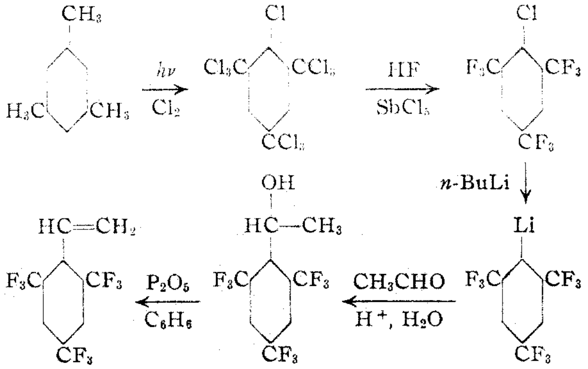
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE PURDUE RESEARCH FOUNDATION, PURDUE UNIVERSITY]

2,4,6-Tris-(trifluoromethyl)-styrene[1]

BY EARL T. McBEE AND ROBERT A. SANFORD[2]

This investigation was conducted to determine whether a styrene monomer with both ortho positions substituted with trifluoromethyl groups would undergo polymerization. Mesitylene was chlorinated photochemically in a single step to give chloro-2,4,6-tris-(trichloromethyl)-benzene which was purified by recrystallization from a mixture of benzene and methanol. This chloro compound was fluorinated with anhydrous hydrogen fluoride in the presence of antimony(V) chloride at atmospheric pressure to yield chloro-2,4,6-tris-(trifluoromethyl)-benzene. The latter compound failed to yield a Grignard reagent, but, when it was subjected to an exchange reaction with butyllithium, it yielded 2,4,6-tris-(trifluoromethyl)-phenyllithium. The addition compound of this lithium derivative and acetaldehyde was hydrolyzed to 2,4,6 - tris - (trifluoromethyl) - α-methylbenzyl alcohol which was dehydrated at room temperature with phosphorus(V) oxide in a benzene medium yielding 2,4,6-tris-(trifluoromethyl)-styrene.

The following series of reactions show the sequence involved in the synthesis of 2,4,6-tris-(trifluoromethyl)-styrene starting with mesitylene.



The structure of 2,4,6-tris-(trifluoromethyl)-phenyllithium was indicated by its hydrolysis to 1,3,5 - tris - (trifluoromethyl) - benzene. This discounted the possibility that butyllithium reacted with fluorine present in the trifluoromethyl groups.

A metal–halogen exchange involving chlorine attached to an aromatic ring is an uncommon reaction.[3,4] A few examples have been reported in which chlorine was exchanged for lithium,[5,6,7] but in general, the reaction requires that the halogen being exchanged be either bromine or iodine.[4] In fact, it is possible to exchange selectively a bromine in a bromochlorobenzene.[8]

All attempts to polymerize 2,4,6-tris-(trifluoromethyl)-styrene were unsuccessful. Apparently, the steric effect of two ortho trifluoromethyl groups is sufficient to prevent polymerization. In fact, this compound seemed to inhibit the polymerization of vinyl acetate when copolymerization experiments were attempted. However, this latter observation may be attributed in part to dilution of the vinyl acetate. 3-Nitrostyrene is the only other styrene known to the authors which has failed to undergo polymerization.[9]

In an attempt to prepare 2,4,6-tris-(trifluoromethyl) - α - methylstyrene, 2,4,6 - tris - (trifluoromethyl)-phenyllithium was treated with dry acetone in ether. Apparently steric factors interfere with the reaction of the carbonyl group in acetone with the organometallic compound, since it failed to give an addition complex after refluxing for twelve hours.

Acknowledgment.—The authors are indebted to Westinghouse Electric Company for the financial support which made this investigation possible.

Experimental

Mesitylene.—Mesitylene, obtained from the University of Illinois, was rectified through a Podbielniak column (Hyper-Cal). The fraction boiling between 162–163° (uncor.) at atmospheric pressure, was used in further synthesis.

Chloro-2,4,6-tris-(trichloromethyl)-benzene.—Mesitylene was chlorinated photochemically using carbon tetrachloride as a solvent following the general procedure of McBee and Leech.[10]

By removing the solvent and increasing the reaction temperature to 130° a substantially quantitative conversion to chloro-2,4,6-tris-(trichloromethyl)-benzene was obtained. It should be noted that no attempt was made to make the equipment and chlorine lines iron free.

Chloro-2,4,6-tris-(trifluoromethyl)-benzene.—Fluorination of chloro-2,4,6-tris-(trichloromethyl)-benzene was conducted at atmospheric pressure.[11] Two successive fluorinations, at 70 and 100°, were required to produce the desired product. Over-all yields of 70–80% were obtained.

2,4,6-Tris-(trifluoromethyl)-α-methylbenzyl Alcohol.—The reaction was conducted under an atmosphere of nitrogen in a 3-necked round-bottom flask, fitted with a separatory funnel, an efficient stirrer and a condenser. Lithium (2.8 g., 0.50 mole) was cut into small pieces and dropped into the reaction flask containing about 300 ml. of anhydrous ether. The *n*-butyl bromide (27.0 g., 0.20 mole)

---

[1] Abstracted from doctoral thesis of Robert A. Sanford.

[2] Sinclair Research Laboratories, Harvey, Illinois.

[3] H. Gilman, W. Langham and F. Moore, THIS JOURNAL, **62**, 2327 (1940).

[4] S. M. Spatz, *Iowa State Coll. J. Sci.*, **17**, 129 (1942).

[5] G. Wittig, G. Harborth and W. Merkle, *Ber.*, **77B**, 315 (1944).

[6] D. S. Melstrom, *Iowa State Coll. J. Sci.*, **18**, 65 (1943).

[7] A. H. Haubein, *ibid.*, **18**, 48 (1943).

[8] H. Gilman and S. Spatz, THIS JOURNAL, **66**, 621 (1944).

[9] C. S. Marvel, C. G. Overberger, R. E. Allen and J. H. Saunders, *ibid.*, **68**, 736 (1946).

[10] E. T. McBee and R. E. Leech, *Ind. Eng. Chem.*, **39**, 394 (1947).

[11] E. T. McBee and O. R. Pierce, *ibid.*, **39**, 397 (1947).

was mixed with an equal volume of ether and added slowly to the reaction flask. The rate of reaction was controlled by the rate of addition of the butyl bromide. Vigorous stirring was used throughout both this step and those following. Lithium bromide precipitated from the ether solution as a chalky white solid.

After the formation of the butyllithium was complete, 47.5 g. (0.150 mole) of chloro-2,4,6-tris-(trifluoromethyl)-benzene, mixed with an equal volume of ether, was added slowly. An exothermic reaction occurred throughout the addition. When no further reaction was apparent, the mixture was refluxed for 0.5 hour and then cooled in an ice-bath. Acetaldehyde (8.8 g., 0.20 mole) was mixed with an equal quantity of ether and added to the solution of organometallic compound. No apparent reaction occurred on mixing. However, on refluxing for 0.5 hour the mixture changed from a pale yellow to a bright orange color. The mixture was hydrolyzed with a saturated solution of ammonium chloride and the ether layer separated, dried, and the ether removed by distillation. Rectification of the remaining organic material yielded 26.4 g. (55.0%) of 2,4,6-tris-(trifluoromethyl)-α-methylbenzyl alcohol, b. p. 71–72° (4 mm.), m. p. 56–56.5°, $n^{26}\text{D}$ 1.4092.

Anal. Calcd. for $C_{11}H_7F_9O$: F, 52.4. Found: F, 51.9.

A small quantity of 2,4,6-tris-(trifluoromethyl)-phenyllithium was prepared as above and hydrolyzed with a saturated solution of ammonium chloride. No unreacted chloro-2,4,6-tris-(trifluoromethyl)-benzene was observed and an 89% yield of 1,3,5-tris-(trifluoromethyl)-benzene was obtained. This discounted the possibility that the butyllithium had attacked fluorine present in the trifluoromethyl groups. The exchange reaction with lithium goes very well, but the reaction of the organometallic compound with the carbonyl compound seems to be a limiting factor in the preparation of 2,4,6-tris-(trifluoromethyl)-α-methylbenzyl alcohol.

2,4,6-Tris-(trifluoromethyl)-styrene.—2,4,6-Tris-(trifluoromethyl)-α-methylbenzyl alcohol (10.0 g., 0.031 mole) was dissolved in 100 ml. of dry benzene contained in a small round-bottom flask and 7.1 g. (0.05 mole) of phosphorus(V) oxide was added as a suspension in benzene. A trace of hydroquinone was added as a polymerization inhibitor and the mixture was shaken vigorously for thirty minutes. The benzene solution was then decanted from the partially hydrated phosphorus(V) oxide and distilled. After the benzene had been removed at atmospheric pressure, the product was rectified under reduced pressure to give 3.4 g. (56.6%) of 2,4,6-tris-(trifluoromethyl)-styrene, b. p. 59° (20 mm.), $n^{27}\text{D}$ 1.3900, $d^{24}{}_4$ 1.4540.

Anal. Calcd. for $C_{11}H_6F_9$: F, 55.6: Found: F, 52.6.

The Attempted Polymerization of 2,4,6-Tris-(trifluoromethyl)-styrene.—Four tests were conducted in sealed tubes. Two were activated with a trace of benzoyl peroxide and two with ultraviolet radiation. They may be summarized as follows: 1. Activated with benzoyl peroxide at 70° for 48 hours: (a) 1 g. of substituted styrene; (b) 1 g. of substituted styrene and 1 g. of vinyl acetate.

2. Activated with ultraviolet radiation at 30° for 70 hours: (a) 1 g. of substituted styrene; (b) 1 g. of substituted styrene and 1 g. of vinyl acetate.

In tests 1a, 2a and 2b, no apparent polymerization occurred. The mobility of each sample remained unaltered throughout the test. Sample 1b, however, polymerized to a highly viscous material. After removal of the volatile starting materials, the sample was analyzed for fluorine. Since none was found, it appears that no copolymerization took place. Rather, the styrene may have exerted a hindering effect upon the polymerization of vinyl acetate as apparently was the case in sample 2b. The inability of 2,4,6-tris-(trifluoromethyl)-styrene to polymerize is not surprising, since it is sterically hindered with two ortho trifluoromethyl substituents.

Attempted Preparation of 2,4,6-Tris-(trifluoromethyl)-α,α-dimethylbenzyl Alcohol.—2,4,6-Tris-(trifluoromethyl)-phenyllithium, 28.8 g., was prepared in an ether solution by means of a butyllithium exchange as discussed previously. Dry acetone, 7 g., was introduced with no evolution of heat or apparent reaction. The mixture was refluxed for five hours, but no color change occurred as in the previously condensation with acetaldehyde. After hydrolysis and isolation of the ether layer, and removal of the ether by distillation, the remaining organic material was distilled. None of the desired product was formed, but due to the hydrolysis of the organometallic compound, 24 g. of 1,3,5-tris-(trifluoromethyl)-benzene, b. p. 118–119° (750 mm.), was obtained. Apparently, the carbonyl group in acetone is unable to react with 2,4,6-tris-(trifluoromethyl)-phenyllithium because of steric effects.

Summary

1. The synthesis and the attempted polymerization of 2,4,6-tris-(trifluoromethyl)-styrene are described.

2. An attempt to prepare 2,4,6-tris-(trifluoromethyl)-α-methylstyrene was unsuccessful.

LAFAYETTE, IND. RECEIVED APRIL 1, 1950

[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

o-Benzylphenol Derivatives. VI.[1] Quaternary Ammonium Halides[2a]

BY WILLIAM B. WHEATLEY, WILLIAM E. FITZGIBBON, WILLIAM F. MINOR, RICHARD R. SMITH, LEE C. CHENEY AND S. B. BINKLEY[2b]

The discovery that dialkylaminoalkyl ethers of *o*-benzylphenol (and substituted *o*-benzylphenols) exhibit potent antihistaminic activities[3] made it worth while to prepare further related compounds. One type which came to mind was the quaternary ammonium halides derived from the tertiary aminoethers. Accordingly, a series of quaternaries has been prepared and evaluated for possible physiological activity. The majority of the quaternary halides prepared were those derived from substituted N,N-dimethyl *o*-benzylphenoxyethylamines, and thus constitute a new class of choline ethers. It is not surprising, therefore, that quaternization was attended by a profound change in physiological behavior. Antihistaminic activity is present in the quaternaries, but to a lesser degree than in the tertiary amines. A noteworthy fact is that the quaternaries possess a high degree of vasopressor activity. A report

---

[1] For paper V in this series, see Wheatley, Cheney, Fitzgibbon and Binkley, THIS JOURNAL, **72**, 4443 (1950).

[2] (a) Presented before the Division of Medicinal Chemistry of the American Chemical Society, Chicago, September 3–8, 1950. (b) University of Illinois College of Medicine, Chicago, Ill.

[3] (a) Cheney, Smith and Binkley, THIS JOURNAL, **71**, 60 (1949); (b) Wheatley, Cheney and Binkley, *ibid.*, **71**, 64, 3795 (1949); (c) Mills, Rohrmann, Dinwiddie and Lee, *Arch. internat. pharmacodyn.*, **80**, 119 (1949).