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Synthesis of 3-Mercapto-2(5*H*)-furanones via Reaction of Dilithio-2,4-thiazolidinedione with α-Halo Ketones.

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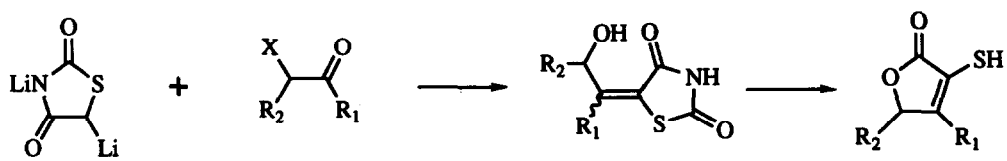
Abstract: A novel synthesis of 3-mercapto-2(5*H*)-furanones is reported based upon the reaction of dilithio-2,4-thiazolidinedione with α-halo ketones. Substitution at the furanone 4- and 5-positions may be controlled by the choice of α-halo ketone.

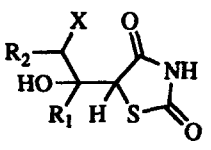
Due to their frequent occurrence in natural products and their synthetic utility, furanones are important synthetic targets and intermediates.[1] The 3-thio-2(5*H*)-furanones are Michael acceptors and annulating reagents useful for the synthesis of complex furanones and natural products.[2] Recently, the corresponding sulfoxides have been utilized for chiral synthesis.[3] To our knowledge the parent 3-mercapto-2(5*H*)-furanones **1** have not been reported in the literature. We report here a synthesis of these compounds via the reaction of dilithio-2,4-thiazolidinedione[4] **2** with α-halo ketones **3**. This reaction produces allylic alcohols **4** which upon base hydrolysis give the corresponding furanones (Scheme 1).[5] Substitution at the furanone 4- and 5-positions may be controlled by the choice of starting α-halo ketone.



2 **3** X=Cl,Br **4** **1**

Scheme 1

The reaction proceeds by nucleophilic addition of dianion **2** to the carbonyl group of α-halo ketone **3** to give a halohydrin intermediate **5** which then cyclizes to an epoxide (e.g. **6**).[6] Under the basic reaction conditions deprotonation of the thiazolidinedione leads to epoxide ring opening and formation of allylic alcohol **4**.[7] Mechanistic evidence was obtained by reaction of the dianion of 5-methyl-2,4-thiazolidinedione with 2-bromoacetophenone to give epoxide intermediate **7** which could not ring open because of the methyl group.[8] In one instance, direct displacement of halogen competed with dianion addition to the carbonyl group; reaction of sterically hindered α-halo ketone **3** (R_1 = *t*-butyl, R_2 = H) gave by-product **8** in 19% yield.



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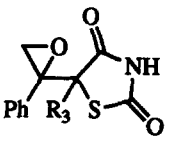
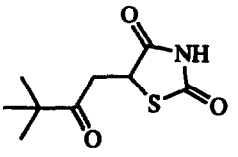


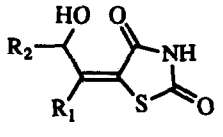
6 R_3 = H

7 R_3 = Me

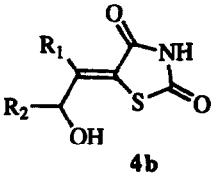


8

The configuration of the intermediate allylic alcohols **4a/4b** is dependent on R_1 and R_2 (Table). If R_1 is large (phenyl or *t*-butyl) a single isomer **4a** was produced. If a less bulky R_1 group was used or if R_2 was not hydrogen the reaction gave a mixture of olefins **4a/4b**.[9] The olefin geometry obtained may be explained by steric interactions between the thiazolidinedione carbonyl and the R_1 and R_2 groups. X-Ray crystallography of **4a** (R_1 = Ph, R_2 = H) provided proof of stereochemistry (Figure).



4a



4b

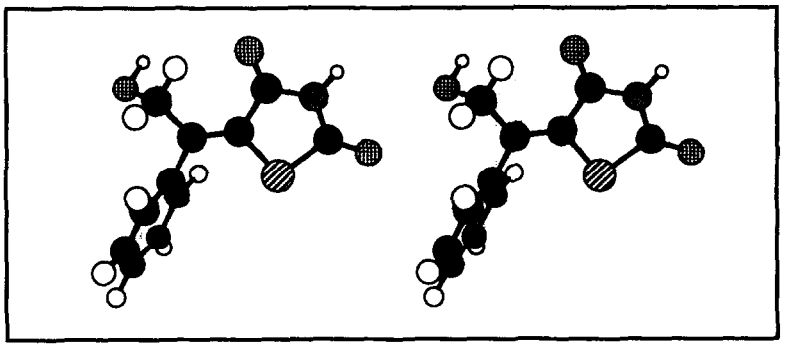
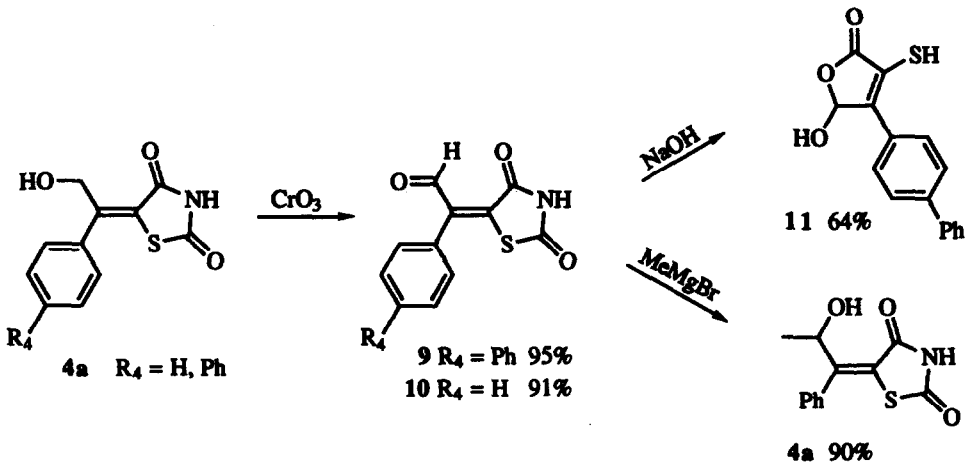


Figure. Stereoview of **4a** (R_1 = Ph, R_2 = H).

Hydrolysis of the allylic alcohols with 1N aqueous sodium hydroxide at 80 °C gave the corresponding 3-mercapto-2(5*H*)-furanones (Table).[10] The reaction proceeds in good yield when R_1 is large; however, yields decrease with decreasing steric bulk. While an aryl or *t*-butyl group is well tolerated, the less bulky *i*-propyl group gave a more moderate yield. A smaller alkyl group such as ethyl gave a low yield and no product was detected when R_1 was methyl.[11]

The 3-mercapto-2(5*H*)-furanones are slowly converted to disulfides upon exposure to air but may be stored indefinitely under nitrogen or converted to the air stable alkylthio analogs. The disulfides may be prepared in quantitative yield by treatment with $Ce(NH_3)_2(NO_2)_4$ (1.1 eq.) in acetonitrile.

Oxidation of the allylic alcohols with excess Jones reagent in acetone at 25 °C gave the corresponding aldehydes (e.g. **9** and **10**) in greater than 90% yield (Scheme 2). Hydrolysis of **9** with 1N NaOH at 80 °C for 45 min gave the 5-hydroxy-3-mercapto-2(5*H*)-furanone **11** in 64% yield. The aldehyde may also be used to introduce substituents at the furanone 5-position. For example, addition of methyl magnesium bromide to the aldehyde **10** in THF gave the allylic alcohol **4a** (R_1 = Ph; R_2 = Me) which may be hydrolyzed to the 5-methyl substituted furanone as before (Table).



Scheme 2

Table. Preparation of Allylic Alcohols and 3-Mercapto-2(5*H*)-furanones.

3			4a/4b		1	
R_1	R_2	X	% yield[a]	ratio[b]	% yield[a]	time (min)
Ph	H	Br	80	100 : 0	83	30
p-Ph-Ph	H	Br	67	100 : 0	62	60
t-Bu	H	Br	55[c]	100 : 0	61	20
1-Naph	H	Br	85	100 : 0	-	-
i-Pr	H	Br	82	79 : 21	34	20
Ph	Me	Br	89	78 : 22	63	180
Et	H	Br	91	72 : 28	10	15
Me	Me	Cl	78	17 : 83	0	20

[a] Yield of purified product. [b] Ratio determined by ^{1}H NMR (ref. 9). [c] **8** isolated in 19% yield

A representative procedure is described: To a 2 L flask containing a solution of 2,4-thiazolidinedione (171 mmol) in THF (1 L) at -78 °C was added *n*-butyllithium (359 mmol, 1.6M in hexane) dropwise over 30 min. The flask was then placed in an ice bath for 45 min to ensure complete formation of dilithio-2,4-thiazolidinedione.[4] Upon cooling to -78 °C a solution of a 2-bromoacetophenone (171 mmol) in THF (200 mL) was added. The reaction mixture was allowed to warm to 25 °C. After 4 h, 1N aqueous HCl was added and the aqueous phase extracted with ether. The ether extracts were dried ($MgSO_4$) and concentrated. Trituration of the resulting gum with EtOAc gave **4a** (R_1 = Ph, R_2 = H) as a solid (23 g). Silica gel chromatography of the washings gave additional product (9 g). ^1H NMR (200 MHz, CD_3CN) δ 4.92 (s, 2H, -CH_2-), 7.3 - 7.5 (m, 5H, PhH). The corresponding furanone was prepared by treatment of **4a** (R_1 = Ph, R_2 = H) (10 g, 42.5 mmol) with 1N aqueous NaOH (200 mL) at 80 °C for 30 min. The mixture was cooled to 0 °C, acidified with HCl (12N, 20 mL) and extracted repeatedly with ether. The ether extracts were concentrated and the resulting solid chromatographed (silica gel) to give **1** (R_1 = Ph, R_2 = H) as a solid (7.0 g). ^1H NMR (200 MHz, $CDCl_3$) δ 4.29 (s, 1H, -SH), 5.17 (s, 2H, -CH_2-), 7.4 - 7.6 (m, 5H, PhH).

In summary, reaction of dilithio-2,4-thiazolidinedione with α-halo ketones leads to an efficient synthesis of substituted 3-mercapto-2(5*H*)-furanones. The corresponding 5-hydroxy-furanones may be prepared by oxidation of the intermediate allylic alcohols to the corresponding aldehydes followed by hydrolysis. In addition, the aldehydes may be used to introduce substituents at the furanone 5-position.

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7. For examples of allylic alcohols formed from α-haloketones and nucleophiles see: De Kimpe, N. and Verhe, R. "The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines"; Patai, S. and Rappoport, Z., Eds.; Wiley: New York, 1988; Chapter 1.
8. Only a single diastereomer was obtained. However, reaction of the dianion with 2-chloroacetophenone gave both epoxide diastereomers.
9. The isomer ratios were determined by ^1H NMR. Allylic protons on groups *cis* to the carbonyl group were assigned the downfield ^1H NMR signals by analogy to known unsaturated carbonyl systems. See for example: Silverstein, R.M.; Bassler, C.G.; Morrill, T.C. "Spectrometric Identification of Organic Compounds", 4th ed.; Wiley: New York, 1981; p 229.
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11. Where low yields were obtained ^1H NMR of the crude reaction mixtures showed complex mixtures of products.

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