was filtered. The solid obtained by removal of the benzene was purified according to the methods utilized in the literature references (*cf.* Table II).

Nitrosation Procedure.—Diethyl malonate, 55.0 g. (0.32 mole), was added dropwise at −40° to a suspension of 72.0 g. (0.45 mole) of complex in 300 ml. of nitroethane in a 500-ml. flask equipped with a dropping funnel, stirrer and reflux condenser. After 45 minutes the blue-colored mixture was allowed to warm to room temperature whereupon an exothermic reaction occurred which required cooling to maintain the temperature below 35°. When the reaction subsided, the mixture was washed with 5% sodium carbonate solution and water, dried and distilled. There were obtained: (a) diethyl mesoxalate, 11 g. (28%), b.p. 95–115° (18 mm.), hydrate m.p. 56°; (b) diethyl oximinomalonate, 25 g. (39%), b.p. 170–180° (18 mm.).

A 90% yield of diethyl mesoxalate was obtained by Curtiss[13] using gaseous N_2O_3 on diethyl malonate in the absence of solvent while Cerchez[6] reported a 50–90% yield of diethyl oximinomalonate using N_2O_3 and sodium ethoxide.

Dimethylaniline, 1.2 g., dissolved in 30 ml. of nitroethane, was added to a suspension of complex in nitroethane at 0–2°. The nitroethane was boiled off after washing with 5% sodium carbonate solution giving 1.5 g. of *p*-nitrosodimethylaniline, m.p. 84°.

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[13] R. S. Curtiss, *Am. Chem. J.*, **35**, 482 (1906).

LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TORONTO]

Triphenylsilyl Phenyl Ketone

BY A. G. BROOK

RECEIVED APRIL 1, 1957

Triphenylsilyl phenyl ketone, the first reported α-silyl ketone, has been prepared. Although not susceptible to thermal rearrangement, it is readily decomposed by base to triphenylsilanol and benzaldehyde. It reacts abnormally with phenylmagnesium bromide and phenyllithium.

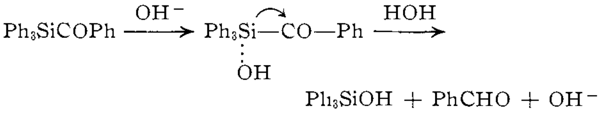
The abnormal behavior of substituents (especially halogen) attached to carbon alpha to a silicon atom has been referred to as the "α-silicon effect."[1,2] It is also apparent that functional groups located alpha to a silicon atom display unusual reactivity: the susceptibility of α-silanecarboxylic acids and their esters both to thermal rearrangement and to base-catalyzed decomposition have been reported recently from this Laboratory.[2] It seemed of interest to see whether this enhanced reactivity was present in other α-silylcarbonyl compounds, to which end the ketone, triphenylsilyl phenyl ketone, has been prepared. No α-silyl ketones have previously been reported in the literature, although indirect evidence for the formation of an α-silylaldehyde has been reported.[3]

Triphenylsilyl phenyl ketone was best prepared from triphenylbenzylsilane. Neither permanganate oxidation nor chromic acid oxidation yielded the desired compound, probably because of its instability, and only triphenylsilanol was isolated. Treatment with two equivalents of N-bromsuccinimide led to triphenylsilyl-α,α-dibromobenzylsilane. This compound was converted readily with silver acetate in an acetone–ethanol–water medium to the yellow ketone, m.p. 102–104°, in good yield. A phenylhydrazone derivative was prepared; attempts to prepare the oxime led to the formation of triphenylsilanol and benzaldehyde.

The ketone was also prepared, but in poor yield, by treatment of benzoyl chloride with an ethereal suspension of triphenylsilylpotassium: attempts to prepare it from triphenylsilane and benzoyl chloride using pyridine, aluminum chloride or boron fluoride as catalysts failed, and only tars or starting materials were isolated.

That the ketone is colored is of interest since organosilicon compounds are generally colorless, a fact generally attributed to the failure of silicon to participate significantly in resonance hybridization.[4] In the present case the color is even more unusual since the carbon analog, β-benzopinacolone, is colorless. The infrared spectrum of the ketone shows apparently normal absorption for the benzoyl group at about 1575 and 1610 cm.$^{-1}$.

The ketone does not rearrange thermally. When heated to 250°, it was recovered almost quantitatively, and when heated to 365°, although some decomposition occurred, no carbon monoxide was eliminated, and 70% of the material was recovered unchanged. However, the compound is extremely labile in basic medium. If a dilute ethanol solution is treated at room temperature with a few drops of aqueous alkali, the yellow color disappears in a few minutes and triphenylsilanol and benzaldehyde are formed. The same reaction occurs when the compound is chromatographed on activated alumina, although it may be recovered by elution from acid-washed alumina. This decomposition is evidently analogous to the base-catalyzed decomposition of triphenylsilanecarboxylic acid and its esters.



$$Ph_3SiCOPh \xrightarrow{OH^-} \underset{\vdots \atop OH}{Ph_3Si}\text{—}CO\text{—}Ph \xrightarrow{HOH} Ph_3SiOH + PhCHO + OH^-$$

When triphenylsilyl phenyl ketone was treated with phenylmagnesium bromide, the expected product of addition to the carbonyl group, triphenylsilyldiphenylcarbinol, was not isolated. Instead, the only product isolated was tetraphenylsilane (5%), other than some recovered ketone and triphenylsilanol, presumably formed by decomposition of the ketone when the reaction mixture

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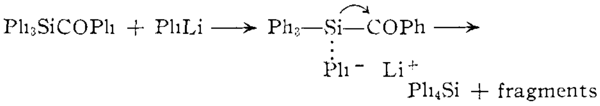
[1] F. C. Whitmore and L. H. Sommer, THIS JOURNAL, **68**, 481 (1946).

[2] A. G. Brook and H. Gilman, *ibid.*, **77**, 2322, 4827 (1955); A. G. Brook and R. J. Mauris, *ibid.*, **79**, 971 (1957).

[3] L. H. Sommer, D. L. Bailey, G. M. Goldberg, C. E. Buck, T. S. Bye, F. J. Evans and F. C. Whitmore, *ibid.*, **76**, 1613 (1954).

[4] For a summary of pertinent evidence and references see H. Gilman and G. E. Dunn, *Chem. Revs.*, **52**, 77 (1953).

was hydrolyzed. The same product was isolated in 10% yield when phenyllithium was used. This product was probably formed by nucleophilic attack on silicon by the organometallic reagent analogously to the reaction described above, although, as will be shown in a forthcoming publication, the addition product triphenylsilyldiphenylcarbinol is itself decomposed by phenyllithium forming tetraphenylsilane in high yield.



$$Ph_3SiCOPh + PhLi \longrightarrow Ph_3\text{—}\underset{\underset{Ph^-\ \ Li^+}{\vdots}}{Si}\text{—}COPh \longrightarrow Ph_4Si + \text{fragments}$$

From this and related work it seems probable that all α-silylcarbonyl compounds will be susceptible to base-catalyzed hydrolysis in which the silicon–carbonyl bond is broken.

Experimental[5]

Triphenyl-α,α-dibromobenzylsilane.—To 4.85 g. (0.0138 mole) of triphenylbenzylsilane[6] in 50 ml. of carbon tetrachloride was added 5.3 g. (0.030 mole) of N-bromosuccinimide. The mixture was refluxed for 18 hr., cooled and 3.05 g. (110%) of crude succinimide, m.p. 117–122°, was filtered off. The filtrate was evaporated to dryness under reduced pressure and the gummy solid recrystallized from ethyl acetate to yield 4.85 g. (70%) of crude white triphenyl-α,α-dibromobenzylsilane, m.p. 112–116°. One additional crystallization raised the melting point to 119–120°.

Anal. Calcd. for $C_{25}H_{20}SiBr_2$: Si, 5.51; Br, 31.5. Found: Si, 5.53; Br (as AgBr), 31.7.

Triphenylsilyl Phenyl Ketone. A. From Triphenyl-α,α-dibromobenzylsilane.—A mixture of 3.0 g. (0.059 mole) of triphenyl-α,α-dibromobenzylsilane and 2.0 g. (0.12 mole) of silver acetate in 40 ml. of ethanol, 15 ml. of water and 30 ml. of acetone was stirred at room temperature for 15 hr. The purplish-gray precipitate was filtered off and washed with acetone to yield 2.31 g. (103%) of silver bromide. The combined filtrates were evaporated to dryness under reduced pressure at room temperature to yield 1.99 g. of yellow powder, m.p. 90–99°. This was twice recrystallized from absolute ethanol to yield 1.67 g. (78%) of yellow needles, m.p. 102–103°.

Anal. Calcd. for $C_{25}H_{20}OSi$: C, 82.4; H, 5.53; Si, 7.70. Found: C, 82.7; H, 5.50; Si, 7.63.

When silver nitrate was used to remove the bromine, the same compound was obtained, but considerable decomposition occurred as indicated by the formation of triphenylsilanol and benzaldehyde (see below).

B. From Triphenylsilylpotassium and Benzoyl Chloride.[7]—To a solution of 2.81 g. (0.02 mole) of benzoyl chloride in 50 ml. of dry ether at 0° was added over an hour a suspension of 0.02 mole of amalgamated triphenylsilylpotassium in 100 ml. of ether. The green suspension was stirred for 14 hr. and then was hydrolyzed with water. Insoluble hexaphenyldisilane, m.p. 353–355°, weighing 1.66 g. (33%) was filtered off and identified by mixed melting point with an authentic specimen.

The ether layer, dried over sodium sulfate, was concentrated and then distilled under reduced pressure (1 mm.). There was isolated 0.13 g. (6%) of benzoyl chloride and 0.90 g. of a yellow solid boiling at 130–170°. Several recrystallizations from carbon tetrachloride and petroleum ether (b.p. 60–70°) yielded 0.28 g. (4%) of triphenylsilyl phenyl ketone, m.p. 102–104°, whose identity was confirmed by a mixed melting point with the material described above.

A phenylhydrazone derivative was prepared by refluxing a mixture of 0.5 g. (0.00137 mole) of the ketone in 8 ml. of ethanol with 0.18 g. of phenylhydrazine and 5 drops of glacial acetic acid for 5 minutes. During this time the yellow color of the original solution faded. On cooling white crystals were deposited which on recrystallization from 1:1 benzene-ethanol yielded 0.35 g. (56%) of almost colorless crystals, m.p. 150–151.5°.

Anal. Calcd. for $C_{31}H_{26}N_2Si$: C, 82.0; H, 5.78; N, 6.17. Found: C, 82.1; H, 5.77; N, 6.33.

Attempts to prepare the oxime by treatment of the ketone with hydroxylamine hydrochloride and pyridine in ethanol-water caused rapid fading of the yellow color. The odor of benzaldehyde was noticeable and a small amount of triphenylsilanol, m.p. 150–151°, was the only product isolated.

Attempted Thermal Rearrangement of Triphenylsilyl Phenyl Ketone.—A 0.5-g. sample of the ketone was heated in a small test-tube to 250° and held at this temperature for 5 minutes. No carbon monoxide[8] was evolved, but a faint odor of benzaldehyde was detected. After cooling the yellow solid melted at 100–102°, and one recrystallization from absolute ethanol gave 0.42 g. (84%) of ketone which melted at 102–103°.

When a 0.1-g. sample was heated at 365° for 10 minutes, no carbon monoxide was evolved, but a strong odor of benzaldehyde was observed and the color of the liquid darkened. The crude material melted at 88–93°, but one recrystallization from ethanol yielded 0.07 g. (70%) of ketone, m.p. 101–102°, identified by mixed melting point with an authentic specimen.

Reaction of Triphenylsilyl Phenyl Ketone with Alkali.—When 0.5 g. (0.00137 mole) of the ketone, dissolved in acetone (or ethanol), was treated with a few drops of 10% aqueous sodium hydroxide at room temperature, the yellow color rapidly faded (2–5 minutes). The odor of benzaldehyde was noticeable. When the solution was drowned in water, a white precipitate formed. After recrystallization from petroleum ether (b.p. 90–100°), this 0.34 g. (89%) of triphenylsilanol melted at 150–152°, and a mixed melting point with an authentic sample was not depressed.

To isolate the benzaldehyde, a hydrolyzed ethanol solution of the ketone was drowned in water and extracted 3 times with ether. The ether solution was treated with 1 ml. of phenylhydrazine, several drops of glacial acetic acid and 10 ml. of ethanol. The solution was boiled to remove the ether and then cooled. Fractional crystallization of the reaction mixture yielded a total of 0.23 g. (85%) of crude benzaldehyde phenylhydrazone, which after recrystallization from ethanol yielded 0.19 g. (70%) of pale yellow needles, m.p. 154–156°, which were identified by mixed melting point with an authentic specimen, m.p. 156–157°. In addition, 0.03 g. (8%) of triphenylsilanol, m.p. 150–152°, was isolated.

Reaction of Triphenylsilyl Phenyl Ketone with Phenylmagnesium Bromide and Phenyllithium.—When 2.0 g. (0.0055 mole) of triphenylsilyl phenyl ketone in 45 ml. of ether was treated with 2.5 ml. of 2.16 *N* phenylmagnesium bromide (0.0055 mole) no apparent change occurred until after 1 hr. when a white precipitate formed. The mixture was stirred for 18 hr. but still gave a positive Color Test I.[9] It was then hydrolyzed with water and acid. The yellow ether layer was worked up yielding a yellow oil which eventually partially crystallized. Recrystallization from benzene gave 0.1 g. (5%) of tetraphenylsilane, m.p. 233–235°, identified by mixed melting point. The residual oil was chromatographed on acid-washed alumina, eluting with petroleum ether (b.p. 60–70°), and although some decomposition occurred as evidenced by the loss of color, 0.18 g. (9%) of the ketone, m.p. 102–104°, was eventually isolated. Finally 0.23 g. (15%) of triphenylsilanol, m.p. 150–152°, was isolated and identified by mixed melting point.

When 2.0 g. (0.0055 mole) of the ketone in 30 ml. of dry ether was treated with 15 ml. of 0.5 *N* phenyllithium (0.0075 mole), the first few drops added caused a color change to orange and then to orange-red. A white solid then precipitated. The mixture was refluxed for 8 hr. at which time a positive Color Test I was obtained. The reaction mixture was poured into cold dilute acid. The only products isolated were 0.64 g. (42%) of crude triphenylsilanol, m.p. 135–145°, which was recrystallized from petroleum ether (b.p. 90–100°) to yield 0.32 g. (21%) of triphenylsilanol,

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(5) Reactions involving organometallic reagents were carried out in a dry, oxygen-free nitrogen atmosphere.

(6) H. Gilman, A. G. Brook and L. S. Miller, THIS JOURNAL, **75**, 3757 (1953).

(7) This run was carried out by Saul Wolfe in this Laboratory.

(8) R. Nowicki, *Chem. Ztg.*, **35**, 1120 (1911).

(9) H. Gilman and F. Schulze, THIS JOURNAL, **47**, 2002 (1925).

m.p. 149–151°, and 0.28 g. (15%) of crude tetraphenylsilane, m.p. 193–208°, which after recrystallization from benzene gave 0.18 g. (10%) of pure tetraphenylsilane, m.p. 230–232°, all products identified by mixed melting point.

Acknowledgment.—The author is indebted to N. Wolfish and M. Gold for technical assistance, to Dr. Henry Gilman and the Institute for Atomic Research, Iowa State College, for the infrared spectrum and to the National Research Council of Canada for a grant supporting this research.

TORONTO, CANADA

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

10-(3-Dimethylaminopropyl)-2-(Trifluoromethyl)-phenothiazine Hydrochloride (VESPRIN[1]) and Related Compounds. I

BY HARRY L. YALE, FRANCIS SOWINSKI AND JACK BERNSTEIN

RECEIVED MARCH 18, 1957

The thionation of 3-(trifluoromethyl)-diphenylamine has yielded 2- and 4-(trifluoromethyl)-phenothiazine. These two nuclei have been allowed to react with various dialkylaminoalkyl chlorides in the presence of sodamide to give 10-dialkylaminoalkyl-2- and 4-(trifluoromethyl)-phenothiazine. Hydrogen peroxide has converted these compounds to various oxygenated derivatives. An improved procedure is described for the preparation of 3-(trifluoromethyl)-phenothiazine. Since this nucleus did not react with dimethylaminopropyl chloride in the presence of sodamide, an indirect procedure was used to prepare the 10-(3-dimethylaminopropyl) derivative.

We have for several years been interested in variously substituted phenothiazine derivatives[2] and wish now to report on a series of 10-dialkylaminoalkyl-2-, -3- and -4-(trifluoromethyl)-phenothiazines and their oxygenated derivatives. Several of these compounds have shown good specificity and high potency as ataractic agents in laboratory animals[3] and are now undergoing clinical evaluation.

The thionation of 3-(trifluoromethyl)-diphenylamine should lead to the formation of both 2-(trifluoromethyl)-phenothiazine and 4-(trifluoromethyl)-phenothiazine. From such a reaction, however, Smith[4] isolated only one (trifluoromethyl)-phenothiazine. This compound showed a deep band in the infrared at 12.17 μ, an absorption band not seen in the spectrum of phenothiazine itself. Since the infrared spectra of asymmetrical trisubstituted benzenes show a characteristic deep band in the region 12.0–12.5 μ while vicinal trisubstituted benzenes show a characteristic deep band in the region 12.5–13.15 μ, Smith concluded that his product was 2-(trifluoromethyl)-phenothiazine. This method of differentiating isomers in monosubstituted phenothiazines received additional support in the observation of Roe and Little[5] that 3-(trifluoromethyl)-phenothiazine, prepared by an unambiguous synthesis, showed a deep band in the infrared at 12.2 μ.

The work of Charpentier[6] has demonstrated that the thionation of 3-substituted diphenylamines, *e.g.*, 3-methyldiphenylamine, leads to 2- and 4-substituted phenothiazines; the less soluble, higher melting isomer (m.p. 187–188°) when heated with copper bronze gave 2-methylcarbazole, while the more soluble, lower melting isomer (m.p. 114–115°) gave 4-methylcarbazole.

We have re-examined the thionation of 3-(trifluoromethyl)-diphenylamine, and have isolated both 2-(trifluoromethyl)-phenothiazine, m.p. 188–189°, in 45% yield, and the hitherto unreported 4-(trifluoromethyl)-phenothiazine, m.p. 72–73° in 32% yield. It is of interest that the latter isomer showed a strong band at 12.7 μ, as anticipated, since it corresponds to a *vicinal* substituted benzene.

3-(Trifluoromethyl)-phenothiazine was prepared in one step in 52% yield by Roe and Little[5] *via* the Smiles rearrangement of 2-formamido-2′-nitro-4′-(trifluoromethyl)-diphenyl sulfide. Based on our own experience, we prefer the two step modification of the Smiles rearrangement, which employed the *2-acetamido derivative* and which gave a 91% yield over-all.

The reactions of 2- and 4-(trifluoromethyl)-phenothiazine with various dialkylaminoethyl chlorides and dialkylaminopropyl chlorides in toluene or xylene, in the presence of sodamide, gave the desired 10-substituted derivatives in good yields. The reaction of 3-(trifluoromethyl)-phenothiazine with dimethylaminopropyl chloride under the same conditions was unsuccessful. Instead of the usual dark brown colored reaction mixtures, deep violet colored solutions were obtained, which, even after prolonged reflux periods, when cooled and hydrolyzed with water became colorless and when worked up in the usual manner yielded only unreacted 3-(trifluoromethyl)-phenothiazine. It became necessary to use the indirect procedure outlined below which gave the desired product.

2-(Trifluoromethyl)-10-phenothiazinepropionitrile[7] and lithium aluminum hydride gave 10-(3-aminopropyl)-2-(trifluoromethyl)-phenothiazine.

The preparation of 10-(4-dimethylaminobutyl)-2-(trifluoromethyl)-phenothiazine followed the sequence of reactions shown below, employing 4-

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(1) VESPRIN is a trademark of the Olin Mathieson Chemical Corporation.

(2) H. L. Yale, THIS JOURNAL, **77**, 2270 (1955).

(3) The tranquilizing activity of 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine hydrochloride was reported by J. C. Burke, H. L. Yale, G. L. Hassert and J. P. High and by J. J. Piala, J. P. High, K. Greenspan and J. C. Burke at the 1956 Meeting of The American Society for Pharmacology and Experimental Therapeutics at French Lick Springs, Indiana, November 8–10, 1956.

(4) N. L. Smith, *J. Org. Chem.*, **15**, 1125 (1950).

(5) A. Roe and W. F. Little, *ibid.*, **20**, 1577 (1955), have discussed the infrared spectra of this compound as well as a number of other fluorine substituted phenothiazines.

(6) P. Charpentier, P. Gailliot, R. Jacob, J. Gaudechon and J. Buisso, *Compt. rend.*, **235**, 59 (1952).

(7) N. L. Smith, *J. Org. Chem.*, **16**, 415 (1951).