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Communications

Selective Reduction of α -Keto Acids to α -Hydroxy Acids by Phosphites

Summary: This paper reports a versatile, selective reduction of α -keto acids to α -hydroxy acids by means of phosphites as reducing agents, which takes place under mild conditions to give products in high yields.

Sir: There are few simple methods for the reduction of α -keto acids to α -hydroxy acids despite their importance in biological as well as organic chemistry.^{1,2} We wish to report a versatile, selective reduction method which employs phosphites as reducing agents.

A typical procedure is as follows. In 3 mL of acetonitrile, pyruvic acid (1a) (5 mmol) and triethyl phosphite (5 mmol)

$$\begin{array}{c|c} \operatorname{RCCO}_2 H & \frac{1. (R'O_{\lambda}P)}{2. \operatorname{NaOH}} & \operatorname{RCHCO}_2 H \\ 0 & OH \\ 1 & 2 \end{array}$$

a, $R = CH_3$; **b**, $R = CH_2CO_2H$; **c**, $R = (CH_2)_2CO_2H$; **d**, $R = C_6H_5$

were dissolved at 0 °C. When the mixture was allowed to warm to room temperature, an exothermic reaction took place. After standing overnight at room temperature, acetonitrile was removed under reduced pressure. The residue was hydrolyzed by stirring with 20 mL of a 2 N NaOH solution at 50 °C for 8 h. Zinc chloride (5 mmol) was added and the mixture was neutralized to precipitate white crystals of the zinc salt. After refrigeration at 0 °C, the salt was filtered, washed two times with cold water, and dried in vacuo to constant weight to give 0.82 g (94%) of $Zn(O_2CCH(OH)CH_3)_2 \cdot 2H_2O$. The salt was identified by comparison of its IR spectrum with that of an authentic sample.³

Similarly, reductions of the other three α -keto acids listed in Table I were carried out by using triethyl phosphite or ethylene phenyl phosphite as reducing agents.

It is known that the phosphorus atom of phosphites reacts with the oxygen atom of carbonyls attached to electronwithdrawing groups.⁵ Analogously, reaction of an α -keto acid (1) with a phosphite is expected to produce a carbanion (3) which rearranges to produce a phosphobetaine 4. In the case of ethylene phenyl phosphite, the betaine 4 is probably in equilibrium with a pentacovalent phosphorane 5. Pentaco-



valent species 6a and 6b have actually been isolated.⁶ Alkaline hydrolysis of either 4 and/or 5 probably produces the α -hydroxy acids 2.



When triethyl phosphite is used, however, the reaction probably proceeds differently after 4 is formed. The betaine species is not stable enough to produce the pentacovalent species 5 (R' = Et) but rather undergoes an Arbuzov-type

$$\begin{array}{c} \stackrel{\text{d}}{\longrightarrow} & \underset{|}{\text{RCHCO}_2 H} + (\text{HO})_3 P = 0 + 3R'OH \\ & \stackrel{|}{\longrightarrow} & \underset{OH}{\text{OH}} \end{array}$$

reaction to produce 7, 8, and 9. In the reaction of triethyl phosphite with pyruvic acid $(R = CH_3)$, 7 and 9 were formed in 22 and 64% yields, respectively. Alkaline hydrolysis produced lactic acid not only from 7 but also from 8 which must be formed in equimolecular amount with 9. Previously, Kamai and Kukhtin⁷ reported only the isolation of triethyl phosphate 9 with pyruvic acid.

Table I. Reduction of α -Keto Acid to α -Hydroxy Acid by Phosphite

	Yield, %, of α -hydroxy acid	
Reaction ^a	(EtO) ₃ P	EPP ^e
1a → 2a ^b	94	99
$1b \rightarrow 2b^c$		78
$1c \rightarrow 2c^{b}$	67	59
$1d \rightarrow 2d^d$	>90	60

^a α -Keto acid (5 mmol) and phosphite (5 mmol) in 3 mL of acetonitrile at room temperature for 12 h. ^b Isolated as zinc salt. ^c Isolated as calcium salt. ^d Isolated as free mandelic acid, mp 120.5 °C.4 e Ethylene phenyl phosphire.

$4 \longrightarrow (EtO)_2 POCHCO_2 Et$	+ $$ $CHCO_2 \rightarrow \overline{n}$	+ $(EtO)_3P=0$
II I OR	 R	9
7	8	

Prior to the present study two methods for reduction of α -keto acids have been reported.^{1,2} Sodium borohydride reduction of 1a and 1d gave 2a and 2d in yields of 61 and 76%,

respectively,¹ whereas hydrogenation of 1a in the presence of Raney nickel afforded 2a in 56% yield.² The present results (Table I) provide a better method for selective reduction of α -keto acids to α -hydroxy acids.

References and Notes

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