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The first example of the generation of azomethine ylides from a fluorocarbene: 1,3-cyclization and 1,3-dipolar cycloaddition

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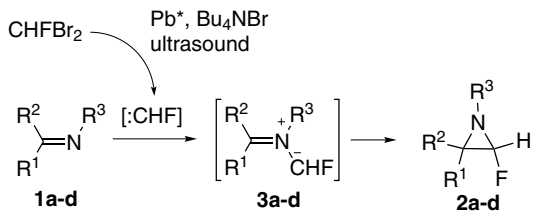
Abstract—The reaction of Schiff bases with fluorocarbene, generated by reduction of dibromofluoromethane with active lead in the presence of Bu_4NBr under ultrasound irradiation, involves the formation of fluoro-substituted azomethine ylides which undergo cyclization into aziridines. 1,3-Cyclization of ylides, generated from *N*-arylimines of benzaldehyde, proceeds stereoselectively. When carrying out the reaction of Schiff bases with fluorocarbene in the presence of dimethyl maleate or dimethyl acetylenedicarboxylate, the products of dehydrofluorination of the primary adducts of the 1,3-dipolar cycloaddition of fluoro-substituted azomethine ylides to multiple bonds of dipolarophiles were obtained. In the case of the reaction of *N*-alkylimines of benzaldehyde the cycloaddition of ylides to dimethyl maleate completely suppressed the cyclization to aziridines.

Nitrogen ylides, which are formed in the reactions of halocarbenes with the C=N bonds of imines and nitrogen heterocycles, are useful synthetic blocks for the preparation of various nitrogenated acyclic and heterocyclic compounds.[1] The reactions of dichloro- and difluorocarbenes with unsaturated nitrogen-containing compounds, giving rise to *gem*-dichloro-[1a,d,2] and *gem*-difluoro-substituted iminium ylides, are of most practical importance.[1d,3] The chemical properties of these species are well documented. Irrespective of their structure, difluoro-substituted azomethine ylides do not cyclize to aziridines, but readily cycloadd to dipolarophiles.[1d,3] On the other hand, *gem*-dichloro ylides, generally provide *gem*-dichloroaziridines in good yields.[1a,d,2a,c–e] The exceptions are ylides generated from dichlorocarbene and ketene imines[1a,d,2a,b] or *N*-(primary-alkyl)imines of benzaldehydes,[1a,d,2c] which are prone to react only via cycloaddition. Whereas for *gem*-chlorofluoroazomethine ylides, generated by the addition of chlorofluorocarbene to Schiff bases, only cyclizations to the corresponding aziridines are known.[4]

It is evident that the nature and number of halogen atoms in *gem*-dihalogenoazomethine ylides largely define their reactivity.[3a,5] When atoms of the most electronegative element, fluorine, are attached to the carbon of a 1,3-dipole one can expect pronounced changes in its chemical behavior that make dipoles, such as *gem*-difluoro- and monofluoroazomethine ylides, a subject of particular interest. Nevertheless, monofluorinated azomethine ylides were unknown up to now. In this work, the first examples of the generation of monofluorosubstituted azomethine ylides and the main routes of their transformation are disclosed.

Known methods for the generation of monofluorocarbene[1b,6] are ineffective for the preparation of monofluorinated azomethine ylides. When a mixture of an *N*-alkyl-*N*-benzhydrylideneamine **1a–d**, dibromofluoromethane, active lead[3e] and tetrabutylammonium bromide in methylene chloride was irradiated with ultrasound at ca. 40 °C, aziridines **2a–d** were formed. They were isolated by column chromatography in 19–47% yields.[7] The reaction sequence leading to the formation of aziridines **2a–d** is depicted in Scheme 1. It involves



Scheme 1.

Keywords: Fluorocarbene; Fluoroaziridines; Azomethine ylides; Cyclization; Cycloaddition.
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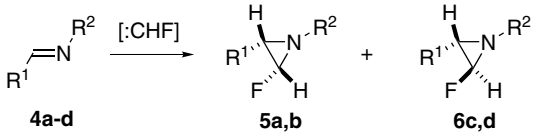
Table 1. Reaction of imines **1a–d** with fluorocarbene

Imine	R^1	R^2	R^3	Yield of **2** (%)
1a	Ph	Ph	Me	**2a**, 47
1b	Ph	Ph	CH_2Ph	**2b**, 34
1c	Ph	Ph	CH_2CO_2Me	**2c**, 47
1d	2,2′-Biphenylene		CH_2CH_2Ph	**2d**, 19



Scheme 2.

attack by the fluorocarbene onto the unshared electron pair of the imine nitrogen to give the azomethine ylides **3a–d** followed by cyclization (Table 1). Fluoroaziridines **2a–d** are thermally stable enough to endure refluxing in 1,4-dioxane or toluene for 2 h without decomposition. They decompose rather rapidly, however, on silica. Thus, isolation of these compounds from the reaction mixture was carried out by use of silica treated with anhydrous Et_3N. Crystalline products, such as aziridines **2a–c**, could be isolated by multiple washing of the reaction mixture with a saturated aqueous solution of Na_2CO_3 followed by crystallization.

1,3-Cyclization of fluorinated ylides, generated from the imines of arenecarbaldehydes **4a–d**, may provide stereoisomeric aziridines **5** and **6**. However, when *N*-aryl-*N*-arylideneamines were reacted with fluorocarbene only the *cis*-aziridines **5a**,**b** were detected by ^{1}H NMR ($J_{vic\text{-}HH} = 4.4$ Hz, $J_{vic\text{-}HF} = 2.5$ Hz, $J_{gem\text{-}HF} = 79$ Hz) in the reaction mixtures (Table 2). The *cis*-configuration of aziridines **5a**,**b** is evident from the values of J_{HF} (2.5 Hz), since *trans*- and *cis*-vicinal $^3J_{HF}$ constants found for monofluoroaziridines are 2.4 and 8.1 Hz, respectively.[8]

It is known that azomethine ylides, generated from dichlorocarbene and *N*-(primary-alkyl)imines of arenecarbaldehydes, like **4c**,**d**, fail to cyclize to aziridines.[1a,d,2c] In contrast, when imines **4c**,**d** were reacted with fluorocarbene, the formation of the corresponding aziridines **6c**,**d** was detected by ^{1}H NMR (Scheme 2).

Aziridine **6c** was isolated as a mixture with the starting material, *N*-benzyl-*N*-benzylideneamine, in 21% yield. The configurations of the products formed from *N*-aryl-*N*-arylideneamine and *N*-alkyl-*N*-arylideneamines

Table 2. Reaction of imines **4a–d** with fluorocarbene

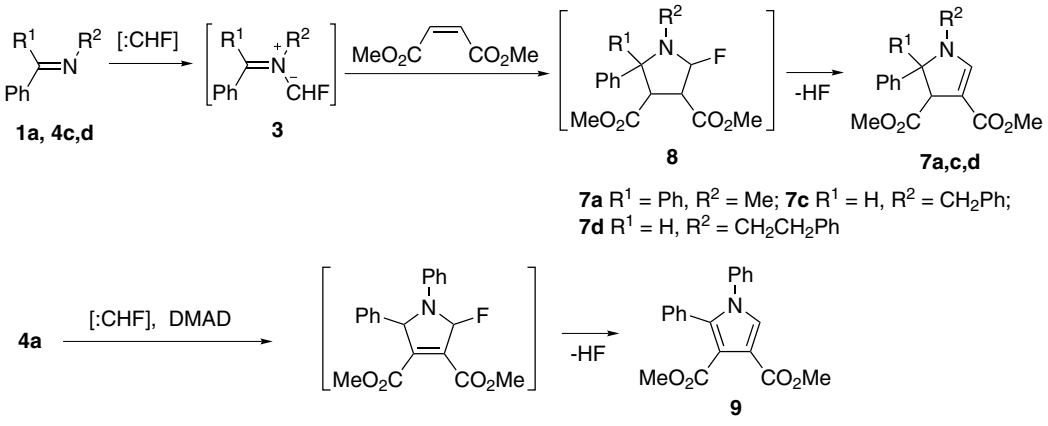
Imine	R^1	R^2	Yield of **5** (%)	Yield of **6** (%)
4a	Ph	Ph	**5a**, 4	
4b	4-ClC_6H_4	4-ClC_6H_4	**5b**, 22	
4c	Ph	CH_2Ph		**6c**,[a] 21
4d	Ph	CH_2CH_2Ph		**6d**[b]

[a] Isolated as a mixture with *N*-benzyl-*N*-benzylideneamine, in a 3:2 ratio.
[b] Detected in the reaction mixture by ^{1}H NMR.

were the opposite (Table 2). In the latter case, only *trans*-aziridines were formed ($J_{vic\text{-}HH} = 0$ Hz, $J_{vic\text{-}HF} = 5.5$ Hz, $J_{gem\text{-}HF} = 79$ Hz).

The intermediate ylides **3** may be trapped by electron deficient alkenes and alkynes. The reactions of imines **4c**,**d** with fluorocarbene in the presence of a 4-fold excess of dimethyl maleate gave rise to isomeric pyrrolidines **7c**,**d** (total yields are 37–38%, trans:cis-isomers ca. 4:1) (Scheme 3). Compounds **7c**,**d** had been formed by dehydrofluorination of the fluoropyrrolidines **8**, which were the 1,3-dipolar cycloadducts of ylides **3** and the C=C bond of dimethyl maleate. Aziridines were not detected under these conditions. However, the competitive formation of the aziridine as well as the product of cycloaddition of ylide **3a** occurred when fluorocarbene was reacted with *N*-benzhydrylidene-*N*-methylamine **1a** in the presence of a 4-fold excess of dimethyl maleate (the ratio of aziridine **2a**:pyrrolidine **7a** was 1:0.9). Pyrrole **9** was isolated in 32% yield from the reaction of imine **4a** with fluorocarbene in the presence of a 2-fold excess of dimethyl acetylenedicarboxylate.

In conclusion, we have demonstrated that a new type of fluorinated azomethine ylide, iminiofluoromethanides,



Scheme 3.

can be generated by the reaction of fluorocarbene with Schiff bases. Ylides generated from *N*-arylimines of benzaldehydes cyclize to *cis*-aziridines, whereas *N*-alkyl-substituted ylides give rise to *trans*-aziridines. The reactions in the presence of dimethyl maleate or acetylenedicarboxylate give rise to the dehydrofluorinated adducts of the fluoro-substituted ylides to the multiple bonds. In the case of *N*-alkylimines of benzaldehydes, cycloaddition to dimethyl maleate completely suppresses cyclization into aziridines, whereas fluorinated ylides from imines of benzophenone react in both directions.

A typical experimental procedure for the reaction of azomethines with fluorocarbene is as follows: a flask containing freshly prepared active lead (2.5 g, 12.1 mmol) and methylene chloride (40 cm^3) was charged with Bu_4NBr (3.87 g, 12.0 mmol), *N*-benzhydrylidene-*N*-methylamine (0.64 g, 3.3 mmol) and $CHFBr_2$ (1.2 cm^3, 14.9 mmol). When the reaction of imines **1a**,**4a**,**c**,**d** was carried out in the presence of dipolarophiles, dimethyl maleate (1.90 g, 13.2 mmol) or dimethyl acetylenedicarboxylate (0.94 g, 6.6 mmol) were also added. The flask was tightly stoppered and the mixture was subjected to ultrasonic irradiation at 40 °C until the lead was completely consumed (ca. 50 h). The solvent was removed under reduced pressure, and the residue was separated by chromatography on silica gel treated with Et_3N.

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7. Data for selected compounds: Compound **2a** mp 29–31 °C (hexane); ^1H NMR (300 MHz, $CDCl_3$): 2.35 (d, 3H, Me, $J_{HF} = 2.2$), 5.23, (d, 1H, H^2, $J_{HF} = 79.3$), 7.2–7.5 (m, 10H, H(Ph)). ^{13}C NMR (75 MHz, $CDCl_3$): 37.4 (d, Me, $J_{CF} = 4.7$), 54.7 (d, C^3, $J_{C-F} = 14.0$), 88.7 (d, C^2, $J_{CF} = 242.9$), 127.2, 127.8, 127.9, 128.6, 128.7, 130.4 (d, $J_{CF} = 2.6$), 135.2, 138.8 (d, $J_{CF} = 3.6$) C(Ph). Anal. Calcd for $C_{15}H_{14}FN$: C, 79.27; H, 6.21; N, 6.16%. Found: C, 79.13; H, 6.22; N, 6.26%. **5b** mp 106–108 °C (hexane); ^1H NMR (300 MHz, $CDCl_3$): 3.28 (dd, 1H, H^2, $J_{HH} = 4.2$, $J_{HF} = 2.5$), 5.19 (dd, 1H, C^3, $J_{HF} = 78.5$, $J_{HH} = 4.2$), 7.03 (d, 2H, H(Ph), $J = 8.8$), 7.28 (d, 2H, H(Ph), $J = 8.8$), 7.39 (d, 2H, H(Ph), $J = 8.6$), 7.44 (d, 2H, H(Ph), $J = 8.6$). ^{13}C NMR (75 MHz, $CDCl_3$): 45.7 (d, C^2, $J_{CF} = 13.5$), 83.0 (d, C^3, $J_{CF} = 247.1$), 120.4, 128.6, 128.9, 129.0, 129.5, 131.7 (d, $J_{CF} = 4.2$), 134.0, 148.0 C(Ph). Anal. Calcd for $C_{14}H_{10}Cl_2FN$: C, 59.60; H, 3.57; N, 4.96%. Found: C, 59.35; H, 3.59; N, 4.91%. *trans*-**7d** colorless oil; IR ν_{max} (CCl_4): 1750, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 2.74–2.87 (m, 2H, CH_2Ph), 3.15–3.33 (m, 2H, CH_2N), 3.66 (s, 3H, Me), 3.77 (s, 3H, Me), 3.87 (d, 1H, H^3, $J = 8.2$), 4.83 (d, 1H, H^2, $J = 8.2$), 7.09–7.34 (m, 10H, H(Ph)), 7.35 (s, 1H, H^5). ^{13}C NMR (75 MHz, $CDCl_3$): 35.0 (CH_2Ph), 49.1, 50.5, 52.3, 55.7 (C^3, CH_2N, $2 \times Me$), 71.2 (C^2), 97.7 (C^4), 126.7, 128.5, 128.7, 129.0, 138.1, 139.7 C(Ph), 151.1 (C^5), 165.7 (C═O), 174.1 (C═O). *cis*-**7d** mp 153–155 °C (Et_2O–hexane); IR ν_{max} (CCl_4): 1755, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 2.75–2.88 (m, 2H, CH_2Ph), 3.08–3.18 (m, 1H, CH_2N), 3.12 (s, 3H, Me), 3.26–3.34 (m, 1H, CH_2N), 3.67 (s, 3H, Me), 4.21 (d, 1H, H^3, $J = 12.5$), 5.01 (d, 1H, H^2, $J = 12.5$), 7.07–7.34 (m,

10H, H(Ph)), 7.40 (s, 1H, H^5); ^{13}C NMR (75 MHz, $CDCl_3$): 34.7 (CH_2Ph), 49.0, 50.6, 51.3, 52.9 (C^3, CH_2N, $2 \times Me$), 69.8 (C^2), 99.5 (C^4), 126.6, 128.0, 128.2, 128.3, 135.3, 138.1 C(Ph), 152.1 (C^5), 165.7 (C═O), 171.0 (C═O). Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83%. Found: C, 72.22; H, 6.41; N, 3.87%.

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