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# A Weinreb Nitrile Oxide and Nitrone for Cycloaddition

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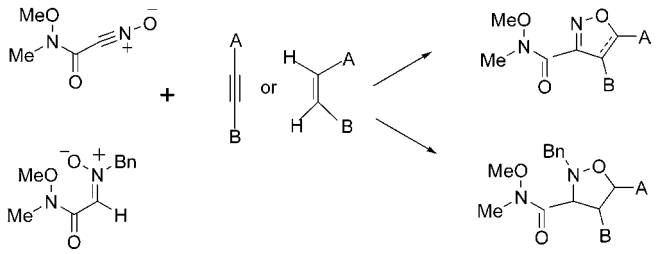
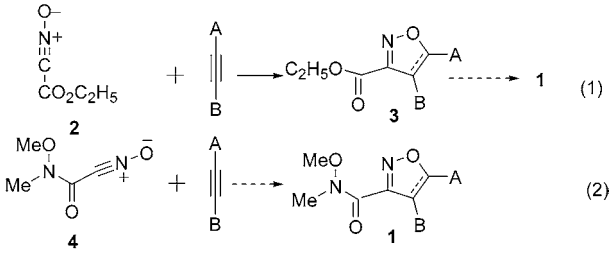
## ABSTRACT



**The cycloaddition of Weinreb amide functionalized nitrile oxide/nitrones with a range of dipolarophiles has been explored.**

This Letter describes the simple preparations and cycloaddition reactions of a new nitrile oxide and nitrone. Our reagent design stemmed from the consideration of three well-known concepts. One idea is the use of heterocycles as peptidomimetics.[1] A second precedent is the preparation of five-membered heterocycles via 1,3-dipolar addition.[2] The third component of our design is the popularity of the *N*-methyl-*N*-methoxyamide (Weinreb amide) as a stable control element for nucleophilic additions to carboxyl derivatives.[3] As a versatile synthon for peptidomimetics to be developed within our neoglycopeptide program,[4] the Weinreb amide isoxazole of generic structure **1** was envisioned. There are two obvious synthetic options for the preparation of **1**, summarized in eqs 1 and 2. Thus, the known ester nitrile oxide **2** could be used to prepare isoxazole **3**, which would then be converted to **1** (eq 1),[5] or the unknown nitrile oxide **4** could be used to produce **1** directly (eq 2). Preliminary studies of the route shown in eq 1 led us to develop the alternate route of eq 2.



The required starting material for both dipolar reactants is the Weinreb aldehyde **8** prepared from commercially

(1) (a) Dragovich, P. S.; Prins, T. J.; Zhou, R.; Webber, S. E.; Marakovits, J. T.; Fuhrman, S. A.; Patick, A. K.; Matthews, D. A.; Lee, C. A.; Ford, C. E. Burke, B. J.; Rejto, P. A.; Hendrickson, T. F.; Tuntland, T.; Brown, E. L.; Meador, J. W., III.; Ferre, R. A.; Harr, J. E. V.; Kosa, M. B.; Worland, S. T. *J. Med. Chem.* **1999**, *42*, 1213−1224. (b) Groutas W. C.; Kuang, R.; Venkataraman, R.; Epp, J. B.; Ruan, S.; Prakash, O. *Biochemistry* **1997**, *36* 4739−4750. (c) Bondebjerg, J.; Xiang, Z.; Bauzo, R. M.; Haskell-Luevano, C.; Meldal, M. *J. Am. Chem. Soc.* **2002**, *124*, 11046−11055. (d) Hoesl, C. E.; Nefzi, A.; Ostresh, J. M.; Yu, Y.; Houghten, R. A. *Methods Enzymol.* **2003**, *369*, 496−517. (e) Lewis, J. G.; Bartlett, P. A. *J. Comb. Chem.* **2003**, *5*, 278−284. (f) Baldwin, S. W.; Long, A. *Org. Lett.* **2004**, *6*, 1653−1656.

(2) (a) Torsell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: Weinheim, 1988. (b) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds; Wiley: Chichester, 2002. (c) Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *164*, 5366−5367. (d) See ref 1f.

(3) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818.

(4) (a) Li, B.; Franck, R. W.; Capozzi, G.; Menichetti, S.; Nativi, C. *Org. Lett.* **1999**, *1*, 111−113. (b) Bartolozzi, A.; Li, B.; Franck, R. W. *Bioorg. Med. Chem.* **2003**, *11*, 3021−3027.

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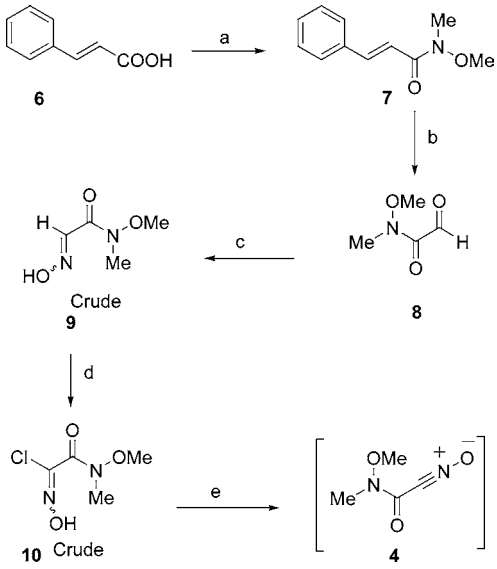
available *trans*-cinnamic acid **6** in two steps. Cinnamic acid derivative **7**[6] is subjected to ozonolysis to produce the desired material isolated as the mixture of aldehyde **8** and its hemiacetal, with methanol used as a cosolvent for the ozonolysis. This inseparable mixture of the desired products, however, was easily separated from benzaldehyde by silica gel chromatography. Treatment of **8** with hydroxylamine hydrochloride produced the crude Weinreb amide-oxime **9** in quantitative yield. The crude oxime **9** can be converted to **4** via the conventional method:[7] chlorination with *N*-chlorosuccinimide followed by removal of HCl by triethylamine (Scheme 1).

**Scheme 1.** Preparation of Weinreb Amide-Nitrile Oxide[a]

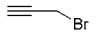
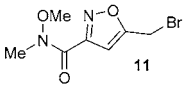
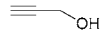
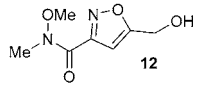
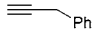
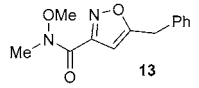
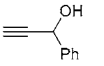
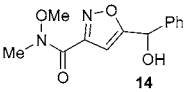
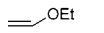
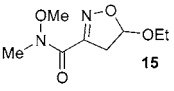
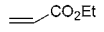
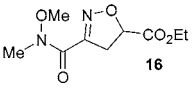



[a] Reagents and conditions: (a) 2-chloro-4,6-dimethoxy-1,3,5-triazine, NMM, Me(MeO)NH·HCl, THF, 10 h, 90%; (b) $O_3$, $CH_2Cl_2$/MeOH, $Me_2S$, 78%; (c) $H_2NOH$·HCl, $NaHCO_3$, ether/$H_2O$, 1 h, 91%; (d) NDS, Pyr, $CHCl_3$; (e) $NEt_3$, $CH_2Cl_2$.

The labile Weinreb amide functionalized nitrile oxide generated in situ was allowed to react with different alkynes (entries 1−4) and alkenes (entries 5 and 6) at room temperature to give substituted isoxazoles and isoxazolines in moderate yield based on oxime. In all cases the reactions are regioselective and give only one product.

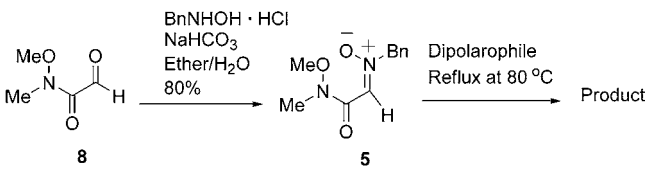
Table 1 records our results from reacting **4** with a range of dipolarophiles.

**Table 1.** [3 + 2] Cycloaddition of Weinreb Amide-Nitrile Oxide

| Entry | Nitrile Oxide | Dipolarophile | Cycloadduct | Yield |
|---|---|---|---|---|
| 1 | **4** |  |  **11** | 55-60% |
| 2 | **4** |  |  **12** | 58% |
| 3 | **4** |  |  **13** | 62% |
| 4 | **4** |  |  **14** | 51% |
| 5 | **4** |  |  **15** | 67% |
| 6 | **4** |  |  **16** | 70% |

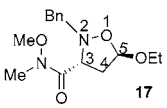
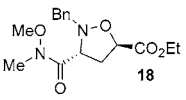
Similarly the Weinreb amide-nitrone **5** was synthesized by treating **8** with *N*-benzyl hydroxylamine hydrochloride (Scheme 2).[8] The crude nitrone was used for cycloadditions

**Scheme 2.** Preparation of Weinreb Amide-Nitrone and Cycloaddition




without further purification (Table 2). In both cases *cis* and *trans* stereoisomers were obtained in a 1:20 ratio favoring the *trans* isomer. The stereochemistry was tentatively assigned from the coupling constant (4 Hz) of the hydrogen at

**Table 2.** [3 + 2] Cycloaddition of Weinreb Amide-Nitrone

| entry | ntrone | dipolarophile | product(major) | yield |
|---|---|---|---|---|
| 1 | **5** |  |  **17** | 84% |
| 2 | **5** |  |  **18** | 82% |

(5) Micetich, R. G.; Shaw, C. C.; Hall, T. W.; Spevak, P.; Fortier, R. A.; Wolfert, P.; Foster, B. C.; Bains, B. K. *Heterocycles* **1985**, *23*, 571−583.

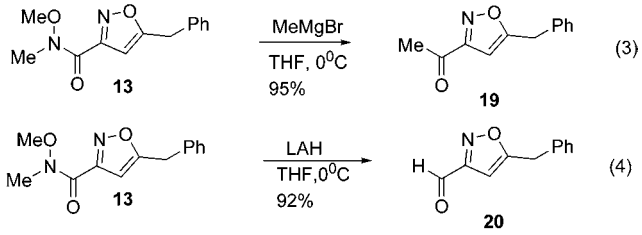
(6) Luca, L. D.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534−2537.

(7) (a) Yin, H.; Franck, R. W.; Chen, S. L.; Quigley, G. J.; Todaro, L. *J. Org. Chem.* **1992**, *57*, 644−651. (b) Jeger, V.; Schohe, R. *Tetrahedron* **1984**, *40*, 2199−2210. (c) Houk, K. N.; Caramella, P.; Cellerinn, G.; Coda, A. C.; Invernizzi, A. G.; Grunanger, P.; Albini, F. M. *J. Org. Chem.* **1976**, *41*, 3349−3357. (d) Jager, V.; Muller, I. *Tetrahedron* **1985**, *41*, 3519−3528. (e) Grunanger, P.; Coda, A. C.; Vernesi, G. *Tetrahedron Lett.* **1966**, 2911−2912.

(8) Deshong, P.; Dicken, C. M. *J. Org. Chem.* **1982**, *47*, 2047−2051.

carbon 5 of the compound **17**. This assignment is based on the work of Deshong[8] and Gómez-Guillén,[9] who had similar isoxazolidines and similar coupling constants at the C-5 hydrogen.

Equations 3 and 4 show that a Weinreb-functionalized isoxazole undergoes reactions with an organolithium and $LiAlH_4$ in the expected manner.[3,10]




In conclusion, two versatile *N*-methyl-O-methyl hydroxamate cycloaddition reagents are available for the synthetic community.

(9) Borrachero, P.; Cabrera-Escribano, F.; Gómez-Guillén, M.; Torres, M. I. *Tetrahedron Lett.* **2004**, *45*, 4835−4839.
(10) Fehrentz, J. A.; Castro, B. *Synthesis* **1983**, 676.

**Acknowledgment.** We dedicate this report to Professor Steven M. Weinreb in recognition of the significance of his amide concept for organic synthesis. This research was supported by NIH grants GM 60271 (R.W.F.), RCMI RR 03037 (Hunter College science infrastructure), and RR 017818 (500 MHz NMR spectrometer).

**Note Added after ASAP Posting.** The footnote for Scheme 1 was missing in the version posted ASAP July 27, 2004; the corrected version was posted August 6, 2004.

**Supporting Information Available:** Experimental procedures and characterization data for compounds **8**, **11**−**14**, and **16**−**20**; copies of the 300 or 500 MHz $^1$H NMR and 75 MHz $^{13}$C NMR spectra of compounds **8**, **12**, **14**, **16**, and **18**−**20**; and (ESI) mass spectra of compounds **18** and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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