

# SYNTHESIS OF 1-PHENYLPROPYLENE-2,3-<sup>13</sup>C<sub>2</sub><sup>1</sup>

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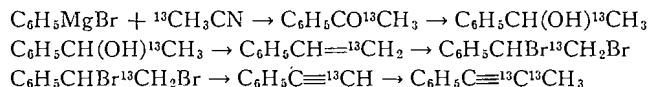
## ABSTRACT

A method of preparing the title compound from methyl-<sup>13</sup>C iodide through acetophenone-2-<sup>13</sup>C, 1-phenylethanol-2-<sup>13</sup>C, styrene-2-<sup>13</sup>C, styrene-2-<sup>13</sup>C dibromide, and 1-phenylacetylene-2-<sup>13</sup>C is described. The overall yield based on methyl-<sup>13</sup>C iodide was 24%.

In connection with the measurement of the spin-spin coupling constants of certain C-C linkages by Bernstein and Frei (1), 1-phenylpropyne-2,3-<sup>13</sup>C<sub>2</sub> with an isotopic abundance of 55% above normal in the marked positions was synthesized.

In a review of the literature up to 1958, Hurd and Tockman (2) record no suitable method for the preparation of 1-phenylpropyne labelled as indicated above. The synthesis reported in that paper is also inconvenient because it would involve the preparation of 1-phenylacetone-2,3-<sup>13</sup>C<sub>2</sub>. The method of Tripett and Gough (3), employing the pyrolysis of  $\alpha$ -phenylacetylidenetriphenylphosphorane, gave 1-phenylpropyne which was very impure and difficult to purify on a small scale.

For these reasons, 1-phenylpropyne-2,3-<sup>13</sup>C<sub>2</sub> was synthesized by the reactions shown below.



The preparation of the intermediates up to and including styrene dibromide by methods already reported requires no special comment.

We attempted initially to prepare 1-phenylpropyne from styrene dibromide in one step, by dehydrobromination with lithium amide in liquid ammonia followed by methylation of the phenylacetylene formed. The product was, however, contaminated with an appreciable amount of styrene. When the reaction was carried out in boiling tetrahydrofuran with only a slight excess of lithium amide the product then contained bromostyrene. However, in the presence of excess lithium amide and only a catalytic amount of ammonia in boiling tetrahydrofuran, a 60% yield of 1-phenylpropyne (98.5% pure as determined by vapor phase chromatography) was obtained, provided an excess of methyl iodide was employed. While this is a satisfactory method of preparing 1-phenylpropyne in one step from styrene dibromide, a rather large amount of expensive methyl-<sup>13</sup>C iodide would be required to prepare the labelled compound. In other words the yield based on methyl iodide is quite low. Consequently, attempts to prepare 1-phenylpropyne in one step were abandoned and attention was directed to the preparation of phenylacetylene.

According to Vaughn, Vogt, and Nieuwland (6) phenylacetylene is obtained in 64% yield by dehydrobromination of styrene dibromide with sodamide in liquid ammonia. Campbell and Campbell (7) report yields of 47-52% in this same preparation. We have repeated the experiments of the authors cited above and observe the formation of appreciable amounts of styrene in this reaction. The similarity in boiling point and refractive

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index of phenylacetylene and styrene prevents the use of these physical constants as criteria of the purity of the phenylacetylene. The presence of styrene in the product was established by vapor phase chromatography of a sample in a Perkin-Elmer Fractometer on a type "O" column at 147°; styrene and phenylacetylene had retention times of 3.5 and 4 min respectively, with good resolution. The formation of olefins in this type of reaction had in fact been reported by Vaughn, Vogt, and Nieuwland (6), who found that stilbene dibromide gave an 83% yield of stilbene rather than diphenylacetylene. It seemed that the preparation of phenylacetylene might best be achieved in good yield by dehydrobromination with excess sodamide in anhydrous ether (or tetrahydrofuran) in the presence of traces of ammonia as described earlier. Phenylacetylene of 96% purity was in fact isolated in 90% yield by this method.

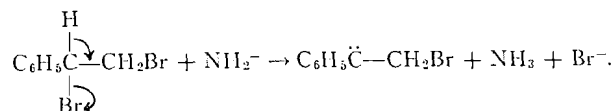
The cobaltous chloride catalyzed reaction between phenylethynyl bromide and methylmagnesium bromide is reported by Kharasch, Lambert, and Urry (4) to give a 62% yield of 1-phenylpropyne, but Black, Horn, and Weedon (5) obtained at best only a 34% yield. Our results agreed with those of Weedon and co-workers and this method was therefore abandoned. The methylation was then carried out with lithium amide in liquid ammonia, and methyl iodide in anhydrous ether. An 80% yield of 1-phenylpropyne, 97% pure, was obtained.

1-Phenylacetylene-2-<sup>13</sup>C and 1-phenylpropyne-2,3-<sup>13</sup>C<sub>2</sub> were prepared in exactly the same way from styrene-2-<sup>13</sup>C dibromide and methyl-<sup>13</sup>C iodide.

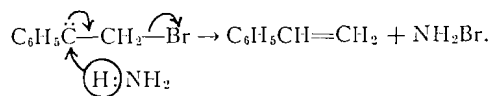
#### DISCUSSION

Conventional elimination mechanisms readily explain the formation of phenylacetylene from styrene dibromide and sodium amide but, to our knowledge, the formation of styrene in this reaction has not been explained. To rationalize this with both sodium amide and ammonia as reagents we suggest the following reactions.

(1) Proton abstraction to yield a methylene (9):



(2) In the absence of ammonia the methylene undergoes dehydrobromination to phenylacetylene, but in its presence addition of a hydride ion takes place and styrene is formed:



#### EXPERIMENTAL

##### *Methyl-<sup>13</sup>C Cyanide*

The nitrile was prepared by the method of Cox, Warner, and Turner reported in *Organic Synthesis with Isotopes* (8, p. 40). Yield: 95%.

##### *Acetophenone-2-<sup>13</sup>C*

The ketone was prepared as described by Brown, Cerwonka, and Anderson in *Organic Synthesis with Isotopes* (8, p. 664). Yield: 60%.

##### *1-Phenylethanol-2-<sup>13</sup>C*

The alcohol was prepared by reducing the ketone with aluminum isopropoxide. Yield: 85%.

*Styrene-2-<sup>13</sup>C*

The alcohol was dehydrated as described by Berstein, Bennett, and Fields (8, p. 1686). Yield: 75%.

*Styrene-2-<sup>13</sup>C Dibromide*

Styrene-2-<sup>13</sup>C (1.2 g; 0.011 mole) was dissolved in 25 ml of chloroform, and a solution of 1.95 g of bromine, also dissolved in chloroform, was added. The dibromide, 3.0 g (93%), was recovered by distilling off the solvent.

*1-Phenylpropyne**1. From Styrene Dibromide and Excess LiNH<sub>2</sub> in Liquid Ammonia*

Lithium amide was prepared in the usual manner from 0.295 g of lithium and 10 ml of liquid ammonia in a flask equipped with a cold finger condenser, which was packed with dry ice and protected from moisture by a drying tube filled with Drierite. After the mixture had been stirred for 15 min, a solution of 3.7 g (0.014 mole) of styrene dibromide in 20 ml of anhydrous ether was added dropwise. The reaction mixture, which turned dark brown, was stirred for 3 h. Methyl iodide (2.3 g; 0.016 mole) in 20 ml of dry ether was added dropwise and the reaction mixture was stirred 2 h under reflux and allowed to stand overnight. In the morning it was decomposed with water. The ether solution was separated, dried over MgSO<sub>4</sub>, and evaporated. The residue was distilled on the vacuum line and analyzed by vapor phase chromatography. The yield of 1-phenylpropyne was 38%, that of styrene 40%, and that of phenylacetylene 22.

A run with a 5 mole excess of lithium amide on the same scale gave an oil which analyzed 22% styrene, 50% phenylacetylene, and only 16% 1-phenylpropyne.

*2. From Styrene Dibromide with an Equivalent Amount of LiNH<sub>2</sub> in Tetrahydrofuran (THF)*

Styrene dibromide (3.58 g; 0.013 mole) was added in portions to 1.1 g (0.05 mole) of lithium amide in tetrahydrofuran and the reaction mixture was heated overnight under reflux with stirring. Methyl iodide (0.5 mole excess) was added to the reaction mixture at ambient temperature. Stirring was continued for 12 h, and then for 1 h under reflux. The tetrahydrofuran was distilled off on the steam bath, and the residue was taken up in ether before adding water. The reaction product was isolated as described in the preceding experiment. The main fraction of material distilled on the vacuum line contained 28.6% monobromostyrene and 27.4% styrene in addition to 33.4% 1-phenylpropyne.

*3. From Styrene Dibromide with Excess LiNH<sub>2</sub> in Tetrahydrofuran, Traces of Ammonia, and Excess CH<sub>3</sub>I*

Lithium amide (1.7 g; 0.074 mole), prepared in the usual manner from lithium and liquid ammonia, was freed of solvent, and 40 ml of dry tetrahydrofuran was added. A trace of dry ammonia was bubbled through the mixture. Styrene dibromide (3.9 g; 0.015 mole) was added in portions over a period of 3 min. The reaction mixture was heated with stirring under reflux overnight. Dry methyl iodide (6.3 g; 0.045 mole) in dry tetrahydrofuran was added, and the reaction mixture was stirred at room temperature for 2 days. The solvent was distilled off on the steam bath, the residue was taken up in ether and worked up as described before. The yield of product, 98.5% pure, was 1.1 g (65%).

Anal. Calc. for C<sub>9</sub>H<sub>8</sub>: C, 93.1; H, 6.85. Found: C, 92.99; H, 6.83. There were traces of styrene and phenylacetylene in the product.

*Phenylacetylene*

Sodamide was prepared in the usual manner from 1.3 g of sodium (0.06 mole). The ammonia was removed by pumping the flask on the vacuum line. Anhydrous ether (50 ml) was added, and a trace of dry ammonia was bubbled through the mixture followed by a solution of 3.7 g (0.012 mole) of styrene dibromide dissolved in 10 ml of ether. The reaction mixture became reddish, turned dark brown, and then turned light brown. White solid LiBr was formed. After the mixture had stood overnight, 4.0 g of ammonium chloride in water was added. The phenylacetylene was isolated in the usual manner. The yield was 1.3 g (90%) of phenylacetylene, which analyzed 96% by vapor phase chromatography. A small amount of styrene was present as an impurity.

1-Phenylacetylene-2-<sup>13</sup>C was prepared in exactly the same way.

*1-Phenylpropyne*

Lithium amide was prepared from 0.16 g (0.023 mole) of lithium (100% excess), 10 ml of liquid ammonia, and a trace of ferric nitrate. After the mixture had been stirred for 30 min, a solution of 1.0 g of phenylacetylene in 50 ml of absolute ether was added with stirring. This was followed by 1.6 g (0.011 mole) of methyl iodide in 25 ml of ether. The ammonia was allowed to evaporate overnight, and the reaction mixture was worked up as before. The yield of 1-phenylpropyne, 97% pure as determined by vapor phase chromatography, was 1.1 ml (80%) after purification by distillation on the vacuum line.

1-Phenylpropyne-2,3-<sup>13</sup>C<sub>2</sub> was prepared in exactly the same way from 1-phenylacetylene-2-<sup>13</sup>C. The overall yield based on methyl-<sup>13</sup>C iodide was 24%.

## ACKNOWLEDGMENTS

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