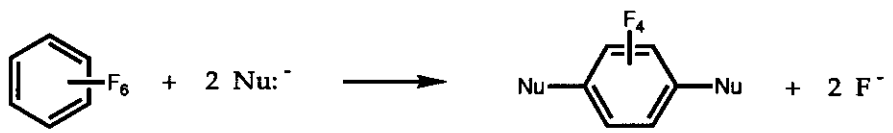
REACTION OF DIAZOLE ANIONS WITH HEXAFLUOROBENZENE: AN UNEXPECTEDLY FACILE ENTRY INTO HEXA(DIAZOL-1-YL)-BENZENES[1]

Robert N. Henrie II* and Walter H. Yeager

FMC Corporation, Agricultural Chemical Group, PO Box 8, Princeton, NJ 08543 USA

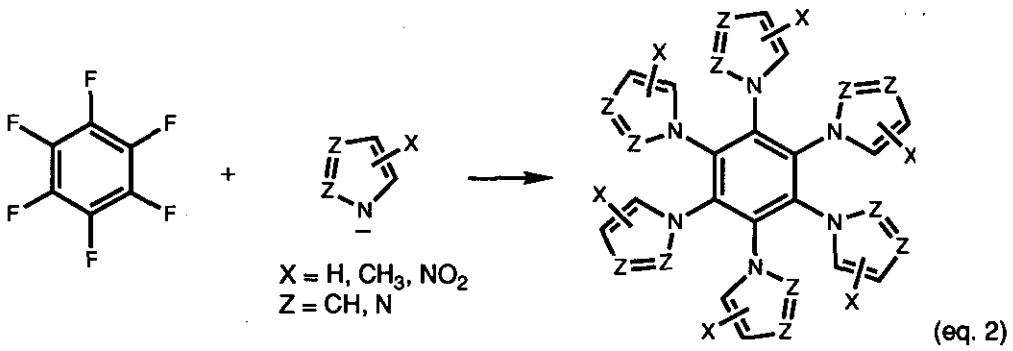
Abstract – Diazole anions react with hexafluorobenzene to give hexa(diazol-1-yl)benzenes in excellent yield, even with unfavorable reaction stoichiometries. In contrast, pyrrole anions give predominantly or exclusively 1,4-disubstituted products. This novel hexasubstitution reaction is discussed in terms of an $S_{RN}1$ mechanism.

During the course of a herbicide discovery project we designed a series of 1,4-bis(azol-1-yl)benzenes as candidate herbicides. Our initial route of entry relied on the well described nucleophilic aromatic substitution chemistry characteristic of perfluoroaromatics[2] and of hexafluorobenzene in particular, generally providing 1,4-disubstituted products (eq. 1).[3]



(eq. 1)

Despite a recent report that imidazole anion fails to react with C_6F_6 even under relatively vigorous conditions (24 h, 80 °C, DMSO or *t*-BuOH)[4], we have found that diazole anions react readily with C_6F_6 at room temperature or slightly above to give the hexasubstitution products irrespective of reaction stoichiometry (eq. 2). Products were characterized chiefly by mass spectrometry, together with ^{19}F nmr and elemental combustion analysis.



(eq. 2)

The preference for the hexasubstituted products is dominant to complete, depending on the diazole anion and reaction conditions, Table I. This was demonstrated by the first attempted reaction. When 2.0 equivalents of pyrazole anion (generated from NaH) in THF were treated with 1.0 equivalent of C_6F_6 at room temperature a mildly exothermic reaction ensued with the immediate precipitation of white solid; after a period of refluxing, tlc indicated that pyrazole had been consumed. The heavy precipitate was discarded assuming that it was NaF and the filtrate was evaporated, but only traces of non-volatile products could be recovered. Repetition of the reaction and examination of the precipitate revealed that it was hexa(pyrazol-1-yl)benzene (**1-6**) produced in excellent yield based on pyrazole anion with only small amounts of lower substitution products being isolable, or even detectable, Table I, entry 1a.

Adjusting the stoichiometry of the reaction to 6:1 diazole anion:C_6F_6 gave the hexasubstituted benzene (**1-6**) quantitatively (Table I, entry 1b). Variously C-substituted pyrazoles also participate in this novel reaction, Table I, entries 2a and 3. The ready reaction of trisubstituted pyrazoles provides confirmation that reaction occurs at the azole nitrogen atom, typical of $S_{RN}1$ reactions of diazoles and triazoles.[5] Acceptable solvents include THF, *N*-methylpyrrolidinone (DMF was generally avoided due to dimethylamine content), and acetonitrile, although with the latter solvent the di-, tetra-, and hexa-substituted products were isolated in nearly equal yield, Table I, entry 2b.

Table I. Reactions of Azole Anions with Hexafluorobenzene

$$C_6F_6 + \text{azole-X}^- \rightarrow (\text{azole})_nC_6F_{6-n}$$

rxn	azole	X	conditions	azole: C_6F_6	time	n: 6, %	5, %	4, %	3, %	2, %	total %
1a	pyrazole	H	THF/Δ	2:1	2 h	**1-6**, 88	nd	**1-4**, 3	nd	**1-2**, 11	102
1b	pyrazole	H	THF/Δ	6:1	6 h	**1-6**, 100	nd	nd	nd	nd	100
1c	pyrazole	H	THF/RT/20 mol % m-dinitrobenzene	6:1	24 h	**1-6**, 75	nd	**1-4**, 1	nd	**1-2**, 17	93
2a	pyrazole	3,5-$(CH_3)_2$	THF/Δ	2:1	6 h	**2-6**, 72	nd	**2-4**, 18-22	nd	**2-2**, 8-9	98-100
2b	pyrazole	3,5-$(CH_3)_2$	CH_3CN/RT	2:1	12 d	**2-6**, 34	nd	**2-4**, 23**	nd	**2-2**, 42**	99
3	pyrazole	3,5-$(CH_3)_2$-4-NO_2	NMP*/RT	5:1	11 d	**3-6**, 100	nd	nd	nd	nd	100
4	imidazole	H	THF+DMF/RT→Δ	2:1	10 d	**4-6**, 100	nd	nd	nd	nd	100
5	pyrrole	H	THF/RT	2:1	24 h	nd	**5-5**, 3	**5-4**, 27	**5-3**, 11	**5-2**, 38	79
6	pyrrole	2,5-$(CH_3)_2$	THF/RT	2:1	24 h	nd	nd	nd	nd	**6-2**, 73	73

RT = room temperature
THF = tetrahydrofuran
nd = not detectable
* NMP = *N*-methylpyrrolidinone; Na salt of the azole is insoluble in THF precluding reaction with C_6F_6
** by nmr integration

The isomeric diazole, imidazole, also participates in the hexasubstitution reaction, Table I, entry 4. Hexa(imidazol-1-yl)benzene (**4-6**) can be recrystallized from small volumes of H_2O. However, all hexasubstitution products, including **4-6**, are exceptionally insoluble in common organic solvents, which may account for the inaccurate literature report noted above.[4] Nmr sectra of the hexasubstitution products were routinely recorded in trifluoroacetic acid.

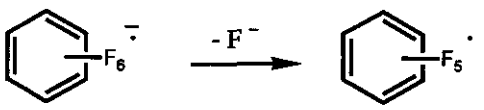
In contrast, pyrrole anion reacted with C_6F_6 exothermically in THF to give the disubstituted derivative (**5-2**) (Table I, entry 5) as the major product with successively lesser amounts of the higher homologs through C_6F(pyrrol-1-yl)$_5$. The hexasubstituted C_6(pyrrol-1-yl)$_6$ could not be detected. Introducing steric hindrance into the pyrrole anion in the form of two flanking methyl groups reduced the reaction course to that originally anticipated--exclusive 1,4-disubstitution, Table I, entry 6.

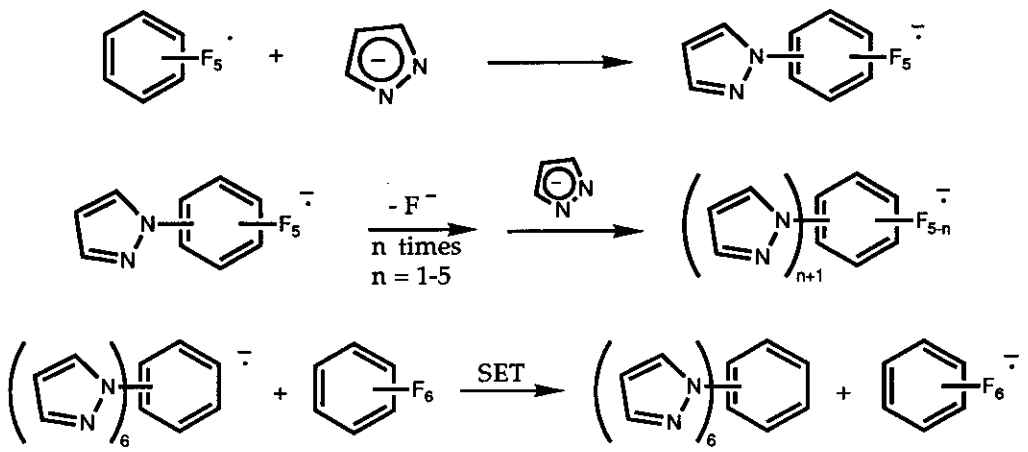
The mechanism of hexasubstitution is clearly not that of the typical nucleophilic aromatic substitution.[2,3] The product profile and mild reaction conditions are also inconsistent with a free radical mechanism.[6] However, we propose that single electron transfer (SET) chemistry, more specifically the $S_{RN}1$ mechanism,[7] is most probably involved, as outlined in Scheme I for pyrazole anion. This is confirmed by an inhibition experiment, Table I, entry 1c, using m-dinitrobenzene as the electron trap.[8] M-Dinitrobenzene is able to disrupt the electron transfer cycle, thereby increasing the yield of disubstitution product at the expense of the hexasubstitution product, even under the optimum 6:1 pyrazole anion:C_6F_6 stoichiometry.

Scheme I

Initiation:

Propagation:





The unique course of this particular $S_{RN}1$ reaction derives from the polyhalogenation of the aromatic acceptor. The ability to successively eject five fluorides from the initial radical anion adduct drives the reaction to the observed hexasubstitution products.

Persubstitution reactions of perhalo aromatics[9] and even perfluoro aliphatics[10, 11b] with alkoxides and mercaptides have been noted previously in the literature. All of these reactions probably proceed via the $S_{RN}1$ mechanism.[11] However, the sole literature reference to the $S_{RN}1$ chemistry of polyhalogenated (both Cl and F) aromatic acceptors that we were able to uncover reported only a monosubstituted product.[12] With regard to the propagation steps outlined in Scheme I, it is known that the C_6F_5 radical is substantially electrophilic.[6,13] In addition the C_6F_5 radical anion bears the extra electron density localized in a C–F σ^*-orbital,[13] enabling rapid cleavage of fluoride ion.

The differing abilities of various azoles to serve as donors is intriguing. Diazole and triazole anions are well-recognized donors in the $S_{RN}1$ reaction with a variety of acceptors.[7c,14] However, pyrrole anion is notably absent from the $S_{RN}1$ literature. This may be due to the unfavorable molecular orbital energy of pyrrole anion to serve as a donor. The proper matching of acceptor and donor properties sets the stage for the currently observed hexasubstitution reaction.[7e]

Alternative syntheses of the 1,4-bis(pyrazol-1-yl)benzenes (**2-2**) and (**3-2**) were achieved by sequential formation of the pyrazole rings from the aryl hydrazines and 2,4-pentanedione, Scheme II. This allowed structure confirmation of **2-2** and documentation that **3-2** was not detectable in the hexasubstitution reaction. Since both ortho and para isomers were obtained by this route, it also conclusively demonstrated that the reactions of azole anions with C_6F_6 provided exclusively the para disubstitution products, when disubstitution products were obtained. The ^{19}F nmr spectra are also diagnostic, Table II. For example, it is clear from the ^{19}F nmr that **5-3** is the 1,2,4-trisubstituted benzene, rather than the 1,3,5- or 1,2,3-pattern. From this evidence one can also conclude that the tetrasubstituted adducts are of the 1,2,4,5-pattern. Only **5-4** shows any evidence of another isomer in the ^{19}F nmr spectrum.

Scheme II

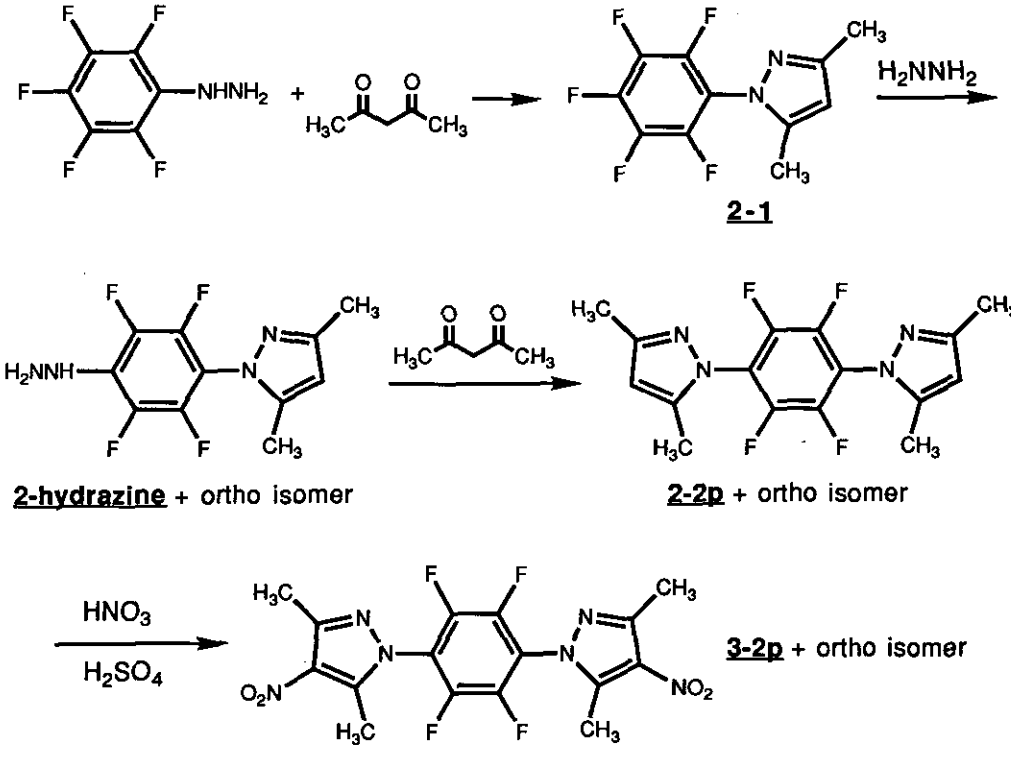


Table II. Physical Data of Compounds

#	molecular formula	C theor	C found	H theor	H found	N theor	N found	F theor	F found	M+	^{19}F nmr	mp °C
1-6	$C_{24}H_{18}N_{12}\cdot H_2O$	58.53	58.78	4.09	3.77	34.13	34.27	0.0	-----	474	-----	>400 sublimes
1-4	$C_{18}H_{12}N_8F_2$									378	-131.2	259-62
1-2	$C_{12}H_6N_4F_4$									282	-147.7	158-60
2-6	$C_{36}H_{42}N_{12}\cdot 0.5H_2O$	66.34	66.23	6.65	6.42	25.79	25.96	0.0	0.10	642	-----	280 with sublimation
2-4	$C_{26}H_{28}N_8F_2$									490	-128.5	200-10
2-2p	$C_{16}H_{14}N_4F_4$									338	-145.6	140-2.5
2-2o	$C_{16}H_{14}N_4F_4$									338	-144.4 -153.2	ni
3-6	$C_{36}H_{26}N_{18}O_{12}\cdot H_2O$	46.45	46.56	4.11	3.82	27.09	25.98	0.0	-----	912	-----	>320
3-2p	$C_{16}H_{12}N_6O_4F_4$									428	-142.6	256-8
3-2o	$C_{16}H_{12}N_6O_4F_4$									428	-141.9 -148.3	108-12
4-6	$C_{24}H_{18}N_{12}\cdot 2H_2O$	56.47	55.76	4.34	4.21	32.92	33.30	0.0	-----	474	nd	348-53 decomp
5-5	$C_{26}H_{20}N_5F$	74.09	75.12	4.78	4.63	16.62	16.18	4.51	5.37	421	-127.5	216-9
5-4	$C_{22}H_{16}N_4F_2$	70.58	69.85	4.31	4.22	14.96	14.68	10.15	9.92	374	-133.9 (-142.3)	238-41
5-3	$C_{18}H_{12}N_3F_3$	66.05	65.61	3.70	3.36	12.84	12.56	17.41	16.81	327	-134.6 -143.7 -148.3	112-5
5-2	$C_{14}H_8N_2F_4$	60.00	59.90	2.88	2.65	10.00	9.85	27.00	25.63	280	-149.5	125-7
6-2	$C_{18}H_{16}N_2F_4$	64.28	65.00	4.80	4.84	8.33	8.37	22.60	-----	336	-145.6	153-5

nd = not detected
ni = not isolated as a pure isomer--cf. Experimental

In summary, an unexpectedly facile entry into hexasubstituted benzenes has been discovered. Complex, high molecular weight, symmetrical products built upon a benzene core can be easily accessed. Single electron transfer (or $S_{RN}1$) mechanisms appear to be general phenomena in heteroaromatic chemistry, the utility of which remains to be explored by synthesis chemists.

EXPERIMENTAL

^{19}F Nmr spectra were recorded on a Nicolet NT-300 spectrometer in a proton decoupled mode using CCl_2F_2 as internal standard, -6.7 ppm. Nmr solvents were trifluoroacetic acid-d for the hexasubstitution products and $CDCl_3$ for all other compounds. Mass spectra were determined on a Varian MAT 311A spectrometer in both EI (70 eV) and CI (isobutane) modes. Melting points are uncorrected. Combustion analyses were performed by the FMC Analytical Services Group.

General procedure for generation of azole anions and reaction with C_6F_6. The Na salt of the azole was prepared by reaction with 1.0 equivalent of NaH (60% oil dispersion) in the indicated solvent, Table I, typically THF, under a nitrogen atmosphere. The suspension was heated to 65 °C to complete salt formation, then cooled to room temperature. C_6F_6 was added by graduated pipette in one portion in the indicated ratio and under the indicated conditions, Table I. In favorable cases a heavy white precipitate began to form almost immediately. The while solid was isolated by filtration and washed with water and THF to give the hexasubstituted products directly as microcrystalline solids. For the isolation of the lower homologs the filtrate was concentrated, diluted with Et_2O, washed with water, and the residue was chromatographed over silica gel using Et_2O/CH_2Cl_2 or CH_2Cl_2/petroleum ether mixtures as eluents.

1-Pentafluorophenyl-3,5-dimethylpyrazole, **2-1**.[15] A solution of 4.94 g (24.9 mmol) of pentafluorophenylhydrazine and 2.5 ml (24.4 mmol) of 2,4-pentanedione in 100 ml of EtOH was

refluxed for 1 h. The dark solution was treated with 0.5 g of activated carbon, refluxed for 1 h and filtered through diatomaceous earth. Removal of the solvent left 5.9 g (92%) of amber liquid. ^{1}H Nmr ($CDCl_3$): δ 2.15 (CH_3, s, 3), 2.30 (CH_3, s, 3), 6.05 (pyrazole 4-H, s, 1). ^{19}F Nmr ($CDCl_3$): -145.7, -152.8, -161.6 ppm. Mass spectrum, M^+: 262.

4-(3',5'-Dimethylpyrazol-1'-yl)-2,3,5,6-tetrafluorophenylhydrazine, **2-hydrazine**. A solution of 3.75 g (14.3 mmol) of the C_6F_5-pyrazole (**2-1**) and 1.0 ml (31.5 mmol) of anhydrous hydrazine in 50 ml of EtOH was stirred at room temperature for 24 h. The precipitated HF salt was removed by filtration and the ethanol was evaporated from the filtrate. The residual brown solid was triturated with 150 ml of water, filtered, washed with water and dried at 60 °C in vacuo providing 3.33 g (84.9%) of the arylhydrazine as an ortho/para isomer mixture (12:88), which was used without further purification. ^{1}H Nmr ($CDCl_3$)–para isomer: δ 6.00 (pyrazole 5-H, s, 1), 5.45 (NH, br s, 1), 4.05 (NH2, br s, 2), 2.29 (CH3, s, 3), 2.12 (CH3, s, 3); ortho isomer: δ 6.02, 5.22, 3.60, respectively. ^{19}F Nmr ($CDCl_3$)–para isomer: -148.6, -160.0 ppm; ortho isomer: -168, -158, -155, -147 ppm.

1,4-Bis(3',5'-dimethylpyrazol-1'-yl)-2,3,5,6-tetrafluorobenzene, **2-2**. A solution of the above hydrazine isomer mixture (1.5 g, 5.5 mmol) and 1.0 ml (9.7 mmol) of 2,4-pentanedione in 50 ml of EtOH was refluxed for 5 h. Removal of solvent in vacuo left a tan solid which was chromatographed over silica gel using 5% Et_2O/CH_2Cl_2. The first fraction contained both ortho and para isomers, 0.38 g (21%). ^{1}H Nmr ($CDCl_3$) of ortho isomer, **2-2o**: δ 5.85 (pyrazole 5-H, s, 2), 2.1, 2.07 (CH_3, s, 12). ^{19}F Nmr ($CDCl_3$): -144.4, -153.2 ppm. The second fraction was pure para isomer, **2-2p**, 1.17 g (63%). ^{1}H Nmr ($CDCl_3$): δ 6.1 (pyrazole 5-H, s, 2), 2.3 (CH_3, s, 6), 2.2 (CH_3, s, 6). ^{19}F Nmr ($CDCl_3$): -145.6 ppm.

1,4-Bis(3',5'-dimethyl-4'-nitropyrazol-1'-yl)-2,3,5,6-tetrafluorobenzene, **3-2p**. Under nitrogen a solution of 1.13 g of **2-2p** in 25 ml of conc H_2SO_4 was treated with a cold mixture of 1.0 ml of 90% HNO_3 in 5 ml of conc H_2SO_4. After standing at room temperature for 19 h, a further 0.5 ml of 90%

HNO_3 was added and the mixture stirred over the weekend. Tlc (CH_2Cl_2) showed the reaction to be complete. The mixture was poured onto 500 ml of ice, and the solid was isolated by filtration. Washing with water and drying at 60 °C in vacuo provided 1.37 g (95.8 %) of white solid. ^1H Nmr ($CDCl_3$): δ 2.6 (CH_3, overlapping singlets). ^{19}F Nmr ($CDCl_3$): -142.6 ppm.
The ortho isomer **3-2o** was prepared analogously. ^1H Nmr ($CDCl_3$): δ 2.40 (CH_3, s, 3), 2.60 (CH_3, s, 3). ^{19}F Nmr ($CDCl_3$): -141.9, -148.3 ppm.

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