A New Synthetic Route to 4-Alkyl-2*H*-1,4-thiazin-3-ones from 2-Methylthiazole

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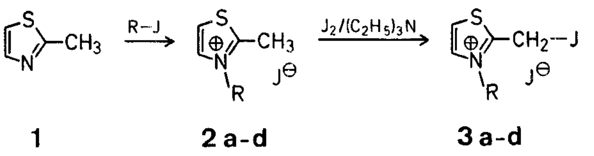
Although 5-methyl[1,2] or 5-pyridyl[2] derivatives of **4** have been synthesized by the reaction of *N*-alkylthioacetamides with chloroacetone or with α-bromoacetylpyridines, respectively, the parent compounds **4** are not accessible in this way.

In connection with some studies in this laboratory, we have found that 4-alkyl-2*H*-1,4-thiazin-3-ones **4** can be prepared easily starting from 2-methylthiazole (**1**).



1 **2a–d** **3a–d** **4a–d**

	a	b	c	d
R	CH_3	C_2H_5	*i*-C_3H_7	$C_6H_5-CH_2$

The key step for this synthesis is a novel skeletal rearrangement of 2-methylthiazole, which proceeds cleanly and the crude products did not show any detectable amounts of other materials as determined by ^{1}H-N.M.R. spectrometry. We now wish to communicate this new synthetic method for the compounds **4**. Conditions for the preparation of **4a–d** are mild and simple, and overall yields are 47–75%. The results are summarized in the Table.

Table. Syntheses of 4-Alkyl-2*H*-1,4-thiazin-3-ones **4**

Product	Yield[a] [%]	b.p./torr	Molecular formula[b]	I.R. (film) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$) δ [ppm]
4a	84 (75)	81°/6	C_5H_7NSO (129.2)	1650	6.26 (d, 1H, *J*=6.9 Hz); 5.61 (d, 1H, *J*=6.9 Hz); 3.31 (s, 2H); 3.13 (s, 3H)
4b	100 (60)	93°/7	C_6H_9NSO (143.2)	1658	6.30 (d, 1H, *J*=7.2 Hz); 5.66 (d, 1H, *J*=7.2 Hz); 3.58 (q, 2H, *J*=7.6 Hz); 3.28 (s, 2H); 1.19 (t, 3H, *J*=7.6 Hz)
4c	85 (47)	115°/7[c]	$C_7H_{11}NSO$ (157.2)	1662	6.36 (d, 1H, *J*=7.7 Hz); 5.66 (d, 1H, *J*=7.7 Hz); 4.92 (d, 1H); 3.28 (s, 2H); 1.17 (d, 6H, *J*=7.1 Hz)
4d	88 (52)	140°/7[c]	$C_{11}H_{11}NSO$ (205.3)	1659	7.26 (s, 5H); 6.26 (d, 1H, *J*=7.2 Hz); 5.63 (d, 1H, *J*=7.2 Hz); 4.74 (s, 2H); 3.35 (s, 2H)

[a] Yield based on **3**; value in brackets is yield based on **1**.

[b] All products give satisfactory microanalyses: (C ±0.2, H ±0.22, N ±0.12, S ±0.3).

[c] Oven temperature.

1,2-Dimethylthiazolium Iodide (2a, R = CH$_3$):

Methyl iodide (182 g, 1.28 mol) is added to a solution of 2-methylthiazole (**1**; 46 g, 0.464 mol) in methanol (100 ml) and the mixture is stirred for 18 h at reflux temperature. After cooling to the room temperature, some ether is added to complete precipitation, then filtration, successive washing with ethanol and ether, and drying in vacuo give the colorless crystalline product; yield: 99.5 g (89%); m.p. 83–84°.

C_5H_8JNS	calc.	C 24.91	H 3.34	J 52.64	N 5.81
(241.1)	found	25.11	3.43	52.41	5.90

^{1}H-N.M.R. (CF$_3$COOH): δ=8.18–7.77 (m, 2H); 4.23 (s, 3H); 3.05 ppm (s, 3H).

1-Methyl-2-iodomethylthiazolium Iodide (3a, R = CH$_3$):

1,2-Dimethylthiazolium iodide (**2a**; 7 g, 29.0 mmol) is suspended in dichloromethane (120 ml) and cooled to 0° in an ice/water bath. With constant stirring, iodine (8.84 g, 34.8 mmol) is added to the suspension and a clear solution is obtained. On adding triethylamine (3.55 g, 34.8 mmol) dropwise to the solution, 1-methyl-2-iodomethylthiazolium iodide precipitates as a brownish yellow powder, which, after filtration and repeated washing with acetone, gives the crude product. Recrystallization from ethanol gives pale yellow needles; yield: 10.7 g (100%); m.p. 115–116° (dec).

$C_5H_7J_2NS$	calc.	C 16.36	H 1.92	H 69.16	N 3.82
(367.0)	found	16.55	2.18	69.01	3.76

^{1}H-N.M.R. (CF$_3$COOH): δ=8.07 (s, 2H); 5.02 (s, 2H); 4.17 ppm (s, 3H).

4-Methyl-2*H*-1,4-thiazin-3-one (4a, R = CH$_3$):

A methanolic solution (40 ml) of potassium hydroxide (1.30 g, 23 mmol) is added to a suspension of 1-methyl-2-iodomethylthiazolium iodide (**3a**; 4.03 g, 11 mmol) in methanol (20 ml) and the mixture is stirred for 30 min at room temperature. After the solvent is removed in vacuo, some water is added to the residue and the whole is extracted with dichloromethane. The crude product (1.19 g, 84%), a dark brown oil and essentially pure (by ^{1}H-N.M.R.), is distilled in vacuo to give pure material; yield: 0.92 g (65%); b.p. 81°/6 torr.

C_5H_7NSO	calc.	C 46.49	H 5.46	N 10.84	S 24.82
(129.2)	found	46.62	5.68	10.96	24.52

M.S.: *m/e* = 129 (M$^+$).

In place of potassium hydroxide in methanol, aqueous solutions of amines (for example, ammonia, *n*-butylamine, or diethylamine) can also be used.

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