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Solid-phase synthesis of benzothiazoles using an alkoxyamine linker

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ABSTRACT

An alkoxyamine linker was applied for the solid-phase synthesis of benzothiazoles. The substrate was anchored by aldoxime linkage and products were cleaved from the solid-support by aldoxime–imine exchange coupled with air-oxidation under the weakly acidic conditions. The tether is highly robust under Mitsunobu reaction, nucleophilic substitution reaction, and Pd-catalyzed reaction conditions.

Solid-phase organic synthesis (SPOS) provides a useful tool for the preparation of a large number of compounds because products are synthesized in easy operations. SPOS has been applied for the synthesis of many nitrogen heterocycles, which are utilized in various fields such as medicinal and material chemistry.[1–3] Linkers, which connect substrates to solid-support, play an important role in SPOS. Linkers, which should be easy to load starting materials onto the solid support, must be stable under the various reaction conditions to construct the desired products as well as must be cleavable without damage to the product at the final stage. Many types of linkers have been developed to efficiently build the desired compounds.[4–6] Previously, we developed a new aniline linker **1** for the solid-phase synthesis of heterocyclic compounds such as 2-substituted benz-fused azoles **7**, quinazolines **8**, and quinazolinones **9** (Scheme 1).[7–9] Linker **1** is characterized as a traceless linker, in which no functional group of the target molecules is necessary to attach to a solid support.[10–12] Substrates are anchored by azomethine linkage and products are released from the solid-support by imine-exchange reaction coupled with air-oxidation in the reaction process. Although this azomethine linkage is stable under some reaction conditions, it is susceptible to cleavage by some nucleophiles.[8] Thus SPOS employing the linker **1** can be applied only to limited reactions.

Recently we reported a new traceless alkoxyamine linker **10**, which can anchor ketones as ketoximes on a solid-support. It was applied to the solid-phase synthesis of benzodiazepins **13** (Scheme 2).[13] In the present study, we investigated the employment of the linker **10** for the preparation of benz-fused azoles by loading benzaldehydes as aldoximes and by releasing the products through aldoxime–imine exchange coupled with air-oxidation. If loading the substrates and releasing the products are performed in the same manner as the alkoxyaniline linker **1**, this methodology would be extended to the preparation of various benz-fuzed azoles because aldoxime linkage is much more robust than azomethine linkage under various conditions.

We first explored the reaction of aldoxime **15** with various 2-substituted anilines **6** in air to afford benzoannelated nitrogen heterocycles **17**, **18**, and **19** by successive aldoxime–imine exchange reaction and air-oxidation. The results are summarized in Table 1. In contrast to the reaction of azomethines with 2-aminothiophenol (**6**, Y = S, Scheme 1), the reaction of **15** with **6** (Y = S) under an atmosphere did not proceed smoothly even at elevated temperature (entries 1 and 2). The yield was drastically improved by addition of trifluoroacetic acid to accelerate aldoxime–imine exchange (entry 3). The reaction was completed within 18 h (entry 4). However, treatment of **15** with 1,2-phenylenediamine **6** (Y = NH) did not give the desired benzimidazole **17** (Y = NH) under the same reaction conditions (entry 6). Synthesis of benzoxazole **17** (Y = O), quinazoline **18**, and quinazolinone **19** were also unsuccessful even in the presence of Darco® KB (entries 7–12), which

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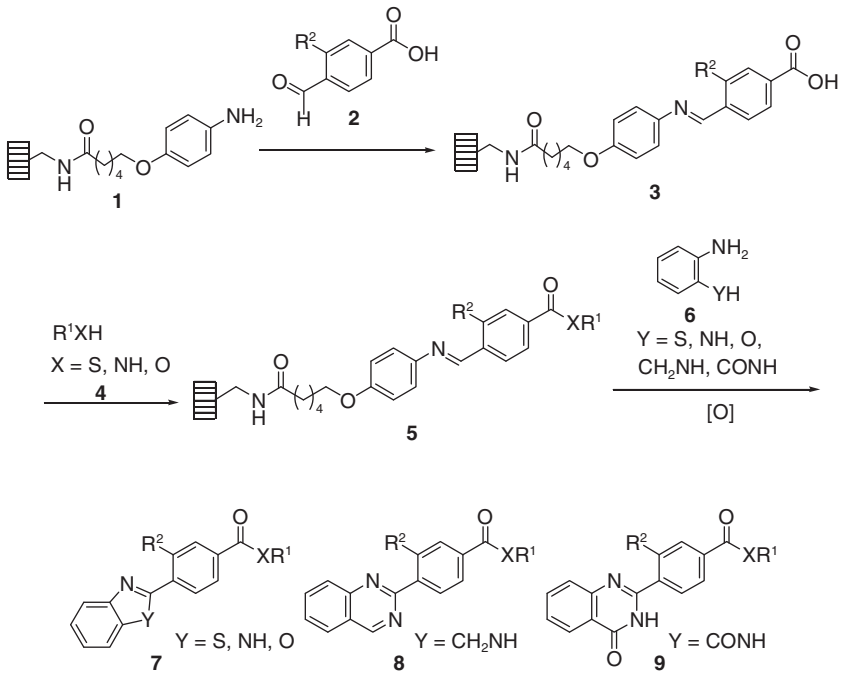
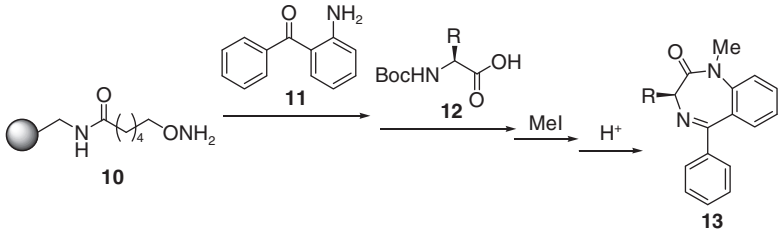


Scheme 1. Combinatorial synthesis of benz-fused heterocycles using alkoxyaniline linker **1**.



Scheme 2. Solid-phase synthesis of benzodiazepins **13** using alkoxyamine linker **10**.

was an effective catalyst for the oxidative cleavage from resin-bound azomethine.[8] Small amount of the products **17** (Y = O) and **19** were obtained at elevated temperature (entries 8 and 12). In entries 6, 8, 10, and 12, 2-substituted anilines **6** were not detected after the reaction. These results indicated that the aldoxime–imine exchange of **15** with **6** was much slower than the imine–imine exchange of **5** with **6** and that oxidative decomposition of **6** proceeded more rapidly than aldoxime–imine exchange at higher temperature. Only the benzothiazole **17** (Y = S) was obtained in good yield because the air oxidation proceeds at rt.

From the preliminary experimental results described above, we focused on the synthesis of benzothiazoles on a solid-support by using alkoxyamine linker **10** shown in Scheme 3. *p*-Anisaldehyde (**14**) was anchored by simple treatment with **10** in DMF at rt. The resulting resin-bound aldoxime **20** was mixed with 4 equiv of 2-aminothiophenol (**21**) in 5% TFA 1,2-dichloroethane solution at rt for 18 h. The desired benzothiazole **22** was obtained in 82% yield.

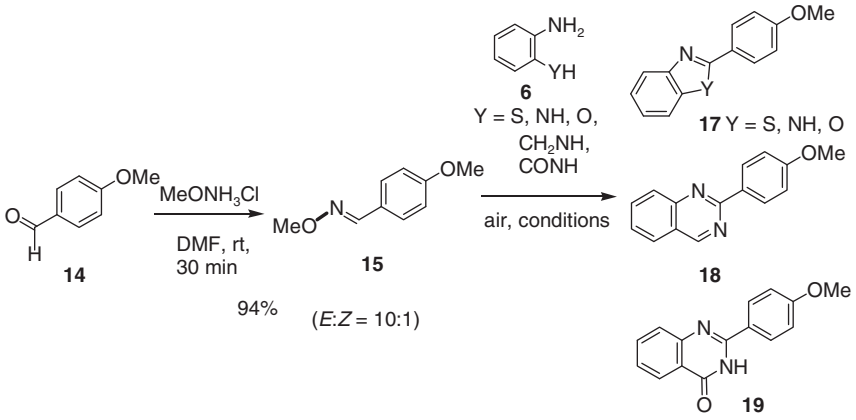
In advance of investigation of some reactions on a solid-support, the reaction conditions were optimized in solution. Two approaches were tried for alkylation of phenolic hydroxy group on **23**. Mitsunobu reaction with 2-butanol smoothly proceeds to give 2-butyl ether **25** at rt in good yield (Scheme 4). *n*-Pentyl ether was also obtained in good yield by alkylation with *n*-pentyl iodide under the basic conditions. The reaction was slower than Mitsunobu reaction.

Two kinds of palladium catalyzed reactions of 4-bromobenzaldehyde aldoxime **28** were also explored. Suzuki–Miyaura coupling of aryl bromide **28** with phenylboronic acid (**29**) proceeded smoothly to give the desired product **30** (Table 2). The reaction was faster by treatment of $Pd(OAc)_2$–PPh_3 (1:3) system than by that of $Pd(PPh_3)_4$ (entries 1 and 2). Employment of $PdCl_2$(dppf) gave **30** in the best yield (97%) (entry 3). Mizoroki–Heck reaction of **28** with *n*-butyl acrylate (**31**) was performed by treating $PdCl_2$(dppf) and triethylamine at 100 °C. The desired product **32** was obtained in acceptable yield (entry 4).

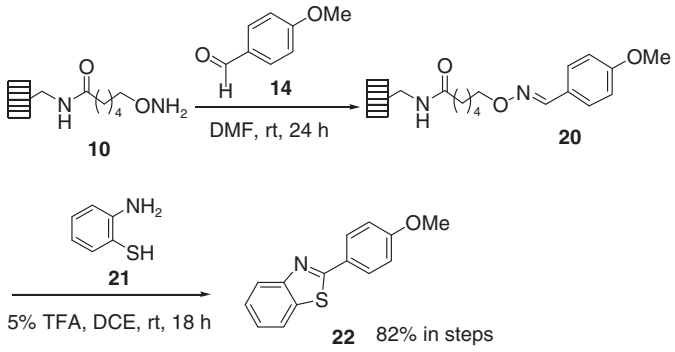
Finally, these optimized conditions were applied to the solid-phase synthesis by using alkoxyamine linker **10**. The yields were compared with that of the reaction using alkoxyaniline linker **1**, which was previously employed for the synthesis of heterocyclic compounds.[8] In case of Mitsunobu reaction on a solid-support, the desired benzothiazole **36** was obtained in 80% yield by successive loading of 4-hydroxybenzaldehyde (**33**), Mitsunobu reaction with 2-butanol (**24**), and aldoxime–imine exchange by using 2-aminothiophenol (**21**) coupled with air-oxidation. Mitsunobu reaction in the second step was completed within 4 h (Table 3, entries 1 and 2). On the other hand, the yields were moderate in the case of using alkoxyaniline linker **1** (entries 3 and 4). Partial alcoholysis of azomethine linkage with 2-butanol may occur during Mitsunobu reaction.

The results for the alkylation of phenolic oxygen on a solid-support with *n*-pentyl iodide under the basic conditions are

Table 1
Scope and limitation of using aldoxime–imine exchange reaction for the synthesis of benz-fuzed heterocyles



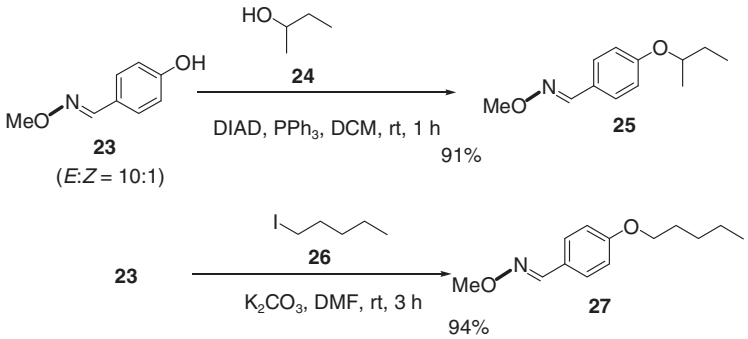
Entry	Y	Additive	Solvent	Temp	Period (H)	Yield (%)
1	S		DMF	100 °C	5	0
2			DCE	Reflux	5	5
3		TFA(5%)	DCE	rt	5	71
4		TFA(5%)	DCE	rt	18	88
5	NH	TFA(5%)	DCE	rt	18	0
6		TFA(5%)	DCE	Reflux	18	0
7	O	TFA(5%)	DCE	rt	18	0
8		TFA(5%), Darco® KB	DCE	Reflux	18	6
9	CH_2NH	TFA(5%)	DCE	rt	18	0
10		TFA(5%), Darco® KB	DCE	Reflux	18	0
11	CONH	TFA(5%)	DCE	rt	18	0
12		TFA(5%)	DCE	Reflux	70	2



Scheme 3. Synthesis of benzothiazole on a solid-support by using **10**.

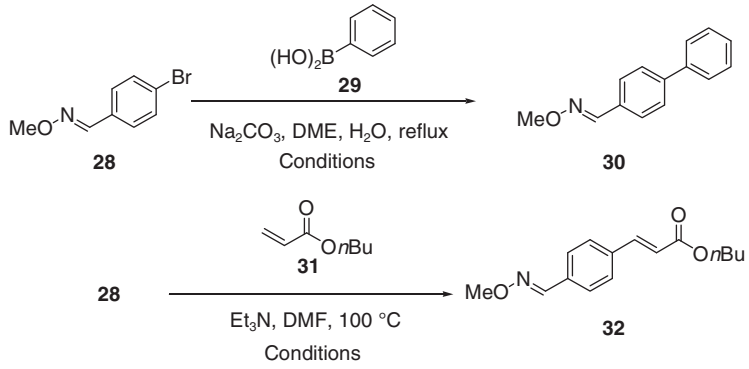
summarized in Table 4. The benzothiazole **37** was obtained in moderate yield when the aldehyde **33** was anchored as aldoxime linkage (entry 1). In our previous study of solid-phase synthesis of benzodiazepins, the reactivity of N-alkylation of *N*-aryl amides highly depended on solid-support. The polystylene resin cross-linked with 1% divinylbenzene was found to be the most suitable resin for the N-alkylation by alkyl halides under the basic conditions.[13] Thus the solid-support was switched to the polystylene resin. The yield was improved to 74% (entry 2). Similar results were obtained when the aldehyde **33** was linked with **1** through azomethine linkage (entries 3 and 4). However the overall yields by using alkoxyaniline linker **1** were lower than that by alkoxyamine linker **10**.

Suzuki–Miyaura coupling on a solid-support also proceeded smoothly using the linker **10**. The results are shown in Table 5.[14] Employment of $PdCl_2$(dppf) as a catalyst rather than $Pd(OAc)_2$–PPh_3 gave better result as well as in solution phase reaction shown in Table 2 (entries 2 and 3). The yields were dropped when 4-bromobenzaldehyde (**38**) was anchored as azomethine using **1** (entries 3 and 4). The substrate might be released during the Suzuki–Miyaura



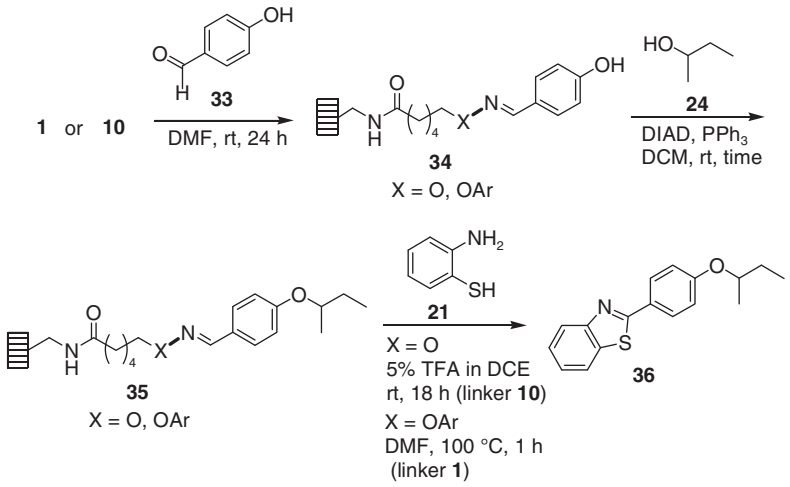
Scheme 4. Alkylation of phenolic hydroxy group on **23**.

Table 2
Suzuki–Miyaura coupling and Mizoroki–Heck reaction of **28**



Entry	Reagent	Catalyst (mol %)	Ligand (mol %)	Period	Yield (%)
1	29	$Pd(PPh_3)_4$ (10)	—	2 h	92
2	29	$Pd(OAc)_2$(10)	PPh_3 (30)	45 min	84
3	29	$PdCl_2$(dppf) (10)	—	45 min	97
4	31	$PdCl_2$(dppf) (20)	—	3 h	78

Table 3
Mitsunobu reaction on a solid-support by using **1** and **10**



Entry	Linker	Period[a] (h)	Yield[b] (%)
1	10	4	80
2		16	80
3	1	4	53
4		16	61

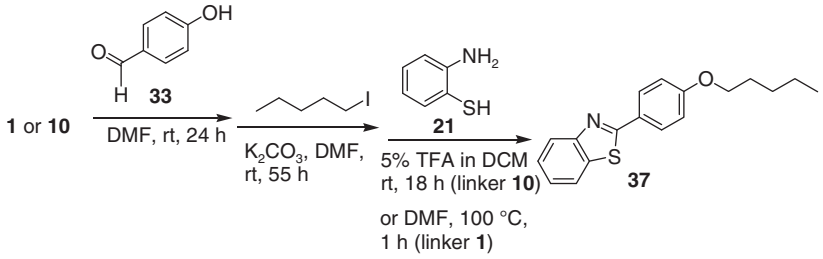
[a] Reaction period for Mitsunobu reaction.
[b] Isolated yield from **1** or **10.**

coupling because unreacted intermediates or decomposed products derived from **38** were not detected in the crude product **39**.

A similar trend was observed in the Mizoroki–Heck reaction on a solid-support (Scheme 5). The desired product **40** was obtained in 68% overall yield by treatment of linker **10**, whereas the yield was decreased to 28% in the case of linker **1**.

In conclusion, we found the alkoxyamine linker **10** is efficient for the solid-phase synthesis of various benzothiazoles. The aromatic aldehydes are tethered as aldoxime linkage and oxidatively cleaved with 2-aminothiophenol under mildly acidic conditions in air. The substrates on a solid-support can be subjected to Mitsunobu reaction, alkylation with alkyl halides, and palladium catalyzed reactions such as Suzuki–Miyaura coupling and Mizoroki–Heck reaction. The tether is highly robust under these reaction conditions in comparison of azomethine linkage formed by aromatic aldehydes and alkoxyaniline linker **1**. Recyclability of the alkoxyamine linker **10** and application to the synthesis of benzothiazole library is currently under investigation.

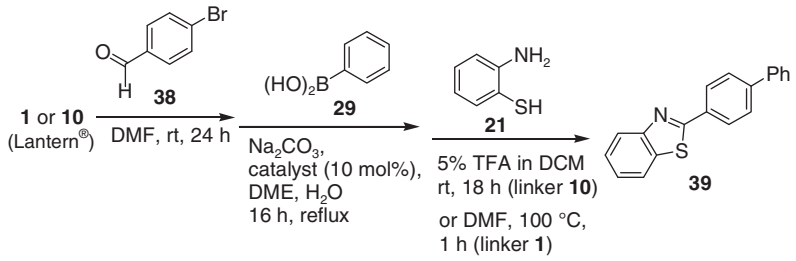
Table 4
Alkylation of phenolic oxygen on a solid-support under the basic conditions by using **1** and **10**



Entry	Linker	Resin	Yield[a] (%)
1	10	Lantern®	52
2		Polystylene	74
3	1	Lantern®	14
4		Polystylene	63

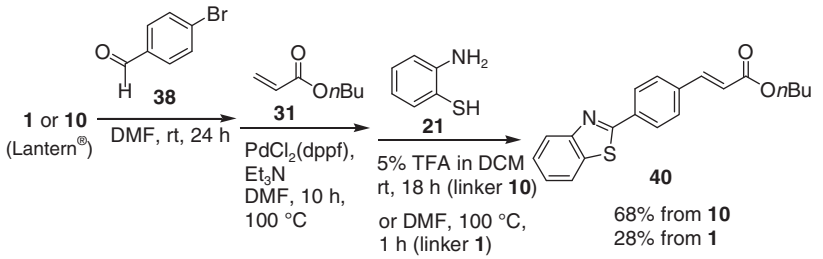
[a] Isolated yield from **1** or **10**.

Table 5
Suzuki–Miyaura coupling on a solid-support by using **1** and **10**



Entry	Linker	Catalyst[a]	Ligand (mol%)[a]	Yield[b] (%)
1	10	$Pd(OAc)_2$	PPh_3 (10)	71
2		$PdCl_2(dppf)$	—	89
3	1	$Pd(OAc)_2$	PPh_3 (10)	38
4		$PdCl_2(dppf)$	—	39

[a] Catalysts and ligands for Suzuki–Miyaura coupling.
[b] Isolated yield from **1** or **10**.



Scheme 5. Mizoroki–Heck reaction on a solid-support by using **1** and **10**.

Acknowledgments

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14. *Representative procedure for the synthesis of benzothiazoles:*
One piece of the solid supported alkoxyamine **10** (loading: 75 μmol)[13] was reacted with 4-bromobenzaldehyde (55 mg, 0.3 mmol, 4 equiv) in DMF solution (3 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 was mixed with phenylboronic acid (55 mg, 0.45 mmol, 6 equiv) and $PdCl_2(dppf)\cdot CH_2Cl_2$ in degassed dimethoxyethane (4.2 mL) and 2 mol L^{-1} aqueous Na_2CO_3 solution (300 μL, 0.6 mmol, 8 equiv). The mixture was refluxed for 16 h. The solution was removed by decantation and the resulting resin was washed with MeOH (3 × 2 min), DMF (3 × 2 min), and DCM (3 × 2 min). The resin was reacted with 2-aminothiophenol (32.7 μL, 0.3 mmol, 4 equiv) in 5% TFA-DCM solution (3 mL) at rt under an air atmosphere for 18 h. The resulting resins were washed with DMF (3 × 2 min) and DCM (3 × 2 min). The combined DMF and DCM solutions were evaporated and purified by silica gel chromatography (hexane/EtOAc = 20/1) to give benzothiazole **39** in 89% yield (19.1 mg, 66.5 μmol,) as a colorless solid (mp 130 °C, dec.).