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THE CONVERSION OF OLEFINS TO β-KETO ESTERS: OZONOLYSIS OF OLEFINS FOLLOWED BY *IN SITU* REDUCTION WITH TIN(II) CHLORIDE IN THE PRESENCE OF ETHYL DIAZOACETATE.

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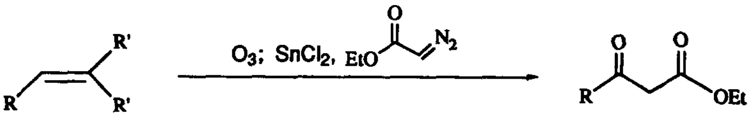
Summary : Trisubstituted olefins are converted to β-keto esters by treatment with ozone followed by the addition of tin(II) chloride and ethyl diazoacetate. Monosubstituted olefins are first treated with ozone in the presence of methanol to generate methoxy hydroperoxides. The hydroperoxides are subsequently reduced with tin(II) chloride in the presence of ethyl diazoacetate to produce β-keto esters.

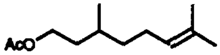
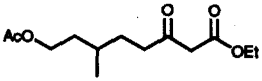
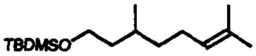
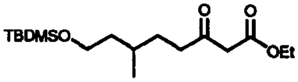
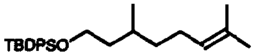
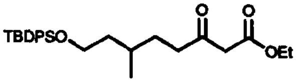
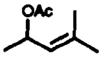
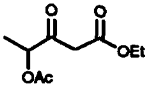
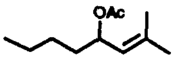
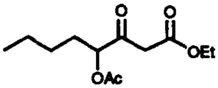
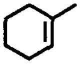
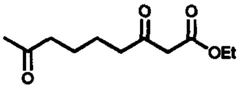
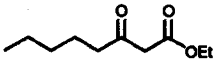
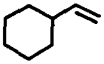
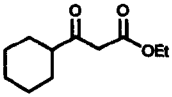
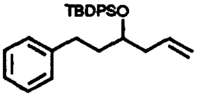
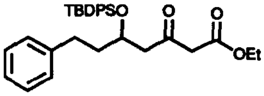
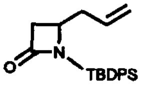
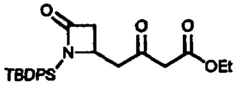
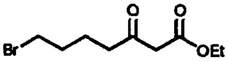
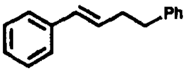
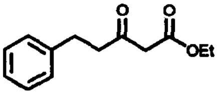
Sir: β-Keto esters are important intermediates in organic synthesis.[1] They are generally prepared from a corresponding ester derivative under basic conditions.[2] Recently, we introduced a new method for the conversion of aldehydes to β-keto esters.[3] A modification of this technology introduces olefins as β-keto ester precursors (eq. 1). The procedure involves three sequential reactions: i) ozonolysis, ii) *in situ* reduction, iii) *in situ* Lewis acid catalyzed addition of ethyl diazoacetate. The tin (II) chloride plays two distinct roles in this sequence, first it acts as a reducing agent and second a Lewis acid catalyst.



(1)

Trisubstituted olefins are converted to β-keto esters in good yields (table 1). For example, when citronellol acetate was treated with ozone followed by tin(II) chloride and ethyl diazoacetate (method A) the corresponding β-keto ester was obtained in 90% yield (entry 1). The reaction conditions are acidic and can result in the partial desilation of t-butyldimethylsilylethers (entry 2). This problem can be remedied by using t-butydiphenylsilylethers (entry 3).[4] Alternative attempts at buffering the pH of the system with sodium acetate or with phosphates only shutdown the reaction. The addition of propylene

Table 1. Conversion of olefins to β-keto esters

	Olefin:	β-Keto ester:	Method A[a]	Method B[a]
1			90 %	77 %
2			71	52[b]
3			85	80
4			86	20
5			80	
6			47	63
7			33	74
8				63
9				60
10				51[c]
11				47
12			45[d]	10[e]

a) Isolated yields; b) deprotected product recovered in 20% yield; c) potassium fluoride omitted from workup; d) 10% ethyl benzoylacetate; e) 15% ethyl benzoylacetate oxide (acid scavenger) had no beneficial effect. We have also observed that cyclic trisubstituted olefins produce ozonides that not efficiently reduced and result in lower overall yields (entry 6).

Method A, (trisubstituted olefins): Ozone was passed through a mixture of citronellol acetate (0.5 g, 2.5 mmol) in dichloromethane (20 mL) at -78°C until the solution remained blue. The reaction was allowed to warm to 0°C after purging the excess ozone with oxygen. Tin (II) chloride (0.71 g, 3.75 mmol) followed by ethyl diazoacetate (0.36 g, 3.13 mmol) were slowly added to the solution and stirring was continued until nitrogen evolution had stopped (~ 30 min to 2 h). Potassium fluoride dihydrate (1.1 g, 12 mmol,) was then added to help polymerise the tin and the mixture stirred for an additional 20 minutes. The reaction was filtered through a plug of silica gel (dichloromethane or ether eluent) and the volatiles were removed *in vacuo* yielding an oil, that was purified by flash chromatography (hexane; ethyl acetate).[5]

Application of method A to terminal olefins, (entry 7) or cyclic olefins (entry 6) resulted in greatly reduced yields of β-keto esters. An examination of the crude products by NMR suggested that a fair amount of ozonide had not been reduced. An alternative procedure using methanol as a co-solvent during the ozonolysis rectified this problem.[6] The methoxy hydroperoxide that is formed by this procedure is more efficiently reduced by tin(II) chloride than the corresponding ozonide. Formaldehyde is also generated from the ozonolysis of terminal olefins, however it is removed when azeotroping the excess methanol. Procedure A can be applied to most trisubstituted olefins unless an α-acetoxy group is present. In this case the α-acetoxy aldehyde that is generated during the ozonolysis forms a relatively stable hemiacetal with methanol. This hemiacetal is not readily converted to a β-keto ester and results in a poor yield of product.[7]

Method B, (cyclic and terminal olefins): Ozone was passed through a solution of 1-heptene (0.24 g, 2 mmol) in dichloromethane (20 mL) and methanol (5 mL) at -78°C until the reaction remained blue. After purging the excess ozone, benzene (20 mL) was added and the volume of the reaction was reduced to ~2 mL. Dichloromethane (25 mL) was then added followed by the slow addition of tin (II) chloride (0.57 g, 3 mmol) and ethyl diazoacetate (0.28 g, 2.5 mmol) at 0°C (see note).[8] The reaction was stirred at 0°C until nitrogen evolution had stopped (~ 30 min to 2 h) and was then worked up as in method A.

Previously, we had observed a remarkable difference in the rates of reaction for saturated aldehydes and aromatic aldehydes.[3] This suggested that aromatic olefins (entry 12) should selectively form β-keto esters. When compound 1,4-diphenyl-1-butene was subjected to method A, ethyl 3-oxo-5-phenylpentanoate and ethyl benzoylacetate were obtained in a 3.2:1 ratio.[9] By method B, the yield fell and a 0.67:1 ratio was obtained. Thus the previously observed selectivity for aldehydes does not hold when they are generated *in situ* from olefins.

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References and notes

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4. Citronellol led to a 16% yield of β-keto ester and unprotected 4-allyl-2-azetidinone produced no β-keto ester.

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6. Claus, R.; Schreiber S. *Org. Syntheses* **1985**, *64*, 150.

7. If an α-acetoxyaldehyde is subjected to methanol in dichloromethane, as in method **B**, the same hemiacetal is formed.

8. With trisubstituted olefins under these conditions, the ozonolysis products are a ketoperoxyacetal and a free aldehyde. A very rapid reaction with vigorous nitrogen evolution will occur unless the ethyl diazoacetate is added dropwise over several minutes. This does not occur with terminal olefins or method A.

9. Benzaldehyde was recovered in 73% yield.

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