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Reports

Solid-Phase Synthesis of Benzofused Tricycles Based on Benzimidazole from Resin-bound 3-(2-aminophenylamino)-2-seleno-ester

Xian Huang,* Jian Cao, and Jianqiang Huang

Department of Chemistry, Zhejiang University (Xixi Campus), Hangzhou 310028, P. R. China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P. R. China

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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.[1] Novel fused heterocyclic ring systems are often considered important scaffolds in medicinal chemistry; therefore, the search for efficient and combinatorial methodologies which allow for the facile synthesis of new scaffolds would be attractive to both organic and medicinal chemists. Benzimidazole is an important heterocyclic nucleus in medicinal chemistry.[2−4] The tricyclic fused scaffolds **1** (Figure 1) incorporating the benzimidazole and a classical heterocyclic moiety, such as pyridine,[5] pyrimidine,[6] pyrazine,[7] and imidazole,[8] have displayed a broad range of biological activities. Therefore, a facile synthesis leading to novel benzofused tricycles based on benzimidazole is highly attractive. Pyrimidin-4(3*H*)-one[9] and 1,4-diazepin-5-one[10] are classical heterocycles present in various biologically active compounds; however, there are rare reports[6] about synthesis of the tricyclic fused scaffolds incorporating the benzimidazole and these heterocycles.

Organoselenium compounds have found a wide range of application in the areas of organic chemistry because of their utility as synthetic intermediates,[11] and it is well-known that the Se−C bond can be easily broken by various methods.[12] Therefore organoselenium resins are ideal linkers and reagents for solid-phase synthesis and for the past decade, a variety of heterocyclic compounds libraries have been constructed from organoselenium resins by several research groups[13] including ours.[14] In a continuation of our efforts toward the solid-phase synthesis of low molecular weight heterocycles, we describe, herein, an efficient approach for the solid-phase synthesis of novel benzofused tricycles pyrimido[1,2-*a*]benzimidazol-2(1*H*)-one **2** and 1,2-dihydro-3*H*-[1,4]diazepino[1,2-*a*]benzimidazol-3-one **3**. The novel tricyclic fused scaffolds were constructed from the new building blocks, resin-bound 3-(2-aminophenylamino)-2-seleno-ester **4** through condensation with isothiocyanates and α-amino-acids (Scheme 1). The polystyrene-supported selenium resins used here not only worked as linkers but also as a part of the building blocks **4** and introduced a new double bond into the target molecules at the cleavage step.

Results and Discussion

Resin-bound 3-(2-aminophenylamino)-2-seleno-esters **4** were easily prepared through two steps (Scheme 2). Poly-

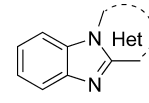

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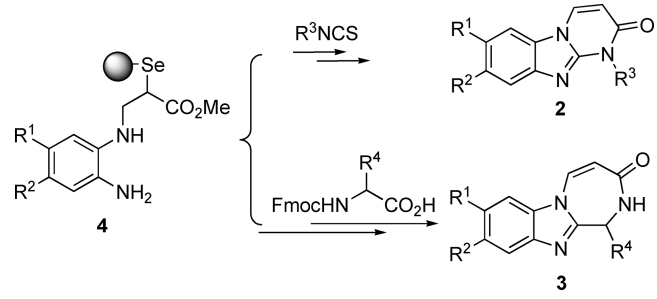
Figure 1

Scheme 1



* huangx@mail.hz.zj.cn.

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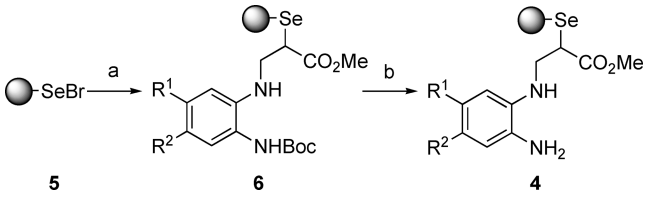
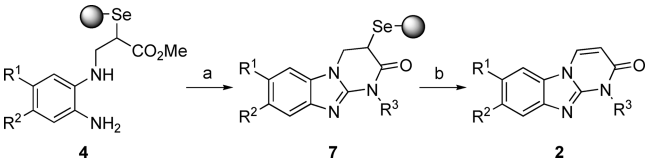
Scheme 2[a]



[a] Reagents and conditions: (a) $ZnCl_2$, $CH_2{=}CHCO_2Me$, THF, rt, 1 h, then mono-Boc-*o*-phenylenediamine, Et_3N, reflux, 24 h; (b) aq HCl, THF, rt, 5 h.

Scheme 3[a]



[a] Reagents and conditions: (a) R^{3NCS}, DIC, DMF, rt, 24 h, then K_2CO_3, rt, 4 h; (b) H_2O_2, THF, rt, 1 h.

Table 1. Synthesis of Substituted Pyrimido[1,2-*a*]benzimidazol-2(1*H*)-one **2a**−**k**

Product	R^1	R^2	R^3	Yield (%)[a]	Purity (%)[b]
2a	H	H	*n*-Pr	61	96
2b	H	H	allyl	69	90
2c	H	H	$PhCHCH_3$	49	76
2d			*n*-Pr	59	94
2e	H	H	4-$MeOC_6H_4$	64	91
2f	H	H	4-MeC_6H_4	61	86
2g	H	H	Ph	52	92
2h	H	H	3-MeC_6H_4	50	90
2i	Me	H	allyl	59	85
2j	Cl	H	allyl	55	83
2k	MeO	H	allyl	61	88

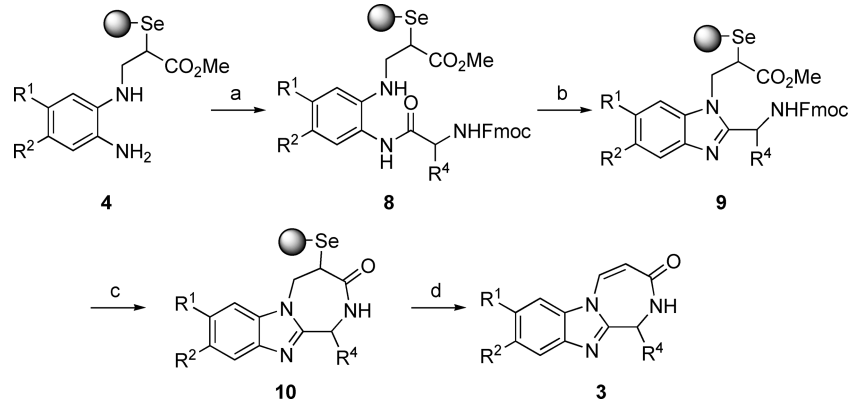
[a] Yield based on the loading of the resin **5**. [b] Determined by HPLC.

styrene-supported selenenyl bromide[13j] (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,[14n] which was reacted with mono-Boc-*o*-phenylenediamine in one pot to give the corresponding yellow resins **6**. FT-IR spectrum showed two strong peaks at about 1733 cm^{-1} and 1717 cm^{-1}. After mild deprotection with aq HCl in THF, resin-bound 3-(2-aminophenylamino)-2-seleno-esters **4** were obtained, which exhibited a single peak at 1729−1733 cm^{-1}. It should be noted that in the cases of R^1 and R^2 were the same groups, symmetrical diamines without Boc group were employed in step a to afford **4** directly.

With resins **4** in hand, we performed cyclization reactions with various reagents to afford the benzofused tricycles. First, isothiocyanates were chosen to form the tricycles incorporating the benzimidazole and a pyrimidinone moiety. As shown in Scheme 3, the resin-bound diamines **4** were reacted smoothly with isothiocyanates and DIC (*N*,*N*′-diisopropylcarbodiimide) to form the 2-amino-benzimidazoles,[15] which were subsequently cyclized to afford the resin-bound tricycles **7** in the presence of K_2CO_3 in a one-pot reaction. FT-IR spectrum showed a strong peak at about 1695 cm^{-1} and the peak at 1729−1733 cm^{-1} disappeared. As expected, the treatment of the newly loaded resins with excess 30% hydrogen peroxide at room temperature resulted in the facile oxidation of the selenides to the corresponding selenoxides. Spontaneous elimination of the selenoxides led to the release of crude products pyrimido[1,2-*a*]benzimidazol-2(1*H*)-ones **2**, which were recrystallized to give the products in moderate yields with good levels of purity (Table 1). The results were satisfactory for various *o*-phenylenediamine (**2a**, **d**, **i**−**k**). Both alkyl and aryl isothiocyanates worked well (**2a**−**c**, **e**−**h**).

For the second strategy, cyclization reactions with α-amino-acids were performed to afford the tricycles incorporating the benzimidazole and a 1,4-diazepin-5-one moiety (Scheme 4). Since optically pure α-amino-acids were readily available, this methodology was suited for the synthesis of optically pure products. The resin-bound diamines **4** were reacted smoothly with Fmoc-α-amino-acids and DIC to form the corresponding amides **8**. FT-IR spectrum showed a strong peak at about 1720 cm^{-1} and a weaker peak at about 1678 cm^{-1}. Then the amides **8** were cyclized in AcOH to give resin-bound benzimidazoles **9**.[16] FT-IR spectrum showed that the peak at about 1678 cm^{-1} disappeared. The resins **9** were deprotected and spontaneously cyclized in piperidine/CH_2Cl_2 to form the tricycles **10**, which exhibited a single peak at

Scheme 4[a]

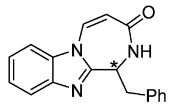


[a] Reagents and conditions: (a) Fmoc-α-amino-acid, DIC, DMF, rt, 12 h; (b) AcOH, 65 °C, 4 h; (c) piperidine, CH_2Cl_2, rt, 6 h; (d) H_2O_2, THF, rt, 1 h.

Table 2. Synthesis of Substituted 1,2-Dihydro-3*H*-[1,4]diazepino[1,2-*a*]benzimidazol-3-one **3a**−**j**

Product	R^1	R^2	α-amino-acid	Yield (%)[a]	Purity (%)[b]
3a	H	H	glycine	64	93
3b			glycine	61	87
3c	Cl	H	glycine	53	92
3d	Me	H	glycine	55	89
3e	H	H	L-alanine	62	89
3f	H	H	L-phenylalanine	59	92
3g	H	H	L-isoleucine	58	86
3h	Me	H	L-phenylalanine	43	91
3i	Me	H	L-isoleucine	40	85
3j	H	H	D-phenylalanine	60	90

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



product	amino-acid	ee (%)[a]	$[\alpha]_D$[b]
3f	*L*-phenylalanine	>99	+12.9
3j	*D*-phenylalanine	>99	-12.1

a. Calculated using HPLC areas.

b. Specific rotations at 20 °C in MeOH.

Figure 2

about 1670 cm^{-1}. Cleavage of resins **10** gave crude products 1,2-dihydro-3*H*-[1,4]diazepino[1,2-*a*]benzimidazol-3-ones **3**, which were recrystallized to give the products in moderate yields with good levels of purity (Table 2).

Finally, it should be demonstrated that the chiral integrity of the starting α-amino acid had been maintained throughout all four synthetic steps. To address this issue, the products **3f** and **3j** were then 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 2.

In summary, we have developed an efficient solid-phase parallel synthetic route to a benzofused tricycles library of pyrimido[1,2-*a*]benzimidazol-2(1*H*)-one and 1,2-dihydro-3*H*-[1,4]diazepino[1,2-*a*]benzimidazol-3-one from the new building blocks, resin-bound 3-(2-aminophenylamino)-2-seleno-esters. The advantages of this method include straightforward operation, lack of odor, good stability of the supported selenium species, and high purities of the products.

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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 **2e**, **2i**, **3b**, and **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Dolle, R. E.; Le Bourdonnec, B.; Morales, G. A.; Moriarty, K. J.; Salvino, J. M. *J. Comb. Chem.* **2006**, *8*, 597–635. (b) Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Salvino, J. M.; Zhang, W. *J. Comb. Chem.* **2007**, *9*, 855–902. (c) Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Thomas, C. J.; Zhang, W. *J. Comb. Chem.* **2008**, *10*, 753–802.

(2) Kubo, K.; Inada, Y.; Kohara, Y.; Sugiura, Y.; Ojima, M.; Itoh, K.; Furukaw, Y.; Nishikawa, K.; Naka, T. *J. Med. Chem.* **1993**, *36*, 1772–1784.

(3) Cheng, J. B.; Cooper, K.; Duplantier, A. J.; Eggler, J. F.; Kraus, K. G.; Marshall, S. C.; Marfat, A.; Masamune, H.; Shirley, J. T.; Tickner, J. E.; Umland, J. P. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1969–1972.

(4) Palmer, B. D.; Smaill, J. B.; Boyd, M.; Boschelli, D. H.; Doherty, A. M.; Hamby, J. M.; Khatana, S. S.; Kramer, J. B.; Kraker, A. J.; Panek, R. L.; Lu, G. H.; Dahring, T. K.; Winters, R. T.; Showalter, H. D. H.; Denny, W. A. *J. Med. Chem.* **1998**, *41*, 5457–5465.

(5) (a) Kotovskaya, S. K.; Baskakova, Z. M.; Charushin, V. N.; Chupakhin, O. N.; Belanov, E. F.; Bormotov, N. I.; Balakhnin, S. M.; Serova, O. A. *Pharm. Chem. J.* **2005**, *39*, 574–578. (b) Wu, W. N.; McKown, L. A.; Melton, J. L.; Reitz, A. B. *J. Pharm. Pharmacol.* **2003**, *55*, 1099–1105.

(6) (a) Shaaban, M. R.; Saleh, T. S.; Farag, A. M. *Heterocycles* **2007**, *71*, 1765–1777. (b) Zanatta, N.; Amaral, S. S.; Esteves-Souza, A.; Echevarria, A.; Brondani, P. B.; Flores, D. C.; Bonacorso, H. G.; Flores, A. F. C.; Martins, M. A. P. *Synthesis* **2006**, 2305–2312.

(7) (a) Demirayak, S.; Abu Mohsen, U.; Cagri Karaburun, A. *Eur. J. Med. Chem.* **2002**, *37*, 255–260. (b) Demirayak, S.; Gueven, K. *Pharmazie* **1995**, *50*, 527–529.

(8) (a) Cavasotto, C. N.; Orry, A. J. W.; Murgolo, N. J.; Czarniecki, M. F.; Kocsi, S. A.; Hawes, B. E.; O'Neill, K. A.; Hine, H.; Burton, M. S.; Voigt, J. H.; Abagyan, R. A.; Bayne, M. L.; Monsma, F. J. *J. Med. Chem.* **2008**, *51*, 581–588. (b) Sondhi, S. M.; Magan, A.; Mahesh, V. K.; Srimal, R. C.; Goel, A. K. *Indian J. Chem., Sect B* **2000**, *62*, 71–76.

(9) (a) Mai, A.; Perrone, A.; Nebbioso, A.; Rotili, D.; Valente, S.; Tardugno, M.; Massa, S.; De Bellis, F.; Altucci, L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2530–2535. (b) Ringom, R.; Axen, E.; Uppenberg, J.; Lundbaeck, T.; Rondahl, L.; Barf, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4449–4452.

(10) Fray, M. J.; Cooper, K.; Parry, M. J.; Richardson, K.; Steele, J. *J. Med. Chem.* **1995**, *38*, 3514–3523.

(11) (a) Mugesh, G.; du Mont, W.-W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125. (b) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev.* **2004**, *104*, 6255.

(12) (a) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22. (b) Liotta, D. *Acc. Chem. Res.* **1984**, *17*, 28. (c) *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley: New York, 1987. (d) Back, T. G. *The Chemistry of Organic Selenium and Tellurium Compounds*, Vol. 2; Patai, S., Ed.; Wiley: Chichester, U.K., 1987; Chapter 3.

(13) (a) Cohen, R. J.; Fox, D. L.; Salvatore, R. N. *J. Org. Chem.* **2004**, *69*, 4265–4268. (b) Fujita, K.; Hashimoto, S.; Oishi, A.; Taguchi, Y. *Tetrahedron Lett.* **2003**, *44*, 3793–3795. (c) Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G. Q.; Affleck, R. L.; Lillig, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 9954–9967. (d) Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G. Q. *J. Am. Chem. Soc.* **2000**, *122*, 9968–9976. (e) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953. (f) Nicolaou, K. C.; Roecker, A. J.; Pfefferkorn, J. A.; Cao, G. Q. *J. Am. Chem. Soc.* **2000**, *122*, 2966–2967. (g) Nicolaou, K. C.; Winssinger, N.; Hughes, R.; Smethurst, C.; Cho, S. Y. *Angew. Chem.* **2000**, *112*, 1126–1130. (h) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao,

G. Q. *Angew. Chem.* **2000**, *112*, 750–755. (i) Laura, A. M.; Rosemary, A. M.; David, J. P. *Tetrahedron* **2005**, *61*, 11527–11576. (j) Nicolaou, K. C.; Pastor, J.; Barluenga, S.; Winssinger, N. *Chem. Commun.* **1998**, 1947–1948.

(14) (a) Wang, Y. G.; Xu, W. M.; Huang, X. *J. Comb. Chem.* **2007**, *9*, 513–519. (b) Wang, Y. G.; Xu, W. M.; Huang, X. *Synthesis* **2007**, 28. (c) Huang, X.; Wang, Y. G. *J. Comb. Chem.* **2007**, *9*, 121–130. (d) Sheng, S. R.; Xin, Q.; Liu, X. L.; Sun, W. K.; Guo, R.; Huang, X. *Synthesis* **2006**, 2293. (e) Qian, H.; Huang, X. *Synthesis* **2006**, 1934. (f) Xu, W. M.; Wang, Y. G.; Miao, M. Z.; Huang, X. *Synthesis* **2005**, 2143. (g) Huang, X.; Tang, E.; Xu, W. M.; Cao, J. *J. Comb. Chem.* **2005**, *7*, 802–805. (h) Xu, W. M.; Huang, X.; Tang, E. *J. Comb. Chem.* **2005**, *7*, 726–733. (i) Xu, W. M.; Tang, E.; Huang, X. *Synthesis* **2004**, 2094–2099. (j) Tang, E.; Huang, X.; Xu, W. M. *Tetrahedron* **2004**, *60*, 9963–9969. (k) Huang, X.; Sheng, S. R. *J. Comb. Chem.* **2003**, *5*, 273–277. (l) Qian, H.; Huang, X. *J. Comb. Chem.* **2003**, *5*, 569–576. (m) Huang, X.; Xu, W. M. *Org. Lett.* **2003**, *5*, 4649–4652. (n) Huang, X.; Cao, J. *Synthesis* **2007**, 2947–2950. (o) Cao, J.; Huang, X. *J. Comb. Chem.* **2008**, *10*, 526–533.

(15) (a) Carpenter, R. D.; DeBerdt, P. B.; Lam, K. S.; Kurth, M. J. *J. Comb. Chem.* **2006**, *8*, 907–914. (b) Smith, J. M.; Gard, J.; Cummings, W.; Kanizsai, A.; Krchnak, V. *J. Comb. Chem.* **1999**, *1*, 368–370.

(16) (a) Balboni, G.; Salvadori, S.; Guerrini, R.; Negri, L.; Giannini, E.; Jinsmaa, Y.; Bryant, S. D.; Lazarus, L. H. *J. Med. Chem.* **2002**, *45*, 5556–5563. (b) Balboni, G.; Onnis, V.; Congiu, C.; Zotti, M.; Sasaki, Y.; Ambo, A.; Bryant, S. D.; Jinsmaa, Y.; Lazarus, L. H.; Trapella, C.; Salvadori, S. *J. Med. Chem.* **2006**, *49*, 5610–5617.

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