

UNITED STATES PATENT OFFICE

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PROCESS OF PRODUCING SUBSTITUTED
2-AMINO-THIAZOLES

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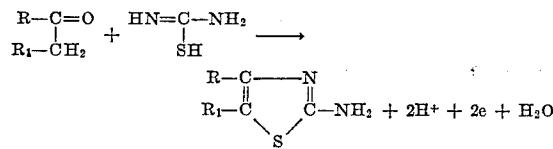
8 Claims. (Cl. 260—302)

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The present invention relates to improvements in the preparation of substituted 2-amino-thiazoles.

In our copending application Serial No. 713,392, filed concurrently with the present application, we have described processes for the production of substituted 2-amino-thiazoles by a reaction between ketones and thiourea or selenourea in the presence of halogens such as chlorine, bromine and iodine.

It has now been found that it is not necessary to have a halogen present, provided that some other substance be present that will accept two electrons for each molecule of 2-aminothiazole formed. Such a reaction will take the following form:

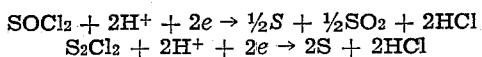


Accordingly, it is an object of the present invention to prepare substituted 2-aminothiazoles by thus reacting suitable ketones with thiourea and oxidizing agents.

Examples of this type of reaction involved the use of a considerable variety of oxidizing agents, namely, sulfonyl chloride, chlorosulfonic acid, thionyl chloride, sulfur monochloride, sulfur trioxide, sulfuric acid, nitric acid, and sulfur. In each case a considerable quantity of 2-amino-4-phenylthiazole was obtained (see the table, hereinbelow). Since some of the above reagents could not possibly produce an intermediary α -haloketone, it is evident that the formation of a

thiazole from a ketone and thiourea can be accomplished by an oxidative process.

In each of the reactions carried out a quantity of sulfur was observed among the by-products. With the exception of reaction 7 (for identification of reactions see the table) in which nitric acid was used as an oxidizing agent, this sulfur could have been formed either from the reduction of the oxidizing agent or from oxidation of thiourea. When sulfonyl chloride (reaction 1) or when chlorosulfonic acid (reaction 2) was used as the oxidizing agent, very little sulfur was formed and the yield of thiazole was good. When thionyl chloride (reactions 3a and 3b) or when sulfur monochloride (reaction 4) was used as the oxidizing agent, a large quantity of sulfur was obtained and a good yield of thiazole was also observed. In these cases, most of the sulfur was probably produced by reduction of the oxidizing agent as follows:



When sulfur trioxide (reaction 5), sulfuric acid (reaction 6) or nitric acid (reaction 7) was used as the oxidizing agent, an appreciable amount of sulfur was formed in each reaction, and in each case the yield of 2-amino-4-phenylthiazole was lower than that obtained with the first four oxidizing agents. In these cases, it appears that two competing reactions are taking place: (1) The reaction of acetophenone with thiourea and the oxidizing agent to form the thiazole, and (2) the direct oxidation of thiourea to form sulfur. This mutual destruction of thiourea and the oxidizing agent could account for the lower yields of 2-amino-4-phenylthiazole obtained in reactions 5, 6, and 7.

TABLE
Summary of reactions ¹

Reaction number	Oxidizing agent	Oxidizing agent, mole	Products			
			2-Amino-4-phenyl thiazole		Sulfur, g.	Other Substances observed
			g.	Per cent ²		
1	SO_2Cl_2	0.2	28.5	81	0.5	$\text{SO}_2, \text{H}_2\text{O}, \text{HCl}$
2	HSO_2Cl	.2	22	63	0.5	Do.
3 (a)	SOCl_2	.2	23	63	3.7	Do.
3 (b)	do.	.1	15.5	58	2.2	Do.
4	S_2Cl_2	.2	27	76	12	$\text{H}_2\text{O}, \text{HCl}$
5	SO_3	.2	11.5	32	5	$\text{SO}_2, \text{H}_2\text{O}$
6	H_2SO_4	.2	15	43	7	Do.
7	HNO_3 (60%)	(excess)	4	11	2	Oxides of nitrogen.
8	S	.2	0.25	0.7	-----	-----

¹ In each reaction 0.2 mole of acetophenone and 0.4 mole of thiourea were used.

² Yield based on ketone or oxidizing agent.

³ Yield based on oxidizing agent only.

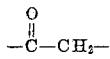
In each case the reaction was carried out as follows: Two-tenths mole of acetophenone and 0.4 mole of thiourea were treated with the indicated amount of the oxidizing agent, and the reaction mixture heated overnight on the steam-bath. The 2-amino-4-phenylthiazole and sulfur were recovered as described by applicants in the Journal of the American Chemical Society, 67, 2242 (1945). The thiazole obtained was compared directly with the 2-amino-4-phenylthiazole produced in accordance with the method described in the copending concurrently filed application. When elementary sulfur was used as the oxidizing agent the reaction mixture was refluxed in Dowtherm, a commercial mixture of diphenyl ether and biphenyl, B. P. ca. 240°.

From the foregoing, it is evident that oxidizing agents are capable of effecting the desired reaction between a ketone such as acetophenone and thiourea. When using some of the other enumerated ketones, corresponding 2-amino-thiazoles are formed by the same reaction, and in good yield.

The products are useful as intermediates in the manufacture of pharmaceutical preparations.

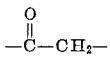
Applicants claim:

1. Process of producing substituted 2-amino-thiazoles which comprises reacting a ketone having the



grouping with thiourea in the presence of a substance capable of accepting two electrons per molecule of the substituted 2 - amino - thiazole formed.

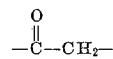
2. Process of producing substituted 2-amino-thiazoles which comprises reacting a ketone having the



grouping with thiourea in the presence of an oxidizing agent.

3. Process of producing 2-amino-4-phenylthiazole which comprises reacting acetophenone with thiourea in the presence of an oxidizing agent.

4. Process of producing substituted 2-amino-thiazoles which comprises reacting one mole of a ketone having the



10 grouping with at least two moles of thiourea in the presence of a substance capable of accepting two electrons for each molecule of the substituted 2-amino-thiazole formed.

15 5. Process of producing 2-amino-4-phenylthiazole which comprises reacting 1 mole of acetophenone with 2 moles of thiourea in the presence of a sulfur-containing oxidizing agent.

20 6. Process of producing 2-amino-4-phenylthiazole which comprises reacting 1 mole of acetophenone with 2 moles of thiourea in the presence of chlorosulfonic acid.

25 7. Process of producing 2-amino-4-phenylthiazole which comprises reacting 1 mole of acetophenone with 2 moles of thiourea in the presence of sulfonyl chloride.

30 8. Process of producing 2-amino-4-phenylthiazole which comprises reacting 1 mole of acetophenone with 2 moles of thiourea in the presence of thionyl chloride.

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REFERENCES CITED

35 The following references are of record in the file of this patent:

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Number	Country	Date
40 554,428	Great Britain	July 2, 1943

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