

α -SUBSTITUTION OF KETONES VIA β -KETO THIOLESTERS

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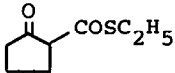
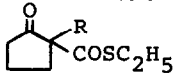
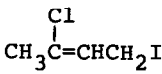
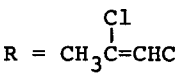
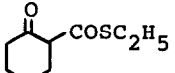
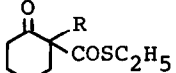
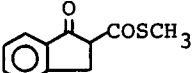
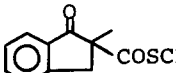
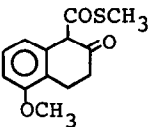
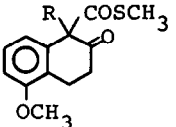
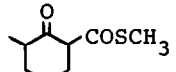
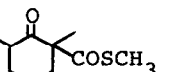
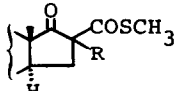
Summary: β -Keto thiolesters readily undergo substitution at the α -carbon and the thiol ester group is easily removed by Ra-Ni.

Use of the β -keto ester function for the regiospecific introduction of a single α -substituent is an important process in organic synthesis¹. The removal of the ester group however is often difficult and requires vigorous reaction conditions¹ under which many functionalities (e.g. a second ester group) are affected. We have found that β -keto thiolesters, like their O-analogs, undergo facile α -substitution and that the thiol ester group can be easily removed by Raney nickel.

β -Keto thiolesters are readily available from dithiol esters via Dieckmann-type condensation² or from ketones by a highly regioselective α -alkylthiocarbonylation process³. In a typical alkylation procedure, sodium hydride (50% oil dispersion; 302 mg, 6.3 mmol) and methyl iodide (895 mg, 6.3 mmol) were added to a solution of 2-methylthiocarbonyl-1-indanone (1 g, 4.85 mmol) in 1,2-dimethoxyethane (20 mL) at 0°C and the reaction mixture was stirred at room temperature under an argon atmosphere for 10 hr. After cooling to 0°C, water was added to destroy the excess NaH and the resulting mixture was poured into ice-cold 1 N aqueous NaOH and extracted with chloroform. The usual work-up of the extracts was followed by column chromatography of the crude product on silica gel. Elution with a solution of 20% ether in n-hexane gave keto thiolester **3**⁴ (896 mg, 84% yield): ir (CHCl₃) 1712 (ketone), 1684 (thiolester), 1600 and 1586 cm⁻¹ (phenyl); nmr (CCl₄) δ 1.52 (s, 3H, CH₃), 2.20 (s, 3H, SCH₃), 2.91, 3.78 (both d, 1H each, J = 18 Hz, CH₂), and 7.24-7.78 (m, 4H, aromatic); ms M⁺ 220.0555 (calcd. for C₁₂H₁₂O₂S: 220.0558).

A variety of β -keto thioesters and alkyl halides were examined, as summarized in Table 1. Elevated temperatures (i.e. refluxing 1,2-dimethoxyethane) were required when less reactive alkyl halides such as ethyl iodide (Entry 6) or isopropyl iodide (Entry 11) were used. Electrophiles other than alkyl halides could also be used. For example, treatment of the carbanion derived from 4-methylthiocarbonyl-5-nonanone (Entry 14) with benzoyl peroxide in benzene at room temperature for 16 hr gave the benzoyloxy derivative **8** in 90% yield.

Table 1. Substitution reactions of β -keto thiolesters.

Entry	β -Keto Thiolester ⁵	Electrophile	Time (hr)	Product (% yield)
1		$C_6H_5CH_2Br$	7	 1 R = $C_6H_5CH_2$ (88)
2		$CH_2=CHCH_2Br$	12	R = $CH_2=CHCH_2$ (88)
3			1	R =  (76)
4		$BrCH_2COOC_2H_5$	16	2 R = $CH_2COOC_2H_5$ (81)
5		CH_3I	2	 R = CH_3 (77)
6		C_2H_5I	3	R = C_2H_5 (85)
7		CH_3I	10	 3 R = CH_3 (84)
8		CH_3I	5	 4 R = CH_3 (88)
9		$BrCH_2COOC_2H_5$	16	5 R = $CH_2COOC_2H_5$ (70)
10		CH_3I	10	 two epimers (2:1) (73)
11	$CH_3(CH_2)_6C(=O)CH_2COSCH_3$	$(CH_3)_2CHI$	16	6 $CH_3(CH_2)_6C(=O)CH(CH_3)COSCH_3$ (88)
12	16-Methylthio-carbonyl-estrone methyl ether	CH_3I	16	 R = CH_3 ⁶ (100)
13		$BrCH_2COOC_2H_5$	16	7 R = $CH_2COOC_2H_5$ ⁶ (97)
14	$CH_3(CH_2)_3C(=O)CH(COSCH_3)(CH_2)_2CH_3$	$(C_6H_5COO)_2$	16	$CH_3(CH_2)_3C(=O)C(OCOC_6H_5)(COSCH_3)(CH_2)_2CH_3$ (90)

Recently we observed that enolizable α -monosubstituted β -keto esters undergo elimination of the thiol ester group when treated with Ra-Ni².

The reductive dealkylthiocarbonylation has now been found to be equally effective for fully substituted compounds.

In all cases (Table 2), the reaction proceeded cleanly and rapidly to completion within 1 hr.

Thus, the reaction of β -keto thiolester 3 (187 mg, 0.85 mmol) with 2 mL (settled volume) of W-2 Ra-Ni⁷ in

benzene (5 mL) carried out at room temperature and under

an argon atmosphere was shown to be complete within 0.5

hr. Filtration (residue washed

thoroughly with benzene and ethanol), concentration, and

column chromatography of the crude product on silica gel

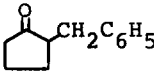
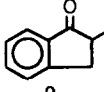
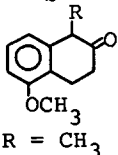
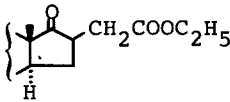
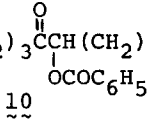
with ether-n-hexane (1:9)

elution gave analytically

pure 2-methyl-1-indanone (9)

in 83% yield.

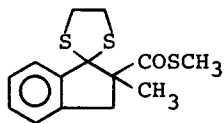
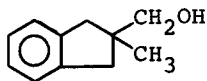
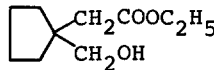
Table 2. Reductive dealkylthiocarbonylation of β -keto thiolesters.

		$\text{RCOCHR}'\text{R}''\text{COSR}''' \xrightarrow[\text{C}_6\text{H}_6; 25^\circ\text{C}]{\text{Ra-Ni (W-2)}} \text{RCOCHR}'\text{R}''$	
Reactant	Time (hr)	Product (% yield)	
<u>1</u>	0.5		(92)
<u>3</u>	0.5		(83)
<u>4</u>	1		(72)
<u>5</u>	0.5	R = $\text{CH}_2\text{COOC}_2\text{H}_5$	(91)
<u>6</u>	0.5	$\text{CH}_3(\text{CH}_2)_6\overset{\text{O}}{\parallel}\text{CCH}_2\text{CH}(\text{CH}_3)_2$	(75)
<u>7</u>	1		(92)
		two epimers (~3:1)	
<u>8</u>	1	$\text{CH}_3(\text{CH}_2)_3\overset{\text{O}}{\parallel}\text{CCH}(\text{CH}_2)_2\text{CH}_3$ 	(91)

The method is operationally simple and employs mild and specific conditions, an essential feature when acid and/or base sensitive functional groups are present. Compounds 5 and 7, for example, underwent smooth demethylthiocarbonylation with the O-ester intact and the reduction of compound 8 gave rise to a 91% yield of α -benzoyloxy ketone 10, a process which may find further use in 1,2-ketone transposition.

Other synthetic applications of β -keto thiolester can easily be anticipated. Transformation of the type $\text{RCOCH}_2\text{R}' \longrightarrow \text{RCH}_2\text{CR}'\text{R}''\text{CH}_2\text{OH}$, for example, can be accomplished in four steps as follows. Thioketalization of 3, prepared in two steps from 1-indanone (*vide supra*), with 1,2-ethanedithiol and boron trifluoride etherate in methylene chloride at 25°C for 20 hr gave quantitatively, thioketal 11 which on treatment with Ra-Ni (16 hr at 25°C) gave alcohol 12 in 75% yield. Similarly, thioketalization of 2 followed by Ra-Ni treatment afforded hydroxy

ester **13**⁸ which on brief treatment (2 hr at 25°C) with 10-camphorsulfonic acid in benzene gave spiro-lactone **14**⁹ in an overall yield of 78%.

**11****12****13****14**

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References and Notes

1. H.O. House, "Modern Synthetic Reactions," 2nd ed., W.A. Benjamin Inc., Menlo Park, CA. 1972, Chapter 9.
2. H.J. Liu and H.K. Lai, *Tetrahedron Lett.*, 1193 (1979).
3. H.J. Liu, S.K. Attah-Poku and H.K. Lai, *Synth. Commun.*, in press.
4. All compounds were adequately characterized by spectroscopic methods and by exact mass measurement and/or elemental analysis.
5. Both 2-ethylthiocarbonylcyclopentanone and 2-ethylthiocarbonylcyclohexanone were prepared by the Dieckmann-type condensation process² and the others by methylthiocarbonylation of the corresponding ketones³.
6. A single isomer was obtained. Its complete stereochemistry remains to be determined.
7. R. Mozingo, *Org. Syn.*, Coll. Vol. 3, 181 (1955).
8. The product is contaminated by a small amount of lactone **14**.
9. It is interesting to note that the nmr spectrum (CCl₄) of this compound showed three singlets at δ 3.99 (2H), 2.31 (2H), and 1.67 (8H).

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