

Utilization of Aryl Sulfide as a Novel Safety-Catch Linker for Solid Phase Organic Synthesis

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The feature of arylthio group was investigated as a new safety catch linker for solid phase organic synthesis. To introduce the aryl sulfide structure, 4-mercaptobenzoic acid (**7**) was immobilized with aminomethyl resin by using WSC to obtain the resin having arylthio group **8**. The precursor of the target compounds, 4-bromobenzyl bromide was reacted with **8** to obtain the resin bound 4-bromobenzyl phenyl sulfide **9**. The generated sulfide was activated to sulfonium salt by CH₃I and AgBF₄. The cleavage can be proceeded at ambient temperature using dibutylamine to obtain 4-bromobenzyl dibutylamine (**11**) in 86% yield.

Key words: sulfonium salt, solid phase organic synthesis, safety-catch linker, nucleophilic substitution,

1. INTRODUCTION

Solid phase organic synthesis (SPOS) has become widely used for preparation of combinatorial libraries. It is indispensable technology for constructing of combinatorial libraries of small molecules. The advantage of SPOS, easy separation can be carried out from excess reagents and solvents by filtration in the reaction mixture. Using the SPOS technology, linkers are required to keep the intermediate bound to the resin support. Linkers should stable under reaction conditions and specific cleavage at the end of a synthesis without damage to the target compound. Various types of linkers have been developed to adapt the broad reaction conditions. To detach from resin support at linker position, various cleaving conditions are used, for example, acid, base, photo irradiation, etc. We have interested in safety-catch linker, which show the dual cleaving steps; 1) activation of linker, and 2) actual cleavage [1]. The main advantage of safety-catch linker is the stability until being activated, but once it is activated, the cleaving reaction is proceeded at mild conditions. Some safety-catch linker has been reported, whereas the use has some limitations for synthetic target. Then, we extend the

utilization of safety-catch linker, arylthio group was examined as a new safety-catch linker for SPOS.

2. EXPERIMENTAL

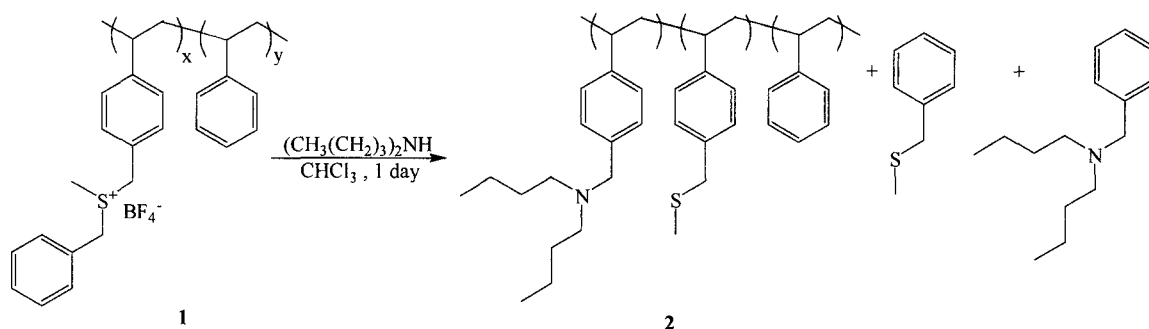
General Procedures.

¹H and ¹³C NMR spectra were recorded in CDCl₃ on a Varian Unity-300 spectrometer using tetramethylsilane (TMS) as an internal standard. FT-IR spectra were obtained with a Shimadzu FT-IR 8200 spectrometer. Gel permeation chromatographic analyses (GPC) were carried out on a Shimadzu LC-10ADVP with a Shimadzu CR-7Aplus integrator, Shimadzu DGU-12A degasser, Shimadzu GO-10AVP column oven, Shimadzu SPD-10ADVP UV-vis detector (254 nm), and a Shimadzu RID-10A refractive index detector (Shim-pack GPC-803, THF as eluent) using polystyrene standards. Gas chromatography (GC) analyses were carried out on Shimadzu GC-17A instrument using Ultra Alloy-7 (15 m x 0.25 mm x 0.25 µm column).

3. RESULTS AND DISCUSSIONS

3.1 Preparation and reaction of poly(sulfonium salt).

Scheme 1 Reaction of poly(sulfonium salt) with dibutylamine

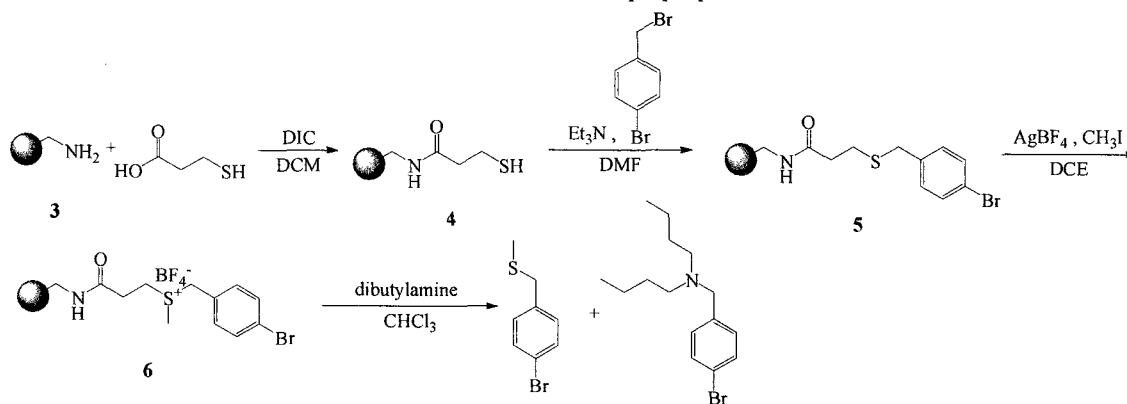


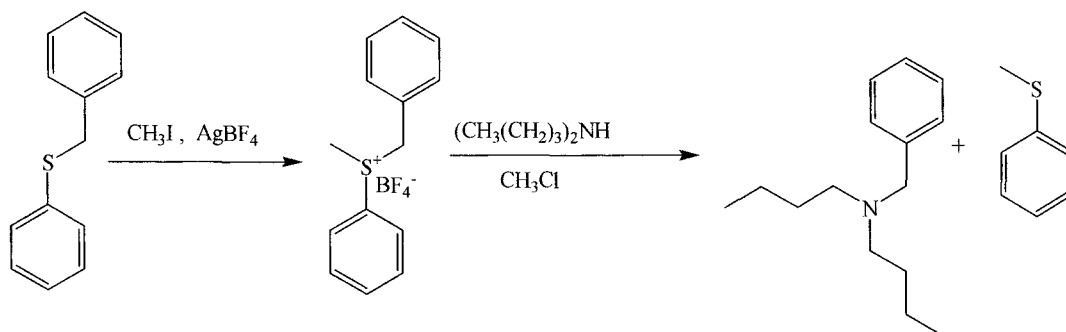
We have reported the reaction of *S*-methylbenzylsulfonium salt with amine nucleophile to produce the corresponding benzyl amine under ambient temperature [2]. So, we investigated the reaction behavior of poly(sulfonium salt) with amine nucleophile. Poly(sulfonium salt) was prepared from the polymer reaction. In order to prepare a polymer having sulfonium moieties, the polymer ($M_n=36,000$, $M_w/M_n=1.2$, $x:y=1:4$) was subjected with CH_3I and AgBF_4 in $\text{CH}_2\text{ClCH}_2\text{Cl}$ at r.t. for 24 h in 73% yield. The poly(sulfonium salt) (1, sulfonium unit: 70%) was reacted with dibutylamine as a nucleophile in CHCl_3 at r.t. for 24 h (Scheme 1). As a result, the obtained polymer (2) has sulfide and *N,N*-dibutylamino group because the nucleophile of dibutylamine attacked to dual benzyl positions of 1. This result shows the linkage of small molecule to polymer support through sulfide, the cleaving reaction will be accomplished under mild conditions. We thought that this type of reaction can be applied for linker of SPOS.

3.2 Application of 3-Mercaptopropionic acid as a Safety-Catch Linker.

To evaluate of 3-mercaptopropionic acid as a linker, aminomethyl resin was used as a solid support 3 (loading: 1.4 mmol/g) [3]. The linker of 3-mercaptopropionic acid was treated with the resin in dichloromethane by using DIC to obtain the resin having thiol group 4 (Scheme 2) [4]. The precursor of the target compounds, 4-bromobenzyl bromide was reacted with 4 to obtain 4-bromobenzyl sulfide 5 [5]. The sulfide 5 was activated to sulfonium salt by using CH_3I - AgBF_4 as an alkylating reagent to obtain the sulfonium resin 6. The cleavage was performed by using dibutylamine to generate the mixture of 4-bromobenzyl methyl sulfide and 4-bromobenzyl dibutylamine. This result shows the nucleophilic cleavage was proceeded at least two positions, i.e., the positions of the neighboring methylene of sulfur and benzyl. So, we changed the linker design to arylthio type.

Scheme 2 Evaluation of 3-mercaptopropionic acid as a linker



Scheme 3 Reaction of benzyl-phenyl sulfonium salt with amine nucleophiles**3.3 Model Reaction by Benzyl Phenyl Sulfide.**

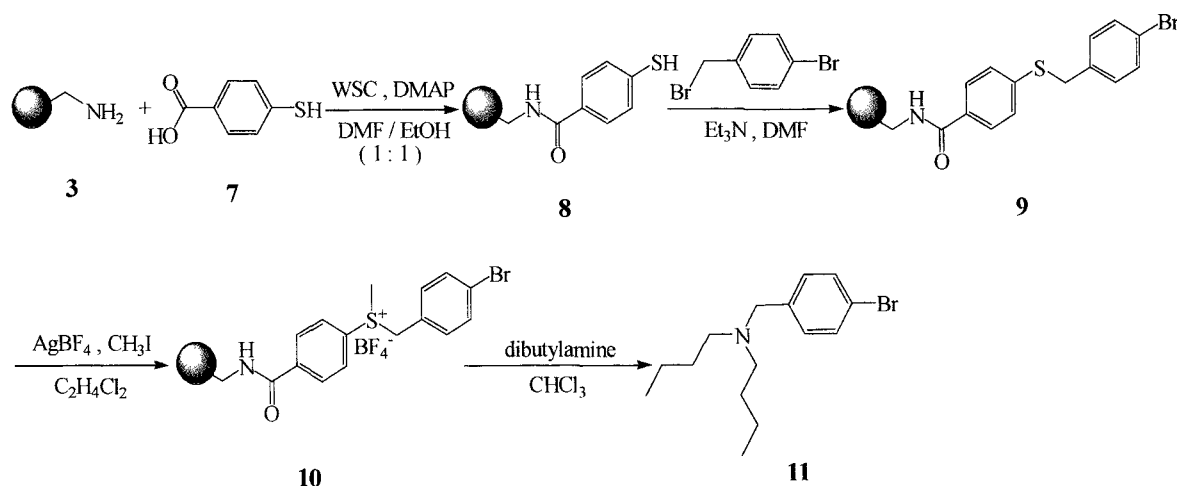
Generally, nucleophilic substitution on aromatic ring cannot be easy. So, 4-mercaptobenzoic acid was investigated as a safety-catch linker. First of all, the reaction was confirmed by using small molecule of sulfide (Scheme 3). Phenyl benzyl sulfide was synthesized as a linker model and preparation of *S*-methyl sulfonium salt was proceeded by the similar conditions for the preparation of **6**. The reaction behavior of model sulfonium salt with dibutylamine was examined. This reaction was completely proceeded and the nucleophilic substitution was only specified at benzyl position. The crude yield and purity determined by GC of *N,N*-dibutylbenzylamine were 95% and 97%, respectively.

3.4 Application of 4-Mercaptobenzoic acid as a Safety-Catch Linker.

By using benzyl phenyl sulfide as a model compound of linker, the target *N,N*-dibutylbenzylamine was

obtained in good yield and purity. So, 4-mercaptobenzoic acid (**7**) was applied as a linker for SPOS. Immobilization and evaluation of the linker was proceeded by the similar method in the case of 3-mercaptopropionic acid. The linker of **7** was treated with the resin **3** in dichloromethane by using DIC to obtain the resin having thiol group **8** (Scheme 4). The precursor of the target compounds, 4-bromobenzyl bromide was reacted with **8** to obtain the resin bound 4-bromobenzyl sulfide **9**. The sulfide was activated to sulfonium salt by using CH_3I - AgBF_4 as an alkylating reagent to obtain the sulfonium resin **10**. The cleavage was performed by using dibutylamine to obtain the 4-bromobenzylidibutylamine (**11**) in 86% yield (>99% purity determined by GC) [6].

In summary, some sulfide linker was evaluated as the safety-catch linker for solid phase organic synthesis. Those linkers were activated to sulfonium salts and cleaved by amine nucleophile under mild condition. In

Scheme 4 Evaluation of 4-mercaptobenzoic acid as a linker

the case of 4-mercaptobenzoic acid as a linker, the synthesized product of 4-bromobenzyl dibutylamine was given in good yield and purity. Now, coupling reaction is examined by using terminal arylbromide position with various aromatic compounds. This type of safety-catch linker would be used for the library synthesis in the near future.

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- [6] The yield was calculated from the basis of the loading of **3**.

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