Novel Alkoxyamine Linker to Load Ketones for Solid-Phase Synthesis: Application of the Synthesis of 1,4-Benzodiazepine-2-ones

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Selection of an adequate linker is important for the solid-phase organic synthesis. Linkers should be easy to load scaffolds onto the solid support, and must be not only stable during the reactions but also cleavable without product damage at the final stage. Much effort has been made to design and synthesize various linkers suitable for loading the scaffolds, as well as for giving desired products.[1] We have previously developed the new alkoxyaniline linker **1**, which is applicable to the solid-phase synthesis of heterocyclic compounds such as 2-substituted benz-fused azoles **6**, quinazolines **7**, and quinazolinones **8**.[2] The 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.[3] The reaction sequence to synthesize these heterocyclic compounds involved loading of the aromatic aldehydes on the solid support by an imine synthesis and oxidative release of resin-bound imines with various 2-substituted anilines. The releasing step includes the equilibrium of the imine-exchange process between **2** and **4** as shown in Scheme 1. Although the stability of compounds **2** and **4** is comparable, the equilibrium can be shifted to the product side by coupling irreversible oxidation process.

In this study, we have focused on an intramolecular imine exchange reaction to expand the utility of our strategy. Releasing product from the solid support by the intramolecular nucleophilic attack of amine group is entropically favorable as a consequence of less adverse ΔS when forming seven-membered ring system. Thus the equilibrium is expected to shift to product side in this process[4] (Scheme 2).
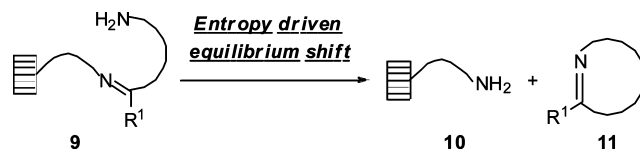
Solid-phase synthesis of 1,4-benzodiazepine-2-ones historically set the stage for the combinatorial synthesis of various small molecules on a solid support.[5] They are classified as privileged structure because of a wide range of their pharmaceutical activities such as hypnosis and anxiolytic actions.[6] Thus we have decided to synthesize 1,4-benzodiazepine-2-ones **18** to demonstrate the validity of our strategy outlined in Scheme 2. According to our synthetic plan as shown in Scheme 3, 2-aminobenzophenones **12** are needed to load on a solid support because the aromatic group at the C-5 position in **18** is essential for the biological activity

of benzodiazepine.[6] After Boc-protected α-amino acids **14** are condensed with **13**, the nitrogen on the aromatic ring is functionalized with alkylating agents. Finally, removal of the

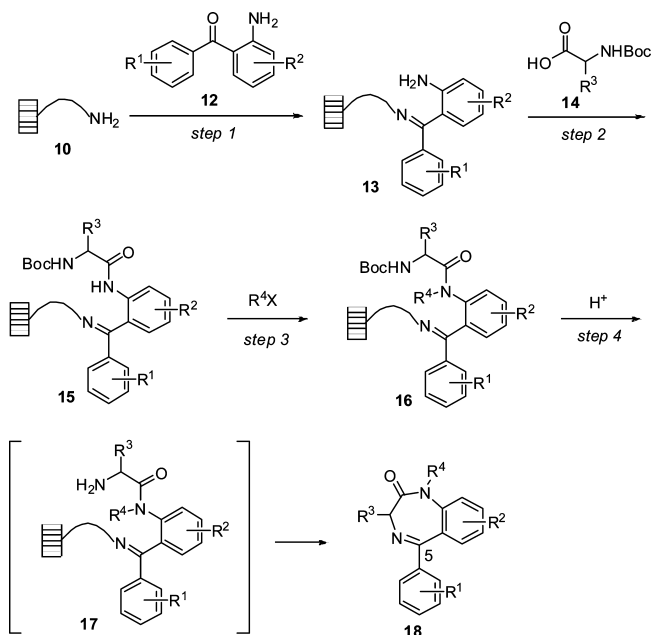**Scheme 1.** Solid-Phase Synthesis of Heterocyclic Compounds by Using a Traceless Alkoxyaniline Linker **1**
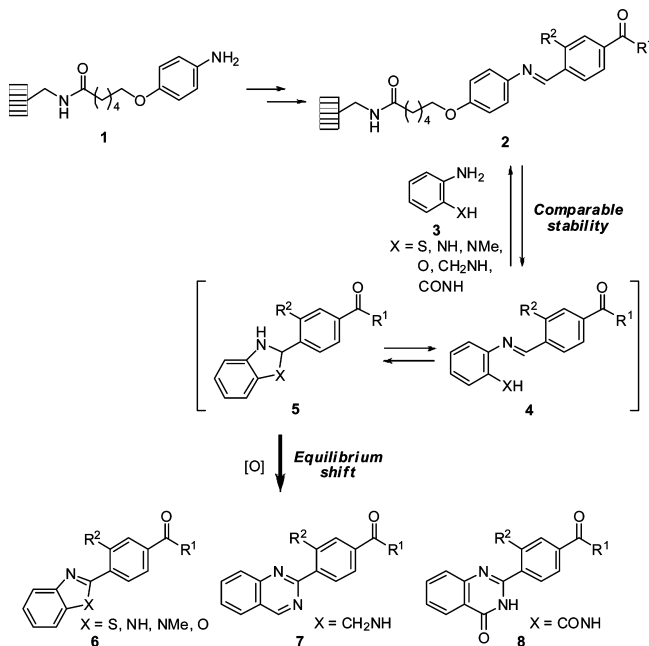
Scheme 2. Strategy for Releasing Product by Intramolecular Imine Exchange Reaction

Scheme 3. Synthetic Plan for the Solid-Phase Synthesis of 1,4-Benzodiazepine-2-ones

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Table 1. Benzophenone Hydrazones and Oximes Formation by Using Various Hydrazines and Alkoxyamines

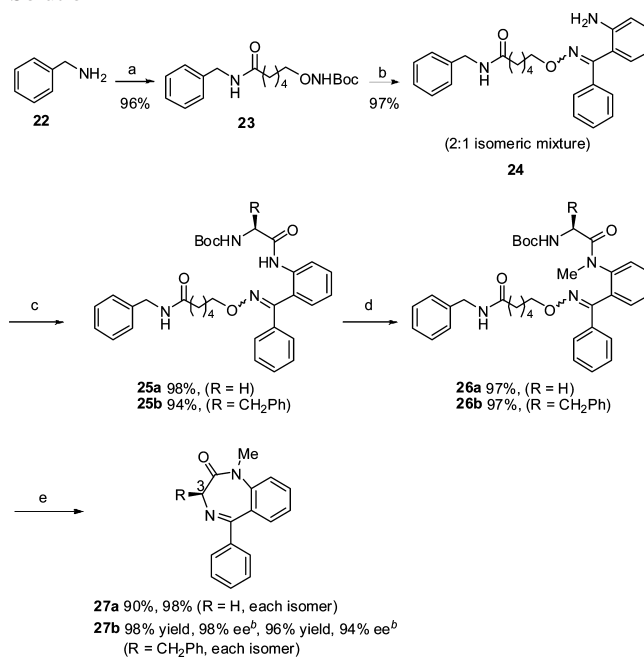| entry	X	R^1	R^2	time (h)	yield (%)
1^a	N	Me	Me	48	0
2^a		Me	H	48	0
3^b		4-methoxyphenyl	H	20	19
4^a		Ph	H	20	42
5^a		2,4-dinitrophenyl	H	48	77
6^a		C$_2$H$_5$OCO	H	40	13
7^c		C$_2$H$_5$NHCO	H	40	98
8^{a,b}	O	Ph		48	0
9^b		Me		20	91

^{a} TsOH was added as an acid catalyst. ^{b} **19** was used as hydrochloride salt. ^{c} **19** was used as trifluoroacetate salt.

Boc group under acidic conditions, together with a subsequent product release by intramolecular imine exchange reaction, would give the desired benzodiazepines **18**.

Since aromatic ketones were not easily loaded on the solid support with the original alkoxyaniline linker **1** by simply heating under the acidic conditions because of their low reactivity,[7] we first explored a suitable linker for loading benzophenones on a solid support. However, the previously known linkers to load ketones are quite limited[8] in contrast to those for amines, carboxylic acids, alcohols, and aldehydes.[1] Ketohydrazones and ketoximes are known to be quite stable, and some of them are simply obtained by heating under the neutral or mild acidic conditions.[9] Therefore, reactions of various hydrazines **19** (X = N) and alkoxyamines **19** (X = O) with benzophenone were examined in solution to afford the corresponding ketohydrazones **21** (X = N) and ketoximes **21** (X = O). Results are summarized in Table 1.

Treatment of benzophenone with *N*-alkyl hydrazines did not give the hydrazones[10] (entries 1 and 2). In the case of *N*-aromatic hydrazines, the desired hydrazones were obtained. Their yields highly depended on the substituents on the aromatic nuclei (entries 3−5). The use of a hydrazine with electron-withdrawing group on the aromatic ring gave higher yield (entry 5). The reaction with ethyl carbazate gave the corresponding hydrazone in only 13% yield (entry 6). On the other hand, the reaction with semicarbazide gave the hydrazone in very good yield (entry 7). In a series of oxime formation, the use of *O*-phenylhydroxylamine was not effective[10] but that of *O*-methylhydroxylamine gave the corresponding oxime in 91% yield (entries 8 and 9). Although the semicarbazide gave the best yield in this screening (entry 7), we chose *O*-alkylhydroxylamine as an appropriate linker to load benzophenones because the hydrazone derived form semicarbazide has highly acidic N−H proton that may cause side reaction, such as *N*-alkylation at this position in the course of further transformation.[11]
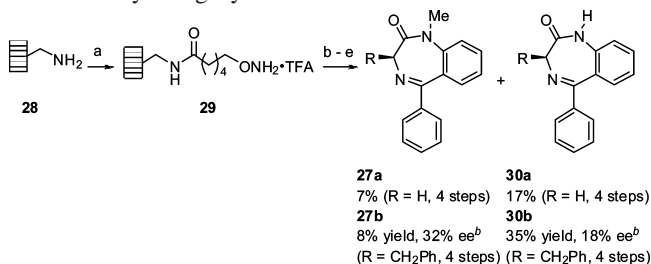
1,4-Benzodiazepine-2-ones **27** were synthesized in solution to optimize the reaction conditions in each step (Scheme 4). Benzylamine **22** was used as a solution model for aminomethylated polystyrene resin. Boc-protected aminooxyhexanoic acid[12] was condensed with **22** to afford **23**. After removal

Scheme 4. Synthesis of 1,4-Benzodiazepine-2-one **27** in Solution^a

27a 90%, 98% (R = H, each isomer)
27b 98% yield, 98% ee^b, 96% yield, 94% ee^b
(R = CH$_2$Ph, each isomer)

^{a} Reagents and conditions: (a) 6-(*N-tert*-butyloxycarbonylaminooxy)hexanoic acid, EDC, DMAP, DCM, rt, 3 h; (b) 15% TFA in DCM, rt, 30 min, then 2-aminobenzophenone, EtOH, reflux, 38 h; (c) Boc-Gly-OH or Boc-Phe-OH, EDC, DMAP, DCM, rt, 4 h; (d) MeI, Cs$_2$CO$_3$, DMF, rt, 4 h; (e) TFA−H$_2$O (4:1), reflux, 24 h. ^{b} Enantiomeric excess was determined by chiral HPLC on the CHIRALCEL OD-H.

of the Boc group, the resulting amine was treated with 2-aminobenzophenone in ethanol under reflux. The desired oxime **24** was obtained in good yield as a 2:1 geometrical isomer, which was used without separation for further reactions. The oxime **24** was subjected to condensation with Boc-protected glycine or phenylalanine. The amides **25a** and **25b** were prepared in good yields. Subsequent *N*-methylation of **25** proceeded smoothly at rt to give **26a** and **26b** in excellent yields. At this stage, two geometrical isomers were separated. Finally, removal of the Boc group and subsequent intramolecular oxime-imine exchange reaction to release the final product were investigated. Desired benzodiazepines were obtained in good yields regardless of the geometry of the oxime bond and substitution at C-3. When R is a benzyl group, **27b** slightly lost their chirality at the C-3 position (**27b** 98% ee and 94% ee for each geometrical isomer around C=N linkage in **26b**).

Next, the optimized reaction conditions described above were applied to the solid-phase synthesis of 1,4-benzodiazepine-2-one (Scheme 5). The aminooxyalkylated resin **29** was synthesized in two steps from aminomethylated Syn-Phase-PS Lantern **28**, which is polystyrene grafted surface, as follows. Boc-protected aminooxyhexanoic acid was loaded through amide linkage, and then the Boc group was removed under acidic conditions to afford TFA salt **29**, which was subjected to further reaction without neutralization. Treatment of **29** with 4 equiv of 2-aminobenzophenone in EtOH under reflux gave the corresponding oxime. The amino group on the aromatic ring was acylated with Boc-protected glycine or phenylalanine.[13] The resulting amides were subjected to *N*-methylation under the same reaction conditions as in solution-phase. Removal of the Boc group triggered benzo-

Scheme 5. Solid-Phase Synthesis of 1,4-Benzodiazepine-2-ones **27** by using SynPhase-PS Lantern[a]

27a
7% (R = H, 4 steps)
27b
8% yield, 32% ee[b]
(R = CH₂Ph, 4 steps)

30a
17% (R = H, 4 steps)
30b
35% yield, 18% ee[b]
(R = CH₂Ph, 4 steps)

[a] Reagents and conditions: (a) 6-(*N-tert*-butyloxycarbonylaminooxy)hexanoic acid, DIC, HOBt, DCM, rt, 24 h then 50% TFA in DCM, rt, 1 h; (b) 2-aminobenzophenone, EtOH, reflux, 48 h; (c) Boc-Gly-OH or Boc-Phe-OH, DIC, DMAP, DCM, rt, 24 h; (d) MeI, Cs₂CO₃, DMF, rt, 3 h; (e) TFA−H₂O (4:1), reflux, 24 h. [b] Enantiomeric excess was determined by chiral HPLC on the CHIRALCEL OD-H.

Table 2. *N*-Methylation on Various Solid Supports

				isolated yield (%)	
entry	resin	composition	cross-linking	**27b**	**30b**
1	Lantern	polystyrene		20	21
2	Lantern	polyacrylamide		29	21
3	polystyrene	polystyrene	macroporous	0.8	5
4	StratoSpheres	polystyrene	1% DVB	50	0
5[a]	StratoSpheres	polystyrene	1% DVB	73[b]	0

[a] Cleavage with 5% TFA in 1,2-dichloroethane at 80 °C for 18 h. [b] Enantiomeric excess was 45% ee, which was determined by chiral HPLC on the CHIRALCEL OD-H.

diazepine formation along with releasing the final products. However, the desired products **27a** and **27b** were generated only in 7% and 8% yields, respectively, along with a large amount of **30a** and **30b**. In addition, considerable racemizations of them (32% ee for **27b** and 18% ee for **30b**) were caused during these reaction sequences. The results indicated that the reaction conditions of these steps in solution were unable to be applied to the solid-phase synthesis.

The reaction conditions of *N*-alkylation were first examined to improve the yields. After numerous trials, we finally found that the *N*-alkylation highly depended on solid-support as shown in Table 2. The *N*-methylation was completed by using polystyrene resin cross-linked with 1% divinylbenzene (entry 4). The reactivity of the *N*-alkylation may be related to swelling capacity of the solid support. Its yield was improved to 73% overall when cleavage from the resin carried out with 5% TFA in 1,2-dichloroethane (entry 5). However, considerable racemization was still observed (45% ee).

The acylation of **32** was examined again to suppress this racemization as shown in Table 3. The use of 1-hydroxy-benzotriazole (HOBt),[14] which is known as a racemization-suppressing agent, drastically increased the enantiomeric excess of **33** to 99%, but decreased chemical yield by 21% (entry 2). Addition of HOAt,[15] which is known to efficiently speed up coupling process and reduce a loss of chiral integrity, gave the desired product **33** in a high enantiomeric

Table 3. Enantiopurity and Isolated Yield of **33** under Various Acylation Conditions

entry	additive	enantiomeric excess (%)[a]	isolated yield (%)
1	DMAP	36	53
2	HOBt	99	21
3	HOAt	99	73

[a] Enantiomeric excess was determined by chiral HPLC on the CHIRALCEL OD-H.

Scheme 6. Solid-Phase Synthesis of 1,4-Benzodiazepine-2-one **27b** under the Optimized Conditions[a]

27b 66% yield, 99% ee[b]
(4 steps)
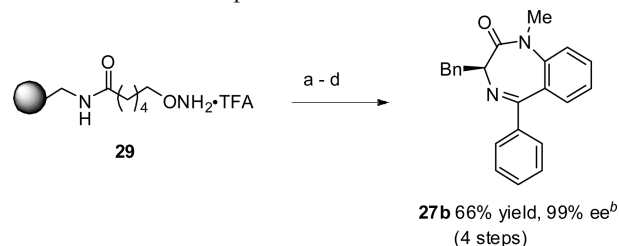
[a] Reagents and conditions: (a) 2-aminobenzophenone, EtOH, reflux, 72 h; (b) Boc-Phe-OH, DIC, HOAt, DCM, rt, 48 h; (c) MeI, Cs₂CO₃, DMF, rt, 48 h; (d) 5% TFA, 1,2-dichloroethane, 80 °C, 18 h. [b] Enantiomeric excess was determined by chiral HPLC on the CHIRALCEL OD-H.

Table 4. Synthesis of 1,4-Benzodiazepine-2-ones **35** using Several α-Amino Acids As Building Blocks

Entry	α-amino acid	R	Isolated yield (%)
1	Boc-Trp(Boc)-OH		62
2	Boc-Asp(OMe)-OH	CH₂COOMe	43
3	Boc-Leu-OH	CH₂CH(CH₃)₂	70
4	Boc-Tyr(*t*Bu)-OH		72

excess and good yield (entry 3, 73% yield and 99% ee). Thus the problems associated with *N*-alkylation and racemization at the C-3 position in the solid-phase synthesis of 1,4-benzodiazepine-2-one have been solved. Benzodiazepine **27b** was also synthesized in 66% yield without racemization under the optimized conditions as shown in Scheme 6.[16]

Finally, several α-amino acids were applied as building blocks at the acylation step to examine the scope of this method. All four benzodiazepines **35** were obtained in moderate to good yields (Table 4).

In conclusion, we have developed a traceless alkoxyamine linker suitable for loading ketones, and it has proved to be useful for the solid-phase synthesis of 1,4-benzodiazepine-2-ones. The reaction sequences involve four steps: loading ketones as oximes, condensation of α-amino acids,

N-alkylation, and cleavage of the products from the resin by intramolecular oxime−imine exchange reaction. The compounds **27b** and **33**, which are representatives of benzodiazepines, were synthesized without racemization in 66% and 73% overall yields, respectively. Although some solid-phase syntheses of 1,4-benzodiazepine-2-ones were reported,[5] our method has the advantages of short reaction sequences, a variety of building blocks available and no functional group attached on solid support. In addition, some other benzodiazepines such as 2,3-benzodiazepine-4-ones[17] and pyrrolo[2,1-*c*][1,4]benzodiazepine-5-ones[18] have been reported to have interesting biological activities such as AMPA receptor antagonists and antibiotic antitumor agents. The solid-phase synthesis of these types of compounds will be also able to be realized utilizing our linker. Synthesis of the combinatorial library of the benzodiazepine family is in progress.

Supporting Information Available. Synthesis and characterization of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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