

SYNLETT Spotlight 262

Ozone: A Versatile Oxidizing Agent in Academic Syntheses and Industrial Processes

Compiled by Giovanni Wilson Amarante



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Giovanni Wilson Amarante was born in 1981 in Campo Belo (MG), Brazil. He received his M.Sc. in Chemistry in 2005 at the Federal University of Juiz de Fora. In the same year, he started his Ph.D. studies at the State University of Campinas under the supervision of Professor Fernando A. S. Coelho. His thesis is focused in the synthesis of bioactive compounds from Morita–Baylis–Hillman adducts.

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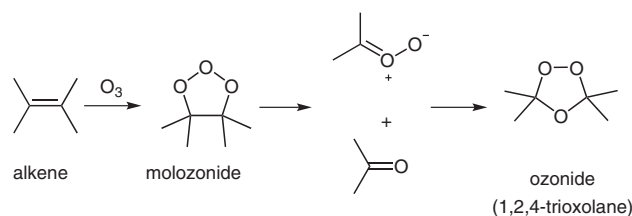
Introduction

Due to its simple preparation (O_3 from O_2) and efficiency, ozone has attracted the attention of academic and industrial sectors as an oxidizing agent, mainly for the clean and efficient oxidative cleavage of double bonds (ozonolysis).¹

Ozone was discovered in 1847 by Schönbein who observed that ozone did not convert organic compounds to the highest oxidation level (CO_2 , H_2O), but led them to intermediate oxidative levels such as carboxylic acids. Some years later, Harries demonstrated the high applicability of ozone in organic reactions, especially with double bond oxidations.²

Based on his own results and data available in the literature, Criegee has proposed a mechanism to explain oxidative cleavage during ozonolysis. According to Criegee, a molozonide and 1,2,4-trioxolane (ozonide) are the intermediates of this reaction. Experimental evidence con-

firmed this proposition and this mechanism is currently accepted (Scheme 1).³



Scheme 1 Mechanistic proposal for ozonolysis

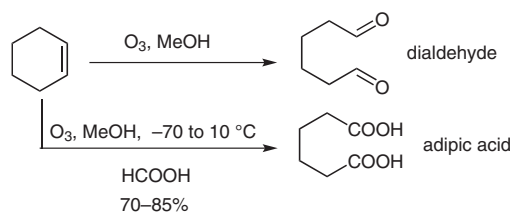
The ozonide intermediate can afford ketones, aldehydes and alcohols after reductive workups, while oxidative conditions can furnish ketones or carboxylic acids.

Ozone has been applied to the development of new synthetic methodologies,⁴ key intermediates in the total synthesis of natural and bioactive compounds⁵ and new protocols in the pharmaceutical industries.⁶

Abstract

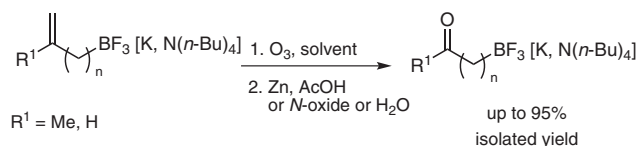
(A) Oxidative Cleavage of Double Bonds:

Ozone is largely used in the cleavage of double bonds of cyclic and acyclic alkenes to furnish aldehydes, dialdehydes or carboxylic acids, in high yields, as in the synthesis of adipic acid and fatty acids.^{5a}

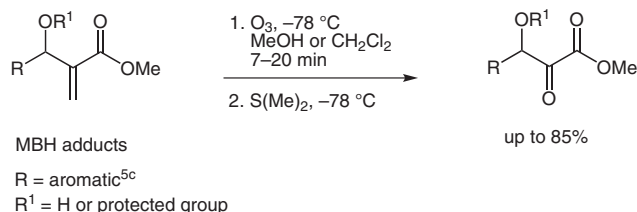


(B) Ozonolysis of Unsaturated Organotrifluoroborates:

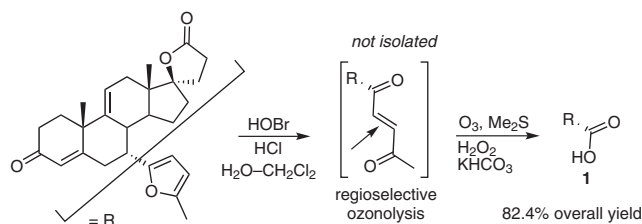
Recently, Molander and Cooper described an elegant method to prepare oxo-substituted organotrifluoroborates by ozonolysis. This strategy permitted the introduction of carbonyl functionality into organoboron reagents in good to high yields.⁴ These reagents can be used to increase the molecular complexity in other transformations, such as cross-coupling.⁷

**(C) Ozonolysis of Morita–Baylis–Hillman (MBH) Adducts:**

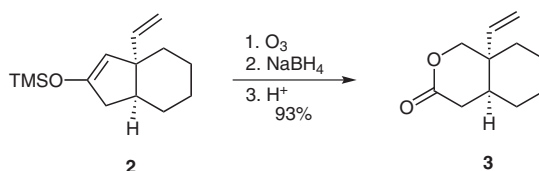
The ozonation of aliphatic MBH adducts was described by Doutheau and co-workers, who prepared highly functionalized α -keto esters in high yields.^{5b} Recently, Coelho and co-workers expanded this method to aromatic derivatives and established an expeditious selective approach for the preparation of α,β -dihydroxy esters.^{5c}

**(D) Selective Cleavage of Double Bonds (Synthesis of Eplerenone):**

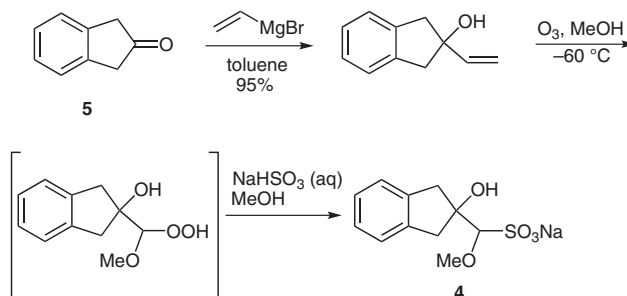
The chemical research division of Pfizer reported a new approach to prepare **1**, an intermediate in the synthesis of eplerenone.⁸ They used highly regioselective ozonolysis conditions to obtain a carboxylic acid function from the furan ring. Intermediate **1** was obtained in high overall yield (82%), in large scale (100 g) after standard crystallization.

**(E) Selective Oxidative Cleavage of Silyloxyalkene:**

Heathcock and Clark showed the potential of ozone in the highly selective oxidation of silyloxyalkenes **2** to lactones **3**, in high yields.⁹ Avery's group used a similar strategy in the last step of the stereoselective total synthesis of (+)-artemisinin from (*R*)-(+)-pulegone.¹⁰

**(F) Ozone in Large-Scale Synthesis:**

The Pfizer process research group prepared bisulfite **4** via an ozonolysis reaction. After experimental optimization, the ozonolysis step was carried out on a three-kilogram scale. The synthesis was performed in 61% overall yield from 2-indanone (**5**), and the product was used as a surrogate aldehyde in a reductive amination reaction.¹¹

**References**

- (1) Ornum, S. G. V.; Champeau, R. M.; Pariza, R. *Chem. Rev.* **2006**, *106*, 2990.
- (2) Rubin, M. B. *Helv. Chim. Acta* **2003**, *86*, 930.
- (3) Criegee, R. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 745.
- (4) Molander, G. A.; Cooper, D. J. *J. Org. Chem.* **2007**, *72*, 3558.
- (5) (a) Bailey, P. S. *Ozonation in Organic Chemistry*, Vol. I; Academic Press: New York, **1978**. (b) Bailey, P. S. *Ozonation in Organic Chemistry*, Vol. II; Academic Press: New York, **1982**. (c) Frezza, M.; Soulère, L.; Queneau, Y.; Doutheau, A. *Tetrahedron Lett.* **2005**, *46*, 6495. (d) Abella, C. A. M.; Rezende, P.; De Souza, M. F. L.; Coelho, F. *Tetrahedron Lett.* **2008**, *49*, 145. (e) White, J. D.; Johnson, A. T. *J. Org. Chem.* **1994**, *59*, 3347.
- (6) (a) Chai, D.; Genders, D.; Weinberg, N.; Zappi, G.; Bernasconi, E.; Lee, J.; Roletto, J.; Sogli, L.; Walker, D.; Martin, C. R.; Menon, V.; Zelenay, P.; Zhang, H. *Org. Process Rev. Dev.* **2002**, *6*, 178; and references cited therein. (b) Cabaj, J. E.; Kairys, D.; Benson, T. R. *Org. Process Res. Dev.* **2007**, *11*, 378. (c) Bandini, M.; Cozzi, P. G.; de Angelis, M.; Umami-Ronchi, A. *Tetrahedron Lett.* **2000**, *41*, 1601.
- (7) Molander, G. A.; Ellis, N. M. *Acc. Chem. Res.* **2007**, *40*, 275.
- (8) Pearlman, B. A.; Padilla, A. G.; Hach, J. T.; Havens, J. L.; Pillai, M. D. *Org. Lett.* **2006**, *8*, 2111.
- (9) (a) Clark, R. D.; Heathcock, C. H. *Tetrahedron Lett.* **1974**, *15*, 2027. (b) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 1396.
- (10) Avery, M. A.; Chong, W. K. M.; Jennings-White, C. *J. Am. Chem. Soc.* **1992**, *114*, 974.
- (11) Ragan, J. A.; am Ende, D. J.; Brenek, S. J.; Eisenbreis, S. A.; Singer, R. A.; Tickner, D. L.; Teixeira, J. J.; Vanderplas, B. C.; Weston, N. *Org. Process Res. Dev.* **2003**, *7*, 155.