Synthesis of β-Keto Esters by the Reformatsky Reaction of 3-Acyloxazolidin-2-ones and -thiazolidine-2-thiones

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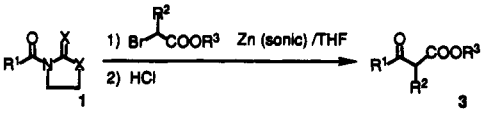
As organozinc reagents are essentially unreactive toward ester carbonyl groups, β-hydroxy esters have been prepared conveniently via the Reformatsky reaction, wherein α-halo esters react with aldehydes and ketones in the presence of zinc.[1] However, the direct synthesis of β-keto esters via the Reformatsky reaction with esters and other carboxylic acid derivatives has never been reported, owing to this property of organozinc compounds.

Recently it was reported that 3-acyloxazolidin-2-ones created a diastereofacial bias by the formation of chelated enolates, which were then utilized in stereoregulated electrophilic reactions[2] and Diels–Alder reactions.[3] These reactions were widely applied to the enantioselective synthesis of various organic substances such as antibiotics[4] and amino acids.[5] Although the acyl group of 3-acyloxazolidin-2-ones is moderately reactive toward nucleophiles, the conversions of 3-acyloxazolidin-2-ones are still limited to the corresponding carboxylic acids, esters, alcohols,[2a] and β-sulfoxy esters.[6] In order to expand the usefulness of these stereoregulated reactions, the development of new conversion reactions for 3-acyloxazolidin-2-ones is highly desirable. Herein, we describe the reactions of various 3-acyloxazolidin-2-ones (**1a–m**) and -thiazolidine-2-thiones (**1n–r**) with organozinc compounds, and in particular the Reformatsky reactions, which give β-keto esters **3**.

3-Acyloxazolidin-2-ones (**1**) were prepared from the corresponding acyl chlorides and oxazolidin-2-one according to Evans' method,[2c] or from the corresponding carboxylic acids **3** in the presence of DCC-DMAP.[7]

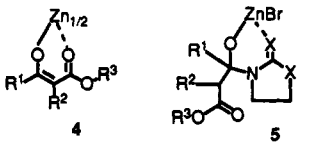
When 3-benzoyloxazolidin-2-one (**1h**) was treated with allylzinc compound, prepared from allyl bromide and zinc,[8] a doubly allylated product, 4-phenyl-1,6-heptadien-4-ol (**2**) was obtained in 91% yield. The reduction of **1h** with zinc borohydride[9] gave benzyl alcohol in 57% yield. These facts seemed to suggest that the reaction of **1** with organozinc compounds proceeds in two steps through keto compounds. On the other hand, **1** was converted into β-keto esters **3** under the Reformatsky reaction conditions, and further reaction with the organozinc compound did not occur. In light of the report that zinc was activated



a: X=O, R¹=Me
b: X=O, R¹=Et
c: X=O, R¹=i-Pr
d: X=O, R¹=t-Bu
e: X=O, R¹=PhCH₂CH₂
f: X=O, R¹=(E)-PhCH=CH
g: X=O, R¹=PhCH₂CH(NHBoc)
h: X=O, R¹=Ph
i: X=O, R¹=p-CH₃C₆H₄
j: X=O, R¹=p-MeOC₆H₄
k: X=O, R¹=MeO
m: X=O, R¹=Me₂N
n: X=S, R¹=Me
p: X=S, R¹=Et
q: X=S, R¹=t-Bu
r: X=S, R¹=Ph

a: R¹=Me, R²=H, R³=Et
b: R¹=Me, R²=H, R³=Bn
c: R¹=Me, R²=Me, R³=Et
d: R¹=Et, R²=H, R³=Et
e: R¹=i-Pr, R²=H, R³=Et
f: R¹=t-Bu, R²=H, R³=Et
g: R¹=PhCH₂CH₂, R²=H, R³=Et
h: R¹=(E)-PHCH=CH, R²=H, R³=Et
i: R¹=PhCH₂CH(NHBoc), R²=H, R³=Et
j: R¹=Ph, R²=H, R³=Et
k: R¹=p-CH₃C₆H₄, R²=H, R³=Et
m: R¹=p-MeOC₆H₄, R²=H, R³=Et
n: R¹=MeO, R²=H, R³=Et
p: R¹=Me₂N, R²=H, R³=Et

by microwave irradiation in the Reformatsky reaction,[10] a mixture of 3-acetyloxazolidin-2-one (**1a**), ethyl bromoacetate, and zinc powder in THF was sonically irradiated and then heated. After workup, ethyl 3-oxobutanoate (**3a**) was obtained as the sole product in high yield. Similarly, oxazolidin-2-ones **1** bearing various acyl groups on the nitrogen atoms were converted into the corresponding β-keto esters **3**. The results are summarized in Table I. From these results, the formation of β-keto esters without further reaction was rationalized by formation of the chelate (**4**) of the resulting β-keto esters with zinc rather than by the formation of zinc chelating intermediate **5**.



Although the use of ethyl and benzyl bromoacetates resulted in the formation of the corresponding β-keto esters in high yields, the yield of β-keto ester was depressed by the use of ethyl 2-bromopropionate. Neither the conjugated double bond, the bulky group, nor the ester carbonyl group on the acyl moiety had any influence on this reaction, and the corresponding β-keto esters were obtained. Even in the cases of 3-(methoxycarbonyl)- (**1k**) and 3-(*N*,*N*-dimethylcarbamoyl)oxazolidin-2-one (**1m**), malonic acid derivatives (**3n** and **3p**, respectively) were exclusively formed. Also, 3-acylthiazolidine-2-thiones (**1n–r**), prepared from thiazolidine-2-thione and acyl chloride, gave the corresponding β-keto esters by treatment with α-bromo esters in the presence of zinc.

When the optically active **1g** (11% ee) was treated with ethyl bromoacetate in the presence of zinc, **3i**, the key

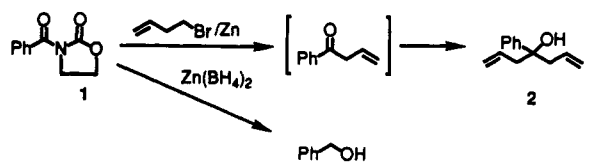


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Table I. Yields of β-Keto Esters 3 by Reformatsky Reaction of 3-Acyloxazolidin-2-ones and -thiazolidine-2-thiones (1)

	1			α-bromo ester		3	
run		X	R^1	R^2	R^3		yield/%[a]
1	1a	O	Me	H	Et	3a	86
2	1a	O	Me	H	Bn	3b	79
3	1a	O	Me	Me	Et	3c	42
4	1b	O	Et	H	Et	3d	64
5	1c	O	*i*-Pr	H	Et	3e	83
6	1d	O	*t*-Bu	H	Et	3f	71
7	1e	O	$PhCH_2CH_2$	H	Et	3g	68
8	1f	O	(*E*)-PhCH=CH	H	Et	3h	51
9	1g	O	$PhCH_2CH(NHBoc)$	H	Et	3i[b]	48
10	1h	O	Ph	H	Et	3j	65
11	1i	O	*p*-$CH_3C_6H_4$	H	Et	3k	67
12	1j	O	*p*-$MeO_2CC_6H_4$	H	Et	3m	40
13	1k	O	MeO	H	Me	3n	53
14	1m	O	Me_2N	H	Et	3p	72
15	1n	S	Me	H	Et	3a	97
16	1n	S	Me	Me	Et	3c	23
17	1p	S	Et	H	Et	3d	39
18	1q	S	*t*-Bu	H	Et	3f	38
19	1r	S	Ph	H	Et	3j	25

[a] Yield was determined by GLC. [b] $[\alpha]^{20}_D$ −6.0° (*c* = 0.74, MeOH). $[\alpha]^{20}_D$ (max) −56.3° (*c* = 2, MeOH) (ref 9).

intermediate in the synthesis of statines,[11] was obtained with 11% ee. This result demonstrated that the present reaction proceeds without any racemization.

It has been demonstrated that the synthetic utility of 3-acyloxazolidin-2-ones and 3-acylthiazolidine-2-thione (1) can be significantly expanded by conversion into the corresponding β-keto esters 3 under the mild Reformatsky conditions.

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Experimental Section

General Procedure. A mixture of 3-acyloxazolidin-2-one or 3-acylthiazolidine-2-thione (1) (2 mmol), zinc powder (1 g), and bromo compound (6 mmol) in dry THF (10 mL) was stirred ultrasonically (30 W, 45 kHz) for 2 h at 30 °C and then refluxed for 18 h under argon. The reaction mixture was acidified, filtered, and extracted with CH_2Cl_2. The organic layer was washed with aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The yields of product were measured by GLC using phenanthrene as an internal standard. Flash column chromatography of the residual crude product on silica gel eluting with benzene–ethyl acetate (30:1 v/v), followed by distillation by Kugelrohr, led to β-keto ester 3. In the case of 2, a hexane–ethyl acetate (10:1 v/v) mixture was used as the eluting solvent. Spectral and chromatographic data of 3 were identical with those of the authentic samples.

4-Phenyl-1,6-heptadien-4-ol (2): bp 200–220 °C (10 mmHg); yield 91%; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.14 (1 H, broad s), 2.66 (4 H, ABX-Oct, *J* = 6.3, 8.2, 12.8 Hz), 5.05–5.12 (4 H, m), 5.53–5.69 (2 H, m), 7.19–7.42 (5 H, m); ^{13}C NMR ($CDCl_3$, 270 MHz) δ 46.8 (CH_2), 75.1 (C), 119.1 (CH_2), 125.3 (CH), 126.6 (CH), 128.1 (CH), 133.4 (CH), 145.7 (C); IR ($CHCl_3$) 3570, 3010 cm^{-1}; MS *m/z* 170 (M^+), 147, 105 (100), 77. Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.68; H, 8.51.

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Supplementary Material Available: ^1H NMR and mass spectral data for 3-acyloxazolidin-2-ones (1a–m), 3-acylthiazolidine-2-thiones (1n–r), and β-keto esters (3a–p) (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.