ORGANIC LETTERS

2004
Vol. 6, No. 1
139−141

Three-Component Homo 3 + 2 Dipolar Cycloaddition. A Diversity-Oriented Synthesis of Tetrahydro-1,2-oxazines and FR900482 Skeletal Congeners

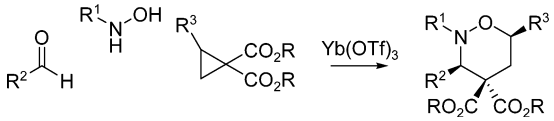
Ian S. Young and Michael A. Kerr*

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

makerr@uwo.ca

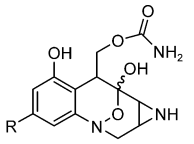
Received November 24, 2003

ABSTRACT

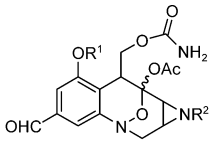


The reaction of nitrones, formed in situ by reaction of hydroxylamines with aldehydes, with 1,1-cyclopropanediesters results in the formation of tetrahydro-1,2-oxazines via a homo 3 + 2 dipolar cycloaddition. This three-component coupling allows for the formation of a diverse array of cycloadducts with excellent diastereoselectivity (>95%) and yields (66–96%). The procedure has been used in the two-step preparation of congeners of the FR900482 skeleton.

The antitumor, antibiotic natural products FR900482[1] and FR66979,[2] structurally related to the anticancer drug mitomycin C, have emerged as promising therapeutic candidates. As with the synthetic derivatives FK317 and FK973, they are thought to act as minor groove-binding cross-linkers.[3] Not surprisingly there has been significant activity toward the synthesis of these molecules[4] in pursuit of preparing analogues with improved biological profiles. An equally compelling motivation for their synthesis lies in their unique and formidable structure, its central feature being the relatively uncommon tetrahydro-1,2-oxazine ring, preparations of which are not abundant.[5] A flexible synthesis of this heterocycle would aid in the synthesis of these natural targets and their evaluation as a drug scaffolds.



FR900482 **1**: R = CHO
FR66979 **2**: R = CH_2OH



FK317 **3**: R^1 = H, R^2 = Ac
FK973 **4**: R^1 = R^2 = Ac

Recently, we reported the first cycloaddition reaction between a nitrone **5** and a 1,1-cyclopropane diester **6** to yield a tetrahydro-1,2-oxazine **7**, always as the cis isomer exclusively (Scheme 1).[6] The exact nature of this fundamentally unique reaction is under investigation (stepwise annulative vs concerted cycloaddition); however, the synthetic utility is clearly evident, with tetrahydro-1,2-oxazines being prepared in excellent yields with virtually complete diastereoselectivity.

(1) Uchida, I.; Shigehiro, T.; Hiroshi, K.; Sumio, K.; Hashimoto, M.; Tada, T.; Shigetaka, K.; Morimoto, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4108−4109.

(2) Terano, H.; Takase, S.; Hosoda, J.; Kohsaka, M. *J. Antibiot.* **1989**, *42*, 145−148.

(3) Judd, T. C.; Williams, R. M. *Org. Lett.* **2002**, *4*, 3711−3714 and references therein.

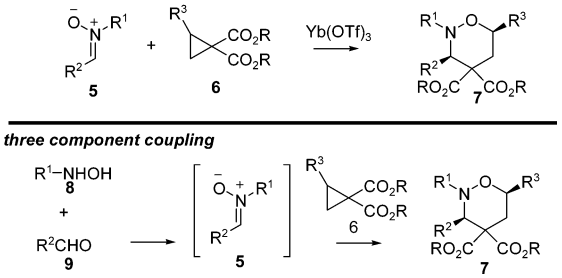
(4) Racemic total syntheses: (a) Fukuyama, T.; Xu, L.; Goto, S. *J. Am. Chem. Soc.* **1992**, *114*, 383−385. (b) Schkeryantz, J. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4722−4723. Enantioselective total syntheses: (c) Kato, T.; Itoh, E.; Yoshino, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10253−10270. (d) Judd, T. C.; Williams, R. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4683−4685. (e) Suzuki, M.; Kambe, J.; Tokuyama, H.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 4686−4688. (f) Paleo, M. R.; Aurrecoechea, N.; Jung, K.-Y.; Rapoport, H. *J. Org. Chem.* **2003**, *68*, 130−138. For a synthesis of related racemic FR66979, see: (g) Ducray, R.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4688−4691.

(5) (a) Tsoungas, P. G. *Heterocycles* **2002**, *57*, 1149−1178. (b) Gilchrist, T. L.; Wood, J. E. In *Comprehensive Heterocyclic Chemistry II*; Elsevier: Oxford, UK, 1996; Vol. 6, pp 279−299, 1177−1307.

(6) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *26*, 3023−3026.

10.1021/ol0362919 CCC: $27.50
Published on Web 12/13/2003

Scheme 1. Reaction of Nitrones with Cyclopropanes



While many nitrones are readily available and stable, some are difficult to prepare or are unstable due to oligomerization under the required Lewis acidic conditions. During efforts to address this, it occurred to us that the nitrone could be prepared in situ from the reaction of a hydroxylamine **8** and an aldehyde **9** in the presence of the Lewis acid, avoiding the isolation or handling of the nitrone at all. In this communication, we report our efforts and success in developing an effective three-component, one-pot protocol, and we showcase it with the efficient synthesis of a diverse selection of tetrahydro-1,2-oxazines. In addition, we report the synthesis of a short array of FR900482 skeletal congeners.

Our study commenced with the selection and preparation of suitable substrates for the development of the cycloaddition (Figure 1). Hydroxylamines[7] and cyclopropanediesters[8]

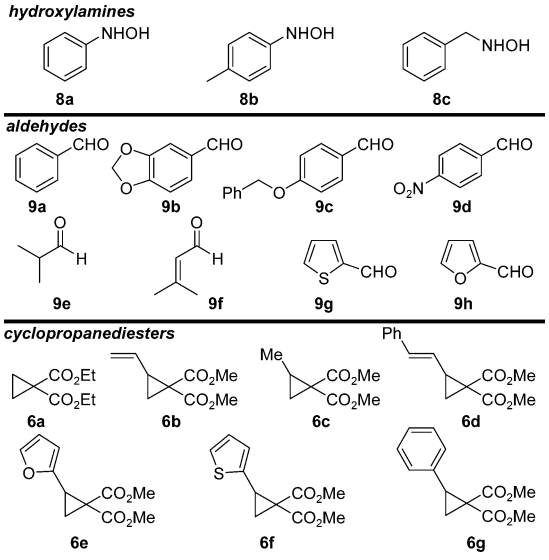


Figure 1. Substrates for three-component coupling reactions.

were prepared via literature methods, while the aldehydes were commercially available. The array of aldehydes include

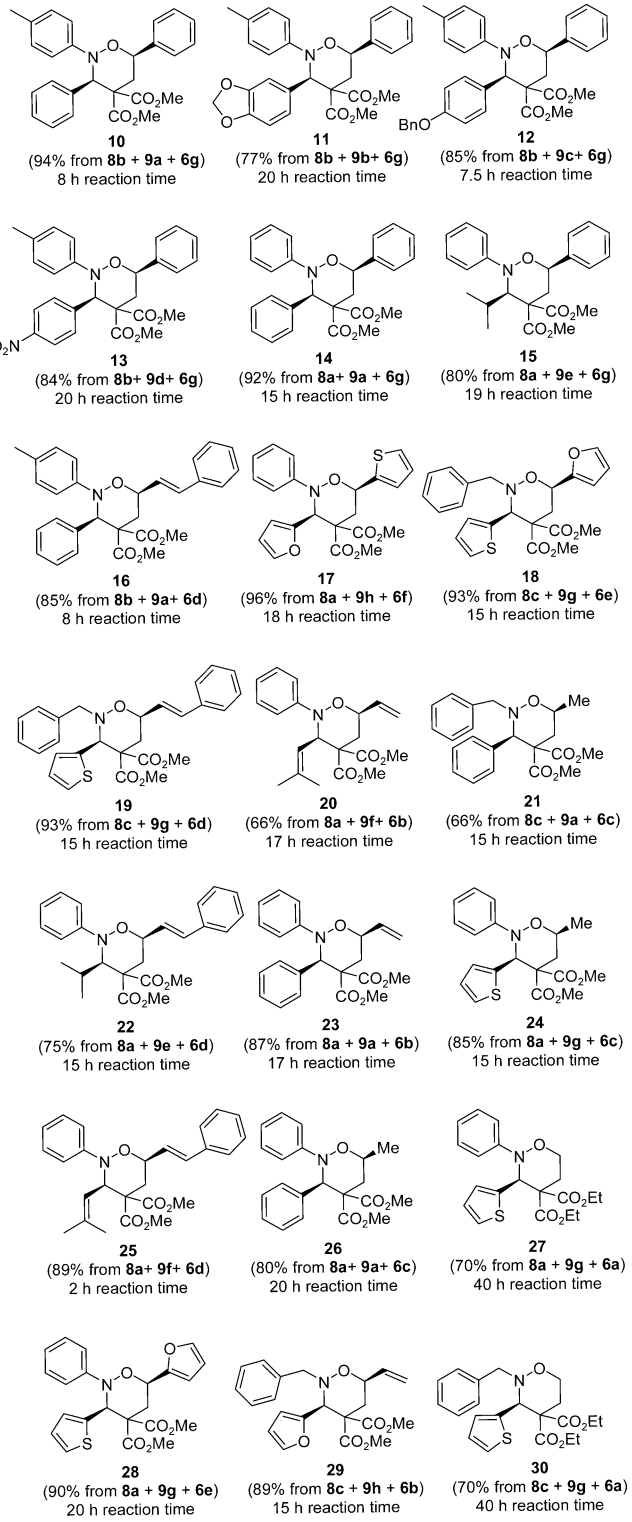


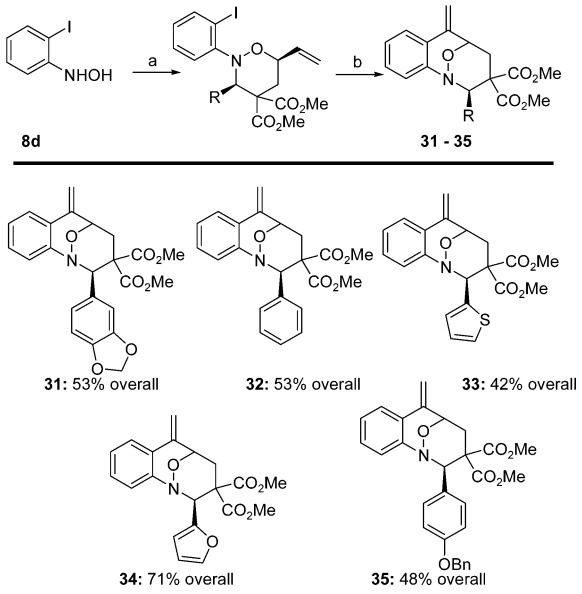
Figure 2. Tetrahydro-1,2-oxazines prepared by three-component coupling.

benzaldehydes (electron rich and poor), an alkenal, an alkanal, and heterocyclic aldehydes. The cyclopropanes bear alkyl, alkenyl, phenyl, and heteroaromatic substituents.

Typically, the hydroxylamine **8** (1.3 equiv) and the aldehyde **9** (1.4 equiv) were combined in toluene in the

(7) **8a** and **8b**: Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1735−1738. **8c**: Maskill, H.; Jencks, W. *J. Am. Chem. Soc.* **1987**, *109*, 2062−2070. **8d**: Crautheson-Chapoulaud, V.; Pandya, S. U.; Cividino, P.; Masson, G.; Py, S.; Vallee, Y. *Synlett* **2001**, 1281−1283.

Scheme 2. Synthesis of FR900482 Congeners[a]



[a] Conditions: (a) **9 (a**−**c**,**g**, or **h**), 10 mol % $Yb(OTf)_3$, 4 Å MS, toluene, 25 °C 30 min, then **6b** 18 h; (b) 20 mol % $Pd(PPh_3)_4$, Et_3N, CH_3CN, 80 °C, 18 h.

presence of 4 Å molecular sieves and catalytic (10 mol %) $Yb(OTf)_3$ (as the hydrate). After 30 min, the cyclopropane **6** (1.0 equiv) was added and the mixture stirred until thin-layer chromatography indicated that the cyclopropane had been consumed. Purification by flash chromatography yielded the heterocycles **10**−**30** (Figure 2). In most cases, the reactions produced only the cis diastereomers shown; however, for **20**, **22**, **23**, **25**, and **26**, a small amount (<5%) of what appears to be the trans isomer was evident in the NMR spectra of chromatographically purified material. Crystallization yielded the pure cis adducts.

It was found to be vital that the hydroxylamine and the aldehyde be mixed together with the catalyst for about 30 min prior to the addition of the cyclopropane, to ensure complete formation of the nitrone. Failure to do so resulted in the ring-opening of the cyclopropane by the hydroxylamine in many cases. As a case in point, in the preparation of compound **28**, only a 6% yield was realized if the three components were mixed at once with the catalyst in contrast to the 90% yield obtained upon premixing the hydroxylamine and the aldehyde prior to addition of the cyclopropane. In the case of the unsubstituted cyclopropane, 20 mol % catalyst was required to effect satisfactory conversion to the product. It should be noted that the times in Figure 2 are not necessarily an accurate description of the time required for complete reaction; the cyclopropane and product coelute in many cases, and the reaction was left to stir for a longer time to ensure complete consumption of the cyclopropane.

As an illustration of the utility and versatility of this process, a series of compounds all possessing the bridged tricyclic skeleton of FR900482 and related molecules (vide supra), was prepared via the sequence of reactions in Scheme 2. 2-Iodophenylhydroxylamine **8d** was treated with a variety of aldehydes (**9a**−**c**,**g**,**h**) followed by the addition of cyclopropane **6b**. The initially formed adducts were treated under Heck conditions to effect cyclization to the desired compounds **31**−**35**, much in the manner of Danishefsky in his synthesis of FR900482.[4b]

In summary, we have reported a convenient preparation of highly substituted tetrahydro-1,2-oxazines. This method should be useful for the preparation of interesting new molecular scaffolds as well as have potential application to the synthesis of FR900482 and related structures. Our efforts toward these goals as well as our studies of the mechanistic aspects will be reported in due course.

Acknowledgment. We gratefully acknowledge the financial support of the Natural Sciences and Engineering Research Council (NSERC), The Ontario Ministry of Science and Technology, and MedMira Laboratories. I.S.Y. is an NSERC PGSA awardee.

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

OL0362919

(8) **6a**: commercially available (Aldrich). **6b**: Kierstead, R. W.; Linstead, R. P.; Weedon, B. C. L. *J. Chem. Soc.* **1952**, 3610−3616. **6c**−**g**: Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353−1364.