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Verdazyl Radicals as Substrates for Organic Synthesis: Unique Access to Tetrahydropyrazolotriazinones, Pyrazolotriazinones and Dihydrotetrazinylacrylonitriles

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1,5-Dimethyl-3-phenyl-6-oxoverdazyl radical was recently shown to undergo a disproportionation reaction to form an azomethine imine, which reacted with a series of dipolarophiles, to form novel tetrahydropyrazolotetrazinone heterocyclic structures, demonstrating for the first time the use of verdazyl radicals as substrates for organic synthesis. Herein, we report on the chemistry of this verdazyl radical with captodative olefins and show that the reactions that occur, either an addition reaction or a hydrogen abstraction reaction followed by a cycloaddition reaction, are defined by the captodative olefin. Also highlighted is an intramolecular rearrangement of initially formed tetrahydropyrazolotetrazinone cycloadducts to either pyrazolotriazinone or tetrahydropyrazolotriazinone structures. While the rearrangement falls under the very general definition of the Dimroth rearrangement, the mechanism that is proposed is distinct and provides the opportunity to go from one particular structural motif to another under mild conditions, expanding the usefulness of this chemistry.

Introduction

We recently proposed a new synthetic strategy for the synthesis of heterocyclic compounds based on the use of verdazyl radicals, a family of stable radicals that can be isolated and stored for extended periods without extensive decomposition.[1] One of the requirements of diversity-oriented synthesis (DOS) is the development of new synthetic strategies that are flexible enough to provide combinatorial libraries of diverse small molecules for biological screening.[2,3] We believe the use of verdazyl radicals will provide this opportunity once the chemistry of these interesting molecules, and the molecular motifs they can provide, has been elucidated.

Our interest in verdazyl radicals began with an investigation of their use as mediators for living-radical polymerizations[4] but that focus shifted to exploring whether they could be used as substrates in organic synthesis. In spite of being discovered over 45 years ago,[1a] surprisingly little is known about the chemistry of verdazyl radicals. However, since they are structurally diverse and contain a wealth of heteroatoms,[5] they would appear to be ideal substrates for preparing novel heterocyclic compounds. From a synthetic chemistry perspective the value of many heterocyclic compounds lies in their propensity to undergo intramolecular rearrangement reactions leading to otherwise hard to obtain structures, a feature highlighted in this submission. Since most synthetic drugs are nitrogen containing heterocyclic compounds,[2] the development of new strategies for the synthesis of heterocyclic structures offers the potential for new drug discovery, the anticipated endgame of this work. Of particular interest are (i) the recent discovery that flat heterocyclic structures can be used to disrupt Myc/Max dimerization, a process implicated in virulent forms of breast cancer[6] and (ii) the use of pyrazolotriazinone compounds in dynamic combinatorial chemistry (DCC).[7,8]

We recently reported that 1,5-dimethyl-3-phenyl-6-oxoverdazyl radical[9] (**1**), where R = Ph, can serve as a precursor to the azomethine imine **1a**. In the presence of electron-poor dipolarophiles, for example acrylates, methacrylates and acrylonitrile, as well as weakly electron-rich dipolarophiles, such as styrene and its derivatives, **1a** undergoes a 1,3-dipolar cycloaddition reaction to give the tetrapyrazolotetrazinone structure **2** (Scheme 1).[10] Herein, we report on the chemistry of verdazyl radicals with the captodative olefins 1-chloroacrylonitrile, 1-acetoxyacrylonitrile, 2-phenyl-1-thiomethylacrylonitrile and methyl α-acetoxyacrylate. In the process, we show that the reaction that occurs, either an addition reaction or a hydrogen abstraction reaction followed by a cycloaddition reaction, is defined by the captodative olefin. Also highlighted is an intramolecular rearrangement of initially formed tetra- or di-hydropyrazolotetrazinone cycloadducts to either tetrahydropyrazolotriazinone or pyrazolotriazinone structures, respectively. While the rearrangement falls under the very general definition of the Dimroth rearrangement,[11,12] it would appear to be mechanistically unique.

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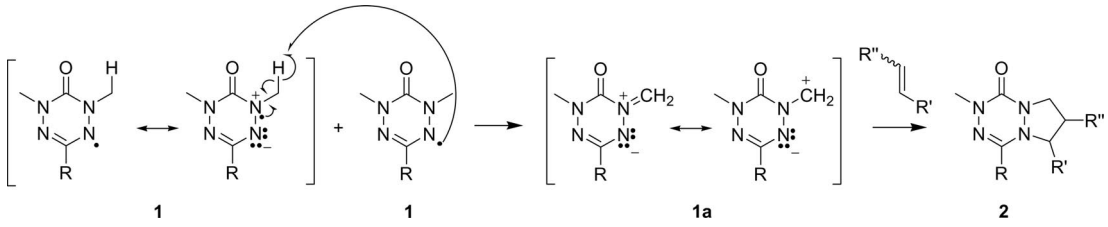


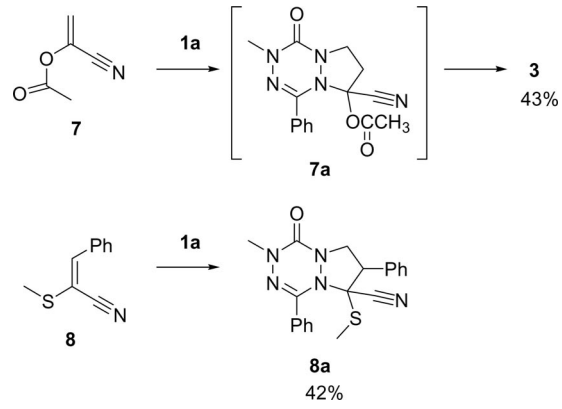
Scheme 1. Formation of tetrahydropyrazolotetrazinone cycloadducts **2** from verdazyl **1**.

Results and Discussion

In an effort to introduce different functionality into the structures produced by the reaction of **1a** with dipolarophiles, **1** was allowed to react in the presence of 1-chloroacrylonitrile, a known ketene equiv.,[13] in anticipation of forming **3** (Scheme 2). However, the reaction yielded less than 5% of **3**. The major product was **4**, with the *E*-configuration as confirmed by single-crystal X-ray diffraction (the crystal X-ray structure of **4** is provided in the Supporting Information). The formation of **4** occurs, we suggest, by the addition of **1** to the double bond of 1-chloroacrylonitrile, giving radical **5**, which is subsequently trapped by another molecule of **1**, affording **6**.[14] Loss of HCl from **6** affords **4**.

The addition of **1** to the double bond of 1-chloroacrylonitrile was somewhat surprising, since in all our previous work with verdazyl radicals as mediators for living-radical polymerizations,[4] and in our initial cycloaddition studies,[10] this type of reaction was not noticed. In hindsight, given that **5** is a captodative radical, the verdazyl radical addition reaction might have been expected. However, methyl methacrylate and methacrylonitrile could conceivably also form captodative radicals but preferred to undergo the cycloaddition reaction in high yield.[10] In these cases the methyl group is a weak electron donor. The captodative radical that would result from these substrates would be less stable than **5** and, therefore, less likely to form.

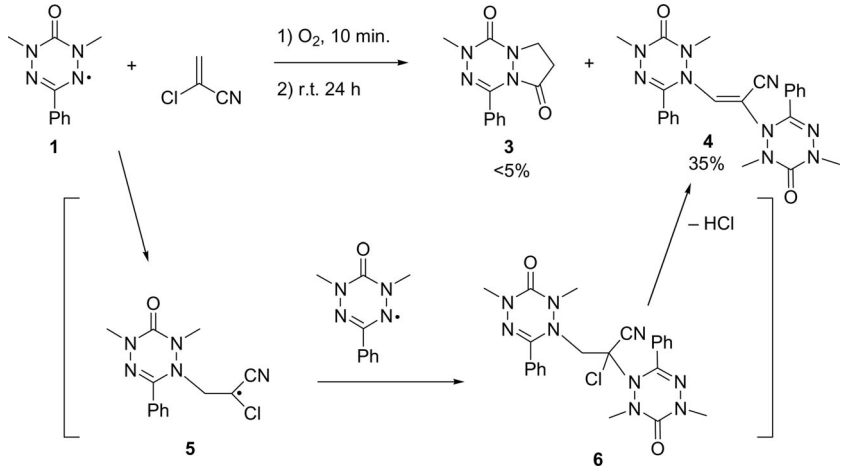
Two other captodative olefins, 1-acetoxyacrylonitrile **7** and (*E*)-2-(methylthio)-3-phenylacrylonitrile **8**, underwent the cycloaddition reaction in modest yields, 43% and 42%, respectively, with **7** providing **3** upon silica gel purification, the product that was initially expected from the reaction with 1-chloroacrylonitrile (Scheme 3).



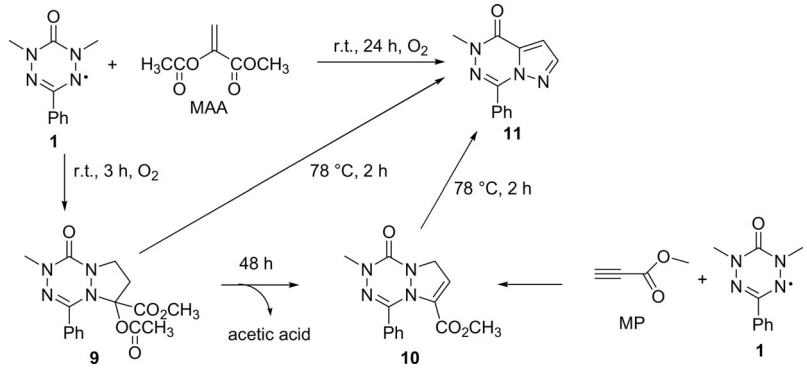
Scheme 3. Cycloaddition reactions between **1a** and 1-acetoxyacrylonitrile **7** and (*E*)-2-(methylthio)-3-phenylacrylonitrile **8**.

Methyl α-acetoxyacrylate (MAA),[15] interestingly, gave neither the anticipated cycloadduct **9** nor the verdazyl radical addition product when stirred with **1** at room temp. for 24 h (Scheme 4). Instead, ^{1}H and ^{13}C NMR suggested that pyrazolotriazinone **11** was the major product. Single-crystal X-ray diffraction confirmed the structure and showed the pyrazolotriazinone moiety to be planar.

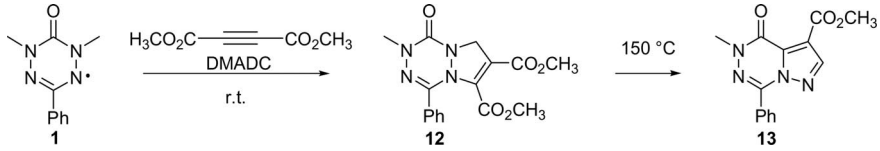
Repeating the reaction of **1** with MAA for only 3 h enabled the isolation of **9** in low yield. As expected **9** was unstable and upon standing in $CDCl_3$ in an NMR tube at room temp. it eliminated acetic acid, evident in the ^{1}H



Scheme 2. Addition of verdazyl **1** to 1-chloroacrylonitrile.



Scheme 4. Reaction of verdazyl **1** with MAA and MP; intermediates and final product.



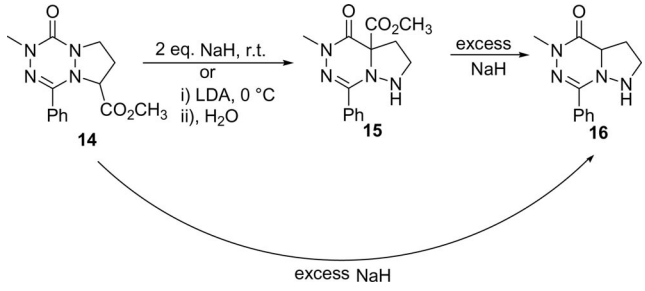
Scheme 5. Reaction of DMADC in the presence of **1** to give **13** via **12**.

NMR spectrum of the reaction mixture, to give **10**. Heating either **9** or **10** in refluxing ethyl acetate gave **11** in 89% yield (Scheme 4). The addition of excess NaH to a solution of **10** in THF resulted in the formation of **11** in 76% yield in 5 h at room temp. (the crystal X-ray structure of **11** is provided in the Supporting Information).

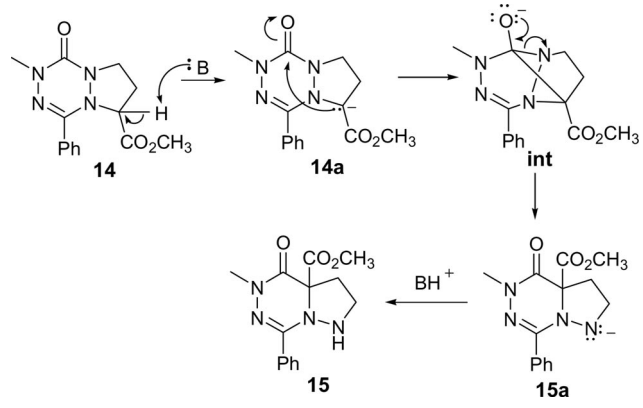
In parallel with the work with the captodative olefins, substituted alkynes were also being investigated as substrates for the cycloaddition reaction. The reaction of methyl propiolate (MP) in the presence of **1** (Scheme 4) gave a small amount of **11** and the α,β-unsaturated ester **10** as the major product, which again was readily converted into **11** in refluxing EtOAc in 76% yield. Using a disubstituted alkyne provided the opportunity to add functionality to the pyrazolotriazinone structure. Thus, the reaction of dimethyl acetylenedicarboxylate (DMADC) in the presence of **1** gave **12**, which subsequently underwent rearrangement upon heating to give **13** in 50% yield (Scheme 5).

While the saturated analogue of **10**, compound **14**, is stable in refluxing EtOAc, it readily rearranges to **15** in 82% yield when treated with 2 equiv. of NaH at room temp. (Scheme 6). Compound **14** is also readily converted into **15** upon treatment with lithium diisopropylamide at 0 °C for 1 h, followed by addition of water, suggesting that the formation of the anion is vital to the success of the reaction.

Scheme 7 outlines a proposed mechanism for the conversion of **14** to **15**. One of the keys to this mechanism is the flexibility of the bicyclic ring system, due to the facile inversion of the ring-junction nitrogen centers allowing the fused rings to approach each other not unlike a butterfly folding it wings, enabling the carbanion to approach and interact with the carbonyl carbon center. DFT calculations show that as the carbanion centre approaches the carbonyl center to form a four atom ring intermediate (**int**) (Figure 1), the C–N bond of the ring lengthens, facilitating it breakage.



Scheme 6. NaH induced rearrangement of **14** and subsequent decarboxylation.



Scheme 7. Proposed mechanism for the rearrangement of **14** to **15**.

Energy levels calculated for the transitions states and intermediate, which would occur with the proposed mechanism, are provided in (Figure 2).

Possibly more interesting at this point is that treatment of **14** or **15** with excess NaH gives the decarboxylated product **16** in 92% and 76% yields, respectively (Scheme 7). Thus, aromatization of the five-membered ring is not the

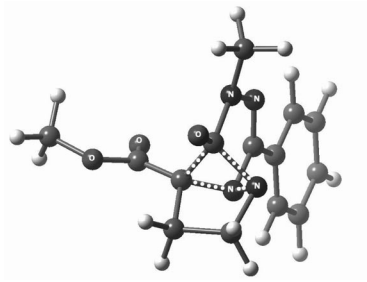


Figure 1. DFT-generated lowest-energy conformation of a four-membered intermediate (**int**) on the pathway from **14** to **15**. The four-membered ring is highlighted with dashed-line bonds.

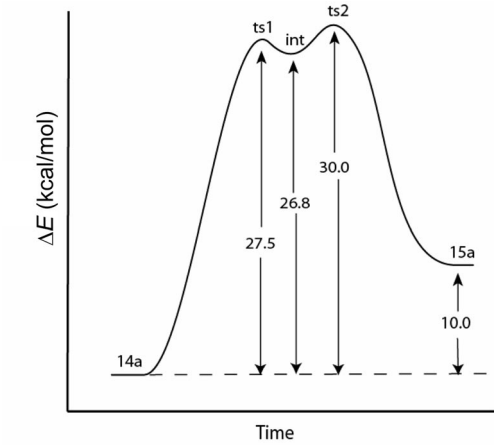
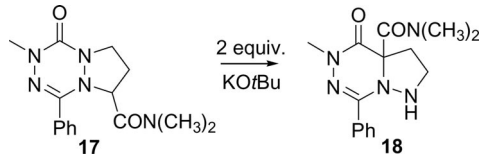


Figure 2. Energy levels to the two transitions states, ts1 and ts2 and the four-membered intermediate (int) determined by DFT calculations. The calculations were carried out at the B3LYP/6-31G+(d,p)//B3LYP/6-31G(d) level using the Gaussian G03W program.[16] Minima on the **14*a*** → **15*a*** reaction pathway potential energy surface were located with the opt = gdiis option and transition states using the QST2 procedure. The nature of the calculated stationary points was tested by frequency analysis and the closed-shell nature of all species determined by wavefunction stability calculations. Relative energies (kcal mol^{-1}) are expressed relative to the energy of **14*a***. ts1,ts2 are transitions states 1 and 2, respectively, while int is the four-membered intermediate depicted in Figure 1.

driving force for this facile decarboxylation reaction, as was first suspected based on previous work showing a decarboxylation reaction leading to aromatic heterocycles.[17] The mild conditions for the decarboxylation leading to saturated heterocycles are interesting, and to the best of our knowledge unprecedented. Further investigation is ongoing with other substrates to determine whether the reaction is general or unique to the substrates used in this work. It would appear that the decarboxylation is not occurring due to NaOH being present in the reaction mixture resulting from NaH reacting over time with trace water since no reaction is observed when **14** is treated with NaOH in THF at room temp. for 24 h.

In testing the generality of this base induced rearrangement reaction, cycloadduct **17** formed from *N*,*N*-dimethylacrylamide was treated with potassium *tert*-butoxide to give **18** (Scheme 8).



Scheme 8. KO*t*Bu-induced rearrangement of **17** to **18**.

Conclusions

While verdazyl radicals are considered stable relative to radicals in general, they are still reactive and, as has been demonstrated herein, can lead to a variety of unique nitrogen-containing small molecules. There is sufficient structural variety in both the verdazyl radical and dipolarophiles to provide a library of diverse compounds enabling this new synthetic strategy to be ideal for DOS. In addition, presently under investigation are two other unique intermolecular rearrangements of our pyrazolotetrazinone structures, dictated by substituents in the molecule and reaction conditions, leading to other structurally interesting motifs. These various rearrangements point to the strength of working with structurally flexible heterocyclic molecules where the nucleophilic heteroatoms are well positioned to react intramolecularly with electrophilic substituents to give strained-ring intermediates that readily collapse to other interesting scaffolds.

Experimental Section

General: All reagents and solvents were purchased from Sigma–Aldrich or Fluka unless otherwise stated. The inhibitor hydroquinone monomethyl ether was removed from acrylates by passing them through a short column packed with inhibitor remover resin purchased from Sigma–Aldrich. Silica gel chromatography was performed with Silica Gel 60 (particle size 40–63 μm) obtained from EMD. Thin-layer chromatrography (TLC) plates were obtained from EMD. Verdazyl radical **1**[18a] and methyl 2-acetoxyacrylate (MAA)[18b] were synthesized according to published procedures.

NMR spectra were recorded on a Varian Unity INOVA spectrometer at 20 °C, operating at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR or a Bruker Avance III spectrometer at 23 °C, operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR spectroscopy. Chemical sifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (δ = 0 ppm) for ^{1}H NMR spectra and $CDCl_3$ (δ = 77.0 ppm) for ^{13}C NMR spectroscopy. Coupling constants (J) are reported in Hertz (Hz).

Mass spectrometry was performed on an AB/Sciex QStar mass spectrometer with an ESI source, MS/MS and accurate mass capabilities, associated with an Agilent 1100 capillary LC system.

X-ray data were collected on a Bruker–Nonius Kappa-CCD diffractometer using monochromated Mo-K_α radiation, and measurements were made using a combination of Φ and ω scans with κ offsets to fill the Ewald sphere. The data were processed using the Denzo-SMN package. Absorption corrections were carried out using SORTAV. The structure was solved and refined using SHELXTL V6.1 for full-matrix least-squares refinement that was based on F^2. All H atoms were included in the calculated positions and allowed to refine in the riding-motion approximation with U_{iso} tied to the carrier atom.

CCDC-766562 (for **4**) and CCDC -766561 (for **11**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for Cycloaddition Reactions: The neat olefin (20 mmol) was placed in a three-neck round-bottomed flask equipped with a septum and an adaptor that was connected to a gas bubbler. Oxygen was bubbled into the reaction flask for 15 min at ambient temperature via a syringe needle pierced through the septum. 1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1 mmol) was added and the reaction solution was stirred at room temp. for 24 h under an atmosphere of O_2. Excess olefin was removed in vacuo and the products were purified by flash silica gel chromatography.

Vinyl Cyanoacetate Cycloadduct 3, Post Hydrolysis: Compound **3** was prepared according to the general procedure. Hydrolysis of the initially formed cycloaddition product appeared to occur during purification by silica gel column chromatography (1:9 ethyl acetate/dichloromethane) to give a white solid (110 mg, 45%); m.p. 108–111 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 7.75–7.65 (m, 2 H, Ph*H*), 7.50–7.35 (m, 3 H, Ph*H*), 4.18 (t, J = 8.14 Hz, 2 H, CH_2), 3.43 (s, 3 H, CH_3), 2.71 (t, J = 8.14 Hz, 2 H, CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3, 156.9, 141.4, 131.3, 128.7, 128.6, 127.5, 42.5, 37.5, 30.2 ppm. HRMS (EI): calcd. for $C_{12}H_{12}N_4O_2$ [M]$^+$ 244.0960; found 244.0960.

Verdazyl Radical Addition Product 4: Compound **4** was prepared according to the general procedure and purified by silica gel column chromatography (1:1 ethyl acetate/hexanes) to give a white solid (160 mg, 35%); m.p. 172–174 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 7.70–7.35 (m, 10 H, Ph*H*), 6.80 (s, 1 H, C=C*H*), 3.32 (s, 3 H, CH_3), 3.26 (s, 3 H, CH_3), 3.19 (s, 3 H, CH_3), 3.15 (s, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.3, 155.2, 142.3, 141.6, 131.8, 130.7, 129.4, 128.8, 127.4, 127.2, 114.3, 91.5, 39.1, 37.5, 36.8, 34.4 ppm. HRMS (EI): calcd. for $C_{23}H_{23}N_9O_2$ [M]$^+$ 457.2000; found 457.1975.

2-Phenyl-1-(methylthio)acrylonitrile Cycloadduct 8a: Compound **8a** was prepared according to the general procedure and purified by silica gel column chromatography (1:4 ethyl acetate/hexanes) to give a white solid (150 mg, 42%); m.p. 144–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.97–7.84 (m, 2 H, Ph*H*), 7.48–7.36 (m, 8 H, Ph*H*), 4.79–4.71 (m, 2 H, CH_2), 3.70–3.55 (m, 2 H, CH_2), 3.45 (s, 3 H, CH_3), 2.07 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2, 143.5, 134.3, 131.4, 129.9, 129.0, 128.9, 128.7, 128.5, 128.3, 113.1, 73.8, 58.3, 50.5, 37.1, 29.6, 16.0 ppm. HRMS (EI): calcd. for $C_{20}H_{19}N_5OS$ [M]$^+$, 377.1310; found 377.1309.

MAA Cycloadduct 9: Compound **9** was prepared according to the general procedure with the modification that the reaction was stopped after 3 h. Purification by silica gel column chromatography (hexanes/ethyl acetate, 3:1) gave **9** as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.65–7.70 (m, 2 H, Ph*H*), 7.45–7.35 (m, 3 H, Ph*H*), 4.37–4.28 (m, 1 H, CH_2), 3.61–3.51 (m, 1 H, CH_2), 3.43 (s, 3 H), 3.21–3.10 (m, 1 H, CH_2), 3.17 (s, 3 H, CH_3), 2.49–2.40 (m, 1 H, CH_2), 2.03 (s, 3 H, CH_3) ppm.

α,β-Unsaturated Ester Cycloadduct 10: Elimination of acetic acid from **9**[18c] occurred in quantitative yield at room temp. over 48 h to give **10** as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.58–7.54 (m, 2 H, Ph*H*), 7.43–7.36 (m, 3 H, Ph*H*), 5.90 (t, J = 2.78 Hz, 1 H, C=C*H*), 4.70 (d, J = 2.78 Hz, 2 H, CH_2), 3.34 (s, 3 H, CH_3), 3.30 (s, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 146.1, 134.2, 131.7, 130.4, 129.4, 128.6, 127.1, 113.3, 52.0, 51.3, 36.8 ppm. HRMS (ESI): calcd. for $C_{14}H_{14}N_4O_3$ [M + H]$^+$ 287.1125; found 287.1138.

α,β-Unsaturated Ester Cycloadduct 10 via Cycloaddition of 1a and Methyl Propiolate: Verdazyl radical **1** (300 mg, 1.5 mmol) was dissolved in methyl propiolate (0.65 mL, 7.5 mmol). The reaction was oxygenated and stirred at room temp. for 48 h. The excess monomer was removed in vacuo. Purification by silica gel chromatography (toluene/ethyl acetate, 17:1) gave **10** (52 mg, 18%) as a colorless liquid.[18d]

5-Methyl-7-phenylpyrazolo[1,5-*d*][1,2,4]triazin-4(5*H*)-one (11): The general procedure was slightly modified such that less MAA (1.065 g, 7.5 mmol) was used relative to 1,5-dimethyl-3-phenyl-6-oxoverdazyl **1** (203 mg, 1.0×10^{-3} mol). The excess monomer was removed in vacuo. Purification by silica gel chromatography (hexanes/ethyl acetate, 3:1) gave the product as a white solid (96 mg, 32%). ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 8.15–8.05 (m, 2 H, Ph*H*), 8.015 (d, J = 1.94 Hz, 1 H, pyr*H*), 7.60–7.50 (m, 3 H, Ph*H*), 7.226 (d, J = 1.94 Hz, 1 H, pyr*H*), 3.83 (s, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.7, 143.7, 138.5, 134.6, 131.0, 129.4, 128.8, 128.5, 106.5, 37.9 ppm. HRMS (ESI): calcd. for $C_{12}H_{11}N_4O$ [M + H]$^+$ 227.0929; found 227.0927.; m.p. 119–121 °C.

Conversion of 10 to 11 via Heating: Product **10** (20 mg, 0.07 mmol) was refluxed in 5 mL of ethyl acetate for 30 min. The solvent was removed in vacuo to give **11** (14 mg, 89%).

Conversion of 10 to 11 Using NaH: Product **10** (20 mg, 0.07 mmol) was dissolved in 3 mL of dry THF. Excess solid sodium hydride (20 mg) was added and the reaction was allowed to proceed for 4 h at room temp. The reaction mixture was cooled in an ice bath and quenched with methanol. The THF was removed in vacuo. The reaction mixture was taken up in ethyl acetate (10 mL) and washed with a cold brine solution (10 mL). The ethyl acetate solution was dried with Na_2SO_4 and evaporated to give **11** (12 mg, 76%) with no starting material remaining according to TLC. Repeating the reaction with no sodium hydride showed only a very faint spot for **11** on a TLC plate when a large amount of the reaction solution was used.[18e]

Cycloadduct of 1a with Dimethyl Acetylenedicarboxylate (12): Verdazyl **1** (300 mg, 1.48 mmol) was dissolved in dimethyl acetylenedicarboxylate (0.9 g, 7.4 mmol) and stirred for 3 d at room temp. under an oxygen atmosphere. The reaction mixture was purified by silica gel column chromatography (1:3 ethyl acetate/hexanes) to give **12** as a yellow oil (209 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 7.60–7.63 (dd, 2 H, Ph*H*), 7.46–7.50 (tt, 1 H, Ph*H*), 7.39–7.43 (tt, 2 H, Ph*H*), 4.84 (s, 2 H, CH_2), 3.72 (s, 3 H, CH_3), 3.39 (s, 3 H, CH_3), 3.25 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 159.5, 156.5, 141.9, 140.4, 131.7, 129.4, 128.8, 128.2, 104.8, 53.0, 52.0, 51.5, 37.5 ppm. HRMS (EI): calcd. for $C_{16}H_{16}N_4O_5$ [M]$^+$ 284.0909; found 284.0903.

Rearrangement of 12 to 13: Cycloadduct **12** (110 mg, 0.32 mmol) was heated at 150 °C neat for 2 d. The reaction mixture was purified by silica gel column (1:3 ethyl acetate/hexanes) to give **13** as a white solid (45 mg, 50%); m.p. 100–103 °C. Unreacted starting material (47 mg, 42%) was recovered. ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 8.37 (s, 1 H, pyr*H*), 8.03–8.05 (m, 2 H, Ph*H*), 7.52–7.57 (m, 3 H, Ph*H*), 3.98 (s, 3 H, CH_3), 3.84 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 151.9, 145.7, 138.2, 133.2, 131.2, 129.6, 128.5, 128.3, 114.8, 52.5, 38.5 ppm. HRMS (EI): calcd. for $C_{14}H_{12}N_4O_3$ [M]$^+$ 345.1193; found 345.1203.

Methyl Acrylate Cycloadduct (14): Compound **14** was prepared according to the general procedure and purified by silica gel column

chromatography (1:1 ethyl acetate/hexanes) to give a white solid (179 mg, 62%); m.p. 115–117 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 7.67–7.62 (m, 2 H, Ph*H*), 7.47–7.42 (m, 1 H, Ph*H*), 7.42–7.37 (m, 2 H, Ph*H*), 4.24 (dd, *J* = 3.9, 9.0 Hz, 1 H, C*H*), 4.22–4.17 (m, 1 H, CH_2), 3.56 (s, 3 H, CH_3), 3.52–3.46 (m, 1 H, CH_2), 3.37 (s, 3 H, CH_3), 2.48–2.39 (m, 1 H, CH_2), 2.27–2.20 (m, 1 H, CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 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 ppm. HRMS (EI): calcd. for $C_{14}H_{16}N_4O_3$ $[M]^+$ 288.1222; found 288.1218. FTIR (KBr): 3041, 2993, 2956, 1738, 1676 cm^{-1}.

Rearranged Methyl Acrylate Cycloadduct Pre-decarboxylation (15): Cycloadduct **14** (140 mg, 0.5 mmol) was dissolved in 15 mL of dry THF in a dry 3-neck round-bottomed flask equipped with a stir bar, cooled to 0 °C and degassed with N_2 for 30 min. Sodium hydride (20 mg, 1.0 mmol) was added. The reaction mixture was warmed to room temp. and then left at that temperature for an additional 0.5 h. Three drops of methanol was added to quench the remaining sodium hydride and the THF was removed in vacuo. The resulting oil was dissolved in ethyl acetate and washed with brine. The organic layer was dried with Na_2SO_4 and the solvents evaporated in vacuo to give **15** (118 mg, 82%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.70–7.62 (m, 2 H, Ph*H*), 7.40–7.32 (m, 3 H, Ph*H*), 5.40 (br., 1 H, N*H*), 3.81 (s, 3 H, CH_3), 3.40–3.30 (m, 1 H, CH_2), 3.21 (dt, *J* = 13, 3 Hz, 1 H, NCH_2), 2.85 (s, 3 H, CH_3), 2.86–2.80 (m, 1 H, CH_2), 2.09 (dt, *J* = 13, 5 Hz, 1 H, NCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 150.2, 147.6, 129.5, 127.9, 127.8, 127.6, 85.6, 52.6, 36.9, 36.7, 27.4 ppm. HRMS (ESI): calcd. for $C_{14}H_{17}N_4O_3$ $[M + H]^+$ 289.1295; found 289.1297.

Rearranged Methyl Acrylate Cycloadduct Pre-decarboxylation (15): Cycloadduct **14** (20 mg, 0.07 mmol) was dissolved in 5 mL of dry THF in a dry 3-neck round-bottomed flask equipped with a stir bar, cooled to 0 °C in an ice bath and degassed with N_2 for 30 min. Lithium diisopropylamide (2 M, 0.1 mL, 0.2 mmol) was added dropwise via syringe over 30 seconds. The reaction mixture was warmed to room temp. after 15 min at 0 °C. The unreacted LDA was destroyed by the careful addition of water to the reaction mixture. TLC (3:1 dichloromethane/ethyl acetate) of the reaction mixture showed no remaining starting material. The THF was removed in vacuo. The resulting solid was washed with $CDCl_3$ and the NMR spectrum of the crude reaction mixture matched the spectrum previously obtained for **15**.

Treatment of 14 with NaOH: Cycloadduct **14** (20 mg, 0.07 mmol) was dissolved in 5 mL of THF in a round-bottomed flask equipped with a stir bar. Aqueous sodium hydroxide (1 M, 1 mL, 1 mmol) was added. The reaction mixture was stirred at room temp. for 24 h. No change was observed by TLC (3:1 dichloromethane/ethyl acetate).

Treatment of 15 with NaOH: Product **15** (20 mg, 0.07 mmol) was dissolved in 5 mL of THF in a round-bottomed flask equipped with a stir bar. An aqueous sodium hydroxide solution (0.1 M, 1 mL, 0.1 mmol) was added. The reaction mixture was stirred at room temp. for 24 h. No change was observed by TLC (3:1 dichloromethane/ethyl acetate).

Rearranged Methyl Acrylate Cycloadduct 16, Post Decarboxylation: Cycloadduct **14** (140 mg, 0.5 mmol) was dissolved in 15 mL of dry THF in a dry 3-neck round-bottomed flask with a stir bar and nitrogen gas was introduced for 30 min at 0 °C. Excess solid sodium hydride (75 mg) was added and the reaction was allowed to proceed for 1 h at 0 °C and 1 h at room temp. The reaction mixture was quenched by the slow addition of methanol until effervescence ceased. The THF was removed in vacuo. The resulting oil was dissolved in ethyl acetate and washed with brine. The organic layer was dried with Na_2SO_4 and the solvents evaporated in vacuo to give **16** (106 mg, 92%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.60–7.65 (m, 2 H, Ph*H*), 7.38–7.44 (m, 3 H, Ph*H*), 4.26 (br., s, 1 H, N*H*), 4.18–4.24 (m, 1 H, CH_2), 3.40 (br., d, *J* = 0.72 Hz, 3 H, CH_3), 3.09 (br., t, *J* = 7.45 Hz, 1 H, C*H*), 2.47–2.70 (m, 3 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 149.1, 132.9, 129.9, 128.3, 128.0, 58.4, 46.3, 36.4, 35.2 ppm. HRMS (EI): calcd. for $C_{12}H_{14}N_4O$ $[M]^+$ 230.1168; found 230.1168.

Conversion of 15 to 16 with NaH: Product **15** (40 mg, 0.14 mmol) was dissolved in 5 mL of dry THF. Excess solid sodium hydride (50 mg) was added and the reaction was allowed to proceed for 4 h at room temp. The reaction mixture was cooled in an ice bath and quenched with methanol. The THF was removed in vacuo. The reaction mixture was taken up in ethyl acetate (10 mL) and washed with a cold brine solution (10 mL). The organic layer was dried with Na_2SO_4 and evaporated to give **16** (28 mg, 76%) with no starting material remaining according to TLC.

***N*,*N*-Dimethylacrylamide Cycloadduct 17:** Compound **17** was prepared according to the general procedure and purified by recrystallization with EtOAc to give a dark yellow solid (253 mg, 84%); m.p. 141–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.70–7.63 (m, 2 H, Ph*H*), 7.47–7.35 (m, 3 H, Ph*H*), 4.58–4.54 (m, 1 H, C*H*), 4.31–4.20 (m, 1 H, CH_2), 3.53–3.43 (m, 1 H, CH_2), 3.38 (s, 3 H, CH_3), 2.71 (s, 3 H, CH_3), 2.51 (s, 3 H, CH_3), 2.40–2.28 (m, 1 H, CH_2), 2.16–2.04 (m, 1 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 153.6, 146.0, 131.4, 130.5, 128.4, 127.7, 59.5, 44.5, 36.7, 36.4, 35.5, 30.0 ppm. HRMS (ESI): calcd. for $C_{15}H_{20}N_5O_2$ $[M + H]^+$ 302.1616; found 302.1611.

Rearranged *N*,*N*-Dimethylacrylamide Cycloadduct 18: Cycloadduct **17** (30 mg, 0.1 mmol) was dissolved in 3 mL of dry THF in a dry 3-neck round-bottomed flask equipped with a stir bar. Potassium *tert*-butoxide (26 mg, 0.2 mmol) was added in small portions. The reaction mixture was stirred at room temp. for 0.5 h. The THF was removed in vacuo. 3 mL of ethyl acetate was added to the remaining solid and three drops of saturated ammonium chloride was added to the suspension. The organic layer was washed twice with brine, dried with Na_2SO_4 and the solvents evaporated in vacuo to give **18** (24 mg, 80%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.73–7.65 (m, 2 H, Ph*H*), 7.42–7.32 (m, 3 H, Ph*H*), 5.06 (br., 1 H, N*H*), 3.43 (dt, *J* = 12.1, 4.6 Hz, 1 H, CH_2), 3.38–3.30 (m, 1 H, CH_2), 3.23 (br., 3 H, CH_3), 3.02 (br., 3 H, CH_3), 2.79 (s, 3 H, CH_3), 2.69 (dd, *J* = 12.5, 3.5 Hz, 1 H, CH_2), 2.11–2.00 (m, 1 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 151.2, 149.1, 129.7, 128.9, 128.0, 127.4, 85.1, 38.1 (br), 37.7 (br), 37.3, 36.5, 25.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{20}N_5O_2$ $[M + H]^+$ 302.1626; found 302.1611.

Supporting Information (see also the footnote on the first page of this article): Spectra of compounds **3**, **4**, **6**, **8a**, **9**–**18** and crystal structures of **4** and **11**.

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