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VICINAL TRICARBONYL PRODUCTS FROM SINGLET OXYGEN REACTIONS. APPLICATION TO THE SYNTHESIS OF CARBACEPHAMS.

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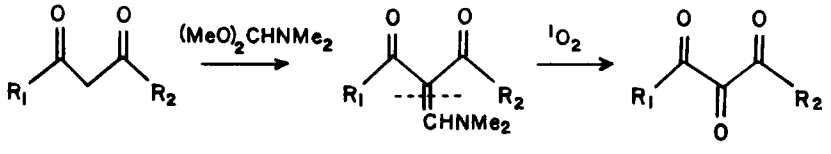
Abstract: Vicinal tricarbonyl systems are readily formed by reacting β-dicarbonyl precursors with DMF acetal to form enamines which are then cleaved by photooxidation. This procedure may be applied to the formation of carbacephams.

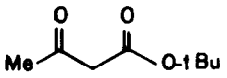
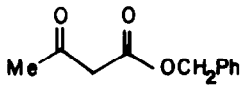
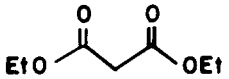
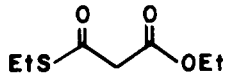
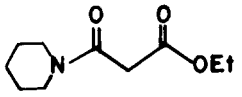
We have recently described a procedure for the formation of α-keto carbonyl derivatives by the conversion of ketones, lactones, esters and lactams[1] to their α-enamino derivatives followed by oxidative cleavage with singlet oxygen. We have now shown that this method may be extended to the generation of vicinal tricarbonyl systems (3) from the corresponding β-dicarbonyl precursors (1) according to the general reaction in Scheme I.[2] With the more reactive methylene groups in the β-diketonic substrates (1), it is possible to form the enamines (2) under very mild conditions, merely by mixing the β-dicarbonyl component with dimethylformamide dimethylacetal at room temperature.[3]



1 2 3

Table I provides information on the β-dicarbonyl substrates, the enamines and the products of photooxidation. Cleavage of 2 to 3 could also be accomplished by ozonolysis [4] but, as shown in the Table, the yields were generally poorer. The following typical experimental procedure is provided for entry #3 in the Table. Diethyl malonate (1, R_1=R_2=OEt) (260 mg, 1.63 mmole) was stirred with dimethylformamide dimethyl acetal[3] (388 mg, 3.26 mmole) for 6h at room temperature. All volatile products were removed in vacuo. The residue was purified by rapid silica gel chromatography, yielding 334 mg (96%) of dimethylaminomethylene (2, R_1=R_2=OEt). This product (313 mg, 1.45 mmole) was then

Table I

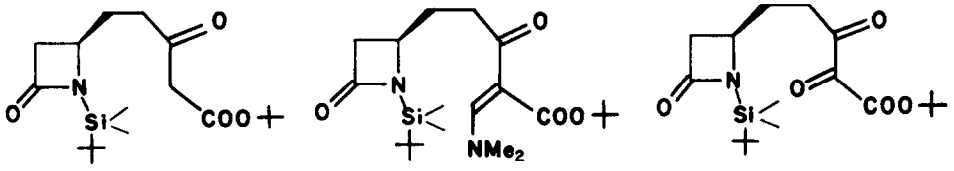
Entry	β-Dicarbonyl Precursor (1)	Enamine (2)(%)	Tricarbonyl Product (3)(%)*	
			singlet oxygen	ozone
1		94	79	55
2		95	83	56
3		96	84	94
4		75	65	54
5		93 **	83	76

* Products were obtained in the hydrated form. They were identified by NMR, IR, and elemental analyses or high resolution mass spectroscopy.

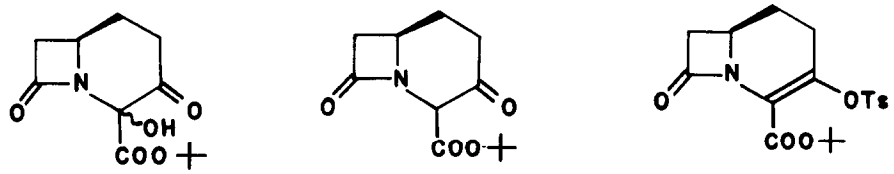
** In this case, reaction with DMF acetal took place at 54°C for 24 h.

dissolved in 20 ml of deuterochloroform and photooxidized at 25°C for 20 h (BANT sensitizer).[1] The solution was then concentrated and the residue purified by silica gel chromatography to afford 235 mg (84%) of diethyl oxomalonate (3, $R_1=R_2=OEt$) (in hydrated form).

This method for the *in situ* generation of vicinal tricarbonyl systems has useful application in synthesis as is illustrated in the formation of the carbacepham (8)[5]. The silylated chiral β-lactam derivative (4) formed by a route analogous to the Merck procedure [6], was treated with N,N-dimethylformamide dimethyl acetal (25°C, 4h), forming the enamino ketone (5) (79%). Oxidation of (5) with singlet oxygen in $DCCl_3$ as described earlier ($^1O_2$, BANT, 19°C, 4h)[1] gave the vicinal tricarbonyl derivative (6). The solvent, ($CDCl_3$) was then replaced with CH_3CN, and desilylation achieved with HF-pyridine complex.[7] The acetonitrile solution was partitioned between ethyl acetate and H_2O, the ethyl acetate layer concentrated, and the oily residue taken up in dry CH_2Cl_2. Stirring the solution in the presence of activated molecular sieves (3Å) followed by silical gel chromatography yielded 7 as a separable mixture of two isomers (32% and 36%) differing in the



4 5 6



7 8 9

α-vs β-orientation of the newly formed hydroxyl group. Reduction of either of the isomers of 7 to a single product, (8), could be accomplished by treatment with trimethylsilyl iodide [8] (2.3 eq., -40°C to 0°C, CH_2Cl_2). Upon aqueous work-up ($K_2S_2O_3$) and without further purification, 8 was treated with Et_3N and p-toluenesulfonyl anhydride to yield the enol tosylate (9) (45% overall yield from either the α-OH or the β-OH form of 7), identical with the product prepared by the Merck procedure[9]. Compound 9 has previously been converted to homothienamycin.[9]

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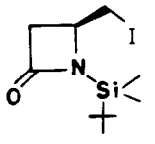

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