ORGANIC
LETTERS

2005
Vol. 7, No. 15
3179−3182

Multicomponent Cascade Reactions: Sequential [1 + 4] and [2 + 3] Cycloadditions for the Generation of Heterocyclic Ring Systems

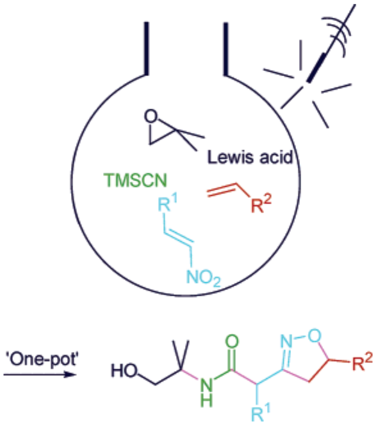
Nicolas M. Fédou,[†] Philip J. Parsons,*,[†] Eddy M. E. Viseux,[†] and Alan J. Whittle[‡]

Department of Chemistry, School of Life Sciences, University of Sussex,
Falmer, Brighton BN1 9QJ, U.K., and Chemistry Laboratories, Maybridge Ltd.,
Trevillet, Tintagel, Cornwall PL34 OHW, U.K.

j.parsons@sussex.ac.uk

Received April 22, 2005

ABSTRACT



A novel intermolecular nitrile oxide cycloaddition sequence has been developed for the formation of highly substituted heterocyclic rings. Reaction of trimethylsilyl cyanide with epoxides generates isonitriles which can react with nitroalkenes to form *N*-(isoxazolylidene)alkylamines. After fragmentation to nitrile oxides, the dipoles can undergo intermolecular 1,3-dipolar cycloadditions with electron deficient dipolarophiles to generate substituted isoxazolines in one synthetic operation.

Multicomponent reactions have attracted considerable attention since an initial report in 1850 by Strecker, who introduced a novel method for the synthesis of amino acids.[1] Passerini[2] further discovered that isonitriles can participate in multicomponent reactions and this finding formed the basis of the well-known Ugi reaction.[3] Almost 50 years later, Saegusa[4] and Foucaud[5,6] reported that nitrile oxides can be generated by the [1 + 4] cycloaddition of isonitriles with nitroalkenes.

The mechanism for the nitrile oxide formation was published by Saegusa in 1972 (Scheme 1).[4]

Although Saegusa reacted the nitrile oxides with a second equivalent of isonitrile in order to generate nitriles, no alkene cyloaddition was reported.

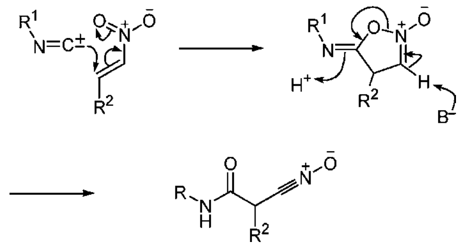
During the course of our studies on the synthetic potential of nitrile oxides, we discovered that *tert*-butyl isonitrile can react with nitroalkene **1** and subsequently fragment to a nitrile

---

[†] University of Sussex.
[‡] Maybridge Ltd.
[1] Strecker, A. *Ann. Chem.* **1850**, *75*, 27.
[2] Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126.
[3] Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8.
[4] Saegusa, T.; Kobayashi, S.; Y., I.; Morino, I. *Tetrahedron* **1972**, *28*, 3389.
[5] Foucaud, A.; Razorilalana-Rabearivony, C.; Loukakou, E.; Person, H. *J. Org. Chem.* **1983**, *48*, 3639.
[6] Person, H.; Delaguilapardo, M.; Foucaud, A. *Tetrahedron Lett.* **1980**, *21*, 281−284.

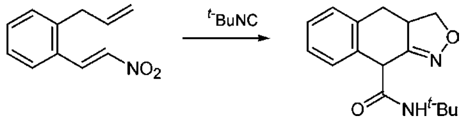
10.1021/ol050892d CCC: $30.25

Scheme 1. Generation of Nitrile Oxides from Isocyanides and Nitro Alkenes



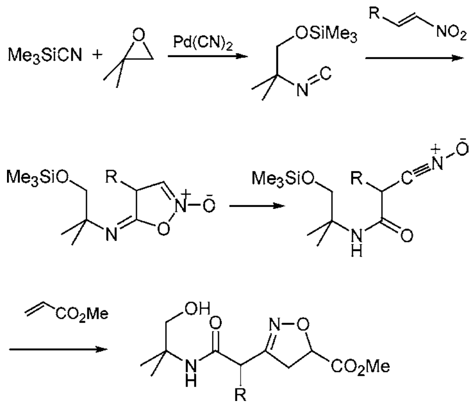
oxide which can be intercepted intramolecularly by 1,3-dipolar cycloaddition with internal alkenes to afford functionalized isoxazolines **2** (Scheme 2).[7]

Scheme 2. Internal Trapping of in Situ Generated Nitrile Oxides



In this paper, we report the elaboration of our original observation to an intermolecular variant which utilizes a four-component reaction sequence to afford heterocyclic rings. In this new cascade (Scheme 3), functionalized isonitriles **5** are generated by the reaction of trimethylsilyl cyanide **3** with substituted epoxides **4**.[8-10]

Scheme 3. Proposed Rationale

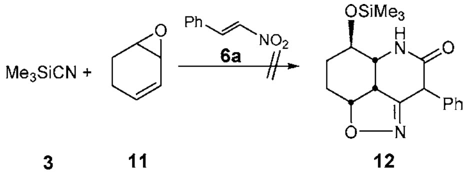


The reaction of isonitrile **5** was investigated with a range of nitroalkenes **6**. Methyl acrylate was chosen for its reactivity toward dipoles of class II (Sustmann's classification), where both the LUMO and the HOMO can be the controlling orbitals during the 6π-aromatic transition state.[11] Various Lewis acids (e.g., $MgBr_2$, $SnCl_2$, $ZnCl_2$, $Sc(OTf)_3$, $Ti(O^i\text{-}Pr)_4$, $Yb(OTf)_3$, $Pd(CN)_2$) were investigated to mediate the formation of isocyanide **5** and to catalyze the dipolar cycloaddition, and palladium cyanide proved to be the most successful. Initial results were capricious, and variable yields of cycloaddition products **10** were isolated. We discovered that lithium perchlorate in acetonitrile (LPAN) improved the yields of cycloadducts **10**, possibly due to the combined effects of solvent polarity increase, increased internal pressure and salt effects.[8] The yield of product **10a** (R = Ph) was increased from 19% (without LPAN) to 58% (5 M LPAN). A range of substituted nitroalkenes was prepared, and the results of the cycloaddition reaction are summarized in Table 1.

The influence of microwave irradiation has also been investigated, and reaction times have successfully been reduced from several hours to 15 min, with yields comparable to the standard thermal conditions.

We are now looking to develop this reaction for intramolecular ring-forming reactions. Addition of trimethylsilyl cyanide to cyclohexadiene oxide gave the expected isonitrile, but this intermediate failed to yield the desired heterocycle **12** (Scheme 4).

Scheme 4. Attempted Intramolecular Cascade



When methyl acrylate **9** was added to the reaction mixture, isoxazoline **18** was isolated in low yield (7%) (Scheme 5). This observation suggests that the cycloaddition could take place before the *N*-(isoxazolidinylidene)alkylamine **16** could

Scheme 5. Proposed Rationale

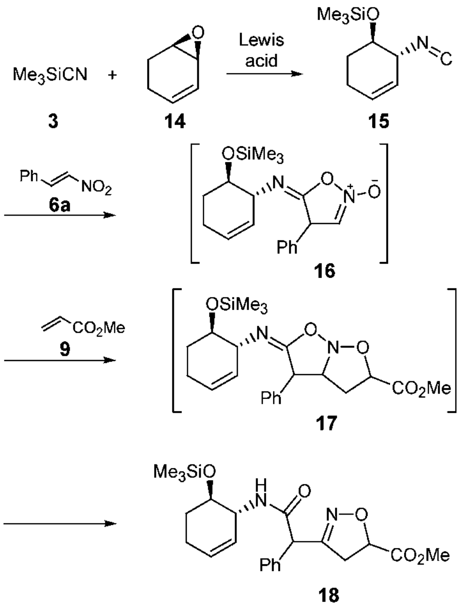
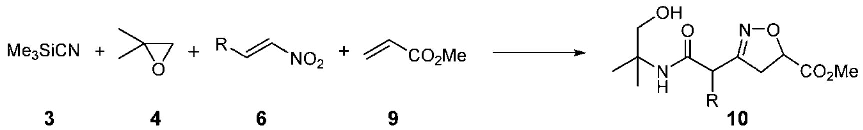
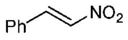
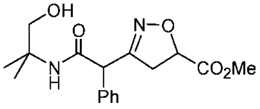
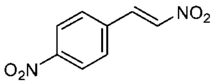
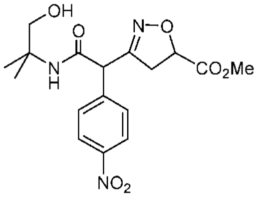
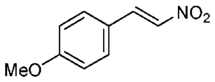
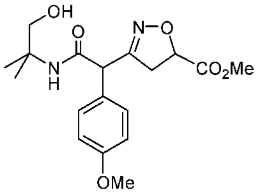
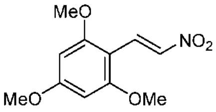
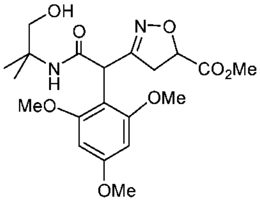
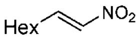
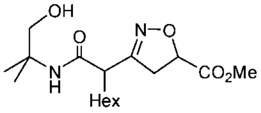


Table 1. Examples for the Multicomponent Cascade Reaction

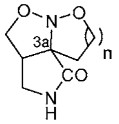


Entry	Nitroalkene	Isoxazolidine product	Yield
1	 **6a**	 **10a**	58[a,c] (37[b,c])
2	 **6b**	 **10b**	33[b,c]
3	 **6c**	 **10c**	31[b,c]
4	 **6d**	 **10d**	18[b,c]
5	 **6e**	 **10e**	33[b,c]

[a] 2 equiv of the isocyanide was used, crude yield. [b] 1.1 equiv of the isocyanide was used, isolated yield. [c] 1:1 ratio of diastereoisomers.

fragment to the corresponding amido nitrile oxide, compromising the intramolecular cycloaddition due to steric impediments. The formation of bicycle **17** is corroborated by previous observations made by Shimizu during the investigation of the cycloaddition of nitrones with dipolarophiles, where tetrahydro-2*H*-isoxazolo[2,3-*b*]isoxazol-1-yl-1-fluorates **13** bearing a quaternary center at position 3a (Figure 1) were isolated.[12]

In conclusion, a novel, efficient and flexible method to access substituted isoxazolines is reported herein, involv-



13

Figure 1. Isolation of tetrahydro-2*H*-isoxazolo[2,3-*b*]isoxazol-1-yl-1-fluorates by Shimizu.

---

(7) Knight, J.; Parsons, P. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 979.

(8) Imi, K.; Yanagihara, N.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 1013.

(9) Gassman, P. G.; Haberman, L. M. *J. Org. Chem.* **1986**, *51*, 5010.

(10) Gassman, P. G.; Haberman, L. M. *J. Am. Chem. Soc.* **1982**, *104*, 5849.

(11) Sustmann, R. *Tetrahedron Lett.* **1971**, 2717.

(12) Shimizu, T.; Hayashi, Y.; Teramura, K. *J. Org. Chem.* **1983**, *48*, 3053.

ing a ‘one-pot’ Lewis acid-catalyzed isocyanide formation/ [1 + 4] cycloaddition/nitrile oxide formation/in situ 1,3-dipolar cycloaddition cascade.

Further investigations of this cascade will be published soon. We are currently investigating the use of chiral catalysts for these tranformations.

Acknowledgment. We gratefully acknowledge support from Maybridge Ltd. and the ESPRC. We thank Dr. Ali Abdul-Sada for mass spectrometry measurements and Dr. Anthony Avent for NMR measurements.

Supporting Information Available: Experimental procedures and spectroscopic data for **10a**−**e** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050892D