Published in final edited form as:

Tetrahedron Lett. 2010 July 1; 51(29): 3789–3791. doi:10.1016/j.tetlet.2010.05.062.

Cyclopropanation of nitroso Diels–Alder cycloadducts and application to the synthesis of a 2',3'-methano carbocyclic nucleoside

Cheng Ji and Marvin J. Miller*

Department of Chemistry and Biochemistry, 251 Nieuwland Science Hall, University of Notre Dame, Notre Dame, Indiana, 46556, United States

Abstract

Treatment of nitroso Diels–Alder cycloadducts **1** with diazomethane in the presence of palladium acetate gives synthetically useful *exo*-6-oxa-7-azatricyclo[3.2.1.0^{2,4}]octane derivatives **7** in good to excellent yield. Using this methodology, a conformationally restricted 2',3'-methano carbocyclic nucleoside was efficiently synthesized from nitroso cycloadduct **1a** in 7 steps.

Nitroso Diels–Alder (NDA) cycloadducts **1**, derived from nitroso agents and cyclopentadiene, are synthetically valuable precursors for many biologically interesting molecules.¹ Site selective modification of **1**, including the separate cleavage of the N–O² or C–O^{3–6} bonds, has been employed in the preparation of various carbocyclic nucleosides⁷ and natural products.⁸

The unsaturated C=C bond in **1** also allows introduction of multiple functionalities in one step (Scheme 1). Previous modifications of the olefin mainly focused on oxidative cleavage,⁹ reduction¹⁰ and dihydroxylation.¹¹ Recently, our group demonstrated that additions of azides to the olefin in nitroso cycloadducts afforded the *exo*-triazoline **5** in excellent yield.¹² Quadrelli *et. al.* also reported formation of isoxazoline **6** by cycloaddition between a nitrile oxide and cycloadduct **1**.¹³ To further explore the synthetic utility of the olefin and expand the versatility of nitroso cycloadducts, here we report a study of Pd-catalyzed cyclopropanation of **1** with diazomethane to form *exo*-6-oxa-7-azatricyclo[3.2.1.0^{2,4}]octane derivatives **7** and demonstrate the utility of the process by the synthesis of a methano carbocyclic nucleoside.

Palladium catalyzed cyclopropanations of strained bicyclic alkenes with diazomethane are known in the literature. Because of its excellent catalytic activity, palladium(II) acetate is a particularly useful and efficient reagent for this transformation. Examples include additions to norbornene,¹⁴ 2-azabicyclo[2.2.1]hept-5-en-3-one (ABH),¹⁵ and 2,3-dioxabicyclo[2.2.1]heptane.¹⁶ However, no report has yet appeared on the catalytic cyclopropanation of bicyclic oxazines, such as nitroso cycloadducts **1**, with diazomethane.

We were pleased to find that by treating *N*-carbamate based nitroso cycloadduct **1a** with 8 equiv of diazomethane in the presence of 5 mol% of Pd(OAc)₂ at 0 °C, *exo* cyclopropane product **7a** was exclusively obtained in 96% yield within 30 min (Table 1, entry 1).¹⁷ To further

© 2010 Elsevier Science. All rights reserved.

*Corresponding author. Tel.: +1 574 631 7571; fax: +1 574 631 6652; mmiller1@nd.edu (M. J. Miller).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

explore the functional group compatibility in this cyclopropanation reaction, a series of *N*-substituted cycloadducts were examined using the same reaction conditions. The results are summarized in Table 1. All of the cycloadducts selected, including acyl (**1c–e**), carbamate (**1a–b**), urea (**1f**), and pyridine (**1g**) derived substrates, reacted quickly and efficiently with diazomethane to afford the corresponding cyclopropanated products **7a–g** in good to excellent yields (Table 1, entries 1–7). This indicates that pendent functional groups on nitroso cycloadducts are well-tolerated in this Pd-catalyzed cyclopropanation.

The *exo*-stereochemistry of the cyclopropanated products was confirmed by 2D NMR experiments and was consistent with previously reported cycloaddition reactions of **1** with azides or nitrile oxides. Interestingly, the ⁴*J*-coupling (“W-coupling”) ¹², ¹³b of H² and H⁴ with H^{8'} which has been often seen in systems like triazoline **5** and isoxazoline **6** was not observed in this case. Nevertheless, ROSEY correlation studies revealed the NOE interaction between H^{3'} and H⁸ (Figure 1), which supported the *exo* configuration of the fused cyclopropane ring.

Carbocyclic nucleosides have attracted much attention in the development of novel antiviral and antitumor agents. The isosteric replacement of an oxygen atom in the parent furanose with a methylene unit confers metabolic stability toward cleavage by nucleoside phosphorylases or hydrolases.¹⁸ However, their bioactivities are often diminished because of the lowered conformational rigidity induced by the methylene function.¹⁹ To overcome this problem, a number of conformationally rigid carbocyclic nucleoside analogs have been designed and synthesized, including nucleosides based on bicyclo[3.1.0]hexane systems which are known as methano carbocyclic nucleosides.^{15,20} The cyclopropanation methodology presented here provides a new synthetic scaffold for quick access 2',3'-methano carbocyclic nucleosides, starting from the cyclopropanated compound **7a** (Scheme 2). Hydrogenation of **7a** catalyzed by 10% Pd/C provided the *N*-Boc protected 1,4-amino alcohol **8** in quantitative yield. Compound **9** was obtained from **8** by acetylation under basic conditions. Subsequent TFA-mediated *N*-Boc removal gave free amine **10**, which was ready to serve as an evolvable scaffold to build various nucleobases. In this case, an adenine ring, as a representative base, was constructed in 3 steps to afford the 2',3'-methano carbocyclic noradenosine **13**.²¹

In summary, an efficient and stereoselective cyclopropanation reaction between nitroso cycloadducts and diazomethane catalyzed by palladium acetate was developed. The resulting cyclopropane product was demonstrated to be a synthetically useful scaffold by the synthesis of a methano carbocyclic nucleoside. Further application of this chemistry for the syntheses of various carbocyclic nucleosides and the biological evaluation of these analogs are in progress.

Acknowledgments

We thank the Lizzadro Magnetic Resonance Research Center at Notre Dame for NMR facilities and Nonka Sevova for mass spectroscopic analyses. We acknowledge The University of Notre Dame and NIH (GM068012) for support of this research.

References and notes

1. (a) Vogt PF, Miller MJ. *Tetrahedron* 1998;54:1317. (b) Samarakoon T, Hanson RR. *Chemtracts* 2007;20:220.
2. (a) Cesario C, Tardibono LP, Miller MJ. *J. Org. Chem* 2009;74:448. [PubMed: 19053586] (b) Shireman BT, Miller MJ. *Tetrahedron Lett* 2000;41:9537. (c) Zhang D, Ghosh A, Söling C, Miller MJ. *Tetrahedron Lett* 1996;37:3799. (d) Keck GE, McHardy SF, Wager TT. *Tetrahedron Lett* 1995;36:7419.
3. (a) Yang BY, Miller MJ. *Tetrahedron Lett* 2010;51:889. [PubMed: 20209116] (b) Machin BP, Howell JH, Mandel J, Bianchard N, Tam W. *Org. Lett* 2009;11:2077. [PubMed: 19361204] (c) Machin BP,

- Ballantine M, Mandel J, Bianchard N, Tam W. J. Org. Chem 2009;74:7261. [PubMed: 19731959] (d) Surman MD, Mulvihill MJ, Miller MJ. Org. Lett 2002;4:139. [PubMed: 11772110] (e) Mulvihill MJ, Surman MD, Miller MJ. J. Org. Chem 1998;63:4874. (f) Surman MD, Miller MJ. J. Org. Chem 2001;66:2466. [PubMed: 11281789] (g) Surman MD, Miller MJ. Org. Lett 2001;3:519. [PubMed: 11178814]
4. Bodnar BS, Miller MJ. Tetrahedron Lett 2009;50:796. [PubMed: 20160837]
5. (a) Surman MD, Mulvihill MJ, Miller MJ. J. Org. Chem 2002;67:4115. [PubMed: 12054945] (b) Surman MD, Mulvihill MJ, Miller MJ. Tetrahedron Lett 2002;43:1131.
6. (a) Cesario C, Miller MJ. J. Org. Chem 2009;74:5730. [PubMed: 19514728] (b) Cesario C, Miller MJ. J. Org. Chem 2009;11:1293.
7. (a) Lin WM, Gupta A, Kim KH, Mendel D, Miller M. J. Org. Lett 2009;11:449. (b) Li FZ, Brogan JB, Gage JL, Zhang DY, Miller MJ. J. Org. Chem 2004;69:4538. [PubMed: 15202916] (c) Kim K-H, Miller MJ. Tetrahedron Lett 2003;44:4571.
8. (a) Li F, Miller MJ. J. Org. Chem 2006;71:5221. [PubMed: 16808509] (b) Li F, Warshakoon NC, Miller MJ. J. Org. Chem 2004;69:8836. [PubMed: 15575765]
9. (a) Nora GP, Miller MJ, Möllmann U. Bioorg. Med. Chem. Lett 2006;16:3966. [PubMed: 16730172] (b) Pepper AG, Procter G, Voyle M. Chem. Commun 2002:1066. (c) Shireman BT, Miller MJ, Jonas M, Wiest O. J. Org. Chem 2001;66:6046. [PubMed: 11529730] (d) Heinz LJ, Lunn WHW, Murff RE, Paschal JW, Spangle LA. J. Org. Chem 1996;61:4838. [PubMed: 11667426]
10. Just G, Cutrone L. Can. J. Chem 1976;54:867.
11. Keck GE, Romer DR. J. Org. Chem 1993;58:6083.
12. Bodnar BS, Miller MJ. J. Org. Chem 2007;79:3929. [PubMed: 17429998]
13. (a) Quadrelli P, Mella M, Paganoni P, Caramella P. Eur. J. Org. Chem 2000;14:2613. (b) Quadrelli P, Bovio B, Piccinini A, Caramella P, De Sarlo F, Machetti F. Tetrahedron 2009;65:10679.
14. (a) Kottwitz J, Vorbrüggen H. Synthesis 1975:636. (b) Dzhemilev UM, Dokichev VA, Sultanov SZ, Khusnutdinov RI, Tomilov YuV, Nefedov OM, Tolstikov GA. Izv. Akad. Nauk SSSR, Ser. Khim 1989;8:1861.
15. Katagiri N, Yamatoya Y, Ishikura M. Tetrahedron Lett 1999;40:9069.
16. Emerzian MA, Davenport W, Song J, Li J, Erden I. Adv. Synth. Catal 2009;351:999.
17. (a) Attempts to decrease the catalyst loading to 1 or 2 mol% led to incomplete reaction. (b) General experimental procedure for Pd(OAc)₂ catalyzed cyclopropanation: To the reaction vessel of a mini Diazald apparatus was added a 3 M KOH solution (9 mL, EtOH/H₂O 5/4) and the condenser was cooled to -78 °C with dry ice/acetone. To a 50 mL round-bottom flask as the receiver were added NDA cycloadduct (0.5 mmol), Pd(OAc)₂ (5.6 mg, 0.025 mmol) and Et₂O (5 mL). This suspension was cooled to 0 °C and stirred vigorously. The reaction vessel was heated with an oil bath to 65–70 °C, before Diazald (1.07 g, 5.0 mmol) in Et₂O (12 mL) was added slowly over a period of 15 min. Diazomethane and Et₂O started to collect immediately. After the addition was complete, another portion of Et₂O (5 mL) was added and allowed to distill over. This step was repeated until the distillate was colorless. Upon completion of the distillation, the solution in receiver flask was stirred for additional 15 min. The reaction mixture was filtered through Celite and concentrated. Purification of the residue by silica gel chromatography (Hexanes/EtOAc) afforded the cyclopropanated product. Spectral data of **7a** (white solid): mp: 83–85 °C; ¹H NMR (600 MHz, CDCl₃) δ 4.76 (m, 1H), 4.54 (m, 1H), 1.53 (d, J=11.4 Hz, 1H), 1.49 (s, 9H), 1.37–1.44 (m, 3H), 0.36–0.38 (m, 1H), 0.31–0.35 (m, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 157.9, 82.0, 80.8, 61.0, 28.4, 27.8, 14.0, 13.0, 4.3; HRMS (FAB) calcd. for C₁₁H₁₇NNaO₃ (M+Na)⁺: 234.1101, found 234.1126.
18. (a) Crimmins MT. Tetrahedron 1998;54:9229. (b) Ferrero M, Gotor V. Chem. Rev 2000;100:4319. [PubMed: 11749350] (c) Jeong LS, Lee JA. Antiviral Chem. Chemother 2004;15:235.
19. (a) Altona C, Sundaralingam M. J. Am. Chem. Soc 1972;94:8205. [PubMed: 5079964] (b) Choi Y, Moon HR, Yoshimura Y, Marquez VE. Nucleosides, Nucleotides & Nucleic Acids 2003;22:547. (c) Marquez VE, Hughes SH, Sei S, Agbaria R. Antiviral Res 2006;71:268. [PubMed: 16730077]
20. (a) Saneyoshi H, Vu BC, Hughes SH, Boyer PL, Sarafianos SG, Marquez VE. Nucleic Acids Symposium Series 2008;No. 52:623. [PubMed: 18776534] (b) Moon HR, Kim KR, Kim BT, Hwang KJ, Chun MW, Jeong LS. Nucleosides, Nucleotides & Nucleic Acids 2005;24:709. (c) Bhushan RG,

- Vince R. Bioorg. Med. Chem 2002;10:2325. [PubMed: 11983530] (d) Choi Y, Sun G, George C, Nicklaus MC, Kelley JA, Marquez VE. Nucleosides, Nucleotides & Nucleic Acids 2003;22:2077.
21. Spectral data of **13** (white solid): mp: 211 °C (dec.); ¹H NMR (600 MHz, CD₃OD) δ 8.54 (s, 1H), 8.21 (s, 1H), 5.03 (d, *J*=7.3 Hz, 1H), 4.35 (d, *J*=5.3 Hz, 1H), 2.18–2.23 (m, 1H), 1.79–1.89 (m, 3H), 0.76–0.80 (m, 1H), 0.25–0.27 (m, 1H); ¹³C NMR (150 MHz, CD₃OD) δ 157.4, 153.4, 150.2, 142.7, 120.2, 74.0, 57.4, 40.5, 27.5, 23.8, 7.5; HRMS (FAB) calcd. for C₁₁H₁₄N₅O (M+H)⁺: 232.1193, found 232.1202.

Figure 1.
Observed NOE in ROSEY spectrum of **7**.

Scheme 1.

Previously reported modifications of the olefin in nitroso Diels-Alder (NDA) cycloadduct **1**.

Scheme 2.

Synthesis of 2',3'-methano carbocyclic noradenosine from **7a**. Reagents and conditions: (a) H_2 , Pd/C, MeOH, rt, 99%; (b) Ac_2O , DMAP, pyridine, rt, 99%; (c) TFA, 0 °C, 1 h; (d) 5-amino-4,6-dichloropyrimidine, Et_3N , *n*-BuOH, 110 °C, 3 d, 32% from **9**; (e) $\text{CH}(\text{OEt})_3$, CSA, rt, 75%; (f) NH_3 , MeOH, 50 °C, 74%.

Table 1

Cyclopropanation of nitroso cycloadducts **1a–g**

Entry	Substrate
1	1a
2	1b
3	1c

$\text{Pd}(\text{OAc})_2$ (5 m)
 CH_2N_2 (8 eq)
Et₂O, 0 °C, 3

Entry	Substrate
4	<p>1d</p>

Entry

Substrate

5

$\text{Pd}(\text{OAc})_2$ (5 m)
 CH_2N_2 (8 eq)
 Et_2O , 0 °C, 3 h

Entry	Substrate
6	<p>Chemical structure 1f: A bicyclic epoxide (norbornene derivative) with a carbamate group ($\text{N}(\text{Boc})_2$) attached to the oxygen atom.</p>
7	<p>Chemical structure 1g: A bicyclic epoxide (norbornene derivative) with a 4-bromopyrrolidin-2-yl group attached to the oxygen atom.</p>