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Synthesis of Polynitroxides Based on Nucleophilic Aromatic Substitution

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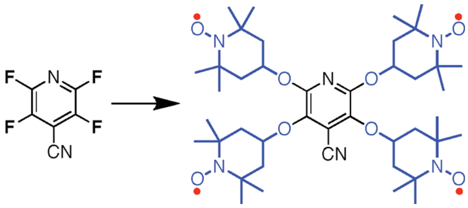
ABSTRACT



The scope and limitations of the synthesis of polynitroxides by nucleophilic substitution of electron-deficient fluorinated aromatic compounds are described. The method provides a facile route to the formation of polynitroxides exhibiting strong electron exchange between nitroxide groups.

Nitroxides are stable, persistent free radicals that are important materials in many fields of science and technology as a result of their electron spin and/or redox properties. For example, nitroxides have been employed as organic ferromagnets, as contrast agents in nuclear magnetic imaging, as labels in electron magnetic resonance imaging, and as radiation protectors during whole brain radiotherapy.[1] We have been interested in the ESR properties of polynitroxides for some time.[2] The ESR properties of polynitroxides differ from those of mononitroxides if sufficient electron spin−electron spin exchange occurs between two or more of the nitroxide moieties. In particular, nitroxides have shown potential use as paramagnetic relaxation agents.[3] The strength of paramagnetic relaxation is proportional to the concentration of magnetic species. In addition, for polynitroxides, the paramagnetic enhancement will depend not only on the concentration of individual molecules but also on the number of nitroxides that are involved in spin−spin interactions. For example, a bis-nitroxide might behave as two independent spin 1/2 species (two doublets) in the same molecule or as a coupled spin 1 species (a triplet). Which situation applies depends on the distance between the unpaired electrons. Recently, polynitroxides have been employed as electron spin agents for dynamic nuclear polarization (DNP) experiments in which the sensitivity of NMR signals has been shown to be enhanced by orders of magnitude.[4] It occurred to us that there was a need for a convenient, general and efficient synthesis of polynitroxides of broad scope that would allow examination of their structure-relaxation agent or structure-DNP agent properties. We report a strategy, along with its scope and limitations, for

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(1) (a) Kovarski, A. L.; Sorokina, O. N. *J. Magn. Magn. Mater.* **2007**, *311*, 155. (b) Crayston, J. A.; Devine, J. N.; Walton, J. C. *Tetrahedron* **2000**, *56*, 7829. (c) Hyodo, F.; Soule, B. P.; Matsumoto, K.; Matsumoto, S.; Cook, J. A.; Hyodo, E.; Sowers, A. L.; Krishna, M. C.; Mitchell, J. B. *J. Pharm. Pharmacol.* **2008**, *60*, 1049. (d) Fuchs, J.; Groth, N.; Herrling, T. *Biol. Magn. Reson.* **2003**, *18*, 483. (e) Metz, J. M.; Smith, D.; Mick, R.; Lustig, R.; Mitchell, J.; Cherakuri, M.; Glatstein, E.; Hahn, S. M. *Clin. Cancer Res.* **2004**, *10*, 6411.

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the synthesis of polynitroxides based on nucleophilic aromatic substitution reactions of fluorinated aromatic substrates **1**−**8** shown in Figure 1.

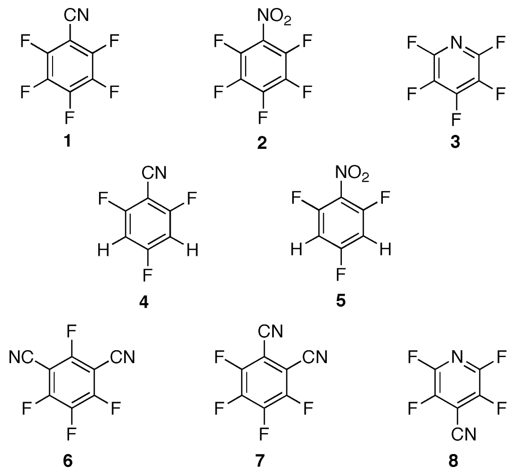
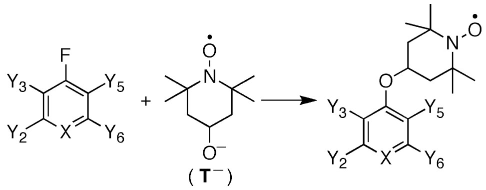


Figure 1. Fluorinated core structures.

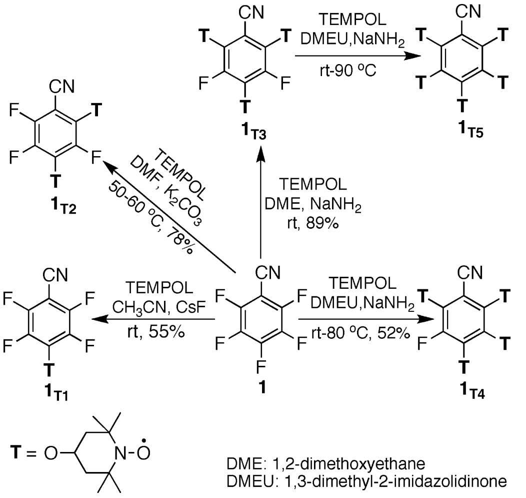
Nucleophilic Substitution of Fluorinated Aromatic Compounds. Fluorinated aromatics possessing strong electron-withdrawing substituents are very reactive toward substitution of the fluorine atom by nucleophiles.[5] Thus, as shown in eq 1, a strategy for the synthesis of polynitroxides involves the use of electron-deficient fluorinated aromatics, such as those in Figure 1, through the substitution of fluorine by the alkoxide anion ($\mathbf{T}^-$) of the mononitroxide, 4-hydroxy-2,2,6,6-tetramethylpiperidine oxide (TEMPOL). The hydroxyl group of TEMPOL is readily converted into the corresponding 4-alkoxide anion ($\mathbf{T}^-$) under basic conditions. In eq 1, the activation for the substitution of fluorine can be provided by an electron-deficient aromatic benzene nucleus (e.g., X = C-CN or C-NO$_2$) or an electron-deficient heteroatom nucleus (e.g., X = N). The Y$_n$ groups in eq 1 can be either potentially substitutable F atoms or further electron-withdrawing groups (e.g., X = C-CN or C-NO$_2$). Other possibilities are shown in Figure 1, which shows the electron-deficient aromatic “cores” selected for this investigation. A set of variations of the core structures **1**−**3** were selected to test the scope of the polynitroxide syntheses. In structures **4** and **5** two fluorine atoms are replaced by hydrogen atoms. In structures **6**−**8** a second electron-withdrawing group (CN) is added to the core.



(1)

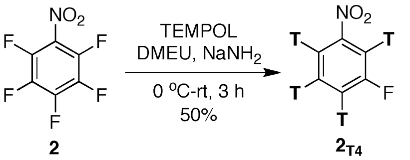
This strategy is of wide scope and flexibility because of the structural variations provided by the X and Y groups associated with the aromatic ring in the generalized substrate of eq 1. Thus, we anticipated that nucleophilic aromatic substitution by $\mathbf{T}^-$ could replace up to five fluorine atoms with nitroxide groups along with mono-, bis-, tris-, and tetra-nitroxides not only as intermediates but also as plausibly synthesizable targets under the proper reaction conditions.

Scheme 1. Preparation of Nitroxides from Fluorinated Core **1**

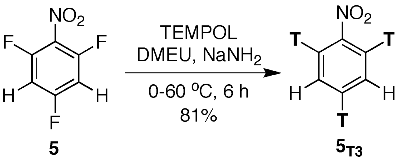


Preparation of Nitroxides from Aromatic Fluorinated Cores. Scheme 1 summarizes the results of nitroxide syntheses with the core aromatic **1** possessing a cyano electron-withdrawing group (Figure 1) as a starting material. Under appropriately controlled reaction conditions, it was possible to synthesize the mononitroxide $\mathbf{1_{T1}}$, the bis-nitroxide $\mathbf{1_{T2}}$, the tris-nitroxide $\mathbf{1_{T3}}$, and the tetra-nitroxide $\mathbf{1_{T4}}$ in moderate to high yields. However, the corresponding penta-nitroxide $\mathbf{1_{T5}}$ could only be synthesized in low yield using $\mathbf{1_{T3}}$ as a starting material.

The results of other attempts to completely substitute fluorine atoms by nitroxide groups are shown in eqs 2−7. From core aromatic **2** possessing a nitro electron-withdrawing group, the tetra-nitroxide $\mathbf{2_{T4}}$ was synthesized in acceptable yield (50%, eq 2).



(2)



(3)

Evidently steric and possibly electronic effects considerably hinder the substitution of the fifth F atom at the mild

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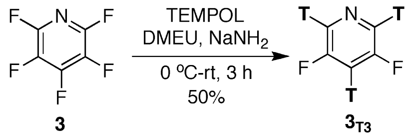
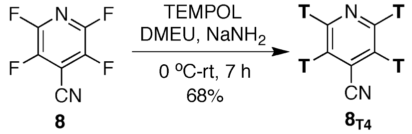
[5] Chambers, R. D.; Hassan, M. A.; Hoskin, P. R.; Kenwright, A.; Richmond, P.; Sandford, G. *J. Fluorine Chem.* **2001**, *111*, 135.

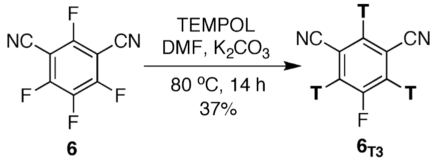
temperatures selected as model conditions for the nitroxide synthesis. In particular, steric hindrance for substituting the fifth F atom of **1** and **2** is confirmed in the case of **5**, in which all three F atoms were substituted to produce the tris-nitroxide $\mathbf{5_{T3}}$ in very good yield (81%, eq 3).



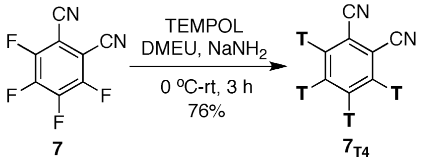
(4)



(5)



(6)

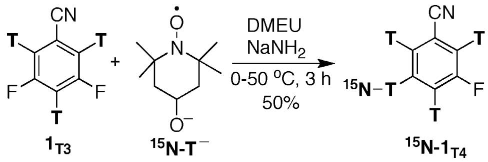


(7)

The scope of the polynitroxide synthesis is demonstrated with the perfluorinated pyridine **3** as a starting material. The tris-nitroxide $\mathbf{3_{T3}}$ was formed in moderate yield (50%, eq 4). In the case of **8**, a pyridine that possesses a second electron withdrawing group (CN) in the 4 position, the tetra-nitroxide $\mathbf{8_{T4}}$ was produced in good yield (68%, eq 5).

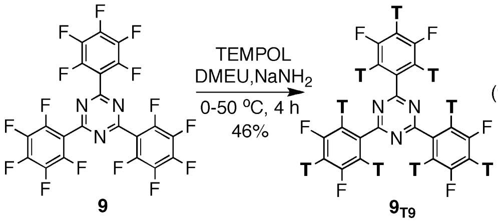
Finally, in the case of the tetrafluorinated structures **6** (eq 6) and **7** (eq 7) possessing two electron-withdrawing groups, the tris-nitroxide $\mathbf{6_{T3}}$ and tetra-nitroxide $\mathbf{7_{T4}}$ were produced, respectively.

The selectivity in the nucleophilic substitution allows for targeted spin labeling of a specific position on the aromatic core with an ^{15}N isotope of **T**. For example, the partly substituted compound $\mathbf{1_{T3}}$ was synthesized at mild temperatures (Scheme 1) followed by substitution of one of the remaining F-atoms with an isotope labeled ^{15}N-T$^-$ at elevated temperatures, which yields a tetra-nitroxide with three ^{14}N nitroxides and one ^{15}N nitroxide ($\mathbf{^{15}N\text{-}1_{T4}}$, eq 8).



(8)

As an extension of the syntheses the method was employed to use 2,4,5-tri(pentafluorophenyl)-triazine **9** as a core, which possesses 15 potentially displaceable F atoms. If nine F atoms were substituted, then a nona-nitroxide, $\mathbf{9_{T9}}$, would be produced (eq 9). The formation of $\mathbf{9_{T9}}$ was confirmed by mass spectrometry.



(9)

Characterization of the Nitroxides. The structures of the nitroxides reported were established by a combination of mass spectrometry, ^{19}F NMR spectroscopy, and EPR spectroscopy. In the case of $\mathbf{1_{T1}}$, $\mathbf{1_{T2}}$, $\mathbf{1_{T3}}$, and $\mathbf{8_{T4}}$, the structures were also determined by single crystal X-ray diffraction, as illustrated for

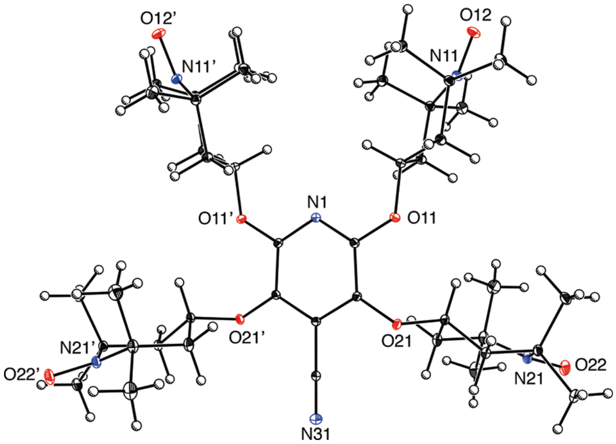


Figure 2. Molecular structure of $\mathbf{8_{T4}}$ as determined by single crystal X-ray diffraction.

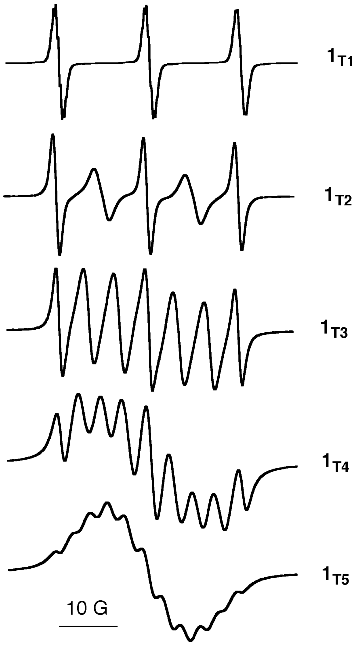


Figure 3. EPR spectra of $\mathbf{1_{T1}}$−$\mathbf{1_{T5}}$ in deoxygenated CHCl$_3$ at room temperature.

$\mathbf{8}_{\mathbf{T4}}$ in Figure 2. Of note, all of the hydrogen atoms were located, and there was no residual electron denisty comparable to that of a hydrogen atom in the vicinity of the oxygen atoms, which thereby provides evidence for the nitroxide formulation. Further evidence for the nitroxide nature of the compound is provided by the fact that there are no short intermolecular oxygen contacts that would have otherwise been expected if there were hydroxy groups present.

A point of considerable interest in the EPR of polynitroxides is the extent of electron spin−spin interactions. If the nitroxide groups of a polynitroxide are significantly coupled by electron exchange, the number of lines in the EPR spectrum is expected to be $2N + 1$, where N is the number of electron exchange coupled nitroxides in the molecule.[6] All of the EPR spectra obtained for the polynitroxides described above were consistent with the $2N + 1$ rule. The EPR spectra of $\mathbf{1}_{\mathbf{T1}}$−$\mathbf{1}_{\mathbf{T5}}$ are shown in Figure 3 as examples. A detailed and quantitative analysis of the EPR spectra of the nitroxides reported here will be the subject of another manuscript.

In summary, we report a direct synthetic procedure employing nucleophilic aromatic substitution for the preparation of polynitroxides starting with the fluorinated cores **1**−**9**. The scope and limitations of the synthetic strategy is elucidated. In general, the yields of polynitroxides are good, except for replacing a final sterically hindered fluorine substituent.

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Supporting Information Available: Synthetic procedures and analysis, and CIF files for X-ray diffraction studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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