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Ozone: a Versatile Reagent for Solid Phase Synthesis

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abstract: ozone is a versatile reagent which is well adapted to solid phase synthesis: terminal double bonds can be efficiently converted into alcohols, aldehydes or carboxylic acids depending on the reaction conditions. © 1997, Published by Elsevier Science Ltd. All rights reserved.

Impressive developments in combinatorial and parallel synthesis have been made recently, underlining the lack of reagents and reactions adapted to solid phase synthesis[2].

In an earlier publication, Fréchet and Schuerch described the use of ozone to release oligosaccharides from a solid support[3]. In this paper we report the use of ozone as an oxidant for solid phase synthesis on Merrifield resins. Ozone is a convenient reagent which is deprived of the usual drawbacks of classical oxidants -*i.e.* low solubility, poor diffusion within the resin matrix or formation of by-products-. It furthermore can be easily eliminated by bubbling argon into the reaction mixture.

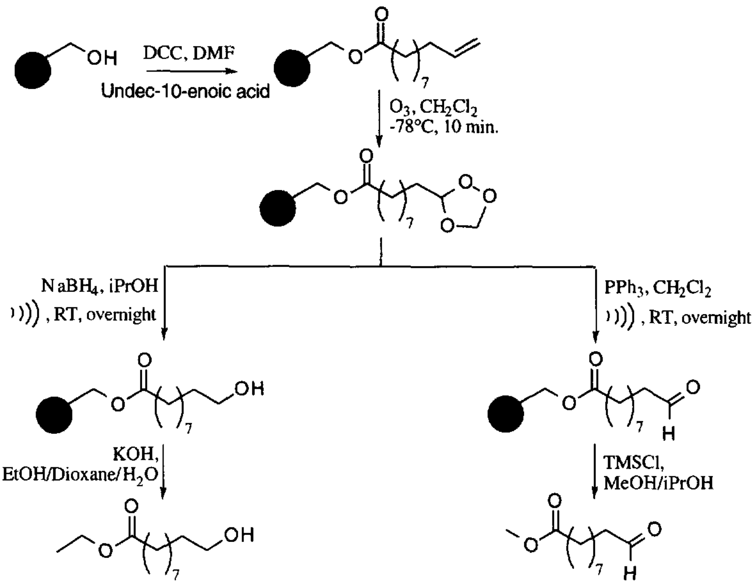
The versatility of ozonolysis is illustrated by the fact that depending on the procedure, a double bond can be transformed into three useful functionalities for combinatorial synthesis: alcohol, aldehyde or carboxylic acid[4].

The stability of the resin toward ozonolysis was checked by subjecting Merrifield resin to three successive ozonolysis processes (10 min. each). While polystyrene beads are known to react with ozone at benzylic position[5], no significant degradation could be observed by IR spectroscopy under our conditions. Relying on this verification we undertook the ozonolysis studies on a model substrate.

Undec-10-enoic acid was coupled to Merrifield hydroxy resin by a classical DCC coupling procedure[6]. The derivatized resin was then subjected to an ozone stream in methylene chloride. Once the reaction mixture turned blue (usually after 10 min.), argon was bubbled through until no traces of ozone could be detected in the gas stream. The ozonide, stable in these conditions, was subsequently treated with various reagents to yield either the alcohol or the aldehyde (scheme 1).

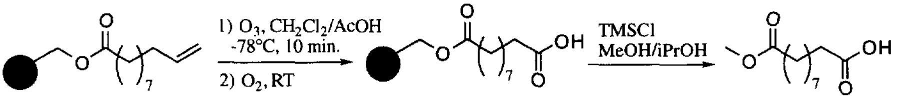
Overnight sonication of the ozonide with sodium borohydride in *iso*propanol allowed the formation of the corresponding alcohol. The isolation of the hydroxy ethyl-ester was performed after treatment with a 0.3 M solution of potassium hydroxide in a mixture of dioxane/ethanol/water (9/1/0.5). Under these conditions, the yields were quantitative and the crude product displayed a purity higher than 95 %.

Treatment of the ozonide with triphenylphosphine quantitatively led to the corresponding aldehyde. Its cleavage from the resin was performed by *trans*-esterification using a mixture of *iso*propanol/methanol/TMSCl (7/3/1)[7]. TMSCl was used to generate HCl *in situ*. This procedure is advantageous compared to the classical basic hydrolysis in that a large amount of degradation products is formed with the latter process. By NMR spectroscopy, the crude methyl ester exhibited more than 95 % purity.



Scheme 1

As for the formation of carboxylic acids, the reaction conditions were slightly modified. The ozonolysis was conducted in a mixture of methylene chloride/acetic acid (7/1) for 10 min. and kept at room temperature overnight under an oxygen atmosphere. The product was released from the resin under the aforementioned conditions affording quantitatively the monomethyl ester with a purity higher than 95 % (scheme 2).



Scheme 2

Ozonolysis of terminal double bonds on solid support is shown here to be a very efficient process to produce alcohols, aldehydes or carboxylic acids in high yield and with high purity.

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