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Solid-phase synthetic method for (±)-α-amino acids via phase-transfer catalytic alkylation

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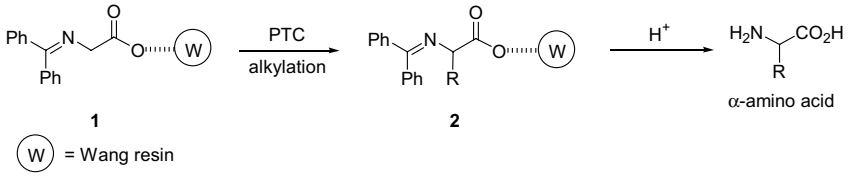
Abstract—A solid supported glycineimine *t*-butyl ester was designed and successfully applied to the synthesis of (±)-α-amino acids. The phase-transfer catalytic alkylation, followed by acidic hydrolysis and benzoylation gave *N*-benzoyl-α-amino acid *tert*-butyl esters in high yields (up to 92%).

Natural and nonnatural (±)-α-amino acids have been regarded as one of the important components for the drug design of peptidomimetics, due to their important role in activity, stability and bioavailability.[1] Among the synthetic methodologies, the solid-phase synthetic methods have been extensively developed and applied to the combinatorial synthesis or parallel synthesis of α-amino acids and peptides.[2] Recently, O'Donnell and Scott reported very efficient solid-phase synthetic methods for α-amino acids and peptides by the phase-transfer alkylation.[3] They used the resin bound diphenylimine-glycine ester (**1**) and successfully applied to the synthesis of natural and nonnatural α-amino acids (Scheme 1). In this letter, we report a new solid-phase synthetic method for α-amino acids via phase-transfer catalytic alkylation.

The connecting point of the linker to the solid support should be chemically stable during the synthesis. Also, its cleavage should be as quantitative as possible at the final stage of the synthesis. Among the various linkers developed over the past 20 years, most of the linkers for the synthesis of α-amino acids and peptides were ester (Scheme 1).[2] Imines have not been popular linkers due to their instability in acidic condition. But it was presumed that aromatic imines could be stable enough to prevent the hydrolysis in the basic conditions of the phase-transfer alkylation. In addition, the aromatic imine linkers themselves could take place of the role of imine moieties in diphenylimine-glycine esters, which could make the α-hydrogen acidic enough to form the corresponding enolate by weak alkali bases.[4] Therefore, the linker was changed from an ester group (**1**) to an imine group (**3**) and the resin bound ester was replaced with *t*-butyl ester, as shown in Scheme 2.

Resin bound *t*-butyl imine esters **8A** and **8B** were prepared from Merrifield resin.[5] The Merrifield resin was oxidized to the corresponding aldehyde **6A** by



Scheme 1.

Keywords: Phase-transfer catalytic alkylation; Solid-phase synthesis; α-Amino acid.
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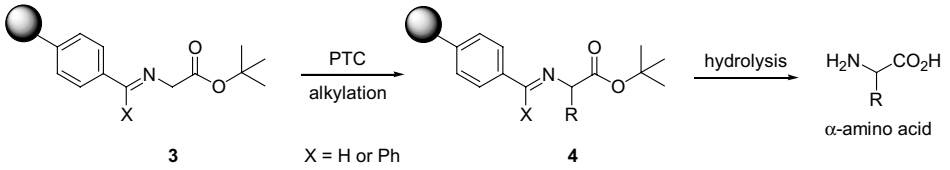
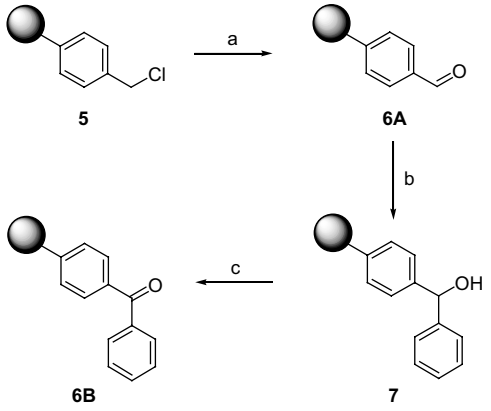
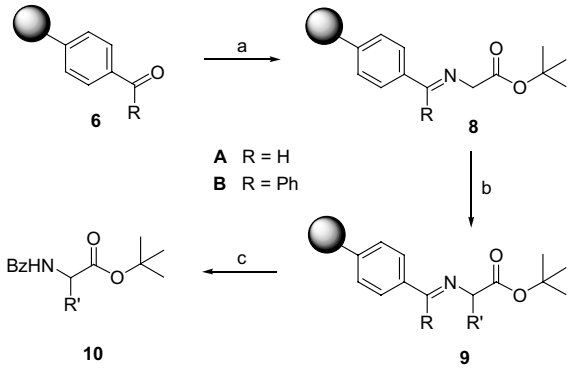


Scheme 2.

dimethylsulfoxide in the presence of $NaHCO_3$.[6] The addition of phenyl Grignard reagent to **6A**, followed by oxidation gave **6B**. The condensation of **6A** and **6B** with glycine *t*-butyl ester gave the corresponding imines **8A** and **8B**, respectively. Their efficiencies for phase-transfer alkylation were evaluated by benzylation.[7] The phase-transfer benzylations of **8A** and **8B** were performed by using 10 mol% of tetrabutylammonium bromide with benzyl bromide (5 equiv) and 50% aqueous KOH (10 equiv) in toluene/chloroform (volume ratio = 7:3) at room temperature for 48 h. The hydrolysis of the α-benzylated ketimine **9B** with 1 N HCl, followed by benzoylation afforded **10** (27%) along the corresponding nonalkylated product (52%). In the case of the α-benzylated aldimine **9A**, **10** (85%) was obtained without any nonalkylated product, showing that the aldimine (**8A**) is a more appropriate substrate than the ketimine (**8B**) in solid-phase alkylation. Notably, there was no dibenzylated product from **8A** in the presence of excess base. Generally, the aldimines have been applied to the synthesis of α,α-dialkylamino acids in solution-phase system.[8] Once the aldimines are alkylated, another α-hydrogen still acidic enough to form the corresponding enolates for the second alkylation in the presence of excess base. However, the solid supported aldimine (**8A**) gave only mono-alkylation. We tentatively propose that the second alkylation might be inhibited by the steric hinderance, involved in solid-supported polymer itself. **8A** was chosen for further investigation with various alkyl halides.[9] The high yields (up to 92%) shown in Table 1 indicate that this solid-phase synthetic method is a very efficient synthetic method for natural and nonnatural (±)-α-amino acids. As one of merits compared to O'Donnell and Scott's method, **6A** could be recovered

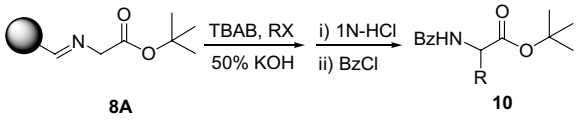


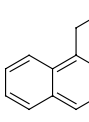
Scheme 3. Reagents and conditions: (a) $NaHCO_3$, DMSO, 150 °C, 15 h; (b) PhMgBr, THF, 0 °C; (c) Dess-martin periodinane, CH_2Cl_2, 0 °C.



Scheme 4. Reagents and conditions: (a) glycine *t*-butyl ester·HCl, Et_3N, C_6H_6, reflux, 27 h, (b) 50% aq KOH, RX, toluene–$CHCl_3$ (7:3), rt (c) (i) 1 N HCl, THF, rt, (ii) BzCl, TEA, CH_2Cl_2, rt, 50–92% from **8**.

Table 1. Phase-transfer catalytic alkylation[a]



Entry	RX	Yield[b] (%)
a	$CH_3(CH_2)_4CH_2I$	50
b		82
c		80
d		85
e		82
f		78
g		88
h		87
i		92
j		85

[a] The reaction was carried out with 5.0 equiv of benzyl bromide and 10.0 equiv of 50% aqueous KOH in the presence of 10.0 mol% of catalyst in toluene/chloroform (7:3) at room temperature for 48 h.
[b] Isolated yield (**10**).

after hydrolysis of **9A** and directly recycled to prepare the substrate **8A**, which could make the imine-linker method more practical for industrial process[10] (Schemes 3 and 4).

In conclusion, a new, efficient solid-phase synthetic methodology for α-amino acids was developed using the phase-transfer catalytic alkylation of resin bound *t*-butyl glycine-imine ester (**8A**), and showed that the aromatic imines could be efficient linkers in the solid-supported phase transfer alkylation. The easy preparation of the solid supported substrate, the high chemical yield, the very mild reaction conditions and the recycling of **6A** could make this method applicable to the combinatorial synthesis or parallel synthesis for α-amino acids.

Acknowledgements

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References and notes

1. For lead references, see: *Asymmetric Synthesis of Novel Sterically Constrained Amino Acids*; Symposium-in-Print, Hruby, V. J.; Soloshonok, V. A., Eds. *Tetrahedron* **2001**, *57*, 6329–6650.
2. (a) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2419; (b) Merrifield, R. B. *Science* **1986**, *232*, 341; (c) Terrett, N. K. *Combinatorial Chemistry*; Oxford University Press: Oxford, 1998; Dörwald, F. Z. *Organic Synthesis on Solid Phase*; Wiley-VCH Verlag: GmbH (Germany), 2000; Bannwarth, W.; Felder, E. *Combinatorial Chemistry*; Wiley-VCH Verlag: GmbH (Germany), 2000; Seneci, P. *Solid-Phase Synthesis and Combinatorial Technologies*; John Wiley and Sons: New York, 2000.
3. (a) O'Donnell, M. J.; Zhou, C.; Scott, W. L. *J. Am. Chem. Soc.* **1996**, *118*, 6070; (b) Scott, W. L.; Zhou, C.; Fang, Z.; O'Donnell, M. J. *Tetrahedron Lett.* **1997**, *38*, 3695; (c) O'Donnell, M. J.; Lugar, C. W.; Pottorf, R. S.; Zhou, C. *Tetrahedron Lett.* **1997**, *38*, 7163; (d) Griffith, D. L.; O'Donnell, M. J.; Pottorf, R. S.; Scott, W. L.; Porco, J. A., Jr. *Tetrahedron Lett.* **1997**, *38*, 8821; (e) Dorminguez, E.; O'Donnell, M. J.; Scott, W. L. *Tetrahedron Lett.* **1998**, *39*, 2167.
4. (a) O'Donnell, M. J.; Boniece, J. M.; Earp, S. E. *Tetrahedron Lett.* **1978**, *19*, 2641; (b) O'Donnell, M. J.; Eckrich, T. M. *Tetrahedron Lett.* **1978**, *19*, 4625; (c) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663; (d) O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3.
5. Procedure for the synthesis of **8A**: To a dimethyl sulfoxide (120 mL) mixture of Merrifield resin (20 g, 0.94 mmol/g, purchased from BEADTECH in Korea) were added sodium bicarbonate (4 g, 7.0 mmol) and the reaction mixture was stirred for 12 h at 155 °C. The resin was then filtrated and washed with a series of solvents: dimethyl sulfoxide, water, a mixture of dioxane and water (2:1), dioxane, acetone, ethanol, dichloromethane. White resin **6A** (18 g) was obtained after drying under vacuum, IR (KBr) 3440, 3022, 2913, 1698, 1602, 1489 cm^{-1}. To an anhydrous benzene (140 mL) mixture of the aldehyde resin **6A** (18 g) and glycine *tert*-butyl ester hydrochloride (9 g, 52 mmol) was added triethylamine (8.7 g, 52 mmol) and the reaction mixture was refluxed for 10 h at 80 °C. The resin was filtrated and washed with a series of solvents: benzene, dichloromethane, a mixture of dichloromethane and methanol (1:1), methanol and dichloromethane. Pale yellow resin **8A** (18 g, 0.26 mmol/g) was obtained after drying under vacuum, IR (KBr) 3441, 3025, 2920, 1736, 1646, 1603 cm^{-1}.
6. Frechet, J. M.; Schuerch, C. *J. Am. Chem. Soc.* **1971**, *93*, 492.
7. Representative procedure for the catalytic phase-transfer alkylation of **8A** (benzylation): To a mixture of aldimine **8A** (300 mg, 0.077 mmol) and tetrabutylammonium bromide (2.6 mg, 0.008 mmol) in 7:3 mixture of toluene and chloroform (2 mL) was added 50% aqueous potassium hydroxide (0.3 mL, 1.0 mmol) and benzyl bromide (0.045 mL, 0.38 mmol). The reaction mixture was stirred vigorously at room temperature for 48 h. The resin was filtrated and washed with methylene chloride and methanol. The yellow coloured resin **9A** was dried under vacuum. To the resin **9A** in tetrahydrofuran (1 mL) was added 1 N HCl (0.5 mL) and the reaction mixture were stirred at room temperature for 1 h. The reaction mixture was filtered and washed with tetrahydrofuran, methylene chloride and methanol. The combined solvent was removed under vacuum, basified with satd aq $NaHCO_3$ (3 mL) and extracted with methylene chloride (5 × 10 mL). The combined methylene chloride was dried over anhydrous $MgSO_4$ and concentrated under vacuum. To the methylene chloride (0.5 mL) solution of the residue was added triethylamine (0.032 mL, 0.24 mmol) and benzoyl chloride (0.013 mL, 0.12 mmol) at 0 °C. The reaction mixture was stirred for 0.5 h and extracted with methylene chloride (5 × 5 mL). The combined methylene chloride was washed with water, dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, hexane–EtOAc = 10:1) to afford the desired product **10d** as white solid.
8. (a) O'Donnell, M. J.; Wu, S. *Tetrahedron: Asymmetry* **1992**, *3*, 591; (b) Lygo, B.; Crosby, J.; Perterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671; (c) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228; (d) Jew, S.-s.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Lee, Y.-J.; Park, B.-s.; Park, H.-g. *J. Org. Chem.* **2003**, *68*, 4514.
9. All new compounds gave satisfactory analytical and spectral data. *Selected data* for **10d**: White solid; mp 61 °C ($CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, J = 8.6 Hz, 2H), 7.33–7.46 (m, 5H), 7.24–7.11 (m, 2H), 6.58 (d, J = 6.8 Hz, 1H), 4.86–4.93 (m, 1H), 3.17 (d, J = 5.3 Hz, 2H), 1.37 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.8, 166.8, 133.7, 131.7, 130.2, 129.6, 128.6, 128.4, 127.0, 82.7, 53.9, 38.0, 28.0 ppm; IR (KBr) 2978, 1723, 1645, 1530, 1488, 1453 cm^{-1}; MS (ESI) *m/z* 348 $[M+Na]^+$, HRMS (FAB) calcd for $[C_{20}H_{22}NO_3]$: 324.3936, found: 325.1679 $[M+H]^+$.
10. The recovered resin **6A** was confirmed by IR spectral data and successfully applied for the synthesis of α-amino acids.