ORGANIC
LETTERS

2012
Vol. 14, No. 2
498–501

Access to Dienophilic Ene-Triketone Synthons by Oxidation of Diketones with an Oxoammonium Salt

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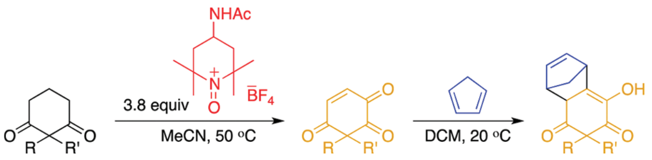
Received November 17, 2011

ABSTRACT



Here we describe the oxidation of 1,3-cyclohexanediones with 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (Bobbitt's salt) to generate 5-ene-1,2,4-triones in moderate-to-good (40−80%) yields. This inexpensive oxidant facilitated an unprecedented cascade of oxidation and elimination to yield novel ene-triketones. The reactivity of these products was explored in the Diels−Alder reaction and provided moderate-to-good yields of cycloaddition products. The products described in this study represent unique, densely functionalized, and versatile building blocks for the synthesis of more complex molecules.

Oxoammonium salts are attractive species because they are easily prepared, environmentally benign, and recyclable compounds.[1,2] Similarly to other nonmetal green oxidants,[3] these oxidants are able to generate aldehydes,[4] esters,[5] and 1,2-diketones.[6] We present here a novel reaction of 2,2-disubstituted 1,3-cyclohexanediones through the use of 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (Bobbitt's salt, **1**) to generate ene-triketones, which are under-investigated but intriguing molecules. This structural motif is found in certain biologically active natural products as either the ene-triketone or a derivative thereof.[7,8] Despite the potential usefulness of ene-triketones as densely functionalized synthons, there are sparse accounts of their synthesis.[7]

We investigated the α-oxidation of 2,2-dimethyl-1,3-cyclohexanedione (**2**), which has been used for the synthesis of bioactive molecules.[9] Our attempts to oxidize

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(1) For reviews on oxidation with oxoammonium salts, see:(a) Merbouh, N.; Bobbitt, J. M.; Bruckner, C. *Org. Prep. Proceed. Int.* **2004**, *36* (1), 1–31. (b) Bobbitt, J. M.; Bruckner, C.; Merbouh, N. *Org. React.* **2010**, *74*, 103–424.

(2) (a) Golubev, V. A.; Zhdanov, R. I.; Protsishin, I. T.; Rozantsev, E. G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1970**, *195*, 952–955. (b) Golubev, V. A.; Rudyk, T. S.; Sen, V. D.; Aleksandrov, A. L. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1976**, *25*, 744–750. (c) Bobbitt, J. M.; Guttermuth, M. C. F.; Ma, Z.; Tang, H. *Heterocycles* **1990**, *30*, 1131–1140. (d) Weik, S.; Nicholson, G.; Jung, G.; Rademann, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1436–1439. (e) Merbouh, N.; Bobbitt, J. M.; Bruckner, C. *J. Carbohydr. Chem.* **2002**, *21*, 65–77. (f) Zakrzewski, J.; Grodner, J.; Bobbitt, J. M.; Karpinska, M. *Synthesis* **2007**, *16*, 2491–2494.

(3) (a) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636–1639. (b) Bisai, A.; Chandrasekhar, M.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 8355–8357. (c) Li, C.; Zheng, P.; Li, J.; Zhang, H.; Cui, Y.; Shao, Q.; Ji, X.; Zhang, J.; Zhao, P.; Xu, Y. *Angew. Chem.* **2003**, *115*, 5217–5220. (d) Noyori, R.; Aoki, M.; Sato, K. *Chem. Commun.* **2003**, 1977–1986. (e) Zhan, B.-Z.; White, M. A.; Sham, T.-K.; Pincock, J. A.; Doucet, R. J.; Rao, K. V. R.; Robertson, K. N.; Cameron, T. S. *J. Am. Chem. Soc.* **2003**, *125*, 2195–2199.

(4) (a) Bobbitt, J. M. *J. Org. Chem.* **1998**, *63*, 9367–9374. (b) Bobbitt, J. M.; Merbouh, N. *Org. Synth.* **2005**, *82*, 80–86.

(5) Merbouh, N.; Bobbitt, J. M.; Bruckner, C. *J. Org. Chem.* **2004**, *69*, 5116–5119.

(6) (a) Golubev, V. A.; Miklyush, R. V. *Zh. Org. Khim.* **1972**, *8*, 1376–1377. (b) Liu, Y.; Ren, T.; Guo, Q. *Chin. J. Chem.* **1996**, *14*, 252–258.

(7) For information on the ene-triketone chromophore's UV-visible and IR spectroscopic properties, see:Martin, H.-D.; Kummer, M.; Martin, G.; Bartsch, J.; Bruck, D.; Heinrichs, A.; Mayer, B.; Rover, S.; Steigel, A.; Mootz, D.; Middelhauve, B.; Scheutzow, D. *Chem. Ber.* **1987**, *120*, 1133–1149.

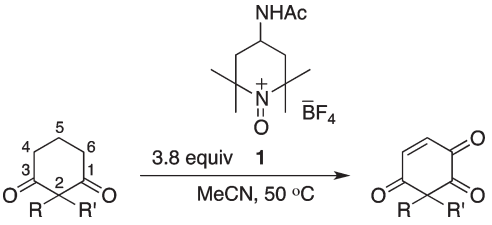
(8) Kong, Z.-L.; Yu, S. C.; Dai, S. A.; Tu, C.-C.; Pan, M.-H.; Liu, Y.-C. *Helv. Chim. Acta* **2011**, *94*, 892–896.

(9) (a) Murai, A.; Tanimoto, N.; Sakamoto, N.; Masamune, T. *J. Am. Chem. Soc.* **1988**, *110*, 1985–1986. (b) Roy, O.; Pattenden, G.; Pryde, D. C.; Wilson, C. *Tetrahedron* **2003**, *59*, 5115–5121.

(10) (a) Gaoni, Y.; Wenkert, E. *J. Org. Chem.* **1966**, *31*, 3809–3814. (b) Rubottom, G. M.; Juve, H. D. *J. Org. Chem.* **1983**, *48*, 422–425.

10.1021/ol2030873

2 with SeO_2, $Pb(OAc)_4$, and Rubottom conditions met with failure.[10] Peroxides caused the formation of the unwanted Baeyer-Villager lactone as the major product. In the absence of peroxides, SeO_2 in refluxing dioxane-water failed to react. $Pb(OAc)_4$ gave low yields of over-acetoxylated products (< 10%) after 24 h of reflux in both benzene and cyclohexane. Seeking alternatives, we turned to the use of oxoammonium salts, which have been reported to promote the α-oxidation of ketones.[6] Using **1**, the desired oxidation was serendipitously accompanied by alkene generation, forming the ene-triketone **3** (Figure 1).



2 **3**

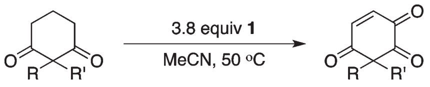
Figure 1. Oxidation of **2** with Bobbitt's salt (**1**).

Table 1. Optimization of the α-Oxidation Reaction[a]

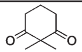
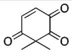
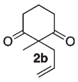
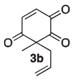
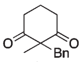
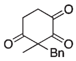
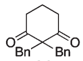
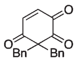
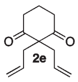
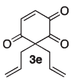
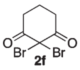
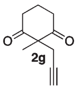
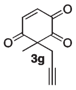
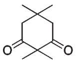
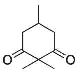
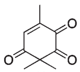
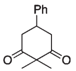
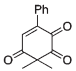
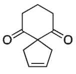
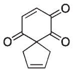
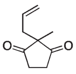
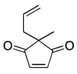
entry	solvent	salt equivalents	temperature (°C)	yield (%)[b]
1	DCM	1	24	—[c]
2	EtOAc	1	24	—[c]
3	MeCN	1	24	—[c]
4	MeCN	1	50	9[d]
5	MeCN	1	reflux	6[d]
6	MeCN	2	50	14
7	MeCN	3	50	53
8	MeCN	3.8	50	65
9	MeCN	4.2	50	44
10	DMF	3.8	50	51

[a] Reactions were performed at 0.2 M on a 1 mmol scale. [b] Refers to isolated yield. [c] No observable reaction. [d] Yield determined by NMR.

Table 2. Scope of the Oxidation for Various Substituted Diketones[a]



2a-l **3a-l**

entry	substrate	product	yield (%)[b]
1	 2a	 3a	65
2	 2b	 3b	56
3	 2c	 3c	58
4	 2d	 3d	36
5	 2e	 3e	48
6	 2f	—	—[c]
7	 2g	 3g	35
8	 2h	—	—[d]
9	 2i	 3i	55
10	 2j	 3j	68
11	 2k	 3k	53
12	 2l	 3l	77

[a] Reactions were performed in anhydrous acetonitrile at 0.2 M and 50 °C on a 2 mmol scale. [b] Refers to isolated yield. [c] No ene-triketone formed. [d] 63% recovered starting material.

We varied solvent, temperature, and oxidant stoichiometry to maximize the yield of **3** (Table 1). No reaction was observed in DCM or EtOAc (Table 1, entries 1 and 2), but the reaction reached completion in 4 h when using anhydrous DMF (Table 1, entry 10) as the solvent.[11] Commonly, silica was added to the mixture at the end of the reaction to allow for facile separation of the desired product from the spent oxidant. Purification of the product from the DMF-silica slurry created complications in successful isolation. In contrast, the use of anhydrous MeCN (Table 1, entries 3–9) for these reactions resulted in successful and facile purification. The optimal reaction temperature was found to be around 50 °C, (Table 1, entries 4 and 6–9).[12] Decreased yields were obtained both at room temperature (Table 1, entry 3) and reflux (Table 1, entry 5). Finally, the effect of varying the stoichiometric equivalents of oxoammonium salt was explored. At oxidant loadings above 4 equiv, yields began to decrease. In contrast, when using 3 equiv or less, the reaction failed to reach completion and gave poor yields. With 3.8 equiv of the oxoammonium salt, the reaction reached completion and gave optimal yield (Table 1, entry 8).[13]

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(11) Determined by TLC and starch paper; a purple coloration to the starch paper is indicative of the presence of oxidant.

(12) The synthesis of the ene-triketones was complished as follows: oven-dried round-bottom flask was cooled under nitrogen, then charged with the 1,3-cyclohexanedione (2 mmol) and anhydrous MeCN (8 mL). Bobbitt's salt (3.8 equiv) was added to the solution and placed into a 50 °C oil bath. The mixture was stirred for 16 h, then allowed to cool. Silica (1–2 weight equiv) was added, and the solvent was removed *in vacuo*. The material was loaded on a short pad of silica gel and eluted with 5–10 volumes of 35% EtOAc/hexanes.

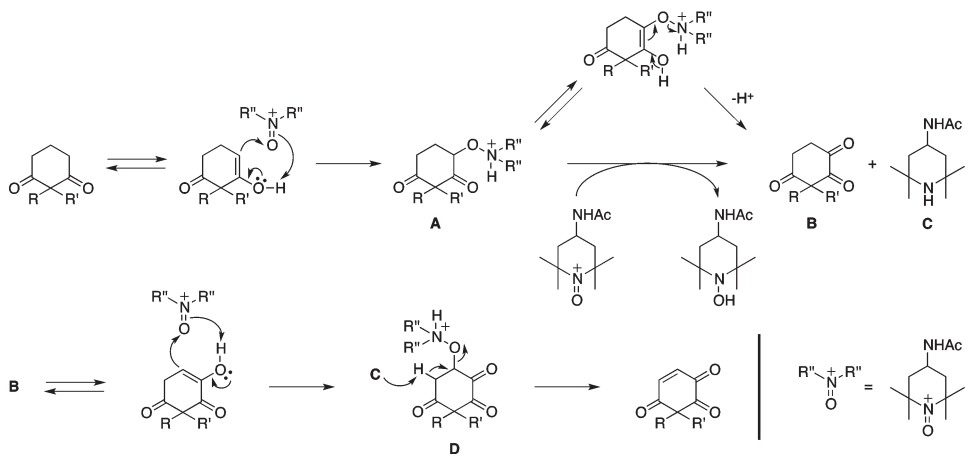

Figure 2. Proposed mechanism for the oxidation of cyclic 1,3-diketones with Bobbitt's salt.

Purity of the oxoammonium salt played a considerable role in the outcome of the reaction. When **1** was allowed to air-dry to constant weight before use, severely diminished yields of **3** (20−30%) were observed. Vacuum-desiccated salt gave fair yields of **3** (40−50%). The best results were obtained from recrystallized and rigorously dried salt (60−80%).[14] These results are in contrast to oxidations of alcohols, where the oxoammonium salt needs no further purification.[4] We attribute the diminished yields observed in our case to residual water in the salt.[15]

With reaction conditions optimized, we screened a series of 1,3-cyclohexanediones to define the scope of the reaction (Table 2). Oxidation of allylic and benzylic methylenes was not observed (Table 2, entries 2−5, 11, and 12), and yields for the dibenzyl diketone (Table 2, entry 4) were reduced. The low yield of this substrate can be attributed to steric shielding caused by one of the benzyl moieties. This is corroborated by the observation of Correa and Mainero of the ^{1}H chemical shifts of the parent compound.[16] Substitution by a propargyl group led to markedly diminished yields (Table 2, entry 7). Disubstitution with methyl groups in the 5 position of the cyclohexanedione (Table 2, entry 8) resulted in no oxidation reaction, likely because of steric hindrance disfavoring the oxidation. To examine the effect of steric hindrance, we exposed the trimethyl (Table 2, entry 9) and dimethylphenyl (Table 2, entry 10) analogs. In the case of **2i** (Table 2, entry 9), we obtained a yield that was comparable to that for the corresponding diketone (Table 2, entry 1) under the same conditions. With **2j** (Table 2, entry 10), the reaction did not reach completion (*ca.* 95% by NMR), but gave good yields. Decreasing the ring from cyclohexanedione to cyclopentanedione (Table 2, entry 12) gave excellent yields of the dehydrogenated product. This result is noteworthy in that it shows that olefin formation seemingly occurs faster than the subsequent oxidation.

We propose the following mechanism for the formation of the ene-triketone products with Bobbitt's salt (Figure 2). An ene-like reaction[17] between the enol form of the diketone and **1** provides intermediate **A**. This mechanism is supported by the data from the solvent screen, in which lower polarity solvents (e.g., DCM and EtOAc) resulted in no reaction, whereas increasing solvent polarity (e.g., MeCN and DMF) facilitated the reaction. This is likely due to the hydrogen-bonding nature of these solvents, which allows for increased concentration of the enol tautomer. **A** undergoes a second oxidation to the ketone **B** concomitantly with the formation of piperidine **C**. The mechanism of the oxidation of **A** to **B** is unclear, although Golubev posited that the counterion can act as a base to facilitate displacement of the piperidinium moiety.[2b] In the present case, this possibility is unlikely due to the nonbasic nature of the tetrafluoroborate anion. Thus, there are two potential pathways through which the reaction could occur: (1) enolization of **A** and rearrangement to **B**; (2) oxidation by a second equivalent of Bobbitt's salt to generate the hydroxyamine. Our optimal conditions necessitated the amount of salt to be greater than 3 equiv, suggesting that, in the case of **1**, the second pathway predominates in the oxidation of **A** to **B**. Tautomerization of **B** to its more stable enol form allows for a second ene-like α-oxidation providing **D** that then undergoes deprotonation by **C**. This occurs through either an E_2 or E_{1cb} pathway to generate the final product, which, as formation of **3l** suggests, is more thermodynamically favored than a subsequent α-oxidation.

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(13) The oxoammonium salt is available commercially, and provides the same yields as the synthesized, unpurified, and undried salt.

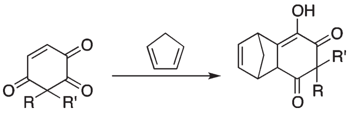
(14) The recrystalization of the oxoammonium salt was accomplished as follows: **1** was dissolved in 1.5 parts of boiling water (solution turns black), plunged in ice and vacuum filtered. The salt was then placed into an Abderhalden and dried under vacuum over KOH with ethanol.

(15) The nitroxide was also considered as a likely impurity. However, when purified 1 was poisoned with 10% (w/w) of the nitroxide, no change in yield was observed and the solution turned black. No observable reaction takes place between the nitroxide and **2** in MeCN, nor is there a reaction between the nitroxide and MeCN. Only trace reaction was observed between **1**, MeCN, and the nitroxide.

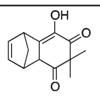
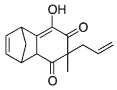
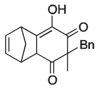
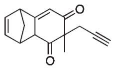
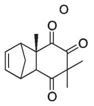
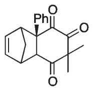
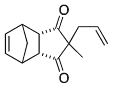
(16) Correa, J.; Mainero, R. M. *J. Org. Chem.* **1969**, *34*, 2192–2195.

(17) Pradhan, P. P.; Bobbitt, J. M.; Bailey, W. F. *Org. Lett.* **2006**, *8*, 5485–5487.

Table 3. Diels–Alder Reaction Between Ene-Triketones and Cyclopentadiene



3a-c,g,i,j,l → 4a-g

entry	substrate	product	yield (%)[b]	endo:exo[c]
1	**3a**[a]	 4a	49	97:3
2	**3b**[a]	 4b	58	95:5
3	**3c**[a]	 4c	45	4:1
4	**3g**[a]	 4d	30	1:1
5	**3i**[d]	 4e	54	3:2
6	**3j**[e]	 4f	39	1:1[f]
7	**3l**[e]	 4g	74	4:1

[a] Reaction performed in DCM at room temperature and 0.5 M on a 1 mmol scale. [b] Refers to isolated yield. [c] Ratio determined by HPLC. [d] Reaction performed in toluene at 22 °C with 20 mol % TiCl$_4$. [e] Reaction performed in toluene at 110 °C. [f] Determined by NMR integrations.

To explore the reactions of the ene-triketone products, the isolated material was reacted with cyclopentadiene. The hope was that the ene-triketones would exhibit selectivity similar to that of analogous benzoquinones.[18] This was indeed found to be the case, as shown in Table 3. The reactions were generally rapid, reaching completion within 3 h in DCM at room temperature. Yields varied based on the substituent, as did the level of diastereoselectivity. No change to the ratios was noted under longer reaction times, suggesting that the kinetic *endo* product is irreversible. In the case of **3a** and **3b** (Table 3, entries 1 and 2) yields were good with excellent selectivity, whereas **3g** (Table 3, entry 4) resulted in both a poor yield and poor selectivity. Substitution at the 5 position of the cyclohexanedione moiety dramatically affected the reaction in terms of rate. Compound **3i** did not react with cyclopentadiene, but, when exposed to 20 mol % TiCl$_4$, the reaction progressed to provide 54% yield of the desired adduct.[19] Under Lewis acid catalysis, **3j** cleanly afforded the desired adduct. It should be noted that compounds **4b**, **c**, **d**, and **g** contain an additional stereogenic center however, their NMR spectra exhibited a simple mixture of *endo* and *exo* adducts, rather than a more complex mixture of all possible products. We believe that the presence of the sterically hindering groups allows for epimeric selection of the dienophile by shielding a single face of the ene-triketone. Shielding of this nature has been shown previously for other chiral substrates.[20]

In summary, we have developed a unique metal-free oxidation of various 1,3-cyclohexanediones with Bobbitt's oxoammonium salt. The reaction tolerates a number of alkyl functionalities in the 2 position of 1,3-cyclohexanedione but does not proceed when the 5 position is disubstituted. The proposed reaction mechanism depends on enol formation and is supported by the solvent screen data. Due to the inherent stability of the 1,2-diketone enol tautomer, further oxidation occurs; however, activated methylene groups tend to favor elimination to generate the olefin. These novel ene-triketones reacted well with cyclopentadiene, providing Diels–Alder adducts in fair-to-good yields with modest-to-good selectivity for the endoexo diastereomers. Further study of these ene-triketones is underway with the hope of developing new synthetic methodologies or accessing intermediates for natural product synthesis.

Acknowledgment. We thank Jay Richardson (University of Connecticut) and Trevor Hamlin (University of Connecticut) for technical assistance, Prof. James M. Bobbitt (University of Connecticut) for helpful discussions, and Evonik-Degussa Corp. and TCI-America for the generous gifts of 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxyl and 4-amino-2,2,6,6-tetramethylpiperidine, respectively. This work was supported by the National Institutes of Health (GM077622 to G.F.) and the National Science Foundation (CAREER award CHE-0847262 to N.E.L.).

Supporting Information Available. Detailed experimental procedures and compound spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Beyler, R. E.; Sarett, L. H. *J. Am. Chem. Soc.* **1952**, *74*, 1397–1401.

(19) (a) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741–761. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92.

(20) (a) McDougal, P. G.; Rico, J. G.; VanDerveer, D. *J. Org. Chem.* **1986**, *51*, 4492–4494. (b) Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257–3262. (c) Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4625–4633. (d) Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1990**, *112*, 6743–6744.