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Formation of β-fluorinated aminoxyl radicals from *N*-arylketonitrones

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The reaction of XeF_2 with several *N*-aryl-*C*,*C*-dialkoxycarbonylnitrones affords *N*-aryl-β-fluorinated aminoxyl radicals in solution by an inverted spin trapping mechanism.

Three different pathways are known to produce aminoxyl radicals from nitrones: (1) spin trapping, in which a transient free radical adds to the double bond of the nitrone;[1–3] (2) the so-called Forrester–Hepburn mechanism, in which a hydroxylamine formed after a nucleophilic attack of the nitrone is oxidised[4] and (3) inverted spin trapping, in which a nitrone can be oxidised to its radical cation, which further reacts with a nucleophile.[5,6] The third mechanism has been used to produce β-fluorinated aminoxyl radicals.[5,7–9] When this method was applied to aldonitrones, it generally resulted in the formation of a mono-fluorinated aminoxyl radical, which was rapidly converted into a difluorinated compound upon standing.[5,7] On the other hand, Grigor'ev and coworkers[8,9] have prepared stable fluorinated aminoxyl radicals bearing an amino group by treatment of cyclic ketonitrones with xenon difluoride. Recently, the synthesis of *N*-aryl-*C*,*C*-dialkoxycarbonylnitrones was performed and their reactivity towards various free radicals was studied by electron spin resonance (ESR) spectroscopy, this paper reporting the very first use of linear ketonitrones as spin trapping agents.[10] To proceed with the study of this class of compounds, we investigated the reactivity of ketonitrones **1**–**7** towards the fluorinating agent XeF_2. The expected reaction, *i.e.*, oxidation of the nitrone by XeF_2 to its radical cation followed by the nucleophilic addition of the fluoride ion, should yield ESR-detectable aminoxyl radicals **8**–**14** bearing a fluorine atom in the β-position towards the nitrogen nucleus (Scheme 1).

Ketonitrones **1**–**7** were synthesised, purified and identified according to methods described previously.[10] Treatment of **1**

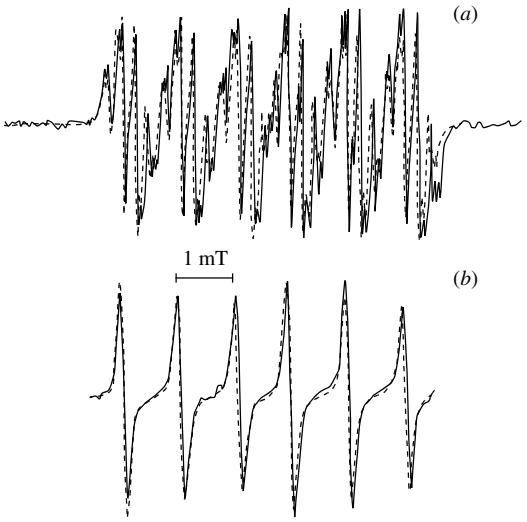
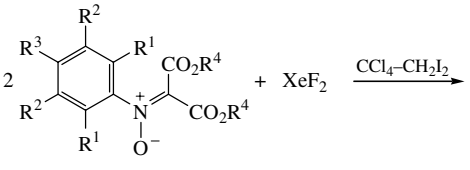


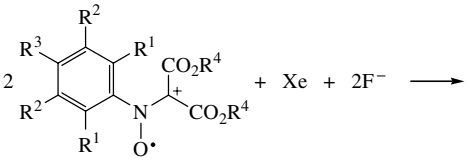
Figure 1 Experimental X-band ESR spectra (solid lines) of aminoxyl radicals (*a*) **8** and (*b*) **13** recorded in CCl_4–CH_2I_2, and their superimposed simulations (dotted lines) obtained using the hfcc listed in Table 1. The ESR instrument settings were as follows: non-saturating microwave power, 20 mW; modulation amplitude, 0.05 mT; receiver gain (*a*) 2.52×10^6 or (*b*) 2×10^5; time constant, (*a*) 81.92 ms or (*b*) 40.96 ms; scan time, (*a*) 42 s or (*b*) 21 s; scan width, (*a*) 9 mT or (*b*) 6 mT; 1 scan.

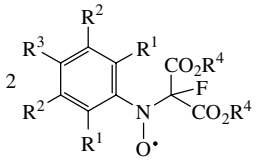
(84.3 mmol dm^{-3} in deoxygenated CCl_4) with an excess of XeF_2 (2.2 mol dm^{-3} in deoxygenated CH_2I_2) produced a very intense ESR spectrum of **8** [Figure 1(*a*)]. Upon standing, this signal kept growing over 30 min and then slowly diminished for *ca.* 1 h. This ESR spectrum, shown in Figure 1(*a*) along with its superimposed simulation, is rather complex. It mainly consists of a doublet of triplets due to hyperfine couplings with the nitrogen and fluorine nuclei, splitted by hyperfine couplings with five aromatic hydrogens. The hyperfine coupling constants



ketonitrone

1–7





aminoxyl radical

8–14

1, **8** $R^1 = R^2 = R^3 = H$, $R^4 = Me$
2, **9** $R^1 = R^2 = R^3 = H$, $R^4 = Et$
3, **10** $R^1 = R^2 = H$, $R^3 = CO_2Me$, $R^4 = Me$
4, **11** $R^1 = R^2 = H$, $R^3 = NMe_2$, $R^4 = Et$
5, **12** $R^1 = H$, $R^2 = R^4 = Me$, $R^3 = OMe$
6, **13** $R^1 = R^2 = R^3 = D$, $R^4 = Me$
7, **14** $R^1 = R^2 = R^3 = D$, $R^4 = Et$

Scheme 1 Synthesis of aminoxyl radicals by inverted spin trapping upon treatment of ketonitrones **1–7** with XeF_2. The formation of aminoxyl radicals **11** and **12** was not observed under these conditions.

Table 1 ESR hyperfine coupling constants of aminoxyl radicals **8–10** and **13–14** in CCl_4–CH_2I_2 (1:1).

Aminoxyl radical	a_N/mT	a_F/mT	a_{Hm}/mT	$a_{Ho,p}$/mT
8	1.06	2.89	0.08 (2H)	0.22 (3H)
9	1.00	2.89	0.08 (2H)	0.23 (3H)
10	0.94	2.70	0.09 (2H)	0.23 (2H)
13	1.01	2.91	—	—
14	1.01	2.93	—	—

(hfcc) a_F, a_N, $a_{Ho,p}$ and a_{Hm}, determined after ESR simulation of this signal using the program elaborated by Duling,[11] are given in Table 1. Contrary to what was observed with aldonitrones such as benzylidene(*tert*-butyl)azane oxide (PBN),[7] aminoxyl radical **8** lacks a hydrogen in the β-position toward the nitrogen, and that precludes the possibility of further oxidation to a difluorinated radical. In addition, this excludes a disproportionation reaction, which often intervenes in the decay of aminoxyl radicals formed from aldonitrones.

The same procedure was then applied to ketonitrones **2** and **3**, thereby leading to aminoxyl radicals **9** and **10**. In each case, the ESR spectral pattern revealed hyperfine couplings with nitrogen (a_N in the range 0.94–1.01 mT), fluorine (a_F in the range 2.70–2.93 mT) and aromatic hydrogen ($a_{Ho,p}$ in the range 0.22–0.23 mT and a_{Hm} in the range 0.08–0.09 mT) nuclei (Table 1). As expected, the ESR spectrum of **9** is almost identical to that of **8**. The ESR spectrum of **10** is simpler because of the lack of a proton in the *para* position and shows lower a_N and a_F values. In this case, the ESR signal observed remains very intense, whereas ketonitrones **4** and **5**, upon treatment with XeF_2, never afforded radicals **11** and **12**. Thus, the presence of an electron-withdrawing *para* substituent on the ketonitrone phenyl ring does not hamper the inverted spin trapping reaction from happening, whereas an electron-donating *para* substituent, such as dimethylamino or methoxyl groups, renders the nitrone oxidation to a radical cation much harder. A thorough examination of published data showed that the only *N*-aryl-β-fluorinated aminoxyl radical ever described to date is {(3,5-di-*tert*-butylphenyl)[2-ethoxy-1-(ethoxycarbonyl)-1-fluoro-2-oxoethyl]amino}oxidanyl radical.[12] This compound was not isolated, but it was transiently observed by ESR spectroscopy when a benzene solution containing diethyl fluoromalonate and 3,5-di-*tert*-butylnitrosobenzene was treated with lead tetraacetate. The hfcc reported for this radical, *i.e.*, $a_N = 1.01$ mT, $a_F = 3.00$ mT and $a_{Ho,p} = 0.23$ mT, are consistent with those given in Table 1 for **8–10**.

Upon reactions of pentadeuterated nitrones **6** and **7** with XeF_2, aminoxyl radicals **13** and **14** were also formed, as observed by ESR spectroscopy [Figure 1(*b*), Table 1]. They showed much simpler ESR spectra consisting of six lines of equal intensities, because of the lack of aromatic hydrogen nuclei. Surprisingly, radicals **13** and **14** were found to decay much more slowly than their non-deuterated analogues **8** and **9** under the same experimental conditions, though at the moment we have no hypothesis to explain this result. The hfcc a_N and, notably, a_F determined from ESR spectra of **13** and **14** were found fairly sensitive to the radical environment. For instance, these hfcc for **14** were $a_N = 1.01$ mT and $a_F = 2.93$ mT in CH_2I_2–CCl_4 (1:1), and $a_N = 0.99$ mT and $a_F = 2.77$ mT in CH_2Cl_2. Similar phenomena were previously observed for stable and persistent β-phosphorated aminoxyl radicals. In this case, the existence of a strong hyperfine coupling with the phosphorus nucleus, very sensitive to the radical conformation, was shown to allow a better and easier localization of the radical in water–micelle or water–liposome media.[13–15] Such a variation in the large hfcc a_F of β-fluorinated aminoxyl radicals could thus be an important advantage for potential applications as spin probes for studies in complex heterogeneous media.[16]

In summary, the reaction of *N*-aryl-*C*,*C*-dialkoxycarbonylnitrones with xenon difluoride allowed us to generate acyclic persistent β-fluorinated aminoxyl radicals by inverted spin trapping, though this synthesis was unsuitable for nitrone substrates bearing an electron-donating substituent in the *para* position on the phenyl ring.

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