Spiroquinazoline Support Studies: New Cascade Reactions Based on the Morin Rearrangement

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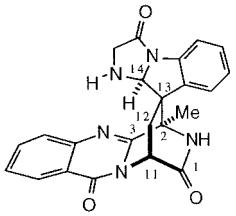
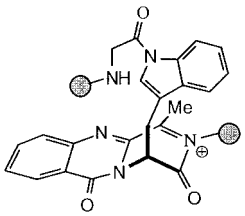
Spiroquinazoline (**1**) is a fungal metabolite produced by *Aspergillus flavipes* that inhibits binding of substance-P to the human NK-1 receptor, a property that renders it a potential lead compound for the preparation of analgesics.[2−5] We have been pursuing a biomimetic approach to spiroquinazoline that involves a projected cascade cyclization of an *N*-acyliminium ion of type **2**. These studies have uncovered an unusual cascade reaction based on the Morin penam−cepham interconversion as described herein.[6]



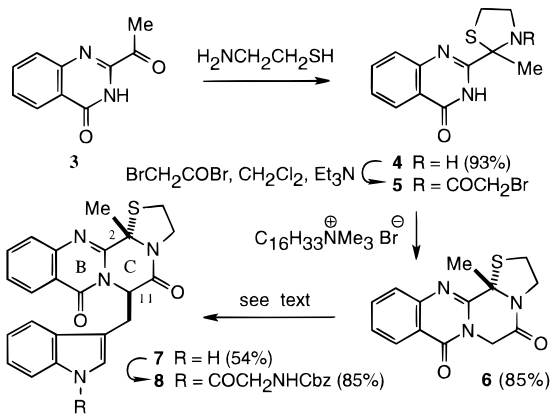
1



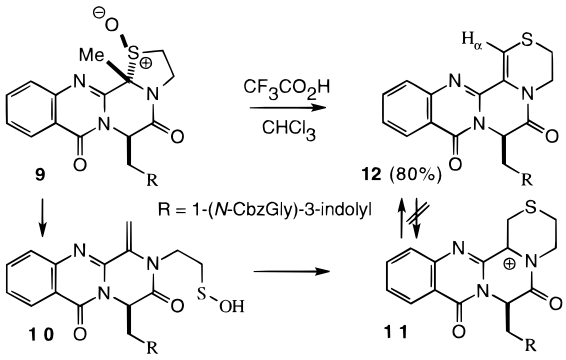
2

Our initial target for synthesis was thiazolidine **8**. It was imagined that ionization of the carbon−sulfur bond would provide an *N*-acyliminium ion of type **2**. A synthesis of racemic **8** is outlined in Scheme 1. Treatment of quinazolinone **3**[7] with 2-aminoethanethiol hydrochloride and triethylamine gave *N*,*S*-acetal **4** in 93% yield. Treatment of **4** with α-bromoacetyl bromide (1.2 equiv) in dichloromethane−aqueous sodium carbonate (1 M) gave **5**. Addition of hexadecyltrimethylammonium bromide (0.05 equiv) directly to the reaction mixture provided **6** in 85% overall yield. Sequential treatment of **6** with lithium diisopropylamide (2.2 equiv) and Li_2CuCl_4 (0.1 equiv) in tetrahydrofuran at −78 °C followed by addition of gramine methosulfate (1.2 equiv) provided a 54% yield of **7** along with 11% of the corresponding C_{11}-diastereomer.[8] The stereochemical assignments for **7** and its C_{11}-diastereomer were based on the chemical shifts of the C_2 methyl groups which appeared at δ 0.86 in **7** and δ 1.83 in its diastereomer.[9] The structure of **7** was also

Scheme 1



Scheme 2



confirmed by X-ray crystallography which indicated that the C-ring folds into a boatlike conformation in which the indole group shields the C_2 methyl group and projects away from the B-ring, as in spiroquinazoline. Treatment of **7** with *p*-nitrophenyl *N*-Cbz-glycinate (1.5 equiv), KF (2.0 equiv), 18-crown-6 (1.0 equiv), and diisopropylethylamine (1.2 equiv) in acetonitrile with sonication gave the target structure **8** in 85% yield along with 13% of recovered **7**.[10] It is notable that the C_2 methyl group in **8** appears at δ 1.73, perhaps a reflection of the electron-withdrawing effect of the *N*-acyl group. It is also notable that X-ray crystallography indicates that in the solid state **8** adopts a conformation in which the C-ring is once again boatlike, but the indole now projects toward the B-ring.

Attempts to ionize **8** in a useful manner have thus far been unsuccessful.[11] However, the behavior of sulfoxide **9**, prepared as a single diastereomer in 92% yield by reaction of **8** with *m*-chloroperoxybenzoic acid at −78 °C in dichloromethane, has been interesting.[12] Warming **9** with chloroform−trifluoroacetic acid (10:1) at reflux for 20 h provided **12** in 80% yield (Scheme 2). The structure of **12** was based on spectroscopic data including the disappearance of the C_2 methyl group and appearance of H_α as a doublet (J = 1.6

(1) This paper is dedicated to Professor Harold Hart on the occasion of his 77th birthday.

(2) Barrow, C. J.; Sun, H. H. *J. Nat. Prod.* **1994**, *57*, 471.

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(4) For synthetic studies on biogenetically related natural products, see: He, F.; Snider, B. B. *Synlett* **1997**, 483. Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432. He, F.; Snider, B. B. *J. Org. Chem.* **1999**, *64*, 1597.

(5) For selected studies that address the problem of addition of electrophiles and nitrogen nucleophiles across the C_2−C_3 bond of indoles, see: Buchi, G.; DeShong, P. R.; Katsumura, S.; Sugimura, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5084. Nakagawa, M.; Taniguchi, M.; Sodeoka, M.; Ito, M.; Yamaguchi, K.; Hino T. *J. Am. Chem. Soc.* **1983**, *105*, 3709. He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417.

(6) Morin, R. B.; Jackson, B. G.; Mueller, R. A.; Lavagnino, E. R.; Scanlon, W. B.; Andrews, S. L. *J. Am. Chem. Soc.* **1969**, *91*, 1401. Morin, R. B.; Spry, D. O. *J. Chem. Soc., Chem. Commun.* **1970**, 335.

(7) Bergman, J.; Brynolf, A. *Tetrahedron* **1990**, *46*, 1295.

(8) Gelin, J.; Mortier, J.; Moyroud, J.; Chene, A. *J. Org. Chem.* **1993**, *58*, 3473.

(9) Anteunis, J. J. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 627.

(10) Klausner, Y. S.; Chorev, M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 627.

(11) Attempts to ionize sulfoxide **9** using a variety of electrophiles such as iodomethane, silver triflate, and mercuric triflate have failed thus far.

(12) The stereochemistry assigned to **9** in Scheme 2 is tentative and only reflects our expectations based on steric considerations.

(13) For relevant studies of the Morin rearrangement, see: Chioccara, F.; Oliva, L.; Prota, G.; Novellino, E. *Synthesis* **1978**, 744. Ueda, N.; Shimizu, H.; Kataoka, T.; Hori, M. *Tetrahedron Lett.* **1984**, *25*, 757. Lee, W. S.; Hahn, H. G.; Nam, K. D. *J. Org. Chem.* **1986**, *51*, 2789. Mah, H. D.; Lee, W. S. *J. Heterocyclic. Chem.* **1989**, *26*, 1447. Mah, H.; Nam, K. D.; Hahn, H.-G. *Heterocycles* **1997**, *45*, 1999.

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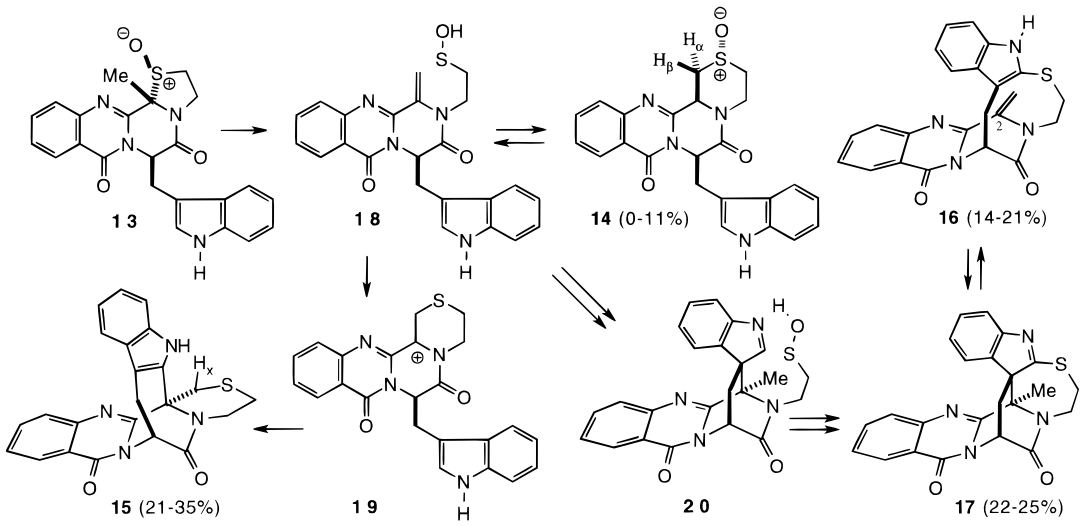
Scheme 3



Hz) at δ 6.89 ($CDCl_3$ at 70 °C). We imagine that **12** is formed by a process that is reminiscent of the Morin penam−cepham interconversion.[6,13] Thus, an elimination reaction could convert sulfoxide **9** into sulfenic acid **10**. Protonation and then electrophilic addition of the sulfenic acid to the resulting olefin would afford an *N*-acyliminium ion, and loss of a proton would afford **12**. Regardless of the mechanism of this rearrangement, we know that conversion of **12** to **11** under the reaction conditions does not occur because treatment of **12** with CF_3CO_2D under the reaction conditions does not result in any exchange of H_α.

Since it was clear that the *N*-acylindole was too electron-deficient to participate in an electrophilic aromatic substitution reaction under the sulfoxide rearrangement conditions, we next examined indole sulfoxide **13**, which lacked the *N*-acyl group. This substrate was prepared in 95% yield by *m*-chloroperoxybenzoic acid oxidation of **7**.[14] Heating **13** in chloroform−trifluoroacetic acid (10:1) for 40−50 h at reflux provided a complex, but clean, mixture of products that could be separated by a combination of chromatography and crystallization (Scheme 3). These products included sulfoxide **14** (0−11%),[15] bridged indoles **15** (21−35%) and **16** (14−21%), and spiro indoline **17** (22−25%).[16] The structures of **14** and **15** were based on spectroscopic data. The stereochemical assignment for **14** was based on the upfield appearance of H_β, adjacent to the sulfoxide, as a doublet of doublets (J = 14, 12 Hz) at δ 0.02 (CD_2Cl_2). The orientation of the indole group in **15** was based on the appearance of a 4% NOE observed at H_x upon irradiation of the indole N−H. The structure of **16** was consistent with spectroscopic data and was ultimately confirmed by X-ray crystallography. The structure of indoline **17** was consistent with spectroscopic data, and its relationship to **16** was established by their interconversion upon treatment with deuteriochloroform−trifluoroacetic acid.[17]

A possible mechanism for the formation of **14**−**17** is outlined in Scheme 3. Generation of sulfenic acid **18** from **13** followed by addition of the sulfenic acid to the resulting double bond with reverse orientation would provide sulfoxide **14**.[18] It is notable that **14** was the major product after only 1 h and that its concentration in the product mixture decreased over time with a corresponding increase in the concentrations of **15**−**17**. Addition of the sulfenic acid to the olefin in **18** followed by an electrophilic aromatic substitution reaction would provide **15**.[19,20] Protonation of **18** by trifluoroacetic acid, followed by trapping of the resulting *N*-acylaminium ion by C_3 of the indole, would provide indoline **20**. Addition of the sulfenic acid to the azomethine would provide an amino sulfoxide, and a Pummerer reaction would then provide **17**.[21] Protonation of the indoline nitrogen followed by a fragmentation would then provide **16**.

Several aspects of the chemistry shown in Scheme 3 are notable. For example, the preparation of **15** represents the first example of trapping, by a carbon nucleophile, of the presumed carbocation intermediate in the Morin rearrangement. From the standpoint of this approach to spiroquinazoline, the preparation of **17** demonstrates that an iminium ion generation−indole spirocyclization−intramolecular azomethine trapping cascade is feasible, but some redesign will be needed if this strategy is to eventually provide access to the natural product. Finally, the interconversion of **16** and **17** suggests that *N*-acyliminium ions of type **2** will be accessible via protonation of C_2 methylidene precursors and that trapping of such cations to provide indolines is feasible. This equilibrium also warns that fragmentation of an intermediate indoline is possible and that success of this strategy will depend on developing an indoline-trapping protocol that drives this equilibrium toward cyclized products.

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Supporting Information Available: ^1H and ^{13}C NMR spectra and experimental procedures for new compounds ORTEP drawings for compounds **7**, **8**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The stereochemistry assigned to **13** in Scheme 3 is tentative and only reflects our expectations based on steric considerations.

(15) Attempts to detect the product analogous to **14** in the rearrangement of **9** were unsuccessful.

(16) The yields represent the range obtained over several runs.

(17) Independent treatment of **16** and **17** with trifluoroacetic acid−chloroform at 65 °C for 30 min provided a 1:2 mixture of **16** and **17**, respectively. Thus, the partitioning of **13** between **16** and **17** appears to reflect the relative thermodynamic stability of these isomers.

(18) This would necessarily provide the sulfoxide stereochemistry shown in Scheme 3. This stereochemistry has not been proven. Cooper, R. D. G. *J. Am. Chem. Soc.* **1970**, *92*, 5010.

(19) It is possible that the conversion of **19** to **15** involves formation of a spiroindoline intermediate followed by a Wagner−Meerwein shift rather than the simple mechanism depicted in Scheme 3.

(20) For a relevant cyclization, see: Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, J. D. M. *J. Org. Chem.* **1982**, *47*, 2147.

(21) For a Pummerer/*N*-acyliminium ion cyclization sequence, see: Padwa, A.; Waterson, A. G. *Tetrahedron Lett.* **1998**, *39*, 8585.