Title
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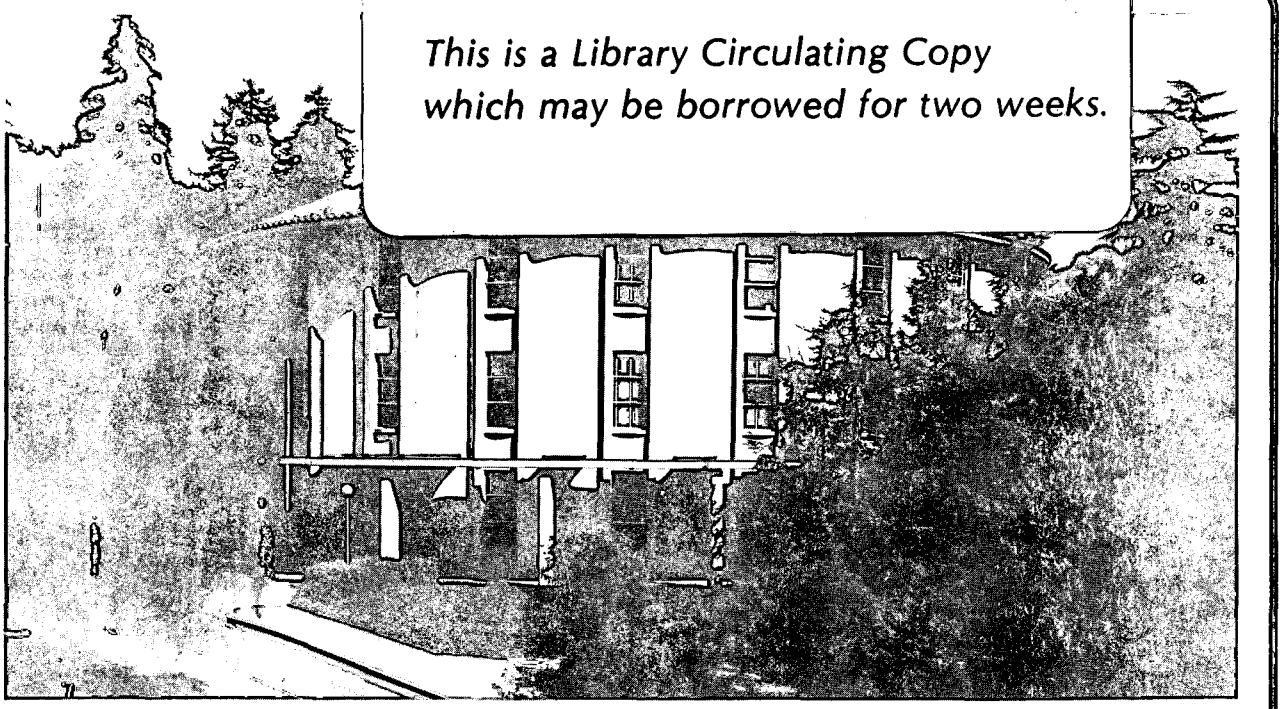

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DISCLAIMER

A NEW ROUTE TOWARDS THE SYNTHESIS OF MULTI-TRITIOMETHYL IODIDE.

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SUMMARY

A new procedure for the synthesis of multi-tritiated methyl iodide is reported. In this procedure trichloromethylphenyl sulfide was prepared and the trichloromethyl group was hydrogenolysed in the presence of 10% Pd/C and an organic base with deuterium gas to give the corresponding deuteriated sulfide as the precursor. Upon heating a mixture of the latter with excess of benzyl iodide in a special apparatus benzylphenyl sulfide remained as a solid by-product and liberated deuteriated methyl iodide was directly reacted with several simple amines to be N-deuteriomethylated. This new synthetic method can be extended to the tritiomethyl labeling of a variety of organic compounds having a methyl group attached to a heteroatom such as N,O and S.

INTRODUCTION

Tritiated compounds specifically labeled in the methyl group as a probe for biological studies have been used in biochemical research for many years (ref.1). Tritiated methyl iodide with low to moderate specific activity has extensively been used as a methylating reagent in the past and we recently reported a new and efficient method for the synthesis of monotritiomethyl iodide with high specific activity (22 Ci/mmol)(ref.2). However, in order to gain insight into the reaction mechanisms, it would be desirable to incorporate more tritium in the compounds of biological interest. One reagent which has been used widely in the past is tritiated methyl iodide with 100% isotopic aboundance which is derived from tritiated methanol (ref.3). Since the generation of tritiated methanol involves stringent conditions it is not applicable in most laboratories and as a part of our ongoing attempt to prepare similar species in an alternative and milder conditions we have recently used trichloromethyl ethers as precursors in our laboratory.

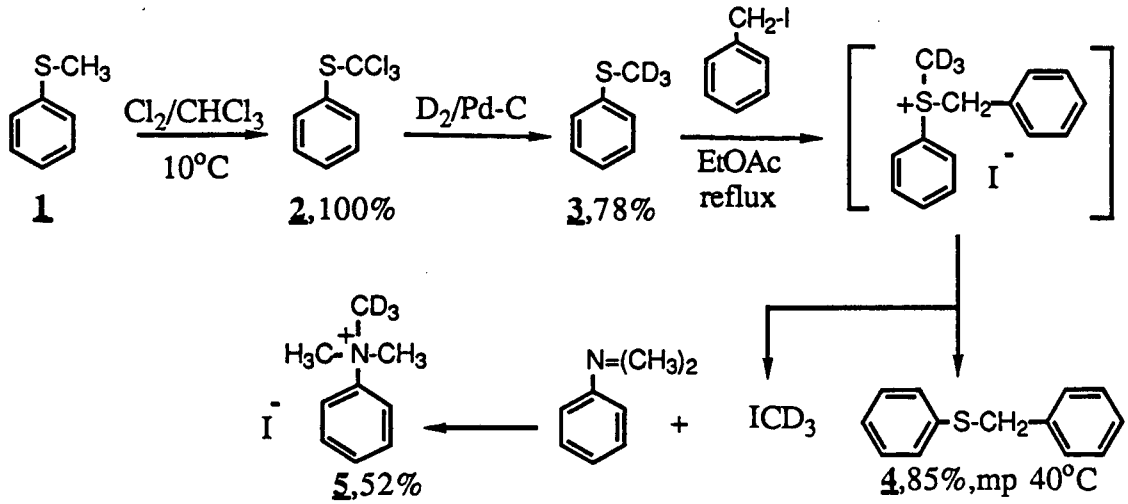
RESULTS AND DISCUSSION

For the synthesis of multi tritiated methyl iodide, our first attempt was to chlorinate the methyl group of anisole by chlorine gas. As it is also reported in the literature (ref.4), our preliminary results showed that even at a relatively high temperature there is little tendency for side-chain chlorination to occur and these alkyl aryl ethers are only chlorinated in the nucleus. However, with 4-chloroanisole a different result was obtained and in the presence of phosphorus pentachloride as the catalyst (ref.5),the reaction was clean with no nuclear substitution. The three hydrogen atoms of the methyl group were replaced successively by chlorine giving 4-chlorophenyl trichloromethyl ether. In this case,the presence of chlorine on the ring precluded any tritiodehalogenation on this compound,because the aromatic chlorine would also be replaced by tritium. Since carbon-flourine

bond has been found very stable under tritiodehalogenation reactions (ref.6) and the presence of a suitable electron withdrawing functionality on the ring was essential for side-chain chlorination,we chlorinated 4-fluoroanisole. It was unfortunate that the effect of fluorine was not strong enough to eliminate nucleus chlorination and a mixture of ring and side chain chlorinated products were formed which were not separatble by chromatographic techniques.

Pursuant to our search to find a suitable ether, we found that aryl methyl sulfides can be chlorinated smoothly and easily at room temperature; the nucleus is unattacked and the three hydrogen atoms of the methyl group are successively replaced by chlorine under very mild conditions(ref.7). An alternative method for the synthesis of this compound is based on the well-documented alkyl and aryl thiolation reactions (ref.8). Based on these reports, trichloromethylphenyl sulfide was synthesised in about 100% yield by the chlorination of thioanisole in chloroform at 10°C. This compound was stable and the first attempt to hydrogenolyse it with deuterium gas and in the presence of an organic base and a heterogeneous catalyst was successful. Surprisingly, the catalyst was not poisoned by the heteroatom through the direct linkage to the metal in this sulfur containing compound and the trichloromethyl group was converted to the corresponding deuteriated methyl group. In the preliminary experiments, the yield of the product was about 20-25% because the precursor was cleaved in the presence of the base to thiophenol. Carefull experiments combined with GC analyses of the products then indicated that elimination of the base from the reaction mixture improves the yield of the reaction, however, the reaction time was longer (two days). Stepwise hydrogenolysis of the trichloro precursor later revealed that the addition of the base after the first step (-CCl_3 to -$CDCl_2$) does not cleave the dichloro species and yield improvement up to 78% can be obtained.(GC evidence).

For the generation of deuteriated methyl iodide from the deuteriated sulfide, we first looked into the halogenolysis of esters by iodide ion as we reported earlier (ref.2) and examination of the mechanism of the reaction indicated that a similar cleavage of alkyl aryl ethers should be possible. Indeed, phenyl methyl ethers can be cleaved with lithium and trimethylsilyl iodides to generate methyl iodide (refs 9-10), but more vigourous conditions are necessary to cleave the S-C bond in the analogous thioethers. Application of the above two reagents gave only partial de-alkylation of the sulfide under forcing conditions in ethylacetate and dimethylformamide, after a long time. Scheme



Finally, synthesis of deuterioalkyl halide from cyclic S-alkylsulfonium salts (ref.11) encouraged us to examine a different aspect of this procedure. In our experiment, after the reaction was complete our first intention was to react the liquid deuteriated sulfide with benzyl iodide to form the corresponding sulfonium salt as a solid precursor, but upon heating the above mixture in ethyl acetate (hydrogenation solvent) a solid product was obtained which was isolated and identified as benzylphenyl sulfide in about 85% yield (scheme). This indicated that multi-deuteriated methyl iodide has been liberated simultaneously in one step synthesis.

We suggest a rather straightforward mechanism for this process. The sulfide reacts with benzyl iodide in a fast and reversible step to produce sulfonium iodide which can then go on to the products (benzylphenyl sulfide and deuteriated methyl iodide) in a slow, irriversible process by an SN_2 mechanism. In the later experiments deuteriated methyl iodide as liberated was trapped in a solution of N,N-dimethylaniline in benzene and formed deuteriated trimethylphenylammonium iodide (mp 215°C). Mass spectral analysis of this compound showed the peaks for several deuterited spicies, D_3-D_1, with D_1 the most aboundant. This indicates that even though the catalyst was extensively evacuated before hydrogenation reaction, hydrogen contribution from the other sources still remains to be the major source of dilution and this is the subject of further investigation before tritiation of the trichloro precursor can be undertaken.

METHODS

a- General Method of Chlorination of Anisoles

Anisole, 4-chloroanisole and 4-fluoroanisole were chlorinated as follows: The compound to be chlorinated (1.75mol) was mixed with phosphorous pentachloride (0.125mol) in a three necked flask fitted with a chlorine gas inlet tube, a thermometer and a reflux condenser. Gaseous chlorine

was introduced during 5 hours at a rate of 100g/hour. The mixture was heated at 190°C during the course of the reactions. After degasing with dry nitrogen the resulting mixtures were fractionally distilled to give the following compounds in each case: nuclear chlorinated anisoles(65%,bp 117-118°C/8mmHg), trichloromethyl 4-chloro anisole(71%,bp 111-113°C/8mmHg) and nuclear and side chain chlorinated 4-fluoroanisoles(55%,bp 112°C/10mmHg) respectively.

b-Chlorination of Methyl Phenyl Sulfide

Methylphenyl sulfide (**1**,7mL) was added to chloroform (70mL) and the reaction vessel was kept in an ice bath. Chlorine gas was introduced into the reaction vessel for 30 min and the colored reaction mixture was left in the refrigerator overnight. The solvent was then evaporated. A white soild was left as the residue:yield 98%, mp 35°C. Anal. Calcd for $C_7H_5Cl_3S$: C,36.7;H,2.2;S,14.4;Cl,46.6 Found: C,36.6; H,2.1; S,14;Cl,45.6. ^1H NMR($CDCl_3$) δ 7.2(m).

c-Hydrogenolysis of Trichloromethyl Phenyl Sulfide

Trichloromethylphenyl sulfide (**2**,80mg) was dissolved in dry purified ethylacetate (2mL) and Pd-C (10%,150mg) was added. The reaction vessel was attached to the hydrogenation line and the content of the flask was frozen in liquid nitrogen. Nitrogen gas was flushed three times and the hydrogenation was carried out under one atmosphere of deuterium gas for 24 hours. At this time triethylamine (180μL) was added to the reaction vessel and the reaction was stirred for an additional 24 hours. The catalyst was then filtered and the solution was analysed by gas chromatography. Deuteriated thioanisole was obtained in 78%. GC chromatogram also showed a few minor products, one of which was identified as thiophenol in 5% yield.

d-Generation of Multi-Deuteriated Methyl Iodide

Deuterited thioanisole (**3**,30μL) in ethylacetate (2mL) was mixed with benzyl iodide (300μL) and the reaction was refluxed for 24 hours. The reaction was monitored by tlc(hexane-chloroform/6:4) and showed a new product (R_f 0.4). Further reaction time did not change the yield of the product. At this time the reaction was discontinued, ethyl acetate and the excess of benzyl iodide were evaporated under vaccum. A solid product was left as the residue:yield 85%, mp 39°C. This compound was identified to be benzylphenyl sulfide[**4**, lit mp 41-43°C (ref.12)]. ^1H NMR ($CDCl_3$) δ 4.1(s,2H), 7.2-7.3(m,10H). This reaction was repeated in a special apparatus and the generated deuteriated methyl iodide as liberated was trapped in a solution of N,N-dimethylaniline(20μL) in benzene (500μL). [^2H]Trimethylphenylammonium iodide (**5**) was precipitated and filtered: yield 52%,mp 215°C, ^2H NMR (H_2O) δ 3.6(s).

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