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1,3-Dipolar Cycloaddition Reactions Initiated with the 1,5-Dimethyl-3-phenyl-6-oxoverdazyl Radical

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The 1,5-dimethyl-3-phenyl-6-oxoverdazyl radical reacts at room temperature in the presence of styrene to give a dihydrotetrazinone heterocyclic structure. We surmise that the reaction occurs by a 1,3-dipolar cycloaddition via the intermediacy of an azomethine imine. While initial reactions under nitrogen gave relatively poor yields (40 %) of the cycloaddition product, improved yields (up to 84 %) were realized when the reaction mixtures were saturated with oxygen. Acrylate, methacrylate, fumarate and maleate dipolarophiles react regioselectively and stereospecifically to provide a series of dihydrotetrazinone heterocyclic structures. These initial results demonstrate the feasibility of using verdazyl radicals as substrates for organic synthesis.

Introduction

While radical molecules are typically transient species, nitroxide and verdazyl radicals are unusual in that they are stable and in many cases can be isolated and stored for long periods without any appreciable decomposition.[1] Historically, these stable radicals have been employed as spin probes[2] or as polymerization inhibitors.[1,3] Recently, they have been successfully used to moderate living-radical polymerizations.[4] Verdazyl radicals, in association with various transition metals, are also showing promise as molecular magnets.[5] To date, however, there are no examples of these stable radicals having been used as substrates for organic synthesis, presumably because of their perceived low reactivity. In fact, it is their inability to initiate the radical polymerization of styrene and acrylate monomers that have enabled them to be so successful in mediating living-radical polymerizations. But certain members of these families have been shown to undergo various transformations under specific conditions. While the chemistry of these transformations is reasonably well known for nitroxides,[1b] the chemistry of verdazyl radicals is largely unexplored. We were intrigued by this latter omission and became interested in seeing if these molecules could find use as substrates for organic synthesis.

Herein, we report the successful use of the 1,5-dimethyl-3-phenyl-6-oxoverdazyl radical (**1**) as a precursor to a structurally unique azomethine imine, which, in the presence of dipolarophiles, undergoes [3+2] cycloaddition reactions to give dihydrotetrazinone heterocyclic structures. Cycloaddition reactions in general constitute one of the most powerful methods for the synthesis of heterocyclic structures often found in therapeutic drugs, natural products and advanced materials.[6]

The use of azomethine imines in 1,3-dipolar cycloaddition (1,3-DC) reactions was highlighted in a seminal paper by Huisgen.[7] Synthetic approaches to azomethine imines include the condensation of pyrazolidinone derivatives with aldehydes[8] or hydrazides with aldehydes,[9] as well as deprotonation of alkylated *N*-nitrosoamines,[10] thermal[11] and acid-catalyzed[12] isomerization of hydrazones and 1,4-silatropic shifts in α-silylnitrosoamines.[13] Recent developments in the chemistry of azomethine imines include an asymmetric variant of the reaction,[14] a formal [3+3][15] and [4+3][16] cycloaddition, and a kinetic resolution of enantiomers using a chiral catalyst.[17]

Results and Discussion

In an ongoing program to synthesize compounds containing a benzylic C–N or C–O σ bond that could mediate living-radical polymerization,[4] we added compound **1** to styrene and benzoyl peroxide (BPO) under N_2 anticipating the formation of **2** [Equation (1)]. However, only a small amount of compound **2** resulted with compound **3** being the major product, although admittedly in modest yield.

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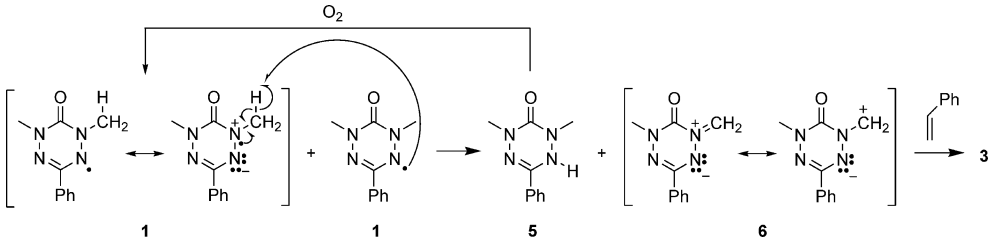
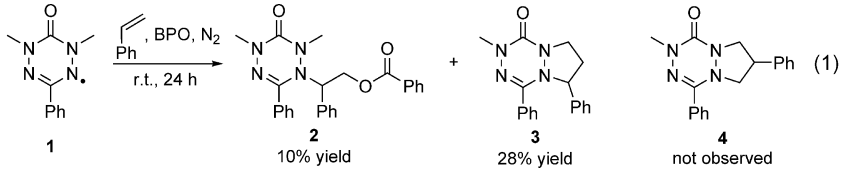


Scheme 1. Proposed reaction mechanism.



We surmised that compound **3** formed by a cycloaddition reaction via an azomethine imine (**6**) (Scheme 1), which in turn, resulted from a disproportionation reaction between two molecules of compound **1** to give leucoverdazyl **5** and compound **6**. Exploratory density functional theory calculations [B3LYP/6-31G(d)] support the hydrogen atom abstraction mechanism leading to the stable intermediates **5** and **6**.[18] Intermediate **6** subsequently undergoes a 1,3-DC reaction with styrene to give compound **3**.[19] The regioisomer **4** was not observed.

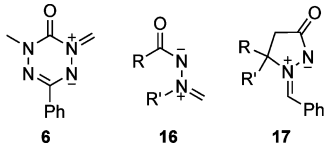
The proposed mechanism suggests that BPO is not part of the reaction sequence and this was verified by repeating the aforementioned reaction in the absence of BPO. After 24 h, a 26% yield of **1** was obtained (Table 1, Entry 1), similar to the yield in the presence of BPO [Equation (1)]. Increasing the reaction time to 96 h gave an improved yield but still less than 50% (Entry 2). Assuming the proposed reaction mechanism is correct this result should not be too surprising since half the verdazyl radical is consumed to form leucoverdazyl **5**, a product that is stable in an inert atmosphere but readily oxidized in air back to the verdazyl radical.[20] The presence of **5** was confirmed indirectly by isolating its benzylated derivative formed, after the cycloaddition reaction was allowed to proceed for 24 h, by adding sodium hydride and benzyl chloride to the reaction mixture.[20] In an attempt to recycle **5** in situ and improve the reaction yields, reactions were performed in air. While a clear improvement in the yield of compound **3** of a 24-h cycloaddition reaction was evident (Table 1, Entry 3), a better result was obtained when the reaction was performed in under O_2 (Entry 4). Extending the reaction time beyond 24 h offered only marginal improvements (Entries 5, 6). Reactions performed in dichloromethane, acetone, and DMSO showed the reaction rate to be relatively insensitive to solvent polarity with isolated yields of compound **3** of 45%, 51% and 53%, respectively. The lower yield in these reactions relative to the reaction in neat styrene (Table 1, Entry 4) can probably be attributed to a dilution effect.

Table 1. Optimization of reaction conditions for the 1,3-dipolar cycloaddition of **1** with styrene.

Entry	Conditions	Time [h]	% Yield of **3**
1	N_2	24	26
2	N_2	96	46
3	air	24	52
4	O_2[a]	24	63
5	O_2[a]	48	66
6	O_2[a]	72	70

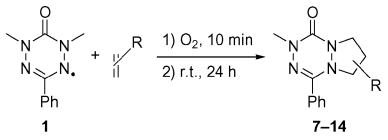
[a] Compressed gas.

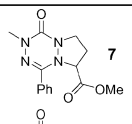
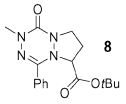
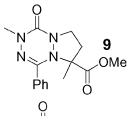
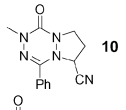
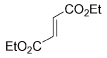
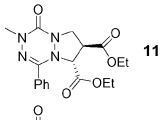
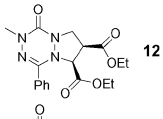
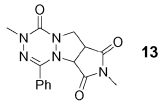
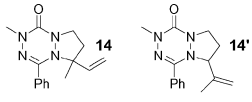
The reaction was subsequently extended to other olefinic substrates (Table 2). Various acrylates reacted smoothly (Entries 1–3) regardless of the steric bulk of the alkoxy moiety (Entry 2) or the presence of a substituent on the α-carbon (Entry 3). Reactions with diethyl fumarate and maleate proceeded stereospecifically to give only one diastereoisomer each (Entries 5,6), while *N*-methylmaleimide afforded a tricyclic product (Entry 7). Reactions with isoprene gave **14** and **14′** (Entries 8,9), with the disubstituted double bond reacting slightly faster than the monosubstituted one. Lower yields were generally observed with acrylonitrile in comparison to styrene, methyl acrylate and methyl methacrylate. (Entry 4). Reactions with unactivated (1-hexene and cyclohexene) or electron-rich (vinyl ethyl ether and *N*-vinylmorpholine) dipolarophiles provided very low or no yield of cyclic products.



As a consequence of forming the azomethine imine from **1**, the structure of **6** differs from previously reported cyclic and acyclic azomethine imines containing a hyrazide backbone. In the ylide resonance forms of the azomethine imines

Table 2. Summarized results from the 1,3-dipolar cycloaddition reaction with various dipolarphiles.[a]



Entry	Substrate	Product	Yield[b]
1		 **7**	74 %
2		 **8**	82 %
3		 **9**	84 %
4		 **10**	62 %
5		 **11**	83 %
6		 **12**	42 %
7[c]		 **13**	56 %
8		 **14** **14'**	40 % (6:4)[e]
9[d]			49 % (6:4)[e]

[a] Reaction conditions: **1** (1.8 mmol) was dissolved in 10 equiv. of substrate, the solution was purged with O_2 for 10 min and the reaction allowed to proceed for 24 h. [b] Isolated yield. [c] Dissolved in 5 mL of dry THF. [d] Reaction performed over 60 h. [e] Ratio of **14**/**14′**.

derived from the hydrazides **16** or the pyrazolidinones **17**, the alkyl substituent is bonded to the β-nitrogen. In contrast, the alkyl group in **6** is situated on the α-nitrogen. The charges on the nitrogen atoms in the ylide structures are therefore transposed (cf. **6** with **16** and **17**), resulting in the cyclic products derived from **6** having a different substitution pattern compared to those from **16** or **17**. The use of **1** as a starting material also enables the incorporation of a novel dihydrotetrazinone moiety into these heterocyclic structures.

Conclusions

As a consequence of forming the azomethine imine from **1**, the structure of **6** differs from previously reported cyclic and acyclic azomethine imines containing a hyrazide backbone. In the ylide resonance forms of the azomethine imines derived from hydrazides **16** or pyrazolidinones **17**, the alkyl substituent is bonded to the β-nitrogen. In contrast, the alkyl group in **6** is situated on the α-nitrogen. The charges on the nitrogen atoms in the ylide structures are therefore transposed (cf. **6** with **16** and **17**), resulting in the cyclic products derived from **6** having a different substitution pattern compared to those from **16** or **17**. The use of **1** as a starting material also enables the incorporation of a novel dihydrotetrazinone moiety into these heterocyclic structures.

In summary, we have demonstrated the use of a verdazyl radical as a precursor for 1,3-DC reactions with various dipolarophiles under mild conditions. The regioselective and stereospecific nature of the cyclization reactions, the various substrate reactivities and the insensitivity to solvent polarity all support the 1,3-DC mechanism. This work provides access to unique bicyclic and tricyclic heterocyclic compounds with structural motifs unattainable by other 1,3-DC reactions. These initial findings lay the foundation for future work in this area. In that regard, an area that is presently been investigated is an interesting and unexpected rearrangement of some of these cyclic structures into a general structure that has been shown to have anti-inflammatory activity.

Experimental Section

Supporting Information (see also the footnote on the first page of this article): Experimental data for cycloadducts and NMR spectra.

Acknowledgments

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[1] a) R. G. Hicks, *Org. Biomol. Chem.* **2007**, *5*, 1231; b) *Synthetic Chemistry of Stable Nitroxides* (Eds.: L. B. Volodarsky, V. A. Reznikov, V. I. Ovcharenko), CRC Press, **1994**.
[2] *Spin Labeling: Theory and Application* (Ed.: L. J. Berliner), vol. 2, Academic Press, New York, **1979**.
[3] M. Kinoshita, Y. Miura, *Makromolekulare Chem.* **1969**, *124*, 211.
[4] E. K. Y. Chen, D. Chan-Seng, P. O. Otieno, R. G. Hicks, M. K. Georges, *Macromolecules* **2007**, *40*, 8609.
[5] For selected examples: a) D. J. R. Brook, S. Fornell, J. E. Stevens, B. Noll, T. H. Koch, W. Eisfeld, *Inorg. Chem.* **2000**, *39*, 562; b) J.-Z. Wu, E. Bouwman, J. Reedijk, A. M. Mills, A. L. Spek, *Inorg. Chim. Acta* **2003**, *361*, 326; c) J. B. Gilroy, B. D. Koivisto, R. McDonald, M. J. Ferguson, R. G. Hicks, *J. Mater. Chem.* **2006**, *16*, 2618.
[6] *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), John Wiley & Sons, New York, **2002**.
[7] a) R. Huisgen, R. Fleischmann, A. Eckell, *Tetrahedron Lett.* **1960**, *1*, 1; b) R. Huisgen, A. Eckell, *Tetrahedron Lett.* **1960**, *1*, 5; c) R. Huisgen, R. Fleischmann, A. Eckell, *Chem. Ber.* **1977**, *110*, 500; d) R. Huisgen, R. Fleischmann, A. Eckell, *Chem. Ber.* **1977**, *110*, 514; e) R. Huisgen, A. Eckell, *Chem. Ber.* **1977**,

110, 522; f) R. Huisgen, A. Eckell, *Chem. Ber.* **1977**, *110*, 540; g) A. Eckell, R. Huisgen, *Chem. Ber.* **1977**, *110*, 559; h) A. Eckell, R. Huisgen, *Chem. Ber.* **1977**, *110*, 571; i) A. Eckell, M. V. Georges, R. Huisgen, A. S. Kende, *Chem. Ber.* **1977**, *110*, 578.
[8] a) H. Dorn, A. Otto, *Chem. Ber.* **1968**, *101*, 3287; b) H. Dorn, A. Otto, *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 214.
[9] W. Oppolzer, *Tetrahedron Lett.* **1970**, *11*, 2199.
[10] a) T. Eicher, S. Hünig, H. Hansen, *Chem. Ber.* **1969**, *102*, 2889; b) P. R. Farina, *Tetrahedron Lett.* **1970**, *11*, 4971.
[11] a) R. Grigg, J. Kemp, N. Thompson, *Tetrahedron Lett.* **1978**, *19*, 2827; b) G. Le Fevre, S. S. J. Hamelin, *Tetrahedron Lett.* **1978**, *46*, 4503 .
[12] G. Le Fevre, S. Sindbandhit, *Tetrahedron* **1979**, *35*, 1821.
[13] M. Komatsu, S. Minakata, Y. Oderaotoshi, *ARKIVOC* **2006**, 370.
[14] a) S. Kobayashi, H. Shimizu, Y. Yamashita, H. Ishitani, J. Kobayashi, *J. Am. Chem. Soc.* **2002**, *124*, 13678; b) R. Shintani, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 10778; c) W. Chen, X. H. Yuan, R. Li, W. Du, Y. Wu, L. S. Ding, Y. C. Chen, *Adv. Synth. Catal.* **2006**, *348*, 1818; d) H. Suga, A. Funyu, A. Kakehi, *Org. Lett.* **2007**, *9*, 97.
[15] a) R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 6330; b) A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 5334.
[16] R. Shintani, M. Murakami, T. Hayashi, *J. Am. Chem. Soc.* **2007**, *129*, 12356.
[17] A. Suarez, W. Downey, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 11244.
[18] An alternative mechanism to form **6** involving a single-electron transfer (SET) process between two molecules of **1** was disregarded due to the low reduction potential of **1**, which makes the SET unlikely to occur. For electrochemical studies on 6-oxoverdazyl radicals, see: J. B. Gilroy, S. D. J. McKinnon, B. D. Koivisto, R. G. Hicks, *Org. Lett.* **2007**, in press. A hydrogen abstraction mechanism similar to that proposed for the verdazyl radical also occurs with nitroxide radicals leading to their decomposition, see: D. F. Bowman, I. Gillian, K. U. Ingold, *J. Am. Chem. Soc.* **1971**, *93*, 6555.
[19] The dimer of **1** has been synthesized by treating **1** with formic acid, albeit in low yield F. A. Neugebauer, H. Fischer, R. Siegel, *Chem. Ber.* **1988**, *121*, 815.
[20] F. A. Neugebauer, *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 455.

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