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Synthesis of 4-Thiazolidinones From Rhodanines by Thiocarbonyl Removal

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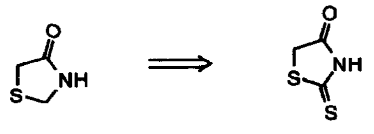
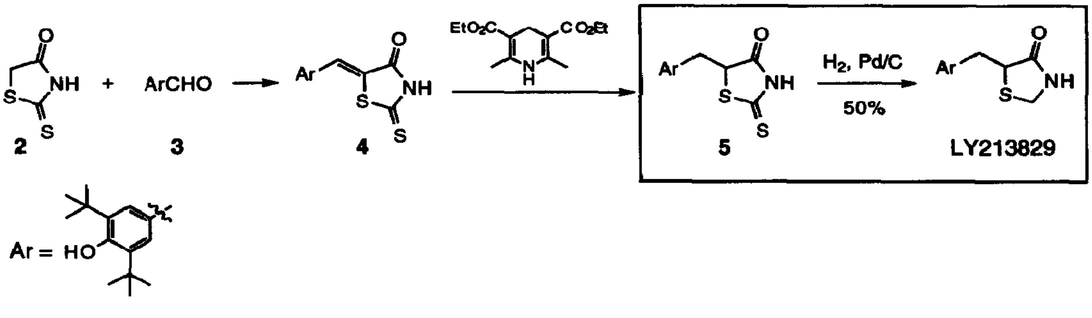
Abstract: A new procedure for synthesis of 4-thiazolidinones from readily available rhodanines is reported. Slow addition of the substrate to excess zinc dust in acetic acid at reflux affords the best yields. Identification of dimeric byproducts led to development of a procedure to suppress their formation.

Thiazolidinones with a carbonyl group at the 2, 4, or 5 position are an important group of heterocyclic compounds with a diverse array of biological activities.[1] Derivatives of 4-thiazolidinone (**1**) in particular have been extensively studied and their chemistry and biology has been reviewed.[2,3] Because rhodanine (**2**) is inexpensive and readily available, it has been used as a precursor to the 4-thiazolidinone ring system as shown in the synthesis of LY213829, which is under investigation for the treatment of inflammatory bowel disease (Scheme I).[4] This general approach is attractive for LY213829 production on larger scale with the exception of the thiocarbonyl removal utilizing hydrogen and palladium on carbon. The reduction requires a large excess of 5% palladium on carbon (340 mass %), harsh conditions (500 psi H_2, 120 °C) and results in only a 50% yield of LY213829.



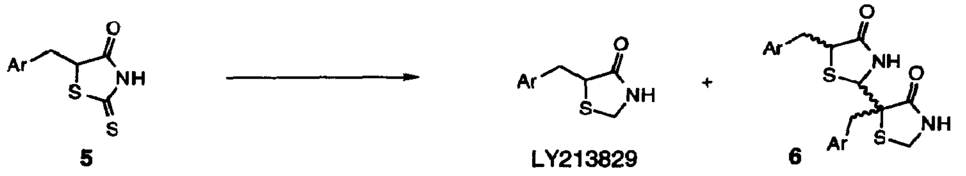
1 **2**

Scheme I



Few other methods are known for conversion of rhodanines to the corresponding 4-thiazolidinone derivatives. Raney nickel reduction affords acceptable yields specifically for 5,5-disubstituted rhodanine derivatives[5] and electrochemical reduction is of questionable practicality.[6] A recent method employing tin hydride to remove a variety of thione groups is ineffective on thioamides that contain an N-H bond as in rhodanine 5.[7] In an isolated example, zinc dust and HCl in ethanol completed the desired transformation, but no yield was given.[8] Application of the zinc/HCl conditions to the conversion of rhodanine 5 to LY213829 led to significant amounts of ring C-S bond cleavage.[9]

Using improved literature procedures,[10] we prepared kilogram quantities of rhodanine 5 for a study of the conversion of 5 to LY213829. When rhodanine 5 was treated with 4 equivalents of zinc dust in acetic acid at reflux for 24 h, complete consumption of rhodanine 5 and formation of LY213829 as the predominant product was observed (eq 1, Procedure A). The reactions were followed closely by HPLC as small amounts of residual 5 were not efficiently removed from the crude product by crystallization. Depending on the activity of zinc dust used, additional zinc dust was required to achieve a level of <1% of rhodanine 5.[11] Two crystallizations of the crude product from ethyl acetate afforded LY213829 (99.5% purity) in 55% yield.



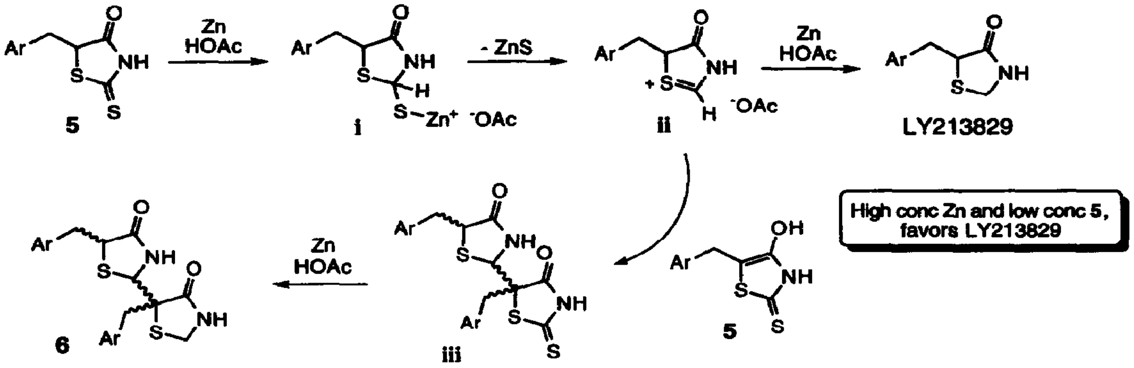
eq 1

Procedure A	4 mol Zn, HOAc, reflux, 24 h	77% (in situ HPLC) 55% crystallized	15% (in situ HPLC)
Procedure B	Add 5 in 5 portions each 1 hr to 5 mol Zn , HOAc, reflux, 16 h	93% (in situ HPLC) 80-85% crystallized	< 2% (in situ HPLC)

Procedure A was effective for production of LY213829 but the isolated yield was only marginal. HPLC analysis of the unpurified product indicated the presence of up to 15% of four major byproducts eluting at a similar HPLC retention time. Two of these four compounds were isolated and identified as stereoisomers with the connectivity shown in structure 6.[12] The stereochemistry of these unique dimeric structures has not been assigned.

A mechanism that could explain formation of compounds 6 is shown in Scheme II. Addition of two electrons from zinc followed by protonation would afford intermediate i. Intermediate i could readily eliminate ZnS to afford the sulfur and nitrogen stabilized carbocation ii. Addition of electrons from zinc followed by protonation would afford the desired product LY213829. However, intermediate ii could react with rhodanine 5 to form the critical C-C bond in the observed byproducts. A subsequent "normal" thiocarbonyl reduction of intermediate iii would afford dimers 6. An implication of this proposed mechanism is that a high concentration of zinc and a low concentration of rhodanine 5 will favor LY213829 formation.

Scheme II



This postulate was readily tested by modifying the reaction conditions as shown in Procedure B (eq 1). Five moles of zinc dust were suspended in acetic acid, and the mixture was heated to reflux. One mole of rhodanine **5** was then added in five equal portions at 1 hour intervals to the reaction mixture. Five equivalents of zinc dust was required to maintain the optimal excess of zinc, presumably because some of the zinc dust is consumed by reaction with acetic acid over the long reaction times. Formation of compounds **6** was dramatically suppressed from 15% to <2% using Procedure B. The crude product was crystallized once from ethyl acetate to afford LY213829 in 80-85% yield.

With efficient conditions for converting rhodanines to 4-thiazolidinones in hand, we applied our method to some additional substrates. The results are summarized in the Table. Noteworthy aspects of the method are: 1) N-H rhodanines, which are not reduced by the tin hydride method,[7] as well as N-alkyl rhodanines are converted to 4-thiazolidinones, 2) 4-thiazolidinone (**1**) can be prepared in higher yield than the literature method,[13] 3) benzylidene rhodanines with and without a conjugated phenol group give different results but neither affords the 4-thiazolidinone cleanly (entries 5 and 6).

General Procedure: To 5 equiv. of zinc dust in acetic acid (5 mL/g of zinc) at reflux, is added 1 equiv. of rhodanine in 5 portions at 30-60 min intervals. After the addition, reflux is continued for 2-24 h. After cooling to 25 °C, Celite is added, and the mixture is filtered through a Celite pad to remove zinc sulfide and zinc acetate. Solvent removal affords the crude products. Due to filtration problems, an alternative procedure is employed for reaction scales of >50 g. Addition of aqueous HCl converts the zinc sulfide to hydrogen sulfide (toxic gas!, scrub with bleach) and the product is isolated by extraction.

In conclusion, a general method has been found for the conversion of readily available rhodanines **2** to 4-thiazolidinones **1** by removal of the thiocarbonyl group with zinc dust in acetic acid. Best yields are obtained using excess zinc dust and adding the substrate in portions to minimize formation of dimeric impurities. Application of this thiocarbonyl removal method to other heterocycles (e.g., hydantoin) and acyclic thioamides and thioimides is under investigation.

ACKNOWLEDGEMENT

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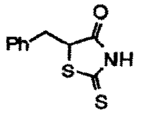
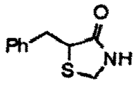
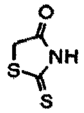
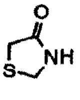
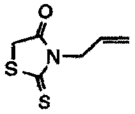
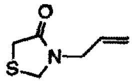
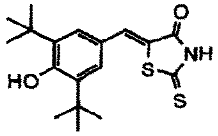
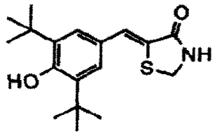
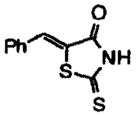
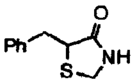
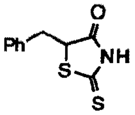
Table. Reduction of Rhodanines With Zn/HOAc, Procedure B

Entry	Substrate	Product(s)	Yield
1	5	LY213829	80-85%
2			92%
3			59%
4			64%
5		LY213829 +  1.5 : 1	90%
6		 +  2 : 1	80%

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7. Williams, D. R.; Moore, J. L. *Tetrahedron Lett.* **1983**, *24*, 339-342.
8. Andreasch, R. *Monatsh. Chem.* **1928**, *49*, 122-132.
9. Phillips, M. L., Eli Lilly and Company, private communication.
10. The procedures disclosed in ref 4 were used except that it was found that silica gel was not required to catalyze step 2 when the concentration of the reaction was increased from 0.07 M to 0.6 M.
11. Suitable quality 325 mesh zinc dust was obtained from Aldrich in the United States and from Southern Zinc Company in Houston, TX. Zinc dust from the Aldrich affiliate in the United Kingdom afforded unacceptably slow reaction rates. Activation by aqueous HCl treatment did not affect the reaction rate. An explanation for this reaction rate dependence on the zinc dust source has not been found.
12. All new compounds were characterized by ^{1}H and ^{13}C NMR, IR and mass spectroscopy as well as elemental analysis.
13. We obtained a 20% yield of 4-thiazolidinone rather than the reported 50% yield by reacting mercaptoacetamide with formaldehyde according to the literature procedure: Ishidate, M.; Hashimoto, Y. *J. Pharm. Soc. Japan* **1956**, *76*, 73-77; Chem. Abstr. **1956**, *50*, 12983.

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