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A MILD, RAPID, AND CONVENIENT ESTERIFICATION OF α-KETO ACIDS

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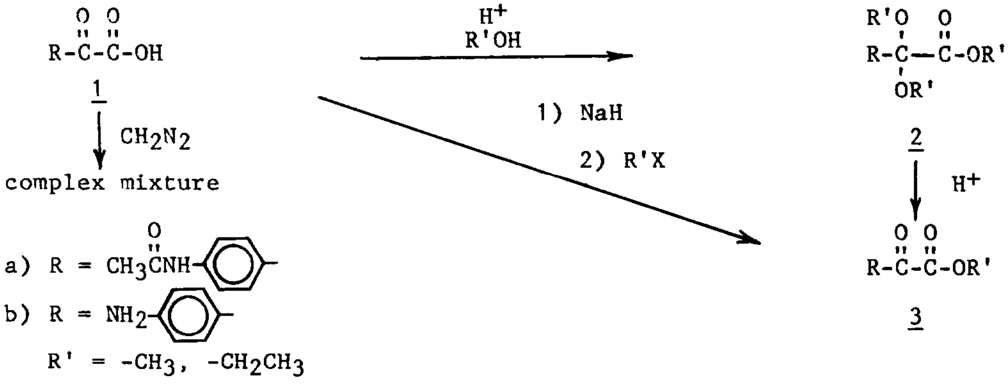
Summary. A new method for the esterification of α-keto acids with alkyl chloroformates is described, which is compatible with many functional groups.

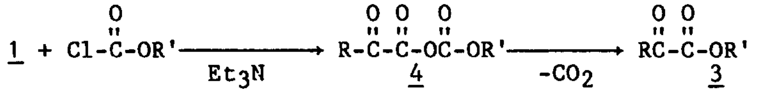
In the course of our research on 4-substituted α-oximinophenylacetic acids,[1] it was often imperative to obtain the corresponding α-keto esters. Although many methods are available for the preparation of certain α-keto esters,[2] none of them utilize, as we required, the α-keto acids themselves as precursors, and most are limited in the number and complexity of the esters derivable.

Furthermore, the common esterification procedures (acid and alcohol or diazomethane) were not compatible with our functional groups. When 4-acetamido-α-oxophenylacetic acid (1a) was treated in alcohol with acid catalysis, the acetyl group was hydrolyzed with concomitant ketalization to give 2b (Scheme 1). Etheral diazomethane gave a complex mixture of products. Some α-keto esters 3 were prepared from the sodium salts of the acids and the appropriate alkyl halides, but long reaction times were required (> 100 h).

Scheme 1



We wish to report that the α-aryl-α-keto acids, 1, (R = Aryl) can be easily converted to the α-keto esters 3 in very good yields by treatment with alkyl chloroformates and triethylamine (Eq. 1).

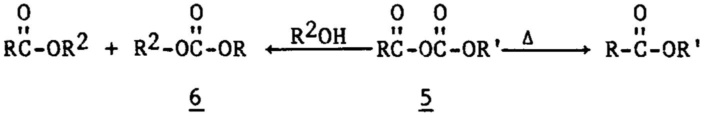


$$\underline{1} + \mathrm{Cl{-}\overset{O}{C}{-}OR'} \xrightarrow[\mathrm{Et_3N}]{} \underset{\underline{4}}{\mathrm{R{-}\overset{O}{C}{-}\overset{O}{C}{-}O\overset{O}{C}{-}OR'}} \xrightarrow[-\mathrm{CO_2}]{} \underset{\underline{3}}{\mathrm{R\overset{O}{C}{-}\overset{O}{C}{-}OR'}} \qquad \text{Eq. 1}$$

The reaction proceeds equally well in H_2CCl_2, $HCCl_3$, DMF, and THF, at ~20°C in 5-20 min, for all chloroformates employed.

The following procedure is representative. To 2.07 g (10.0 mmol) of 1a in 50 ml of dichloromethane was added 1.39 ml (1.0 eq) of triethylamine. To this mixture, 0.77 ml (1.0 eq) of methyl chloroformate was added at 20°C. The loss of CO_2 was complete in 10 min. Extraction at pH 7.0, drying ($MgSO_4$), and concentration gave 2.11 g (95%) of methyl 4-acetamido-α-oxophenylacetate (3a).

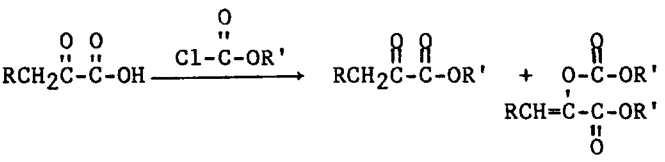
Tarbell[3] has reported the preparation of esters from the thermal (150-175°C) decomposition of mixed anhydrides 5 (Eq. 2). Apparently, the presence of the α-keto group in 4 facilitates the rapid loss of CO_2 even at -30°C.



$$\mathrm{R\overset{O}{C}{-}OR^2} + \underset{\underline{6}}{\mathrm{R^2{-}O\overset{O}{C}{-}OR}} \xleftarrow{\mathrm{R^2OH}} \underset{\underline{5}}{\mathrm{R\overset{O}{C}{-}O\overset{O}{C}{-}OR'}} \xrightarrow{\Delta} \mathrm{R{-}\overset{O}{C}{-}OR'} \qquad \text{Eq. 2}$$

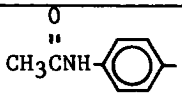
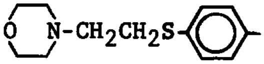
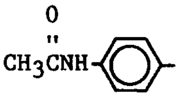
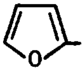
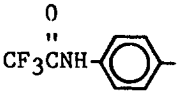
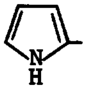
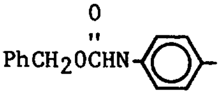
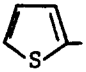
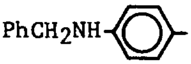
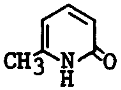
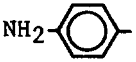
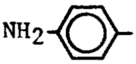
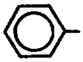
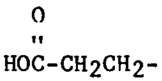
In theory, mixed anhydrides such as 5 can be converted to esters by treatment with alcohols. In practice however, the desired esters are often contaminated with unreacted alcohol (a problem for nonvolatile alcohols) and mixed carbonates, 6.

The reaction was less satisfactory for α-alkyl-α-keto acids, 1, (R = RCH_2-) where any enol is present. Although the mixed anhydrides form and decompose as described (Eq. 1), the process is slower and some chloroformate reacts with the enol (Eq. 3). Purification of these mixtures is therefore required lowering the yields of ester to between 40-65%.



$$\mathrm{RCH_2\overset{O}{C}{-}\overset{O}{C}{-}OH} \xrightarrow{\mathrm{Cl{-}\overset{O}{C}{-}OR'}} \mathrm{RCH_2\overset{O}{C}{-}\overset{O}{C}{-}OR'} + \begin{array}{c} \mathrm{O{-}\overset{O}{C}{-}OR'} \\ | \\ \mathrm{RCH{=}C{-}\underset{O}{C}{-}OR'} \end{array} \qquad \text{Eq. 3}$$

Table 1. Preparation of α-Keto Esters 3 from α-Keto Acids 1.

Entry[a]	R	R'	Entry[a]	R	R'
a		$-CH_3$	j		$-CH_3$
b		$-CH_2CCl_3$	k		$-CH_2CCl_3$
c		$-CH_2CH_3$	l		$-CH_2Ph$
d		$-CH_3$	m		$-CH_2CH_3$
e		$-CH_3$	n		$-CH_2CH_3$
f		$-CH_2CCl_3$	o[b]	CH_3-	$-CH_2Ph$
g		$-CH_2Ph$	p[c]	$PhCH_2-$	$-CH_2CH_3$
h		$-CH_2Ph$	q[d]	 $HO\overset{O}{\overset{\parallel}{C}}-CH_2CH_2-$	$-CH_2CH_3$
i		$-CH_2CH(CH_3)_2$	r[e]	CH_3CH_2-	$-CH_2CCl_3$

a) All yields are between 93-99% unless otherwise noted. All products had satisfactory elemental analysis. For the preparation of the keto acids see ref. 4-7. b) 60% yield; c) 40% yield; d) 44% yield; e) 65% yield.

References and Notes

1. J. M. Domagala and T. H. Haskell, submitted for publication.

2. From α-haloacetophenones, J. P. Schaefer, and E. J. Corey, J. Org. Chem., 24, 1825 (1959). (This procedure failed for our α-haloacetophenones.) From acylation of acyl anion equivalents, W. E. Truce and F. E. Roberts, J. Org. Chem, 28, 961 (1963); K. Ogura, N. Katoh, I. Yoshimura, and G. Tsuchihashi, Tetrahedron Lett., 375 (1978). From Friedel-Crafts reaction with ethyl oxalylchloride, and from mandelic acid esters, A. G. Long, E. M. Wilson, and W. G. Pinner, U.S. Patent 3,573,294 (1971).

3. D. S. Tarbell and E. J. Longosz, J. Org. Chem., 24, 774 (1959). For a similar process giving thiol esters, see R. A. Gorski, D. J. Dagli, V. A. Patronik, and J. Wemple, Synthesis, 811 (1974).

4. The keto acids 1a, 1c, 1d, 1i, and 1m were obtained from oxidation of the corresponding methyl ketones with selenium dioxide. 1h and 1o-1r were commercially available. 1f was prepared from 1a. 1e was prepared from 2b by reductive amination. 1j was prepared from 1i by fluorine displacement. 1l, 1k, and 1n were prepared following the procedures in references 5-7.

5. G. R. Birchall and A. H. Rees, Can. J. Chem., 49, 919 (1971).

6. W. J. Gottstein, U. K. Patent 1,557,423 (1977).

7. H. H. Showalter, J. Org. Chem., in press.

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