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Preparation of 2-Styrylthiazoles from 2-Methylthiazoles: An Improved Procedure and Mechanistic Aspects

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A Contribution from Pharmaceutical Process Development† and Vitamin Process Research and Development‡

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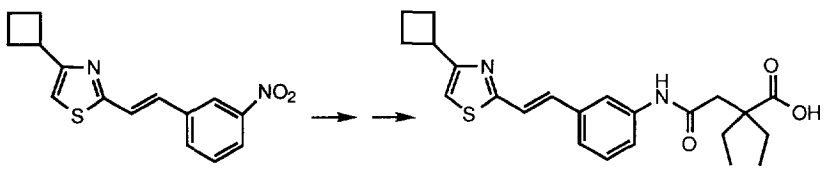
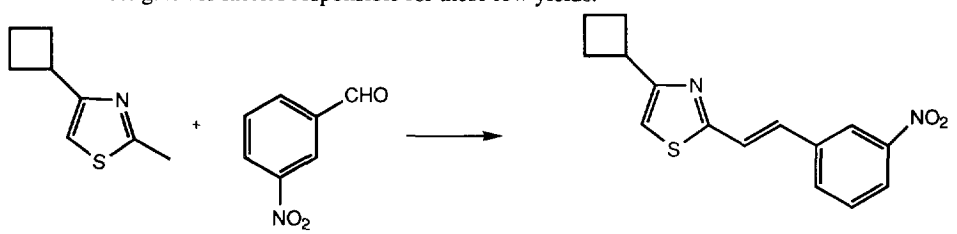
Abstract: *An improved procedure for the preparation of styrylthiazoles from 2-methylthiazoles is described. Using acetic acid as the solvent and the catalyst, yields of 49-80% of styrylthiazoles are obtained. A plausible mechanism is proposed.* Copyright © 1996 Elsevier Science Ltd

Styrylthiazoles and their quaternary salts are important compounds in the industrial preparation of dyes as well as pharmaceuticals.[2,3,4] During development studies on the synthesis of leukotriene antagonist, Ro 24-5913 (**1**), our task was to develop a process for the key intermediate, (E)-4-cyclobutyl-2-[2-(3-nitrophenyl)-ethenyl]-thiazole (**2a**).[3]



2a **1**

A review of the literature for the preparation of styrylthiazoles indicated that a particularly efficient route would be the condensation of 4-cyclobutyl-2-methylthiazole (**3**) with 3-nitrobenzaldehyde. Unfortunately, our survey also revealed that yields in this type of coupling were, in general, consistently less than 50%. For example, in the reaction of 4-substituted-2-methylthiazoles with 3-nitrobenzaldehyde in refluxing acetic anhydride, the yield of the desired alkene ranged from 23-30%.[4] Similar yields were reported by early workers for 2-methylthiazole using zinc chloride as a catalyst.[5] Despite this history, the attractiveness of this route propelled us to investigate the factors responsible for these low yields.

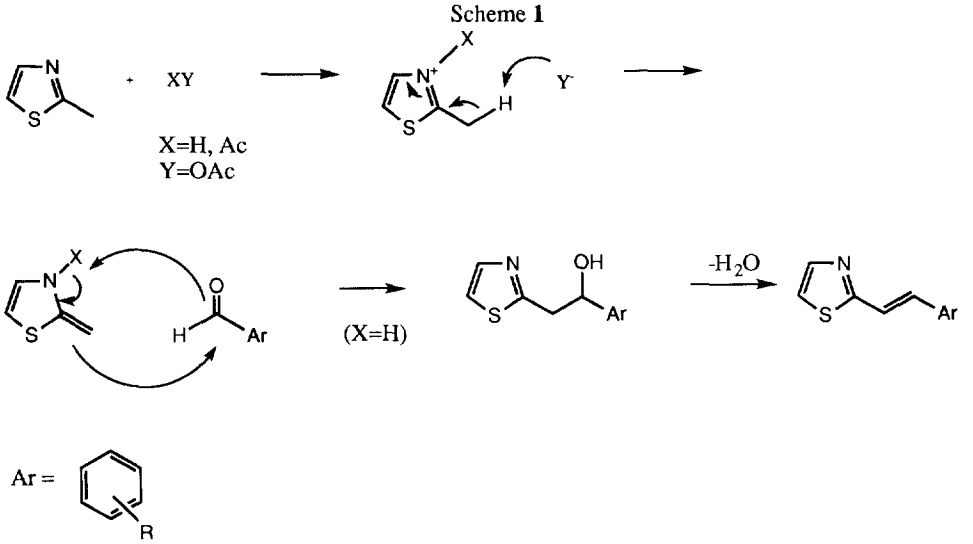


3 **2a**

While this manuscript was in preparation, Pagani and others described the condensation of bis(2-benzothiazolyl)methane with aromatic aldehydes in the presence of sodium acetate with acetic acid as solvent. Good yields (69-78%) of the condensed products were obtained. Owing to the presence of two acidifying thiazole groups, a Knoevenagel-like mechanism was suggested.[6]

Although unsubstituted 2-methylthiazoles are typically deprotonated by strong bases[7], Pagani's work coupled with the traditional acetic anhydride-catalyzed approach to styryl thiazoles led us to consider an alternative role for the electrophilic reagent in this reaction. Our tentative mechanism is shown in Scheme **1**.

Scheme **1**



We rationalized that the electrophilic reagent may serve a dual purpose of acidifying the 2-methyl position of the thiazole ring via complexation with the ring nitrogen[8] and of giving rise to counter ion Y^- which can function as a base to generate the putative enamine intermediate. In the case where X is H, reaction of this intermediate with the aldehyde in an ene-like fashion yields the carbinol. Subsequent dehydration affords the desired alkene.

In the event, reaction of thiazole **3** in the presence of sodium acetate and acetic acid and with an excess of 3-nitrobenzaldehyde afforded a 74% yield of styrylthiazole **2a**.[9-11] Moreover, this reaction could be extended to other aromatic aldehydes. Table I shows the influence of substituents on the conversion and yield. The data shows that increasing the electrophilicity of the aldehyde increases the reaction rate and the yield.

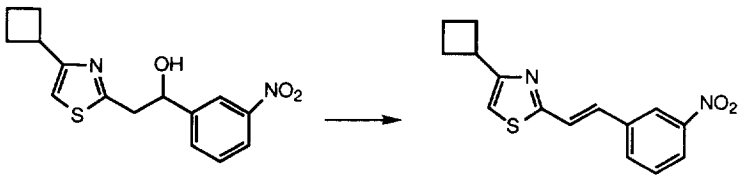
Table I

R	Product	Time	Conversion[a]	Isolated Yield[12,13]
4-NO_2	**2b**	17 hr	100%	80%
3-NO_2	**2a**	28 hr	76%	74%
4-Br	**2c**	48 hr	85%	61%
H	**2d**	96 hr	70%	65.5%
4-OCH_3	**2e**	168 hr	83%	49%
4-$N(CH_3)_2$	**2f**	144 hr	0%	0%

[a]By integrated intensity of the C_5 proton of the starting material and the product.

If our hypothesis was correct regarding the role of the acid catalyst, hydrogen-deuterium exchange should be observed when thiazole **3** was heated in acetic acid-d4. As evident by the integrated intensity of the cyclobutyl methine proton versus the C_2-methyl, greater than 90% exchange occurred in less than 30 minutes at reflux. Interestingly, the rate of this exchange was not influenced by added sodium acetate and this result suggests that internal deprotonation of the complex was faster than external deprotonation by added sodium acetate.

The rapid rate of hydrogen-deuterium exchange and the rate dependency of the condensation reaction on the aromatic aldehyde strongly suggests that the rate determining step was either formation of the carbinol or dehydration of the alcohol. Indeed, by careful chromatography of the reaction mixture during the preparation of **2a** in the early stages of the condensation, we were able to isolate and characterize the intermediate alcohol **4a**.[12] Further, by monitoring the reaction by ^1H NMR, the concentration of this alcohol was shown not to exceed 15% and it was not present at the end of the reaction. The kinetics of the overall reaction are dictated by the condensation step and are consequently determined by the amount and kind of aromatic aldehyde.



4a **2a**

In summary, an improved procedure for the preparation of styryl thiazoles has been described. Of particular note is the use of acetic acid as both solvent and catalyst for this condensation.

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References and Endnotes

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7. For a review see Gschwend, H.W.; Rodriguez, H.R. *Org. React.* **1979**, *26*, 1.

8. The pK_a of 2,4-dimethylthiazole is 3.91. For a discussion see, Metzger, J.V.; Vincent, E.J. "Properties and Reactions of Thiazoles" in *Chemistry of Heterocyclic Compounds, Part One* (J.V. Metzger, Ed.) John Wiley & Sons: New York, 1979.

9. For example **2a**, the hydrobromide salt was used and neutralized *in situ.* It was prepared by the reaction of bromomethyl cyclobutyl ketone and thioacetamide.

10. Except in the case of anisaldehyde, the excess aldehyde was removed by conversion to its bisulfite adduct.

11. **2a** was isolated as its hydrochloride salt.

12. The following is a representative example: Under a nitrogen atmosphere, 3.51 g (0.015 moles) of hydrobromide salt of **3**, 6.80 g (0.045 moles) of 4-nitrobenzaldehyde, 5.05 g (0.06 moles) of sodium acetate in 30 mL of glacial acetic acid were combined and heated to reflux. The course of the reaction was monitored by ^1H NMR. After 17 hours, the reaction was complete and mixture was cooled. Ethyl acetate was added and the reaction was extracted with water and saturated sodium bicarbonate. Excess aldehyde was removed by extraction with saturated sodium bisulfite solution. Chromatographic purification (20% ethyl acetate/ hexane) yielded 3.45 g (80%) of **2b**. An analytical sample was prepared by recrystallization with ethanol and **2b** was obtained as an orange yellow solid (MP 91-93°C).

13. All new compounds gave satisfactory spectral data and either correct microanalysis or high resolution mass spectral data.

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