ORGANIC LETTERS

2011
Vol. 13, No. 15
4012–4015

A Cycloisomerization/Friedel–Crafts Alkylation Strategy for the Synthesis of Pyrano[3,4-*b*]indoles

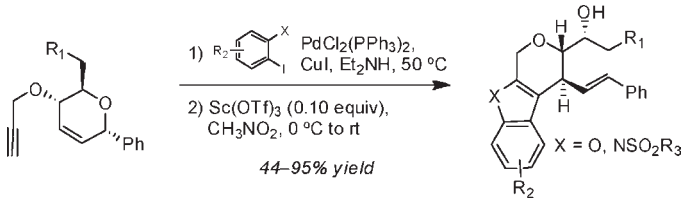
Matthew R. Medeiros, Scott E. Schaus,* and John A. Porco Jr.*

Chemistry Department, Center for Chemical Methodology and Library Development, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215, United States

seschaus@bu.edu; porco@bu.edu

Received June 8, 2011

ABSTRACT



The synthesis of pyrano[3,4-*b*]indoles is described. The reaction sequence involves Sonogashira coupling of dihydropyran propargyl ether scaffolds with iodoanilines to afford intermediate indoles. Lewis acid-catalyzed ionization of the dihydropyrans, followed by intramolecular C3 alkylation of the indole, provides the title compounds.

It is well established that compounds containing the "privileged" indole motif exhibit a myriad of biological activities.[1] Building upon our recently reported study of dihydropyran rearrangements,[2] we developed a program focused on the synthesis of molecules comprising the pyrano[3,4-*b*]indole framework. Compounds having this skeleton have been used as anti-inflammatory and analgesic agents as exemplified by etodolac (**1**) and pemedolac (**2**) (Figure 1).[3] More recently these compounds have shown promise as inhibitors of hepatitis C virus (HCV) NS5B polymerase (**3**)[4] and as potential treatments for lymphoma.[5]

A SciFinder search[6] of known compounds having the pyrano[3,4-*b*]indole skeleton revealed 2726 structures with only 55 (2%) bearing substitution at C3 and C4 (*cf.* **1**, Figure 1). Accordingly, methodology providing functionalization at these positions will serve to increase the diversity of this chemotype. Herein, we describe a cycloisomerization/alkylation strategy that affords pyrano[3,4-*b*]indoles exhibiting both stereochemistry and useful functional groups at C3 and C4.

We envisioned a strategy to pyranoindoles of the type **4** involving intramolecular Friedel–Crafts cyclization of indole **5** (Scheme 1a). Alkylation of allylic alcohol **6** with a substituted bromomethylindole (**7**) would provide the desired cyclization precursor. Considering our interest in library synthesis, and identifying the indole fragment as a diversity element, we were

(1) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361.

(2) Medeiros, M. R.; Narayan, R. S.; McDougal, N. T.; Schaus, S. E.; Porco, J. A., Jr. *Org. Lett.* **2010**, *12*, 3222–3225.

(3) (a) Demerson, C. A.; Humber, L. G.; Philipp, A. H.; Martel, R. R. *J. Med. Chem.* **1976**, *19*, 391–395. (b) Katz, A. H.; Demerson, C. A.; Shaw, C.-C.; Asselin, A. A.; Humber, L. G.; Conway, K. M.; Gavin, G.; Guinosso, C.; Jensen, N. P.; Mobilio, D.; Noureldin, R.; Schmid, J.; Shah, U.; Van Engen, D.; Chau, T. T.; Weichman, B. M. *J. Med. Chem.* **1988**, *31*, 1244–1250.

(4) (a) Gopalsamy, A.; Lim, K.; Ciszewski, G.; Park, K.; Ellingboe, J. B.; Insaf, S.; Upeslacis, J.; Mansour, T. S.; Krishnamurthy, G.; Damarla, M.; Pyatski, Y.; Ho, D.; Howe, A. Y. M.; Orlowski, M.; Feld, B.; O'Connell, J. *J. Med. Chem.* **2004**, *47*, 6603–6608. (b) LaPorte, M. G.; Draper, T. L.; Miller, L. E.; Blackledge, C. W.; Leister, L. K.; Amparo, E.; Hussey, A. R.; Young, D. C.; Chunduru, S. K.; Benetatos, C. A.; Rhodes, G.; Gopalsamy, A.; Herbertz, T.; Burns, C. J.; Condon, S. M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2968–2973.

(5) Nardella, F. A. U.S. Patent 6573292, 2003.

(6) A structure search for the pyrano[3,4-*b*]indole skeleton was conducted on March 14, 2011 using the web-based SciFinder Scholar Database.

(7) (a) Nagarathnam, D. *Synthesis* **1992**, 743–745. (b) Bélanger, G.; Larouche-Gauthier, R.; Ménard, F.; Nantel, M.; Barabe, F. *J. Org. Chem.* **2006**, *71*, 704–712. (c) Monhanakrishnan, A. K.; Ramesh, N. *Tetrahedron Lett.* **2005**, *46*, 4231–4233.

(8) (a) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Org. Lett.* **2006**, *8*, 2803–2805. (b) Isono, N.; Lautens, M. *Org. Lett.* **2009**, *11*, 1329–1331. (c) Martínez, C.; Álvarez, R.; Aurrecoechea, J. M. *Org. Lett.* **2009**, *11*, 1083–1086. (d) Yin, Y.; Ma, W.; Chai, Z.; Zhao, G. *J. Org. Chem.* **2007**, *72*, 5731–5736.

10.1021/ol201532k
Published on Web 07/08/2011

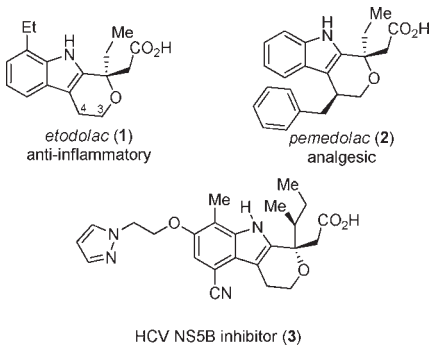
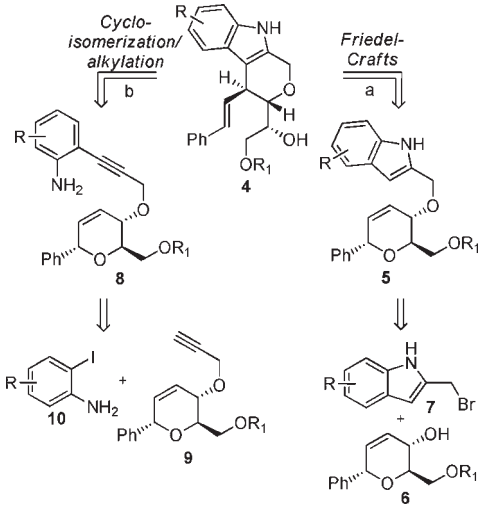


Figure 1. Biologically active pyrano[3,4-*b*]indoles.

concerned with the availability and preparation of diverse bromomethylindoles.[7]

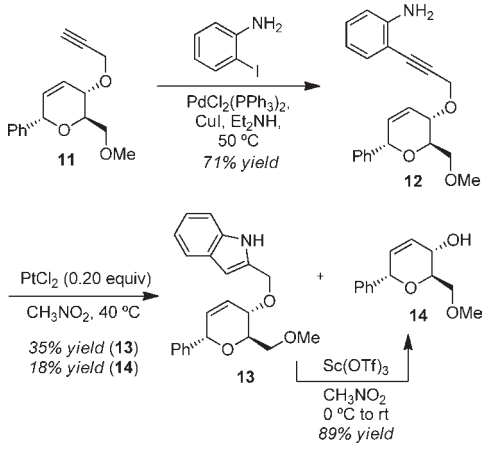
Alternatively, reports of the intermolecular, electrophilic alkylation of the intermediate metal vinylidenes resulting from metal-catalyzed cycloisomerization of *o*-alkynylanilines[8] inspired us to pursue an intramolecular cycloisomerization/alkylation strategy employing *o*-alkynylanilines (**8**) (Scheme 1b). Sonogashira coupling[9] of terminal alkynes (**9**) with readily available iodoanilines (**10**) would serve to generate the desired cycloisomerization precursors.

Scheme 1. Proposed (a) Intramolecular Indole Alkylation and (b) Cycloisomerization/Alkylation Strategies



Investigation of our proposed cycloisomerization approach commenced with Sonogashira coupling of terminal alkyne **11** and 2-iodoaniline to provide *o*-alkynylaniline **12** (Scheme 2).[10] A variety of conditions have been reported to effect cycloisomerization of *o*-alkynylanilines.[8,11] Our desire to conduct a tandem process and prior experience with related rearrangements[2] led us to explore conditions that would allow both alkyne activation and ring opening of the dihydropyran. A preliminary screen revealed $PtCl_2$ and $Ph_3PAuCl/AgSbF_6$ as candidate catalysts for the transformation. However, upon further investigation, we did not observe the desired pyranoindole. Rather, we isolated both indole **13** and alcohol **14**, the latter presumably arising from β-elimination. Furthermore, exposure of indole **13** to $Sc(OTf)_3$ in CH_3NO_2 resulted in exclusive formation of elimination product **14**.

Scheme 2. Attempted Cycloisomerization/Alkylation Using an Unprotected *o*-Alkynylaniline



Encouraged by the isolation of indole **13**, we anticipated that deactivation of the indole moiety with an electron-withdrawing group on the nitrogen would abrogate the formation of alcohol **14**. Accordingly, sulfonylation of aniline **12** under standard conditions provided sulfonamide **15** (Scheme 3). A brief catalyst screen revealed a marked dependence of product formation on catalyst choice. Use of π-philic catalysts such as $PtCl_2$ and Ph_3PAuCl[12] generated the desired pyranoindole **16** along with a small amount of the intermediate indole **17** (entries 1 and 2). Alternatively, treatment of **15** with $Sc(OTf)_3$ and $In(OTf)_3$, both known to be oxophilic Lewis acids,[13] provided tetrahydrofuran **18** (stereochemistry not determined).[10] Presumably, tetrahydrofuran **18** arises from initial ionization of the dihydropyran followed by nucleophilic attack by the pendant alkyne to form the C3−C8 bond. The resulting vinyl carbocation may finally be quenched by water present

(9) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470. (b) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922.

(10) See Supporting Information for complete experimental details.

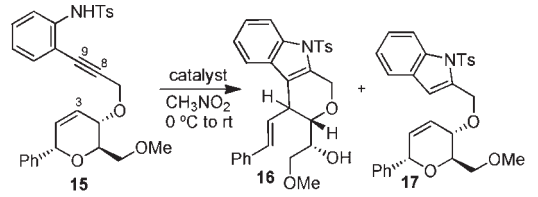
(11) (a) Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071–4078. (b) Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. *Angew. Chem.* **2007**, *119*, 1913–1916. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309. (d) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843–3846.

(12) (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403 and references therein. (c) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817–7831.

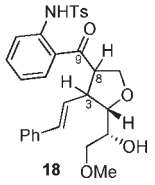
(13) (a) Tsuruta, H.; Yamaguchi, K.; Inamoto, T. *Chem. Commun.* **1999**, 1703–1704. (b) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227–2302.

(14) See Supporting Information for a graphical representation of the proposed mechanism.

Scheme 3. Catalyst Role in the Tandem Cycloisomerization/ Friedel–Crafts Rearrangement[a]



entry	catalyst	yield (%) 16	17	18
1	$PtCl_2$	–	trace[b]	–
2	$Ph_3PAuCl/AgSbF_6$	33	27	<10
3	$Sc(OTf)_3$	–	–	50
4	$In(OTf)_3$	–	–	81

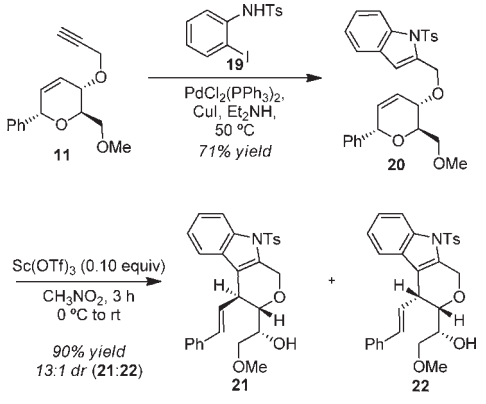


[a] Conditions: substrate (0.10 mmol), catalyst (0.010 mmol), CH_3NO_2 (1 mL), 3 h. [b] Starting material recovered.

in the reaction medium. Tautomerization of the intermediate enol affords the C9 ketone.[14]

We desired to streamline the synthesis of the cycloisomerization precursors (**15**) in order to provide a route amenable to library preparation. Accordingly, we considered protection of the iodoaniline prior to the Sonogashira coupling in order to provide a more convergent process and to increase the flexibility of protecting groups (Scheme 4). However, we did not observe any of the expected protected alkynyl aniline after Sonogashira coupling of alkyne **11** and sulfonamide **19**. Instead, we only observed formation of indole **20** arising from cycloisomerization.[15]

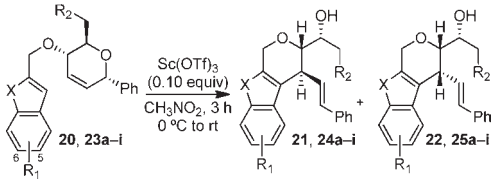
Scheme 4. Synthesis of Pyranoindoles **21** and **22**



Subsequent exposure of indole **20** to $Sc(OTf)_3$ in CH_3NO_2 provided pyranoindoles **21** and **22** in 90% combined yield and 13:1 diastereomeric ratio favoring the *trans* isomer. An X-ray crystal structure of the analogous methanesulfonyl-protected derivative confirmed the stereochemistry of the major isomer.[10] Due to the convenience and high yield of the two-step procedure, we pursued this strategy for the remainder of our study.

An investigation of the scope of the reaction revealed that indoles containing electron-withdrawing (Table 1, entries 1–5) or electron-donating groups (entry 6) provided the desired pyranoindoles in good yields. The reaction conditions were tolerant of both azide and bromide substituents at R^2 (entries 7–8). Furthermore, use of iodophenols as coupling partners in the Sonogashira reaction provided intermediate benzofurans, which were smoothly transformed to pyrano[3,4-*b*]benzofurans[16] using identical conditions (entries 9–10).

Table 1. Scope of the $Sc(OTf)_3$-Catalyzed Cyclization[a]



entry	substrate (**20**,**23**)	X	R_1	R_2	yield (%)	dr[b]
1	**20**	NHT_S	H	OMe	90	13:1
2	**23a**	NHM_S	5-F	OMe	95	4:1
3	**b**	NHT_S	5-CF_3	OMe	95	2:1
4	**c**	NHT_S	5-NO_2	OMe	88	1:1
5	**d**	NHM_S	6-Cl	OMe	77	4:1
6	**e**	NHT_S	5-OMe	OMe	49	>20:1
7	**f**	NHT_S	H	Br	74	17:1
8	**g**	NHM_S	H	N_3	44	5:1
9	**h**	O	H	OMe	80	3:1
10	**i**	O	5-CO_2Me	OMe	60	1:1

[a] See Supporting Information for detailed experimental procedures. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture.

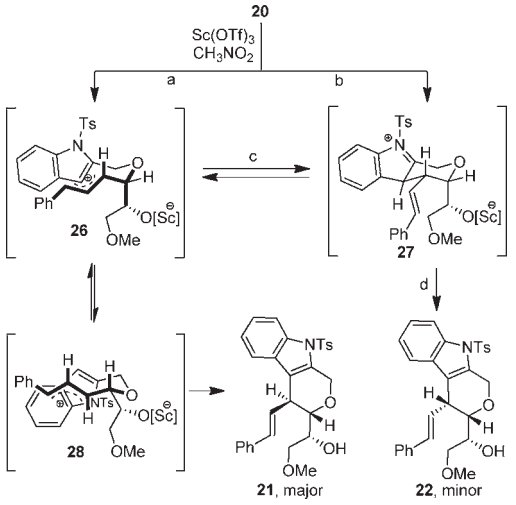
An investigation of the reaction scope revealed an interesting relationship between the electronic nature of the indole and the diastereoselectivity of the reaction. Analysis of the results in Table 1 reveals that a decrease in the electron density of the indole is accompanied by a decrease in the diastereoselectivity of the reaction. Our rationale for this trend is illustrated in Scheme 5. We envision two initial pathways for the reaction. Lewis acid mediated ionization of the dihydropyran may afford the open intermediate **26** (pathway *a*). Alternatively, S_N2' attack of the indole on the activated dihydropyran would lead to iminium **27** (pathway *b*). Bond rotation in **26** to relieve $A^{1,3}$-strain would provide **28**, which upon ring closure and rearomatization would yield *trans*-pyranoindole **21**. Iminium **27** could also undergo two possible reaction pathways, the

(15) (a) Xiong, X.; Pirrung, M. C. *Org. Lett.* **2008**, *10*, 1151–1154. (b) For examples of cycloisomerization occuring under Sonogashira conditions, see: Chen, Y.; Markina, N. A.; Larock, R. C. *Tetrahedron* **2009**, *65*, 8908–8915. (c) Heravi, M. M.; Sadjadi, S. *Tetrahedron* **2009**, *65*, 7761–7775.

(16) (a) Brown, G. R.; Foubister, A. J. *Eur. J. Med. Chem.* **1992**, *27*, 723–727. (b) Gopalsamy, A.; Aplasca, A.; Ciszewski, G.; Park, K.; Ellingboe, J. W.; Orlowski, M.; Feld, B.; Howe, A. Y. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 457–460.

first being C−C bond cleavage to return to the open intermediate **26** (pathway *c*). A second reaction manifold (pathway *d*) involves deprotonation to furnish *cis*-pyranoindole **22**. We hypothesize that the electron deficiency of the aromatic ring decreases the pK_a of the indolic proton prior to rearomatization making pathway *d* more favorable in these cases, thereby, increasing the proportion of the *cis*-isomer. Increasing electron density of the indole may favor S_N2' pathway *b*. However, based on our results we believe that stereodifferentiation to access *cis*-pyranoindole isomers (*cf.* **22**) occurs during pathways *c* and *d*.

Scheme 5. Proposed Mechanism for Pyranoindole Formation



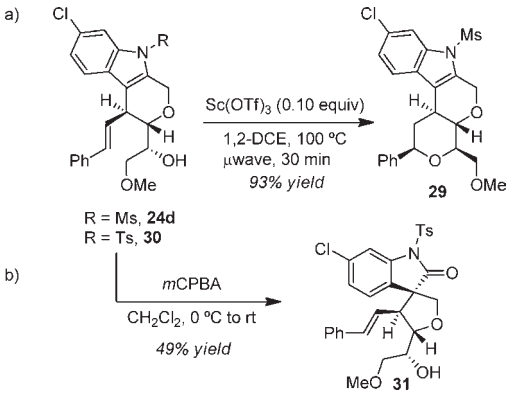
In order to increase the diversity of structures accessed using this methodology, we proceeded to investigate further reactions of the pyranoindole scaffolds. Precedent for the etherification of alkenols using metal triflates prompted us to investigate further cyclization of **24d** (Scheme 6a).[17] Indeed, microwave heating of **24d** in the presence of a catalytic amount of $Sc(OTf)_3$ in 1,2-dichloroethane provided *bis*-pyran **29** in 93% yield as a single diastereomer. The corresponding *cis*-isomer (**25d**) did not cyclize under these conditions and decomposed upon increasing the temperature and catalyst loading.

(17) (a) Coulombel, L.; Weïwer, M.; Duñach, E. *Eur. J. Org. Chem.* **2009**, 5788–5795. (b) Dzudza, A.; Marks, T. *Chem.—Eur. J.* **2010**, *16*, 3403–3422.

(18) (a) Adams, L. A.; Valente, M. W. N.; Williams, R. M. *Tetrahedron* **2006**, *62*, 5195–5200. (b) Movassaghi, M.; Schmidt, M. A.; Ashenhurst, J. A. *Org. Lett.* **2008**, *10*, 4009–4010.

Reports of the oxidative rearrangement of 2,3-substituted indoles prompted our investigation of the oxidation of pyranoindole **30** (Scheme 6b).[18] We anticipated that selective epoxidation of the indole 2,3-π bond, followed by ring contraction, would provide a rearranged spirooxindole. Indeed, subjection of pyranoindole **30** to *m*CPBA in CH_2Cl_2 produced spirooxindole **31** in 49% yield.

Scheme 6. (a) Etherification and (b) Oxidative Rearrangement of Pyranoindoles



In conclusion, we have developed syntheses of pyrano[3,4-*b*]indoles and pyrano[3,4-*b*]benzofurans containing an uncommon C3−C4 substitution pattern. The two-step procedure involves Sonogashira coupling of dihydropyran propargyl ether scaffolds with iodoanilines followed by Friedel−Crafts alkylation. Conditions to convert pyranoindoles into other scaffolds, including a *bis*-pyran and a spirooxindole, were also devised. Further studies using the methodology to access diverse chemical architectures are currently underway and will be reported in due course.

Acknowledgment. We gratefully acknowledge financial support from the NIGMS CMLD initiative (P50-GM67041). We also thank Drs. Paul Ralifo and Norman Lee (Boston University) for assistance with instrumentation and Dr. Jeffrey W. Bacon (Boston University) for X-ray crystallographic analysis.

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