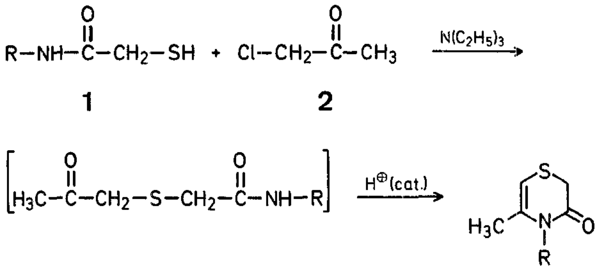
An Improved Method for the Preparation of 5-Methyl-2*H*-1,4-thiazin-3(4*H*)-one and its N-Alkyl Analogs

G. Venkat Rao, K. Szabo, and D.W. Grisley, Jr.

Syracuse Univ. Research Corp., Syracuse, N.Y. 13210, U.S.A.

The title compounds (**3**) were prepared by the reaction of mercaptoacetamides (**1**) with chloroacetone (**2**) and triethylamine:



$$R{-}NH{-}\overset{O}{\overset{\|}{C}}{-}CH_2{-}SH + Cl{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}CH_3 \xrightarrow{N(C_2H_5)_3}$$

$$\left[H_3C{-}\overset{O}{\overset{\|}{C}}{-}CH_2{-}S{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}NH{-}R\right] \xrightarrow{H^{\oplus}(cat.)}$$

3

Conditions for our preparation of **3** are mild, and easily duplicated. In contrast, several attempts to repeat the briefly worded synthesis of the parent heterocycle (**3**, R = H) by the one-step reaction of chloroacetone (**2**) with mercaptoacetamide (**1**, R = H, thioglycolamide) previously reported[1] were unsuccessful in our laboratory. The heterocyclic structure (**3**) for the products was supported by elemental analysis, I.R., and U.V. spectra.

5-Methyl-2*H*-1,4-thiazin-3(4*H*)-one (3, R = H):

A solution of chloroacetone (18.6 g, 0.21 mol) in ether (50 ml) was added during 2 hr to a stirred solution of mercaptoacetamide (18.3 g, 0.20 mol) and triethylamine (20.2 g, 0.20 mol) in absolute ethanol (200 ml) at 5–10° in a dry atmosphere. The stirred reaction mixture was allowed to warm to 20° during 2 hr. The volatiles were evaporated at 50° in vacuo to yield a greasy solid. The solid was triturated with acetone (150 ml), the mixture was filtered, and the solid was washed with acetone. The filtrate was evaporated in vacuo to yield a viscous oil (26 g) [I.R.: 3300 cm^{-1} (NH) and 1640 cm^{-1} (C=O)]. *p*-Toluenesulfonic acid hydrate (0.6 g) was added to a solution of the oil in absolute ethanol (150 ml); the solution was acidic to pH paper. The mixture was heated on the steam bath to 60–70° for 10 min, and cooled in an ice bath; crystallization ensued rapidly. The mixture was filtered to give the crystalline product; yield: 12.7 g (49%); m.p. 143–144° (Ref.[1], m.p. 144°).

I.R. (KBr): ν_{max}, 3015 (NH), 1660 cm^{-1} (C=O).

U.V. (C_2H_5OH): λ_{max}, 295 mμ (ε = 2428).

4,5-Dimethyl-2*H*-1,4-thiazin-3(4*H*)-one (3, R = CH$_3$):

Chloroacetone (0.41 mol) was reacted with N-methyl-mercaptoacetamide (0.4 mol)[3] and triethylamine (0.4 mol) in the usual manner. *p*-Toluenesulfonic acid hydrate (2 g) was added to a solution of the product in toluene (250 ml). The mixture was heated under reflux for 6 hr with the use of a Dean-Stark water separator. The reaction mixture was cooled, and was washed with water (3 × 100 ml). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated in vacuo to yield a red-brown oil. The oil was distilled to give a light-yellow fraction; yield: 35 g (61%); b.p. 88–90°/0.1–0.4 mm; m.p. 32–34° (Ref.[2], b.p. 98°/0.6 mm).

C_6H_9NOS	calc.	C 50.3	H 6.6	N 9.8
	found	50.1	6.4	9.7

I.R. (neat): broad peak at 1665–1670 cm^{-1} (C=O), no absorption in the NH region.

U.V. (C_2H_5OH): λ_{max}, 295 mμ (ε = 2330).

4-Isopropyl-5-methyl-2*H*-1,4-thiazin-3(4*H*)-one (3, R = *i*-C$_3$H$_7$):

N-Isopropyl-mercaptoacetamide was prepared *in situ*[3]. The product was prepared in the same manner as the 4-methyl derivative; yield: 65%; b.p. 102–104°/1–1.2 mm.

$C_8H_{13}NOS$	calc.	C 56.1	H 7.7	N 8.2
	found	55.8	7.7	8.2

I.R. (neat): peak at 1665–1670 cm^{-1} (CO), no NH absorption.

U.V. (C_2H_5OH): λ_{max}, 295 mμ (ε = 2309).

Attempted Preparation of Compound 3 (R = H) according to the Procedure of Sokol and Ritter[1]:

Chloroacetone (9.3 g) was added all at once to powdered mercaptoacetamide (9 g) at room temperature in a dry atmosphere in a flask fitted with a condenser. No external cooling was used. Within 5 min, the temperature of the mixture rose to 114°; gas evolution was vigorous and the reaction mixture was a dark-colored mass. Ice water (50 g) was added to the dark liquid and a dark-colored stiff tar separated. The tar was repeatedly rubbed with a glass rod. No crystallization occurred. The water was decanted and ethanol (25 ml) was added to the tar. The tar dissolved and a negligible amount of solid, m.p. 180°, separated. The experiment was discontinued. – From this and another modified experiment we conclude, that in the procedure given by Sokol and Ritter important experimental details must have been omitted. Thus, the results given in Ref.[1] are impossible to duplicate without rediscovering the conditions used by these authors.

This work was supported by the Esso Research and Engineering Co., Linden, N.J.

Received: October 10, 1971

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