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

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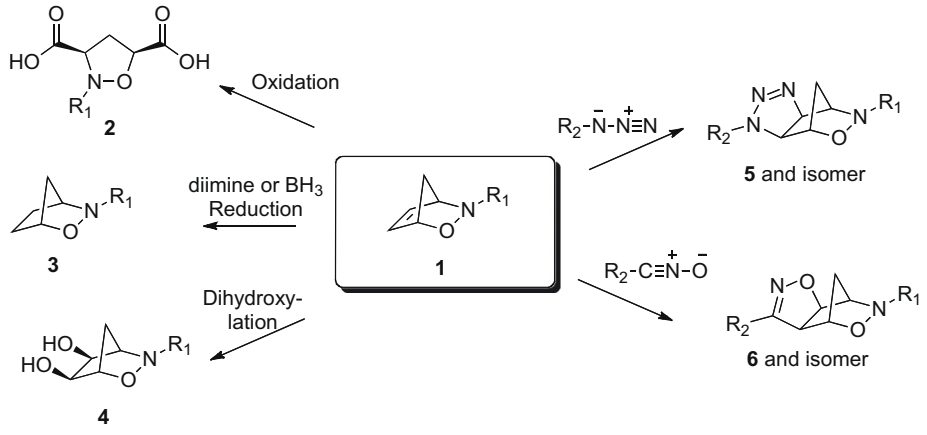
ABSTRACT

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 seven 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–O[2] or C–O[3–6] bonds, has been employed in the preparation of various carbocyclic nucleosides[7] 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] reduction[10], 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 the 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, herein 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-



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

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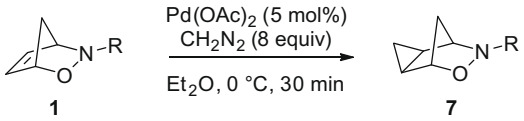
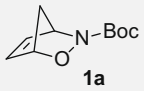
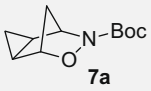
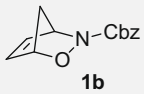
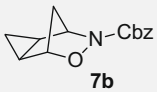
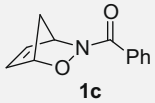
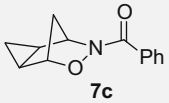
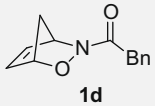
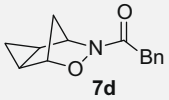
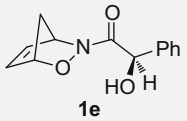
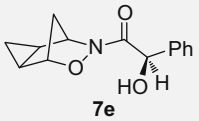
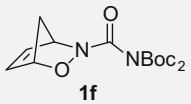
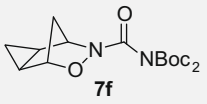
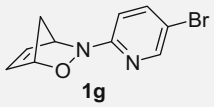
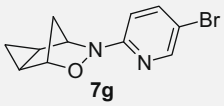
Table 1
Cyclopropanation of nitroso cycloadducts **1a–g**



Entry	Substrate	Product	Isolated yield (%)
1	 **1a**	 **7a**	96
2	 **1b**	 **7b**	84
3	 **1c**	 **7c**	88
4	 **1d**	 **7d**	89
5	 **1e**	 **7e**	73
6	 **1f**	 **7f**	80
7	 **1g**	 **7g**	78

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 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 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 ^4J-coupling ('W-coupling')[12,13b] of H^2 and H^4 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 H^8 (Fig. 1), which supported the *exo* configuration of the fused cyclopropane ring.

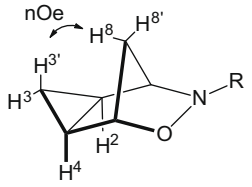
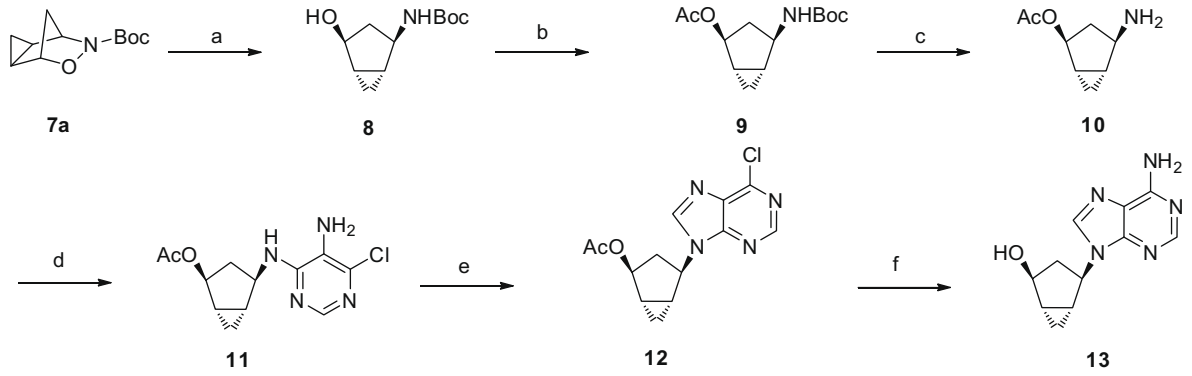


Figure 1. Observed NOE in ROSEY spectrum of **7**.

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 ob-



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) $CH(OEt)_3$, CSA, rt, 75%; (f) NH_3, MeOH, 50 °C, 74%.

tained 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 three 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

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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/H_2O 5:4) and the condenser was cooled to −78 °C with dry ice/acetone. To a 50 mL round-bottomed flask as the receiver were added NDA cycloadduct (0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), and Et_2O (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 Et_2O (12 mL) was added slowly over a period of 15 min. Diazomethane and Et_2O started to collect immediately. After the addition was complete, another portion of Et_2O (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; ^{1}H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.9, 82.0, 80.8, 61.0, 28.4, 27.8, 14.0, 13.0, 4.3; HRMS (FAB) calcd for $C_{11}H_{17}NNaO_3$ $(M+Na)^+$: 234.1101, found: 234.1126.
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21. Spectral data of **13** (white solid): mp: 211 °C (dec); ^{1}H NMR (600 MHz, CD_3OD) 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); ^{13}C NMR (150 MHz, CD_3OD) 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 $C_{11}H_{14}N_5O$ $(M+H)^+$: 232.1193, found: 232.1202.