JOURNAL OF combinatorial CHEMISTRY

Volume 12, Number 1 January/February 2010

Report

Solid-Phase Synthesis of Bis-Heterocyclic Compounds with Skeletal Diversity from Resin-Bound 3-Propargylamino-2-seleno-ester

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Received July 30, 2009

Heterocyclic compounds have attracted considerable attention for being broadly useful as therapeutic agents, especially privileged heterocycles which are capable of binding to multiple receptors with high affinity.[1] Combination of two privileged heterocycles in one molecule can construct a novel system of a bis-heterocycle which may potentially create new entities with unusual bioproperties through a synergistic effect. In fact recent reports described libraries where the most active compound was a bis-heterocycle,[2] and an average six publications in every issue of the *Journal of Medicinal Chemistry* reported bis-heterocycles as being the most potent ones in 2008.[3] Uracil,[4] benzofuran,[5] indole,[6] and diazepinedione[7] are privileged heterocycles known for a wide range of biological activities, which have been found in clinically accepted drugs as well. Particularly, molecules containing two of these privileged heterocycles were reported to show special biological activities. For example, uracil-benzofuran bis-heterocycle **1** (Figure 1) displayed a potent anti-HIV-1 activity,[8] while uracil-indole **2** was found to be a potential neoplasm inhibitors[9] and **3** was reported to show serotonergic activity.[10] Because of potential biological and pharmacological applications of these bis-heterocyclic compounds, it is considered worthwhile to develop a general and effective method for the construction of a bis-heterocyclic compounds library.

Organoselenium resins are ideal linkers and reagents for solid-phase synthesis because organoselenium compounds are important synthetic intermediates, and the Se−C bond can be easily broken by various methods.[11] Recently several research groups[12] including ours[13] were interested in the preparation of heterocyclic libraries from organoselenium resins. In a continuation of our efforts toward the solid-phase synthesis of bis-heterocyclic compounds,[14] we describe, herein, an efficient approach for the solid-phase synthesis of a bis-heterocycles system consisting of uracil/diazepinedione and benzofuran/indole. The overall strategy is based on the resin-bound intermediate **4** (Scheme 1), in which the 3-amino-2-seleno-ester moiety is transformed to uracil or diazepinedione through condensation with isocyanate or α-amino-acid and oxidative elimination of selenium linker and the terminal acetylene moiety is transformed to benzofuran or indole through a sonogashira/annulation reaction with 2-iodophenol or 2-iodoaniline. The strategy opens the way to the

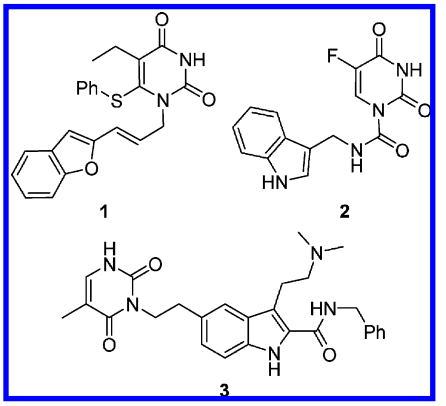

Figure 1

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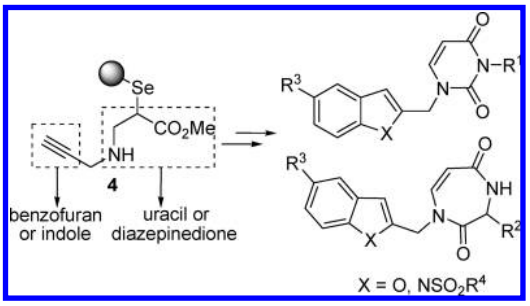
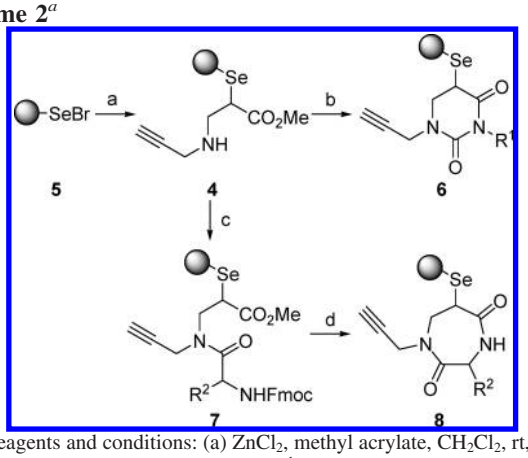
10.1021/cc900112s CCC: $40.75
Published on Web 11/06/2009

Scheme 1

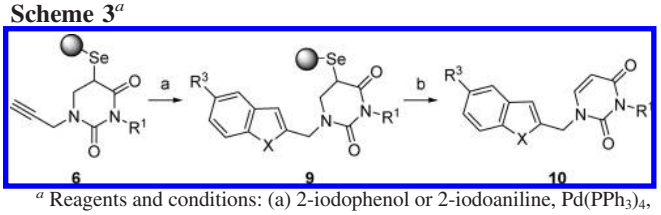


Scheme 2[a]



[a] Reagents and conditions: (a) $ZnCl_2$, methyl acrylate, CH_2Cl_2, rt, 0.5 h, then propargylamine, 24 h; (b) K_2CO_3, R^1NCO, DMF, 65 °C, 5 h; (c) Fmoc-α-amino-acid, DIC, THF, rt, 24 h; (d) piperidine/CH_2Cl_2 (1:4), rt, 12 h.

Scheme 3[a]



[a] Reagents and conditions: (a) 2-iodophenol or 2-iodoaniline, $Pd(PPh_3)_4$, CuI, Et_3N, DMF, 65 °C, 24 h; (b) H_2O_2, THF, rt, 1 h.

construction of a bis-heterocyclic compounds library with skeletal diversity (four different heterocycles).

Results and Discussion

Resin-bound 3-propargylamino-2-seleno-ester **4** was prepared according to our previous report.[13k] Polystyrene-supported selenenyl bromide (resin **5**) (Br: 1.18 mmol/g) was smoothly reacted with methyl acrylate in the presence of $ZnCl_2$ at room temperature to afford the corresponding resin-bound 3-bromo-2-seleno ester, which was reacted with propargylamine in one pot to give the corresponding yellow resin **4** (Scheme 2). The Fourier transform infrared (FT-IR) spectrum showed a strong peak of the carbonyl absorptions at 1730 cm^{-1}.

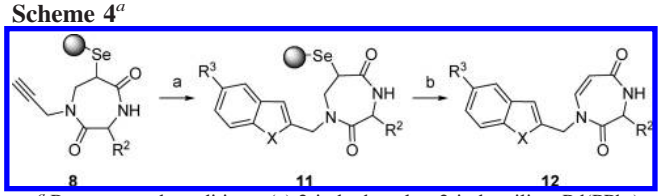
With resin **4** in hand, we performed cyclization reactions with isocyanates and α-amino-acids to afford the dihydrouracils **6** and 1,4-diazepane-2,5-diones **8**. First, in the presence of K_2CO_3, resin **4** was reacted with isocyanates in DMF at 65 °C for 5 h to afford the corresponding resin-bound N1-propargyl 5,6-dihydrouracils **6**.[13k] The FT-IR spectrum showed two strong peaks for the carbonyl absorptions at 1729−1734 and 1665−1679 cm^{-1}, respectively. Second,

Table 1. Synthesis of Bis-Heterocycles of Uracil and Benzofuran/Indole **10a**−**n**

product	R^1	R^3	X	yield (%)[a]	purity (%)[b]
10a	*n*-Bu	H	O	43	82
10b	Ph	H	O	45	89
10c	Ph	Me	O	41	86
10d	*p*-tol	H	O	53	91
10e	*p*-tol	Me	O	46	84
10f	*p*-tol	*t*-Bu	O	56	92
10g	3-MeC_6H_4	H	O	44	83
10h	4-$MeOC_6H_4$	H	O	51	86
10i	*n*-Bu	H	NMs	42	80
10j	Ph	H	NMs	46	84
10k	Ph	Cl	NMs	40	81
10l	*p*-tol	H	NMs	47	85
10m	*p*-tol	Me	NMs	39	78
10n	Ph	H	NSO_2Ph	37	79

[a] Yield of the crude product based on the loading of the resin **5**. [b] Determined by HPLC.

Scheme 4[a]



[a] Reagents and conditions: (a) 2-iodophenol or 2-iodoaniline, $Pd(PPh_3)_4$, CuI, Et_3N, DMF, 65 °C, 24 h; (b) H_2O_2, THF, rt, 1 h.

Table 2. Synthesis of Bis-Heterocycles of Diazepinedione and Benzofuran/Indole **12a**−**j**

product	α-amino-acid	R^3	X	yield (%)[a]	purity (%)[b]
12a	glycine	H	O	39	81
12b	glycine	Me	O	42	83
12c	D-phenylalanine	H	O	45	85
12d	L-alanine	Me	O	49	84
12e	L-isoleucine	H	O	52	90
12f	glycine	H	NMs	38	80
12g	glycine	Me	NMs	44	86
12h	glycine	Cl	NMs	35	77
12i	D-phenylalanine	H	NSO_2Ph	31	76

[a] Yield of the crude product based on the loading of the resin **5**. [b] Determined by HPLC.

resin **4** was condensed with Fmoc-α-amino-acids to form 1,4-diazepane-2,5-diones **8** under standard peptide synthesis conditions. Resin **4** was reacted smoothly with Fmoc-α-amino-acids and DIC (*N*,*N*′-diisopropylcarbodiimide) to form the corresponding amides **7**. Then the amides **7** were deprotected and spontaneously cyclized in piperidine/CH_2Cl_2 to form the 1,4-diazepane-2,5-diones **8**, which exhibited a strong peak at 1661−1673 cm^{-1} and a weaker peak at 1689−1700 cm^{-1}. Oxidative cleavage of a small aliquot of resins **6** and **8** with 30% H_2O_2 and subsequent ^1H NMR spectroscopic analysis of the products showed that the steps above succeeded.

We then sought to construct the benzofuran and indole moiety. It is well-known that benzofuran and indole could be synthesized through a sonogashira/annulation reaction with 2-iodophenol or 2-iodoaniline and terminal acetylene,[15] and the method has been applied to solid-phase synthesis successfully with various linkers[16] including the selenium linker.[12e] Therefore we performed the sonogashira/annulation reaction to form the benzofuran and indole moiety. Under classical Pd/Cu and Et_3N catalytic condition, resins **6** were

reacted with 2-iodophenol smoothly to afford bis-heterocycle **9** (Scheme 3). After 24 h, IR analysis revealed the complete disappearance of the terminal alkyne C−H vibration (3297 cm^{-1}), and oxidative cleavage of resins **9** with 30% H_2O_2 showed the sonogashira/annulation reaction succeeded and no uncyclized 2-ethynylphenol was found. Screening the reaction conditions showed that other conditions (catalyst, base, and temperature) did not improve the yields and purities dramatically. Then a series of isocyanates and 2-iodophenols were chosen to perform the reaction (Table 1, products **10a**−**10h**). The results were satisfactory for various 2-iodophenols. Both alkyl and aryl isocyanates worked well. Thus, bis-heterocycles of uracil and benzofuran were constructed successfully.

Inspired by the results above, we performed the sonogashira/annulation reaction to form the indole moiety. For activating the amino group,[16a] *N*-sulfonyl-2-iodoanilines were chosen to react with resins **6**. The reaction proceeded smoothly under the same condition, and the results were similar to benzofuran (Table 1, products **10i**−**10n**). Both alkyl and aryl sulfonyl-2-iodoanilines worked well, and R^3 could be H, alkyl, and Cl. Unfortunately, replacing the sulfonyl group with another activating group (i.e., trifluoroacetyl) resulted in failure to form indole (only uncyclized sonogashira products were found).

Finally, bis-heterocycles of diazepinedione and benzofuran/indole were constructed through the sonogashira/annulation reaction with resins **8** and 2-iodophenol or 2-iodoaniline (Scheme 4). The results were satisfactory for various α-amino-acids (Table 2). Because of the ready availability of chiral α-amino-acid, this methodology was suited for the synthesis of optically pure products. To demonstrate that the chiral integrity of the starting α-amino acid had been maintained throughout all four synthetic steps, the product **12c** was then analyzed by chiral HPLC, compared with the racemic product, and found to be optically pure (ee >99%).

In summary, we have developed an efficient solid-phase parallel synthetic route to a bis-heterocycles library of uracil/diazepinedione and benzofuran/indole from resin-bound 3-propargylamino-2-seleno-ester. Efforts to construct a library with this method are still underway in this laboratory.

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

Supporting Information Available. General procedures for the synthesis of the library, spectral data, ^1H NMR and ^{13}C NMR spectra of all the products, and parts of HPLC spectra of **10d**, **10n**, **12d**, and **12i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC900112S