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Photochemistry of Fluorophenyl Azides in Diethylamine. Nitrene Reaction Versus Ring Expansion

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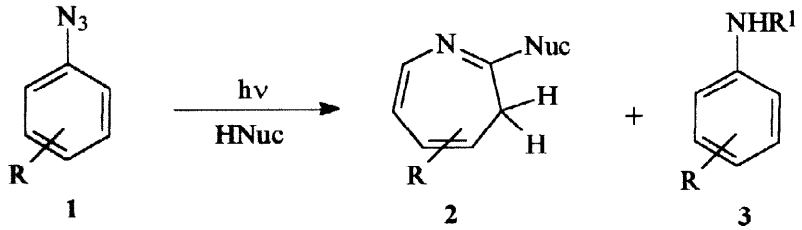
Abstract: Several fluorophenyl azides were photolyzed with diethyl amine at room temperature. Pentafluoro and 2,6-difluorophenyl azides gave hydrazines as the major products. On the other hand, several mono- and difluorophenyl azides gave azepines under similar conditions. Ortho-fluoro singlet phenyl nitrene produces the azirine by ring closure away from the substituent.

Aryl azides have been used for fotoaffinity labeling of enzymes, a technique used to determine the amino acid residues in the active sites.[1] This application is most efficient when intermolecular insertion reactions of the aryl nitrenes, formed upon photolysis of the aryl azides, are faster than their intramolecular rearrangements.[2] Fluorine substituents have been found to slow the rate of intramolecular rearrangements[3] and fluorophenyl azides have become the most popular reagents for photoaffinity labelling.[1]

It is well established that irradiation of an aryl azide **1** at room temperature in the presence of a nucleophile (HNuc) such as diethylamine gives a variety of products among them the ring expanded azepine **2**.[4-13]



1 **2** **3**

R = H, Halogen, NO_2 R1 = H, alkyl, Nuc

This reaction has been studied for more than 60 years and a variety of reaction pathways have been proposed to explain the products formed. Improved spectroscopic techniques have allowed direct observation of intermediates with short lifetimes (nanoseconds and picoseconds).[10,14,15,21] The singlet nitrene ^{1}**4** (Scheme 1) is considered to be the first intermediate formed upon photolysis of phenyl azide.[15,24] However, the nature of the intermediate (s) involved in the ring expansion is still under debate. Early studies on the photolysis of phenyl azide by Huisgen suggested that the first intermediate formed from the singlet phenyl nitrene ^{1}**4** was the bicyclic azirine **7**.[16] Later studies in the photochemistry of matrix isolated phenyl azide by Chapman and Le Roux gave IR spectroscopic evidence for the formation of the didehydroazepine **5**.[17]

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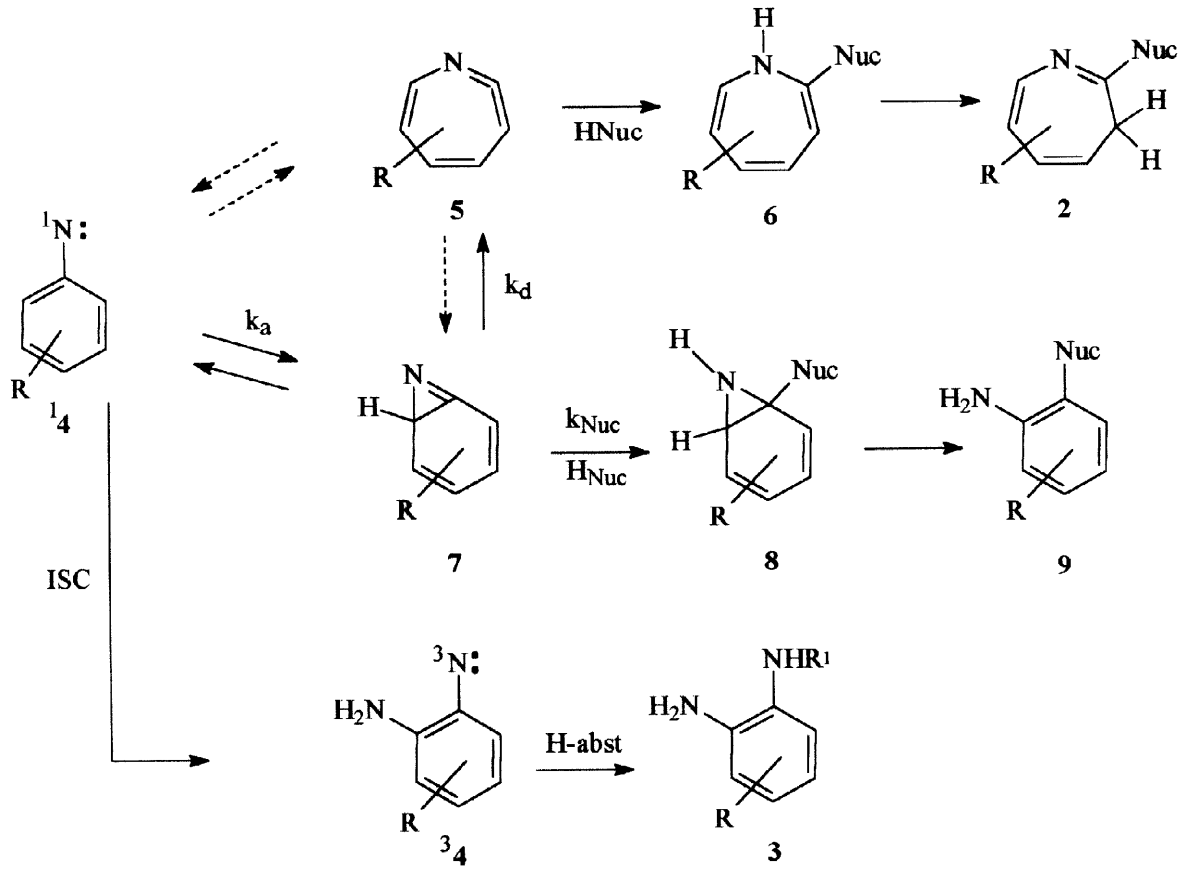
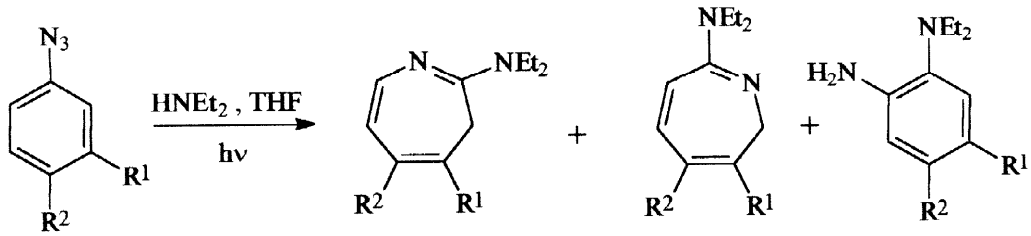


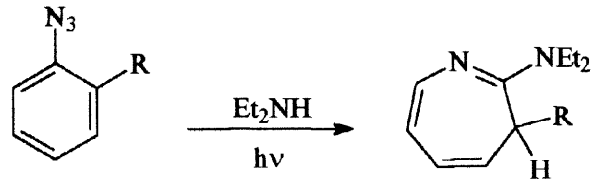
Scheme 1

In a recent study by Younger and Bell,[18] the photolysis of aryl azide **10** gave a long lived azirine intermediate **7**, which was in equilibrum with the initially formed nitrene and subsequently rearranged to the didehydroazepine intermediate **5**. The two intermediates, azirine **7** and didehydroazepine **5**, were trapped with diethylamine.



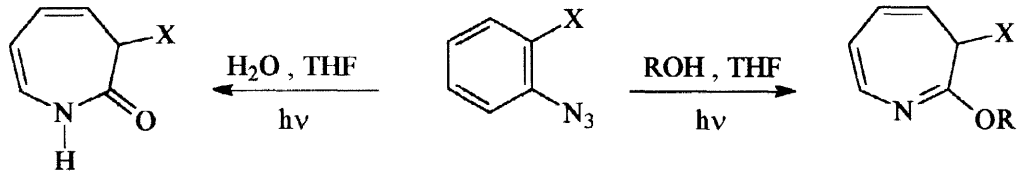
R1 = NHCOMe
R2 = NHCOCF3

Several ortho-substituted (R = CH_3, C_2H_5, i-C_3H_7, C_6H_5) aryl azides **14** gave a single isomeric azepine **15** upon photolysis in diethylamine. [7]



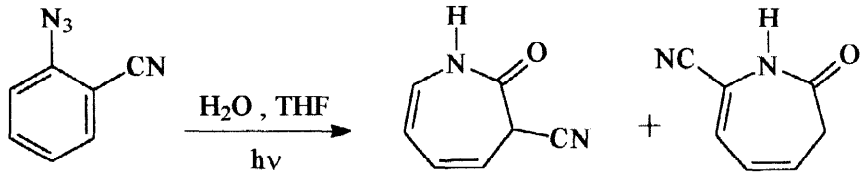
14 **15**

The photo-induced ring expansion of an aryl azide in the presence of a nucleophile is particularly efficient for some aryl azides **16** with an electron-withdrawing ortho-substituent (X=CO_2Me, SO_2NH_2, CO_2H, CONHR). All of these azides gave a single isomeric azepine in good yields.[19,20,21]



17 **16** **18**

There are a few cases in which two isomeric azepines are obtained upon photolysis of an aryl azide with an electron-withdrawing ortho-substituent.[22]



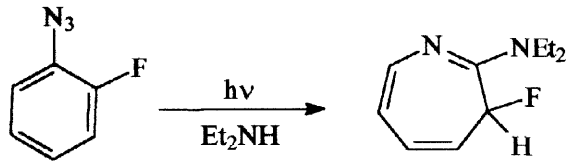
19 **20** **21**

30 % 16 %

We have reported that the rate of ring expansion of a singlet aryl nitrene ^{1}**4** to didehydroazepine **5** is strongly dependent on the temperature.[23,24] At room temperature, singlet phenyl nitrene undergoes ring expansion to didehydroazepine which is subsequently trapped with diethylamine to give the corresponding azepine. At 77K, the singlet phenyl nitrene undergoes intersystem crossing to triplet phenyl nitrene and only the products derived from this intermediate are obtained. More recently, we studied the photochemistry of several fluorinated aryl azides by laser flash photolysis using the pyridine ylide probe method.[14] We reported that two fluorine substituents, ortho and ortho' relative to the azide group, are required to retard ring expansion and allow bimolecular capture of the singlet nitrene. Therefore, the rate of ring expansion of a given aryl azide is affected by the steric and electronic effects of the substituents. In order to investigate the fluorine effect on the singlet nitrene ring expansion further, we studied the photochemistry of several fluorophenyl azides in diethylamine.

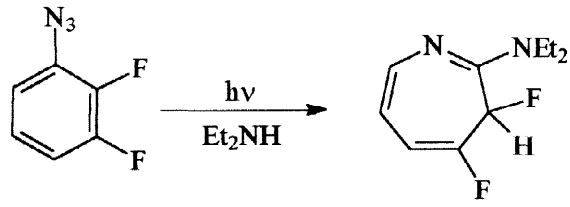
Photolysis of ortho-fluorophenyl azides

Irradiation of 2-fluorophenylazide **22** in cyclohexane containing diethylamine gave 3-(diethylamino)-3-fluoro-3H-azepine **23** in 25% yield.



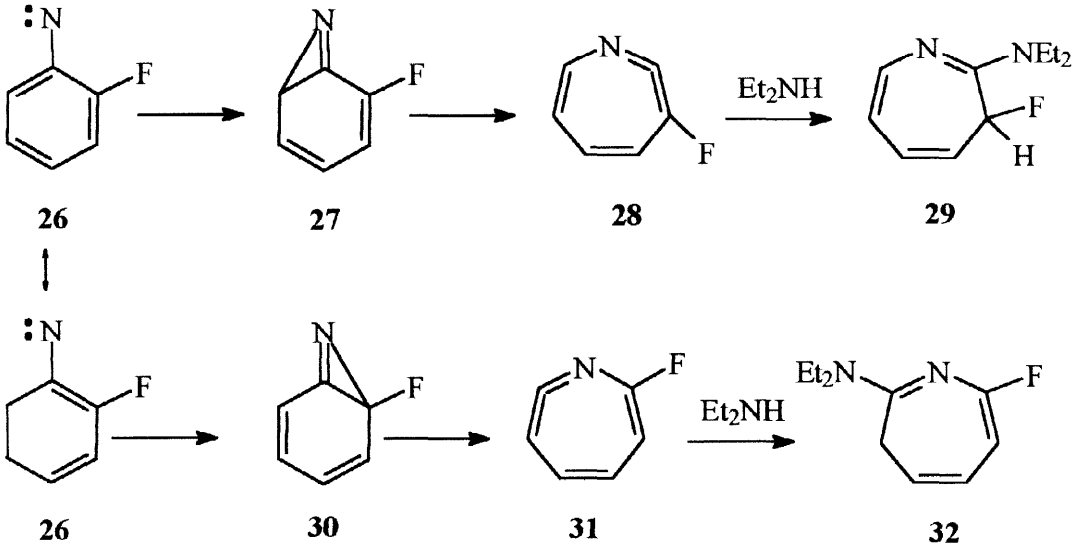
22 **23**

Under the same conditions, irradiation of 2,3-difluorophenylazide **24** in cyclohexane containing diethylamine gave 2-(diethylamino)-3,4-difluoro-3H-azepine **25** in 22% yield.



24 **25**

Two benzazirine isomers (**27** and **30**) are possible from an ortho-fluorophenyl azide **26**, but only one product, namely, the 3-fluoro-3H-azepine **29** was obtained. These results are in agreement with earlier observations by Sundberg with ortho alkyl groups.[7] Very recently, Karney and Borden have predicted that ortho-fluoro singlet phenyl nitrene **26** preferentially forms the azirine **27** by ring closure away from the substituent.[25] They also predicted that the ring expansion of a singlet aryl nitrene is a stepwise process involving an azirine intermediate.[26] Their computational results are in excellent agreement with the laser flash photolysis studies by Platz and collaborators.[15]

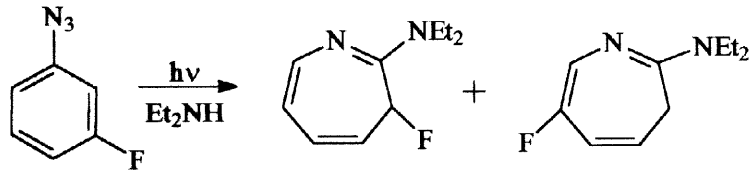


26 **27** **28** **29**

26 **30** **31** **32**

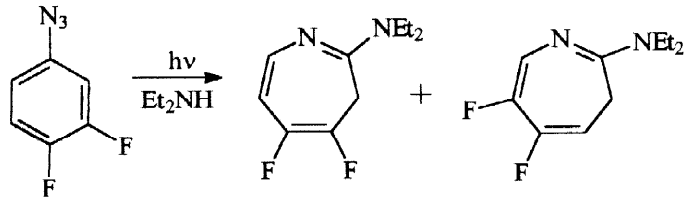
Photolysis of meta-fluorophenyl azides

Irradiation of 3-fluorophenylazide **33** in cyclohexane containing diethylamine gave an oil (31% yield) containing the two azepine isomers **34** and **35** (in a 2:1 mixture on the basis of their ^{1}H NMR spectra).



33 **34** **35**

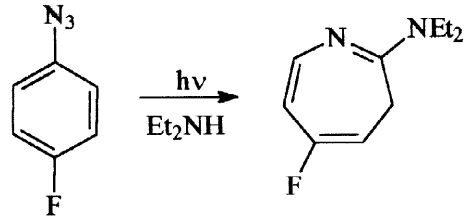
Under standard conditions, irradiation of 3,4-difluorophenylazide **36** in cyclohexane containing diethylamine gave an oil (20% yield) containing the two azepine isomers **37** and **38** (in a 2:1 mixture on the basis of their ^{1}H NMR spectra).



36 **37** **38**

Photolysis of para-fluorophenyl azides

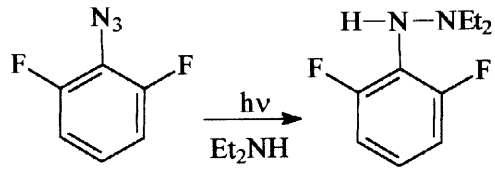
Irradiation of 4-fluorophenylazide **39** in cyclohexane containing diethylamine produced 2-(diethylamino)-5-fluoro-3H-azepine **40** in 35% yield.



39 **40**

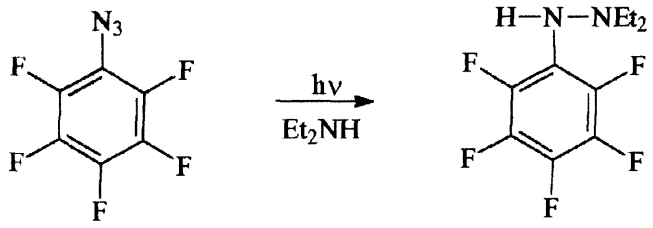
Photolysis of 2,6-difluorophenylazide and pentafluorophenyl azide

Irradiation of 2,6-difluorophenylazide **41** in diethylamine gave the hydrazine **42** in 57% yield.



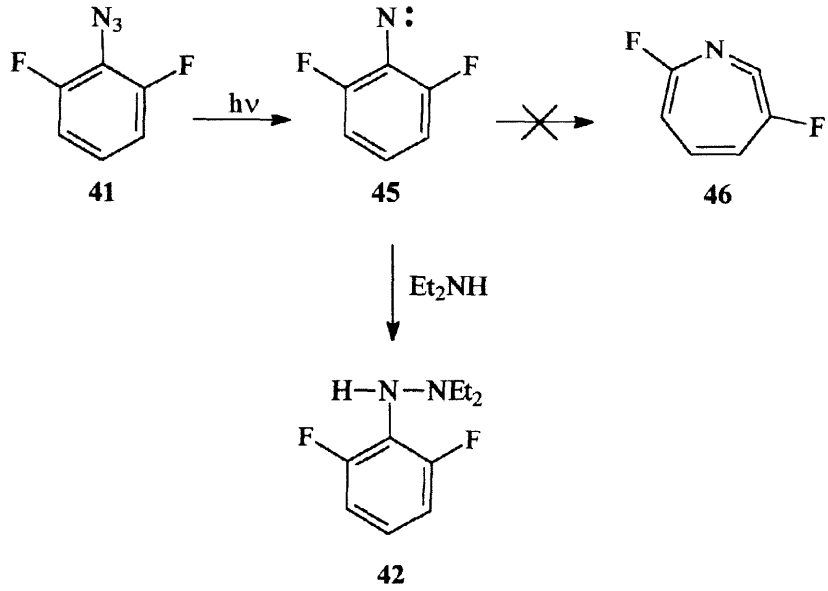
41 **42**

Utilizing the same reaction conditions, pentafluorophenylazide **43** in diethylamine generated hydrazine **44** in 46% yield.[3]



43 **44**

Only in those azides where the two ortho positions are occupied by fluorine atoms will the ring expansion to the didehydroazepine **46** be sufficiently inhibited to allow singlet nitrene reaction with diethylamine. Fluorination dramatically raises the barrier to rearrangement of singlet aryl nitrene **45** which must surmount a 8.8 kcal/mol barrier to cyclize and eventually form didehydroazepine **46**. [15]



41 **45** **46** **42**

Conclusions

In our studies, we observed that o-fluorophenyl azides produce an azepine by ring closure of the singlet phenyl nitrene away from the substituent. O, o'-difluorophenyl azides produce hydrazines by singlet phenyl nitrene N-H insertion reactions. Our product studies are in good agreement with Karney and Borden's calculation.[25,26] They have indicated that in the transition states for cyclizations, an ortho-fluoro substituent interacts in an sterically repulsive manner with the attacking nitrogen favoring cyclization away from the substituent. They also indicated that in o'o-difluoro substituted systems, such as pentafluorophenylnitrene and 2,6-difluorophenyl nitrene, this repulsion leads to a considerably higher barrier to ring expansion than in phenyl nitrene.

Experimental

General methods. All ^1H NMR and ^{19}F NMR spectra were recorded on a Bruker AM-250 (250 MHz) spectrometer. All ^1H NMR chemical shifts are reported relative to TMS. All ^{19}F NMR spectra were proton decoupled. The ^{19}F NMR chemical shifts are reported relative to hexafluorobenzene (162.9 ppm) as an internal standard. IR spectra were recorded on a Perkin-Elmer model 1710 IRFT spectrometer. Mass Spectra and exact masses were obtained on a VG 70-2505 or a Kratos MS-30 mass spectrometer.

Preparation of compounds. The fluoroarylazides were prepared from the corresponding fluoroanilines following the procedure described by Smith[27] with only minor modifications as previously described.[28]

Photolysis of fluoroarylazides. A cyclohexane solution of the arylazide (1g, 10^{-2}M) containing diethylamine (2.0M) was irradiated with 350-nm light in a Southern New England Rayonet photoreactor for 48 hours. The solution was purged with N_2 during the irradiation. The solvent was removed to yield a brown oil. The oil was purified by column chromatography with neutral alumina using a mixture of ethyl acetate (1%) in hexane as the solvent. Aryl azides (**41** and **43**) were photolyzed in neat diethylamine. In addition to azepines or hydrazines, the product mixtures contained tar and traces of fluoroanilines and fluoroazobenzenes.

2-(diethylamino)-3-fluoro-3H-azepine 23. Light brown oil; yield 25%; IR (neat, cm^{-1}) 1600 (N=C); ^1H NMR (CCl_4, δ) 1.20 (t, 6H, CH_3), 2.63 (q, 4H, CH_2), 4.32 (d.d, 1H, CH), 4.64(d.d, 1H, CH), 5.57 (t.d, 1H, CH), 7.42 (m, 1H, CH), 8.09 (d.t, 1H, CH); ^{19}F NMR (CCl_4, ppm) -122.90 (b.s, 1F); MS m/e calculated for $C_{10}H_{15}N_2F$: 182.1219, observed: 182.1185.

2-(diethylamino)-3,4-difluoro-3H-azepine 25. Light brown oil; yield 22%; IR (neat, cm^{-1}) 1600 (N=C); ^1H NMR (CCl_4, δ) 1.03 (t, 6H, CH_3), 2.51 (q, 4H, CH_2), 4.16 (d.d, 1H, CH), 4.52 (d.d, 1H, CH), 5.41 (t.d, 1H, CH), 7.69 (d.t, 1H, CH); ^{19}F NMR (CCl_4, ppm) -137.84 (d, J=21.3 Hz, 1F) -142.22 (d, J=21.3 Hz, 1F); MS m/e calculated for $C_{10}H_{14}N_2F_2$: 200.1125, observed: 200.1110.

2-(diethylamino)-4-fluoro-3H-azepine 34. Pale yellow oil; yield 31% (as a 2:1 mixture of **34** and **35** isomers); IR (neat, cm^{-1}) 1600 (N=C); ^1H NMR (CCl_4, δ) 1.58 (t, 6H, CH_3), 3.17 (d, 2H, CH_2), 3.80 (q, 4H, CH_2), 5.77 (m, 1H, CH), 6.23 (m, 1H, CH), 7.26 (d, 1H, CH); ^{19}F NMR (CCl_4, ppm) -104.49 (b.s, 1F); MS m/e calculated for $C_{10}H_{15}N_2F$: 182.1219, observed: 182.1245.

2-(diethylamino)-6-fluoro-3H-azepine 35. ^1H NMR (CCl_4, δ) 1.54 (t, 6H, CH_3), 3.02 (b.s, 2H, CH_2), 3.73 (q, 4H, CH_2), 5.45 (m, 1H, CH), 6.72 (m, 1H, CH), 7.48 (d, 1H, CH); ^{19}F NMR (CCl_4, ppm) -136.06 (b.s, 1F); MS m/e calculated for $C_{10}H_{15}N_2F$: 182.1219, observed: 182.1245.

2-(diethylamino)-4,5-difluoro-3H-azepine 37. Pale yellow oil; yield 20% (as a 2:1 mixture of **37** and **38** isomers); IR (neat, cm^{-1}) 1600 (N=C); ^1H NMR (CCl_4, δ) 1.37 (t, 6H, CH_3), 2.86 (d.d, 2H, CH_2), 3.60 (q, 4H, CH_2), 5.63 (q, 1H, CH), 7.07 (m, 1H, CH); ^{19}F NMR (CCl_4, ppm) -133.86 (d, J=17 Hz, 1F), -140.19 (d, J=17 Hz, 1F); MS m/e calculated for $C_{10}H_{14}N_2F_2$: 200.1125, observed: 200.1114.

2-(diethylamino)-5,6-difluoro-3H-azepine 38. ^1H NMR (CCl_4, δ) 1.31 (t, 6H, CH_3), 2.15 (b.s, 2H,CH_2), 3.53 (q, 4H, CH_2), 4.92 (m, 1H, CH), 7.38 (d.d, 1H, CH); ^{19}F NMR (CCl_4, ppm) -130.44 (d, J=28 Hz, 1F), -155.05 (d, J=28 Hz, 1F); MS m/e calculated for $C_{10}H_{14}N_2F_2$: 200.1125, observed: 200.1114.

2-(diethylamino)-5-fluoro-3H-azepine 40. Pale yellow oil; yield 35%; IR (neat, cm^{-1}) 1600 (N=C); ^1H NMR (CCl_4, δ) 1.36 (t, 6H, CH_3), 2.61 (b.s, 2H, CH_2), 3.56 (q, 4H, CH_2), 4.76 (q, 1H, CH), 5.71 (t, 1H, CH), 7.19 (d.d, 1H, CH); ^{19}F NMR (CCl_4, ppm) -113.45 (b.s, 1F); MS m/e calculated for $C_{10}H_{15}N_2F$: 182.1219, observed: 182.1206.

Hydrazine 38. Yellow oil; yield 30%; IR (neat, cm^{-1}) 3300 (N-H), 3090, 3070, 3030 (aromatic C-H), 2980, 2950, 2880, 2820 (aliphatic C-H); ^1H NMR (CCl_4, δ) 1.2 (t, 6H, CH_3), 2.7 (q, 4H, CH_2), 4.1 (s, 1H, N-H), 6.0-6.7 (m, 3H, aromatic); ^{19}F NMR (acetone-d_6, ppm) 57 (s, 2F, aromatic); MS m/e calculated for $C_{10}H_{14}N_2F_2$: 200.1125, observed: 200.1123.

Acknowledgement

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