Tetrahedron Letters 55 (2014) 5680–5682

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Bromolactonization of alkenoic acids mediated by V_2O_5 via bromide to bromenium in situ oxidation

McKenzie L. Campbell [†], Samuel A. Rackley [†], Lauren N. Giambalvo, Daniel C. Whitehead [*]

Department of Chemistry, Clemson University, Clemson, SC 29634, USA

ARTICLE INFO

Article history:
Received 23 July 2014
Revised 12 August 2014
Accepted 18 August 2014
Available online 28 August 2014

Keywords:
Bromolactonization
Halenium equivalent
Alkenoic acid
Vanadium oxide

ABSTRACT

An efficient protocol for the bromolactonization of alkenoic acids is presented that obviates the use of molecular bromine or exogenous bromenium sources. Vanadium (V) oxide catalyzes the in situ oxidation of bromide salts to bromenium (Br^+) in a process mediated by urea–hydrogen peroxide complex. Initial mechanistic investigations indicate that the presence of urea does not accelerate the halolactonization reaction.

Marine algae have evolved impressive metalloenzymes that make use of the mM concentration of bromide in ocean water as a terminal halogen source for the electrophilic bromination of secondary metabolites. The so-called haloperoxidase enzymes feature a vanadium (V) oxo active site that promotes the oxidation of bromide to bromenium (Br^+) mediated by hydrogen peroxide as the terminal oxidant.[1] Building on our previous work on vanadium (V) oxide-mediated oxidations,[2] we present here a bio-inspired approach toward the bromolactonization of alkenoic acids mediated by a similar V_2O_5-catalyzed in situ oxidation of bromide to bromenium. Previous attempts at exploiting haloperoxidase-like chemistry with V_2O_5 in different transformations have been stymied by very high catalyst loadings (i.e., >0.5 equiv relative to substrate).[3] In the case of our method, V_2O_5 (~$0.25/g) is employed in a reasonable 0.05 equiv loading with 3 equiv of urea–hydrogen peroxide complex as the terminal oxidant. The protocol is operationally simple, often returning products after acid–base extraction without the need for column chromatography. This method represents an attractive alternative to bromolactonizations that employ molecular bromine or other exogenous bromenium sources (i.e., NBS, 1,3-dibromo-5,5-dimethylhydantoin, etc.), particularly in light of instances such as the 2011 accidental release of approximately 50 L of molecular bromine in Chelyabinsk, Russia that resulted in the hospitalization of 40 people.[4]

We began our investigation by evaluating the bromolactonization of 4-phenyl-4-pentenoic acid (**1**). We were encouraged by our ability to effect the desired bromolactonization to return γ-bromolactone **2** in 84% yield mediated by 0.5 equiv of V_2O_5 in an ACN/H_2O/H_2O_2 (6:1:1) solvent system with NH_4Br as the terminal bromine source (Table 1, entry 1).

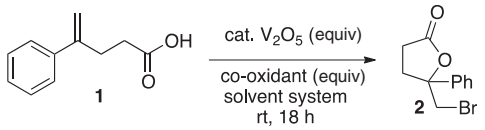
Similar conditions with NaBr as the bromine source returned **2** in a reduced 73% yield (entry 2). Reducing the catalyst loading to 0.2 or 0.1 equiv V_2O_5 (entries 3–7) resulted in reduced yields with both NH_4Br and NaBr. A notable exception was the acceptable 89% yield with 0.2 equiv V_2O_5 and 5 equiv NH_4Br that resulted from warming the reaction mixture to 65 °C (entry 5). An extensive solvent and co-oxidant screen finally returned conditions whereby lactone **2** was isolated in 93% yield with as low as 0.1 equiv of V_2O_5 (entries 8 and 9). Ammonium bromide was confirmed as the halide source of choice, given that NaBr returned bromolactone in an unacceptable 43% yield coupled with significant formation of the corresponding dibromo carboxylic acid product resulting from the rupture of the bromonium intermediate with bromide (entry 10). In all cases, regardless of conditions, the reactions were homogenous.

The catalyst loading could be further lowered to 0.05 equivalents with only a marginal decrease in yield of **2** to 90% (entry 11). In the event, the optimal conditions were found to be 0.05 equiv V_2O_5, 3 equiv of urea–hydrogen peroxide complex (UHP), and 3 equiv of NH_4Br in a 6:1 mixture of acetone and water at room temperature (entry 11, highlighted in bold). Further reduction in the catalyst loading to 0.01 equiv V_2O_5 resulted in a poor yield of 12% of lactone **2** coupled with significant formation of the vicinal dibromo by-product (entry 12). Conducting the reaction in the absence of V_2O_5 confirmed that any background reaction resulting from direct H_2O_2-mediated oxidation of bromide was negligible (entry 13).

* Corresponding author.
E-mail address: dwhiteh@clemson.edu (D.C. Whitehead).
† These authors contributed equally.

http://dx.doi.org/10.1016/j.tetlet.2014.08.071
0040-4039/

Table 1
Optimization of V_2O_5 promoted bromolactionization



Entry	V_2O_5 (equiv)	Solvent	Oxidant (equiv)	Br^- source (equiv)	Yield (%)
1	0.5	ACN/H_2O (6:1)	H_2O_2 (aq)[a]	NH_4Br (5)	84
2	0.5	ACN/H_2O (6:1)	H_2O_2 (aq)	NaBr (5)	73
3	0.2	ACN/H_2O (6:1)	H_2O_2 (aq)	NH_4Br (5)	65
4	0.2	ACN/H_2O (6:1)	H_2O_2 (aq)	NaBr (5)	75
5	0.2	ACN/H_2O (6:1)	H_2O_2 (aq)	NH_4Br (5)	89[b]
6	0.1	ACN/H_2O (6:1)	H_2O_2 (aq)	NaBr (5)	59
7	0.1	ACN/H_2O (6:1)	H_2O_2 (aq)	NH_4Br (5)	54
8	0.2	Acetone/H_2O (6:1)	UHP (3)	NH_4Br (3)	92
9	0.1	Acetone/H_2O (6:1)	UHP (3)	NH_4Br (3)	93
10	0.1	Acetone/H_2O (6:1)	UHP (3)	NH_4Br (3)	43
11	**0.05**	**Acetone/H_2O (6:1)**	**UHP (3)**	**NH_4Br (3)**	**90**
12	0.01	Acetone/H_2O (6:1)	UHP (3)	NH_4Br (3)	12
13	0.0	Acetone/H_2O (6:1)	UHP (3)	NH_4Br (3)	0

[a] H_2O_2 denotes a 30% aq solution of H_2O_2 employed as a co-solvent in a 6:1:1 ratio with ACN and water, respectively.
[b] Reaction was warmed to 65 °C. Isolated yields after acid–base extraction.

Next we turned to a brief exploration of the substrate scope of the transformation (Chart 1). Under our optimal conditions (Table 1, entry 11), lactone **2** was returned in an average isolated yield of 90%. Similarly, γ-lactones **3**–**6** were returned in yields ranging from 83% to 96% depending on the electron donating ability of the arene *para* substituent.

The corresponding δ-lactone **7** was isolated in a modest 50% yield (with a higher 0.1 equiv catalyst loading). In this case a substantial portion of the starting material was converted to the vicinal dibrominated by-product, reflecting the slower cyclization of six versus five-membered rings. The *gem*-dimethyl derivative **8** was returned in an excellent yield of 97%, taking advantage of the Thorpe–Ingold effect. Unsubstituted γ-bromolactone **9** was isolated in 50% yield from 4-pentenoic acid. Benzolactone **10** was isolated in 93% yield from the corresponding 2-allylbenzoic acid. Finally, *trans*-bromolactone **11** was returned in 63% yield on the reaction of *trans*-styrylacetic acid in the presence of 0.1 equiv catalyst. In this singular example, we found it necessary to include 3 equiv of *p*-toluenesulfonic acid as an additive to prevent the formation of the butenolide elimination product.

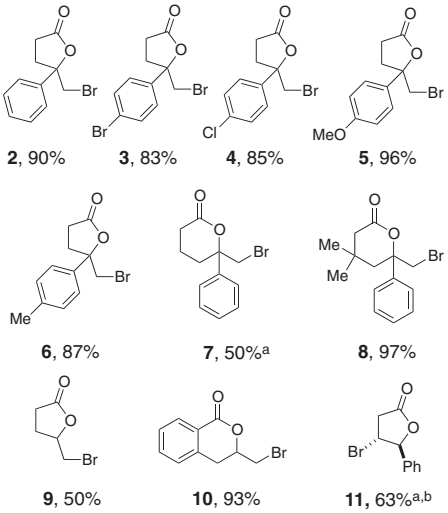
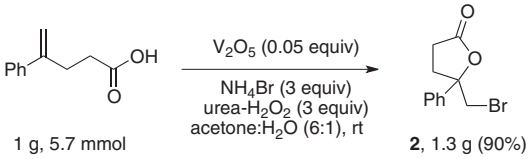


Chart 1. Substrate scope. [a]Reaction conducted with 0.1 equiv V_2O_5. [b]Reaction conducted with 3 equiv *p*-toluenesulfonic acid as an additive.

Finally, the reaction performs well at larger scale. Using our standard reaction conditions, 1 g (5.7 mmol) of alkenoic acid **1** was converted to 1.3 g of γ-bromolactone **2** (90% yield, Eq. 1). This scaled experiment highlights the synthetic ease of our protocol. Pure lactone product was returned after acid–base extraction of the reaction mixture without recourse to column chromatography.



(1)

A number of methods with the aim of effecting brominations while circumventing the use of molecular bromine have appeared, and an assessment of our method compared to the prior art seems appropriate. A number of methods promote the in situ oxidation of inorganic bromide salts to molecular bromine or bromenium (Br^+). Notable oxidants include sodium perborate,[5] lead acetate,[6] ceric ammonium nitrate,[7] sodium periodate,[8] and Selectfluor®.[9] While effective, these methods rely on expensive and relatively environmentally unfriendly oxidants (as compared to the ideal cases of hydrogen peroxide or molecular oxygen). One of the most routinely employed methods for promoting the oxidation of bromide to bromenium is the treatment of sodium or ammonium bromide with Oxone®.[10] These methods suffer from the use of stoichiometric or superstoichiometric loadings of Oxone,® a triple salt of the composition $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$, which yields a significantly large salt waste stream per unit of active oxidant. Additionally, Oxone® is a powerful oxidant that has been demonstrated to react with a number of functional groups,[11] highlighting the potential for the formation of undesirable by-products.

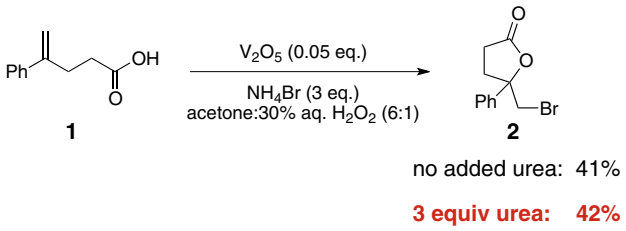
The use of hydrogen peroxide as the terminal oxidant in these transformations is particularly appealing from an environmental standpoint. Owing to its reduced reactivity relative to Oxone,® early examples employing hydrogen peroxide resorted to the use of strongly acidic conditions including H_2O_2/H_2SO_4[12] and H_2O_2/HBr[13] reagent combinations. Detty and coworkers have pioneered the use of various selenoxides, selenic acids, diselenides, and organotellurides as catalysts for the oxidation of bromide mediated by hydrogen peroxide.[14] Additionally, the aerobic oxidation of HBr catalyzed by sodium nitrite has been reported.[15] Finally, sodium bromide has been oxidized in situ by the action of a super-stoichiometric loading of an organic sulfoxide and TMSOTf.[16]

We were intrigued by the better performance of our method in the presence of urea–hydrogen peroxide complex in lieu of 30% aqueous hydrogen peroxide (see Table 1). We wondered whether urea might be playing a catalytic role in our system. Indeed, Braddock and co-workers observed that various N-containing nucleophiles, including dimethyl amides (e.g., DMF) and tetramethylguanidine significantly accelerate bromolactonizations mediated by *N*-bromosuccinimide.[17] To probe whether a similar catalytic process was at play in our system, we compared the bromocyclization of **1** in the presence of 30% aqueous H_2O_2 with and without 3 equiv of added urea (Scheme 1). These experiments represent a slight modification of our optimal conditions, whereby we replaced the water in the solvent system with an equal volume of 30% aqueous H_2O_2. Using these modified conditions, the bromolactonization is not as efficient. Nonetheless, bromolactone **2** was returned in a nearly identical 42% and 41% yield with and without added urea, respectively. These data suggest that urea does not play a catalytic role in our system, and the reason for the benefit of utilizing urea–hydrogen peroxide complex in lieu of aqueous H_2O_2 remains unclear.

The method disclosed herein compares favorably with many of the aforementioned protocols for the in situ generation of molecular bromine or bromenium based on the fact that it employs hydrogen peroxide as the terminal oxidant (albeit as the convenient, shelf-stable urea–H_2O_2 complex). This has marked advantages over early advances in the field that employed less environmentally friendly oxidants. Our catalyst, V_2O_5, is cheap (~$0.25/g), relatively benign, and can be used in a reasonable 5 mol % loading. Finally, our method also has the added benefit of returning the organic products without recourse to chromatographic purification.

Nonetheless, our method suffers from some unfortunate drawbacks including the necessity to employ 3 molar equivalents of both the oxidant and halide source. Indeed, in some instances our method may prove less economical than the use of molecular bromine to promote bromolactonization. This fact, however, is a common issue for the 'alternative bromine' field as a whole. In fact, a 2008 study[18] that evaluated nineteen alternative methods for brominations (in lieu of molecular bromine) revealed that the HBr/H_2O_2 reagent combination[13] was the *only* known method that compared favorably with the use of Br_2 in terms of cost despite considerable attention from the synthetic community. It seems that our method shares similar limitations to many of the other methods described in the prior art, but does, nonetheless offer the significant advantage of circumventing chromatographic purification of products. We are actively pursuing means to further optimize our protocol to address some of its limitations. Nevertheless, it compares favorably with other known means for the in situ generation of Br^+.

In conclusion, we have developed a novel approach toward bromolactonization that exploits the haloperoxidase-like activity of catalytic loadings of V_2O_5 in the presence of urea–hydrogen peroxide complex and ammonium bromide. The process hinges on the in situ oxidation of bromide to bromenium, thus obviating the use of toxic, volatile molecular bromine or other exogenous bromenium sources. The method is synthetically feasible, often returning the desired products after simple acid–base extraction without the need for column chromatography. Current efforts are directed at expanding the utility of this novel reagent combination as well as exploring related haloperoxidase-like activity with chloride.



Scheme 1. Evaluating the role of urea.

Acknowledgments

The authors gratefully acknowledge Clemson University for generous start-up funds. The authors wish to thank Rieke Metals, Inc. and Oakwood Chemical for their generous donation of a substrate precursor in support of this effort.

Supplementary data

Supplementary data (general experimental details and spectral data for all reported compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.071.

References and notes

1. (a) Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937–1944; (b) Butler, A. *Curr. Opin. Chem. Biol.* **1998**, *2*, 279–285; (c) Butler, A. *Coord. Chem. Rev.* **1999**, *187*, 17–35.
2. Drew, E. T.; Yang, Y.; Russo, J. A.; Campbell, M. L.; Rackley, S. A.; Hudson, J.; Schmuki, P.; Whitehead, D. C. *Catal. Sci. Technol.* **2013**, *3*, 2610–2613.
3. (a) Chaudhuri, M. K.; Khan, A. T.; Patel, B. K.; Dey, D.; Kharmawophlang, W.; Lakshmiprabha, T. R.; Mandal, G. C. *Tetrahedron Lett.* **1998**, *39*, 8163–8166; (b) Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T.; Patel, B. K. *Org. Lett.* **2000**, *2*, 247–249; (c) Mondal, E.; Bose, G.; Sahu, P. R.; Khan, A. T. *Chem. Lett.* **2001**, 1158–1159; (d) Mondal, E.; Sahu, P. R.; Bose, G.; Khan, A. T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1026–1028; (e) Bujar Barua, P. M.; Sahu, P. R.; Mondal, E.; Bose, G.; Khan, A. T. *Synlett* **2002**, 81–84; (f) Khan, A. T.; Goswami, P. *Tetrahedron Lett.* **2005**, *46*, 4937–4940; (g) Khan, A. T.; Goswami, P.; Choudhury, L. H. *Tetrahedron Lett.* **2006**, *47*, 2751–2754; (h) Kikushima, K.; Moriuchi, T.; Hirao, T. *Tetrahedron Lett.* **2010**, *51*, 340–342; (i) Kikushima, K.; Moriuchi, T.; Hirao, T. *Tetrahedron* **2010**, *66*, 6906–6911.
4. BBC News: Europe: 'Bromine chemical leak in Russian city of Chelyabinsk'. http://www.bbc.co.uk/news/world-Europe-14755874 (accessed July 1, 2014).
5. Kabalka, G. W.; Yang, K.; Reddy, N. K.; Narayana, C. *Synth. Commun.* **1998**, *28*, 925–929.
6. Muathen, H. A. *Synth. Commun.* **2004**, *34*, 3545–3552.
7. Nair, V.; Panicker, S. P.; Augustine, A.; George, T. G.; Thomas, S.; Vairamani, M. *Tetrahedron* **2001**, *57*, 7417–747422.
8. Dewkar, G. K.; Narina, S. V.; Sudalai, A. *Org. Lett.* **2003**, *5*, 4501–4504.
9. Ye, C.; Shreeve, J. M. *J. Org. Chem.* **2004**, *69*, 8561–8563.
10. (a) Kennedy, R. J.; Stock, A. M. *J. Org. Chem.* **1960**, *25*, 1901–1906; (b) Dieter, R. K.; Nice, L. E.; Velu, S. E. *Tetrahedron Lett.* **1996**, *37*, 2377–2380; (c) Ross, S. A.; Burrows, C. J. *Tetrahedron Lett.* **1997**, *38*, 2805–2808; (d) Lee, K.-J.; Lin, K. W.; Chi, D. Y. *Bull. Korean Chem. Soc.* **2001**, *22*, 549–550; (e) Lee, K.-J.; Cho, H. K.; Song, C.-E. *Bull. Korean Chem. Soc.* **2002**, *23*, 773–775; (f) Koo, B.-S.; Lee, C. K.; Lee, K.-J. *Synth. Commun.* **2002**, *32*, 2115–2123; (g) Narender, N.; Srinivasu, P.; Prasad, M. R.; Kulkarni, S. J.; Raghavan, K. V. *Synth. Commun.* **2002**, *32*, 2313–2318; (h) Kumar, M. A.; Rohitha, C. N.; Kulkarni, S. J.; Narender, N. *Synthesis* **2010**, 1629–1632; (i) Yakura, T.; Ozono, A.; Morimoto, K. *Chem. Pharm. Bull.* **2011**, *59*, 132–134; (j) Wang, G.-W.; Gao, J. *Green Chem.* **2012**, *14*, 1125–1131; (k) Macharla, A. K.; Nappunni, R. C.; Marri, M. R.; Peraka, S.; Nama, N. *Tetrahedron Lett.* **2012**, *53*, 191–195; (l) Parida, K. N.; Jhulki, S.; Mandal, S.; Moorthy, J. N. *Tetrahedron* **2012**, *68*, 9763–9768; (m) Kumar, M. A.; Naresh, M.; Rohitha, C. N.; Narender, N. *Synth. Commun.* **2013**, *43*, 3121–3129.
11. Hussain, H.; Green, I. R.; Ahmed, I. *Chem. Rev.* **2013**, *113*, 3329–3371.
12. Ying, T. K.; Bao, W. L.; Zhang, Y. M. *J. Chem. Res.* **2004**, 806–807.
13. Barhate, N. B.; Gajare, A. S.; Wakharkar, R. D.; Bedekar, A. V. *Tetrahedron* **1999**, *55*, 11127–11142.
14. (a) Higgs, D. E.; Nelen, M. I.; Detty, M. R. *Org. Lett.* **2001**, *3*, 349–352; (b) Abe, M.; You, Y.; Detty, M. R. *Organometallics* **2002**, *21*, 4546–4551; (c) Drake, M. D.; Bateman, M. A.; Detty, M. R. *Organometallics* **2003**, *22*, 4158–4162; (d) Goodman, M. A.; Detty, M. R. *Organometallics* **2004**, *23*, 3016–3020; (e) Bennett, S. M.; Tang, Y.; McMaster, D.; Bright, F. V.; Detty, M. R. *J. Org. Chem.* **2008**, *73*, 6849–6852; (f) Alberto, E. E.; Braga, A. L.; Detty, M. R. *Tetrahedron* **2012**, *68*, 10476–10481.
15. Podgorsek, A.; Eissen, M.; Fleckenstein, J.; Stavber, S.; Zupan, M.; Iskra, J. *Green Chem.* **2009**, *11*, 120–126.
16. Klimczyk, S.; Huang, X.; Fares, C.; Maulide, N. *Org. Biomol. Chem.* **2012**, *10*, 4327–4329.
17. Ahmad, S. M.; Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Tetrahedron Lett.* **2007**, *48*, 915–918.
18. Eissen, M.; Lenoir, D. *Chem. Eur. J.* **2008**, *32*, 9830–9841.