Alkylation of Benzene with Triphenylmethyl Chloride

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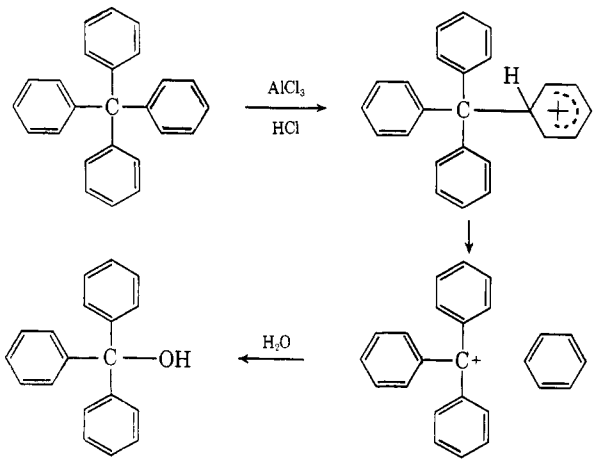
It is common knowledge that benzene and similar aromatic compounds may be readily alkylated with an alkyl halide under Friedel–Crafts conditions. It is, however, a curious fact that tetraphenylmethane cannot be prepared by such direct alkylation procedures.[1] Triphenylmethyl chloride fails to alkylate benzene as do similar systems which presumably involve an intermediate triphenylmethyl cation. Arguments have been presented[2] that this cannot be due to steric hindrance nor to instability of tetraphenylmethane for this substance is "thermally stable."

It appeared reasonable that the thermal stability of tetraphenylmethane should have little or no relationship to the failure of the Friedel–Crafts alkylation reaction but rather the product might well be unstable with respect to reactants under the alkylating conditions. The alkylation process is acknowledged as being in some measure reversible; hence one might anticipate fairly ready dealkylation of the substituted benzene to generate the relatively stable triphenylmethyl cation and benzene. Accordingly we allowed tetraphenylmethane to react with anhydrous aluminum chloride and hydrogen chloride in benzene solution. Hydrolysis of the reaction mixture gave an almost quantitative yield of triphenylcarbinol thus indicating facile dealkylation of the substituted benzene.



In contrast to its ready fragmentation in the presence of aluminum chloride, tetraphenylmethane appears to undergo very little change in concentrated sulfuric acid at room temperature. At higher temperatures the characteristic ultraviolet spectrum of the triphenylmethyl cation could be detected in the solution although the bulk of the tetraphenylmethane could be recovered unchanged from the solution.

The observance of similar behavior in related substances is to be anticipated.

(1) C. A. Thomas, "Anhydrous Aluminum Chloride," Reinhold Publishing Co., New York, N. Y., 1941, p. 116.

(2) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 357.

One might now postulate that the triphenylmethyl cation will alkylate benzene but due to an unfavorable equilibrium one fails to obtain significant quantities of product. As a simple test of this hypothesis we allowed 4-methyltriphenylmethyl chloride[3] to react with benzene in the presence of aluminum chloride. If reversible alkylation and dealkylation occurs one would expect to generate a mixture of benzene, toluene, triphenylmethyl cation, and the cation derived from the original reactant. Such was evidently the case for hydrolysis of the reaction mixture afforded triphenylcarbinol, diphenyl-4-tolylcarbinol, and a liquid fraction containing largely benzene but in which toluene could be identified by vapor phase chromatography.

Experimental

Dealkylation of Tetraphenylmethane.—A solution of 1.60 g. (0.005 mole) of tetraphenylmethane in 20 ml. of anhydrous benzene was saturated with anhydrous hydrogen chloride. Upon addition of 2 g. of anhydrous aluminum chloride the colorless mixture turned deep red in color. The mixture was warmed briefly on a steam cone, poured into water, and extracted with ether. Evaporation of the ether extract left a yellow solid residue which, upon decolorization with charcoal and crystallization, afforded 1.25 g. of triphenylcarbinol, m.p. 162–163°. Admixture with authentic triphenylcarbinol gave no melting point depression. The infrared spectrum was identical with that of authentic material.

Attempted Alkylation of Benzene.—A solution of 5.8 (0.02 mole) of 4-methyltriphenylmethyl chloride and 4 g. of anhydrous aluminum chloride in 20 ml. of dry benzene was stirred for 6 hr. at room temperature and then warmed briefly on a steam cone and poured into ice–water. The organic material was extracted with ether and the extract was carefully fractionated by distillation to give an aromatic fraction which by vapor phase chromatography analysis contained a small but definite quantity of toluene. The distillation residue afforded 0.47 g. of authentic triphenylcarbinol after much tedious handling. Somewhat impure diphenyl-4-tolylcarbinol was also recovered and identified by its infrared spectrum.

(3) A. Bistrzycki and J. Gyr, *Ber.*, **37**, 655 (1904).

t-Butyl S-Methyl and S-Phenyl Thiolcarbonates[1]

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Since the first report[2] in 1956 describing the use of the carbo-*t*-butoxy protective group its numerous advantages over other protective groups have become clear. Sufficient effort has been expended regarding the introduction and removal of this function that it has become one of the most valuable of all amino-protecting groups.[3,4]

(1) Supported by a grant (RG-9706) from the National Institutes of Health.

(2) L. A. Carpino, Abstracts of the 129th National Meeting of the American Chemical Society, Dallas, Tex., April, 1956, p. 59N.

(3) For references to earlier work, see L. A. Carpino, *J. Am. Chem. Soc.*, **82**, 2725 (1960).

(4) For recent examples of the advantageous utilization of the carbo-*t*-butoxy group in the synthesis of complex polypeptides and references to earlier work of the Swiss group, see R. Schwyzer and A. Tun-Kyi, *Helv. Chim. Acta*, **45**, 859 (1962).

It is, therefore, of interest to describe a simple method for the preparation of the heretofore difficultly accessible thiol ester, *t*-butyl S-methyl thiolcarbonate, undoubtedly the best of the currently available intermediates for the preparation of *t*-butyl carbazate,[5] precursor of one of the most important carbo-*t*-butoxylating agents, *t*-butyl azidoformate.[10,11]

An earlier described synthesis[3] of *t*-butyl S-methyl thiolcarbonate suffers from the disadvantage that expensive, relatively inaccessible gaseous carbonyl sulfide is required. It has now been shown that the thiol ester is readily obtained by reaction of commercially available methyl chlorothiolformate[12] with *t*-butyl alcohol in refluxing chloroform in the presence of pyridine.[13] The corresponding S-phenyl ester was also obtained in analogous fashion in 61% yield from phenyl chlorothiolformate. Use of *t*-butyl S-phenyl thiolcarbonate might offer some advantage over the use of the methyl ester in the preparation of *t*-butyl carbazate by virtue of its increased reactivity toward hydrazine. The greater acidity of benzenethiol *vs.* phenol allows clean separation of the resultant *t*-butyl carbazate and the coproduct benzenethiol thus avoiding a difficulty which arises in the use of the corresponding oxygen analog, *t*-butyl phenyl carbonate.[3,6]

Experimental[14]

t-Butyl S-Methyl Thiolcarbonate.—To a solution of 53.6 ml. of pyridine and 62.6 ml. of *t*-butyl alcohol in 200 ml. of chloroform which was stirred mechanically at room temperature there was added dropwise over 15–20 min. 66.4 g. of methyl chlorothiolformate.[12] The mixture was stirred and refluxed for 24 hr. and then washed in a separatory funnel with two 200-ml. portions of water, three 100-ml. portions of 5% hydrochloric acid, and finally 100 ml. of 1 *M* sodium bicarbonate. The solution was dried over magnesium sulfate and most of the solvent removed by distillation at atmospheric pressure followed by the use of a water aspirator.

Distillation of the residue gave 61.5 g. (69%) of the ester, b.p. 62–65° (24 mm.). Redistillation through a 30-cm. helices-packed column gave 50 g. (56%) of the ester, b.p. 60–63° (24 mm.), lit.[3] b.p. 60–62° (20 mm.). Conversion of this ester to *t*-butyl carbazate by heating in an oil bath at 105–110° for 24 hr. has already been described.[3]

t-Butyl S-Phenyl Thiolcarbonate.—A solution of 62.6 ml. of *t*-butyl alcohol and 53.6 ml. of pyridine dissolved in 200 ml. of chloroform was treated at room temperature with stirring over a period of 10 min. with 103.4 g. (81.6 ml.) of phenyl chlorothiolformate.[12] The solution was refluxed with stirring for 55 hr. and worked up essentially as given for the corresponding methyl ester. Distillation from an ordinary Claisen flask gave 70 g. (61%) of the thiol ester, b.p. 88.5° (1.2 mm.) to 102° (1.9 mm.). A center cut for analysis, distilled through a 30-cm. helices-packed column (95% recovery) had b.p. 86° (0.9 mm.).

Anal. Calcd. for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71. Found: C, 63.23 H, 7.02.

Conversion of *t*-Butyl S-Phenyl Thiolcarbonate to *t*-Butyl Carbazate.—A mixture of 21 g. of *t*-butyl S-phenyl thiolcarbonate and 10 g. of 64% hydrazine was heated in a water bath to 85–90° with swirling for a few minutes until the two phases coalesced. The resulting solution was warmed in the water bath at 75–80° for 3 hr. and then poured into a solution of 8 g. of sodium hydroxide in 250 ml. of water. The resulting cloudy mixture was treated with decolorizing carbon at room temperature with occasional stirring for 1 hr. and filtered. The clear filtrate was extracted with ether in a continuous extractor for 48 hr.

Evaporation of the dried (magnesium sulfate) ether extract from a water bath with the aid of a water aspirator gave a colorless oil which solidified on cooling or seeding to give 10.5–11 g. (80–83%) of snow white crystals of *t*-butyl carbazate, m.p. 39.5–41° (lit.[6] m.p. 41–42°).

(5) Other methods which have been recommended for the synthesis of *t*-butyl carbazate involve acylation of hydrazine by means of *t*-butyl phenyl carbonate,[6] *t*-butyl *p*-nitrophenyl carbonate,[7,8] and N-*t*-butyloxycarbonylimidazole.[9]

(6) L. A. Carpino, *J. Am. Chem. Soc.*, **79**, 98 (1957).

(7) G. W. Anderson and A. C. McGregor, *ibid.*, **79**, 6180 (1957).

(8) F. Eloy and C. Moussebois, *Bull. soc. chim. Belges*, **68**, 409 (1959).

(9) W. Klee and M. Brenner, *Helv. Chim. Acta*, **44**, 2151 (1961).

(10) L. A. Carpino, C. A. Giza, and B. A. Carpino, *J. Am. Chem. Soc.*, **81**, 955 (1959), and earlier papers cited therein.

(11) R. Schwyzer, P. Sieber, and H. Kappeler, *Helv. Chim. Acta*, **42**, 2622 (1959).

(12) We acknowledge with thanks generous gifts of methyl, ethyl, and phenyl chlorothiolformates from The Stauffer Chemical Co., New York, N. Y.

(13) A number of other bases and solvents proved to be unsatisfactory in the conversion, giving lower yields or other products. These included dimethylaniline, quinoline, triethylamine or pyridine in methylene dichloride, triethylamine in benzene, and trimethylamine or pyridine in dimethylformamide. We are indebted to David Collins for checking some of the preparations.

(14) Analyses are by Galbraith Laboratories, Knoxville, Tenn.

Reductions of 3,6-Diphenyl-*s*-tetrazine[1,2]

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In the course of attempting to prepare 3,6-bis(hydroxymethyl)-*s*-tetrazine *via* the reduction of 3,6-bis(carboxy)-*s*-tetrazine with lithium aluminum hydride, it became apparent that the tetrazine ring was cleaved. In order to facilitate the study of this reduction, 3,6-diphenyl-*s*-tetrazine[2] (I) was utilized instead of the 3,6-bis(carboxy)-*s*-tetrazine since the former is much easier and cheaper to prepare.

When I is slowly added to an ether solution of lithium aluminum hydride, there is an immediate loss of red color. Hydrolysis of the reaction mixture gives a yellow, ether-soluble product. This product has been identified as benzalazine by means of melting point, nitrogen analysis, and mixture melting point with an authentic sample of benzalazine. The infrared spectrum of this material is identical with that of benzalazine.

Hydrazine is identified as one of the products by the addition of benzaldehyde to the aqueous hydrolyzate. A yellow solid is recovered from this reaction and is identified as benzalazine. Ammonia is not observed as a product of the reduction. Sodium borohydride gives essentially the same results in this reaction. The reaction of I with sodium dithionite gives only 1,2-dihydro-3,6-diphenyl-*s*-tetrazine.[2,3] The reduction of this dihydrotetrazine with lithium aluminum hydride gives benzalazine. Benzalazine is not changed when an ether solution of it and lithium aluminum hydride are refluxed overnight. The reduction of 3,6-diphenyl-*s*-tetrazine or 1,2-dihydro-3,6-diphenyl-*s*-tetrazine with zinc dust and acetic acid gives 3,5-diphenyl-1,2,4,4*H*-triazole.[4] This triazole is not changed when it is warmed with lithium aluminum hydride overnight.

(1) Supported by a grant (CY3908) from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare, Bethesda, Md. Presented at the Southwest Regional Meeting of the American Chemical Society, Dallas, Tex., December, 1962.

(2) A. Pinner, *Ber.*, **26**, 2126 (1893).

(3) P. Chabries and S. H. Renard, *Compt. rend.*, **230**, 1673 (1950).

(4) R. Huisgen, J. Sauer, and M. Seidel, *Ann. Chem.*, **654**, 146 (1962).