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Fluorinated 4*H*-1,3-diazepines by reaction of difluorocarbene with 2*H*-azirines

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Abstract—5,7-Diaryl-2-fluoro-4*H*-1,3-diazepines have been synthesized from 3-aryl-substituted 2*H*-azirines and difluorocarbene. The reaction involves isomerization of azirinium ylide into a 2-aza-1,3-diene which undergoes [4+2]-cycloaddition with the starting azirine followed by ring expansion and dehydrofluorination.
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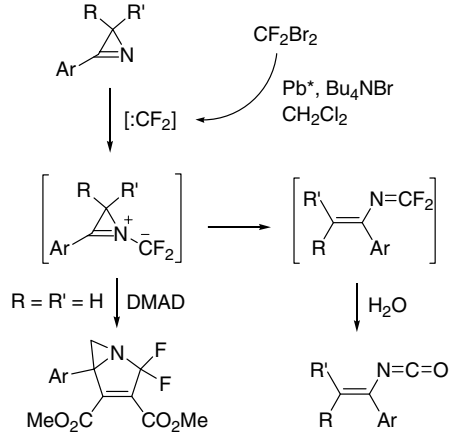
Structural features of 2*H*-azirines predetermine their high reactivity and substantial synthetic potential.[1–4] Notwithstanding the fact that the chemistry of 2*H*-azirines attracts much interest, their reactions with electrophilic carbenes, leading to the formation of unusual strained azomethine ylides, have scarcely been explored.[5,6]

Recently, we detected the formation of fluorine-substituted azirinium ylides in the reaction of 2*H*-azirines with difluorocarbene via 1,3-dipolar cycloaddition.[7,8] It was established that the reactivity of these unstable intermediates depends on the character of substitution in azirinium ring. Ylides obtained from 2,3-disubstituted and 2,2,3-trisubstituted azirines, both in the absence and in the presence of a dipolarophile, undergo azirine ring opening to form unstable azadienes, which are hydrolyzed to stable isocyanates (Scheme 1). 3-Monosubstituted azirinium ylides, unlike di- and trisubstituted ylides, can enter 1,3-dipolar cycloadditions with electron-deficient alkynes, alkenes, and aldehydes and thus present interest as synthetic blocks for preparing azirinopyrrole, pyridine, and morpholine derivatives.[7,8]

In this work, we investigated the reaction of 3-aryl-2*H*-azirines with difluorocarbene in the absence of effective dipole traps and present the first results of the application of azirinium ylides in the synthesis of fluorinated 4*H*-1,3-diazepines. Unlike fused 1,3-diazepines,[9] monocyclic 1,3-diazepines are poorly studied, though some perhydro-derivatives have received considerable attention recently as compounds with potential anti-AIDS activity.[10] It is known that a few reactions lead to non-fused 1,3-diazepines: photolytic ring expansion of 2-azido- or tetrazolopyridines,[11] reaction of 2*H*-azirines with 1,2,4-triazine[12] or 1,3-oxazine derivatives,[13] and reaction of diazirines with cyclobutadienes.[14] These new fluorinated 4*H*-1,3-diazepines are interesting as potential bioactive compounds and useful synthetic blocks.



Scheme 1.

In continuation of our investigations of 1,3-dipolar cycloadditions of azirinium ylides to multiple bonds, we generated ylide **2a** from 3-phenyl-2*H*-azirine **1a** and difluorocarbene in the presence of furfural in order to obtain azirinooxazolidine **3a**, or the ring expansion product, 1,4-oxazin-3(4*H*)-one **4a** (Scheme 2).[7,8] Azirine

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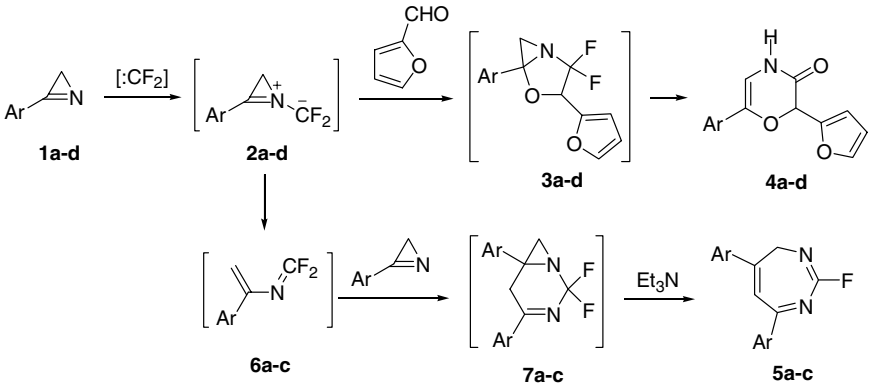


5a: Ar = Ph (41%); **5b**: Ar = 4-ClC_6H_4 (16%); **5c**: Ar = 4-BrC_6H_4 (11%); **4d**: Ar = 4-$MeOC_6H_4$ (4%)

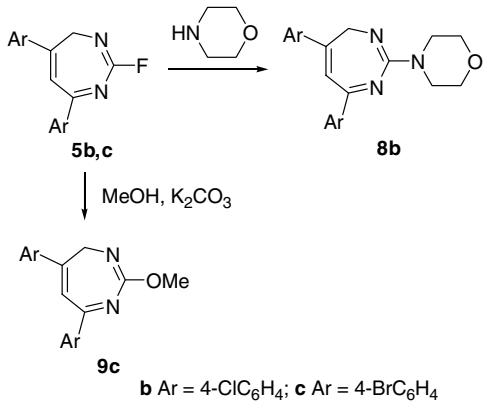
Scheme 2. Reagents and conditions: CF_2Br_2, active lead, Bu_4NBr, furfural, CH_2Cl_2, 40–45 °C, 6 h.

1a is a readily available compound and was synthesized from styrene in two steps in 63% yield.[15] Difluorocarbene was generated in situ by the reduction of dibromodifluoromethane with active lead[16] in the presence of tetrabutylammonium bromide.[17] However, contrary to expectations, the reaction gave 4*H*-1,3-diazepine **5a** in 41% yield. This product was isolated by treatment of a fraction of the chromatographic eluate, whose R_f was the same as that of furfural, with dry Et_3N. Analogous products **5b**,**c** were obtained from azirines **1b**,**c**. An addition product of ylide **2d** to furfural, oxazine **4d**,[18] could only be isolated in trace amounts when 4-methoxyphenyl-substituted azirine was used as the reactant.

The structures of compounds **5a**–**c** were proved from their IR, ^1H and ^{13}C NMR spectra,[19] as well as from chemical transformations. The ^1H NMR spectra of **5a**–**c** contain, along with aryl proton signals, a singlet at δ 4.08–4.13 ppm, assignable to the CH_2 protons, and a signal at δ 6.82–6.91 ppm (singlet or doublet, J_{HF} 0.9 Hz), assignable to the H^6 proton. The ^{13}C NMR spectra of diazepines **5a**–**c** display signals for the diazepine ring carbons at δ 46.6–46.7 (d, C^4, J_{CF} 14.4–14.8 Hz), δ 120.3–120.6 (C^6), δ 152.2–153.2 (d, C^5, J_{CF} 3.3–3.5 Hz), δ 157.7–157.8 (d, C^2, J_{CF} 217–220 Hz), and δ 172.7–174.1 (d, C^7, J_{CF} 14.9 Hz).

Diazepines **5a**–**c** contain a fairly labile fluorine atom, which has the ability to be changed to another functional group or heterocyclic moiety. Thus, treatment of compound **5b** with excess morpholine gave 2-morpholino-substituted diazepine **8b**[20] in 71% yield, while treatment of diazepine **5c** with anhydrous K_2CO_3 in methanol gave 2-methoxy-substituted diazepine **9c** (39%)[21] (Scheme 3).

The most probable mechanism of the formation of diazepines **5a**–**c** involves isomerization of ylides **2a**–**c** into azadienes **6a**–**c** followed by [4+2]-cycloaddition of the latter to azirines **1a**–**c** to form compounds **7a**–**c** (Scheme 2). Recently, the [2+4]-cycloaddition of methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate to electron-rich 2-azadienes has been reported.[22,23] Under the action of the base, 1,3-diazabicyclo[4.1.0]heptane derivatives **7a**–**c** underwent ring expansion and dehydrofluorination



b Ar = 4-ClC_6H_4; **c** Ar = 4-BrC_6H_4

Scheme 3.

to give diazepines **5a**–**c**. Furfural is an inactive dipolarophile due to the electron-rich nature of the furan ring and reacts poorly with ylides **2a**–**c**. However, in the absence of furfural, diazepines **5a**–**c** are impossible to isolate. At the same time, these products can be obtained if furfural is added to the reaction mixture before chromatographic purification. From azirine **1c**, using the general procedure with addition of furfural after reaction completion, compound **5c** was obtained in 21% yield. The role of furfural, which was used in the experiments in an 11-fold excess, is to stabilize difluorides **7a**–**c** during chromatographic purification. Since it has the same R_f in the hexane–ethyl acetate eluting system as compounds **7a**–**c** it prevents decomposition of the latter on silica gel.

It should be noted that the yields of adducts of some 1,3-dipolar cycloadditions of *gem*-difluoro-substituted azirinium ylides **2** generated from 3-aryl-2*H*-azirines **1** and difluorocarbene are frequently low, which may imply the occurrence of side reactions.[7,8] The resulting data led us to conclude that this fact is associated with the competitive isomerization of azirinium ylides into 1,1-difluoro-2-aza-1,3-dienes. The latter compounds under the reaction conditions, undergo [4+2]-cycloaddition to the starting azirines to form diazabicyclo[4.1.0]heptane derivatives like **7** that tend to decompose when isolated by chromatography on silica gel. Chromatography with

stabilizing additives followed by treatment with base allows unstable compounds **7** to be converted into relatively stable 2-fluoro-1,3-diazepines **5**. The use of two different azirines to realize cross-reaction of 1,3-diazepine formation is under investigation.

Acknowledgements

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17. A typical experimental procedure for the reaction of difluorocarbene with 3-aryl-2*H*-azirines is as follows: azirine **1a** (0.74 g, 6.31 mmol), Bu_4NBr (3.96 g, 14.89 mmol), furfural (7 g, 72.84 mmol), and CF_2Br_2 (1.41 mL, 15.52 mmol) were added to a flask charged with freshly prepared active lead (2.41 g, 11.65 mmol) under a layer of CH_2Cl_2 (25 mL). The flask was closed with a stopper which was fixed so as to keep a slight excess pressure and the reaction mixture was magnetically stirred at 40–45 °C until the lead disappeared completely (6 h). The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel (hexane–EtOAc, 10:1). A fraction containing furfural was collected and the furfural was rapidly evaporated under reduced pressure (0.1 mmHg) at 30–40 °C. Dry Et_3N, 0.5 mL, was immediately added to the residue, and the mixture was left overnight at 5 °C. Evaporation of Et_3N, repeated chromatography, and recrystallization gave 0.34 g (41%) of diazepine **5a**.
18. Compound **4d** was obtained from azirine **1d** (0.5 g, 3.4 mmol) by the general procedure using hexane–EtOAc mixture (10:1) for chromatography, 0.035 g (4%) of oxazine **4d** was obtained as a colorless solid; mp 151–153 °C (Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$): 3.81 (s, 3H, Me), 5.70 (s, 1H, H^2), 6.19 (d, 1H, H^5, $J = 4.8$ Hz), 6.37 (dd, 1H, H^4 furyl, $J = 3.5$, 1.3 Hz), 6.53 (d, 1H, H^3 furyl, $J = 3.5$ Hz), 6.87 (d, 2H, H_{Ar}, $J = 8.9$ Hz), 7.38 (d, 2H, H_{Ar}, $J = 8.9$ Hz), 7.48 (s, 1H, H^5 furyl, $J = 1.3$ Hz), 8.18 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$–DMSO-d_6): 54.1 (Me), 70.7 (C^2), 100.8 (C^5), 108.9, 109.4 (C^3 furyl, C^4 furyl), 112.7, 124.1, 136.0 (C_{Ar}), 142.4 (C^5 furyl), 147.4 (C^2 furyl), 158.1 (C_{Ar}), 161.3 (C^3). Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.83; N 5.16. Found: C, 66.27; H, 4.82; N, 4.92.
19. Data for compounds **5a**–**c**. Compound **5a**: pale yellow needles, mp 71–73 °C (hexane–Et_2O). IR ($CHCl_3$): 1620, 1660 (C=C, C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 4.13 (s, 2H, H^4), 6.91 (d, 1H, H^6, $J = 0.9$ Hz), 7.46–7.66 (m, 8H, H_{Ph}), 8.05–8.08 (m, 2H, H_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$): 46.7 (d, C^4, $J_{CF} = 14.8$ Hz), 120.6 (C^6), 126.9, 128.1, 128.4, 128.6, 129.6, 132.6, 136.5, 137.2 (C_{Ph}), 153.2 (d, C^5, $J_{CF} = 3.4$ Hz), 157.8 (d, C^2, $J_{CF} = 217$ Hz), 174.1 (d, C^7, $J_{CF} = 14.9$ Hz). Anal. Calcd for $C_{17}H_{13}FN_2$: C, 77.26; H, 4.96; N, 10.60. Found: C, 77.38; H, 5.01; N, 10.43. Compound **5b**: pale yellow solid, mp 158–160 °C (hexane–Et_2O). IR ($CHCl_3$): 1600, 1630, 1670 (C=C, C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 4.09 (s, 2H, H^4), 6.83 (s, 1H, H^6), 7.43–7.58 (m, 6H, H_{Ar}), 7.98–8.01 (m, 2H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): 46.7 (d, C^4, $J_{CF} = 14.9$ Hz), 120.3 (C^6), 128.2, 128.8, 128.9, 129.5, 134.8, 135.5, 135.9, 139.1 (C_{Ar}), 152.2 (d, C^5 $J_{CF} = 3.5$ Hz), 157.7 (d, C^2, $J_{CF} = 220$ Hz), 172.7 (d, C^7, $J_{CF} = 14.9$ Hz). Anal. Calcd for $C_{17}H_{11}Cl_2FN_2$: C, 61.28; H, 3.33; N, 8.41. Found: C, 61.32; H, 3.41; N, 8.30. Compound **5c**: pale yellow solid, mp 181–183 °C (Et_2O). IR ($CHCl_3$): 1635, 1660, 1670 (C=C, C=N). ^{1}H NMR (300 MHz, $CDCl_3$): 4.08 (s, 2H, H^4), 6.82 (s, 1H, H^6), 7.47–7.93 (m, 8H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): 46.6 (d, C^4, $J_{CF} = 14.4$ Hz), 120.3 (C^6), 124.3, 127.8, 128.5, 129.6, 131.8, 131.9, 135.2, 136.0 (C_{Ar}), 152.3 (d, C^5, $J_{CF} = 3.3$ Hz), 157.7 (d, C^2, $J_{CF} = 219$ Hz), 172.8 (d, C^7, $J_{CF} = 14.9$ Hz). Anal. Calcd for $C_{17}H_{11}Br_2FN_2$: C, 48.37; H, 2.63; N 6.64. Found: C, 48.35; H, 2.64; N, 6.65.
20. Compound **8b**: A mixture of diazepine **5b** (20 mg, 0.06 mmol) and dry morpholine (0.4 mL) was allowed to stand at 20 °C for a week and then poured into 5 mL of water. A precipitate formed, which was filtered off, washed with 5 mL of water, dried in air, and recrystallized to afford 23 mg (71%) of diazepine **8b** as a colorless solid, mp 157–161 °C (dec., hexane–Et_2O). IR ($CHCl_3$): 1590, 1600, 1640 (C=C, C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 3.49 (t, 4H, CH_2, $J = 4.6$ Hz), 3.75 (t, 4H, CH_2, $J = 4.6$ Hz), 3.98 (s, 2H, H^4), 6.68 (s, 1H, H^6), 7.40–7.93 (m, 8H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): 45.9 (CH_2), 48.0 (C^4), 66.4 (CH_2), 119.2 (C^6), 128.1, 128.6, 128.9, 135.1, 136.1, 136.2, 137.7 (C_{Ar}), 154.2 (C^5), 159.6 (C^2),

168.3 (C^7). Anal. Calcd for $C_{21}H_{19}Cl_2N_3O$: C, 63.01; H, 4.78; N, 10.50. Found: C, 63.06; H, 4.83; N, 10.24.

21. Compound **9c**: A mixture of diazepine **5c** (20 mg, 0.047 mmol) and calcined K_2CO_3 (35 mg, 0.265 mmol) in absolute methanol (1 mL) was stirred for 2 h and then poured into 5 mL of water. A precipitate formed which was filtered off, dried in air, and recrystallized from Et_2O to give 8 mg (39%) of diazepine **9c** as a colorless solid, mp 169–171 °C (Et_2O). IR ($CHCl_3$): 1610, 1640, 1655 (C=C, C=N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 3.79 (s, 3H, CH_3), 4.02 (s, 2H, H^4), 6.71 (s, 1H, H^6), 7.51–7.90 (m, 8H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): 47.1 (C^4), 54.7 (Me), 119.9 (C^6), 123.7, 126.7, 128.4, 129.4, 131.6, 131.8, 136.1, 136.5 (C_{Ar}), 153.3 (C^5), 161.6 (C^2), 170.0 (C^7). Anal. Calcd for $C_{18}H_{14}Br_2N_2O$: C, 49.80; H, 3.25; N 6.45. Found: C, 49.61; H, 3.28; N, 6.45.
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