ORGANOPENTAFLUOROSILICATES: REAGENTS FOR RAPID AND EFFICIENT INCORPORATION OF NO-CARRIER-ADDED RADIOBROMINE AND RADIOIODINE

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SUMMARY

An investigation exploring the utility of organopentafluorosilicates as intermediates for the site specific incorporation of no-carrier-added radiobromine or radioiodine into organic molecules was carried out. Some simple alkyl- and arylpentafluorosilicates were synthesized and reacted with in situ generated [^{77}Br]BrCl and [^{131}I]ICl. The radiohalogenations of aryl- and primary alkylpentafluorosilicates were found to be complete within 10 minutes at room temperature, with radiochemical yields of 74-96%. Radiohalogenations of a secondary alkylpentafluorosilicate, cyclohexylSiF_5K_2, gave lower radiochemical yields and required higher reaction temperatures.

Key Words: Radiohalogenation, Bromine-77, Iodine-131, Organopentafluorosilicates

INTRODUCTION

Organopentafluorosilicates are air- and moisture-stable dianionic complexes (salts) in which the valency of silicon has expanded from the usual tetravalent to hexavalent (1,2). Kumada, et al. (3,4) have reported that these coordinatively saturated organosilicon compounds readily undergo cleavage by halogens to yield alkyl or aryl organohalides. Our investigations (5,6) of no-carrier-added (nca) radiohalogenations (7) using aryltrimethylsilyl intermediates have demonstrated that good radiochemical yields can be obtained for both nca radiobrominations and radioiodinations of aromatic rings. Unfortunately, the nca radioiodinations of some aryl rings requires relatively harsh reaction conditions to obtain good radiochemical yields (i.e., 1-2 hours in HOAc at 60°C). Furthermore, the trimethylsilyl moiety can not be used to radiohalogenate alkyl groups. Because of these shortcomings of organotrimethylsilanes, we undertook an investigation of the applicability of organopentafluorosilicates to incorporate nca radiobromine and radioiodine into organic molecules. The investigation employed a variety of simple organopentafluorosilicates as model compounds. That investigation is described herein.

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RESULTS AND DISCUSSION

Initial experiments were conducted to determine if the mixed halogens, BrCl and ICl, could be generated and reacted in the presence of organopentafluorosilicates. The results of these experiments were important to the radiohalogenations as *in situ* generation of mixed halogens has proven to be the most efficient method for reactions involving *nca* radiohalogens. Also, Kumada (3) has reported that reactions of the mixed halogen, BrI, with alkylpentafluorosilicates yielded both alkylbromides and alkyliodides. Similar results for the mixed halogens employed in this study would decrease the radiolabeling efficiencies.

Non-radioactive mixed halogen reactions were carried out on an arylpentafluorosilicate, *para*-tolylSiF_5K_2 **6**, and an alkylpentafluorosilicate, n-hexyl-SiF_5K_2 **2**. The mixed halogens were generated in a variety of solvents (e.g., MeOH, HOAc, THF, DME) by oxidizing sodium bromide or sodium iodide with N-chlorosuccinimide (NCS) (8) or *tert*-butylhypochlorite (TBHC). Reactions of NCS/halide in the presence of a suspension of organopentafluorosilicate yielded yellow-orange solutions, which became colorless within 15 minutes. Likewise, use of TBHC as the oxidant yielded colored solutions which became colorless within 5 minutes at room temperature. Analyses of the reaction mixtures by HPLC and capillary GC indicated that only one product was formed in each reaction. The product was identical to either the corresponding bromide or iodide derivatives by chromatographic retention time. No chlorinated products were seen in any of the stoichiometric *in situ* generated mixed halogen reactions (9), even though the organopentafluorosilicates were readily chlorinated by TBHC.

Following the initial studies, some additional organopentafluorosilicates were synthesized, and all of the compounds, **1**-**7**, were investigated in radiohalogenation reactions. *In situ* generated mixed halogen radiohalogenations were carried out using *nca* sodium [^{77}Br]bromide and *nca* sodium [^{131}I]iodide. The results of the radiohalogenations are given in Table I. The radioiodinations

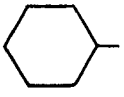
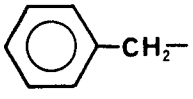
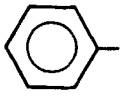
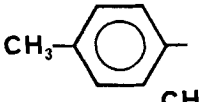
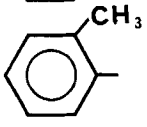
were quite facile, leading to only one product using NCS as the oxidant. Contrary to this, very poor radiochemical yields were obtained when NCS was used in the radiobrominations. Therefore, TBHC was used as the oxidant for the radiobrominations. This same result has been observed for nca radiobrominations of aryltrimethylsilanes. Unfortunately, the use of TBHC results in the formation of chlorinated products in the reaction mixtures, as the oxidant is used in large excess over the radionuclide. Reactions employing NCS as the oxidant have a distinct advantage in that NCS reacts very slowly with the organopentafluorosilicates.

All of the radiohalogenation reactions gave very good radiochemical yields within 10 minutes at room temperature, except reaction of 3. The effect of a highly steric environment, such as a cyclohexyl group, on a backside attack (S_E2-inversion reaction) of the electrophile has been previously noted as a cause of poor yields in the halogen cleavages of organopentafluorosilicates. We found that the radiohalogenation of primary alkylpentafluorosilicates were best carried out in protic solvents and the secondary alkylpentafluorosilicate, 3, was best reacted in aprotic solvents. Interestingly, these are the exact opposite results observed by Kumada, et al. (3). Elevation of the reaction temperature in the radiohalogenations gave improved radiochemical yields for the radiobromination, but not for the radioiodination (10).

The difference in the reaction mechanisms for alkyl- and arylpentafluorosilicates can be readily seen in the reactions of ortho-tolylSiF$_5$K$_2$, 7, as this reaction is at least as fast as the less sterically encumbered para-tolylSiF$_5$K$_2$. Unlike the reactions of the aryltrimethylsilanes, no difference in the reaction yields were observed between the use of MeOH or HOAc as solvents. In fact, reactions with nca radiohalides could be carried out by adding a small aliquot of the radiohalide solution as obtained, without neutralizing the base present (usually 0.1N NaOH).

Table I: Radiohalogenations of Organopentafluorosilicates[a]

$$R\text{-}SiF_5K_2 \xrightarrow{oxid/{}^*X^{\ominus}} R\text{-}{}^*X$$

Compound	R	Radiochemical Labeling Efficiencies (%)[b] TBHC/^{77}Br	NCS/^{131}I
1	CH_3CH_2-	86 (MeOH) 82 (HOAc)	96 (MeOH) 89 (HOAc)
2	$CH_3(CH_2)_4CH_2-$	81 (MeOH) 82 (HOAc)	77 (MeOH) 84 (HOAc)
3		58 (THF)[c] 70 (DME)[c]	24 (HOAc)
4		81 (MeOH)	--[d]
5		90 (MeOH) 86 (HOAc)	86 (MeOH) 74 (HOAc)
6		89(MeOH) 85 (HOAc)	88 (MeOH) 86 (HOAc)
7		94% (MeOH)	91% (MeOH)

[a]Reactions were run at room temperature except where noted. Reaction times were <5 min for radiobromination and <10 min for radioiodinations. [b]Radiochemical labeling efficiencies are taken as percentages of total activity on radiochromatograms that are associated with the product. [c]Fifteen minutes at 55°C. [d]Reaction not run due to expected instability of product.

The organopentafluorosilicates, like the aryltrimethylsilanes, are easily synthesized. The syntheses begin with the preparation of organotrichlorosilanes. These compounds are conveniently prepared in high yield from the reaction of Grignard reagents with tetrachlorosilanes (11), or by the process of hydrosilation of alkenes (12) or alkynes (13) with trichlorosilane and peroxides

or chloroplatinic acid (14). The organotrichlorosilanes can be readily converted to organopentafluorosilicates in high yields by their reaction with fluoride salts (usually potassium) in H_2O at 0-10°C (4). The organopentafluorosilicates are solid white precipitates which are quite insoluble in most solvents.

Reactions of the organopentafluorosilicates gave high radiochemical yields for radiohalogenations of primary alkyl groups. They also gave regiospecific aromatic substitutions under milder reaction conditions, with higher radiochemical yields, than the corresponding aryltrimethylsilanes. However, the use of organopentafluorosilicates for nca radiobrominations and radioiodinations will ultimately depend on the compound under study. While trimethylsilyl derivatives can be carried through on entire synthetic scheme, a major drawback to the use of organopentafluorosilicates may be that they must be put into molecules at the final step of a synthesis. This comes about by the fact that the organopentafluorosilicates are quite insoluble in most solvents, and their immediate precursors, organotrichlorosilanes, are very reactive species. However, the organopentafluorosilicates may have an advantage over organotrimethylsilanes in the purification process due to their insolubility and dianionic nature. While the organopentafluorosilicates were not found to be completely insoluble in the solvents employed, the reaction mixtures can be cleared of a large portion of starting material by filtration through a 0.2 micron Millipore filter. Additional purification may be readily available by ion chromatography.

Our studies of the radiohalogenations of organopentafluorosilicates, as well as purificaton of products, are continuing.

EXPERIMENTAL

All of the requisite organotrichlorosilanes needed to synthesize compounds 1-7 were purchased from Petrarch Systems, Inc. (Bristol, PA), with the exception of ortho-trichlorosilyltoluene. The synthesis of this compound is described below. The organotrichlorosilanes were converted to organopentafluorosilicates

by reaction of KF in H_2O at 0°C as previously described (4). All of the non-radioactive reagents and solvents were at least analytical reagent grade and were used as obtained. The sodium [^{131}I]iodide solution used was obtained from New England Nuclear (Boston, MA) containing 20 mCi activity in 500 μL of a 0.1N NaOH solution. The sodium [^{77}Br]bromide solution used was made by bombardment of a molybdenum target by medium energy protons (spallation reactions) at this facility as previously described (15).

Chromatography. Analyses of the non-radioactive reaction mixtures of compounds 2, 6, and 7 were performed on a Varian 3700 gas chromatograph using FID detection, coupled to a Spectra Physics 4100 integrator/plotter. Separations were accomplished on a 50-m SE-30 capillary column (J&W), using a temperature program of 50°C (5 min) to 150°C at 10°C/min for compound 2 and 5°C/min for compounds 6 and 7 (necessary to check regiospecificity).

Analyses of all of the reaction mixtures were performed with Waters Associates Liquid Chromatograph with 6000A pumps, U6K injector, Model 450 UV detector (at 254 nm), system controller, and data module. Separations were obtained with a reverse-phase (Radial Pak C-18) column on a Radial Compression Module, eluting with 60:40 CH_3CH/H_2O at a flow rate of 2 mL/min. Analyses of radiohalogenation reaction mixtures were performed on the HPLC system with a radioactivity detection system. This system consists of a 2-in NaI crystal coupled to an Ortec power bin, high voltage supply, ratemeter, amplifier, counter and timer, and line printer.

Radiohalogenations. Reactions were carried out with 1-2 mg of compounds 1-7 suspended in 100 μL solvent (e.g., MeOH, HOAc, THF, or DME) in 1 mL conical bottomed vials. Radiobrominations of these compounds were carried out by addition of 1-2 μL of the nca sodium [^{77}Br]bromide solution (300-500 μCi) followed by addition of 1 μL neat TBHC. Radioiodination of the compounds were carried out by addition of 1 mg NCS followed by 3-5 μL nca sodium [^{131}I]iodide solution (120-200 μCi). Reaction progress was followed by radioHPLC.

Synthesis of ortho-trichlorosilyltoluene. Reaction of 25 g ortho-bromotoluene to make the Grignard reagent was accomplished as previously described (16).

The Grignard reagent was then added to a solution of two equivalents of tetrachlorosilane in THF at such a rate as to keep the reaction temperature below 40°C (cooling by ice/H_2O bath needed at times). After the addition was complete, the reaction mixture was stirred at room temperature for an hour. Filtration of the white salts from a cooled reaction solution (ice/H_2O bath) and evaporation of the THF solvent under vacuo yielded a light yellow oil. Purification of the oil by Kugelrohr distillation at 55°C/100 μ Hg gave a colorless oil in 76% yield.

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