A Convenient Synthesis of 2-Acylmethyl-4,4-dimethyl-2-oxazolines. Useful Reagents for β-Keto Ester Synthesis

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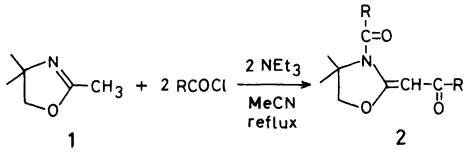
Synopsis. Acylation of 2,4,4-trimethyl-2-oxazoline with acid chlorides having no α-proton and triethylamine gave *C,N*-diacylated products. Hydrolysis of the products with potassium hydroxide gave the enols of 2-acylmethyl-oxazolines, which were selectively *C*-monoalkylated by alkyl halides.

β-Keto esters have been well known as useful starting materials for organic syntheses, and various synthetic methods of β-keto esters were developed.[1] Although 2-oxazoline is also known as the protecting group of carboxylic acids,[2] oxazoline derivatives of β-keto acids are scarcely known. Since 2-oxazoline group can be converted into a variety of functional groups more easily than esters,[3-6] the oxazoline derivatives of β-keto acids are expected to be more versatile starting materials than the corresponding β-keto esters. Here we report a convenient synthesis of this class of compounds by acylation of 2,4,4-trimethyl-2-oxazoline (**1**), which is easily obtained from acetic acid.[7]

Results and Discussion

When **1** was refluxed with two equivalents of benzoyl chloride in the presence of triethylamine in acetonitrile for 3 h, diacylated product **2a** was obtained in 97% yield. By the similar treatment of **1** with other acid chlorides having no α-proton, **1** was converted into the corresponding products **2b—2d** in good yields (Eq. 1). The acid chlorides having α-protons such as acetyl and isobutyryl chlorides did not give **2** due to decomposition of the reagents under the reaction conditions. IR spectra (Table 1) of **2a—2c** show carbonyl bands at 1675—1690 cm^{-1}, which indicate that they are amides (*C,N*-diacylated products) rather than esters (*C,O*-diacylated products). NMR spectra (Table 2) of **2a—2c** suggest that they are mixtures of two geometrical isomers in the solutions. The carbonyl band of **2d** is found at higher frequency, 1750 cm^{-1}. This can be attributed to poor conjugation between the oxazoline nitrogen and the bulky pivaloyl group.

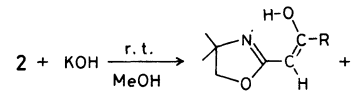


(1)

1 2

2a (R = C_6H_5) 97%, **2b** (R = $C_6H_4NO_2$-p) 99%,
2c (R = 2-furyl) 82%, **2d** (R = t-C_4H_9) 90%.

The diacylated products, **2a—2c** were easily converted into unique enols (**3a—3c**) of 2-acylmethyl-2-oxazolines in good yields by treatment with excess methanolic potassium hydroxide at room temperature (Eq. 2). Hydrolysis of **2d** was carried out by refluxing with potassium hydroxide in ethanol for 30 h. The structure of **3** was determined based on the results of IR, NMR, and elemental analyses (Tables 1 and 2).



(2)

3

3a (R = C_6H_5) 93%, **3b** (R = $C_6H_4NO_2$-p) 95%,
3c (R = 2-furyl) 88%,
3d (R = t-C_4H_9) 57% (under reflux in ethanol).

2-Ethyl-4,4-dimethyl-2-oxazoline was also benzoylated to **3e** (76%) by the similar treatment without isolation of intermediate **2e**. The treatment of 2-benzyl-4,4-dimethyl-2-oxazoline with benzoyl chloride and triethylamine gave **2f** (96%). Hydrolysis of **2f**

TABLE 1. IR SPECTRA AND ELEMENTAL ANALYSES OF THE OXAZOLINES

Compd	Mp θm /°C	IR spectra (Nnjol) ν/cm⁻¹ ν(O–H)	ν(C=O)	ν(C=N or C=C)	Found/% C	H	N	Calcd/% C	H	N
2a	119-120	—	1675	1643	74.71	6.05	4.14	74.74	5.96	4.36
2b[a]	184-185.5	—	1680	1640	58.31	4.35	11.23	58.40	4.32	11.35
2c	148-149 5	—	1690	1640	63.39	5.01	4.58	63.78	5.02	4.65
2d	75-75.5	—	1750	1660	68 10	9.67	4.90	68.29	9.67	4.98
2f	149-152	—	1675	1640	78.75	5.83	3.53	78.57	5.83	3.52
3a	100.5-101	3220	—	1620	72.15	7.00	6.46	71.86	6.96	6.45
3b	163-164.5	3270	—	1620	59.68	5.36	10.74	59.53	5.38	10.68
3c	104-105	3220	—	1635	63 90	6 38	6.67	63.76	6.32	6.76
3d	94.5-95	3290	—	1635	66.86	9.79	7.04	66.97	9.71	7.10
3e	91-93	3240	—	1620	72.89	7 47	6.07	72.70	7.41	6.06
3f	185-186.5	3240	—	1625	78.07	6.65	4.76	77.79	6.53	4.77
3g	106-108.5	3180	—	1615	73 15	7 78	5 41	73.44	7.81	5.71
3h	156-158	3220	—	1635	77 87	6.88	4.45	78.15	6.89	4.56
3i	90-91	—	1690	1660	73.19	7.83	5.70	73.44	7.81	5.71

a) Containing a half molecule of acetonitrile.

TABLE 2. NMR SPECTRA OF THE OXAZOLINE

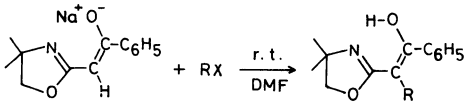
Compound	Isomer[a]	Chemical shifts (δ) in $CDCl_3$: Oxazoline ring protons $(CH_3)_2$	CH_2	α-Proton of 2-substituent	Other protons
2a	A[b]	1.28 (s, 6H)	3.89 (s)	6.37 (s)	7.2-7 8 (m, 10H).
	B	1.66 (s, 6H)	4 36 (s)	5.04 (s)	7.2-7.8 (m, 10H).
2b[c]	A	1 48 (s, 6H)	4.41 (s)	6.10 (s)	7.3-8.4 (m, 8H).
	B	1.59 (s, 6H)	4.51 (s)	4.96 (s)	7.3-8.4 (m, 8H).
2c	A	1 46 (s, 6H)	4.03 (s)	6.01 (s)	6.3-7.6 (m, 6H).
	B	1.60 (s, 6H)	4.30 (s)	5 14 (s)	6.3-7.6 (m, 6H).
2d	A[b]	1.26 (s, 6H)	3.86 (s)	5.78 (s)	1.13 (s, 9H), 1.31 (s, 9H).
2f	A[b]	1.23 (s, 6H)	3.88 (s)	—	7.1-7.7 (m, 13H), 8.0-8.2 (m, 2H).
3a	E[b]	1.42 (s, 6H)	4.12 (s)	5.55 (s)	7.3-7.5 (m, 3H), 7.7-7.9 (m, 2H).
3b	E[b]	1.48 (s, 6H)	4.23 (s)	5.55 (s)	7.98 (d, 2H, J=8.5 Hz), 8.24 (d, 2H, J=8.5 Hz), 10.5 (broad, 1H).
3c	E[b]	1.41 (s, 6H)	4.13 (s)	5.50 (s)	6.47 (dd, 1H, J=3.4 and 1.7 Hz), 6.97 (dd, 1H, J=3.4 and 0.8 Hz), 7.46 (dd, 1H, J=1.7 and 0.8 Hz).
3d[d]	E[b]	1.39 (s, 6H)	3.96 (s)	4.84 (s)	1.05 (s, 9H), 10.1 (broad, 1H).
3e	E[b]	1.41 (s, 6H)	4.13 (s)	—	1.80 (s, 3H), 7.3-7.6 (m, 5H), 10.4 (broad, 1H).
	K	1.19 (s, 3H) 1.22 (s, 3H)	3.85 (s)	4.35 (q, 1H J=6.6 Hz)	1.49 (d, 3H, J=6.6 Hz), 7.3-7.6 (m, 3H), 7.9-8.1 (m, 2H).
3f	E[b]	1.49 (s, 6H)	4.14 (s)	—	7.0-7.2 (m, 10H), 11 (broad, 1H).
3g	E[b]	1.43 (s, 6H)	4.14 (s)	—	0.94 (t, 3H, J=7.3 Hz), 2.22 (q, 2H, J=7.3 Hz), 7.37 (s, 5H), 11.0 (s, 1H)
3h	E[b]	1.46 (s, 6H)	4.10 (s)	—	3.63 (s, 2H), 7.1-7.3 (m, 10H), 11.0 (s, 1H).
	K	1.05 (s, 3H) 1.35 (s, 3H)	3.79 (s)	4.63 (t, 1H, J=7.7 Hz)	3.34 (d, 2H, J=7.7 Hz), 7.0-7.6 (m, 8H), 7.9-8.2 (m, 2H).
3i	K[b]	1.29 (s, 6H)	3.80 (s)	—	1.60 (s, 6H), 7.2-7.5 (m, 3H), 7.9-8.1 (m, 2H).

a) A and B are geometrical isomers. E is an enol isomer and K is a keto isomer. b) Crystals of the compounds consist of only this isomer. c) Measured in DMSO-d_6. d) Measured in CCl_4.

by refluxing with triethylamine in methanol for 3 h gave **3f** in 75% yield. However, a similar treatment of 2-isopropyl-4,4-dimethyl-2-oxazoline with benzoyl chloride gave a ring opening product, 2-benzoylamino-1-isobutyryloxy-2-methylpropane in 67% yield, not *C*-acylated product. The results may be interpreted in terms of lower acidity of the α-proton of the isopropyl group and its higher steric hinderance. A six-membered analogue of **1**, 2,4,4,6-tetramethyl-5,6-dihydro-4*H*-1,3-oxazine was found to be less reactive to the acylating reagent.[8]

A plausible mechanism of the formation of **2** from **1** is as follows: The 2-methyl protons of **1** are activated by quaternarization of the ring nitrogen, and subsequent abstraction of the proton by triethylamine gives a nucleophilic ketene *N,O*-acetal intermediate. The lower reactivity of the dihydrooxazine may be attributed to the more crowded nitrogen. The intermediate is *C*-acylated, and the abstraction of the second α-proton gives less nucleophilic product **2**. When **1** was treated with an equimolar amount of benzoyl chloride and triethylamine, monoacylated product **3a** was not obtained at all, and the yield of **2a** was reduced to 20%. This fact is also consistent with the above mechanism.

On treatment of sodium salt of **3a** with three molar amounts of alkyl halides in DMF at room temperature, *C*-monoalkylated products (**3e**, **3g**, and **3h**) were selectively obtained in good yields (Eq. 3). Since hydroxyl bands, not carbonyl band, are observed at about 3200 cm^{-1} in the IR spectra of **3e—3h**, they are also enols in crystals. The NMR spectra show that they are in the keto-enol equilibria in solutions. Further methylation of **3e** by the similar treatment as above gave the *C,C*-dimethylated product, **3i**, in 78% yield. However, the reaction of **3a** with excess methyl iodide and sodium ethoxide in ethanol gave neither **3e** nor **3i**, but **3a** was recovered. This fact shows that the α-protons of the 2-acylmethyl group of **3** are not so activated as those of β-keto esters. Subsequently, selective monoalkylation can be more easily achieved for **3**.



(3)

3e, **3g**, **3h**

3e (78%, RX=MeI),
3g (92%, RX=EtI; 55%, RX=EtBr),
3h (89%, RX=$C_6H_5CH_2Br$).

These results indicate that the oxazoline derivatives, **3**, of β-keto acids obtained by this method are versatile reagents for β-keto ester synthesis.

Experimental

All the melting points were uncorrected. NMR spectra were recorded on a Hitachi R-20B spectrometer. IR spectra were recorded on a Hitachi infrared spectrophotometer model 260-10. Physical properties of the oxazolines are summarized in Tables 1 and 2.

Benzoylation of 2,4,4-Trimethyl-2-oxazoline 1. Benzoyl chloride (28.4 g, 200 mmol) was added to a solution of **1** (11.3 g, 100 mmol) and triethylamine (25.3 g, 250 mmol) in acetonitrile (200 ml) at room temperature. The mixture was refluxed for 3 h, and the solvent was removed by a rotary evaporator. To the residue 100 ml of water was added and **2a** was extracted with chloroform. The organic layer was washed with 5% aqueous sodium carbonate and water, and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded the crude product. Recrystallization from hexane–benzene (1:1) gave 31.1 g (97%) of pale yellow prisms (**2a**).

2-(β-Hydroxystyryl)-4,4-dimethyl-2-oxazoline (3a). To 100 ml of 1.5 M (1 M=1 mol dm^{-3}) methanolic potassium hydroxide 3.21 g (10 mmol) of **2a** was added at room temperature. After 6 h, precipitates were filtered off, and water was added to the filtrate. The mixture was extracted with chloroform and the organic layer was washed with water, and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation and the residue was recrystallized from hexane–benzene (4:1) to give 2.02 g (93%) of colorless prisms (**3a**).

2-(β-Hydroxy-α-methylstyryl)-4,4-dimethyl-2-oxazoline (3e). To an equimolar amount of sodium ethoxide in ethanol 0.434 g (2 mmol) of **3a** was added and the solvent was removed by rotary evaporation. To the residue 0.85 g (6 mmol) of methyl iodide in 20 ml of DMF was added and the mixture was allowed to stand at room temperature for 5 h. The solvent was removed *in vacuo*, and 5% aqueous sodium carbonate was added to the residue. The mixture was extracted with chloroform. The extract was dried and the solvent was removed. The crude solid was recrystallized from hexane–benzene (4:1) to give 0.360 g (1.56 mmol) of colorless needles (**3e**).

2-(1-Benzoyl-1-methylethyl)-4,4-dimethyl-2-oxazoline (3i). Sodium salt of **3e** prepared from 0.462 g of **3e** and equimolar sodium ethoxide was treated with 0.85 g of methyl iodide in 20 ml of DMF at room temperature for 5 h. The usual workup yielded 0.426 g of colorless needles (**3i**) (87%).

References

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8) Reaction of 2,4,4,6-tetramethyl-5,6-dihydro-4*H*-1,3-oxazine with benzoyl chloride by the similar treatment yields the corresponding diacylated product (mp 166—167 °C) in 11% yield. Hydrolysis of the product to the corresponding enol (mp 81.5—83 °C) required refluxing with ethanolic potassium hydroxide for 5 h (yield 92%).