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Solid-phase synthesis of benzazoles, quinazolines, and quinazolinones using an alkoxyamine linker

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ABSTRACT

An alkoxyamine linker was applied for the solid-phase synthesis of benzazoles, quinazolines, and quinazolinones. Aromatic aldehydes were anchored by aldoxime linkage. After some reactions on a solid support, the products were cleaved with paraformaldehyde under the acidic conditions to afford the corresponding aldehydes, which were subsequently subjected to oxidative coupling with 2-substituted anilines under air atmosphere to give the desired compounds.

Nitrogen-containing heterocyclic compounds, such as benzazoles, quinazolines, and quinazolinones are an important class of compounds. They can be utilized as not only a wide variety of biologically active and medicinally significant compounds[1] but also as advanced materials including non-linear optics (NLO),[2] organic light-emitting diodes (OLED),[3] and liquid crystals.[4] Hence, facile preparation of these derivatives for rapid discovering of new drugs and materials is highly desirable. Solid-phase combinatorial synthesis is effective in providing a large number of compounds. Therefore, solid-phase combinatorial syntheses of these compounds have been reported by some groups.[5] The selection of an adequate linker in the solid-phase synthesis is one of the key factors for efficiently building the desired libraries.[6] A connection between a linker and substrates must be stable under the various reaction conditions to construct the desired products. Meanwhile, the linkage must be cleavable without damage to the product at the final stage.

We previously reported a new traceless alkoxyamine linker **1**, which can anchor ketones and aldehydes as ketoximes or aldoximes on a solid-support. It was applied to the solid-phase synthesis of benzodiazepins[7] and benzothiazoles.[8] The oxime linkage formed by anchoring carbonyl compounds on **1** has been shown to be more robust than the azomethine linkage prepared from our previously reported alkoxyaniline linker **2**[9] under the various reaction conditions such as Mitsunobu reaction, nucleophilic substitution reaction, and Pd-catalyzed reactions (Fig. 1).

The reaction sequence to synthesize benzothiazoles **5** is shown in Scheme 1. The desired benzothiazoles **5** were released in good yields by exchange reaction between solid-supported aldoxime **4** and 2-amino-thiophenol coupled with air-oxidation under the weakly acidic conditions. However, treatment of **4** with other 2-substituted anilines such as 1,2-phenylenediamine, 2-aminobenzylamine, and 2-aminobenzamide did not give the corresponding benzimidazole, quinazoline, and quinazolinone due to the resistance to aldoxime–azomethine exchange.[8]

Hence, we investigated the cleavage conditions how the linker **1** can be effectively employed for the preparation of these heterocyclic compounds. The key in the synthesis is the cleavage conditions at the final stage. The products must be released without damage

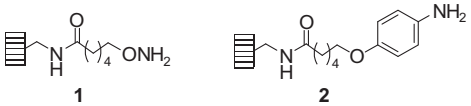

Figure 1. Two traceless linkers which can anchor ketones and aldehydes as oximes or azomethines.

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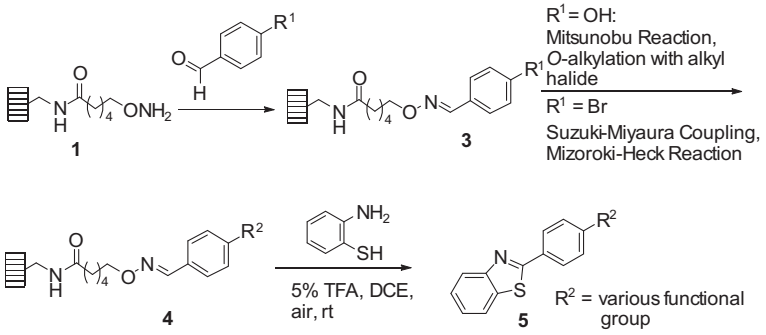


Scheme 1. Solid-phase synthesis of benzothiazoles **5** using an alkoxyamine linker **1**.

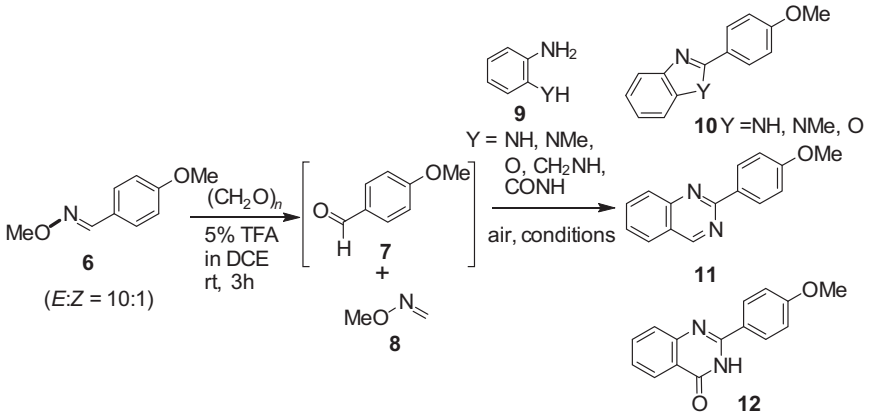
from the highly robust aldoxime linkage on a solid-support. Sakamoto and Kikugawa reported mild deoximation using paraformaldehyde in the presence of Amberlyst® 15 (acidic ion exchange resins).[10] We have envisioned that this deoximation condition would be applied to the cleavage step.

In advance of investigation on a solid-phase synthesis, the cleavage conditions were optimized in solution. TFA was employed instead of Amberlyst® 15 as acidic catalyst because solid catalyst could not be applied for solid-phase reaction. Aldoxime **6** was treated with paraformaldehyde in 1,2-dichloroethane (DCE) solution containing 5% TFA. Desired 4-methoxybenzaldehyde **7** was observed by TLC as expected. After 3 h at room temperature, TFA and the solvent were removed under reduced pressure. The residue was successively treated with various 2-substituted anilines **9** under air atmosphere at 100–120 °C to drive **7** to Schiff base formation and sequential oxidative cyclization. The results are summarized in Table 1.

Treatment of crude 2-methoxybenzaldehyde **7** with 4-equivalent of 1,2-phenylenediamine **9** (Y = NH) at 100 °C for 18 h gave the corresponding benzimidazole **10** (Y = NH) in 77% yield (entry 1). N-methyl-2-arylbenzimidazole **10** (Y = NMe) was also obtained in good yield although much longer reaction time was required (entries 2 and 3). However, treatment of crude **7** with 2-aminophenol **9** (Y = O), did not give benzoxazole **10** (Y = O) even in the presence of Darco® KB, which was an effective catalyst for the oxidative coupling between aromatic aldehydes and 2-aminophenol **9** (Y = O).[11] Oxidative decomposition of 2-aminophenol **9** (Y = O) occurred in preference to oxidative coupling. Desired benzoxazole **10** (Y = O) was obtained in 12% yield at elevated temperature. The yield was improved to 53% in xylene (entries 4 - 6). In case of quinazoline synthesis, yields were improved from 27% to 80% when crude **7** was treated with 2-aminobenzylamine **9** (Y = CH_2NH) for 18 h to form N,N-cyclic acetal before addition of Darco® KB which caused oxidative decomposition of unreacted 2-aminobenzylamine **9** (Y = CH_2NH) (entries 7 and 8). Quinazolinone **12** was also obtained in good yield even without pretreatment with 2-aminobenzamide **9** (Y = CONH) due to its resistance for oxidative decomposition (entry 9).

On the basis of the preliminary experimental results in solution, we investigated the solid-phase synthesis of these heterocycles by using the alkoxyamine linker **1**. After loading 4-methoxy benzaldehyde **7**, the resin **13** was treated under the same conditions as

Table 1
Deoximation of **6** using paraformaldehyde under the acidic conditions and successive oxidative coupling with various 2-substituted anilines **9**



Entry	Y	Additive	Solvent	Temp (°C)	Period (h)	Yield (%)
1	NH		DMF	100	18	77
2	NMe		DMF	100	48	41
3			DMF	100	72	79
4	O	Darco® KB	DMF	100	18	0
5		Darco® KB	DMF	120	18	12
6		Darco® KB	Xylene	120	18	53
7	CH_2NH	Darco® KB	DMF	100	18	27
8[1]		Darco® KB	DMF	100	18	80
9	CONH	Darco® KB	DMF	100	18	83

[1] Darco® KB was added after stirring **7** with 2-aminobenzylamine **9** (Y = CH_2NH) at rt for 18 h.