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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

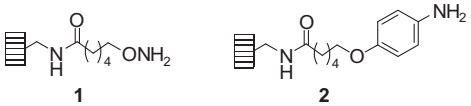

Figure 1. Two traceless linkers which can anchor ketones and aldehydes as oximes or azomethines.

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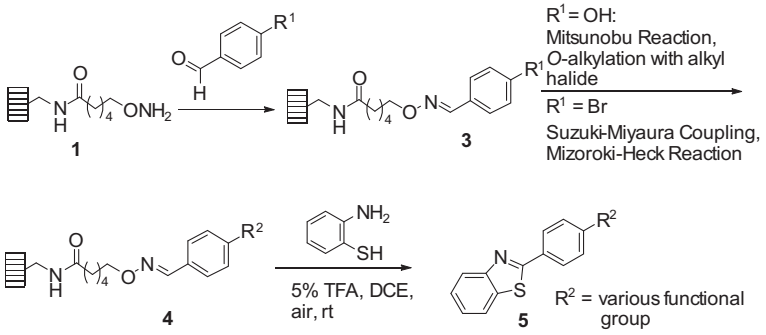


Scheme 1. Solid-phase synthesis of benzothiazoles **5** using an alkoxyamine linker **1**.

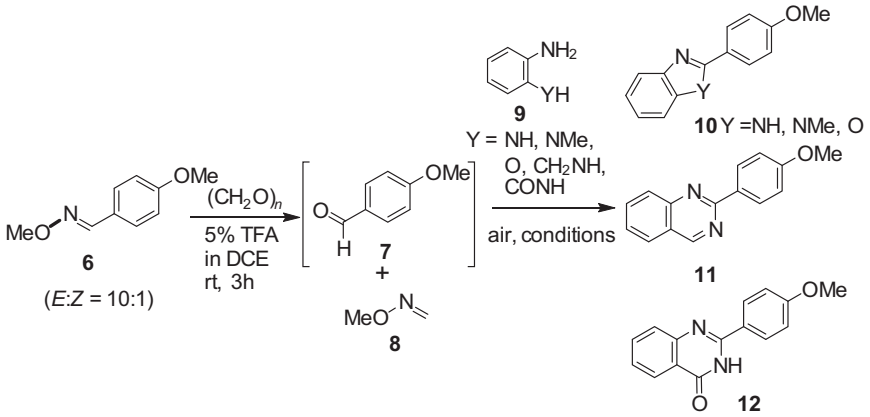
from the highly robust aldoxime linkage on a solid-support. Sakamoto and Kikugawa reported mild deoximation using paraformaldehyde in the presence of Amberlyst® 15 (acidic ion exchange resins).[10] We have envisioned that this deoximation condition would be applied to the cleavage step.

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

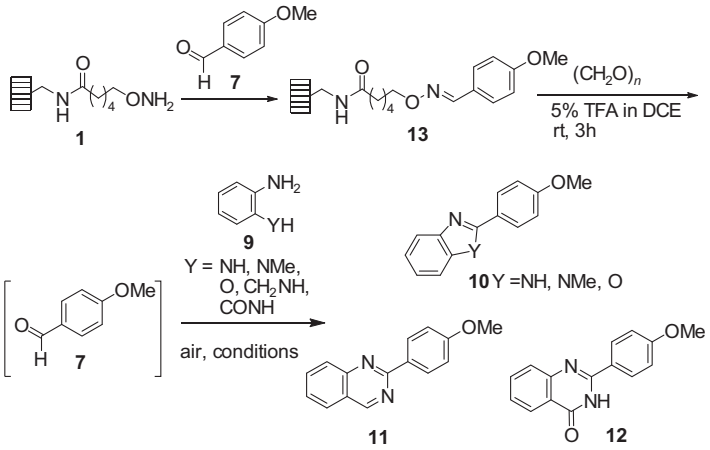
Table 1
Deoximation of **6** using paraformaldehyde under the acidic conditions and successive oxidative coupling with various 2-substituted anilines **9**



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.

Table 2
Solid-phase synthesis of benzimidazoles **10** (Y = NH, NMe), benzoxazole **10** (Y = O), quinazoline **11**, and quinazolinone **12** using the alkoxyamine linker **1**



Entry	Y	Additive	Solvent	Temp (°C)	Period (h)	Yield (%)
1	NH	—	DMF	100	18	75
2	NMe	—	DMF	100	72	73
3	O	Darco® KB	xylene	120	18	35
4[1]	CH_2NH	Darco® KB	DMF	100	18	75
5	CONH	Darco® KB	DMF	100	18	77

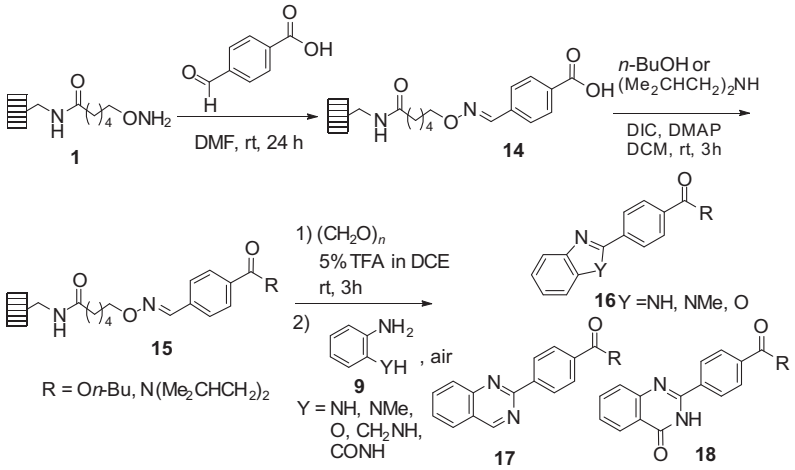
[1] Darco® KB was added after stirring **7** with 2-aminobenzylamine **9** (Y = CH_2NH) at rt for 18 h.

solution-phase synthesis for cleavage of the benzaldehyde **7** and oxidative coupling with 2-substituted anilines **9**. The isolated yields of corresponding heterocycles from **1** are shown in Table 2. The yields were comparable to those in solution-phase synthesis (Table 1).

To test the utility of the linker, some reactions on a solid-support were explored. After 4-formyl benzoic acid was loaded on **1**, oxime **14** was condensed with *n*-butanol or diisobutylamine. Finally, desired esters or amide was released from **15** under the optimized reaction conditions described above. Table 3 summarizes the yields, which were compared with those for the reaction using the alkoxyaniline linker **2**. In the series of *n*-butyl esters, they were comparable to those using the alkoxyaniline linker **2**. On the other hand, the yields of amide **16**–**18** (R = $N(Me_2CHCH_2)_2$) were improved by using the linker **1** because aldoxime **14** is more stable for the undesirable aminolysis of C = N linkage in **14** by diisobutylamine than corresponding azomethine formed by aromatic aldehydes and alkoxyaniline linker **2**.

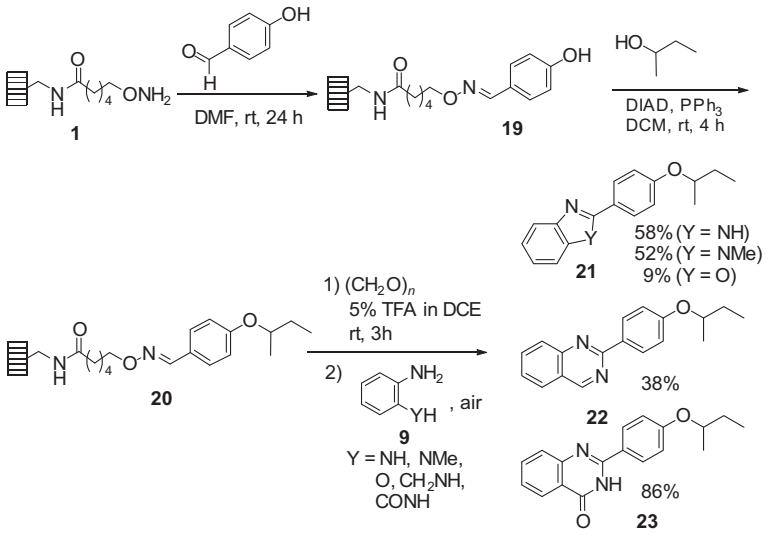
4-Hydroxy benzaldehyde was loaded onto **1** to explore Mitsunobu reaction of phenol with 2-butanol on a solid-support. The

Table 3
Condensation with *n*-butanol, diisobutylamine on a solid-support



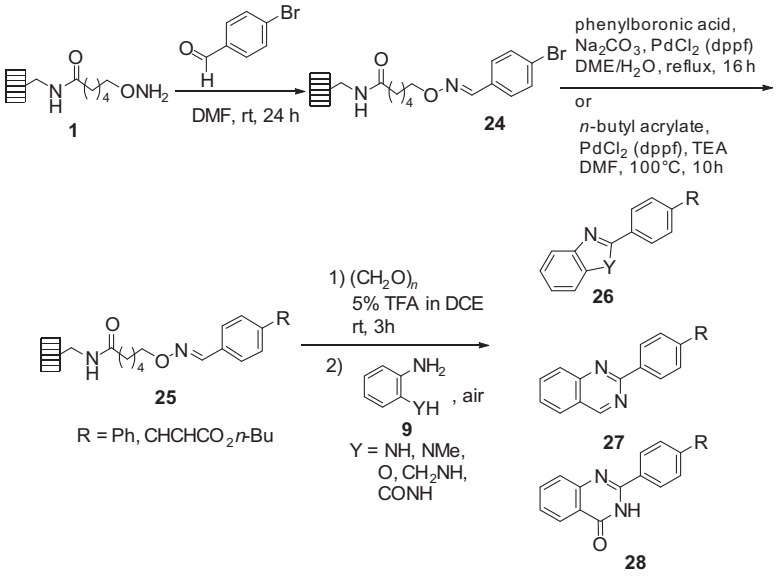
R	Yields from **1**[1] (%)				
	Y				
	NH	NMe	O	CH_2NH	CONH
O*n*-Bu	76 (84)	84 (77)	57 (58)	82 (82)	95 (74)
$N(Me_2CHCH_2)_2$	73 (40)	53 (47)	16 (15)	61 (33)	48 (39)

[1] Values in parenthesis refers to a yield when the alkoxyaniline linker **2** was applied for the synthesis.



Scheme 2. Mitsunobu reaction with 2-butanol on a solid-support.

Table 4
Suzuki–Miyaura coupling with phenylboronic acid and Mizoroki–Heck reaction with *n*-butyl acrylate on a solid-support



R	Yields from **1** (%)				
	Y				
	NH	NMe	O	CH_2NH	CONH
Ph	72	76	48	79	76
$CHCHCO_2n$-Bu	56	64	27	23	47

overall yield of heterocycles from **1** is shown in Scheme 2. Desired products **21**–**23** except benzoxazole **21** (Y = O) were obtained in moderate to good yields.

Finally, 4-bromobenzaldehyde was linked with **1** to examine two kinds of palladium catalyzed reactions.[12] The aldoxime on a solid-support **24** was subjected to Suzuki–Miyaura coupling with phenylboronic acid. Mizoroki–Heck reaction with *n*-butyl acrylate was also applied to **24**. Desired products **26**–**28** were obtained from **25** under the optimized conditions described above. Yields are summarized in Table 4. Suzuki–Miyaura couplings were shown to proceed smoothly on a solid support by comparing the coupling yields with those of simple loading, cleavage, and oxidative coupling (Table 2). However, yields were slightly reduced in Mizoroki–Heck reaction on a solid-support.

In conclusion, we found the alkoxyamine linker **1** to be an efficient traceless linker used for the solid-phase synthesis of not only benzothiazoles and benzodiazepins but also other benz-fuzed azoles, quinazolines, and quinazolinones. The aldoximes on a solid support are robust under some reaction conditions such as condensation with alcohols and amines, Mitsunobu reaction, and palladium catalyzed reactions. Meanwhile, the corresponding aldehydes were easily cleaved under the mild conditions using paraformaldehyde in weakly acidic solvent. The aldehydes can be oxidatively coupled with 2-substituted anilines under air

atmosphere without purification. Application to the synthesis of other heterocycles using the alkoxyamine linker **1** is currently under investigation.

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12. *Representative procedure for the synthesis:* Three pieces of the solid supported alkoxyamine **1** (loading: 3 × 75 μmol)[7] were reacted with 4-bromobenzaldehyde (167 mg, 0.90 mmol, 4 equiv) in DMF solution (8 mL) at rt for 24 h. The solution was removed by decantation and the resulting resins were washed with DMF (3 × 2 min) and DCM (3 × 2 min). The resulting solid supported aldoxime **24** was mixed with phenylboronic acid (165 mg, 1.35 mmol, 6 equiv) and $PdCl_2$ (dppf) CH_2Cl_2 (18.3 mg, 22.5 μmol, 0.1 equiv) in degassed dimethoxyethane (8 mL) and 2 mol L^{-1} aqueous Na_2CO_3 solution (900 μL, 1.80 mmol, 8 equiv) under argon atmosphere. The mixture was refluxed for 16 h. The solution was removed by decantation and the resulting resins were washed with MeOH (3 × 2 min), DMF (3 × 2 min), and DCM (3 × 2 min). The resins 24 (R = Ph) were reacted with paraformaldehyde (33.9 mg, 1.13 mmol, 5 equiv) in 5% TFA-1,2-DCE solution (8 mL) at rt under argon atmosphere for 3 h. The resulting resins were washed with DCM (3 × 2 min), DMF (3 × 2 min), and DCM (3 × 2 min). The combined DCM and DMF solutions were evaporated and the residue was treated with 1,2-phenylenediamine **9** (Y = NH) (97.3 mg, 0.90 mmol, 4 equiv) in DMF (3 mL) at 100 °C for 18 h. The reaction mixture was concentrated and purified by silica gel chromatography (hexane/EtOAc = 1/1) to give benzimidazole **26** (R = Ph, Y = NH) in 72% yield (44.0 mg, 163 μmol) as flesh color solid (mp 276-277 °C).