ORGANIC LETTERS

2006
Vol. 8, No. 17
3777−3779

Synthesis and Cross-Coupling Reactions of 7-Azaindoles via a New Donor–Acceptor Cyclopropane

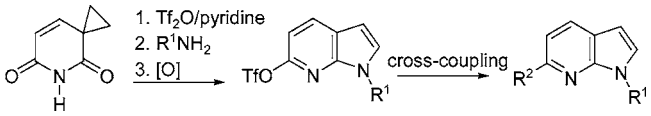
Xiaomei Zheng and Michael A. Kerr*

Department of Chemistry, The University of Western Ontario, London, Ontario, Canada N6A 5B7

makerr@uwo.ca

Received June 6, 2006

ABSTRACT



A new type of donor–acceptor cyclopropane has been prepared from commercially available cyclopropane-1,1-diesters. This cyclopropane reacts with triflic anhydride to produce an isolable tristrifloxy intermediate which when treated with primary amines gives 6-trifloxy-7-azaindolines which in turn can be dehydrogenated to the azaindoles. The 6-trifloxy substituent can be used to introduce diversity at this position via a variety of cross-coupling reactions thus preparing potentially interesting compounds based on the important 7-azaindole pharmacophore.

The importance of the indole moiety in both natural products and pharmaceutical chemistry is well understood, due in no small part to the vast number of bioactive natural products as well as medicinally important unnatural compounds based on the benzopyrrole skeleton.[1] Some of the drawbacks of the indole as a pharmacophore, such as poor water solubility, are being addressed by the investigation of azaindoles, where one or more of the carbons of the indole ring system have been replaced by a nitrogen atom.[2] 7-Azaindoles, in particular, are of interest because the proximity of the two nitrogen atoms allows this ring system to mimic purines in its role as a hydrogen-bonding partner. Although a relatively few natural products contain the 7-azaindole motif (variolin B is one of the few[3]), it is the subject of pharmaceutical patent literature too extensive to reference here, although the HIV attachment inhibitor BMS-378806[4] and the kinase inhibitors investigated by Johnson and Johnson[5] stand as examples of unnatural bioactive 7-azaindoles (Figure 1).

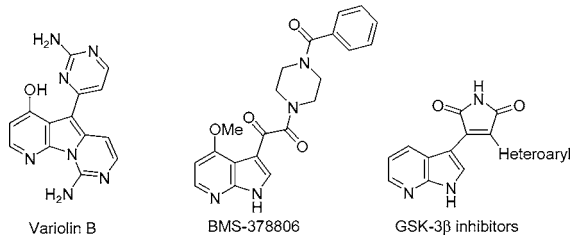


Figure 1. Representative 7-azaindoles.

In our continuing investigation into the chemistry of donor−acceptor cyclopropanes, we had hypothesized that a cyclopropane such as **1** would react with nitrones or imines in a manner we have described previously,[6] to afford spiroadducts such as **2** or **3** (Scheme 1). Our interest lay in the fact that this substructure is present in a target of interest

(1) (a) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry*, 2nd ed.; Pergammon Press: New York, 1996; Vol. 2, pp 203−257. (b) Snieckus V. A. In *The Alkaloids*; Academic Press: New York, 1968; Vol. 11, Chapter 1.

(2) For a recent synthesis of 7-azaindoles with leading references concerning both synthesis and pharmaceutical aspects, see: Schirok, H. *Synlett* **2005**, 1255−1258.

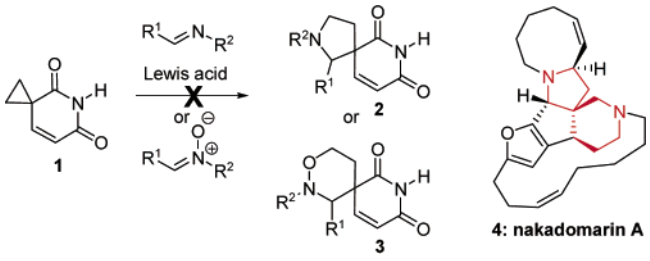
(3) Anderson, R. J.; Hill, J. B.; Morris, J. C. *J. Org. Chem.* **2005**, *70*, 6204−6212 and references therein.

(4) Yang, A.; Zadjura, L.; D'Arienzo, A. M.; Santone, K.; Llunk, L.; Green, D.; Lin, P.-F.; Colonno, R.; Wang, T.; Neanwell, N.; Hansel, S. *Biopharm. Drug Dispos.* **2005**, *26*, 387−402.

(5) O'Neill, D. J.; Shen, L.; Prouty, C.; Conway, B. R.; Westover, L.; Xu, J. Z.; Zhang, H.-C.; Maryanoff, B. E.; Murray, W. V.; Demarest, K. T.; Kuo, G.-H. *Bioorg. Med. Chem.* **2004**, *12*, 3167−3185.

10.1021/ol061379i CCC: $33.50
Published on Web 07/29/2006

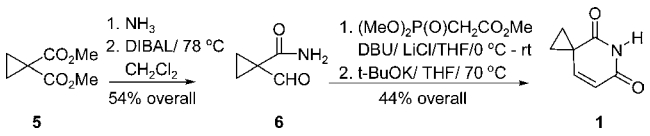
Scheme 1. Proposed Synthesis of a Nakadomarin A Substructure



to us, namely, nakadomarin A (**4**). We were disappointed to discover that these cycloadditions which had proceeded so smoothly with other substrates, failed with this cyclopropane. We were, however, able to activate this cyclopropane toward nucleophilic ring opening with various amines under the influence of triflic anhydride. This communication describes this chemistry and a novel, flexible, and efficient synthesis of 7-azaindoles.

Cyclopropane **1** was prepared from the commercially available 1,1-dicarbomethoxy cyclopropane **5** in the manner shown in Scheme 2. Monoammonolysis of the diester moiety

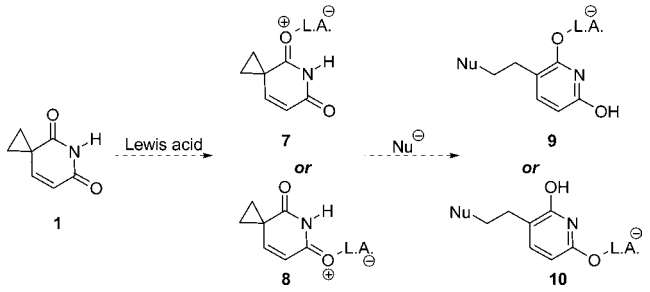
Scheme 2. Preparation of Cyclopropane **1**



followed by DIBAL reduction produces amido aldehyde **6** in 54% overall yield. Horner−Emmons olefination of the aldehyde followed by a base-induced ring formation produces the target cyclopropane **1**.

Our initial attempts to activate **1** toward ring-opening reactions with Lewis acids were met with unequivocal failure. We had envisioned an activated complex such as **7** or **8** (Scheme 3) which would, in the presence of a suitable

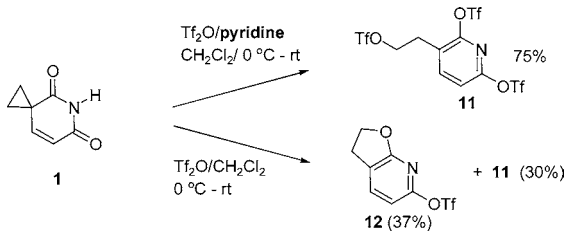
Scheme 3. Proposed Ring Opening of Cyclopropane **1**



nucleophile, open to form an aromatically stabilized anion such as **9** or **10**. Lanthanide triflates and magnesium iodide, which had served us so well previously for the activation of cyclopropane diesters, led to no reaction at ambient temperature and decomposition at higher temperatures. Stronger Lewis acids such as BF_3 etherate or $TiCl_4$ led to decomposition.

At this time, we turned to an alternative activation via triflic anhydride.[7] Treatment of **1** with Tf_2O and pyridine in CH_2Cl_2 led to relatively clean formation of the tristriflate **11** (Scheme 4). In the absence of pyridine, the reaction

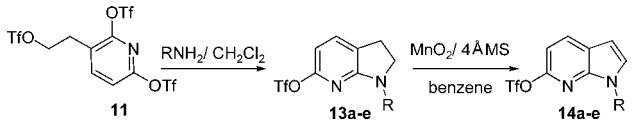
Scheme 4. Reaction of **1** with Triflic Anhydride



produced in a near 1:1 mixture of **11** and the dihydrofuranopyridine **12**.

The synthetic utility of **11** with its three potential electrophilic sites was immediately obvious. It was felt that treatment of **11** with a nucleophile capable of a double displacement would first react with the 1° triflate via an S_N2 process followed by an intramolecular S_NAr reaction. To this end, **11** was treated with a variety of 1° amines in CH_2Cl_2. The result was the clean formation of 6-trifloxy-7-azaindolines in 76−88% yields (Scheme 5). The adducts could be

Scheme 5. Synthesis of 7-Azaindolines and 7-Azaindoles



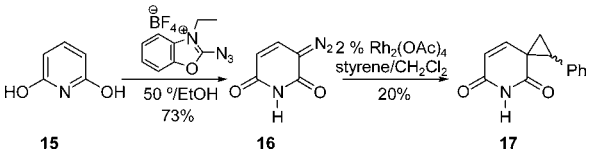
dehydrogenated with MnO_2 in benzene to yield the 7-azaindoles in 79−91% yields. It is interesting, but not totally unexpected, that a second S_NAr reaction of the other aryl triflate moiety did not occur. Clearly, the intramolecular S_NAr reaction was faster, and moreover, the replacement of one trifloxy group with an amino group deactivated the ring toward subsequent nucleophilic attack.

(6) (a) Wanapun, D.; Van Gorp, K. A.; Mosey, N. J.; Kerr, M. A.; Woo, T. K. *Can. J. Chem.* **2005**, *83*, 1752−1767. (b) Carson, C. A.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 8242−8244. (c) Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953−955. (d) Ganton, M. D.; Kerr, M. A. *J. Org. Chem.* **2004**, *69*, 8554−8557. (e) Young, I. S.; Kerr, M. A. *Org. Lett.* **2004**, *6*, 139−141. (f) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023−3026.

(7) The activation of amides with triflic anhydride of pyridine has been well documented. See, for example: (a) DeRoy, P. L.; Charette, A. B. *Org. Lett.* **2003**, *5*, 4163−4165 and references therein. (b) Mahuteau-Betzer, F.; Ding, P.-Y.; Ghosez, L. *Helv. Chim. Acta* **2005**, *88*, 2022−2031 and references therein.

With the aim of preparing more substituted 7-azaindoles, we investigated the preparation of the cyclopropane **17** (Scheme 6). Diazo transfer to **15** using 2-azido-3-ethylbenzothiazolium tetrafluoroborate resulted in the preparation of **16** in 73% yield. A rhodium-catalyzed carbenoid insertion to styrene resulted in the formation of the target compound albeit in low yield.[8] All attempts to employ **17**[9] in ring-opening chemistry met with failure.

Scheme 6. Preparation of Cyclopropane **1**



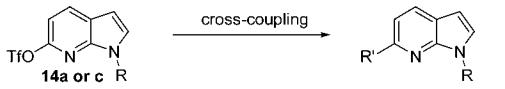
With 7-azaindoles **14a**−**f** in hand, we sought to utilize the remaining trifloxy group toward the installation of diversity via either S_NAr or cross-coupling reactions. Treatment of 6-trifloxy-7-azaindoles such as **14** with a variety of nucleophiles under even forcing conditions failed to produce substitution products. Cross-coupling reactions, however, were far more productive. Table 1 shows a variety of cross-coupling reactions of trifloxy-7-azaindoles **14a** or **14c**. Suzuki, Sonogashira, Stille, Heck, and carbonylation reactions were all successful in the installation of functionality at position-6. This cross-coupling study is only a survey, and one may imagine that, considering the advances in cross-coupling chemistry, an enormous degree of molecular diversity may be installed.

In conclusion, we have prepared a new donor−acceptor cyclopropane and probed its reactivity in ring-opening reactions. Triflic anhydride was effective in activating the cyclopropane toward ring opening. The product of ring opening was shown to be a useful synthetic intermediate for the preparation of a variety of 7-azaindoles bearing a trifloxy substituent at the 6-position. The triflate proved to be a useful handle for building molecular complexity via a variety of cross-coupling reactions.

(8) One of the reviewers has suggested the use of a bulkier rhodium catalyst to suppress suspected carbenoid dimerization side reactions. This will be explored in future studies.

(9) The relative stereochemistry of **17** was not determined because the stereochemistry would have been lost upon success in the intended reaction.

Table 1. Cross-Coupling of 7-Azaindoles



entry	triflate	conditions	product (yield)
1	**14c**	$PhB(OH)_2$/ LiCl Na_2CO_3/ DMF $Pd(PPh_3)_4$	**18** (89%)
2	**14a**	Phenylacetylene Et_3N/ CuI/ LiCl $Pd(PPh_3)_2Cl_2$	**19** (87%)
3	**14a**	TMSacetylene Et_3N/ CuI/ LiCl $Pd(PPh_3)_2Cl_2$	**20** (86%)
4	**14a**	CH_2=CHSnBu_3 DMF/ LiCl $Pd(PPh_3)_2Cl_2$	**21** (70%)
5	**14a**	Me_4Sn/DMF/ LiCl $Pd(PPh_3)_2Cl_2$	**22** (81%)
6	**14a**	methylacrylate Et_3N/ DMF $Pd(PPh_3)_2Cl_2$	**23** (78%)
7	**14a**	methylvinylketone Et_3N/ DMF $Pd(PPh_3)_2Cl_2$	**24** (93%)
8	**14a**	CO/ MeOH $Pd(PPh_3)_2Cl_2$ Et_3N/ DMF	**25** (72%)

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada and Boehringer Ingelheim Canada for funding. We are grateful to Mr. Doug Hairsine (University of Western Ontario) for performing MS analyses.

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

OL061379I