PRESSURE SYNTHESIS OF THIOFORMAMIDE

Eugene H. Axelrod

Merck & Co., Inc.
Rahway, New Jersey 07065

Thioformamide, the simplest of the thioamides, is a low-melting crystalline compound of importance as a synthetic intermediate. FIGURE 1 illustrates the use of thioformamide in its most characteristic role as a starting material for the synthesis of heterocycles.

Simple heating with chloroacetone gives, in virtually quantitative yield, 4-methylthiazole, a pharmaceutical intermediate, and a solvent and weakly basic catalyst with properties similar to those of pyridine. Analogously, reaction with 3-chloro-5-hydroxy-2-pentanone gives 5-hydroxyethyl-4-methylthiazole, immediately convertible to the vitamin thiamine by quaternization of the thiazole nitrogen with the appropriate halomethylpyrimidine.

On the lower left of the Figure is a characteristic pyrimidine-forming reaction,[1] occurring with loss of H_2S. Finally, condensation[2] with an unsaturated ester affords the dihydrothiazine ring system closely related to that of the Cephalosporin antibiotics (the last reaction actually proceeds better with higher thioamides, e.g., thioacetamide). Industrial use of thioformamide has been limited by its instability and by the difficulty of its preparation.

The pure compound[3] is stable at low temperatures, but at ordinary temperatures rapidly melts and polymerizes, with the evolution of hydrogen sulfide, ammonia, and hydrogen cyanide. Both acids and bases catalyze the decomposition, and ammonia evolved during the decomposition causes the decomposition to appear autocatalytic. On the other hand, pure solutions of thioformamide are highly stable. Industrial manufacture (FIGURE 2) involves[3] interaction of formamide and phosphorus pentasulfide, a reaction that has been known for a long time and is rather general for thioamides. Basic by-products lower the yield and, because the product is also not completely stable to the reaction conditions, yields are rarely higher than 50%. Separation from finely divided phosphorus pentoxide introduces further technical problems.

On the laboratory scale, a new, convenient method[4] comprises reaction of ammonia with ethyl thioformate. The product forms in high yield uncontaminated with by-products and thus is obtained in a stable form. The cost of ethyl thioformate unfortunately makes this a high-cost route to thioformamide.

For thioamides in general, another old and useful mode of preparation consists of contacting a basic solution of the corresponding nitrile with hydrogen sulfide; yields are normally quite high (FIGURE 3). The reaction proceeds by addition of hydrosulfide anion to the nitrile followed by proton transfers.

However, in the case of formonitrile, that is, hydrogen cyanide, two difficulties arise. In the first place, hydrosulfide anion must be generated in the presence of unionized HCN, because addition to cyanide ion is an unlikely process. In principle this is possible because H_2S ($pk_1 = 7.2$) is more acidic than HCN ($pk = 9.1$). Nevertheless, the range of useful bases is restricted.

Second, HCN is notoriously subject to base-catalyzed polymerization, and the usual result of placing HCN in contact with base is a more or less rapid

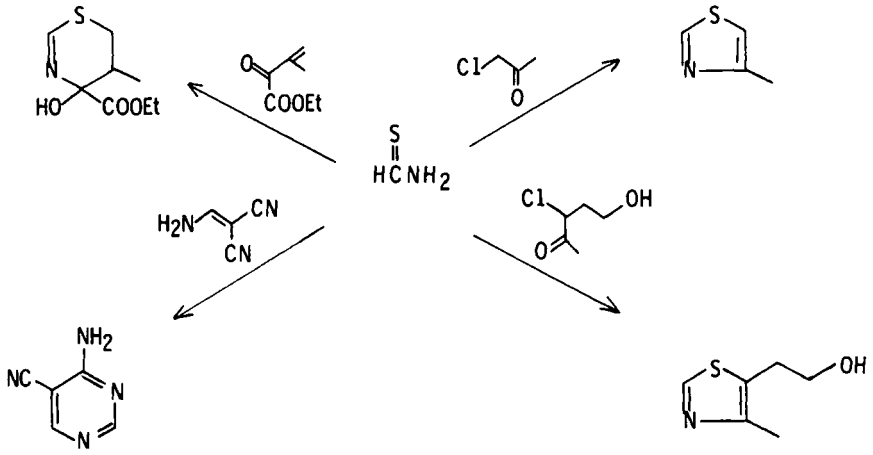

FIGURE 1. Formation of heterocycles from thioformamide.

polymerization to a brownish black amorphous material. Völker[5] formulates the polymerization (FIGURE 4) as proceeding via formation of the (never isolated) dimer, chain-growth, and, perhaps concomitantly, ring closure on one side of the backbone (as illustrated) or on both sides of the backbone. The entire process is first order in base and HCN concentrations.

In agreement with these ideas, attempts to add H_2S to HCN have led mainly to HCN polymer. However, Tull and Weinstock[6] recently reported the successful production of thioformamide through this reaction by using ammonia or tertiary amines as bases. With 15–100 mole% of the basic catalyst, yields as high as 70% of thioformamide were obtained. Judging from the dark colors produced and the cessation of the reactions after several hours, the balance of the HCN is converted to polymer.

In attempting to use this method of preparation, we found great difficulty in isolating thioformamide from solution with reasonable recoveries. The presence of the basic catalyst also destabilized the product solution and suppressed rather completely its further reaction with, for example, chloroacetone.

In an effort to produce base-free solutions of thioformamide, weakly basic ion-exchange resins were tried as catalysts; rather unexpected dividends were obtained in yield and purity. Some typical results are shown in FIGURE 5. The experiment consisted of dissolving liquid HCN in a solvent, here isopropanol,

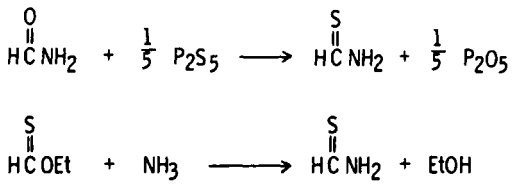

FIGURE 2. Preparation of thioformamide.

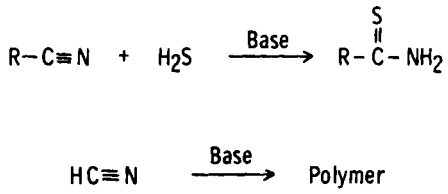

FIGURE 3. General preparation of thioamides.

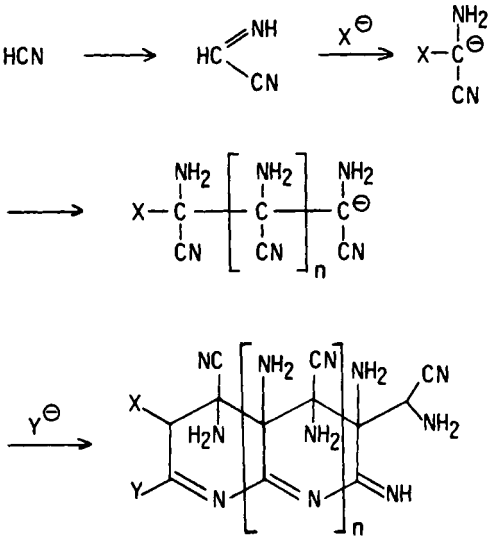

FIGURE 4. Polymerization of hydrogen cyanide (adapted from Reference 5).

Time (hrs)	Temp.	Mole % Resin	HCN Concentration (v/v)	Conversion	Yield
17	22	50	10%	30%	95%
7	35	50	10	35	93.5
17	22	100	10	61	~78
17	22	150	10	60	~76

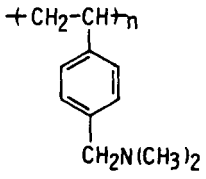

FIGURE 5. Synthesis of thioformamide (50 psig, isopropanol).

adding the resin, pressurizing with H_2S, and shaking under constant H_2S pressure for several hours. Isolation involved a simple filtration from the resin.

The particular macroreticular resin shown contains the dimethylbenzylamine moiety, formed from polystyrene cross-linked with several percent divinylbenzene. The third and fourth entries are not much different from results obtained with soluble amine catalysts, but the first two entries show that very high yields are obtainable by restricting the conversions. Furthermore, the small amount of polymer that does form under these conditions is entirely contained on the resin. This was demonstrated by the use of ^{14}C-labeled HCN. Radioactivity occurring in the product solution was exactly equal to that expected for the sum of the recovered HCN and thioformamide product.

As anticipated, the product solutions, being free of by-products, were completely stable. Also, condensation with chloroacetone, for example, no longer required prior isolation of the product.

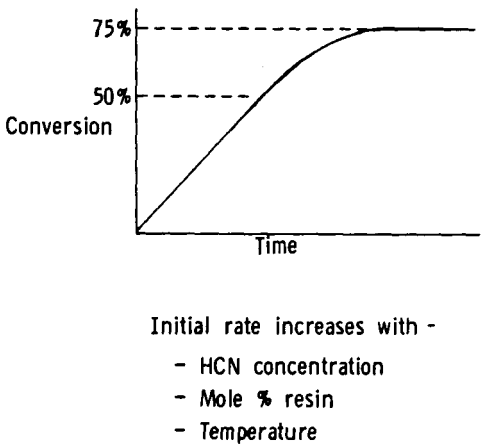

FIGURE 6. Kinetics of resin-catalyzed thioformamide synthesis (schematic).

Weak-base resins, in general, proved to be good catalysts for this reaction; however, there were substantial differences in reaction time and in yield and purity of the product. Insoluble weak bases of other types were much less effective in promoting the desired reaction to the exclusion of HCN polymerization. Among these poor catalysts were weak and strong acid salts of various amines, sodium acetate, phosphines, and the like.

To gain some insight into the mode of action of the resin, some rough kinetic studies were undertaken. Typical results are shown (FIGURE 6) in a schematic manner. The graph refers to an experiment in which a large excess of H_2S was used to simulate constant partial pressure of H_2S. Periodic assays for thioformamide showed a linear time dependence, up to approximately 50% conversion. Within this linear range, the reaction is, therefore, zero order in HCN concentration.

Exploration of the operating parameters showed first that H_2S pressure has little effect on rate, although, of course, ease of handling large quantities of

H_2S dictates the use of pressure. However, the rate increased with temperature in a typical fashion, approximately doubling with a 10° C temperature rise. The rate also increases with the mole percent of resin used, approximately doubling when the mole percent is doubled, although this effect appears to become minor beyond 100 mole% resin.

These results suggest that the reaction rate is controlled by some sort of diffusion process involving the resin. Although no definitive explanation is available, it is reasonable to suppose that it is diffusion of the largest species, thioformamide, away from the resin surface, that is rate limiting.

The suppression of HCN polymerization may also be due to a surface effect: The growing ends of polymer chains that are entangled in the resin beads become unusually inaccessible to further attachment of HCN molecules.

Although these explanations are offered as speculations, they serve to point out once again the difficulty of separating the acid-base properties of a resin from those properties connected in a more complicated manner with its surface geometry.

Thus, thioformamide can be prepared in high yield and purity from hydrogen cyanide and hydrogen sulfide. Although discussed as a batch process, the method is readily adaptable to continuous operation. Limited experimentation also suggests that the method will prove to be a general way for preparing thioamides.

References

1. Baddiley, J., B. Lythgoe & A. R. Todd. 1943. J. Chem. Soc. **1943:** 386.
2. Green, D. M., A. G. Long, P. J. May & A. F. Turner. 1964. J. Chem. Soc. **1964:** 766.
3. Hurd, R. N. & G. Delamater. 1960. Chem. Rev. **60:** 45.
4. Mayer, R. & J. Orgis. 1964. Z. Chem. **4:** 457.
5. Völker, Th. 1960. Angew. Chem. **72:** 379.
6. Tull, R. J. & L. M. Weinstock. 1967. U.S. Patent 3,346,632; 1969. Angew. Chem. Int. Ed. Eng. **8:** 278.

Discussion

Dr. W. Perlman (*Parke Davis, Ann Arbor, Mich.*): You implied that you could apply this reaction to other nitriles. Have you done this? Do you have any yield data?

Dr. Axelrod: The yields refer to only two compounds under one set of conditions per compound. They were good. Acetylnitrile reacts cleanly and so does methylene glutaronitrile, but these are easy compounds to convert to thioamides. Use of a weakly basic amine causes the reaction to be very slow. With these compounds, you can use strong bases, and it probably would have been more efficient to have used a strongly basic amine.

Dr. W. H. Jones: Isn't there an assumingly simple reaction between H_2S and HCN? Hasn't this been studied thoroughly?

Dr. Axelrod: Well, there are reports, attempts to add potassium sulfide to HCN or treat hydrogen sulfide with potassium cyanide and so forth, but only HCN polymer and some oligomers have been isolated.

DR. B. SELIGMAN (*Consultant*): To demonstrate whether or not this is diffusion controlling, did you change the particle size of the resin in any of these experiments?

DR. AXELROD: I did.

DR. SELIGMAN: Or change the agitation?

DR. AXELROD: Increasing the agitation in a couple of experiments in a stirred autoclave did, in fact, increase the rate of the reaction. The results on changing the particle size are not acceptable under these conditions. The particles break up, and it was never clear to me what particle size I had; that is, this factor is more effectively studied in a column without shaking the particles, which are too sensitive to attrition.

DR. W. S. KNOWLES: What happens to your resin after it picks up a lot of polymer? Does it become deactivated quickly? Or does it last for a long time?

DR. AXELROD: It does become deactivated, and if one works at high conversions where a lot of polymer is formed, it eventually becomes impossible to regenerate the resin. But, as long as you maintain a 30–35% conversion, the activity decreases slowly from batch to batch when the same catalyst is used; that is, 35% conversion under one set of conditions, then 33%, then 31%, and so on. However, simple hydroxide treatment always regenerates the resin completely if deactivation does not proceed too far.