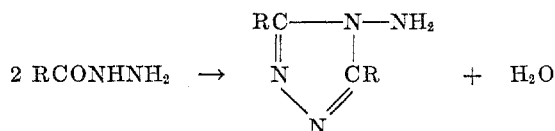


STUDIES ON THE FORMATION OF 4-AMINOTRIAZOLE DERIVATIVES FROM ACYL HYDRAZIDES

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In the course of investigations of polynitrogen heterocyclic systems it became of interest to prepare a number of 4-amino-3,5-dialkyl-1,2,4-triazoles. A search of the literature revealed that no single investigator had prepared a continuous series, nor had any single method been applied to the synthesis of a group of these compounds. The most generally useful reaction appeared to be the self-condensation of monoacyl hydrazides at elevated temperatures with the elimination of water (1-4).



As generally applied the method is rather tedious and involves the preparation of the monoacyl hydrazide by interaction of an ester with hydrazine followed by the thermal self-condensation. For instance, the preparation of 4-amino-1,2,4-triazole (5) requires four to five days. Although the sequence of reactions has almost always been performed in stepwise fashion, there was no apparent reason for not combining hydrazide formation and triazole formation into a single operation.

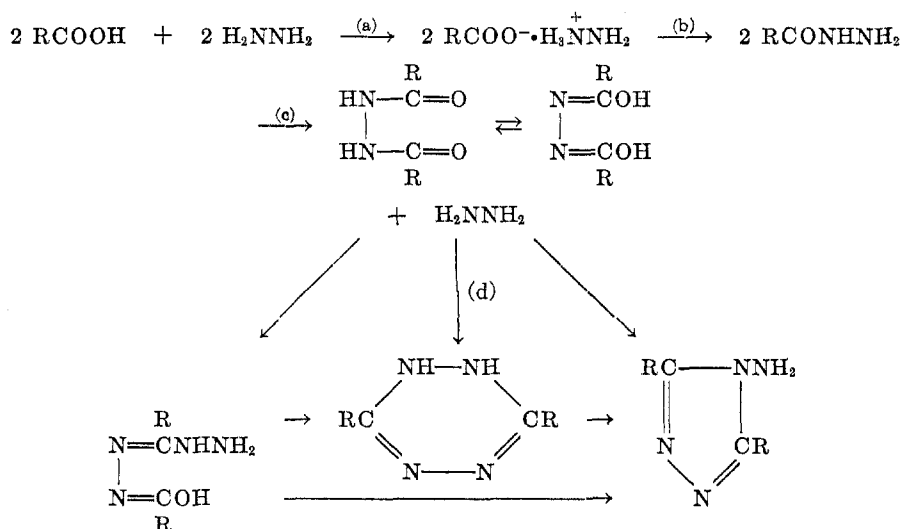
Amide formation can be accomplished easily in many instances by the thermal dehydration of ammonium salts. Since hydrazide formation from hydrazinium salts is essentially analogous to amide formation, it seemed reasonable to anticipate that 4-amino-1,2,4-triazoles could be prepared in a single operation by simply heating a mixture of hydrazine and a carboxylic acid until triazole formation was complete.

When formic acid was heated with an excess of hydrazine hydrate in aqueous solution under conditions permitting the continuous elimination of water by distillation, the formation of formohydrazide and its conversion to 4-amino-1,2,4-triazole were complete in about six hours. The distillation of water and the temperature of the reaction mixture were quite closely associated with the several steps in the reaction. The yield of pure 4-amino-1,2,4-triazole obtainable in this way was about 80%. Acetic acid, propionic acid, and *n*-butyric acid reacted in a similar manner to form the respective 4-amino-3,5-dialkyl-1,2,4-triazoles. The yield, however, decreased progressively as the molecular weight of the acid increased. Steric factors may also influence the yield, since with isobutyric acid

¹ Based on a thesis submitted by James A. Garrison to the School of Graduate Studies at Michigan State College in December 1951 in partial fulfillment of the requirements for the degree of Master of Science.

only diisobutyryl hydrazide could be isolated consistently from the reaction products obtained by this technique. Actually some aminotriazole appeared to be formed but only in one instance could it be separated from the diisobutyryl hydrazide. With benzoic acid and hydrazine hydrate solution only about 10% of the aminotriazole was isolated; the major product was dibenzoyl hydrazide.

Formation of 4-aminotriazoles from carboxylic acids and hydrazine might involve the following steps: (a) Formation of the hydrazinium salt. (b) Dehydration of the hydrazinium salt to form the monoacyl hydrazide. (c) Decomposition of the monoacyl hydrazide with formation of hydrazine and a diacyl hydrazide. (d) Aminotriazole formation by interaction of the diacyl hydrazide, either in the lactam or the lactim form, with hydrazine. Acylated hydrazidines and dialkyl-dihydro-1,2,4,5-tetrazines may be intermediates in this last step. In this connection it may be observed that the formation of 4-amino-3,5-dimethyl-1,2,4-triazole (6) and of 4-amino-3,5-diphenyl-1,2,4-triazole (7) from acyl hydrazidines has been reported.

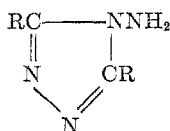


The diacyl hydrazides formed in the reactions with isobutyric and benzoic acid are probably intermediates, as indicated in step c of the reaction scheme, rather than by-products. The formation of little or no 4-aminotriazole derivative in these two instances might be due to a slow reaction between the diacyl hydrazide and hydrazine, possibly due to steric factors, thus permitting too much hydrazine to be removed by distillation. To verify this point it was established that benzhydrazide was converted extensively into dibenzoyl hydrazide on heating at 180° in a sealed tube. No aminotriazole could be isolated from the reaction mixture. Monoisobutyryl hydrazide behaved in the same way. Since hydrazine could not escape under these conditions, another factor, possibly water, which was not present in the sealed tube experiments appeared to be necessary. When either dibenzoyl hydrazide or diisobutyryl hydrazide, as well

as the di-*n*-butyryl and dipropionyl hydrazides were heated with hydrazine hydrate solution in sealed tubes at 180°, approximately 60% yields of the respective aminotriazoles were obtained in each instance. These observations support the postulation of diacyl hydrazides as intermediates during aminotriazole formation from monoacyl hydrazides.

Comparative yields of aminotriazoles obtained by the distillation and by the sealed tube technique are given in Table I. For the lower fatty acids the simplicity of the distillation technique and the availability of starting materials make this the procedure of choice.

TABLE I
FORMATION OF 4-AMINO-3,5-DIALKYL-1,2,4-TRIAZOLES



R	YIELD, %	
	Distillation technique	Sealed tube technique
H	89	—
CH ₃	75	—
C ₂ H ₅	68	64
<i>n</i> -C ₃ H ₇	48	59
iso-C ₃ H ₇	(31) ^a	62
C ₆ H ₅	10	58

^a Obtained in one experiment; in subsequent attempts none of the product could be separated from the reaction mixture.

Although it has been reported that 4-amino-3,5-dimethyl-1,2,4-triazole can be prepared in a single operation from ethyl acetate and hydrazine hydrate at 130° (8), application of this technique to ethyl benzoate did not give satisfactory results. When ethyl benzoate and hydrazine hydrate were heated in a sealed tube at 195° for five days, only 22% of 4-amino-3,5-diphenyl-1,2,4-triazole could be isolated. It was accompanied by an almost equal amount of 3,5-diphenyl-1,2,4-triazole. The latter may have been formed by the reductive deamination of the 4-amino-3,5-diphenyl-1,2,4-triazole, or by condensation of benzhydrazide and its reductive deamination product, benzamide. Alteration of the conditions served only to decrease the yields.

EXPERIMENTAL²

REACTIONS BETWEEN CARBOXYLIC ACIDS AND HYDRAZINE

4-Amino-1,2,4-triazole. Formic acid (51 g., 1 mole of 90%) and 85 g. (1.5 moles) of 85% hydrazine hydrate solution were mixed cautiously with cooling. The flask containing the mixture was arranged for distillation and was heated slowly in an oil-bath until the temperature of the mixture was 200°. Heating was controlled so that water and excess hydrazine

² All melting points were taken in open capillaries; temperatures are corrected.

distilled slowly. Distillation started when the reaction mixture reached 116°. During about 75 minutes 62 g. of distillate was collected and the temperature of the mixture rose to 127°. During the next 25 minutes the temperature rose to 144° while 18 g. of distillate collected. In another 25 minutes the temperature had risen to about 200° while only 8-9 g. of distillate collected. The reaction mixture was kept at about 200° for four hours. Although this temperature is not critical, temperatures above 220° caused excessive decomposition. Occasionally the reaction mixture turned pink on cooling after four hours at 200°. This was an indication of incomplete reaction. Another hour at 200° usually sufficed to complete the reaction in these instances. The crude product was dissolved in 75 ml. of 95% ethanol and treated with an equal volume of ethyl ether. The product separated as a liquid that solidified rapidly in the cold. After recrystallization from another portion of the same solvent mixture, the product was transferred immediately to a vacuum desiccator and dried. Yield 89%, m.p. 79-80.5° (5).

4-Amino-3,5-dimethyl-1,2,4-triazole was prepared in essentially the same manner from 60 g. (1 mole) of glacial acetic acid and 85 g. (1.5 moles) of 85% hydrazine hydrate solution. The reaction mixture was heated slowly in an oil-bath until its temperature reached 220-230° where it was maintained for five hours. The mixture was allowed to cool to about 100° when it was taken up in 150 ml. of 99% isopropyl alcohol from which the product crystallized on cooling. The crude product was recrystallized from the same solvent and the mother liquors were concentrated to small volumes for complete isolation of the product. Yield 75%, m.p. 196.5-197.5° (1, 6, 8).

4-Amino-3,5-diethyl-1,2,4-triazole was prepared from 18.5 g. (0.25 mole) of propionic acid and 21.5 g. (0.4 mole) of 85% hydrazine hydrate solution as described in the preceding examples. The reaction mixture was kept at 220-230° for five hours. The product was recrystallized from ethyl acetate, yield 68%, m.p. 165.5-166.5° (9).

4-Amino-3,5-di-n-propyl-1,2,4-triazole was prepared from 22 g. (0.25 mole) of *n*-butyric acid and 21.5 g. (0.4 mole) of 85% hydrazine hydrate solution as in the foregoing examples. The reaction mixture was heated to 270° for 5-6 hours. The product was recrystallized from ethyl acetate, yield 48%, m.p. 182-183° (10).

Isobutyric acid with hydrazine. An attempt was made to prepare an aminotriazole from 22 g. (0.25 mole) of isobutyric acid and 21.5 g. (0.4 mole) of 85% hydrazine hydrate solution by the above procedure keeping the reaction mixture at 270° for 5-6 hours. The cooled reaction mixture was dissolved in hot isopropyl alcohol. Diisobutyl hydrazide, m.p. 238-239° (11) crystallized from the solution; yield 25-50% in different experiments. Concentration of the mother liquors gave additional material melting over a range, 190-210°. Efforts to separate pure products from this mixture were unsuccessful. Extraction of the aminotriazole by virtue of its solubility in aqueous hydrochloric acid failed because the diisobutyl hydrazide, although practically insoluble in water or dilute hydrochloric acid, showed marked solubility in the aqueous, acid solutions of the aminotriazole. In one experiment under the same conditions a 31% yield of 4-amino-3,5-diisopropyl-1,2,4-triazole, m.p. 228.5-230° (11), separated from the concentrated isopropyl alcohol solution but this result could not be repeated.

Benzoic acid with hydrazine. Aminotriazole formation from 31 g. (0.25 mole) of benzoic acid and 21.5 g. (0.4 mole) of 85% hydrazine hydrate solution was attempted at 270° as in the preceding examples. The cold reaction mixture was extracted with several portions of 3 *N* hydrochloric acid. The acid extracts upon neutralization with aqueous ammonia gave 4-amino-3,5-diphenyl-1,2,4-triazole, recrystallized from 95% ethanol, yield 10%, m.p. 259-260° (7, 12). The material insoluble in aqueous hydrochloric acid was dibenzoyl hydrazide, recrystallized from 95% ethanol, yield 50-60% in several experiments, m.p. 238-239° (13).

DECOMPOSITION OF MONOACYL HYDRAZIDES

Isobutyl hydrazide (5 g.) was heated at 180° in a sealed tube for 24 hours. The product was crystallized from isopropyl alcohol. Yield of diisobutyl hydrazide 50-60%, m.p. 237-239° (11). No 4-amino-3,5-di-isopropyl-1,2,4-triazole could be isolated.

Benzhydrazide (10 g.) was heated at 180° in a sealed tube for 24 hours. Recrystallization of the product from 95% ethanol gave 50-60% of dibenzoyl hydrazide in several experiments, m.p. 237-238° (13). No 4-amino-3,5-diphenyl-1,2,4-triazole could be extracted from the reaction mixture with dilute hydrochloric acid.

FORMATION OF 4-AMINOTRIAZOLES FROM DIACYL HYDRAZIDES

4-Amino-3,5-diethyl-1,2,4-triazole. Dipropionyl hydrazide (14) (14.2 g, 0.1 mole) and 5.7 g. (0.1 mole) of 85% hydrazine hydrate solution were heated in a sealed tube for 48 hours at 180°. The liquid reaction mixture was suspended in toluene and water was removed by distillation. 4-Amino-3,5-diethyl-1,2,4-triazole precipitated from the toluene and was twice recrystallized from ethyl acetate, yield 64%, m.p. 165.5-166.5° (9).

Anal. Calc'd for $C_8H_{12}N_4$: N, 40.0. Found: N, 39.9.

4-Amino-3,5-di-n-propyl-1,2,4-triazole was prepared in the same way from 17.2 g. (0.1 mole) of di-*n*-butyryl hydrazide (14) and 5.7 g. (0.1 mole) of 85% hydrazine hydrate solution. The crude solid product was recrystallized from ethyl acetate, yield 59%, m.p. 182-183° (10).

Anal. Calc'd for $C_8H_{16}N_4$: N, 33.3. Found: N, 33.1.

4-Amino-3,5-diisopropyl-1,2,4-triazole was obtained from 17.2 g. (0.1 mole) of diisobutyryl hydrazide and 5.7 g. (0.1 mole) of 85% hydrazine hydrate solution as described in the preceding instances. The crude product was crystallized from isopropyl alcohol, yield 62%, m.p. 228.5-230° (11).

Anal. Calc'd for $C_9H_{16}N_4$: N, 33.3. Found: N, 33.2.

4-Amino-3,5-diphenyl-1,2,4-triazole was prepared from 12 g. (0.05 mole) of dibenzoyl hydrazide and 5.7 g. (0.1 mole) of hydrazine hydrate solution as just described. Recrystallization was from 95% ethanol, yield 58%, m.p. 259-260° (7, 12).

Anal. Calc'd for $C_{14}H_{12}N_4$: N, 23.7. Found: N, 23.8.

In experiments using equimolar amounts of hydrazine and dibenzoyl hydrazide a much lower yield of the aminotriazole was obtained. This was due possibly to the physical characteristic of dibenzoyl hydrazide which is a very light, fluffy material that may not have become completely wetted by the hydrazine solution.

REACTION OF ETHYL BENZOATE WITH HYDRAZINE

A mixture of 30 g. (0.2 mole) of ethyl benzoate and 12 g. (0.22 mole) of 85% hydrazine hydrate solution was heated at 195° for five days in a sealed tube. The reaction mixture was taken up in 50 ml. of hot 95% ethanol. On cooling 4-amino-3,5-diphenyl-1,2,4-triazole separated, m.p. 259-260° after a second crystallization from 95% ethanol, yield 5.3 g. Concentration of the alcoholic solution of the reaction mixture to half its volume and dilution with water caused the separation of 3,5-diphenyl-1,2,4-triazole, m.p. 190° (15), after recrystallization from 50% ethanol, yield 4.3 g.

When the reaction was run with a larger excess (100%) of hydrazine hydrate, or for a shorter time (three days), or at a lower temperature (160°), or with the addition of sufficient ethanol to make the mixture homogeneous, the yield of 4-amino-3,5-diphenyl-1,2,4-triazole was markedly decreased. Some 3,5-diphenyl-1,2,4-triazole could be isolated in each instance.

SUMMARY

Convenient methods of preparation of 4-amino-3,5-dialkyl-1,2,4-triazoles have been described. When the alkyl groups are small, the aminotriazoles can be prepared from the free fatty acid and hydrazine hydrate in an ordinary distillation apparatus. Higher molecular weight aminotriazoles can be prepared by heating diacyl hydrazides and hydrazine hydrate solution in sealed tubes.

A mechanism for the formation of aminotriazoles has been proposed involving

(a) hydrazinium salt formation, (b) dehydration of the hydrazinium salt to form a monoacyl hydrazide, (c) decomposition of the monoacyl hydrazide to a diacyl hydrazide and hydrazine, and (d) interaction of the diacyl hydrazide, possibly in the lactim form, with hydrazine to form the aminotriazole directly or through intermediates such as acyl hydrazidines or dihydrotetrazines.

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