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

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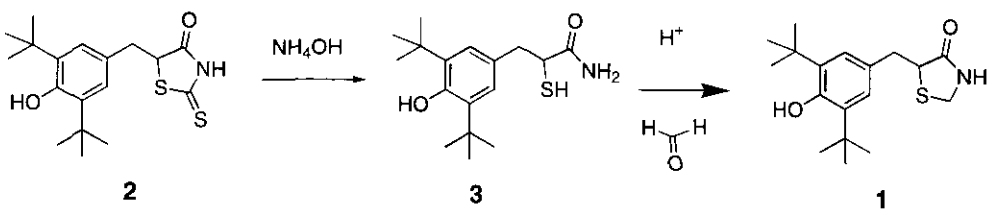
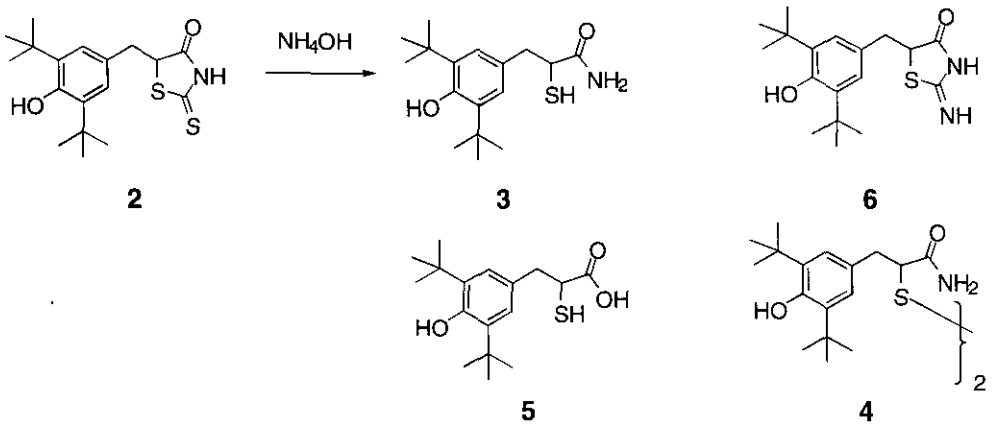
**Abstract** - Treatment of mercapto amide (**3**) with formaldehyde and acid or base results in products whose structures are a function of the reaction conditions. Lactone (**8**), hemithioacetal (**9**), and dimer (**7**) were formed in good yields under acidic reaction conditions. In addition, dienenone (**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 thiocarbonyl[2] 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-




**2** **3** **1**

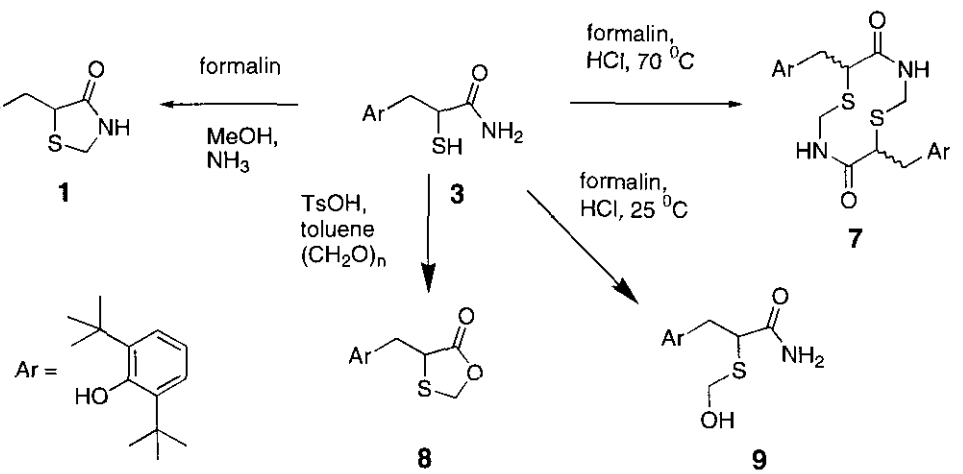
**Scheme 1**




**Scheme 2**

products under these conditions. However, (**4**) could be minimized by the exclusion of oxygen from the reaction vessel. Mercapto acid (**5**) was soluble in the mother liquors and was separated by the crystallization of (**3**). Compound (**6**), isolated from the product by preparative HPLC, could be minimized by extension of the reaction time.[6]

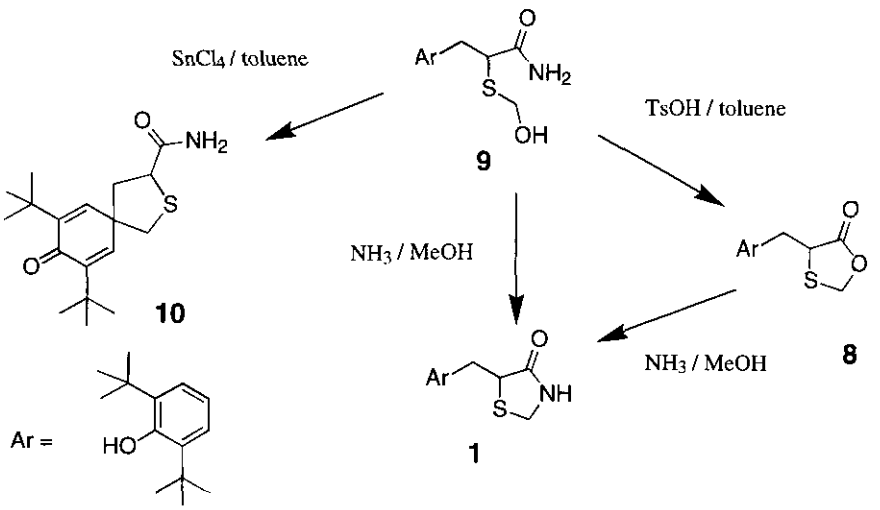
The formation of the 4-thiazolidinone ring system from α-mercapto amides was precedented in the literature. These conditions utilized either tosic acid in benzene at reflux[7a-d] or aqueous hydrochloric acid in dioxane.[6e] However, attempts to cyclize (**3**) according to the literature protocols produced unexpected results (Scheme 3 and Table 1). Attempts to form the 4-thiazolidinone ring under acidic conditions




**Scheme 3**

resulted in predominant formation of either lactone (**8**), hemithioacetal (**9**) or dimer (**7**) as a mixture of diastereomers.[8] The desired product (**1**) was formed in only minor amounts. The presence of excess ammonia was required to produce (**1**) in high yield.

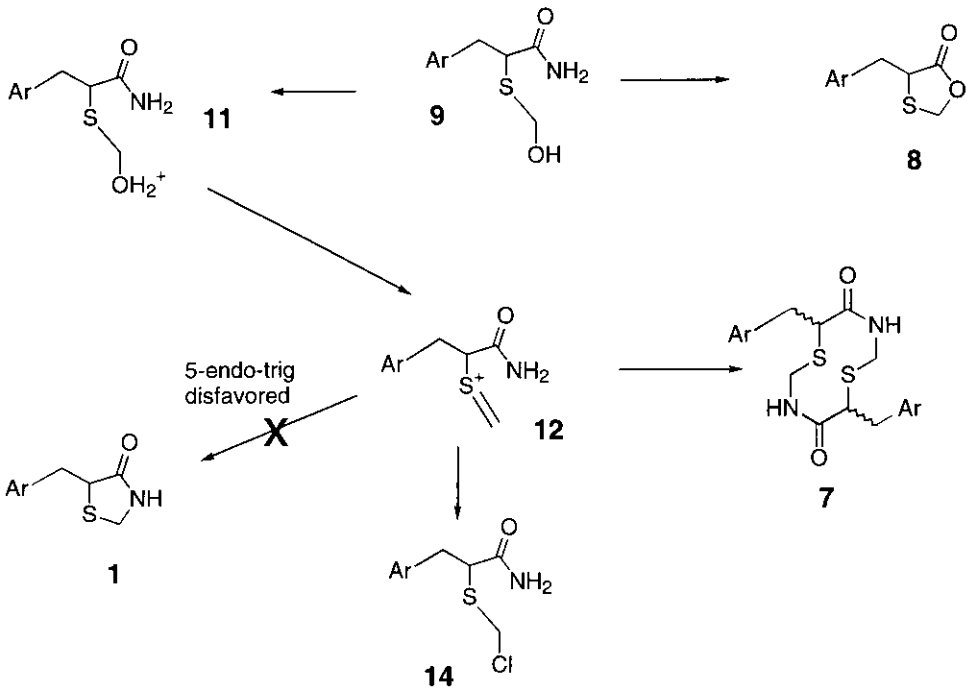
Hemithioacetal (**9**) was examined as a possible intermediate for the preparation of (**1**). Treatment of (**9**) with protic acids resulted in formation of lactone (**8**). The use of coordinating Lewis acids ($SnCl_4$ or $TiCl_4$) produced spiroketone (**10**) (Scheme 4 and Table 1).[9] However,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



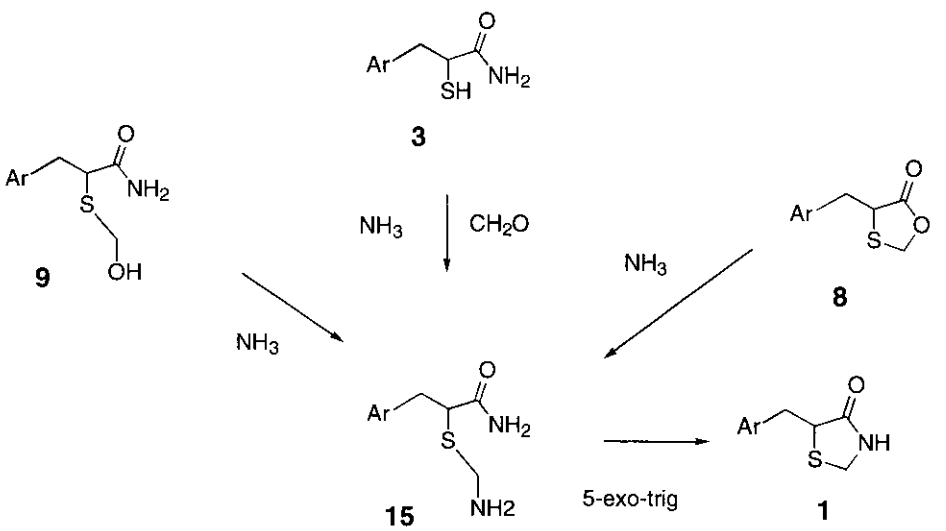

**Scheme 4**

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 nucleophilicty 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.




**Scheme 5**




**Scheme 6**

**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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3. M. L. Phillips, D. M. Berry and J. A. Panetta, *J. Org. Chem.*, 1992, **57**, 4047.
4. $^1$H 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. $^1$H 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); $^1$H 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); $^1$H 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.
7. a) R. K. Clarke Jr. and J. R. Schenk, *Arch. Biochem. Biophys.* 1952, **40**, 270; b) M. Ishidate and Y.Hashimoto, *J. Pharm. Soc. Japan,* 1956, **76**, 73; c) F. C. Pennington, W. D. Celmer, W. M. McLamore, V. V. Bogert and I. A. Solomons, *J. Am. Chem. Soc.*, 1953, **75**, 109; d) T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, T. Kohagizawa and H. Inoue, *Heterocycles,* 1978, **9**, 831; e) G. S. Skinner and J. C. James, *J. Org. Chem.*, 1961, **26**, 1450.
8. $^1$H 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;$CDCl_3$): 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; $d^6$ 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;$CDCl_3$): 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).
10. A. H. Harhash, M. H. Elnagdi and S. O. Abdallah, *Indian J. Chem.*, 1973, **11**, 128.
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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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