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THE CLAISEN REARRANGEMENT USING β-ALKYLTHIO-β,γ-UNSATURATED ALCOHOLS. A NEW METHOD FOR THE PREPARATION OF FURANS AND γ-OXOCARBOXYLIC ESTERS

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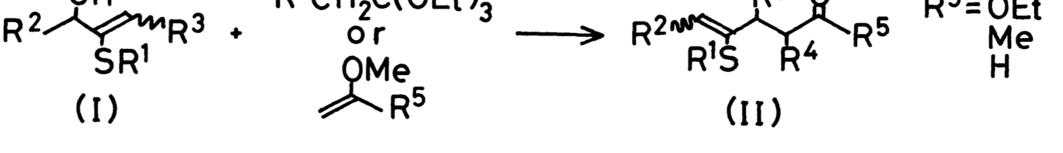
Various furans and γ-oxocarboxylic esters were prepared by the pivalic acid-promoted Claisen rearrangement using β-alkylthio-β,γ-unsaturated alcohols followed by the treatment of the rearrangement products with an acid catalyst such as hydrochloric acid or sulfuric acid in good yields.

Although the Claisen rearrangement utilizing β-alkylthio-β,γ-unsaturated alcohols (I) (eq 1) is one of the most useful methods for the preparation of the masked 1,4-dicarbonyl compounds (γ-alkylthio-γ,δ-unsaturated carbonyl compounds (II)), only one example using mercuric acetate as a catalyst was reported.[1] Recently, we showed that various β-alkylthio-β,γ-unsaturated alcohols (I) were easily synthesized by the reaction of aldehydes with (1-alkylthio)vinyllithium reagents, which prepared by treatment of β-methoxyethyl sulfides with twice molar amounts of butyllithium in the presence of N,N,N',N'-tetramethylethylenediamine.[2] In this communication, we wish to report the pivalic acid-promoted Claisen rearrangement utilizing β-alkylthio-β,γ-unsaturated alcohols (I) and a simple procedure for the conversion of the rearrangement products (II) to furans (III) or γ-oxocarboxylic esters (IV).

It has been reported that β-alkylthio-β,γ-unsaturated alcohols (I) easily isomerized to α-alkylthio ketones in the presence of hydrochloric acid or p-toluenesulfonic acid.[3] In fact, when 3-hydroxy-2-methylthio-3-phenylpropene was allowed to react with triethyl orthoacetate using p-toluenesulfonic acid as a catalyst, the corresponding γ-methylthio-γ,δ-unsaturated carboxylic ester could not be isolated, but α-(methylthio)propiophenone was obtained as a major product. After several attempts, it was found that pivalic acid was especially effective for the conversion of I to II (Table I).



(eq 1)

Table I. The reaction of 3-hydroxy-2-methylthio-3-phenylpropene with triethyl orthoacetate

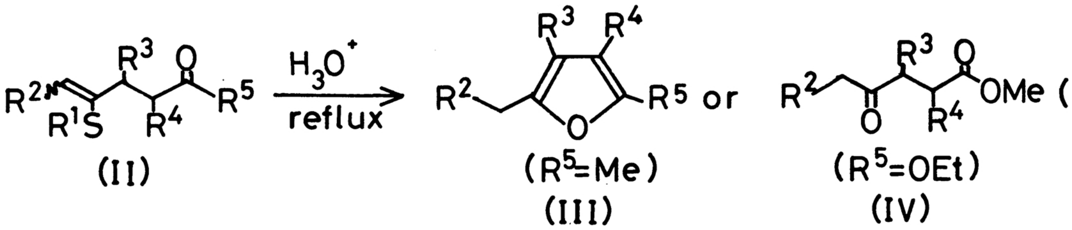
Catalyst	(mol%)	Solvent	Time(h)	Temp(°C)	Yield(%)[4]
TsOH	(10)	DMF	17	100	0
$CH_3(CH_2)_2COOH$	(10)	DMF	12	100	12
$CH_3(CH_2)_2COOH$	(10)	PhH	30	reflux	10
$(CH_3)_3CCOOH$	(10)	$PhCH_3$	2.5	reflux	54
$(CH_3)_3CCOOH$	(30)	$PhCH_3$	3.5	reflux	82

The experimental procedure is as follows: A toluene (5 ml) solution of 3-hydroxy-2-methylthio-3-phenylpropene (361 mg, 2 mmol), triethyl orthoacetate (649 mg, 4 mmol), and pivalic acid (61 mg, 0.6 mmol) was refluxed for 3.5 h. The reaction mixture was washed with 5% $NaHCO_3$ aqueous solution and the aqueous layer was extracted with AcOEt. The extracts were combined, dried over Na_2SO_4 and condensed under reduced pressure. The residue was chromatographed on silica gel (AcOEt-hexane) and ethyl 4-methylthio-5-phenyl-4-pentenoate (410 mg) was isolated in 82% yield.

In a similar manner, various γ-alkylthio-γ,δ-unsaturated carbonyl compounds (II) were synthesized in good to high yields (Table II).

One of the advantages of the present method for the preparation of furans (III) and γ-oxocarboxylic esters (IV) is facility of the hydrolysis of the vinyl sulfide group of <u>II</u>. It is well known that mercuric chloride[5] or titanium tetrachloride[6] is indispensable for the hydrolysis of the vinyl sulfide to carbonyl group and drastic reaction conditions are required without these salts.[7] We found that γ-alkylthio-γ,δ-unsaturated ketones (II;R^5=Me) were easily converted to furans (III) on treatment with p-toluenesulfonic acid or hydrochloric acid in good yields. The typical experimental procedure is as follows: A benzene solution of 8-phenyl-4-(2-phenylethyl)-5-phenylthio-5-octen-2-one (207 mg, 0.5 mmol) and p-toluenesulfonic acid monohydrate (9.5 mg, 0.05 mmol) was refluxed for 1 h. The reaction mixture was washed with 1M NaOH solution to remove benzenethiol and aqueous layer was extracted with AcOEt. The extracts were combined, dried over Na_2SO_4 and condensed under reduced pressure. The residue was purified by preparative TLC (AcOEt-hexane) to give 2-methyl-4-(2-phenylethyl)-5-(3-phenylpropyl)furan (114 mg) in 75% yield.

On the other hand, methyl γ-oxocarboxylates (IV) were obtained by treatment of γ-alkylthio-γ,δ-unsaturated carboxylic esters (II;R^5=OEt) with sulfuric acid in methanol in good yields (eq 2). These results are summarized in Table III.



(eq 2)

Table II. Synthesis of γ-alkylthio-γ,δ-unsaturated carbonyl compounds (II)

R^1	R^2	R^3	Ortho ester or Vinyl ether	Time(h)	Yield(%)[4)]
Me	Et	H	$CH_3C(OEt)_3$	3.5	78
	Et	H	$CH_3CH_2C(OEt)_3$	2.5	78
	$(CH_3)_2CHCH_2$	H	$CH_3C(OEt)_3$	3.3	80
	$Ph(CH_2)_2$	H	$CH_3C(OEt)_3$	2.3	76
	Ph	H	$CH_3C(OEt)_3$	3.5	82
	Ph	H	$CH_3CH_2C(OEt)_3$	2.5	88
Ph	Et	$Ph(CH_2)_2$	$CH_3C(OEt)_3$	3.0	80
	Et	$Ph(CH_2)_2$	$CH_3CH_2C(OEt)_3$	3.0	89
	Ph	$Ph(CH_2)_2$	$CH_3C(OEt)_3$	2.5	70
	Ph	$Ph(CH_2)_2$	$CH_3CH_2C(OEt)_3$	3.0	85
	Ph	$(CH_3)_2CHCH_2$	$CH_3C(OEt)_3$	2.0	71
	Ph	$(CH_3)_2CHCH_2$	$CH_3CH_2C(OEt)_3$	1.5	83
Me	Et	H	$CH_2=C(OMe)CH_3$	5.5	78[a)b)]
	$(CH_3)_2CHCH_2$	H	$CH_2=C(OMe)CH_3$	4.0	81[a)b)]
	$Ph(CH_2)_2$	H	$CH_2=C(OMe)CH_3$	4.0	78[a)b)]
	Ph	H	$CH_2=C(OMe)CH_3$	4.0	81[a)b)]
	Ph	H	$CH_2=C(OMe)H$	18	56[a)c)]
Ph	Et	$Ph(CH_2)_2$	$CH_2=C(OMe)CH_3$	15	93[a)b)]
	$(CH_3)_2CHCH_2$	$Ph(CH_2)_2$	$CH_2=C(OMe)CH_3$	15	74[a)b)]
	$Ph(CH_2)_2$	$Ph(CH_2)_2$	$CH_2=C(OMe)CH_3$	15	76[a)b)]
	$Ph(CH_2)_2$	$(CH_3)_2CHCH_2$	$CH_2=C(OMe)CH_3$	15	93[a)b)]
	Ph	$Ph(CH_2)_2$	$CH_2=C(OMe)CH_3$	15	79[a)b)]
	Ph	$(CH_3)_2CHCH_2$	$CH_2=C(OMe)CH_3$	15	88[a)b)]

a)The reaction was carried out in a sealed tube.
b)Six equiv of vinyl ether and 5 mol% of the catalyst were used.
c)Eight equiv of vinyl ether and 1 mol% of the catalyst were used.

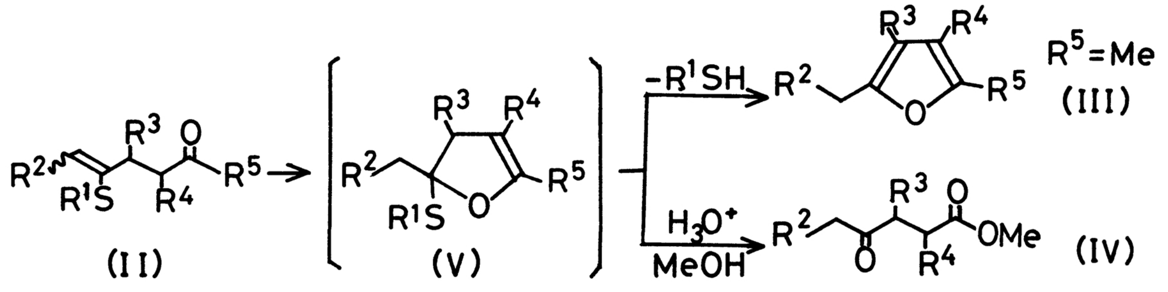
It is suspected that the facility of the present hydrolysis of the vinyl sulfide is due to the neighboring group participation by the carbonyl group. Namely, the hydrolysis proceeds through an initial formation of the dihydrofuran (V) by the addition of the enol to the vinyl sulfide. The intermediate (V) affords furan (III) by the elimination of thiol and γ-oxocarboxylate (IV) is produced by the methanolysis of V as shown in the following scheme.

Table III. Synthesis of furans (III) and methyl γ-oxocarboxylates (IV)

R^1	R^2	R^3	R^4	R^5	Solvent	Catalyst	Time(h)	Yield(%)[4)]
Ph	Et	$Ph(CH_2)_2$	H	Me	CH_2Cl_2	TsOH	2	75
	Ph	$Ph(CH_2)_2$	H	Me	PhH	TsOH	2	61
	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Me	PhH	TsOH	1	75
					MeOH	HCl	1	67[a)]
	$Ph(CH_2)_2$	$(CH_3)_2CHCH_2$	H	Me	PhH	TsOH	1	89
					MeOH	HCl	1	74[a)]
	$(CH_3)_2CHCH_2$	$Ph(CH_2)_2$	H	Me	PhH	TsOH	1	62[a)]
					MeOH	HCl	1	74[a)]
Me	$(CH_3)_2CHCH_2$	H	H	Me	PhH	TsOH	2	61
	$Ph(CH_2)_2$	H	H	Me	PhH	TsOH	1	52
Ph	Ph	$(CH_3)_2CHCH_2$	H	OEt	MeOH	H_2SO_4	5	84[b)]
	Et	$Ph(CH_2)_2$	H	OEt	MeOH	H_2SO_4	2	79[b)]
	Et	$Ph(CH_2)_2$	Me	OEt	MeOH	H_2SO_4	2	71[b)]
Me	Ph	H	H	OEt	MeOH	H_2SO_4	1	80[b)]
	$(CH_3)_2CHCH_2$	H	H	OEt	MeOH	H_2SO_4	2	85[b)]

a)The reaction was carried out by refluxing a methanol solution (0.083 mol/l) of the ketone (II) with concd hydrochloric acid (1 ml/1 mmol of II).

b)The reaction was carried out by refluxing a methanol solution (0.091 mol/l) of the ester (II) with concd sulfuric acid (1 ml/1 mmol of II).



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4) All compounds exhibited ir and nmr spectral data in accordance with the assigned structures.

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