

THE ASYMMETRIC SYNTHESIS OF AMINO ACIDS UNDER POLYMER-SUPPORTED PHASE TRANSFER CATALYTIC CONDITION*

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Abstract The optical α -amino acids were synthesized under room temperature by alkylation of N-(diphenyl methylene) glycine *t*-butyl ester under polymer-supported phase transfer conditions using polymer-supported cinchonine (or quinine) alkaloids as chiral phase transfer catalysts and dichloromethane as solvent, followed by hydrolysis of the above intermediates introduced to the final products—optical α -amino acids. This is a new method for the asymmetric synthesis of α -amino acids. The influences of catalyst, temperature, substrates, and organic solvents on the chemical yield and optical purities of products were studied.

Keywords Asymmetric organic synthesis; Polymer supported phase transfer catalysts (PS-PTC); α -Amino acids

INTRODUCTION

α -Amino acids are important physiological active substances for the existing of human being. Only racemates can be obtained when the general chemical synthesis methods are used. The investigation of the asymmetric synthesis of α -amino acids appears more and more important for the organists.

Asymmetric synthesis of α -amino acids by polymer supported phase transfer catalytic alkylation using a chiral catalysis and a prochiral protected glycine derivatives would give a particularly attractive method for the preparation of optically active α -amino acids. There are several practical advantages when PS-PTC are used e.g. the

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isolation of product is simplified, the catalyst can be easily recovered and possibly reused et al..^[1~3].

In this paper the polymer supported cinchonine alkaloids have been used as PS-PTC in order to carry out the asymmetric alkylation of a prochiral protected glycine derivatives.

EXPERIMENTAL

Materials

P-Nitrobenzyl bromide, *p*-chlorobenzyl chloride and *m*-chloro benzyl bromide, (analytical grade) from Aldrich Co. were used without further purification. Benzyl bromide, methyl iodide, *n*-propyl bromide, allyl bromide, (chemical grade) available commercially were used without further purification.

Apparatus

¹H-NMR spectra were recorded on a Jeol FX-90Q NMR spectrometer and MS spectra were recorded on 7070-HE Mass spectrometer, the Elemental analyses were conducted on a PE-240 CHN analyzer. The optical rotation was conducted on WZZ-1 polarimeter, Physical Optical Instrument Plant, Shanghai, China.

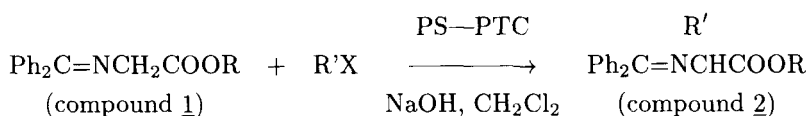
Typical procedure for the synthesis of polymer-supported cinchonine (or quinine) alkaloids

20g chlormethylated styrene-divinylbenzene copolymer bead (2.91 mmol CL/g) and 100mL chloroform were placed into a 250 mL 3-necked flask. After 2~3 h of swelling, 16 g (54.3 mmol) cinchonine was added. The flask was heated under refluxing for about 50 h. During this course the color of the copolymer bead turned into dark red. After cooling, the copolymer bead were filtered out and washed with ethanol and pure water, extracted with chloroform in a Soxhlet extractor for 72 h.

Typical procedure for the synthesis of prochiral protected glycine derivatives (compound 1)

20 g (0.11 mol) benzophenone imine^[6], 18.5 g (0.11 mol) *t*-butyl glycine hydrochloride acid and 400 mL dichloromethane were placed in a 500 mL flask protected by calcuinm chloride dry tube, the reaction was carried out at room temperature accompanied with a vigorous stirring, filtered out the ammonium chloride and removed the solvent by rotary evaporator. The crude product was dissolved in 400 mL diethylether and washed with water, the oil layer was dried with magnesium sulfate anhydrous over night, recrystallized using ether/hexane as the solvents, 26.1 g pure product was obtained m.p. 113~115°C, yield 80%.

Typical procedure for the alkylation of compound 1 under PS-PTC condition.



0.84g (1.6mmol) PS-CN and 60mL dichloromethane were placed in a 250mL 3-necked flask, was followed. After one hour of swelling the compound 1, the alkylation agents and 50% sodium hydroxide were added. The reaction was carried out at room temperature accompanied with vigorous mechanical stirring, and monitored by TLC, 20h are generally needed for finishing the reaction. After the reaction came to completion, a proper amount of water and dichloromethane was added, filtered out the resin catalyst and washed with dichloromethane.

The organic layer was separated and dried with magnesium sulfate anhydrous over night. After the solvent was removed a silica gel column chromatograph was used for separate the product (1:4 of dichloromethane: 60 ~ 90°C petrol. ether as eluent).

The typical procedure for the hydrolysis of compound 2

About 3g compound 2 was charged into 50 mL Erlenmeyer's flask and refluxed under 15 mL 6N hydrochloric acid for 4 ~ 5h monitored by TLC. After the compounds decomposed completely the water phase was washed with 15 mL ether twice and dried in magnesium sulfate anhydrous, recrystallized by C₂H₅OH/water to obtain the products.

RESULTS AND DISCUSSION

The result of elemental microanalysis of resin catalysts is shown in Table 1

Table 1 The Elemental microanalysis of resin*

Code	Carbon (%)	Hydrogen (%)	Nitrogen (%)	Capacity (meq./g)
PS-CN	80.925	7.468	5.6055	2.002
PS-QN	80.636	7.440	5.0165	1.792

*PS-CN: polymer supported cinchonine; PS-QN: polymer supported quinine

The alkylation reaction condition of prochiral protected glycine derivatives, the chemical and the optical yield, the configuration of the products were given in Table 2 and the results of their ¹H-NMR spectra, the MS and the elemental analysis were given in Table 3.

Table 4 shows the optical yields and other physicochemical properties of the final α-amino acids. It was found in both Table 2 and Table 4 that the optical yield of the

products is not very high as compared with that in the Ref.7, the similar reaction catalyzed by small molecular analogue.

Table 2 The alkylation of prochiral protected glycine derivatives*

RX	PS-PTC	<i>t</i> (h)	Chemical yields (%)	$[\alpha]_D^{20}$	Excess config. of
Benzyl bromide	PS.CN.	20	48	+1.2	R
	PS.QN	15	51	-0.84	S
Methyl iodide	PS.CN	35	32	+0.21	R
	PS.QN	30	29	-0.08	S
Allyl bromide	PS.CN	24	40	+56	R
	PS.QN	25	38	-6.32	S
iso-Propyl bromide	PS.CN	35	35	+3.4	R
	PS.QN	35	38	-2.6	S
<i>p</i> -Chlorobenzyl chloride	PS.CN	35	55	+2.17	R
	PS.QN	30	52	-1.88	S
Propyl bromide	PS.CN	30	31	+4.8	R
	PS.QN	30	30	-2.5	S
<i>p</i> -Nitrobenzyl bromide	PS.CN	15	68	+0.6	R
<i>m</i> -Chlorobenzylbromide	PS.CN	35	48	+1.65	R
<i>o</i> -Chlorobenzylbromide	PS.CN	35	50	+1.78	R

* The solvent used in this reaction is CH₂Cl₂-H₂O and the reaction temperature is 20°C.

The influence of the alkylation reagents on the chemical and optical yields

It was found that during the alkylation reaction, the easier the carbenium ion could be formed from the alkylation reagents. The higher the chemical yields could be achieved. e.g. by comparing the allyl bromide and *n*-propyl bromide the former one is more active than the latter one, so the chemical yield is more higher when the allyl bromide was used. Another example was *p*-nitro benzyl bromide and benzyl bromide, the former one is more active so the chemical yield is higher.

The optical yield is another important factor for the reaction, it was found the bulk factor is very obvious. Larger alkylation reagents would give pretty good optical yield but the small one would give poor result. e.g. isopropyl bromide is better than methyl iodide. Also the reaction speed is more important, generally the relation between the reaction speed and the optical yield is in reverse order, i.e faster reaction speed would introduce poor optical yield.

Table 3 The chemical shift of ^1H -NMR, the Mass spectrum and microanalysis of alkylated prochloral glycine derivatives

Chemical structure	Molecular formula	Elemental analysis (%)	^1H -NMR chemical shift (δ^{**})	MS m/z (Relative abundance)
$\text{Ph}_2\text{C}=\text{NCHCOOC}(\text{CH}_3)_3$			1.5 (9H, s, $\text{C}(\text{CH}_3)_3$) 4.2 (2H, s, CH_2) 7.3~7.8 (10H, m, Ph_2)	
$\text{Ph}_2\text{C}=\text{NCHCOOC}(\text{CH}_3)_3$ CH_2Ph	$\text{C}_{26}\text{H}_{27}\text{NO}_2$	80.84 6.94 3.64 (81.00) (7.00) (3.60)	1.4 (9H, s, $\text{C}(\text{CH}_3)_3$) 3.25 (2H, t, CH_2) 4.1 (1H, q, CH) 6.5 ~ 7.6 (15H, m, Ph_3)	385 (M^+ , 2.24) 294 (M^+ , $-\text{CH}_2\text{Ph}$, 26.1), 284 (M^+ , $-\text{COOC}_4\text{H}_9$, 100)
$\text{Ph}_2\text{C}=\text{NCHCOOC}(\text{CH}_3)_3$ $\text{CH}_2\text{CH}=\text{CH}_2$	$\text{C}_{22}\text{H}_{25}\text{NO}_2$	78.89 7.55 4.31 (78.81) (7.46) (4.18)	1.42(9H, s, $\text{C}(\text{CH}_3)_3$) 2.62 (2H, q, CH_2) 4.1 (1H, t, CH) 5.1 (2H, m, $=\text{CH}_2$) 5.7 (2H, m, $\text{CH}=\text{CH}_2$) 7.14 ~ 7.85 (10H, m, Ph_2)	335 (M^+ , 13.18) 234 (M^+ , $-\text{COOC}_4\text{H}_9$, 100)
$\text{Ph}_2\text{C}=\text{NCHCOOC}(\text{CH}_3)_3$ CH_3	$\text{C}_{20}\text{H}_{23}\text{NO}_2$	77.04 7.45 4.24 (77.67) (7.44) (4.53)	1.5 (9H, s, $\text{C}(\text{CH}_3)_3$) 1.4(3H, d, CH_3) 4.1 (1H, q, CH) 7.0 ~ 7.8 (10H, m, Ph_2)	309 (M^+ , 0.62) 294 (M^+ , $-\text{CH}_3$, 0.57) 208 (M^+ , $-\text{COOC}_4\text{H}_9$, 100)
$\text{Ph}_2\text{C}=\text{NCHCOOC}(\text{CH}_3)_3$ $\text{CH}_2\text{C}_6\text{H}_4\text{NO}_2$	$\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_4$	72.32 6.63 6.33 (72.56) (6.05) (6.51)	1.42(9H, s, $\text{C}(\text{CH}_3)_3$) 3.2~3.4 (2H, d, CH_2) 4.2 (1H, t, CH) 6.7 ~ 7.7 (14H, m, Ph_3)	430 (M^+ , 0.12) 329 (M^+ , $-\text{COOC}_4\text{H}_9$, 100) 294 (M^+ , $-\text{CH}_2\text{C}_6\text{H}_4\text{NO}_2$, 9.81)
$\text{Ph}_2\text{C}=\text{NCHCOOC}(\text{CH}_3)_3$ $\text{CH}_2\text{C}_6\text{H}_4\text{Cl}$	$\text{C}_{26}\text{H}_{26}\text{NO}_2\text{Cl}$	74.81 6.50 3.42 (74.37) (6.20) (3.34)	1.42(9H, s, $\text{C}(\text{CH}_3)_3$) 3.2 (2H, d, CH_2) 4.1 (1H, q, CH) 6.7 ~ 7.6 (14H, m, Ph_3)	419 (M^+ , 0.78) 318 (M^+ , $-\text{COOC}_4\text{H}_9$, 84.99) 294 (M^+ , $-\text{CH}_2\text{C}_6\text{H}_4\text{Cl}$, 33.62)
$\text{Ph}_2\text{C}=\text{NCHCOOC}(\text{CH}_3)_3$ $\text{CH}_2\text{CH}_2\text{CH}_3$	$\text{C}_{22}\text{H}_{27}\text{NO}_2$	78.26 8.03 4.18 (78.34) (8.01) (4.15)	1.7(9H, s, $\text{C}(\text{CH}_3)_3$) 1.1 (3H, t, CH_3) 1.3 (2H, m, CH_2) 2.1 (2H, m, CH_2) 4.2 (1H, t, CH) 7.2~7.8 (10H, m, Ph_2)	337 (M^+ , 1.60) 280 (M^+ , $-\text{C}(\text{CH}_3)_3$, 2.98) 236 (M^+ , $-\text{COOC}_4\text{H}_9$, 100)

* The data in brackets are calculated value; ** CDCl_3 as solvent

Table 4 The physicochemical properties of the final products

CODE	PS-PTC	$[\alpha]_D^{20}$	Optical yield %	Major config.	M.P. (°C)
Phenylalanine	PS-CN	+3.08	8.82	D	268~ 272
	PS-QN	-2.1	6.2	L	270 ~ 273
Alanine	PS-CN	-0.21	1.48	D	287 ~ 293
	PS-QN	+0.09	0.61	L	290 ~ 294
Valine	PS-CN	-3.42	12.5%	D	> 300
	PS-QN	+2.6	9.4%	L	> 300
2-Amino-4-pentenoic acid	PS-CN	+9.78		D	260 ~ 265
	PS-QN	-4.15	11.5%	L	263 ~ 267
<i>p</i> -Chloro phenylalanine	PS-CN	+2.24	9.5%	D	234 ~ 237
	PS-QN	-1.95	8.48	L	236~ 240
<i>p</i> -Nitrophenylalanine	PS-QN	1.36			238 ~ 240
<i>o</i> -Chlorophenylalanine	PS-CN	2.76			
<i>m</i> -Chlorophenylalanine	PS-CN	3.23			

CONCLUSION

Asymmetric synthesis of α -amino acids under polymer-supported phase transfer catalytic condition is innovatory to obtain the chiral product. This reaction was carried out under mild reaction condition and the operation procedure was convenient.

The polymeric catalyst can be recovered and reused easily. But the chemical yield especially the optical yield is not very satisfactory at the moment.

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