Tetrahedron Letters 53 (2012) 6846–6848

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Effects of N1 and N5 alkyl substituents on the stability of 6-oxoverdazyl radicals

Matthew Bancerz *, Michael K. Georges

Department of Chemical and Physical Sciences, University of Toronto at Mississauga, 3359 Mississauga Road, Mississauga, Ontario, Canada, L5L 1C6

ARTICLE INFO

Article history:
Received 22 September 2012
Accepted 8 October 2012
Available online 16 October 2012

Keywords:
Verdazyl
Disproportionation
Cycloaddition
Radical Stability, Sterics

ABSTRACT

A series of 1,5-dialkyl-6-oxoverdazyl radicals with differing N1 and N5 substituents were synthesized as a means to observe the effects of different alkyl groups on the reactivity of verdazyl radicals towards disproportionation with a methyl group as the benchmark. Using previously described cycloaddition chemistry with verdazyl radical-derived azomethine imines via disproportionation, methyl acrylate was used to trap the disproportionation products in situ in order to observe the N1 versus N5 site-selectivity of this process. Surprisingly, in most cases the larger alkyl groups proved to be the more reactive as compared to methyl explained by the weakening of the C–H bond involved in a hydrogen atom abstraction as part of the disproportionation. These results contrast with the idea that greater steric bulk generally makes radicals less reactive.

Verdazyl radicals, first described by Kuhn and Trischmann [1] in 1963, make up a family of remarkably stable radicals characterized by their 6-membered ring containing four nitrogen atoms. Their stability is attributed to the delocalization of the unpaired electrons among the four nitrogen atoms. Beyond this common structure, verdazyl radicals are highly modular with a wide variety of substitution patterns described in the literature. Their properties as stable radicals have been exploited in the fields of polymer, material, physical and inorganic chemistry.[2] They have not been used however, purposefully as substrates for organic synthesis until 2008. Georges and co-workers[3] reported a disproportionation of 1,5-dimethyl-3-phenyl-6-oxoverdazyl radicals forming azomethine imines capable of 1,3-dipolar cycloaddition reactions with various dipolarophiles. The resultant cycloadducts of these reactions were shown to act as precursors in the syntheses of several classes of N-heterocycles.[4]

With the recent development of a new synthetic methodology for the synthesis of 1,5-dialkyl-6-oxoverdazyl radicals, the choice of alkyl substituents on the N1 and N5 positions of verdazyl radicals is no longer limited to options given by commercially available mono-alkyl hydrazines.[5] In addition, this new synthetic route allows for the synthesis of verdazyl radicals with different alkyl substituents on the N1 and N5 positions, in effect generating 'unsymmetrical' examples (Fig. 1). These unsymmetrical verdazyl radicals provide a means to study the site selectivity of the disproportionation reactions observed in the formation of verdazyl radical-derived azomethine imines with respect to different alkyl groups.

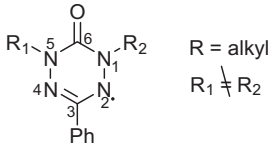


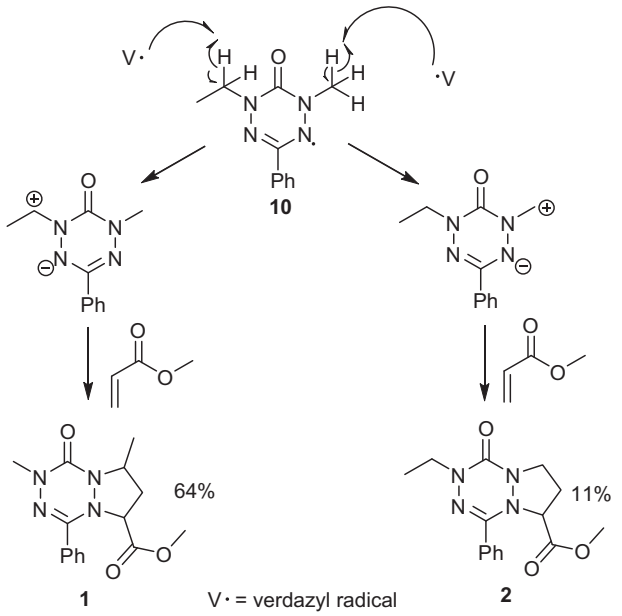
Figure 1. Structure and number scheme of unsymmetrical 1,5-dialkyl-6-oxoverdazyl radicals.

To study the reactivity of different alkyl substituents towards undergoing disproportionation (via hydrogen atom abstraction) we synthesized a series of 1-alkyl-5-methyl-3-phenyl-6-oxoverdazyl radicals and exposed them to our cycloaddition conditions.[4] The methyl group was chosen as the standard with which to compare other alkyl groups. By allowing these unsymmetrical verdazyl radicals to undergo disproportionation to azomethine imines in a solution of methyl acrylate (a dipolarophile), we trapped the azomethine imines formed and inferred the reactivity of different alkyl groups towards disproportionation by the product distribution of the resultant cycloadducts (Scheme 1).

The results we observed were somewhat surprising. We had assumed that the methyl substituent, given its small size would be the most accessible to hydrogen atom abstraction. On the contrary, in most cases sterically bulkier groups preferentially underwent hydrogen atom abstraction and were the source of the major cycloaddition reaction products compared to the methyl substituent. These results seem to go against the paradigm that radicals with sterically bulkier substituents are less reactive. The most marked case involved the 1-ethyl-5-methyl-3-phenyl-6-oxoverdazyl radical depicted in Scheme 1, that showed a preference to form azomethine imine from the ethyl substituent by a factor of 5.8 compared

* Corresponding author.
E-mail address: matthew.bancerz@utoronto.ca (M. Bancerz).

0040-4039/$ - see front matter Crown Copyright © 2012 Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.10.031



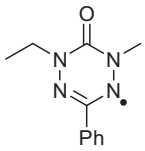
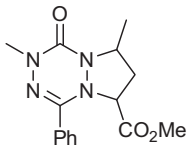
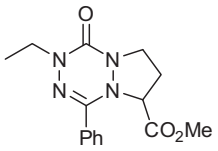
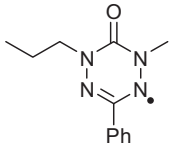
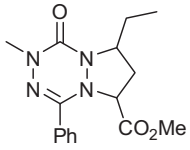
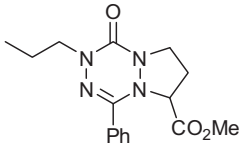
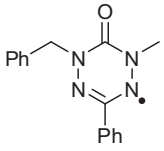
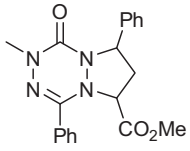
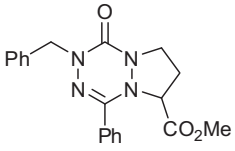
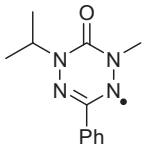
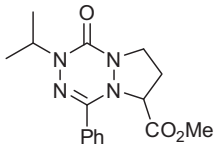
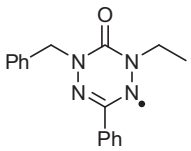
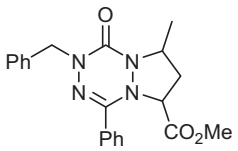
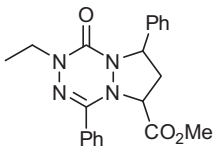
Scheme 1. The two possible disproportionation routes of 1-ethyl-5-methyl-3-phenyl-6-oxoverdazyl radicals to form their respective azomethine imines and undergo 1,3-dipolar cycloaddition.

to methyl. The results of these cycloadditions are summarized in Table 1.

The resulting product distributions indicate that the steric bulk of alkyl substituents is not the only property that affects the propensity of the parent verdazyl radical to undergo disproportionation. Because a hydrogen atom abstraction is involved, the bond dissociation energy (BDE) of the C–H bond in question should be considered when predicting reactivity. BDE is easiest to use as a rationale for product distributions observed with radical **12**, where the competing reaction pathways involve an aliphatic C–H bond versus a significantly weaker benzylic C–H bond. The resultant cycloaddition products show that the hydrogen atom abstraction occurs favourably on the benzylic site by a factor of 2.8 as compared to methyl despite the steric bulk of a benzyl group.

The largest preference away from methyl-side disproportionation is seen with radical **10**, with 5.8:1 ethyl versus methyl-derived cycloaddition product distribution. The BDE of the C–H bond of interest on the ethyl substituent is only slightly weaker (being a 2° site compared to 1°) but at the same time the additional steric impedance is quite small. It would seem therefore that an ethyl group as a substituent has a good balance between BDE and sterics to promote hydrogen atom abstraction and disproportionation in verdazyl radicals. Radical **11** with the *n*-propyl group gave a slightly lower selectivity of 4.5:1, which was anticipated given that *n*-propyl is a slightly larger group but with a nearly identical BDE to the ethyl group case. Example **14** illustrates a direct comparison between a benzyl and ethyl substituent showing that despite the benzyl group having a much weaker C–H bond, the approach of another radical is hindered enough to favour ethyl-side H-abstraction by a factor of 1.7.

Table 1
Unsymmetrical verdazyl radical-derived cycloaddition reaction products with methyl acrylate and their product ratios

Verdazyl radical	Major cycloadduct	Minor cycloadduct	Ratio
 **10**	 **1**	 **2**	5.8:1
 **11**	 **4**	 **3**	4.5:1
 **12**	 **6**	 **5**	2.8:1
 **13**	 **9**	N/A	N/A
 **14**	 **7**	 **8**	1.7:1

Radical **13** was an interesting example to explore given that 1,5-diisopropyl-3-phenyl-6-oxoverdazyl radicals have already been reported and characterized as being more stable than their 1,5-dimethyl counterparts by Hicks and co-workers.[6] Due to the limitations of being able to use only 1° alkyl groups in the synthetic scheme used for the other unsymmetrical examples, Brook's modified Milcent methodology was applied to synthesize example **13**.[7] After allowing **13** to react, only methyl-side cycloadduct was isolated with no evidence of isopropyl side azomethine imine formation. It appears that despite the latter group's weaker abstractable C–H bond (a 3° alkyl centre); the sterics involved were too much to overcome. Isopropyl is indeed less prone to H-abstraction and Hicks' assertion of the increased stability afforded by substituting isopropyl groups for methyl in 6-oxoverdazyl radicals is consistent with our results.

It should be noted that the rationale presented herein for the site-selectivity of the azomethine imine formation is qualitative and made with the assumption that the disproportionation is not a reversible process. The possibility of the azomethine imine formation being reversible should not be ruled out and further study of the kinetics of this disproportionation is warranted. In the case where this process would be reversible, an alternative explanation of the results presented here could be given that equilibrium is established between the two possible azomethine imines and the more stable of the two, being in higher concentration in a solution of dipolarophile is accountable for the majority of cycloaddition products observed.

In conclusion, a series of unsymmetrical verdazyl radical examples using a recently developed synthetic scheme was generated in order to observe how different alkyl groups on the N1 and N5 positions of 6-oxoverdazyl radicals affected their stability, specifically towards disproportionation. By allowing these verdazyl radicals to disproportionate in a solution of methyl acrylate, the disproportionation products, namely azomethine imines, could be efficiently trapped via a 1,3-dipolar cycloaddition reaction. The distribution of the cycloadduct products shows the site-selectivity of the disproportionation reaction based on differing alkyl groups. The results were somewhat surprising, showing that in most cases the sterically larger alkyl substituents proved to be more reactive than the benchmark methyl group. Despite the greater sterics involved with the larger alkyl groups, which would otherwise be assumed to have a stabilizing effect on the radical, the C–H bond of interest in the disproportionation reaction was weaker with the larger alkyl groups given that it resided on a 2° Centre versus a 1° Centre with methyl.

Acknowledgements

Support was provided by the National Science and Engineering Research Council of Canada. M.B. gratefully acknowledges the University of Toronto (UT) fellowship and a Helen Sawyer Hogg Graduate Admission UT Fellowship.

Supplementary data

Supplementary data (experimental details, analytical data and NMR spectra for compounds **1**–**9**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.031. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Kuhn, R.; Trischmann, H. *Angew. Chem.* **1963**, *75*(6), 294–295.
2. Koivisto, B. D.; Hicks, R. G. *Coord. Chem. Rev.* **2005**, *249*, 2612–2630.
3. Yang, A.; Kasahara, T.; Chen, E. K. Y.; Hamer, G. K.; Georges, M. K. *Eur. J. Org. Chem.* **2008**, 4571–4574.
4. (a) Chen, E. K. Y.; Bancerz, M.; Hamer, G. K.; Georges, M. K. *Eur. J. Org. Chem.* **2010**, 5681–5687; (b) Bancerz, M.; Georges, M. K. *J. Org. Chem.* **2011**, *76*(15), 6377–6382.
5. Bancerz, M.; Youn, B.; DaCosta, M. V.; Georges, M. K. *J. Org. Chem.* **2012**, *77*(5), 2415–2421.
6. McKinnon, S. D. J.; Patrick, B. O.; Lever, A. B. P.; Hicks, R. G. *Chem. Commun.* **2010**, *46*, 773–775.
7. Brook, D. J. R.; Richardson, C. J.; Haller, B. C.; Hundley, M.; Yee, G. T. *Chem. Commun.* **2010**, *46*, 6590–6592.