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gem-Difluorosubstituted NH-azomethine ylides in the synthesis of 4-fluorooxazolines via the three-component reaction of imines, trifluoroacetophenones and CF_2Br_2

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Abstract

A simple one-step synthesis of a new class of fluorinated heterocycles, 4-fluoro-3-oxazolines, from diarylmethanimines, trifluoroacetophenones and CF_2Br_2 is described. The reaction proceeds via the sequential formation of difluorocarbene and a *gem*-difluorosubstituted NH-azomethine ylide, followed by 1,3-dipolar cycloaddition with a ketone.

1,3-Dipolar cycloaddition of azomethine ylides with compounds containing carbon–carbon and carbon–oxygen multiple bonds is an attractive synthetic approach to pyrrole and oxazole derivatives. Such a strategy has the advantage of synthetic efficiency and high regio- and stereoselectivity. Most syntheses have been realized using N-substituted azomethine ylides, resulting in the formation of *N*-aryl or *N*-alkyl heterocycles.[1] For the synthesis of N-unsubstituted azaheterocycles via 1,3-dipolar cycloaddition, NH-azomethine ylides[2] or the so-called N-metallated azomethine ylides[1c,3] can be used. Furthermore, N-unsubstituted azomethine ylides with good leaving groups (CN, OTMS, STMS, SCH_3, $SSnBu_3$, etc.) are nitrile ylide equivalents[4] and can be used for the preparation of pyrroline,[5] oxazoline,[6] and other heterocycles.[7]

The known methods for the generation of NH-azomethine ylides involve desilylation of nitrogen-containing silanes,[2b] ring opening of aziridines,[8] prototropy of azomethines,[2a,c,d] 1,2- and 1,4-silatropy of α-silylimines and α-silylamides, respectively,[5a,9] 1,4-stannotropy of *N*-(stannylmethyl)thioamides,[10] decarboxylation of α-amino acids,[11] and condensation of aldehydes with N-unsubstituted α-amino acids,[12] making it possible to introduce CO_2R, CN, NRR′, and =NR functional groups into the target heterocycles. C-Halogen-substituted NH-azomethine ylides are unknown though the corresponding N-substituted iminium ylides are widely used for the synthesis of halogenated, and in particular, fluorinated heterocycles.[13]

In this work, we report the first example of the generation of *gem*-difluorosubstituted NH-azomethine ylides, their trapping by 1,3-dipolar cycloaddition with trifluoroacetophones and their utilization for the synthesis of a new class of fluorinated heterocycles-4-fluoro-3-oxazolines.

The only method for the generation of fluorinated azomethine ylides is the reaction of fluoro- and difluorocarbenes with compounds containing C=N bonds.[13a] Difluorocarbene was generated in situ by the reduction of dibromodifluoromethane with lead in the presence of tetrabutylammonium bromide.[13b] To form *gem*-difluorosubstituted NH-azomethine ylides, we used diphenylmethanimine **1a** as the starting imine, and α,α,α-trifluoroacetophenone **2a** was used for trapping dipole **4a**. Stirring a mixture of imine **1a**, α,α,α-trifluoroacetophenone, CF_2Br_2, lead filings, and Bu_4NBr in dichloromethane in the ratio 1:1:1:1:1:120 for 42 h gave rise to fluoro-oxazoline **3a** in 15% yield after chromatographic purification

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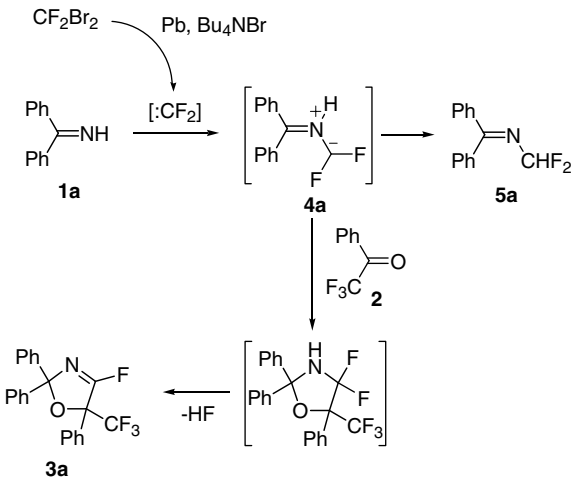


Scheme 1. The reaction of diphenylmethanimine **1a** with difluorocarbene.

(Scheme 1).[14] This three-component reaction proceeds via two reactive intermediates—difluorocarbene and the *gem*-difluorosubstituted NH-ylide **4a**. The NH-ylide then participates in a 1,3-dipolar cycloaddition to give an intermediate, which undergoes dehydrofluorination.

The structure of compound **3a** was determined from IR, ^{1}H, ^{13}C, and ^{19}F NMR spectra, and confirmed by single crystal X-ray data (Fig. 1).[15]

The second product of the reaction was the unstable difluoroimine **5a**, formation of which was detected by chromatographic and NMR methods. This compound easily hydrolyses but it is possible to isolate it by flash chromatography on silica with 10% of benzophenone. The difluoromethyl group of difluoroimine **5a** was apparent in the ^{1}H NMR spectrum as a triplet at δ 6.35 ($^{1}J_{HF}$ 70.6 Hz). The triplet signal for the carbon of this fragment in the ^{13}C NMR spectrum was found at δ 115.2 ($^{1}J_{HF}$ 232 Hz). The triplet at δ 176.7 ($^{1}J_{HF}$ 15.7 Hz) was attributed to the imine function. Difluoroimine **5a** is the product of a formal 1,2-H-shift in azomethine ylide **4a**. To improve the yield of oxazoline **3a** and to diminish the formation of by-product **5a** we performed the reaction of imine **1a** with difluorocarbene under different conditions, varying the concentrations of reagents, their ratio, and dispersiveness of lead (lead filings or active pyrophoric lead). The optimization of conditions and the results are summarized in Table 1. The best yield of oxazoline **3a** was obtained with the molar ratio of reagents $Ph_2C{=}NH{:}CF_2Br_2{:}Pb{:}Bu_4NBr{:}PhCOCF_3{:}CH_2Cl_2$ equal

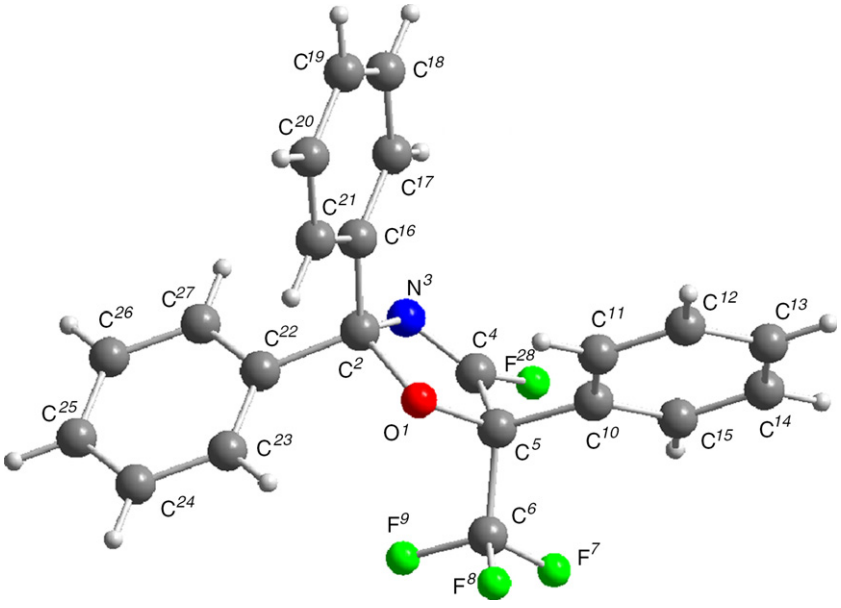
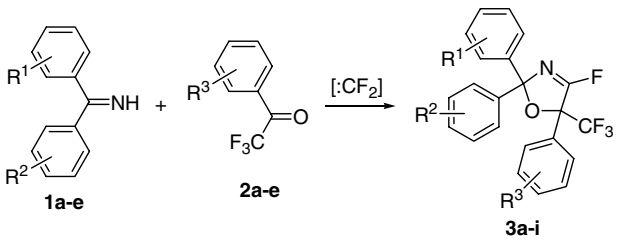


Fig. 1. X-ray structure of compound **3a**.

Table 1
Optimization of the reaction conditions for the synthesis of oxazoline **3a** from diphenylmethanimine **1a** and trifluoroacetophenone **2a**

Entry	Imine (mmol)	Pb (mmol)	Bu_4NBr (mmol)	CF_2Br_2 (mmol)	$PhC(O)CF_3$ (mmol)	CH_2Cl_2 (mL)	Generation of CF_2	Reaction time (h)	Yield of **3a** (%)
1	6	6	6	6	6	25	A	42	15
2	2	6	6	6	6	10	A	6	66
3	4	12	12	12	10	20	B	18	38
4	1	3	3	3	3	3	A	168	50
5	1	3	3	3	6	3	C	120	37

Reaction conditions: A: (lead/ultrasound irradiation); B: (active lead/magnetic stirring without ultrasound irradiation); C: (lead/magnetic stirring without ultrasound irradiation).



Scheme 2. The synthesis of fluorooxazolines **3a–i**.

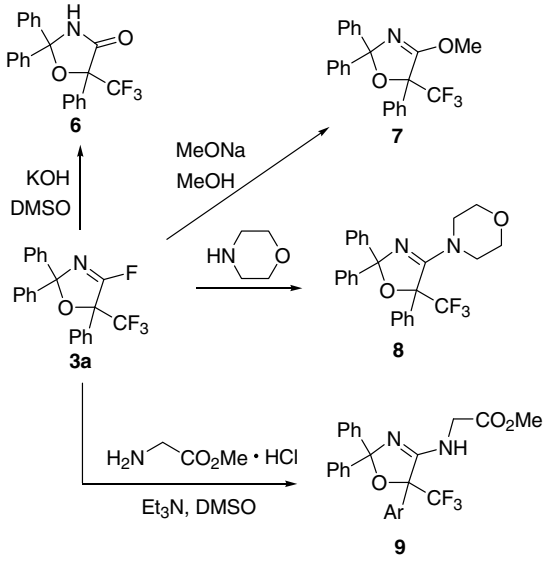
Table 2
Preparation of fluoro-oxazolines **3a–i**

Imine	R^1	R^1	Ketone	R^3	Oxazoline	Yield (%)
1a	H	H	**2a**	H	**3a**	66
1b	4-Cl	4-Cl	**2a**	H	**3b**	61
1c	4-Cl	4-CN	**2a**	H	**3c**	10[a]
1d	4-CF_3	4-CF_3	**2a**	H	**3d**	12
1e	3-CF_3	3-CF_3	**2a**	H	**3e**	38
1a	H	H	**2b**	4-CH_3	**3f**	63
1a	H	H	**2c**	4-Cl	**3g**	54
1a	H	H	**2d**	4-F	**3h**	76
1a	H	H	**2e**	3-CF_3	**3i**	74

[a] Mixture of stereoisomers.

to 1:3:3:3:3:78 with ultrasonication of the reaction mixture at 40 °C (entry 2). The use of active lead did not increase the yield of the desired product in contrast to the results obtained earlier for N-substituted imines.[13b] With optimized conditions in hand, we synthesized oxazolines **3b–i** starting from substituted diarylmethanimines **1b–e** and acetophenones **2b–e** (Scheme 2 and Table 2).[14]

The decrease in yield of oxazolidines having electron-withdrawing substituents on the phenyl rings is probably accounted for by the increase of the acidity of ylides **4** derived from imines **1c–e** and this increase of acidity facilitates isomerization of the ylides to the corresponding difluoroimines **5**.



Scheme 3. The reactions of fluoro-oxazoline **3a** with *O*- and *N*-nucleophiles.

It was found that fluorooxazolines **3** were stable under acidic conditions. For example, compound **3f** did not decompose in refluxing conc. hydrochloric acid over 8 h. At the same time, the fluorine can be easily replaced via reaction with nucleophilic reagents (Scheme 3). Treatment of oxazoline **3a** with potassium hydroxide in DMSO gave rise to lactam **6** in 91% yield. Methoxy-derivative **7** was obtained as a product of the reaction of oxazoline **3a** with sodium methoxide in methanol in 94% yield. *N*-Nucleophiles easily react with compound **3a** at room temperature. Treatment of oxazoline **3a** with morpholine for 2 days gave rise to compound **8** in 76% yield. Compound **9** was obtained in 88% yield via reaction of oxazoline **3a** with methyl glycinate hydrochloride in a mixture of Et_3N and DMSO.

In summary, a simple one-step synthesis of a new class of fluorinated heterocycles, 4-fluoro-3-oxazolines, from diarylmethanimines, trifluoroacetophenones, and CF_2Br_2 is described. This three-component reaction proceeds via two reactive intermediates—difluorocarbene and a *gem*-difluorosubstituted NH-azomethine ylide. Besides the main reaction—cycloaddition with the C=O bond—*gem*-difluorosubstituted NH-ylides undergo a formal 1,2-H-shift with the formation of *N*-(difluoromethyl)diarylmethanimines. This isomerization explains the decrease in yield of oxazolidines from imines which contain strong electron-withdrawing substituents on the phenyl rings.

Acknowledgment

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14. A typical experimental procedure for the synthesis of fluoro-oxazolines **3a**–**i** is as follows. A flask containing freshly prepared lead filings (0.64 g, 6 mmol) and dichloromethane (10 mL) was charged with Bu_4NBr (1.93 g, 6 mmol), diarylmethanimine (2 mmol), aryltrifluoromethyl ketone (6 mmol) and CF_2Br_2 (0.55 mL, 6 mmol). The flask was tightly stoppered, immersed in an ultrasonic cleaner (160 W) and irradiated with ultrasound at 40 °C until the lead was consumed completely (6–20 h). The solvent was removed under reduced pressure, and the residue was separated by column chromatography on silica to afford oxazolines **3a**–**i**. Crystalline products were recrystallised from hexane or a mixture of hexane–Et_2O.
15. Data for selected compounds: **3a** (colourless solid), mp 111–112 °C (hexane–Et_2O). IR ($CHCl_3$): 1740 (C=N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.23–7.69 (m, 15H, H_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$): 84.9 (quintet, C^5, $^2J_{CF} = 32.9$ Hz), 107.5 (d, C^2, $^3J_{CF} = 21.9$ Hz), 122.1 (qd, CF_3, $^1J_{CF} = 287.2$ Hz, $^3J_{CF} = 4.9$ Hz), 125.8, 128.2, 128.3, 128.6, 129.8, 130.9, 131.0, 141.8, 142.2 (C_{Ph}), 157.9 (d, C^4, $^1J_{CF} = 298.7$ Hz). ^{19}F NMR (188 MHz, $CDCl_3$, ext. standard C_6F_6): 80.0 (q, F–C^4, J_{FF} 3.2 Hz), 86.7 (d, CF_3, J_{FF} 3.2 Hz). Anal. Calcd for $C_{22}H_{15}F_4NO$: C, 68.57; H, 3.92; N, 3.63. Found: C, 68.53; H, 4.07; N, 3.42. X-ray data for compound **3a**: $C_{22}H_{15}F_4NO$, $M = 385.36$, monoclinic, space group $P21/c$, $a = 9.0134(10)$, $b = 22.6457(19)$, $c = 9.8100(10)$ Å, $\beta = 117.129(8)°$, $V = 1782.07(30)$ Å^3, $Z = 4$, $d = 1.436$ g/cm^3, MoK_α radiation, $\lambda = 0.71073$ Å, $T = 133$ K. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC-666525. Compound **7**: (colourless solid), mp 129.5–130 °C (methanol). ^1H NMR (300 MHz, $CDCl_3$): 4.16 (s, 3H, CH_3), 7.19–7.69 (m, 15H, H_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$): 57.9 (OCH_3), 86.1 (q, C^5, $^2J_{CF} = 31.3$ Hz), 108.7 (C^2), 122.7 (q, CF_3, $^1J_{CF} = 287$ Hz), 125.9, 126.0, 127.5, 127.6, 127.9, 128.0, 129.1, 132.7, 143.7, 144.1 (C_{Ph}), 162.9 (C^4). Anal. Calcd for $C_{23}H_{18}F_3NO_2$: C, 69.52; H, 4.57; N, 3.52. Found: C, 69.51; H, 4.63; N, 3.54. Compound **8**: (colourless solid), mp 142–143 °C (hexane–Et_2O). IR ($CHCl_3$): 1650 (C=N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.19–7.6 (m, 15H, H_{Ph}), 3.29–3.73 (m, 8H, CH_2).^{13}C NMR (75 MHz, $CDCl_3$): 47.6 (CH_2), 66.1 (CH_2), 89.4 (q, C^5, $^2J_{CF} = 29.3$ Hz), 110.1 (C^2), 123.59 (q, CF_3, $^1J_{CF}$ 288 Hz), 126.1, 126.3, 127.4, 127.5, 127.6, 127.6, 128.2, 128.3, 129.3, 129.8, 135.1, 145.9, 146.3 (C_{Ph}), 157.24 (C^4). Anal. Calcd for $C_{26}H_{23}F_3N_2O_2$: C, 69.02; H, 5.12; N, 6.19. Found: C, 69.14; H, 5.13; N, 6.29.