Solid-Phase Synthesis of 2,5-Dihydro-1*H*-pyrroles, 1,3-Dioxo-2,3,5,7*a*-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazoles and 1,4-Dioxo-1,2,3,4,6,8*a*-hexahydropyrrolo[1,2-*a*]pyrazines Using a Supported Selenium Resin

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Received October 6, 2008

A versatile combinatorial approach was developed for the rapid synthesis of 2,5-dihydro-1*H*-pyrroles, 1,3-dioxo-2,3,5,7*a*-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazoles, and 1,4-dioxo-1,2,3,4,6,8*a*-hexahydropyrrolo[1,2-*a*]pyrazines libraries. The synthetic strategy includes electrophilic addition, dehydrohalogenation, 1,3-dipolar cycloaddition, N-acylation, amino carbonylation−cyclization, N-alkylation, lactamization, and oxidation−elimination.

Introduction

Combinatorial chemistry and related parallel synthesis techniques are important tools for lead generation, target validation, and lead optimization in drug discovery.[1] Solid-phase organic synthesis (SPOS), which is regarded as the core technology of combinatorial chemistry, has attracted much attention in building libraries of biologically relevant and structurally diverse molecules.[2] It is well-known that compounds with biological activity are often derived from heterocyclic structures. Thus it is not surprising that in recent years, various protocols for the construction of heterocyclic compounds via solid-phase strategies have been developed.[3]

Among the heterocyclic templates, 3-pyrrolines, hydantoins, and 2,5-diketopiperazines exist in many biologically active compounds. The 3-pyrrolines structural motif may be found in a large number of pharmaceutical agents where they function as MAO inhibitors,[4a−c] NMDA receptor agonists,[4d] K-agonists,[4e] and tumor inhibitors.[4f] Many compounds having hydantion scaffolds display the properties of antidiabetic,[5a] anti-inflammatory,[5b] antiviral,[5c] GHS[5d] and CB_1 receptor antagonists,[5e] and of inhibitors of LFA-1,[5f] FAAH,[5g] and EGFR.[5h] The pharmaceutical compounds having the 2,5-diketopiperazine unit show great biological activities, such as antitumor,[6a] antiviral,[6b] antifungal,[6c] antibacterial,[6d] and antihyperglycaemic[6e] agents and show affinities for calcium channels and opioid,[6f] GABAergic,[6g] serotoninergic 5-HT1A,[6h] and oxytocin receptors.[6i] As a result, they and their fused derivatives are interesting targets for the research of solid-phase synthetic methodology.

An important aspect of solid-phase methodology is the choice of the linker, which is crucial for the attachment and detachment of the requisite substrates to and from the resin respectively. The ease of loading, a wide tolerance of a broad variety of reaction conditions, and the efficient release of products under mild conditions are some of the characteristics that make organoselenium a convenient linker in solid-phase synthesis. Recently, several research groups,[7] including ours,[8] were interested in the preparation of heterocyclic libraries from organoselenium resins. As a continuation of our ongoing efforts to generate pharmaceutically interesting heterocyclic compounds on solid phase, herein, we report an efficient synthetic method for 2,5-dihydro-1*H*-pyrroles, 1,3-dioxo-2,3,5,7*a*-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazoles, and 1,4-dioxo-1,2,3,4,6,8*a*-hexahydropyrrolo[1,2-*a*]pyrazines from a supported selenium resin, with the advantages of straightforward synthetic sequence, low odor, good stability of the supported selenium species, and high purities of the products.

Results and Discussion

Initially, polystyrene-supported selenenyl bromide **1**[7a] (dark-red resin; Br 1.07 mmol/g) was reacted for 1 h with methyl acrylate in the presence of $ZnCl_2$, giving the corresponding resin **2** smoothly. The progress of the reaction was monitored by measuring the growth of strong carbonyl absorption at 1737 cm^{-1}. Resin **2** then was stirred with triethylamine in one pot for another 2 h to afford the desired resin-bound methyl 2-seleno acrylate **3**.[9] With resin **3** in hand, we explored 1,3-dipolar cycloaddition reaction to furnish a polystyrene-supported pyrrolidine moiety, which could be further elaborated for diversity and complexity. After the mixture was stirred with excess azomethine ylide for 48 h at room temperature, resin **3** was successfully converted into the polystyrene supported pyrrolidine-substituted selenide resin **4** (Scheme 1).[10] Because of the

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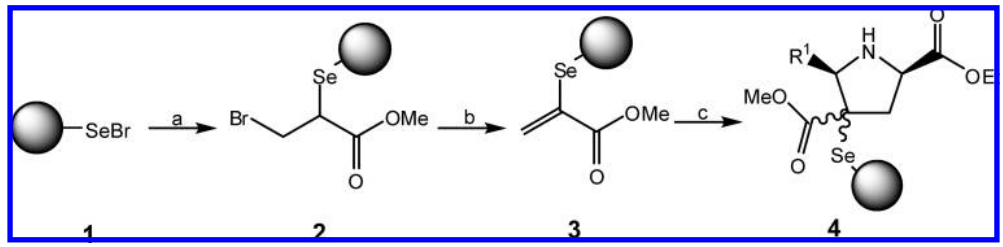
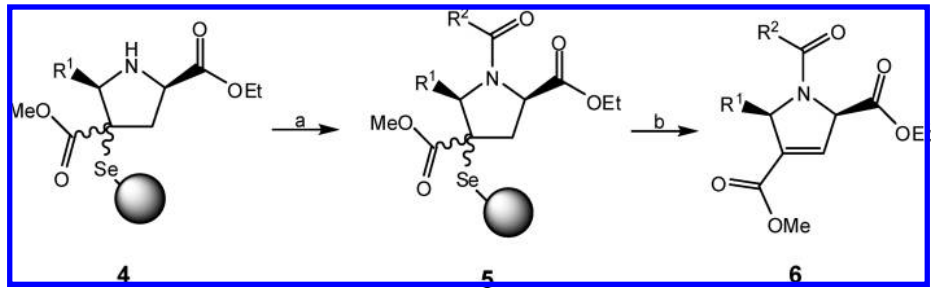
10.1021/cc800161g CCC: $40.75
Published on Web 02/16/2009

Scheme 1[a]



[a] Reagents and conditions: (a) $ZnCl_2$, $CH_2{=}CHCO_2Me$, CH_2Cl_2, rt, 1 h; (b) Et_3N, rt, 2 h; (c) $R^1CH{=}NCH_2COOEt$, AgOAc, Et_3N, THF, rt, 48 h.

Scheme 2[a]



[a] Reagents and conditions: (a) R^2COCl, Et_3N, CH_2Cl_2, rt, 24 h; (b) H_2O_2, THF, rt, 1 h.

Table 1. Synthesis of Substituted 2,5-Dihydro-1*H*-pyrroles **6a**−**6m**

product	R^1	R^2	yield (%)[a]	purity (%)[b]
6a	Ph	Me	73	85
6b	Ph	$ClCH_2$	63	86
6c	Ph	*i*-Pr	67	88
6d	Ph	*t*-Bu	61	86
6e	Ph	4-$MeOC_6H_4CH_2$	58	78
6f	4-$MeOC_6H_4$	Me	74	94
6g	4-MeC_6H_4	Me	69	92
6h	4-ClC_6H_4	Me	62	81
6i	4-BrC_6H_4	Me	66	89
6j	3-BrC_6H_4	Me	67	84
6k	2-BrC_6H_4	Me	57	78
6l	1-Nph	Me	64	96
6m	2-Furyl	Me	68	88

[a] Yield of the crude product based on the loading of the resin **1**. [b] Determined by HPLC.

effect of silver acetate, the stereochemistry of resin **4** would be cis-cycloadducts, which is the same as other cycloaddition reactions.[11]

Further experimentation showed that resin **4** could be acylated smoothly with different acyl chlorides in the presence of triethylamine at room temperature.[12] FTIR showed two strong peaks of carbonyl absorptions at 1734−1737 and 1670−1677 cm^{-1}, respectively. The resulting resin **5** was then treated with excess 30% hydrogen peroxide to form the corresponding selenoxide in situ, and spontaneous elimination of the selenoxide led to the release of corresponding 2,5-dihydro-1*H*-pyrroles **6** (Scheme 2) in moderate to good yields with good levels of purities (Table 1).

To prepare the hydantoin scaffold, the regular route of urea formation followed by cyclization was adopted.[13] The reaction of resin **4** with isocyanates in toluene for 12 h afforded urea resin **7**. Their FTIR spectra showed a new carbonyl absorpotion at 1677−1680 cm^{-1}. Then 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) was added to the suspension, and the temperature was raised to 80 °C. After 6 h, resin-bound hydantions **8** were obtained, which then reacted with excess 30% hydrogen peroxide to give the corresponding 1,3-dioxo-2,3,5,7*a*-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazoles **9** (Scheme 3 and Table 2). The FTIR spectra of resins **8** demonstrated a strong absorption at 1725−1730 cm^{-1} and a weak absorption at 1777−1780 cm^{-1}, with the disappearance of absorptions at 1733−1736 and 1677−1680 cm^{-1}. During the hydantoin cyclization step, the use of strong base DBU and heat caused the epimerization of the C2−H at the pyrrolidine ring to give the thermodynamically preferred products **8**.[10b]

In addition to the two scaffolds above, the 2,5-diketopiperazine ring system was also explored.[14] Resin **4** was treated with 2-chloroacetyl chloride to form the amide resin **10**. The resin **10** was then refluxed with various amines for 10 h, yielding 2,5-diketopiperazine analogs. After oxidation and syn-elimination, the cleavage of resin **11** afforded the final products 1,4-dioxo-1,2,3,4,6,8*a*-hexahydropyrrolo[1,2-*a*]pyrazines **12** in moderate yields with good purities (Scheme 4, Table 3).

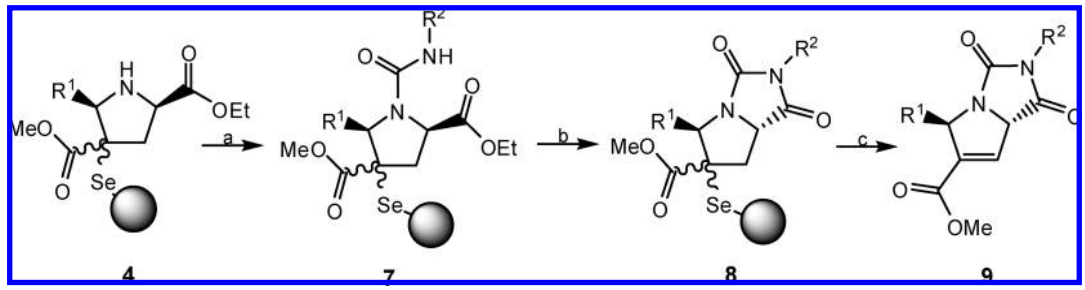
Conclusions

In summary, we have developed an efficient solid-phase parallel synthetic route to prepare libraries of 2,5-dihydro-1*H*-pyrroles, 1,3-dioxo-2,3,5,7*a*-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazoles, and 1,4-dioxo-1,2,3,4,6,8*a*-hexahydropyrrolo[1,2-*a*]pyrazines based on a polystyrene-supported selenium resin. The advantages of this method include straightforward synthetic sequence, low odor, good stability of the supported selenium species, and high purities of the products. In addition, the easy workup procedure makes the method suitable for building parallel libraries.

Experimental Section

General Methods. Starting materials were obtained from commercial suppliers and were used without further purifica-

Scheme 3[a]



[a] Reagents and conditions: (a) R^2NCO, toluene, rt, 12 h; (b) DBU, 80 °C, 6 h; (c) H_2O_2, THF, rt, 1 h.

Table 2. Synthesis of Substituted 1,3-Dioxo-2,3,5,7*a*-tetrahydro-1*H*-pyrrolo[1,2-*c*] imidazoles **9a**−**9q**

product	R^1	R^2	yield (%)[a]	purity (%)[b]
9a	Ph	4-$MeOC_6H_4$	63	89
9b	Ph	4-MeC_6H_4	60	85
9c	Ph	Ph	58	80
9d	Ph	3-ClC_6H_4	59	79
9e	Ph	*n*-Bu	66	94
9f	4-ClC_6H_4	4-$MeOC_6H_4$	60	81
9g	4-ClC_6H_4	4-MeC_6H_4	56	83
9h	4-ClC_6H_4	Ph	61	82
9i	4-ClC_6H_4	3-ClC_6H_4	59	81
9j	4-ClC_6H_4	*n*-Bu	67	85
9k	4-$MeOC_6H_4$	*n*-Bu	70	95
9l	4-MeC_6H_4	*n*-Bu	68	92
9m	4-BrC_6H_4	*n*-Bu	62	91
9n	3-BrC_6H_4	*n*-Bu	56	84
9o	2-BrC_6H_4	*n*-Bu	53	78
9p	1-Nph	*n*-Bu	64	93
9q	2-Furyl	4-$MeOC_6H_4$	57	80

[a] Yield of the crude product based on the loading of the resin **1**. [b] Determined by HPLC.

tion. THF and toluene were 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 (1.07 mmol of Br/g) according to the procedure described by Nicolaou and co-workers[7a] 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 × 150 mm; mobile phase, MeOH/H_2O, 90/10 (v/v); flow rate, 1.0 mL/min; detector, UV 254 nm). Purities reported were determined by HPLC analysis of crude products. Yields are calculated by mass recovery of the crude products based on the loading of the resin **1**. NMR, MS, FT-IR, EA, and the melting points are determined from the purified products obtained by purification using thin-layer chromatography (TLC) on silica gel with ethyl acetate and light petroleum (1:1−1:4) as eluent. The melting points are uncorrected.

Typical Procedure for the Preparation of Resin-Bound 2,3,5-Trisubstituted Pyrrolidine 4. To a suspension of the swollen resin **1**[7a] (1.0 g, 1.07 mmol of Br/g) in CH_2Cl_2 (20 mL) was added $ZnCl_2$ (0.2 mmol). After the mixture was stirred for 10 min at room temperature, methyl acrylate (4 mmol) was added, and the mixture was stirred for 1.0 h. Then triethylamine (4 mmol) was added, and the reaction mixture was stirred for another 2.0 h. The resin was filtered and washed successively with H_2O (20 mL × 2), THF (10 mL × 2), THF/H_2O (2:1) (30 mL × 2), DMF (10 mL × 2), H_2O (20 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2) and then dried under vacuum overnight to afford resin **3**.

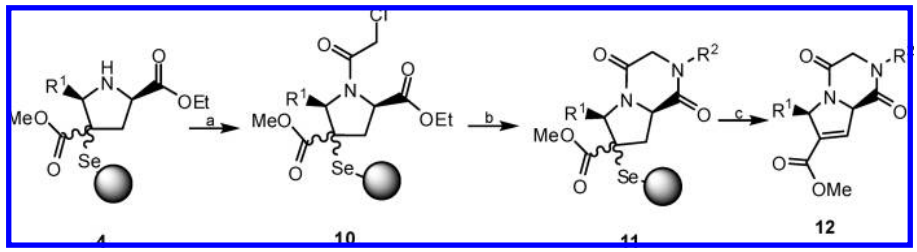
Under a positive pressure of nitrogen, to a suspension of the swollen polystyrene resin **3** (1.0 g) in anhydrous THF (20 mL) was added azomethine imine (3 mmol), silver acetate (3 mmol), and triethylamine (3 mmol); the mixture was stirred for 48 h at room temperature. Resin **4** was filtered, washed with THF (10 mL × 2), 3 N aqueous HNO_3 (10 mL × 2), H_2O (10 mL × 2), DMF (10 mL × 2), H_2O (10 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2), and then dried in vacuo.

Typical Procedure for the Preparation of the Substituted 2,5-Dihydro-1*H*-pyrroles 6 (Products 6a−6m). To a suspension of the swollen resin **4** (1.0 g) in CH_2Cl_2 (15 mL) was added triethylamine (3 mmol), and a solution of acyl chloride (3 mmol) in CH_2Cl_2 (5 mL) was slowly added dropwise in 2 h. After the mixture was stirred for another 24 h at room temperature, resin **5** was filtered and washed with THF (10 mL × 2), H_2O (10 mL × 2), DMF (10 mL × 2), H_2O (10 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2).

The washed resin was suspended in THF (10 mL); 30% 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 over $MgSO_4$, and evaporated to dryness under vacuum to obtain the crude products **6**. Further purification was via thin-layer chromatography with light petroleum/EtOAc (2:1 v/v) as the eluent for NMR and other microanalysis.

Typical Procedure for the Preparation of the Substituted 1,3-Dioxo-2,3,5,7*a*-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazoles 9 (Products 9a−9q). Under a positive pressure of nitrogen, to a suspension of the swollen polystyrene resin **4** (1.0 g) in anhydrous toluene (20 mL) was added isocyanate (3 mmol); the mixture was stirred at room temperature for 12 h, and then in the same pot, DBU (3 mmol) was added. The mixture was then heated to 80 °C and stirred for another 6 h. Resin **8** was filtered and washed with THF (10 mL ×

Scheme 4[a]



[a] Reagents and conditions: (a) $ClCH_2COCl$, Et_3N, CH_2Cl_2, rt, 24 h; (b) R_2NH_2, Et_3N, MeOH/THF, reflux, 10 h; (c) H_2O_2, THF, rt, 1 h.

Table 3. Synthesis of Substituted 1,4-Dioxo-1,2,3,4,6,8*a*-hexahydropyrrolo[1,2-*a*]pyrazines **12a**−**12h**

product	R^1	R^2	yield (%)[a]	purity (%)[b]
12a	4-MeC_6H_4	*n*-Pr	51	80
12b	4-MeC_6H_4	Allyl	54	78
12c	4-MeC_6H_4	Bn	60	87
12d	4-MeC_6H_4	$PhCH_2CH_2$	57	82
12e	4-$MeOC_6H_4$	Bn	61	90
12f	3-BrC_6H_4	Bn	49	77
12g	1-Naph	Bn	58	93
12h	2-Furyl	Bn	53	79

[a] Yield of the crude product based on the loading of the resin **1**. [b] Determined by HPLC.

2), H_2O (10 mL × 2), DMF (10 mL × 2), H_2O (10 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2).

The washed resin was suspended in THF (10 mL), and 30% H_2O_2 (1.0 mL) was added; then 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 **9**. Further purification was via thin-layer chromatography with light petroleum/EtOAc (4:1 v/v) as the eluent for NMR and other microanalysis.

Typical Procedure for the Preparation of the Substituted 1,4-Dioxo-1,2,3,4,6,8*a*-hexahydropyrrolo[1,2-*a*] pyrazines 12 (Products 12a−12h). To a suspension of the swollen resin **4** (1.0 g) in CH_2Cl_2 (15 mL) was added triethylamine (3 mmol), and a solution of 2-chloroacetyl chloride (3 mmol) in CH_2Cl2 (5 mL) was slowly added dropwise in 2 h. After the mixture was stirred for another 24 h at room temperature, resin **10** was filtered and washed with THF (10 mL × 2), H_2O (10 mL × 2), DMF (10 mL × 2), H_2O (10 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2).

To a suspension of the swollen resin **10** (1.0 g) in MeOH/THF (20 mL 3:1 v/v) was added triethylamine (3 mmol) and primary amine (3 mmol); the mixture was then heated to reflux for 10 h, and the resin **11** was filtered and washed with THF (10 mL × 2), H_2O (10 mL × 2), DMF (10 mL × 2), H_2O (10 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2).

The washed resin was suspended in THF (10 mL); 30% 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 MgSO4, and evaporated to dryness under vacuum to obtain the crude products **12**. Further purification was via thin-layer chromatography with light petroleum /EtOAc (1:1 v/v) as the eluent for NMR and other microanalysis.

Acknowledgment. We are grateful to the National Natural Science Foundation of China (Project Nos. 20672095, 20732005), National Basic Research Program of China (973 Program, 2009CB825300), and CAS Academician Foundation of Zhejiang Province for financial support.

Supporting Information Available. ^1H NMR and ^{13}C NMR spectra data of all the products and parts of HPLC spectra of **6j**, **6l**, **9b**, **9e**, **12a**, and **12d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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