in the reaction.

Solid base ratio is also an important factor influencing reaction yield. When the suitable ratio of mixed base (KOH/K_2CO_3 = 1.5/3.0) is used, the reaction works best.

The kinetics curve of the benzylation shows that the reaction seems to undergo two stages, i.e., slow induction period and fast-action procedure to the end. The formation of 4k and the disappearance of the substrate 3k or benzyl bromide proceed with the same exchange.

Scheme 3. The kinetic curve of the benzylation

Diagram A.



HPLC conditions:
Equipment: Backman 334
Detector: UV_{254} X 0.04 AUFS
Column: Porasil (300 X 4 mm)
Eluent: MeCOOEt(5%)/Hexane/DMF(0.5%)
Volume of flow: 0.4 ml/min
Retention time: (3k) 12'24"
(4k) 11'32"

Diagram B.

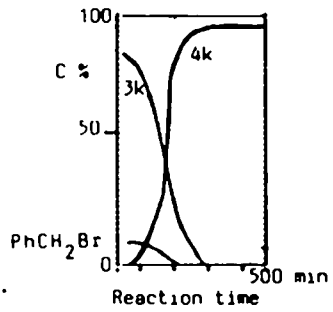


Diagram A: Working curve of 4k.
Diagram B: Kinetic curve of the solid-liquid PTC benzylation.

Having considered all the above results obtained by using the HPLC method, we conclude that the PTC benzylation of aldimine 3k has the characteristics of surface reactions and autocatalytic reactions. A possible mechanism of the alkylation is proposed as follows:

Scheme 4. A possible mechanism of solid-liquid PTC alkylation

$$SubH_{(liquid)} \equiv\equiv\equiv SubH_{(surface)} \quad (1)$$

$$Q^+X^-_{(sf.)} \equiv\equiv\equiv Q^+X^-_{(l.)} \quad (2)$$

$$SubH_{(sf.)} + KB_{(sf.)} \equiv\equiv\equiv K^+Sub^-_{(sf.)} + HB_{(sf.)} \quad (3)$$

$$K^+Sub^-_{(sf.)} + Q^+X^-_{(l.)} \equiv\equiv\equiv Sub^-Q^+_{(l.)} + KX_{(sf.)} \quad (4)$$

$$Sub^-Q^+_{(l.)} + RX_{(l.)} \equiv\equiv\equiv SubR_{(l.)} + Q^+X^-_{(l.)} \quad (5)$$

The reaction starts with the extension and absorption of the substrate (SubH) from the solution onto the solid base surface. The α-hydrogen of the substrate absorbed on the solid base surface is broken giving rise to the carbanion of the substrate which is also absorbed onto the solid surface. The procedure-(3) may be the slowest step due to including the destruction of the chemical bond and the change of solid crystal lattice energy. The carbanion on the surface is then attracted by the PTC catalyst (Q^+X^-) and the ion pair (Sub^-Q^+) formed is quickly transfered into the solution. The ion pair in the solution reacts with alkyl halide (RX) to give the alkylated product (SubR) and the catalyst is regenerated. In such a way, the reaction is continuously recycled until the end.

EXPERIMENTAL

Materials and methods. All melting points were recorded on a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded on a Microlab ^{IM}620 MX spectrophotometer. PMR spectra were measured on an F180A instument. Chemical shifts are recorded as δ values in ppm relative to TMS. Mass spectra were obtained employing a VG 70/70 instrument. Analytical TLC was carried out with precoated 0.25 mm thick silica gel plates with fluorescent indicator (E. merck). High pressure liquid chromatography was performed with a Backman 334 gradual liquid chromatographer. All solvents were dried prior to use unless otherwise noted.

Preparation of aldimine 3. Starting aldimine 3 was prepared by the procedure detailed by the Ref. 2, 19, 20. Thus, condensation of benzaldehyde and amino acid esters gave rise to the aldimine 3 in excellent yield at room temperature.

General procedure for solid-liquid PTC alkylation of aldimine 3. To a mixture of the inorganic base and the catalyst TEBAC in methylene chloride or acetonitrile was added a solution of aldimine 3 and alkylated reagent in the reaction solvent. The reaction mixture was stirred for 6-20 hours at room temperature except for 4d at 50 C. The reaction was monitored by TLC. After being filtered and washed with acetonitrile, the filtrate was concentrated under reduced pressure and the residue was taken up in ether. The ether solution was washed saturated sodium chloride solution and dried by $MgSO_4$. After removing ether, the alkylated product 4 was obtained.

The details of 4c-4f and 4k-4o had been given in the Ref. 19, 20.

4a: The mixture of K_2CO_3 (2.20g, 15 mmol), KOH (0.50g, 8.9mmol), TEBAC (0.14g, 0.61 mmol), ethyl N-benzylidene amino acetate (1.4g, 7.3 mmol) and benzyloxymethyl chloride in 40 ml acetonitrile was stirred for 14 hours at room temperature. The product 4a(1.82g) was obtained as an oil. Yield 80%. IR(film) 3020, 1740, 1645, 1580, 1500, 1250, 1110, 760, 690 cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.50(3H, CH_3), 4.10(2H, $OC\underline{H}_2Me$), 4.50(4H, $C\underline{H}_2O\underline{CH}_2Ph$), 5.00(1H, CH), 6.80-7.20(10H, 2 C_6H_5), 8.30(1H, N=CH); m/z 311 (M^+) ($C_{19}H_{21}NO_3$ requires 311).

4b: The similar reaction of ethyl N-benzylidene amino acetate with 4-methoxybenzyl chloride afforded 4b as an oil in 75% yield. IR(film) 3020, 1740, 1640, 1590, 1500, 1450, 1180, 1110, 850, 750, 700 cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.20(3H, CH_3), 3.40(2H, CH_2), 3.80(3H, $\cap CH_3$), 4.10(2H, OCH_2) 4.50(1H, CH), 6.80(4H, C_6H_4), 7.40-7.70(5H, C_6H_5), 8.50(1H, N=CH); m/z 331 (M^+).

4g: The reaction of methyl N-benzylidene alaninate and benzyloxymethyl chloride provided 4g as a colorless oil in 90% yield. IR(film) 3020, 1740, 1640, 1580, 1500, 1250, 1110, 755, 700 cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.50(3H, CH_3), 3.70(3H, OCH_3), 4.50(4H, $C\underline{H}_2O\underline{CH}_2Ph$), 6.80-7.30(10H, 2 C_6H_5), 8.30(1H, N=CH); m/z 311 (M^+) ($C_{19}H_{21}NO_3$ requires 311).

4h: The reaction of methyl N-benzylidene alaninate with 4-methoxybenzyl chloride produced 4h in 92% yield. IR(film) 3010, 1735, 1640, 1590, 1500, 1458, 1250, 1110, 850, 755, 700 cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.40(3H, CH_3), 3.20(2H, CH_2), 3.70(3H, OCH_3), 3.90(3H, OCH_3), 6.80(4H, C_6H_4), 7.40-7.70(5H, C_6H_5), 8.20(1H, N=CH); m/z 311 (M^+) ($C_{19}H_{21}NO_3$ requires 311).

4i: The alkylation of methyl N-benzylidene alaninate by 3,4-di-methyl-benzyl bromide yielded oil 4i in 92% yield. IR(film) 3020, 1730, 1640, 1580, 1500, 1450, 870, 755, 700 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.40(3H, CH_3), 2.10(6H, 2 Ar-CH_3), 3.20(2H, CH_2), 3.70(3H, OCH_3), 6.80(3H, C_5H_3), 7.3-7.70(5H, C_6H_5), 8.10(1H, N=CH); m/z 309 (M^+) ($C_{20}H_{23}NO_2$ requires 309).

4j: Yield 90%. IR(film) 1730, 1640, 1610, 1510, 1450, 1250, 1130, 800, 755, 700 cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.50(3H, CH_3), 3.20(2H, CH_2), 3.60(3H, OCH_3), 3.85(6H,2-OCH_3), 6.60(3H, C_6H_3), 6.8-7.40(4H, C_6H_4), 8.30(1H, N=CH); m/z 342 (M^+) ($C_{20}H_{23}NO_4$ requires 341).

4c: The action of ethyl N-benzylidene amino acetate with propene bromide gave 4c in 89% yield. IR(film) 3020, 1735, 1645, 1670, 1580, 1495, 1200, 1115, 995, 925, 755, 700 cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.20(3H, CH_3), 2.50(2H, CH_2), 4.00(2H, OCH_2), 5.10(2H, CH=$C\underline{H}_2$), 5.60(1H, $C\underline{H}$=CH_2),

7.30-7.70(5H, C_6H_5), 8.30(1H, N=CH); m/z 230(M^+) ($C_{14}H_{17}NO_2$ requires 231).

General procedure for hydrolysis of the alkylated product 4. 4 mmoles of the alkylated product 4 was dissolved in 15 ml of ether and 10ml of hydrochloric acid(1N). The solution was stirred for 12 hours at room temperature, and the ether was separated, solution was concentrated to dry in vacuuo. Then 15 ml of hydrochloric acid(6N) was added, refluxed for 4 hours. Followed by evaporation and addition of 20 ml ethanol and 10 ml of propene oxide to residue, the solution was heated to reflux for 15 min., and precipitate was filtered, recrystallized with H_2O-EtOH-Et_2O to give amino acid 5. Or after removing excess hydrochloric acid, the solution was taken to the isoelectric point with ammonia.

5a: Yield: 10%; IR(KBr) 3200-2400, 3400, 1650, 1620, 1510, 1420 cm^{-1}; ^{1}H-NMR(CF_3COOH) 3.36 (2H,CH_2), 3.96(1H,CH), 5.60(1H,OH), 6.67(3H,N^+H_3); $C_3H_7NO_3$ (found: C, 34.27; H, 6.75; N, 13.35. calc: C, 34.28; H, 6.61; N, 13.33).

5b: Yield: 41%; IR(KBr) 3200-2400, 1620, 1605, 1500, 1450, 1245, 850 cm^{-1}; ^{1}H-NMR(D_2O) 3.10 (2H, CH_2), 3.58(1H, CH), 5.60(1H, OH), 6.67(3H, N^+H_3); $C_3H_7NO_3$(found: C, 61.13; H, 6.40; N, 7.20. calc: C, 61.53; H, 6.65; N, 7.17).

5c: Yield: 50%; IR(KBr) 3200-2400, 1620, 1520, 1580, 1400, 995, 920 cm^{-1}; ^{1}H-NMR(D_2O) 2.60 (2H, CH_2), 3.70(1H, CH), 5.30(2H, CH_2=CH), 5.60(1H, CH=CH_2); $C_5H_9NO_2$ (found: C, 52.08; H, 7.55 N, 11.56. Calc: C, 52.17; H, 7.83; N, 12.17).

The details of 5d-5f and 5k-5o had been given in the Ref. 19 and 20.

5g: Yield: 44%; IR(KBr) 3400, 3200-2400, 1600, 1620, 1510, 1410 cm^{-1}; ^{1}H-NMR(CF_3COOH) 2.86 (3H, CH_3), 3.54(2H, CH_2), 5.61 (1H, OH), 6.42(3H, N^+H_3); $C_4H_9NO_3$(found: C, 40.46; H, 7.55; N, 11.51. calc: C, 40.33; H, 7.56; N, 11.76).

5h: Yield: 45%; IR(KBr) 3200-2400, 1650, 1610, 1510, 1460, 1400, 1250, 840 cm^{-1}; ^{1}H-NMR (D_2O) 1.71(3H, CH_3), 3.10(2H, CH_2), 3.90(3H, OCH_3), 6.70-7.25(4H, C_6H_4); $C_{11}H_{15}NO_3$ (found: C, 64.04; H, 7.33; N, 6.32. calc: C, 63.25; H, 7.17; N, 6.69).

5i: Yield: 47%; 3200-2400, 1620, 1600, 1520, 1460, 1400, 870 cm^{-1}; ^{1}H-NMR(D_2O + DCl) 1.40 (3H, CH_3), 2.00(6H, 2 Ar-CH_3), 2.70(2H, CH_2), 6.70-6.90(3H, C_6H_3); $C_{12}H_{17}NO_2$ (found: C, 69.50; H, 8.49; N, 6.76. calc: C, 68.52; H, 8.24; N, 6.76).

5j: Yield: 41%; IR(KBr) 3200-2400, 1605, 1620, 1500, 1405, 870, 1260 cm^{-1}; ^{1}H-NMR(D_2O) 1.71(3H, CH_3), 3.10(2H, CH_2), 3.72(3H, OCH_3), 3.90(6H, 2 OCH_3), 6.91-7.12(3H, C_6H_3); $C_{12}H_{17}NO_4$ (found: C, 60.25; H, 7.11; N, 6.52. calc: C, 59.84; H, 6.84; N, 5.95).

General procedure for nucleophilic addition of aldimine 3. Method A: A mixture of 0.28g(2.0mmol) K_2CO_3, 0.23g(1.0mmol) of TEBAC, 10mmoles of aldimine, and equivalent of electrophilic olefin in acetonitrile (10 ml) was stirred at room temperature until it solidified. After standing overnight, water (100 ml) was added, the separated solid filtered, washed carefully with water and dried. The crude product was purified by recrystalization in methanol or ethanol. In the cases where the reaction mixture did not solidify, after removal of solvent in vacuo, the residue was extracted with ether and dried with $MgSO_4$, the solvent was removed and the crude product was taken up in methanol so that it became solid or purified by passing chromatography. Method B: A mixture of 0.28g(2.0mmol) K_2CO_3, 10 mmoles of aldimine and the corresponding electrophilic olefin (10 mmol) in 10 ml of methanol or ethanol (dependent on R^2) was stirred until it completely solidified (about 5-30 minutes). After standing overnight, the crude product was obtained in nearly quantitative yield, then purified by recrystalization in methanol or absolute ethanol. In the non-crystalline cases the treatment is the same as method A.

6a The condensation of methyl N-benzylidene glycinate (10 mmol) with methyl acrylate (20 mmol) in method B gave 6a as an oil in 82% yield. IR(film) 1730(C=O), 1640(C=N), 750, 650(Ph) cm^{-1}; ^{1}H-NMR($CDCl_3$) 2.1-2.4(8H, m, 2 CH_2CH_2), 3.6, 3.7(9H, ss, 3 OCH_3), 8.25(1H, s, N=CH); (found: C, 61.54; H, 6.45; N, 4.10. calc for $C_{18}H_{23}NO_6$ C, 61.90; H, 6.30; N, 4.01).

6b: The condensation of methyl N-benzylidene glycinate (10 mmol) with acryonitrile(20 mmol) in the presence of K_2CO_3 in methanol gave 6b as an oil in 72% yield. IR(film) 2240(CN), 1730(C=O), 1640(C=N) cm^{-1}; ^{1}H-NMR($CDCl_3$) 2.2-2.6(8H, m, 2 CH_2CH_2), 3.8(3H, s, OCH_3), 8.25(1H, s, N=CH); (found: C, 67.39; H, 6.21; N, 14.92. calc for $C_{16}H_{17}N_3O_2$ C, 67.84; H, 6.01; N, 14.84).

6c: The reaction of methyl N-benzylidene alaninate with equivalent amount of methyl acrolate afforded 6c as a colorless oil. Yield: 92% from method A and 85% from method B; IR(film) 1725 (C=O), 1640(C=N), 1200(OCH_3), 750, 690(Ph) cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.50(3H, s, CH_3), 2.20-2.50(4H, m, CH_2CH_2), 3.60, 3.70(6H, ss, 2 OCH_3), 7.40-7.70(5H, m, C_6H_5), 8.30(1H, s, N=CH); (found: C, 65.25; H, 7.04; N, 5.06. calc for $C_{15}H_{19}NO_4$ C, 64.98; H, 6.86; N, 5.05).

6d: Yield: 90% from method A and 80% from method B; IR(film) 2240(CN), 1725(C=O), 1640(C=N), 1230(OMe), 750, 690(Ph) cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.50(3H, s, CH_3), 2.35-2.60(4H, m, CH_2CH_2), 3.70 (3H, s, OCH_3), 7.35-7.70(5H, m, C_6H_5), 8.30(1H, s, N=CH); (found: C, 63.77; H, 6.45; N,10.39. calc for $C_{14}H_{16}N_2O_2$ C, 68.85; H, 6.56 ; N, 11.48).

6e: Yield: 94% from method A; IR(film) 1725, 1705(C=O), 1640(C=N), 1160(OCH_3), 750, 690 (C_6H_5) cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.50(3H, s, CH_3), 2.90(1H, m, CH), 3.30(2H, t, CH_2), 3.60(3H, s, OCH_3), 3.70(3H, s, OCH_3), 7.30-7.70(10H, m, 2 C_6H_5), 8.30(1H, s, N=CH); (found: C, 70.38; H, 6.16; N, 3.55. calc for $C_{21}H_{23}NO_4$ C, 71.39; H, 6.52; N, 3.55).

6f: Yield: 87% from method B; IR(KBr) 1745(C=O), 1725(C=O), 1630(C=N) cm^{-1}; ^{1}H-NMR($CDCl_3$) 3.4, 3.5(6H, ss, 2 OCH_3), 2.75(2H, q, CH_2), 8.05(1H, s, N=CH); (found: C, 70.54; H, 6.23; N, 4.32. calc for $C_{20}H_{21}NO_4$ C, 70.79; H, 6.19; N, 4.13).

6g: Yield: 63% from method B; m.p. 132-134 °C (recrystalized in methanol); IR(KBr) 1745(CO-OMe), 1680(COPh), 1635(C=N) cm^{-1}; ^{1}H-NMR($CDCl_3$) 3.50(3H, s, OCH_3), 3.65(2H, d, CH_2), 3.85(1H, m CHPhCl), 5.15(1H, d, CHCOO), 7.0-8.05(15H, m, 2 C_6H_5, C_6H_4, N=CH); (found: C, 71.17; H, 5.18; N, 3.27. calc for $C_{25}H_{22}NO_3Cl$ C, 71.51; H, 5.24; N, 3.34).

6h: The monoaddition of ethyl N-benzylidene glycinate with methyl acrylate in the presence of excess amount of K_2CO_3 (3.0 molar ratio) provided the monoadduct 6h as an oil in 93% yield. IR(film) 1725(C=O), 1645(C=N), 1200(OEt), 750, 690(Ph) cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.20(3H, t, CH_3), 2.30(4H, m, 2 CH_2CH_2), 3.60(3H, s, OCH_3), 4.20(2H, q, OCH_2), 4.35(1H, m, CHCOO), 7.30-7.70(5H, m, C_6H_5), 8.30(1H, s, N=CH); (found: C, 64.62; H, 6.97; N, 5.06. calc for $C_{15}H_{19}NO_4$ C, 64.98; H 6.86; N, 5.06).

6i: The equimolar addition of ethyl N-benzylidene glycinate with acryonitrile via method A (3.0 molar ratio K_2CO_3) yielded the monoadduct 6i of 92%. IR(film) 2240(CN), 1725(C=O), 1645 (C=N), 1200(OEt), 745, 690(C_6H_5) cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.20(3H, t, CH_3), 2.35(4H, m, CH_2CH_2), 4.2 (2H, q, OCH_2), 4.35(1H, m, CHCOO), 7.30-7.70(5H, m, C_6H_5), 8.30(1H, s, N=CH); (found: C, 68.61; H, 6.77; N, 11.16. calc for $C_{14}H_{16}N_2O_2$ C, 68.85; H, 6.56; N, 11.48).

8a: Yield: 82% from method B; m.p. 105-106 °C (recrystalized in methanol); IR(film) 3240(NH) 1730(COOMe), 1670(COPh), 1180(OMe), 1030, 835, 760, 700(Ar) cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.25(3H, s,CH_3) 2.95(1H, s, NH), 3.65(3H, s, OCH_3), 3.75(3H, s, OCH_3), 4.30(1H, d, CHPhOMe), 4.80(1H, q, CHCOPh) 4.85(1H, d, NCHPh), 6.10-7.55(14H, 2 C_6H_5, C_6H_4); (found: C, 75.73; H, 6.36; N, 3.27. calc for $C_{27}H_{27}NO_4$ C, 75.52; H, 6.29; N, 3.26).

8b: Yield: 34% from method A and 85% from method B; m.p. 175-176 °C (recrystalized in methanol); IR(KBr) 3340(NH), 1745(COOMe), 1675(COPh), 1600, 1260, 1035, 760, 700 cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.25(3H, s, CH_3), 2.85(1H, s, NH), 3.25(3H, s, OCH_3), 4.35(1H, d, CHPh), 4.85(2H, m, NCHPh, CH-COPh), 6.95-7.60(15H, m, 3 C_6H_5); ^{13}C-NMR($CDCl_3$) 22.0($\underline{C}H_3$), 52.5($O\underline{C}H_3$), 55.0($\underline{C}HPh$), 56.7($N\underline{C}HPh$) 64.1($\underline{C}HCOPh$), 68.7($\underline{C}HPh$), 175.6($\underline{C}OO$), 197.7($\underline{C}OPh$); (found: C, 77.89; H, 6.18; N, 3.45. calc for $C_{26}H_{25}NO_3$ C, 78.20; H, 6.26; N, 3.52).

8c: Yield: 37% from method A and 87% from method B; m.p. 162-164 °C (methanol); IR(film) 3330(NH), 1740(COOMe), 1670(COPh), 1595, 1495, 1260, 1020, 830, 760, 700 cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.30(3H, s, CH_3), 3.05(1H, s, NH), 3.75(3H, s, OCH_3), 4.85(1H, d, CHPhCl), 4.90(2H, m, NCHPh, CHCOPh), 6.90-7.60(14H, m, C_6H_4, 2 C_6H_5); (found: C, 72.08; H, 5.57; N, 3.22; calc for

$C_{26}H_{24}ClNO_3$ C, 71.97; H, 6.00; N, 3.23).

8d: Yield: 63% from method B; m.p. 146-147°C (methanol); IR(film) 3340(NH), 1725(COOMe), 1675(COPh), 1605, 1490, 1260, 1170, 1005, 765, 695 cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.25(3H, s, CH_3), 2.95 (1H, s, NH), 3.50-4.00(1H, CH-C=C), 3.75(3H, s, OCH_3), 4.35(1H, t, CHCOPh), 4.85(1H, d, NCHPh), 6.10-6.60(2H, m, CH=C), 6.90-7.70(15H, m, 3 C_6H_5); (found: C, 79.63; H, 6.45; N, 3.32. calc for $C_{28}H_{27}NO_3$ C, 79.65; H, 6.35; N, 3.29).

8e: 85% from method B; m.p. 101-102°C (ethanol); IR(KBr) 3280(NH), 1735(COOMe), 1675(COPh), 1615, 1600, 1515, 1185, 1040, 830, 750, 700 cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.15(3H, t, CH_3), 2.95(1H, s, NH), 3.70(3H, s, OCH_3), 4.05(3H, m, CH-$COOCH_2$), 4.45(1H, m, CHCOPh), 4.90(1H, d, NCHPh), 6.40-7.55(14H, m, 2 C_6H_5, C_6H_4); (found: C, 75.35; H, 6.49; N, 3.19; calc for $C_{27}H_{27}NO_4$ C, 75.52; H, 6.29; N, 3.26).

8f: Yield: 90% from method A; IR(film) 3320(NH), 1740(COOMe), 1200, 750, 700 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.90(1H, s, NH), 1.30(3H, s, CH_3), 1.50(3H, d, CH_3), 2.00-2.90(2H, m, CH_2), 3.10-3.65 (3H, ss, OCH_3); 3.70(3H, s, OCH_3), 4.00, 4.65(1H, ss, NCHPh), 7.20(5H, s, C_6H_5); m/z 291 (M^+), 232(M^+-COOMe, base peak); (found: C, 65.27; H, 6.96; N, 4.89. calc for $C_{16}H_{21}NO_4$ C, 65.72; H, 7.22; N, 4.89).

8g: Yield: 92% from method A; IR(film) 3350(NH), 1730(COOMe), 1700, 2730(CH=O), 1150, 750, 700 cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.10(3H, m, CH_3), 1.40(3H, s, CH_3), 1.70(1H, m, NH), 2.75(1H, m, CH), 3.45(1H, m, CH), 3.75(3H, m, OCH_3), 4.50(1H, m, CH), 7.60(5H, q, C_6H_5), 9.75(1H, s, CHO); m/z 361 (M^+), 246(M^+-CH_3), 232(M^+-CHO), 202(M^+-COOMe, base peak).

9a: Yield: 95% from method A and 92% from method B; m.p. 103-105°C (recrystalized in ethanol); IR(film) 3320(NH), 1725(COOEt), 1650(weak, C=N), 1225, 1075, 855, 700 cm^{-1}; ^{1}H-NMR($CDCl_3$) 0.85, 0.95(3H, tt, CH_3), 3.55, 3.90(4H, m, NH, $CHCOOCH_2$), 5.05(1H, m, $CHPhNO_2$), 5.25, 6.05(1H, ss, CHPh), 6.90-7.95(9H, m, C_6H_4, C_6H_5); m/z 341 (M^+), 269(M-COOEt); (found: C, 62.31; H, 5.50; N, 8.66. calc for $C_{18}H_{18}N_2O_5$ C, 62.16; H, 5.26; N, 8.19).

9b: Yield: 75% from both method A and method B; m.p. 99-101°C (ethanol-hexane); IR(KBr) 3325(NH), 1735(COOEt), 1650(weak, C=N), 1200, 1050, 825, 750, 690 cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.25(3H, m, CH_3), 2.55(1H, s, NH), 3.70-4.40(3H, m, $CHCOOCH_2$), 4.95, 5.15(1H, tt, $CHPhCl$), 5.70, 5.85 (1H, dd, CHPh), 7.10-7.75(9H, m, C_6H_4, C_6H_5); m/z 332 (M^+ + H), 258(M-COOEt, base peak); (found: C, 65.43; H, 5.46; N, 4.22. calc for $C_{18}H_{18}ClNO_3$ C, 65.16; H, 5.43; N, 4.22).

9c: The crude yield: 64% from method A and 70% from method B; It was directly hydrolyzed to yield 10c.

9d: The crude yield: 82% from method A and 80% from metnod B; It was directly hydrolyzed to 10d.

Hydrolysis of the carbonyl addition product 9. In the same treatment as hydrolysis of the alkylated product 4, β-hydroxy-α-amino acid 10 was obtained by hydrolysis of the carbonyl adduct 9.

10a: Yield: 64%; m.p. 180-183°C(dec); IR(KBr), 3570(OH), 3200-2400(N^+H_3), 824(C_6H_4) cm^{-1}; ^{1}H-NMR(CF_3COOD) 3.35(1H, d, CH), 4.55(1H, d, CH), 6.80-7.20(4H,q, C_6H_4); (found: C, 47.67; H, 4.42; N, 12.06. calc for $C_9H_{10}N_2O_5$ C, 47.79; H, 4.42; N, 12.39).

10b: Yield 43%; m.p. 153-155°C (dec.); IR(KBr) 3400(OH), 3100-2500(N^+H_3), 1630(COO^-), 830 (C_6H_4) cm^{-1}; ^{1}H-NMR(D_2O) 4.10(1H, d, CHCOO), 5.35(1H, t, CHAr), 7.50(4H, s, C_6H_4); (found: C, 47.87; H, 4.86; N, 5.95. calc for $C_9H_{10}ClNO_3$ C, 50.12; H, 4.64; N, 6.50).

10c: Yield: 10% from 9c of method A and 7% from 9c of method B; m.p. 190-192°C; IR(KBr) 3400(OH), 3100(N^+H_3), 1610(COO^-), 700(C_6H_5) cm^{-1}; ^{1}H-NMR(D_2O) 4.00(1H, d, CH), 5.25(1H, s,CHAr) 7.90(5H, s, C_6H_5); (found: C, 59.50; H, 6.31; N, 7.68. calc for $C_9H_{11}NO_3$ C, 56.97; H, 6.08; N, 7.73).

10d: Yield: 56%; m.p. 253°C; IR(KBr) 3400(OH), 3100-2400(NH_3^+), 1610(COO^-) cm^{-1}; ^{1}H-NMR(D_2O) 1.45(3H, s, CH_3), 3.80(2H, q, CH_2); (found: C, 39.83; H, 7.84; N, 11.45. calc for $C_4H_9NO_3$ C, 40.33; H, 7.56; N, 11.76).

Acknowledgments: The authors are grateful to National Nature Science Foundation of China and Youth Prizing Research Fund of the Chinese Academy of Sciences as well as Humboldt Foundation of West Germeny for supporting this research work.

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