JOC*Note*

Reduction of Pyrrolyl- and Indolylamides with $BH_3 \cdot THF$: Cyclodeoxygenation versus Deoxygenation

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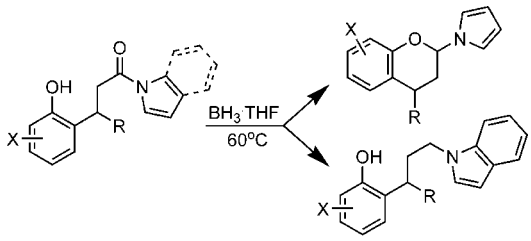
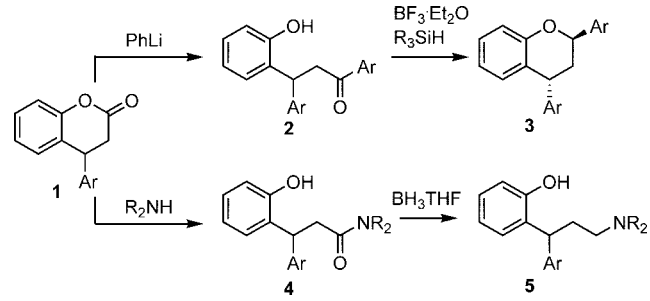


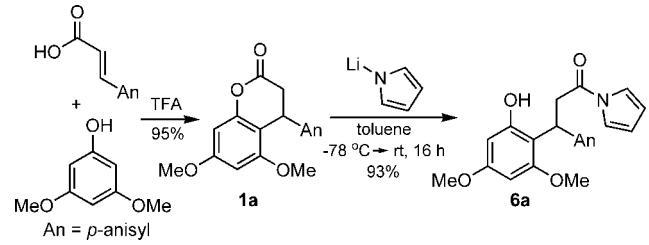
Herein we report that borane reductions of acylpyrroles and acylindoles that contain a pendant phenol take two different paths. Acylpyrroles undergo a reductive cyclization to make unusual chromanyl pyrroles. Treatment of related acylindoles under identical conditions results in deoxygenation without cyclization. The results are interpreted in terms of relative rates of cyclization and reduction of intermediate carbenium ions, where cyclization of the indole-stablized carbenium ion is slower.

Previously, we have reported that 2,4-diaryl chromans **3** can be conveniently obtained from phenols by a three-step procedure involving hydroarylation of cinnamic acids,[1] nucleophilic ring opening of the resulting lactone, and diastereoselective reduction using $BF_3 \cdot OEt_2/R_3SiH$.[2,3] While the reductive deoxygenation of the phenolic ketone **2** proceeds via a cyclodeoxygenation path, the reductive deoxygenation of the related amides provides the open-chain amines exclusively.[4] Given our interest in exploring the biological activity of these derivatives,[5] we became interested in extending this protocol to the use of heteroaromatic arenes. Herein we report an interesting bifurcation in the pathway of reductive deoxygenation of heteroaromatic amides with a pendant phenol.

SCHEME 1



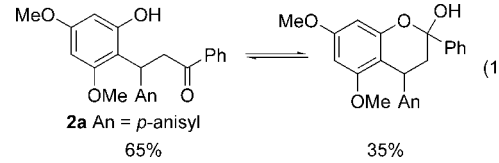
SCHEME 2



To begin, we synthesized dihydrocoumarin **1a** using our acid-catalyzed hydroarylation of phenols.[1] Next, we investigated the ring opening of the lactone with pyrrolyl lithium.[6] Overall, the two-step process provided acylpyrrole **6a** in 88% yield (Scheme 2).

With these conditions in hand, we extended the ring opening to the reaction of pyrrolyllithium with several different dihydrocoumarins. The results of the ring opening are summarized in Table 1.

The yields of the ring-opening products seem quite dependent on the substituents on the dihydrocoumarin core but are generally acceptable and can be quite high. In addition, performing the acyl substitution with indolyl lithium reagents gives yields that are comparable to those obtained using pyrrolyl lithium (**7a,b**, Table 1).[7] It is interesting that ^1H NMR spectroscopic analysis shows that these products all exist primarily as the open-chain phenolic amides **6**. This is in contrast to the analogous benzenoid ketones (**2**), which exist in equilibrium with the cyclic hemiacetal (eq 1).[2] It is perhaps even more surprising in light of the remarkable stability exhibited by tetrahedral intermediates derived from acylpyrroles and acylindoles.[8]



Next, we subjected the *N*-acylpyrrole **6a** to the conditions that we had used previously for the reductive deoxygenation of aliphatic amides (**4**).[4a] To our surprise, the major product of

(1) Li, K.; Tunge, J. A. *J. Org. Chem.* **2005**, *70*, 2881–2883.
(2) Li, K.; Tunge, J. A. *Org. Lett.* **2006**, *8*, 4711–4714.
(3) (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978. (b) Wang, Y.; Babirad, S. A.; Kishi, Y. *J. Org. Chem.* **1992**, *57*, 468–481. (c) Ellsworth, B. A.; Doyle, A. G.; Patel, M.; Caceres-Cortes, J.; Meng, W.; Deshpande, P. P.; Pullockaran, A.; Washburn, W. N. *Tetrahedron: Asymmetry* **2003**, 3242–3247. (d) Terauchi, M.; Abe, H.; Matsuda, A.; Shuto, S. *Org. Lett.* **2004**, *6*, 3751–3754.
(4) (a) Li, K.; Tunge, J. A. *J. Comb. Chem.* **2008**, *10*, 170–174. (b) Bussolari, J. C.; Rehborn, D. C.; Combs, D. W. *Tetrahedron Lett.* **1999**, *40*, 1241–1244.

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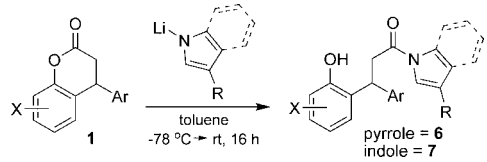
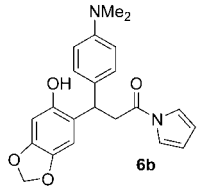
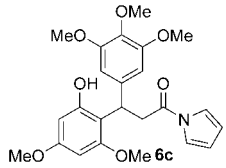
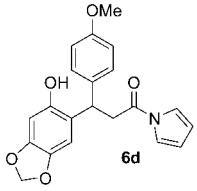
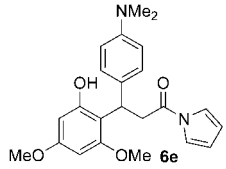
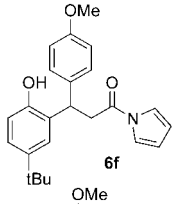
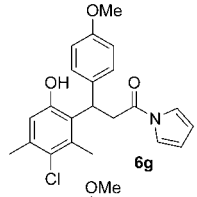
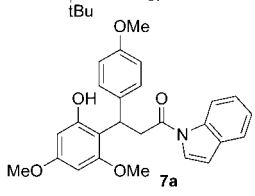
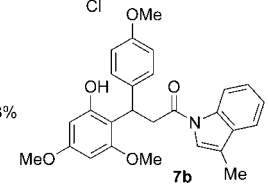
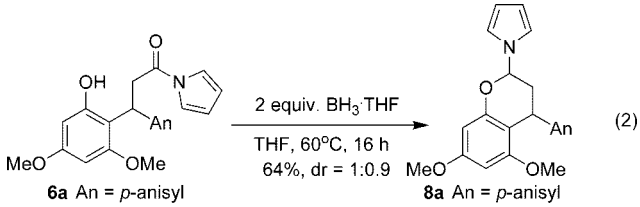
TABLE 1. Synthesis of Acylpyrroles and Acylindoles



Product	Yield	Product	Yield
 **6b**	82%	 **6c**	48%
 **6d**	56%	 **6e**	91%
 **6f**	52%	 **6g**	46%
 **7a**	73%	 **7b**	86%

the reduction was that of reductive cyclization to form the chroman derivative **8a** as a 1:0.9 mixture of diastereomers (eq 2).

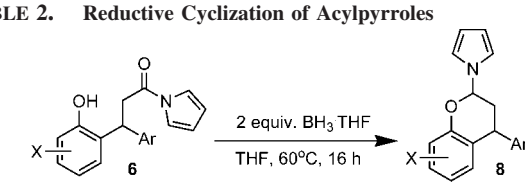


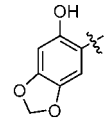
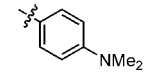
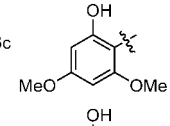
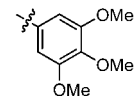
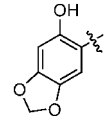
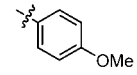
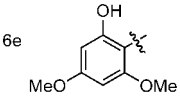
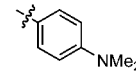
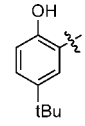
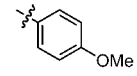
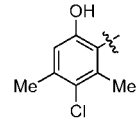
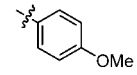
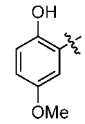
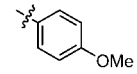
(2)

Given that we had previously shown that aromatic ketones undergo reductive cyclization under typical $BF_3 \cdot OEt_2/R_3SiH$ deoxygenation conditions,[2,3] we hypothesized that acylpyrroles behave more like aromatic ketones than amides. However, treatment of substrate **6a** with $BF_3 \cdot OEt_2/Et_3SiH$, which effected the reductive cyclization of related aromatic ketones, led to a complex mixture that did not contain any of the reductive cyclization product **8a**. Similarly, the arylketone substrates (**2**) do not give cyclized products when treated with BH_3. These results indicate that the reduction of arylketones and acylpyrroles proceed via different mechanisms.

Next, we briefly investigated the generality of the reductive cyclization; the results are shown in Table 2. All substrates react

TABLE 2. Reductive Cyclization of Acylpyrroles



substrate	phenol	Ar	yield	dr
6b			65%	1:0.6
6c			68%	1:0.8
6d			77%	1:0.6
6e			60%	1:0.6
6f			60%	1:0.7
6g			86%	1:0.9
6h			74%	1:0.7

to give chromanyl pyrroles, and the yields are generally good, ranging from 60% to 86%.[9] Unfortunately, the diastereoselectivities are generally poor, and the pattern of substituents on the arene rings has little effect on the diastereomeric ratios. Nonetheless, (pyrrolyl)tetrahyrdropyrans of this type are quite rare in the literature,[10,11] yet they may find uses similar to those found for the more common (indolyl)tetrahydropyrans.[12]

With the goal of accessing the (indolyl)benzopyrans through the same methodology, we treated the acylindole species (**7**) under the same conditions that gave rise to reductive cyclization

(5) Chromans are biologically "privileged" structures: Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.

(6) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440–1456.

(7) (a) Nakagawa, M.; Sodeoka, M.; Yamaguchi, K.; Tohru, H. *Chem. Pharm. Bull.* **1984**, *32*, 1373–1384. (b) Katritzky, A. R.; Robinson, R. *J. Chem. Soc.* **1955**, 2481–2485.

(8) (a) Arai, E.; Tokuyama, H.; Linsell, M. S.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 71. (b) Evans, D. A.; Borg, G.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3188–3191.

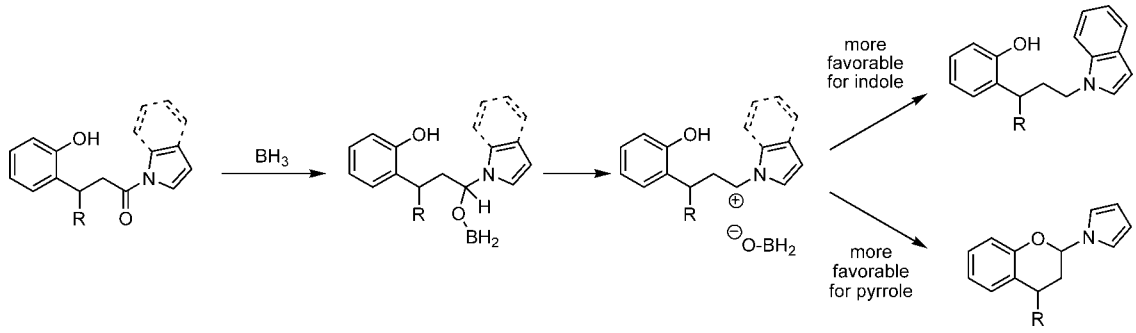
(9) For the synthesis of chromenylpyrroles, see: (a) Nahas, N. M.; Abdel-Hafez, A. A. *Heterocycl. Commun.* **2005**, *11*, 263–272.

(10) (a) Kawana, M.; Sakae, E. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3539–3546. (b) Kawana, M.; Sakae, E. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2552.

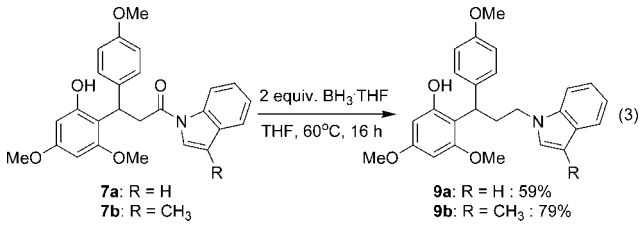
(11) For related tetrahydrofuran derivatives, see: (a) Kawana, M. *Chem. Lett.* **1981**, 1541–1542. (b) Kawana, M.; Sakae, E. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3539–3546.

(12) (a) Reyes, F.; Fernandez, R.; Rodriguez, R.; Santiago, B.; de Eguilior, C.; Francesch, A.; Cuevas, C. *J. Nat. Prod.* **2008**, *71*, 1046–1048. (b) Bouchikhi, F.; Anizon, F.; Moreau, P. *Eur. J. Med. Chem.* **2008**, *43*, 755–762. (c) Mukherjee, D.; Sarkar, S. K.; Chowdhury, U. S.; Taneja, S. C. *Tetrahedron Lett.* **2007**, *48*, 663–667. (d) Libnow, S.; Hien, M.; Michalik, D.; Langer, P. *Tetrahedron Lett.* **2006**, *47*, 6907–6909.

SCHEME 3



of the acylpyrroles (eq 3). Interestingly, these substrates react to provide the open-chain indole derivatives (**9**) that are aromatic derivatives of the antimuscarinic pharmaceutical tolterodine.[13,14] Thus, the reactivity that is observed for the acylindoles is that expected for the "standard" reductive deoxygenation of amides with $BH_3 \cdot THF$.[15]



Finally, we would like to explain the interesting bifurcation in reaction paths taken by acylindoles and acylpyrroles. Our failure to achieve reductive cyclization of acylpyrroles using Et_3SiH/BF_3 suggests that the cyclization does not take place via lactol and oxocarbenium ion intermediates.[2] Thus, the mechanism for reduction of acylpyrroles and acylindoles likely proceeds through free carbenium ion intermediates. The stabilized carbenium ions can form after hydride reduction of the carbonyl followed by ionization of the resulting borate (Scheme 3). At this point, the pyrrole stabilized carbenium ion is expected to be more reactive and more sterically accessible than the indole-stabilized carbenium ion.[16] Thus, intramolecular trapping of the carbenium ion by the phenol is rapid. In contrast, the more stabilized and sterically larger indolyl carbenium ion does not cyclize; rather it reacts with the small borane reducing agent.

In conclusion, we have developed a reductive cyclization of acylpyrroles that gives rise to chromanyl pyrroles. Evaluation of the biological activities of compounds having this uncommon scaffold is ongoing.

Experimental Section

General Procedure for the Addition of Lithium Pyrrol-1-ide to Dihydrocoumarins. Pyrrole (0.48 mL, 0.96 mmol) was dissolved in THF (2 mL) and cooled to −78 °C, and LDA (0.48 mL, 0.96 mmol) was added. The resulting solution of pyrrolyl lithium was added dropwise to a suspension of dihydrocoumarin **1** (0.64 mmol) in toluene (15 mL) at −78 °C. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 16 h. At this point, the reaction was quenched by addition of saturated $NaHCO_3$ (10 mL) and extracted with EtOAc (50 mL). The resulting organic layer was dried ($MgSO_4$) and concentrated on a rotary evaporator. The residue was purified by flash column chromatography.

General Procedure for the Borane Reduction of Substrates 6 and 7. The heteroaromatic amide **6** or **7** (0.15 mmol) was dissolved in THF (2 mL), and $BH_3 \cdot THF$ (1 M, 2 equiv) was added dropwise. The resulting solution was heated to 60 °C for 16 h. At this point the reaction was quenched with methanol (1 mL), and the solvents were removed under vacuum. The remaining residue was purified by flash column chromatography.

Acknowledgment. We acknowledge support of this work by the National Institutes of Health (KU Chemical Methodologies and Library Development Center of Excellence, P50 GM069663). We are grateful for the analytical assistance of Ben Neuenswander.

Supporting Information Available: General experimental, complete compound characterization data, and copies of NMR spectra and chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801627Z

(13) (a) Appell, R. A. *Urology* **1997**, *50*, 90–96. (b) Modiri, A. R.; Alberts, P.; Gillberg, P. G. *Urology* **2002**, *59*, 963–968.

(14) Related acylaniline derivatives also undergo reductive deoxygenation without cyclization.

(15) Brown, H. C.; Heim, P. *J. Org. Chem.* **1978**, *38*, 912–916.

(16) Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem. Eur. J.* **2003**, *9*, 2209–2218.