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cine-Substitution of the nitro group in 2,4-disubstituted nitroarenes with carbanions of aryl alkyl sulfones

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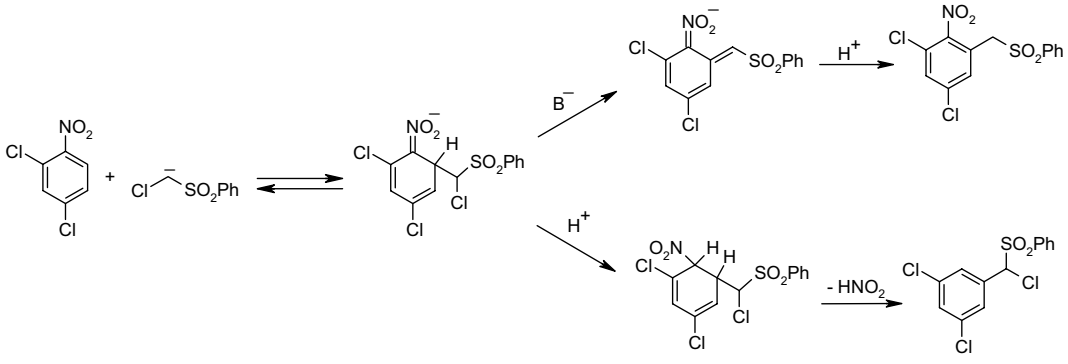
Abstract—Rapid protonation of short lived σ^H adducts of carbanions of aryl alkyl sulfones to 2,4-disubstituted nitrobenzenes results in elimination of nitrous acid giving 1,3,5-trisubstituted benzenes as products of *cine*-substitution of the nitro group.

Addition of nucleophilic agents to electrophilic arenes, for example, nitroarenes, proceeds preferentially in positions occupied with hydrogen giving σ^H adducts. These adducts can dissociate to starting components or can be converted into products of nucleophilic substitution of hydrogen.[1–3] While hydride ion is unable to depart spontaneously, conversion of σ^H adducts into products of nucleophilic substitution of hydrogen can be accomplished in many different ways. Oxidation of σ^H adducts with external oxidants leads to products of oxidative substitution of hydrogen.[4] When nucleophiles contain leaving groups X at the nucleophilic center, the σ^H adducts undergo β-elimination of HX giving the products of vicarious nucleophilic substitution, VNS.[5] There are also other, less common ways of converting σ^H adducts into stable products such as *cine*- and *tele*-substitution,[2,6] intramolecular redox processes leading to nitrosoarenes,[7] etc.

In our recent paper on the effect of halogens on reactions of carbanions with halonitroarenes we reported that under certain reaction conditions, the VNS reaction of chloromethyl phenyl sulfone with 2,4-dichloronitrobenzene is accompanied by the formation of a considerable amount of (3,5-dichlorophenyl)methyl phenyl sulfone.[8] This unexpected side product was observed only when the reaction mixture was quenched after a very short time, thus we concluded that it is formed via protonation of the intermediate σ^H adduct followed by elimination of nitrous acid (Scheme 1). This



Scheme 1.

Keywords: Carbanions; Nitroarenes; Sulfones; *cine*-Substitution.
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unprecedented *cine*-substitution could give additional information on the behavior of anionic σ^H adducts and is also of practical interest. In this communication we present preliminary results on our studies of this process.

The success of this reaction relies on there being a sufficiently high concentration of the σ^H adduct at the moment of the acidic quench, which can be achieved when the rate of formation of the σ^H adduct is higher than the combined rates of its subsequent transformation (VNS) and dissociation to the starting components. Apparently, these requirements are met, to some extent, in the addition of the chloromethyl sulfone carbanion to the *ortho* position of the highly electron-deficient nitroarene in Scheme 1. Since β-elimination of HCl from σ^H adducts of secondary carbanions is usually a fast reaction, it was reasonable to assume that better results could be obtained in reactions of tertiary carbanions of chloroalkyl sulfones, or carbanions of alkyl aryl sulfones lacking such good leaving groups as halogens, thus the arylsulfonyl group is the only one prone to base-promoted elimination. These expectations were fully corroborated by the results presented in this paper.

We have found that *cine*-substitution in nitrobenzenes **1a**–**c** substituted with two electron-withdrawing groups in positions 2 and 4 proceeds efficiently with carbanions of aryl alkyl sulfones **2**–**6**, containing additional stabilizing substituents such as Cl, Ph, and CH=CH_2 at the carbanion center (Table 1). The reaction time was carefully optimized for each individual case to minimize the subsequent VNS reaction and to obtain the highest possible yields of the *cine*-substitution products.

The effect of the prolonged time of the reaction and of the amount of the base used on the product distribution is exemplified for the selected reaction in Table 2. From these data it can be seen that σ^H adducts of tertiary α-halocarbanions formed in positions *ortho* to the NO_2 group are relatively long-lived species, particularly in the absence of a strong base. This observation supports the earlier supposition that β-elimination of HCl from such σ^H adducts is greatly decelerated due to steric hindrance.[5]

The essential element of the reaction procedure is the acidic quench of the reaction mixture. When it was quenched with saturated aqueous NH_4Cl or acetic acid, the starting materials: $ArNO_2$ and the sulfone were mostly recovered. On the other hand, the products of *cine*-substitution were obtained when protonation of the σ^H adducts was performed with dilute strong acids such as HCl or H_2SO_4.

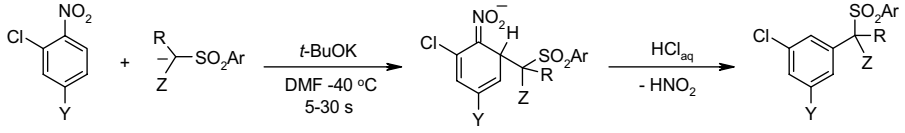
It appears that under weakly acidic conditions the anionic σ^H adducts, being weak bases, are protonated slowly and/or incompletely, thus fast protonation of the starting carbanions—much stronger bases—shifts the addition equilibrium to the left leading to the starting sulfone and $ArNO_2$.

Table 2. Effect of time and amounts of *t*-BuOK on the reaction of **1a** with **4**[a]

Time [s]	Yield (%)	
	4a	VNS
5	75 (22)	3 (19)
30	74 (15)	9 (39)
60	70 (9)	12 (54)
300	61 (1)	17 (58)
900	46 (0)	20 (68)

[a] Ratio *t*-BuOK:**4** = 1.25 and 2.5 (in parentheses).

Table 1. The *cine*-substitution of the nitro group in 2,4-disubstituted nitrobenzenes



1a - c **2 - 6** **2a - 6a, 4b, 5b, 4c**

Entry	$ArNO_2$		Sulfone				Reaction[a] time (s)	Product[b] no	Yield[c] (%)
	No	Y	No	Ar	R	Z			
1	**1a**	Cl	**2**	Ph	H	Cl	5	**2a**	21[d]
2	**1a**	Cl	**3**	Ph	Me	Cl	10	**3a**	67
3	**1a**	Cl	**4**	Ph	Et	Cl	5	**4a**	75
4	**1a**	Cl	**5**	*p*-Tol	H	Ph	15	**5a**	52
5	**1a**	Cl	**6**	*p*-Tol	H	CH=CH_2	30	**6a**	63
6	**1b**	CF_3	**4**	Ph	Et	Cl	5	**4b**	65
7	**1b**	CF_3	**5**	*p*-Tol	H	Ph	5	**5b**	59
8	**1c**	CN	**4**	Ph	Et	Cl	5	**4c**	45

[a] For general reaction conditions and selected spectral data, see Ref. 9.
[b] The VNS products were observed also in yields below 9%.
[c] Determined by GC using diphenyl sulfone as an internal standard.
[d] The previously reported result (isolated yield 28%)[8] was obtained in a reaction with a large excess of **1a**.

The presented results show, that under certain circumstances, a high equilibrium concentration of σ^H adducts is attained in the course of the VNS reaction. Furthermore, parallel observations have been made in the reactions of chloromethyl phenyl sulfone with substituted nitrobenzene derivatives, carried out in dilute solutions, when quantitative formation of σ^H adducts was observed spectroscopically and the addition rate constants were measured.[10]

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9. Typical reaction procedure: To a stirred solution of *t*-BuOK (35 mg, 0.31 mmol) in a mixture of dry DMF (6 mL) and THF (0.5 mL) at −40 °C was added a solution of sulfone **4** (55 mg, 0.25 mmol) in DMF (1 mL) and after 1 min nitroarene **1a** (48 mg, 0.25 mmol) in DMF (1 mL) was added. After 5 s the reaction mixture was quenched with HCl_{aq} (1:10, 4 mL). The mixture was diluted with water and extracted with CH_2Cl_2. The yields of the products were determined by GC analysis using diphenyl sulfone as an internal standard. Analytically pure samples were obtained as white solids (except **4b**, a colorless oil) by column chromatography or simple crystallization. Selected spectral data: **3a**, mp 166–168 °C (MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 3H), 7.36–7.41 (m, 3H), 7.48–7.52 (m, 2H), 7.63–7.71 (m, 3H); MS (EI) m/z 348 (M^+, 0.6), 207 (100), 173 (21), 136 (13), 102 (6), 77 (9), 51 (9); HRMS (ESI) calcd for $C_{14}H_{11}O_2NaSCl_3$ 370.9438, found 370.9458. Compound **4a**, mp 124–126 °C (MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, $J = 7.30$, 3H), 2.46–2.55 (m, 1H), 2.84–2.93 (m, 1H), 7.33 (d, $J = 1.81$, 2H), 7.34 (t, $J = 1.81$, 1H), 7.43–7.47 (m, 2H), 7.56–7.60 (m, 2H), 7.63–7.67 (m, 1H); MS (EI) m/z 362 (M^+, 0.2), 221 (100), 185 (31), 150 (29), 115 (19), 77 (18); HRMS (ESI) calcd for $C_{15}H_{13}O_2NaSCl_3$ 384.9594, found 384.9616. Compound **5a**, mp 114–116 °C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H), 5.17 (s, 1H), 7.20 (d, $J = 8.20$, 2H), 7.31–7.35 (m, 4H), 7.42–7.45 (m, 4H), 7.50 (d, $J = 8.20$, 2H); MS (EI) m/z 235 (M^+-SO_2Tol, 100), 200 (25), 165 (47), 91 (3), 65 (3); HRMS (ESI) calcd for $C_{20}H_{16}O_2NaSCl_2$ 413.0140, found 413.0161. Compound **6a**, mp 120–122 °C (MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (s, 3H), 4.58 (d, $J = 8.90$, 1H), 5.25 (d, $J = 16.95$, 1H), 5.45 (d, $J = 10.24$, 1H), 6.14–6.23 (m, 1H), 7.14 (s, 1H), 7.26 (s, 1H), 7.29 (d, $J = 8.16$, 2H), 7.33 (br s, 1H), 7.56 (d, $J = 8.16$, 2H); MS (EI) m/z 340 (M^+, 0.5), 185 (100), 150 (33), 115 (28), 91 (8), 65 (6); HRMS (ESI) calcd for $C_{16}H_{14}O_2NaSCl_2$ 362.9984, found 362.9990. Compound **4b**, oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, $J = 7.32$, 3H), 2.52–2.60 (m, 1H), 2.91–3.00 (m, 1H), 7.42–7.47 (m, 2H), 7.50 (s, 1H), 7.53–7.56 (m, 2H), 7.62–7.67 (m, 2H), 7.69 (br s, 1H); MS (EI) m/z 255 (M^+-SO_2Ph, 100), 219 (27), 193 (23), 143 (19), 115 (7), 77 (13), 51 (9); HRMS (ESI) calcd for $C_{16}H_{13}O_2F_3NaSCl_2$ 418.9858, found 418.9877. Compound **5b**, mp 114–116 °C (MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H), 5.26 (s, 1H), 7.19 (d, $J = 8.27$, 2H), 7.33–7.37 (m, 3H), 7.45–7.48 (m, 2H), 7.49 (d, $J = 8.27$, 2H), 7.57 (br s, 2H), 7.80 (br s, 1H); MS (EI) m/z 269 (M^+-SO_2Tol, 100), 249 (5), 234 (20), 214 (4), 165 (14), 91 (2); HRMS (ESI) calcd for $C_{21}H_{16}O_2F_3NaSCl$ 447.0404, found 447.0417. Compound **4c**, mp 138–141 °C (MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (t, $J = 7.31$, 3H), 2.46–2.54 (m, 1H), 2.88–2.96 (m, 1H), 7.46–7.51 (m, 2H), 7.59–7.62 (m, 2H), 7.65–7.67 (m, 2H), 7.67–7.71 (m, 1H), 7.74 (m, 1H); MS (EI) m/z 212 (M^+-SO_2Ph, 100), 176 (25), 150 (29), 77 (20), 51 (13); HRMS (ESI) calcd for $C_{16}H_{13}NO_2NaSCl_2$ 375.9936, found 375.9951.
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