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The Preparation of 1,2,3-Triazole[1]

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A new synthesis of 1,2,3-triazole suitable for reasonably large scale preparation has been developed. Acetylenedicarboxylic acid is converted to 1-benzyl-1,2,3-triazole-4,5-dicarboxylic acid in 92% yield. This dicarboxylic acid is decarboxylated in 77% yield to 1-benzyl-1,2,3-triazole which then is debenzylated in 47% yield (77% conversion) to 1,2,3-triazole.

In spite of numerous recorded[3-11] syntheses 1,2,3-triazole is not an easily available compound. This inaccessibility has so hindered the study of the chemistry of 1,2,3-triazole that little has been learned about this compound in the last 40 years. The syntheses by direct reaction[3] of hydrogen azide with acetylene under pressure at 100° is an unattractive method for large scale preparation because both components are explosive. The synthesis[4] which involves the preparation, from glyoxal bis (benzoylhydrazone), of 1-amino-1,2,3-triazole[4] and its deamination with nitrous acid is tedious and has several incompletely described steps including the last one. The syntheses which involve the decarboxylation of 1,2,3-triazole-4-carboxylic acid[5,6,7,11] or of 1,2,3-triazole-4,5-dicarboxylic acid[8] require the preparation of these acids by the addition of hydrogen azide to the acetylenic acids[10] or by the oxidation of various substituted triazoles.[5,6,7,8,9,11] The hydrogen azide additions are slow and the preparation and use of hydrogen azide in 1–5 mole quantities is a very hazardous operation. The oxidative methods are very difficult to run on a large scale because of the nature of permanganate oxidations and because most of the starting materials are themselves difficult of access. Furthermore, the isolation of triazolecarboxylic acids from solutions containing large quantities of sodium and potassium salts is neither convenient nor efficient. Although some of these syntheses might be improved by systematic study, we have chosen to investigate new synthetic routes to 1,2,3-triazole and wish to report the results of these studies at this time.

The common starting material for our syntheses is the known[12] 1-benzyl-1,2,3-triazole-4,5-dicarboxylic acid(I). Curtius and Raschig prepared this acid by the reaction of benzyl azide with the methyl ester of acetylenedicarboxylic acid with subsequent saponification. We have prepared it more directly and in better yield (92%) from acetylenedicarboxylic acid. Four procedures for converting this acid to 1,2,3-triazole have been studied in detail. These involve alternative decarboxylations and debenzylations of this acid. The debenzylation of the acid to 1,2,3-triazole-4,5-dicarboxylic acid (II) with (1) sodium in liquid ammonia or (2) by catalytic hydrogenation prior to decarboxylation is complicated by difficulties in isolation of the acid (II).

The decarboxylation of the acid (I)[12] gives 1-benzyl-1,2-3-triazole (III) in essentially quantitative yield. The sodium and catalytic debenzylation of this substance gave 1,2,3-triazole (IV) directly. Of these four variant routes, although all of them gave debenzylated product, the catalytic debenzylation of 1-benzyl-1,2,3-triazole seems the best. The most surprising aspect of this hydrogenation is the high temperature necessary for reaction. We were not able to demonstrate significant hydrogen absorption with a palladium on charcoal catalyst below about 150°. The reaction is best carried out at 165–175°. Even at these temperatures and at hydrogen pressures of the order of 1000 p.s.i. the reaction takes 3–4 days. Whether or not this hydrogenation could be speeded up by use of a different catalyst and higher hydrogen pressures is uncertain, but the use of temperatures much higher than 175° seems inadvisable.

Even with this rather slow hydrogenation step the over-all synthesis is rapid. Benzyl azide can readily be made in 100–1000-g. quantities by overnight refluxing. The reaction of benzyl azide with acetylenedicarboxylic acid and the decarboxylation of the product to 1-benzyltriazole can be carried out in one working day, so that the whole synthesis can be carried out in about one week. The amount of triazole produced in the last step is limited by the size of the bomb. A 300-ml. bomb gives about 30 g. of triazole.

Some notes on the preliminary steps are in order.

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(2) Eli Lilly Company Pre-doctoral research assistant.

(3) Dimroth and Fester, *Ber.*, **43**, 2222 (1910).

(4) Von Pechmann and Bauer, *Ber.*, **42**, 673 (1909); *Cf.* Stollé, *Ber.*, **59**, 1743 (1926).

(5) Baltzer and Von Pechmann, *Ann.*, **262**, 320 (1891).

(6) Zincke, *Ann.*, **311**, 310 (1900).

(7) Dimroth, *Ber.*, **35**, 1045 (1902).

(8) Bladin, *Ber.*, **26**, 545, 2737 (1893).

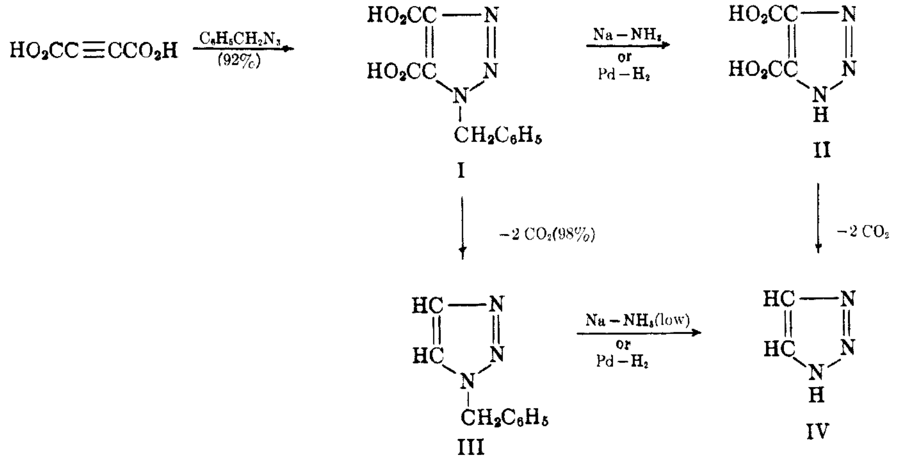
(9) Michael, Luehn, and Higbee, *Am. Chem. J.*, **20**, 389 (1898).

(10) Oliveri-Mandalà and Coppola, *Atti Real. Acad. Lincei*, [5] **19**, I, 565 (1910).

(11) Wiley, Smith, Johnson, and Moffat, *J. Am. Chem. Soc.*, **76**, 4933 (1954); *Cf.* Hüttel, *Ber.*, **74**, 1680 (1941).

(12) Curtius and Raschig, *J. prakt. Chem.*, [2] **125**, 466 (1930).

Curtius[13] used an excess of sodium azide in the preparation of benzyl azide. From the point of view of cost it is better to use an excess of benzyl chloride particularly since it is neither easy nor necessary to purify the benzyl azide for use in the next step. The distilled material used in our studies undoubtedly contained benzyl chloride. We have found, as would be expected on mechanistic grounds that the reaction of alkyl azides with acetylenes is much more rapid in acetone than in the less polar ethyl ether.



EXPERIMENTAL

The *benzyl azide* was prepared by the method of Curtius and Ehrhart[13] except that equimolar quantities of reagents were used and methanol was used instead of ethanol. Although all the benzyl azide used in the present work was vacuum distilled this operation seems to serve no useful purpose. The palladium on charcoal was a commercial (Matheson-Coleman and Bell Company) material.

1-Benzyl-1,2,3-triazole-4,5-dicarboxylic acid (I). To a solution of 88 g. (0.65 mole) of acetylenedicarboxylic[14] acid in 200 ml. of acetone was added 120 g. (0.90 mole) of crude benzyl azide (containing benzyl chloride) and 40 ml. of acetone. The solution heated up to reflux rapidly and required external cooling for control. The product began to crystallize from the solution almost immediately. After standing overnight the mixture was filtered and the filtrate concentrated to a small volume and refiltered. The total yield of pure product was 183.5 g. (92.5%), m.p. 183°. Reported m.p. 183°.[12]

1-Benzyl-1,2,3-triazole (II). The diacid was heated under a vacuum in a Claisen flask with an air condenser. After evolution of carbon dioxide was complete the product was distilled at *ca.* 160°/1 mm. or 210°/20 mm., and then was crystallized from ethyl ether at *ca.* −20°. The yield was from 89 g. (98%) from 144 g. of acid to 2.5 g. (85%) from 4.5 g. of acid. The losses seem to be purely mechanical; practically no forerun or residue was observed. M.p. 61°; reported m.p. 61°.[12]

1,2,3-Triazole-4,5-dicarboxylic acid. A. With sodium in liquid ammonia. To a solution of 14 g. (0.6 mole) of sodium in 500 ml. of liquid ammonia was added slowly with stirring a solution of 49.4 g. (0.2 mole) of 1-benzyl-1,2,3-triazole-4,5-dicarboxylic acid in 100 ml. of ammonia. The acid is very soluble in liquid ammonia. Since the blue sodium color was discharged before the addition was complete an additional 5 g. of sodium was added. At the end of the addition excess ammonium chloride was added and the ammonia was allowed to evaporate. The residue was dissolved in 300 ml. of water and extracted with ether to remove toluene and bibenzyl. Acidification, decolorization, chilling, and filtration gave 23.1 g. of crude product. The potentiometric titration curve showed this to be 86% pure monosodium salt of 1,2,3-triazole-4,5-dicarboxylic acid which is equivalent to a yield of 55%. Triazoledicarboxylic acid titrates as a tribasic acid with breaks at *p*H's 3.8, 7.2, and 10.5.

B. By catalytic reduction. Attempts to reduce 1-benzyl-1,2,3-triazole-4,5-dicarboxylic acid with palladium on charcoal at 30–45 p.s.i. hydrogen pressure were completely unsuccessful. Hydrogenation in water solution at 1000 p.s.i. hydrogen pressure and temperatures of from 150° to 200° gave the theoretical absorption of hydrogen in about one hour. However, the product attacked the bomb so that only 10% of the 1,2,3-triazole-4,5-dicarboxylic acid was isolated as such. The other 90% was converted to the very insoluble ferrous salt a part of which "enameled" the inside of the bomb forming a very adherent hard surface which was removed only with difficulty. The use of a glass liner did not completely remove this difficulty since a part of the solution foamed out of the liner during the reaction. No further study of this reaction was made.

1,2,3-Triazole. A. With sodium in liquid ammonia. Reduction of 1-benzyl-1,2,3-triazole (II) with sodium in liquid ammonia gave significant quantities of bibenzyl in addition to some toluene. The separation of triazole from this mixture by simple distillation is not easy since triazole distills in part with the toluene, and bibenzyl distills with the triazole. Both of these contaminants can be removed by solution of the triazole in water, but the isolation of triazole from such solutions is tedious. It should be noted here that despite the published report[4] triazole is not extracted by ether from a water solution saturated with potassium carbonate. It can be extracted from water solutions saturated with neutral salts such as potassium chloride. The reported isolation must have been fortuitous. Probably the solution from which these workers extracted triazole was mostly a solution of potassium nitrite. Because of the difficulties of isolation, no definitive work was done on this reaction but the yield at best was no more than 50%.

B. By catalytic reduction. In a 300-ml. steel bomb 157.6 g. of 1-benzyl-1,2,3-triazole (III) was hydrogenated with 1 g. of 50% palladium on charcoal catalyst at 175°. The pressure of hydrogen varied from *ca.* 1200 p.s.i. to *ca.* 400 p.s.i. It was necessary to repressure the bomb with hydrogen several times introducing a large error into the measurement of pressure change. Two 1-g. portions of fresh catalyst were added during the reaction. After 84 hours the reaction was stopped, and the reaction mixture was dissolved in ether, filtered, and distilled. After the ether and toluene were

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[13] Curtius and Ehrhart, *Ber.*, **55**, 1565 (1922).

[14] The authors wish to thank the National Aniline Division of Allied Chemical and Dye Corporation for furnishing samples of this acid.

removed through a six-inch glass helix-packed column the triazole was distilled without fractionation. The unreacted 1-benzyl-1,2,3-triazole was recovered by vacuum distillation of the residue. The yield of triazole, b.p. 208–210°, was 32.3 g. (47%). Since 61.2 g. of 1-benzyl-1,2,3-triazole was recovered, the yield is 77% corrected for the recovered starting material.

It should be noted that it is not safe to superheat triazole vapors.[5] Although the exact conditions for explosive decomposition are not known it seems inadvisable to heat it much over its boiling point. Careful fractionation should be carried out at reduced pressure.

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