Pergamon

Tetrahedron Letters 40 (1999) 7955–7959

TETRAHEDRON LETTERS

Synthesis and 1,3-dipolar cycloaddition reactions of 4-methyl-1-nitromethyl-2,6,7-trioxabicyclo[2.2.2]octane

Christopher J. Fenk *

Department of Chemistry, Kent State University-East Liverpool Campus, East Liverpool, OH 43920, USA

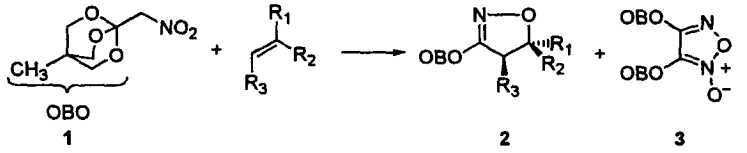
Received 27 July 1999; accepted 24 August 1999

Abstract

The preparation of novel 3-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octyl)-Δ^2-isoxazolines **2** via nitrile oxide cycloaddition chemistry is described. The target compounds were produced in moderate to good yields using only 2.2 equivalents of alkene and without the need for slow addition of reagents. Cycloaddition reactions were conducted using modified Mukaiyama conditions that included a convenient dehydration reagent which significantly simplified product isolation.

Keywords: cycloadditions; nitrile oxides; orthoesters; isoxazolines.

Study of the biological, synthetic and commercial applications of 2,6,7-trioxabicyclo[2.2.2]octanes has received renewed attention since the development of a new and versatile synthesis of these compounds was reported by Corey and Raju in 1983.[1] Compounds containing the 2,6,7-trioxabicyclo[2.2.2]octane sub-unit (OBO esters) have been shown to be useful as synthetic intermediates, pesticides, artificial sweeteners, dental adhesives, polymers, and liquid crystals.[2,3] The present study demonstrates the synthetic utility of 4-methyl-1-nitromethyl-2,6,7-trioxabicyclo[2.2.2]octane (**1**) as part of a cycloaddition approach for the preparation of 3-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octyl)-Δ^2-isoxazolines 2 (3-OBO-Δ^2-isoxazolines) (Scheme 1).[4]



1 2 3

Scheme 1.

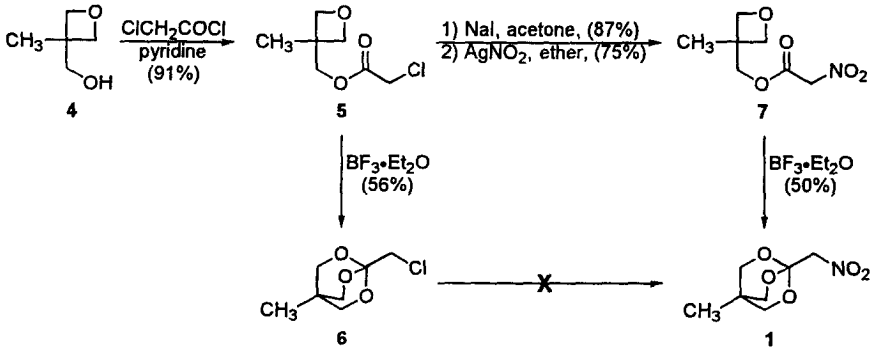
There are several advantages to developing highly functionalized cycloaddition reagents such as orthoester **1**. 3-OBO-Δ^2-Isoxazolines have not been previously reported. OBO esters serve as a convenient carboxyl protecting group since they are resistant to attack by strong nucleophiles and are readily

* Corresponding author.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01656-1

hydrolyzed under relatively mild reaction conditions.[5] 1,3-Dipolar cycloaddition reactions of nitrile oxides with olefins are stereospecific and are not significantly hindered by incorporation of sterically bulky substituents.[6,7] In fact, sterically large nitrile oxide substituents are known to inhibit the formation of undesired by-products such as furoxan **3**.[6a] Finally, the synthetic potential of these compounds may be considerable as indicated by Kozikowski's work with 3-carbethoxy-Δ^2-isoxazolines.[8]

Nitrile oxides are typically generated in situ either by dehydration of primary nitro paraffins according to the method of Mukaiyama, or by the dehydrohalogenation of hydroxamic acid halides.[4] In order to take advantage of the benefits offered by sterically congested nitrile oxides and the convenience of the Mukaiyama protocol for in situ generation of nitrile oxides from nitro alkanes, orthoester **1** was selected as the direct precursor for the synthesis of 3-OBO-Δ^2-isoxazolines. Incorporating the work of Corey and Raju,[1] the title compound **1** was readily prepared using a four-step sequence (Scheme 2).



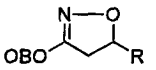
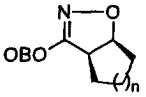
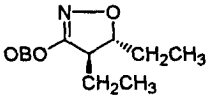
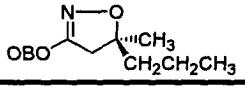
Scheme 2.

Reaction of 3-hydroxymethyl-3-methyl oxetane (**4**) with chloroacetyl chloride and pyridine in methylene chloride at 0°C provided chloro ester **5** in 91% yield. Cyclization of **5** using $BF_3 \cdot Et_2O$ in CH_2Cl_2 at 0°C provided orthoester **6** in 56% yield. Unfortunately, all efforts to react **6** with sodium nitrite to provide 4-methyl-1-nitromethyl-2,6,7-trioxabicyclo[2.2.2]octane (**1**) were unsuccessful. Indeed, orthoester **6** even failed to react with sodium iodide. Consequently, an alternative route to the desired compound was developed.

Kornblum et al. have shown that α-iodo esters react with $AgNO_2$ to produce α-nitro esters while the corresponding α-chloro and α-bromo esters were virtually non-reactive.[9] Therefore, chloro ester **5** was treated with sodium iodide in acetone at room temperature to give the corresponding iodo ester in 87% yield. Subsequent reaction with silver nitrite in ether at room temperature for 48 h gave nitro ester **7** in 75% yield. Cyclization of **7** was complicated by the presence of the nitro group and reaction attempts using catalytic amounts (25 mol%) of $BF_3 \cdot Et_2O$ were unsuccessful. However, reaction of **7** with 1.25 equivalents of $BF_3 \cdot Et_2O$ in CH_2Cl_2 at 5°C for 24 h gave the desired orthoester **1** in 50% yield as a white crystalline solid. This compound is remarkably stable when stored at −20°C and exhibited no detectable decomposition even after three years.

With the requisite nitro compound in hand, a detailed study was undertaken to unveil the optimum 1,3-dipolar cycloaddition reaction conditions (Scheme 1). Surprisingly, **1** underwent rather sluggish cycloaddition reactions when employing 'standard' Mukaiyama dehydration conditions.[10] Two methods were ultimately developed that maximized the yield of cycloadduct and minimized the reaction time. Cycloaddition was accomplished in a sealed pressure tube by heating a solution of orthoester **1**, olefin, phenyl isocyanate and triethylamine in benzene for 30 h at 135°C (Method A).[11] Alternatively, the reaction could be conducted at atmospheric pressure by refluxing a solution of **1**, olefin, methylenebis(phenyl isocyanate) (MDI), and triethylamine in toluene for 90 h (Method B).[12] Upon completion, water was

Table 1
3-OBO-Δ^2-Isoxazolines

Olefin	Cycloadduct	Method	Yield[15]
styrene	 R = Ph	A	73%
1-hexene	R = Bu	B	74%
cyclopentene	 n = 1	A	80%
cyclohexene	n = 2	B	55%
trans-3-hexene		B	75%
2-methyl-1-pentene		B	62%

Method A: **1**, 2.2 eq. olefin, 3.0 eq. PhNCO, 1.0 eq. Et_3N, benzene (sealed tube), 135°C, 30 h.
Method B: **1**, 2.2 eq. olefin, 3.0 eq. MDI, 1.0 eq. Et_3N, refluxing toluene, 90 h.

added to the reaction mixtures to consume any unreacted isocyanate. The cycloadducts formed using Method A were purified by flash chromatography[13] and recrystallization. Due to the polymeric nature of the urea formed from MDI in Method B, the desired cycloadducts could often be purified simply by filtration and recrystallization. Even in cases where chromatographic purification was required, the often tedious task of separating the product from the urea by-product was eliminated.[14] Both procedures were effective and provided the desired cycloadducts in yields ranging from 55–80% (Table 1).[15]

Several aspects of these cycloaddition reactions are of interest and deserve comment. Typically, in cycloaddition reactions involving nitrile oxides, yields of Δ^2-isoxazoline are optimized by utilizing large excesses of olefin and/or syringe pump addition of reagents. Furthermore, while monosubstituted and 1,1-disubstituted alkenes generally provide good yields of cycloadduct, 1,2-disubstituted alkenes tend to be poorer dipolarophiles.[4] The cycloaddition reactions described in this report do not require large excesses of reagents or slow addition techniques in order to achieve satisfactory product yields. All of the reaction yields listed in Table 1 were accomplished using only 2.2 equivalents of alkene. Note also that even expectedly poor dipolarophiles such as cyclohexene and *trans*-3-hexene provided satisfactory product yields.

Most notable is the quantity of base used for these cycloaddition reactions. While a catalytic amount of base is normally used when applying Mukaiyama's procedure, all of the reported isoxazolines were prepared using a stoichiometric amount of base. Fortunately, the excess base served only to accelerate the cycloaddition reactions and did not promote the formation of significant quantities of furoxan **3**. Indeed, furoxan **3** has yet to be isolated using this protocol.

In summary, 1,3-dipolar cycloaddition reactions of a new carbalkoxy nitrile oxide equivalent were reported. The resulting 3-OBO-Δ^2-isoxazolines were isolated in moderate to good yield without resorting to large olefin excesses or slow reagent addition techniques. The mechanics of product isolation were greatly simplified by use of methylenebis(phenyl isocyanate) as the dehydration reagent in the cycloaddition reactions. The method for synthesis of 3-OBO-Δ^2-isoxazolines described here has considerable

potential to be exploited in the synthesis of α-keto acids and α-amino acids. Work along these lines is currently in progress.

Acknowledgements

Thanks to the Kent State University Research Council and regional campuses for funding of this work. Drs. Richard A. Conley and Paul Sampson are also gratefully acknowledged for numerous discussions, advice and encouragement during the development of this project. Special thanks to Dr. Mahinda Gangoda for providing analytical support.

References

1. Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571–5574.
2. (a) Casida, J. E. *Arch. Insect Biochem.* **1993**, *22*, 13–23. (b) Goodman, M.; Oh, Y. S. U.S. Patent 529827, 1994; *Chem. Abstr.* 121:107045. (c) Tokuyama Soda Co. Ltd., Japan JP 58213781, 1983; *Chem. Abstr.* 100:197826. (d) Paschke, R.; Zaschke, H.; Hauser, A.; Demus, D. *Liquid Crystals* **1989**, *6*, 397–407. (e) Corey, E. J.; Shimoji, K. *J. Am. Chem. Soc.* **1983**, *105*, 1662–1664. (f) Corey, E. J.; De, B. *J. Am. Chem. Soc.* **1984**, *106*, 2735–2736. (g) Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339–4341. (h) Ishizone, T.; Tominaga, T.; Kitamura, K.; Hirao, A.; Nakahama, S. *Macromolecules* **1995**, *28*, 4829–4836.
3. For reviews on the syntheses and uses of ortho esters, see: (a) Pindur, U.; Müller, J.; Flo, C.; Witzel, H. *Chem. Soc. Rev.* **1987**, 75–87. (b) Pavlova, L. A.; Davidovich, Yu. A.; Rogozhin, S. V. *Russ. Chem. Rev.* **1986**, *55*, 1026–1041. (c) DeWolfe, R. H. *Synthesis* **1974**, 153-172.
4. For reviews on the synthetic utility of Δ^2-isoxazolines and cycloaddition reactions involving nitrile oxides, see: (a) Curran, D. P. *Advances in Cycloaddition*; JAI: Greenwich CN, 1988; pp. 129–189. (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988. (c) Kanemasa, S.; Tsuge, O.; *Heterocycles* **1990**, *30*, 719–736. (d) Grunanger, P.; Vita-Finzi, P. In *The Chemistry of Heterocyclic Compounds*; Wiley (Interscience): New York, 1991; Vol. 49, Part 1. (e) Easton, C. J.; Hughes, C. M. M.; Savage, G. P.; Simpson, G. W. In *Advances in Heterocyclic Chemistry*; Katritzky, A. Ed.; Academic: New York, 1994; Vol. 60, pp. 261–327.
5. (a) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: Stuttgard, New York, 1994 and references cited therein. (b) For a kinetic study on the relative stability of cyclic ortho esters, see: Atkins, M. P.; Golding, B. T.; Howes, D. A. *J. Chem. Soc., Chem. Commun.* **1980**, 207–208.
6. (a) Curran, D. P.; Scanga, S. A.; Fenk, C. J. *J. Org. Chem.* **1984**, *49*, 3474–3478. (b) Martin, S. F.; Dupre, B. *Tetrahedron Lett.* **1983**, *24*, 1337–1340. (c) Barrow, S. J.; Easton, C. J.; Savage, G. P.; Simpson, G. W. *Tetrahedron Lett.* **1997**, *38*, 2175–2178.
7. (a) Grudmann, C.; Grünhanger, P. *The Nitrile Oxides*; Springer-Verlag: New York, 1971. (b) Caramella, P.; Grünhanger, P. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984.
8. (a) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410–416. (b) Kozikowski, A. P.; Adamczyk, M. *J. Org. Chem.* **1983**, *48*, 366–372.
9. Kornblum, N.; Chalmer, M. E.; Daniels, R. *J. Am. Chem. Soc.* **1955**, *77*, 6654–6655.
10. Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339–5342.
11. Method A, cyclopentene adduct. A solution of **1** (48 mg, 0.25 mmol), cyclopentene (48 μL, 0.55 mmol), phenyl isocyanate (82 μL, 0.75 mmol) and triethylamine (32 μL, 0.25 mmol) in benzene (0.75 ml) was placed into a glass pressure tube and heated to 135°C for 30 h. Water (13.5 μL, 0.75 mmol) was added to react with the excess phenyl isocyanate. The mixture was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The product was purified by flash chromatography (20% EtOAc/hexanes) and recrystallization to give 48 mg (80% yield) white crystals. Mp 158–160°C (ether/hexanes); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 4.97 (1H, dd, J=5.0 Hz), 3.93 (6H, s), 3.66 (1H, t, J=8.6 Hz), 2.07 (1H, m), 1.87 (1H, m), 1.60 (3H, m), 1.18 (1H, m), 0.78 (3H, s); ^{13}C NMR (DMSO-d_6, 125.7 MHz) δ 155.4, 104.8, 86.9, 72.0, 51.5, 35.0, 30.5, 29.9, 22.8, 13.6; IR ($CHCl_3$) 3021 (m), 2967 (m), 2884 (m), 1407 (m), 1266 (w), 1117 (s), 998 (s) cm^{-1}; MS *m/z* 239 (M^+, 3), 210 (3), 209 (27), 165 (12), 164 (9), 150 (6), 149 (4), 140 (9), 139 (100), 138 (25), 136 (5), 111 (10), 108 (7), 94 (5), 92 (5), 82 (15), 79 (9), 70 (11), 67 (25). Anal. calcd for $C_{12}H_{17}NO_4$; C, 60.24; H, 7.16; found C, 60.09; H, 7.25.

12. Method B, *trans*-3-hexene adduct. To a solution of **1** (96 mg, 0.50 mmol), *trans*-3-hexene (137 μL, 1.10 mmol) and MDI (375 mg, 1.50 mmol) in toluene (5.0 ml) was added triethylamine (70 μL, 0.50 mmol). The solution was heated to reflux for 90 h and then cooled to room temperature. Water (30 μL, 1.67 mmol) was added and stirring was continued for 12 h. The product mixture was dried ($MgSO_4$), filtered through Celite® and the solvent was removed under reduced pressure. The product was purified by recrystallization to give 96 mg (75% yield) white crystals. Mp 102–104°C (ether/hexanes). ^1H NMR (DMSO-d_6, 400 MHz) δ 4.21 (1H, q (overlapping dt), J=8.3 Hz), 3.94 (6H, s), 2.86 (1H, m), 1.69 (1H, m), 1.41 (3H, m), 0.83 (3H, t, J=6.7 Hz) overlapping 0.82 (3H, t, J=6.7 Hz), 0.79 (3H, s); ^{13}C NMR (DMSO-d_6, 125.7 MHz) δ 157.2, 140.3, 87.4, 73.2, 53.7, 31.1, 28.6, 24.6, 14.8, 11.6, 10.1; IR ($CHCl_3$) 3017 (m), 2968 (s), 2938 (m), 2882 (m), 1460 (m), 1405 (m), 1114 (m), 993 (s); MS *m/z* 255 (M^+, 7), 226 (11), 225 (24), 181 (15), 180 (7), 171 (10), 166 (5), 156 (11), 155 (100), 154 (22), 152 (6), 129 (6), 125 (5), 124 (7), 122 (5), 114 (7), 108 (6), 98 (36), 85 (14), 71 (13), 70 (33), 69 (38), 68 (15), 67 (20). Anal. calcd for $C_{13}H_{21}NO_4$; C, 61.16; H, 8.29; found C, 61.00; H, 8.34.
13. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
14. Use of tolylene 2,4-diisocyanate and phenylene 1,4-diisocyanate have also been reported as dehydration agents, see: (a) Dawson, I. M.; Johnson, T.; Paton, R. M.; Rennie, R. A. *C. J. Chem. Soc., Chem. Commun.* **1988**, 1339–1340. (b) Jäger, V.; Müller, I. *Tetrahedron* **1985**, *41*, 3519–3528.
15. Isolated yields. New compounds were characterized by ^1H NMR, ^{13}C NMR, IR, MS, and elemental analysis.