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A NEW METHOD FOR THE PREPARATION OF α-HYDROXY KETONES

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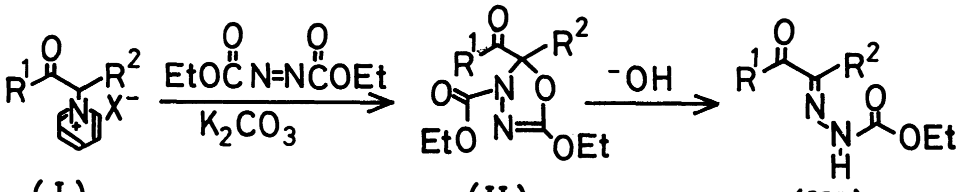
Various α-hydroxy ketones were prepared in good yields by reduction of α-ethoxycarbonylhydrazono ketones with $NaBH_4$, followed by acid hydrolysis. α-Ethoxycarbonylhydrazono ketones were obtained in good yields by the treatment of Δ^2-1,3,4-oxadiazolines, prepared from 1-(2-oxoalkyl)pyridinium salts and diethyl azodicarboxylate, with aqueous sodium hydroxide.

Concerning the preparation of α-hydroxy ketones, there have been reported a number of methods, for example, acyloin condensation,$^{1)}$ hydrolysis of α-halo ketones$^{1)}$ and recently the reactions of carbonyl compounds with several acyl anion equivalents.$^{2)}$

In the present communication, we wish to report a useful synthetic route for the preparation of α-hydroxy ketones from pyridinium salts of α-halo ketones which involves the transposition of carbonyl group.

Recently we reported a facile synthesis of Δ^2-1,3,4-oxadiazolines(II) by the reaction of 1-(2-oxoalkyl)pyridinium salts(I) with diethyl azodicarboxylate.$^{3)}$ The oxadiazolines(II) were converted to α-ethoxycarbonylhydrozono ketones(III) in good yields by the treatment with aqueous sodium hydroxide(eq.-1). A similar reaction of forming 9-fluorenone ethoxycarbonylhydrazone from 9-diazofluorene has been reported by Staudinger and Gaule.$^{4)}$



(I) (II) (III)

The typical reaction procedure is described for the preparation of 3-ethoxycarbonylhydrazono-2-pentanone: to an acetonitrile (7 ml) solution of 1-(1-ethylacetonyl)pyridinium bromide (0.5 mmol) and diethyl azodicarboxylate (0.55 mmol) was added K_2CO_3 (0.55 mmol) at room temperature under an argon atmosphere and the mixture was stirred overnight. After 10 ml of 0.5N NaOH was added to the solution at 0°C, the reaction mixture was stirred for 1 hr at room temperature. Then the mixture was acidified with hydrochloric acid and extracted with ether. The extract was dried over anhydrous Na_2SO_4 and condensed under reduced pressure. The residue was chromatographed on silica gel and 3-ethoxycarbonylhydrozono-2-pentanone was isolated in 86% yield.

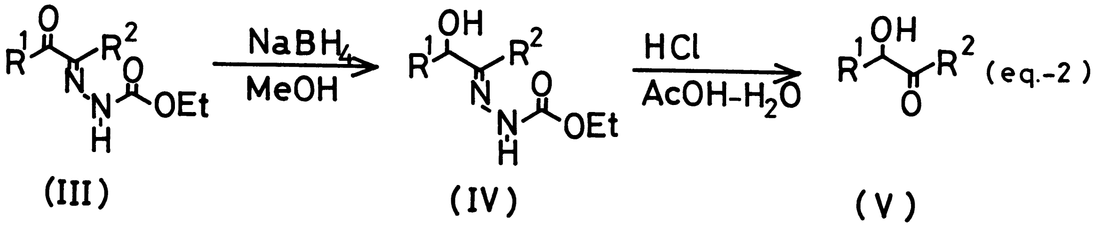
Table I. Synthesis of α-ethoxycarbonylhydrazono ketones (III)[a)]

			Reaction conditions				
			Synthesis of the Δ^2-1,3,4-oxadiazoline		The treatment with aq.NaOH		
R^1	R^2	X	Temp(°C)	Time(hr)	Time(min)	Yield(%)	Mp(°C)
CH_3-	$CH_3(CH_2)_9$	Br	r.t.	overnight	120	61	40-42
CH_3-	$CH_3(CH_2)_7$	Br	48	2.0	70	81	61-63
CH_3-	CH_3CH_2-	Br	r.t.	overnight	60	86	66-68
CH_3CH_2-	CH_3-	Br	r.t.	overnight	60	84	139-140
CH_3-	CH_3-	Br	r.t.	overnight	35	74	140-141
		Cl	50	3.7	20	48	
CH_3-	$PhCH_2$-	Br	40	2.5	30	73	70-72
Ph-	CH_3CH_2-	Br	r.t.	5.5	120	76	106-107
Ph-	CH_3-	Br	r.t.	6.0	150	80	107
		Cl	r.t.	6.6	20	49	
Ph-	Ph-	Cl	r.t.	overnight	100	77	125-127
		I	r.t.	overnight	120	84	
$CH_3(CH_2)_3$	$CH_3(CH_2)_2$	I	r.t.	overnight	60	43	63-64

a) The structures of these compounds are supported by ir and nmr spectra and elemental analysis.

In a similar manner, various α-ethoxycarbonylhydrazono ketones(III) were obtained in good yields without isolation of the intermediates, Δ^2-1,3,4-oxadiazolines(II) (Table I).

The synthetic utility of α-ethoxycarbonylhydrazono ketones(III), regarded as selectively protected α-diketones, was shown in the synthesis of α-hydroxy ketones(V); the hydroxyl group is obviously originated from the carbonyl group of the starting materials, the pyridinium salts of α-halo ketones(I) (eq.-2).



α-Ethoxycarbonylhydrazono ketones(III) were reduced with sodium borohydride in methanol to give the corresponding α-hydroxy ketone ethoxycarbonylhydrazones(IV). These hydrazones(IV) were readily hydrolyzed with hydrochloric acid to produce the corresponding α-hydroxy ketones(V).

The typical reaction procedure is as follows: to a methanol (3 ml) solution of 2-ethoxycarbonylhydrazono-1-phenyl-1-butanone (1 mmol) was added $NaBH_4$ (2 mmol) at 0°C. After stirring for 1 hr, a mixture of conc. HCl, acetic acid and water (3 ml each) was added and stirred for 1.5 hr at room temperature. The reaction mixture was extracted with ether and the extract was washed with aqueous $NaHCO_3$ solution. After drying over anhydrous Na_2SO_4, the extract was condensed under reduced pressure. The residue was chromatographed on silica gel and 1-hydroxy-1-phenyl-2-butanone was isolated in 83% yield.

In this manner, various α-hydroxy ketones(V) were obtained in good yields without isolation of α-hydroxy ketone ethoxycarbonylhydrazone(IV) (Table II). The isomerization of α-hydroxy ketones concerning the positions of hydroxyl group and carbonyl group was not observed under the present reaction conditions.

Table II. Synthesis of α-hydroxy ketones(V)[a)]

R^1	R^2	Reaction time (hr) Reduction	Hydrolysis	Yield(%)
Ph-	Ph-	1.0	1.5	91
Ph-	CH_3CH_2-	1.0	1.5	83
Ph-	CH_3-	1.5	1.0	85
CH_3-	$PhCH_2$-[b)]	1.0	1.5	80
CH_3-	$CH_3(CH_2)_9$	1.5	1.0	66
$CH_3(CH_2)_3$	$CH_3(CH_2)_2$	1.0	1.5	81

a) Each product gave satisfactory spectral data.

b) α-Methoxycarbonylhydrazono ketone

Further study on the synthetic utility of the α-ethoxycarbonylhydrazono ketones is now under investigation.

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