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Reactions of Nitroheteroarenes with Carbanions: Bridging Aromatic, Heteroaromatic, and Vinylic Electrophilicity

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Dedicated to Professor Helmut Schwarz on the occasion of his 65th birthday

Abstract: The relative rate constants for the vicarious nucleophilic substitution (VNS) of the anion of chloromethyl phenyl sulfone ($\mathbf{1}^-$) with a variety of nitroheteroarenes, for example, nitropyridines, nitropyrroles, nitroimidazoles, 2-nitrothiophene, and 4-nitropyrazole, have been determined by competition experiments. It was shown that nitropyridines are approximately four orders of magnitude more reactive than nitrobenzene. Among the five-membered heterocycles 2-nitrothiophene is the most active followed by nitroimidazoles and 4-nitropyrazole. Nitropyrroles are the least electrophilic nitroheteroarenes with reactivities comparable to nitrobenzene. Quantum chemically calculated methyl anion affinities (B3LYP/6–311G(d,p)//B3LYP/6–31G(d)) of the nitroarenes correlated only moderately with the partial relative rate constants. The correlation of these activities with the LUMO energies of nitroarenes is even worse. By measuring the second-order rate constants of the addition of $\mathbf{1}^-$ to nitroarenes and to diethyl arylidenemalonates **10**, it was possible to link the electrophilic reactivities of nitroheteroarenes with the comprehensive electrophilicity scale based on the linear-free-energy-relationship $\log k(20\,^\circ\mathrm{C}) = s(N + E)$.

Keywords: aromatic vicarious nucleophilic substitution · density functional calculations · heterocycles · kinetics · linear free energy relationships

Introduction

The concept of vicarious nucleophilic substitution (VNS) of hydrogen in electron-deficient arenes was developed three decades ago.[1,2] Since then this method has been thoroughly studied and has become a versatile tool for the introduction of a variety of substituents into aromatic or heteroaromatic nitro compounds.[3–6]

In general, the reaction proceeds by fast and reversible addition of a carbanion, bearing a leaving group X (e.g. halogen) at the carbanion center, to a nitroarene, followed by base-induced β-elimination of H–X from the resultant σ_H-adduct. At least two equivalents of base are necessary for the reaction to proceed, one for the deprotonation of the CH-acid to form the carbanion and the second for inducing the β-elimination of H–X. After final protonation, the substituted nitroarene or -heteroarene is obtained (Scheme 1).[7–10]

It has been reported that the solvent, the nature and concentration of the base, and the steric demand of the carbanion have a considerable influence on the ratio of isomeric products.[11] When there is a high excess of the base, H–X elimination is faster than the retroaddition of the σ_H-adduct, and the formation of the σ_H-adducts becomes irreversible. Nitro-substituted heteroarenes, similar to their carbocyclic analogues, readily enter the VNS reaction giving products that are important building blocks in organic synthesis.[12] Therefore, it is of interest to determine their electrophilic activities and compare them with those of typical aliphatic electrophiles.

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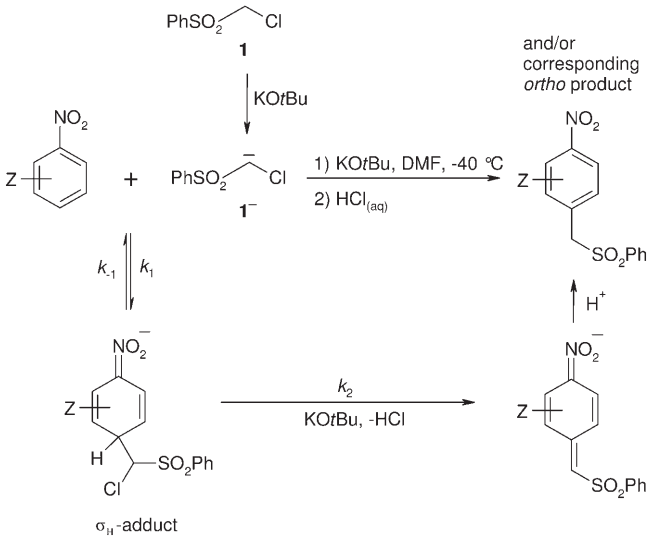


Scheme 1. Mechanism of the vicarious nucleophilic substitution in nitroarenes with the anion of chloromethyl phenyl sulfone ($\mathbf{1}^-$).

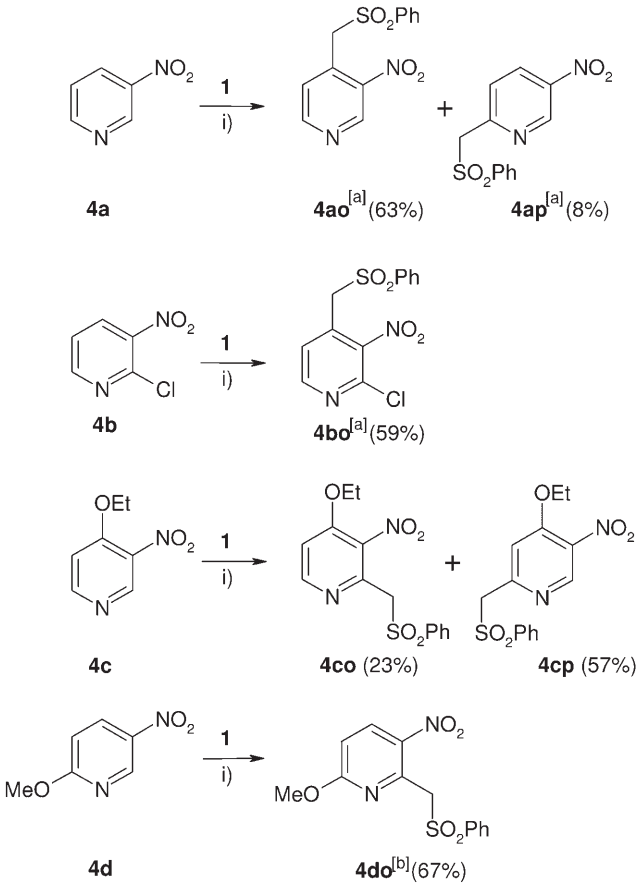
Understanding and predicting the influence of substituents will help to control regioselectivity in nucleophilic aromatic displacement reactions. Analogous substituent effects on the electrophilic activities of nitro-substituted benzenoid arenes have already been studied earlier.[13,14]

Results and Discussion

Product studies: As shown previously, the anion of chloromethyl phenyl sulfone ($\mathbf{1}^-$) undergoes VNS reactions with a broad variety of electron-deficient arenes[15,16] and was used as a substrate in earlier mechanistic studies.[7–10,13,14] Accordingly, it was chosen as the reference nucleophile also in this work. For the determination of relative electrophilic reactivities of various heteroarenes toward $\mathbf{1}^-$ by competition experiments, it was necessary to have samples of all VNS products, which were synthesized as described in Schemes 2 and 3. Some of these products were described earlier, as specified in the schemes.

The ratios of isomeric products obtained by VNS reactions of 3-nitropyridine (**4a**),[18] 2-chloro-3-nitropyridine (**4b**),[18] and 2-methoxy-5-nitropyridine (**4d**)[20] with the sulfonyl carbanion $\mathbf{1}^-$ agree with those reported in the literature (Scheme 2). Compound **4c** is predominately attacked by $\mathbf{1}^-$ at position 6 to yield **4cp** as the major product (Scheme 2) in accordance with the quantitative competition experiments discussed below. In contrast, the reaction of $\mathbf{1}^-$ with 4-methoxy-3-nitropyridine was reported to yield only the corresponding 2-substitution product.[20]

In the presence of strong bases, 1-unsubstituted nitropyrroles, nitroimidazoles, and nitropyrazoles are converted into the corresponding anions, which do not react with nucleophiles. Therefore we used the non-acidic 1-methylated derivatives **5**–**7** for our competition experiments.



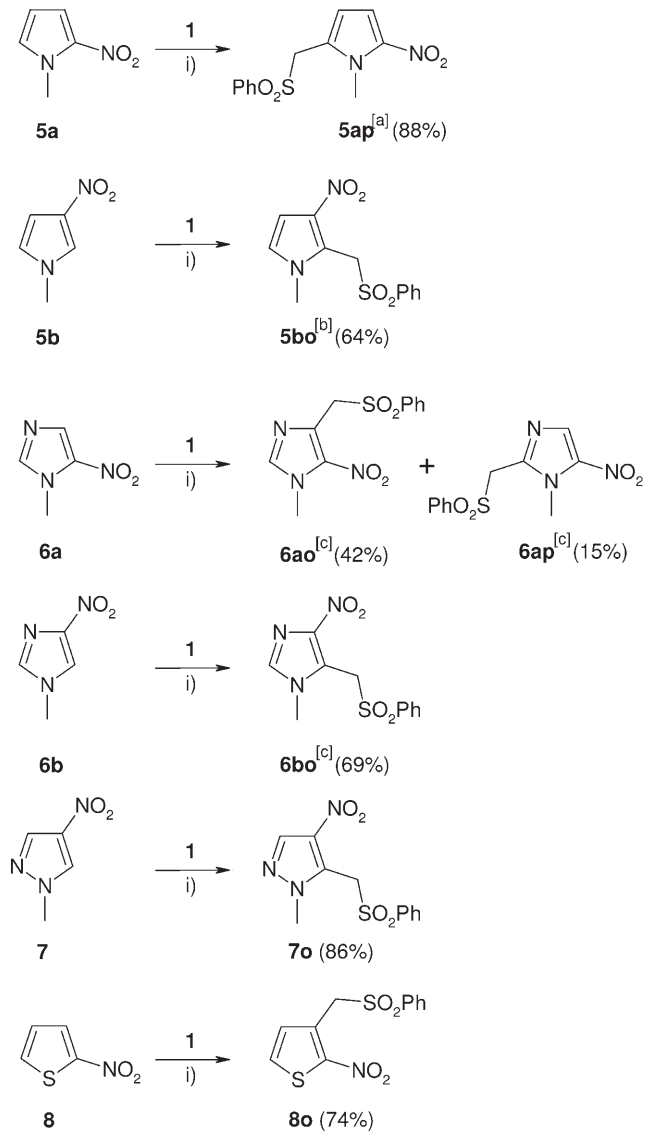
Scheme 2. VNS reactions of 3-nitropyridines **4a**–**d** with the anion of chloromethyl phenyl sulfone ($\mathbf{1}^-$).[17] i) 1. DMF, KO*t*Bu, −40 °C, 5 min; 2. $HCl_{(aq)}$. [a] Ref. [18]. [b] Ref. [19,20]

The VNS reactions of $\mathbf{1}^-$ with *N*-methyl-2-nitropyrrole (**5a**) and *N*-methyl-3-nitropyrrole (**5b**) gave only single regioisomers (Scheme 3).[21,22]

While Crozet and co-workers[24–26] reported the exclusive formation of **6ao**, when **6a** was treated with **1** and potassium hydroxide in DMSO at room temperature, we isolated a mixture of 4-benzenesulfonylmethyl-1-methyl-5-nitroimidazole (**6ao**, 42%) and 15% of the corresponding 2-isomer (**6ap**, Scheme 3) in accordance with earlier reports.[23] Only one regioisomer was obtained in the reaction of 1-methyl-4-nitroimidazole (**6b**, Scheme 3) with $\mathbf{1}^-$.

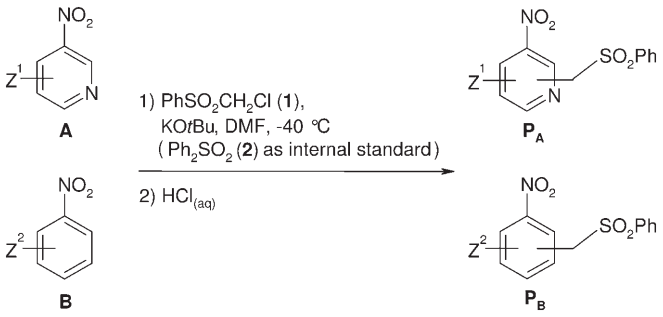
1-Methyl-4-nitropyrazole (**7**) was exclusively attacked at position 5 to give 5-benzenesulfonylmethyl)-1-methyl-4-nitro-1*H*-pyrazole (**7o**) in 86% yield (Scheme 3), in analogy to previously reported reactions of **7** with other carbanions.[27,28] In contrast to the regioselectivity of the reaction of **5a** with $\mathbf{1}^-$ (see above), 2-nitrothiophene (**8**) is selectively attacked at the 3-position by $\mathbf{1}^-$ (Scheme 3).[22,29]

Competition experiments: For the determination of the relative electrophilic reactivities of the electron-deficient arenes **3**–**8**, a mixture of two nitroheteroarenes was treated with chloromethyl phenyl sulfone (**1**) and KO*t*Bu. The products, obtained after treatment of the reaction mixtures with dilut-



Scheme 3. VNS reactions of five-membered heterocycles **5**–**8** with the anion of chloromethyl phenyl sulfone ($\mathbf{1}^-$). i) 1. DMF, KO*t*Bu, −40 °C, 5 min; 2. $HCl_{(aq)}$. [a] Ref. [21]. [b] Ref. [22]. [c] Ref. [23].

ed hydrochloric acid, were extracted with chloroform and analyzed by GC and/or HPLC (Scheme 4).



Scheme 4. Competition experiment for determining the relative electrophilic reactivities of two nitroarenes **A** and **B**.

A low reaction temperature (−40 °C) and a high concentration of potassium *tert*-butoxide (four equivalents) guaranteed the reaction to proceed under kinetic control with irreversible formation of the σ_H-adduct (Scheme 1). Because β-elimination of HCl from the σ_H-adducts is much faster than the reverse reaction ($k_2[B] \gg k_{-1}$),[13,14] the ratio of the isolated products reflects the ratio of the addition rate constants k_1. As competitors for the nitroheteroarenes we used the *para*-substituted nitrobenzenes **3b**–**d** (formula see Figure 1) and 1-nitronaphthalene (**3e**), which allowed us to combine the relative reactivities of this work with those of earlier studies.[13,14] A summary of all relative reactivities determined in this investigation is shown in Table 1. If there is more than one reaction center in the nitroheteroarenes, also the chromatographically determined product ratios are given. The results obtained by HPLC analysis are in good agreement with those from GC measurements. Whereas the results of the two methods differ by 25% for the first entry of Table 1, the deviation for all other systems is less than 10%. For further evaluation only the results obtained by GC are considered.

Table 1. Reactivity ratios derived from competition experiments.

A	B	Analysis	$\kappa^{[a,b]}$	Regioselectivity
4a	**3e**	GC	17 ± 1	[**4ao**]:[**4ap**] = 12 ± 2
		HPLC[c]	13 ± 1	[**4ao**]:[**4ap**] = 12 ± 2
4b	**3e**	GC	19 ± 1	
		HPLC[c]	21 ± 0.1	
4c	**3d**	GC	4.5 ± 0.4	[**4cp**]:[**4co**] = 2.0 ± 0.1
		HPLC[c]	4.2 ± 0.3	[**4cp**]:[**4co**] = 2.6 ± 0.1
3e	**4c**	GC[d]	4.8 ± 0.1	
4d	**3e**	GC	3.7 ± 0.2	
		HPLC[c]	3.7 ± 0.5	
3b	**5a**	GC	2.2 ± 0.1	
5b	**5a**	GC	5.0 ± 0.3	
5b	**3b**	GC	2.8 ± 0.3	
		HPLC[c]	3.1 ± 0.4	
6a	**3b**	GC	11 ± 1	[**6ao**]:[**6ap**] = 1.00 ± 0.03
		HPLC[e]	9.9 ± 1.4	[**6ao**]:[**6ap**] = 0.87 ± 0.11
3c	**6a**	GC	7.0 ± 0.3	[**6ao**]:[**6ap**] = 0.90 ± 0.04
6b	**3c**	GC	5.7 ± 0.4	
		HPLC[c]	6.2 ± 0.5	
6b	**3d**	GC	1.8 ± 0.1	
7	**3c**	GC	1.0 ± 0.1	
		HPLC[c]	1.1 ± 0.02	
3d	**7**	GC	2.7 ± 0.3	
8	**3e**	GC	3.9 ± 0.5	
		HPLC[c]	4.1 ± 0.7	

[a] $\kappa = k_A/k_B$ (ratio of the overall reactivity of **A** and **B**). [b] The indicated errors refer to the reproducibility of the chromatographic analysis, deviations between the results obtained by different methods show that the absolute errors are bigger. [c] Analysis at 264 nm. [d] Amount of *ortho* product of **4c** is estimated on the basis of [**4cp**]:[**4co**] = 2.0 ± 0.04. [e] Analysis at 280 nm.

Equation (1) represents the logarithm of the competition constants $k_A/k_B = \kappa$. By expressing all available competition constants (GC) in this way, an overdetermined set of linear equations [Eq. (1)] was obtained, which is solved by least squares minimization[30] to give the k_{rel} values listed in Figure 1. The activity of one *ortho*-position in nitrobenzene

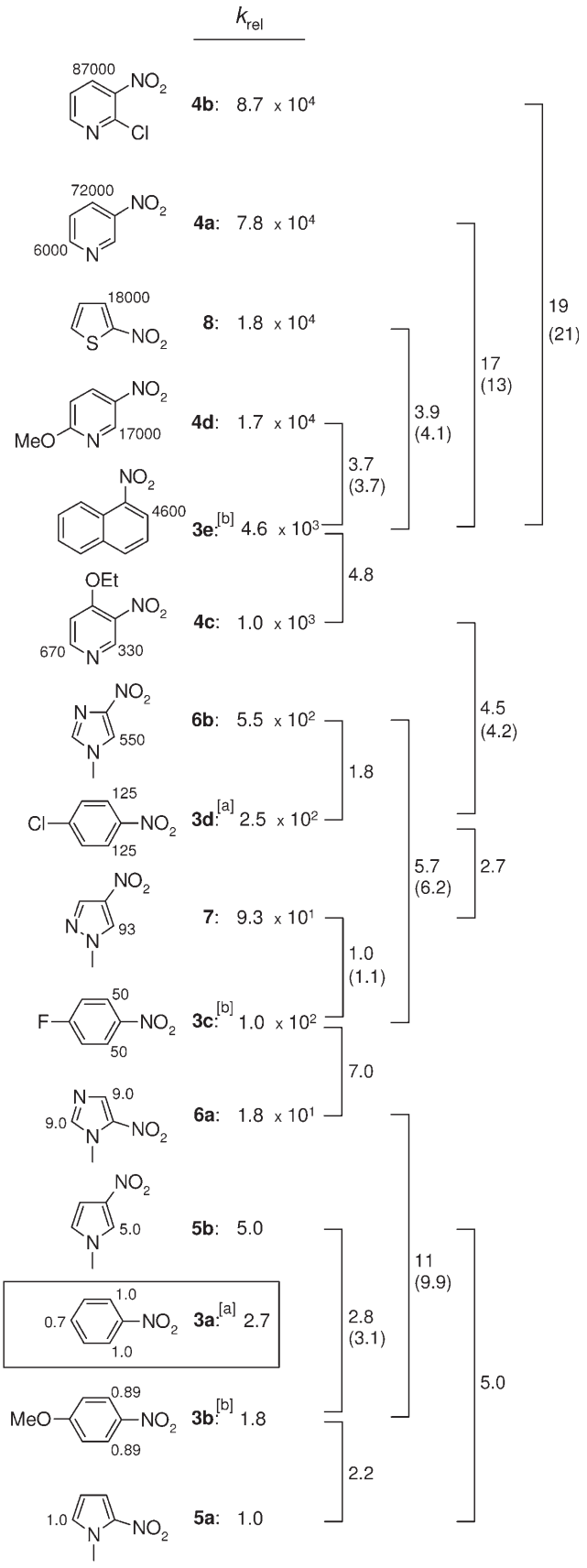


Figure 1. Overall relative reactivities k_{rel} (−40 °C) of nitroheteroarenes toward the anion of chloromethyl phenyl sulfone (**1**$^-$) based on κ values (Table 1) in relation to nitrobenzene (**3a**, $k_{rel}=2.7$).[13] The numbers in the formula give the relative reactivities of the corresponding positions with respect to one *ortho*-position of nitrobenzene. The numbers in parentheses indicate HPLC results, all other numbers result from GC analysis. [a] Ref. [13]. [b] Ref. [14].

(**3a**) was defined as 1.0,[13] and the previously reported overall activities of 4-chloronitrobenzene (**3d**, $k_{rel}=250$),[13] 4-methoxynitrobenzene (**3b**, $k_{rel}=1.8$),[14] 4-fluoronitrobenzene (**3c**, $k_{rel}=100$),[14] and 1-nitronaphthalene (**3e**, $k_{rel}=4600$)[14] were treated as invariable.

$$\log k_A - \log k_B = \log \kappa \quad (1)$$

The reactions of 5-nitrofuran-2-carbonitrile, 2-bromo-5-nitrothiophene, and 5-nitrothiazole with **1**$^-$ gave complex mixtures of products, which could not be analyzed quantitatively by GC and HPLC. Their electrophilic reactivities could, therefore, not be determined by analogous competition experiments. In line with these observations, nitrothiazoles have previously been reported to decompose in the presence of alkoxides.[31–33]

Direct rate measurements: In 2003, Lemek et al. showed that the reactions of α-halocarbanions with 4-methoxynitrobenzene (**3b**) yield persistent σ_H-adducts in DMF at −40 °C.[8] The second-order rate constants for these additions were determined by UV/Vis spectroscopy. Analogously, we determined the rate constants for the additions of **1**$^-$ to **3b**, **3d**, and 2,4-dichloronitrobenzene (**3f**, studied in refs. [13] and [14]) by following the absorbance of the σ_H-adduct at 425 nm (Table 2). To inhibit the elimination of HCl from the σ_H-adducts, chloromethyl phenyl sulfone (**1**) was used in slight excess over KO*t*Bu. Entries 1/2 and 3/4 of Table 2 show that the second-order rate constants determined for these additions do not depend on the reaction conditions, that is, which of the two reagents is used as the major com-

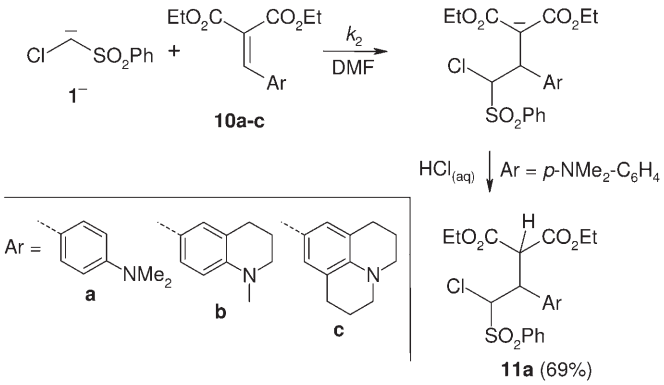
Table 2. Second-order rate constants k_2 of the reactions of carbanion **1**$^-$ with vinylic and aromatic electrophiles in DMF at −40 °C.

Entry	**A**[a]	**B**	k_2 (−40 °C) [$M^{-1}s^{-1}$][b]
1[c]	**1**$^-$	**3b**	**(2.26±0.12)×10^{-1}**
2[c]	**3b**	**1**$^-$	(2.34±0.17)×10^{-1}
3[c]	**1**$^-$	**3d**	(2.95±0.11)×10^{1}
4[c]	**3d**	**1**$^-$	**(2.77±0.08)×10^{1}**
5[c]	**3f**[d]	**1**$^-$	(1.95±0.11)×10^{2}
6[e]	**1**$^-$	**10a**	(1.01±0.03)×10^{1}
7[e]	**1**$^-$	**10b**	4.65±0.31[f]
8[e]	**1**$^-$	**10c**	2.64±0.12

[a] Compound used in excess to ensure pseudo-first-order kinetics. [b] Bold values are considered to be more reliable and are used for further calculations. [c] Exponential increase of the σ_H-adduct (425 nm) is followed. [d] **3f**: 2,4-dichloro-nitrobenzene. [e] Exponential decrease of the electrophile band is followed. [f] $\Delta H^{\neq}=(28.3\pm1.1)$ kJ mol^{-1} and $\Delta S^{\neq}=(-111\pm5)$ J mol^{-1} K^{-1}.

ponent under pseudo-first-order conditions. The ratio of the directly measured rate constants ($k_{3d}/k_{3b}=123$, from Table 2) is in good agreement with the relative reactivities determined by competition experiments ($k_{3d}/k_{3b}=139$, from Figure 1). Thus, the consistency of the two independent methods of reactivity studies is confirmed.

To compare the reactivities of aliphatic and aromatic electrophiles, the kinetics of the additions of $\mathbf{1}^-$ to diethyl benzylidenemalonates **10a–c** (Scheme 5) were studied analogously



Scheme 5. Reactions of carbanion $\mathbf{1}^-$ with Michael acceptors **10a–c**.

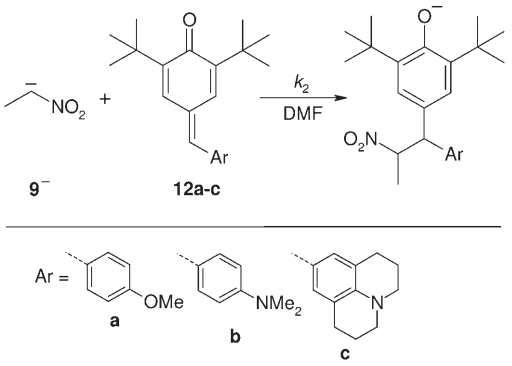
(Table 2, entries 6–8). The electrophiles **10a–c** show strong absorption bands in the UV/Vis spectra at $\lambda_{max}=400$–420 nm. When treated with an excess of $\mathbf{1}^-$, complete decolorization of the solutions was observed, indicating quantitative reactions. From the exponential decay of the absorbances of **10a–c**, the pseudo-first-order rate constants were derived and plotted against the variable concentrations of $\mathbf{1}^-$ to give the second-order rate constants listed in Table 2 (entries 6–8).[34]

The reaction course proposed in Scheme 5 was confirmed by the isolation of **11a**, which was obtained by protonation of the adduct of $\mathbf{1}^-$ and benzylidenemalonate **10a**.

Kinetic studies of the reaction of $\mathbf{1}^-$ with diethyl benzylidenemalonate **10b** at various temperatures yielded the Eyring activation parameters $\Delta H^{\neq}=(28.3\pm1.1)$ kJ mol^{-1} and $\Delta S^{\neq}=(-111\pm5)$ J mol^{-1} K^{-1}.

To link the kinetic data in Figure 1 and Table 2 to our comprehensive reactivity scales,[35] we also studied the kinetics of the additions of nitroethyl anion ($\mathbf{9}^-$) to **10a–c** and the quinone methides **12a–c** in DMF (Scheme 6) at various temperatures. From the second-order rate constants, the Eyring activation parameters and the second-order rate constants at −40 °C were derived (Table 3).

Relative reactivities of heteroarenes: As pyridine is well known to be π-electron deficient compared to benzene, it is not surprising that the nitropyridines **4a–d** are more electrophilic than analogously substituted nitrobenzenes.[36–38] The introduction of a ring nitrogen into nitrobenzene (**3a**) and 4-methoxynitrobenzene (**3b**) increases the electrophilic reactivity by four orders of magnitude: 3-Nitropyridine (**4a**) is



Scheme 6. Reaction of the nitroethyl anion ($\mathbf{9}^-$) with the quinone methides **12a–c**.

Table 3. Second-order rate constants k_2 and Eyring activation parameters of the reactions of the nitroethyl anion ($\mathbf{9}^-$) with quinone methides **12a–c** and diethyl benzylidenemalonates **10a–c** in DMF. The exponential decrease of UV/Vis absorbances of the electrophile was followed.

	k_2 (20 °C) [M^{-1} s^{-1}]	$\Delta H^{\neq}$ [kJ mol^{-1}]	$\Delta S^{\neq}$ [J mol^{-1} K^{-1}]	k_2 (−40 °C) [M^{-1} s^{-1}][a]
10a	$(4.52\pm0.18)\times10^{-1}$	44.4 ± 1.7	-101 ± 6	$(3.01\pm0.57)\times10^{-3}$
10b	$(2.46\pm0.02)\times10^{-1}$	45.4 ± 0.8	-102 ± 3	$(1.56\pm0.15)\times10^{-3}$
10c	1.76×10^{-1}	46.1 ± 0.4	-102 ± 1	$(1.01\pm0.05)\times10^{-3}$
12a	$(1.15\pm0.04)\times10^{3}$	33.3 ± 0.5	-73 ± 2	$(2.55\pm0.23)\times10^{1}$
12b	$(1.94\pm0.10)\times10^{2}$	30.2 ± 1.9	-98 ± 6	6.15 ± 1.52
12c	$(8.97\pm0.46)\times10^{1}$	31.1 ± 1.5	-101 ± 5	2.62 ± 0.53

[a] Calculated from Eyring parameters.

about 29000 times more reactive than nitrobenzene (**3a**, Figure 1) and the 2-position of **4d** is 19000 times more reactive than one of the corresponding positions of **3b**.

The overall reactivity of 4-ethoxy-3-nitropyridine (**4c**, $k_{rel}=1000$) towards $\mathbf{1}^-$ is approximately 17 times lower than the activity of 2-methoxy-5-nitropyridine (**4d**). With the assumption that the electronic effects of methoxy and ethoxy are similar (Hammett σ), the comparison of compounds **4c** and **4d** shows that the activating effect of a nitro group is more reduced by alkoxy groups in the *ortho*-position than by alkoxy groups in the *para*-position. Similar effects were observed for 2- and 4-methoxynitrobenzenes.[14]

2-Chloro-3-nitropyridine (**4b**, $k_{rel}=87000$) is only 1.1 times more reactive than 3-nitropyridine (**4a**), indicating a neglible activating effect by chlorine. On the other hand, chlorine has a noticeable activating effect in the benzene series, and 2-chloro-nitrobenzene is 6.4 times more reactive towards $\mathbf{1}^-$ than nitrobenzene (**3a**).[13,14] The preferred attack of $\mathbf{1}^-$ at position 4 in 3-nitropyridine (**4a**) is in good agreement with the relative reactivities of different chloro-substituted 3-nitropyridines in nucleophilic aromatic substitutions of chloride.[39] 4-Chloro-3-nitropyridine reacts 16 times faster with pyridine than 2-chloro-5-nitropyridine and 31 times faster than 2-chloro-3-nitropyridine.

Pyrrole is around 10^{10} times more nucleophilic than benzene,[40] due to its higher π-electron density and lower aromaticity. Remarkably, in the case of vicarious nucleophilic substitution the electrophilicities of the nitropyrroles **5a** and

5b are comparable to that of nitrobenzene (**3a**), indicating that the increased electron density in pyrroles is compensated by the reduced aromaticity. Thereby, 1-methyl-3-nitropyrrole (**5b**, $k_{rel}=5.0$) is five times more reactive than its 2-nitro isomer **5a** ($k_{rel}=1.0$).

The same ranking of reactivity was found for the two isomers of 1-methyl-nitroimidazole (**6a** and **6b**, Scheme 1). The 4-nitro compound **6b**, which is structurally related to **5b**, reacts 31 times faster with $\mathbf{1}^-$ than 1-methyl-5-nitroimidazole (**6a**, $k_{rel}=18$).

Figure 2 illustrates that replacement of a CH group by nitrogen generally increases the electrophilicity of the aromatic ring towards $\mathbf{1}^-$. This effect is much larger in the six-membered than in the five-membered rings. Whereas 3-nitropyridine (**4a**) is 29000 times more active than nitrobenzene (**3a**), nitroimidazole **6a** is only activated by a factor of 18 in relation to nitropyrrole **5a**. Important is also the position at which the additional nitrogen atom is located in the ring: 1-Methyl-4-nitroimidazole (**6b**) is activated by a factor of 110, whereas the isomeric nitropyrazole **7** is only 19 times more reactive than **5b**.

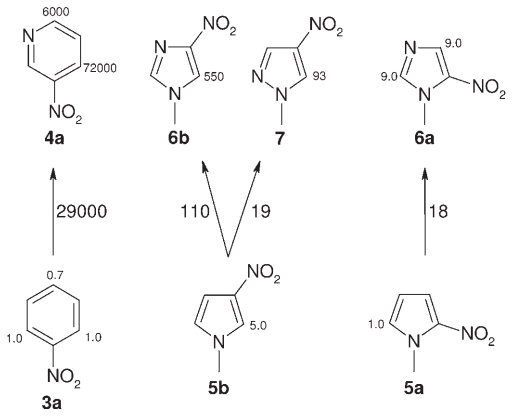


Figure 2. Effect of an additional nitrogen atom in the ring on the overall activity towards $\mathbf{1}^-$.

Although thiophene is considerably more nucleophilic than benzene, acceptor-substituted thiophene derivatives are also known to be more active in S_NAr reactions than analogously substituted benzene derivatives.[41–43] The activity of 2-nitrothiophene (**8**) in the VNS reaction with $\mathbf{1}^-$ follows this pattern. With $k_{rel}=18000$, compound **8** is the most active five-membered heterocycle of Figure 1, comparable to the nitropyridines **4a–d**. Possibly the low aromaticity of thiophene and the ability of sulfur to expand its electron octet facilitates the accommodation of the negative charge in the σ_H-adduct and therefore enhances the activity in nucleophilic addition reactions.

Quantum chemical calculations: The nitroheteroarenes **3–8** and the corresponding methyl anion adducts have been calculated with Gaussian03.[44] Structures were optimized at the B3LYP level using the 6–31G(d) basis set. Single-point energies have then been calculated at the B3LYP/6–311+G(d,p) level. Combination of these energies with thermochemical corrections derived from a harmonic vibrational frequency analysis at the B3LYP/6–31G(d) level yield the enthalpies H_{298} at 298 K. For detailed information, see the Supporting Information.

A plot of the logarithms of the partial rate constants versus the calculated methyl anion affinities shows a moderate correlation (Figure 3). Multiplication of log k_{rel} with 2.303 RT converts the y axis of Figure 3 into relative activation free energies $\Delta\Delta G^{\neq}$. The resulting slope $\Delta\Delta G^{\neq}/\Delta\Delta H_{rxn}(CH_3^-)=0.29$ indicates that approximately 30% of the calculated differences in gas-phase methyl anion affinities are reflected by the relative activation energies in solution. A quantitative interpretation of this ratio is problematic, because it is well-known that the differences of ion stabilization in the gas phase are generally attenuated in solution.[45]

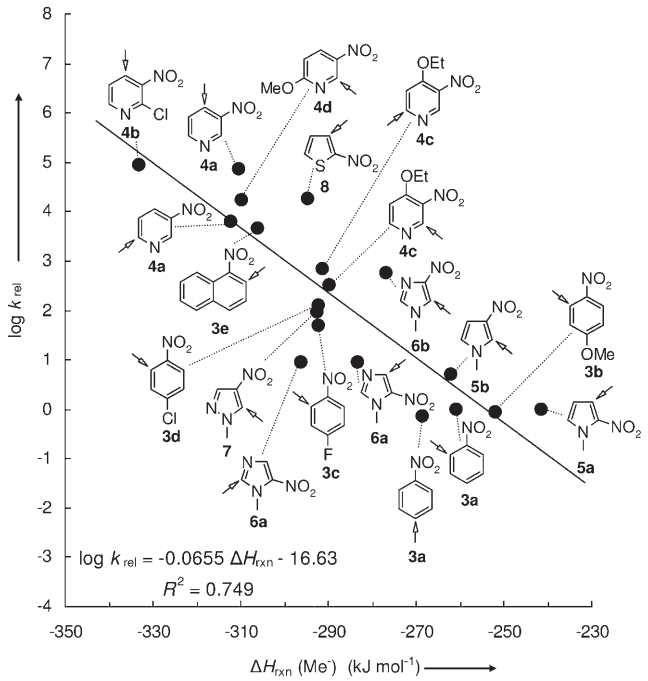


Figure 3. Correlation of logarithmic relative partial reactivities (−40 °C) of nitroheteroarenes versus their methyl anion affinities (B3LYP/6–311+G(d,p)//B3LYP/6–31G(d)).

From the small size of this ratio and the significant scatter shown in Figure 3 one can conclude, however, that the electrophilicities of the nitroarenes depend on the relative stabilities of the σ-adducts but that other, transition-state specific, properties contribute.

The correlation between the relative reactivities and the LUMO energies of the nitroarenes is even worse ($R^2=0.31$, Figure 4). Nitrobenzene (**3a**), one of the least reactive electrophiles, and 2-methoxy-5-nitropyridine (**4d**), one of the most reactive electrophiles, have almost the same LUMO energies. Thus, LUMO energies by themselves are also not suitable for predicting the relative reactivities of nitrohetero-

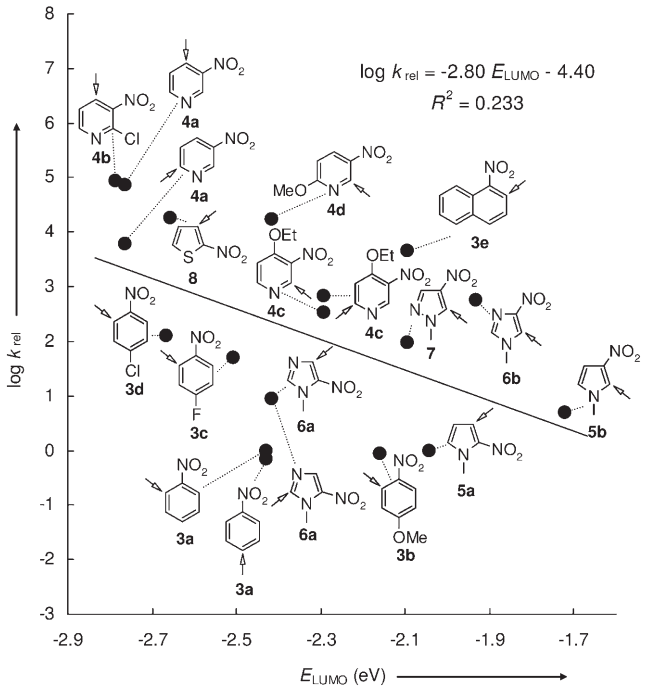


Figure 4. Correlation of logarithmic relative partial reactivities (−40 °C) of nitroheteroarenes versus the corresponding LUMO energy (B3LYP/6–31G(d)).

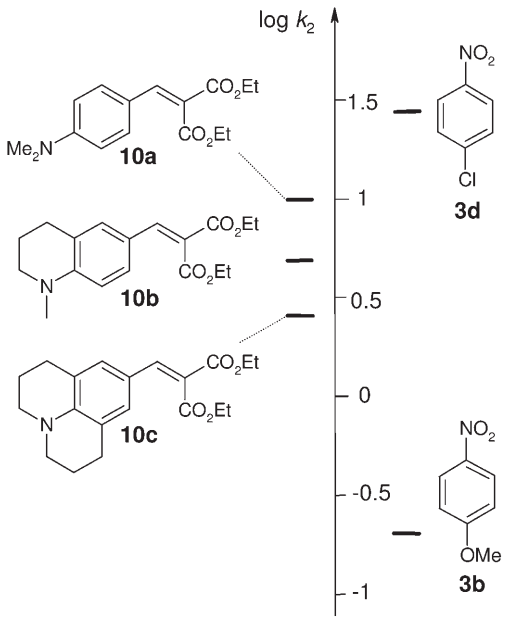


Figure 5. Second-order rate constants (L mol^{-1} s^{-1}) for the additions of $\mathbf{1}^-$ to aromatic and vinylic electrophiles (DMF, −40 °C).

arenes. Despite the poor correlations, one observation might be significant: Systems, which strongly deviate in a positive or negative direction from the correlation in Figure 3 usually deviate in the same direction in the (log k_{rel})/E_{LUMO} correlation (Figure 4). One, therefore, might argue that systems where the $\Delta G°$ and frontier orbital term enforce each other, give rise to the deviations in one or the other direction. We hesitate to interpret these data more quantitatively, because neither the relative stabilities of the adducts (Figure 3) nor the relative magnitudes of the LUMO coefficients (see Supporting Information) can correctly predict the regioselectivity of the nucleophilic attack at compounds **3a**, **4a**, **4b**, and **6a**. A special effect directing into the *ortho*-position of the nitro group seems to be operating. Though one might consider the positive counter ions being responsible for this orientation, the independence of the rate constants of the nature of the counter ion argues against this interpretation.

Comparison of aromatic and aliphatic electrophiles: From the second-order rate constants k_2 of the reactions of $\mathbf{1}^-$ with **10a–c** and **3b**,**d** at −40 °C in DMF (Table 2), one can derive that the electrophilicities of the benzylidenemalonates **10a–c** are in between those of **3b** and **3d** (Figure 5).

Because electrophilicity parameters E for compounds **10a–c** have recently been determined,[46] we can now include the nitroarenes **3–8** (Figure 1) into the comprehensive electrophilicity scale based on the correlation Equation (2):[35]

$$\log k_2\ (20\,^\circ\mathrm{C}) = s\,(N + E) \qquad (2)$$

where s = nucleophile-specific slope parameter, N = nucleophilicity parameter, E = electrophilicity parameter.

For that purpose, the relative rate constants at −40 °C given in Figure 1 have to be converted into second-order rate constants (L mol^{-1} s^{-1}) at 20 °C. From the ratio k_2 (Table 2)/k_{rel} (Figure 1) for the reaction of $\mathbf{1}^-$ with **3b** (0.126) and **3d** (0.111) one can derive that multiplication of k_{rel} from Figure 1 with the average value 0.119 yields the second-order rate constants (−40 °C, DMF) for the reactions of $\mathbf{1}^-$ with the nitroarenes **3–8**.

From the temperature dependence of the reaction of $\mathbf{1}^-$ with **10b** in DMF an activation entropy of $\Delta S^{\neq} = -111$ J mol^{-1} K^{-1} was determined (see footnote [f] of Table 2). As expected, this value is of the same order of magnitude as those for other combinations of carbanions with neutral electrophiles in DMF (Table 3) and was, therefore, used to transform the second-order rate constants at −40 °C into values at 20 °C (for details see the Supporting Information p. S76).

Figure 6 shows a linear correlation between the rate constants (log k_2) of the reactions of $\mathbf{1}^-$ with **10a–c** at 20 °C (from Table 4, last column) versus the E parameters of these electrophiles. According to Equation (2), the slope yields s = 0.64, and the intercept on the abscissa gives N = 26.64 for the carbanion $\mathbf{1}^-$ in DMF.

Substitution of N and s for $\mathbf{1}^-$ and the value of log $k_{2,\,calcd}$ (20 °C) from Table 4 into Equation (2) allows one to calculate the electrophilicity parameters E for the nitroheteroarenes **3–8**, which are depicted in Figure 7 along with several previously characterized electrophiles.

It should be noted that the slope parameter s for the carbanion $\mathbf{1}^-$ was derived from only three rate constants with electrophiles in a relatively narrow range of reactivity. For

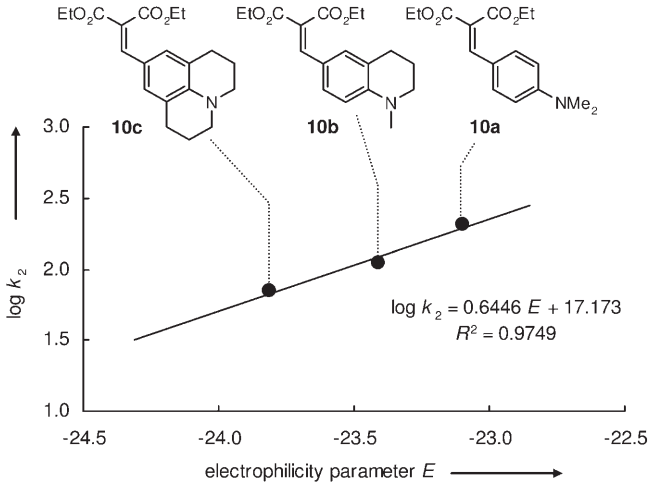


Figure 6. Plot of log k_2 for the reactions of $\mathbf{1}^-$ with **10a–c** (20 °C, DMF, Table 4) versus the electrophilicity parameters E of the benzylidenemalonates **10a–c**.

Table 4. Calculation of second-order rate constants k_2 (DMF, 20 °C) for the reactions of the carbanion $\mathbf{1}^-$ with the nitroarenes **3–8** and benzylidenemalonattes **10** from the corresponding relative rate constants at −40 °C.

	k_{rel} (−40 °C)[a]	k_2 (−40 °C)[b] [$M^{-1}s^{-1}$]	$k_{2,\,calcd}$ (−40 °C)[c] [$M^{-1}s^{-1}$]	$k_{2,\,calcd}$ (20 °C)[d] [$M^{-1}s^{-1}$]
4b	8.7×10^4	–	1.0×10^4	5×10^4
4a	7.8×10^4	–	9.3×10^3	5×10^4
8	1.8×10^4	–	2.1×10^3	1×10^4
4d	1.7×10^4	–	2.0×10^3	1×10^4
3e	4.6×10^3	–	5.5×10^2	5×10^3
3f	–	1.95×10^2	2.0×10^2	2×10^3
4c	1.0×10^3	–	1.2×10^2	2×10^3
6b	5.5×10^2	–	6.6×10^1	9×10^2
3d	2.5×10^2	2.77×10^1	3.0×10^1	5×10^2
3c	1.0×10^2	–	1.2×10^1	2×10^2
7	9.3×10^1	–	1.1×10^1	2×10^2
10a	–	10.1	1.0×10^1	2×10^2
10b	–	4.65	4.7	1×10^2
10c	–	2.64	2.6	7×10^1
6a	1.8×10^1	–	2.1	6×10^1
5b	5.0	–	6.0×10^{-1}	2×10^1
3a	2.7	–	3.2×10^{-1}	1×10^1
3b	1.8	2.26×10^{-1}	2.1×10^{-1}	1×10^1
5a	1.0	–	1.2×10^{-1}	6

[a] From competition experiments (Figure 1). [b] From direct rate measurements (Table 2). [c] Calculated by multiplication of k_{rel} with the average factor 0.119. [d] Calculated with $\Delta S^{\neq} = -111\,J\,mol^{-1}K^{-1}$ (for details see the Supporting Information).

that reason, the E values for electrophiles, which differ by several orders of magnitude from those of compounds **10a–c**, should be treated with caution.

Conclusion

The UV/Vis spectroscopically determined second-order rate constants for the reactions of the sulfonyl-stabilized carbanion $\mathbf{1}^-$ with the aromatic (**3b**, **3d**) and nonaromatic electrophiles (**10a–c**) can be used to link the manifold of relative

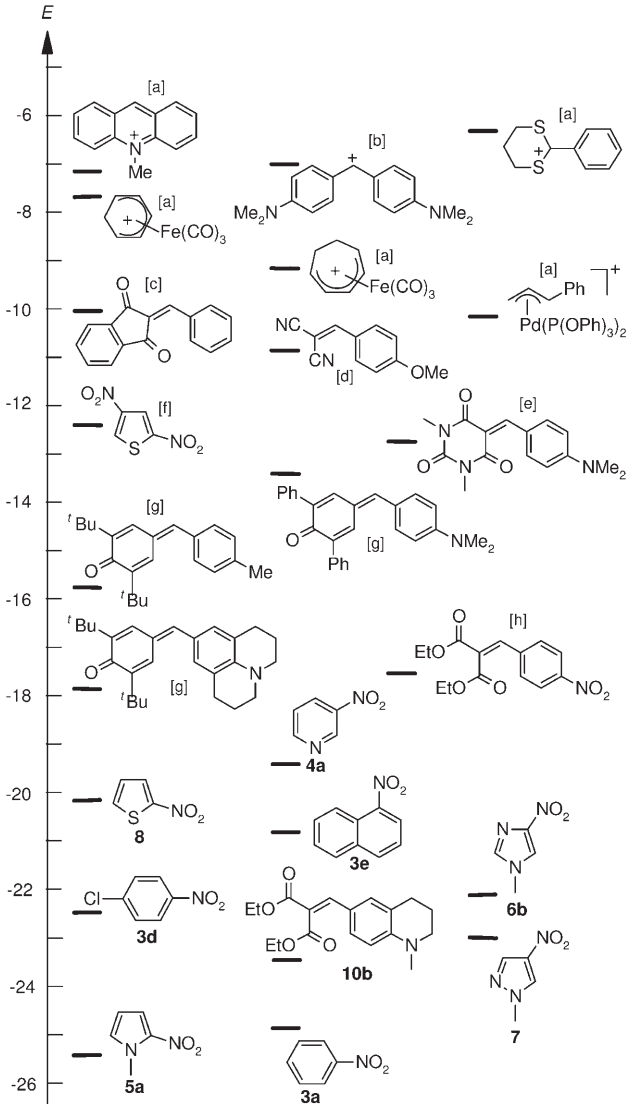


Figure 7. Electrophilicity scale according to Equation (2). [a] Ref. [47]. [b] Ref. [40]. [c] Ref. [34a]. [d] Ref. [48]. [e] Ref. [34b]. [f] Ref. [49]. [g] Ref. [50]. [h] Ref. [46].

electrophilic reactivities of nitroheteroarenes in VNS reactions, which were determined by competition experiments, with the comprehensive electrophilicity scale based on Equation (2). Because of the uncertainty in the nucleophilicity parameters N and s for carbanion $\mathbf{1}^-$ in DMF, the E parameters given in Figure 7 should be considered preliminary. However, the comparison of aromatic and nonaromatic electrophiles shown in Figure 7 provides a reliable orientation, which can be used to guide synthetic studies until more reliable electrophilicity parameters E for these compounds become available.

Experimental Section

General: ^1H and ^{13}C NMR chemical shifts are expressed in ppm and refer to TMS. DEPT and HSQC experiments were employed to assign

the signals. Syringes used to transfer reagents were purged with dry nitrogen prior to use. All competitive and preparative VNS reactions were carried out with magnetic stirring in flame-dried glassware under an atmosphere of dry nitrogen. Dry DMF was purchased (< 50 ppm H_2O). Cooling of the reaction vessels was performed by the use of a cryostat unit. The yields of the products in competitive experiments were determined either by gas chromatography or HPLC using diphenyl sulfone as an internal standard. GC was performed with nitrogen as mobile phase and FID detector on a Thermo Electron Focus apparatus equipped with an MN 25 m × 0.25 mm stainless column packed with fused-silica and an automatic injection unit (temperature gradient: 150 °C [2 min]–8 °C/min–280 °C [10 min]). For HPLC a CC 250/4 Nucleosil 120–3 normal-phase column and *n*-heptane and ethyl acetate as mobile phase (gradient: 0–100 % ethyl acetate or 0–50 % ethyl acetate in 45 min, detector: UV/Vis) were used. The following starting materials were prepared according to the published procedures: Chloromethyl phenyl sulfone (**1**),[15] 1-methyl-2-nitropyrrole (**4a**),[51] 1-methyl-3-nitropyrrole (**4b**),[51] 1-methyl-5-nitroimidazole (**6a**),[52] 1-methyl-4-nitroimidazole (**6b**),[53] 1-methyl-4-nitropyrazole (**7**),[54] 2-nitrothiophene (**8**),[55] 2-bromo-5-nitrothiophene,[56] 5-nitrothiazole.[57,58]

The product mixtures were analyzed by gas chromatography and high-performance liquid chromatography. The product ratios were determined relative to diphenyl sulfone (**2**) as an internal standard. To guarantee the reproducibility of the obtained results, all examined VNS products were first isolated on a preparative scale and characterized. Figure 8 and Figure 9 show typical GC and HPLC chromatograms obtained for a VNS experiment, in which 1-methoxy-4-nitrobenzene (**3b**) was competing with *N*-methyl-3-nitropyrrole (**5b**) for $\mathbf{1}^-$.

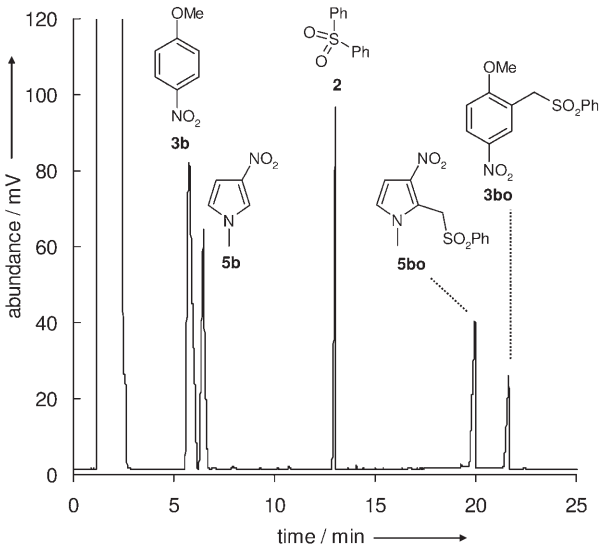


Figure 8. GC analysis of the product mixture obtained in an experiment in which 1-methoxy-4-nitrobenzene (**3b**) and 1-methyl-3-nitropyrrole (**5b**) competed for $\mathbf{1}^-$ (diphenyl sulfone (**2**) as internal standard).

The relative activities determined for particular pairs of nitroheteroarenes were calculated from the observed product ratios with Equation (3).

$$\frac{k_A}{k_B} = \frac{\ln\left(\frac{[A]_0 - \sum[P_A]}{[A]_0}\right)}{\ln\left(\frac{[B]_0 - \sum[P_B]}{[B]_0}\right)} \qquad (3)$$

$[A]_0$ and $[B]_0$ are starting concentrations of the nitroheteroarenes; $[P_A]$ and $[P_B]$ are the concentrations of reaction products of nitroarenes A and B, respectively.

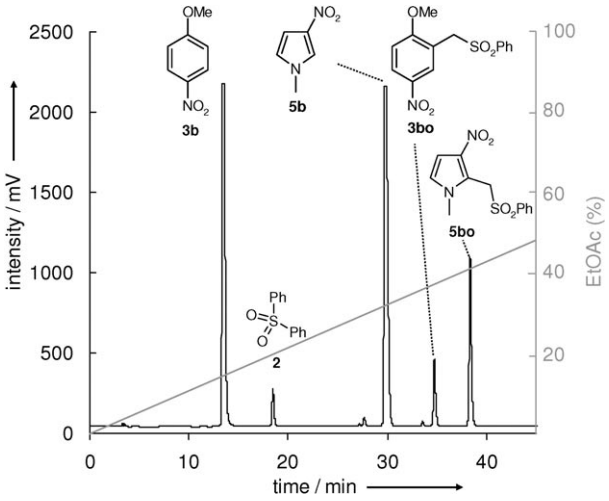


Figure 9. HPLC analysis of the product mixture obtained in an experiment in which 1-methoxy-4-nitrobenzene (**3b**) and 1-methyl-3-nitropyrrole (**5b**) competed for $\mathbf{1}^-$ (diphenyl sulfone (**2**) as internal standard).

General procedure for preparative VNS reactions: A solution of KO*t*Bu (452 mg, 2.50 mmol) in DMF (6 mL) was added to a solution of **1** (307 mg, 1.61 mmol) in DMF (5 mL) cooled to −40 °C and the mixture was stirred for 30 s. A solution of the appropriate arene or heteroarene in DMF (2 mL) was added and the mixture was stirred for a further 5 min at −40 °C, then 1 M HCl (15 mL) was added. The mixture was then extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The pure products were isolated by column chromatography over silica gel or recrystallization from EtOH.

General procedure for competitive VNS reactions: Chloromethyl phenyl sulfone (95.3 mg, 0.500 mmol), diphenyl sulfone (43.7 mg, 0.200 mmol), and the appropriate competing arenes/heteroarenes were dissolved in DMF (4 mL) in a 10 mL round-bottomed Schlenk flask. A 1 mL portion of this mixture was transferred to another 10 mL round-bottomed Schlenk flask and cooled to −40 °C. Then a 0.6 M KO*t*Bu solution in THF (0.84 mL, 0.50 mmol) was added and the mixture was stirred for 15 s at −40 °C. 1 M HCl (5 mL) and water (5 mL) were added and the mixture was extracted with CH_2Cl_2 (4 mL). The organic layer was dried over $MgSO_4$ and then subjected to GC (injection volume: 1 μL) or HPLC (injection volume: 10 μL). The reaction was repeated three times for every pair.

2-Benzenesulfonylmethyl-4-ethoxy-3-nitropyridine (4co): Colorless crystals, 23 % yield, m.p. 146–147 °C (EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (t, ^3J = 7.2 Hz, 3H; CH_2CH_3), 4.21 (q, ^3J = 7.2 Hz, 2H; CH_2CH_3), 4.73 (s, 2H; CH_2), 6.96 (d, ^3J = 5.7 Hz, 1H; 5-H), 7.52–7.80 (m, 5H; C_6H_5), 8.42 ppm (d, ^3J = 5.9 Hz, 1H; 6-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.1 (CH_3), 60.2 (CH_2-S), 66.0 (CH_2CH_3), 108.9 (C-5), 128.4 (C_{Ar}-H), 129.2 (C_{Ar}-H), 134.1 (C_{Ar}-H), 138.5 (C_{Ar}), 139.5 (C_{Ar}), 142.5 (C_{Ar}), 151.9 (C-6), 157.5 ppm (C_{Ar}); MS (ESI): 667.4 [2*M*+Na]$^+$, 345.3 [*M*+Na]$^+$, 323.3 [*M*H]$^+$; MS (EI): *m/z* (%): 323 (3) [*M*H]$^+$, 257 (11), 241 (23), 213 (21), 171 (10), 165 (30), 154 (12), 153 (32), 141 (11), 125 (12), 110 (17), 107 (11), 95 (32), 83 (20), 77 (100), 55 (18), 54 (11), 52 (18), 51 (37); elemental analysis calcd (%) for $C_{14}H_{14}N_2O_5S$ (322.3): C 52.17, H 4.38, N 8.69, S 9.95; found: C 52.08, H 4.40, N 8.68, S 10.14.

2-Benzenesulfonylmethyl-4-ethoxy-5-nitropyridine (4cp): Pale yellow crystals, 57 % yield, m.p. 150–151 °C (EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53 (t, ^3J = 7.2 Hz, 3H; CH_2CH_3), 4.30 (q, ^3J = 7.0 Hz, 2H; CH_2CH_3), 4.57 (s, 2H; CH_2-S), 7.23 (s, 1H; 6-H), 7.53–7.74 (m, 5H; C_6H_5), 8.74 (s, 1H; 3-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.1 (CH_3), 64.3 (CH_2-S), 66.2 (CH_2CH_3), 111.1 (C-3), 128.3 (C_{Ar}-H), 129.3 (C_{Ar}-H), 134.2 (C_{Ar}-H), 136.1 (C_{Ar}), 137.9 (C_{Ar}), 146.5 (C-6), 154.6 (C_{Ar}), 158.5 ppm (C_{Ar}); MS (ESI): 667.4 [2*M*+Na]$^+$, 345.3 [*M*+Na]$^+$, 323.4 [*M*H]$^+$; MS (EI): *m/z* (%): 258 (52), 257 (100), 230 (11), 229 (63), 183

(16), 107 (17), 78 (11), 77 (66), 51 (29), 39 (14); elemental analysis calcd (%) for $C_{14}H_{14}N_2O_5S$ (322.3): C 52.17, H 4.38, N 8.69, S 9.95; found: C 52.04, H 4.41, N 8.79, S 10.03.

5-Benzenesulfonylmethyl-1-methyl-4-nitro-1*H*-pyrazole (7o): Pale green crystals, 86% yield, m.p. 193–195°C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.10$ (s, 3H; CH_3), 4.95 (s, 2H; CH_2), 7.49–7.72 (m, 5H; C_{Ar}-H), 8.01 ppm (s, 1H; 3-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 38.8$ (CH_3), 51.4 (CH_2), 128.5 (2 C_{Ar}-H), 129.4 (2 C_{Ar}-H), 129.7 (2 C_{Ar}), 134.9 (C_{Ar}-H), 136.0 (C_{Ar}-H), 136.9 ppm (C_{Ar}); elemental analysis (%) calcd for $C_{11}H_{11}N_3O_4S$: C 46.97, H 3.94, N 14.94, S 11.40; found: C 47.04, H 3.95, N 14.92, S 11.76.

2-[2-Benzenesulfonyl-2-chloro-1-(4-dimethylaminophenyl)ethyl]malonic acid diethyl ester (11a): A 0.52 M solution of KO*t*Bu in DMF (0.96 mL, 0.50 mmol) was added slowly to a solution of **1** (0.50 mmol) in DMF (5 mL) at −40°C. The mixture was stirred for 2 min before a solution of **10a** (0.50 mmol) in DMF (2.5 mL) was added dropwise within 1 min. After 20 min the mixture was allowed to warm up to 0°C, poured into cooled 3% aqueous HCl (100 mL), and then extracted with ethyl acetate (3×20 mL). After drying over $MgSO_4$ and removal of the solvent in vacuo at room temperature, purification of the residue by column chromatography (SiO_2, hexane/ethyl acetate 3:1) gave a yellow oil in 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.04$ (t, $^3J = 7.2$ Hz, 3H; CH_2CH_3), 1.24 (t, $^3J = 7.2$ Hz, 3H; CH_2CH_3), 2.91 (s, 6H; $N(CH_3)_2$), 3.97 (q, $^3J = 7.2$ Hz, 2H; CH_2CH_3), 4.18 (q, $^3J = 7.2$ Hz, 2H; CH_2CH_3), 4.20 (dd, $^3J = 9.2$ Hz, $^3J = 6.2$ Hz, 1H; CH), 4.53 (d, $^3J = 9.0$ Hz, 1H; CH), 5.59 (d, $^3J = 6.3$ Hz, 1H; CH), 6.56 (d, $^3J = 8.7$ Hz, 2H; C_{Ar}H), 7.24 (d, $^3J = 9.0$ Hz, 2H; C_{Ar}H), 7.43–7.60 (m, 3H; C_{Ar}-H), 7.74–7.77 ppm (m, 2H; C_{Ar}H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 13.9$ (CH_2CH_3), 14.1 (CH_2CH_3), 40.5 ($N(CH_3)_2$), 47.3 (CH), 55.4 ($CH(CO_2Et)_2$), 61.6 (CH_2), 62.0 (CH_2), 76.0 (CHCl), 112.0 (2×C_{Ar}-H), 121.9 (C_{Ar}), 129.1(C_{Ar}-H), 129.3 (C_{Ar}-H), 131.0 (2×C_{Ar}-H), 134.1 (C_{Ar}-H), 137.9 (C_{Ar}-S), 150.4 (C_{Ar}-N), 167.6 (CO_2Et), 168.2 ppm (CO_2Et); MS (EI): *m/z* (%): 481.1 (22) [M^+], 341.1 (21), 340.1 (17), 339.1 (77), 293.2 (16), 292.2 (100), 219.1 (28), 183.1 (25), 182.1 (14), 181.1 (97), 180.1 (20), 174.1 (31), 158.1 (25), 146.1 (12), 145.1 (18), 144.1 (15), 77.0 (15): HR-MS (EI): calcd for $C_{23}H_{28}ClNO_6S$: 481.1326, found: 481.1313.

Acknowledgements

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[17] Following notations are used throughout this paper: **3a**, **3b**, **3c**, .., **4a**, **4b**, .., **7**, etc. denote the nitro(hetero)arene. The additional letter (o = *ortho*, p = *para*, or *pseudo-para*) indicates the position of the CH_2SO_2Ph substituent in relation to the nitro group.
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