ORGANIC LETTERS

2009
Vol. 11, No. 11
2389−2392

Total Synthesis of Siphonazoles by the Use of a Conjunctive Oxazole Building Block

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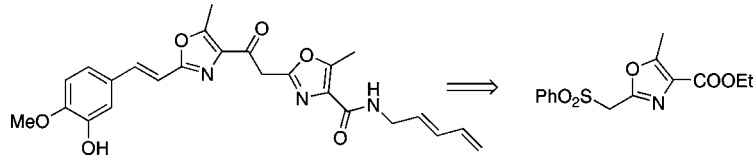
Received March 4, 2009

ABSTRACT

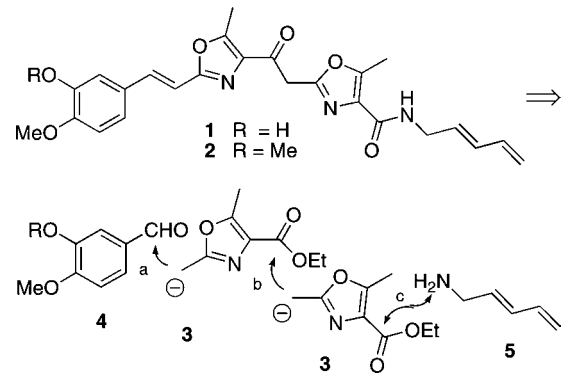


The preparation of 4-carbethoxy-5-methyl-2-(phenylsulfonyl)methyloxazole and its use in the elaboration of more complex oxazoles are described. A total synthesis of the unique natural products, siphonazoles A and B, illustrates an application of the new building block.

Siphonazole, **1**, and its methylated congener, **2** (Scheme 1), are structurally novel natural products isolated from a Gram-negative filamentous gliding bacterium of the *Herpetosiphon* genus.[1] Their uniqueness derives from the fact that they incorporate a pair of oxazole subunits connected by a two-carbon tether. As of yet, no information is available concerning the bioactivity of **1**−**2**, which we propose to distinguish with the names siphonazole A, **1**, and siphonazole B, **2**.

The unusual structure of siphonazoles has not escaped the attention of the synthetic community, and efforts in this field have recently culminated in Moody's landmark syntheses of **1**−**2**.[2] This successful route to the target molecules demonstrates yet another application of elegant oxazole-forming processes, which rely on the reaction of a ketocarbenoid with an amide[3] or a nitrile.[4] On the other hand, siphonazoles provide ample opportunity for further methodology development. To illustrate (Scheme 1), an alternative avenue could be envisioned based on the iterative use of oxazole nucleophile **3**. This synthon would enable both the olefination of aldehyde **4** (bond-forming step *a*), resulting in formation of a 1,2-diarylethylene motif and the condensation with an ester, yielding a (2-oxazolyl)methyl ketone (step *b*). The product of C−C bond-forming steps *a* and *b* would then be advanced to the ultimate **1** or **2** by condensation with amine **5** (step *c*).

Scheme 1. Structure and Retrosynthetic Disconnection of Siphonazoles A and B



(1) Nett, M.; Erol, Ö; Kehrhaus, S.; Köck, M.; Krick, A.; Eguereva, E.; Neu, E.; König, G. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3863.

(2) (a) Linder, J.; Moody, C. J. *Chem. Commun.* **2007**, 1508. (b) Linder, J.; Blake, A. J.; Moody, C. J. *Org. Biomol. Chem.* **2008**, *6*, 3908.

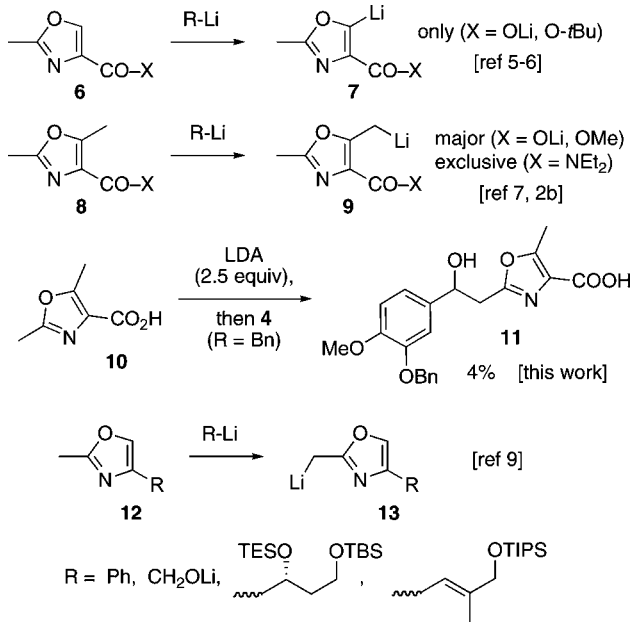
(3) Davies, J. R.; Kane, P. D.; Moody, C. J. *Tetrahedron Lett.* **2004**, *60*, 3967 See refs 2 for a thorough bibliography.

(4) Connell, R. D.; Tebbe, M.; Helquist, P.; Åkermark, B. *Tetrahedron Lett.* **1991**, *32*, 17 See also refs 2.

10.1021/ol900455m CCC: $40.75
Published on Web 04/27/2009

Precedent foreshadowed numerous difficulties with the strategy depicted in Scheme 1. Briefly, the oxazole C-4 carboxy substituent opposes the formation of anion **3**. As shown in Scheme 2, metalation of 2-methyloxazole-4-

Scheme 2. Problematic Behavior of Oxazole-4-carboxylic Acid Derivatives



carboxylic acid[5] or the corresponding *tert*-butyl ester[6] (**6**) occurs exclusively at the unsubstituted C-4 ring position (**7**). Deprotonation of 2,4-dimethyloxazole-4-carboxylic acid or ester (**8**) takes place preferentially (ca. 2:1) at the C-4 methyl group (**9**),[7,2b] while the corresponding diethylamide is metalated exclusively there.[7] Finally, and in accord with Moody,[2b] we found that deprotonation of **10**, followed by capture of the intermediate organometallic species with aldehyde **4**, resulted in a complex mixture of products from which adduct **11** was isolated in 4% yield.[8] The behavior of 2-methyloxazole-4-carboxylic acid derivatives thus deviates from that of analogues lacking the 4-carboxy group. The latter, e.g., **12**, are smoothly deprotonated at the C-2 Me group, and the ensuing anions **13** perform well in nucleophilic processes, including olefination reactions.[9]

(5) (a) Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1981**, *22*, 3163. (b) Meyers, A. I.; Lawson, J. P.; Walker, D. G.; Lindermann, R. J. *J. Org. Chem.* **1986**, *51*, 5111.

(6) (a) Nagao, Y.; Yamada, S.; Fujita, E. *Tetrahedron Lett.* **1983**, *24*, 2287. (b) Nagao, Y.; Yamada, S.; Fujita, E. *Tetrahedron Lett.* **1983**, *24*, 2291.

(7) Cornwall, P. Dell, C. P. Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2417. These authors report that under particular conditions it is possible to generate a 1:1 mixture C-2 and C-4 lithiomethyl derivatives of the oxazole 4-carboxylic acid.

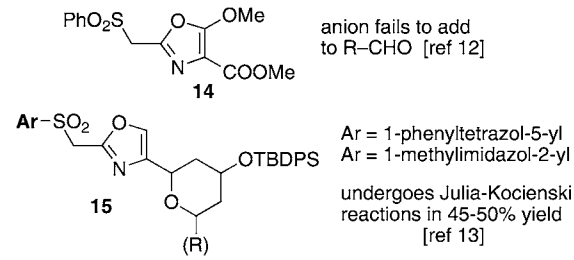
(8) These difficulties may be ascribed to the unfavorable positioning of the 4-COOR substituent: the 5-COOR isomer is smoothly deprotonated at the C-2 Me group (ref 7), arguably because of good mesomeric stabilization of the resulting anion. In a later step of the synthesis of **1** and **2** (ref 2), Moody bypassed the problem by employing an organozinc reagent prepared from the 2-(iodomethyl) analogue of oxazole **8**.

(9) Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87.

In principle, the foregoing ills could be cured by activating the C-2 Me with an appropriate anion-stabilizing unit. A sulfonyl group would be a logical choice, given that the acylation of a 2-(arylsulfonyl)methyl oxazole, in a fashion reminiscent of step *b* in Scheme 1, finds precedent in the work of Fujita,[6] and that a sulfonyl group should permit the execution of step *a* in a Julia[10] mode.

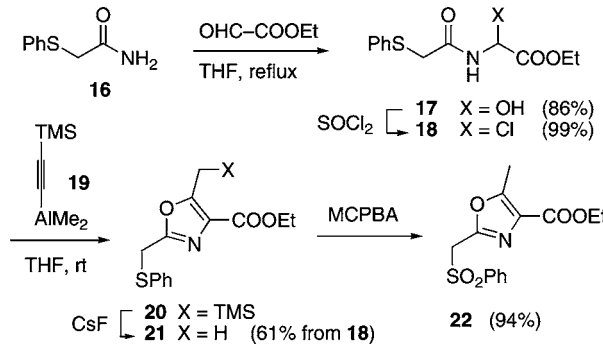
In practice, such a remedy creates a new set of problems. The exiguous volume of literature on the chemistry of 2-(sulfonyl)methyloxazole-4-carboxylates[11] suggests that the anions of these species are exceedingly poor nucleophiles. To wit, the anion of **14** (Scheme 3) fails to add to

Scheme 3. Problematic Behavior of 2-(Sulfonyl)methyloxazole-4-carboxylic Acid Derivatives



aldehydes,[12] preventing the occurrence of Julia reactions. Once again, the peculiar behavior of these compounds is attributable to the effect of the 4-COOR functionality in that analogues lacking a 4-carbonyl group, e.g., **15**, do participate in Julia-type processes,[13] though not very efficiently. Indeed, Wittig technology is superior for olefination reactions involving 2-methyloxazole donors.[12−14] Clearly, in order to reach **1**−**2** by the intended route, it was necessary to circumvent the unfavorable reactivity profile of 2-(sulfonyl)methyloxazole-4-carboxylates.

Scheme 4. Preparation of Building Block **22**

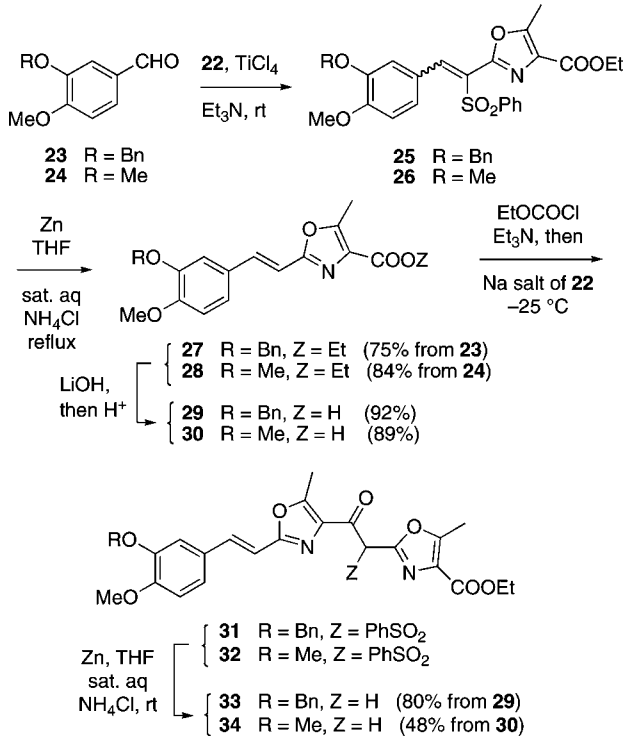


The first goal of this study was oxazole conjunctive agent **22** (Scheme 4). The synthesis of this material relied on an oxazole-forming reaction developed in this laboratory.[15] Accordingly, addition of 2-(phenylthio)acetamide **16** to ethyl

glyoxylate provided **17**, which was then converted into chloride **18** in excellent yield. The action of alkynylaluminum reagent **19** on **18** resulted in formation of an alkynylglycinate intermediate, which is isolable, but that in the present case was more conveniently allowed to cyclize in situ to oxazole **20**. The desired **22**, a white solid of mp 154−155 °C, emerged upon desilylation and *m*-CPBA oxidation of **20**.

Both **21** and **22** underwent facile deprotonation of the activated C-2 substituent upon exposure to LDA (**21**) or NaH (**22**).[16] While the anion of **21** added to aldehydes to form the anticipated adducts in modest yield,[17] that of sulfone **22** failed to undergo the same reaction. This is in accord with the observations of Hoffmann.[12] Fortunately, it transpired that the combination of $TiCl_4$ and Et_3N promotes a smooth Knoevenagel-type condensation of **22** with aldehydes, leading to alkylidene derivatives in excellent yield, albeit as mixtures of geometric isomers. This is exemplified in Scheme 5 by the conversion of aldehydes **23** and **24** into olefinic

Scheme 5. Preparation of Key Intermediates **29** and **30**



sulfones **25** (1:5 mixture of *E*- and *Z*-isomers) and **26** (4:5 mixture of *E*- and *Z*-isomers), respectively. These conditions are reminiscent of the Masamune−Roush variant of the Wadsworth−Emmons olefination reaction.[18] However, we are unable to find literature precedent for the application of a similar protocol in the Knoevenagel-like condensation of sulfones with aldehydes. The closest recorded example involves the reaction of an activated sulfone with PhCHO in the presence of piperidine.[19] With less reactive sulfones, bases such as BuLi,[20] LiHMDS,[21] NaH,[22] tBuOK,[23] or NaOH[24] are necessary, though in one case, the weaker base, TBAF,[25] did promote condensation in modest yield.

A potential drawback of the above process is that the release of the sulfonyl group from the olefinic products may be difficult. However, such a concern proved to be unfounded: efficient reduction of **25**−**26** to olefins **27**−**28** was readily achieved by treatment with Zn and aqueous saturated NH_4Cl solution in THF. This technique for the desulfonylation of olefinic sulfones such as **25**−**26** appears to be undocumented. When the reaction was carried out at room temperature for 30 min, the emerging **27**−**28** were obtained as mixtures of *E*- and *Z*-isomers, but conduct of the same step in refluxing THF for 6 h afforded exclusively (within the limits of 300 MHz ^1H NMR spectroscopy) the *E*-isomer of the products. The chemistry of Scheme 5 had thus resolved all the reactivity issues outlined earlier.

The weak nucleophilicity of the anion of **22** precluded a direct condensation with esters **27**−**28**. Therefore, the corresponding carboxylic acids **29**−**30**, prepared by the customary LiOH saponification of the esters, were activated with EtOCOCl/Et_3N, and the resulting mixed anhydrides were intercepted in situ with sodiated **22**, which had been generated separately by deprotonation of the parent compound with NaH. The ensuing Fujita-like reaction[6] resulted in the formation of α-sulfonyl ketones **31**−**32**, which existed as mixtures of keto (shown) and enol tautomers in a ratio that appeared to be a function of solvent, moisture content, time and pH. Inferior results were obtained in this step when the acids were activated as the corresponding acyl chlorides ($SOCl_2$) or imidazole derivatives (CDI).[26] Desulfonylation of **31**−**32** was once again best carried out by treatment with

(10) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833 Reviews. (b) Kelly, S. E. Alkene Synthesis. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 1, pp 729−817. (c) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.

(11) Comprehensive bibliography beyond refs 6 and 12: (a) Fujita, E. *Heterocycles* **1984**, *21*, 41. (b) Yokoyama, M.; Menjo, Y.; Ubukata, M.; Irie, M.; Watanabe, M.; Togo, H. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2219. (c) White, J. D.; Kranemann, C. L.; Kuntiyong, P. *Org. Synth.* **2003**, *79*, 244. In addition, the following patents describe the preparation of some 2-(arylsulfonyl)methyloxazole-4-carboxylic esters: (d) Jpn. Kokai Tokkyo Koho (1984) JP 59108772 A 19840623 Showa (Taiho Pharmaceutical Co., Ltd.), CAN 101:171238. (e) Dehmlow, H.; Kuhn, B.; Masciadri, R.; Panday, N.; Ratni, H.; Wright, M. B. U.S. Pat. Appl. Pub. (2005), US 2005215577 A1 20050929, CAN 143:347051.

(12) (a) Wolbers, P.; Misske, A. M.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1999**, *40*, 4527. (b) Wolbers, P.; Misske, A. M.; Hoffmann, H. M. R. *Synlett* **1999**, 1808.

(13) Williams, D. R.; Clark, M. P. *Tetrahedron Lett.* **1999**, *40*, 2291.

(14) Paterson, I.; Arnott, E. A. *Tetrahedron Lett.* **1998**, *39*, 7185.

(15) (a) Coqueron, P. Y. Didier, C. Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1411. See also: (b) Sano, S. Shimizu, H. Kim, K. Lee, W. S. Shiro, M. Nagao, Y. *Chem. Pharm. Bull.* **2006**, *54*, 196. Reference a above contains an extensive bibliography of oxazole-forming reactions. Subsequent representative examples of oxazole construction via the cyclization of *N*-propargylamide intermediates. (c) Wipf, P. Aoyama, Y. Benedum, T. E. *Org. Lett.* **2004**, *6*, 3593. (d) Hashmi, A. S. K. Weyrauch, J. P. Frey, W. Bats, J. W. *Org. Lett.* **2004**, *6*, 4391. (e) Milton, M. D. Inada, Y. Nishibayashi, Y. Uemura, S. *Chem. Commun.* **2004**, 2712. (f) Hashmi, A. S. K. Rudolph, M. Schymura, S. Visus, J. Frey, W. *Eur. J. Org. Chem.* **2006**, 4905. (g) Kang, J.-E. Kim, H.-B. Lee, J.-W. Shin, S. *Org. Lett.* **2006**, *8*, 3537. (h) Merkul, E. Grotkopp, O. Müller, T. J, J. *Synthesis* **2009**, 502. It is important to note that among these methods only the chemistry of refs a and b permits access to the 2,5-dialkyloxazole-4-carboxylate series.

(16) The deprotonation of **22** with NaH is in accord with ref 6.

(17) These results shall be detailed in a forthcoming full paper.

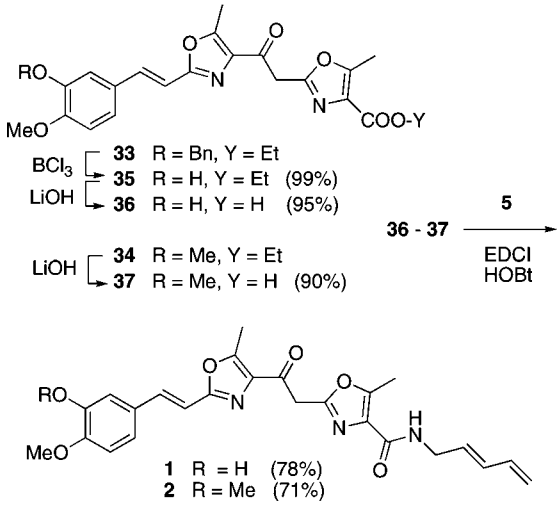
(18) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, 2183.

(19) Nikolae, A.; Florea, S.; Rudorf, W.-D.; Perjessy, A. *Rev. Chim.* **2005**, *56*, 524; CAN 144:412344.

Zn/NH_4Cl. Contrary to the case of **25**−**26**, the desulfonylation of α-sulfonyl ketones by this method finds precedent in the work of Holton.[27] Reductants like Na/Hg amalgam or SmI_2 performed poorly in the present case. Ketones **33**−**34** and derivatives thereof, including the ultimate **1**−**2**, existed in equilibrium with the relative enols, the proportion of which once again varied as a function of experimental parameters (solvent, temperature, etc.).

The synthesis of siphonazoles was completed as delineated in Scheme 6. Compound **33** was debenzylated (BCl_3) to

Scheme 6. Total Synthesis of Siphonazoles A and B



afford ester **35**. The latter as well as its congener **34** underwent saponification to the corresponding acids, **36** and **37**, which combined with dienic amine **5**[2,28] under the influence of EDCI to deliver fully synthetic **1** and **2**, respectively. The ^1H and ^{13}C NMR spectra of siphonazoles A and B thus obtained (mostly keto tautomers)[29] were identical to the published spectra of the natural products.[1,2]

Synthetic siphonazoles were tested for antibiotic activity against representative pathogens. However, a standard paper disk assay (10 μg/mL) showed no activity against typical Gram-positive [methycillin-sensitive *Staphylococcus aureus* (MSSA)] or Gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*) bacteria, as well as fungi (*Candida albicans*).

In summary, a straightforward synthesis of siphonazoles has been completed by the iterative use of the oxazole conjunctive reagent **22**. Additional aspects of the chemistry of this reagent and of the synthesis of siphonazoles will be discussed in detail in a forthcoming full paper.

Acknowledgment. We thank the University of British Columbia, the Canada Research Chair Program, CFI, BCKDF, NSERC, CIHR, and MerckFrosst Canada for financial support. We are grateful to Dr. Elena Polishchuk and the staff of the Chemistry Department's Biological Services for testing the siphonazoles for bioactivity.

Supporting Information Available: Experimental procedures and characterization data for new compounds, plus hardcopy NMR (^1H and ^{13}C) spectra of several molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Holton, R. A.; Crouse, D. J.; Williams, A. D.; Kennedy, R. M. *J. Org. Chem.* **1987**, *52*, 2317.

(28) Grieco, P. A.; Galatsis, P.; Spohn, R. F. *Tetrahedron* **1986**, *42*, 2847.

(29) The enol tautomer of **1**−**2** was recognizable from a characteristic ^{13}C signal at 85 ppm. See the spectra provided in the Supporting Information.