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DEHYDROGENATIONS WITH LEAD TETRAACETATE. KETONE TO ENONE TRANSFORMATIONS IN THE 2-(AMINOCARBONYL)- AND 2-(CARBALKOXY)CYCLOALKANONE SERIES

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Abstract: Cyclic β-ketoesters and β-ketoamides are converted to 2-(carbalkoxy)- and 2-(aminocarbonyl)-2-cycloalken-1-ones by treatment with $Pb(OAc)_4$ and $Cu(OAc)_2$ in benzene.

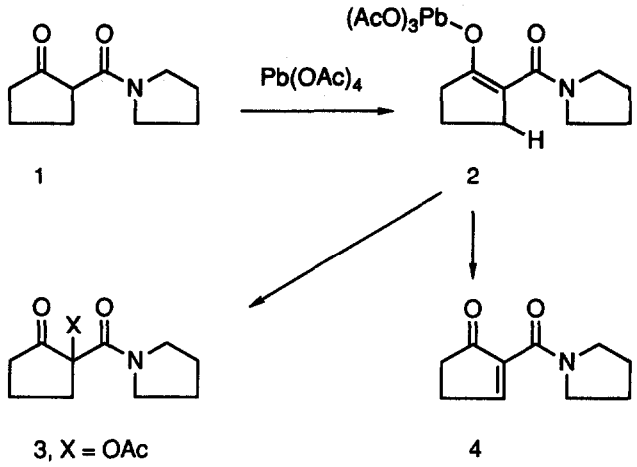
In connection with a project directed at the development of asymmetric conjugate addition reactions, we required a method for conversion of readily available 2-(carbalkoxy)cycloalkanones to their corresponding chiral 2-(aminocarbonyl)-2-cycloalken-1-ones.[1] The 4-dimethylamino-pyridine-catalyzed aminolysis of β-ketoesters[2] provided an efficient preparation of the substrates to be subjected to dehydrogenation; however, attempted utilization of known methods for the conversion of ketones to enones failed to provide 2-(aminocarbonyl)-2-cycloalken-1-ones free of by-products and in quantities necessary for synthetic studies. Except for (2'S)-2-[[2'-(methoxy-methyl)pyrrolidinyl]carbonyl]-2-cyclohexen-1-one and a related substrate, both prepared by Birch reduction of aromatic precursors,[1] examples of 2-(aminocarbonyl)-2-cycloalken-1-ones appear to be absent from the chemical literature.[3]

Lead tetraacetate has been reported to effect transformations of steroidal and related cyclohexenones to 2,5-cyclohexadien-1-ones in yields ranging from 1.5 to 20%.[4] The major products obtained from these reactions are the result of selective oxidation at the α'-position of the cyclohexenone ring. Indeed, α'-oxidation of enones with lead tetraacetate is a well-established procedure for preparation of α'-acyloxyenones.[5]

Prior experience suggested that substrates containing a β-dicarbonyl unit should be more receptive to dehydrogenation with lead tetraacetate.[6] In fact, treatment of ketoamide **1** with ~1 equiv of lead tetraacetate in acetic acid gave a mixture of 2-acetoxyketoamide **3**[7] and a small amount of the desired cyclopentenone **4** (Scheme 1). Changing the solvent from acetic acid to

benzene reduces the importance of α-acetoxylation in favor of enone formation. Addition of catalytic quantities of $Cu(OAc)_2$[8] provided the highest yields of enone.

Scheme 1



1 2

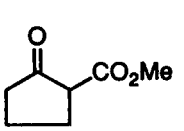
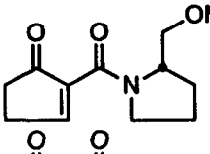
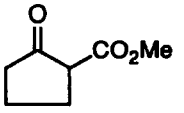
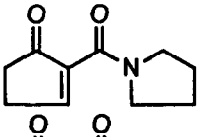
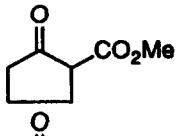
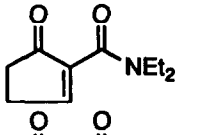
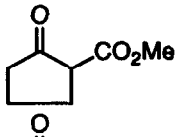
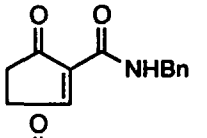
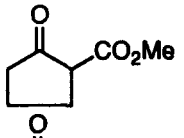
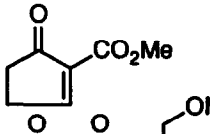
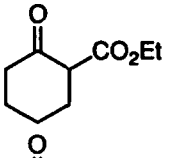
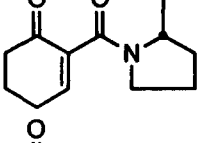
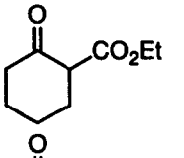
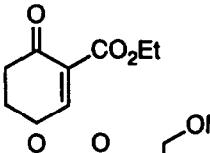
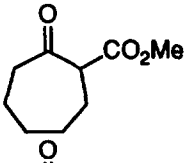
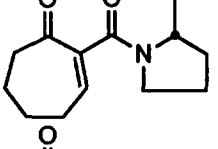
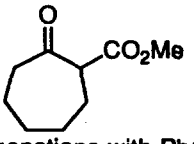
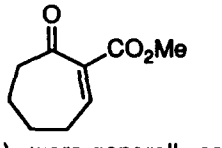
3, X = OAc 4

Reaction Conditions	3 (% Yield)	4 (% Yield)
$Pb(OAc)_4$ in HOAc	42	6
$Pb(OAc)_4$ in benzene	15	29
$Pb(OAc)_4$ + $Cu(OAc)_2$ in benzene	5	67

Results of the $Pb(OAc)_4$ oxidation of several cyclic ketoamides and ketoesters are shown in Table I. Yields for dehydrogenation of ketoamides are better than those for ketoesters, except for the synthesis of 2-carbomethoxy-2-cyclohepten-1-one (entry 9). Dehydrogenation of the 2-(aminocarbonyl)cyclohexanone occurs without secondary oxidation to the phenol (entry 6). The preparation of (2'S)-2-[[2'-(methoxymethyl)pyrrolidinyl]carbonyl]-2-cyclohexen-1-one in two steps from 2-carboethoxycyclohexanone (52% overall yield) represents an alternative synthesis of this important substrate for asymmetric conjugate additions;[1] remarkably, only trace quantities of the corresponding ester are obtained (entry 7). Entry 4 demonstrates that secondary ketoamides are effective substrates for conversion to the enone.

Representative Experimental Procedure. 2-Carbomethoxycycloheptanone (200 mg, 1.18 mmol), benzene (50 mL) and $Cu(OAc)_2 \cdot 2\ H_2O$ (6 mg, 0.03 mmol) were combined and stirred for 30 min. $Pb(OAc)_4$ (524 mg, 1.18 mmol) was added and the mixture was stirred for 48 h. Ethylene glycol was added until the solution became clear. The solvent was removed under reduced

Table I. Conversions of 2-(Carbalkoxy)cycloalkanones to 2-(Aminocarbonyl)-2-cycloalken-1-ones and 2-(Carbalkoxy)-2-cycloalken-1-ones[a]

entry	ketoester[b]	enone (% yield)[c]	reaction time (h)	2-acetoxyketone (% yield)[c]
1		 (62)	10	(11)
2		 (67)	4	(5)
3		 (72)	4	(25)
4		 (48)[d]	6	(26)
5		 (20)[d]	3	---
6		 (55)	96	(19)
7		 (trace)	4	---
8		 (41)	2[e]	(25)
9		 (78)	48	---

[a]Dehydrogenations with $Pb(OAc)_4$ were generally carried out as described in the representative experimental procedure with variations in reaction time indicated in the table. [b]Ketoesters were converted to ketoamides by heating a solution of the ketoester, the corresponding amine and 4-dimethylaminopyridine in toluene to reflux for 12 hours; see ref. 2. [c]Yields for the oxidation with $Pb(OAc)_4$ are for analytically pure materials isolated by flash chromatography on silica gel. [d]0.5 to 1.0 equiv $Cu(OAc)_2$ utilized in these experiments. [e]Reaction mixture heated to reflux.

pressure, water was added, and the mixture was extracted with CH_2Cl_2 (5 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Flash chromatography (ether/hexane, 1:1) afforded 2-carbomethoxy-2-cyclohepten-1-one as a colorless oil (155 mg, 78%). This procedure gave the enone in 60% yield on a 10 g reaction scale.

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