[3+2] Cycloaddition Reactions of Proline Benzyl Ester Nitrone with Alkenes and Alkynes

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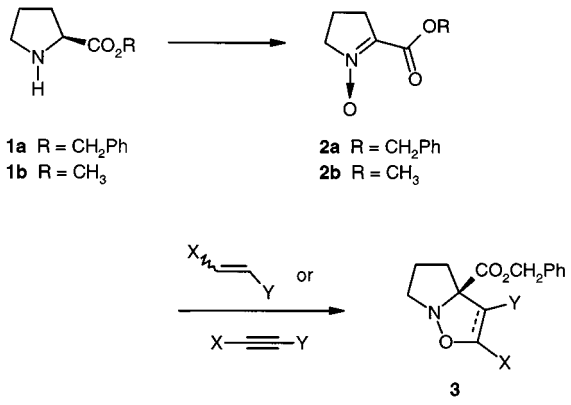
Abstract: Proline-based nitrone **2a** has been synthesized. It readily underwent [3+2] cycloadditions with a variety of alkene and alkyne substrates to give isoxazolidines and isoxazolines, respectively, with good to excellent regio- and diastereoselectivity.

Key words: [3+2] cycloaddition, isoxazolidine, isoxazolin, nitrone

As part of an effort to build combinatorial libraries of various chemical classes, we have investigated potential scaffolds which would lead to molecules with at least two sites for chemical modification. Nitrones represent attractive scaffolds since they undergo [3+2] cycloaddition reactions with a diverse range of alkenes and alkynes to afford versatile isoxazolidine and isoxazoline-type products.[1] These cycloadducts are useful intermediates for the creation of chemical libraries because they are readily modified by reduction,[2] oxidative alkylation,[3] and even oxidation to other nitrones.[4] Therefore the cycloadducts represent a key branch point toward chemical diversity. One appealing scaffold candidate is cyclic nitrone **2a**, closely related to known **2b** (Scheme 1).[5] The latter nitrone has been synthesized several times but, to our knowledge, it has not been utilized in cycloaddition reactions. Reaction of **2a** with various substrates and subsequent reductive cleavage of cycloadducts **3** would produce α-substituted proline derivatives. While cycloadditions of this achiral nitrone to achiral substrates would afford racemic mixtures, our initial efforts focused on this simpler system with the expectation of a future chiral version. We report here the synthesis of **2a** and its cycloaddition reactions with a range of substrates, supporting the use of nitrones as building blocks for combinatorial libraries.[6]



Scheme 1

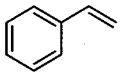
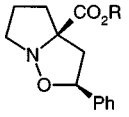
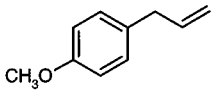
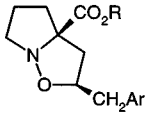
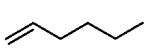
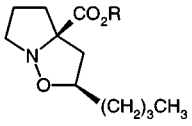
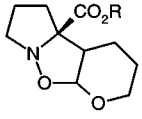
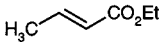
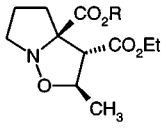
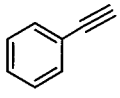
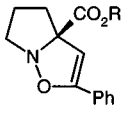
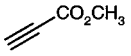
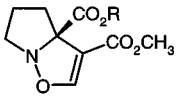
The benzyl ester of proline was chosen as the starting material since it was commercially available and the benzyl group provided a convenient handle during synthetic manipulations. Direct oxidation of proline benzyl ester **1a** was accomplished using a Na_2WO_4-catalyzed hydrogen peroxide oxidation[7] to give nitrone **2a** in 30-40% yield as a low melting solid. When a sample of **2a** was heated under nitrogen in d_8-toluene for 2 days at 110 °C, no decomposition was detected by ^1H or ^{13}C NMR.

With **2a** in hand, we examined its cycloaddition reactions with alkenes and alkynes (Table 1). Substrates for cycloaddition included simple alkenes such as 1-hexene and 4-allylanisole, aryl substituted alkenes such as styrene, and Michael acceptors such as ethyl crotonate. Alkyne substrates included phenyl acetylene and methyl propiolate. In a typical procedure, the nitrone and 2-4 equivalents of substrate were heated in toluene under nitrogen at 80-110 °C. Concentration of the reaction mixture followed by flash chromatography afforded the purified products.

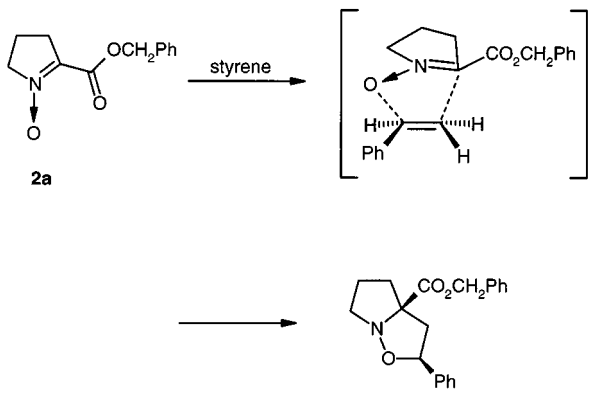
Not surprisingly, reaction times varied considerably depending on the substrate. In general, Michael-type systems such as methyl propiolate and ethyl crotonate reacted fastest, with the cycloaddition essentially complete after just 1-3 hours. Alkynes also reacted rather quickly, possibly helped by both the minimal steric demands of the linear alkyne group and its increased reactivity. Monosubstituted alkenes were considerably slower to undergo cycloaddition, typically requiring 1 to 2 days at reflux in toluene to near completion. The most hindered alkene, tetrahydropyran, gave only a 14% yield of the cycloadduct even after 2 days at reflux. The product, of undetermined stereochemistry, appeared to slowly revert to starting materials in $CDCl_3$ as determined by ^1H NMR analysis. Traces of acid in the solvent may have contributed to the cycloreversion.

The regioselectivity and diastereoselectivity of the cycloadditions was determined using NMR, including extensive NOE and NOESY analysis of cycloadducts **3**.[8] The cycloadditions exhibited very high regioselectivity affording the products anticipated.[8,9] Specifically, the nitrone oxygen added to the end of the multiple bond at which the substitutent either stabilizes formation of partial positive charge (e.g. alkyl, aromatic and alkoxy) or is less destabilizing (e.g. away from the ester). Steric factors may also contribute to the regioselectivity.

Table 1. Cycloadditions of nitrone **2a** with alkenes and alkynes

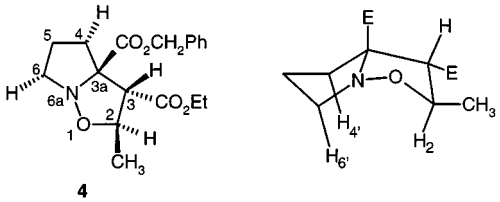
Substrate	Equivalents Substrate	Reaction Temp./Time	Cycloadduct R = CH_2Ph	Ratio (exo:endo)	% Yield
	4	110°C/21 h		>98:2	65
	2	110°C/7 h		>98:2	80
	excess	65°C/24 h		>98:2	60
	as solvent	100°C/48 h		one isomer, not assigned	14
	6	110°C/3 h		>98:2	83
	3	80°C/8 h		----	84
	3.4	80°C/1 h		----	64

The cycloadditions of nitrone **2a** were essentially diastereospecific. Ample precedent exists for diastereoselectivity in cycloadditions of other cyclic nitrones.[10] These reactions generally favor *exo*-mode addition consistent with our observed diastereomer preference (Scheme 2). However, certain cycloadditions are reversible and therefore the product distribution may reflect thermodynamic rather than kinetic control.[9,11]



Scheme 2

In conclusion, we have synthesized nitrone **2a** and investigated its [3+2] cycloaddition reactions with alkenes and alkynes. The nitrone reacted with a variety of substrates to give a diverse set of cycloadducts. The cycloadditions proceeded with excellent regioselectivity and diastereoselectivity. Since the cycloadducts are immediate precursors to α-substituted proline derivatives, the methodology should allow the synthesis of proline derivatives not readily accessible by other methods.[12] Experiments are underway to develop a chiral version of the nitrone to address the limitation of obtaining achiral products. The results of this investigation will be reported in due course.



Figure

References and Notes

(1) Confalone, P. N.; Huie, E. M. in *Organic Reactions*, Vol. 36, 1-158 and reference 11.

(2) LeBel, N. A.; Balasubramanian, N. *J. Am. Chem. Soc*. **1989**, *111*, 3363-3368 and Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351-3354.

(3) Murahashi, S.-I.; Kodera, Y.; Hosomi, T. *Tetrahedron Lett.* **1988**, *29*, 5969-5952.

(4) See LeBal, N. A.; Spurlock, L. A. *J. Org. Chem.* **1964**, *29*, 1337-1339, Holmes, A. B.; Hughes, A. B.; Smith, A. L. *Synlett*. **1991**, 47-48 and de March, P.; Figueredo, M.; Font, J.; Milan, S.; Alvarez-Larena, A.; Piniella, J. F.; Molins, E. *Tetrahedron* **1997**, *53*, 2979-2988.

(5) Marcantoni, E.; Petrini, M.; Polimanti, O. *Tetrahedron Lett*. **1995**, *36*, 3561-3562, Murahashi, S.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem*. **1990**, *55*, 1734-1744, Goti, A.; Nannelli, L. *Tetrahedron Lett*. **1996**, *37*, 6025-6028, Murray, R. W.; Iyanar, K. *J. Org. Chem*. **1996**, *61*, 8099-8102. A 3,4-disubstituted analog of **2b** has recently been reported, but was not used in cycloaddition reactions: see Maeda, H.; Kraus, G. A. *J. Org. Chem*. **1997**, *62*, 2314-2315.

(6) 1,3-Dipolar cycloadditions have been used to make combinatorial libraries on solid support. See Hollinshead, S. P. *Tetrahedron Lett*. **1996**, *37*, 9157-9160.

(7) Murahashi, S.-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem*. **1990**, *55*, 1736-1744.

(8) For a discussion of the stereochemistry of alkene-cyclic nitrone reactions see: Tufariello, J. T. *Accts. Chem. Res*. **1979**, *12*, 396-403.

(9) For reviews, see Bianchi, G.; De Micheli, C.; Gandolfi, R. *Angew. Chem., Int. Ed. Engl*. **1979**, *18*, 721-738 and Bianchi, G.; Gandolfi, R. "1,3-Dipolar Cycloreversions" in *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley Interscience: New York, 1984; Vol. 2, p. 451.

(10) Tamura, O.; Gotanda, K.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Masanori, S. *Chem. Commun*. **1996**, 1861-1862.

(11) For leading references see: Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in OrganicSynthesis*; VCH: New York, 1988; p 22.

(12) See Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704-2708.

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