REACTION OF 1-SUBSTITUTED PYRROLES WITH N-FLUORODIBENZENESULFONIMIDE: EFFECT OF HALOGEN ON ELECTROPHILIC SUBSTITUTION BY ADDITION-ELIMINATION

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Abstract-The reaction of 1-substituted pyrroles (1-methyl, 1-ethyl and 1-phenyl) with N-fluorodibenzenesulfonimide (NFSi) gave N-(1-substituted 1H-pyrrol-2-yl)dibenzenesulfonimides as products by addition elimination. Defluorination of NFSi was the only competing reaction. In contrast the reaction of 1-t-butylpyrrole with NFSi gave a mixture of fluoropyrroles. This is attributed to a steric interaction between the t-butyl group and the phenyl groups on NFSi. N-Chlorodibenzenesulfonimide was found to dechlorinate under all conditions studied and it was not possible to compare its reactivity with that of NFSi. The results of this study support our hypothesis that the observation of addition-elimination in pyrroles is related to the π-electron donating ability of the halogen initially introduced into the ring.

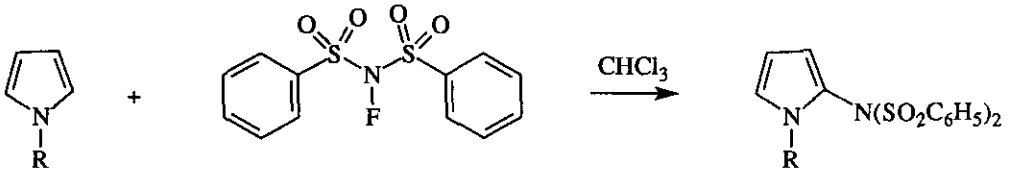
In 1986 we reported the first example of electrophilic substitution by addition-elimination in pyrrole chemistry.[1] The reaction of 1-methylpyrrole with N-chloroacetanilide gave a product in which the acetanilide moiety became attached to the pyrrole ring by a process of addition-elimination. It was proposed that addition-elimination occurred because the 2-chloro substituent effected the aromaticity of the pyrrole ring making it more dienic in character. Addition of the acetanilide anion to the initially formed σ-complex then became competitive with deprotonation.[1] Calculations, by Radom and coworkers, on the effect of substituents on the aromatic character of the pyrrole ring indicated that π-electron donors at C-2 increased the dienic character of the pyrrole ring.[2] This suggested that addition-elimination should depend on the π-electron donating ability of the halogen. To this end a study of the reaction of N-haloimides (Cl,Br and I) with 1-methylpyrrole was carried out.[3] Essentially no addition-elimination reaction was observed with the N-bromo and N-iodo derivatives. These results supported our hypothesis that there is a relationship between the π-electron donating ability of the halogen and the observation of addition-elimination.

Fluorine is the strongest π-electron donator of the halogens. It would be interesting to see how N-fluoro derivatives reacted with 1- substituted pyrroles. But at the time of the 1988 study suitable N-fluoro

derivatives were not readily available.[3] Recently N-fluorodibenzenesulfonimide[4] became commercially[5] available. This compound has been reported to fluorinate anisole.[4] Mechanistic studies[6] indicated that fluorine transfer occurred by an S_N2 process analogous to the proposed[7] first step in electrophilic substitution by addition-elimination in pyrroles. In this study the reaction of N-fluorodibenzenesulfonimide with 1-substituted pyrroles is examined. A process which is analogous to the reaction of N-chloro-N-(4-substituted phenyl)benzenesulfonamides[8] with 1-methylpyrrole to give addition-elimination products.

RESULTS

The reaction of pyrroles (**1**-**4**) with N-fluorodibenzenesulfonimide (NFSi) was studied in $CHCl_3/CDCl_3$.



1, R = CH_3
2, R = CH_3CH_2
3, R = C_6H_5
4, R = t-C_4H_9

5, R = CH_3
6, R = CH_3CH_2
7, R = C_6H_5

Reaction conditions were worked out using 1-methylpyrrole (**1**) as a model system. Pyrrole (**1**) was combined with NFSi in $CDCl_3$ and the reaction was over in 12 h (negative KI/starch test). A gas was produced which was identified as HF based on its reaction with pH indicator paper. The ^1H nmr spectrum of the reaction mixture showed addition-elimination product (**5**) (62 %) and starting pyrrole (**1**) to be the only compounds present. Reaction mixtures were black and this suggested the possibility of product decomposition. To check this 2-methylnaphthalene was added to the reaction mixture and product yields were determined by quantitative ^1H nmr. No evidence for product decomposition was found.

It appeared that the HF generated in the addition-elimination reaction was causing the defluorination of NFSi. Base ($NaHCO_3$)[7] was added to the reaction in $CDCl_3$ to trap the HF generated. The ^1H nmr spectrum of the reaction mixture indicated a slight increase in the addition-elimination product but the reaction was not as clean and at least three additional products were observed by ^1H nmr spectroscopy. Sodium fluoride was added to the reaction mixture as an HF trap. Yields of the the addition-elimination product increased and an equimolar amount of NaF had the same effect on the yield as a ten-fold excess. Bis-trimethylsilylacetamide (BSTA), recently used to trap HCl,[9] was added to the reaction mixture as a possible HF scavenger but the yield of addition-elimination product decreased and other products were observed.The highest yields of addition-elimination product (**5**) were obtained with NaF (equimolar) as the HF trap and reactions with pyrroles (**2**-**4**) were carried out under these conditions. Results of the various reactions are summarized in Table 1.

Preparative reactions were run in $CHCl_3$ and the addition-elimination products were isolated by column chromatography, recrystallized from ethanol and identified by their respective spectral properties and elemental analysis.

Table 1
Reaction of N-Fluorodibenzenesulfonimide with 1-Substituted Pyrroles

R	Trapping Agent	Yield (%)
CH_3	none	62[a]
CH_3	$NaHCO_3$	50[a]
CH_3	NaF (1 equiv.)	76[a]
CH_3	NaF (10 equiv.)	72[a]
CH_3	BSTA (1 equiv.)	42[a]
CH_2CH_3	none	34[b]
CH_2CH_3	NaF (1 equiv.)	65[b]
C_6H_5	none	79[b]
C_6H_5	NaF (1 equiv.)	85[b]
t-C_4H_9	none	0[a]
t-C_4H_9	NaF (1 equiv.)	0[a]

[a]*Yields determined by* ^1H *nmr and are* ± 5 %. [b]Isolated product before chromatography and recrystallization. Material is essentially pure by ^1H nmr.

No addition-elimination product was observed by ^1H nmr when 1-t-butylpyrrole (4) was reacted with NFSi either in the presence or absence of NaF. The ^1H nmr spectra of the reaction mixtures showed the presence of starting (4) and at least four products. It appeared that in this system fluorination had taken place. This was confirmed by the ^{19}F nmr spectrum of the reaction mixture which showed a complex mixture of fluorine containing compounds. *Steric effects have been observed in previous studies and it was found that when a large* steric effect was present the addition-elimination product did not form.[7,10] It is proposed that there exists a steric interaction between the the t-butyl group on the σ-complex and the phenyl groups on the sulfonimidyl anion which prevents ion-pair (σ-complex/nitrogen anion) collapses to give the 2,5-addition product. Deprotonation of the σ-complex becomes more favorable and fluorination of the pyrrole ring is observed.

As noted above it has been proposed that addition-elimination depends on the π-electron donating ability of the halogen.[3] In order to test this further N-chlorodibenzenesulfonimide (NClSi) was prepared in order to compare its reactivity with that of N-fluorodibenzenesulfonimide. NClSi was prepared by reacting dibenzenesulfonimide

with t-butylhypochlorite in methanol. N-Chlorodibenzenesulfonimide precipitated out of solution and contained 90% active chlorine. This material decomposed on attempted recrystallization and the dried material was used without further purification.

N-Chlorodibenzenesulfonimide was reacted with 1-methylpyrrole (**1**) in $CDCl_3$ containing $NaHCO_3$.[7] The ^1H nmr spectrum indicated only the presence of starting pyrrole (**1**). A gas was produced which gave a positive KI/starch paper test and was identified as chlorine. When the reaction was carried out without added base, HCl gas was detected and the ^1H nmr spectrum indicated the presence of starting pyrrole (**1**) and small amounts of what appeared to be chlorination products. No evidence for the formation of the addition-elimination product (**5**) was found under any of the reactions conditions used. These results indicated that N-chlorodibenzenesulfonimide dechlorinated faster than it reacted with the pyrrole ring and therefore it was not possible to compare the reactivity of the N-fluoro and N-chloro derivatives of dibenzenesulfonimide.

CONCLUSION

For pyrroles (**1-3**) the only observable products were formed by addition-elimination. Defluorination of NFSi was the only competing process. Based on unreacted starting material, the yields of addition-elimination product in these reactions were essentially quantitative. These results support out hypothesis that the observation of addition-elimination in pyrroles is related to the π-electron donating ability of the halogen initially introduced into the ring.

EXPERIMENTAL

A Varian EM-360 and a Bruker AM 200 were used to record ^1H nmr spectra. ^{19}F Nmr spectra were taken on a Bruker AM 200 operating at 188.18 MHz. Mass spectra were taken with a Hitachi-Perkin Elmer RMU-6H spectrometer. Melting points were taken on a Meltemp and are uncorrected. Pyrroles (**1-4**) were commercially available and used without further purification. Iodometric analysis indicated that N-fluorodibenzenesulfonimide (AlliedSignal Inc.) contained 95+% active fluorine.

Preparation of N-Chlorodibenzenesulfonimide: Dibenzenesulfonimide (0.983 g, 3.31 mmol) was dissolved in 10 ml of methanol and a slight excess (0.370 g, 0.339 mmol) of t-butylhypochlorite[11] was added. Reaction was immediate and the product precipitated out of solution. The product was isolated by suction filtration and dried overnight in a vacuum desiccator. Recrystallization from either methanol or toluene resulted in decomposition of the product. A 65% yield of N-chlorodibenzenesulfonimide (90% chlorine), mp 111-115 °C was obtained and used without further purification.

General Reaction Procedure: Nmr scale reactions were run in 2.0 ml of $CDCl_3$ to which were added 0.4 mmol of NFSi/NClSi, the trapping agent/base (if any) and 0.04 mmol of the pyrrole. Reactions were over in 12 h (negative KI/starch test) and were then analyzed by ^1H nmr. Preparative scale reactions were run in 25 ml of $CHCl_3$ to which were added 5.46 mmol of NFSi, the trapping agent (if any) and 5.46 mmol of the pyrrole.

Reactions were over in 12 h (negative KI/starch test). The reaction mixture was filtered under suction, the filtrate was washed twice with 5% aqueous NaOH solution and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure to give a black crude reaction mixture. It was washed with a small amount of

petroleum ether (35-60 °C) to remove unreacted pyrrole and any halopyrroles which might be present. This material was purified by column chromatography on silica gel with $CHCl_3$ as the eluent. All the addition-elimination products were recrystallized from ethanol.

N-(1-methyl-1H-pyrrol-2-yl)dibenzensulfonimide (**5**): mp 113-116 °C; 200 MHz ^1H nmr ($CDCl_3$) δ 7.94-7.48 (m, 10 arom H), 6.66 (dd, J_{4-5} = 2.9 Hz, J_{3-5} = 1.9 Hz, C5H), 6.09 (dd, J_{4-5} = 2.9 Hz, J_{3-4} = 4.0, C4H), 5.78 (dd, J_{3-4} = 4.0 Hz, J_{3-5} = 1.9 Hz, C3H), 3.22 (s, CH_3); Anal. Calcd for $C_{17}H_{16}N_2O_4S_2$: C, 54.24; H, 4.28; N, 7.44. Found: C, 53.92; H, 4.27; N, 7.35.

N-(1-ethyl-1H-pyrrol-2-yl)dibenzensulfonimide (**6**): mp 124-126 °C; 200 MHz ^1H nmr ($CDCl_3$) δ 7.98-7.47 (m, 10 arom H), 6.79 (dd, J_{4-5} = 3.0 Hz, J_{3-5} = 1.8 Hz, C5H), 6.13 (dd, J_{4-5} = 3.0 Hz, J_{3-4} = 3.8, C4H), 5.74 (dd, J_{3-4} = 3.8 Hz, J_{3-5} = 1.8 Hz, C3H), 3.57 (q, J = 8.9 Hz, CH_2), 1.26 (t, J = 8.9 Hz, CH_3); Anal. Calcd for $C_{18}H_{18}N_2O_4S_2$: C, 55.37; H, 4.65; N, 7.17. Found: C, 54.86; H, 4.45; N, 6.92.

N-(1-phenyl-1H-pyrrol-2-yl)dibenzensulfonimide (**7**): mp 153-155 °C; 200 MHz ^1H nmr ($CDCl_3$) δ 7.75-7.30 (m, 15 arom H), 6.94(dd, J_{4-5} = 3.2 Hz, J_{3-5} = 1.9 Hz, C5H), 6.24 (dd, J_{4-5} = 3.2 Hz, J_{3-4} = 3.9, C4H), 5.79 (dd, J_{3-4} = 3.9 Hz, J_{3-5} = 1.9 Hz, C3H); nmr ($CDCl_3$); Anal. Calcd for $C_{22}H_{18}N_2O_4S_2$: C, 59.80; H, 4.14; N, 6.39. Found: C, 59.69; H, 4.15; N, 6.22.

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