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^{1}H NMR aided elucidation of products derived from photodegradation of ethyl 3-azido-4,6-difluorobenzoate in 2,2,2-trifluoroethanol

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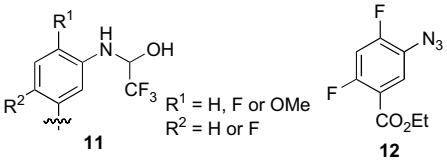
ABSTRACT

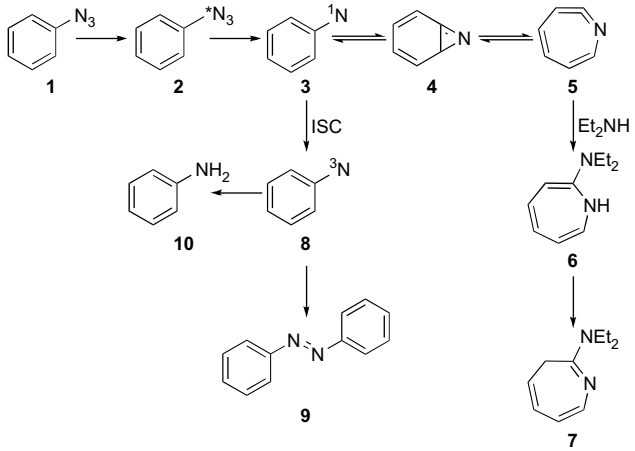
The major products formed upon photolysis of ethyl 3-azido-4,6-difluorobenzoate in 2,2,2-trifluoroethanol-d_3 has been elucidated by ^{1}H NMR analysis of the product mixture. Among the products formed and structurally elucidated was a hitherto unreported product formed during photolysis of aryl azides, namely azoxybenzene **19**. The structural assignments of the major components of the reaction mixture were aided by comparison with ^{1}H NMR data from synthetic reference materials and compound isolation. MS, MS/MS, and HPLC analysis as well as UV spectroscopy was also employed in order to confirm and aid the structural analysis.

1. Introduction

The photodegradation of aryl azides has been extensively examined over the last 80 years.[1] It is commonly understood that upon irradiation with UV light phenyl azide **1** is converted to singlet phenylnitrene **3** with the loss of N_2 via excited azide **2** (Scheme 1).[2] At temperatures above 165 K phenylnitrene **3** rapidly ring-expands via benzazirine **4** to ketenimine **5**.[3] Intermediate **5** can be trapped by the addition of diethylamine, thus forming the corresponding 2-diethylamino-1*H*-azepine **6**, which quickly rearranges to 2-diethylamino-3*H*-azepine **7**.[4] At moderate concentrations and in the absence of a suitable trapping agent ketenimine gives predominantly polymeric tar.[5] At temperatures below 165 K intersystem crossing (ISC) dominates generating triplet phenylnitrene **8** from singlet phenylnitrene **3**, which can dimerize in order to form the corresponding azobenzene **9** or the corresponding aniline **10** via photoreduction.[6]



11 **12**



Scheme 1. Mechanism for the photodegradation of phenyl azide and some of the products formed when conducted in the presence of diethylamine.

Recently we reported that hemiaminal **11** (general structure shown) was formed when a range of aryl azides, non-fluorinated or fluorinated [including ethyl 3-azido-4,6-difluorobenzoate (**12**)], was irradiated with a high-pressure mercury lamp (350 nm) at ambient temperature in 2,2,2-trifluoroethanol (TFE) at a concentration of 2.0 mM.[7] The structural assignment in the previous work was predominantly conducted by using nano-LC-ESI-Q-TOF-MS and -MS/MS. In the work presented herein the photolysis of aryl azide **12** was performed at a much higher concentration (13.75 mM) enabling the reaction to be monitored by ^{1}H NMR spectroscopy.

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2. Results and discussion

Photolysis of a 13.75 mM degassed (degassed by sonication) solution of ethyl 3-azido-4,6-difluorobenzoate (**12**) in 2,2,2-trifluoroethanol-d_3 (TFE-d_3) contained in a Pyrex NMR tube (no additional filter was used) with a low-pressure mercury lamp (254 nm) at ambient temperature resulted in the formation of at least five products. In order to aid assignment of signals in the ^{1}H NMR spectra of the reaction mixture as well as in the HPLC chromatograms we prepared synthetic samples of products known from previously to be formed during photolysis of aryl azide **12**.[7] The compounds we decided to prepare were azobenzene **13** and hydrazine **14**. In addition we had a sample of the corresponding aniline **15**, viz. ethyl 3-amino-4,6-difluorobenzoate, from our previous work.

2.1. Synthesis of reference material

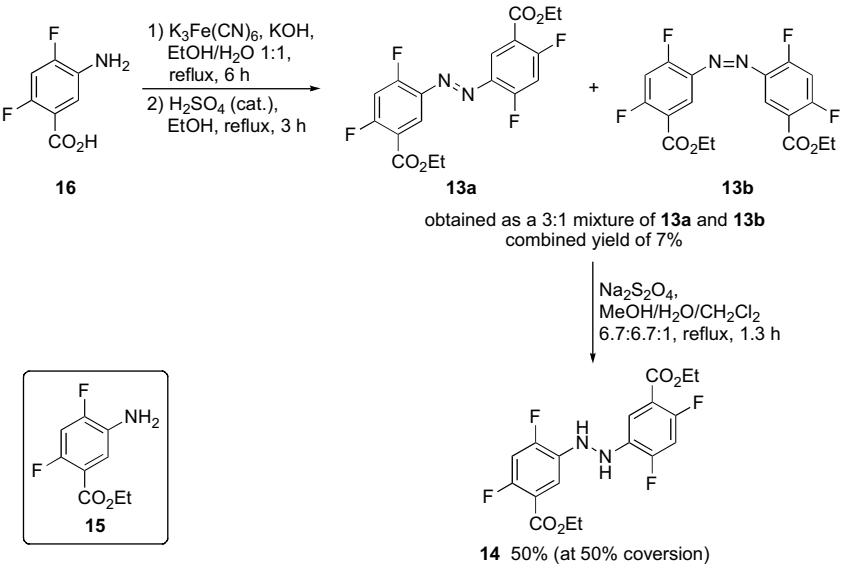
We found azobenzene **13** to be a rather difficult compound to prepare due to the fact that several of the potential starting materials are activated toward S_NAr reactions. However, after some experimentation we were able to obtain the desired substrate, although in poor yield, by using a method reported by Leyva and co-workers[8] To this end, aniline **16** was treated with potassium ferricyanide [$K_3Fe(CN)_6$] and potassium hydroxide in ethanol/water (1:1), thus forming azobenzene carboxylic acid, which was directly converted to the corresponding ethyl ester prior to column chromatography. Concentration of the relevant fractions gave a 3:1 mixture of the *E* and *Z* isomer of azobenzene, viz. compounds **13a** and **13b**, respectively, in a combined yield of 7% (yield not optimized) (Scheme 2). The major isomer was assigned to be the *E*-isomer based on literature precedent stating that generally the *E*-isomer is the most stable of the two possible isomers.[9] Part of the aforementioned mixture was then converted to the corresponding hydrazine **14** upon exposure to sodium dithionite in water/methanol/dichloromethane 6.4:6.4:1 at reflux by using a method reported recently by Sydnes and co-workers.[10] By such means compound **14** could be obtained in 50% yield at 50% conversion (yield not optimized). Although the yield of **13a** and **13b** was low it still provided us with sufficient amount of material for our purpose.

2.2. Photolysis

With the reference data in hand work could shift toward the photolysis experiments. A 13.75 mM degassed solution (degassed by sonication) of ethyl 3-azido-4,6-difluorobenzoate (**12**) in TFE-d_3 was irradiated with a low-pressure mercury lamp in a Pyrex NMR tube (no additional filter was used during these experiments). The reaction was monitored by conducting ^{1}H NMR experiments after 2, 4, 6, 8, 10, 14, 18, 22, and 26 min. Simultaneously samples for analytical HPLC analysis were collected and frozen on dry ice. These samples were analyzed shortly thereafter. From the ^{1}H NMR spectra and HPLC chromatograms we could see that the concentration of the products slowly increased until ca. 18 min and then leveled off.

The ^{1}H NMR spectrum and HPLC chromatogram after 26 min irradiation showed that there was significant amount of unreacted starting material left in the reaction mixture. Further irradiation of the solution did not increase the conversion of the starting material. Most likely due to the dark color of the reaction mixture functioning as a filter, thus blocking out most of the light. Based on the data for the reference material of azobenzenes **13a** and **13b** we could easily determine that both *E*- and *Z*-azobenzene were formed during the photolysis (see Figs. 1 and 2). We could also conclude that hydrazine **14** was not formed under these conditions. This conclusion was based on the fact that we could not see a triplet in the ^{1}H NMR spectrum at 7.49 ppm and no signal in the HPLC chromatogram at t_R 9.62 min [HPLC conditions: Develosil ODS-UG-5 (4.6×250 mm i.d.), CH_3CN/H_2O 4:1, 0.5 mL/min]. The fact that compound **14** was not formed in this work, but was formed in our previous work[7] could be due to a concentration effect and/or an effect due to the change of light source (350 nm→254 nm). In our previous work the photolysis was conducted predominantly with a high-pressure mercury lamp and with a sample concentration of 2.0 mM.

The product in the reaction mixture with t_R 9.51 min was assigned to be hemiaminal **17** based on its UV spectrum obtained by HPLC analysis. The UV spectrum of compound **17** (Fig. 3A) is very similar to the UV spectrum we obtained for hemiaminal **18** (Fig. 3B) in our previous work.[7] In our previous work the structure of compound **18** was securely proved by ESI-Q-TOF-MS and -MS/MS including proton/deuterium (H/D) exchange experiments followed by MS and MS/MS analysis.[7] We therefore assign the structure as



Scheme 2. Synthesis of azobenzene **13** and hydrazine **14** and the structure of aniline **15**.

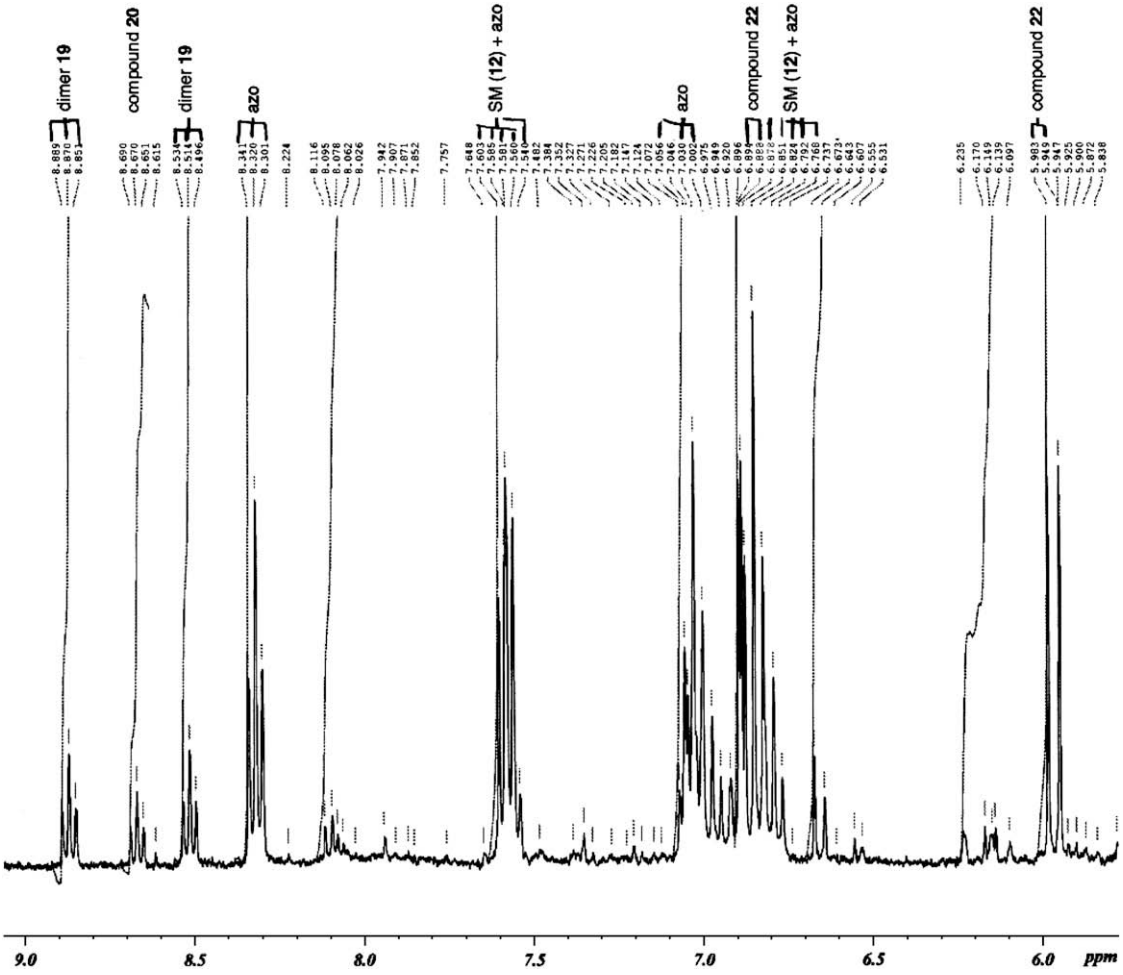
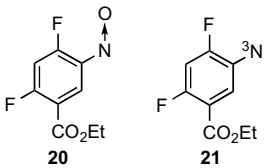


Figure 1. ^{1}H NMR spectrum (9.0–5.8 ppm) obtained after 26 min irradiation of a 13.75 mM solution of ethyl 3-azido-4,6-difluorobenzoate (**12**) in TFE-d_3. The signals derived from the various compounds are assigned at the top of the spectrum.

depicted for compound **17** based on analogy with hemiaminal **18**. In order to further prove the structural assignment of the compound we calculated the UV spectrum for compound **17** using SPARTAN. As we can see from the calculated UV spectrum depicted in Figure 3C it matches well with the UV spectrum obtained for hemiaminal **17** (Fig. 3A). It was not possible to discern the signals derived from compound **17** in the ^{1}H NMR spectrum most likely due to overlapping signals. Due to the unstable nature of hemiaminals in general we did not attempt to isolate this compound.

The compound with t_R 13.1 min in the HPLC chromatogram was isolated by utilizing a reversed phase column (see Experimental part for details) in order to help structural assignment. ^{1}H NMR analysis of the product in TFE-d_3 showed four sets of down field triplets (8.87, 8.51, 7.04, and 6.97 ppm integrating for one proton each) in addition to two quartets (4.33 and 4.31 ppm integrating for two protons each) and two triplets (1.29(8) and 1.29(7) ppm integrating for three protons each). ^{19}F NMR analysis in $CDCl_3$ revealed that the compound contained four fluorine atoms and low resolution MS (EI) showed a molecular ion at m/z 414. Subjection of this molecular ion to high resolution MS gave the molecular formula $C_{18}H_{14}F_4N_2O_5$. The molecular mass was also confirmed by ESI-Q-TOF-MS, and a proton/deuterium exchange experiment followed by MS analysis, using our well established method.[7,11] The proton/deuterium exchange experiment revealed a molecular mass of m/z 416 $(M+D)^+$ confirming that the product had no exchangeable proton. Unfortunately due to the small amount of available compound it was not possible to obtain a ^{13}C NMR spectrum. Nevertheless, based on the information at hand we concluded that the structure of the compound is as depicted for azoxybenzene **19**. Comparison of the UV spectrum of compound **19** ($\lambda_{max} \approx 310$ nm) (Fig. 4) with similar compounds from the literature shows a good match.[12]

It is plausible that substrate **19** was formed from azobenzene **13a** and/or **13b** by oxidation,[13] however, a different mode of formation is also plausible. It is possible that compound **19** was formed upon reaction between *N*-oxide **20** and triplet phenylnitrene **21**. In an attempt to verify any of the intermediates en route to compound **19** we subjected the photolysis mixture to nano-LC-ESI-Q-TOF-MS. And indeed we were able to find a compound with mass m/z 216 $(M+H)^+$, which could stem from the *N*-oxide **20**. The compound giving rise to the triplet at 8.67 ppm in the ^{1}H NMR spectrum (see Fig. 1) (the remaining signals could not be discerned due to overlapping) could possibly be derived from *N*-oxide **20**.



20 **21**

Regardless of if compound **19** was formed by oxidation of azobenzene or via a reaction between compounds **20** and **21** we still could not unambiguously point out the oxygen source for this

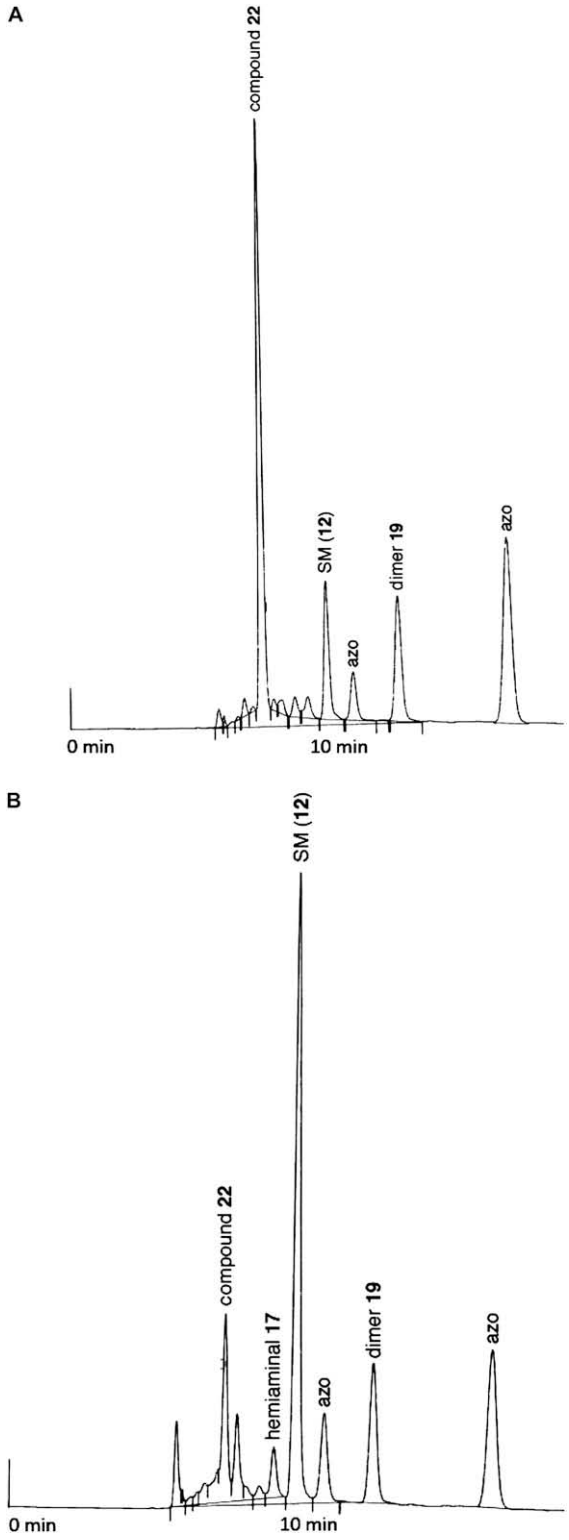


Figure 2. HPLC chromatogram [HPLC conditions: Develosil ODS-UG-5 (4.6×250 mm i.d.), CH_3CN/H_2O 4:1, 0.5 mL/min] of the reaction mixture obtained after 26 min irradiation of a 13.75 mM solution of ethyl 3-azido-4,6-difluorobenzoate (**12**) in TFE-d_3: (A) analyzed at 295 nm; (B) analyzed at 254 nm. The signals derived from the various compounds are assigned on the top of the chromatograms. The t_R for the respective compounds are as follows: compound **22** 7.73 min, hemiaminal **17** 9.51 min, SM (**12**) 10.30 min, azo 11.32 min, dimer (azoxybenzene) **19** 13.08 min, and azo 17.35 min.

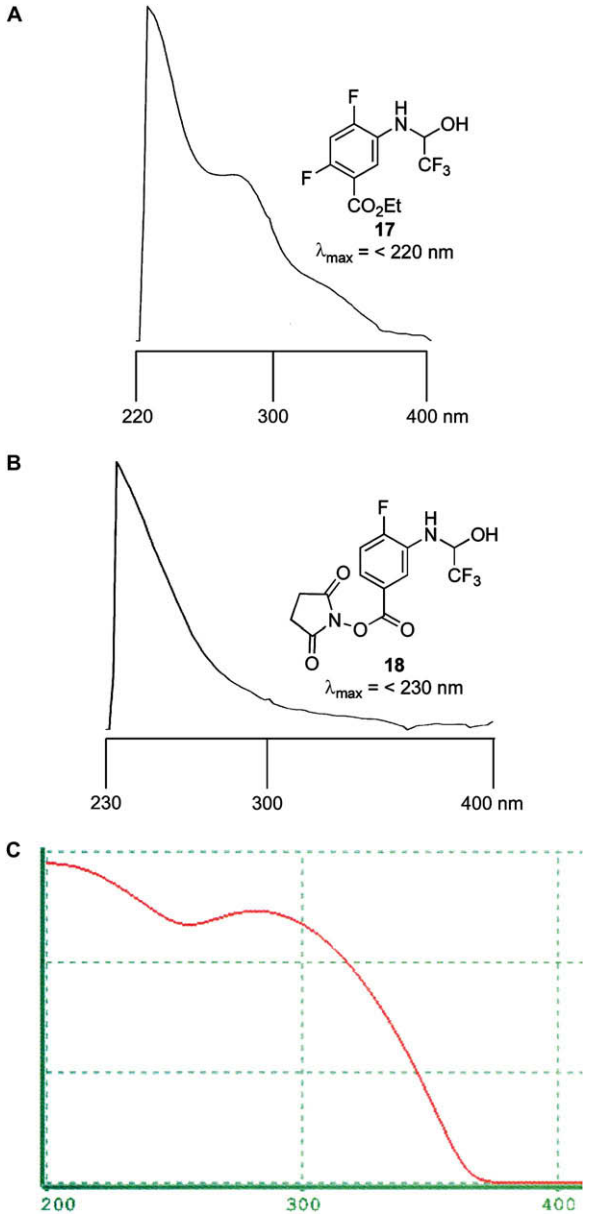


Figure 3. (A) UV spectrum of hemiaminal **17**; (B) UV spectrum of hemiaminal **18** (data taken from Ref. 7); (C) calculated UV spectrum for compound **17** using SPARTAN.

reaction. A few experiments were therefore conducted in order to try to shade some light on this question. Initially we envisaged three potential sources for the oxygen: (1) the oxygen came from trace of water in the solvent; (2) the oxygen originated from the solvent; (3) molecular oxygen that still remained dissolved in the solvent due to poor degassing prior to photolysis. First the photolysis was conducted in a mixture of ethanol/$H_2^{18}O$ water 95:5 followed by isolation of azoxybenzene **19** by preparative HPLC. Submission of the isolated product to MS (EI) analysis failed to show any enhancement of ^{18}O in the compound, thus ruling out water as the oxygen source. Next we tested if the source of oxygen was the solvent. Indeed, when the reaction was conducted in other solvents, 1,1,1,3,3,3-hexafluoropropan-2-ol, 2,2,2-trichloroethanol, and ethanol, we did see the formation of compound **19**. However, when the reaction was performed in non-degassed acetonitrile still some azoxybenzene was formed. These results together with the former points toward oxygen in the air as the source of oxygen in this reaction. Finally when acetonitrile was degassed very carefully the formation of compound **19** dropped to almost zero proving that the fifth oxygen in azoxybenzene **19** stems from oxygen in the air. A final experiment was conducted where oxygen was bubbled

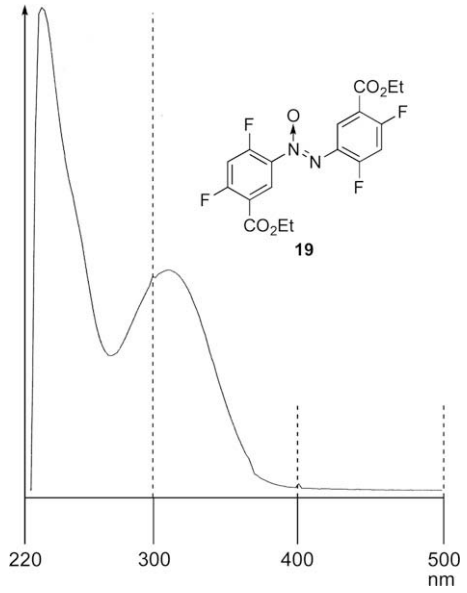


Figure 4. UV spectrum for compound **19**.

through the sample during photolysis. Under these conditions we did not observe an increase in the formation of azoxybenzene **19**, rather the contrary, as evident from HPLC analysis. In fact, bubbling oxygen through the sample during the photolysis gave only trace amount of compound **19**. However, under these conditions we did see a dramatic increase in the amount of the compound with t_R 7.73 min in the HPLC chromatogram. The fact that azoxybenzene **19** was not formed in a significant amount when oxygen was bubbled through the reaction mixture during photolysis serves as evidence that the compound most likely is formed via a triplet process. The fact that oxygen is a triplet quencher[14] results in this process almost totally stopping up when oxygen is bubbled through the sample solution during photolysis. While conducting the experiments in different solvents we found that the highest yield of compound **19** (15%) was obtained when ethanol was used as the solvent. Using ethanol as the solvent also resulted in an increased formation of aniline **15**, which was only formed in trace amount at this concentration when TFE was used as solvent, as evident from HPLC analysis.

Interestingly the yield of azoxybenzene **19** was reduced to half when the reaction concentration was doubled, viz. 27.5 mM. Despite the fact that generally a concentration increase would result in an increased rate of dimerization. One probable explanation for this could be that the solution turns very dark colored during the photolysis, thus forming a filter blocking out the light and by such means hampering further reaction. From our previous work[7] we know that compound **19** is not formed under rather dilute conditions, namely 2.0 mM, so a higher concentration is essential in order for this compound to be formed.

The compound giving rise to the two doublets at 6.88 and 5.96 ppm and with a t_R 7.73 in the HPLC chromatogram was formed in an 18% yield after 26 min irradiation together with a range of other products (Figs. 1 and 2). Fortunately this compound (referred to as compound **22** from this point onwards) was the predominant product after 2 min irradiation, however, the yield was very low (**12**/**22** 1:0.04). As alluded to previously the yield of this compound could be improved (**12**/**22** 5:1) when photolysis was conducted for 2 min with oxygen bubbling through the sample solution. By such means it was possible to obtain good ^{1}H NMR data for compound **22** (Fig. 5).

The ^{1}H NMR spectrum of compound **22** shows two down field doublets at 6.88 and 5.96 ppm integrating for one proton each with

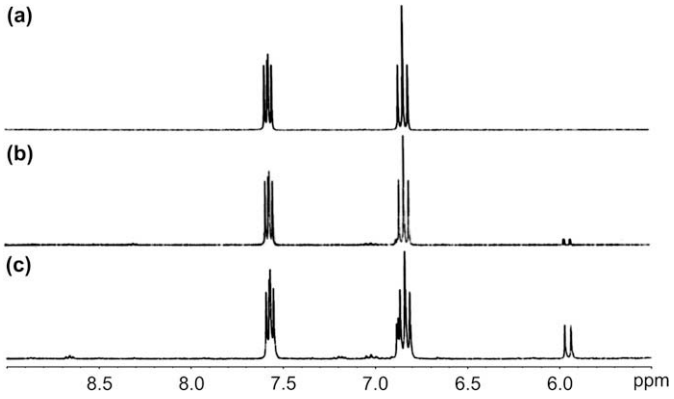


Figure 5. ^{1}H NMR spectra of photolysis mixture (400 MHz, TFE-d_3, room temperature) (9.0–5.5 ppm shown). (A) Aryl azide **12** prior to photoirradiation; (B) after 2 min irradiation (the sample was degassed before photoirradiation) (**12**/**22** 1:0.04); (C) after 2 min irradiation with oxygen bubbling through the sample (**12**/**22** 5:1).

coupling constant (J) 3.2 Hz and 13.6 Hz, respectively. Furthermore, the spectrum also shows, as expected, two signals resulting from the ethyl ester [4.20 ppm (q, J=7.2 Hz, 2H) and 1.19 ppm (t, J=7.2 Hz, 3H)]. The rather small coupling (J) constant (3.2 Hz) for the doublet at 6.88 ppm and the fact that both the down field protons appeared as doublets was intriguing. Further analysis by ^{13}C NMR only enabled us to discern the signals for six out of the nine carbons embodied in compound **22** (see Experimental for details). Syringe injection ESI-Q-TOF-MS revealed a molecular ion with mass m/z 200 for compound **22**. Subjection of this molecular ion to MS/MS gave rise to the following fragments, m/z 173, 171, and 170. The fragment at m/z 173 probably arises from loss of HCN, while m/z 171 and 170 are derived from loss of ethyl radical and ethane, respectively. We then submitted the sample to our standard H/D exchange conditions,[7,11] which confirmed that the product had no exchangeable proton. Furthermore, the fragments at m/z 171 and m/z 170 both had a mass increase of 1 Da, thus further confirming that the product had no exchangeable proton. The UV spectrum of the product is depicted in Figure 6 and shows a red shift relative to the starting material ($\lambda_{max} \approx 290$ nm).

At this stage we suspected that this compound might be the corresponding ketenimine **23** (Fig. 7), however, its long lifetime (slowly decomposing over two weeks when stored at room temperature) in TFE-d_3 suggested otherwise. Furthermore, the ^{1}H NMR spectrum shows two down field doublets, which do not, at least at first glance, match the expected ^{1}H NMR spectrum of the ketenimine. It was at least expected that the proton between the two fluorine atoms should give rise to a doublet of doublets or a triplet due to coupling with the two fluorines. However, some solvated form of ketenimine, such as indicated in structure **24** (Fig. 7), should not be totally ruled-out.

There is previously only one report of low temperature (−86 °C) ^{13}C NMR analysis of ^{13}C enriched ketenimine **5** incorporated into hemicarcerand.[15]

The remarkable long lifetime for compound **22** at room temperature in TFE could be explained by the unique physical properties of this solvent, such as low nucleophilicity.[16] It has been reported that another fluorinated alcohol, namely 1,1,1,3,3,3-hexafluoropropan-2-ol, increases the half-lives of radical cations dramatically.[17] It is likely that TFE can have a similar effect on intermediates formed during photolysis given that the physical properties of the two alcohols are similar.[16]

Ketenimines are known to be readily trapped by diethylamine, thus forming the corresponding 2-diethylamino-3*H*-azepine.[4] A sample mixture containing compound **22** generated by irradiation of azide **12** in TFE with oxygen bubbling through the sample

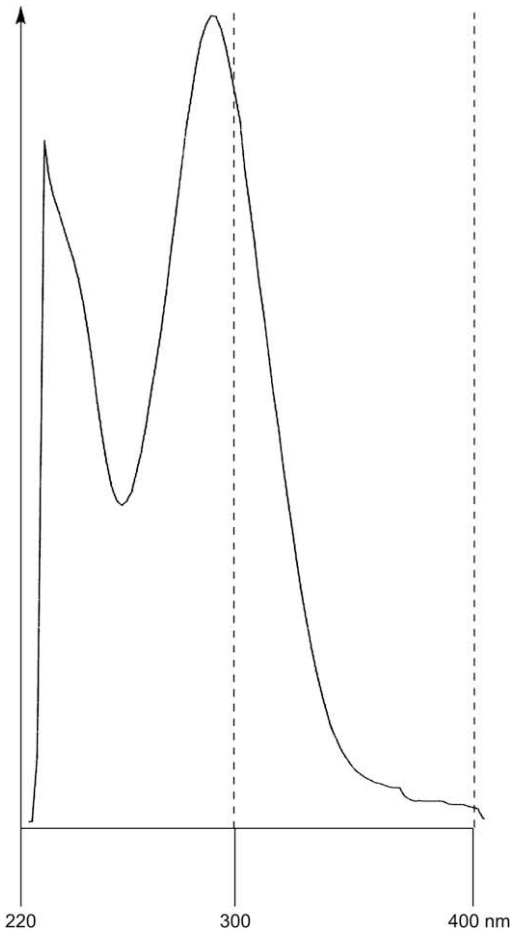
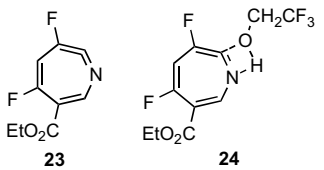


Figure 6. UV spectrum of compound **22**.

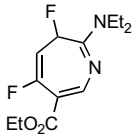
(26 min irradiation) was treated with excess diethylamine. By HPLC analysis we could determine that the intermediate **22** was fully converted to other products after 1.5 h at room temperature. The reaction mixture, which contained several new compounds as evident from HPLC analysis, was then subjected to ESI-Q-TOF-MS analysis. These analysis revealed the formation of a compound with m/z 273 $(M+H)^+$ corresponding to the mass of the expected diethylamine insertion product **25** derived from ketenimine **23**. Subjecting this molecular ion to MS/MS analysis displayed the structurally important fragment at m/z 200, which most likely corresponds to ketenimine **23**. ^{1}H NMR analysis of the reaction mixture was not attempted due to the complexity of the reaction mixture and the high concentration of diethylamine in the solution. However, the MS/MS data obtained for the compound strongly suggest that the substrate giving rise to the mass m/z 273 $(M+H)^+$ is azepine **25**.

Even though some of the data reported herein points toward ketenimine **23** as the most likely candidate for compound **20**, there are also, on the other hand, facts that suggests otherwise. Further analysis is therefore required in order to draw a conclusion as to the actual structure of compound **22**.



23 **24**

Figure 7. Possible structures for compound **22**.



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3. Conclusion

The work reported herein represents the first thorough analysis by ^{1}H NMR of products derived from photodegradation of aryl azide. We have shown that ^{1}H NMR is an excellent analytical method to investigate the products formed upon photolysis of ethyl 3-azido-4,6-difluorobenzoate. The strategy employed in this work has broad generality for the analysis of products derived from photolysis of aryl azides. ^{1}H NMR supported by MS, MS/MS, and UV analysis enabled firm confirmation of four out of the five major products formed. In order to unambiguously prove the structure of compound **20** further work is required.

4. Experimental section

4.1. General experimental

Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel coated glass plates $60F_{254}$ using UV light as visualizing agent and basic $KMnO_4$ solution followed by heating as developing agent. Silica gel 60 (particle size 0.063–0.2 mm ASTM) was used for flash chromatography. Ethyl 3-azido-4,6-difluorobenzoate (**13**) was prepared according to our previously reported method.[8] Solvents and reagents for LC/MS were purchased and prepared as follows: acetonitrile (hypergrade for LC/MS, Merck, Germany), CF_3CO_2D (D=99.8%) (Merck, Germany), trifluoroacetic acid (Nacalai tesque, Japan), deuterium oxide (D_2O=99.9%, Cambridge Isotope Laboratory, USA) and water were of MilliQ grade. Deuterated solvents were freshly opened prior to use and was used for 1 day when capped under an atmosphere of argon.

4.2. Instrumentation

NMR chemical shifts are reported as δ values in parts per million (ppm) using tetramethylsilane (δ=0.00 ppm) or 2,2,2-trifluoroethanol-d_3 (δ=5.02 ppm) as internal standard for proton (^{1}H) NMR and residual chloroform (δ=77.0 ppm) or residual 2,2,2-trifluoroethanol (δ=126.3 ppm) as internal standard for carbon (^{13}C) NMR. Fluorine (^{19}F) NMR spectra were referenced externally to 1,1,1-trifluorotoluene at δ=0.00 ppm. HPLC analysis of reaction mixtures derived from photolysis experiments was analyzed by HPLC; Develosil C30-UG-5 (4.6×250 mm i.d.), CH_3CN/H_2O 4:1, 1 mL/min and the effluent were monitored at both 295 and 254 nm.

MS analysis was conducted utilizing a Q-TOF mass spectrometer (Micromass, Manchester, UK) equipped with a Z-spray type ESI source. Data were acquired and processed using MassLynx version 3.4. All samples were desalted and separated by non-split type prepacked gradient (PPG) system and appropriately assembled nano-HPLC system (JASCO, Tokyo, Japan) using a Develosil ODS-HG-5 column (Nomura, 150 mm×0.3 mm i.d.) before on-line ESI-MS and MS/MS analysis. For H-MS and H-MS/MS analysis the column was equilibrated with 260 μL water containing 0.025% trifluoroacetic acid at a flow rate of 10 μL/min and then developed using a linear gradient from 0 to 100% of acetonitrile containing 0.025% trifluoroacetic acid for 40 min at a flow rate of 5 μL/min. For the H/D

exchange experiments (D-MS and D-MS/MS) the column was equilibrated with 260 μL D_2O containing 0.025% D-trifluoroacetic acid at a flow rate of 10 μL/min and then developed using a linear gradient from 0 to 100% acetonitrile containing 0.025% D-trifluoroacetic acid at a flow rate of 5 μL/min. The column effluent was monitored at 210 nm and then introduced into the electrospray nebulizer without splitting. For H-MS and H-MS/MS the column was equilibrated with isocratic 40% acetonitrile/water containing 0.025% trifluoroacetic acid at a flow rate of 5 μL/min. For the proton exchange experiments (D-MS and D-MS/MS) the column was equilibrated with isocratic 40% acetonitrile/D_2O containing 0.025% D-trifluoroacetic acid at a flow rate of 5 μL/min. Selected MS and MS/MS spectra were also measured utilizing syringe injection ion trap HCT Plus mass spectrometer (Bruker Daltonics, Bremen, Germany) equipped with an orthogonal ESI source. Data were acquired and processed using Compass version 1.2 (esquireControl™ and DataAnalysis™ version 3.2) (Bruker Daltonics, Bremen, Germany), respectively. All MS experiments were preformed in the positive ion mode.

4.3. Ethyl 3-azido-4,6-difluorobenzoate (12)

^{1}H NMR (CF_3CD_2OD, 400 MHz) δ 7.57 (dd, J=7.0 and 9.0 Hz, 1H), 6.84 (t, J=10.6 Hz, 1H), 4.28 (q, J=7.2 Hz, 2H), 1.27 (t, J=7.2 Hz, 3H). For the remaining spectroscopic data see Ref. 8.

4.4. Ethyl 3-amino-4,6-difluorobenzoate (15)

^{1}H NMR (CF_3CD_2OD, 400 MHz) δ 7.40 (dd, J=7.2 and 9.6 Hz, 1H), 6.77 (t, J=10.6 Hz, 1H), 4.25 (q, J=7.2 Hz, 2H), 1.26 (t, J=7.2 Hz, 3H). For the remaining spectroscopic data see Ref. 8.

4.5. Azobenzenes 13a and 13b

To a stirred solution of amine **16** (62.3 mg, 0.309 mmol) was added a solution of KOH (47.4 mg, 0.845 mmol in 1.5 mL EtOH/water 1:1) followed by slow addition of potassium ferricyanide (408.3 mg, 1.24 mmol). The resulting reaction mixture was heated at reflux for 7 h before being cooled to room temperature, filtered, and diluted with CH_2Cl_2 (10 mL). The aqueous phase was acidified with 1 N HCl and extracted with CH_2Cl_2 (3×10 mL). The combined organic fractions were dried over Na_2SO_4. Filtration and concentration under reduced pressure gave a dark orange oil, which was diluted with EtOH (20 mL) and H_2SO_4 (10 drops) was added. The resulting reaction mixture was heated at reflux for 3 h before being cooled to room temperature and diluted with EtOAc (40 mL). The organic phase was washed with brine/water (1×10 mL of a 1:1 mixture) and brine (1×10 mL) before being dried over Na_2SO_4. Filtration and concentration gave a dark yellow oil, which was subjected to flash chromatography (silica, hexane/EtOAc/Et_3N 90:9.95:0.05→85:14.95:0.05). Concentration of the relevant fractions (R_f 0.4 in hexane/EtOAc 85:15) gave 4.1 mg (7%) of the desired product as a yellow solid and as a 3:1 mixture of *E* (**13a**) and *Z* (**13b**) isomer. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (t, J=8.2 Hz, 2H, *E*-isomer), 7.67 (t, J=7.8 Hz, 2H, *Z*-isomer), 7.11 (t, J=10.2 Hz, 2H, *E*-isomer), 6.81 (t, J=9.6 Hz, 2H, *Z*-isomer), 4.43 (q, J=7.2 Hz, 4H, *E*-isomer), 4.37 (q, J=7.2 Hz, 4H, *Z*-isomer), 1.42 (t, J=7.2 Hz, 6H, *E*-isomer), 1.37 (t, J=7.2 Hz, 6H, *Z*-isomer); ^{1}H NMR (CF_3CD_2OD, 400 MHz) δ 8.32 (t, J=8.0 Hz, 2H, *E*-isomer), 7.55 (t, J=7.6 Hz, 2H, *Z*-isomer), 7.02 (t, J=10.4 Hz, 4H, *E*-isomer), 6.79 (t, J=10.0 Hz, 2H, *Z*-isomer), 4.31 (q, J=7.2 Hz, 4H, *E*-isomer), 4.23 (q, J=7.2 Hz, 4H, *Z*-isomer), 1.29 (t, J=7.2 Hz, 6H, *E*-isomer), 1.23 (t, J=7.2 Hz, 6H, *Z*-isomer); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 164.1 (dd, J_{C-F}=12 and 270 Hz, *E*-isomer), 162.7 (dd, J_{C-F}=12 and 269 Hz, *E*-isomer), 163.0 (dd, J_{C-F}=4 Hz, *E*-isomer), 162.3 (dd, J_{C-F}=5 Hz, *E*-isomer), 125.9 (*Z*-isomer), 122.3 (*E*-isomer), 106.7 (dd, J_{C-F}=24 and 27 Hz, *E*-isomer), 61.8(9) (*Z*-isomer), 61.8(6) (*E*-isomer), 14.2 (*E*-isomer), 14.1 (*Z*-isomer), five signals from the aromatic rings associated with the *Z*-isomer and the signal from the carbonyl carbon associated with both isomers could not be discerned; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −36.3 (*E*-isomer), −40.1 (*Z*-isomer), −49.2 (*Z*-isomer), −46.5 (*E*-isomer); MS (EI$^+$) m/z 398 ($M^{+\bullet}$, 68%), 353 (22), 213 (86), 185 (46), 157 (98), 140 (100), 112 (97), 101 (77), 51 (37); HRMS (EI$^+$) found: $M^{+\bullet}$, 398.0872. $C_{18}H_{14}F_4N_2O_4$ requires $M^{+\bullet}$, 398.0890; t_R in HPLC 17.75 min (*E*-isomer) and 11.48 min (*Z*-isomer).

4.6. Hydrazine 14

Sodium dithionite (13.6 mg, 0.0782 mmol) was added to a solution of azobenzenes **13a** and **13b** (3.0 mg, 0.00753 mmol) stirred at reflux in a mixture of MeOH/H_2O/CH_2Cl_2 (1.0 mL/1.0 mL/0.15 mL). The resulting reaction mixture was heated at reflux for 1.3 h before being cooled to room temperature and poured into ice-water (10 mL). The aqueous phase was extracted with Et_2O (2×20 mL) and the combined organic fractions were dried over Na_2SO_4. Filtration and concentration gave a dark yellow oil, which was subjected to preparative TLC (hexane/EtOAc 4:1) to afford fractions A and B.

Concentration of fraction A (R_f 0.46) gave 1.1 mg (37%, recovery) of compound **13a** as a yellow solid, which was identical, in all respects, with the starting material.

Concentration of fraction B (R_f 0.38) gave 1.9 mg of a 3.8:1 mixture of hydrazine **14** and starting material **13a** as a yellow solid. This implements that 1.5 mg (50%, at 50% conversion) of the desired hydrazine **14** was formed. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (dd, J=6.8 and 9.6 Hz, 2H), 6.91 (dd, J=10.0 and 10.8 Hz, 2H), 4.34 (q, J=7.2 Hz, 4H), 1.35 (t, J=7.2 Hz, 6H); ^{1}H NMR (CF_3CD_2OD, 400 MHz) δ 7.49 (t, J=8.2 Hz, 2H), 6.81 (t, J=10.6 Hz, 2H), 4.20 (q, J=7.2 Hz, 4H), 1.20 (t, J=7.2 Hz, 6H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −53.5, −61.3; MS (EI$^+$) m/z 400 ($M^{+\bullet}$, 20%), 200 (28), 155 (100), 127 (82), 101 (32), 100 (22); HRMS (EI$^+$) found: $M^{+\bullet}$, 400.1003. $C_{18}H_{16}F_4N_2O_4$ requires $M^{+\bullet}$, 400.1046; t_R in HPLC 9.62 min.

4.7. Isolation of azoxybenzene 19

The photolysis mixture was purified by HPLC (Cosmosil 5C18-AR (10×250 nm), CH_3CN/H_2O 4:1, 2.0 mL/min, 295 nm). Concentration of the relevant fraction under reduced pressure gave a light-yellow oil. ^{1}H NMR (CF_3CD_2OD, 400 MHz) δ 8.87 (t, J=8.0 Hz, 1H), 8.51 (t, J=7.6 Hz, 1H), 7.04 (t, J=10.2 Hz, 1H), 6.97 (t, J=10.4 Hz, 1H), 4.33 (q, J=7.2 Hz, 2H), 4.31 (q, J=7.2 Hz, 2H), 1.29(8) (t, J=7.2 Hz, 3H), 1.29(7) (t, J=7.2 Hz, 3H); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.04 (t, J=8.0 Hz, 1H), 8.64 (t, J=7.8 Hz, 1H), 7.11 (t, J=9.8 Hz, 1H), 7.04 (t, J=10.2 Hz, 1H), 4.44 (q, J=7.2 Hz, 2H), 4.42 (q, J=7.2 Hz, 2H), 1.42 (t, J=7.2 Hz, 3H), 1.41 (t, J=7.2 Hz, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −35.5, −37.7, −41.1, −44.6; MS (EI$^+$) m/z 414 ($M^{+\bullet}$, 100%), 394 (85), 369 (63), 213 (37), 199 (88), 157 (79), 140 (46), 115 (43), 101 (37); MS (ESI) m/z 415 ($[M+H]^+$, 100%), 395 (4); HRMS (EI$^+$) found: $M^{+\bullet}$, 414.0828. $C_{18}H_{14}O_5N_2F_4$ requires $M^{+\bullet}$, 414.0839.

4.8. Compound 22

^{1}H NMR (CF_3CD_2OD, 400 MHz) δ 6.88 (d, J=3.2 Hz, 1H), 5.96 (d, J=13.6 Hz, 1H), 4.20 (q, J=7.2 Hz, 2H), 1.19 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 164.3 (d, J_{C-F}=2 Hz), 139.3 (d, J_{C-F}=20 Hz), 119.9 (d, J_{C-F}=4 Hz), 104.2 (dd, J_{C-F}=33 and 79 Hz), 65.5, 14.1, three signals were overlapping or obscured; MS (ESI): m/z 200 ($(M+H)^+$, 100%), 173 (8), 171 (42), 170 (34).

4.9. Compound 25

MS (ESI): m/z 273 ($(M+H)^+$, 100%), 247 (10), 200 (5), 86 (90), 74 (25).

4.10. General procedure for photolysis experiments (no oxygen bubbling through the solution during irradiation)

A degassed solution of aryl azide **12** (13.75 mM) in 2,2,2-trifluoroethanol-d_3 (for ^{1}H NMR experiments) or 2,2,2-trifluoroethanol (for other experiments) was irradiated at ambient temperature for the required time in a Pyrex NMR tube by using a low-pressure mercury lamp. The samples were then subjected to ^{1}H NMR and/or MS and MS/MS analysis.

4.11. General procedure for photolysis experiments with oxygen bubbling through the solution during irradiation

A solution of aryl azide **12** (13.75 mM) in 2,2,2-trifluoroethanol-d_3 (for ^{1}H NMR experiments) or 2,2,2-trifluoroethanol (for other experiments) was irradiated at ambient temperature for the required time in a Pyrex NMR tube while bubbling oxygen through the sample by using a low-pressure mercury lamp. The samples were then subjected to ^{1}H NMR and/or MS and MS/MS analysis.

4.12. Procedure for treating compound 22 with diethylamine

A solution of aryl azide **12** (13.75 mM) in 2,2,2-trifluoroethanol was irradiated for 26 min at ambient temperature in a Pyrex NMR tube while bubbling oxygen through the sample by using a low-pressure mercury lamp. Diethylamine (1.0 mL, 9.67 mmol) was then added to the reaction mixture and the resulting reaction mixture was thoroughly shaken. The NMR tube was then left in the dark at room temperature for 1.5 h when all of the intermediate had reacted as judged by HPLC analysis. A sample of the reaction mixture was then subjected to MS and MS/MS analysis.

4.13. General procedure for the preparation of samples for MS and MS/MS analysis

All samples for H-MS and H–MS/MS were further diluted with methanol/acetonitrile (1:1) to 500 pmol μL^{-1} and all samples for D-MS and D–MS/MS were further diluted with methanol-d_4/acetonitrile to 500 pmol μL^{-1}.

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