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A facile tandem carbene-ylide route to 2-fluoropyrrole derivatives

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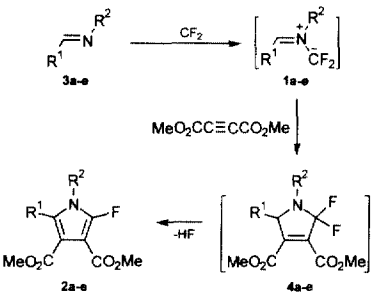
Abstract

2-Fluoropyrroles were synthesised via 1,3-dipolar cycloaddition of iminiodifluoromethanides derived from corresponding imines and difluorocarbene to dimethyl acetylenedicarboxylate.

Keywords: 2-Fluoropyrroles; Azomethine ylides; Difluorocarbene; Cycloaddition

1. Introduction

Fluoro-containing pyrroles are attractive synthesis targets for groups interested in fluorinated bioactive compounds. [1–6]. However, pyrroles bearing fluorine atoms directly linked to the nucleus are rare owing to the lack of convenient synthetic methods. Thus, direct fluorination of the pyrrole ring with xenon difluoride [7–9] and fluoro-decarboxylation of pyrrolecarboxylic acids [10] still remain practically the sole synthetic routes to 2-fluoropyrroles. Earlier, we reported the facile carbene-ylide synthesis of fused 2-chloropyrroles (indolizine derivatives), which involved the addition of dichlorocarbene to a nitrogenated heterocycle followed by 1,3-dipolar cycloaddition of the ylide formed to an alkene or alkyne [11–15]. Unfortunately, extension of this protocol to the synthesis of unfused 2-chloropyrroles gave unsatisfactory results because iminiodichloromethanides of type **1** (Cl instead of F) preferred to undergo cyclisation to the corresponding aziridines rather than participating in a 1,3-dipolar cycloaddition [16]. Recently, we have found that difluoro-substituted azomethine ylides generated by reaction of difluorocarbene with azomethines exhibit a diametrically opposite chemistry [17,18]. This led us to investigate whether this feature might form the basis for a convenient synthetic approach to 2-fluoropyrrole derivatives.



We present here our preliminary results on the synthesis of 2-fluoropyrrole derivatives **2a–e** based on the tandem iminiodifluoromethanide generation—1,3-dipolar cycloaddition reaction onto dimethyl acetylenedicarboxylate (DMAD). Iminiodifluoromethanides **1a–e** are unstable ylides, so they were generated in situ by the addition of difluorocarbene to imines **3a–e** in the presence of an excess of DMAD. Two methods of generation of difluorocarbene were examined: reduction of CBr_2F_2 with lead in the presence of tetrabutylammonium bromide (Method A) and reduction of CBr_2F_2 with activated zinc dust under ultrasound irradiation (Method B). The results obtained are presented in the Table 1. In all cases, the corresponding 2-fluoropyrroles **2a–e** were isolated. When the Pb-mediated carbene generation method was used, primary cycloaddition adducts **4a–e** underwent dehydrofluorination during the reaction, while in the case of the Zn-mediated procedure the reaction mixture should be additionally treated with Et_3N.

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Table 1
Reactions of imines **3a–e** with difluorocarbene in the presence of DMAD

Imine **3**	R^1	R^2	Method of: CF_2 generation	Yield of **2**, %[a]
a	Ph	Ph	A	58
a	Ph	Ph	B	15
b	Ph	4-$MeOC_6H_4$	A	30
c	Ph	4-ClC_6H_4	A	61
d	2,4-$Cl_2C_6H_3$	Ph	A	68
e	2-furyl	Ph	A	30
e	2-furyl	Ph	B	11

[a]Yields are based on the imine **3**.

2. Experimental

All reactions were carried out in dried solvents under nitrogen or argon, using rigorously dried glassware. Zinc dust was activated by treatment with 2% HCl aq. then washed with water, ethanol and ether (in that order) and then dried in vacuo. Zinc dust and lead were obtained from Merck.

Melting points were determined with a hot stage microscope (Boetius) and are uncorrected. Microanalyses were obtained using a Hewlett-Packard 185B CHN-analyser. IR spectra were obtained with a Carl-Zeiss UR-20 spectrophotometer. ^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded on a Bruker AMX 250 instrument (^{1}H, 250 MHz, internal standard TMS; ^{13}C, 62.9 MHz, internal standard $CHCl_3$) or Varian VXR 500S (^{19}F, 470.3 MHz, internal standard $CFCl_3$). Mass spectra were obtained using a HP-59970C instrument. Column chromatography separations were performed on silica gel LS 5/40 (Chemapol) with hexane–diethyl ether mixture as eluant.

2.1. General procedure

2.1.1. Method A

Lead powder (1.2 g, 5.8 mmol), tetrabutylammonium bromide (2.0 g, 6.0 mmol), CH_2Cl_2 (7 ml), Schiff base **3** (2.7 mmol), DMAD (0.98 g, 6.9 mmol), and CBr_2F_2 (1.92 g, 9.2 mmol) were placed in succession into a tube (or into a flask) filled with argon, after which the tube was sealed (or the flask was tightly stoppered). The mixture was stirred by rotation or shaking at 45°C until the lead was consumed completely (ca. 60 h). The reaction mixture was diluted with Et_2O (10 ml), filtered, and the solvent was removed under reduced pressure. Purification by chromatography on silica gel and recrystallisation from Et_2O–CH_2Cl_2 gave pyrrole **2**.

2.1.2. Method B

A mixture of Schiff base **3** (2.7 mmol), DMAD (0.98 g, 6.9 mmol) activated Zn dust (0.70 g, 10.8 mmol), and CBr_2F_2 (1.92 g, 9.2 mmol) in dry THF (10 ml) was immersed in a sonic cleaner and irradiated with ultrasound for 7.5 h. Then Et_3N (1 ml) was added dropwise under stirring and cooling with water. After additional stirring for 10 min the solvent was evaporated, and the residue was purified by chromatography on silica gel and recrystallisation from Et_2O to give pyrrole **2**.

2.2. Dimethyl 2-fluoro-1,5-diphenylpyrrole-3,4-dicarboxylate (2a)

Analysis: Found: C, 67.87; H, 4.64; N, 3.78%; $C_{20}H_{16}NFO_4$ requires: C, 67.98; H, 4.56; N, 3.96%. Mp 132–134°C. IR ($CHCl_3$) $\upsilon_{max.}$ 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.75 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 7.07–7.35 (m, 10H, H_{Ph}) ppm. ^{13}C NMR ($CDCl_3$) δ: 51.73 (CH_3), 52.18 (CH_3), 94.43 (d, $^2J_{CF}$ = 5.1 Hz, 3-C), 112.85 (5-C), 127.43 (C_{Ph}), 127.57 (d, $^3J_{CF}$ = 2.8 Hz, 4-C), 127.97, 128.35, 128.74, 128.85, 129.24, 130.34, 133.23 (C_{Ph}), 147.49 (d, $^1J_{CF}$ = 278 Hz, 2-C), 162.26 (d, $^3J_{CF}$ = 5.0 Hz, (3-C)-$\underline{C}$O), 165.19 (d, $^4J_{CF}$ = 2.5 Hz, (4-C)-$\underline{C}$O) ppm; ^{19}F NMR ($CDCl_3$) δ: −126 ppm; Mass spectrum (m/z, %) (EI, 70 eV) 353 (91) $[M]^+$, 322 (100) $[M\text{-}CH_3O]^+$, 77 (15) $[Ph]^+$.

2.3. Dimethyl 2-fluoro-1-(4-methoxyphenyl)-5-phenylpyrrole-3,4-dicarboxylate (2b)

Analysis: Found: C, 65.73; H, 4.74; N, 3.54%; $C_{21}H_{18}NFO_5$ requires: C, 65.79; H, 4.73; N, 3.65%. Mp 145–147°C. IR ($CHCl_3$) $\upsilon_{max.}$ 1735, 1720 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.73 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 6.80–7.26 (m, 9H, H_{Ph}) ppm. ^{13}C NMR ($CDCl_3$) δ: 51.66 ($CO_2\underline{C}H_3$), 52.12 ($CO_2\underline{C}H_3$), 55.39 (OCH_3), 94.21 (d, $^2J_{CF}$ = 5.4 Hz, 3-C), 112.51 (5-C), 114.38 (C_{Ph}), 125.79 (C_{Ph}), 127.75 (4-C), 127.94, 128.25, 128.51, 128.82, 130.32 (C_{Ph}), 147.63 (d, $^1J_{CF}$ = 277 Hz, 2-C), 159.59 (C_{Ph}), 162.24 (d, $^3J_{CF}$ = 5 Hz, (3-C)-$\underline{C}$O), 165.26 (d, $^4J_{CF}$ = 2.8 Hz, (4-C)-$\underline{C}$O) ppm.

2.4. Dimethyl 1-(4-chlorophenyl)-2-fluoro-5-phenylpyrrole-3,4-dicarboxylate (2c)

Analysis: Found: C, 61.58; H, 4.07; N, 3.21%; $C_{20}H_{15}NClFO_4$ requires: C, 61.95; H, 3.90; N, 3.61% Mp. 139–141°C. IR ($CHCl_3$) $\upsilon_{max.}$ 1730 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.72 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 7.00–7.32 (m, 9H, H_{Ph}) ppm. ^{13}C NMR ($CDCl_3$) δ: 51.69 (CH_3), 52.11 (CH_3), 94.65 (d, $^2J_{CF}$ = 5.2 Hz, 3-C), 113.11 (5-C), 127.43 (d, $^3J_{CF}$ = 3.0 Hz, 4-C), 128.09, 128.37, 128.51, 128.54, 129.48, 130.29, 131.66, 134.83 (C_{Ph}), 147.5 (d, $^1J_{CF}$ = 279 Hz, 2-C), 161.99 (d, $^3J_{CF}$ = 5.0 Hz, (3-C)-$\underline{C}$O), 164.87 (d, $^4J_{CF}$ = 2.5 Hz,(4-C)-$\underline{C}$O) ppm.

2.5. Dimethyl 5-(2,4-dichlorophenyl)-2-fluoro-1-phenylpyrrole-3,4-dicarboxylate (2d)

Oil. IR ($CHCl_3$) $\upsilon_{max.}$ 1720 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.68 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 7.09–7.34 (m, 8H, H_{Ph}) ppm. ^{13}C NMR ($CDCl_3$) δ: 51.80 (CH_3), 51.86 (CH_3), 94.87 (d, $^2J_{CF}$ = 5.0 Hz, 3-C), 113.31 (5-C), 125.48 (4-C),

126.69, 126.96, 127.26, 129.19, 132.61, 134.10, 135.83, 136.12 (C_{Ph}), 147.36 (d, $^1J_{CF}$=278 Hz, 2-C), 162.09 (d, $^3J_{CF}$=4.8, (3-C)-CO), 163.69 (d, $^4J_{CF}$=2.7 Hz, (4-C)-CO) ppm.

*2.6. Dimethyl 2-fluoro-5-(fur-2-yl)-1-phenylpyrrole-3,4-dicarboxylate (**2e**)*

Analysis: Found: C, 63.30; H, 4.07; N, 4.04%; $C_{18}H_{14}NFO_5$ requires: C, 62.97; H, 4.11; N, 4.08%. Mp 113–116°C. IR ($CHCl_3$) $\upsilon_{max.}$ 1730 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.85 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 6.08 (d, ^1H, J=2.5 Hz, 3′-H), 6.25 (dd, ^1H, J=3.8, 2.5 Hz, 4′-H), 7.20–7.47 (m, 6H, 5′-H, H_{Ph}) ppm. ^{13}C NMR ($CDCl_3$) δ: 51.72 (CH_3), 52.44 (CH_3), 94.55 (d, $^2J_{CF}$=5 Hz, 3-C), 110.86, 111.06 (3′-C, 4′-C), 113.43 (5-C), 117.67 (d, $^3J_{CF}$=1.5 Hz, 4-C), 127.21, 129.39, 127.26, 129.49, 133.39 (C_{Ph}), 142.49 (2′-C), 142.89 (5′-C), 147.73 (d, $^1J_{CF}$=279 Hz, 2-C), 161.89 (d, $^3J_{CF}$=5 Hz, (3-C)-CO), 164.97 (d, $^4J_{CF}$=2. 6 Hz, (4-C)-CO) ppm.

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References

[1] J.T. Welch, S. Eswarakrishnan (Eds.), Fluorine in Bioorganic Chemistry, Wiley, New York, 1991.
[2] K.L. Kirk, Biochemistry of Halogenated Organic Compounds, Plenum, New York, 1991.
[3] M.E. Crestoni, S. Fornarini, Gazzetta Chim. Ital. 119 (1989) 203.
[4] Z.-M. Qiu, D.J. Burton, Tetrahedron Lett. 35 (1994) 4319.
[5] J. Leroy, C. Wakselman, Tetrahedron Lett. 35 (1994) 8605.
[6] Z.-M. Qiu, D.J. Burton, Tetrahedron Lett. 36 (1995) 5119.
[7] M.N. Chang, T. Biftu, D.A. Boulton, P.E. Finke, M.L. Hammond, A.A. Pessolano, R.A. Zimbias, P. Bailey, M. Goldenberg, A. Rackham, Eur. J. Med. Chem.- Chim. Ther. 21 (1986) 363.
[8] J. Wang, A.I. Scott, Tetrahedron Lett. 35 (1994) 3679.
[9] J. Wang, A.I. Scott, Tetrahedron 50 (1994) (1994) 6181.
[10] J. Wang, A.I. Scott, J. Chem. Soc., Chem. Commun., 1995, 2399.
[11] A.F. Khlebnikov, R.R. Kostikov, Khim. Geterotsikl. Soedin., 1987, 856.
[12] A.F. Khlebnikov, R.R. Kostikov, Chem. Heteroc. Comp., 1987, 708.
[13] A.F. Khlebnikov, E.I. Kostik, and R.R. Kostikov, Khim. Geterotsikl. Soedin., 1990, 355.
[14] A.F. Khlebnikov, E.I. Kostik, R.R. Kostikov, Chem. Heteroc. Comp., 1990, 304.
[15] A.F. Khlebnikov, E.I. Kostik, and R.R. Kostikov, Synthesis, 1993, 568.
[16] R.R. Kostikov, A.F. Khlebnikov, V.Ya. Bespalov, J. Phys. Org. Chem. 6 (1993) 83.
[17] M.S. Novikov, A.F. Khlebnikov, A.E. Masalev, R.R. Kostikov, Tetrahedron Lett. 38 (1997) 4187.
[18] A.F. Khlebnikov, M.S. Novikov, R.R. Kostikov, Mendeleev Comm., 1997, 145.