A Novel Strategy for the Solid-Phase Synthesis of Substituted Indolines

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Combinatorial chemistry has become an important tool in both drug discovery and chemical biology, and its continued success is dependent, in part, on further advances in solid-phase organic synthesis (SPOS).[1] As the demand for drug-like and/or natural product-like libraries continues to grow, there is an increased need for the development of reaction sequences and linking strategies that allow complex and diverse targets to be constructed efficiently and reliably. Toward this end, there has been particular interest in developing linking strategies whereby the loading and cleavage step(s) contribute to the complexity of the target structure rather than merely constituting extraneous manipulations.[2]

Recently, we reported a selenium-based approach for the solid-phase combinatorial synthesis of benzopyran-containing natural products, utilizing a novel cycloloading strategy.[3] Given the versatility of this approach, we sought to extend it toward the solid-phase synthesis of other heterocycles. It was envisaged that substituted *o*-allyl anilines (**1**, Figure 1) might be cycloloaded onto a polystyrene-based selenenyl bromide resin[4a] via a 5-*exo*-trig cyclization to afford resin-bound indoline scaffolds (**2**). Elaboration of **2** would provide structures such as **3** that could be tracelessly cleaved[4a−c] providing access to 1-methyl indolines (**5**), a structural class from which several drug candidates have emerged including antineoplastic sulfonamides,[5a] 5-hydroxytryptamine receptor antagonists (5-HT3),[5b] and muscarine receptor agonists and antagonists.[5c] Moreover, it was envisaged that the ability of this selenium tether to generate a carbon-centered radical upon cleavage might also be utilized to create additional complexity in the target structure concomitant with release.[6] Specifically, if an intramolecular radical acceptor could be positioned in proximity to this radical (i.e. **4**), then relatively complex polycyclic indolines (**6**) could be constructed. Herein we describe our preliminary efforts aimed at the loading, elaboration, and cleavage of such substituted indolines.[7]

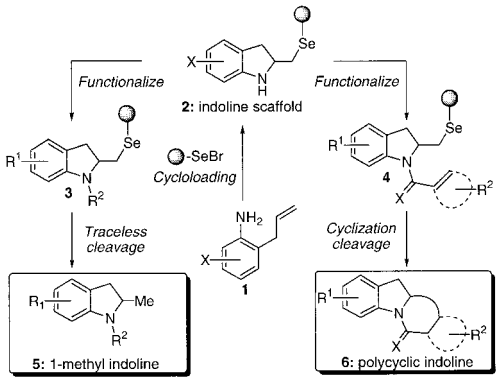
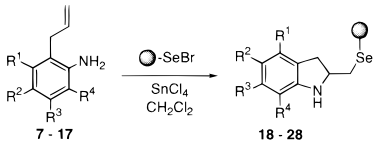


Figure 1. General strategy for the solid-phase cycloloading, functionalization, and cleavage of substitute indolines.

Table 1. Selenium-Mediated Loading[a] of *O*-Allyl Anilines[b]



entry	aniline	R^1	R^2	R^3	R^4	product	temp (°C)	time (h)	purity (%)[b]
1	**7**	H	H	H	H	**18**	−20	0.5	89
2	**8**	H	Me	H	H	**19**	−20	0.5	85
3	**9**	Me	H	Me	H	**20**	−20	0.5	92
4	**10**	H	*t*-Bu	H	H	**21**	−20	0.5	92
5	**11**	H	F	H	H	**22**	−20	0.5	86
6	**12**	H	Cl	H	H	**23**	−20	0.5	94
7	**13**	H	Br	H	H	**24**	−20	0.5	89
8	**14**	H	CN	H	H	**25**	0	1.0	95
9	**15**	H	CO_2Me	H	H	**26**	0	1.0	95
10	**16**	H	NO_2	H	H	**27**	0	1.0	n/a
11	**17**	H	OMe	H	H	**28**	−20	0.5	n/a

[a] Loading ranged from 54 to 87% as determined by weight of cleavage product. [b] Reaction conditions: 1.0 equiv of selenenyl bromide resin (0.75 mmol/g), 3.0 equiv of *o*-allyl aniline, 3.0 equiv of $SnCl_4$. [c] Purities estimated by cleavage (*n*-Bu_3SnH, AIBN, 90 °C), polarity-based purification, and ^1H NMR analysis.

It was first necessary to define conditions for the cycloloading of *o*-allyl anilines.[8] Preliminary solution phase studies with *o*-allyl aniline (**7**, Table 1) revealed that such unprotected anilines would undergo a selenium-mediated cyclization with PhSeBr in the presence of suitable Lewis acid catalysts. Hence, we attempted the corresponding reaction on solid support by treatment of a suspension of selenenyl bromide resin[4a] and aniline **7** with $SnCl_4$ at −20 °C which resulted in rapid resin decolorization. Subsequent treatment of this resin with *n*-Bu_3SnH and AIBN at 90 °C followed by polarity-based removal[9] of the reaction byproducts afforded indoline **18** in 89% purity with an approximate loading of 87%.[10] As shown in Table 1, a series of functionalized anilines were then prepared and tested for loading.[11] Substrates **8**−**13**,

(1) (a) Balkenhohl, F.; von dem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288−2337. (b) Watson, C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1903−1908. (c) Schreiber, S. L. *Bioorg. Med. Chem.* **1998**, *6*, 1127−1152.

(2) For a review, see: van Maarseveen, J. H. *Comb. Chem. High Throughput Screening* **1998**, *1*, 185−214.

(3) (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q. *Angew. Chem., Int. Ed.* **2000**, *39*, 734−739. (b) Nicolaou, K. C.; Cao, G.-Q.; Pfefferkorn, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 739−743.

(4) (a) Nicolaou, K. C.; Pastor, J.; Barluenga, S.; Winssinger, N. *Chem. Commun.* **1998**, 1947−1948. For preparations of related selenium-based resins, see: (b) Ruhland, T.; Andersen, K.; Pedersen, H. *J. Org. Chem.* 1**998**, *63*, 9204−9211. (c) Fujita, K.; Watanabe, K.; Oishi, A.; Ikeda, Y.; Taguchi, Y. *Synlett* **1999**, *11*, 1760−1761.

(5) (a) Yoon, S. J.; Chung, Y.; Lee, M. S.; Choi, D. R.; Lee, J. A.; Yun, D. K.; Moon, E. Y.; Hwang, H. S.; Choi, C. H.; Jung, S. H. Patent. WO 9807719 (Dong Wha Pharm. Ind. Co., Ltd., S. Korea); *Chem. Abstr.* **1998**, *128*, 204885. (b) Bermudez, J.; Dabbs, S.; Joiner, K. A.; King, F. D. *J. Med. Chem.* **1990**, *33*, 1929−1932. (c) Adachi, S.; Koike, K.; Takayanagi, I. *Pharmacology* **1996**, *53*, 250−258.

(6) To our best knowledge, this is the first example whereby radical cleavage from a solid support is accompanied by subsequent intramolecular cyclization to afford an additional ring system in the target molecule. Solid-phase *non-releasing* radical cyclizations have been described previously; for examples, see: (a) Du, X.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5678−5679. (b) Watanabe, Y.; Ishikawa, S.; Takao, G.; Toru, T. *Tetrahedron Lett.* **1999**, *40*, 3411−3414. In addition, traceless radical cleavages of selenium resins have been described, see references 4a−c.

(7) For a previous method for the solid-phase synthesis of indolines, see: Wang, Y.; Huang, T.-N. *Tetrahedron Lett.* **1998**, *39*, 9605−9608.

(8) For solution-phase precedent, see: (a) Clive, D. L. J.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. C. S. Chem. Commun.* **1978**, 379−380. (b) Clive D. L. J.; Farina, V.; Singh, A.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Org. Chem.* **1980**, *45*, 2120−2126. (c) Danishefsky, S.; Berman, E. M.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891−3898.

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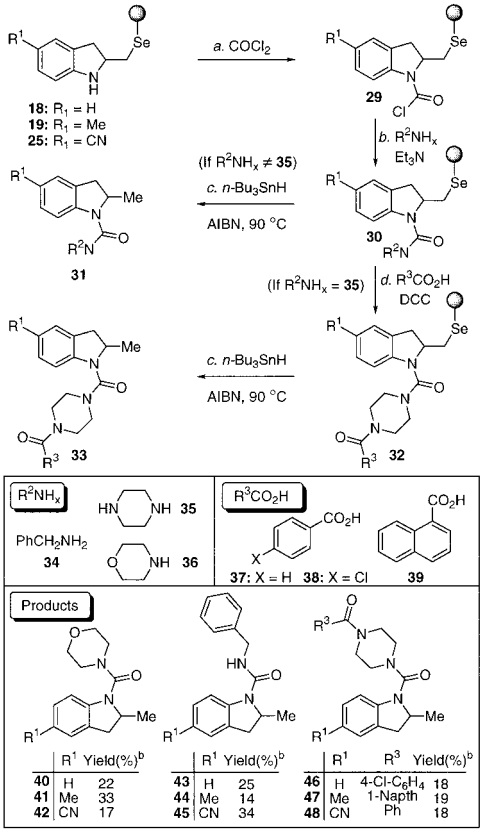
Scheme 1. Parallel Synthesis of 1-Methyl Indolines[a]



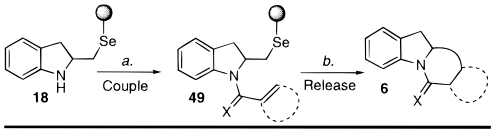
[a] Reaction conditions: (a) 27.0 equiv of $COCl_2$, CH_2Cl_2, 0 °C, 1 h; (b) 10.0 equiv R_2NH_x, 27.0 equiv of Et_3N, CH_2Cl_2, 25 °C, 12 h; (c) 4.0 equiv of *n*-Bu_3SnH, 1.3 equiv of AlBN, toluene, 90 °C, 2 h; (d) 10.0 equiv of R_3CO_2H, 10.0 equiv of DCC, 1.3 equiv of 4-DMAP, CH_2Cl_2, 25 °C, 16 h. [b] Isolated yields over four steps (**40**−**45**) or five steps (**46**−**48**) based on 0.75 mmol/g loading.

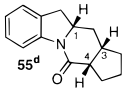
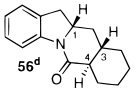
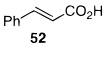
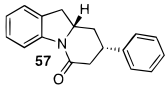
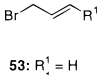
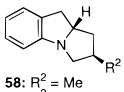
bearing alkyl substituents or halogens, underwent facile loading under these conditions (−20 °C, 0.5 h), whereas those with electron-withdrawing groups (**14** and **15**) required slightly modified conditions (0 °C, 1 h). The only failures noted were 4-nitro aniline **16** and 4-methoxy aniline **17**.

With this collection of resin-bound indolines (**18**−**26**) now in hand, we set out to test their proposed applications. First, we undertook the solid-phase synthesis of a collection of 1-methyl indolines resembling previously reported 5-HT3 receptor antagonists[5b] to demonstrate how the current linking strategy might be employed in combinatorial synthesis. The generalized synthetic strategy is outlined at the top of Scheme 1. Hence, resin-bound indolines were converted to acyl chlorides (**29**) by treatment with phosgene, and these acyl chlorides were then reacted with various amines (R^2NH_x) to afford ureas (**30**).[5b] If the amine used was piperazine (**35**), the remaining secondary amine was then coupled with a carboxylic acid (R^3CO_2H). All of the resulting indolines (**30** or **32**) were tracelessly cleaved to produce compounds of type **31** or **33**. The parallel application of this sequence to indoline scaffolds **18**, **19**, and **25**, amines **34**−**36**, and carboxylic acids **37**−**39** resulted in the formation of 1-methyl indolines **40**−**48**.

Notwithstanding the utility of these 1-methyl indolines, our second goal was to develop a more functional cleavage protocol

Table 2. Release and Cyclization of Polycyclic Indolines[a]



Entry	Olefin	Coupling procedure[a]	Product	Yield (%)[b,c]
1	 **50**	A	 **55**[d]	26
2	 **51**	A	 **56**[d]	36
3	 **52**	A	 **57**	13
4	 **53**: R^1 = H	B	 **58**: R^2 = Me	18
5	**54**: R^1 = Me	B	**59**: R^2 = Et	19

[a] Reaction conditions: (a) Coupling procedure A: 10.0 equiv of acid, 10.0 equiv of DCC, 1.3 equiv of 4-DMAP, CH_2Cl_2, 25 °C, 24 h; coupling procedure B: 10.0 equiv of alkenyl bromide, 20.0 equiv of NaH, DMF, 60 °C; (b) 4.0 equiv of *n*-Bu_3SnH, 1.3 equiv of AlBN, toluene, 90 °C, 4 h. [b] Products obtained as single diastereomers with relative stereochemistry shown as determined by ^1H NMR and ROESY analysis unless otherwise noted. [c] Isolated yield over three steps based on 0.75 mmol/g loading. [d] See Supporting Information for discussion of stereochemical assignment.

by taking better advantage of the ability of this selenium tether to generate a carbon-centered radical. Hence, the secondary nitrogen of indoline (**18**, Table 2) was coupled to a series of olefinic acceptors via either amide or alkyl linkages to form derivatives of type **49** which could be cleaved with concomitant cyclization to provide polycyclic indolines of type **6**. For example, DCC coupling of indoline **18** with 1-cyclopentene-1-carboxylic acid **50** afforded the corresponding amide which was then suspended in toluene at 90 °C and a solution of *n*-Bu_3SnH and AIBN was slowly added over a 4 h interval. Gratifyingly, tetracycle **55** was released as the sole product and a single diastereomer in 26% yield over three steps. Coupling of **18** with 1-cyclohexene-1-carboxylic acid **51** and *trans*-cinnamic acid **52** followed by release afforded tetracycle **56** and tricycle **57** in 36 and 13% yields, respectively. over three steps. In addition, alkylation (NaH, DMF, 60 °C) of indoline **18** with either allyl or crotyl bromide (**53** and **54**) led to the formation of tricycles **58** and **59** in 18 and 19% yields, respectively.

In conclusion, we have described a highly efficient method for the solid-phase synthesis of substituted indoline scaffolds which can be elaborated and tracelessly cleaved providing access to members of the medicinally important 1-methyl indoline class. Moreover, this linking strategy also allows for a novel cleavage approach whereby additional ring systems can be formed through a radical cyclization during the release step. The use of this latter cleavage option in conjunction with the development of highly functionalized indoline scaffolds should allow for the construction of complex natural product-like compound libraries.

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Supporting Information Available: Representative procedures and physical data for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Separation of the desired indoline cleavage products from organotin byproducts represents an obstacle to the combinatorial use of this methodology. The polarity-based purification used here relies on the desired product being prontonated and taken into the aqueous phase such that the organotin species can be removed with the organic phase. For a review of other applicable methods, see: Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1174−1196.

(10) Purities of products are estimated based upon integration of ^1H NMR signals of isolated cleavage products after polarity-based[9] purification.

(11) See Supporting Information for preparation of *o*-allyl anilines.