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A CONVENIENT SYNTHESIS OF 5-ETHOXY-4-(TRIFLUOROMETHYL)-2-OXAZOLECARBOXYLIC ACID AND RELATED TRIFLUOROMETHYL SUBSTITUTED HETEROCYCLIC COMPOUNDS

GUOQIANG SHI, YUANYAO XU* and MING XU†

Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Academia Sinica, 345 Lingling Lu, Shanghai 200032 (China)

SUMMARY

5-Ethoxy-4-(trifluoromethyl)-2-oxazolecarboxylic acid **4** has been obtained from the corresponding ethyl ester prepared by rhodium-catalysed reaction of ethyl 3,3,3-trifluoro-2-diazopropionate **1** with ethyl cyanoformate. Starting from this acid, a number of its ester and amide derivatives have been prepared in good yields. The acid **4** was found to decarboxylate readily on heating to give the simple CF_3-substituted oxazole **5**, which was further utilized as an aza-diene for the synthesis of 3-hydroxy-2-trifluoromethyl-4-pyridinecarboxylic acid from acrylic acid.

INTRODUCTION

Heterocyclic compounds bearing a trifluoromethyl group are of potential interest as intermediates for pharmaceuticals and agrochemicals [1]. Burger *et al.* [2] have reported that some CF_3-substituted oxazole derivatives, which were synthesized in several steps starting from hexafluoroacetone, could be used as herbicides. Meanwhile, we have recently developed a convenient preparation of a CF_3-containing diazo compound, *i.e.* ethyl

†Undergraduate participant from the College of Pharmacy, Shanghai Medical University.

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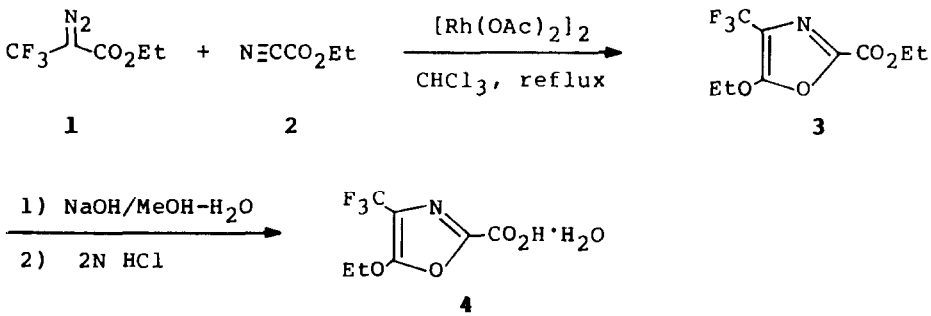
3,3,3-trifluoro-2-diazo-propionate **1** and briefly demonstrated its synthetic utility for the preparation of a number of CF_3-substituted oxazole derivatives by carrying out its rhodium-catalysed reaction with some nitriles [3]. The ease with which the CF_3-substituted oxazoles were formed from **1** and the need of preparing more oxazole derivatives for agrochemical screening have now prompted us to synthesize a hitherto unknown CF_3-substituted oxazolecarboxylic acid from **1** and further derivatives thereby.

RESULTS AND DISCUSSIONS

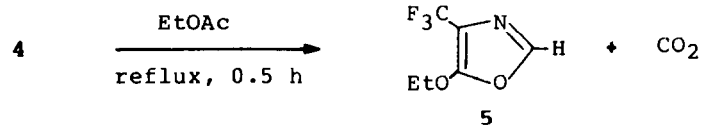
To obtain a CF_3-substituted oxazole carboxylic acid, we extended our previous reaction to a special 'nitrile', i.e. ethyl cyanoformate **2** (Mander's reagent). Although the electronic properties of the cyano group of **2** might have been considerably altered by its direct connection to the carboethoxy group, the rhodium-catalysed reaction of the CF_3-containing diazo compound **1** with **2** proceeded readily and afforded the expected oxazole product **3** in good yield. Compound **3** was easily hydrolyzed to furnish the corresponding oxazole carboxylic acid **4** which was found to exist in a monohydrated form (Scheme 1).



Scheme 1.

The carboxylic acid **4** has been found to be thermally unstable and decarboxylation occurred readily upon refluxing **4** in ethyl acetate to result in the clean formation of a simple CF_3-substituted oxazole **5**. This instability has

frustrated the attempt to remove the water of crystallisation from **4**. Consequently, the acid had to be used in its hydrated form.



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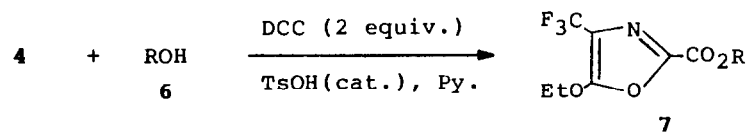
With the hydrated parent acid **4** in hand, we then sought to prepare its ester and amide derivatives which might possess some intriguing biological activities. The preparation of the acid derivatives of **4** turned out not to be trivial because the rather unstable character of **4** has precluded the use of conventional methods.

For direct esterification of **4** with alcohols, a very mild and efficient method has been chosen using a slightly modified procedure developed by Holmberg and Hansen [4]. Thus reaction of **4** with a slight excess of alcohol in pyridine promoted by two equivalents of dicyclohexyl carbodiimide(DCC) and a catalytic amount of p-toluenesulfonic acid took place smoothly at room temperature and afforded the CF_3-substituted oxazolecarboxylate **7** in high yields (Scheme 2). In this reaction, the use of two



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Scheme 2.

TABLE 1

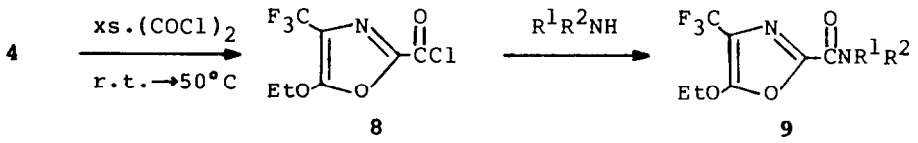
5-Ethoxy-4-(trifluoromethyl)-2-carboxylates Prepared

Entry	Products 7		Yields(%)[a]	m.p.(°C)
	R=			
1	Ph	**7a**	88	42-43
2	$PhCH_2$	**7b**	81	68-69
3	$PhCH=CHCH_2$	**7c**	85	69-70

[a] Yields of isolated products based on **4**.

equivalents of DCC was necessitated by both the dehydration of the starting acid **4** and the subsequent esterification process. The results were summarized in Table 1.

In order to prepare amido derivative of **4**, we first tried the direct condensation of **4** with appropriate organic amines in the presence of DCC, a reagent widely employed for peptide synthesis; unfortunately, the yields of the amides were very poor presumably because of side reactions [5]. The preparation of the acyl chloride from **4** and its subsequent treatment with amines were then examined. Thionyl chloride turned out to be unsuitable for the conversion of **4** to the acyl chloride because of the moderate reaction temperature at which decarboxylation of **4** occurs. Use of the milder reagent oxalyl chloride permitted the conversion to be carried out quickly and efficiently at a temperature tolerated by the thermally labile acid **4**. Without isolation the crude acyl chloride prepared was directly treated with appropriate amines to afford the desired CF_3-substituted oxazolecarboxamides in fairly good yields (Scheme 3 and Table 2).



Scheme 3.

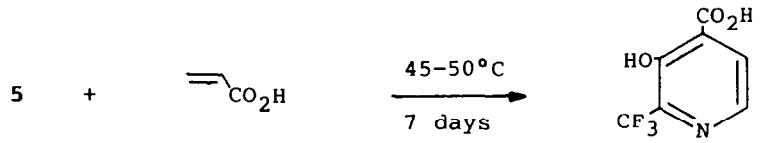
TABLE 2

5-Ethoxy-4-(trifluoromethyl)-2-oxazolecarboxamides

Entry	Products 9			Yields(%)[a]	m.p.(°C)
	R^1=	R^2=			
1		$-(CH_2)_4-$	**9a**	83	77-78
2		$-(CH_2)_5-$	**9b**	87	26-27
3	H	$(CH_3)_2CHCH_2$	**9c**	77	51-52
4	H	p-BrC_6H_4	**9d**	78	139-141

[a] Yields of isolated products based on **4**.

Finally, we briefly examined the potential of the CF_3-substituted oxazole **5** as an aza-diene for a Diels-Alder reaction [6]. Thus, prolonged heating of a mixture of **5** and an excess of acrylic acid afforded the CF_3-substituted pyridine derivative **10** in reasonable yield. However, cycloaddition of **5**



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with other olefins, such as ethyl acrylate, maleic anhydride, N-phenyl maleimide, 2,5-dihydrofuran and 2-buten-4-olide, which have been successfully employed in the reaction with the nonfluorinated counterpart of **5**, i.e. 4-ethoxy-5-methyl-oxazole [6], did not take place to any appreciable extent presumably because of the deactivation of the oxazole ring by a strongly electron-withdrawing CF_3 group.

EXPERIMENTAL

^1H NMR spectra were obtained on a Varian EM-360L spectrometer with Me_4Si as the internal standard. ^{19}F NMR spectra were recorded on a Varian EM-360A spectrometer with trifluoroacetic acid(δ 0.00) as the external standard; downfield shifts were designated negative. Infrared spectra were taken on a Shimadzu 440-IR spetrometer and mass spectra on a Finnigan 4021/GC/MS/DC instrument with an ionizing potential of 70 eV. Melting points were uncorrected. Ethyl cyanoformate was prepared according to the procedure described by Childs and Weber [7] and rhodium(II) acetate was obtained by the method of Wilkinson [8]. Chloroform (analytical grade) was first shaken with concentrated sulfuric acid and washed with water to remove traces of ethanol, then dried over $CaCl_2$, and finally distilled. Ethyl 3,3,3-trifluoro-2-diazo-propionate **1** was prepared as described in our previous paper [9].

Preparation of Ethyl 5-Ethoxy-4-(trifluoromethyl)-2-oxazole-carboxylate(**3**)

Ethyl cyanoformate (5.70 g, 58 mmol) and rhodium(II) acetate (0.33 g, 0.75 mmol) were dissolved in ethanol-free chloroform (10 mL) and the resulting solution was stirred and heated under reflux until the solution became homogeneously purple. The mixture was kept at reflux and a solution of **1** (13.65 g, 75 mmol) in chloroform (60 mL) was then added over 8 h. The reaction mixture was passed through a short column of silica gel and the filtrate was concentrated and distilled to afford **3** in 90% yield, b.p.: 82-83°C/2.5 mmHg. ^{1}H NMR(CCl_4) δ 1.26 (t,J=7.2Hz, 3H), 1.39 (t,J=7.2Hz,3H), 4.20 (q,J=7.2Hz,2H), 4.40 (q,J=7.2Hz, 2H); ^{19}F NMR(CCl_4) δ -15.4(s); IR(neat) 1740(s); MS, m/z (relative intensity) 253(M, 45), 225(100), 197(44), 180(29), 169(12), 153(99), 133(96), 69(31). Anal. calcd for $C_9H_{10}F_3NO_4$: C, 42.68; H, 3.95; N, 5.53; F, 22.53%. Found: C, 42.53; H, 3.91; N, 5.09; F, 22.89%.

Preparation of 5-Ethoxy-4-(trifluoromethyl)-2-oxazolecarboxylic Acid Monohydrate(**4**)

A solution of **3** (12.65 g, 50 mmol) in 80% aqueous methanol (80 mL) containing sodium hydroxide (4 g) was stirred at room temperature for 30 min. The reaction mixture was then acidified with 2 N HCl solution(100 mL), and extracted with ether (4× 50 mL). The ether extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford **4** as a crystalline mass in quantitative yield. An analytical sample was prepared by recrystallization from ethyl ether-hexane, m.p.: 55-56°C. ^{1}H NMR ($CDCl_3$) δ 1.26(t, J=7.2Hz, 3H), 4.25(q, J=7.2Hz, 2H), 5.4-5.8 (br s, 2H); ^{19}F NMR($CDCl_3$) δ -15.6(s); MS, m/z(relative intensity) 225(M-H_2O, 23), 197(83), 153(35), 133(45), 96(75), 77 (100), 69(51), 45(72); IR(nujol) 3450(s), 2000-3000(s), 1710(s). Anal. calcd for $C_7H_8F_3NO_5$:C, 34.56; H, 3.29; N, 5.76; F, 23.45%. Found: C, 34.86; H, 3.11; N, 5.36; F, 23.14%.

Preparation of 5-Ethoxy-4-(trifluoromethyl)-2-oxazole (**5**)

A solution of **4** (2.43 g, 10 mmol) in ethyl acetate (20 mL) was refluxed for 30 min. and then washed with brine and dried over Na_2SO_4. Removal of the solvent in vacuo gave essentially

pure **5** in 98% yield. ^{1}H NMR(CCl_4) δ 1.40(t,J=7.2Hz,3H), 4.30 (q,J=7.2Hz,2H), 7.25(s,1H); ^{19}F NMR(CCl_4) δ -15.4(s); MS, m/z (relative intensity) 181(M, 55), 162(11), 153(100), 133(69), 96 (51), 69(35). Anal. calcd for $C_6H_6F_3NO_2$: C, 39.78; H, 3.31; N, 7.73; F, 31.49%. Found: C, 39.29; H, 3.21; N, 7.82; F, 31.19%.

General Procedure for the Preparation of 5-Ethoxy-4-(trifluoromethyl)-2-oxazolecarboxylates (7a-c)

The acid 4 (0.49 g, 2 mmol), the alcohol(2.4 mmol) and dicyclohexyl carbodiimide (0.86 g, 4.2 mmol) were mixed in dry pyridine(4 mL) containing a few crystals of p-toluenesulfonic acid (ca. 20 mg) and the resulting mixture was stirred at room temperature overnight with the exclusion of moisture. The insoluble materials were filtered off and the filtrate was concentrated. The residual oil was subjected to silica gel chromatography **using 6:1 petroleum ether (60-90°C)/ethyl acetate as the eluent.**

7a: ^{1}H NMR(CCl_4) δ 1.45(t,J=7.2Hz,3H), 4.50(q,J=7.2Hz,2H), 7.13(s,5H); ^{19}F NMR(CCl_4) δ -15.6(s); IR(nujol) 1740(s); MS, m/z (relative intensity) 302(M+1, 37), 301(M, 7), 273(9), 227(35), 208(15), 180(49), 132(31), 94(100), 77(42), 65(20). Anal. calcd for $C_{13}H_{10}F_3NO_4$: C, 51.82; H, 3.32; N, 4.65; F, 18.94%. Found: C, 51.77; H, 2.82; N, 4.65; F, 18.95%.

7b: ^{1}H NMR(CCl_4) δ 1.45(t,J=7.2Hz,3H), 4.50(q,J=7.2Hz,2H), 5.32(s,2H), 7.20-7.40(m,5H); ^{19}F NMR(CCl_4) δ -15.7(s); IR (nujol) 1730(s); MS, m/z(relative intensity) 315(M, 3), 271 (31), 224(2), 209(5), 181(10), 107(55), 91(100), 77(5), 65(15). Anal. calcd for $C_{14}H_{12}F_3NO_4$: C, 53.33; H, 3.81; N, 4.44; F, 18.10%. Found: C, 53.05; H, 3.65; N, 4.20; F, 18.34%.

7c: ^{1}H NMR(CCl_4) δ 1.45(t,J=7.2Hz,3H), 4.45(q,J=7.2Hz,2H), 4.85(d,J=7.0Hz, 2H), 6.16(dt,J=7.0 and 15.5Hz, 1H), 6.66(d, J= 15.5HZ, 1H), 7.18(s, 5H); ^{19}F NMR(CCl_4) δ -15.7(s); IR(nujol) 1740(s); MS, m/z(relative intensity) 341(M, 6), 268(12), 224 (2), 180(5), 133(64), 117(100), 91(17). Anal. calcd for $C_{16}H_{14}F_3NO_4$: C, 56.30; H, 4.11; N, 4.11; F, 16.72%. Found: C, 56.24; H, 4.07; N, 3.95; F, 16.99%.

General Procedure for the Preparation of 5-Ethoxy-4-(trifluoromethyl)-2-oxazolecarboxamide (9a-d)

To the ice-cooled reaction flask containing the acid **4** (0.97 g, 4 mmol) oxalyl chloride (2 mL) was added via syringe

over 5 min.; and the reaction mixture was then stirred at room temperature for 1 h and finally at 50°C for 20 min. After removal of the excess oxalyl chloride in vacuo (50°C/2 mmHg), the residual oil was taken up in 10 ml of dry benzene and the resulting solution was treated with the organic amine (8 mmol). The reaction mixture was poured into 1 N HCl solution (30 mL) and extracted with ether(3×20 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. The residual oil was chromatographed on silica gel using 2:1 petroleum ether(60-90°C)/ethyl acetate as the eluent.

9a: ^{1}H NMR(CCl_4) δ 1.45(t,J=7.2Hz,3H), 1.80(m,4H), 3.40(t, J=7.0Hz,2H), 3.81(t,J=7.0Hz,2H), 4.45(q,J=7.2Hz,2H); ^{19}F NMR (CCl_4) δ -15.6(s); IR(nujol) 1650(s); MS, m/z(relative intensity) 278(M, 37), 249(4), 180(3), 98(100), 70(71), 55(66). Anal. calcd for $C_{11}H_{13}F_3N_2O_3$: C, 47.48; H, 4.68; N, 10.07; F, 20.50%. Found: C, 47.67; H, 4.39; N, 9.55; F, 20.14%.

9b: ^{1}H NMR(CCl_4) δ 1.45(t,J=7.2Hz,3H), 1.45-1.70(m,6H), 3.35-3.63(m,2H), 3.75-4.00(m,2H), 4.45(q,J=7.2Hz,2H); ^{19}F NMR (CCl_4) δ -15.6(s); IR(nujol) 1660(s); MS, m/z(relative intensity) 293(M+1,100), 112(10), 84(38). Anal. calcd for $C_{12}H_{15}F_3N_2O_3$: C, 49.32; H, 5.14; N, 9.59; F, 19.52%. Found: C, 49.02; H, 5.17; N, 9.52; F, 19.48%.

9c: ^{1}H NMR(CCl_4) δ 0.95(d,J=7.0Hz,6H, $CH(\underline{CH_3})_2$), 1.45(t,J= 7.2Hz,3H,$OCH_2\underline{CH_3}$), 1.65-1.98(m,1H,$\underline{CH}(CH_3)_2$), 3.15(dd,J=6.9 and 7.0Hz,2H,$NH\underline{CH_2}CH$), 4.45 (q,J=7.2Hz,2H,$O\underline{CH_2}CH_3$), 6.80-7.20(m,1H, $CO\underline{NH}CH_2$); ^{19}F NMR(CCl_4) δ -15.5(s); IR(nujol) 1680(s); MS, m/z(relative intensity) 281(M+1, 100), 280(M, 37), 237(17), 209 (29), 180(18), 153(20), 57(35). Anal. calcd for $C_{11}H_{15}F_3N_2O_3$: C, 47.14; H, 5.36; N, 10.00; F, 20.36%. Found: C, 47.44; H, 5.69; N, 10.22; F, 20.98%.

9d: ^{1}H NMR($CDCl_3$) δ 1.45(t,J=7.2Hz,3H), 4.45(q,J=7.2Hz,2H), 7.25-7.50(m,4H), 8.62(br s,1H); ^{19}F NMR($CDCl_3$) δ -15.6(s); IR(nujol) 1705(s); MS, m/z(relative intensity) 380(M+2, 74), 378(M, 100), 352(11), 350(10), 199(42), 197(40), 172(23), 170 (29). Anal. calcd for $C_{13}H_{10}BrF_3N_2O_3$: C, 41.20; H, 2.60; N, 7.40; F, 15.04%. Found: C, 41.17; H, 2.42; N, 7.31; F, 15.10%.

Preparation of 3-Hydroxy-2-trifluoromethyl-4-pyridinecarboxylic Acid (10)

A solution of 5 (0.73g, 4mmol) in acrylic acid (2 ml) was heated at 45-50°C for a week during which a white precipitate was formed. The white solid was collected on a Buchner funnel, washed with ether and dried to give **10** in 64% yield, m.p.: 199-201°C. ^{1}H NMR(CD_3OD) δ 8.00(d,J=5.0Hz,1H), 8.28(d,J=5.0Hz,1H); ^{19}F NMR(CD_3OD) δ -8.5(s); IR(nujol) 2000-3000(s), 1680(s); MS, m/z(relative intensity) 207(M, 78), 189(100), 161(63), 133(28), 69(17). Anal. calcd for $C_7H_4F_3NO_3$: C, 40.57; H, 1.93; N, 6.76; F, 27.54%. Found: C, 40.56; H, 1.80; N, 6.64; F, 27.62%.

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