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α-HYDROXYLATION OF β-DICARBONYL COMPOUNDS

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Summary : Various β-dicarbonyl compounds can be hydroxylated as their silyl enol ethers by m-chloroperbenzoic acid (MCPBA).

In the course of the total syntheses of the indole alkaloids vindorosine 1a and vindoline 1b [1], we had to introduce a hydroxyl group at C-16 of β-keto ester derivatives 2a and 2b. Two modes of hydroxylation of β-keto esters have been used in the past. In one procedure, β-Keto esters are treated sequentially with a strong base (t-BuOK [2] or KH [3]) and with an oxidative reagent (H_2O_2 [2] or m-chloroperbenzoic acid [3]). The second method involvesfluoride ion induced hydrogen bonding on the enol form of β-keto ester followed by an oxidative step performed with O_2 [4,5].

In connection with the usual hydroxylation of silyl enol ethers of ketones with MCPBA [6], we tested this reagent on silyl enolethers derived from β-keto esters in which the electron rich double bond is conjugated with an electron withdrawing group. Despite this opposing feature, the unstable silyl enol ethers 3a and 3b led to the anticipated hydroxylated compounds 4a and 4b.

In the present communication, we describe further scope and limitation of this reaction (Table). The silyl enol ether intermediates have been prepared by different methods as referenced in the table.

The hydroxylation procedure described here is rather general and has been applied successfully to β-keto esters, β-diketone and β-ester lactam. In the case of compound 10a which was less reactive, the hydroxylation was carried out at 90°C in 1,2-dichloroethane in the presence of MCPBA and small amount of 4,4'-thiobis (6-t-butyl-3-methylphenol) [18]. The failure of the hydroxylation of ethyl 2-methyl acetoacetate 9a could be due to the low stability of the t-butyl dimethyl silyl enol ether derivative in the reaction condition. β-Keto ester 9a was the only product recovered after treatment with MCPBA.

Isolation of some amount of trialkylsilyloxy derivatives 8c and 10c suggests that these compounds could be one of the intermediates involved in the hydroxylation process [19].

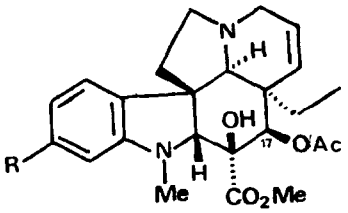
TABLE

β-dicarbonyl compound (Ref.)	Preparation of silyl enol ether (Ref.)	MCPBA equiv.	Hydroxylated products (Yield %) [17]	^{13}C NMR (δ : PPM., TMS = 0) OH bearing C
2a [1]	(8)	2	4a (88)	
2b [1]	(8)	2	4b (89)	83.1
5a [7]	(8)	2	5b (76)	80.7
6a [9]	(8)	2	6b (70)	83.2
7a [10]	(11)	2.5	7b (80)	68.1
8a [12]	(13)	1.5	8b (33)	85.3
			8c (17)	88.4
9a [12]	(14)	2	9b (0)	
10a [15]	(16)	2	10b (7)	
			10c (21)	82.2

General procedure :

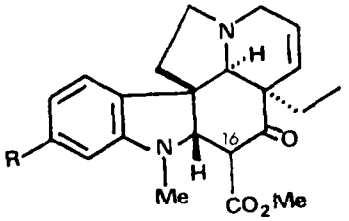
Preparation of 2-hydroxy-2-methoxycarbonyl cyclohexanone 5b.

A solution of MCPBA (20 mmol ; 3.4 g) in 1,2-dichloroethane (80 ml) was added at 0°C to a solution of silyl enol ether (10 mmol ; 2g) obtained from 5a in 1,2-dichloroethane. The reaction mixture was stirred at room temperature and monitored by TLC. After 1 hour, the precipitate of m-chlorobenzoic acid was filtered off. The resulting filtrate was diluted with dichloromethane, washed three times with an aqueous solution of Na_2CO_3 (10%) and with water, dried over $MgSO_4$ and evaporated under vacuum after filtration. The residual oil after silica gel chromatography (pentane-ether : 70-30) afforded pure 5b (1.3 g ; 76%).



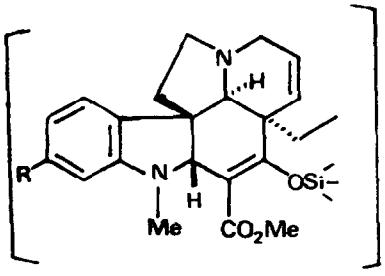
1a ; R=H

1b : R=OMe



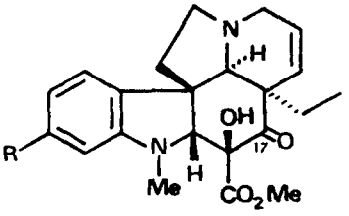
2a : R=H

2b : R=OMe



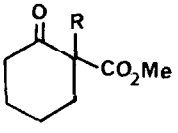
3a : R=H

3b : R=OMe



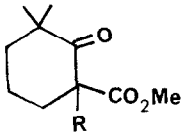
4a : R=H

4b : R=OMe



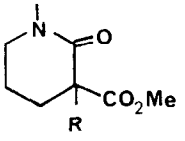
5a : R=H

5b : R=OH



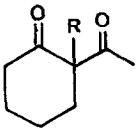
6a : R=H

6b : R=OH



7a : R=H

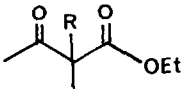
7b : R=OH



8a : R=H

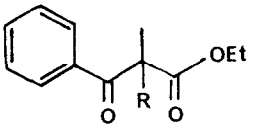
8b : R=OH

8c : R=OSiMe$_3$



9a : R=H

9b : R=OH



10a : R=H

10b : R=OH

10c : R=OSitBuMe$_2$

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9. i, 2-Methylcyclohexanone, NaH, MeI ; ii, NaH, dimethylcarbonate. (70%).
10. 1-Methyl piperidone, LDA(1.2 equiv.), $ClCO_2Me$ (1.2 equiv.), THF, -70°C, 2 h. Yield 50%.
11. LDA (1.25 equiv.), t-$BuMe_2SiCl$ (1.25 equiv.), THF, -40°C, 30' ; then, 20°C, 5 h.
12. Purchase from Aldrich.
13. S. Torkelson and C. Ainsworth, Synthesis, 722 (1976).
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15. Ethyl benzoyl acetate, NaOEt (1.5 equiv.), IMe (1.1 equiv.), EtOH, Rfx, 20 h. Yield 40%.
16. NaH (1.1 equiv.), t-$BuMe_2SiCl$ (1.1 equiv.), THF, 0°C, 2 h.
17. Over all yields of hydroxylated products from β-dicarbonyl compounds after purification by chromatography.
18. Y. Kishi, M. Aratani, T. Fukayama, F. Nakabutso, T. Goto, S. Inoue, H. Tanino, S. Sugiura and M. Kakoi, J. Am. Chem. Soc., 94, 9217 (1972).
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