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A SIMPLE AND GENERAL SYNTHESIS OF α-KETO ESTERS

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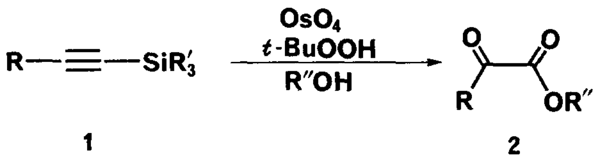
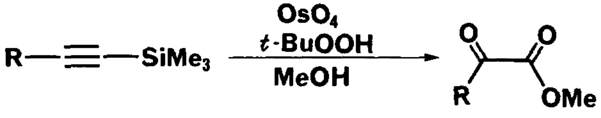
Abstract : *α-Keto esters may be prepared directly in good yields by the osmium tetroxide catalysed oxidation of trimethylsilyl acetylenes.*

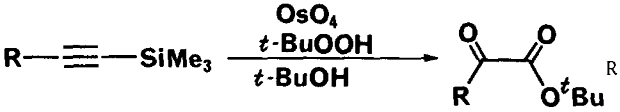
α-Keto acids are important in a number of biosynthetic and respiratory pathways, for example in the pyridoxal-dependant biosynthesis of α-amino acids and in the biosynthesis of fats, carbohydrates, proteins, porphyrins and nucleic acids.[11] Several synthetic routes are available for the laboratory preparation of α-keto acids and α-keto esters,[1,2,3] including synthesis via metalloaldimines,[4] Ritter reactions,[5] selective decarboxylation of a β-keto ester,[1] and hydrolysis of a dithiane,[6] however all suffer from lack of generality, experimental inconvenience, multistep sequences, or variable yields.

We are pleased to report a new, general, and simple procedure for the preparation of α-keto esters in good yield. Treatment of the readily available trimethylsilyl acetylenes (1) with osmium tetroxide (5% w/w) and t-butyl hydroperoxide (5 equiv .) in the appropriate alcoholic solution at 0°C affords α-keto esters (2) directly.



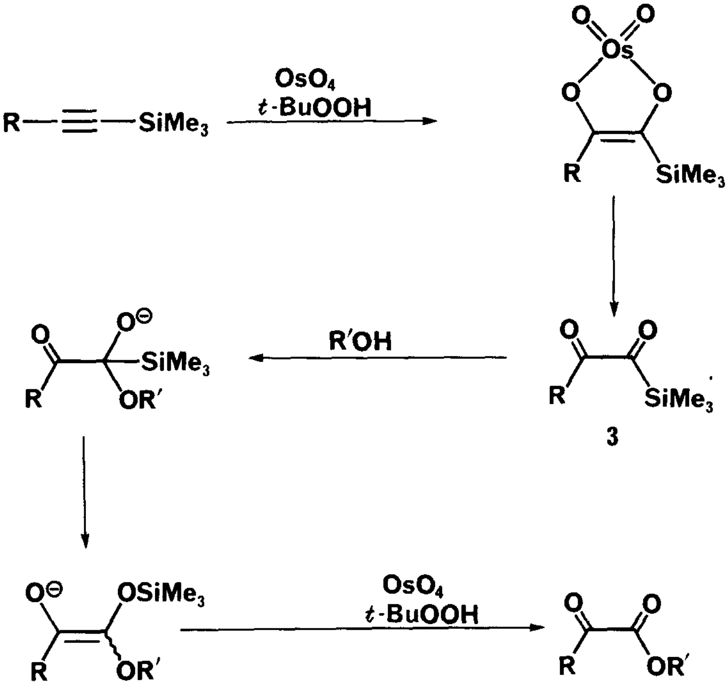


R = Ph	61%
R = $CH_3(CH_2)_4$	55%[†]
R = $CH_3(CH_2)_5$	54%[†]



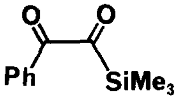
R = Ph	58%

The reaction of osmium tetroxide with dialkyl acetylenes is known to yield the corresponding α-diketones[7] and we believe the present reaction proceeds through the intermediacy of an α-keto acylsilane (Scheme).



SCHEME

Attack of alcohol at the more electrophilic carbonyl group of acyl silane (3) and subsequent Brook-type rearrangement[8] would be followed by further osmium tetroxide catalysed oxidation. Breakdown of the osmate ester so formed would lead directly to the α-keto ester. Reaction mixtures display the deep pink colour characteristic of α-keto acyl silanes;[9] further, treatment of benzoyl acyl silane (4)[††] with osmium tetroxide under identical reaction conditions using methanol as solvent provides methyl phenylglyoxylate (5) in 45% yield. Presence of water in the reaction mixture or use of water in place of alcoholic solvent does not result in the isolation of α-keto acids. Although a pink colouration develops during the course of the reaction oxidative cleavage occurs to give the corresponding carboxylic acids as the sole isolable products in good yield.



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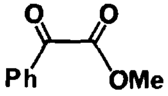

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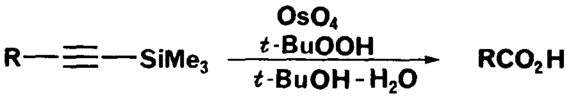

R = Ph	58%
R = $CH_3(CH_2)_4$	61%
R = $CH_3(CH_2)_5$	62%

It is interesting to note that, in accordance with a report by Griffith,[10] when phenylacetylene was treated with osmium tetroxide in a similar reaction no pink colour was observed and only benzoic acid could be isolated.

A typical experimental procedure is given below.

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METHYL PHENYLGLYOXYLATE

Trimethylsilylphenylacetylene (2.0g, 11.5 mmoles) was dissolved in methanol (50 ml) and cooled to 0°C under an argon atmosphere. A solution of t-butyl hydroperoxide in toluene (4.5M, 12.8 ml, 57.6 mmoles) was added followed by osmium tetroxide (100 mg, 0.39 mmoles). The reaction mixture was stirred at 0°C until all the starting material was consumed. A saturated aqueous solution of sodium metabisulphite (10 ml) was added and the bulk of the solvents removed *in vacuo*. A saturated aqueous solution of ammonium chloride (50 ml) was added to the residue and the mixture was extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with water (2 x 20 ml) and dried over magnesium sulphate. The solvents were removed under reduced pressure and the residue purified by flash chromatography (Merck 9385) to give methyl phenylglyoxylate (1.15g, 61%).

† Yield based on recovered starting material.

†† Prepared by *cis*-hydroxylation and Swern oxidation of vinyl silane (6).

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