Syntheses of Novel 1,3-Oxathiolan-5-one Derivatives

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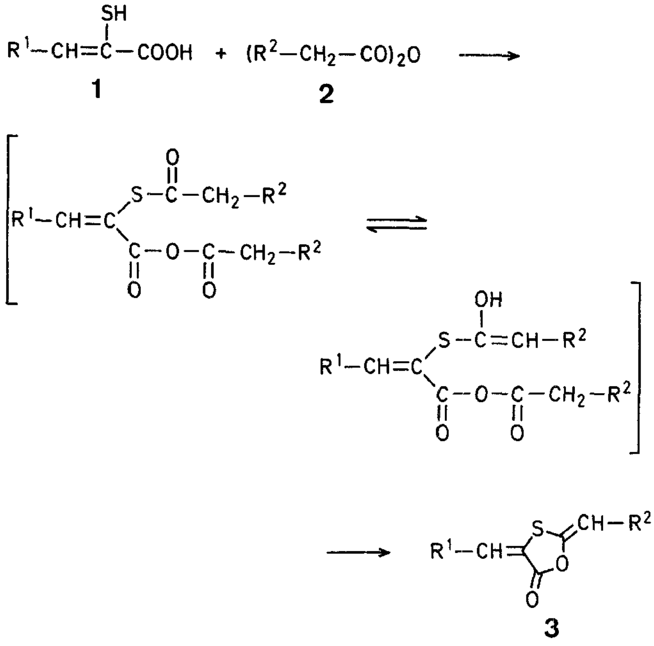
We have shown that β-(3-methyl-5-isoxazolyl)-acrylic acid possesses hypoglycemic and hypolipidemic activities[1]. During our investigations on the synthesis of isoxazolylacrylic acid derivatives and in expectation of stronger activities, we have found that the reaction of α-mercapto-β-(3-methyl-5-isoxazolyl)-acrylic acid (**1a**) with an excess of acetic anhydride (**2**; $R^2 = H$) gave a novel heterocyclic compound, 2-methylene-4-(3-methyl-5-isoxazolylmethylene)-1,3-oxathiolan-5-one (**3a**) in 44% yield. In this paper we report a general procedure for the synthesis of 2-alkylidene -4-arylidene-1,3-oxathiolan-5-ones **3** and their stereochemistry.

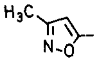
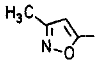
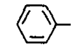
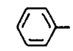
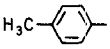
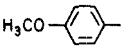
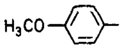
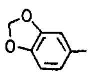
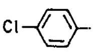
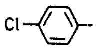
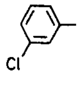


The reaction of β-aryl-α-mercaptoacrylic acids **1** with aldehydes yielding 4-arylidene-1,3-oxathiolan-5-one derivatives is known[2], but hitherto the reaction of the acids **1** with alkanoic acid anhydrides **2** has not been reported. The reaction of several β-aryl-α-mercaptoacrylic acids **1** with alkanoic acid anhydrides **2** were performed and the products characterized by their spectral data and microanalysis (Table). The reaction probably proceeds via the formation of mixed acid anhydride followed by intramolecular acylation.

We have studied the ^{1}H- and ^{13}C-N.M.R. of compounds **3** in detail, especially to determine the stereochemistry of the products. The geometry around R^1 in **3** has only one form because the α-mercaptoacrylic acid (**1**) is fixed predominantly in the (*Z*)-form[3]. Thus, the ^{1}H-N.M.R. spectrum of **3a** showed only one singlet for the vinyl proton on the isoxazolylmethylene group at $\delta = 7.37$ ppm. The signals for the exocyclic vinyl protons appeared at $\delta = 4.65$ and 5.18 ppm as doublets each with $J = 4$ Hz. The presence of the exocyclic double bond at position 2 was also proved by analyzing the ^{13}C-N.M.R. spectrum of **3a**. The signal for a secondary carbon which appeared at $\delta = 89.5$ ppm (singlet on decoupling conditions) split into a triplet on application of off-resonance technique.

The 1,3-oxathiolan-5-one **3b** obtained from the reaction of propanoic anhydride and **1** is an isomeric mixture of **3b′** and **3b″** as shown by its ^{1}H-N.M.R. spectrum. Unfortunately,

Table. 1,3-Oxathiolan-5-one Derivatives **3** prepared

Product No.	R^1	R^2	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3/TMS_{int}$) δ [ppm]
3a		H	44	143–145° (CCl_4)	$C_9H_7NO_3S$ (209.3)	1778	2.35 (s, 3H); 4.65 (d, 1H, $J = 4$ Hz); 5.18 (d, 1H, $J = 4$ Hz); 6.28 (s, 1H); 7.37 (s, 1H)[b]
3b		CH_3	58[c]	133–136° (CCl_4)	$C_{10}H_9NO_3S$ (223.3)	1776	1.74 (d, 3H, $J = 7$ Hz); 1.89 (d, 3H, $J = 7$ Hz); 2.35 (s, 3H); 2.36 (s, 3H); 4.91 (q, 1H, $J = 7$ Hz); 5.64 (q, 1H, $J = 7$ Hz); 6.31 (s, 1H); 6.36 (s, 1H); 7.41 (s, 1H); 7.42 (s, 1H)
3c		H	42	57–59° (CCl_4)	$C_{11}H_8O_2S$ (204.3)	1775	4.51 (d, 1H, $J = 4$ Hz); 5.06 (d, 1H, $J = 4$ Hz); 7.33 (s, 5H); 7.54 (s, 1H)
3d		CH_3	65[d]	45–46° (CCl_4)	$C_{12}H_{10}O_2S$ (218.3)	1772	1.69 (d, 3H, $J = 7$ Hz); 1.85 (d, 3H, $J = 7$ Hz); 4.78 (q, 1H, $J = 7$ Hz); 5.48 (q, 1H, $J = 7$ Hz); 7.1–7.45 (m, 5H); 7.46 (s, 1H); 7.51 (s, 1H)
3e		H	70	91–93° (C_2H_5OH)	$C_{12}H_{10}O_2S$ (218.3)	1774	2.32 (s, 3H); 4.51 (d, 1H, $J = 4$ Hz); 5.05 (d, 1H, $J = 4$ Hz); 7.0–7.4 (m, 4H); 7.55 (s, 1H)
3f		H	42	94–95° (C_2H_5OH)	$C_{12}H_{10}O_3S$ (234.3)	1772	3.8 (s, 3H); 4.51 (d, 1H, $J = 4$ Hz); 5.06 (d, 1H, $J = 4$ Hz); 6.39 (d, 2H, $J = 8$ Hz); 7.35 (d, 2H, $J = 8$ Hz); 7.55 (s, 1H)
3g		CH_3	76[d]	94–96° (C_2H_5OH)	$C_{13}H_{12}O_3S$ (248.3)	1772	1.66 (d, 3H, $J = 7$ Hz); 1.81 (d, 3H, $J = 7$ Hz); 3.8 (s, 3H); 4.8 (q, 1H, $J = 7$ Hz); 5.48 (q, 1H, $J = 7$ Hz); 6.86–7.45 (m, 4H); 7.47 (s, 1H); 7.49 (s, 1H)
3h		H	45	139–141° (CH_3OH)	$C_{12}H_8O_4S$ (248.3)	1775	4.5 (d, 1H, $J = 4$ Hz); 5.05 (d, 1H, $J = 4$ Hz); 5.96 (s, 2H); 6.72–6.96 (m, 3H); 7.42 (s, 1H)
3i		H	30	132–134° (C_2H_5OH)	$C_{11}H_7ClO_2S$ (238.7)	1770	4.56 (d, 1H, $J = 4$ Hz); 5.13 (d, 1H, $J = 4$ Hz); 7.44 (s, 4H); 7.58 (s, 1H)
3j		CH_3	60[d]	116–119° (C_2H_5OH)	$C_{12}H_9ClO_2S$ (252.7)	1770	1.7 (d, 3H, $J = 7$ Hz); 1.85 (d, 3H, $J = 7$ Hz); 4.84 (q, 1H, $J = 7$ Hz); 5.54 (q, 1H, $J = 7$ Hz); 7.4 (s, 4H); 7.46 (s, 4H); 7.52 (s, 1H); 7.54 (s, 1H)
3k		H	50	109–110° (C_2H_5OH)	$C_{11}H_7ClO_2S$ (238.7)	1771	4.6 (d, 1H, $J = 4$ Hz); 5.13 (d, 1H, $J = 4$ Hz); 7.1–7.45 (m, 4H); 7.51 (s, 1H)

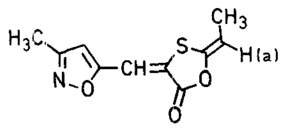
[a] Satisfactory microanalyses obtained: C, ±0.23, H, ±0.26, N, ±0.11; exception: **3a**, C –0.46.

[b] ^{13}C-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 10.7$ (q), 89.5 (t); 106.8 (d); 112.4 (d); 125.0 (s); 145.1 (s); 148.7 (s); 159.3 (s); 163.3 ppm (s).

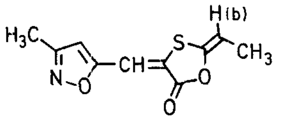
[c] (E/Z)-Ratio around $R^2 = 1.6$.

[d] (E/Z)-Ratio around $R^2 = 1.0$.

these isomers could not be seperated by column chromatography. The estimation of the geometry, (Z)- or (E)-form, around R^2 were performed by the known principle[4]. Namely, the theoretical δ value of proton H(a) for **3b′** and that of proton H(b) for **3b″** in the ^{1}H-N.M.R. spectra, calculated according to the literature[4], are $\delta = 5.28$ and 4.81 ppm, respectively. On the other hand, the signals of the vinyl protons appeared in the ^{1}H-N.M.R. spectrum of the product **3b** at $\delta = 5.64$ (q, $J = 7$ Hz) and 4.91 ppm (q, $J = 7$ Hz) in an integrated ratio of 3 : 5. Thus, the δ-values of the chemical shift for the vinyl protons H(a) and H(b) of **3b** are very similar to that of the theoretical values.



(Z)-**3b′**



(E)-**3b″**

All melting points were recorded with a Yanagimoto micromelting point apparatus and were uncorrected. Spectral data were obtained as follows: I.R. with Hitachi 260-50 spectrophotometer; M.S. with JEOL JMS-01G-2 spectrometer; ^{1}H-N.M.R. and ^{13}C-N.M.R with JEOL-FX 100 spectrometer.

The β-aryl-α-mercaptoacrylic acids **1a–g** were prepared by literature procedure[2]; all are known compounds except **1a**.

α-Mercapto-β-(3-methyl-5-isoxazolyl)-acrylic Acid (1a):

A mixture of 5-(3-methyl-5-isoxazolylmethylene)-rhodanine[5] (16.0 g, 0.07 mol), prepared from 3-methyl-5-isoxazolylcarboxyaldehyde[6] and rhodanine (2-thioxo-4-thiazolidinone), and 15% sodium hydroxide (100 ml) is heated at 90–100 °C for 1 h. After cooling, the mixture is poured into an excess of ice-cold concentrated hydrochloric acid (30 ml). The precipitate formed is collected and recrystallized from methanol/water (1 : 1) to give yellow crystals of **1a**; yield: 9.0 g (69%); m.p. 119–120 °C.

$C_7H_7NO_3S$	calc.	C 45.40	H 3.81	N 7.56
(185.3)	found	45.11	4.28	7.81

I.R. (KBr): $\nu = 2900–2550$ (OH), 1700 cm^{-1} (C=O).

M.S.: (m/e) = 185 (M^+).

2-Alkylidene-4-arylidene-1,3-oxathiolan-5-ones 3; General Procedure:

A solution of β-aryl-α-mercaptoacrylic acid **1** (0.05 mol) in an excess of alkanoic anhydride **2** (50 ml) is heated at 120 °C for 1 h. After cooling, the mixture is concentrated to about 5 ml and poured into ice-cold water (100 ml). The precipitate formed is collected by suction, dried, and recrystallized (Table).

The low melting products **3c** and **3d** are extracted with chloroform (3 × 50 ml), the organic phase is washed with water (50 ml), and dried with sodium sulfate. The residue obtained after removal of the solvent is chromatographed on silica gel column (eluent: chloroform) and recrystallized.

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