ORGANIC LETTERS

2009
Vol. 11, No. 15
3458−3461

An Interrupted Fischer Indolization Approach toward Fused Indoline-Containing Natural Products

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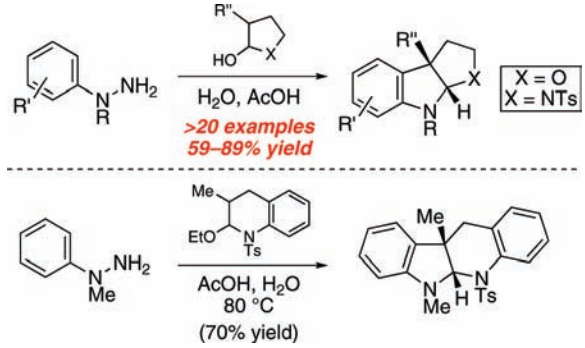
Received June 19, 2009

ABSTRACT



An efficient method to access the fused indoline ring system present in a multitude of bioactive molecules has been developed. The strategy involves the condensation of hydrazines with latent aldehydes to ultimately deliver indoline-containing products by way of an interrupted Fischer indolization sequence. Our studies show that the approach will likely be amenable to the synthesis of complex targets, such as the communesin natural products.

The discovery of efficient methods to synthesize complex bioactive molecules continues to be a vital area of research.[1] A subset of compounds that have received substantial interest due to their medicinal properties and impressive structures are those that possess a fused indoline motif of the type **1** shown in Figure 1. Such compounds include the acetylcholinesterase inhibitors physovenine (**2**) and physostigmine (**3**)[2,3] and the anticancer agents diazonamide A (**4**),[4] bipleiophylline (**5**),[5] communesin B (**6**),[6] aspidophylline A (**7**),[7] and echitamine chloride (**8**).[8] The importance of indoline-containing compounds has prompted the development of a number of methods to access such motifs, with numerous studies particularly in the area of pyrrolidinoindoline synthesis. In most cases, the fused indoline ring systems are assembled in a stepwise fashion by the initial synthesis of a substituted indole[9] or oxindole[10] intermediate, which is then further elaborated to the target **1**. Herein, we report a

(1) (a) Hudlicky, T.; Reed, J. W. *The Way of Synthesis*; Wiley-VCH: Weinheim, 2007. (b) Wender, P. A.; Verman, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40–49.

(2) For a review of these alkaloids, see: Takano, S.; Ogasawara, K. *Alkaloids* **1989**, *36*, 225–251.

(3) Physostigmine (**3**) has been used to treat glaucoma, Alzheimer's disease, and myasthenia gravis. For a pertinent review, see: Triggle, D. J.; Mitchell, J. M.; Filler, R. *CNS Drug Rev.* **1998**, *4*, 87–136.

(4) For biological studies, see: (a) Williams, N. S.; Burgett, A. W. G.; Atkins, A. S.; Wang, X.; Harran, P. G.; McKnight, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 2074–2079. (b) Wang, G.; Shang, L.; Burgett, A. W. G.; Harran, P. G.; Wang, X. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 2068–2073. For a review of synthetic studies, see: (c) Lachia, M.; Moody, C. J. *Nat. Prod. Rep.* **2008**, *25*, 227–253.

(5) Kam, T.-S.; Tan, S.-J.; Ng, S.-K.; Komiyama, K. *Org. Lett.* **2008**, *10*, 3749–3752.

(6) (a) Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355–2358. (b) Jadulco, R.; Edrada, R. A.; Ebel, R.; Berg, A.; Schaumann, K.; Wray, V.; Steube, K.; Proksch, P. *J. Nat. Prod.* **2004**, *67*, 78–81. For a comprehensive review, see: (c) Siengalewicz, P.; Gaich, T.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 8170–8176.

10.1021/ol901383j CCC: $40.75
Published on Web 07/14/2009

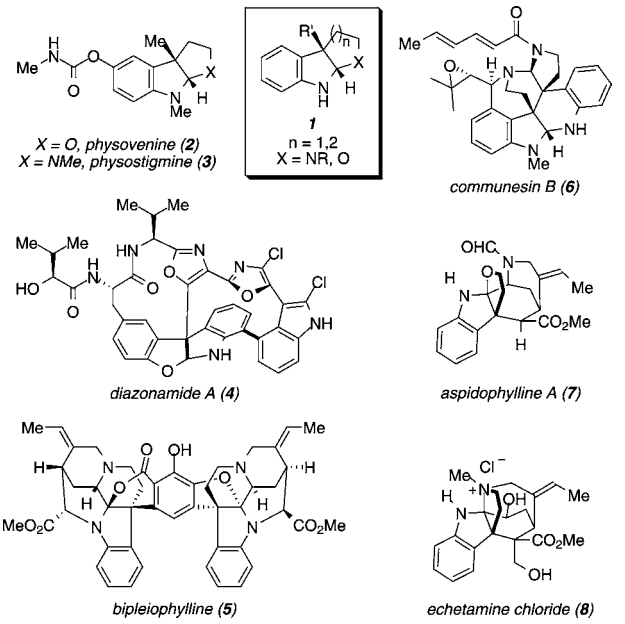


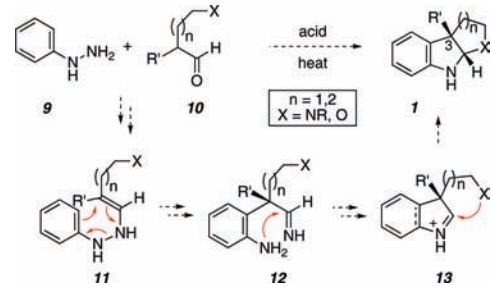
Figure 1. Parent indoline **1** and representative natural products **2**−**8**.

powerful cascade reaction that allows direct access to **1** from simple starting materials under mild aqueous conditions.

Our approach to the indoline scaffold **1** of compounds **2**−**8** is inspired by the classic Fischer indole synthesis[11,12] and is presented in Scheme 1. We envisaged that phenylhydrazine (**9**) and an α-disubstituted aldehyde **10** would react in the presence of acid to afford enamine intermediate **11**. Subsequent [3,3]-sigmatropic rearrangement and rearomatization would provide aniline **12**, which in turn would cyclize with loss of NH_3 to furnish transient indolenine **13**. Intramolecular attack by a proximal heteroatom substituent (X = NR or O) would deliver the desired product **1**. The successful implementation of this interrupted Fischer indolization process would lead to the formation of three new bonds, two heterocyclic rings, and two stereogenic centers, one of which is quaternary (C3).

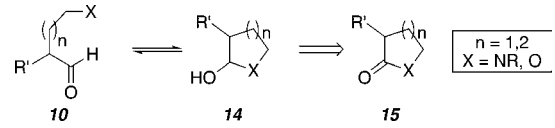
Although scattered examples of interrupted Fischer indolization reactions have been reported in the literature over

Scheme 1. Proposed Cascade Sequence To Access Indoline **1**



the past 50 years,[13−15] most notably by Grandberg[13] and Takano,[14] a general and mild method to access compounds of type **1** using the strategy outlined in Scheme 1 has not been discovered. Moreover, the notion that such a method could be used to prepare the indoline scaffold present in a multitude of complex biologically important compounds (e.g., **4**−**8**) has not been realized. In this paper, we describe the development and scope of this powerful cascade reaction, which provides access to an array of indoline scaffolds, including the complex polycyclic framework observed in communesin B. In addition, a one-step formal total synthesis of physovenine is disclosed.

Scheme 2. Lactols and Hemiaminals as Latent Aldehydes



Our studies commenced with the identification of an efficient method for accessing the key substituted aldehyde reaction partners **10** (Scheme 2). It was noted that isomeric lactols and hemiaminals **14** would likely serve as suitable aldehyde surrogates in the desired transformation, following a strategy sometimes employed in modifications of the Fischer indole synthesis.[16] This approach was considered

(7) Subramaniam, G.; Hiraku, O.; Hayashi, M.; Koyano, T.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1783–1789.

(8) (a) Jagetia, G.; Baliga, M. S.; Venkatesh, P.; Ulloor, J. N.; Mantena, S. K.; Genebriera, J.; Mathuram, V. *J. Pharm. Pharmacol.* **2005**, *57*, 1213–1219. (b) Ramírez, A.; García-Rubio, S. *Curr. Med. Chem.* **2003**, *10*, 1891–1915.

(9) For examples of pyrrolidinoindoline and furoindoline syntheses from substituted indoles, see: (a) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953–11963. (b) Austin, J. F.; Kim, S. G.; Sinz, C. J.; Xiao, W. J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482–5487. (c) Movassaghi, M.; Schmidt, M. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3725–3728. (d) Kim, J.; Ashenhurst, J. A.; Movassaghi, M. *Science* **2009**, *324*, 238–241.

(10) For examples of pyrrolidinoindoline and furoindoline syntheses from substituted oxindoles, see: (a) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500–6503. (b) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590–4591.

(11) For reviews, see: (a) Robinson, B. *Chem. Rev.* **1963**, *63*, 373–401. (b) Robinson, B. *Chem. Rev.* **1969**, *69*, 227–250.

(12) (a) Fischer, E.; Jourdan, F. *Ber.* **1883**, *16*, 2241–2245. (b) Fischer, E.; Hess, O. *Ber.* **1884**, *17*, 559–568.

(13) In a seminal study, Grandberg demonstrated that a C2-substituted pyrrolidinoindoline could be prepared by the reaction of phenylhydrazine and 5-chloro-3-methylpentan-2-one. However, this method is not applicable to the synthesis of furoindolines or to the more complex ring systems encountered in numerous natural products, such as **4**−**7**; see: (a) Grandberg, I. I.; Zuyanova, T. I.; Afonina, N. I.; Ivanova, T. A. *Dokl. Akad. Nauk SSSR* **1967**, *176*, 583−585. For a synthesis of furoindolines, albeit in modest yield, see: (b) Grandberg, I. I.; Tokmakov, G. P. *Khim. Geterotsikl. Soedin.* **1975**, 207–210.

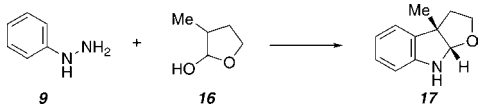
(14) Takano has synthesized a pyrrolidinoindoline product using an interrupted Fischer indolization reaction; see: (a) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K. *Chem. Lett.* **1990**, 109–112. (b) Takano, S.; Ogasawara, K.; Iwabuchi, R.; Moriya, M. JP 03112989 A 19910514, 1991.

(15) For other examples, see: (a) Tsuji, R.; Nakagawa, M.; Nishida, A. *Heterocycles* **2002**, *58*, 587–593. (b) Britten, A. Z.; Bardsley, W. G.; Hill, C. M. *Tetrahedron* **1971**, *27*, 5631–5639. (c) Rosenmund, P.; Sadri, E. *Liebigs Ann. Chem.* **1979**, 927–943. (d) Rosenmund, P.; Gektidis, S.; Brill, H.; Kalbe, R. *Tetrahedron Lett.* **1989**, *30*, 61–62. (e) Nishida, A.; Ushigome, S.; Sugimoto, A.; Arai, S. *Heterocycles* **2005**, *66*, 181–185.

ideal for the present study because of the ready availability of substituted lactones and lactams **15**, which would serve as precursors to the desired substrates. Thus, a variety of substrates of the type **14** were accessible in a straightforward fashion.[17]

The feasibility of the proposed cascade reaction sequence of Scheme 1 was established from the reaction between commercially available phenylhydrazine (**9**) and latent aldehyde **16** (1 equiv) under a variety of acidic conditions (Table 1). Lewis acids were examined and found to be ineffective (entries 1 and 2). However, use of *p*-toluenesulfonic acid, trifluoroacetic acid, or HCl each afforded the desired product **17** in modest yield (entries 3−5). Sulfuric acid-mediated reaction conditions were also explored and ultimately provided the desired product in 87% yield (entry 6). Recognizing that a milder acid source would be more generally useful, acetic acid was examined. Although the use of neat acetic acid afforded modest product yields (entry 7), employment of a 1:1 mixture of acetic acid and water at 60 °C furnished indoline **17** in 89% isolated yield (entry 8).[18]

Table 1. Survey of Acids To Promote Furoindoline Synthesis



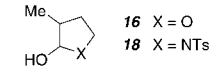
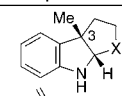
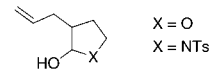
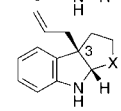
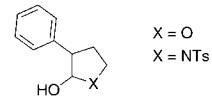
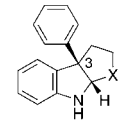
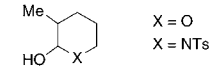
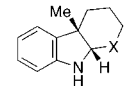
9 **16** **17**

entry	acid source	conditions	yield[a] (%)
1	PCl_3	benzene, 60 °C	<5
2	$ZnCl_2$	EtOH, 100 °C	<5
3	TsOH	EtOH, H_2O, 60 °C	51
4	TFA	CH_3CN, 60 °C	64
5	5% HCl	CH_3CN, 60 °C	70
6	4% H_2SO_4	CH_3CN, 60 °C	87
7	AcOH	AcOH, 60 °C	52
8	AcOH	1:1 AcOH/H_2O, 60 °C	89[b]

[a] Unless otherwise noted, yields determined by ^1H NMR analysis. [b] Isolated yield.

Having identified suitable conditions for indoline formation, we evaluated the scope of the transformation. Gratifyingly, both lactols and hemiaminal substrates could be utilized,[19] thereby furnishing oxygen- and nitrogen-containing indoline products, respectively (Table 2). For both classes of compounds, fused indolines possessing methyl, allyl, and phenyl substituents at C3 could be prepared in good yields (entries 1−6). Of note, these furoindoline and pyrrolidinoindoline motifs are present in an array of medicinally important compounds, such as physovenine (entry 1), physostigmine (entry 2),[2] flustramine B (entry 4),[20] and the hodgkinsine alkaloids (entry 6).[21] Furthermore, 6-membered homologues of the furoindoline and pyrrolidinoindoline frameworks were accessible using this methodology (entries 7 and 8).

Table 2. Variation of the Surrogate Aldehyde Coupling Partner

entry	aldehyde surrogate		product	yield[c]
1[a]		***16*** X = O ***18*** X = NTs		89% 88%
2[b]				
3[a]		X = O X = NTs		89% 68%
4[b]				
5[a]		X = O X = NTs		75% 70%
6[b]				
7[a]		X = O X = NTs		65% 81%
8[b]				

[a] Conditions: **9** (1 equiv), 1:1 AcOH/H_2O, 60 °C. [b] Conditions: **9** (1 equiv), 1:1 AcOH/H_2O, 100 °C. [c] Isolated yield.

As shown in Table 3, the transformation is broad in scope with respect to the hydrazine component.[22] *N*-Methyl- and *N*-benzyl-substituted hydrazines were deemed competent coupling partners (entries 1−4). Whereas the *N*-benzyl group can be used as a protective group in multistep synthesis, the *N*-Me group is present in a number of natural products (e.g., **2**, **3**, and **6**, Figure 1). In addition, para and ortho substituents were tolerated under the reaction conditions (entries 5−14). Importantly, use of chlorohydrazines furnished haloindolines (entries 9−12), which could be further functionalized by transition-metal-catalyzed cross-coupling chemistry. Finally, the transformation proceeded smoothly with *p*-methoxyphenylhydrazine as a substrate, thus affording C5-oxygenated products in good yields (entries 13 and 14).[23]

Several significant features of the reactions shown in Tables 2 and 3 should be noted: (a) both coupling partners employed are readily accessible entities (i.e., substituted hydrazines and aldehyde surrogates), (b) the reaction conditions employed (i.e., aqueous acetic acid) are inexpensive, operationally simple, and do not require costly transition-metal catalysts, and (c) the strategy is convergent, broad in

(16) (a) Campos, K. R.; Woo, J. C. S.; Lee, S.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 79–82. (b) Brodfuehrer, P. R.; Chen, B.-C.; Sattelberg, T. R.; Smith, P. R.; Reddy, J. P.; Stark, D. R.; Quinlan, S. L.; Reid, J. G.; Thottathil, J. K.; Wang, S. *J. Org. Chem.* **1997**, *62*, 9192–9202. (c) Adachi, H.; Palaniappan, K. K.; Ivanov, A. A.; Bergman, N.; Gao, Z.-G.; Jacobson, K. A. *J. Med. Chem.* **2007**, *50*, 1810–1827.

(17) See the Supporting Information for details.

(18) For the use of H_2O/AcOH to facilitate the Fischer indole synthesis, see: (a) Desaty, D.; Kegleviæ, D. *Croat. Chem. Acta* **1964**, *36*, 103–109. (b) Kegleviæ, D.; Stojanac, N.; Desaty, D. *Croat. Chem. Acta* **1961**, *33*, 83–88.

(19) All lactol and hemiaminal substrates were employed as an inconsequential mixture of diastereomers.

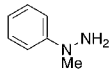
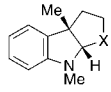
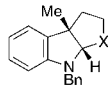
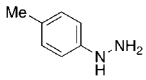
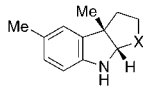
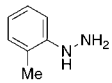
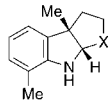
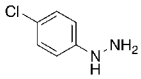
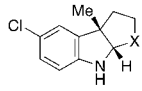
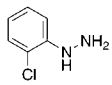
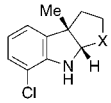
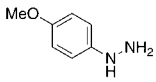
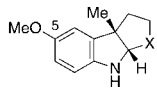
(20) Carle, J. S.; Christophersen, C. *J. Am. Chem. Soc.* **1979**, *101*, 4012–4013.

(21) Guéritte-Voegelein, F.; Sévenet, T.; Pusset, J.; Adeline, M.-T.; Gillet, B.; Beloiel, J.-C.; Guénard, D.; Potier, P.; Rasolonjanahary, R.; Kordon, C. *J. Nat. Prod.* **1992**, *55*, 923–930.

(22) Hydrazines could be employed in either free-base form or as the hydrochloric acid salts; see the Supporting Information for details.

(23) Use of *p*-(trifluoromethyl)phenylhydrazine as a substrate afforded low yields of product.

Table 3. Variation of the Hydrazine Coupling Partner

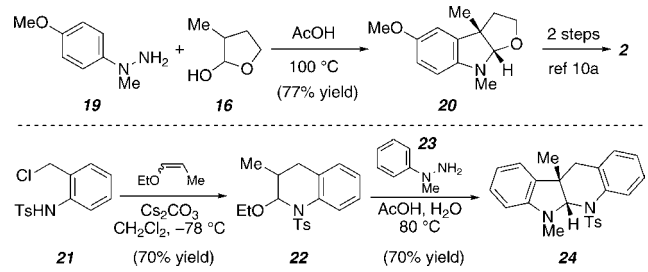
entry[a]	hydrazine	aldehyde surrogate	product		yield[f]
1[b]		***16***		X = O	70%
2[c]		***18***		X = NTs	81%
3		***16***		X = O	59%
4[d]		***18***		X = NTs	83%
5		***16***		X = O	60%
6[d]		***18***		X = NTs	71%
7		***16***		X = O	62%
8[d]		***18***		X = NTs	73%
9		***16***		X = O	67%
10[d]		***18***		X = NTs	77%
11		***16***		X = O	60%
12[d]		***18***		X = NTs	84%
13		***16***		X = O	75%
14[e]		***18***		X = NTs	70%

[a] Conditions unless otherwise noted: 1:1 ratio of hydrazine to **16** or **18**, 1:1 AcOH/H_2O, 60 °C. [b] AcOH. [c] AcOH, 23 °C. [d] 100 °C. [e] 75 °C. [f] Isolated yield.

scope, and therefore, could be used to prepare libraries of compounds possessing the biologically privileged indoline motif.

As shown in Scheme 3, the methodology is effective in more complex settings. Reaction of hydrazine **19** with lactol **16** in AcOH furnished furoindoline **20** in 77% yield, which constitutes a formal total synthesis of physovenine (**2**).[10a,24,25] In addition, known sulfonamide **21**[26] was reacted with 1-ethoxypropene in the presence of Cs_2CO_3 to afford hetero-

Scheme 3. Formal Total Synthesis of Physovenine (**2**) and Synthesis of the Communesin Indoline Scaffold



Diels−Alder product **22**, following the general procedure described by Corey.[26] Gratifyingly, exposure of **22** to *N*-methylphenylhydrazine (**23**) in 1:1 AcOH/H_2O delivered indoline **24**, which possesses the 6,5,6,6-ring system of the communesin natural products.[27]

In summary, we have developed an efficient method to access the fused indoline ring systems present in a variety of natural products. The strategy involves the condensation of readily available hydrazines with latent aldehydes to ultimately deliver indoline-containing products by way of an interrupted Fischer indolization sequence. The method is convergent, mild, operationally simple, and broad in scope. In addition, our studies show that the approach would likely be amenable to the synthesis of complex targets, such as the communesin natural products. The development of diastereo- and enantioselective variants of the newly described transformation is currently underway in our laboratory, along with related studies in the realm of natural product total synthesis.

Acknowledgment. We are grateful to the University of California, Los Angeles and Boehringer Ingelheim for financial support. We thank Professors Harran (UCLA) and Houk (UCLA) for pertinent discussions, the Garcia-Garibay laboratory (UCLA) for the generous access to instrumentation, and Dr. John Greaves (UC Irvine) for mass spectra.

Supporting Information Available: Detailed experimental details and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) For asymmetric routes to **20** (7 and 18 steps, respectively), see ref 10a and: ElAzab, A. S.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 2757–2759.

(25) Physovenine can be resolved readily, on preparative scale, using column chromatography with cellulose triacetate; see: Yu, Q.; Liu, C.; Brzostowska, M.; Chrisey, L.; Brossi, A.; Greig, N. H.; Atack, J. R.; Soncrant, T. T.; Rapoport, S. I.; Radunz, H. *Helv. Chim. Acta* **1991**, *74*, 761–766.

(26) Steinhagen, H.; Corey, E. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1928–1931.

(27) Indoline **24** has previously been prepared by an intermolecular aza-Diels−Alder strategy; see: May, J. A.; Stoltz, B. M. *Tetrahedron* **2006**, *62*, 5262–5271.