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Convenient synthesis of 5-perfluoroalkylsubstituted isoxazoles

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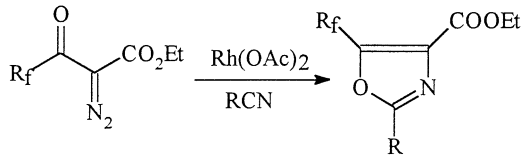
Abstract—5-Perfluoroalkylsubstituted isoxazoles are prepared readily from the reaction of nitrile oxide generated in situ from RCH_2NO_2, TEA and $POCl_3$ with ethyl 3-perfluoroalkyl-3-pyrrolidino-acrylates, which were obtained by treatment of α-perfluoroalkyl ethyl acetate with pyrrolidine in the presence of base.

Isoxazoles are well known compounds and structural parts of numerous natural products, drugs, polymers and other useful compounds.[1] Owing to their unique biological activities such as pharmaceuticals and agrochemicals,[2] and the novel chemical and physical properties, as dyes, electric insulating oils and high temperature lubricants,[3] many methods have been developed for their preparation.[1] We are interested in synthesis of fluorine-containing isoxazoles as they could be key intermediates in the preparation of fluorine-containing β-amino alcohol, β-hydroxyl ketone and other fluorine-containing heterocycles which are intriguing targets for medical treatment.[1,4]

However, some methods for preparation of isoxazoles do not work well for fluorine-containing analogues.[5] Recently we have reported the preparation of a series of 5-perfluoroalkyl-1,3-oxazoles via the rhodium catalyzed heterocycloaddition of ethyl 2-diazo-fluoroalkylacetoacetate with nitrile (Scheme 1):[6]

Herein we wish to report the synthesis of ethyl 3-perfluoroalkyl-3-pyrrolidino-acrylates and their reactions with nitrile oxides obtained in situ from nitro compounds to give 5-perfluoroalkylsubstituted isoxazoles.



Scheme 1.

1. Result and discussion

It is well known that 1,3-dipolar cycloaddition reactions between an open chain building block including a double bond, and nitrile oxide as dipole produced in situ is a versatile route to isoxazoles. An electron donating group on one side of the double bond controls the regioselectivity in the reaction.[7] We therefore synthesized a fluorine-containing building block with an electron donating group attached to one end of the double bond. A preparation of ethyl 3-trifluoromethyl-3-pyrrolidino-acrylate has been reported.[8] However, the starting material (ethyl 4,4,4-trifluoroacetoacetate) is comparatively an expensive reagent.

Firstly, we prepared α-fluoroalkyl substituted ethyl acetates **3** from the reaction of vinyl ethyl ether **2** and readily available perfluoroalkylhalide **1** using the method of Huang.[9] Under basic conditions treatment of **3** with pyrrolidine at ambient temperature gave ethyl 3-perfluoroalkyl-3-pyrrolidino-acrylates **4** as a mixture of *Z* and *E* isomers in high yield (Scheme 2).

The formation of perfluoroalkylated acrylates **4** from **3** involves three reaction steps in one pot: (i) elimination of HX; (ii) Michael addition of pyrrolidine to the acrylate ester and (iii) elimination of HY.

It was noted that in the preparation of **4** (Scheme 2) two stereoisomers (**4***Z*/**4***E*) are formed. For example, when **3c** was treated with pyrrolidine, ^{19}F NMR spectra showed two peaks at −60.2 and −65.5 ppm, respectively, in a ratio of 7:6 after **3c** was consumed. According to the literature,[10] when the CF_3 and ester groups are *trans*, the chemical shift of the CF_3 is at higher field, so in our case the higher field chemical shift (at −65.5 ppm) should arise from the *Z* isomer.

Attempts to separate the two isomers by flash chromatography using silica gel (washed with TEA before use) failed.

Keywords: synthesis; fluorine-containing isoxazole; nitrile oxide; 1,3 dipolar cycloaddition; enamine.

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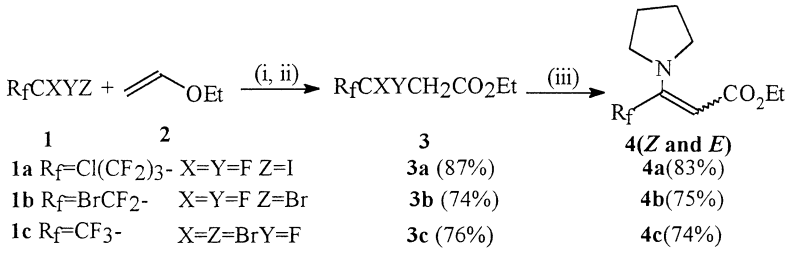


Scheme 2. Reaction conditions and reagents: (i) $Na_2S_2O_4$, $NaHCO_3$, C_2H_5OH, 50°C; (ii) $(NH_4)_2S_2O_8/H_2SO_4/H_2O$; (iii) TEA, $NaHCO_3$, pyrrolidine/diethyl ether.

Table 1. Reaction of α-fluoroalkyl ethyl acetates **3** with pyrrolidine in the presence of base

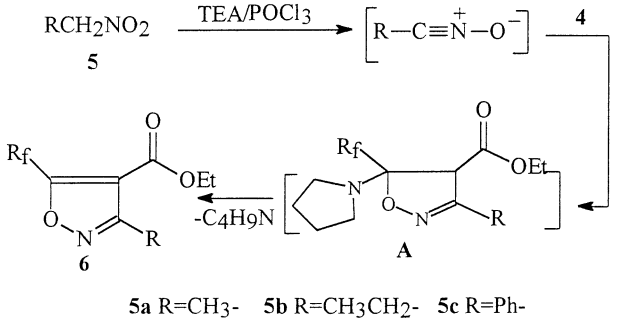
Entry	Reactant (**3**)	Product (**4**)	*E*:*Z*[a]	Yield (%)[b]
1	**3a**	**4a**	1:2	83
2	**3b**	**4b**	2:5	75
3	**3c**	**4c**	7:6	74

[a] Determined by ^{19}F NMR spectroscopy.
[b] Isolated yield (*Z* isomer only after Vacuum distillation).

It was found that the *E* isomer transformed partly to the *Z* isomer on the silica gel column. It was also observed that the ratio of *Z* isomer in the two isomers mixture increased after standing for several days at room temperature. The *Z* isomer is thermodynamically more stable. Eventually, vacuum distillation gave pure acrylates **4** as the *Z* isomer alone. The reaction result of α-fluoroalkyl ethyl acetates **3** with pyrrolidine is tabulated in Table 1.

The reaction of ethyl 3-perfluoroalkyl-3-pyrrolidino-acrylates **4** with nitrile oxide formed in situ from the reaction of RCH_2NO_2 with TEA and $POCl_3$ proceeded smoothly as shown by TLC analysis. However, the conversions of the acrylates observed by ^{19}F NMR spectroscopy were ranged from 30 to 60%. Even by raising the reaction temperature or prolonging the reaction time, the fluorinated acrylates did not react more completely. Addition of more reagents or changing the ratio of RCH_2NO_2, TEA and $POCl_3$, did not increase the conversion. As it is known that the nitrile oxide is liable to dimerisation, [11] we tried to reduce its concentration in the reaction system by slowing down the speed of addition of phosphorus oxychloride and increasing the amount of solvent used. The conversions increased only a little.

The optimum reaction conditions are described in the experimental section. The reaction mixture was stirred at room temperature for three days, then excess TEA was added to quench the reaction. The solvent was then evaporated, and 1N HCl was added to the residue. The remaining acrylate was hydrated to the F-alkyl β-keto ester after several hours, then the reaction mixture was extracted with diethyl ether. After general work up, chromatography afforded the expected isoxazoles **6**.



Scheme 3.

The addition product **A** from 1,3 dipole nitrile oxide with fluoroalkylated acrylates **4** could not been detected by ^{19}F NMR spectroscopy or TLC analysis (Scheme 3). Consequently, the pyrrolidine moiety was readily lost after the concerted cycloaddition reaction. The moderate conversion should be attributed to the comparatively low reactivity of the acrylate to the nitrile oxide because of the electron withdrawing character of the perfluoroalkyl group and the comparatively high liability of nitrile oxide to dimerisation.[11] It can also explain the fact that α-nitro acetate acid methyl ester had no reaction with the fluorinated acrylates **4**. The conversions were 60, 55 and 35% for the **4c** (R_f=CF_3–), **4b** (R_f=$BrCF_2$–) and **4a** (R_f=ClC_3F_6–), respectively. The different steric effect of perfluoroalkyl groups could account for the difference in the conversion. The preparation of 5-perfluoroalkyl substituted isoxazoles is summarised in Table 2.

Table 2. Preparation of 5-perfluoroalkyl substituted isoxazoles **6**

Entry	Reactant (**4**)	Regent (**5**)	Product (**6**)[a]	Yield (%)[b]
1	**4a**	**5a**	**6aa**	85
2	**4a**	**5b**	**6ab**	92
3	**4a**	**5c**	**6ac**	81
4	**4b**	**5a**	**6ba**	84
5	**4b**	**5b**	**6bb**	61
6	**4b**	**5c**	**6bc**	72
7	**4c**	**5a**	**6ca**	76
8	**4c**	**5b**	**6cb**	69
9	**4c**	**5c**	**6cc**	89

[a] The reaction conditions are described in the Experimental section.
[b] Isolated yield based on the conversions.

In summary we have synthesized a series of ethyl 3-perfluoroalkyl-3-pyrrolidino-acrylates **4** in high yield and with high steroselectivity. They readily undergo 1,3-dipolar cycloaddition with nitrile oxide produced in situ to afford 5-perfluoroalkyl substituted isoxazoles **6**.

2. Experimental

^1H- and ^{19}F NMR spectra were recorded on Varian-360L

spectrometer instruments with TMS and TFA ($\delta_{CFCl3}=\delta_{TFA}-76.8$ ppm, with high field negative) as internal and external standards, respectively. NMR spectra were recorded in $CDCl_3$ unless otherwise stated. The IR spectra were obtained with a Perkin–Elmer 983G spectro-photometer on KBr disks. Low and high resolution mass spectra were obtained in a HP 5989a and Finngan MAT Instruments, respectively. This institute performed elemental analysis. Solvent and reagents were commercially available and purified before use.

2.1. General procedure for preparation of the ethyl 3-perfluoroalkyl-3-pyrrolidino-acrylates 4

To a suspension of α-perfluoroalkyl ethyl acetate **3** (10.0 mmol), sodium bicarbonate (1.26 g, 15.0 mmol) and triethylamine (2.09 mL, 15.0 mmol) in diethyl ether (50 mL) at 0–5°C, with stirring, added a solution of pyrrolidine (1.00 mL, 12.0 mmol) in diethyl ether (10 mL) by drop funnel in 1 h, then the mixture was stirred at ambient temperature for 24 h. ^{19}F NMR spectroscopy showed the reaction was completed. Then the mixture was poured into water (60 mL), the organic layer was separated, the water layer was extracted with diethyl ether (40 mL×3). The organic layers were combined, washed with brine (40 mL×2) and dried (Na_2SO_4). After removal of solvent, vacuum distillation afforded the ethyl 3-perfluoroalkyl-3-pyrrolidino-acrylates.

2.1.1. (*Z*) Ethyl 3-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-3-pyrrolidino-acrylate 4a. (Yield: 83%); light yellow oil; bp 88°C/0.5 Torr; [Found: C, 40.69; H, 3.99; N, 4.11. $C_{12}H_{14}ClF_6NO_2$ requires C, 40.75; H, 3.99; N, 3.96%]; ν_{max} (liquid film) 2979, 1681, 1597, 1047–1287, 789 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 5.18 (1H, s, C=C*H*), 4.13 (2H, q, *J*=9.3 Hz, –OCH_2CH$_3$), 3.28–3.68 (4H, m, 2×NCH_2CH$_2$–), 1.73–2.23 (4H, m, 2×NCH$_2$CH_2–), 1.28 (3H, t, *J*=9.3 Hz, –OCH$_2$CH_3); δ_F (54.7 MHz, $CDCl_3$) −66.4 (2F, s, ClCF_2CF$_2$CF$_2$–), −105.5 (2F, s, ClCF$_2$CF$_2$CF_2–) [$\delta_F=-102.4$ for *E*-**4a**], −119.8 (2F, s, ClCF$_2$CF_2CF$_2$–) [$\delta_F=-116.4$ for *E*-**4a**]; *m/z* (EI): 353/355 (8.56/2.93 M^+), 324/326 (100.00/33.35), 308/310 (34.78/11.45), 280/282 (10.27/3.39%).

2.1.2. (*Z*) Ethyl 3-bromodifluoromethyl-3-pyrrolidino-acrylate 4b. (Yield: 75%); light yellow oil; bp 100°C/1 Torr; [Found: C, 40.42; H, 4.77; N, 4.85. $C_{10}H_{14}BrF_2NO_2$ requires C, 40.28; H, 4.73; N, 4.70%]; ν_{max} (liquid film) 2976, 1693, 1597, 1145–1262 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 5.10 (1H, s, C=C*H*), 4.08 (2H, q, *J*=10.0 Hz, –OCH_2CH$_3$), 3.26–3.64 (4H, m, 2×NCH_2CH$_2$–), 1.73–2.08 (4H, m, 2×NCH$_2$CH_2–), 1.23 (3H, t, *J*=10.0 Hz, –OCH$_2$CH_3); δ_F (54.7 MHz, $CDCl_3$) −46.1 [$\delta_F=-43.0$ for *E*-**4b**]; *m/z* (EI): 298/300 (10.10/8.80 M^+), 268/270 (9.44/9.34), 252/254 (47.38/43.62), 188 (100.00%).

2.1.3. (*Z*) Ethyl 3-trifluoromethyl-3-pyrrolidino-acrylate 4c. (Yield: 74%); light yellow oil; bp 78°C/3 Torr; [Found: C, 50.31; H, 6.02; N, 6.00. $C_{10}H_{14}F_3NO_2$ requires C, 50.67; H, 5.95; N, 5.91%]; ν_{max} (liquid film) 2980, 1681, 1615, 1123–1274 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 5.21 (1H, s, C=C*H*), 4.14 (2H, q, *J*=11.0 Hz, –OCH_2CH$_3$), 3.26–3.78 (4H, m, 2×NCH_2CH$_2$–), 1.76–2.15 (4H, m, 2×NCH$_2$CH_2–), 1.28 (3H, t, *J*=11.0 Hz, –OCH$_2$CH_3); δ_F (54.7 MHz, $CDCl_3$) −64.6 [$\delta_F=-59.6$ for *E*-**4b**]; *m/z* (EI): 237 (22.10 M^+), 192 (37.04), 208 (100.00%).

2.2. General procedure for the synthesis of 5-perfluoroalkylsubstituted isoxazoles 6

Under nitrogen atmosphere and with stirring, to a mixture of ethyl 3-perfluoroalkyl-3-pyrrolidino-acrylate **4** (1.0 mmol), primary nitro compound **5** (1.1 mmol) and triethylamine (0.42 mL, 3.0 mmol) in anhydrous chloroform (15 mL) at 0°C was added for about 3 h, via dropping funnel, a solution of phosphorus oxychloride (0.11 mL, 1.2 mmol) in anhydrous chloroform (10 mL). The mixture was stirred at ambient temperature for about 72 h before TEA (5 mL) was added to quench the reaction. The solvent was evaporated out in vacuo, the residue was submitted to ^{19}F NMR spectroscopy, then poured into 1N HCl (25 mL) and stirred for 7–8 h at room temperature. The organic layer was separated, the water layer was extracted with CH_2Cl_2 (25 mL×3). The organic layers were combined, washed with brine (40 mL×2) and dried (Na_2SO_4). After removal of solvent, column chromatography (with petroleum ether and ethyl acetate as the eluent) afforded the title compounds.

2.2.1. 4-Ethoxycarbonyl-3-methyl-5-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-isoxazole 6aa. Eluent: *n*-hexane/ethyl acetate 30:1 (R_f=0.2–0.3); (yield: 85%); light yellow oil; [Found: C, 35.60; H, 2.31; N, 4.30. $C_{10}H_8ClF_6NO_3$ requires C, 35.37; H, 2.37; N, 4.12%]; ν_{max} (liquid film) 2986, 1728, 1615, 1125–1306, 776 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 4.40 (2H, q, *J*=7.2 Hz, –OCH_2CH$_3$), 2.17 (3H, s, –CH_3), 1.28 (3H, t, *J*=7.2 Hz, –OCH$_2$CH_3); δ_F (54.7 MHz, $CDCl_3$) −66.8 (2F, s, ClCF_2CF$_2$CF$_2$–), −108.8 (2F, s, ClCF$_2$CF$_2$CF_2–), −119.2 (2F, s, ClCF$_2$CF_2CF$_2$–); *m/z* (EI): 339/341 (7.19/2.29 M^+), 331/333 (7.38/8.36), 294/296 (100.00/32.81), 154 (15.41%).

2.2.2. 4-Ethoxycarbonyl-3-ethyl-5-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-isoxazole 6ab. Eluent: *n*-hexane/ethyl acetate 15:1 (R_f=0.2–0.3); (yield: 92%); light yellow oil; [Found: C, 37.61; H, 2.89; N, 4.19. $C_{11}H_{10}ClF_6NO_3$ requires C, 37.36; H, 2.85; N, 3.95%]; ν_{max} (liquid film) 2920, 1729, 1600, 1093–1293, 786 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 4.40 (2H, q, *J*=6.2 Hz, –OCH_2CH$_3$), 3.00 (2H, q, *J*=7.1 Hz –CH_2CH$_3$), 1.09–1.54 (6H, m, –OCH$_2$CH_3 and –CH$_2$CH_3); δ_F (54.7 MHz, $CDCl_3$) −66.5 (2F, s, ClCF_2 CF$_2$CF$_2$–), −108.2 (2F, s, ClCF$_2$CF$_2$CF_2–), −118.4 (2F, s, ClCF$_2$CF_2CF$_2$–); *m/z* (EI): 354/356 (57.32/18.25 M^+), 326/328 (14.99/4.77), 307/309 (95.59/34.72), 94 (100.00%).

2.2.3. 4-Ethoxycarbonyl-3-phenyl-5-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-isoxazole 6ac. Eluent: *n*-hexane/ethyl acetate 30:1 (R_f=0.2–0.3); (yield: 81%); light yellow oil; [Found: C, 45.08; H, 2.65; N, 3.67. $C_{15}H_{10}ClF_6NO_3$ requires C, 44.85; H, 2.51; N, 3.48%]; ν_{max} (liquid film) 2985, 1737, 1623, 1124–1309, 774 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 7.33–7.73 (5H, m, Ph), 4.33 (2H, q, *J*=6.2 Hz, –OCH_2CH$_3$), 1.28 (3H, t, *J*=6.2 Hz, –OCH$_2$CH_3); δ_F (54.7 MHz, $CDCl_3$) −66.3 (2F, s, ClCF_2CF$_2$CF$_2$–), −109.1 (2F, s, ClCF$_2$CF$_2$CF_2–), −119.1 (2F, s, ClCF$_2$CF_2CF$_2$–); *m/z* (EI): 401/403 (72.00/27.82 M^+),

356/358 (61.97/21.52), 216 (75.00), 77 (45.85), 114 (100.00%).

2.2.4. 4-Ethoxycarbonyl-3-methyl-5-bromodifluoromethyl-isoxazole 6ba. Eluent: *n*-hexane/ethyl acetate 20:1 (R_f=0.2–0.3); (yield: 84%); light yellow oil; [Found: C, 33.75; H, 2.89; N, 4.71. $C_{15}H_{10}BrF_2NO_3$ requires C, 33.83; H, 2.84; N, 4.93%]; ν_{max} (liquid film) 2920, 1731, 1600, 1140–1290 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 4.40 (2H, q, J=7.2 Hz, $-OCH_2CH_3$), 2.53 (3H, s, $-CH_3$), 1.40 (3H, t, J=7.2 Hz, $-OCH_2CH_3$); δ_F (54.7 MHz, $CDCl_3$) −47.3 (s, $BrCF_2$); *m/z* (EI): 284/286 (7.89/7.37 M^+), 238/240 (23.68/23.16), 204 (22.19), 176 (100.00%).

2.2.5. 4-Ethoxycarbonyl-3-ethyl-5-bromodifluoromethyl-isoxazole 6bb. Eluent: *n*-hexane/ethyl acetate 20:1 (R_f=0.2–0.3); (yield: 61%); light yellow oil; [Found: C, 36.42; H, 3.59; N, 5.04. $C_9H_{10}BrF_2NO_3$ requires C, 45.10; H, 2.91; N, 4.00%]; ν_{max} (liquid film) 2910, 1720, 1600, 1142–1290 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 4.40 (2H, q, J=8.0 Hz, $-OCH_2CH_3$), 2.97 (2H, q, J=7.1 Hz $-CH_2CH_3$), 1.23–1.53 (6H, m, $-OCH_2CH_3$ and $-CH_2CH_3$); δ_F (54.7 MHz, $CDCl_3$) −46.9 (s, $BrCF_2$); *m/z* (EI): 298/300 (11.87/11.02 M^+), 251/253 (18.42/19.63), 224/226 (22.98/19.99), 162 (100.00%).

2.2.6. 4-Ethoxycarbonyl-3-phenyl-5-bromodifluoromethyl-isoxazole 6bc. Eluent: *n*-hexane/ethyl acetate 20:1 (R_f=0.2–0.3); (yield: 72%); light yellow oil; [Found: C, 45.26; H, 3.11; N, 4.30. $C_{13}H_{10}BrF_2NO_3$ requires C, 36.30; H, 3.38; N, 4.70%]; ν_{max} (liquid film) 2910, 1730, 1600, 1130–1297 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 7.37–7.90 (5H, m, Ph), 4.37 (2H, q, J=7.4 Hz, $-OCH_2CH_3$), 1.52 (3H, t, J=7.4 Hz, $-OCH_2CH_3$); δ_F (54.7 MHz, $CDCl_3$) −46.6 (s, $BrCF_2$); *m/z* (EI): 345/347 (34.72/34.94 M^+), 317/319 (1.22/1.21), 300/302 (16.77/16.52), 216 (75.68), 144 (100.00%).

2.2.7. 4-Ethoxycarbonyl-3-methyl-5-trifluoromethyl-isoxazole 6ca. Eluent: *n*-hexane/ethyl acetate 20:1 (R_f=0.2–0.3); (yield: 76%); light yellow oil; [HMRS (EI): M^+, Found 223.05023. $C_8H_8F_3NO_3$ requires 223.04563.]; ν_{max} (liquid film) 2961, 1732, 1617, 1023–1262 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 4.30 (2H, q, J=7.1 Hz, $-OCH_2CH_3$), 2.47 (3H, s, $-CH_3$), 1.30 (3H, t, J=7.1 Hz, $-OCH_2CH_3$); δ_F (54.7 MHz, $CDCl_3$) −61.8 (s, CF_3); *m/z* (EI): 224 (11.41 M^+), 195 (28.09), 178 (82.68), 154 (20.69), 128 (100), 69 (24.02%).

2.2.8. 4-Ethoxycarbonyl-3-ethyl-5-trfluoromethyl-isoxazole 6cb. Eluent: *n*-hexane/ethyl acetate 40:1 (R_f=0.2–0.3); (yield: 69%); light yellow oil; [HMRS (EI): M^+, Found 237.06174. $C_9H_{10}F_3NO_3$ requires 237.06128.]; ν_{max} (liquid film) 2961, 1732, 1617, 1023–1298 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 4.25 (2H, q, J=10.0 Hz, $-OCH_2CH_3$), 2.85 (2H, q, J=10.0 Hz $-CH_2CH_3$), 1.10–1.46 (6H, m, $-OCH_2CH_3$ and $-CH_2CH_3$); δ_F (54.7 MHz, $CDCl_3$) −61.8 (s, CF_3); *m/z* (EI): 238 (6.96 M^++1), 209 (5.13), 191 (100.00), 164 (65.13), 69 (17.82%).

2.2.9. 4-Ethoxycarbonyl-3-phenyl-5-trfluoromethyl-isoxazole 6cc. Eluent: *n*-hexane/ethyl acetate 30:1 (R_f=0.2–0.3); (yield: 89%); light yellow oil; [Found: C, 55.05; H, 3.79; N, 5.21. $C_{13}H_{10}F_3NO_3$ requires C, 54.70; H, 3.53; N, 4.91%]; ν_{max} (liquid film) 2920, 1730, 1600, 1160–1319 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 7.37–7.87 (5H, m, Ph), 4.24 (2H, q, J=7.5 Hz, $-OCH_2CH_3$), 1.20 (3H, t, J=7.5 Hz, $-OCH_2CH_3$); δ_F (54.7 MHz, $CDCl_3$) −61.0 (s, CF_3); *m/z* (EI): 285 (5.29 M^+), 240 (3.38), 216 (5.80), 149 (100), 69 (13.46%).

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