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# Charge Control in the $S_NAr$ Reaction. *Meta* Substitution with Respect to the Activating Nitro Group in 3,4-Dihalogenonitrobenzenes.§

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***Abstract*** : The reactions of 3-fluoro-4-chloronitrobenzene and of 3,5-difluoro-4-chloronitrobenzene with thiophenoxide anion lead to predominant substitution of the chlorine atom through $S_NAr$ orbital-controlled processes. However, when harder nucleophiles (methoxide anion) are used, the substitution of a fluorine atom *meta* with respect to the activating nitro group becomes apparent in the reaction of 3-fluoro-4-chloronitrobenzene, predominant in the reaction of 5-fluoro-4-chloro-3-methoxynitrobenzene, and almost exclusive in the reaction of 3,5-difluoro-4-chloronitrobenzene. Kinetic measurements and theoretical calculations indicate that the observed *meta* substitution of a fluorine atom is a $S_NAr$ charge-controlled reaction with a loosely bonded transition state.

## INTRODUCTION

Non-electron-defficient benzene derivatives are intrinsically reluctant to participate in $S_NAr$ reactions. Introduction of substituents such as $NO_2$ has the effect of reducing the electron density of the benzenoid system, especially at the *ortho* and *para* carbons, thus favoring the nucleophilic attack at these positions.[1] Concomitantly, electron-withdrawing groups, especially the $NO_2$ group, have a strong stabilizing effect on the intermediate anionic σ-complexes (Meisenheimer complexes), and this stabilization increases in the order *meta* << *ortho* < *para*.[2] It is therefore expected that $S_NAr$ reactions will preferentially occur at the *para* and *ortho* positions of a substituted nitrobenzene derivative, and this is what is experimentally found.

The chlorine atom of nitrochloro-substituted aromatic compounds, when occupying a conjugate position relative to the nitro group, has a significant mobility in $S_NAr$ reactions, being in most cases the only atom substituted by different nucleophiles.[3] On the other hand, among the halogens, fluoro is generally a much better leaving group than the other halogens in kinetically controlled (first step as rate determining step) $S_NAr$ reactions, especially when hard nucleophiles are used.[4] It has also been reported that fluorine has a promoting effect in the reactions of polyfluorobenzenes with nucleophiles varying the effect in the series *meta* > *ortho* > *para*-fluorine, whereas in similar processes with polyfluoro-pyridines and -pyrimidines, the greatest acceleration effect is produced by *ortho*-fluorines.[5,6] This behavior has been explained considering ion-dipole interactions that lead to an early formation of the transition state and to σ-complex stabilization by *ortho*-fluorine atoms.[6] Theoretical calculations indicate that although most π-donor substituents exert a destabilizing effect on the cyclohexadienyl anions when placed in the *ortho* and *para* positions, *ortho*-fluorine acts in the opposite way.[2]

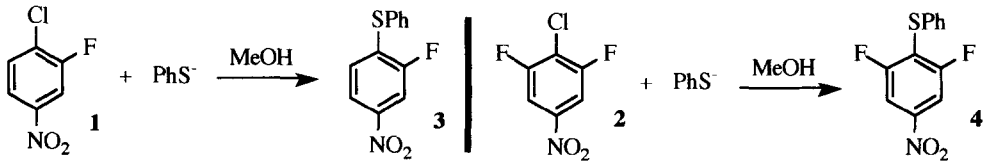
§Devoted to the memory of the late Professor Felix Serratosa.

In order to get some extra information on the factors that govern the regioselectivity of $S_NAr$ reactions where fluorine substituents are involved,[7] we decided to test the effect that fluorine atoms *ortho* to chlorine produce in the nucleophilic aromatic substitution reactions of 4-chloronitrobenzene with various nucleophiles. If a comparable mobility of the chlorine and fluorine atoms is achieved, and the mechanism remains invariable, the predominant direction of nucleophilic attack may be determined by the properties of the nucleophile, in particular, by the ratio of contributions of electrostatic and orbital terms into the energy of interaction with the substrate.[8,9,10] A related reasoning has been used in the literature to justify the substitution of the nitro group by hard oxyanions in 1,4-nitrochloroanthraquinone.[11]

In this article we wish to report that in our case (4-chloronitrobenzene), and contrary to some observations described in the literature for some other systems (non-nitro-substituted aromatics),[5,6] fluorine (and other resonance electron donor groups) substituents *ortho* to the carbon under attack inhibit the attack by hard nucleophiles. On the other hand, a fluorine (and other electronegative groups) substituent *meta* to the carbon under attack shows the opposite effect, enhancing the attack by hard nucleophiles. Combining these properties with the ability of the fluorine atom as a leaving group and the strong polarization of the C-F bond compared with other carbon-halogen bonds, $S_NAr$ substitution *meta* with respect to an activating nitro group can be achieved in the presence of a good leaving group in the *para* position providing the reaction is controlled by the electrostatic term.[10]

## EXPERIMENTAL RESULTS

In the scheme 1 the reactions of 3-fluoro-4-chloronitrobenzene, **1**, and 3,5-difluoro-4-chloronitrobenzene, **2**, with thiophenoxide anion as representative nucleophile of the soft type are described. Exclusive substitution of the chlorine atom in the *para* position with respect to the nitro group is observed in both cases.



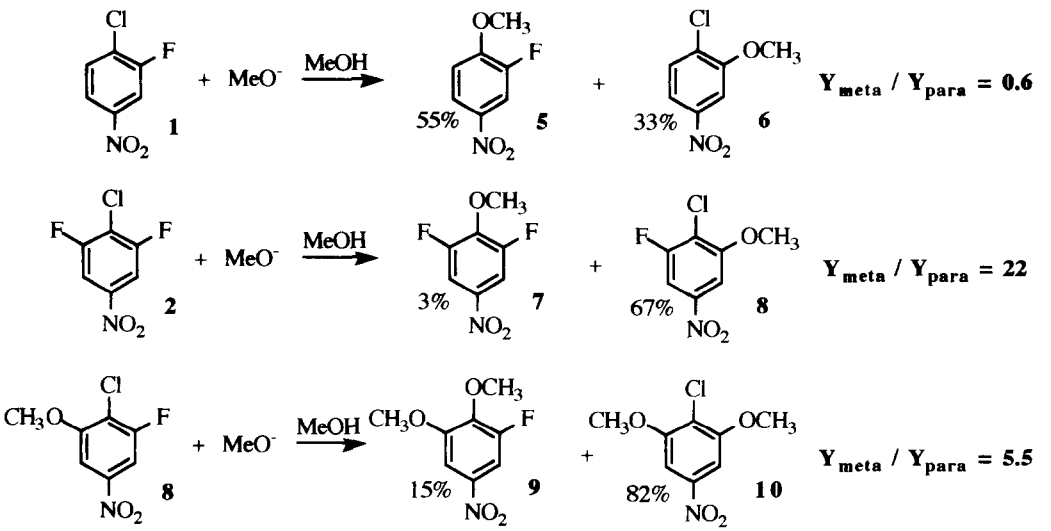

**Scheme 1**

In the scheme 2 the corresponding reactions of substrates **1** and **2** with methoxide anion as representative nucleophile of the hard type are depicted. In the reaction of 4-chloro-3-fluoronitrobenzene, **1**, in addition to the "normal" *para* substituted product (2-fluoro-4-nitroanisole, **5**), significant amounts of the product corresponding to fluorine substitution in the *meta* position with respect to the nitro group are obtained (2-chloro-5-nitroanisole, **6**). This trend becomes more evident in the reaction of 4-chloro-3,5-difluoronitrobenzene, 2, that leads almost exclusively to the *meta* substituted product, 4-chloro-5-fluoro-3-methoxynitrobenzene, **8**. This *meta* fluorine atom substitution is also observed in the reaction of 4-chloro-5-fluoro-3-methoxynitrobenzene, **8**, with methoxide anion, being the observed selectivity in between the obtained in the reactions of substrates **1** and **2** (scheme 2).

*Mechanistic studies.*

The regioselectivity of fluorine *vs.* chlorine substitution in $S_NAr$ reactions can depend on the reaction mechanism.[12] Thus, in the reaction of pentafluorochlorobenzene with carbanions the limiting stage is the formation of the σ-complex with rapid loss of the fluoride ion, whereas in the reaction with iron carbonilate,

the limiting stage corresponds to chloride ion elimination.[13] Another possibility to consider is a change from a polar to an electron transfer mechanism[14] (we have reported such a behavior in related photochemical $S_NAr$ reactions)[15]. In order to stablish if the regioselectivity changes just described were due to a change of mechanism the effect of different conditions and additives, and the kinetics of our reactions were studied.




**Scheme 2**

Reactions of 4-chloro-3,5-difluoronitrobenzene, **2**, with methoxide and thiophenoxide anions were carried out in inert atmosfere, in the presence of radical scavengers such as *m*-dinitrobenzene or galvinoxyl, and also under irradiation with visible light, but no significant differences with the standard reactions (schemes 1 and 2) were observed.

**Table 1.** Pseudo-first-order Rate Constants ($k_{obs}$) and Second Order Rate Constants ($k_2$) for the Reactions of 4-Chloro-3,5-difluoronitrobenzene, **2** (0.01M), with Methoxide (35°C) and Thiophenoxide (10°C) Anions in Methanol.

| [MeO⁻] mol $l^{-1}$ | $10^5k_{obs}$ $s^{-1}$ | $10^5k_2$ l $mol^{-1}s^{-1}$ | [PhS⁻] mol $l^{-1}$ | $10^5k_{obs}$ $s^{-1}$ | $10^5k_2$ l $mol^{-1}s^{-1}$ |
|---|---|---|---|---|---|
| 0.30 | 17.5±0.4 | | 0.10 | 33.6±0.6 | |
| 0.45 | 27.7±0.3 | 70.6 | 0.20 | 73.4±0.5 | 40.6 |
| 0.60 | 38.7±0.3 | | 0.25 | 94.7±0.3 | |

Kinetic data are recorded in Tables 1 and 2. Thus, using 4-chloro-3,5-difluoronitrobenzene, **2**, as a substrate and methoxide and thiophenoxide anions as a nucleophiles in methanol as a solvent under pseudo-first-order conditions, good straight lines were obtained to at least 80% completion (the starting material disappearance was monitored by HPLC). The observed rates constants ($k_{obs}$) for these reactions are recorded in Table 1 together with the obtained $k_2$ values (35°C in the case of methoxide anion and 10°C in the case of thiophenoxide). In Table 2 the obtained $k_{obs}$ ([**2**] = 0.01M, [MeO⁻] = 0.3, [PhO-] = 0.1M) at different temperatures together with the calculated activation parameters (using the Eyring equation)[16] are shown.

**Table 2.**- Activation Parameters for the Reactions of 4-Chloro-3,5-difluoronitrobenzene, **2**, with Methoxide and Thiophenoxide Anions in Methanol.

| Exp. | Nucleophile[a] | Temperature °C | $10^5 k_{obs}$ $s^{-1}$ | $\Delta H^{\dagger}$ kJ mol-1 | $\Delta S^{\dagger}$ J $mol^{-1}$ $K^{-1}$ |
|---|---|---|---|---|---|
| 1 | $MeO^-$ | 15 | 1.81±0.01 | 81.9 | -43.8 |
| 2 | | 25 | 5.76±0.03 | | |
| 3 | | 30 | 10.17±0.08 | | |
| 4 | | 35 | 17.5±0.4 | | |
| 5 | $PhS^-$ | 10 | 33.6±0.6 | 60.5 | -77.3 |
| 6 | | 15 | 56.2±1.3 | | |
| 7 | | 17 | 67.0±0.4 | | |
| 8 | | 20 | 88.9±0.8 | | |

[a][**2**] = 0.01M, [MeO-] = 0.3M, [PhS-] = 0.1M.

## THEORETICAL CALCULATIONS AND DISCUSSION

The reactions of substrate **1** with both nucleophiles lead, as expected, to predominant substitution of the chlorine atom in the *para* position with respect to the nitro group. However, the regioselectivity is much more evident when the thiophenoxide anion acts as a nucleophile (scheme 1). Methoxide anion shows a higher tendency than thiophenoxide anion to substitute the fluorine atom, thus the observed regioselectivity is reduced (scheme 2). The substitution of the hydrogen *ortho* to the chlorine atom by groups with strong inductive electron-atracting and resonance electron-donor properties (F, substrate **2**) produces no significant effect in the reactions with thiophenoxide anion being still the substitution of the chlorine atom the exclusive observed process (scheme 1). However, an important effect is observed in the reactions with methoxide anion as a nucleophile. In these cases (scheme 2), the reaction shows an inverted regioselectivity (substitution of the fluorine atom *meta* with respect to the nitro group) that is very well defined in the case of substrate **2**. As far as we know, this result is a unique example of regioselectivity change (*para* to *meta* with respect to the nitro group) in a ground state nucleophilic aromatic substitution.

Our mechanistic studies in different conditions and in the presence of additives indicate that the change in regioselectivity (scheme 1 *vs.* scheme 2) is not due to a change of mechanism from an electron-transfer to a polar one. This comes supported by the described kinetic studies (Tables 1 and 2). Thus, the studied reactions show good second order (first order in each of the reactants) kinetic behavior, the activation enthalpy is similar in both reactions (methoxide or thiophenoxide anions as a nucleophiles), and the entropy of activation has the expected values ($\Delta S^{\dagger} << 0$) for a first stage rate determining $S_NAr$ mechanism in both cases.[17] However, and interestingly enough, the activation entropy is significantly more negative for the reaction with thiophenoxide anion .

In Figures 1 and 2, the results of semiempirical AM1[18] (implemented in the AMPAC[19] program) theoretical calculations on 4-chloronitrobenzene, 4-chloro-3-fluoronitrobenzene, **1**, 4-chloro-5-fluoro-3-methoxynitrobenzene, **8**, and 4-chloro-3,5-difluoronitrobenzene, **2**, are summarized. Net charges (Figure 1) and LUMO (Figure 2) coefficients are indicated for the ring carbons. The results reported in Figure 1 show an increase in electronic density at C-4 (the one that bears the chlorine atom) upon the introduction of fluorine atoms in its *ortho* positions. In an opposite way, C-3 becomes positively charged when linked to a fluorine atom and it becomes more positive when an electronegative substituent is introduced at C-5, being the effect observed directly related to the electronegativity value of the substituent (stronger effect for fluorine than for methoxy). On the other hand, the LUMO coefficient is always larger at C-4 than at C-3 (Figure 2).

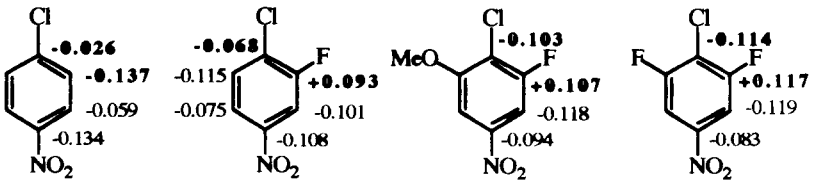



**Figure 1.**- Net charges on the ring carbons of 4-chloronitrobenzene, 3-fluoro-4-chloronitrobenzene, **1**, 4-chloro-5-fluoro-3-methoxynitrobenzene, **8**, and 4-chloro-3,5-difluoronitrobenzene, **2.**

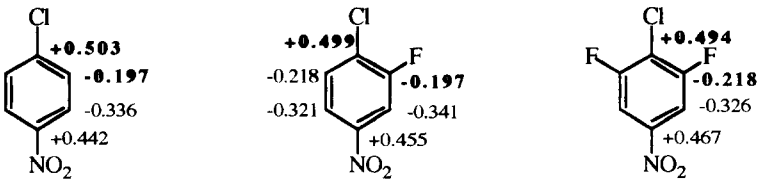



**Figure 2.**- Coefficients of the LUMO orbitals of 4-chloronitrobenzene, 4-chloro-3-fluoro-nitrobenzene, **1**, and 4-chloro-3,5-difluoronitrobenzene, **2.**

After considering the obtained kinetic results and theoretical calculations, our interpretation for the regioselectivity change in the reactions described in the schemes 1 and 2 is that both reactions follow the same mechanism (first stage rate determining $S_NAr$), being the "normal" *para* substitution with thiophenoxide anion as nucleophile, an example of orbital controlled reaction (with an important contribution of the relative stability of the intermediate σ-complex), and the *meta* substitution observed when methoxide anion (hard) is used as nucleophile, the result of a charge controlled reaction leading to the less stable σ-complex intermediate. It is interesting to notice that the activation entropy values (Table 2) indicate that the formation of the new aryl-nucleophile bond is more advanced in the transition state of the thiophenoxide anion reactions (*para* substitution, Scheme 2) than in the reactions of methoxide (*meta* substitution, Scheme 2). This means that in the first case, the structure of the transition state is more related to the structure of the σ-complex, and therefore, the contribution of the relative stability of the σ-complex to the energy of the transition state more important than when methoxide anion is the nucleophile (loosely bonded transition state), thus justifying the evolution of the later to the less stable σ-complex.

From the results reported in the schemes 1 and 2, and from the results of our theoretical calculations it becomes clear that for the regioselectivity change to be observed it is necessary the presence of a strong inductive electron-atracting and resonance electron-donor group (F better than MeO) in *ortho* position with respect to the chlorine substituent. Resonance effects of this group are only apparent in the *ortho* position (chlorine substituent) whereas the inductive effects are transmitted to the *ortho* (overcome by the resonance effects) and the *meta* position (with respect to the substituent), making the electronic density in the positions *para* and *meta* with respect to the nitro group different enough to justify the observed *meta* substitution in a charge controlled reaction.

In spite of the apparent contradiction between our results and the reported by Chambers *at al.*[5,6] (activating properties of the *ortho* fluorine substituents in the reactions of polyfluorobenzenes and polyfluoropyridines with methoxide anion in methanol)[5,6], a coherent general picture can be obtained by using the Hammond[20] postulate. Thus, nitro-substituted substrates are more reactive in front of nucleophiles, and therefore, our reactions, specially with hard nucleophiles, must have an earlier transition state with a less advanced formation of the new aryl nucleophile bond (the activation entropy values shown in Table 2 are

significantly less negative than the values reported by Chambers *et al.*[5] for the reactions of polyfluoropyridines with sodium methoxide in methanol). This means in our case, an almost exclusive dependence of the energy of the transition state on the energy of interaction[10] substrate-nucleophile (the electrostatic term in our reactions with methoxide anion) with a very reduced contribution from the relative stability of the intermediate σ-complex. On the other hand, less reactive substrates (Chamber's cases)[5,6] will have transition states with a much greater contribution from the relative stabilities of the σ-complexes, probably higher when fluorine atoms are in the *ortho* positions with respect to the carbon atom under attack.[2]

## EXPERIMENTAL PART

All melting points are uncorrected. $^1H$ NMR were recorded at 250 MHz and the $^{13}C$ NMR at 62.5 MHz. The coupling constants with fluorine are indicated in the $^{13}C$ NMR spectra.

*4-Chloro-3-fluoronitrobenzene, 1.* In a 250 mL flask, 2.082 g (10 mmol) of $PCl_5$ and 4.5 g (30 mmol) of *p-tert*-butylphenol were introduced. After connecting a acid vapors tramp the mixture was heated to 130-140 °C for 1.5 h. The mixture was cold down to room temperature and then 1.570 g (10 mmol) of 2-fluoro-4-nitrophenol were added and the mixture heated again to 130-140 °C for 2 h. A dark brown slurry was obtained. Next, the flask was sealed and the mixture heated to 230-240 °C for 40 min. Column chromatograpy of the reaction crude, through silica gel using mixtures hexane/chloroform as eluent, afforded 1.070 g (61% yield) of 4-Chloro-3-fluoronitrobenzene, **1**, mp 56-7 °C (lit.[21] mp 41 °C): IR (KBr) 3105, 3047, 2927, 1592, 1536, 1477, 1417, 1353, 1301, 1241, 1137, 1055, 938, 883, 833, 810, 737, 696 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.6 (dd, J=8.2 Hz, J=7.9 Hz, 1H), 7.98 (m, 2H); $^{13}C$ NMR ($CDCl_3$) δ 112.35 (d, J=25.7 Hz), 119.88 (d, J=3.7 Hz), 128.75 (d, J=17.4 Hz), 131.18 (d, J=2.75 Hz), 136.35, 157.66 (d J=252.7 Hz); MS m/e (relative intensity) 177 (M+2, 31) 175 (M, 97), 147 (16), 145 (51), 131 (33), 129 (100), 119 (15), 117 (47), 111(14), 109 (41), 94 (32) 92 (41), 74 (23).

*4-Chloro-3,5-difluoronitrobenzene, 2.* The procedure just described for the preparation of substrate **1** was followed starting from 2,6-difluoro-4-nitrophenol, affording a 19% yield of 4-chloro-3,5-difluoronitrobenzene, **2**, mp 37-38 °C: IR (KBr) 3106, 2921, 1548, 1534, 1473, 1443, 1351, 1042, 881, 785 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.91 (d, J=6.1 Hz, 2H); $^{13}C$ NMR ($CDCl_3$) δ 108.02 (dd, J=27 Hz, J=3 Hz), 117.85 (t, J=20 Hz), 146.36, 158.55 (dd, J=255 Hz, J=3 Hz); MS m/e (relative intensity) 195 (M+2, 35), 193 (M, 100), 165 (9), 163 (32), 149 (27), 147 (91), 137 (10), 135 (30), 112 (46), 99 (24), 97 (60), 81 (22), 62 (37); Calculated for $C_6H_2ClF_2NO_2$: C, 37.23; H, 1.04; N, 7.23. Found: C, 36.93; H, 0.97; N, 7.19.

*Reaction of 4-chloro-3-fluoronitrobenzene, 1, with sodium thiophenoxide in anhydrous methanol.* In a 100 mL round bottom flask 0.235 g (1.28 mmol) of 4-chloro-3-fluoronitrobenzene, 1.693 g (12.8 mmol) of sodium thiophenoxide and 50 mL of anhydrous methanol were introduced. The mixture was kept at room temperature for 5 h. After that, the reaction was quenched with $I_2$. The reaction crude was extracted with chloroform and a solution of sodium bisulfite in water. The organic layer was washed several times with water, dried and evaporated, affording a residue that was column chromatographed through silica gel using mixtures of hexane/chloroform as eluent. 3-Fluoro-4-thiophenoxynitrobenzene, **3** (0.238 g, 78% yield) bp 175 °C oven temperature, 0.5 Torr, was obtained: IR (film) 3098, 2929, 1592, 1523, 1469, 1440, 1415, 1342, 1224, 1054, 1025, 937, 883, 809, 743, 692 cm-$^1$; $^1H$ NMR ($CDCl_3$) δ 6.83 (dd, J=8.7 Hz, J=8.4 Hz, 1H), 7.45 (m, 5H), 7.76 (ddd, J=0.7 Hz, J=2.2 Hz, J= 8.4 Hz, 1H), 7.83 (dd, J=2.2 Hz, J=9.5 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 110.70 (d, J=25.7 Hz), 119.47 (d, J=3.7 Hz), 127.79 (d, J=2.7 Hz), 128.45, 129.89, 130.07, 134.92, 136.30 (d, J=16.5 Hz), 145.75 (d, J=3.6 Hz), 157.45 (d, J=247.22 Hz); MS m/e (relative intensity) 250 (M+1, 15), 249 (M, 100), 219 (11), 203 (23), 202 (64), 170 (12); Calculated for $C_{12}H_8FNO_2S$: C, 57.83; H, 3.21; N, 5.62. Found: C, 57.47; H, 3.10; N, 5.62.

*Reaction of 4-chloro-3,5-difluoronitrobenzene, 2, with sodium thiophenoxide in anhydrous methanol.* The procedure described in the previous paragraph was followed starting from 4-chloro-3,5-difluoronitrobenzene, **2**, keeping a constant temperature of -6 °C for 2h. A 30% yield (99% based on non recovered starting material) of 3,5-difluoro-4-thiophenoxynitrobenzene, **4**, mp 66-67 °C (Hexane) was obtained: IR (KBr) 3093, 2931, 2650, 1600, 1532, 1476, 1427, 1342, 1180, 1025, 885, 787, 744, 688 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.33 (m, 5H), 7.28-7.40 (d, J=9.5 Hz, 2H); $^{13}C$ NMR ($CDCl_3$) δ 107.81 (complex abs.) 120.41 (t, J= 21.5 Hz), 128.14, 129.32, 130.96, 132.06, 147.83 (t, J=10.4 Hz), 161.9 (dd, J=253 Hz, J=5 Hz); MS m/e (relative intensity) 269 (M+2, 6), 268 (M+1, 4), 267 (M, 100), 221 (37), 220 (54), 188 (12), 157 (14), 77 (15), 51 (16); Calculated for $C_{12}H_7F_2NO_2S$: C, 53.93; H, 2.62; N, 5.24. Found: C,53.99; H, 2.51; N, 5.27.

***Reaction of 4-chloro-3-fluoronitrobenzene, 1, with sodium methoxide in anhydrous methanol.*** In a 100 mL round bottom flask, 0.087 g (0.5 mmol) of 4-Chloro-3-fluoronitrobenzene, **1**, 0.340 g of sodium methoxide (6.3 mmol) and 50 mL of anhydrous methanol were introduced. The mixture was kept under reflux for 12 h. Then, the solution was cooled and after addition of 100 mL of 0.1M HCl, extracted with dichlorometane. The organic layer was dried and the solvent evaporated. The residue was column chromatographed through silica gel using mixtures of hexane/dichloromethane as eluent, affording 28.7 mg of the starting material 4-chloro-3-fluoronitrobenzene (33%), 31.05 mg (37% yield, 55% based on non recovered starting material) of 2-fluoro-4-nitroanisole, **5**, mp 98-101 °C (lit.[22] 104-5 °C): IR (KBr) 3094, 2945, 1605, 1515, 1504, 1462, 1453, 1355, 1285, 1180, 1009, 938, 886, 767, 745, 634 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.96 (s, 3H), 7.00 (dd, J=8.8 Hz, J=9.1 Hz, 1H), 7.91 (dd, J=10.6 Hz, J=2.6 Hz, 1H), 8.01 (ddd, J=9.1 Hz, J=2.6 Hz, J=1.5 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 56.61, 112.17, (d, J=10.2 Hz), 119.7 (d, 9.2 Hz), 120.88 (d, J=3.7 Hz), 140.79, 151.08 (d, J=251.5 Hz), 153.36 (d, J=10.18 Hz); and 20.34 mg (22% yield, 33% based on non recovered starting material) of 2-chloro-5-nitroanisole, **6**, mp 76-9 °C (lit.23 83 °C): IR (KBr) 3107, 3001, 2958, 1581, 1519, 1349, 1317, 1256, 1066, 1025, 868, 804, 738, 707, 612 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.00 (s, 3H), 7.51 (d, J=8.05 Hz, 1H), 7.78 (s, 1H), 7.80 (m, 1H); $^{13}C$ NMR ($CDCl_3$) δ 56.56, 106.70, 116.14, 116.18, 129.90, 130.31, 155.37; MS m/e (relative intensity) 189 (M+2, 23), 187 (M, 100), 142 (11, 141 (22), 131 (11), 129 (35), 126 (43), 113 (11), 111 (24), 98 (15), 77 (27).

***Reaction of 4-chloro-3,5-difluoronitrobenzene, 2, with sodium methoxyde in anhydrous methanol.*** In a 100 mL round bottom flask, 0.095 g (0.49 mmol) of 4-Chloro-3,5-difluoronitrobenzene, **1**, 0.265 g of sodium methoxyde (4.9 mmol) and 50 mL of anhydrous methanol were introduced. The mixture was kept under stirring at room temperature for 2 h. Then, the solution was cooled and after addition of 100 mL of 0.1M HCl, extracted with dichlorometane. The organic layer was dried and the solvent evaporated. The residue was column chromatographed through silica gel using mixtures of hexane/dichloromethane as eluent, affording 24.7 mg of the starting material 4-chloro-3,5-difluoronitrobenzene, **2**, (26%), 50.0 mg (50% yield, 67% based on non recovered starting material) of 4-chloro-3-fluoro-5-methoxynitrobenzene, **8**, mp 76-77 °C (hexane): IR (film) 3112, 2923, 1615, 1509, 1425, 1360, 1332, 1207, 1100, 866, 745 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.04 (s, 3H), 7.64 (t, J=2 Hz, 1H), 7.68 (dd, J=8 Hz, J=2.5 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 57.00, 102.36 (d, J=2 Hz), 104.46 (d, J= 28 Hz), 117.9 (d, J=20 Hz), 146.65 (d, J=.10.1 Hz), 156.72 (d, J=4.6 Hz), 158.34 (d, J=251 Hz); MS m/e (relative intensity) 207 (M+2, 31), 205 (M, 100), 175 (12), 159 (19), 147 (34), 144 (38), 116 (19), 95 (27), 81 (45); Calculated for $C_7H_5ClFNO_3$: C, 40.88; H, 2.43; N, 6.81. Found: C, 40.90; H, 2.47; N, 6.80; and 2.0 mg (2% yield, 3% based on non recovered starting material) of 2,6-difluoro-4-nitroanisole, **7**, mp 36-37 °C (lit.[24] 37-8 °C): IR (KBr) 3095, 2966, 1533, 1510, 1351, 1255, 1049, 991, 744 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.1 (t, J=1.8 Hz, 3H), 7.85 (d, J=8.7 Hz, 2H); $^{13}C$ NMR ($CDCl_3$) δ 61.60 (t, J=3.3 Hz), 107.78 (m), 140.75 (broad), 142. 31 (t, J=12.9 Hz),153.81 (dd, J=252 Hz, J=6.5 Hz); MS m/e (relative intensity) 190 (M+1, 8), 189 (M, 100), 159 (38), 144 (13), 143 (21), 128 (37), 124 (42), 113 (36), 100 (58), 99 (25), 95 (26), 81 (28).

***Reaction of 4-chloro-3-fluoro-5-methoxynitrobenzene, 8, with sodium methoxide in anhydrous methanol.*** In a 100 mL round bottom flask, 0.039 g (0.19 mmol) of 4-Chloro-3,5-difluoronitrobenzene, **1**, 0.421 g of sodium methoxyde (7.8 mmol) and 25 mL of anhydrous methanol were introduced. The mixture was kept under reflux for 15 h. Then, the solution was cooled and after addition of 50 mL of 0.1M HCl, extracted with dichlorometane. The organic layer was dried and the solvent evaporated. The residue was column chromatographed through silica gel using mixtures of hexane/dichloromethane as eluent, affording 21.8 mg of the starting material 2-chloro-3-fluoro-5-nitroanisole, **8**, (56%), 15.1 mg (37% yield, 82% based on non recovered starting material) of 4-chloro-3,5-dimethoxynitrobenzene, **10**, mp 138-140 °C (hexane): IR (KBr) 3111, 2986, 1525, 1468, 1441, 1408, 1336, 1218, 1122, 1063, 1025, 849, 783, 742, 712 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.99 (s, 6H), 7.48 (s, 2H); $^{13}C$ NMR ($CDCl_3$) δ 56.78, 99.71, 117.96, 146.87, 156.09; MS m/e (relative intensity) 219 (M+2, 31), 217 (M, 100), 189 (15), 172 (13), 171 (21), 161 (13), 159 (41), 156 (39), 143 (21), 141 (44), 128 (12), 126 (23), 113 (33), 97 (19), 87 (10), 85 (25), 77 (27); Calculated for $C_8H_8ClNO_4$: C, 44.15; H, 3.67; N, 6.44. Found: C, 44.59; H, 3.53, N, 6.51; and 2.6 mg (7% yield, 15% based on non recovered starting material) of 3-fluoro-5-nitroveratrole, **9**, mp 59-60 °C (hexane): IR (KBr) 3092, 2950, 1507, 1430, 1355, 1311, 1254, 1210, 1103, 989, 875, 802, 769, 741, 543 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.97 (s, 3H), 4.07 (d, J=2.2 Hz, 3H), 7.62 (d, J=2.6 Hz, J= 1.5 Hz, 1H), 7.67 (dd, J=2.6 Hz, J=10.78 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 56.58, 61.55 (d, J=5.6 Hz), 103.37 (d, J=2.8 Hz), 105.99 (d, J=25.0 Hz), 136.92, 142.88 (d, J=12.0 Hz), 153.01 (d, J=6.5 Hz), 154.11 (d, J=247.8 Hz); MS m/e (relative intensity) 202 (M+1, 9), 201 (M, 100), 171 (18), 155 (11), 125 (10), 97 (26), 69 (19).

***Kinetic measurements (Tables 1 and 2).*** In a typical run, 50 mL of methanol and 97 mg (0.5 mmol) of 4-chloro-3,5-difluoronitrobenzene, **2**, were introduced in a thermo-static vessel (HAAKE F-8). The solution was left under stirring until the

appropriate temperature was achieved and then 810 mg (15 mmol) of previously prepared sodium methoxide were added. Samples were taken at different times and analyzed by HPLC [3.9 x 150 mm Nova-Pak C18 Waters column, using acetonitrile-water (1:1) as eluent, with a pressure of 1400 psi] using $\lambda$ = 262 nm (sodium thiophenoxide) and $\lambda$ = 280 nm (sodium methoxide) as the kinetic wavelength. Kinetics were followed monitoring the decrease of absorbance of the 4-chloro-3,5-difluoronitrobenzene, **2**, at the kinetic wavelength ($\varepsilon$ = 2600 at $\lambda$ = 262 nm and $\varepsilon$ = 2550 at $\lambda$ = 280 nm). In typical runs under pseudo-first-order conditions the concentration of the substrate was 0.01 M, while those of the nucleophiles varied from 0.3 M to 0.6 M for methoxide and from 0.1 M to 0.25 M for thiophenoxide. Pseudo-first-order rate constants were calculated from the slope of conventional plots of ln ($C_0/C_i$) *versus* time (irreversible process). Such plots were linear to at least 80% completion. Activation parameters (Table 2) were obtained (using the Eyring equation)[10] from linear plots of ln ($k_2/T$) versus 1/T.

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## REFERENCES

1. Terrier, F. *Nucleophilic Aromatic Displacement. The Influence of the Nitro Group*; VCH Publishers, Inc.. New York **1991**, p. 4-11.
2. Birch, A.J.; Hinde, A.L.; Radom, L.J. *J. Am. Chem. Soc.* **1980**, *102*, 6430.
3. Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, New York, 1968. p. 139.
4. a) Bartoli, G.; Todesco, P.E. *Acc. Chem. Res.* **1977**, *10*, 125. b) Ritchie, C.D.; Sawada, M.J. *J. Am. Chem. Soc.* **1977**, *99*, 3754. c) Bordwell, F.G.; Hughes, D.L. *J. Am. Chem. Soc.* **1986**, *108*, 5991.
5. Chambers, R.D.; Close, D.; Williams, D.L.H. *J. Chem. Soc. Perkin Trans 2* **1980**, 778.
6. Chambers, R.D., Seabury, M.J.; Williams, D.L.H.; Hughes, N. *J. Chem. Soc. Perkin Trans 1* **1988**, 255.
7. Vlasov, V.M. *J. Fluorine Chem.* **1993**, *61*, 193.
8. Wosniak, M.; Baranski, A.; Nowak, K.; Van der Plas, H.C. *J. Org. Chem.* **1987**, 52, 5643.
9. Shigeru, O.; Norihiro, Y.; Ken, F.; Osamy, K. *Bull. Chem. Soc. Jpn*, **1983**, *56*, 248.
10. Hudson, R.F. in *Chemical Reactivity and Reaction Paths*, ed. Klopman, G.. Wiley, New York **1974**, ch. 5.
11. Tabatskaya, A.A.; Kutasheva, E.F.; Vlasov, V.M. *Mendeleev Commun.* **1993**, 163.
12. Broxton, T.J.; Muir, D.M.; Parker, A.J. *J. Org. Chem.* **1975**, *40*, 3230.
13. Artamkina, G.A.; Milchenko, A.Y.; Beletskaya, I.P.; Reutov, O.A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1988**, 2826.
14. a) Bacaloglu, R.; Blaskó, A.; Bunton, C.; Dorwin, E.; Ortega, F.; Zucco, C. *J. Am. Chem. Soc.* **1992**, *114*, 7708. b) Bacaloglu, R.; Blaskó, A.; Bunton, C.; Dorwin, E.; Ortega, F.; Zucco, C. *J. Am. Chem. Soc.* **1991**, *113*, 238.
15. a) Cantos, A.; Marquet, J.; Moreno-Mañas, M.; Gonzalez-Lafont, A.; Lluch, J.M.; Bertrán, J. *J. Org. Chem.* **1990**, *55*, 3303. b) van Eijk, A.M.J.; Huizer, A.H.; Varma, C.A.G.O.; Marquet, J. *J. Am. Chem. Soc.* **1989**, *111*, 88. c) Cantos, A.; Marquet, J.; Moreno-Mañas, M.; Castelló, A. *Tetrahedron*, **1988**, *44*, 2606.
16 Moore, J.W.; Pearson, R.G. *Kinetics and Mechanism*; 3rd ed. Wiley: New York, **1981**; pp. 159-181.
17. a) de Rosi, R.H.; Veglia, A.J. *J. Org. Chem.* **1983**, *48*, 1879. b) Burdon, J.; Hollyhead, W.B.; Patrick, C.R.; Wilson, K.V. *J. Chem. Soc.* **1965**, 6375.
18. a) Dewar, M.J.S.; Storch, D.M. *J. Am. Chem. Soc.* **1985**, *107*, 3898. b) Dewar, M.J.S.; Zoebisch, E.F.; Healy, E.F.; Stewart, J.J.P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
19. Liotard, D.A.; Healy, E.F.; Ruiz, J.M.; Dewar, M.J.S. AMPAC-version 2.1 *Quantum Chemistry Program Exchange, program 506, QCPE Bull.*, **1989**, *9*, 123.
20. Hammond, G.S. *J. Am. Chem. Soc.* **1955**, *77*, 334.
21. Rinkes, I.J. *Chem.Weekblad II*, **1914**, 360.
22. Elderfield, R.C.; Gensleg, W.J.; Williamson, T.A.; Griffing, J.M.; Kupchan, S.M.; Maynard, J.T.; Kreysa, F.J.; Wrinht, J.B. *J. Am. Chem. Soc.* **1946**, *68*, 1584.
23. Brieux, J.A.; Deulofeu, V. *J. Org. Chem.* **1954**, *19*, 2519.
24. Niemann, C.; Benson, A.A.; Neal, J.F. *J. Am. Chem. Soc.* **1941**, *63*, 2204.

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