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Generation and cycloadditions of azirinium difluoromethanides—strained azomethine ylides

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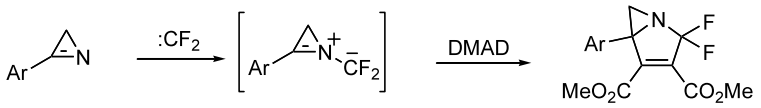
Abstract—The reaction of 3-aryl-2*H*-azirines with difluorocarbene involves the formation of azirinium difluoromethanides—the first strained azomethine ylides which undergo 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate, giving rise to fluorinated fused azirinopyrrole derivatives.

The chemistry of azirines has long attracted considerable interest because of the high reactivity of these strained nitrogen unsaturated heterocycles towards electrophiles, nucleophiles, as well as dipoles and dienes, in cycloaddition reactions.[1] However, the reactions of azirines with electrophilic carbenes, which might give rise to unusual strained azomethine ylides—azirinium methanides, are practically unknown. No evidence has so far been reported for the existence of systems in which the carbon–nitrogen bond of a 1,3-dipole is incorporated into a three-membered ring. There has been a sole work of Hassner et al. who showed that the reaction of dichlorocarbene with azirines proceeds with opening of the three-membered ring to provide *N*-vinyl-*N*-dichloromethyleneamines, presumably through formation of the corresponding azirinium dichloromethanides and subsequent rearrangement of the latter, directly or through cyclization, into transient 1-azabicyclobutane.[2] Trapping of dichloro-substituted ylides by 1,3-dipolar cycloaddition often fails because of their tendency for 1,3-cyclization into aziridines.

Earlier we found that reaction pathways of halogenocarbene-derived ylides are highly halogen-dependent.[3] Quantum-mechanical calculations revealed that introduction of two geminal fluorine atoms influences the ylide geometry, and this shows up in a great difference in reactivity between iminiodifluoromethanides and their close analogue iminiochlorofluoromethanides and iminiodichloromethanides.[4] Actually, as predicted by the calculations difluoroylides (irrespective of substituent at nitrogen) undergo 1,3-dipolar cycloaddition onto multiple bonds rather than cyclization into aziridines,[5] and with dichloroylides and chlorofluoroylides the situation is the opposite.[6] These findings led us to suppose that difluorocarbene would react with azirines to give the corresponding azirinium difluoromethanides which might be fixed as adducts of 1,3-dipolar cycloadditions to suitable dipolarophiles.

We found that the reaction of 3-aryl-2*H*-azirines with difluorocarbene proceeds through formation of difluorosubstituted azirinium ylides—the first strained azomethine ylides which can be trapped with DMAD and benzaldehyde as dipolarophiles to obtain fused azirinopyrrole or azirinoxazole derivatives. Difluorocarbene was produced by reduction of CF_2Br_2 with active lead in the presence of tetrabutylammonium bromide.[5d]



1a-f **2a-f** **3a-f**

Ar = (**a**) Ph (36%), (**b**) 4-MeC_6H_4 (28%), (**c**) 4-$MeOC_6H_4$, (**d**) 4-ClC_6H_4 (34%), (**e**) 4-BrC_6H_4 (40%), (**f**) 3,4-$Cl_2C_6H_4$ (27%)

Scheme 1.

Keywords: azirines; difluorocarbene; strained azomethine ylides; cycloaddition; azirinopyrroles.

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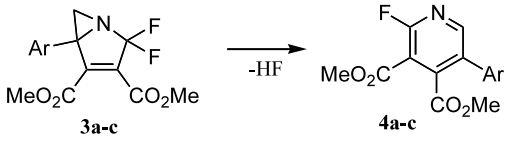
The reaction of 3-aryl-2*H*-azirines **1a–f** with difluorocarbene in the presence of dimethyl acetylenedicarboxylate as a dipolarophile yields azirino[1,2-*a*]pyrroles **3a**,**b**,**d–f** (Scheme 1) which were fully characterised using standard spectral and analytical methods.[7] The modest yields of the products can be rationalised by their partial decomposition on silica during chromatographic purification. In fact, the primary products of cycloaddition of difluorosubstituted azomethine ylides to multiple carbon–carbon bonds are usually not isolable compounds because of their propensity to dehydrofluorinate into pyrroles[5a,5c,5e] or hydrolyse into lactams.[5b,5d,5e] In contrast, *gem*-difluorinated azirinopyrroles **3** being isolated as solids or an oil are fairly stable and can be stored indefinitely at –20°C. However, when kept at room temperature they quantitatively transformed to 2-fluoropyridines[7] **4** by ring expansion and dehydrofluorination (Scheme 2). Of all the azirines studied, only azirine **1c** gave a cycloadduct which proved to be not stable enough to withstand chromatographic work-up and directly transforms into pyridine **4c** (isolable yield 36%).

Cycloaddition of azirinium difluoromethanide **2a** to benzaldehyde proceeds completely regioselectively. However, the corresponding primary cycloadduct **5** is unstable and undergoes hydrolysis to give 42% of morpholinone[7] **7**, probably through the 3-fluoromorpholine derivative **6** (Scheme 3). The regioselectivity of cycloaddition of azirinium difluoromethanides to carbonyl group is the same as in intermolecular cycloaddition of unstrained fluorinated azomethine ylides.[5c]



3a-c **4a-c**

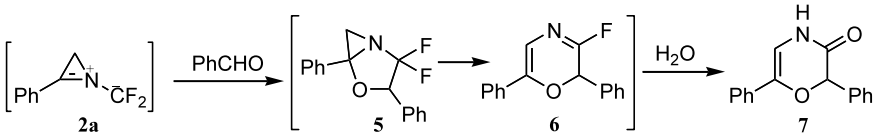
Ar = (**a**) Ph, (**b**) 4-MeC$_6$H$_4$, (**c**) 4-MeOC$_6$H$_4$

Scheme 2.

An important feature of the 2,2-difluoro-1-azabicyclo[3.1.0]hex-3-enes **3** synthesised is their ability to undergo transformations with preservation of the three-membered ring. Thus, azirinopyrroles **3** react with primary amines with preservation of the strained bicyclic skeleton (Scheme 4). The products are amino-substituted azirinopyrroles **8** which are probably formed by *tele*-substitution (S_N2' reaction) of one fluorine in compounds **3** with amine, followed by *ipso*-substitution of the second fluorine through the addition-elimination sequence. The structure of the products was proved by ^{1}H, ^{13}C NMR and IR spectroscopy and elemental analysis.[7] The *trans*-arrangement of the aryl and methoxycarbonyl groups follows from the chemical shifts of CH_3O protons[6a,8] and the NOESY spectrum of compound **8a**.

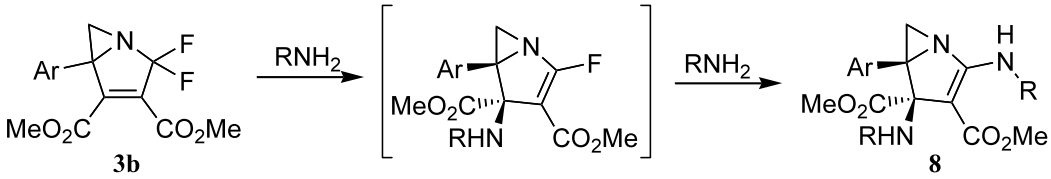
In conclusion, we have demonstrated that a new type of azomethine ylide, strained azirinium difluoromethanides, can be generated by the reaction of difluorocarbene with 3-aryl-2*H*-azirines. The azirinium methanides can be used as synthetic equivalents both of -C$^+$-N-C$^-$ and -C$^+$-C-N-C$^-$-synthons in the carbene-derived ylide methodology of preparation of heterocycles containing an unusual combination of structural fragments: a strained ring and fluorine.

A typical experimental procedure of the reaction of azirines **1** with difluorocarbene in the presence of dipolarophiles is as follows. A flask containing a freshly prepared active lead (1.7 g, 8.2 mmol) and methylene chloride (20 cm^3) was charged with Bu_4NBr (2.79 g, 10.5 mmol), imine **1a** (0.52 g, 4.44 mmol), DMAD (1.89 g, 13.3 mmol), and CBr_2F_2 (1 cm^3, 10.9 mmol). The flask was tightly stopped, and the mixture was magnetically stirred at 45°C until the lead was consumed completely (ca. 4 h). The solvent was removed under reduced pressure, and the residue was separated by chromatography on silica gel.



2a **5** **6** **7**

Scheme 3.



3b **8**

8 Ar = 4-MeC$_6$H$_4$; (**a**) R = Me, (**b**) R = PhCH$_2$

Scheme 4.

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7. Data for selected compounds: **3a** mp 70–72°C (Et_2O/pentane); IR ν_{max} (CCl_4): 1670, 1755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 7.41–7.36 (m, 5H, PhH), 3.85 (s, 3H, MeO), 3.76 (s, 3H, MeO), 2.85 (d, $J_{H\text{-}F}=1.5$ Hz, 1H, 1-H), 2.69 (d, $J_{H\text{-}F}=2.5$ Hz, 1H, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$): 162.3 (C=O), 159.7 (t, C=O, $J_{C\text{-}F}=2.6$ Hz), 154.8 (t, C^5, $J_{C\text{-}F}=4.5$ Hz), 124.0 (dd, C^4, $J_{C\text{-}F}=30$, 38 Hz), 129.1 (dd, C^3, $J_{C\text{-}F}=245$, 255 Hz), 131.2 (d, C^{Ph}, $J_{C\text{-}F}=3.5$ Hz), 129.0, 128.5, 127.8 (C^{Ph}), 55.0 (t, C^{5a}, $J_{C\text{-}F}=2.9$ Hz), 49.2 (t, C^1, $J_{C\text{-}F}=3.5$ Hz), 52.6, 52.4 (MeO). Anal. Calcd for $C_{15}H_{13}F_2NO_4$: C, 58.26; H, 4.24; N, 4.53. Found: C, 58.11; H, 4.34; N, 4.34: **4a** (mp 68°C, EtOH); IR ν_{max} (CCl_4): 1760, 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 8.38 (s, 1H, C^6), 7.46–7.33 (m, 5H, PhH), 3.97 (s, 3H, MeO), 3.70 (s, 3H, MeO); ^{13}C NMR (75 MHz, $CDCl_3$): 165.5 (C=O, $J_{C\text{-}F}=4.4$ Hz), 162.9 (C=O, $J_{C\text{-}F}=6.6$ Hz), 159.5 (C^2, $J_{C\text{-}F}=247$ Hz), 150.9 (C^6, $J_{C\text{-}F}=15$ Hz), 145.1 (C^4, $J_{C\text{-}F}=2.2$ Hz), 133.3 (C^5, $J_{C\text{-}F}=5.5$ Hz), 134.2, 128.5, 128.4, 128.2 (C_{Ar}), 111.7 (C^2, $J_{C\text{-}F}=31$ Hz), 52.9, 52.6 (MeO). Anal. Calcd for $C_{15}H_{12}FNO_4$: C, 62.28; H, 4.18; N, 4.84. Found: C, 62.00; H, 4.24; N, 4.69; **7** mp 190–192°C (CH_2Cl_2); IR ν_{max} ($CHCl_3$): 3415, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 8.92 (br. s, 1H, NH), 7.54–7.28 (m, 10H, ArH), 6.31 (d, $J=4.7$ Hz, 1H, 5-H), 5.68 (s, 1H, 2-H); ^{13}C NMR (75 MHz, $CDCl_3$): 165.1 (C=O), 138.2 (C^6), 134.8, 132.0 (Ph-*ipso*), 128.6, 127.7 (Ph-*p*), 128.3, 128.2, 126.6, 123.3 (Ph-*o*,*m*), 102.0 (C^5), 78.0 (C^2). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.11; N, 5.68; **8a** (mp 158°C, AcOEt/hexane); IR ν_{max} ($CHCl_3$): 3415, 3345, 1740, 1675, 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 7.46 (br. s, 1H, HN), 7.32 (d, $J=7.9$ Hz, 2H, ArH), 7.14 (d, $J=7.9$ Hz, 2H, ArH), 3.88 (s, 3H, MeO), 3.63 (s, 3H, MeO), 3.22 (d, $J=5.3$ Hz, 3H, MeN), 2.59 (s, 1H, 1-H), 2.34 (s, 3H, Me), 2.15 (s, 1H, 1-H), 2.06 (br. s, 1H, HN), 1.98 (s, 1H, MeN); ^{13}C NMR (75 MHz, $CDCl_3$): 174.0, 173.5 (C=O), 167.8 (C^3), 136.7, 133.0, 128.6, 126.4 (C^{Ph}), 84.0 (C^4), 72.6 (C^5), 54.9 (C^{5a}), 46.0 (C^1), 52.2 (MeO), 50.1 (MeO), 20.8 (Me), 28.5 (MeN), 29.1 (MeN). Anal. Calcd for $C_{18}H_{23}N_3O_4$: C, 62.59; H, 6.71; N, 12.17. Found: C, 62.62; H, 6.74; N, 12.29.
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