Notes A department for short papers of immediate interest.

Use of Amines in the Glaser Coupling Reaction

MARGARET D. CAMERON[1] AND GEORGE E. BENNETT

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The reaction in which a compound containing an acetylenic hydrogen is coupled *via* oxidation of the copper(I) acetylide was discovered by Carl Glaser in 1869.[2] Subsequent workers have found the reaction applicable not only to ethynyl hydrocarbons but to a wide variety of organic compounds possessing the ethynyl group. The catalyst most often employed for Glaser coupling consists of a mixture of copper(I) chloride, ammonia, and ammonium chloride. Occasional references to the use of silver salts instead of copper ones are found, but the previously reported modifications of the Glaser reaction usually involve variations in the oxidant.[3]

In the course of a general investigation of the Glaser reaction, the effect was determined of substituting amines for ammonia in the catalyst mixture. Table I summarizes the results obtained when propargyl alcohol (I) was coupled by oxygen in the presence of several amines; the method of Run 1 was employed as the standard from which the indicated deviations were made. It is apparent that *t*-butylamine, ethylenediamine, and (to a limited extent) pyridine aid in the catalysis of the oxidation of propargyl alcohol (I) to 2,4-hexadiynediol (II) and that triethylamine does not.

TABLE I

EFFECT OF SEVERAL AMINES ON GLASER COUPLING OF PROPARGYL ALCOHOL

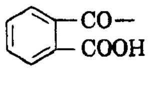
Run	Cu Ratio[a]	Amine[b]	Amine Ratio[a]	Amine.-HCl Ratio[a]	Solvent[b]	Yield, Diol II (%)[c]
1	1.3	NH_3	0.9	3.8	H_2O	83
2	1.3	py	0.9	3.8	H_2O	42
3	1.3	en	0.9	3.8	H_2O	81
4	0.2	en	0.3	0.4	H_2O	17
5	1.3	*t*-bu	0.9	3.8	H_2O	92
6	0.2	*t*-bu	0.2	0.7	H_2O	41
7	1.3	et_3	0.9	3.8	H_2O	0
8	1.3	NH_3	0.9	3.8	THF	68
9	1.3	en	0.9	3.8	THF	79

[a] Ratios expressed as equivalents/mole propargyl alcohol. [b] Abbreviations: py, pyridine; en, ethylenediamine; *t*-bu, *t*-butylamine; et_3, triethylamine; THF, tetrahydrofuran. [c] All runs made at room temperature (25 ± 5°); the same apparatus and identical oxygen pressures and stirrer settings were used.

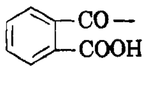
$$2ROCH_2C{\equiv}CH \xrightarrow[\text{catalyst}]{O_2} ROCH_2C{\equiv}C{-}C{\equiv}CCH_2OR$$

I R=H— II R=H—

III R=



IV R=



Previous investigators[4] have found that in the presence of ammonia or ammonium chloride 0.2–0.5 equivalents of copper(I) per mole of ethynylcarbinol are required for the Glaser coupling reaction, while even higher ratios are desirable.[5] A comparison of Runs 3 and 4 and of Runs 5 and 6 indicates that these observations hold for the use of organic amines as well.

An interesting application of the utility of *t*-butylamine in the Glaser catalyst was found in coupling propargyl hydrogen phthalate (III). While an ammonia-containing catalyst (as in Run 1) gave a 53% yield of 2,4-hexadiyne-1,6-diol di-(hydrogen phthalate) (IV), an 83% yield was obtained using *t*-butylamine (as in Run 5).

EXPERIMENTAL

2,4-Hexadiyne-1,6-diol (II). The following examples are typical of the runs summarized in Table I:

Run 1. Propargyl alcohol (11.2 g., 0.20 mole) was added with stirring to a mixture of 25 g. copper(I) chloride (0.13 mole), 40 g. ammonium chloride (0.75 mole), 12.5 ml. concentrated ammonium hydroxide (0.18 mole NH_3), and 200 ml. water. The mixture was stirred under a slight (ca. 30 mm.) positive pressure of oxygen for 20 hr. The blue-green reaction mixture was acidified with dilute hydrochloric acid, diluted to 750 ml. with water and extracted with ether in a continuous extractor for 24 hr. Evaporation of ether from the extract left a solid which, when recrystallized from hot water, gave 9.1 g. (83%) of 2,4-hexadiyne-1,6-diol, m.p. 111.5–112°.

Run 9. Propargyl alcohol (11.2 g., 0.20 mole) was added with stirring to a mixture of 25 g. copper(I) chloride (0.13 mole), 5.4 g. ethylenediamine (0.09 mole), 50.6 g. ethylenediamine dihydrochloride (0.38 mole), and 200 ml. tetrahydrofuran. The mixture was stirred under a slight positive pressure of oxygen for 20 hr. and the volatile portion removed by evaporation under reduced pressure. Water (200 ml.) was added, the mixture was acidified and extracted with ether for 20 hr. in a continuous extractor. Evaporation

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[1] Present address: Department of Chemistry, Lamar State College of Technology, Beaumont, Tex.

(2) C. Glaser, *Ber.*, **2**, 422 (1869).

(3) R. A. Raphael, *Acetylenic Compounds in Organic Synthesis*, Academic Press, New York, 1955, p. 127.

(4) K. Bowden, I. Heilbron, E. R. H. Jones, and K. H. Sargent, *J. Chem. Soc.*, 1579 (1947); J. W. Copenhaver and M. H. Bigelow, *Acetylene and Carbon Monoxide Chemistry*, Reinhold, New York, 1949, p. 121 give unpublished work from I. G. Farbenindustrie laboratories.

(5) J. B. Armitage, C. L. Cook, N. Entwistle, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 1998 (1952).

of the ether and recrystallization of the resulting solid from hot water gave 8.7 g. (79%) yield of 2,4-hexadiyne-1,6-diol (II).

Propargyl hydrogen phthalate (III). Phthalic anhydride (148 g., 1.00 mole) and 84 g. propargyl alcohol (1.50 moles) were stirred together and heated gradually to 110° over a period of 4 hr. After allowing it to cool overnight, the mixture was filtered and the solid portion recrystallized from benzene to give 186 g. (91.2%) propargyl hydrogen phthalate (III), m.p. 106–107°.

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.71; H, 3.95. Found: C, 64.71; H, 4.26.

2,4-Hexadiyne-1,6-diol di-(hydrogen phthalate) (IV). Propargyl hydrogen phthalate (20.4 g., 0.10 mole) was added to a stirred mixture of 12.5 g. copper(I) chloride (0.065 mole), 34.4 g. *t*-butylamine (0.47 mole), 63 mole of 6*N* hydrochloric acid (0.38 mole) and 100 ml. water. The mixture was stirred under a slight positive pressure of oxygen for 20 hr., the solid removed by filtration and triturated with 250 ml. sulfuric acid (3*N*). The acid mixture was filtered and the solid recrystallized from aqueous acetone to give 16.7 g. (82%) yield of 2,4-hexadiyne-1,6-diol di-(hydrogen phthalate), m.p. 145.5–147°.

Anal. Calcd. for $C_{22}H_{14}O_8$: C, 65.17; H, 3.48. Found: C, 65.07; H, 3.67.

A run with propargyl hydrogen phthalate (0.10 mole), cuprous chloride (0.065 mole), ammonia (0.09 mole), ammonium chloride (0.038 mole) under the same reaction and work-up conditions gave a 10.7 g. (53%) yield of 2,4-hexadiyne-1,6-diol (IV), m.p. 145.5–147°.

CENTRAL RESEARCH DEPARTMENT
RESEARCH AND ENGINEERING DIVISION
MONSANTO CHEMICAL COMPANY
DAYTON, OHIO

Mercaptotriazolopyrimidines[1,2]

CARL TABB BAHNER, DOROTHY ELLIS BILANCIO, EMMA BROWN SENTER, SARA HUMPHRIES, RONALD NATIONS, WILLIAM PORCH, AND JOAN WILSON

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Synthesis of triazolopyrimidines containing sulfur at the 5- or 7- position[3–5] has been continued in order that the action of these compounds on tumors might be compared with the effects of 6-mercaptopurine and 8-azaguanine.

Kidder, Dewey, Parks, and Woodside[6] reported that 5-mercapto-7-amino-1-v-triazolo[d]pyrimidine (I) was not an inhibitor of the growth of Adenocarcinoma 755, but they did not give data on the preparation or other properties of the compound. A later paper[7] has described the preparation of a material which gave a volumetric chloride analysis corresponding to the dihydrochloride salt of I and was a strong inhibitor of the growth of *Streptococcus faecalis R.* The free compound I has now been prepared in this laboratory and its ultraviolet absorption has been determined. Boiling dilute hydrochloric acid converted it into a yellow solid that gave a Volhard analysis very close to that reported for the supposed dihydrochloride of I, but was found to have the ultraviolet absorption maxima characteristic of 5-mercapto-7-hydroxy-1-v-triazolo[d]pyrimidine (II), not I. An explanation of the apparently inconsistent observations was found when it was discovered that under the conditions of the Volhard analysis, II reacted with silver nitrate in a 1:1 molar ratio to form a precipitate, probably through forming the silver salt of the —SH group, whereas I did not. Since the equivalent weights of $II \cdot 2H_2O \cdot HCl$, molecular weight 240.6, and $I \cdot 2HCl$, molecular weight 241.1, thus happen to be almost identical, the Volhard analysis was in agreement with either formula. (Both 5-mercapto-1-v-triazolo[d]pyrimidine and 7-mercapto-1-v-triazolo[d]pyrimidine behaved like II in this respect.) In view of these facts it appears likely that the material previously referred to as I dihydrochloride was actually a hydrated monohydrochloride of II. Probably the inhibition of *Streptococcus faecalis R* was due to II, formed from I during the heating.

The replacement of the amino group in I by a hydroxyl group suggested that 5-hydroxy-7-mercapto-1-v-triazolo[d]pyrimidine (III) might be formed as a by-product under the acid conditions encountered in the preparation of 5-amino-7-mercapto-1-v-triazolo[d]pyrimidine and 5,7-dimercapto-1-v-triazolo[d]pyrimidine. A solid which appeared to be the oxidation product of III was found among the reaction products.

EXPERIMENTAL

5-Mercapto-7-amino-1-v-triazolo[d]pyrimidine, I. A solution of 3.5 g. of KNO_2 in 110 ml. of H_2O was added to 10 g. of 4,5,6-triamino-2-mercaptopyrimidine hydrosulfate in 3.5 l. of H_2O. The crystals of I were filtered off after stirring 20 min. and were washed with methanol and acetone.[8] The analysis values for C, H, and N were a fraction of a per cent low. Accordingly the product was purified by dissolving in 0.05*N* potassium hydrosulfide, neutralizing the solution with acetic acid, filtering, washing the precipitate with 3% acetic acid, and drying. Ultraviolet absorption: at *p*H 6.5 log ϵ_{256} 4.18, log ϵ_{310} 3.98; at *p*H 10 log ϵ_{255} 4.26, log ϵ_{307} 3.95.

Anal. Calcd. for $C_4H_4N_6S$: C, 28.56; H, 2.31. Found: C, 28.46, 28.69; H, 2.31, 2.19.

When a sample of I was tested by the Volhard method

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(2) Part of this paper was presented before the Tennessee Academy of Science at Cookeville, Tenn., December 3, 1955.

(3) C. T. Bahner and D. E. Bilancio, *J. Am. Chem. Soc.*, **75**, 6038 (1953).

(4) C. T. Bahner, B. Stump, and E. M. Brown, *J. Am. Chem. Soc.*, **75**, 6301 (1953).

(5) C. T. Bahner, D. E. Bilancio, and E. M. Brown, *J. Am. Chem. Soc.*, **76**, 1370 (1954).

(6) G. W. Kidder, V. C. Dewey, R. E. Parks, Jr., and G. L. Woodside, *Cancer Research*, **11**, 204 (1951).

(7) C. T. Bahner, H. A. Rutter, Jr., and J. R. Totter, *J. Tenn. Acad. Sci.*, **27**, 179 (1952).

(8) On standing in air, I formed what appeared to be an oxidation product having a strong absorption peak at 236 mμ at *p*H 6.5, from which I was obtained again by reduction with NaSH.