

THE FLUORINATION OF 1,3-BIS-(TRIFLUOROMETHYL)- BENZENE OVER POTASSIUM TETRAFLUOROCOBALTATE(III)

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(Received January 31, 1972)

SUMMARY

1,3-Bis-(trifluoromethyl)benzene has been fluorinated over potassium tetrafluorocobaltate under conditions where the bulk of the products are lightly fluorinated. Two aromatic products, 1-fluoro-2,4-bis-(trifluoromethyl)benzene and 1-fluoro-3,5-bis-(trifluoromethyl)benzene, are formed initially, the two associated 1,4-dienes being also found. The mechanistical implications are discussed, along with probable further reaction pathways.

INTRODUCTION

No studies of the mild fluorinations of simple derivatives of benzene using high-valency transition metal fluorides have been reported. Our recent rationalisation¹ of fluorination reaction pathways prompted us to investigate such fluorinations in order to examine the attractive idea that they are closely akin to electrophilic substitution. For this purpose it is important to select substituents likely to be impervious to fluorination: the trifluoromethyl group is an outstanding candidate.

Previous work² on the fluorination of benzotrifluoride over cobalt trifluoride has shown that although the actual intermediates were not isolated the products can all be explained *via* an initial *meta* attack, followed by attack *para* to the ring fluorine atom and saturation³ (Fig. 1).

If this postulated pathway is correct, then 1,3-bis-(trifluoromethyl)benzene should follow a pathway *via* 1-fluoro-3,5-bis-(trifluoromethyl)benzene, since the fluorine is then attacking *meta* to both trifluoromethyl groups. Accordingly, since the products were expected to be symmetrical and hence easily identified, the reaction between 1,3-bis-(trifluoromethyl)benzene and potassium tetrafluorocobaltate(III)⁴ (KCoF₄) has been studied under mild conditions (220°).

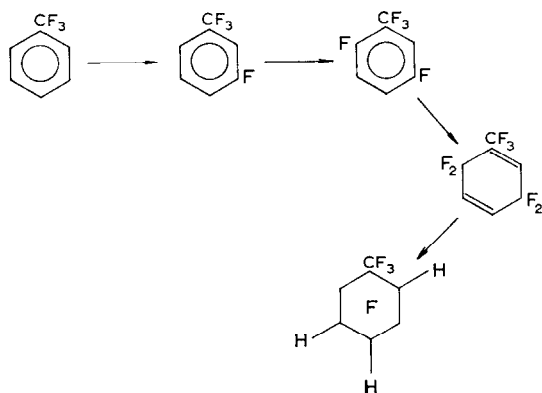


Fig. 1. Major fluorination pathway for benzotrifluoride over cobalt trifluoride.

RESULTS AND DISCUSSION

The reaction was carried out and worked up as usual³; the recovery was not very high but this is not unusual for so mild a fluorination.

The product mixture contained about a dozen major peaks, the biggest of which by far was starting material. Separation of individual components was achieved by distillation followed by GLC; the recoveries from the GLC separations were very variable, and the percentages of the components in the product mixture have been calculated by triangulation on a GLC trace; they are presumed to be molar. Although this is not an entirely satisfactory way of calculating these percentages it is probably the best available for a complex mixture with small amounts of minor components; clearly, however, not too much reliance should be placed on exact figures, although the bulk of the mixture was identified.

The compounds identified and their percentages in the mixture are shown in Table I. All the identifications rest primarily upon spectroscopic evidence, and this is discussed in the NMR section (see later). The present discussion concentrates mainly upon the major components of this reaction mixture, whose structures are not in doubt.

TABLE I

COMPOUNDS IDENTIFIED IN THE FLUORINATION MIXTURE

No.	Compound	% ^a in mixture
(I)	1,3-Bis-(trifluoromethyl)benzene	31
(II)	1-Fluoro-2,4-bis-(trifluoromethyl)benzene	14
(III)	1-Fluoro-3,5-bis-(trifluoromethyl)benzene	11
(IV)	1,2-Difluoro-3,5-bis-(trifluoromethyl)benzene	9
(V)	1,1,4,4-Tetrafluoro-3,5-bis-(trifluoromethyl)cyclohexa-2,5-diene	5
(VI)	1,1,4-Trifluoro-2,4-bis-(trifluoromethyl)-cyclohexa-2,5-diene	5
(VII)	1 <i>H</i> ,4 <i>H</i> -2,6-bis-(trifluoromethyl)hexafluorocyclohex-1-ene	8
(VIII)	1 <i>H</i> -2,4-bis-(trifluoromethyl)heptafluorocyclohex-3-ene	6

^a Calculated as in text.

The most surprising thing about this reaction is that two positions of initial attack are about equally favoured, and that one of them is *ortho* to one trifluoromethyl and *para* to the other, in sharp contrast with prediction based on the behaviour of the trifluoromethyl group in electrophilic aromatic substitution⁵. Clearly, either or both monofluoroaromatics may react to give 1,2-difluoro-3,5-bis-(trifluoromethyl)benzene by routes similar to those outlined below.

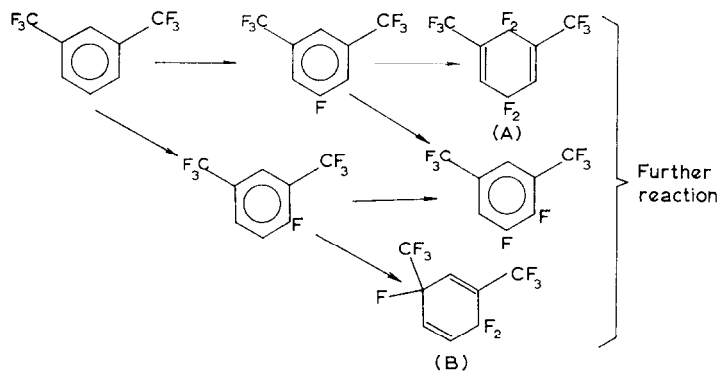


Fig. 2. Early stages in the fluorination pathway.

A possible explanation of this apparent anomaly lies in the stabilities of the Wheland intermediates, which may be good models for product-determining transition states in these reactions: after initial formation of the cation-radical¹ from the aromatic, quenching (assumed to be by F•) may plausibly give one of two Wheland intermediates (Fig. 3).

Quenching at C₅ gives intermediate (C), which may readily collapse (*via*

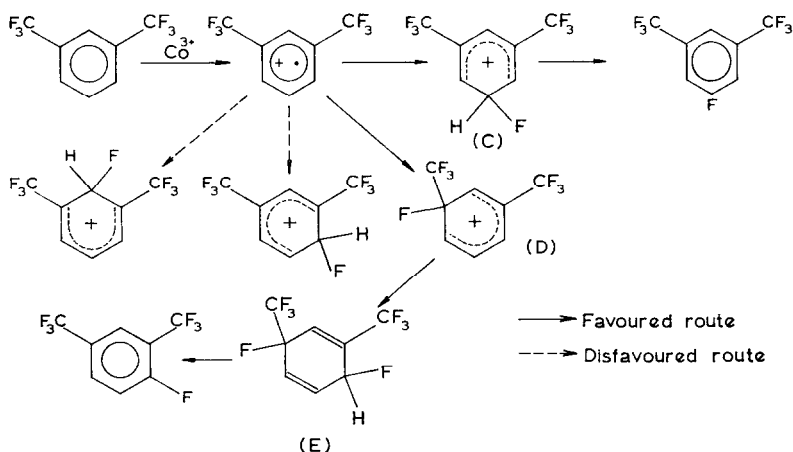


Fig. 3. Routes to the monofluorinated aromatics.

fluoride-ion abstraction of H^+) to 1-fluoro-3,5-bis-(trifluoromethyl)benzene, the expected primary product. However, (C) is not necessarily the most stable intermediate, since it bears two CF_3 groups on the π system, whereas quenching at C_1 gives (D), with only one CF_3 group on the π system. However, (D) cannot now collapse to an aromatic as simply as can (C), but must itself be quenched with fluoride ion to give (E), which may now collapse by loss of the originally attacking fluorine as HF to give 1-fluoro-2,4-bis-(trifluoromethyl)benzene.

The isolation of both monofluorinated aromatics makes it quite plain that reaction *via* (D), which would not ordinarily be expected in electrophilic attack, must be about as rapid as reaction *via* (C). Indeed, according to the argument advanced above, reaction *via* (D) ought to be more favourable than reaction *via* (C), although this may be offset by the attack on the radical-cation being reversible in this case, the quenching with fluoride ion now being rate-determining, in contrast to the pathway *via* (C). This is not unreasonable, since abstraction of H^+ (as HF) from (C) with concomitant aromatisation (total energy gain $\simeq 150$ kcal mole $^{-1}$, excluding any inorganic energetics) may quite plausibly be supposed to be faster than attack of F^- on (D), with no aromatisation (total energy gain $\simeq 100$ kcal mole $^{-1}$, without any inorganic energetics).

It is noteworthy here that (A) and (B) are only the second and third intermediates of this type to be reported in fluorinations of benzenes^{3, 4, 6}.

Further steps down the pathways from (A) and (B) are not well defined by the present work, and are not extensively discussed here. It may be pointed out, however, that (A) is expected to be less reactive than (B), since in the former case both double bonds bear CF_3 groups and will therefore⁷ have higher ionisation potentials than the unsubstituted one in (B). This may serve to explain the observation that the more highly fluorinated products derive more straightforwardly from (B) than from (A): on the other hand, it is quite possible that fluoride-ion catalysed rearrangements⁸ account for this.

In summary, the reaction of $KCoF_4$ with 1,3-bis-(trifluoromethyl)benzene proceeds *via* initial attack, as expected, at C_5 and, less predictably, C_1 . Both attacks give monofluoroaromatics and hence the appropriate cyclohexa-1,4-dienes. This pattern of reactivities has been rationalised on the basis of the relative stabilities of the Wheland intermediates involved, but some doubts remain as to the soundness of this approach in the case of reaction *via* attack at C_1 .

EXPERIMENTAL

All boiling points are uncorrected. Infrared spectra were measured on a Perkin-Elmer 257 or a Unicam SP200 machine, UV spectra on a Unicam SP800. NMR spectra were run on dilute CCl_4 solns on a Perkin-Elmer R10 instrument operating at 60 MHz (1H) and 56.4 MHz (^{19}F). Mass spectra were run on Metropolitan Vickers MS9 or MS2 instruments.

Two instruments were employed for gas chromatographic measurements in this work. Instrument A was a Perkin-Elmer F11 gas chromatograph employing a 100 m capillary column packed with UCON oil LB-550-X. Instrument B was a Pye 104 gas chromatograph employing a 10 m × 9 mm glass column packed with UCON LB on chromasorb P (20%). In each case the temperature employed and N₂ pressure are given.

Fluorination of 1,3-bis-(trifluoromethyl)benzene over potassium tetrafluorocobaltate(III)

The aromatic (Koch Light Labs. Ltd.) (150 g) was fluorinated in the usual way⁴, at 200°, in a reactor packed with 7 kg of KCoF₄. The apparatus and technique have been described before³. The product (109 g) was trapped out in a copper vessel at -78° and washed with aqueous NaHCO₃ solution before weighing. GLC (A; 80°, 30 psi) showed that the material was largely unfluorinated and the product was therefore re-fluorinated at 220° and worked up as before to give 93.7 g of more highly fluorinated material. GLC (A; 80°, 30 psi) showed 13 major peaks, with starting material \approx 30% of the mixture.

The product was washed once more with H₂O, dried (MgSO₄), filtered and distilled up a spinning-band column (Nester-Faust Corp.; *ca.* 35 theoretical plates) to give the fractions listed in Table 2.

TABLE 2
SPINNING-BAND DISTILLATION

Fraction No.	B.p. range (°C)	Weight (g)
1	85-95	6.7
2	95-100	0.9
3	100-103	5.0
4	103-104	3.0
5	104-105	4.8
6	105-107	6.3
7	107	5.5
8	107-110	1.4
9	110-112	4.6
10	112-113	5.4
11	113-114	4.2
12	114-115	3.8
13	115	5.6
14	115-116	4.3
15	116-119	4.4
16	119	3.9
17	119-121	1.1
Pot residue		4.8

Each fraction was examined by GLC and suitable fractions were separated on a semi-preparative (\approx 100 mm³) scale to give the major components. The components identified and the fractions from which they were isolated are shown

below. All these isolations were performed on column B; the temperature and N₂ pressure are given in each case. The peaks are listed in order of increasing retention time.

Peak 1 was isolated from the first fraction (No. 1) (50°, 15 psi), and shown to be a mixture of at least three compounds (by NMR spectroscopy). It was not further separated.

Peak 2 was isolated from the first fraction (No. 1) (50°, 15 psi) and proved to be largely 2*H*-1,3-bis-(trifluoromethyl)heptafluorocyclohex-1-ene by NMR spectroscopy (see NMR section); the IR spectrum showed no strong band in the 1680–1800 cm⁻¹ region.

Peak 3 was isolated from the second fraction (No. 2) (65°, 20 psi) and shown to be a stereoisomer of 4*H*-1,3-bis-(trifluoromethyl)heptafluorocyclohex-1-ene by NMR spectroscopy (see NMR section); the IR spectrum showed a strong band at 1707 cm⁻¹ ($\text{F}_3\text{C}-\text{C}=\text{C}-\text{F}$).

Peak 4 was isolated from fraction 6 (80°, 25 psi) and shown to be a stereoisomer of 2*H*,5*H*-bis-(trifluoromethyl)hexafluorocyclohex-1-ene (nc), b.p. 105°. (Found: C, 29.1; H, 0.8; F, 69.3. C₈F₁₂H₂ requires C, 29.4; H, 0.6; F, 69.8%.) NMR spectral evidence is given in the NMR section; IR spectroscopy showed no strong band between 1650 and 1800 cm⁻¹.

Peak 5 was isolated from fraction 6 (80°, 25 psi) and shown to be 1,1,4,4-tetrafluoro-2,5-bis-(trifluoromethyl)cyclohexa-1,4-diene (nc), b.p. 112°. (Found: C, 32.9; H, 0.8; F, 66.4. C₈F₁₀H₂ requires C, 33.3; H, 0.6; F, 66.1%.)

Peak 6 was isolated in very small amount and shown to be a mixture of three compounds (NMR spectroscopy). It was not investigated further.

Peak 7 was isolated from fraction 6 (80°, 25 psi) and shown to be 1-fluoro-3,5-bis-(trifluoromethyl)benzene (nc), b.p. 114°. (Found: C, 41.4; H, 1.6; F, 57.2. C₈H₃F₇ requires C, 41.3; H, 1.3; F, 57.2%.) NMR spectral evidence is given in the NMR section; IR spectroscopy showed three medium strength bands at 1605, 1615 and 1630 cm⁻¹ (fluoroaromatic).

Peak 8 was isolated from fraction 12, (80°, 25 psi) and shown to be 1,2-difluoro-3,5-bis-(trifluoromethyl)benzene, b.p. 115°. (Found: C, 38.7; H, 1.1; F, 60.8. C₈H₂F₈ requires C, 38.4; H, 0.8; F, 60.8%.)

Peak 9 was isolated in small amount from fraction 7 (80°, 25 psi) and shown to be 2,2,4-trifluoro-4,6-bis-(trifluoromethyl)cyclohexa-1,4-diene (nc), (see NMR section). Insufficient material was available for combustion analysis, but mass spectroscopy showed a weak molecular ion at 270 a.m.u., together with strong ones at 250 (M–F)⁺ and 201 (M–CF₃)⁺. UV spectroscopy showed no strong absorption down to 220 mμ.

Peaks 10 and 11 could not be isolated.

Peak 12 was isolated from several fractions and shown to be starting material (IR spectroscopy).

Peak 13 was obtained from fraction 17, which was a pure sample, and shown to be 1-fluoro-2,4-bis-(trifluoromethyl)benzene (nc), b.p. 122°. (Found: C, 40.9; H, 1.4; F, 57.7. C₈H₃F₇ requires C, 40.3; H, 1.3; F, 57.2%.)

NMR spectroscopy

The empirical formulae of the compounds were, in most cases, checked by elemental analyses and mass spectroscopy, and are therefore not in doubt. The precise structures have been allocated by a mixture of NMR and IR spectroscopic studies, on the assumption that there has been no migration of trifluoromethyl groups under the mild conditions employed.

It is known⁹ that, in polyfluorocyclohexanes, CF₃ resonances are split by α -fluorines ($J \approx 13.5$ Hz) and by the *gem* fluorine ($J \approx 6$ Hz). By extension, it is reasonable to presume that only these types of fluorine show large couplings with CF₃ groups in cyclohexenes. The structures given are based as far as possible on this, although there is at least one exception to this rule in Table 3. The chemical shifts of CF₃ on sp³ carbon (≈ 60 – 65ϕ) and on sp² carbons (≈ 75 – 80ϕ) are quite distinct, and therefore it is possible to assign the position of any double bonds and hydrogens by a "fluorine count" round each CF₃. The structures thus obtained are tabulated below.

TABLE 3

NMR SPECTRA OF COMPOUNDS CHARACTERISED IN THIS WORK

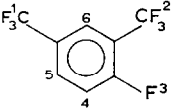
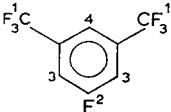
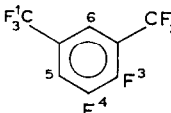
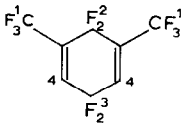
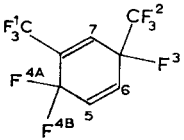
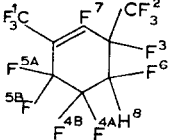
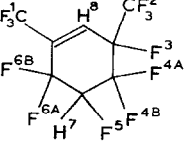
Compound	Nucleus	Shift ^a	Couplings (Hz)
 (II) ^b	1 2 3 4, 5, 6	63.0 62.4 108.6	$J(2,3) = 11$ others not available Very complex multiplet, consisting of rough (apparent) triplet, centred at 2.70, and an uneven doublet, centre of gravity at ~ 2.1 .
 (III)	1 2 3 and 4	64.3 108.3	$J(2,3) = 8$ Apparent 1 : 1 : 1 triplet centred at 2.40.
 (IV)	1 2 3 5, 6	63.8 62.5 132.2	$J(2,3) = 14$ Narrow multiplet at 2.34

TABLE 3 (continued)

Compound	Nucleus	Shift ^a	Couplings (Hz)
 (V)	1	65.3	$J(1,2) = 8.0$
	2	102.0	$J(1,4) = 0$
	3	97.0	$J(3,4) = 5.0$
	4	3.15	
 (VI)	1	65.3	
	2	79.9	
	3	164.2	
	4A	92.7	$J(A,B) = 341$
	4B	99.7	
	5, 6, 7		Very complex multiplet, with lines at 2.35, 3.20, 3.60, intensities 2 : 9 : 12, further split.
 (VII)	1	59.7	$J(1,5), J(1,5), J(1,7) = 5, 10, 14$
	2	72.9	$J(2,3) = 8, J(2,7) = 16, J(2,6) = 11$
	3	168.7	$J(2,7) = 16$
	4A	121.8	
	4B	133.6	$J(A,B) = 279$
	5A	102.2	$J(A,B) \text{ (assumed)} = 285$
	5B	104.2	
	6	211.5	$J(6,8) = 45$
	7	119.0	
	8	4.29	
 (VIII)	1*	65.9	$J(1,6A,6B) = 5, 10$
	2	78.9	$J(2,4A) = 11, J(2,4B) = 19, J(2,3) = 5$
	3	159.5	
	4A	124.1	$J(A,B) = 300$
	4B	134.2	
	5	213.5	$J(5,7) = 47$
	6A	105.7	$J(A,B) = 322$
	6B	126.6	
7	4.87		
8	3.22		

* 1 shows another coupling of ~ 5 Hz, which is not assigned.

^a ¹⁹F shifts in ϕ (ppm upfield from CCl₃F), ¹H shifts in τ .

^b Reference numbers from Table 1.

ACKNOWLEDGEMENTS

The author wishes to thank Professor J. C. Tatlow for his interest in this work Dr. J. Burdon for helpful discussions.

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