Diastereoselective Solid-Phase Radical Addition to Oxime Ether Anchored to Polymer Support

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Stereocontrol in radical reactions of oxime ether anchored to polymer support was studied. Highly diastereoselective solid-phase radical reaction was achieved by using triethylborane and diethylzinc as a radical initiator at low reaction temperature, providing a novel method for the synthesis of the α-amino acid derivatives with excellent diastereoselectivities.

Key words solid-phase; radical reaction; oxime ether; diastereoselective

Combinatorial chemistry has become a core technology for the rapid development of novel lead compounds in the pharmaceutical industry and for the optimization of therapeutic efficacy.2–9 Therefore, the development of solid-phase radical reactions is a new subject of considerable interest as a carbon–carbon bond-forming method on solid support.10–19 Some recent reports have shown that radical reactions could be performed on solid supports by using AIBN or Sml, as a radical initiator. We have also demonstrated that triethylborane or diethylzinc have the potential to induce intermolecular radical reactions on solid support.20–22

Stereocontrol in free radical-mediated reactions has been of great importance in organic synthesis. In recent years, a high degree of stereocontrol in solution-phase radical reactions has been achieved at low reaction temperature mainly by using triethylborane as a radical initiator. We have recently demonstrated that the employment of triethylborane or diethylzinc, particularly at low reaction temperature, facilitated the control of stereoechemistry in solid-phase radical reaction.20–23 We report here in detail the triethylborane- or diethylzinc-induced diastereoselective radical reaction of Oppolzer’s camphorsultam derivatives of oxime ether anchored to polymer support.23

Results and Discussion

Our recent studies showed that triethylborane has the potential to induce solid-phase radical reaction of oxime ether (TYPE 1) on solid support even at −78 °C and acts multiply as a radical initiator, a Lewis acid, and a radical terminator (Chart 1).20 Based on these results, we next investigated the control of stereocchemistry in solid-phase reactions of oxime ether (TYPE 2) by using triethylborane and diethylzinc at low reaction temperature.23 The auxiliary of choice was Oppolzer’s camphorsultam since it had shown good characteristics in our previous work on solution-phase radical reactions.24,25

Preparation of chiral oxime ether 1 anchored to a polymer support is shown in Chart 2. Treatment of p-xylene glycol 2 with TBSCI and imidazole gave the r-butyldimethylsilylated p-xylene glycol derivative 3 in 62% yield. Mesylation of 3 in the presence of triethylamine in CH2Cl2 followed by treatment with N-hydroxysulfamide in one-pot afforded the desired imide 5 in 79% yield.26 One-pot preparation of oxime ether 7 was achieved by treatment of imide 5 with hydrazine monohydrate in MeOH and subsequent condensation with 2-hydroxy-2-methoxyacetic acid methyl ester.27 Treatment of oxime ether 7 with (1R)-(+)2,10-camphorsultam in the presence of trimethyl aluminum in boiling dichloroethane gave oxime ether 8 having sultam in quantitative yield as a single E isomer. Treatment of 8 with pyridinium p-toluensulfonate in EtOH at 60 °C gave deprotected alcohol 9 in 89% yield. Treatment of alcohol 9 with glutaric anhydride gave carboxylic acid 10 in 99% yield. The carboxylic acid 10 could be attached to Wang resin by the treatment with DCC in the presence of DMAP in CH2Cl2 at 20 °C for 12 h to give the resin-bound oxime ether 1.28 The loading level of the resin-bound glyoxyllic oxime ether 1 was determined to be 0.83 mmol/g by quantification of nitrogen by elemental analysis.

Expecting that the direct comparison of the solid-phase radical reactions with the solution-phase radical reactions would lead to informative and instructive suggestions regarding reactivity and stereoselection in solid-phase reaction, we also investigated the solution-phase radical addition to oxime ether 10 (Chart 3). We first investigated the simple addition of an ethyl radical, generated from triethylborane and O2, to the oxime ether 10 in CH2Cl2 at −78 °C (Table 1, entry 1). As expected, the reaction proceeded smoothly to give the eth-
ylated product 11a in 91% yield. The diastereomeric purity was found to be not less than 95% de. The absolute configuration of major product was assigned to be R since their 1H-NMR data showed similarity with that of major product in solution-phase radical reaction showed in our recent report.24,25) The replacement of CH2Cl2 with toluene as a solvent were also effective for the reaction (entry 2). The development of tin-free radical reactions has generated considerable interest from both economical and environmental points of view. We recently reported the solution-phase radical addition to oxime ethers in the absence of Bu3SnH and by using Et3B or Et2Zn,29,30) which acts multiply as a Lewis acid, a radical initiator, and a terminator. Thus, we next investigated the isopropyl radical addition to oxime ether 10 in the absence of tributyltin hydride under the iodine atom-transfer reaction conditions (entry 3). The isopropyl radical addition to 10 was carried out with isopropyl iodide (30 equiv) and triethylborane (5 eq) in CH2Cl2 at 0 °C for 30 min. After purification, the desired isopropylated amino acid 11b was obtained in 86% combined yield and in 90% de. The addition of a clohexyl radical also proceeded smoothly under the same reaction conditions to give the clohexylated product 11c in 79% yield with good diastereoselectivity (entry 4).

We next investigated the ethyl radical addition to the Wang resin-bound oxime ether 1 (Chart 4). To a flask containing oxime ether 9 and undegassed CH2Cl2 was added a commercially available 1.0 M solution of triethylborane in hexane, and then the reaction mixture was stirred at −78 °C for 30 min (Table 2, entry 1). The resin 12a was then filtered and washed successively with CH2Cl2 and AcOEt, and the subsequent cleavage of the resin with trifluoroacetic acid (TFA)/CH2Cl2 (1:5, v/v) gave the crude ethylated α-amino acid derivative which was purified by the preparative TLC (hexane/AcOEt 2:3, v/v) to afford the amino acid derivative 11a in 74% isolated yield. The absolute configuration of major product was R and the diastereomeric purity was not less than 95% de. The solid-phase reaction of 1 in toluene also proceeded smoothly under similar reaction conditions (entry 2). Recently, Ryu and Komatsu reported that diethylzinc-air system can serve as an initiator of tin hydride-mediated radical reaction as well as triethylborane.31) In order to test the viability of diethylzinc, we next investigated the ethyl radical addition to oxime ether 1 using a commercially available 1.0 M solution of diethylzinc at −78 °C (entries 3, 4). Diethylzinc could also be utilized to achieve a high degree of stereocontrol in solid-phase radical reaction of 1 to afford the ethylated product 11a in good isolated yields with excellent diastereoselectivities. It is noteworthy that diethylzinc works well as an effective radical initiator for the solid-phase radical reaction without interference of polystyrene skeleton of the resin, and good chemical yield was observed even at low reaction temperature.

To test the generality of the solid-phase radical reaction of 1, we next investigated the reaction using different radical

Table 1. Solution-Phase Radical Addition to 10

<table>
<thead>
<tr>
<th>Entry</th>
<th>RI</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Selectivity (de)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>None</td>
<td>CH2Cl2</td>
<td>−78</td>
<td>11a</td>
<td>91</td>
<td>&gt;95% de</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>None</td>
<td>Toluene</td>
<td>−78</td>
<td>11a</td>
<td>82</td>
<td>&gt;95% de</td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>i-PrI</td>
<td>CH2Cl2</td>
<td>0</td>
<td>11b</td>
<td>86</td>
<td>90% de</td>
</tr>
<tr>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>c-Hexyl</td>
<td>CH2Cl2</td>
<td>0</td>
<td>11c</td>
<td>79</td>
<td>91% de</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were carried out with Et3B (5 eq) in CH2Cl2 or toluene at −78°C.
<sup>b</sup> Reactions were carried out with RI (30 eq) and Et3B (5 eq) in CH2Cl2 at 0 °C.
<sup>c</sup> Isolated yields.
<sup>d</sup> Diastereoselectivities were determined by 1H-NMR analysis.
precursors under the stannyl radical-mediated reaction conditions (Chart 5). However, the reactivity of oxime ether 1 anchored to polymer support was quite different from that of oxime ether 10 in solution-phase reactions. In the case of the isopropyl radical addition to 1 in the presence of Bu₃SnH (10 eq) at −78 °C, the addition of ethyl radical, generated from triethylborane, competed with the stannyl radical-mediated isopropyl radical addition to give a small amount of the isopropylated product 11b and a large amount of the undesired ethylated product 11a in 43% combined yield (Table 3, entry 1). The formation of 11b was found to be dependent on the reaction temperature, thus changing the temperature from −78 °C to 0 °C led to an effective increase in the ratio 11b/11a to 1:1 (entry 2). The addition of a bulky cyclohexyl radical proceeded in low chemical efficiency under the same reaction conditions to give the cyclohexylated product 11c in 58% isolated yield (entry 2). Diethylzinc worked well under similar reaction conditions to give the alkylated products with good selectivity (entries 3, 4). In the solid-phase reactions, the often tedious workup to remove excess reagents from reaction mixture was eliminated by washing of the resin with solvents. Additionally, the carbon–carbon bond-forming solid-phase radical reactions are run without any special precautions such as dry, degassing and purification of solvents and reagents. Thus, employment of a neutral species such as an uncharged free radical would overcome the tedious operations with organometallic reagents on solid-phase reactions.

In conclusion, we have demonstrated the utility of triethylborane in RI/toluene (4 : 1, v/v) at 0 °C (Chart 6). The isopropyl radical addition to 1 in i-PrI/toluene (4 : 1, v/v) proceeded smoothly to give the isopropylated product 11b in 69% isolated yield with good diastereoselectivity after purification by the preparative TLC (Table 4, entry 1). The addition of a bulky cyclohexyl radical proceeded in slightly low chemical efficiency under the same reaction conditions to give the cyclohexylated product 11c in 58% isolated yield (entry 2). Diethylzinc worked well under similar reaction conditions to give the alkylated products with good selectivity (entries 3, 4).

Experimental

**General** Melting points are uncorrected. ¹H- and ¹³C-NMR spectra were recorded at 200 or 300 MHz and at 50 or 125 MHz, respectively. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by electron ionization (EI), chemical ionization (CI), or secondary ion (SI)-MS methods. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck 60F254). Flash column chromatography was performed using E. Merck Kieselgel 60 (230—400 mesh).

4-(t-Butyl(dimethylsiloxy)methyl)phenylmethanol (3) To a solution of p-xylene glycol (1.0 g, 7.2 mmol) and imidazole (1.2 g, 18 mmol) in N,N-dimethylformamide (DMF) (3 ml) was added dropwise a solution of t-butyldimethylsilyl chloride (1.1 g, 7.3 mmol) in DMF (5 ml) under a nitrogen at-
mosphere at 20°C. After the reaction mixture was stirred at the same temperature for 3 h, the reaction mixture was diluted with Et2O. The organic phase was washed with water and brine, dried over MgSO4, and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 5:1) afforded 3 (1.1 g, 62%) as a colorless oil and 1,4-di-(butylidimethylsiloxymethyl)benzene (0.26 g, 10%) as a white solid. 3. IR (CHCl3) cm⁻¹: 2958, 2928, 2875, 2830, 2725, 1457. 1H-NMR (CDCl3) δ: 7.29 (4H, m), 4.73 (2H, s), 4.62 (2H, br s), 0.94 (9H, s), 0.09 (6H, s). 13C-NMR (CDCl3) δ: 140.7, 139.4, 126.8, 126.1, 65.0, 64.6, 25.8, 18.2, —5.4, high resolution (HR)-MS m/z: 252.1554 (Calcd for C19H34O2Si: 252.1544).

N-(4-Butylidimethylsiloxymethyl)phenothiazine (5) To a solution of 3 (7.3 g, 29 mmol) and Et3N (4.4 ml, 32 mmol) in CH2Cl2 (40 ml) was added dropwise mesyl chloride (2.5 ml, 32 mmol) under a nitrogen atmosphere at 0°C. After being heated at reflux for 8 h, the solvent was evaporated at reduced pressure. After the resulting residue was dissolved in AcOEt, the organic phase was washed with 1 N NaHCO3, and then was concentrated at reduced pressure. Purification of the residue by recrystallization (hexane/AcOEt) afforded 5 (9.0 g, 79%) as colorless crystals: mp 82—84°C (hexane/AcOEt); IR (CHCl3): cm⁻¹: 2956, 1737, 1649. 1H-NMR (CDCl3) δ: 7.68—7.81 (4H, m), 7.50, 7.33 (each 2H, d, J=8.0 Hz), 5.20, 4.74 (each 2H, s), 0.93 (9H, s), 0.08 (6H, s). 13C-NMR (CDCl3) δ: 163.3, 142.6, 134.2, 131.2, 129.7, 128.7, 125.9, 73.9, 65.4, 25.7, 18.2, —5.5. HR-MS m/z: 397.1711 (Calcd for C25H24N2O2Si: 397.1700). Anal. Calcd for C25H24N2O2Si: C, 66.47; H, 6.85; N, 3.53. Found: C, 66.30; H, 6.82; N, 3.38.

Methyl (E)-2-[4-(Butylidimethylsiloxymethyl)benzoyl]oxetane (7) To a solution of 5 (12 g, 30 mmol) in MeOH (200 ml) was added a solution of hydrazine hydrate (1.7 g, 33 mmol) in MeOH (10 ml) under a nitrogen atmosphere at 20°C. After being stirred at the same temperature for 1 h, a solution of 2-hydroxy-2-methoxyacetic methyl ester (7.2 g, 60 mmol) in MeOH (10 ml) was added to the reaction mixture at 20°C. After being stirred at the same temperature for 8 h, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 10:1) afforded 7 (9.4 g, 93%) as a colorless oil: IR (CHCl3) cm⁻¹: 2956, 1737, 1600, 1467. 1H-NMR (CDCl3) δ: 7.54 (1H, s), 7.33 (4H, m), 5.28, 4.74 (each 2H, s), 3.85 (3H, s), 0.94 (9H, s), 0.10 (6H, s). 13C-NMR (CDCl3) δ: 162.3, 141.8, 140.7, 134.3, 128.4, 126.1, 77.9, 64.5, 52.3, 25.8, 18.2, —5.4. HR-MS m/z: 337.1698 (Calcd for C16H24NO2Si: 337.1689).

N-(E)-2-[4-(Butylidimethylsiloxymethyl)benzoyl]oxetan-10,2-sultam (8) To a solution of 7 (11.7 g, 20.2 mmol) in MeOH (100 ml), saturated aqueous NaHCO3, and water, dried over MgSO4, and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 3:2) afforded 8 (9.1 g, 99%) as a colorless oil: [α]D25 +67.1 (c=0.92, CHCl3). IR (CHCl3) cm⁻¹: 3684, 2969, 1732, 1586, 1519. 1H-NMR (CDCl3) δ: 8.20 (1H, s), 7.40—7.31 (4H, m), 5.31, 5.11 (each 2H, s), 3.98 (1H, dd, J=6.8, 5.6 Hz), 3.52, 3.46 (each 1H, d, J=6.8 Hz), 2.45—2.36 (4H, m), 2.13—1.90 (7H, m). 13C-NMR (CDCl3) δ: 176.0 (1C, s), 153.9, 128.7, 128.3, 77.7, 65.8, 65.1, 52.9, 48.8, 47.7, 44.6, 38.1, 33.0, 32.8, 26.2, 20.7, 19.73, 19.67. HR-MS m/z: 520.1903 (Calcd for C26H24N2O3S: 520.1877).

Attachment of the Sultam Derivative to Water Resin To a suspension of Wang resin (0.83 mmol/g, 6.0 g, 5.0 mmol) in CH2Cl2 (100 ml) were added 10 (5.2 g, 10 mmol), DCC (5.1 g, 25 mmol) and DMAP (0.3 g, 2.5 mmol) under a nitrogen atmosphere at 20°C. After the reaction mixture was stirred at the same temperature for 1 h and then stood for 11 h, the resin was filtered, washed well with CH2Cl2, AcOEt followed by MeOH and then dried in vacuo.
Ethyl Radical Addition to Oxime Ether 1 (Table 2). To a suspension of oxime ether 1 (0.83 mmol/g, 200 mg, 0.166 mmol) in CH₂Cl₂ (10 ml) was added Et₃B or Et₂Zn (1.0 mmol, 0.83 ml) under a nitrogen atmosphere at −78 °C. After the reaction mixture was stirred at the same temperature for 30 min, the resin was filtered, washed well with CH₂Cl₂ and AcOH, and then dried in vacuo. To a flask with the resulting resin was added TFA/CH₂Cl₂ (1:5, v/v, 5.0 ml) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 30 min, the reaction mixture was filtered and washed with CH₂Cl₂ (50 ml), and the filtrate was concentrated at reduced pressure. After the resulting residue was dissolved in CH₂Cl₂, the organic phase was washed with diluted aqueous NaHCO₃, and water, dried over MgSO₄, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 3:2, 3-fold development) afforded the α-amino acid derivative 11a (68 mg, 74%) in the case of Et₃B or (61 mg, 67%) in the case of Et₂Zn.

Alkyl Radical Addition to Oxime Ether 10 (Table 3). To a suspension of oxime ether 1 (0.83 mmol/g, 200 mg, 0.166 mmol), Bu₃SnH (0.45 ml, 1.66 mmol) and RI (4.98 mmol) in CH₂Cl₂ (10 ml) was added Et₃B (1.0 mmol in hexane, 0.83 ml, 0.83 mmol) under a nitrogen atmosphere at −78 or 0 °C. After the reaction mixture was stirred at the same temperature for 30 min, the resin was filtered, washed well with CH₂Cl₂ and AcOE, and then dried in vacuo. To a flask with the resulting resin was added TFA/CH₂Cl₂ (1:5, v/v, 5.0 ml) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 30 min, the reaction mixture was filtered and washed with CH₂Cl₂ (50 ml), and the filtrate was concentrated at reduced pressure. After the resulting residue was dissolved in CH₂Cl₂, the organic phase was washed with diluted aqueous NaHCO₃, and water, dried over MgSO₄, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 3:2, 3-fold development) afforded the α-amino acid derivatives 11b and 11c.

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