ORGANIC LETTERS

2000
Vol. 2, No. 6
827−829

Aberrant S$_{\mathrm{RN}}$1 Reaction of 4-Aminophenol with α,*p*-Dinitrocumene: EPR Observation of Intermediates

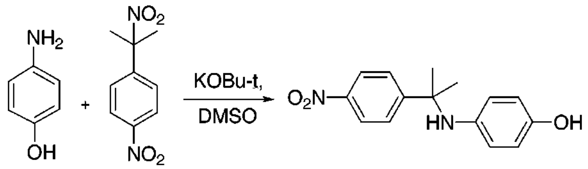
**Richard G. Scamehorn,[*,†,‡] Lisa A. Mahnke,[‡] Renee D. Krause,[‡] Brian L. Frey,[‡]
Deborah L. Hendriksen,[‡] Kelly S. Jahn,[‡] Steven G. Kultgen,[‡] and
John C. Walton[*,§]**

*Department of Chemistry, Ripon College, Ripon, Wisconsin 54971, and University of
St. Andrews, School of Chemistry, St. Andrews, Fife, United Kingdom KY16 9ST*

jcw@st-and.ac.uk

Received January 21, 2000

ABSTRACT



The *tert*-butoxide-induced substitution of α,*p*-dinitrocumene by 4-aminophenol unexpectedly afforded the N-coupled product, 2-(4-hydroxyanilino)-2-(4-nitrophenyl)propane. EPR observations revealed arylaminyl radical intermediates as well as coupled anion radicals, hence the normal S$_{\mathrm{RN}}$1 process may compete with an alternative nonchain reaction pathway.

Interest in the scope of electron transfer induced nucleophilic substitutions and in the factors controlling them has intensified recently due to imaginative exploitations of inter- and intramolecular versions of this reaction in new synthetic procedures.[1a−f] The substitution of NO$_2$ in α,*p*-dinitrocumene [2-nitro-2-(4-nitrophenyl)propane **1**] by sundry nucleophiles is regarded as a representative S$_{\mathrm{RN}}$1 process.[1,2] Kornblum and co-workers studied the reaction of **1** with carbon-centered nucleophiles, thiolate, CN$^-$, N$_3^-$, amines, and 1-methyl-2-naphtholate anion some time ago.[3,4] According to the orthodox S$_{\mathrm{RN}}$1 mechanism the process is initiated by electron transfer to **1**, followed by rapid and irreversible decomposition of the resulting radical anion **2** to give the 4-nitrocumyl radical (**3**) and nitrite ion. The key step is coupling of a nucleophile (ArO$^-$) with **3** to produce the radical anion of the substitution product (**4**). Rapid electron transfer from **4** to more **1** yields the substitution product **5** and generates a new α,*p*-dinitrocumene radical anion ready to propagate further chains (Scheme 1).

We found that a range of aryloxide nucleophiles **6a**−**e** reacted readily with **1** in DMSO to afford aryl ether type substitution products (**5**) together with some elimination product [2-(4-nitrophenyl)propene]. For example, 4-methoxyphenol reacted rapidly with **1** in the presence of KOBu-*t* (all 0.1 M) in DMSO in the dark at room temperature to produce **5b** (58%) plus 2-(4-nitrophenyl)propene (25%). We attempted to identify radical intermediates by using 9 GHz

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[†] scamehornr@mail.ripon.edu.

[‡] Ripon College.

[§] University of St. Andrews.

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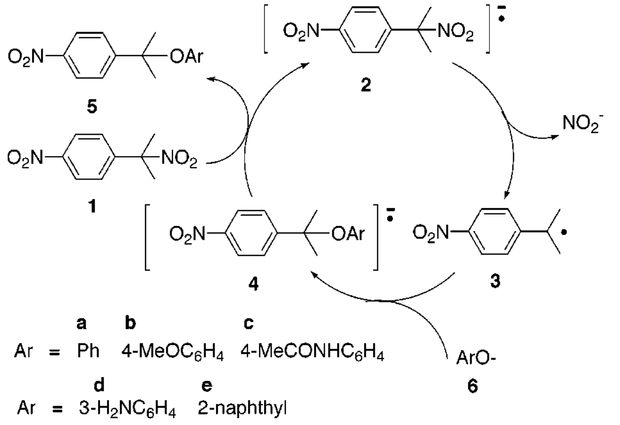
10.1021/ol005573v CCC: $19.00

Scheme 1. $S_{RN}1$ Reaction of Aryloxy Anions with α,*p*-Dinitrocumene



EPR spectroscopy. The reactants were mixed under nitrogen in a quartz capillary tube which was immediately placed in the resonant cavity of the spectrometer; however, no signals developed.

The *tert*-butoxide induced reaction of 4-aminophenol (**7**) with **1** was expected to produce the analogous ether product because the hydroxyl hydrogen is at least 10 p*K* units more acidic than the amino hydrogens.[5] Treatment of **1** and freshly purified 4-aminophenol with KOBu-*t*, under identical reaction conditions, led to a very rapid reaction from which 92% of the substitution and 3% of the elimination product were isolated. Surprisingly, however, the substitution product proved to be the amine **10** rather than the anticipated ether. In separate reactions carried out over times ranging from 60 s to 48 h, yields of **10** were always ≥ 85%. This indicated that **10** was inert under the reaction conditions.

When the reaction was monitored by EPR spectroscopy a well-resolved, although slightly anisotropic, spectrum was obtained immediately on mixing (within 60 s) which persisted for several hours before all signals disappeared. This spectrum contained two components and the major one was well matched by a computer simulation with the following hyperfine splittings (hfs): $a(\mathrm{N}) = 10.6$, $a(2\mathrm{H}) = 3.34$, $a(2\mathrm{H}) = 1.2$, $a(\mathrm{N}) = 1.2$ G (see Supporting Information). The EPR spectra of radical anions derived from nitrobenzene,[6] 4-nitrocumene,[7] and related nitroaromatics display hfs of very similar magnitudes for N and the two sets of ring hydrogens, and hence we assign our spectrum to the radical anion **9**. The fact that a small hfs from an additional N was observed confirmed that the nucleophile was attached via the NH group in the radical anion. Our EPR spectroscopic observations of such coupled radical anions during $S_{RN}1$ reactions in solution is unique, apart from three-line nitroxide spectra reported by Tamura et al.[8] Radical anions derived from 4-nitrocumyl and related systems by electron capture have been extensively studied by EPR spectroscopy at 77 K.[2d,9] To determine if spectra could be obtained by use of other N-centered nucleophiles, the *tert*-butoxide-promoted reaction of *p*-anisidine with **1** in DMSO was examined. A very similar EPR spectrum was obtained [$a(\mathrm{N}) = 10.2$, $a(2\mathrm{H}) = 3.3$, $a(2\mathrm{H}) = 1.0$, plus small unresolved hfs], which we attribute to an analogous coupled radical anion.

The lifetimes of both O-coupled (**4**) and the N-coupled (**9**) radical anions would probably be long enough for them to be spectroscopically detected. First, because the unpaired spin is localized in the nitroaromatic ring and second, because EPR spectra of many diverse persistent analogues, including nitroaromatic radical anions containing β-alkoxy substituents as well as β-aminyl substituents, have been reported.[10] The fact that only the N-coupled variety could be detected by EPR spectroscopy in our *tert*-butoxide-promoted reactions is most probably related to differences in their rates of formation. The relative reactivities of **6b** and **7** were estimated from competition experiments in which excess quantities of the two nucleophiles were reacted with **1** and the amounts of the two substitution products were determined. This showed that the 4-aminophenol (**7**) reacted more than 100 times as fast as 4-methoxyphenol. Relative reactivities determined competitively in this way are a measure of the relative rates of coupling of nucleophiles with the 4-nitrocumyl radical (**3**).[11,12,13] This coupling reaction is known to occur near the diffusion-controlled limit for many nucleophiles,[11,12] and hence the observed difference in reactivity suggests that the oxanion (**6b**) coupling with **3** may be much slower. This may account for the lack of EPR spectra with the oxanions.

There are several possible ways in which formation of product **10** and radical anion **9** could be accounted for. First, the initial oxanion **8** (Scheme 2) could be transformed to the N-centered tautomer by proton transfer and, although **8** will be in large excess, if the N-centered anion reacts much more rapidly with **3** this could explain the formation of **9**. If this possibility were correct, then it seems probable that the *m*-isomer **6d** should also yield N-coupled product; contrary to what was observed. Second, **9** could be formed by direct N-coupling of oxanion **8** and **3** followed by tautomerization. However, we are not aware of other examples of direct coupling of **8** through N according to this second possibility.[14] Third, **8** could couple with **3** to give the O-coupled product which then rearranges in some as yet unknown way to afford **9**. This seems unlikely because there is no evidence of O-coupled products being unstable, and none was detected in reactions carried out over times ranging from 1 min to 48

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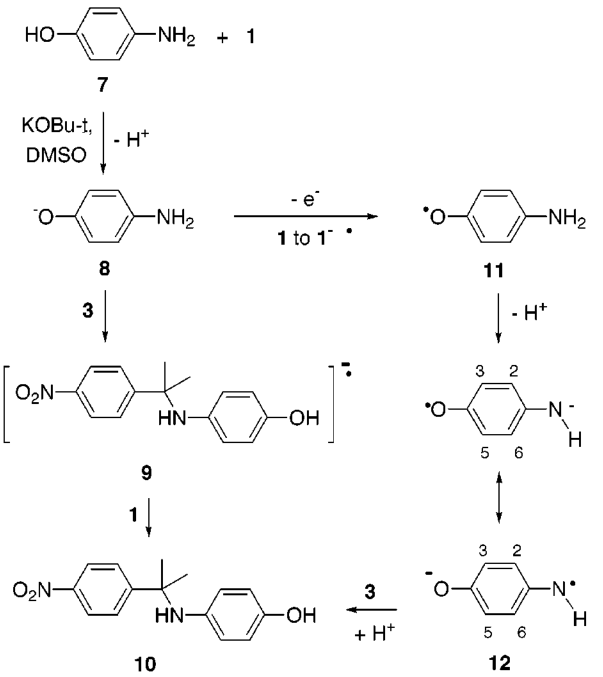
[14] Treatment of **8** with acetic anhydride under these reaction conditions gave only O-acetylation products.

h. Fourth, N-coupled product **10** might be produced by a different route and then transformed to **9** by electron transfer (see below and Scheme 2).

Scheme 2. Mechanisms for the Substitution of α,*p*-Dinitrocumene by 4-Aminophenol



On mixing 4-aminophenol (**7**) (5 μmol) with *tert*-butoxide (6 μmol) in DMSO (30 μL), in the absence of **1**, the well-resolved EPR spectrum shown in the figure was obtained at room temperature. Computer simulation using the hfs recorded in Table 1 produced good correspondence with experiment (see Figure 1). The hfs are similar to those of related monoarylaminyl radicals,[15] and hence we attribute this spectrum to phenoxide−aminyl radical **12** formed from **7** by deprotonation and loss of a hydrogen atom.

Table 1. EPR hfs of 4-Phenoxide−Aminyl Radical **12** in DMSO at 300 K Compared with Ab Initio B3LYP Computed hfs

hfs/G	N	(N)H	H(2)	H(6)	H(3)	H(5)
exp	6.2	±9.5	±3.4	±3.4	±1.01	±0.84
B3LYP	9.4	−11.2	−3.4	−3.2	−1.79	−0.96

Ab initio DFT computations [B3LYP with a 6-31G* basis set] indicated a planar ground-state structure for **12** with the N−H group in the same plane as the ring. This asymmetry of the structure explains the nonequivalent ring hydrogens, as revealed by the two small H-hfs (Table 1). The computed hfs were in reasonable accord with experiment (Table 1). The computations also showed the charge to be almost equally distributed between the O and N atoms.

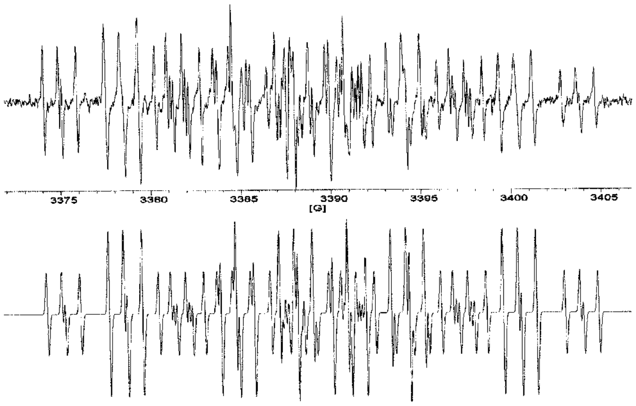


Figure 1. (Upper panel) 9.5 GHz EPR spectrum obtained from 4-aminophenol and KOBu-*t* in DMSO at 290 K in the dark, under N_2 and (lower panel) computer simulation with the hfs recorded in Table 1 and $\Delta H_{pp} = 0.11$ G.

It is highly probable therefore that some radicals **12** were generated during the *tert*-butoxide-mediated reaction of 4-aminophenol with **1**. Combination of radical **12** with the 4-nitrocumyl radical (**3**) will lead to formation of the anion of **10** and hence this offers an alternative, rapid, nonchain route to the coupled product, which may compete with the normal $S_{RN}1$ route (Scheme 2). The fact that the radical anion **9** was spectroscopically observed might indicate that reaction via radical **12** was minor.

Alternatively, however, the nonchain process in which oxanion **8** loses an electron to give phenoxyl radical **11**, which deprotonates to yield resonance-stabilized radical anion **12**, could be a major reaction channel. Loss of a proton from **11** is expected to be very rapid, as is coupling of **12** with the 4-nitrocumyl radical (**3**). In the absence of **1** radical anion **12** might form by electron transfer from **8** to the solvent, or possibly by a disproportionation.

The base-induced substitution of α,4-dinitrocumene by 4-aminophenol unexpectedly occurs via nitrogen, much more rapidly than with other phenols. The EPR observation of arylaminyl radical **12** as well as the coupled radical anion **9** suggested that the normal $S_{RN}1$ process may be accompanied by, if not replaced by, an alternative path embodying combination of phenoxide-aminyl **12** with the 4-nitrocumyl radical.

Acknowledgment. We thank the EPSRC (grant GR/L49185), NSF (grants CHE-9724425 and 8418622), and the ACM Minority Scholars Program for financial support.

Supporting Information Available: General experimental procedure for a typical $S_{RN}1$ reaction; specific experimental details, characterization data, and NMR spectra for the reactions of **6b** and **7** with **1**; and sample EPR spectrum for radical anion **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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