SUPPORTING INFORMATION

Title: 1,3-Dipolar Cycloaddition Reactions Initiated with the 1,5-Dimethyl-3-phenyl-6-oxoverdazyl Radical *Author(s):* Angela Yang, Takahito Kasahara, Eric K. Y. Chen, Gordon K. Hamer, Michael K. Georges* *Ref. No.:* O200800687

General: All reagents and ACS grade solvents were purchased from Sigma-Aldrich and used as received unless otherwise noted. tert-Butylcatechol was removed from styrene and isoprene, while hydroquinone monomethyl ether was removed from methyl acrylate, n-butyl acrylate, t-butyl acrylate, methyl methacrylate and acrylonitrile by passing them through a short column packed with the appropriate inhibitor remover resin purchased from Sigma-Aldrich. Flash column chromatography was performed using Silica Gel 60 (particle size 40-63 μ m) purchased from EMD Chemicals. Thin layer chromatography analyses were performed using aluminum plates coated with silica (pore size of 60Å) and fluorescent indicator, purchased from Sigma-Aldrich, and visualized under UV (254 nm) light. Oxygen (U.S.P. \geq 99%) was purchased from BOC Canada.

NMR spectra were recorded on a Varian Unity INOVA-500 spectrometer at 20 °C, operating at 500 MHz for ¹H NMR and 125 MHz for ¹C NMR. Chemical sifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (0 ppm) for ¹H NMR spectra and CDCl₃ (77.0 ppm) for ¹S NMR. Coupling constants (*J*) are reported in hertz (Hz). Spin multiplicities are indicated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Low resolution mass spectra (LRMS) and accurate mass determinations (HRMS) were obtained from AIMS laboratory, Department of Chemistry, University of Toronto using a Micromass 70S-250 sector mass spectrometer or ABI/Sciex Qstar mass spectrometer. Elemental analysis was performed by the ANALEST facility, Department of Chemistry, University of Toronto on a 2400 Series II CHNS analyzer. FTIR spectra were acquired on a Nicolet Avatar 360 spectrometer using pellets prepared with KBr or as thin films on NaCl cells. Melting points were determined on an Electrothermal capillary melting point apparatus and are uncorrected.

N,N'-Dimethylcarbonohydrazide

The title compound was synthesized by a slightly modified procedure from the literature. Caution should be taken when working with triphosgene or methyl hydrazine as they are highly toxic.

Methyl hydrazine (18.6 g, 0.40 mol), dissolved in 200 mL of dichloromethane, was added to a three neck round bottom flask equipped with an overhead stirrer, addition funnel and a gas inlet. The addition funnel was charged with a solution of triphosgene (10 g, 33.8 mmol) in 125 mL of dichloromethane. The reaction flask was immersed in a cool bath (dry ice/acetone, -78 °C) and the reaction mixture was purged with argon for 15 min while stirring. Triphosgene was added dropwise over a period of 4 h while maintaining the temperature at -78 °C. When addition was completed the reaction mixture was gradually warmed to room temperature and allowed to continue to stir overnight. The resulting white hydrazine salts were filtered and washed three times with 10 mL of CH₂Cl₂. The filtrate was concentrated under reduced pressure to give the title compound as a yellow oil (11.3 g, 95%).² ¹H NMR (500 MHz, CDCl₃, δ): 4.14 (br, 5H), 3.07 (s, 6H). ¹³C NMR (125 MHz, CDCl₃, δ): 166.0, 42.0. HRMS (ESI): calculated for C₃H₁₁N₄O [M+H]⁺, 119.0927; found, 119.0931.

2,4-Dimethyl-6-phenyl-1,2,4,5-tetrazinan-3-one

The title compound was synthesized according to a slightly modified procedure reported in the literature.³

Dimethylcarbonohydrazide (11.3 g, 0.096 mmol), dissolved in 200 mL of methanol, was added to a round bottom flask containing an egg shaped stirring bar. A solution of benzaldehyde (9.0 g, 0.08 mol) in 110 mL of methanol was added dropwise over a period of 6 h while the reaction mixture was stirred vigorously and maintained at 55°C. Stirring was continued for 30 min after the addition of the benzaldehyde solution had been completed, afterwhich the reaction mixture was concentrated under reduced pressure. The product was recrystalized from ethyl acetate to give white crystalline needle (10.3 g, 59%). ¹H NMR (500 MHz, CDCl₃, δ): 7.56-7.51 (m, 2H), 7.41-7.33 (m, 3H), 5.02 (apparent t, J = 9.7, 1H), 4.05 (apparent d, J = 9.7, 2H), 3.15 (s, 6H). ¹³C NMR (125 MHz, CDCl₃, δ): 155.3, 135.0, 128.6, 128.6, 126.4, 69.3, 38.0. HMRS (ESI): calculated for $C_{10}H_{15}N_4O$ [M+H]⁺, 207.1240; found, 207.1242. FTIR (KBr): 3063, 3028, 2962, 2895, 1723, 1673 cm⁻¹. mp: 128-129 °C (lit. ⁴ 138-139 °C).

1,5-Dimethyl-3-phenyl-6-oxo-verdazyl radical (1)

Compound 1 was synthesized according to a literature procedure.³

From 9.9 g (0.048 mol) of tetrazinone, **1** was isolated as an orange powder (9.53 g, 98%). HRMS (EI): calculated for $C_{10}H_{11}N_4O$ [M]⁺, 203.0933; found, 203.0938. FTIR (KBr): 3564, 3502, 2945, 1689, 1672 cm⁻¹. mp: 65-66 °C (lit.³ mp: 72-73 °C).

Reaction of 1 in the presence of styrene and BPO

To a three neck round bottom flask equipped with a gas inlet, thermometer and an egg-shaped stirring bar, **1** (1 g, 4.9 mmol) was dissolved in styrene (10 mL, 0.09 mol). The reaction solution was purged with nitrogen for 20 min. BPO (1 g, 4.1 mmol) was added to the reaction mixture producing an exotherm of about 10 °C 2 min after the addition. The reaction was allowed to continue at room temperature for 24 h after which the excess styrene was removed by a stream of air. Silica gel column chromatography of the resulting reaction mixture (3:7 ethyl acetate/hexane) gave **2** (220 mg, 10%) as a pale powder and **3** (422 mg, 28%) as yellow crystals. Due to restricted slow rotation about the N-CPh bond at room temperature, the ¹H and ¹³C NMR spectra were recorded at -20 °C.

BSV unimer (2)⁵

¹H NMR (500 MHz, CDCl₃, -20 °C, δ): major conformer (78%), δ 2.65 (s, 3H), 3.34 (s, 3H), 4.50 (dd, J = 4.1, 10.8, 1H), 4.63 (dd, J = 4.1, 11.9, 1H), 5.04 (dd, J = 10.8, 11.9, 1H), 7.2-8.2 (m, 15H); minor conformer (22%), 2.71 (s, 3H), 3.05 (s, 3H), 4.53 (dd, J = 3.8, 11.6, 1H), 4.77 (dd, J = 3.8, 10.3, 1H), 5.08 (dd, J = 10.3, 11.6, 1H), 7.2-8.2 (m, 15H). ¹³C NMR (125 MHz, CDCl₃, -20 °C, δ): major conformer, 166.1, 157.2, 147.2, 135-127, 64.3, 62.2, 40.4, 35.6; minor conformer, 166.0, 159.4, 149.2, 136-127, 63.8, 63.2, 40.0, 36.7. mp: 97-98 °C.

Styrene cycloadduct (3)

¹H NMR (500 MHz, CDCl₃, δ): 7.44-7.38 (m, 2H), 7.45-7.28 (m, 1H), 7.26-7.20 (m, 2H), 7.18-7.11 (m, 3H), 6.92-6.86 (m, 2H), 4.71 (dd, J = 4.9, 8.6, 1H), 4.37-4.30 (m, 1H), 3.64-3.57 (m, 1H), 3.19 (s, 3H), 2.58-2.49 (m, 1H), 2.22-2.14 (m, 1H). ¹³C NMR (125 MHz, CDCl₃, δ): 155.0, 147.3, 139.4, 131.5, 130.1, 128.2, 128.1, 127.8, 127.4, 127.2, 66.0, 44.8, 36.4, 33.2. HRMS (ESI): calculated for C₁₈H₁₉N₄O [M+H]⁺, 307.1553; found, 307.1551. FTIR (KBr): 3065, 3026, 2953, 1674 cm⁻¹. mp: 58-60 °C.

Reaction of 1 in the presence of styrene and in the absence of BPO.

The above reaction was repeated in the absence of BPO. The reaction was allowed to continue at room temperature for 24 h after which the excess styrene was removed by a stream of air. Silica gel column chromatography of the resulting reaction mixture (3:7 ethyl acetate/hexane) **3** (393 mg, 26%) as yellow crystals.

Benzylation of leucoverdazyl

Following the general procedure to synthesize methyl methacrylate adduct, the reaction was setup with the modification of purging the reaction for 20 min using argon. After 24 h a solution of NaH (250 mg, 10.4 mmol) in 3 mL of THF was added via syringe, followed about 5 min. later by the addition of benzyl bromide (0.88 mL, 7.4 mmol) also via syringe. After 20 min. the reaction mixture was quenched with a few drops of methanol, a saturated ammonium chloride solution (5 mL) was added and the reaction mixture was concentrated under reduced pressure. The reaction mixture was then extracted with ethyl acetate (3 x 5 mL) and the organic layers were collected, dried over NaSO₄, and concentrated under reduced pressure. Upon purification by column chromatography (2:3 ethyl acetate/hexane) the title compound was isolated as a white solid (157 mg, 36%)

¹H NMR (500 MHz, CDCl₃, δ): 7.93-7.88 (m, 2H); 7.48-7.43 (m, 3H); 7.37-7.31 (m, 3H); 7.27-7.26 (m, 2H), 4.06 (s, 2H); 3.04 (s, 3H), 2.98 (s,3H).

¹³C NMR (125 MHz, CDCl₃, δ): 156.2, 147.5, 134.9, 130.8, 130.4, 129.8, 128.8, 128.4, 128.3, 127.2, 55.3, 36.3, 35.7.

HRMS (ESI) (m/z): calculated for $C_{17}H_{19}N_4O$ [M+H]⁺, 295.1553; found, 295.1560.

FTIR (KBr): 3056, 3026, 2941, 1669 cm⁻¹.

mp: 80-83 °C.

Solvent effect studies for the cycloadditon reaction with 1 and styrene

To a 50 mL round bottom flask equipped with an egg-shaped magnetic stirring bar, 1 (300 mg, 1.47 mmol) was dissolved in 10 equiv of styrene and 0.5 mL of a given solvent. The flask was capped with a rubber septum and purged with oxygen for 10 min. The reaction was then allowed to proceed for 24 h at room temperature. For the reactions performed in acetone and CH₂Cl₂, the solvent was evaporated upon reaction completion and the crude mixture was passed through a slica gel column (2:3 ethyl acetate/hexane). In the case of DMSO, the reaction mixture was diluted with 10 mL of water and extracted with 10 mL of ethyl acetate. The ethyl acetate layer was collected and the DMSO/H₂O layer was washed twice with 5 mL of ethyl acetate. The ethyl acetate layers were combined, dried over Na₂SO₄ and concentrated under reduced pressure. The crude mixture was purified by column chromatography (2:3 ethyl acetate/hexane).

Solvent used	Yield of 3
Acetone	51%
DMSO	53%
CH_2Cl_2	45%

General procedure for the 1,3-DC reaction of 1 with various dipolarophiles

To a 50 mL round bottom flask equipped with an egg-shaped magnetic stirring bar, 1 (300 mg, 1.47 mmol) was dissolved in 10 equiv of a dipolarophile. The flask was capped with a rubber septum and purged with oxygen for 10 min. The reaction was then allowed to proceed for 24 h at room temperature.

Styrene cycloadduct

The title compound was synthesized according to the general procedure. Purification by flash column chromatography $(2:3 \rightarrow 1:1 \text{ ethyl acetate/hexane})$ gave the product as a yellow solid (285 mg, 63%).

Methyl acrylate cycloadduct

The title compound was synthesized according to the general procedure. Purification by flash column chromatography (2:3 ethyl acetate/CH₂Cl₂) afforded the product as yellow crystals (315mg, 74%). 1 H NMR (500 MHz, CDCl₃, δ): 7.67-7.62 (m, 2H), 7.47-7.42 (m, 1H), 7.42-7.37 (m, 2H), 4.24 (dd, J = 3.9, 9.0, 1H), 4.22-4.17 (m, 1H), 3.56 (s, 3H), 3.52-3.46 (m, 1H), 3.37 (s, 3H), 2.48-2.39 (m, 1H), 2.27-2.20 (m, 1H). 13 C NMR (125 MHz, CDCl₃, δ): 171.3, 154.2, 146.0, 130.9, 130.9, 128.7, 127.5, 62.1, 52.4, 44.1, 36.7, 29.8. HRMS (EI): calculated for C₁₄H₁₆N₄O₃ [M]⁺, 288.1222; found, 288.1218. FTIR (KBr): 3041, 2993, 2956, 1738, 1676cm⁻¹. mp: 115-117 °C.

t-Butyl acrylate cycloadduct

The title compound was synthesized according to the general procedure. Purification by flash column chromatography (10% ethyl acetate/CH₂Cl₂) gave the product as a yellow powder. (375mg, 77%). 1 H NMR (500 MHz, CDCl₃, δ): 7.67-7.63 (m, 2H), 7.46-7.42 (m, 1H), 7.42-7.37 (m, 2H), 4.28-4.21 (m, 1H), 4.17-4.11 (dd, J = 3.9, 8.6, 1H), 3.43-3.36 (m, 1H), 3.34 (s, 3H), 2.45-2.36 (m, 1H), 2.25-2.17 (m, 1H), 1.32 (s, 9H). 13 C NMR (125 MHz, CDCl₃, δ): 169.9, 154.3, 145.9, 130.9, 130.8, 128.6, 127.6, 82.7, 63.1, 44.3, 36.7, 29.8, 27.7. HRMS (EI): calculated for $C_{17}H_{22}N_4O_3$ [M] $^+$, 330.1692; found, 330.1694. FTIR (KBr): 3064, 2977, 2934, 1726, 1677 cm $^{-1}$. mp: 109-110 °C.

Methyl methacrylate cycloadduct

The title compound was synthesized according to the general procedure. Upon reaction completion the reaction mixture was filtered to give the title compound as a yellow solid (375mg, 84%). 1 H NMR (500 MHz, CDCl₃, δ): 7.66-7.61 (m, 2H), 7.46-7.41 (m, 1H), 7.41-7.35 (m, 2H), 4.01-3.93 (m, 1H), 3.83-3.75 (m, 1H), 3.63 (s, 3H), 3.35 (s, 3H), 2.58-2.50 (m, 1H), 1.97-1.89 (m, 1H), 1.29 (s, 3H). 13 C NMR (125 MHz, CDCl₃, δ): 172.6, 155.4, 146.8, 132.1, 130.6, 128.4, 128.1, 69.7, 52.3, 44.0, 38.5, 36.7, 23.4. FTIR (KBr): 3031, 2984, 2946, 1737, 1685, 1667 cm⁻¹. HRMS (ESI): calculated for $C_{15}H_{19}N_4O_3$ [M+H]⁺, 303.1451; found, 303.1459. mp: 122-125 °C.

Acrylonitrile cycloadduct

The title compound was synthesized according to the general procedure. Purification by flash column chromatography (5% ethyl acetate/ CH_2Cl_2) gave the title compound as a pale powder (234 mg, 62%). 1H NMR (500 MHz, $CDCl_3$, δ): 7.79-7.74 (m, 2H), 7.52-7.47 (m, 1H), 7.47-7.42 (m, 2H), 4.44-4.37 (m, 1H), 4.32 (dd, J = 3.4, 9.2, 1H), 3.50-3.43 (m, 1H), 3.39 (s, 3H), 2.56-2.48 (m, 1H), 2.45-2.38 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 153.4, 143.9, 131.4, 129.9, 128.9, 127.4, 117.1, 50.3, 44.1, 37.1, 30.5. HRMS (EI) (m/z): calculated for $C_{13}H_{13}N_5O$ [M $^+$], 255.1120; found, 255.1127. FTIR (KBr): 3005, 2972, 2227, 1673 cm $^{-1}$. mp: 184-186 °C.

Dimethyl fumarate cycloadduct

The title compound was synthesized according to the general procedure. Purification by flash column chromatograph (3:7 ethyl acetate/hexane) gave the title compound as a yellow oil (459 mg, 83%). 1 H NMR (500 MHz, CDCl₃, δ): 7.74-7.70 (m, 2H), 7.48-7.39 (m, 3H), 4.64 (d, J = 3.3, 1H), 4.52 (dd, J = 9.0, 11.8, 1H), 4.27 (dq, J = 1.4, 7.1, 2H), 4.05 (dq J = 0.5, 7.1, 2H), 3.67 (dd, J = 5.5, 11.8, 1H), 3.53-3.48 (m, 1H), 3.35 (s, 3H), 1.33 (t, J = 7.1, 3H), 1.13 (t, J = 7.1, 3H). 13 C NMR (125 MHz, CDCl₃, δ): 170.4, 169.5, 153.8, 145.4, 130.9, 130.5, 128.7, 127.4, 64.6, 62.1, 62.0, 47.4, 47.1, 36.7, 14.1, 13.8. HRMS (EI): calculated for $C_{18}H_{22}N_4O_5$ [M $^+$], 374.1590; found, 374.1593. FTIR (thin film): 3060, 2982, 2939, 1747, 1682 cm $^{-1}$.

Diethyl maleate cycloadduct

Diethyl maleate was first purified by column chromatography (8:1 hexane/ethyl acetate). The title compound was synthesized according to the general procedure with the modification of using 8 equiv of purified diethyl maleate. The crude mixture was purified by flash column chromatography (7:3 hexane/ethyl acetate) giving the product as a yellow oil (132 mg, 24%). ¹H NMR (500 MHz, CDCl₃, δ): 7.65-7.60 (m, 2H), 7.48-7.44 (m, 1H), 7.43-7.38 (m, 2H), 4.46 (dd, J = 8.8, 11.3, 1H), 4.38 (d, J = 7.9, 1H), 4.14 (q, J = 7.1, 2H), 4.12 (qd, J = 7.1, 10.8, 1H), 4.04 (dq, J = 7.1, 10.8, 1H), 3.83 (dd, J = 9.7, 11.3, 1H), 3.64 (q, J = 8.6, 1H), 3.31 (s, 3H), 1.22 (t, J = 7.1, 3H), 1.17 (t, J = 7.2, 3H). ¹³C NMR (125 MHz, CDCl₃, δ): 168.5, 168.3, 154.4, 144.7, 131.0, 130.6, 128.7, 127.4, 63.1, 61.9, 61.6, 47.1, 46.5, 36.8, 13.9, 13.8. HRMS (EI): calculated for $C_{18}H_{22}N_4O_5$ [M $^+$], 374.1590; found, 374.1582. FTIR (thin film): 3060, 2982, 2939, 1747, 1682 cm $^{-1}$.

N-Methyl maleimide cycloadduct

The title compound was synthesized according to the general procedure with the modification of adding 5 mL of THF to the reaction mixture. Upon reaction completion, the crude mixture was concentrated under reduced pressure. Purification by flash column chromatography (20% ethyl acetate/CH₂Cl₂) gave the title compound as a white power (260 mg, 56%). 1 H NMR (500 MHz, CDCl₃, δ): 7.86-7.82 (m, 2H), 7.53-7.47 (m, 2H), 7.47-7.44 (m, 1H), 4.82 (dd, J = 0.8, 12.4, 1H), 4.41 (d, J = 7.7, 1H), 3.57 (apparent t, 7.9, 1H), 3.44 (dd, J = 8.5, 12.4, 1H), 3.30 (s, 3H), 2.91 (s, 3H). 13 C NMR (125 MHz, CDCl₃, δ): 153.4, 143.9, 131.4, 129.9, 128.9, 127.4, 117.1, 50.3, 44.1, 37.1, 30.5. HRMS (ESI) (m/z): calculated for $C_{15}H_{16}N_5O_3$ [M+H] $^+$, 314.1247; found, 314.1262. FTIR (KBr): 3046, 2992, 2944, 1782, 1709, 1670 cm $^{-1}$. mp: 224-226 °C.

Isoprene cycloadducts

The general procedure was followed with the modification of using 60 equiv of isoprene, cooling the reaction mixture in an ice bath (ice/ H_2O , 0 °C), attaching a balloon filled with oxygen which allowed O_2 to be slowly bubbled into the reaction solution throughout the course of the reaction, and allowing the reaction to go for 60 h. After completion, the mixture was concentrated under reduced pressure and purified by flash column chromatography (5% ethyl acetate in CH_2Cl_2) to give the combined products as a yellow oil (194 mg, 61:39 ratio of A/B, 49%).

Isoprene cycloadduct A

Appears as a pale oil in pure form. ^{1}H NMR (500 MHz, CDCl₃, δ): 7.67-7.64 (m, 2H), 7.43-7.39 (m, 1H), 7.37-7.33 (m, 2H), 5.85 (dd, J = 10.7, 17.3, 1H), 4.95 (d, J = 10.7, 1H), 4.88 (d, J = 17.3), 4.01 (m, 1H), 3.62 (m, 1H), 3.32 (s, 3H), 2.12 (m, 1H), 1.93 (m, 1H), 1.22 (s, 3H). ^{13}C NMR (125 MHz, CDCl₃, δ): 156.5, 147.8, 140.8, 133.2, 130.5, 128.8, 128.0, 114.5, 69.5, 43.9, 39.0, 36.9, 24.2. HRMS (ESI) (m/z): calculated for $C_{15}H_{19}N_4O$ [M+H]⁺, 271.1553; found, 271.1542. FTIR (thin film): 3506, 3339, 3060, 2973, 1678, 1604.

Isoprene cycloadduct B

Appears as a bright yellow oil in pure form. ^{1}H NMR (500 MHz, CDCl₃, δ): 7.61 (m ,2H), 7.43-7.38 (m, 1H), 7.38-7.33 (m, 2H), 4.65 (t, J = 1.3, 1H), 4.62 (s, 1H), 4.28 (dd, J = 5.2, 8.6, 1H), 3.94 (m, 1H), 3.62 (m, 1H), 3.32 (s, 3H), 2.22 (m, 1H), 1.95 (m, 1H), 1.60 (br s, 3H). ^{13}C NMR (125 MHz, CDCl₃, δ): 155.5, 148.7, 142.2, 131.9, 130.5, 128.3, 127.7, 115.3, 67.3, 44.5, 36.6, 30.1, 17.4. HRMS (EI) (m/z): calculated for $C_{15}H_{18}N_{4}O$ [M $^{+}$], 270.1481; found, 270.1485. FTIR (thin film): 3500, 3339, 3060, 1677.

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