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Deprotection of Carboxylic Acids from their Phenacyl Esters by $Cu(II)/O_2/DMF\text{-}H_2O$: Unusual Formation of Benzaldehyde from the Phenacyl Group

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Abstract: Phenacyl esters gave the deprotected carboxylic acids, alongwith $PhCO_2H$, PhCHO and CO_2 on heating with $CuCl_2$ or $CuSO_4$ in aqueous DMF (50% v/v) at reflux with continuous bubbling of O_2.

Phenacyl esters are used as protected carboxylic acids in organic synthesis.[1] They are generally solids, soluble in common solvents, easy to prepare, purify and handle.[1b] They are stable to acidic conditions[1a] and therefore are suitable for orthogonal protection of the carboxyl group in the presence of acid labile protecting groups.[1b,c] They are particularly useful in peptide synthesis.[1b-d] Phenacyl ester linkage is also used to anchor the peptide chain to the polymer support in solid phase peptide synthesis.[1c] Phenacyl esters are cleaved to the parent acids by Zn/AcOH, H_2/Pd-C, NaSPh, PhSeH,[1a] KCN/18- crown-6,[1d] hydrazine[2] and n-$Bu_4NF.3H_2O$.[3] α-Methyl-and p-methoxy-phenacyl esters can be cleaved photochemically.[1a] Most of these reagents show limited selectivity with respect to other esters[4] (such as alkyl, benzyl, trichloroethyl), and/or other protecting and sensitive groups.[5] In fact, the strongly basic n-$Bu_4NF.3H_2O$ is so indiscriminate that it has been used for the final deprotection of the peptide chain during peptide synthesis to remove several protecting groups in a single step.[1c] Moreover, silicon based protecting groups are also vulnerable to this reagent. Recently, this reagent has been moderated to some extent by using it in combination with 1-octanethiol.[6]

Our interest in metal-ion promoted synthetically useful hydrolytic reactions[7] led us to explore the possibility of hydrolysing phenacyl esters by Cu(II) ion. It was expected that chelation through the phenacyloxy oxygens would activate the ester carbonyl as well as stabilise the leaving group in the transition state during the hydrolysis. The reported efficacy of $Cu(II)/O_2$ system to form α-hydroperoxyketones from enolisable ketones[8] was also envisaged to lead to the desired cleavage by hydroperoxidation at the phenacyl methylene followed by dehydration[8] or disproportionation[9] of the α-ketohydroperoxide intermediate to give readily hydrolysable mixed anhydride or hemiacetal type derivative, ultimately releasing the acid. We are pleased to report that when the phenacyl esters were heated with hydrated $CuCl_2$ or $CuSO_4$ in aqueous DMF at gentle reflux with continuous bubbling of O_2, the carboxylic acids were obtained in high yields. Benzoic acid and benzaldehyde, apparently arising from the phenacyl group, were also isolated and evolution of CO_2 detected. The results are compiled in the Table. The reaction also occurs with catalytic amount (20 mol%) of Cu(II). No reaction occurs in the absence of Cu(II). In the absence of O_2, the blue-green colour of Cu(II) was discharged and the reaction proceeded very slowly indicating that a redox reaction

was involved. α-Methylphenacyl toluate and ethyl and benzyl benzoates did not react under the present conditions showing the selectivity of the reaction. The method is complementary to the Zn/AcOH reductive method. The present reaction conditions are normally not encountered in common synthetic sequences and therefore there is little chance of interference with the synthetic planning and execution. The work-up procedure is simple when the regenerated acid is sparingly soluble in water because the impurity of benzoic acid is removed by simply washing with water. However, for water soluble acids, the purification may be complicated.

Table : Cleavage of the Phenacyl esters with $CuCl_2.2H_2O$

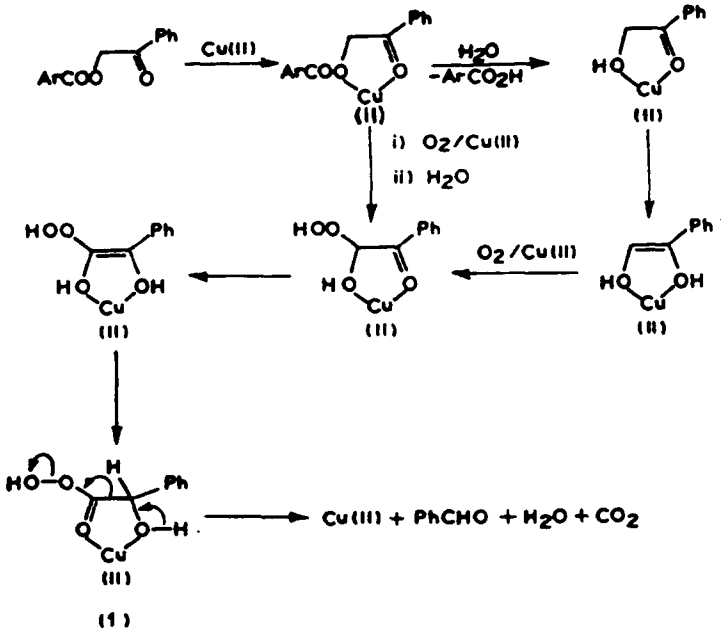
$$ArCO_2CH_2COPh \xrightarrow[DMF-H_2O]{CuCl_2/O_2} ArCO_2H + PhCHO + PhCO_2H + CO_2$$

Entry	Phenacyl esters ($ArCO_2CH_2COPh$)		Molar ratio ester: $CuCl_2.2H_2O$	Reflux time(h)	Recovered starting ester (%)	Isolated yields of products[a] (%)		
						$ArCO_2H$	$PhCO_2H$	PhCHO[b]
1.	Ar = C_6H_5		1:1.1	3.5	-	45[c]		5
2.	C_6H_5		5:1	8.0	-	48[c]		5
3.	C_6H_5		-	5.0	80	-	-	-
4.	4-CH_3-C_6H_4		1:1.1	4.5	-	78	7	5
5.	4-CH_3-C_6H_4		1:1[d]	8.0	-	85	10	4
6.	4-CH_3-C_6H_4		1:1.1[e]	10.0	70	23	3	-
7.	C_6H_4-CH=CH		1:1.1	4.5	-	92	5	2
8.	4-NO_2.C_6H_4		1:1.1	9.0	-	88	9	3
	other esters $ArCO_2R$							
	Ar	R						
9.	4-CH_3-C_6H_4	$CH(CH_3)CO$-C_6H_5	1:1.1	12	93	6	-	-
10.	C_6H_5	C_2H_5	1:1.1	5.0	90	-	-	-
11.	C_6H_5	CH_2-C_6H_5	1:1.1	5.0	80	-	-	-

a: yields are not optimised; b: isolated as semicarbazone; c: assuming that two moles of benzoic acid are otained from one mole of phenacyl benzoate; d: $CuSO_4.5H_2O$ was used in place of $CuCl_2.2H_2O$. e: anhydrous $CuCl_2$ and dry DMF (7.5 ml) were used in this case.

The mechanism of the reaction has not been studied in detail. Benzoic acid may arise by partial oxidation of benzaldehyde or, alongwith the deprotected acid, by other reported modes of fragmentation of the α-ketohydroperoxide intermediate.[10] But the formation of benzaldehyde is unusual. The keto group gets converted to carboxyl group and not aldehydic group in the reported

Cu(II) promoted oxidative cleavage of ketones.[8,11] The reaction occurs only very slowly under anhydrous conditions with high recovery of the starting ester in comparable amount of time which shows that the water independent mechanism is not important. From a separate reaction of phenacyl alcohol under identical conditions, benzoic acid and benzaldehyde were isolated and CO_2 detected. Of the other intermediates as the plausible sources of benzaldehyde, phenylglyoxal has already been reported not to give benzaldehyde under similar conditions,[11] and benzoylformic acid and mandelic acid (which might arise from phenylglyoxal[11]) did not yield benzaldehyde when subjected to the present reaction conditions rather benzoic acid alongwith small amount of the starting material (only in the case of mandelic acid) were isolated. Thus, the dehydration or disproportionation of the α-ketohydroperoxide intermediate, as envisaged earlier is not significant for the formation of benzaldehyde, but might be occuring only as a competing reaction leading to the formation of other observed products. Considering these, the following mechanism is proposed for the formation of benzaldehyde.



The above mechanism is supported by the following literature precedents. Chelation is known to promote enolisation.[12] Thus, the mildly basic conditions reported for α-hydroperoxidation of non-chelating ketones[8] may not be necessary here. Phenacyl ethers are known to be weaker chelating ligands than phenacyl alcohol,[12] thus explaining the slower reaction rate under anhydrous conditions. α-Methylphenacyl toluate does not react probably because of inhibition of chelation and tautomerisations due to steric and inductive effects respectively.

One curious aspect of the present study is that phenylglyoxal could not be isolated from the reactions of phenacyl esters and phenacyl alcohol, whereas phenacyl alcohol has been reported to give phenylglyoxal by Cu(II) oxidation of its ethanolic solution.[12] Perhaps the solvent system used in the present study has an important role to play, such as, in the chelation, tautomerisations and

in the cleavage of (1) as indicated by the fact that no reaction occurred in other solvents, such as, CH_3CN and aqueous CH_3CN.

General Procedure: A solution of the phenacyl ester (5 mmol) and $CuCl_2.2H_2O$ (5.5 mmol) in 10 ml of DMF -H_2O (50%v/v) was heated at gentle reflux with stirring and continous bubbling of a slow stream of O_2 for the time indicated in the Table. The insoluble blue residue was filtered and washed with ether. The aqueous filtrate was extracted with the ethereal washings and then with fresh ether (20 x 2 ml). The combined ethereal extract was washed with saturated $NaHCO_3$ solution (20 X 3 ml) and then once with water, dried (Na_2SO_4) and evaporated to give benzaldehyde which was derivatised as its semicarbazone. The bicarbonate layer was neutralised, filtered and washed with water to give the regenerated acid which was recrystallised. Benzoic acid being more soluble in water, went into the filtrate from which it was obtained by addition of solid NaCl followed by extraction with ether.

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