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Progress toward Synthesis of Diazonamide A. Preparation of a 3-(Oxazol-5-yl)-4-trifluoromethyl-sulfonyloxyindole and Its Use in Biaryl Coupling Reactions

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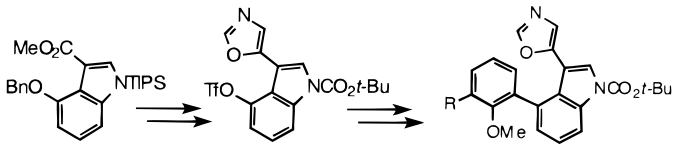
ABSTRACT



The synthesis of a 3-oxazol-5-yl-indole-4-triflate is described, featuring a Schöllkopf reaction to prepare the oxazole. In addition, the participation of this intermediate in biaryl coupling reactions toward the total synthesis of the natural product diazonamide A is presented.

Diazonamide A (**1**) (Scheme 1) is a highly potent cytotoxic isolate of the colonial ascidian *Diazona chinesis*.[1] Several groups including our own have initiated strategies based on palladium-catalyzed aryl coupling reactions to assemble the C(16)−C(18) bond of **1**.[2] In the preceding communication we described the stereoselective synthesis of **2**, an appropriately substituted benzofuranone intermediate possessing the required C(10) quaternary center and a C(16) halogen substituent.[3] The latter provides the means for eventual conversion into a reactive organometallic derivative suitable for coupling to C(18). We now present the preparation of an indole−oxazole conjugate **3** and demonstrate its ability to participate in biaryl coupling reactions corresponding to the formation of the C(16)−C(18) linkage in **1**.

Our first approach to a 3-(oxazol-5-yl)indole was based on the Schöllkopf reaction of indole-3-carboxylates with $LiCH_2NC$. The prospects were tested in a model study using **4** as the substrate.[4] Indole nitrogen was protected with the bulky triisopropylsilyl (TIPS) group because *N*-TIPS substitution in pyrroles and indoles is known to prevent deprotonation at C(2).[5] By using this strategy, the addition of **4** to 5 equiv of $LiCH_2NC$ at −78 °C in THF resulted in an 85% yield of **5** with concomitant cleavage of the silylamine upon workup.

We then attempted to apply this transformation to the corresponding 4-iodo indole **6.** The latter was prepared by the directed electrophilic aromatic substitution of 3-formylindole with thallium(III) trifluoroacetate,[6] followed by sodium chlorite oxidation of the formyl group to the acid,

(1) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303.

(2) (a) Moody, C. J.; Doyle, K J.; Elliott, M. C.; Mowlem, T. J. *Pure Appl. Chem.* **1994**, *66*, 2107. (b) Konopelski, J. P.; Hottenroth, J. M.; Oltra, H. M.; Veliz, E. A.; Yang, Z.-C. *Synlett* **1996**, 609. (c) Moody, C. J.; Doyle, K. J.; Elliott, M. C.; Mowlem, T. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2413. (d) Boto, A.; Ling, M.; Meek, G.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 8167. (e) Wipf, P.; Yokokawa, F. *Tetrahedron Lett.* **1998**, *39*, 2223. (f) Hang, H. C.; Drotleff, E.; Elliott, G. I.; Ritsema, T. A.; Konopelski, J. P. *Synthesis* **1999**, 398. (g) Jeong, S.; Chen, X.; Harran, P. G. *J. Org. Chem.* **1999**, *63*, 8640. (h) Magnus, P.; Kreisberg, J. D. *Tetrahedron Lett.* **1999**, *40*, 451. Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **1200**, *41*, 831. Chan, F.; Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **1200**, *41*, 835.

(3) Vedejs, E.; Wang, J. *Org. Lett.* **2000**, *2*, 1031.

(4) Schöllkopf, U.; Schröder, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 333.

(5) Pyrroles: (a) Kozikowski, A. P.; Cheng, X. M. *J. Org. Chem.* **1984**, *49*, 3239. Indoles: (b) Amat, M.; Sathyanarayana, S.; Hadida, S.; Bosch, J. *Heterocycles* **1996**, *43*, 1713. (c) Iwao, M. *Heterocycles* **1993**, *36*, 29 and references therein.

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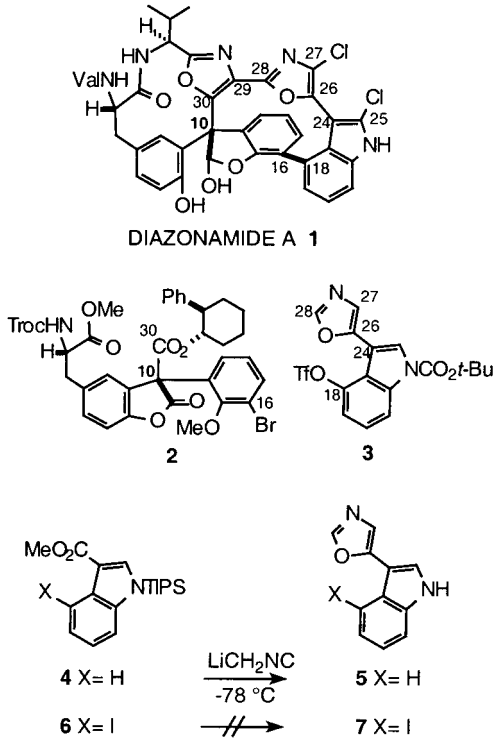
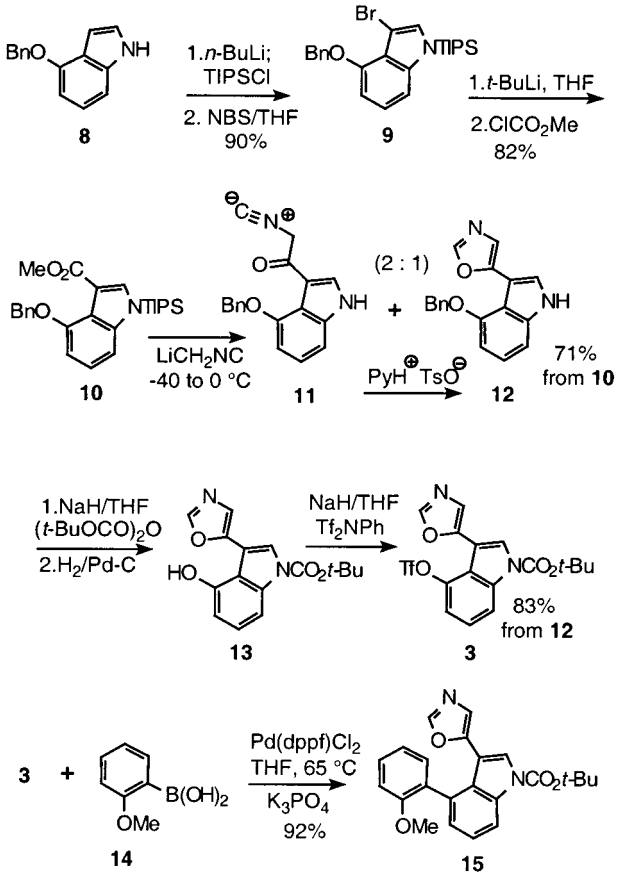
Scheme 1



Scheme 2



conversion to the methyl ester with $TMSCHN_2$, and introduction of the TIPS group. However, attempts to effect the Schöllkopf reaction of **6** using the same conditions as before resulted in rapid decomposition, and none of the expected product **7** could be isolated. Evidently, the 4-iodo substituent impedes the desired addition at the ester carbonyl group.

At this point, attention was turned to the use of a triflate as the activating group at C(18) (diazonamide numbering). The triflate approach (Scheme 2) has the advantage that indoles containing the C(4) oxygen (indole numbering) are commercially available and can be prepared conveniently using the Leimgruber−Batcho procedure.[7] Benzyloxyindole **8** was chosen as the starting material and was converted to the TIPS silylamine. Bromination at C(3) with NBS in THF then occurred efficiently to give **9** (90% overall from **8**).[8] Subsequent low-temperature lithium−halogen exchange with *t*-BuLi, followed by reaction with methyl chloroformate, resulted in **10** in 82% yield.

The Schöllkopf reaction of **10** was carried out using the same conditions that had been developed for the C(4)-unsubstituted indole ester **4**. In contrast to **4**, the 4-benzyloxyindole **10** gave a 2:1 mixture of the keto isocyanide **11** and the desired oxazole **12** (71% combined yield). If the mixture of **11** and **12** was subjected to mild acid treatment (pyridinium toluenesulfonate, CH_2Cl_2), **11** was completely converted to **12** with no need for isomer separation. Ultimately, the oxazolyl indole **12** was obtained in 71% overall yield from **10**. Further elaboration to the aryl triflate **3** could then be carried out in three steps. First, the indole nitrogen was protected using NaH and Boc_2O to produce the *N*-BOC derivative. The benzyl ether was cleaved (Pd/C, H_2) to the free phenol **13** (quantitative) and treatment with NaH and $(F_3CSO_2)_2NPh$ (**14**) gave the triflate **3** in 81% yield from **12.**

To test the reactivity of a 4-trifluoromethylsulfonyloxyindole for the desired cross coupling, **3** was submitted to Suzuki coupling conditions with boronic acid **14**.[9] The best results were obtained using $Pd(dppf)Cl_2/K_3PO_4$ in refluxing anhydrous THF.[10] This procedure gave an excellent 92% yield of the biaryl product **15**. Aqueous solvent combinations were not suitable for the coupling reaction because of rapid cleavage of the *N*-BOC protecting group.

The final series of experiments was designed to test the feasibility of indole triflate coupling with an aryl boronic acid **22** (Scheme 3) that mimics the benzofuranone environment of **2**. Strategic considerations suggested that it would be desirable to convert the C(16) bromide into a boronic acid substituent *prior* to the incorporation of a carboxyl group at C(10). The main advantage of this plan is that the high

(6) (a) Hollins, R. A.; Colnago, L. A.; Salim, V. M.; Seidl, M. C. *J. Heterocycl. Chem.* **1979**, *16*, 993. (b) Somei, M.; Yamada, F.; Kunimoto, M.; Kaneko, C. *Heterocycles* **1984**, *22*, 797.

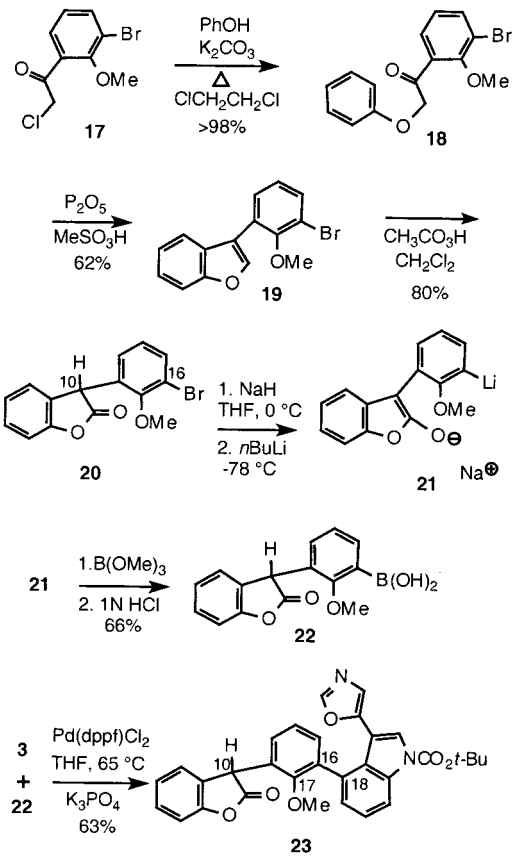
(7) Batcho, A. D.; Leimgruber, W. *Org. Synth.* **1985**, *63*, 214.

(8) Amat, M.; Hadida, S.; Pshenichnyi, G.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3158.

(9) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Josephy, P. D.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763.

(10) For a review of Suzuki coupling reactions, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

Scheme 3



acidity of the benzofuranone C(10)-H in **20** provides a simple means for lactone carbonyl protection as the enolate **21** during the conversion of C(16)-Br into an activated organometallic intermediate.

Benzofuranone **20** was prepared using a sequence based on the synthesis of **2**[3] (Scheme 3; 50% over three steps from the chloromethyl ketone **17**[11]). Next, protection of the lactone carbonyl was accomplished by treatment of **20** with 2 equiv of NaH at 0 °C in THF to generate **21**. Subsequent addition of 2 equiv of *n*-BuLi at −78 °C and quenching with 3 equiv of $B(OMe)_3$ gave the boronic acid **22** with minimal damage to the lactone ring (66% of **22** isolated).

The cross coupling reaction of **3** and **22** was investigated using the same conditions that had been optimized in the simpler example (**14**). A coupling product was isolated in 63% yield, and NMR spectra demonstrated that the crucial C(16)−C(18) bond had been formed. However, the spectra also provided clear evidence that two isomeric structures were present in a 1:1 ratio. Thus, two signals were observed for the methoxy group at C(17), for the methine hydrogen at C(10), and also for several of the aromatic C−H bonds. Because the model compound **15** has a relatively simple spectrum (singlets for oxazole C−H; methoxy; *tert*-butoxy protons), hindered rotation of the oxazole is not a likely explanation for the doubling of signals observed for **23**. We conclude that the two species are the atropisomers corresponding to two possible orientations of the indole ring with respect to the stereocenter at C(10). The isomeric species should therefore interconvert thermally by rotation about the C(16)−C(18) bond. Supporting evidence for the presence of atropisomers was obtained from NMR experiments performed in deuterated DMSO in the temperature range from 70 to 115 °C. The first indications of signal broadening were detected at 90 °C, and coalescence was seen at 105 and 115 °C for the C(10) methine and methoxy signals, respectively, corresponding to a free energy of activation of ca. 19 kcal/mol for the interconversion process.

Other groups have investigated mechanistically similar biaryl coupling reactions en route to potential precursors of diazonamide A,[2b−e] However, our results represent the first Suzuki coupling reactions of a 4-trifluoromethylsulfonyloxyindole. It is significant that the hindered triflate **3** participates efficiently in these reactions and that lactone functionality is compatible with the activation and coupling sequence. Furthermore, this route allows assembly of the oxazole prior to the coupling reaction with an advanced, lactone-containing boronic acid fragment. It also provides potential flexibility for introduction of a carbon substituent at diazonamide C(28) or a chloride at diazonamide C(27) at several stages of the synthesis using lithiooxazole chemistry.[12] Some progress with the chlorination of a lithiated oxazole has already been made in preliminary studies.[13] The alternative of electrophilic ring halogenation of an oxazolyl indole is also available from studies by Wipf et al.[2e]

In conclusion, a practical method for the preparation of 4-substituted 3-(oxazol-5-yl)indoles has been demonstrated and shown to be useful in the synthesis of a model compound corresponding to the biaryl and 3-(oxazol-5-yl)indole segment of diazonamide A. Future progress toward this end will be reported in due course.

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

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(11) Structure **6**, preceding paper. See ref 3.

(12) (a) Vedejs, E.; Monahan, S. D. *J. Org. Chem.* **1996**, *61*, 5192. (b) Vedejs, E.; Luchetta, L. M. *J. Org. Chem.* **1999**, *64*, 1011.

(13) According to the method of ref 12b, treatment of the 3-(oxazol-5-yl)indole **24** with 2.15 equiv *n*-butyllithium in THF/DMPU at −78 °C followed by slow addition of *N*-chlorosuccinimide in dichloromethane and warming to room temperature gave **25** in 60% yield: Vedejs, E.; Zajac, M., unpublished results.