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The first example of intramolecular cycloaddition of carbene-derived azomethine ylides in a domino reaction of difluorocarbene with Schiff bases

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Abstract—Domino reactions of difluorocarbene with Schiff bases containing a tethered olefinic or acetylenic dipolarophile moiety involve intramolecular 1,3-dipolar cycloaddition of iminiodifluoromethanides and yield chromeno[4,3-*b*]pyrrole derivatives.

Intramolecular 1,3-dipolar cycloaddition of azomethine ylides is a powerful synthetic approach to fused, bridged, and caged nitrogen-containing heterocycles.[1] Such reactions are quite attractive as they generally occur with high stereocontrol and make the achievement of a strong increase in molecular complexity possible. Functionally substituted ylides supply the cycloadducts with groups available for further chemical transformations. However, the azomethine ylides used so far in intramolecular reactions only allow a limited number of functional groups to be introduced.[2] Specifically, halogenated ylides have never been employed in such reactions despite the fact that intermolecular 1,3-dipolar cycloaddition of dihalogenomethylides to alkenes,[3–5] alkynes,[5–7] and carbonyl compounds[8] give rise to nitrogen-containing heterocycles with such useful functional groups as carbonyl, fluorine and chlorine. The only known method for generation of halogenated azomethine ylides is reaction of dihalogenocarbenes with C=N compounds.[9,10]

In this communication, we wish to report the first example of intramolecular 1,3-dipolar cycloaddition of azomethine ylides generated by a carbenic method, namely by reaction of difluorocarbene with Schiff bases containing a tethered dipolarophile moiety. Schiff bases **1a**–**c** provided lactams **2a**–**c** and fluoropyrrolines **3a**,**c** as the result of reaction with difluorocarbene, followed by chromatographic isolation (Scheme 1). The domino reaction is triggered by an attack of difluorocarbene on the nitrogen lone pair, resulting in formation of azomethine ylides **4a**–**c**; intramolecular cycloaddition of the latter to the activated double bond gives difluoropyrrolidines **5a**–**c**. These compounds are labile both under the reaction conditions, undergoing dehydrofluorination to pyrrolines (**3a**,**c**), and under chromatographic purification, hydrolyzing to lactams **2a**–**c**. Fluoropyrrolines, too, tend to hydrolyze on silica gel to the corresponding compounds **2a**–**c**. Therefore, the chromatographic isolation of the products should be performed as quickly as possible. Apparently, the strong tendency for hydrolysis prevented isolation of methylpyrroline **3b**. Difluorocarbene was produced by reduction of CF_2Br_2 with active lead in the presence of tetrabutylammonium bromide. Active lead was prepared by reduction of lead acetate with sodium borohydride just before use.[7] The use of metallic lead instead of active lead for difluorocarbene generation reduced the yield of product **2b** from 55 to 32% and increased the reaction time from 2 to 34 h.

Earlier we showed that intermolecular cycloaddition of difluoro-substituted azomethine ylides to unsymmetrical dipolarophiles, such as ethyl acrylate or methyl methacrylate, results in preferential or exclusive formation of a regioisomer with the CO_2R and CF_2 groups *meta* to each other.[4] Had such regioselectivity of cycloaddition been retained in the intramolecular reaction of difluoroazomethine ylides **4a**–**c**, bridged regioisomers **6a**–**c** would have been formed. However, the reaction yields exclusively fused regioisomers **5a**–**c**. The reversed regioselectivity can be explained in terms of the rigorous conformational restrictions the 4-atom tether poses on the geometry of the transition state.

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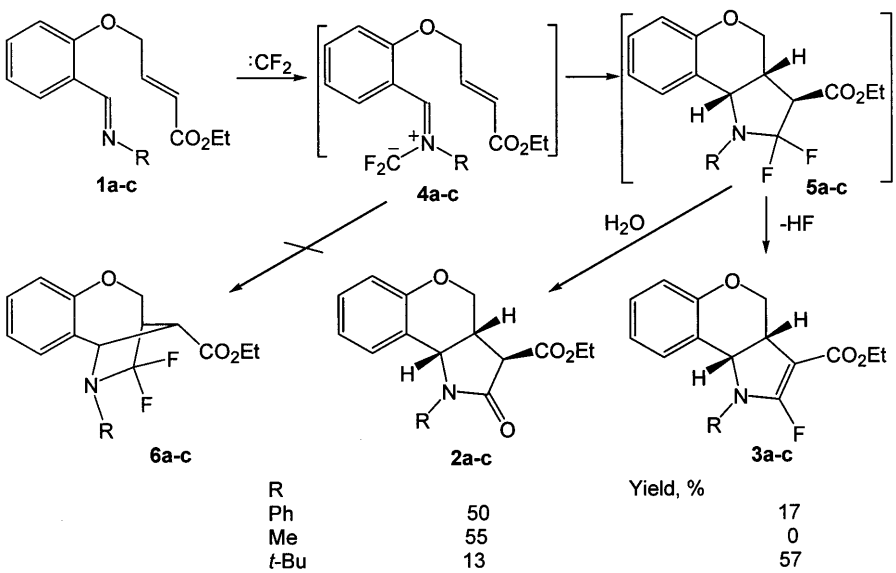


R	Yield, %	
Ph	50	17
Me	55	0
t-Bu	13	57

Scheme 1.

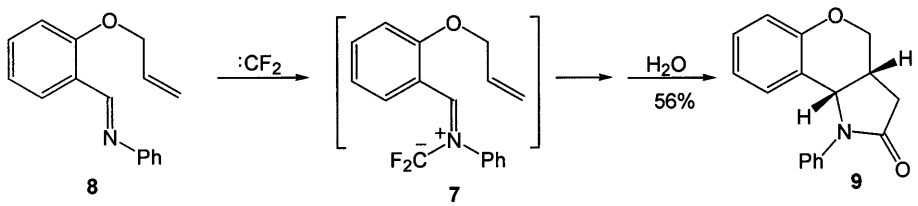
The above methodology was successfully extended to ylides containing nonactivated tethered dipolarophile moieties, such as monosubstituted double and triple bonds.

Thus, ylide **7** derived from imine **8** readily adds to a terminal C=C bond, providing the chromenopyrrole derivative **9** in 56% yield after hydrolysis on silica (Scheme 2).

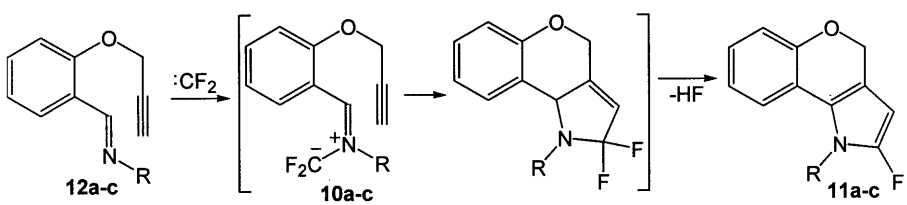
It is known that the intramolecular cycloadditions of azomethine ylides with formation of 5- and 6-fused systems can occur both with high stereocontrol to give *cis*-fused[2d,e] or *trans*-fused[2g] products and without any stereocontrol.[2b,h] The stereoselectivity is frequently reduced by increasing substitution at the dipolarophilic C=C bond.[2b,d] In our case, however, the cycloaddition of difluoro-substituted ylides both to a terminal double bond (ylide **7**) and to a disubstituted double bond (ylides **4a**–**c**) occurs completely stereoselectively, yielding *cis*-fused products.

Intramolecular cycloaddition of ylides **10a**–**c** containing a terminal triple bond as a dipolarophile is accompanied by dehydrofluorination under reaction conditions, resulting in formation of 2-fluorochromenopyrrole derivatives **11a**–**c**. The relatively low yields of pyrroles **11b**,**c** are explained by incomplete conversion of parent imines **12b**,**c** (the yield per reacted imine is 54% for both substrates) (Scheme 3).

The compounds synthesized were all previously unknown.[11] The *cis*-fusion of pyran and pyrrolidine rings in lactams **2a**–**c** is evident from the coupling constant (6.6–7.2 Hz) between 3a-H and 9b-H.[2b] The *trans*-configuration of C^3–C^{3a} bond is assessed from nOe data.[12]



Scheme 2.



R = Ph (69%) (**a**), Me (49%) (**b**), *t*-Bu (31%) (**c**)

Scheme 3.

A typical experimental procedure is as follows. A flask containing freshly prepared active lead (2.0 g, 9.7 mmol) and methylene chloride (12 cm^3) was charged with Bu_4NBr (3.4 g, 10.0 mmol), the imine **1a** (0.93 g, 3.0 mmol) and CBr_2F_2 (1.2 cm^3, 13.1 mmol). The flask was tightly stopped, and the mixture was magnetically stirred at 45°C until the lead was consumed completely (ca. 2 h). The solvent was removed under reduced pressure, and the residue was separated by chromatography on silica gel.

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11. The data for selected compounds are: **2a** (mp 148–150°C Et_2O); IR ν_{max} ($CHCl_3$): 1730, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 7.5–6.5 (m, 9H, ArH), 5.44 (d, $J = 7.5$ Hz, 1H, 9b-H), 4.33 (m, 2H, CH_2), 4.22 (dd, $J = 11.9$, 3.5 Hz, 1H, 4-H), 4.18 (dd, $J = 11.9$, 4.9 Hz, 1H, 4-H), 3.77 (d, $J = 8.4$ Hz, 1H, 3-H), 3.44 (dddd, $J = 8.4$, 7.5, 4.9, 3.5 Hz, 1H, 3a-H), 1.37 (t, $J = 7.1$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 168.5, 167.8, 154.4, 137.0, 129.7, 129.2, 129.0, 127.0, 126.3, 120.8, 119.7, 117.3, 64.8, 61.6, 55.8, 49.6, 35.9, 13.8. Anal. calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 70.88; H, 5.63; N, 4.16. **3a** (oil); IR ν_{max} ($CHCl_3$) cm^{-1}: 1735, 1715; ^1H NMR (300 MHz, $CDCl_3$): 7.5–6.4 (m, 9H, ArH), 4.98 (d, $J = 8.8$ Hz, 1H, 9b-H), 4.38 (dd, $J = 10.9$, 4.4 Hz, 1H, 4-H), 4.25 (m, 2H, CH_2), 4.12 (dd, $J = 10.9$, 9.4 Hz, 1H, 4-H), 3.59 (m, 1H, 3a-H), 1.33 (t, $J = 7.1$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 163.8 (d, $^3J_{CF} = 6.1$ Hz), 163.0 ($^1J_{CF} = 291$ Hz), 155.9, 136.9, 130.7, 129.5, 129.2, 127.8, 127.4, 120.1, 118.0, 117.3, 79.4 ($^2J_{CF} = 3.9$ Hz), 65.1 ($^3J_{CF} = 3.3$ Hz), 59.7, 59.2, 35.7 ($^3J_{CF} = 3.9$ Hz), 14.2. **11a** (mp 76–78°C, hexane); ^1H NMR (300 MHz, $CDCl_3$): 7.6–6.3 (m, 9H, ArH), 5.56 (d, $^3J_{HF} = 4.0$ Hz, 1H, 3-H), 5.23 (s, 2H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$): 152.4 ($^6J_{CF} = 2.2$ Hz), 148.5 ($^1J_{CF} = 265$ Hz), 135.0, 129.1, 128.4, 127.3, 125.8, 120.8, 119.4, 117.9, 116.6, 115.8, 113.8 ($^3J_{CF} = 5.0$ Hz), 82.4 ($^2J_{CF} = 12.7$ Hz), 65.1 ($^4J_{CF} = 2.8$ Hz). Anal. calcd for $C_{17}H_{12}FNO$: C, 76.97; H, 4.56; N, 5.28. Found: C, 76.81; H, 4.59; N, 5.30.
12. ^1H nOe (%) for **2a**: irradiation of 3a-H resulted in enhancement of 9b-H (14) and 3-H (2). For comparison, ^1H nOe (%) for 3,3a-*cis*, 3a,9b-*trans* isomer of lactam **2a**: irradiation of 3a-H resulted in enhancement of 9b-H (11) and 3-H (12).