

Synthesis of Deuteriomethyl Aromatic Hydrocarbons by Exchange with Dimethylsulfoxide-D₆

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SUMMARY

Deuterium exchange between dimethylsulfoxide-D₆ (DMSO-D₆) and methyl substituted aromatic hydrocarbons such as toluene, the xylenes, mesitylene, methylnaphthalenes and methylphenanthrenes is a convenient general method of preparing the CD₃ analogues.

INTRODUCTION.

Present methods of synthesizing aromatic compounds containing CD₃ groups are relatively few in number and lack generality:

- (1) reduction of a carboalkoxy group with LiAlD₄ to the alcohol, conversion of the alcohol into the chloride or bromide by concentrated acid, formation of the Grignard reagent from the halide, and decomposition with deuterium oxide ⁽¹⁾.
- (2) reductive dechlorination of the trichloromethyl derivative with zinc dust and acetic acid-D ⁽²⁾.
- (3) conversion of a bromide or iodide into the lithio derivative with n-butyl lithium and addition of CD₃Br or CD₃I ⁽³⁾.
- (4) reaction of deuteriomethylpyrium salts prepared by acid-catalyzed exchange with certain reagents ⁽⁴⁾.

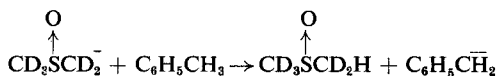
Each of these methods has serious limitations. The first depends upon the availability of the esters. In the benzene series this requirement presents no problem but the naphthalene- and phenanthrene-carboxylic acids and their esters are few in number. The second method is severely restricted by the small number of available or readily prepared trichloromethyl derivatives. In fact, none of these is known in the naphthalene or phenanthrene series. Method 3 is subject to the same limitations because of the small number of bromo- (or iodo-) naphthalenes and phenanthrenes; in addition, the method fails in the case of o-dibromo derivatives. Method 4 has so far been confined to the preparation of benzene-1, 3,5-CD₃ naphthalene-1,3-CD₃ and others issued as NRC No. 11370 compounds with active CH₃ groups.

During extensive studies on electrophilic substitution at saturated carbon, Cram, Kingsbury and Rickborn⁽⁵⁾ observed that optically active 1-deuterio-1-phenylbutane suffered 37% loss of D when heated in DMSO containing potassium tert-butoxide as well as racemization. This result was attributed to the formation of the anion by loss of D. Other examples were also reported in the same paper. Subsequently, Corey and Chaykowsky⁽⁶⁾ reported incorporation of 42% deuterium in triphenylmethane when a solution of the hydrocarbon in DMSO containing the methyl sulfinyl carbanion ($\text{CH}_3\text{-SO-CH}_2^-$) was treated with deuterium oxide. Deuteration was attributed to the formation of trityl carbanion. A few years later, Hoffman, Müller and Schriesheim⁽⁷⁾ utilized base-catalyzed exchange between toluene and other methylbenzenes and tritiated DMSO for measuring the ionization rates of extremely weak acids. These workers made the important observation that only benzylic protons participate in the exchange reaction, a fact of considerable importance from a practical standpoint. While our work was in progress a critical review on tritium labelling of compounds by exchange in strongly basic media appeared⁽⁸⁾. Our contribution in this area stresses the practical aspect of this exchange reaction.

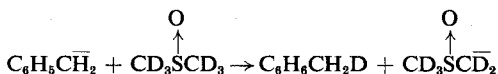
Additional motivation for this work was provided by the discovery a few years ago of rapid exchange of methyl protons in tetramethylammonium hydroxide in deuterium oxide at 125-140° C through the agency of the ylide $\text{C}\text{H}_2\text{N}^+(\text{CH}_3)_3$ ⁽⁹⁾. It led us to investigate the possibility of promoting exchange, in toluene for instance, via the anion $\text{C}_6\text{H}_5\text{CH}_2^-$ in deuterated DMSO in the presence of $\text{CD}_3\text{SCD}_2\text{Na}$. If the ion $\text{C}_6\text{H}_5\text{CH}_2^-$ were formed even in very low



concentration by the reaction



it should be possible to obtain $\text{C}_6\text{H}_5\text{CD}_3$ by repeated exchange with basic DMSO- D_6 via the reaction



It has now been found that toluene recovered after heating for 24 hours at 150-160° C in DMSO- D_6 in the presence of a small amount of sodium hydride is deuterated to the extent of 75% in the CH_3 group exclusively as determined by IR and NMR spectra. Two more exchanges were sufficient to raise the CD_3 content to 99%.

This initial success led us to extend the investigation to the xylenes, trimethylbenzenes, durene, mono- and polymethylnaphthalenes and phenanthrenes with the same result.

It was found that reaction temperature is an important factor in obtaining deuteration exclusively, or almost so, in the methyl groups. Temperatures near or at the boiling point of DMSO tend to favor slight exchange of the ring protons as well as rapid exchange of the methyl group protons. Thus, exchange of *m*-xylene at 170° C leads to 14 % exchange on the ring as judged by NMR spectra while at 100° C there is virtually no exchange in these positions. Some additional examples are provided in Table 1.

TABLE 1. Base-catalyzed Exchange of Methylbenzenes with DMSO-D₆.

Compound	Reaction Temperature °C	Number of Exchanges	Exchange on Methyl Group H %	Exchange on Aromatic Ring %
Toluene	170	2	97.9	7.0
Toluene	135	2	0	0
<i>o</i> -Xylene	170	2	96.8	~0
<i>o</i> -Xylene	170	3	98.2	~0
<i>m</i> -Xylene	170	3	96.2	14.0
<i>m</i> -Xylene	170	3	97.8	6.5
<i>m</i> -Xylene	110	3	97.6	~0
<i>p</i> -Xylene	150	3	97.8	9.5
<i>p</i> -Xylene	125	3	98.3	~0
Hemimellitene	170	4	97.5	~0
Pseudocumene	170	3	95.3	10.0
Pseudocumene	105	3	0	0
Mesitylene	150	3	98.7	13.0
Mesitylene	125	3	98.7	4.0
Mesitylene	100	3	98.5	~0

EXPERIMENTAL.

Infrared spectra were measured on a Perkin-Elmer, Model 237. NMR spectra were measured on a Varian Associates A-60 instrument in CDCl₃ using TMS as internal standards.

Toluene-α-D₃. One gram of 1 : 1 sodium hydride paraffin suspension was added to 10.0 ml (11.0 g; 0.08 mole) of 99.5 atom % D dry dimethylsulfoxide (Merck, Sharp and Dohme, Montreal, Canada) and 5.0 ml (4.6 g; 0.05 mole) of toluene and the solution was heated under reflux or at the optimum temperature shown in the table for 24 hours. Volatile materials (exchanged toluene and DMSO) were distilled off at 50° in a vacuum line into a trap cooled in dry

ice and acetone to -78°C . After thawing, the distillate was transferred to a separatory funnel and treated with 20 ml of D_2O to precipitate out exchanged toluene. The recovered solution of DMSO was saved and used later to exchange fresh DMSO. The toluene was washed with ordinary water and dried over sodium before repeating the exchange with fresh deuterated DMSO. Recovery of toluene in each exchange is nearly quantitative.

The IR spectrum of thrice exchanged toluene showed CH_3 stretching vibrations at 2850 cm^{-1} and 2950 cm^{-1} completely absent while corresponding CD_3 bands appeared at 2050 cm^{-1} and 2200 cm^{-1} . In the NMR the signal at 7.63τ due to the methyl group was nearly absent while the signal at 2.8τ due to the ring protons retained its initial intensity. The isomeric xylenes and trimethylbenzenes were exchanged in the same manner under the conditions indicated in Table I.

For the less volatile hydrocarbons such as the dimethylnaphthalenes and phenanthrenes, work-up of the reaction mixture had to be modified. In these cases the solution of DMSO-D_6 was diluted with deuterium oxide and extracted with ether or benzene. The aqueous layer was drawn off and distilled to recover deuterated DMSO and deuterium oxide. The ether or benzene solution was washed with water, dried over potassium carbonate, and freed of solvent. The residue was purified by bulb to bulb distillation on the vacuum line. Recovery of hydrocarbon from each exchange was nearly quantitative.

1-Methyl and 2-methylnaphthalenes, 1,3-dimethylnaphthalene, 2,7-dimethylnaphthalene, 1,3,6,8-tetramethylnaphthalene, 2-methylphenanthrene and 2,8-dimethylphenanthrene were converted into their CD_3 analogues by this modified method.

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