Regiospecificity in Nucleophilic Displacement of Aromatic Nitro-groups

Fabio Benedetti,[a] Donald R. Marshall,[a] Charles J. M. Stirling,*[a] and John L. Leng[b]

[a] *School of Physical and Molecular Sciences, University College of North Wales, Bangor, Gwynedd LL57 2UW, U.K.*

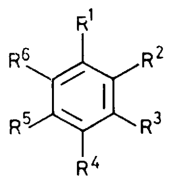
[b] *I.C.I. Organics Division, Blackley, Manchester M9 3DA, U.K.*

Displacement of nitro-groups by thiolate ions from aromatic polynitro-compounds is highly selective for nitro-groups adjacent to alkyl groups except when the thiolate ion is bulky, the alkyl group is bulky, or both.

Displacement of nitro-groups from aromatic nuclei by nucleophiles is a familiar reaction[1] and such reactions with thiolate ions have recently been reported.[2] We now report on the regiospecificity of this reaction, the results of which have considerable potential for synthesis of benzothiophens and related compounds.[1,3]

A series of polynitro-compounds (Table 1) has been treated with lithium alkanethiolates in hexamethylphosphoramide (HMPA). In each nitro-compound (**1**)—(**7**), an alkyl group is situated adjacent to one or more of the nuclear nitro-groups. In each case in which the alkyl group is methyl and the nucleophile is ethanethiolate, displacement of the nitro-group adjacent to the alkyl group is overwhelmingly preferred. When, however, as in compound (**6**) the alkyl group is bulky, regiospecificity disappears and when the thiolate ion is also bulky, displacement of the non-adjacent nitro-group is preferred and reaction is much slower than with the ethanethiolate. It is notable that while activation by an electron-accepting conjugative group is required for the displacement of nitro-groups,[1] it is not necessary for this group to be located *o*- or *p*- to the nucleofuge [*cf.* compounds (**3**), (**5**), (**6**), (**7**), and earlier work[2]].

Table 1. Reactions of polynitrobenzenes with lithium thiolates in HMPA.[a]



	Nitro-compound						Thiolate ion[b,c]	Product(s)						% Yield[d]
	R^1	R^2	R^3	R^4	R^5	R^6		R^1	R^2	R^3	R^4	R^5	R^6	
(**1**)	Me	NO_2	H	H	H	H	$\mathrm{Et\bar{S}}$			[e]				
(**2**)	Me	NO_2	NO_2	H	H	H	$\mathrm{Et\bar{S}}$	Me	SEt	NO_2	H	H	H	100
(**3**)	Me	NO_2	H	NO_2	H	H	$\mathrm{Et\bar{S}}$	Me	SEt	H	NO_2	H	H	94[f]
(**4**)	Me	NO_2	H	H	NO_2	H	$\mathrm{Et\bar{S}}$	Me	SEt	H	H	NO_2	H	97[f]
(**5**)	Me	NO_2	H	H	H	NO_2	$\mathrm{Et\bar{S}}$	Me	SEt	H	H	H	NO_2	99[f], 100[g]
(**6**)	Bu^t	NO_2	H	NO_2	H	H	$\mathrm{Et\bar{S}}$	Bu^t	SEt	H	NO_2	H	H	51
								Bu^t	NO_2	H	SEt	H	H	49
							$\mathrm{Bu^t\bar{S}}$	Bu^t	Bu^tS	H	NO_2	H	H	0
								Bu^t	NO_2	H	Bu^tS	H	H	60[h], 10[i]
(**7**)	Me	NO_2	H	NO_2	H	NO_2	$\mathrm{Et\bar{S}}$	Me	SEt	H	NO_2	H	NO_2	75.6
								Me	NO_2	H	SEt	H	NO_2	0.9
								Me	SEt	H	NO_2	H	EtS	9.2 78[j]
								Me	SEt	H	SEt	H	NO_2	0.6, 13[j]

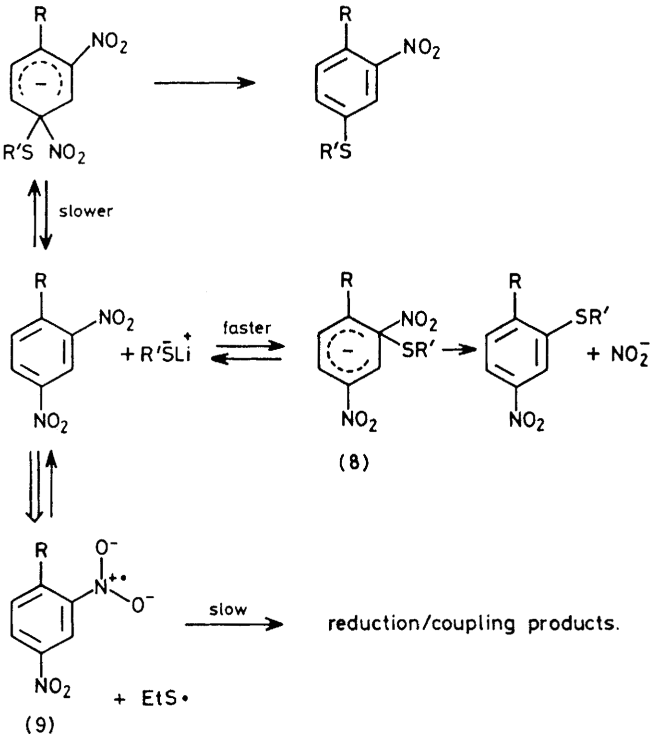
[a] At 20 °C. [b] 1 mol per mol of nitro-compound. [c] Reagent from thiol and LiOH in HMPA. [d] Isolated; products were characterised by elemental analysis of sulphide or derived sulphone and by ^{13}C and ^{1}H n.m.r. spectroscopy. [e] No product of nitro-group displacement. [f] No other product detected in product mixture before purification. [g] *S*-Methyl compound with MeSH. [h] Conversion. [i] Yield with 5 : 1 mol ratio of thiol to nitro-compound. Azoxy- and hydrazo-compounds also isolated; 80% yield of Bu^tSSBu^t. [j] Yield with thiol: nitro-compound mol ratio of 2 : 1.

These results are to be interpreted as follows: a nuclear nitro-group adjacent to a nuclear methyl group is out of the plane of the nucleus by about 35°;[4] attack by the nucleophile at such a nitro-group is preferred as formation of the Meisenheimer complex requires the lesser perturbation of the impaired interaction of this nitro-group with the nucleus. Nitro-groups elsewhere in the molecule lie in the plane of the nucleus. Displacement of the out-of-plane nitro-group is reinforced by activation from the in-plane nitro-group, although when this is in the *meta*-position this activation is not entirely understood. Displacement of an in-plane nitro-group, while being possible [*cf.* reactions with (**6**) and (**7**)] is less well activated by an out-of-plane nitro-group.†

When the alkyl group is very bulky, as in (**6**), a compromise is struck between steric acceleration of formation of the Meisenheimer complex and steric interference with access of the nucleophile. When the alkyl group and the thiolate ion are *both* bulky, the net effect is to direct attack to an in-plane substituent in a poorly activated process.

While these reactions occur most readily in HMPA, dimethyl sulphoxide (DMSO) can also be employed as a solvent, and ^{1}H n.m.r. examination of a mixture of lithium ethanethiolate and *o*-nitrotoluene (**1**) in DMSO suggests that there is a rapidly established equilibrium with a radical anion of type (**9**); all aromatic protons disappear, but reappear on quenching. With these reagents, there is no nitro-group displacement, but similar behaviour is seen for reactions with trinitrotoluene (**7**) in which displacement of nitrite *does* occur. The products of nitrite displacement therefore appear to be formed by relatively slow leakage *via* a Meisenheimer intermediate such as (**8**), from the rapidly established equilibria *e.g.* (**3**) $\rightleftharpoons$ (**9**) (Scheme 1). When formation of the Meisenheimer intermediate is slow, as with a bulky nucleophile or sterically hindered electrophilic site, the normally slow decay of the radical ion (**9**) to the familiar products of one-electron transfer reactions becomes a significant pathway.

Such reduction products thus accompany the slow displacement of the *para*-nitro group in 2,4-dinitro-t-butylbenzene by the t-butylthiolate ion (Table 1), and when an excess of thiolate over nitro-compound is employed, most of the thiolate is oxidised to disulphide and nitro-group displacement is depressed. Formation of disulphide and reduction of the nitro-compound also occurs when *m*-dinitrobenzene reacts with an excess of thiolate ion in HMPA.[2] In this case, the poorly activated displacement of the second nitro-group is slow, as in the reaction of compound (**6**) with the t-butylthiolate ion. The radical anion-reduction pathway is thus able to compete.



Scheme 1

This work was funded by the I.C.I. Joint Research Scheme and by I.C.I. Organics Division.

Received, 19th March 1982; Com. 321

References

1 J. R. Beck, *Tetrahedron*, 1978, **34**, 2057.
2 P. Cogolli, L. Testaferri, M. Tingoli, and M. Tiecco, *J. Org. Chem.*, 1979, **44**, 2636.
3 F. Benedetti, D. R. Marshall, J. L. Leng, and C. J. M. Stirling, to be published.
4 B. A. Arbuzov, A. P. Timosheva, S. G. Vul'fson, and A. N. Vereschagin, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1976, 2007.

---

† We thank a referee for directing our attention to the work of J. F. Bunnett and J. D. Reinheimer (*J. Am. Chem. Soc.*, 1959, **81**, 315) in which it was shown that London dispersion forces favoured the attack of polarisable nucleophiles adjacent to methyl groups in aromatic substitution. The relevant reactivity enhancements were fairly small (*ca.* 4) but we propose to quantify their significance in the present reactions in future work. Surprisingly, the Bunnett-Reinheimer work has not been cited since 1963.