Novel Synthesis of α-Amino Acid Derivatives through Triethylborane-Induced Solid-Phase Radical Reactions

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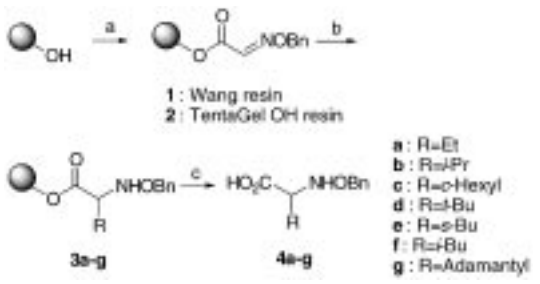
Combinatorial chemistry has became a core technology for the rapid development of novel lead compounds in the pharmaceutical industry and for the optimization of therapeutic efficacy.[1] The extension of radical reactions to solid-phase reactions would allow further progress in combinatorial organic synthesis. Thus, the development of solid-phase radical reactions is a new subject of considerable interest. A few reports have recently demonstrated that radical cyclization could be performed on solid supports by using AIBN or SmI_2 as a radical initiator.[2−4] Sibi's group more recently reported the first studies on the solid-phase intermolecular radical reaction using allyl stannanes and AIBN.[5] Triethylborane has the potential to induce solution-phase radical reactions at low reaction temperature, and a wide range of synthetically useful reactions using triethylborane as a radical initiator are available.[6] In conjunction with our studies on the triethylborane-induced radical chemistry in solution,[7] we now report the results of experiments to probe the utility of triethylborane in the solid-phase intermolecular radical reactions. As shown below, the intermolecular carbon radical addition to the carbon−nitrogen double bond of the glyoxylic oxime ethers anchored to a polymer support provides a new efficient carbon−carbon bond-forming method for the synthesis of α-amino acid derivatives.[8]

As a preliminary experiment, we chose two simple glyoxylic oxime ethers **1** and **2** anchored to a polymer support as a model substrate and investigated several reaction conditions for attachment of the glyoxylic oxime ether to Wang resin and TentaGel OH resin (Scheme 1).[9] The glyoxylic oxime ether ($HO_2CC{=}NOBn$) could be attached to Wang resin by the treatment with DCC in the presence of DMAP in CH_2Cl_2 at 20 °C for 12 h to give the resin-bound glyoxylic oxime ether **1** in ca. 70% loading level.[10] The loading level of the Wang resin-bound glyoxylic oxime ether **1** was determined to be 0.83 mmol/g by quantification of nitrogen by elemental analysis. TentaGel OH resin-bound glyoxylic oxime ether **2** was prepared from $HO_2CC{=}NOBn$ in ca. 90% loading level by the treatment with 2,6-dichlorobenzoyl chloride in the presence of pyridine in DMF at 20 °C for 12 h.

Scheme 1[a]



[a] Key: (a) $HO_2CC{=}NOBn$, DCC, DMAP, CH_2Cl_2, 20 °C, 12 h (for **1**); $HO_2CC{=}NOBn$, 2,6-dichlorobenzoyl chloride, Py, DMF, 20 °C, 12 h (for **2**); (b) Et_3B, 1 h; or RI, Bu_3SnH, Et_3B, 1 h; (c) TFA/$CHCl_3$ (1:3, v/v), 20 °C, 30 min.

Table 1. Ethyl Radical Addition to 1 and 2[a]

entry	oxime	solvent	*T* (°C)	product	yield[b] (%)
1	**1**	CH_2Cl_2	20	**4a**	71
2	**2**	CH_2Cl_2	20	**4a**	57
3	**1**	toluene	20	**4a**	83
4	**1**	CH_2Cl_2	−78	**4a**	61

[a] All reactions were carried out with Et_3B in hexane (3.6 equiv). [b] Yields of isolated product **4a** from **1** or **2**.

To test the viability of triethylborane as a radical initiator on solid support, we first investigated the simple addition of an ethyl radical, generated from triethylborane and O_2, to the Wang resin-bound glyoxylic oxime ether **1** (Table 1, entry 1). To a flask containing glyoxylic oxime ether **1** and undegassed CH_2Cl_2 was added a commercially available 1.0 M solution of triethylborane in hexane, and then the reaction mixture was stirred at 20 °C for 1 h. The resin **3a** was then filtered and washed successively with CH_2Cl_2, AcOEt, and then MeOH, and the subsequent cleavage of the resin with

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TFA/$CHCl_3$ (1:3, v/v) gave the crude ethylated α-amino acid **4a** as a TFA salt. Purification of the resulting α-amino acid **4a** was accomplished by a combination of Amberlite IR-120B (eluting with MeOH) and the preparative TLC (MeOH/$CHCl_3$ 1:10, v/v) to afford the free amino acid **4a**.[11] In this reaction, triethylborane acts as not only a radical initiator but also a terminator to trap the intermediate benzyloxyaminyl radical without interference of the polystyrene skeleton of the resin. Thus, the radical reaction cycle involving the regeneration of the ethyl radical proceeds by this quite simple procedure, which does not require the use of moisture-sensitive irritant tin hydride. The important role of triethylborane has been already explained by two groups.[7,12] The ethyl radical addition to TentaGel resin-bound glyoxylic oxime ether **2** proceeded also in slightly low chemical efficiency under the same reaction conditions (Table 1, entry 2). In regard to the solvent effect, the replacement of CH_2Cl_2 with a nonpolar aromatic solvent such as toluene was found to be also effective for triethylborane-induced solid-phase radical reactions to give the ethylated products **4a** in 83% yield from **1** (Table 1, entry 3). It is important to note that good chemical yield was observed at −78 °C (Table 1, entry 4). These results suggest that triethylborane works well as an effective radical initiator for the solid-phase radical reaction even at low reaction temperature.

To test the generality of the solid-phase radical reaction using triethylborane, we investigated the reaction using different radical precursors that afforded moderate to good yields of alkylated products **4b**−**g** (Table 2). As in the case of **4a**, to a flask containing glyoxylic oxime ether **1** and undegassed CH_2Cl_2 were successively added isopropyl iodide, tributyltin hydride, and triethylborane as a radical initiator, and then the reaction mixture was stirred at 20 °C for 1 h. The isopropylated α-amino acid derivative **4b** was obtained in 66% yield from **1** after cleavage of the resin followed by purification, accompanied with a small amount of the ethylated product **4a**, which was formed by the competitive reaction with the ethyl radical generated from triethylborane (Table 2, entry 1). The often tedious workup to remove excess tin residues from the reaction mixture is eliminated in the solid-phase methodology by washing of the resin with solvents. Not only secondary alkyl radicals such as isopropyl, cyclohexyl, and *sec*-butyl radicals but also a bulky *tert*-butyl radical worked well under similar reaction conditions, allowing facile incorporation of structural variability (Table 2, entries 1−5). This reaction will be particularly useful because there currently exists no general synthetic method for the construction of a wide range of aliphatic α-amino acids using glyoxylic imines as the starting material.[13] The unstable primary alkyl radicals such as isobutyl radical and a more bulky adamantyl radical were less effective for the present solid-phase intermolecular radical reaction (Table 2, entries 6 and 7).

Table 2. Solid-Phase Synthesis of α-Amino Acids 4b−g[a]

entry	RI	solvent	product[b]	yield[c] (%)
1	*i*-PrI	CH_2Cl_2	**4b**	66
2	*i*-PrI	toluene	**4b**	42
3	*c*-hexyl I	CH_2Cl_2	**4c**	61
4	*t*-BuI	CH_2Cl_2	**4d**	78
5	*s*-BuI	CH_2Cl_2	**4e**	71
6	*i*-BuI	CH_2Cl_2	**4d**	24
7	adamantyl I	CH_2Cl_2	**4g**	28

[a] All reactions were carried out with RI (7.1 equiv), Bu_3SnH (2.1 equiv), and Et_3B in hexane (1.1 equiv) at 20 °C. [b] The ethylated product **4a** was obtained in ca. 5−30% yields. [c] Yields of isolated products **4b**−**g** from **1**.

In conclusion, we have demonstrated that triethylborane can be applied to the solid-phase radical reaction. Furthermore, the radical addition to glyoxylic oxime ethers anchored to a polymer support provides direct access to unnatural α-amino acids as useful building blocks exemplified by the recent progress in the fields of combinatorial chemistry and drug discovery. The newly found solid-phase radical reactions are run without any special precautions such as drying, degassing, and purification of solvents and reagents and are thus readily adaptable to parallel synthesis.[14]

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Supporting Information Available: Experimental procedures and NMR spectra for obtained compounds.

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(11) All compounds **4a**−**g** were characterized by ^1H NMR, ^{13}C NMR, and HRMS.

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(13) Glyoxylic imines are convenient starting materials for the synthesis of α-amino acids through ene reactions, cycloadditions, or the nucleophilic additions of organometallic reagents or enolate anion equivalents.

(14) All reactions were run in commercially available solvents and with reagents without requiring any special precautions.