Solid-Phase Synthesis of 2-Pyridones, 1,4-Diazepines, and 1,4-Oxazepines from Resin-Bound 3-Amino-2-seleno Ester

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A versatile combinatorial approach was developed for the rapid synthesis of 2-pyridones, 1,4-diazepines, and 1,4-oxazepines libraries. The synthetic strategy includes electrophilic addition, nucleophilic substitution, amine-acid condensation, Dieckmann condensation, lactamization, ester hydrolysis, lactonization, and oxidation−elimination.

Introduction

The rapid synthesis of diverse libraries of organic compounds for drug candidate screening is an important facet of modern drug discovery programs. As one of the most powerful tools in small-molecule library preparation, solid-phase organic synthesis (SPOS) has attracted much attention from both chemists and pharmaceutists.[1] Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents. As a result, an increasing range and number of pharmaceutically useful heterocyclic compounds have been prepared using the solid-phase methodology.[2]

2-Pyridones, 1,4-diazepines, and 1,4-oxazepines are three kinds of heterocycles that exist in various biologically active compounds. The 2-pyridone structural motif is found in a large number of pharmaceutical agents where they function as inhibitors of the *Bacillus anthracis* enoyl-ACP reductase,[3a] inhibitors of HCV genotype 1NS5B RNA-dependent RNA polymerase,[3b] inhibitors of Receptor Tyrosine Kinase c-Kit,[3c] Calcitonin gene-related peptide (CGRP) receptor antagonists,[3d] inhibitors of Mitogen-Activated Protein Kinase Kinase,[3e] and HIV-1 reverse transcriptase inhibitors.[3f] The pharmaceutical compounds having the 1,4-diazepine unit show great biological activities such as HDM2 antagonists.[4] The 1,4-oxazepines scaffold also play important role as pharmacophores in many pharmaceuticals.[5] Therefore, all of them are interesting targets to be prepared through solid-phase synthetic methodology.

Organoselenium compounds have been widely applied in organic synthesis,[6] because the relative weak bond energy of the C−Se bond makes it possible to conduct various reactions.[7] Therefore, organoselenium resins are ideal linkers and reagents for solid phase synthesis. During the past decade, several research groups[8] including ours[9] have constructed a variety of heterocyclic compounds libraries from organoselenium resins. As the continuation of our ongoing efforts to generate pharmaceutically interesting heterocyclic compounds on solid phase, herein, we wish to report an efficient method for the parallel synthesis of 2-pyridones, 1,4-diazepines, and 1,4-oxazepines. In our strategy, the easily achieved and useful building block resin-bound 3-amino-2-seleno ester **1** is reacted with functionalized acid to form amide resin **2**. According to the differences of the functional groups on the acid, resin **2** then has two choices as follows. (path a) The α carbon of the amide **2** attacks the carbonyl group of ester to get a six-membered ring 2-pyridones **3**. (path b) The β position of the amide **2** attacks the carbonyl group of ester to give a seven-membered ring 1,4-diazepines **4** or 1,4-oxazepines **5**, respectively (Scheme 1).

Results and Discussion

3-Amino-2-seleno ester resins **1** were synthesized by reported protocols.[9e] Polystyrene-supported seleneyl bromide **6**[8a] (Br: 1.04 mmol/g) was reacted with methyl acrylate and primary amine successively in one pot to afford the desired yellow resins **1** (Scheme 2).

With resins **1** in hand, we explored Dieckmann condensation to prepare the 2-pyridone ring system.[10] Resins **1** were first reacted with malonic monoester and diisopropyl carbodiimide (DIC) for 24 h to give the amide resins **7**. FTIR showed a new carbonyl absorption at 1655−1658 cm^{-1}. Under a positive pressure of nitrogen, resins **7** were stirred with potassium *tert*-butoxide for 2 h at −78 °C to afford the lactam resins **8**. FTIR showed that the original strong absorption of the carbonyl group at 1728−1731 cm^{-1} became much weaker. The resulting resins **8** were then treated with excess 30% hydrogen peroxide to form selenoxide in situ, and spontaneous elimination of the selenoxide led to the release of corresponding 2-pyridones **3** (Scheme 3) in moderate to good yields with good levels of purities (Table 1).

Amine-acid condensation was a classic method in heterocycle formation;[11] here, we utilized this strategy to prepare

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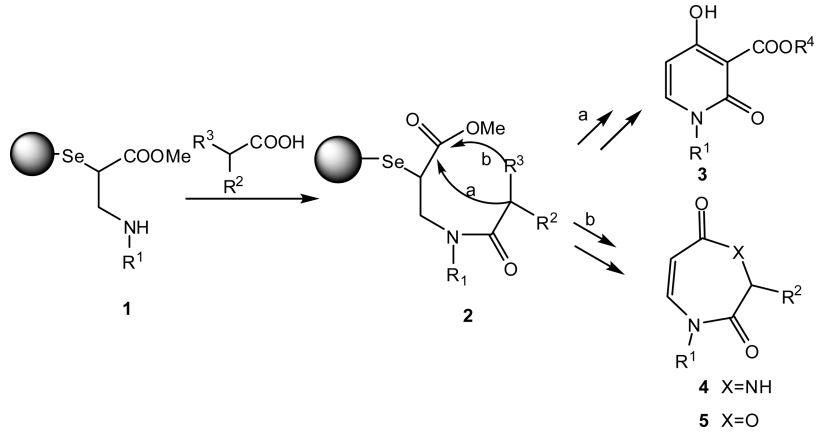
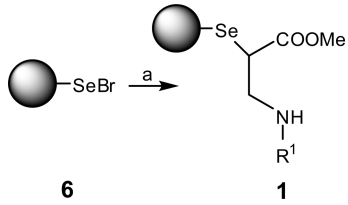
Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) $ZnCl_2$, $CH_2{=}CHCO_2Me$, CH_2Cl_2, rt, 0.5 h, then R^1NH_2, rt, 24 h.

Table 1. Synthesis of 2-Pyridones **3**

product	R^1	R^2	yield (%)[a]	purity (%)[b]
3a	Bn	Et	57	92
3b	Pr	Et	51	85
3c	allyl	Et	43	78
3d	Cy	Et	55	94
3e	$PhCH_2CH_2$	Et	50	92
3f	*i*-Bu	Et	49	83
3g	Bn	Me	63	89
3h	Cy	Me	58	86
3i	Pr	Me	55	82

[a] Yield of the crude product based on the loading of the resin **6**. [b] Determined by HPLC (UV 254 nm).

the 1,4-diazepine scaffold in the solid phase. At room temperature, resins **1** were treated with Fmoc-α-amino-acids and DIC for 24 h to form the amide resins **9** smoothly. Resins **9** then were deprotected and spontaneously cyclized in piperidine/CH_2Cl_2 to give the resin-bound 1,4-diazepane-2,5-diones **10**; FTIR showed the disappearance of the carbonyl absorption peak at 1730−1735 cm^{-1}. After oxidation and *syn*-elimination, the cleavage of resin **10** afforded the final products 1,4-diazepines **4** in moderate to good yields with good levels of purities (Scheme 4, Table 2).

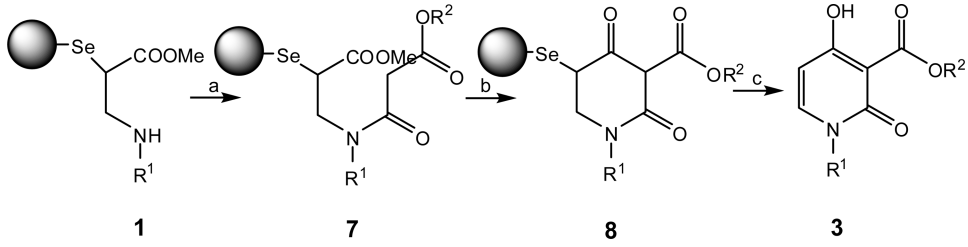
Further experiment showed that throughout all these three steps, the chiral integrity of the starting α-amino acid had been maintained. To address this issue, the products **4e** and **4f** were analyzed by chiral HPLC and found to be optically pure. The calculated enantiomeric excess (ee) and measured optical rotation for each enantiomer are given in Figure 1. Therefore, this methodology was very suitable for the synthesis of optically pure products due to the easy availabilities of chiral α-amino-acids.

When Fmoc-α-hydroxy-acids were used instead of Fmoc-α-amino-acids, after deprotecting, the seven-membered ring 1,4-oxazepane did not formed spontaneously. The reason may be that the nucleophilicity of oxygen is not as strong as that of nitrogen. As a consequence, other alternative procedures had to be adopted. The newly formed amide resins **11** were stirred in piperidine/CH_2Cl_2 to free the hydroxyl group to form resins **13**. Resins **13** were then treated with aqueous LiOH in THF to undergo a hydrolysis step; FTIR showed that the carbonyl absorption at 1732−1735 cm^{-1} moved to 1715−1718 cm^{-1}. Under the assistance of DIC, the resulting resins **14** performed intramolecular condensation to afford the 1,4-oxazepane resins **12**, which were then reacted with excess 30% hydrogen peroxide to give the corresponding 1,4-oxazepines **5** in moderate yields with good levels of purities (Scheme 5, Table 3).

Conclusions

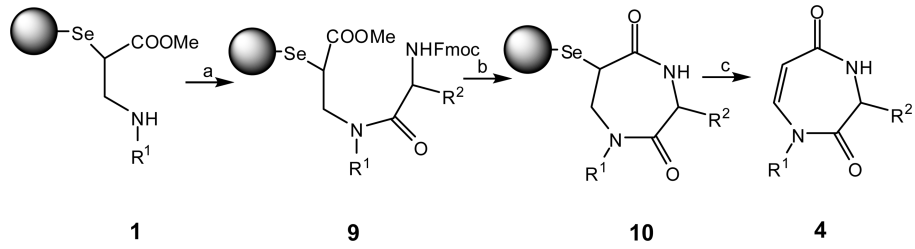
In summary, we have developed an efficient solid-phase parallel synthetic route to prepare libraries of 2-pyridones, 1,4-diazepines, and 1,4-oxazepines based on a polystyrene-supported selenium resin. The advantages of this method include straightforward synthetic sequence, lack of odor,

Scheme 3[a]



[a] Reagents and conditions: (a) $HOOCCH_2COOR^2$, DIC, THF, rt, 24 h; (b) *t*-BuOK, *t*-BuOH/THF, −78 °C, 2 h; (c) H_2O_2, THF, rt, 1 h.

Scheme 4[a]

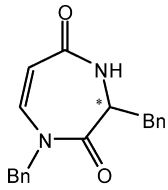


[a] Reagents and conditions: (a) Fmoc-α-amino-acid, DIC, THF, rt, 24 h; (b) piperidine/CH_2Cl_2(1:4), rt, 12 h; (c) H_2O_2, THF, rt, 1 h.

Table 2. Synthesis of 1,4-Diazepines **4**

product	R^1	α-amino-acid	yield (%)[a]	purity (%)[b]
4a	Bn	glycine	73	96
4b	Bn	L-alanine	68	88
4c	Bn	L-isoleucine	65	91
4d	Bn	L-proline	63	87
4e	Bn	L-phenylalanine	70	85
4f	Bn	D-phenylalanine	68	93
4g	Pr	L-phenylalanine	71	85
4h	allyl	L-phenylalanine	66	84
4i	Cy	L-phenylalanine	75	89
4j	Pr	L-alanine	60	87
4k	allyl	L-isoleucine	65	91
4L	Cy	glycine	77	97
4m	$PhCH_2CH_2$	glycine	57	83

[a] Yield of the crude product based on the loading of the resin **6**. [b] Determined by HPLC (UV 254 nm).



Product	α-amino-acid	ee (%)[a]	$[\alpha]_D$[b]
4e	L-phenylalanine	>99	+364.1
4f	D-phenylalanine	>99	-361.6

a. Calculated using HPLC areas.

b. Specific rotations at 20 °C in CH_2Cl_2.

Figure 1

good stability of the supported selenium species, and high purities of the products.

Experimental Section

General Methods. Starting materials were obtained from commercial suppliers and were used without further purification. THF was distilled from sodium/benzophenone immediately prior to use. Polystyrene (H 1000, 100−200 mesh, cross-linked with 1% divinylbenzene) was used for the preparation of selenenyl bromide resin (1.04 mmol of Br/g) according to the procedure described by Nicolaou and coworkers[8a] and was purchased from commercial sources (Nankai University). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance spectrometer using $CDCl_3$ as the solvent and TMS as an internal standard. Mass spectra (EI, 70 eV) were recorded on an Agilent 5975 inert mass selective detector. Infrared spectra were recorded on a Bruker Vector22 spectrometer. High resolution mass spectrometry (HRMS) was performed on a Waters Micromass GCT instrument. HPLC was performed on an Agilent 1100 (column, Eclipse XDB-C18 5 μm, 4.6 mm × 150 mm; mobile phase, MeOH/H_2O, 90/10 (v/v); flow rate, 1.0 mL/min; detector, UV 254 nm). The chiral chromatographic conditions (HPLC) were as follows: column OD 250 mm × 4.6 mm; mobile phase, isopropyl alcohol/hexane, 15/85 (v/v); flow rate 1.0 mL/min; detector UV 254 nm. Purities reported were determined by HPLC analysis of crude products. Yields were calculated by mass recovery of the crude products based on the loading of the resin **6**. NMR, MS, FTIR, HRMS, and the melting points were determined from the purified products. The melting points were uncorrected.

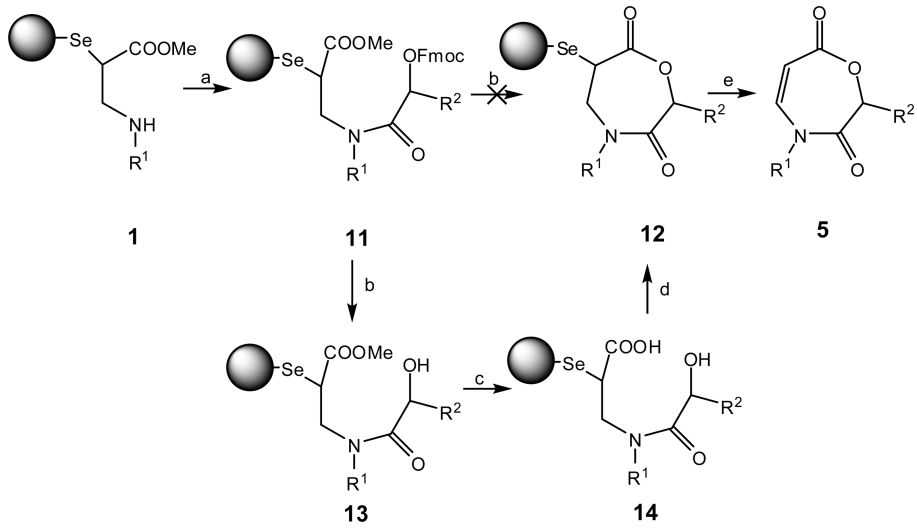
Typical Procedure for the Preparation of Polystyrene-Supported 3-Alkylamino-2-seleno-ester Resin 1. To a suspension of the swollen polystyrene-supported selenenyl bromide resin **6** (1.0 g, 1.04 mmol Br/g) in CH_2Cl_2 (20 mL) was added $ZnCl_2$ (0.2 mmol) and methyl acrylate (3 mmol), and the mixture was stirred for 0.5 h at room temperature. Then, primary amine (6 mmol) was added. After 24 h, the resin was filtered and washed successively with H_2O (20 mL × 2), THF (10 mL × 2), DMF (10 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2) and then dried under vacuum overnight to afford resin **1**.

Typical Procedure for the Preparation of Substituted 2-Pyridones 3 (Products 3a−i). To a suspension of the swollen resin **1** (1.0 g) in anhydrous THF (20 mL) was added malonic monoester (3 mmol) and DIC (3 mmol), and the mixture was stirred for 24 h at room temperature. Then, the resin was filtered and washed successively with THF (10 mL × 2), H_2O (20 mL × 2), DMF (10 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2), and then dried under vacuum overnight to afford resin **7**.

Under a positive pressure of nitrogen, to a suspension of the swollen polystyrene resin **7** (1.0 g) in anhydrous THF (20 mL) was added potassium tert-butoxide (2 mmol) in tert-butyl alcohol solution (1 M) at −78 °C; the mixture was stirred for 2 h at that temperature. Then, the resin was filtered and washed successively with saturated NH_4Cl (20 mL × 2), THF (10 mL × 2), H_2O (20 mL × 2), DMF (10 mL × 2), acetone (10 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2) to afford resin **8**.

The washed resin **8** was suspended in THF (10 mL), 30% aqueous H_2O_2 (1.0 mL) was added, and the mixture was stirred for 1 h at room temperature. Then, the mixture was filtered, and the resin was washed with CH_2Cl_2 (20 mL × 2). The filtrate was washed with H_2O (30 mL × 2), dried

Scheme 5[a]



[a] Reagents and conditions: (a) Fmoc-α-hydroxy-acid, DIC, THF, rt, 24 h; (b) piperidine/CH_2Cl_2(1:4), rt, 12 h; (c) LiOH, THF/H_2O, rt, 6 h; (d) DIC, THF, rt, 24 h; (e) H_2O_2, THF, rt, 1 h.

Table 3. Synthesis of 1,4-Oxazepines **5**

product	R^1	R^2	yield (%)[a]	purity (%)[b]
5a	Bn	Me	37	87
5b	Pr	Me	31	77
5c	allyl	Me	33	78
5d	Cy	Me	40	81
5e	$PhCH_2CH_2$	Me	42	73
5f	Bn	Ph	30	83
5g	$PhCH_2CH_2$	Ph	37	84

[a] Yield of the crude product based on the loading of the resin **6**. [b] Determined by HPLC (UV 254 nm).

over $MgSO_4$, and evaporated to dryness under vacuum to obtain the crude products **3**. Further purification was via flash chromatography with light petroleum/EtOAc (2:1 v/v) as the eluent for NMR and other microanalyses.

Typical Procedure for the Preparation of Substituted 1,4-Diazepines 4 (Products 4a−m). To a suspension of the swollen resin **1** (1.0 g) in anhydrous THF (20 mL) was added Fmoc-α-amino-acid (3 mmol) and DIC (3 mmol), and the mixture was stirred for 24 h at room temperature. Then, the resin was filtered and washed successively with THF (10 mL × 2), H_2O (20 mL × 2), DMF (10 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2) to afford resin **9**.

To a suspension of the swollen resin **9** (1.0 g) in CH_2Cl_2 (10 mL) was added piperidine (2.5 mL), and the mixture was stirred for 12 h at room temperature. Then the resin was filtered and washed successively with THF (10 mL × 2), H_2O (20 mL × 2), DMF (10 mL × 2), H_2O (20 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2) to afford resin **10**.

The washed resin **10** was suspended in THF (10 mL), 30% aqueous H_2O_2 (1.0 mL) was added, and the mixture was stirred for 1 h at room temperature. The mixture was filtered, and the resin was washed with CH_2Cl_2 (20 mL × 2). The filtrate was washed with H_2O (30 mL × 2), dried over $MgSO_4$, and evaporated to dryness under vacuum to obtain the crude products **4**. Further purification was via flash chromatography with light petroleum/EtOAc (1:2 v/v) as the eluent for NMR and other microanalysis.

Typical Procedure for the Preparation of Substituted 1,4-Oxazepines 5 (Products 5a−g). To a suspension of the swollen resin **1** (1.0 g) in anhydrous THF (20 mL) was added Fmoc-α-hydroxy-acid (3 mmol) and DIC (3 mmol), and the mixture was stirred for 24 h at room temperature. Then, the resin was filtered and washed successively with THF (10 mL × 2), H_2O (20 mL × 2), DMF (10 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2) to afford resin **11**.

To a suspension of the swollen resin **11** (1.0 g) in CH_2Cl_2 (10 mL) was added piperidine (2.5 mL), and the mixture was stirred for 12 h at room temperature. Then, the resin was filtered and washed successively with THF (10 mL × 2), H_2O (20 mL × 2), DMF (10 mL × 2), H_2O (20 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2) to afford resin **13**.

Under a positive pressure of nitrogen, to a suspension of the swollen polystyrene resin **13** (1.0 g) in THF (20 mL) was added an LiOH−water sloution (1M) 2 mL; the mixture was stirred for 6 h at room temperature. Then, the resin was filtered and washed successively with H_2O (20 mL × 2), HCl (1N) (20 mL × 2), THF (10 mL × 2), H_2O (20 mL × 2), DMF (10 mL × 2), acetone (20 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2) and then dried under vacuum overnight to afford resin **14**.

To a suspension of the swollen resin **14** (1.0 g) in anhydrous THF (20 mL) was added DIC (3 mmol), and the mixture was stirred for 24 h at room temperature. Then, the resin was filtered and washed successively with THF (10 mL × 2), acetone (20 mL × 2), DMF (10 mL × 2), CH_3OH (20 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2) to afford resin **12**.

The washed resin **12** was suspended in THF (10 mL), 30% aqueous H_2O_2 (1.0 mL) was added, and the mixture was stirred for 1 h at room temperature. The mixture was filtered, and the resin was washed with CH_2Cl_2 (20 mL × 2). The filtrate was washed with H_2O (30 mL × 2), dried over $MgSO_4$, and evaporated to dryness under vacuum to obtain the crude products **5**. Further purification was via flash

chromatography with light petroleum/EtOAc (2:1 v/v) as the eluent for NMR and other microanalysis.

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Supporting Information Available. ^{1}H NMR and ^{13}C NMR spectral data of all the products and parts of the HPLC spectra of **3d**, **3e**, **4c**, **4e**, **5d**, and **5f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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