Tetrahedron. Vol. 25, pp. 5771 to 5776. Pergamon Press 1969. Printed in Great Britain

WURTZ–FITTIG SYNTHESES OF MIXED TRIDEUTEROMETHYL AND METHYL DERIVATIVES OF BENZENE

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(*Received in the UK* 25 *July* 1969; *Accepted for publication* 19 *August* 1969)

Abstract—In the Wurtz–Fittig reaction of an aryl bromide with methyl iodide no rearrangement products are produced. All reaction mechanisms involving radical intermediates are contrary to experimental results and should be rejected. Selective or even specific adsorption dominates the sequence of the Wurtz–Fittig reactions:

Aryl tribromide ≫ aryl dibromide ≫ aryl monobromide ≫ alkyl iodide, although chemical reactivity with sodium is in the reverse order, the higher ranking molecule reacting much slower. This effect may be important in other surface-localized reactions also.

By the method described, it is possible to introduce any number of trideuteromethyl groups at predetermined locations in the phenyl nucleus. Thus fifteen trideuteromethyl derivatives and mixed trideuteromethyl and methyl derivatives of benzene have been prepared (see Tables).

INTRODUCTION

A NUMBER of trideuteromethyl analogues of the Me derivatives of benzene, in which CD_3 as well as Me is present in the molecule were required.[1] As this type of compound has not been mentioned in the literature, the synthesis was investigated. Catalytic deuterium-proton exchange,[2] a very useful reaction, can, however, only produce all-CD_3 derivatives. The Friedel–Crafts[3] synthesis was ruled out on account of unavoidable rearrangement reactions. Contrary to the current general opinion, we found the Wurtz–Fittig[3] synthesis promising and it was therefore investigated in detail.

$$\text{Aryl bromide} + \text{Alkyl iodide} + 2\,\text{Na} \rightarrow \text{Aryl-Alkyl} + \text{NaBr} + \text{NaI}$$

In this paper a method is described for the introduction of any number of trideuteromethyl and Me groups at predetermined locations in the phenyl nucleus.

RESULTS

Selectivity. The usual procedure for the Wurtz-Fittig reaction includes the destruction of unreacted alkali metal by subsequent addition of alcohol and water. The reaction of *o*-bromotoluene with methyl iodide at 40° in cyclohexane gave a clear mixture which by gas chromatography showed the presence of the expected *o*-xylene, and some ethane, toluene and reagents, but it did not show any trace of *m*-xylene, *p*-xylene or ethylbenzene. After the addition of alcohol, however, a number of additional components were found, thus proving that the Wurtz–Fittig reaction itself is free from rearrangement reactions:

a. All reaction mechanisms involving radical intermediates[3] do not agree with the experimental results and should be rejected.

b. The product should be extracted with an intert solvent prior to the addition of alcohol.

Generally, a measurable reaction at the sodium surface resulted in the parent aryl compound, apparently formed from the corresponding aryl bromide, and in addition, a very strong pungent garlic-like odour was always detected. The mechanism for these side reactions is not clear. Ethane was always present, but diphenyl or symmetrical diphenyl derivatives could not be detected with certainty.

Substituent effect. 2,4-Dibromo-1,3,5-trimethylbenzene does not react with trideuteromethyl iodide at 40° in cyclohexane solution, the sodium retaining its metallic lustre for 2 months. At 80°, in mesitylene, a slight bluish stain on the sodium surface developed during 2 months, and a trace of trideuteropentamethylbenzene was detected in the gaschromatogram corresponding to a conversion of 0·01% after 60 days. Compounds having no interfering Me groups such as *o*-dibromo, *m*-dibromo- and *p*-dibromobenzene with trideuteromethyl iodide in cyclohexane at 80° produced the corresponding xylenes slowly but in usable yields.

1,3,5-Tribromobenzene or 3,6-dibromo-1,2,4,5-tetramethylbenzene did not react with trideuteromethyl iodide in mesitylene at 40°, the metallic surface of sodium remaining bright even after 2 months. In contrast, the reaction of 2-bromo-1,3,5-trimethylbenzene or 4-bromo-2-trideuteromethyl-1,3,5-trimethylbenzene reacted with trideuteromethyl iodide at 40° giving yields of approximately 40% after 48 hr. Therefore, Me substituents, and more strongly, additional bromo substituents have a retarding effect on the Wurtz–Fittig reaction. In our experience, a hetero-coupling reaction appeared essential before any homo-coupling reaction could take place.*

Isotope effect. The reaction of bromobenzene with methyl iodide produced toluene in 80% yield after 1 hr at 20°. This is a far greater yield than expected from random hetero- and homo-coupling. It thus indicates a highly selective hetero-coupling reaction.

The reaction of bromobenzene with trideuteromethyl iodide produced the corresponding trideuterotoluene in 60% yield after 24 hr. The isotope substitution thus resulted in a very much slower and a less selective reaction.

Experiments with mixtures of arylbromides. A mixture of *o*-bromo- + *m*-bromo- + *p*-bromotoluenes with methyl iodide in cyclohexane solution at 20° showed reaction rates with a spread of less than a factor of four. Under similar conditions, the Wurtz-Fittig reactions of a mixture of *o*-dibromo- + *m*-dibromo- + *p*-dibromobenzene with methyl iodide showed a difference of approximately a factor of two in the rates of formation of the xylene isomers. The three isomers of mono bromotoluene were also formed. Their initial concentrations were low, but increased during practically the whole course of the reaction.

A mixture of equimolar amounts uf *m*-bromotoluene + *m*-dibromobenzene subjected to the Wurtz–Fittig reaction with methyl iodide produced only a trace of *m*-xylene during the first 8 hr. In the period between 20 and 70 hr, the concentration of dibromobenzene dropped to less than 20% of its original value, and considerable amounts of *m*-xylene were formed, whereas the concentration of *m*-bromotoluene was practically unchanged during this time. These experiments suggest that the dibromo compound reacts preferentially to form xylene in one tandem step, the small amount of bromotoluene which escaped from the sodium surface into the liquid

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* This interesting effect has not been reported in literature before. A detailed investigation of this and other unexpected effects on the Wurtz–Fittig reaction is in progress.

TABLE 1. PREPARATION OF BROMO COMPOUNDS

Starting derivative of benzene	Product	Yield, %	Analysis†		
			log α K 56, 150°	log α K 109, 150°	log α K 109, 125°
Benzene	1-Br	80	0·472	0·847	—
	1,4-di Br	70	1·119	1·344	—
1,4-di CD_3	*2-Br-1,4-di CD_3	60	1·019	—	—
2-NH_2-1-CH_3	2-Br-1-CH_3	20	0·764	1·071	1·368
1-CH_3	2-Br-1-CH_3	20	0·764	1·071	1·368
	4-Br-1-CH_3	40	0·764	1·062	1·354
(Messrs. Fluka AG)	3-Br-1-CH_3	—	0·764	1·078	1·378
1.4-di CH_3	2-Br-1,4-di CH_3	60	1·039	1·305	—
1,3-di CH_3	4-Br-1,3-di CH_3	53	1·039	1·396	1·805
	2-Br-1,3-di CH_3	7	1·039	1·304	1·579
1,2-di CH_3	3-Br-1,2-di CH_3	15	1·118	1·393	1·668
	4-Br-1,2-di CH_3	45	1·118	1·410	1·699
(Messrs. Fluka AG)	1,3-di Br	—	1·189	1·488	—
(Messrs. Fluka AG)	1,2-di Br	—	1·223	1·719	—
1,3,5-tri CH_3	2-Br-1,3,5-tri CH_3	60	1·320	—	—
	2,4-di Br-1,3,5-tri CH_3	50	2·055	—	—
2-CD_3-1,3,5-tri CH_3	*4-Br-2-CD_3-1,3,5-tri CH_3	50	1·705	—	—
	n-octane	—	0·000	0·000	0·000
	n-decane	—	0·516	0·511	0·570
	n-dodecane	—	1·039	—	1·138

* This compound has not been described before.

† The coupling constants and the integrals of the proton signals in the NMR spectra correspond to the values that should be expected from the structure of the products.

All deuterated products show strong CD_3 steching bands between 2228 and 2070 cm^{-1} in their IR spectra.

Log α is the logarithm of the relative retention on a non-polar liquid gas-chromatographic column (Apiezon L, K 56) and a solid gas-chromatographic column (Bentone 34, K 109), values of the normal alkanes are given as reference.

(together with bromotoluene that has been specifically added to the solution) being excluded from any reaction by dibromo compound present.

This seemingly complex state of affairs is probably due to highly competitive reactions. Selective or even specific adsorption dominates the sequence of the Wurtz–Fittig reactions in the following order:

Aryl tribromide $\gg$ aryl dibromide $\gg$ aryl monobromide $\gg$ alkyl iodide.

By comparison the chemical reactivity with sodium is in the reverse order:

Aryl monobromide $\gg$ aryl dibromide $\gg$ aryl tribromide.

The aryl sodium reaction with methyl iodide is much faster than with aryl bromide.

Reaction scheme for syntheses of trideuteromethyl compounds. The reaction routes shown in Tables 1 and 2 are self-evident and are not discussed in detail. Some compounds were synthesized by more than one route, and thus their identity was confirmed. In all cases the Wurtz–Fittig reaction produced no rearrangement products.

TABLE 2. PREPARATION OF DEUTERATED COMPOUNDS

Starting bromo benzene	Deuterated product	Yield, %	Analysis†	
			$\log(\alpha/\alpha_B)$	$\alpha_{D,H}$
1-Br	1-CD_3	60	0·3151	0·9810
1,4-di-Br	1,4-di CD_3	20	0·6281	0·9605
2-Br-1,4-di CD_3	*1,2,4-tri CD_3	10	1·0057	0·9354
2-Br-1-CH_3	*2-CD_3-1-CH_3	20	0·7260	0·9805
4-Br-1-CH_3	*4-CD_3-1-CH_3	7	0·6489	0·9808
3-Br-1-CH_3	*3-CD_3-1-CH_3	60	0·6473	0·9792
2-Br-1,4-di CH_3	*2-CD_3-1,4-di CH_3	40	1·0508	0·9786
4-Br-1,3-di CH_3	*4-CD_3-1,3-di CH_3	8	1·0523	0·9801
2-Br-1,3-di CH_3	*2-CD_3-1,3-di CH_3	4	1·1460	0·9808
3-Br-1,2-di CH_3	*3-CD_3-1,2-di CH_3	6	1·1443	0·9791
4-Br-1,2-di CH_3	*4-CD_3-1,2-di CH_3	6	1·0508	0·9786
1,3-di Br	1,3-di CD_3	7	0·6247	0·9573
1,2-di Br	1,2-di CD_3	4	0·7051	0·9602
2-Br-1,3,5-tri CH_3	*2-CD_3-1,3,5-tri CH_3	60	1·4625	0·9793
4-Br-2-CD_3-1,3,5-tri CH_3	*2,4-di CD_3-1,3,5-tri CH_3	20	1·9278	0·9590
	benzene	—	0·0000	—
	n-octane	—	0·3792	—
	n-decane	—	1·0118	—

* This compound has not been described before.

† All deuterated products show strong CD_3 stretching bands between 2228 and 2070 cm^{-1} in their IR spectra. Values of chemical shifts and integrals of proton signals in NMR correspond to values that should be expected by comparison with NMR spectra of fully protonated analogues. Log (α/α_B) is logarithm of retention relative to benzene on an Apiezon L GLC column (K 47) at 95°.

$\alpha_{D,H}$ is retention of deuterated product relative to its fully protonated analogue on an Apiezon L column (K 47) at 95°.

The following set of reactions is suggested to fit the experimental data.

$$(1)\quad \mathrm{BrC_6H_4Br}\ \text{(sol)}\ \underset{k_1'}{\overset{k_1}{\rightleftarrows}}\ \mathrm{BrC_6H_4Br}\ \text{(ads)}\qquad \frac{k_1}{k_1'} \gg \frac{k_7}{k_7'};\ k_1 \gg k_1'$$

$$(2)\quad \mathrm{BrC_6H_4Br}\ \text{(ads)}\ \xrightarrow[k_2]{\mathrm{Na}}\ \mathrm{NaC_6H_4Br}\ \text{(ads)}\qquad k_2 \ll k_8;\ k_1' \ll k_2$$

$$(3)\quad \mathrm{NaC_6H_4Br}\ \text{(ads)}\ \underset{k_3}{\overset{k_3'}{\rightleftarrows}}\ \mathrm{NaC_6H_4Br}\ \text{(sol)}$$

$$(4)\quad \mathrm{NaC_6H_4Br}\ \text{(ads)}\ \xrightarrow[k_4]{\mathrm{CH_3I}}\ \mathrm{CH_3C_6H_4Br}\ \text{(ads)}\qquad k_3' \ll k_4$$

$$(5)\quad \mathrm{NaC_6H_4Br}\ \text{(ads)}\ \xrightarrow[k_5]{\mathrm{CH_3C_6H_4Br}}\ \mathrm{CH_3C_6H_4C_6H_4Br}\ \text{(etc)}\qquad k_4 \gg k_5$$

$$(6)\quad \mathrm{NaC_6H_4Br}\ \text{(ads)}\ \xrightarrow[k_6]{\mathrm{BrC_6H_4Br}}\ \mathrm{BrC_6H_4C_6H_4Br}\ \text{(etc)}\qquad k_4 \gg k_6$$

$$(7)\quad \mathrm{CH_3C_6H_4Br}\ \text{(ads)}\ \underset{k_7}{\overset{k_7'}{\rightleftarrows}}\ \mathrm{CH_3C_6H_4Br}\ \text{(sol)}\qquad k_7 \gg k_7'$$

$$(8)\quad \mathrm{CH_3C_6H_4Br}\ \text{(ads)}\ \xrightarrow[k_8]{\mathrm{Na}}\ \mathrm{CH_3C_6H_4Na}\ \text{(ads)}\qquad k_7' \ll k_8$$

$$(9)\quad \mathrm{CH_3C_6H_4Na}\ \text{(ads)}\ \underset{k_9}{\overset{k_9'}{\rightleftarrows}}\ \mathrm{CH_3C_6H_4Na}\ \text{(sol)}$$

$$(10)\quad \mathrm{CH_3C_6H_4Na}\ \text{(ads)}\ \xrightarrow[k_{10}]{\mathrm{CH_3J}}\ \mathrm{CH_3C_6H_4CH_3}\qquad k_9' \ll k_{10}$$

$$(11)\quad \mathrm{CH_3C_6H_4Na}\ \text{(ads)}\ \xrightarrow[k_{11}]{\mathrm{CH_3C_6H_4Br}}\ \mathrm{CH_3C_6H_4C_6H_4CH_3}\qquad k_{10} \gg k_{11}$$

$$(12)\quad \mathrm{CH_3C_6H_4Na}\ \text{(ads)}\ \xrightarrow[k_{12}]{\mathrm{BrC_6H_4Br}}\ \mathrm{BrC_6H_4C_6H_4CH_3}\ \text{(etc)}\qquad k_{10} \gg k_{12}$$

$$(13)\quad \mathrm{CH_3I}\ \text{(sol)}\ \underset{k_{13}'}{\overset{k_{13}}{\rightleftarrows}}\ \mathrm{CH_3I}\ \text{(ads)}\qquad \frac{k_1}{k_1'} \gg \frac{k_7}{k_7'} \gg \frac{k_{13}}{k_{13}'}$$

(sol) molecule in solution
(ads) molecule absorbed on sodium surface
(etc) molecule may undergo further reactlon
reactions 5, 6, 11 and 12 yield the same hydrocarbon.

EXPERIMENTAL*

Conditions for chromatography. Chromatograph, Hewlett–Packard/F&M, Model 5750; detector, flame ionization detector; recorder, Hewlett-Packard, −0·05 to 1 mV, 1 sec; carrier gas, He at 100 ml/min; sample size, 0·01 to 0·10 mg per component.

Column K 47.9 m × 0·5 cm i.d. copper coiled tube filled with Apiezon L (5:95) on Chromosorb P DMCS (100/120 Mesh), efficiency circa 12,000 theoretical plates; analysis temp 95°; analysis time 550 min for pentamethylbenzene.

Column K 56.4 m × 0·5 cm i.d. stainless steel 316 coiled tube filled with Apiezon L (5:95) on Chromosorb P DMCS (100/120 Mesh), efficiency circa 6000 theoretical plates; analysis temp 150°; analysis time 29 min for 4-Br-1,2-di CH_3-benzene.

Column K 109.5 m × 0·5 cm i.d. stainless steel coiled tube filled with a mixture of Apiezon L and Bentone 34 (5:15:80) on Chromosorb W (45/60 Mesh); efficiency circa 4000 theoretical plates; analysis temp 125° and 150°; analysis time 127 and 44 min respectively for 4-Br-1,2-di CH_3-benzene.

Synthesis of aryl bromides. A number of simple aryl bromides were commercially available. We found that under mild reaction conditions aryl monobromides were formed preferentially during the early stages of the bromination, substantial quantities of dibromo compounds being formed only after most of the hydrocarbon had disappeared, while no tribromo compounds could be detected. As this aspect is especially

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* Synthesis and purification were performed with the assistance of Miss M. C. Hazeleger. Gaschromatographic separation of some isomeric aryl bromides were performed with the assistance of Mr. D. L. J. Remeeus.

important in the bromination of the deutero compounds, the usual bromination procedures[3] were modified. To a dilute soln of aryl hydrocarbon (10%) and dry pyridine (1%) in Na-dried cyclohexane in an ice-bath, 0·60 equivs of dilute Br_2 (1% by volume) in dry cyclohexane were carefully added. When the vigorous reaction subsided after approx 2 hr, the mixture was first neutralized with solid Na_2CO_3, and then unreacted Br_2 was reduced by the addition of $Na_2S_2O_5$. All manipulations were performed under green dark-room lighting, by the operator wearing a gas mask. Normal lighting was allowed only after all the Br_2 was reduced. This avoided bromination of the Me substituents or the cyclohexane solvent. The cyclohexane soln was washed free of sulfite with small amounts of water and dried successively over $MgSO_4$ and molecular sieve 5 A. It was either used as such for the Wurtz–Fittig synthesis or purified by means of gas chromatography.

Wurtz–Fittig synthesis. In a typical procedure aryl bromide was dissolved (10% by volume) in dry cyclohexane in a 10–25 ml pear-shaped flask fitted with a condensor and a $CaCl_2$ tube.

Metallic Na was cut in thin slices (approximately 10 cm^2 per gram) and added to the soln (50% excess). The calculated equiv amount of CD_3I (99% isotopic purity) was added from a Hamilton 500 microliter syringe keeping the needle tip below the liquid surface. All manipulations were performed in a glove-box under dry N_2. The reaction was first allowed to proceed at room temp but if this was slow the temp was raised to 40°. Reaction time was 24 to 170 hr. The yields varied between 4% and 60%.

The organic products and solvent were separated from inorganic material by means of high vaccum low temp distillation (boiler at room temp, receiving flask in liquid N_2).

Alternatively the soln was separated from the inorganic material using a Hamilton 500 microliter syringe. The insoluble material was rinsed twice with cyclohexane. The products were separated and purified from the solutions by means of gas chromatography.

Analysis

(a) *NMR spectra.** As a Br atom introduces strong anisotropy in the molecule, the signals of the aromatic protons in *ortho*, *meta* and *para* position to the Br atom could be distinguished from each other. Their coupling constants correspond to those expected from the structure. The Br atom also contributes to the chemical shift of the Me groups, thus additional information with regard to the relative position of the Me groups was obtained. In this way the structure of the bromo compounds given in Table 1 were determined unambiguously. As the Wurtz–Fittig reaction is free from rearrangement products, the structure of the mixed trideuteromethyl and Me derivatives of benzene in Table 2 correspond to the structure of the starting bromo compounds. This was confirmed by comparing the NMR spectra of the deuterated compounds with those of their fully protonated analogues.

(b) *IR spectra* of all trideuteromethyl derivatives in Tables 1 and 2 show strong CD_3 stretching bands at 2232 ± 5, 2210 ± 5, 2132 ± 6 and 2060 ± 10 cm^{-1}.

(c) *Gas chromatography.* Gas chromatographic relative retention data of the compounds are shown in Tables 1 and 2.

The separation of isomeric bromo compounds of Table 1 was achieved by gas–solid chromatography. In the Bentone 34 column K 109 a non-polar liquid was added to eliminate tailing.

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* Detailed assignments have not been described in literature. A paper is in preparation.