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Synthesis of novel nitroso acetal derivatives via tandem 6π-electrocyclization/ [3+2]-cycloaddition of 1-nitro-2-methyl-1,3 butadiene

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Abstract: Novel nitroso acetal derivatives (4-methyl-2,3,3a,6-tetrahydroisoxazolo[2,3-b][1,2]oxazine) were synthesized through 6π-electrocyclization/[3+2]-cycloaddition reaction of several dionophiles with 1-nitro-2-methyl-1,3-butadiene. Structures of the synthesized compounds were determined by ^{1}H-NMR, ^{13}C-NMR, IR and GC-MS analyses.

Keywords: Nitrodiene; nitroso acetal; 6π-electrocyclization; [3 + 2] cycloaddition; pericyclic reactions.

1. Introduction

Pericyclic reactions are among miscellaneous conversions in synthetic organic chemistry,[1] which rapidly produce complex molecules from basic starting materials in a single step, often resulting in predictable and well-defined stereochemistry. Pericyclic reactions could be turned into some useful reactions when combined with domino processes, product of the previous reaction of which serves as a substrate for the following reaction(s).[2]

Pericyclic reactions might be realized applying sigmatropic rearrangement, cycloaddition or electrocyclization,[3] among which electrocyclization has been studied relatively less.[4]

Nitroso acetals have already been shown to be precious precursors for the synthesis of pyrrolizidinone and pyrrolizidine skeletons. Thus, nitroso acetals could be utilized as precursors in the synthesis of novel heteroaromatic-substituted pyrrolizidinones and pyrrolizidines.[5] Although nitroso acetals are quite infrequent molecules, their preparation and potential for organic syntheses have attracted remarkable attention in recent years.[6]

Recently, Kwon group has developed 6π-electrocyclization of cyclic nitrodienes, which involved trapping the intermediate nitronates via [3+2] cycloaddition reaction. Two rings were created with one quaternary center and, typically, the products were obtained as one diastereomer in good to excellent yields in this one-pot domino process.[2] Considering these stereochemically well-defined intermediates, resulting from a 6π-electrocyclization/[3+2] dipolar cycloaddition reaction, one can envision assembling the pyrrolizidine alkaloids heliotridane or pseudoheliotridane.[7]

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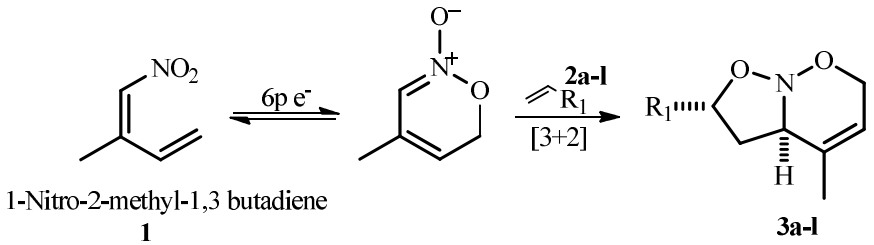


Figure 1. Synthesis of nitroso acetal derivatives

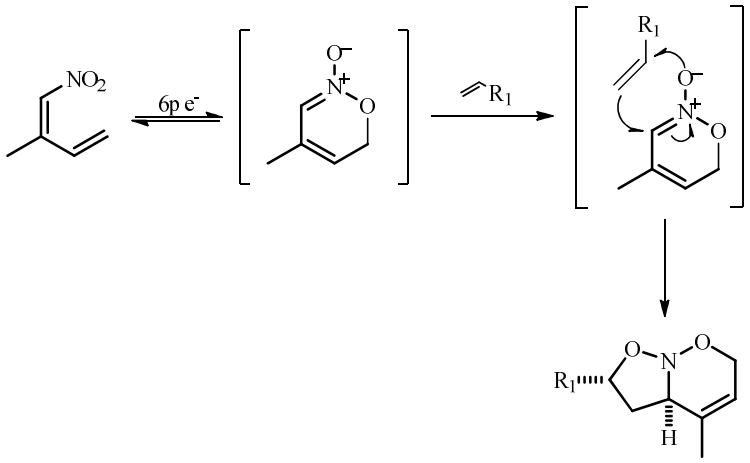


Figure 2. [3+2]-Cycloaddition reaction mechanism of nitrodiene with dienophile

The aim of this work is to synthesize novel nitroso acetal derivatives **3a-l** using tandem 6π-electrocyclization/[3+2] cycloaddition reactions of several dionophiles with acyclic nitrodiene and 1-nitro-2-methyl-1,3-butadiene (Figure 1). Structures of the synthesized compounds were determined by ^{1}H-NMR, ^{13}C-NMR, IR and GC-MS analyses.

2. Experimental

2.1. General

IR spectra (KBr disc) were recorded on a Jasco FT/IR-430 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance DPX-400 instrument. As internal standards, TMS (δ 0.00) for ^{1}H NMR and $CDCl_3$ (δ 77.0) for ^{13}C NMR spectroscopy were used. Their *J* values are given in Hz. The multiplicities of the signals in ^{1}H NMR spectra were abbreviated by s = singlet, d = doublet, t = triplet, q = quarted, m = multiplet, br = broad and combinations thereof. Melting points were recorded using an Electrothermal 9100 apparatus. Elemental analyses were obtained from a LECO CHNS 932 Elemental Analyzer.

2.2. Chemistry

*2.2.1. General Procedure for Nitroso Acetals (**3a-l**):*

1-Nitro-2-methyl-1,3 butadiene (**1**), (2 g, 0.018 mol, 1 equiv) was added via syringe in one portion to a mixture of $NaHCO_3$ (1.81 g, 0.02 mol, 1.2 equiv), 4-methoxyphenol (MEHQ) (0.9 g, 7 mmol, 0.4 equiv), distilled dichloroethane and methyl acrylate (5 mL, 0.05 mol, 3 equiv). The mixture was placed in an oil bath (90 °C) and stirred for 18 h. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography, using EtOAc/hexanes (1:9) mixture as an eluent.

*Ethyl 4-methyl-2,3,3a,6-tetrahydroisoxazolo[2,3-b][1,2]oxazine-2-carboxylate (**3a**)*: ^{1}H and ^{13}C NMR data of compound **3a** is in agreement with the literature data.[7]

*Propyl 4-methyl-2,3,3a,6-tetrahydroisoxazolo[2,3-b][1,2]oxazine-2-carboxylate (**3b**)*: Colorless liquid, Yield**,** 74%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.52-5.51 (m, 1H), 5.11-5.02 (m, 2H), 4.55-4.51 (m, 1H), 4.17-4.12 (m, 1H), 3.74-3.70 (m, 1H), 2.56-2.40 (m, 2H), 1.80 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 170.04, 130.38, 119.72, 81.29, 70.28, 69.26, 66.99, 34.53, 21.67, 21.65, 20.42. IR (KCl, cm^{-1}): 2981, 2938, 2881, 2838, 1737, 1683, 1646, 1554, 1467, 1450, 1375, 1288, 1209, 1106, 1072, 925, 827, 543, 484. GC/MS (*m/z*): 227 (M^+, 10%), 110 (100%), 94 (40%).

*Methyl 4-methyl-2,3,3a,6-tetrahydroisoxazolo[2,3-b][1,2]oxazine-2-carboxylate (**3c**)* : ^{1}H and ^{13}C NMR data of compound **3c** are in agreement with the literature data.[7]

*2-Bromo-4-methyl-2,3,3a,6-tetrahydroisoxazolo[2,3-b][1,2]oxazine (**3d**)*: Colorless liquid, Yield**,** 65%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.53–5.52 (m, 1H), 5.01-4.95 (m, 1H), 4.57–4.52 (m, 1H), 4.19-4.14 (m, 1H), 3.74 (t, *J* = 9.2 Hz, 1H), 2.39-2.24 (m, 2H), 1.79 (s, 3H, $-CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 130.97, 119.43, 82.39, 70.69, 66.85, 34.72, 20.46. IR (KCl, cm^{-1}) 2925, 1691, 1635, 1552, 1434, 1376, 1280, 1230, 1079, 1000, 916, 811, 738, 659, 555. GC/MS (*m/z*): 218 (M^+, 50%), 126 (100%), 114 (80%).

*4-Methyl-2-phenyl-2,3,3a,6-tetrahydroisoxazolo[2,3-b][1,2]oxazine (**3e**)*: Colorless liquid, Yield, 85%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.38 (s, 5H), 5.76 (dd, *J* = 9.6; 4.4 Hz, 1H), 5.57-5.55 (m, 1H), 4.64-4.59 (m, 1H), 4.26-4.20 (m, 1H), 3.89-3.85 (m, 1H), 2.65-2.60 (m, 1H), 2.40-2.34 (m, 1H), 1.78 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 140.60, 131.19(2C), 128.60, 128.01(2C), 126.34, 119.48, 85.11, 71.07, 66.89, 38.77, 20.52. IR (KCl, cm^{-1}): 3064, 3033, 2969, 1689, 1494, 1378, 1286, 1027, 927, 700, 605. GC/MS (*m/z*): 217 (M^+, 10%), 105 (80%), 77 (100%, C_6H_5).

*(2R, 3R, 3aR)-dimethyl 4-methyl-2,3,3a,6-tetrahydroisoxazolo[2,3-b][1,2]oxazine-2,3-dicarboxylate (**3f**)*: Colorless liquid, Yield: 79%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.86-5.85 (m, 1H), 5.58-5.57 (m, 1H), 4.60-4.55 (m, 1H), 4.25-4.18 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.68-3.63 (m, 1H), 3.02-2.95 (m, 1H), 1.59 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 173.22, 171.85, 127.94, 119.95, 84.25, 69.92, 67.04, 52.81, 52.38, 39.92, 20.43. IR (KCl, cm^{-1}): 2976, 2882, 1754, 1540, 1501, 1444, 1348, 1292, 1208, 1185, 1088, 1053, 929, 815, 669, 649.

*(4aR,4bS,7aR)-4-methyl-2,4a,4b,7a-tetrahydrofuro[3',4':4,5]isoxazolo[2,3-b][1,2]oxa zine-5,7-dione (**3g**) :* Colorless liquid, Yield: 60%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.97-5.92 (m, 1H), 5.58-5.57 (m, 1H), 4.59-4.54 (m, 1H), 4.19-4.14 (m, 1H), 3.77-3.73 (m, 1H), 3.11-3.05 (m, 1H), 2.14 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 154.40, 134.90, 129.96, 83.81, 70.97, 66.98, 35.68, 20.37, 18.10. IR (KCl, cm^{-1}): 2971, 1646, 1635, 1556, 1519, 1344, 1064, 917, 744, 547.

*(4aR,4bS,7aR)-4,6-dimethyl-2,4a,4b,7a-tetrahydro-5H-pyrrolo[3',4':4,5]isoxazolo[2,3-b][1,2]oxazine-5,7(6H)-dione (**3h**):* Colorless liquid, Yield, 67%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.93-5.92 (d, *J* = 7.2 Hz, 1H), 5.35-5.34 (m, 1H), 4.16-4.11 (m, 1H), 3.96-3.93 (m, 1H), 3.38-3.34 (m, 1H), 3.01 (s, 3H), 2.77-2.71 (m, 1H), 2.37 (s, 3H), ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 174.28, 171.26, 129.51, 120.66, 83.29, 82.51, 73.68, 67.10, 52.12, 19.81. IR (KCl, cm^{-1}): 2981, 2886, 2834, 1772, 1704, 1552, 1436, 1384, 1265, 1130, 997, 740, 568, 497.

*(4aR,4bS,8aR)-4-methyl-2,4a,4b,8a-tetrahydrobenzo[4,5]isoxazolo[2,3-b][1,2]oxazine-5,8-dione(**3i**):* Colorless liquid, Yield, 54%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 4.4 Hz, 1H), 7.22 (d, *J* = 4.4 Hz, 1H), 5.58-5.57 (m, 1H), 5.23-5.20 (m, 1H), 4.60-4.55 (m, 1H), 4.23-4.18 (m, 1H), 3.70-3.65 (m, 1H), 2.59-2.54 (m, 1H), 2.25 (s, 3H), ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 173.22, 171.85, 148.36, 135.56, 130.24, 119.94, 84.25, 69.92, 67.04, 35.49, 20.42. IR (KCl, cm^{-1}): 2971, 2938, 2881, 2838, 1646, 1554, 1519, 1436, 1380, 1346, 1070, 838, 811, 759, 547, 482, 457.

3. Results and Discussion

In this work, novel nitroso acetal derivatives were synthesized using the methods described in the literature.[2] Nitroso acetals were obtained from the reaction of 1-nitro-2-methyl-1,3-diene with acrylates in the presence of MeQH and $NaHCO_3$. The reaction was conducted at an elevated temperature of 90 ^oC and the products were isolated in moderate to good yields.

Electron-deficient olefins, ethyl acrylate, isopropyl acrylate and methyl acrylate formed the nitroso acetals **3a, 3b** and **3c** with reasonable diastereoselectivity (entry 1, 2 and 3) in good yield, 71%, 74% and 81%, respectively. Styrene (electron-neutral) was also found to be an excellent dipolarophile, producing the nitroso acetal **3e** in 85% yield as a single diastereoisomer (entry 5).

Reaction of allyl bromide, *N*-methylmaleimide and 1,4-benzoquinone afforded the nitroso acetals **3d, 3h** and **3i** (65%, 67% and 54%, respectively) as a single diastereoisomer (entry 4, 8 and 9). In addition, *trans*-disubstituted olefin dimethyl fumarate provided nitroso acetal **3f** in 79% yield as a single diastereoisomer (entry 6). On the other hand, its *cis* isomer, dimethyl maleate, gave rearranged nitroso acetal **3g** instead of expected nitroso acetal **3g-1** (entry 7) (Figure 3).

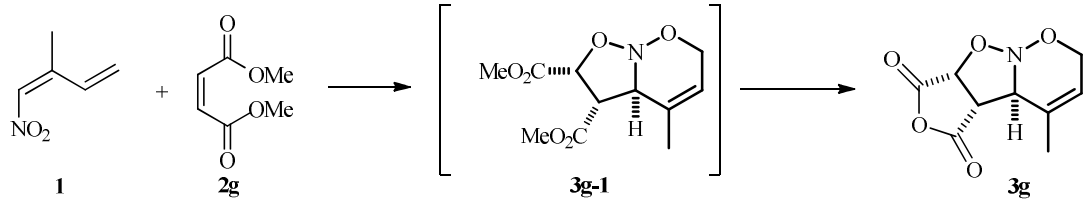


Figure 3. Rearrengement nitroso acetal **3g**

In the same manner, when the reactions were repeated with maleic anhydride, acrylonitrile or dimethyl acetylenedicarboxylate, polymeric products instead of the expected nitroso acetal derivatives, were obtained. Structures of the synthesized compounds were assigned by ^{1}H-NMR, ^{13}C-NMR, IR and GC-MS analaysis.

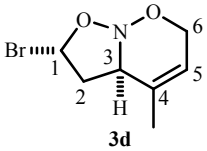
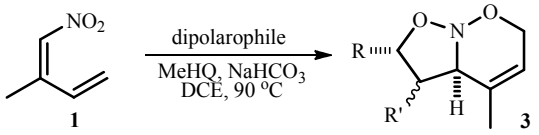


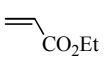
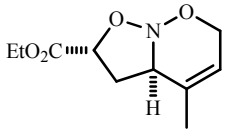
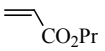
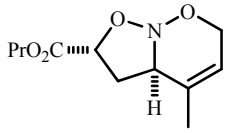
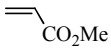
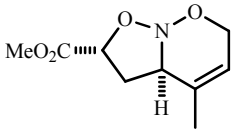
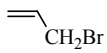
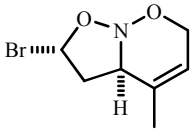
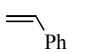
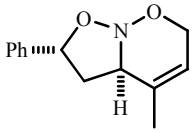
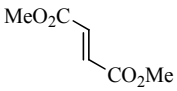
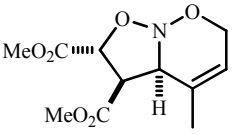
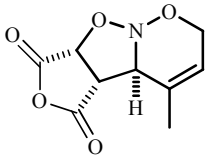
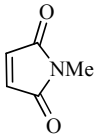
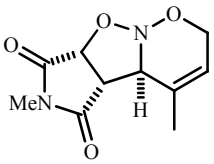
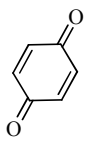
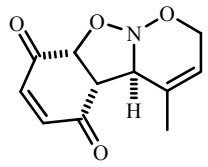
Figure 4. Structure of **3d**

In the ^{1}H-NMR spectra of **3d**, an olefinic hydrogen of C-5 showed a multiplet at 5.51 ppm. Hydrogen of C-1 resonated as a multiplet at 5.98 ppm. Two hydrogens at C-6 produced an AB system (A and B parts of AB system, as multiplets) at 4.55 and 4.17 ppm. The hydrogen attached to the bridge at C-3 showed a triplet (t, J = 9.2 Hz) at 3.74 ppm. Two hydrogens attached to C-2 gave a multiplet at 2.30 ppm and the methyl protons were recorded as a singlet at 1.79 ppm (Figure 4).

Table 1. Electrocyclization/cycloadditions of nitrodiene **1**. All compounds **3a-i** are in racemic form, and the stereochemistry of the atoms or groups are relative to each other.



1 **3**

entry	dipolarophile	nitroso acetal **3**	yield[a]	exo/endo
1	 **2a**	 **3a**	71%	1:11
2	 **2b**	 **3b**	74%	1:11
3	 **2c**	 **3c**	81%	1:11
4	 **2d**	 **3d**	65%	exo
5	 **2e**	 **3e**	85%	exo
6	 **2h**	 **3f**	79%	exo
7	 **2i**	 **3g**	60%	exo
8	 **2j**	 **3h**	67%	exo
9	 **2l**	 **3i**	54%	exo

[a] Isolated yields after chromatographic purification.

The stereochemistry of the hydrogens, H1 and H3, was found to be always in *trans* form with a good agreement with the syntheses available in the literature[2]. Thus, we presumed that the substituents of the products, obtained in this study, had the same stereochemistry.

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