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A Novel Synthesis of 1,3,5-Triazine Derivative under High Pressure

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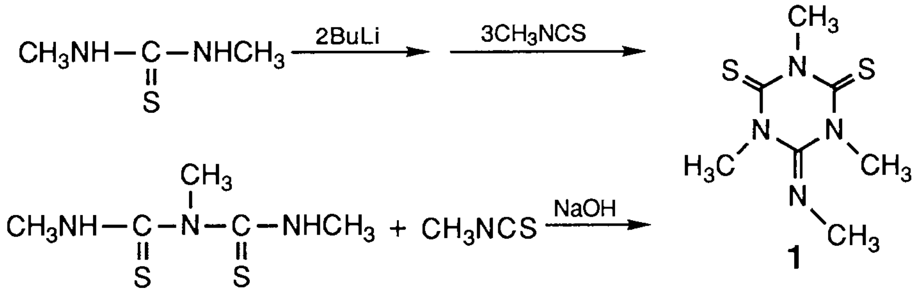
5,6-Dihydro-1,3,5-trimethyl-6-methylimino-1,3,5-triazine-2,4-(*1H,3H*)-dithione (**1**) was synthesized by the reaction of methyl isothiocyanate under high pressure in the presence of Et_3N and H_2O. The yield and selectivity of **1** were seriously effected by pressure, reaction temperature, solvent, and the amount of H_2O.

A large number of studies have been undertaken to prepare 1,3,5-triazine derivatives because they have many applications to various fields.$^{1)}$ The synthetic methods of **1** were reported by Matsumura$^{2)}$ and Joshua,$^{3)}$ however, these methods need strong base and thiourea or dithiobiuret besides methyl isothiocyanate.



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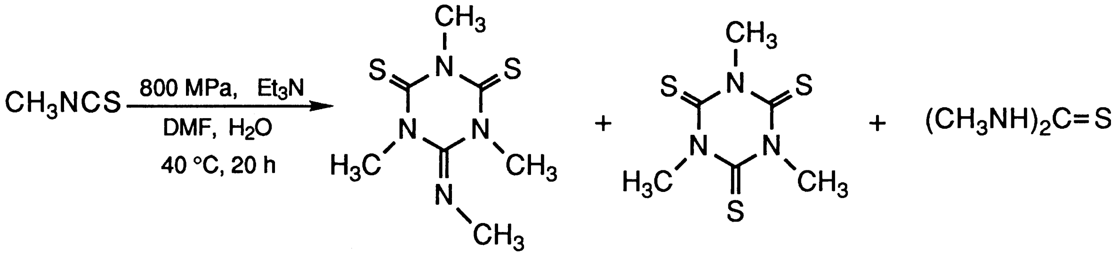
Here we report a convenient preparation of **1** from methyl isothiocyanate under high pressure. A typical procedure was as follows: A homogeneous mixture of methyl isothiocyanate (5 mmol), triethylamine (0.5 mmol), H_2O (10 µl), and DMF (dimethylformamide, 3 ml) in a sealed teflon tube was compressed to 800 MPa, at 40 °C, and for 20 h in a high pressure equipment.$^{4)}$ The resulting mixture was subjected to evaporation and the residue was distilled with Kugelrohr. The distillate, a mixture of **1**, 1,3,5-trimethyl -1,3,5-triazine-2,4,6-(*1H,3H,5H*)-trithione (**2**), and *N,N'*-dimethylthiourea (**3**), was separated by column chromatography on silica gel using a mixture of benzene and ethyl acetate (10:1 v/v) as an eluent.$^{5)}$



1 52% **2** 10% **3** 15%

Table 1 shows the effects of pressure, reaction temperature, reaction time, catalyst, and solvent. The reaction under ordinary pressure gave no products (Run 1), and products of **1**-**3** were formed under 400 MPa (Run 2). This shows that all of **1**-**3** were accelerated by compression, but the yields of **2** and **3** did not increase on the reaction under 800 MPa (Run 4). It is considered that pressure was most effective on the formation of **1**. Product **2** was afforded as a main product at high temperature (Run 5), or using non polar solvent (Run 10, 11). The reaction in the absence of H_2O gave **2** as a main product (Run 7). This agrees with the results of previous report,$^{5)}$ and it means that the formation of **1** was seriously affected by the presence of H_2O.

Table 1. Effects of reaction conditions on the reaction of methyl isothiocyanate under high pressure$^{a)}$

	Press.	Temp	Time	Et_3N	H_2O		Yield/%		
Run	MPa	℃	h	mmol	µl	Solvent	**1**	**2**	**3**
1	0.1	40	20	0.5	10	DMF	0	0	0
2	400	40	20	0.5	10	DMF	17	21	14
3	610	40	20	0.5	10	DMF	48	16	15
4	800	40	20	0.5	10	DMF	52	10	15
5	800	100	20	0.5	10	DMF	6	41	13
6	800	40	1	0.5	10	DMF	33	6	4
7	800	40	20	0.5	0	DMF	4	28	0
8	800	40	20	0	10	DMF	0	0	0
9	800	40	20	0.5	10	CH_3CN	31	15	14
10	800	40	20	0.5	10	IPE$^{b)}$	2	17	21
11	800	40	20	0.5	10	Benzene$^{c)}$	12	68	4
12	1200	30	3	0.1	2	DMF	80	2	trace

a) CH_3CN 5 mmol, catalyst 0.5 mmol, H_2O 10 µl, solvent 3 ml. b) Diisopropyl ether.

c) Solution was inhomogeneous.

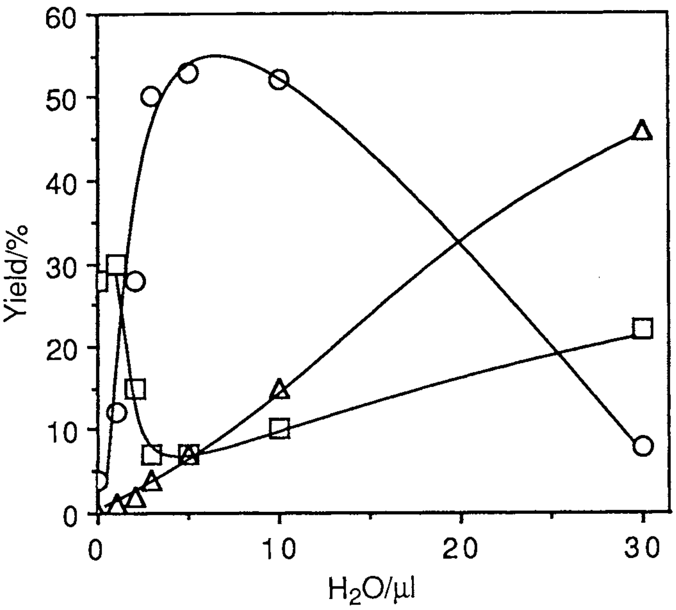
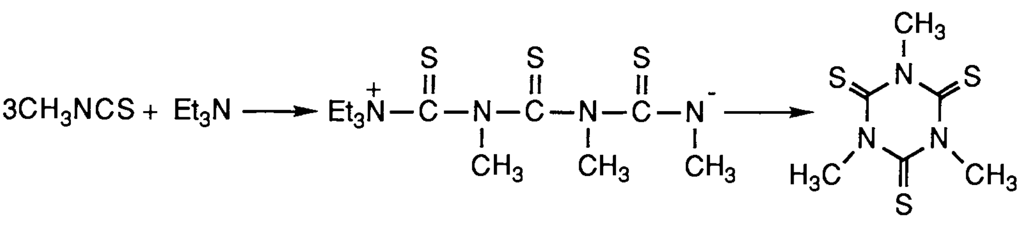


Fig. 1. Effect of amount of H_2O.
CH_3NCS 5 mmol, Et_3N 0.5 mmol,
DMF 3 ml, 800 MPa, 40 °C, 20 h

○ 1
□ 2
△ 3

Figure 1 shows the effect of the amount of H_2O on the reaction of methyl isothiocyanate under high pressure. Yields of **1** and **2** were altered dramatically by addition of H_2O. The yield of **1** increased with amount of H_2O, and got to maximum in the range of 5 µl to 10 µl (0.3-0.6 mmol). It means that about equimolar of H_2O to Et_3N was used. The yield of **2** decreased in inversely proportional to the yield of **1**. Further much amount of H_2O lowered the yield of **1**. The yield of **3** increased in proportional to amount of H_2O. On the base of these results, the reaction of methyl isothiocyanate in the presence of 0.1 mmol of Et_3N and 2 µl of H_2O was carried out under 1200 MPa, and 80% yield of **1** was obtained (Run 12).

The formation of **2** in the presence of triethylamine seems to proceed as follows: At first, triethylamine add to methyl isothiocyanate, and stepwise addition of methyl isothiocyanate and ring closure are followed. This



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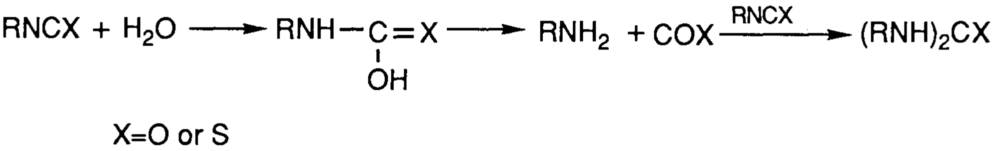

$$RNCX + H_2O \longrightarrow RNH-\underset{\displaystyle OH}{\underset{|}{C}}=X \longrightarrow RNH_2 + COX \xrightarrow{RNCX} (RNH)_2CX$$

X=O or S

mechanism has been estimated on the trimerization reaction of isocyanates7) and isothiocyanates5) under high pressure. It is well known that isocyanates and isothiocyanates react with H_2O to give ureas and thioureas through carbamic acids and thiocarbamic acids. Although the behaviour of H_2O on the formation of **1** was not clear, it seems that H_2O act catlytically since a little amount of H_2O formed **1** in high yield (Table 1, Run 12), and that there is some interaction between H_2O and triethylamine (Fig. 1). Some mechanisms on the formation of **1** can be considered,8) but further study is nescesaly to determine it's mechanism.

Further investigations are in progress in our laboratory on the determination of formation mechanism of **1** and on the applications of this reaction to various isothiocyanates.

References

1) For example: J. M. E. Quirke, "Comprehensive Heterocyclic Chemistry," ed by A. Katritzky and C. W. Rees, Pergamon Press, New York (1984), Vol 3, p457.

2) N. Matsumura, M. Tomura, R. Mando, Y. Tsutiya, and S. Yoneda, *Bull. Chem. Soc. Jpn.*, **59**, 3693 (1986).

3) C. P. Joshua and S. K. Thomas, *Synthesis*, **1982**, 1070.

4) On the apparatus see, M. Kurabayashi, K. Yanagiya, and M. Yasumoto, *Bull. Chem. Soc. Jpn.*, **44**, 3413 (1971); M. Yasumoto, N. Asou, Y. Taguchi, T. Tsuchiya, I. Shibuya, and K. Yonemoto, *Kagaku Gijutu Kenkyusyo Hokoku*, **86**, 163 (1991).

5) The spectral data of **1** agreed with the previous reports.2,3) The structure of **2** has been already determined.6) Product **3** was idetical to the standard sample which was made on the reaction of methyl isothiocyanate with H_2O.

6) Y. Taguchi, M. Yasumoto, T. Tsuchiya, I. Shibuya, and K. Yonemoto, *Nippon Kagaku Kaishi*, **1992**, 383.

7) Y. Taguchi, I. Shibuya, M. Yasumoto, T. Tsuchiya, and K. Yonemoto, *Bull, Chem, Soc Jpn.*, **63**, 3486 (1990).

8) For example, the tetramerization of methyl isothiocyanate followed by cyclization and reconstruction, and the [2+2] cycloaddition of **1** with methyl isothiocyanate followed by reconstruction can be considered.

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