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Synthesis of Fused 4,5-Disubstituted Indole Ring Systems by Intramolecular Friedel−Crafts Acylation of 4-Substituted Indoles

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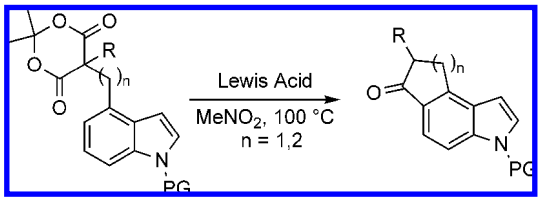
Received December 4, 2007



4-Substituted indoles containing a variety of electrophiles and *N*-substituents undergo Friedel−Crafts acylation to give exclusively the products of cyclization at the 5-position of indole. These indanones and tetralones have been scarcely prepared and are subunits in natural products and analogues of potential biological significance.

Indole-containing natural products and bioactive molecules represent a substantial portion of alkaloids, and as such have been the subject of innumerable synthetic forays. We were particularly interested in 3,4-bridged and 4,5-fused indole-containing molecules (indole numbering), which include the ergot alkaloids[1] (such as festuclavine) and hapalindoles/ambiguines[2] and lolitrems and lolicines,[3] respectively (Figure 1).

Retrosynthetically, intramolecular Friedel−Crafts (FC) acylation of 4-substituted indoles appears to be a logical disconnection to access these ring systems. FC acylation has been among the most powerful and widely used means of functionalizing arenes, which makes the lack of examples of this reaction as it pertains to 4-substituted indoles surprising.[4,5] FC acylation with Vilsmeier−Haack reagents derived from *N*,*N*-dimethylamides, reported by Ishikawa,[6] and carboxylic acids, reported by Spadoni,[7] cyclize from the 4- to the 3-position of indole exclusively (Scheme 1a).[8] In both of these cases, the indole nitrogen was unprotected, although in the latter case the 5-position was blocked. Boger disclosed the cyclization of an acid chloride to the 5-position in a comparatively deactivated 2-carbomethoxyindole (Scheme 1b). Indoles containing this 4,5-indanone motif are of medicinal relevance as such a substructure, appended to the CPI unit of CC-1065, greatly increases the cytotoxicity of the analogues.[9]

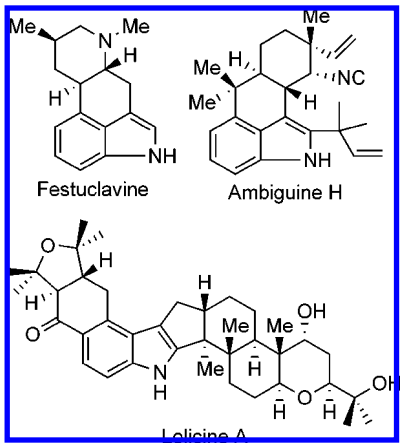
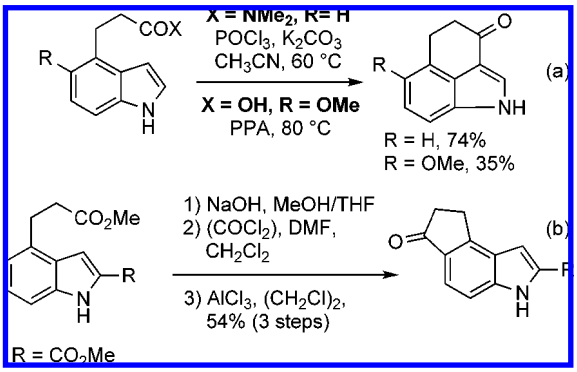


FIGURE 1. Examples of 3,4- and 4,5-substituted indole natural products.

SCHEME 1. Intramolecular FC Acylation of 4-Substituted Indoles To Yield 3,4-Bridged and 4,5-Fused Products



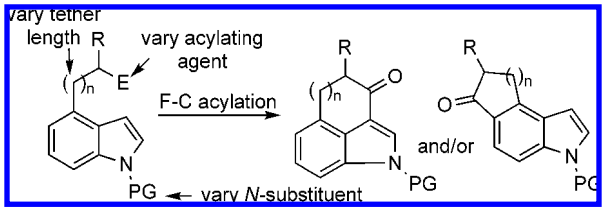
Based on this precedent, the factors affecting the regioselectivity of the acylation are unclear. Considering the potentially wide range of products available by these routes, we undertook a study of the regioselectivity of FC acylations of 4-substituted indoles. These studies focused on the effect of changing the electrophile, the *N*-protecting group, and the tether length (Scheme 2).

The intramolecular FC acylation of Meldrum's acid derivatives was chosen as the initial probe reaction, as the molecules are easily prepared and functionalized, but are highly reactive FC acylating agents.[10] These are conveniently synthesized by Knoevenagel condensation of an aldehyde with Meldrum's acid (**3**).[11] In this case, the π-nucleophilicity of indole-4-carboxal-

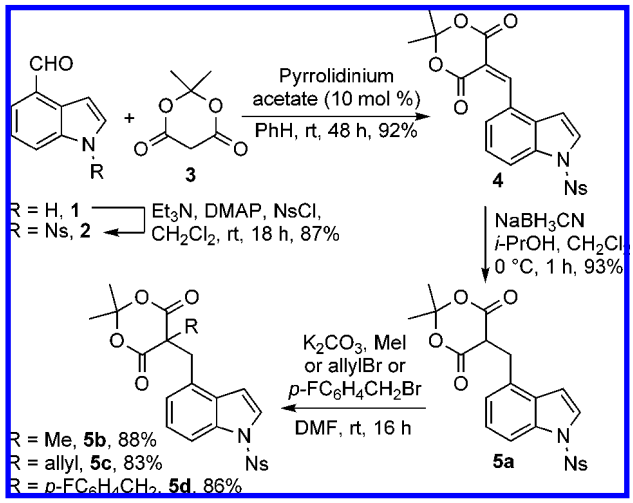
(1) Řeháček, Z.; Sajdl, P. *Ergot Alkaloids: Chemistry, Biological Effects, Biotechnology*; Elsevier: New York, 1990.
(2) Isolation of ambiguine H: Smitka, T. A.; Bonjouklian, R.; Doolin, L.; Jones, N. D.; Deeter, J. B. *J. Org. Chem.* **1992**, *57*, 857−861.
(3) Isolation of lolicine A: Munday-Finch, S. C.; Wilkins, A. L.; Miles, C. O. *J. Agric. Food Chem.* **1998**, *46*, 590−598.
(4) Examples of FC alkylation of 4-substituted indoles: (a) Natsume, M.; Muratake, H. *Tetrahedron Lett.* **1989**, *30*, 1815−1818. (b) Matsumoto, M.; Watanabe, N.; Kobayashi, H. *Heterocycles* **1987**, *26*, 1479−1482.
(5) A related anionic cyclization of a 4-substituted indole to the 3-position was reported in a total synthesis of lysergic acid: Hendrickson, J. B.; Wang, J. *Org. Lett.* **2004**, *6*, 3−5.
(6) Kurokawa, M.; Watanabe, T.; Ishikawa, T. *Helv. Chim. Acta* **2007**, *90*, 574−587.
(7) Spadoni, G.; Balsamini, C.; Diamantini, G.; Di, Giacomo, B.; Tarzia, G.; Mor, M.; Plazzi, P. V.; Rivara, S.; Lucini, V.; Nonno, R.; Pannacci, M.; Fraschini, F.; Stankov, B. M. *J. Med. Chem.* **1997**, *40*, 1990−2002.
(8) For an example of cyclization from the 3- to the 4-position of indole, see: Komoda, T.; Nakatsuka, S. *Heterocycl. Commun.* **2003**, *9*, 119−122.
(9) Boger, D. L. Int. Patent WO2004101767, 2004.

10.1021/jo702591p CCC: $40.75
Published on Web 03/06/2008

SCHEME 2. Planned Study of FC Acylation of 4-Substituted Indoles



SCHEME 3. Preparation of *N*-Ns-indolyl Meldrum's Acid Derivatives



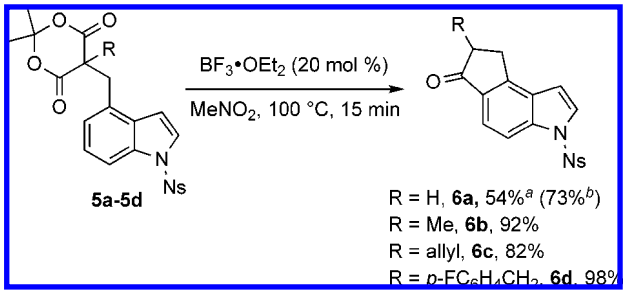
dehyde (**1**) was attenuated by protection as the 4-nitrophenylsulfonyl (Ns) derivative **2** to prevent intermolecular FC alkylation of indole by the alkylidene Meldrum's acid, a reaction which occurs readily.[12] Condensation of **2** proceeded cleanly, and reduction of **4** with $NaBH_3CN$ and alkylation with various electrophiles gave substrates **5a**−**d** suitable for Lewis acid-catalyzed FC acylation (Scheme 3).

Acylation was performed under conditions previously used for reaction of phenyl-containing Meldrum's acid derivatives.[10] Under BF_3•OEt_2 catalysis, all substrates cyclized exclusively at the 5-position of indole; in no case were the products of 3-position cyclization detected in the ^1H NMR of the crude reaction mixture. Enolizable Meldrum's acid **5a** reacted in much lower yield; the yield increased under $Yb(OTf)_3$ catalysis and with equal selectivity (Scheme 4).

The same regioselectivity was observed in spirocyclic Meldrum's acid derivative **7**. This was obtained by thermal Diels−Alder reaction of alkylidene Meldrum's acid **4** followed by BF_3•OEt_2-promoted FC acylation in 1,2-dichloroethane (Scheme 5).[13] At this point, it was clear that substitution of groups not directly involved in the acylation had no effect on the regioselectivity.

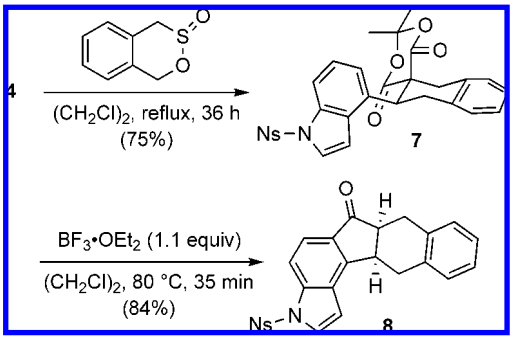
Therefore, deprotection of the Ns group[14] to give more electron-rich *N*-H indoles was performed in order to determine

SCHEME 4. Intramolecular FC Acylation of Meldrum's Acid Derivatives

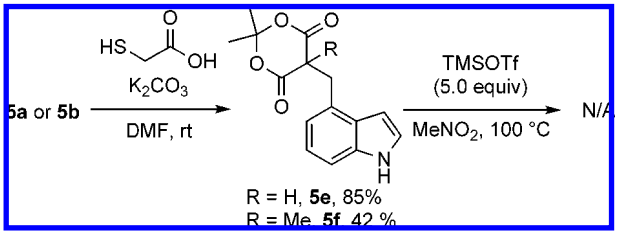


[a] Reaction time 30 min. [b] Reaction performed with 10 mol % of $Yb(OTf)_3$, heating for 6 min.

SCHEME 5. Intramolecular FC Acylation of Spiro Meldrum's Acid Derivatives



SCHEME 6. Attempted FC Acylation of *N*-H Indoles



the extent to which regioselectivity is controlled by π-nucleophilicity. However, under conditions previously successful for the FC acylation of reactive-nitrogen containing aromatics with Meldrum's acid derivatives,[10a] no cyclized products could be isolated from the reactions of **5e** and **5f**. Rather, a complex mixture indicative of decomposition was produced (Scheme 6).

The propensity of these acylations to occur at the 5-position is in one sense counterintuitive, in that the 3-position is typically the most electron-rich and π-nucleophilic portion of indoles.[15] As well, we had previously shown that 6-membered rings form faster than 5-membered ones in FC acylation using Meldrum's acid derivatives.[10a] However, intermolecular FC reactions of indoles can occur with unexpected regioselectivity depending on the electrophile and *N*-substituent.[16]

Because of a lack of precedent for FC acylations of *N*-Ns indoles, it was not clear if this deactivating protecting group was altering 3-position nucleophilicity in favor of a more

(10) (a) Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. *J. Org. Chem.* **2005**, *70*, 1316−1327. (b) Fillion, E.; Fishlock, D. *Org. Lett.* **2003**, *5*, 4653−4656.

(11) Dumas, A. M.; Seed, A.; Zorzitto, A. K.; Fillion, E. *Tetrahedron Lett.* **2007**, *48*, 7072−7074.

(12) (a) Boisbrun, M.; Jeannin, L.; Toupet, L.; Laronze, J.-Y. *Eur. J. Org. Chem.* **2000**, 3051−3057. (b) Jeannin, L.; Nagy, T.; Vassileva, E.; Sapi, J.; Laronze, J.-Y. *Tetrahedron Lett.* **1995**, *36*, 2057−2058. (c) Oikawa, Y.; Hirasawa, H.; Yonemitsu, O. *Tetrahedron Lett.* **1978**, *20*, 1759−1762.

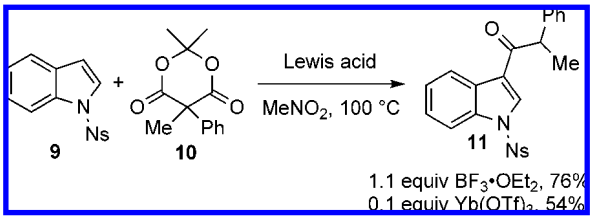
(13) Fillion, E.; Dumas, A. M.; Hogg, S. A. *J. Org. Chem.* **2006**, *71*, 9899−9902.

(14) Davies, J. R.; Kane, P. D.; Moody, C. J.; Slawing, A. M. Z. *J. Org. Chem.* **2005**, *70*, 5840−5851.

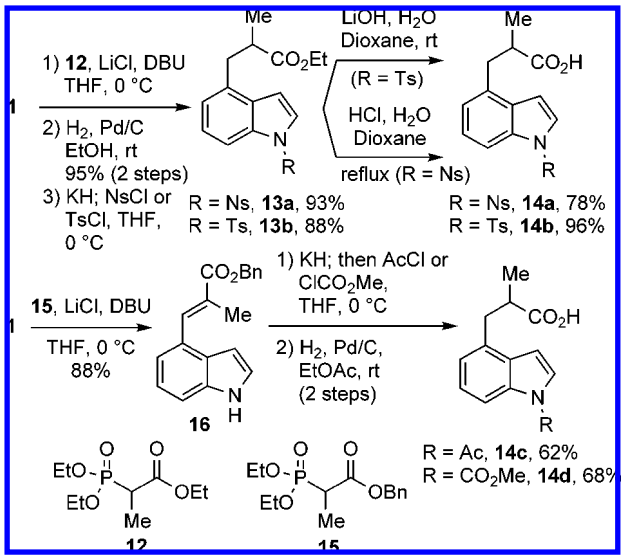
(15) Lakhdar, S.; Westermaier, M.; Terrier, F.; Goumont, R.; Boubaker, T.; Ofial, A. R.; Mayr, H. *J. Org. Chem.* **2006**, *71*, 9088−9095.

(16) Sundberg, R. J. *Best Synthetic Methods: Indoles*; Academic Press: San Diego, CA, 1996; pp 136−137.

SCHEME 7. Intermolecular FC Acylation of *N*-Ns Indole



SCHEME 8. Preparation of 3-(4-Indolyl)propanoic Acid Derivatives

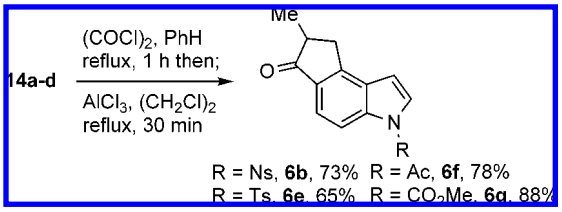


reactive 5-position. However, *intermolecular* FC acylation of *N*-Ns indole **9** with disubstituted Meldrum's acid derivative **10**, promoted by either BF_3•OEt_2 or $Yb(OTf)_3$, gave the 3-acylated product **11** exclusively (Scheme 7).[17] This suggests that although the 3-position in *N*-Ns indoles **5a**−**d** is more nucleophilic than the 5-position, the difference in nucleophilicity is insufficient to overcome the kinetic preference for formation of the 4,5-fused product.

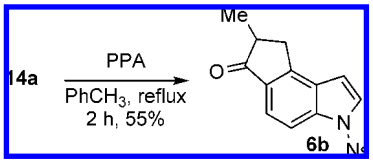
To explore the effect of different electrophiles and *N*-protecting groups, 3-(4-indolyl)propanoic acids were synthesized (Scheme 8). α-Secondary carboxylic acids were used to be as similar to the Meldrum's acid substrate **5a** as possible. All were prepared from indole-4-carboxaldehyde by various routes outlined in Scheme 8. Substrates containing *N*-sulfonamide indoles were synthesized by HWE reaction and hydrogenation of the crude unsaturated ester in high yield. Subsequent *N*-protection, followed by base hydrolysis of **13b** gave the carboxylic acid. Acid hydrolysis of **13a** was needed to avoid cleaving the sensitive *N*-Ns derivative.[18] A shorter route was developed to prepare *N*-carbonyl derivatives **14c** and **14d**, as both *N*-Ac and *N*-CO_2Me groups were cleaved by acid or base hydrolysis. Therefore, the unsaturated benzyl ester **16** was prepared; *N*-protection and simultaneous reduction of the alkene and benzyl ester gave **14c** and **14d**.

FC acylation of these substrates was performed by derivatization to the acid chloride, followed by treatment with $AlCl_3$ in refluxing $(CH_2Cl)_2$. Both the *N*-sulfonamide and *N*-carbonyl derivatives reacted to give the substituted indanones **6b/6e**−**g** as the only detectable cyclized product (Scheme 9). This corresponds with the results of Boger,[6] in that 3-(4-indolyl)-propanoyl chlorides containing electron-withdrawing substituents cyclize at the 5-position.

SCHEME 9. FC Acylation of Various *N*-Protected 3-(4-Indolyl)propanoyl Chlorides



SCHEME 10. FC Acylation of *N*-Ns 3-(4-Indolyl)propanoic Acid



These results, in comparison with the reactions of Meldrum's acid derivatives **5a**−**d**, suggest that the nature of the electrophile plays a less important role in determining the regioselectivity than do the substituents on the indole. In this regard, it was concluded that electron-withdrawing *N*-substituents favor cyclization at the 5-position. This was further confirmed by the direct acylation of the carboxylic acid **14a** with PPA, which again cyclized exclusively at the 5-position (Scheme 10).

The above examples all involved the competitive formation of either a six-membered 3,4-substituted or five-membered, 4,5-substituted indole. However, it was unknown whether a longer chain length (extended by one methylene unit) would affect the regioselectivity of the FC acylation. A Meldrum's acid derivative with the appropriate tether length was synthesized from known and easily prepared *N*-tosyl-4-cyanomethylindole **17**.[19] Acid hydrolysis of the nitrile, followed by DCC-promoted condensation of indoleacetic acid **18** with Meldrum's acid and *in-situ* reduction of the resulting alkylidene with $NaBH_4$, gave the enolizable Meldrum's acid derivative **19a**.[20] Methylation under standard conditions gave the quaternized product **19b** (Scheme 11).

Meldrum's acid substrates **19a** and **19b** were cyclized under $Yb(OTf)_3$-catalysis in $MeNO_2$ at 100 °C. In both cases, the products were exclusively the result of acylation at the 5-position to give tetralones **20a** and **20b** (Scheme 12). This motif is a privileged substructure of the tremorgenic natural product family, and as such a convenient and simple route is potentially of value.[21]

These results clearly demonstrate that cyclization of 4-substituted indoles to the 5-position is the preferred mode for indoles

(17) The position of acylation was determined unambiguously based on the disappearance of the signal for the C-3 proton and $^1H-^1H$ COSY correlations.

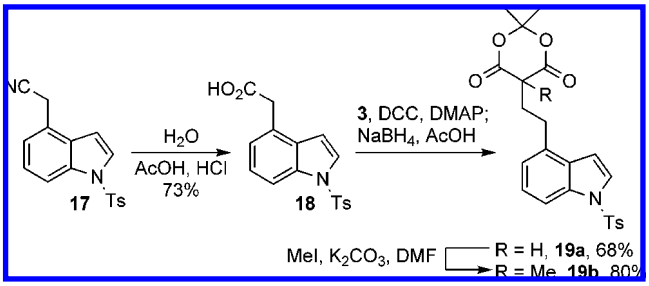
(18) For example, *N*-Ns indole **9** is rapidly (3 h) and quantitively deprotected by aqueous LiOH in DMF or 1,4-dioxane at rt.

(19) Ponticello, G. S.; Baldwin, J. J. *J. Org. Chem.* **1979**, *44*, 4003−4005.

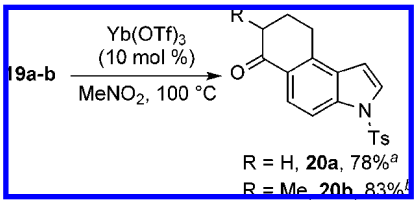
(20) (a) Hin, B.; Majer, P.; Tsukamoto, T. *J. Org. Chem.* **2002**, *67*, 7365−7368. (b) Smrcina, M.; Majer, P.; Majerová, E.; Guerassina, T. A.; Eissenstat, M. A. *Tetrahedron* **1997**, *53*, 12867−12874.

(21) The only other reported route to these tetralones was disclosed by Kerr, who prepared an acyclic 4,5-disubstituted indole and built the tetralone by a clever domino process involving the non-aromatic portions of the molecule. See: England, D. B.; Magolan, J.; Kerr, M. A. *Org. Lett.* **2006**, *8*, 2209−2212.

SCHEME 11. Preparation of Extended Tether FC Acylation Substrates



SCHEME 12. Synthesis of 4,5-Disubstituted Indolyl Tetralones



[a] Reaction time 1.75 h. [b] Reaction time 30 min.

protected with electron-withdrawing *N*-substituents. This selectivity is general across a range of electrophiles, Lewis acids, *N*-protecting groups, and tether lengths. The regioselectivity observed for these substrates is noteworthy, as in no case was there evidence of the 3,4-disubstituted product. Therefore, the intramolecular FC acylation of 4-substituted indoles is a convenient means of preparing *N*-protected, 4,5-fused indole ring systems. As some of these motifs have potential medical applications, and considering that the scarcity of reported procedures for their preparation has limited biological evaluation of these structures, this methodology may be of further use.

Experimental Section

General Procedure A: FC Acylation of Meldrum's Acid Derivatives 5a−d. An oven-dried Schlenk flask cooled under nitrogen was charged with Meldrum's acid derivative (0.2 mmol, 1.0 equiv) and dissolved in 0.8 mL of $MeNO_2$. $BF_3{\cdot}OEt_2$ (5.0 μL, 0.04 mmol, 0.2 equiv) was washed into the flask with 0.5 mL of $MeNO_2$. The flask was sealed tightly and placed in a temperature controlled oil bath at 100 °C. After 15 or 30 min, the flask was removed from the bath and cooled to rt. The contents were rinsed into a round-bottom flask with CH_2Cl_2 and concentrated. Purification by flash column chromatography yielded the cyclized products.

General Procedure B: FC Acylation of Carboxylic Acids 14a−d. Carboxylic acid (0.1 mmol, 1.0 equiv) was dissolved in benzene (1.0 mL) in a flask equipped with an oven-dried, water-cooled condenser. To this was added distilled $(COCl)_2$ (35 μL, 0.4 mmol, 4.0 equiv) at rt, and the solution heated to reflux for 1 h. The flask was removed from heat, cooled to rt, and concentrated by rotary evaporation. The residue was dissolved in benzene (2 mL) and concentrated, followed by the same procedure with $(CH_2Cl)_2$ (2 × 2 mL). The resulting crude acid chloride was dissolved in $(CH_2Cl)_2$ (2 mL) at rt, and $AlCl_3$ (40 mg, 0.3 mmol, 3.0 equiv) was added. The suspension was heated to reflux for 30 min, cooled to rt, and quenched with saturated $NaHCO_3$ (10 mL). The reaction was poured into a separatory funnel and the layers separated; the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography or recrystallization yielded the indanones.

Cyclized product **6b** was obtained as an off-white powder in 92% yield (68 mg) from **5b** by procedure A and in 73% yield (27 mg) from **14a** by procedure B: mp 189−191 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.28 (dd, J = 7.0, 1.9 Hz, 2H), 8.06 (dd, J = 7.0, 1.9 Hz, 2H), 7.99 (d, J = 8.6 Hz, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.67 (d, J = 3.7 Hz, 1H) 6.95 (d, J = 3.6 Hz, 1H), 3.49 (dd, J = 17.4, 7.6 Hz, 1H), 2.83−2.73 (m, 2H), 1.31 (d, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.2 (C), 150.9 (C), 148.7 (C), 143.1 (C), 137.9 (C), 132.6 (C), 128.2 (overlapping C and 2 × CH), 127.1 (CH), 124.7 (2 × CH), 120.7 (CH), 113.0 (CH), 108.4 (CH), 41.9 (CH), 33.4 (CH_2), 16.5 (CH_3); HRMS(EI) *m/z* calcd for $C_{18}H_{14}N_2O_5S$ (M^+) 370.0623, found 370.0631.

Acknowledgment. This work was supported by the Merck Frosst Centre for Therapeutic Research, AstraZeneca Canada Inc., NSERC, CFI, OIT, and the University of Waterloo. A.M.D. thanks the Governments of Canada and Ontario and the University of Waterloo for graduate scholarships.

Supporting Information Available: Procedures for preparation of all new starting materials and products and characterization and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702591P