ORGANIC LETTERS

2007
Vol. 9, No. 19
3857−3858

Hydroxyl-Directed Nitrile Oxide Cycloaddition Reactions with Cyclic Allylic Alcohols

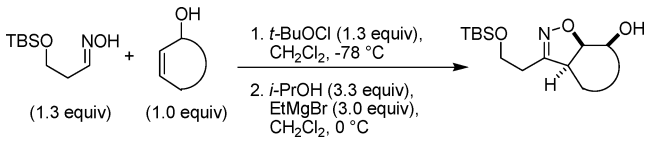
Nina Becker and Erick M. Carreira*

Laboratorium für Organische Chemie, ETH Zurich, CH-8093 Zürich, Switzerland

carreira@org.chem.ethz.ch

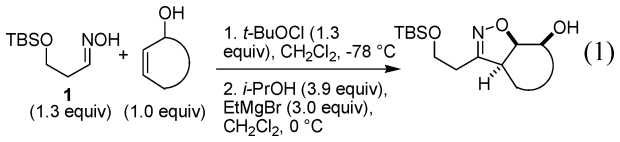
Received July 27, 2007

ABSTRACT



Diastereoselective cycloaddition reactions between a nitrile oxide and cyclic allylic alcohols are reported. The products isolated are densely functionalized building blocks that are not otherwise easily accessed with existing methods and concepts previously established for the construction of acyclic polyketides.

We have previously conducted an in-depth study on the hydroxyl directed cycloaddition reaction of acyclic allylic alcohols and nitrile oxides.[1] This approach provides access to a wide range of acyclic polyketide arrays. Herein we document the cycloaddition reaction of cyclic allylic alcohols, which proceeds in useful yields and high levels of diastereocontrol (eq 1). The isolated adducts provide access to an unusual set of densely functionalized polyketide building blocks.



(1)

The use of acyclic allylic alcohols in diastereoselective nitrile oxide cycloaddition reactions first described by Kanemasa[2] has been subsequently investigated and showcased in the context of complex molecule syntheses in our group. By contrast the use of cyclic allylic alcohols lacks relevant precedence, despite the fact that their utility would considerably expand the scope of building blocks available. The cycloaddition of cyclohex-2-enol was reported to give a complex mixture of many products.[2c] Additionally, Kim reported two examples of aromatic nitrile oxides reacting with tertiary cyclic allylic alcohols;[3] the reactions, however, were slow (48 h).[4] Moreover, it was far from clear whether the cycloaddition reaction would be amenable to generalization. Additionally, the implementation of the cycloaddition would benefit from the use of aliphatic nitrile oxides, which are more capricious and prone to dimerization than the aromatic counterparts. Thus, we have focused on the use of the nitrile oxide generated from **1** and a collection of cyclic allylic alcohols (eq 1). As shown in Table 1, cycloadditions can be effected with five-, seven-, or eight-membered cyclic allylic alcohols displaying various substitution patterns. The typical reaction conditions involve the use of 1.3 equiv of nitrile oxide, 3.3 equiv of isopropyl alcohol, and 3.0 equiv

(1) (a) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082. (b) Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611. (c) Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410. (d) Fader, L. D.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 2485. (e) Muri, D.; Lohse, N.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4036.

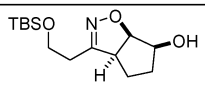
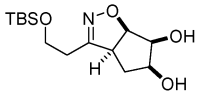
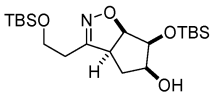
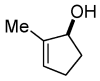
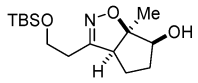
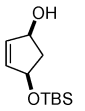
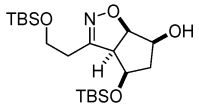
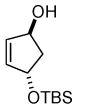
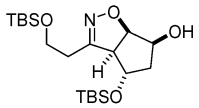
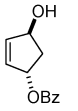
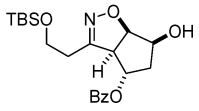
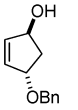
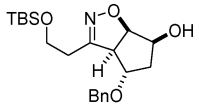
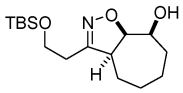
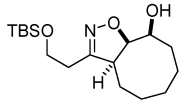
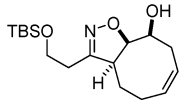
(2) (a) Kanemasa, S.; Kobayashi, S.; Nishiuchi, M.; Yamamoto, H.; Wada, E. *Tetrahedron Lett.* **1991**, *32*, 6367. (b) Kanemasa, S.; Nishiuchi, M.; Wada, E. *Tetrahedron Lett.* **1992**, *33*, 1357. (c) Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324.

(3) Kim, H. R.; Song, J. H.; Rhie, S. Y.; Ryo, E. K. *Synth. Commun.* **1995**, *25*, 1801.

(4) (a) For diastereoselective nitrile oxide cycloadditions with 3-alkyl-4-hydroxycyclopenten-2-ones, which proceed largely on the basis of sterics differences, see: Adembri, G.; Giorgi, G.; Lampriello, R. L.; Paoli, M. L.; Sega, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2649. (b) Basra, S. K.; Drew, M. G. B.; Mann, J.; Kane, P. D. *J. Chem. Soc., Perkin Trans 1* **2000**, 3592.

10.1021/ol7017032 CCC: $37.00
Published on Web 08/23/2007

Table 1. Cycloadditions of Cyclic Allylic Alcohols (Eq 1)[a]

entry	alcohol	cycloadduct	yield
1			66%
2			63%
3			69%
4			44%
5			61%
6			78%
7			61%
8			66%
9			61%[b]
10			88%
11			55%

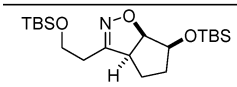
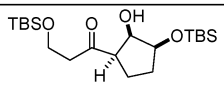
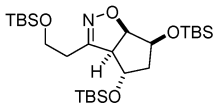
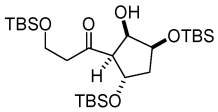
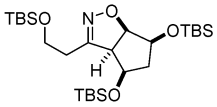
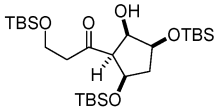
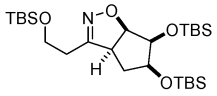
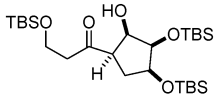
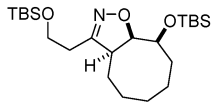
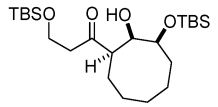
[a] The typical reaction was conducted with 1.3 equiv of nitrile oxide, 3.9 equiv of isopropyl alcohol, and 3.0 equiv of EtMgBr at 0 °C and employed racemic allylic alcohols. All adducts were obtained as single diastereomers, as determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture. The configuration of the cycloadducts was confirmed by 1D NOEs; see the Supporting Information. [b] 2.4 equiv of EtMgBr were employed.

of EtMgBr in CH_2Cl_2 at 0 °C. We have noted that the isoxazolines are uniformly isolated as single regio- and diastereomers, as determined by NMR spectroscopy, favoring the *syn* cycloadduct.

A few entries in Table 1 merit additional commentary. In analogy to our previous work, we believe that stereocontrol is under the exclusive dictate of the allylic stereocenter, which is validated by the results in entries 5 and 6. A substrate incorporating a trisubstituted double bond also forms cycloadduct, albeit in diminished yield (entry 4). The cycloadduct derived from cyclooct-2,6-dienol was obtained chemoselectively, without any evidence of competing reaction at the homoallylic double bond. This outcome allows the remaining resident C=C to function as a handle for further synthetic elaborations. A key limitation we have observed is that cyclohexenols are unreactive.

Although isoxazolines themselves are useful and versatile synthetic scaffolds, their straightforward conversion to the corresponding β-hydroxy ketone derivatives would enhance their utility and inherent value. As exemplified in Table 2,

Table 2. Reductive Opening of Isoxazolines with Raney-Ni[a]

isoxazoline	product	yield
		63%
		80%
		62%
		72%
		69%

[a] Reductive opening was conducted in MeOH/H_2O with 10 equiv of boric acid and Ra-Ni under an atmosphere of H_2.

reductive opening of various adducts with Raney-Ni using conditions developed by Curran[5] leads to β-hydroxy ketones in good yield.

In conclusion, we have documented that the hydroxyl-directed cycloaddition reaction of an aliphatic nitrile oxide with five-, seven-, and eight-membered cyclic allylic alcohols provides isoxazoline cycloadducts in useful yields as single diastereomers. Additionally, the corresponding hydroxy ketones can easily be obtained by straightforward reduction. The products obtained constitute highly functionalized ring systems which should be of great value as building blocks in organic synthesis.

Acknowledgment. We thank the ETH for support of this research in the form of a TH-Gesuch. We are grateful to F. Hoffmann-LaRoche, Lilly, and Boehringer Ingelheim for generous support of our research program.

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

OL7017032

(5) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024.