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[3+2] Cycloaddition reactions of diethyl (*E*)-2-fluoromaleate

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ABSTRACT

Diethyl *E*-2-fluoromaleate has been prepared in a pure state in 89% yield by a Horner–Wadsworth–Emmons Wittig procedure. The *E* configuration was determined by NMR spectroscopy. Diethyl E-2-fluoromaleate undergoes [3+2] cycloadditions with a series of aromatic α-iminoesters and aromatic nitrones. The yields of purified cyclic products ranged from 65 to 80%.

1. Introduction

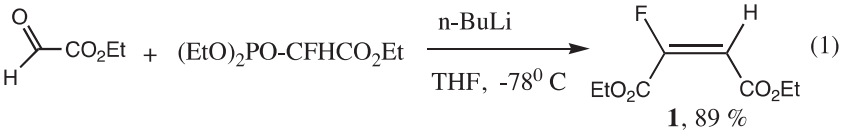
Cycloaddition reactions of fluorinated alkenes represent an important new methodology for the preparation of fluorinated carbocycles [1,2] and fluorinated heterocycles. [3].

Following our studies of Diels–Alder reactions of fluoroalkenes [4], we now extend our research to include [3+2] cycloadditions. Although Huisgen's methodology is long known [5], very little is reported on the preparation of ring-fluorinated heterocycles by [3+2] cyclizations [2]. We chose to focus on reactions of azomethine ylides [6] and nitrones [7,8] with fluoromaleate (**1**). We recently developed a new and convenient preparation of **1** in 89% yield by the reaction of ethyl glyoxylate in the Horner–Wadsworth–Emmons reaction with triethyl 2-fluoro-2-phosphoethanoate as shown in equation (1).

The concept of [3+2] cycloaddition reactions was reviewed in 1963 by Huisgen [5]. Many new materials with widespread biological use have been prepared by this cycloaddition method. We thus felt that the use of **1** in cycloadditions could be very useful for the preparation of a wide variety of fluorinated heterocyclic compounds with applications in biological sciences.

2. Results and discussion

For this study we have used aromatic α-imines, **2a** and 2**b**, obtained from the condensation of glycine methyl or ethyl ester hydrochlorides with aromatic aldehydes following the method of Longmire [6]. Aromatic nitrones, **3a, 3b, 3c** and **3d**, were obtained by condensation of methyl hydroxylamine with aromatic aldehydes.



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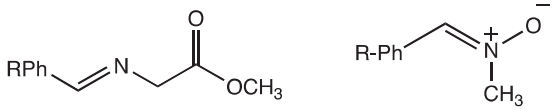


2a, R = H
2b, R = *p*-Cl

3a, R = H
3b, R = *p*-OCH_3
3c, R = *p*-Cl
3d, R-Ph = 2-furyl

Cyclization of **1** with the α-imines (**2**) was accomplished in 65 and 77% yield by refluxing the components in toluene with silver acetate catalyst to give **4a** and **4b**.

The protons H_2 and H_4 in **4a** couple equally with the fluorine atom (J = 26.0 Hz) and establish that the H and F atoms are *cis* to each other. The COSY spectrum shows that H_5 and H_4 are adjacent to each other and confirms the regiochemistry of the cycloaddition. The absence of any NOE between H_5 and H_4 indicates that these two atoms are *trans* to each other, as shown in **4a** and **4b**.

The regioselectivity observed between **1** and the α − imines can be explained as shown by the proposed mechanism in Fig. 1. In the cyclization the imine bears a partial negative charge which adds to the carbon *alpha* to the fluorine atom.

The cyclization of **1** with the nitrones (**3**) to give **5a–5d** was accomplished by refluxing the materials in toluene for 20 h. The cycloadducts were formed in 70–78% yield.

The regiochemistry and stereochemistry of **5a–5b** were established also by ^{1}H NMR. Protons H_3 and H_4 are adjacent to each other by COSY, but do not show a NOE effect. Proton H_4 is coupled with F into a doublet (J = 22.6 Hz), and F shows no further coupling. The selectivity in the reaction of the nitrones with **1** is explained from calculations which show that the reaction is controlled by the HOMO of the nitrone and the LUMO of **1**. This interaction predicts that the oxygen of the nitrone will add to the carbon of **1** that has the F atom. (Fig. 2).

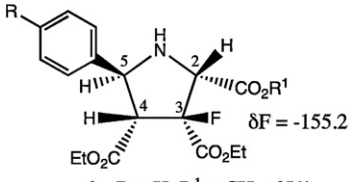
This methodology is simple and regioselective and opens new avenues for the preparation of fluorinated heterocycles that have potential use in medicinal chemistry.

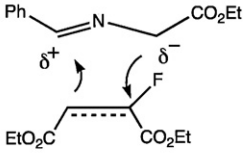
3. Experimental procedure

3.1. General

^{1}H NMR data were recorded at 300.0 MHz with tetramethylsilane (δ = 0.00 ppm) as internal reference. ^{13}C NMR spectra were recorded at 75.5 MHz with deuterated chloroform ($CDCl_3$ δ = 77.0 ppm) as internal reference. ^{19}F NMR spectra were recorded at 282.3 MHz with trifluoroacetic acid (TFA δ = 0.00 ppm) as external reference, and are corrected to $CFCl_3$. Deuterated chloroform was the solvent in all cases.

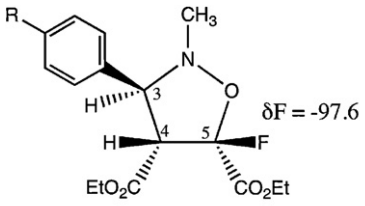
The mixtures were purified by flash column chromatography on silica gel with hexane/ethyl acetate mixtures as the eluent solvents.

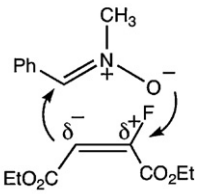




4a, R = H, R^1 = CH_3, 65%
4b, R = *p*-Cl, R^1 = Et, 77 %

Fig. 1. Proposed mechanism for α-imine cyclization.





5a, R = H, 76 %
5b, R = *p*-Cl, 78 %
5c, R = *p*-OCH_3 , 70 %
5d, RPh = 2-furyl, 70 %

Fig. 2. Proposed mechanism for nitrone cyclization.

3.2. Diethyl (E)-2-fluoromaleate (1)

A three necked 100-mL flask fitted with a magnetic stirrer was flamed dried and kept under nitrogen atmosphere. Triethyl 2-fluoro-2-phosphonethonate (4.6 g, 1.7 mmol) in 20 mL of anhydrous tetrahydrofuran was injected into the flask. The solution was cooled to −78° with a dry ice–acetone bath. n-Butyllithium (1.6 M, 12.5 mL in hexane) was gradually added to the flask. The bright yellow solution was stirred for 20 min, and ethyl glyoxylate (5.15 g, 5.0 mmol) was added by syringe. The mixture was stirred at −78° C for 1 h and then allowed to warm to room temperature. The solution was quenched with 80 mL of cold water. The contents were extracted three times (20 mL) of ether and dried with $MgSO_4$. The solvent was removed to give 3.18 g (89%) of **1**. ^{1}H NMR data were fully consistent with reported values [9]. ^{19}F NMR δ −112 3 (d, J = 15.7 Hz) [lit. 9 δ ^{19}F −109 J = 15.7 Hz].

3.3. The α-imines were prepared by standard literature procedures by condensing glycine ester hydrochlorides with aromatic aldehydes [6]

Benzylideneamino acetic acid methyl ester (**2a**)*:* 77%, ^{1}H NMR δ 3.74 (s, 3H, CH_3), 4.38 (s), 7.4–7.8 (m, 5H, aromatic) 8.3 (s, 1H, CH). ^{13}C NMR δ 52.33 (OCH_3), 62.2 (CH_2), 127.9–140.8 (aromatic), 165.7 (CH), 170.8 (C=O).

4-Chlorobenzylidineamino acetic acid ethyl ester (**2b**): 65%, ^{1}H NMR δ 1.95 (t, 3H, CH_3, J = 5 Hz), 4.24 (s, 2H, CH_2), 7.2–7.8 (m, aromatic, 4H), 8.24 (s, CH, 1H). ^{13}C NMR d 14.3 (CH_3), 61.3 (OCH_2), 127.9–139.7 (aromatic), 164.2 (CH), 170.1 (C=O).

3.4. Nitrones (3a–3d)

The nitrones were prepared by heating at reflux a mixture of N-methylhydroxylamine and the aromatic aldehyde for 18 h. The nitrones were purified by flash chromatography.

N-methylphenylnitrone (**3a**): ^{1}H NMR δ 3.8 (CH_3, 3H), 7.31 (m, 5H, aromatic) 8.09 (m, 1H, CH). **N-methyl-4-methoxyphenylnitrone** (**3b**): ^{1}H NMR δ 3.8 (s, CH_3) 3.9 (CHN), 6.9–7.3 (m, 4H, aromatic), 8.1 (m, 1H, CH). **N-methyl-4-chlorophenylnitrone (3c):** ^{1}H NMR δ 3.8 (s, 3H, CH_3), 7.4 (d, J = 2 Hz) and 8.2 (d, J = 2 Hz), 7.08 (s,1H, CH). **N-methyl-2-furanylnitrone (3d):** ^{1}H NMR δ 3.8 (s, 3H, CH_3), 6.5, 7.4–7.7 (m, 3H, furan), 7.8 (m, 1H CH).

3.5. Cyclization of 1 with 2a and 2b to produce pyrrolidines 4a and 4b

3,4-Diethyl 2-methyl 3-fluoro-5-phenylpyrrolidine-2,3,4-tricarboxylate (4a). To a mixture of imine 2(88 mg, 0.45 mmol) and silver acetate (2.3 mg) in 2 mL of dry toluene was added 1 (90 mg, 0.68 mmol) and diisopropylamine (8 μL) in 3 mL of dry toluene. The reaction was heated at reflux for 20 h. The mixture was concentrated and chromatographed (hexane/EtOAc, 3/1) to give pure **4a** (65%). ^{1}H NMR δ 0.88 (t, 3H, CH_3, J = 5 Hz), 1.2 (t, 3H, CH_3,

J = 5 Hz), 3.7 (s, 3H, OCH_3), 3.8 (t, 2H, CH_2, J = 5 Hz), 4.2 (t, 2H, CH_2, J = 5 Hz), 4.4 (d, H2, J = 2 Hz), 4.6 (d, 1H, J = 4 Hz, H5), 7.2–7.5 (m, 5H, aromatic). ^{13}C NMR δ 13.8 (d,) 53.2 (OCH_3), 58.5 (C5) 61.0 (C2), 62.0, (CH_2), 101.4 (C3, d, J_{CF} = 289 Hz), 128–140 (Aromatic), 164, 171, 171.7 (C=O). ^{19}F NMR δ −155.2. *m/z* calcd. 367.140: found: 367.142.

Triethyl 5-(p-chlorophenyl)-3-fluoropyrrolidine-2,3,4-tricarboxylate (4b) was prepared in 77% yield as described for **4a**: ^{1}H NMR δ 1.3 (m 6H, CH_3 of ethyl), 3.8–4.0 (m, 3H, CH_3 of 3-ethyl), 4.2 (m, CH_2 of 2,3-diethyl 6H), 4.6 (d, 1H, H5), 7.2–7.9 (dd, 4H, J_{HH} = 2 Hz, aromatic). ^{13}C NMR δ 14.8 (3 s, CH_3), 50.2 (C2), 54.3 (C5), 58.6 (CH_2), 59.5 (CH_2), 62.0 (CH_2), 102 (d, J_{CF} = 290 Hz), 128–141.0 (several singlets, aromatic), 168.0, 172.4, 172.7 (three C=O of esters). ^{19}F NMR δ −155.8 (CF, J = 27.8 Hz). *m/z* calcd for 401.810: found 401.797.

3.6. Cyclization of 1 with nitrones 3a–3d to produce isoxazolidines 5a–5d

Diethyl 5-fluoro-2-methyl-3-phenylisoxazolidine-4,5-dicarboxylate (5a). Nitrone **3a** (1 mmol) and diethyl (*E*)-2-fluoromaleate (**1**) were allowed to reflux in toluene (4 mL) for 20 h. The toluene was removed under vacuum and the product was chromatographed on silica gel to give pure **5a** (76%): ^{1}H NMR δ 1.3, 1.8 (two triplets, 6H, CH_3, of ester, *Js* = 5 Hz), 2.7 (s, NCH_3, 3H), 3.84–3.96 (dd, H4, H5, *Js* = 3 Hz), 4.1 and 4.3 (q, CH_2, of ethyl), 7.3–7.5 (m, 5H, aromatic). ^{13}C NMR δ 14.0 (CH_3 of ethyls), 43.4 (NCH_3), 61 (C4), 76.1 (C3), 117 (d, CF, J = 300 Hz), 128.4 (m, aromatic) 135, (aromatic), 164 (d, CFC=O, J = 6 Hz), 167.0 (C=O). ^{19}F NMR δ −97.6. *m/z* calcd for 325.130: found: 325.136.

Diethyl 3-(p-chlorophenyl)-5-fluoro-2-methylisoxazolidine-4,5-dicarboxylate (5b).

^{1}H NMR δ 1.2 (t, 3H, CH_3), 1.38 (t, 3H, CH_3), 2.7 (s, 3H, NCH_3), 3.8 (dd, H3 and H4, 2H, *Js* = 4 Hz)), 4.2 (q, 2H, CH_2), 4.3 (q, 2H, CH_2), 7.4–7.6 (dd, aromatic). ^{13}C NMR δ 14.1 (CH_3 of ethyl), 43.3 (NCH_3) 61.8 (d, J = 25 Hz, C4), 76.1 (C3), 117.1 (d, J_{CF} = 300 Hz, CF), 130.1 (m, aromatic) 135, 137 (aromatic), 164 (CFC=O), 167.2 (C=O). ^{19}F NMR δ −97.5. *m/z* calcd for 359.09: found: 359.079.

Diethyl 3-(p-methoxyphenyl)-5-fluoro-2-methylisoxazolidine-4,5-dicarboxylate (5c).

^{1}H NMR δ 1.2 (t, 3H, CH_3), 1.39 (t, 3H, CH_3), 2.7 (s, 3H, NCH_3), 3.8 (s, 3H, OCH_3), 3.9 (dd, H3, H4, 2H), 4.2 (q, 2H, CH_2), 4.35 (q, 2H, CH_2), 6.8–7.3 (m, 4H, aromatic). ^{13}C NMR δ 14.2 (CH_3), 43.5 (NCH_3), 55.5 (OCH_3), 61.9 (d, J = 27 Hz, C4), 76.8 (C3), 118.1 (d, CF, J_{CF}= 300 Hz), 130, 138, 139 (aromatic), 164 (CFC=O) 167 (C=O). ^{19}F NMR δ −97.9. *m/z* calcd. For 355.141: found: 355.134; Calcd. For 355.141.

Diethyl 5-fluoro-3-(2-furanyl)-2-methylisoxazolidine-4,5-dicarboxylate (5d).

^{1}H NMR δ 1.2 (t, 3H, CH_3, J = 5 Hz), 1.38 (t, 3H, CH_3, J = 5 Hz), 2.8 (s, NCH_3), 4.1 (q, CH_2) 4.21 (m, H3, H4, 2H), 4.4 (q, CH_2), 6.2, 6.5, 7.2, 7.4 (furan). ^{13}C NMR δ 14.1 (CH_3), 43.5 (NCH_3), 55.5 (OCH_2), 62.0 (d, C4), 63.5 (OCH_2), 76.1 (C3), 115 (d, J = 300 Hz, CF), 116,.0 143.2, 139.0, 145.5 (furanyl), 164.1 (d, C3, C=O, J = 7 Hz), 166.3 (d, C4, C=O). ^{19}F NMR δ −97.5. *m/z* calcd for 315.113: found. 315.121.

References

[1] G. Haufe, in: V.A. Soloshonok (Ed.), Vinyl Fluorides in Cycloaddition in Fluorine Containing Synthons, ACS Symposium Series 911, 2005, Ch 5.
[2] Y.-H. Lam, S.J. Stanway, V. Gouverneur, Tetrahedron 65 (2009) 9905.
[3] W.R. Dolbier, in: M. Hudlicky, A.E. Pavlath (Eds.), Cycloadditions Forming Five- and Six-Membered Rings in Chemistry of Organic Fluorine Compounds II, ACS, Washington DC, 1995, , ACS Monograph 187.
[4] T.B. Patrick, J. Neuman, A. Tatro, Journal of Fluorine Chemistry 132 (2011) 779.
[5] R. Huisgen, Angewandte Chemie International Edition^pV 2 (1963) 565.
[6] J.M. Longmire, B. Wang, X. Zhang, Journal of American Chemical Society 124 (2002) 13400.
[7] A. Brandi, F. Cardona, S. Cicchi, F. Cardero, A. Goti, Chemistry: A European Journal 15 (2009) 7808.
[8] R.C.F. Jones, J.N. Martin, in: A. Padwa, W.H. Pearson (Eds.), Synthetic applications of 1,3-dipolar cycloaddition chemistry toward heterocycles and natural products, Wiley, New York, NY, 2002, pp. 1–81.
[9] J. Cousseau, P. Albert, Bulletin de la Société Chimique de France 6 (1986) 910.