

**PRODUCT STRUCTURE AS A FUNCTION OF REACTION
CONDITIONS IN THE REACTION OF FORMALDEHYDE WITH AN
ALPHA-MERCAPTO AMIDE**

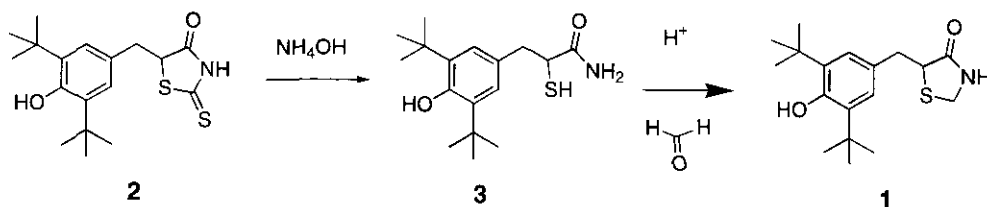
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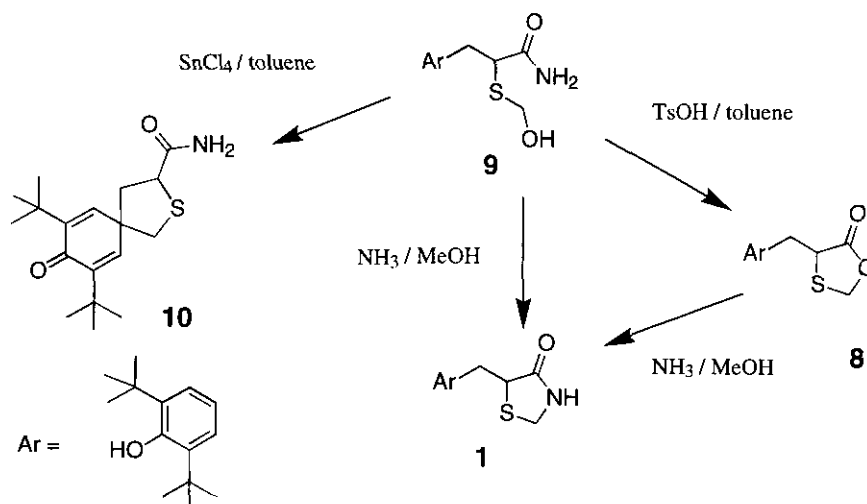
Abstract - Treatment of mercapto amide (**3**) with formaldehyde and acid or base results in products whose structures are a function of the reaction conditions. Lactone (**8**), hemithioacetal (**9**), and dimer (**7**) were formed in good yields under acidic reaction conditions. In addition, dienenone (**10**) was produced from the treatment of (**9**) with strongly coordinating Lewis acids. Treatment of (**9**) with NH_3/MeOH gave the desired thiazolidinone (**1**) in moderate yield.

The BHT-derivative (**1**) is a potent antioxidant and 5-lipoxygenase inhibitor.¹ A previous synthesis of (**1**) utilized a zinc reduction of the thiocarbonyl² of the readily available benzylrhodanine (**2**).³ In order to circumvent the waste disposal issues of the zinc reduction, this effort focused on testing the concept of ammonolysis of (**2**), followed by reaction of (**3**) with formaldehyde to form the thiazolidinone (**1**) (Scheme 1). Preparation of α -mercapto amide (**3**)⁴ was accomplished in 91% yield by treatment of (**2**) with concentrated ammonium hydroxide (Scheme 2). Compounds (**4**, **5**, and **6**)⁵ were formed as by-



Scheme 1

Hemithioacetal (**9**) was examined as a possible intermediate for the preparation of (**1**). Treatment of (**9**) with protic acids resulted in formation of lactone (**8**). The use of coordinating Lewis acids (SnCl_4 or TiCl_4) produced spiroketone (**10**) (Scheme 4 and Table 1).⁹ However, treatment of (**9**) with ammonia



Scheme 4

did result in the formation of (**1**). Subjecting lactone (**8**) to the same reaction conditions also resulted in the production of (**1**) by treatment with ammonia as reported for a similar compound by Abdallah.¹⁰ Some insight into the character of the intermediates in these reactions may be gained by application of Baldwin's rules of ring closure to these observations.¹¹ Under acidic conditions, thioxonium ion (**12**) is a possible intermediate competing with intermediates (**11**) or (**14**) (Scheme 5). Ring closure of (**12**) to (**1**) would require a disfavored 5-endo-trig process. Therefore, (**1**) would not be formed if (**12**) was the intermediate. The minor amounts (<5%) of (**1**) formed under these conditions could result from intermediates (**11**) or (**14**) reacting in a favored 5-exo-tet process. The formation of dimeric structure (**7**) at the expense of formation of the desired 5-membered ring from (**12**) is possible because the formation of (**7**) would not have the same trajectory constraints. The presence of strongly coordinating Lewis acids TiCl_4 or SnCl_4 impact the reaction pathways. Formation of compound (**10**) from (**12**) requires a 5-exo-tet process. This suggest the character of the intermediate is similar to structure (**11**) or (**14**). In addition, this reaction pathway may result from a relative decrease in nucleophilicity of the carboxamide functionality relative to the aromatic ring due to coordination with the Lewis acid. Favored closure of intermediate alcohol (**9**) via a 5-exo-trig process produces lactone (**8**). Formation of (**1**) from compounds (**3**), (**8**) and (**9**) when the reaction mixtures contain ammonia may proceed through a common intermediate, (**15**) (Scheme 6).¹² Table 1 is a summary of the products and yields from the various reactions of (**3**) and (**9**).

In summary, the original goal of synthesizing (**1**) *via* the route in Scheme 1 was realized only under basic conditions. Analysis of the products of this reaction through application of Baldwin's rules suggests different reaction intermediates result from acid and basic reaction conditions.

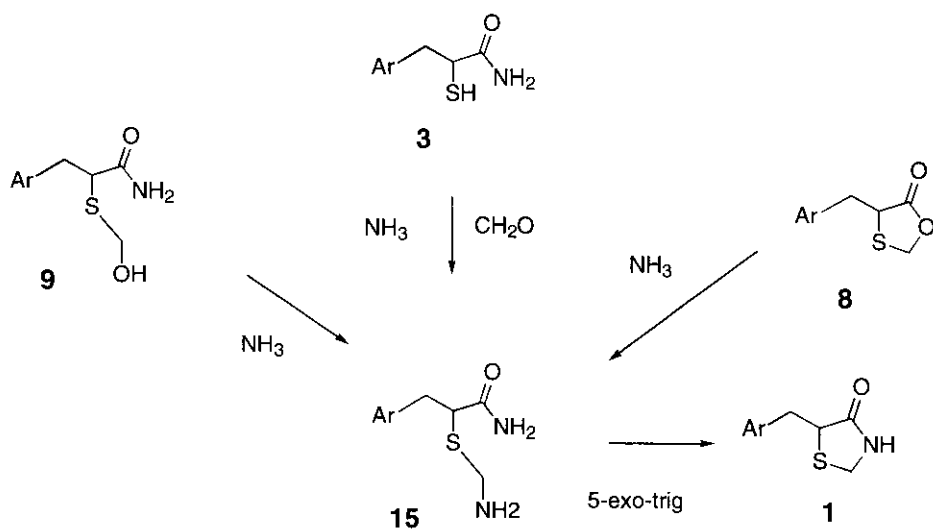
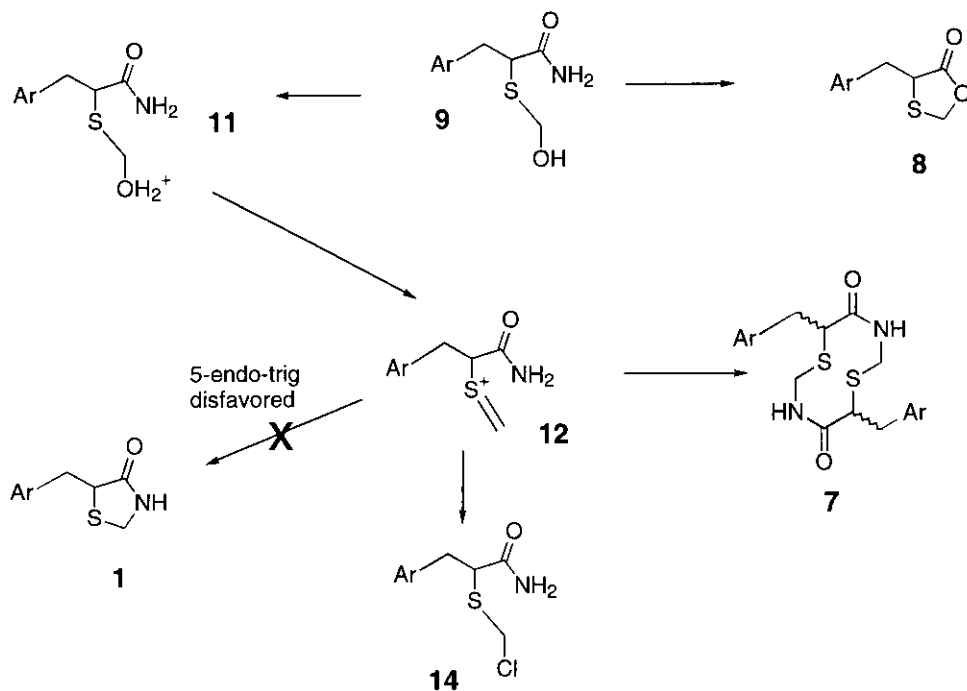


Table 1. A Summary of the Yields of the Products Isolated from Reactions of **3** and **9**

Entry	Starting Material and Reaction Conditions	Product	% Yield
1	3 , paraformaldehyde, toluene TsOH, Δ	8	64
2	3 , formalin, anhydrous NH_3 , MeOH, sealed tube, 60 °C	1	70
3	3 , formalin, HCl (12 M), 70 °C, dioxane	7	99
4	3 , formalin, HCl (12 M), 25 °C, dioxane	9	99
5	9 , SnCl_4 , toluene, 25 °C	10	83
6	9 , TsOH, toluene, D	8	74
7	9 , NH_3 , MeOH, D	1	60

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4. ^1H NMR spectrum of **3**: (300 MHz; CDCl_3): δ 1.42 (s, 18 H), 2.0 (d, 1 H, J = 8.25 Hz), 3.01-2.96 (dd, 1 H, J = 7, 14 Hz), 3.21-3.19 (dd, 1 H, J = 6.5, 14 Hz), 3.5 (m, 1 H), 5.02 (broad s, 1H), 6.08 (broad s), 6.15 (broad s 1 H), 7.01 (s, 2H); IR (CM^{-1}): 1685 (CO), 3641 (OH), 2508, 3406 (amide II); MS: 309 (parent ion).
5. ^1H NMR spectrum of **4**: (300 MHz; CDCl_3): δ 1.4 (s 18 H), 2.8 (dd 1 H, J = 7.6, 14 Hz), 3.1 (dd 1 H, J = 7.3, 14 Hz), 3.4 (overlapping dd 1 H, J = 7.6, 7.3 Hz), 5.13 (s 1 H), 5.6 (broad s 1 H), 5.7 (broad s 1 H), 7.0 (s 2H); IR (CM^{-1}): 1685 (CO), 3640 (OH), 3495, 3382 (amide II), MS: 616 (parent ion); ^1H NMR spectrum of **5**: (300 MHz; CDCl_3): δ 1.41 (s, 18 H), 2.2 (d, 1 H, J = 8.25 Hz), 2.9-3.0 (dd, 1 H, J = 7, 14 Hz), 3.19-3.21 (dd, 1 H, J = 6.5, 14 Hz), 3.58 (m 1 H), 5.19 (s 1 H), 7.0 (s 2 H); IR (CM^{-1}): 1712 (CO) 3641 (OH); MS: 310 (parent ion); ^1H NMR spectrum of **6** (300 MHz; CDCl_3): δ 1.35 (s, 18 H), 2.68-2.77 (dd 1H, J = 10.5, 8.7 Hz) 3.26-3.33 (dd 1 H, J = 3.6, 14 Hz), 4.43-4.48 (dd 1 H, J = 3.6, 10.4 Hz, 6.8 (s 1 H), 6.95 (s 2 H), 8.6 (broad s 1 H), 8.9 (1 H); IR (CM^{-1}): 1680 (CO) 1643 (C=N); MS: 334 (parent ion);
6. Base hydrolysis of this type of chemical system has been previously reported. See: G. S. Skinner, J. S. Elmslie and J. D. Gabbert, *J. Am. Chem. Soc.*, 1959, **81**, 3756.
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8. ^1H NMR spectrum of **7** (300 MHz; d^6 DMSO): δ 1.34 (s 36 H), 2.57 (m 1 H), 2.68 (M 1 H), 2.87-2.92 (m 2 H), 3.62 (t 1 H, J = 2.6 HZ), 3.72 (t 1 H, J = 2.6 HZ), 3.87 (d 1 H, J = 8 HZ), 4.10 (m 1 H),

- 4.49 (broad s 1 H), 4.83 (broad s 1 H), 6.72 (s 2 H), 6.89 (s 4 H), 8.05 (s 1 H), 8.18 (s 1 H); IR (CM⁻¹): 1630 (CO), 3230 (OH), 3620 (NH); MS: 643 (parent peak);); ¹H NMR spectrum of **8** (300 MHz;CDCl₃): δ 1.4 (s 18 H), 3.0 (dd 1H, J = 14, 8.8 Hz), 3.3 (dd 1H, J = 14, 3.8 Hz), 4.0 (dd 1 H,J = 8.8, 3.8 Hz), 4.7 (d 1 H, J = 6.7 Hz) 5.0 (d 1 H, J = 6.7 Hz), 5.2 (s 1 H), 7.1 (s 2 H);); IR (CM⁻¹): 1770 (CO), 3640 (OH); MS: 323 (M+1 parent ion); ¹H NMR spectrum of **9** (300 MHz; d⁶ DMSO): δ 1.4 (s 18 H), 2.9 (dd 1 H, J = 5, 14 H), 3.2 (dd 1 H, J = 9,14 Hz), 3.6 (dd 1 H, J = 5,9 Hz), 4.8 (dt 2 H, J = 6,16 Hz), 5.8 (t 1 H), 6.8 (s 1 H), 7 (s 2 H) 7.08 (broad s 1 H) 7.45 (s 1 H); IR (CM⁻¹): 1672 (CO) 3644, 3627 (OH), 3327, 3135 (amide II); MS: 339 (parent ion).
9. ¹H NMR spectrum of **4**: (300 MHz;CDCl₃): δ 1.22 (s 9 H) 2.2 (dd 1 H, J = 7.2 13 Hz), 2.4 (dd 1 H, J = 8.2, 13 Hz), 2.8 (d 1 H, J = 10.9 Hz), 3.2 1 H, J = 10.9 Hz), 4.1 (dd (overlapping, appears as a triplet) 1 H, J = 7.2, 8.2 Hz), 6.13 (broad s 1 H), 6.63 (broad s 1 H), 6.5 (d 1 H, J = 3 Hz), 6.7 (d 1 H, J = 3 Hz); IR (CM⁻¹):1680, 1658 (CO), 3503 (amide II), MS: 321 (parent ion).
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12. Under the conditions of the reaction, it is possible that **16** is formed from the reaction of the thiol with the imine of formaldehyde generated in situ from **9**.

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