SHORT PAPER

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Synthesis of fluoro-substituted 4,5-dihydro-1,2,4-oxadiazoles *via* 1,3-dipolar cycloadditions†

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4,5-Dihydro-1,2,4-oxadiazoles have been prepared by regiospecific 1,3-dipolar cycloaddition of nitrile oxides with fluoro-substituted aldimines.

Keywords: cycloaddition, fluoro compounds, 1,2,4-oxadiazoles, imines, nitrile oxides

The importance of fluoro-heterocycles is widely acknowledged in many fields, such as medicine and agrochemistry, due to their peculiar properties and biological activity.[1] Among them, many fluoro-substituted, fully unsaturated 1,2,4-oxadiazoles are described in the literature, owing to their interest as pesticides and insecticides[2] or in medicinal chemistry[3], *e.g.* as antiviral agents. Nevertheless, only very few examples of the corresponding fluoro-substituted partially hydrogenated 4,5-dihydro-1,2,4-oxadiazoles are known.[4]

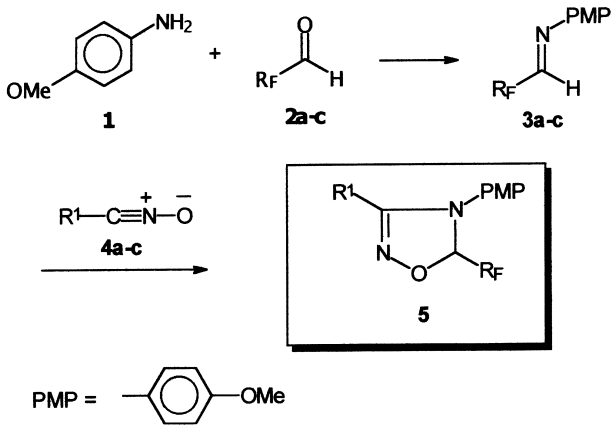
For the construction of heterocyclic systems several methods are available: among these, 1,3-dipolar cycloadditions occupy a preeminent place, owing to their versatility and to the high regio- and stereo-chemical control that can be involved in such reactions.[5]

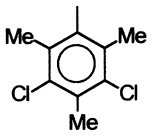
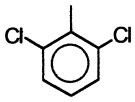
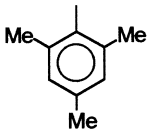
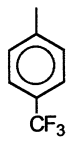
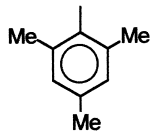
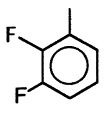
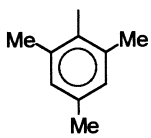
Within a research program aimed to the synthesis of fluorinated heterocycles of biological interest *via* 1,3-dipolar cycloadditions,[6] we thought to devise a cycloadditive route to 4,5-dihydro-1,2,4-oxadiazoles, starting from common 1,3-dipoles and easily accessible fluorinated dipolarophiles. The present paper describes the synthesis of 5-trifluoromethyl- and 5-(fluoroaryl)-4,5-dihydro-1,2,4-oxadiazoles through the cyclo-addition of the aromatic nitrile oxides **4** with fluoro-substituted aldimines **3** (Scheme 1).

Results and discussion

The synthesis of fluoro-substituted aldimines **3a–c** was performed in good yield (75–90%) through the condensation of 4-methoxybenzenamine **(1)** with fluoroaldehydes **2a–c** in the presence of an acidic ion-exchange resin (Dowex W X 8-400). Subsequently, the nitrile oxides **4a–c** were treated with a 1.2:1 molar excess of the fluoro-substitued aldimines **3a–c** in a CCl_4 solution: after 3 to 10 days at room temperature, the cycloadducts **5** were isolated in moderate to good yields as the only regioisomers. The assigned structures rely upon analytical and spectral data (Table 1): in particular the ^{13}C NMR signals of the sp^3 ring carbon atom, ranging from 91 to 97 ppm (see Experimental), are evidence of its position between an oxygen and a nitrogen atom; the observed regiochemical orientation, that can be ascribed mainly to electronic factors, is also in agreement with literature data on the 1,3-dipolar cycloadditions of nitrile oxides with C=N bonds.[7]

Owing both to the great variety of fluorinated aldimines that can be prepared by the above described method, and to the number of available nitrile oxides, the reported reactions can constitute an effective and versatile cycloadditive route to a



	R_F	R^1
5aa	CF_3	
5ab	CF_3	
5ac	CF_3	
5bc		
5cc		

Scheme 1

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

Table 1 ^{1}H and ^{19}F NMR data of 4,5-dihydro-1,2,4-oxadiazoles **5**

Product	δ_H (ppm), *J* (Hz)	δ_F (ppm), *J* (Hz)
5aa	7.02 and 6.74 (m, 4 H, ArH), 6.18 (q, 1 H, $^3J_{H,F}$ 4.2, CHN), 3.72 (s, 3 H, OMe), 2.51, 2.46 and 2.26 (s, 9 H, 3×Ar*Me*)	–83.52 (d, 3 F, $^3J_{F,H}$ 4.2, CF_3)
5ab	7.4-7.1 and 6.78 (m, 7 H, ArH), 6.08 (q, 1 H, $^3J_{H,F}$ 4.1, CHN), 3.74 (s, 3 H, OMe)	–83.56 (d, 3 F, $^3J_{F,H}$ 4.1, CF_3)
5ac	7.08, 6.92, 6.82 and 6.80 (m, 6 H, ArH), 6.81 (q, 1 H, $^3J_{H,F}$ 4.6, CHN), 3.68 (s, 3 H, OMe), 2.36, 2.20 and 2.08 (br s, 9 H, 3×Ar*Me*)	–82.91 (d, 3 F, $^3J_{F,H}$ 4.6, CF_3)
5bc	7.70, 7.67, 6.80, 6.65 and 6.60 (m, 10 H, ArH), 6.88 (s, 1 H, CHN), 3.63 (s, 3 H, OMe), 2.45, 2.24 and 2.20 (br s, 9 H, 3×Ar*Me*)	–63.2 (br s, 3 F, CF_3)
5cc	7.6–6.5 (m, 9 H, ArH), 7.23 (s, 1 H, CHN), 3.63 (s, 3 H, OMe), 2.49, 2.24 and 2.15 (s, 9 H, 3×Ar*Me*)	–138.9 and –145.8 (m, 2 F, 2×ArF)

class of fluoro-substituted heterocycles of biological interest. As a further development of this work, we are now considering the use as dipolarophiles of fluoro-substituted aldimines bearing also a chiral and enantiomerically pure sulfinyl function.[8] The asymmetric induction that this chiral auxiliary is able to exert in the cycloadditions[9] could allow the preparation of enantiopure fluoro-substituted 4,5-dihydro-1,2,4-oxadiazoles. These reactions are in progress and will be reported in due course.

Experimental

Melting points were obtained using a capillary apparatus and are uncorrected. Analytical TLCs were performed with Merck silica gel 60 F_{254} plates. Flash column chromatographies were performed with silica gel 60 (230-400 ASTM mesh). ^{1}H, ^{13}C and ^{19}F NMR spectra were obtained on a Bruker AC 250L spectrometer, operating at 250.13, 62.89 and 235.35 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts are expressed in ppm (δ), using tetramethylsilane (TMS) as internal standard for ^{1}H and ^{13}C nuclei (δ_H and δ_C = 0.00), whilst C_6F_6 was used as external standard (δ_F = –162.90) for ^{19}F. Coupling constants are expressed in Hertz (Hz). In the ^{13}C NMR signal assignment, capital letters refer to the pattern resulting from directly bonded (C,H) couplings and lower case letters to that from (C,F) couplings. Mass spectra were registered on a TSQ 70 Finnigan Mat three-stage quadrupole instrument. DIS (Direct Inlet System) was used for pure compounds. Infrared spectra were obtained using a Perkin-Elmer System 2000 FT-IR.

Commercially available reagents and solvents were employed without further purification. Trifluoroacetaldehyde **2a** was directly used in the commercial hydrate form. Nitrile oxides **4a**[10] and **4c**[11] were prepared by standard literature methods. Nitrile oxide **4b** was generated *in situ* by treatment of the corresponding chlorooxime[12] with an excess of triethylamine.

*Fluoro-substituted aldimines **3**. General procedure:* To a solution of 4-methoxybenzenamine 1 (0.96 g, 7.75 mmol) in benzene (9.4 ml) fluoroaldehydes **2a–c** (7.04 mmol) were added, followed by a catalytic amount of Dowex 50 W X 8-400 ion-exchange resin. The mixture was refluxed for 2 hours, collecting the water of condensation by a Dean-Stark apparatus. After filtering off the catalyst and evaporating the solvent under reduced pressure, the residue was distilled *in vacuo* **(3a)** or flash chromatographed on a silica gel column **(3b,c)** with hexane-ethyl acetate mixtures, affording fluoro-substituted aldimines **3a–c**, in yields ranging from 75 to 90%. Physical properties of the aldimines **3a**[13] and **3b**[14] were consistent with literature data.

N-*(4-Methoxyphenyl)-2,3-difluorobenzaldimine* **3c:** yield 88%; m.p. 53–54°C; ν_{max} (KBr) 1623 cm^{-1}. δ_H 8.78 (s, 1 H, CH=N); 7.93 (dddd, 1 H, *J* 7.9, 5.9, 1.9, 1.7), 7.22 (dddd, 1 H, *J* 9.6, 7.8, 7.5, 1,9) and 7.16 (dddd, 1 H, *J* 7.9, 7.8, 5.0, 1.6): H-4, H-5 and H-6; 7.27 and 6.94 (m, 4 H, ArOMe*H*); 3.85 (s, 3 H, OMe). δ_F -139.75 (dddd, 1 F, *J* 20.0, 9.6, 5.0, 1.7) and -147.86 (dddd, 1 F, *J* 20.0, 7.5, 5.9, 1.6): F-2 and F-3. δ_C 155.88 (S, C-4'); 150.73 (Sdd, $J_{C,F}$ 256 and 13) and 150.63 (Sdd, $J_{C,F}$ 249 and 12): C-2 and C-3; 149.83 (Dt, $J_{C,F}$ 4.5, CH=N); 144.24 (S, C-1'); 126.36 (Sbrd, $J_{C,F}$ 7.5, C-1); 124.24 (Ddd, $J_{C,F}$ 7 and 5), 122.39 (Dm) and 119.24 (Dbrd, $J_{C,F}$ 17.5): C-4, C-5 and C-6; 122.45 and 114.45 (D, ArOMe*C*H); 55.52 (Q, OMe). *m/z* (%) 247 (M$^+$, 100), 232 (70), 134 (5), 107 (8), 77 (18). (Found: C, 66,23; H, 4.59; N, 6.06. $C_{14}H_{11}F_2NO$ requires: C, 66.36; H, 4.72; N, 5.96).

*4,5-Dihydro-1,2,4-oxadiazoles **5**. General procedure:* A solution of nitrile oxide **4** (0.50 mmol) and aldimine **3** (0.60 mmol) in CCl_4 (5.0 ml) was stirred at room temperature for a time ranging from 2 to 9 days. After removal of the solvent under reduced pressure, the residue was flash chromatographed on a silica gel column with hexane-ethyl acetate mixtures, affording 4,5-dihydro-1,2,4-oxadiazoles **5** (see Scheme 1 and Table 1).

3-(3,5-Dichloro-2,4,6-trimethylphenyl)-4-(4-methoxyphenyl)-5-trifluoromethyl-4,5-dihydro-1,2,4-oxadiazole **5aa:** reaction time 3 days; yield 34%; m.p. 134–135°C. δ_C 159.2 (S), 154.5 (S), 137.2 (S), 134.9 (2×S), 133.8 (2×S), 128.7 (S), 127.5 (2×D), 122.3 (S), 121.6 (Sq, $^1J_{C,F}$ 287.5), 114.9 (2×D), 91.9 (Dq, $^2J_{C,F}$ 35.5), 55.4 (Q), 19.0 (Q), 18.8 (Q), 18.3 (Q). *m/z* (%) 434 (40), 432 (M$^+$, 60), 363 (43), 335 (30), 134 (68), 122 (100), 108 (38). (Found: C, 52.49; H, 4.04; N, 6.32. $C_{19}H_{17}Cl_2F_3N_2O_2$ requires: C, 52.67; H, 3.95; N, 6.47).

3-(2,6-Dichlorophenyl)-4-(4-methoxyphenyl)-5-trifluoromethyl-4,5-dihydro-1,2,4-oxadiazole **5ab:** reaction time 4 days; yield 67%; m.p. 123–124°C. δ_C 159.4 (S), 152.2 (S), 136.3 (S), 136.2 (S), 132.4 (2×D), 128.5 (2×D), 128.4 (D), 128.2 (S), 122.6 (S), 121.6 (Sq, $^1J_{C,F}$ 293.0), 114.7 (2×D), 92.4 (Dq, $^2J_{C,F}$ = 35.5), 55.4 (Q). *m/z* (%) 392 (65), 390 (M$^+$, 100), 321 (92), 293 (94), 134 (37), 122 (80), 108 (60) (Found: C, 49.01; H, 2.95; N, 7.03. $C_{16}H_{11}Cl_2F_3N_2O_2$ requires: C, 49.13; H, 2.83; N, 7.16).

4-(4-Methoxyphenyl)-5-trifluoromethyl-3-(2,4,6-trimethylphenyl)-4,5-dihydro-1,2,4-oxadiazole **5ac:** reaction time 2 days; yield 81%; oil. δ_C 158.6 (S), 154.9 (S), 140.4 (S), 138.2 (2×S), 130.1 (S), 128.8 (2×D), 126.7 (2×D), 122.0 (Sq, $^1J_{C,F}$ 288.5), 119.4 (S), 114.7 (2×D), 91.6 (D, $^2J_{C,F}$ 35.5), 55.3 (Q), 21.1 (Q), 20.0 (Q), 19.6 (Q). *m/z* (%) 365 (18), 364 (M$^+$, 100), 295 (60), 267 (10), 134 (40), 122 (24) (Found: C, 62.85; H, 5.08; N, 7.49. $C_{19}H_{19}F_3N_2O_2$ requires: C, 62.63; H, 5.26; N, 7.69).

4-(4-Methoxyphenyl)-5-(4-trifluoromethylphenyl)-3-(2,4,6-trimethylphenyl)-4,5-dihydro-1,2,4-oxadiazole **5bc:** reaction time 7 days; yield 27%; oil. δ_C 157.2 (S), 154.3 (S), 141.7 (S), 140.0 (S), 137.8 (2×S), 132.1 (Sq, $^2J_{C,F}$ 33), 129.9 (S), 128.6 (2×D), 128.2 (Sq, $^1J_{C,F}$ 275), 128.1 (2×D), 125.7 (2×Dq, $^3J_{C,F}$ 5), 124.3 (2×D), 120.9 (S), 114.4 (2×D), 96.7 (D), 55.3 (Q), 21.2 (Q), 20.0 (2×Q). *m/z* (%) 440 (M$^+$, 30), 279 (38), 266 (100), 265 (32), 134 (68), 251 (21) (Found: C, 67.96; H, 5.40; N, 6.48. $C_{25}H_{23}F_3N_2O_2$ requires: C, 68.17; H, 5.26; N, 6.36).

5-(2,3-Difluorophenyl)-4-(4-methoxyphenyl)-3-(2,4,6-trimethylphenyl)-4,5-dihydro-1,2,4-oxadiazole **5cc:** reaction time 12 days; yield 31%; oil. δ_C 157.1 (S), 154.0 (S), 150.4 (Sm), 149.5 (Sm), 140.0 (S), 137.9 (2×S), 129.7 (S), 128.6 (2×D), 127.5 (Sm), 124.6 (Dm), 124.5 (Dm), 123.9 (2×D), 120.9 (S), 118.5 (Dm), 114.3 (2×D), 91.2 (D), 55.2 (Q), 21.2 (Q), 19.9 (2×Q). *m/z* (%) 408 (M$^+$, 38), 266 (90), 265 (100), 247 (80), 232 (70), 161 (18), 147 (37), 141 (43), 130 (25), 92 (15), 77 (10) (Found: C, 70.34; H, 5.31; N, 6.73. $C_{24}H_{22}F_2N_2O_2$ requires: C, 70.58; H, 5.43; N, 6.86).

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