Journal of Fluorine Chemistry, 67 (1994) 119–123

The activation of S_NAr reactions by the superstrong electron-withdrawing substituent $CF_3S(O)=NSO_2CF_3$

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(Received January 13, 1993; accepted July 9, 1993)

Abstract

The chlorine lability of the 2-nitrochlorobenzene derivative which contains the superstrong electron-withdrawing substituent $CF_3S(O)=NSO_2CF_3$ in position 4 has been compared with the analogous 4-trifluoromethylsulphonyl derivative and picryl chloride in nucleophilic substitution. During interaction with hard nucleophilic agents, the effect of one superstrong substituent approximately corresponds to the influence of two nitro groups in positions 2 and 4. With soft reagents, picryl chloride is more active than the compound containing the $CF_3S(O)=NSO_2CF_3$ group, polarizable only with difficulty.

Introduction

The introduction of fluorine atoms into aromatic substituent groups has a strong influence on the properties of these compounds. Recently, the principle for the construction of superstrong groups involving displacement of an oxygen atom [=O] in different groups by the fragment [$=NSO_2CF_3$] was formulated by one of us [1]. Previously, over the whole Hammett scale, the σ_p constants did not exceed the value of 1.1 for substituents which were stable under ordinary conditions. Superstrong substituents of the above type have σ_p constant values within the range 1.3–1.75, which means that they correspond to two or even three nitro groups in their influence on an aromatic ring. Thus, the σ_p constant of the CF_3SO_2 group equals 1.04 but its NSO_2CF_3 analogue $CF_3S(O)=NSO_2CF_3$ has a σ_p value of 1.40.

The σ constants alone do not always give the correct indication of the reactivity of a molecule. Their values, especially those calculated from ^{19}F NMR data, reflect the static molecular state. Under dynamic reaction conditions, the rates and direction of the reaction do not sometimes correspond to these values [2, 3].

Results and discussion

We have studied the nucleophilic substitution of chlorine in *N*-trifluoromethylsulphonyl-*S*-trifluoromethyl-*S*-(3-nitro-4-chlorophenyl)sulphoximide (**I**). The chlorine lability has been compared with that of two other substrates: 3-nitro-4-chlorophenyl trifluoromethyl sulphone (**II**) and picryl chloride (**III**). The results are summarized in Table 1.

Owing to the presence of the superstrong electron-withdrawing substituent $CF_3S(O)=NSO_2CF_3$ in sulphoximide **I**, a high reactivity is exhibited. For example, the chlorine atom is substituted almost quantitatively on reaction with aniline or trifluoroethanol in the presence of Et_3N, whereas under the same conditions sulphone **II** does not react with aniline at all and the corresponding trifluoroethyl ether in only 7% yield forms with trifluoroethyl alcohol and Et_3N.

The observed results indicate that in full accord with the σ constants, the $CF_3S(O)=NSO_2CF_3$ group shows considerably greater electron-attracting power then the previous strongest electron-withdrawing substituent, i.e. the SO_2CF_3 group.

In order to understand the character of the electron-attracting group and its specificity in forming a reactive molecular centre, it is necessary to carry out a comparison with substrates whose reactivity is close to that of the compound studied. As shown above for the $CF_3S(O)=NSO_2CF_3$ group, the σ-constant value is virtually equal to the sum of the effect of two nitro groups. For this reason, we have made a comparative study of the chlorine lability in sulphoximide **I** and picryl chloride (**III**) using different nucleophiles, i.e. CH_3OH and CF_3CH_2OH in the presence of bases, azide and iodide anions, and *p*-nitroaniline.

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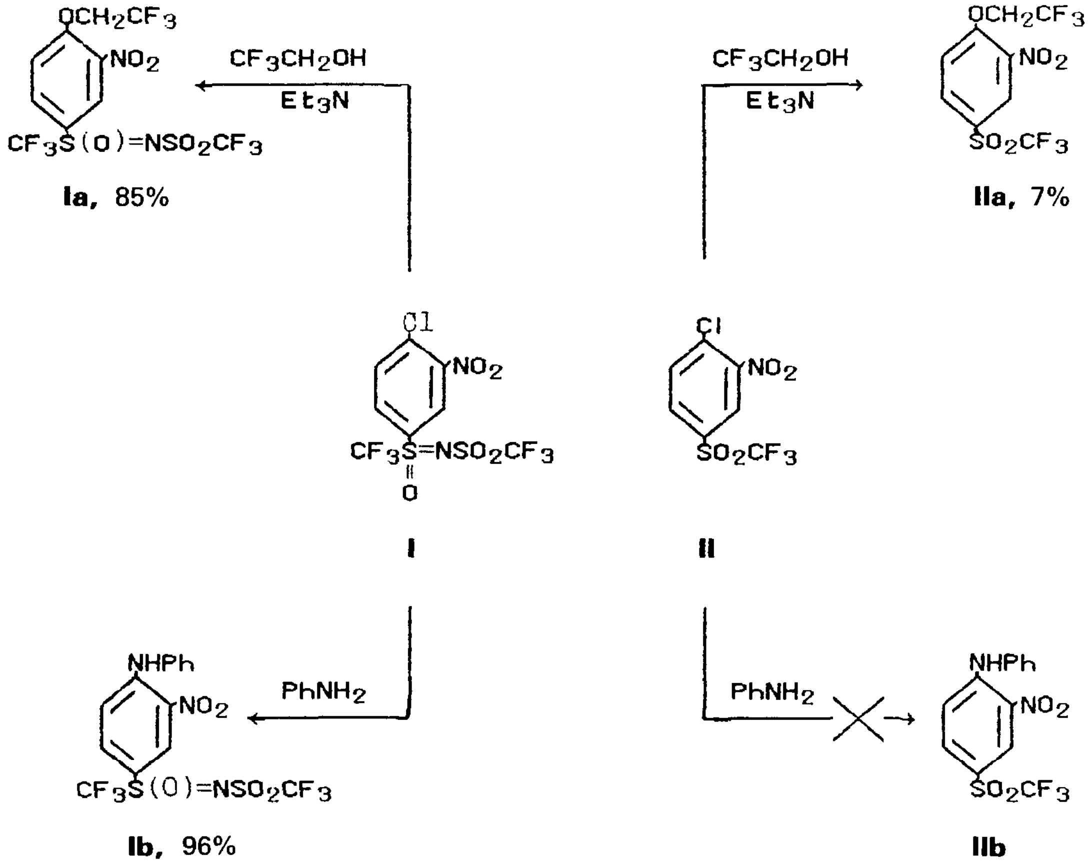
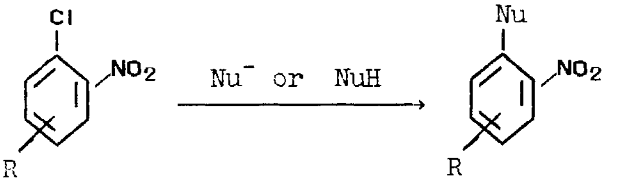
0022-1139/94/$07.00
SSDI 0022-1139(93)02959-I

TABLE 1. The comparative nucleophilic substitution of chlorine in sulphoximide **I**, sulphone **II** and picryl chloride (**III**)

Nucleophile	Substrate	Reaction conditions	Product	Composition of reaction mixture (%)[a]		Yield (%)[b]	
				Substrate	Product	Substrate	Product
$CF_3CH_2O^-$	**I**	CF_3CH_2OH, Et_3N, 25 °C, 3 h	**Ia**	–	100	0	84.9
	II		**IIa**	90	10	75	6.8
$C_6H_5NH_2$	**I**	CH_3CN, 25 °C, 5 min	**Ib**	0	100	0	96.4
	II		**IIb**	100	0	96.6	0
CH_3O^-	**I**	CH_3OH, $KHCO_3$, 25 °C, 3 h	**Ic**	20	80	18.1	73.1
	III		**IIIc**	40–45	55–60	40.3	55.5
$CF_3CH_2O^-$	**I**	CF_3CH_2OH, $KHCO_3$, 25 °C, 21 h	**Ia**	45	55	46.5	49.3
	III		**IIIa**	40	60	41.3	49.3
N_3^-	**I**	CH_3CN/Et_2O, NaN_3, 25 °C, 30 min	**Id**	75	25	69.1	22.7
	III		**IIId**	50	50	49.5	48.3
$NH_2C_6H_4NO_2$-*p*	**I**	CH_3CN, 25 °C, 19 h	**Ie**	90	10	73.5	6.6
	III		**IIIe**	25	75	24.1	51.4
I^-	**I**	CH_3COCH_3/CH_3COOH, NaI, 25 °C, 30 min	**If**	100	0	96.4	0
	III		**IIIf**	0	100	0	66.4

[a] As estimated by NMR spectroscopy.
[b] Calculated from NMR data.





I, III **Ia–IIIf**

[R = 4-$CF_3S(O)=NSO_2CF_3$ (**I, Ia, Ic–f**); 4,6-$(NO_2)_2$ (**III, IIIa, IIIc–f**); Nu = CF_3CH_2O (**Ia, IIIa**); CH_3O (**Ic, IIIc**); N_3 (**Id, IIId**); *p*-$O_2NC_6H_4NH$ (**Ie, IIIe**); I (**If, IIIf**)]

Although the reaction conditions with each nucleophile were different, they were the same for the two substrates **I** and **III**. Analysis of the reaction mixture and the product yields arising from chlorine substitution were based on ^1H and ^{19}F NMR spectral studies. The results are summarized in Table 1.

From these data it is clear that the reactivity of sulphoximide **I** on interaction with alcoholates is about equal to, or slightly exceeds, the activity of picryl chloride. With other reagents, **I** is less reactive than picryl chloride.

It should be noted that sulphoximide **I** does not react with I^- under those conditions where picryl chloride readily forms picryl iodide (**IIIf**). For other nucleophilic agents, on the basis of the substitution yields, imide **I** is clearly more reactive with alcoholates but picryl chloride is more reactive with the less basic azide ion and *p*-nitroaniline. This dependence is made more obvious by comparing the relative degree of reactions with different nucleophiles (Table 2).

The relative lability of chlorine in compound **I** compared with picryl chloride (**I/III** value) gradually decreases on moving from alcoholates (~1) to I^- (0). The nucleophilicity is known to be a function of two components, i.e. basicity and polarizability. As seen from Table 2, the relative reactivity (**I/III** value) changes in the same order as the pK_a values of the conjugate acids of the anionic nucleophiles and *p*-nitroaniline. In accord with such basicity, the nucleophilic reagents may be arranged in the order: $I^- < p\text{-}O_2NC_6H_4NH_2 < N_3^- < CF_3CH_2O^- < CH_3O^-$. The relative lability of the chlorine in compound **I** increases in the same order in comparison with picryl chloride, i.e. as the ratio **I/III**. It should be noted that these values correlate to each other with the exception of I^- (Fig. 1).

The influence of the second component, i.e. the polarizability (*P*), is not so straightforward, probably owing to the approximate nature of the calculated value (**P**). The change in **P** and the ratio **I/III** are opposite to each other (Table 2). However, the polarizability of the nucleophilic reagents increases on moving from alcoholates to nitroaniline and I^-, and is in agreement with the increase in chlorine lability in picryl chloride (**III**) relative to sulphoximide **I** (magnitude **III/I**, Table

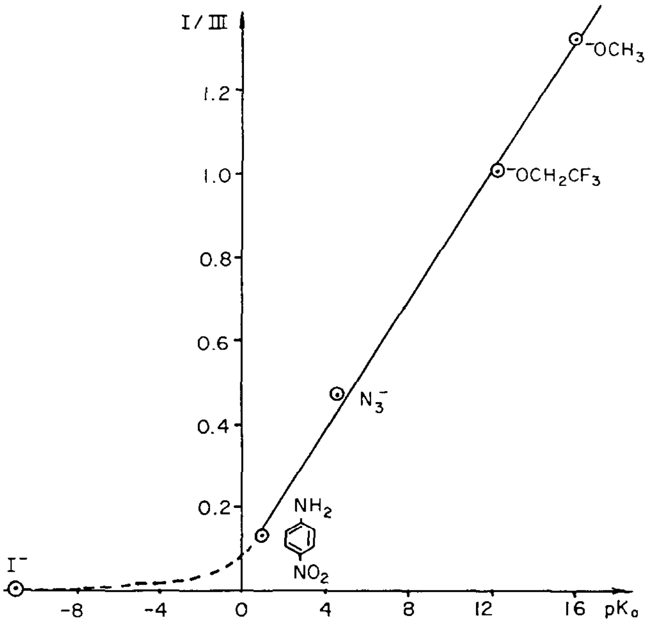


Fig. 1. Plot of relative yields for chlorine substitution in sulphoximide (I) and picryl chloride (III) versus nucleophile basicity.

TABLE 2. Relative yields for chlorine substitution in sulphoximide **I** and picryl chloride (**III**) together with the parameters of the nucleophilic agents

Nucleophilic reagent	Yields of **Ia–f** related to yields of **IIIa–f** (**I/III**)	pK_a of conjugated acid	P^a	Yields of **IIIa–f** related to yields of **Ia–f** (**III/I**)
CH_3O^-	1.32	16	0.40	0.76
$CF_3CH_2O^-$	1.0	12.37	0.55	1.00
N_3^-	0.47	4.59	0.52	2.13
p-$O_2NC_6H_4NH_2$	0.13	1.02	1.00	7.80
I^-	0.0	~ −11	0.72	∞

[a] P = polarizability factor taken from ref. 4 or calculated from the formula $P = \log(R/R_{H_2O})$, where R is a molecular or group refraction; the calculated averaged R values were obtained via an additive procedure [5].

TABLE 3. Characterization of products

Compound	Isolated yield (%)	Melting point (°C) (solvent)	^1H NMR (δ, ppm; *J*, Hz)				^{19}F NMR[a] (δ, ppm)		Analytical data (Calc./found)			
			H^3	H^5	H^6	Other protons	$O=SCF_3$	SO_2CF_3	C (%)	H (%)	N (%)	F (%)
Ia	85	122–123 (benzene/ hexane)	8.81 (d, $J=2.8$)	8.58 (dd, $J=$ 9.2, 2.8)	8.01 (d, $J=9.2$)	5.19 (q, CH_2)	−74.9	−78.7	24.79 24.90	1.04 1.05		35.30 35.34
Ib	94	125–126 (hexane)	8.86 (d, $J=2.4$)	8.00 (dd, $J=$ 9.2, 2.4)	7.36 (d, $J=9.2$)	7.4–7.55 (m, 5H); 10.44 (1H, NH)	−76.24	−78.90	35.22 34.48	1.90 1.85	8.80 8.63	23.88 23.70
Ic	85.4	86–87 (benzene/ hexane)	8.72 (d, $J=2.6$)	8.48 (dd, $J=$ 9.4, 2.6)	7.90 (d, $J=9.4$)	4.23 (s, CH_3)	−75.34	−78.77	25.96 26.08	1.44 1.39	3.08 3.09	27.40 27.01
Id	79	80–81 (decomp.)	8.78 (d, $J=2.4$)	8.51 (dd, $J=$ 8.8, 2.4)	8.13 (d, $J=8.8$)		−74.69	−78.64	22.49 22.16	0.71 0.72	16.39 16.07	26.68 26.37
Ie	80	201–202 (benzene)	8.58	8.35	7.76	9.55 (NH); 7.30 (dd, C_6H_4)	−75.86	−78.84	32.18 32.07	1.53 1.45	10.73 10.52	21.84 21.70
IIa	91	92–93 (benzene/ hexane)	8.57 (d, $J=2.4$)	8.33 (dd, $J=$ 8.8, 2.4)	7.88 (d, $J=8.8$)	5.12 (q, CH_2)		−78.4	30.60 29.91	1.43 1.31	3.97 3.87	32.28 30.86
IIb	87	98–99 (benzene/ pentane)						−77.93				
IIIa	78	107–108 (benzene/ hexane)	9.12	9.12		4.94 (q, CH_2)						
IIIc	86.2	68–69	9.01	9.01		4.11 (s, CH_3)						
IIId	81	92–93	9.04	9.04								
IIIe	75	214–215	9.08	9.08		10.18 (NH); 7.79 (dd, C_6H_4)						
IIIf	78	164–165										

[a] ^{19}F NMR signal of OCH_2CF_3 group in compound **Ia**, −73.3 (t, $J=$ 8 Hz) ppm; in compound **IIa**, −73.4 (t, $J=8$ Hz) ppm.

2). In comparison to compound **I**, picryl chloride reacts preferentially with soft reagents such as nitroaniline and the I^- anion.

Thus the present investigation has confirmed the view that the formation of the reaction centre in the aromatic ring is dependent on the nature of the electron-withdrawing groups [6]. Since it is a superstrong electron-withdrawing substituent similar to SO_2CF_3, and in contrast to the nitro group, the sulphoximide group, $CF_3S(O)=NSO_2CF_3$ exhibits a low polarizability. This is the reason why chemical reactions proceeding on a reaction centre activated by a hard group such as $CF_3S(O)=NSO_2CF_3$ are subjected strongly to charge control but not to orbital influence.

Experimental

^1H NMR and ^{19}F NMR spectra were obtained on Gemini 200 Varian and Bruker WP-200 (188.28 MHz for ^{19}F) spectrometers with acetone-d_6 as the solvent and HMDS and CCl_3F as internal standards.

$2\text{-}NO_2\text{-}4\text{-}[SO(CF_3)=NSO_2CF_3]C_6H_3OCH_2CF_3$ (*Ia*)

Chloride **I** (1 mmol) was dissolved in 20 ml of CF_3CH_2OH, 1 g of Et_3N was added and mixture stirred for 3 h at 25 °C. Trifluoroethanol was removed *in vacuo* and the residue diluted with dilute aqueous acid. The product was extracted with ether and the latter removed.

$2\text{-}NO_2\text{-}4\text{-}[SO(CF_3)=NSO_2CF_3]C_6H_3NHC_6H_5$ (*Ib*)

Chloride **I** (0.2 mmol) was dissolved in 20 ml of CH_3CN and 2.4 mmol of aniline added. After 5 min, acetonitrile was removed *in vacuo* and the residue dissolved in benzene and washed with dilute aqueous acid. The benzene solution was dried and benzene removed.

$2\text{-}NO_2\text{-}4\text{-}[SO(CF_3)=NSO_2CF_3]C_6H_3OCH_3$ (*Ic*)

Chloride **I** (2.5 mmol) was dissolved in 20 ml of methanol, 2.5 mmol of $KHCO_3$ added and the mixture stirred for 24 h at 25 °C. The methanol was removed *in vacuo*. The product was extracted with ether and the solvent removed.

$2\text{-}NO_2\text{-}4\text{-}[SO(CF_3)=NSO_2CF_3]C_6H_3N_3$ (*Id*)

NaN_3 (1 mmol) was dissolved in 30 ml of CH_3OH and 1 mmol of chloride **I** was added. After 30 min stirring, the reaction mixture was diluted with water and the product extracted with ether, dried and the ether removed.

$2\text{-}NO_2\text{-}4\text{-}[SO(CF_3)=NSO_2CF_3]C_6H_3NHC_6H_4NO_2$-p (*Ie*)

Chloride **I** (1.5 mmol) was dissolved in 10 ml of CH_3CN, 3.3 mmol of *p*-nitroaniline added and the reaction solution boiled for 24 h. Acetonitrile was removed *in vacuo*, the residue dissolved in benzene and washed with dilute aqueous acid. The solution was dried and the benzene removed.

$2\text{-}NO_2\text{-}4\text{-}SO_2CF_3C_6H_3OCH_2CF_3$ (*IIa*)

Chloride **II** (1 mmol) was dissolved in 2 ml of CF_3CH_2OH, 1 g of Et_3N added and the reaction solution boiled for 4 h. Trifluoroethanol was distilled *in vacuo* and the residue diluted with dilute aqueous acid. The product was extracted with benzene and the latter removed.

The yields, ^1H and ^{19}F NMR spectra and analytical data for the products thus prepared are summarized in Table 3. The conditions of the comparative experiments for studying substrate reactivity are presented in Table 1. The quantity of nucleophilic (basic) agents used as a comparative basis to 1 mol of substrate was 1 mol for $KHCO_3$ and NaN_3, 2 mol for *p*-$O_2NC_6H_4NH_2$ and NaI, and 11–12 mol for Et_3N and $C_6H_5NH_2$.

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