

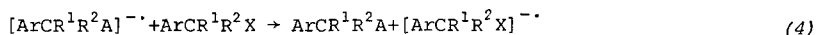
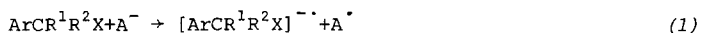
STERIC AND ELECTRONIC LIMITATIONS OF THE $S_{RN}1$ REACTION BETWEEN *p*-NITROBENZYLIC SUBSTRATES
AND TERTIARY CARBANIONS^{1,2}

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Summary: The $S_{RN}1$ reaction between sterically hindered *p*-nitrobenzyl substrates and tertiary carbanions gives *C*-alkylated products whose yields depend on the steric bulk of both the benzylic substrate and the carbanion, and on the nature of the groups in the carbanion.

The $S_{RN}1$ mechanism^{3,4} for substitution in *p*-nitrobenzyl substrates is given in equations (1)-(4).²



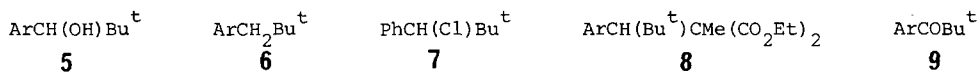
Our particular interest has been in the effect of steric hindrance on the rate and regiochemistry of this reaction. We have found that branching at the carbon α to the benzylic site can cause a reduction in the rate of dissociation of the radical anions from *p*-nitrobenzyl halides⁵ and also causes a change in the regiochemistry of association of *p*-nitrobenzyl radicals with *aci*-nitronate ions, from a *C*-alkylation to an *O*-alkylation process.⁶⁻⁹ Although guidelines for prediction of the regiochemistry of reaction with *aci*-nitronate ions have been published,⁹ no corresponding information has been presented for other potentially ambident nucleophiles. This hiatus and a recent report on the reaction of some α -functionalized derivatives of *p*-nitrobenzyl chloride with nucleophiles¹⁰ prompts us to report some observations on the utility and limitation of the $S_{RN}1$ reaction of the derivatives 1-4 with a variety of tertiary carbanions (see Table). These reactions proceed very smoothly in hexamethylphosphoramide (HMPA) at temperatures near 60°. The reaction times are appreciably shorter than for the corresponding reactions in dimethyl sulfoxide (DMSO). The reaction in expt 7, for example, is complete in 1.5 hours whereas in DMSO it was still incomplete after 11 days.⁷

The two main types of products¹¹ formed in the reactions reported in the Table were "C-alkylates", formally produced by replacement of the nucleofuge at the benzylic position by the tertiary carbanion, with formation of a C-C bond, and "reduced" products in which the nucleofuge has been replaced by hydrogen. Other products, usually in amounts less than 10%, were benzylic alcohols and other α -oxygenated compounds. The proportion of these compounds could be minimized by rigorous exclusion of oxygen from the solvents and nitrogen atmosphere during the

course of reactions. Even with these precautions, however, α -oxygenated derivatives sometimes were formed if the reaction mixtures were not quenched under a nitrogen atmosphere, with deoxygenated water. For example the reaction reported in expt 7 with all of the above precautions gave less than 2% of the alcohol 5. If the reaction mixture was quenched without exclusion of oxygen, however, 5-6% yields of the alcohol 5 and only trace amounts of the reduced compound 6 were obtained. It is quite possible that the conjugate bases of the reduced compounds, produced by the process in eqn (5) [cf. eqn (3)], are the species being oxidized.



The formation of the C-alkylation products in the reactions reported in the Table was shown to be the result of $S_{\text{RN}}1$ processes by the usual methods.^{3,4} Thus the reaction of chloro compound 7 did not give any C-alkylation products with any of the carbanions used in this work. When a reaction was carried out as described in expt 7 but with a stream of dry oxygen passing through the solution, formation of the C-alkylated product 8 was completely prevented. Instead,



after 3 hours, unchanged starting material 1 (2%), alcohol 5 (55%) and the ketone 9 (31%) were obtained. Compounds 5 and 9 had been isolated previously in a similar reaction of 1 but under nitrogen in DMSO.⁷ Their formation was attributed to incursion of O-alkylation processes,⁷ or to trapping of the intermediate benzylic radical by the sulfoxide-oxygen of DMSO.¹³ We now believe that compounds 5 and 9 arose, in the earlier experiment,⁷ from reaction with oxygen in the nitrogen supply.¹⁴

From the results presented in the Table, it can be seen that increasing the size of the alkyl groups attached to the benzylic or anionic carbons in the substrates causes substantial decreases in the proportions of C-alkylates formed. This is evident, for example, in the reactions of anions of α -alkylmalononitriles with 1 (expts 1-4) and 4 (expts 22-24). When alkyl groups are interchanged between the benzylic component and the carbanion, C-alkylation occurs to a similar extent (expts 3 and 14). The increasing steric demand in the series 2<1<3<4 is seen in their reactions with various α -alkylmalononitrile anions (expts 14, 4, 3, 17 and 24).

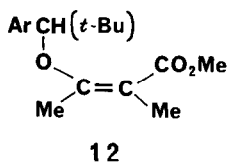
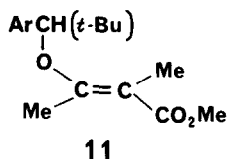
The electronic nature of the groups attached to the anionic carbon also effects the proportion of C-alkylate. Acetyl groups clearly disfavour C-alkylation processes (expts 11-13, 20 and 21). The amount of C-alkylate formed in the reaction of 1 with a series of α -methylated carbanions, in which steric interactions are reasonably similar (expts 1, 5, 7, 11-13), decreases when the stabilizing substituents on the carbanion are changed from cyano, to alkoxy-carbonyl to acetyl.

By way of contrast with the reaction of *p*-nitrobenzylic substrates with *aci*-nitronates,⁶⁻⁹ increasing the steric bulk of the carbanion and/or benzylic substrate does not in general lead to significant formation of O-alkylated material, but leads instead to formation of reduced products and/or highly polar intractable products. In only one of the reactions presented in the Table was direct evidence for occurrence of O-alkylation processes found. An inseparable mixture of the isomers 11 and 12 was isolated (in 7% yield) in expt 11.

TABLE : REACTION OF *p*-NITROBENZYLIC SUBSTRATES WITH TERTIARY CARBANIONS.^a

No.	Substrate (RX)		Expt No.	Time (h) ^b	Carbanion (A ⁻)	Products (%) ^c	
	R	X				C-Alkylate (RA)	Reduced (RH)
1	ArCH(Bu ^t)	Cl	1	0.5	Me(NC) ₂ C ⁻	>95	
			2	1.0	Et(NC) ₂ C ⁻	>95	
			3	2.0	<i>iso</i> -Pr(NC) ₂ C ⁻	59	2
			4	24	<i>tert</i> -Bu(NC) ₂ C ⁻	0	8
			5	0.5	Me(NC)(EtO ₂ C)C ⁻	92 ^d	
			6	10	<i>iso</i> -Pr(NC)(EtO ₂ C)C ⁻	36 ^d	14
			7	1.5	Me(EtO ₂ C) ₂ C ⁻	73	4
			8	6	Et(EtO ₂ C) ₂ C ⁻	54	5
			9 ^e	28	<i>iso</i> -Pr(EtO ₂ C) ₂ C ⁻	0	7
			10 ^e	48	<i>tert</i> -Bu(EtO ₂ C) ₂ C ⁻	0	9
			11	7	Me(Ac)(MeO ₂ C)C ⁻	2	45
			12	1.5	Me(Ac) ₂ C ⁻	0	56
			13 ^f	6	Me(Ac) ₂ C ⁻	0	76
2	ArCH(Pr ⁱ)	Cl	14	4	<i>tert</i> -Bu(NC) ₂ C ⁻	52	10
			15	14	<i>iso</i> -Pr(EtO ₂ C) ₂ C ⁻	0	
3	ArCMe(Pr ⁱ)	NO ₂	16	1	Et(NC) ₂ C ⁻	>90	2
			17	72	<i>iso</i> -Pr(NC) ₂ C ⁻	18	26
			18	7	Me(NC)(EtO ₂ C)C ⁻	31	10
			19	13	Me(EtO ₂ C) ₂ C ⁻	20	13
			20	20	Me(Ac)(MeO ₂ C)C ⁻	0	29
			21	24	Me(Ac) ₂ C ⁻	0	36
4	ArCMe(Bu ^t)	Cl	22	2.5	Me(NC) ₂ C ⁻	>90	
			23	4	Et(NC) ₂ C ⁻	73	
			24	26	<i>iso</i> -Pr(NC) ₂ C ⁻	0	40

^aReactions were carried out at 55-60°C with substrate (2.5 mmol) and the sodium salt (10.0 mmol) in hexamethylphosphoramide (10 ml) under a nitrogen atmosphere and with irradiation from a 500-W sunlamp placed 20 cm from the reaction vessel. ^bTime taken for complete disappearance of starting material (by t.l.c.). ^cYields were estimated by ¹H n.m.r. spectroscopy; isolated yields were normally within 15% of the estimated yields. ^dMixture of (separable) diastereoisomers. ^eEntrained by addition of lithium 2-nitropropan-2-ide (0.1-0.4 mmol). ^fIn hexamethylphosphoramide (20 ml).



Although this work shows that the $S_{\text{RN}}1$ reaction is prone to steric limitations, it should be stressed that most of the *C*-alkylated products obtained in this study are nevertheless extremely sterically congested molecules, whose preparation would be difficult by other methods. ^1H N.m.r. spectroscopy clearly indicates that rotation about the benzylic carbon-aromatic carbon bond in most of the *C*-alkylates is restricted. An analysis of the dynamics of this rotation process in these crowded molecules, by d.n.m.r. spectroscopy, is in progress.

FOOTNOTES and REFERENCES

1. This study was supported by a grant from the Australian Research Grants Scheme (to R.K.N.).
2. Throughout this paper, the abbreviation "Ar" is used to represent the $p\text{-O}_2\text{NC}_6\text{H}_4$ group.
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10. R. Beugelmans, A. Lechevallier, and H. Rousseau, *Tetrahedron Lett.*, **25**, 2347 (1984).
11. All new compounds gave satisfactory elementary analyses and had the expected spectroscopic (i.r., u.v., m.s. and ^1H n.m.r.) properties.
12. A similar process has been suggested when A^- is an *aci*-nitronate ion.⁹
13. N. Kornblum, P. Ackermann, and R.T. Swiger, *J. Org. Chem.*, **45**, 5294 (1980).
14. Also see footnote on p. 1488 in ref.⁷

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