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Facile regio- and stereospecific 1,3-dipolar cycloaddition of metallo-azomethine ylides to ethyl (*E*)-4,4,4-trifluorobut-2-enoate

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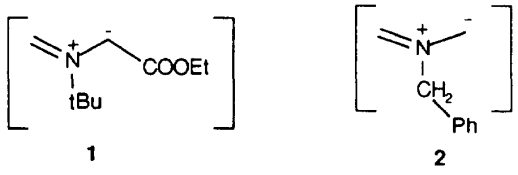
Summary – Ethyl (*E*)-4,4,4-trifluorobut-2-enoate undergoes regio- and stereospecific cycloaddition with metallo-azomethine ylides generated from the imines of glycine or alanine esters in the presence of silver acetate to give trifluoromethylpyrrolidines in excellent yields. This methodology has been applied to the synthesis of a range of substituted trifluoromethylpyrrolidines.

ethyl (E)-4,4,4-trifluorobut-2-enoate / metallo-dipole / azomethine ylide / cycloaddition / pyrrolidine / trifluoromethyl proline

Although the 1,3-dipolar cycloaddition of nonstabilized and stabilized azomethine ylides with alkenes for the synthesis of pyrrolidines is well documented [1-6], to our knowledge there are only two reports of this reaction with fluorinated alkenes [7, 8]. The first example was reported by Leroy *et al* [7] and involved the reaction of the stabilized azomethine ylide **1** generated by the thermal opening of an aziridine to give pyrrolidines in low yield without stereo- and regioselectivity. More recently, we have reported that the nonstabilized azomethine ylide **2** [9-11] reacts with a variety of trifluoromethylated alkenes at room temperature to give the corresponding pyrrolidines in good yields [8]. Herein we wish to report our investigations into the synthesis of trifluoromethylated polyfunctionalized pyrrolidines through 1,3-dipolar cycloaddition reactions with stabilized azomethine ylides.



1 **2**

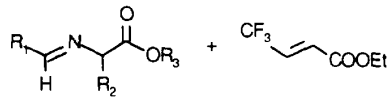
Fig 1

It has been reported [12-14] that imines of α-amino esters of type **3** undergo cycloaddition reactions with electron-deficient alkenes in the presence of a range of metal salts. The high regio- and stereospecificity observed, coupled with the possibility of controlling the regiochemistry by the appropriate choice of metal salt [12, 13] prompted us to investigate the reactivity of these *N*-metallated azomethine ylides towards ethyl (*E*)-4,4,4-trifluorobut-2-enoate **4** as a route to highly functionalized fluorinated pyrrolidines.

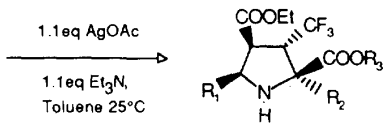
The investigations were carried out in the presence of silver acetate, which has been shown to give the highest regio- and stereoselectivity provided the reactions are performed in toluene [12]. The use of polar solvents greatly accelerates the rate of reaction but decreases selectivity [12, 13]. Thus, toluene was chosen as a solvent for our investigations. The treatment of imines of glycine and alanine esters **3a-e** in toluene with 1.1 equivalents of triethylamine and 1.3 equivalents of silver acetate in the presence of **4** resulted in good to excellent yields of the desired pyrrolidines (table I). The imines derived from alanine esters were found to be more reactive as indicated by the shorter reaction times, suggesting that the rate of reaction is determined by the energy level of the ylide and not by steric hindrance.

The structure of the pyrrolidine **5b** was determined by X-ray crystallography (fig 2) [15] and the structures of all other cycloadducts were elucidated using high-field NMR, in particular NOE homo- and heteronuclear decoupling experiments, and by comparison with the known **5b**. In **5a-c**, J_{HF} coupling constants between CF_3 and CH_3 indicate the relative regiochemistry. Furthermore, an enhancement of the CH_3 signal when the fluorine atoms are irradiated (heteronuclear NOE experiments) indicates a spatial proximity and thus a *cis* relationship between the CF_3 and CH_3 groups. In **5d** and **5e** homonuclear decoupling experiments, irradiation of H5 results in an enhancement of the H2 and H4 signals, indicating spatial proximity.

* Correspondence and reprints



3a-e 4



5a-e

Table I.

Imine	R1	R2	R3	Reaction Time H	Yield %[a,b] 5a-e
3a	Cyclohexyl	CH_3	Me	18	83
3b	Phenyl	CH_3	Me	18	88
3c	2-Furyl	CH_3	Me	24	83
3d	Phenyl	H	Me	36	60
3e	2-Furyl	H	Et	36	68

[a] Yields refer to chromatographically pure compounds. [b] Before chromatography a second isomer (2-5%) was observed by ^{19}F NMR, which was not isolated.

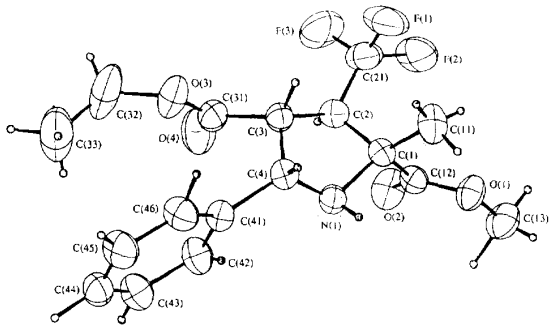


Fig 2

The regiochemistry observed for **5** is the same as that observed when methyl acrylate is used as the dipole [12, 13]. Despite of the presence of the CF_3 group, the regiochemistry of the addition of the alkene is determined by the ester group, as previously observed in other cycloaddition reactions with trifluorocrotonates [8, 16, 17]. The *trans* relationship between the CF_3 group and the ester group at C-3 is due to retention of the configuration of the alkene. It has been postulated [12] that the metallo-dipole in toluene adopts a W conformation with a coordination between the silver atom and both the nitrogen atom and an oxygen of the ester group, which induces the stereochemistry at both the C-2 and C-5 positions (fig 3). The relative stereochemistry at C-4, C-5 centers and C-2, C-3 centers indicates the preferred *endo* approach of the ester group of the alkene in the cycloaddition reaction [8, 17].

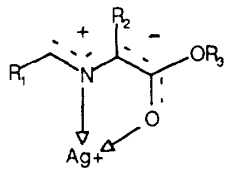


Fig 3

After the success of the cycloaddition reactions performed in the presence of silver acetate, we turned our attention to the possibility of reversal of regiochemistry by the use of another metal salt. We employed $Ti(OPr^i)_3Cl$ which has been reported to form a coordination complex between the ester group of the dipole and the ester group of the methyl acrylate, thus reversing the regiochemistry of the reaction [18]. No reaction occurred with **4**. This lack of reactivity can be explained by steric hindrance of both the alkene and the metallo-dipole.

In summary we have shown that the 1,3-dipolar cycloaddition of metallo-azomethine ylides generated with silver acetate to **4** proceeds with high regio- and stereoselectivity and is a general synthetic route to highly substituted trifluoromethyl pyrrolidines.

Experimental section

^1H, ^{13}C and ^{19}F NMR spectra were measured as solutions in $CDCl_3$ with a Bruker ARX400 instrument (400 MHz) or a Bruker AC200 (200 MHz) using TMS or $CFCl_3$ respectively, as internal standards. IR spectra were obtained on a Perkin-Elmer 841 spectrophotometer. Column chromatography was performed with silica gel 60 (230-400 mesh, Merck). Starting materials were commercially available from Lancaster or Aldrich chemical company and solvents were distilled on sodium before use. Aldimines **3a**, **3b** and **3d** were prepared by literature procedures [12, 19]; **3c** and **3e** were prepared by a modified described procedure.

Methyl N-*(furan-2-ylmethylidene)alaninate* **3c**

A mixture of alanine methyl ester hydrochloride (2.1 g, 0.02 mol), triethylamine (3 mL, 0.022 mol) and furan-2-carbaldehyde (1.9 g, 0.02 mol) in methanol (50 mL) was stirred at room temperature. After 1 h, the solvent was removed under reduced pressure, and then anhydrous diethyl ether was added. The suspension was filtered and evaporated under reduced pressure to give **3c** (3.1 g, 86%) which was used without further purification.

IR neat 1 738 cm^{-1} (υ C=O), 1 639 cm^{-1} (υ C=N).

^1H NMR δ 1.5 (d, J = 7.3 Hz, 3H), 3.7 (s, 3H), 4.1 (q, J = 7.3 Hz, 1H), 6.4 (dd, J = 3.3 Hz, J = 1.8 Hz, 1H), 6.75 (d, J = 3.3 Hz, 1H), 7.4 (d, J = 1.8 Hz, 1H), 8.0 (s, 1H).

^{13}C NMR δ 19.5, 52.4, 68.0, 112.0, 115.1, 145.0, 151.5, 172.5, 177.3.

Ethyl N-*(furan-2-ylmethylidene)glycinate* **3e**

According to the same procedure as for **3c**, glycine ethyl ester hydrochloride (2.8 g, 0.02 mol), triethylamine (3 mL, 0.022 mol) and furan-2-carbaldehyde (1.9 g, 0.02 mol) in methanol (50 mL) gave after work-up **3e** (3.0 g, 90%).

IR neat 1 745 cm^{-1} (υ C=O), 1 640 cm^{-1} (υ C=N).

^1H NMR δ 1.25 (t, J = 7.1 Hz, 3H), 4.1 (q, J = 7.1 Hz, 2H, 4.4 (s, 2H), 6.5 (dd, J = 3.4 Hz, J = 1.8 Hz, 1H), 6.75 (d, J = 3.4 Hz, 1H), 7.45 (d, J = 1.8 Hz, 1H), 8.1 (s, 1H).

^{13}C NMR δ 15.5, 60.7, 61.7, 111.7, 115.1, 145.2, 152.5, 170.4, 171.7.

4-Ethyl 2-methyl 5-cyclohexyl-2-methyl-3-(trifluoromethyl)pyrrolidine-2,4-dicarboxylate **5a**

To a mixture of methyl *N*-(cyclohexylmethylidene)alaninate **3a** (1 g, 5 mmol), silver acetate (1.1 g, 6.5 mmol) and triethylamine (0.8 mL, 6 mmol) in anhydrous toluene under an atmosphere of argon was added ethyl (*E*)-4,4,4-trifluorobut-2-enoate **4** (1.0 g, 6 mmol) in toluene. The suspension was stirred at room temperature for 18 h and then the solvent was removed under reduced pressure to give a yellow residue (1.7 g), which was dissolved in anhydrous diethyl ether and filtered through celite. Flash chromatography (eluent : pentane/diethyl ether 90:10) gave the pure cycloadduct **5a** (1.52 g, 83%).

IR neat 3 316 cm^{-1} (υNH), 1 731 cm^{-1} (υ C=O).

^{19}F NMR δ −66.6 (qd, $^3J_{HF}$ = 10.8 Hz, $^5J_{HF}$ = 1.5 Hz).

^1H NMR δ 1.0 (m, 2H cyclohexyl), 1.2 (m, 4H, cyclohexyl), 1.25 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.3 (m, 1H, cyclohexyl), 1.5 (q, $^5J_{HF}$ = 1.5 Hz, 3H), 1.7 (m, 2H cyclohexyl), 1.9 (m, 2H, cyclohexyl), 2.65 (bs, 1H, N*H*), 3.1 (dd, J = 6.8 Hz, J = 9.7 Hz, 1H, *H*5), 3.2 (dd, J = 6.8 Hz, J = 4 Hz, 1H, *H*4), 3.5 (dq, J_{HH} = 4 Hz, $^3J_{HF}$ = 10.8 Hz, 1H, *H*3), 3.8 (s, 3H, OCH_3), 4.2 (m, 2H, OCH_2).

^{13}C NMR δ 14.3, 20.8, 25.5, 25.6, 26.1, 30.9, 31.0, 39.1, 49.0 (*C*4), 52.8 (OCH_2), 54.2 (q, J_{CF} = 26.5 Hz, *C*3), 61.0, 66.4 (*C*5), 66.5 (*C*2), 126.2 (q. J_{CF} = 279 Hz, CF_3), 172.8, 174.1.

Anal calc for $C_{17}H_{26}F_3NO_4$: C 55.9, H 7.2, N 3.8. Found : C 55.9, H 7.3, N 3.7%.

4-Ethyl 2-methyl 2-methyl-5-phenyl-3-(trifluoromethyl) pyrrolidine-2,4-dicarboxylate **5b**

According to the same procedure as for **5a**, methyl *N*-benzylidene alaninate **3b** (1 g, 5.2 mmol), silver acetate (1.1 g, 6.5 mmol), triethylamine (0.8 mL, 6 mmol) and ethyl (*E*)-4,4,4-trifluorobut-2-enoate **4** (1.0 g, 6 mmol) were stirred for 18 h ; work-up gave a colorless solid (1.8 g) (a 96:4 mixture of isomers was observed by ^{19}F NMR). Recrystallization (pentane) gave the pure cycloadduct **5b** (1.65 g, 88%). Mp = 43-45°C.

IR neat 3 350 cm^{-1} (υ NH), 1 734 cm^{-1} (υ C=O).

^{19}F NMR δ −67.1 (qd, $^3J_{HF}$ = 9.8 Hz, $^5J_{HF}$ = 2 Hz).

^1H NMR δ 0.75 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.6 (q, $^5J_{HF}$ = 2 Hz, 3H, CH_3), 2.8 (bs, 1H, N*H*), 3.5 (dd, J = 7.4 Hz, J = 8.5 Hz, 1H, *H*4), 3.6 (m, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 3.9 (dq, $^3J_{HF}$ = 9.8 Hz, J_{HH} = 7.4 Hz, 1H, *H*3), 4.8 (d, J = 8.5 Hz, 1H, *H*5), 7.3 (m, 5H).

^{13}C NMR δ 13.2, 19.8, 50.5 (*C*4), 51.6 (q, J_{CF} = 27 Hz, *C*3), 52.7 (OCH_3), 60.7, 62.7 (*C*5), 65.8 (*C*2), 125.8 (q, J_{CF} = 283 Hz, CF_3), 127.2, 127.9, 137.7, 172.8, 173.4.

Anal calc for $C_{17}H_{20}F_3NO_4$: C 56.8, H 5.6, N 3.9. Found C 57.0, H 5.75, N 3.75%.

4-Ethyl 2-methyl 5-(furan-2-yl)-2-methyl-3-(trifluoromethyl)pyrrolidine-2,4-dicarboxylate **5c**

According to the same procedure as for **5a**, methyl *N*-(furan-2-ylmethylidene)alaninate **3c** (0.5 g, 2.76 mmol), silver acetate (0.6 g, 3.5 mmol) triethylamine (0.5 mL, 3.75 mmol) and ethyl (*E*)-4,4,4-trifluorobut-2-enoate **4** (0.5 g, 3 mmol) were stirred for 24 h; work-up gave a pale yellow oil (0.85 g) (a 95:5 mixture of isomers was observed by ^{19}F NMR). Flash chromatography (eluent : pentane/diethyl ether 90:10) gave the pure cycloadduct **5c** (0.8 g, 83%).

IR neat 3 354 cm^{-1} (υ NH), 1 742 cm^{-1} (υ C=O).

^{19}F NMR δ −65.6 (qd, $^3J_{HF}$ = 10.8 Hz, $^5J_{HF}$ = 1.7 Hz).

^1H NMR δ 1.0 (t, J = 7 Hz, 3H, OCH_2CH_3), 1.5 (q, $^5J_{HF}$ = 1.7 Hz, 3H, CH_3), 2.8 (bs, 1H, N*H*), 3.5 (t, J = 8.5 Hz, 1H, *H*4), 3.75 (s, 3H, OCH_3), 3.8-4 (m, 3H, OCH_2 and H_3), 4.75 (d, J = 8.5 Hz, *H*5), 6.2 (d, J = 3.3 Hz, 1H), 6.25 (dd, J = 3.3 Hz, J = 1.8 Hz, 1H), 7.2 (d, J = 1.8 Hz, 1H).

^{13}C NMR δ 13.7, 21.5, 49.6, 50.5 (q, J_{CF} = 27 Hz, *C*3), 53.1, 57.0, 61.4, 66.1, 107.7, 110.3, 126.0 (q, J_{CF} = 279 Hz, CF_3), 142.2, 151.6, 174.6, 177.4.

Anal calc for $C_{15}H_{18}F_3NO_5$: C 48.0, H 5.6, N 4.3. Found C 47.8, H 5.7, N 4.15%.

4-Ethyl 2-methyl 5-phenyl-3-(trifluoromethyl)pyrrolidine-2,4-dicarboxylate **5d**

According to the same procedure as for **5a**, methyl-N-benzylidene glycinate **3d** (1.2 g, 7 mmol), silver acetate (1.1 g, 6.5 mmol), triethylamine (1 mL, 7.5 mmol) and ethyl (*E*)-4,4,4-trifluorobut-2-enoate **4** (1.1 g, 6.6 mmol) were stirred for 36 h ; work-up gave a colorless liquid (1.35 g) (a 96:2 mixture of isomers was observed by ^{19}F NMR). Flash chromatography (eluent : pentane/diethyl ether 90:10) gave the pure cycloadduct **5d** (1.15 g, 60%).

IR neat 3 373 cm^{-1} (υ NH), 1 740 cm^{-1} (υ C=O).

^{19}F NMR δ −71.6 (d, J_{HF} = 9.7 Hz).

^1H NMR δ 0.75 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.9 (bs, 1H, N*H*), 3.35 (dd, J = 3.4 Hz, J = 7.5 Hz, 1H, *H*4), 3.6 (ddq, $^3J_{HF}$ = 10 Hz, J_{HH} = 6.4 Hz, J_{HH} = 3.4 Hz, 1H, *H*3), 3.65 (m, 2H), 3.8 (s, 3H, OCH_3), 4.0 (d, J = 6.4 Hz, 1H, *H*2), 4.6 (d, J = 7.5 Hz, 1H, *H*5), 7.3 (m, 5H).

^{13}C NMR δ 13.6, 50.5 (q, J_{CF} = 27.3 Hz, *C*3), 50.8 (*C*4), 52.7 (OCH_3), 60.3 (*C*2), 60.9, 65.7 (*C*5), 126.3 (q, J_{CF} = 280.5 Hz, CF_3), 126.6, 126.9, 128.2, 136.7, 170.8, 171.1.

Anal calc for $C_{16}H_{18}F_3NO_4$: C 55.65, H 5.25, N 4.0. Found C 55.7, H 5.4, N 3.9%.

Diethyl 5-(furan-2-yl)-3-(trifluoromethyl)pyrrolidine-2,4-dicarboxylate **5e**

According to the same procedure as for **5a**, methyl *N*-(furan-2-ylmethylidene)glycinate **3e** (1 g, 5.5 mmol), silver acetate (1.1 g, 6.5 mmol), triethylamine (1 mL, 7.5 mmol) and ethyl (*E*) 4,4,4-trifluorobut-2-enoate **4** (1 g, 6 mmol) were stirred for 36 h ; work-up gave a pale-yellow oil (1.5 g) (a 95:5 mixture of isomers was observed by ^{19}F NMR). Flash chromatography (eluent : pentane/diethyl ether 90:10) gave the pure cycloadduct **5e** (1.3 g, 68%).

IR neat 3 361 cm^{-1} (υ NH), 1 743 cm^{-1} (υ C=O).

^{19}F NMR δ −70.5 (d, $^3J_{HF}$ = 10.8 Hz).

^1H NMR δ 1.0 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.35 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.9 (bs, 1H, N*H*), 3.4 (dd, J = 5.3 Hz, J = 7.4 Hz, 1H, *H*4), 3.8 (ddq, $^3J_{HF}$ = 9.5 Hz, J_{HH} = 3.8 Hz, J_{HH} = 5.3 Hz, 1H, *H*3), 3.9 (m, 2H, CH_2O), 4.15 (d, J = 3.8 Hz, *H*2), 4.2 (m, 2H, OCH_2), 4.6 (d, J = 7.4 Hz, 1H, *H*5), 6.2 (d, J = 3.3 Hz, 1H), 6.25 (dd, J = 3.3 Hz, J = 1.8 Hz), 7.27 (d, J = 1.8 Hz).

^{13}C NMR δ 13.6, 13.9, 49.3 (q, J_{CF} = 30 Hz, *C*3), 49.6 (*C*4), 59.4, 60.2 (*C*2, *C*3), 61.2 (CH_2), 61.8 (CH_2), 107.4, 110.2, 126.7 (q, J_{CF} = 262 Hz), 142, 151, 170, 171.

Anal calc for $C_{15}H_{18}F_3NO_5$: C 51.6, H 5.2, N 4.0. Found C 51.4, H 5.3, N 3.9%.

Acknowledgments

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