Aryne Chemistry. Part IX.[1] Cycloaddition Reactions of the Isomeric Trifluorobenzynes

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The isomeric trifluorobenzynes have been generated from tetraflurophenyl-lithium reagents in the presence of furan and afford good yields of the expected products. Reaction with aromatic substrates gives considerably lower yields of the isomeric trifluoro-1,4-dihydro-1,4-ethenonaphthalenes than are obtained in analogous reactions with tetrafluorobenzyne.

BENZYNE, generated by the thermal decomposition of benzenediazonium-2-carboxylate in suspension in benzene, in the presence of silver ions, reacts with benzene to give very low yields of 1,2- and 1,4-addition products (8% and 2% respectively).[2] Friedman has recently shown that the 1,4-addition reaction predominates in the absence of silver ions.[3] No addition reactions have been observed between benzyne generated from Grignard and organolithium reagents and aromatic substrates. However, we have recently shown that tetrafluorobenzyne,[4] and tetrachlorobenzyne [5] form 1,4-adducts in high yield (~80%) with a wide variety of aromatic compounds.

The reactivity of partially fluorinated benzynes towards 1,4-addition to aromatic hydrocarbons might be expected to be intermediate between the reactivities of tetrafluorobenzyne and benzyne itself. It was of interest, therefore, to study the relationship between extent and position of fluorine substitution in the benzyne intermediate, and reactivity towards aromatic hydrocarbons. The present paper deals with the two possible trisubstituted benzyne intermediates.

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[1] Part VIII, I. F. Eckhard, H. Heaney, and B. A. Marples, *Tetrahedron Letters*, 1967, 4001.

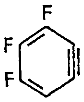
[2] R. G. Miller and M. Stiles, *J. Amer. Chem. Soc.*, 1963, **85**, 1798.

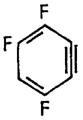
[3] L. Friedman, *J. Amer. Chem. Soc.*, 1967, **89**, 3071.

[4] (*a*) J. P. N. Brewer and H. Heaney, *Tetrahedron Letters*, 1965, 4709; (*b*) J. P. N. Brewer, I. F. Eckhard, H. Heaney, and B. A. Marples, *J. Chem. Soc.*, in the press.

[5] H. Heaney and J. M. Jablonski, *Tetrahedron Letters*, 1966, 4529.

Lithium-bromine exchange with 1-bromo-2,3,4,5-tetrafluorobenzene and 1-bromo-2,3,5,6-tetrafluorobenzene gave the corresponding tetrafluorophenyl-lithium compounds which at *ca.* −5° generated 3,4,5-trifluorobenzyne (I) and 3,4,6-trifluorobenzyne (II), respectively, in the presence of a suitable co-reactant. That the benzynes were, in fact, being generated was shown by reaction with furan. In each case a crystalline 1,4-epoxytrifluoro-1,4-dihydronaphthalene was isolated in *ca.* 60% yield. That the yield should be comparable with that of the adduct formed from tetrafluorobenzyne is not surprising as furan is a sufficiently reactive trapping agent to give a 76% yield of adduct with benzyne itself.[6]


(I)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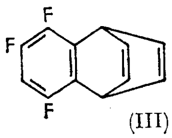
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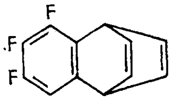

(IV)

When 3,4,6-trifluorobenzyne was generated in benzene a syrupy mixture was obtained from which the 1,4-adduct (III) could be sublimed as a crystalline solid in 16% yield. Gas chromatographic analysis showed that the residue contained a mixture of higher molecular weight compounds. When, however, 3,4,5-trifluorobenzyne was formed in benzene solution a very complex mixture resulted which was shown by analytical gas chromatography to contain the 1,4-benzyne adduct in not more than 1·5% yield. This adduct, 5,6,7-trifluoro-1,4-dihydro-1,4-ethenonaphthalene (IV), was independently prepared by debromination, *via* metallation and hydrolysis, of 5-bromo-6,7,8-trifluoro-1,4-dihydro-1,4-ethenonaphthalene.

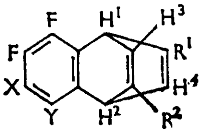
Generation of 3,4,6-trifluorobenzyne in *p*-xylene solution produced the corresponding adduct in 16% yield showing little variation from the benzene reaction. The structures of the adducts were confirmed by analysis and ^{1}H n.m.r. spectroscopy and in the benzene reaction by reduction, with uptake of 2 moles of hydrogen, to give a crystalline compound.

The drop in yield of the 1,4-benzene adduct in going from tetrafluorobenzyne (50%) to 3,4,6-trifluorobenzyne (16%) is large, and confirms that the presence of fluorine atoms in the 4 and 5 positions in a benzyne molecule is important to its electrophilic reactivity. Far more dramatic, however, is the low yield of 1,4-benzene-adduct (*ca.* 1·5%) from 3,4,5-trifluorobenzyne which contains an *ortho*-fluorine atom less than tetrafluorobenzyne. This yield of 1,4-benzene-adduct suggests that the presence of two *ortho*-fluorine atoms is essential to the high reactivity of fluorinated benzynes. As it is presumably the inductive effect of fluorine which contributes to the increased electrophilicity of the 'triple bond' it is not surprising that this effect should be much greater when fluorine is in the nearest position to the reactive centre.

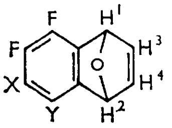
In view of the rapid drop in 1,4-adduct formation in moving from the tetrafluoro- to trifluoro-benzyne, it is unlikely that di- or mono-fluorobenzynes will show appreciable reactivity of this type. The 2,5-difluorobenzyne, however, in which both *ortho*-fluorines are still present might be of interest and we are currently investigating possible syntheses of this intermediate.

In order to study the relative ease of formation of 3,4,5- and 3,4,6-trifluorobenzynes from 2,3,4,6-tetrafluorophenyl-lithium, lithium fluoride was eliminated from the latter compound in the presence of furan. The furan adducts were found, by gas chromatographic analysis, to be present in the ratio of 3 : 1, and in a combined yield of *ca.* 90%. That 2,3,4,6-tetrafluorophenyl-lithium should preferentially lose fluoride ion from the 6-position in benzyne formation is understandable in view of the inductive effect of the fluorine at position 3 which would hinder loss of fluoride ion from position 2.

^{1}H N.m.r. Spectra.—The ^{1}H n.m.r. spectra of the trifluorobenzyne adducts contain the following points of general interest.



(V)



(VI)

Spectra of compounds of the type (V; X = Y = F) have already been discussed,[4b] and the trifluorobenzyne adducts (either X or Y = H) differ mainly in the removal of symmetry caused by replacement of one of the aromatic fluorines by hydrogen. In the tetrafluorobenzyne adduct the bridgehead protons H^{1} and H^{2} occur as a multiplet at τ 4·6—4·9. Compound (V; X = H, Y = F, R^{1} = R^{2} = H) still shows a broad multiplet at τ 4·5—5·0 but compound (V; X = F, Y = H, R^{1} = R^{2} = H) has two distinct multiplets at τ 4·6—4·9 and τ 5·0—5·4 for H^{1} and H^{2} respectively. Thus, a bridgehead proton is deshielded by *ca.* 0·4 p.p.m. by an opposed fluorine atom on the benzene nucleus. Similarly the furan adduct (VI; X = H, Y = F) shows H^{1} and H^{2} as a multiplet at τ 4·0—4·2 while in (VI; X = F, Y = H) H^{1} and H^{2} are separated to τ 4·1—4·2 and τ 4·4—4·5 respectively.

The bridgehead protons of the 3,4,6-trifluorobenzyne-*p*-xylene adduct (V; X = H, Y = F, R^{1} = R^{2} = Me) occur as an octet at τ 5·17—5·42 with peaks in the approximate ratio of 1 : 2 : 2 : 3 : 3 : 2 : 2 : 1. This can be explained on a first-order basis as a superposition of two identical sextets with coupling constants $J_{H(1)H(3)}$ =

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[6] G. Wittig and L. Pohmer, *Chem. Ber.*, 1956, **89**, 1334; H. Gilman and R. D. Gorsich, *J. Amer. Chem. Soc.*, 1957, **79**, 2625.

$J_{H(2)H(4)}$ 6·0 c./sec., $J_{H(1)H(4)} = J_{H(2)H(3)}$ 2·0 c./sec., and $J_{H(1)-F} = J_{H(2)-F}$ 2·0 c./sec. and with chemical shifts of τ 5·25 and 5·32 for H^1 and H^2 respectively. Such coupling constants are reasonable and in accord with those derived for the tetrafluorobenzyne–benzene adduct. It is also reasonable that H^2 should be less deshielded than H^1 because of the replacement at X of a fluorine by a hydrogen atom.

The aromatic proton X in the benzene adduct (V; $X = H$, $Y = F$, $R^1 = R^2 = H$) appeared as an octet of equal peaks centred on τ 3·5. First-order analysis gives $J^1_{o(HF)}$ 10 c./sec.; $J^2_{o(HF)}$ 8 c./sec.; $J_{m(HF)}$ 5·5 c./sec. which lies within the expected range. An identical aromatic pattern occurred in the reduced benzene adduct, the furan adduct (VI; $X = H$, $Y = F$) and the *p*-xylene adduct (V; $X = H$, $Y = F$, $R^1 = R^2 = Me$) although in the last compound half the octet was obscured by the vinyl proton multiplet.

The vinylic protons ($H^3H^4R^1R^2$) in the tetrafluorobenzyne–benzene adduct (V; $X = Y = F$, $R^1 = R^2 = H$) have been analysed as the AA′ portion of an AA′XX′ system, where $J_{XX'} = 0$ c./sec. The 60 Mc. spectrum shows two small outlying peaks flanking an intense triplet the middle line of which is resolved into a doublet on scale expansion. In the trifluorobenzyne–benzene adduct (V; $X = H$, $Y = F$, $R^1 = R^2 = H$) the unexpanded spectrum is very similar but expansion fails to resolve the middle peak and also shows considerable perturbation. The loss of symmetry relative to the tetrafluorobenzyne adduct has clearly resulted in loss of magnetic equivalence of H^1 and H^2 with resultant complication of the spectrum.

The fluorine F^{19} spectra of the two furan adducts (VI; X or $Y = H$) were analysed by first-order methods to give values of coupling constants in accord with the literature.

EXPERIMENTAL

Preparation of 1-*Bromo*-2,3,5,6-*tetrafluorobenzene*.[7]—1,2,4,5-Tetrafluorobenzene (4·5 g.) in dry ether (30 ml.) was stirred at −70° under an atmosphere of nitrogen. n-Butyl-lithium [N-solution in hexane–ether (30 ml.)] was added dropwise during ½ hr. and the mixture was maintained at −70° for a further 1 hr. Bromine (5·3 g.) was added dropwise during ½ hr. and again the mixture was kept at −70° for a further 1 hr. The solution was allowed to warm to room temperature, and was then washed with sodium thiosulphate solution, water, and finally dried ($MgSO_4$). Concentration at atmospheric pressure gave an oil which was distilled, b.p. 142—145°, (5·7 g.) to give an oil. Redistillation, b.p. 142—144°, gave 1-bromo-2,3,5,6-tetrafluorobenzene (5·1 g., 74%) which was shown by g.l.c. to contain less than 2% impurity, and was used for further preparations.

Reaction of 3,4,6-*Trifluorobenzyne with Furan*.—1-Bromo-2,3,5,6-Tetrafluorobenzene (5·0 g.) in furan (redistilled; 25 ml.) and dry ether (10 ml.) was stirred at −70° in an atmosphere of dry nitrogen. n-Butyl-lithium (2·54N-solution in hexane; 9·0 ml.) was added dropwise during ½ hr. The stirred mixture was set aside at −70° for 2 hr. and then allowed to warm to room temperature overnight. The reaction mixture was diluted with ether (50 ml.), well washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to a syrup (3·9 g.) which slowly crystallised. Recrystallisation from ethanol gave 1,4-*Epoxy*-5,6,8-*trifluoro*-1,4-*dihydronaphthalene*, m.p. 67—68° (2·5 g., 58%), $\gamma_{max.}$ 3130, 3100, 3060, 1655, 1635, 1510, 1290, and 1280 cm.$^{-1}$ (Found: C, 60·75; H, 2·45; F, 28·4. $C_{10}H_5F_3O$ requires C, 60·6; H, 2·55; F, 28·8%).

Reaction of 3,4,5-*Trifluorobenzyne with Furan*.—1-Bromo-2,3,4,5-tetrafluorobenzene (5·0 g.) was treated with n-butyl-lithium (2·54N-solution in hexane; 9·0 ml.) in furan–ether as described for 2,3,5,6-tetrafluorobromobenzene. A yellow syrup (4 g.) was obtained which was distilled, b.p. 58°/0·4 mm.) to give a crystalline product (3·3 g.) which from ethanol gave 1,4-*Epoxy*-5,6,7-*trifluoro*-1,4-*dihydronaphthalene* (2·7 g., 62%), m.p. 51—53°, $\gamma_{max.}$ 3120, 3110, 3020, 1640, 1510, 1295, and 1285 cm.$^{-1}$ (Found: C, 60·5; H, 2·65; F, 28·9. $C_{10}H_5F_3O$ requires C, 60·6; H, 2·55; F, 28·8%).

Reaction of 3,4,6-*Trifluorobenzyne with Benzene*.—1-Bromo-2,3,5,6-Tetrafluorobenzene (15 g.) in dry benzene (70 ml.) and dry light petroleum (30 ml.) was stirred at −10° under an atmosphere of dry nitrogen. n-Butyl-lithium (2·54N, 25·5 ml.), was added dropwise during 1·5 hr. The mixture was maintained at −10° for a further 4·5 hr. and then allowed to warm to room temperature overnight. The reaction mixture was washed with 2N-hydrochloric acid and water and dried ($MgSO_4$). Concentration under reduced pressure gave a syrup (10·5 g.) which was placed on an alumina column and eluted with light petroleum. Concentration of this elute gave a syrup (5·8 g.) which, on analytical g.l.c. (column A^{4b}; 180°), showed a single peak of low retention time and a broad peak of much higher retention time in the approximate ratio of 1 : 2. The first compound was isolated by sublimation (70°/0·5 mm.) from the syrup, to give fine needles of 5,6,8-*trifluoro*-1,4-*dihydro*-1,4-*ethenonaphthalene*, m. p. 73—74° from methanol (2·2 g., 16%), $\nu_{max.}$ 3090, 3010, 1640, 1630, 1615, 1590, 1515, 840, 770, and 700 cm.$^{-1}$ (Found: C, 69·35; H, 3·5; F, 27·5. $C_{12}H_7F_3$ requires C, 69·25; H, 3·35; F, 27·4%).

Reaction of 3,4,6-*Trifluorobenzyne with* p-*Xylene*.—2,3,5,6-Tetrafluorobenzyne (15 g.) was treated with n-butyl-lithium (2·54N; 25·5 ml.) in toluene–light petroleum as described for the benzene adduct. Concentration of the washed and dried reaction mixture gave a syrup (11 g.) which was chromatographed on alumina with light petroleum as eluant to give a yellow syrup (6·1 g.). Distillation (b.p. 60°/0·4 mm.) gave a syrup (2·5 g.) which crystallised and this after recrystallisation from methanol, gave 5,6,8-*trifluoro*-1,4-*dihydro*-2,10-*dimethyl*-1,4-*ethenonaphthalene*, m.p. 46—48°, (2·2 g., 14%), $\nu_{max.}$ 3110, 3050, 1645, 1625, 1510, 955, 890, 850, 830, 790, 735, and 690 cm.$^{-1}$ (Found: C, 71·0; H, 4·6; F, 24·6. $C_{14}H_{11}F_2$ requires C, 71·2; H, 4·65; F, 24·15%).

Reduction of 5,6,8-*Trifluoro*-1,4-*dihydro*-1,4-*ethenonaphthalene*.—5,6,8-Trifluoro-1,4-dihydro-1,4-ethenonaphthalene (0·42 g.) in methanol (25 ml.) containing palladium–charcoal (5%, 0·05 g.) was stirred at room temperature in an atmosphere of hydrogen under a slight excess of pressure. After 1 hr. the uptake of hydrogen had ceased. The catalyst was filtered off and the filtrate was concentrated to give a crystalline residue. Recrystallisation from

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[7] J. F. Tilney-Bassett, *Chem. and Ind.*, 1965, 693.

ethanol gave 5,6,8-*tetrafluoro*-1,2,3,4-*tetrahydro*-1,4-*ethanonaphthalene*, m.p. 63—65° (from ethanol) (0·21 g., 50%) $\nu_{max.}$ 3110, 3090, 1660, 1620, 1525, 1515, 970, 850, 810, 730, and 660 cm.$^{-1}$ (Found: C, 67·8; H, 5·25; F, 26·6; $C_{12}H_{11}F_3$ requires C, 67·95; H, 5·2; F, 26·9%).

Reaction of 3,4,5-*Trifluorobenzyne with Benzene*.—1-Bromo-2,3,4,5-tetrafluorobenzene (15 g.) was treated with n-butyl-lithium (2·54N; 25·5 ml.) in benzene–light petroleum as described for the 3,4,6-trifluorobenzyne reaction. Concentration of the washed and dried reaction mixture gave a syrup (10·4 g.) which after chromatography on an alumina column with light petroleum yielded a further syrup (6·4 g.). Distillation allowed separation of three broad fractions: (a) 60—100°/0·4 mm. (0·9 g.), (b) 100—160°/0·4 mm. (1·5 g.), and (c) residue (3·8 g.).

Analytical g.l.c. on column A^{4b} (180°) showed all the fractions to be mixtures. Fraction (a) contained components of shorter retention time and showed a peak comprising approximately 20% of this fraction which had identical retention time to that of 5,6,7-trifluoro-1,4-dihydro-1,4-ethenonaphthalene, prepared by an independent route.

Preparation of 5,6,7-*Trifluoro*-1,4-*dihydro*-1,4-*ethenonaphthalene*.— 5-Bromo-6,7,8-trifluoro-1,4-dihydro-1,4-ethenonaphthalene (0·91 g.) in dry ether was stirred at −70° under an atmosphere of dry nitrogen. n-Butyl-lithium (2·54N; 1·25 ml.) was added dropwise during 10 min.; stirring was continued at −70° for 2·5 hr. Water (1 ml.) in tetrahydrofuran (10 ml.) was added dropwise and the mixture was stirred at −60° for a further 1 hr. The reaction mixture was allowed to warm to room temperature, washed well with water, dried ($MgSO_4$), and concentrated under reduced pressure to give a syrup (0·6 g.) which was distilled (b.p. 54—56°/0·3 mm.) to give 5,6,7-*trifluoro*-1,4-*dihydro*-1,4-*ethenonaphthalene* as an oil (0·4 g., 61%), $\gamma_{max.}$ 3065, 2980, 1615, 1495, 1460, 1330, 1070, 870, 750, and 710 cm.$^{-1}$, n_D^{28} 1·5168 (Found: C, 69·15; H, 3·4; F, 27·6. $C_{12}H_7F_3$ requires C, 69·25; H, 3·35; F, 27·4%).

Preparation of 2,3,4,6-*Tetrafluorobromobenzene*.—1,2,3,5-Tetrafluorobenzene (45 g.) in dry ether (500 ml.) was cooled to −70° and stirred in an atmosphere of dry nitrogen. n-Butyl-lithium [(1N-solution in hexane (300 ml.)] was added dropwise during 1·5 hr. The mixture was stirred at −70° for a further 1 hr. Bromine (52·8 g.) was added dropwise during 1 hr. and the mixture maintained at −70° for a further ½ hr. The reaction mixture was allowed to warm to room temperature and then washed well with water, sodium thiosulphate solution, and again with water, and finally dried ($MgSO_4$). Concentration at atmospheric pressure yielded a syrup which was distilled, b.p. 138—150°/760 mm., to give an oil (50 g.). Redistillation (b.p. 141—146°/760 mm.) gave 2,3,4,6-tetrafluorobromobenzene (42 g., 61%) as a liquid. Analytical g.l.c. (column A^{4b} showed that $<1\%$ impurity was present and this material was used in the following metallation experiment.

Reaction of Furan with Benzyne Intermediates from 1-*Bromo*-2,3,4,6-*Tetrafluorobenzene*.— 2,3,4,6-Tetrafluorobromobenzene (15 g.) in furan (redistilled; 70 ml.) and dry ether (30 ml.) was stirred at −70° in an atmosphere of dry nitrogen. n-Butyl-lithium [2·54N-solution in hexane (25·8 ml.)] was added dropwise during 40 min. The reaction mixture was stirred at −70° for a further 2 hr. and then allowed to warm to room temperature. The mixture was diluted with ether, well washed with water, and dried ($MgSO_4$). Concentration under reduced pressure gave a syrup (12 g.). Analytical g.l.c. (column A^{4b}) showed the presence of two components only in the ratio of 3 : 1. Standard comparison showed these to be 1,4-epoxy-5,6,7-trifluoro-1,4-dihydro-naphthalene and 1,4-epoxy-5,6,8-trifluoro-1,4-dihydronaphthalene respectively.

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