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New Reagents for the Reductive Quenching of Ozonolysis Reactions

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NEW REAGENTS FOR THE REDUCTIVE QUENCHING OF OZONOLYSIS REACTIONS

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Abstract: 3,3'-Thiodipropionic acid and its salts were found to be effective reductive quench reagents in the ozonolysis of olefins. They were as effective as methyl sulfide without its drawbacks. A polymer-bound form of 3,3'-thiodipropionic acid was also effective.

Ozonolysis of cyclic alkenes in a protic solvent, followed by a reductive quench of the resultant hydroperoxides¹, is a classical method for the synthesis of dialdehydes.² This general method was under investigation for the synthesis of 3-ethoxycarbonylglutaric dialdehyde (2) via ozonolysis of ethyl 3-cyclopentenecarboxylate (1).

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Dialdehyde 2 is an intermediate in the synthesis of dolasetron mesylate, the active drug substance in ANZEMET[®] anti-emetic.



Dolasetron Mesylate

A variety of reagents exist for the reductive quenching of ozonolysis reactions. Examples include catalytic hydrogenation³, zinc-acetic acid⁴, phosphines⁵, amines⁶ and sulfides⁷. Most, however, are not amenable for use in the large-scale synthesis *via* ozonolysis, due in part to economics, toxicity and processability. In the classical procedure⁷, methyl sulfide is used in the reduction of the intermediary methoxyhydroperoxide produced on ozonolysis of the alkene in methanol.

Methyl sulfide has a number of unwanted physical and chemical properties. It is a very volatile (bp= 38 °C), flammable (Fp= -34 °F) and foul smelling material. These problems, along with the fact that large excesses must typically be used to give good yields of aldehyde, make methyl sulfide undesirable for larger scale production of dialdehyde 2. A reagent which overcomes these problems and still gives good yields of the desired dialdehyde was therefore needed.

3,3'-Thiodipropionic acid (3) is used as an anti-oxidant in the food industry.⁸ It is odorless, has low toxicity⁸, is inexpensive and is widely available on large scale. These qualities, as well as the ability to remove the post-reaction sulfur-containing byproducts by aqueous extraction, make 3 an excellent candidate

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for the replacement of methyl sulfide for the reductive quenching of ozonolysis reactions.

3,3'-Thiodipropionic acid (3) and its mono- and disodium salts, 4 and 5 respectively, were compared to methyl sulfide as quench reagents for the ozonolysis of ethyl 3-cyclopentenecarboxylate (1). In a typical procedure, ozone enriched air was bubbled through a 10 wt% solution of 1 in 2:3 methanol-water cooled to -10 °C containing sufficient Sudan Red to give a pink colored solution. The reaction was complete when the pink color disappeared.⁹ Excess ozone was removed from the reaction by purging with air for 15 min. The appropriate reductive quench reagent was added and the mixture was stirred at room temperature until the solution tested negative for peroxides.¹⁰ A summary of results is given in Table 1. Yields were determined by GC using an internal standard and were not optimized.

While a large excess of methyl sulfide (Entry 1) gave 2 in high yield, two equivalents of the reagent (Entry 2) gave only moderate yields (64%) of the dialdehyde. A large excess of methyl sulfide is, therefore, necessary to obtain high yields. The use of 3 itself in the reaction (Entry 3) leads to long peroxide quenching times, significant acetal formation and lower yields. This was believed to be due in part to the acidity of the quench solution (pH = 2.5).

The monosodium salt 4 or disodium salt 5 can be produced by adding one or two equivalents of sodium hydroxide, respectively, to a solution of 3.



3 X=H,H
4 X=Na,H
5 X=Na,Na

A solution of the monosodium salt 4 has a nearly neutral pH and quenches the ozonolysis reaction (Entry 4) quickly (1.5 h) and in high yield (90%). The disodium salt 5 (Entry 5, pH = 7.8) quenched the reaction very quickly (<1 h) giving the dialdehyde 2 in 92% yield. The work-up for these reactions, consisting of methanol evaporation and ethyl acetate extraction, gave ethyl acetate solutions of 2 essentially free of 3 and its oxidation product(s)!

To demonstrate the generality of these new quenching reagents, this method was used in the ozonolysis of a number of acyclic alkenes. In each case, two molar equivalents of quench reagent were used. The results of these experiments are given in Table 2. The products were identified by comparison with authentic

Entry	Quench Reagent	Molar Equivalents	Rxn. Time ^a	Yield of 2 ^b
1	Me ₂ S	8	< 1 hr	high ^c
2	Me ₂ S	2	1.5 hr	60%
3	3	2	18 hr	62%
4	4	2	1.5 hr	90%
5	5	2	< 1 hr	93%

 TABLE 1

 Ozonolysis of Ethyl 3-Cyclopentenecarboxylate

^a Time needed for complete reduction of peroxides. ^b GC yields. ^c No yield determined.

TABLE 2

Ozonolysis of Acyclic Alkenes						
Entry	Substrate	Product	Quench Reagent	Yield ^a		
1	1-Octene	Heptanal	4	54%		
2	1-Octene	Heptanal	5	67%		
3	1-Undecene	Decanal	Me ₂ S	b		
4	1-Undecene	Decanal	3	b		
5	1-Undecene	Decanal	5	95%		
6	Styrene	Benzaldehyde	4	71%		
7	Styrene	Benzaldehyde	5	64%		
8	3,4-Dimethoxy- propenylbenzene	Veratraldehyde	4	84%		
9	3,4-Dimethoxy- propenylbenzene	Veratraldehyde	5	74%		

a. GC Yield. b. Mostly decanal dimethyl acetal. No yield determined.

commercial materials. As before, yields were determined by GC using an internal standard and were not optimized.

Good to excellent yields were obtained when salts 4 or 5 were used for the reductive quench. In the case of 1-undecene, the use of methyl sulfide (Entry 3) or thiodipropionic acid (Entry 4) gave very little decanal, instead giving mostly decanal dimethyl acetal (no yield determined). In contrast, the formation of acetals using 4 or 5 was not significant (< 5%).

Polymer-bound reductive quench reagents offer the advantage of very simplified reaction work-up.¹¹ Filtration is all that is necessary to completely remove the quench reagent, giving a solution of desired ozonolysis product. This is exemplified by the use of polymeric triphenylphosphine.¹¹ However, this reagent is prohibitively expensive,¹² useful only for small-scale syntheses.

Polymer-bound 3,3'-thiodipropionic acid (6), made by treating DOWEX[®] SBR resin (in the hydroxide form) with an excess of 3 in methanol, was shown to be quite effective in the reductive quenching of ozonolysis reactions.



Two equivalents of **6** added to the ozonolysis reactions of ethyl 3cyclopentenecarboxylate (1) gave the dialdehyde 2 in 92% yield after reacting overnight. Simple filtration gave a sulfur-free solution of **2** in methanol-water. It would be expected that an additional advantage of using **6** would be that the quench reagent could be readily regenerated by eluting the oxidation products of **3** from the resin with acid, followed by regenerating **6** first with caustic and then with fresh thiodipropionic acid. The use of resin **6** has all of the advantages of resin-bound reagents without the exorbitant costs.¹³

In conclusion, 3,3'-thiodipropionic acid (3), and its mono- and disodium salts (4 and 5, respectively) have been demonstrated as being new and superior replacements for methyl sulfide as a reductive quench reagent for hydroperoxides produced on ozonolysis of olefins. 3-Ethoxycarbonylglutaric dialdehyde (2) was produced in 92% yield on ozonolysis of ethyl 3-cyclopentenecarboxylate (1), followed by quenching with the disodium salt of 3. Polymer-bound 3 quenched the same reaction efficiently, giving a solution of 2 in 92% yield, which was sulfurfree after simple filtration. The general utility of these new quench reagents was

demonstrated when applied to the ozonolysis of 1-undecene, octene, styrene and 1,2-dimethoxy-4-propenylbenzene, giving the expected aldehyde in good to excellent yields.

EXPERIMENTAL

1-Undecene, 1-octene, styrene, 1,2-dimethoxy-4-propenylbenzene, decanal, heptanal, benzaldehyde, veratraldehyde, 3,3'-thiodipropionic acid, Sudan Red and reagent grade solvents were purchased from Aldrich Chemical Co. and used without purification. DOWEX[®] SBR-OH (3.8 meq/g) was obtained from The Dow Chemical Company. Ozone was generated with a Welsbach Model T-816 laboratory Ozonator (115 Volts, 7.5 psi, 1.5-2.0 slpm) using air passed through a molecular sieve drying column. Analysis by gas chromatography (GC) was performed on a Hewlett Packard 5890 using a DB-5 capillary column.

GENERAL PROCEDURE:

Synthesis of 3-Carboethoxycarbonyl Glutaric Dialdehyde (2)

Ethyl 3-cyclopentenecarboxylate 1 (11.66 g, 83.3 mmol) and Sudan Red (-2 mg) in 2:3 methanol-water (100 mL) was treated with ozone/air at -10 °C until the pink color of the mixture faded. Excess ozone was removed from the reaction by purging with air for 15 min. A solution of 3,3'-thiodipropionic acid (31.0 g, 174 mmol) and 5N NaOH (62 mL) and enough 2N NaOH to give a pH of 7.6 (~17 mL) was added and the solution was stirred at room temperature until peroxide-free (1.0 h). The bulk of the methanol was removed *in vacuo* at < 30 °C. The remaining aqueous solution was saturated with sodium chloride and extracted with ethyl acetate (1x70 mL, 2x40 mL). The extract contained 13.14 g (92% yield) of dialdehyde **2** by GC assay.

Synthesis of Resin-bound 3,3'-Thiodipropionic Acid (6)

A column of DOWEX[®] SBR-OH resin (176 ml wet volume, 1.29 meq/ml, 227 meq) was slowly eluted with a solution of 3,3'-thiodipropionic acid (3, 54.5 g, 306 mmol) in ethanol 2-B (100 ml). The resin was then rinsed with ethanol 2-B (2x50 ml). The eluted fraction was concentrated *in vacuo* leaving 5.98 g (33.6 mmol) of

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the 3. This left 48.5 g (273 mmol) of 3 on the resin. The resin was dried with a stream of nitrogen leaving 105.0 g resin-bound 3. The resin contained 2.60 meq of quench reagent per gram of resin.

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