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A convenient one-pot synthesis of 5-carboxyisoxazoles: trichloromethyl group as a carboxyl group precursor

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Abstract

The one-pot synthesis of ten 5-carboxyisoxazoles from the cyclocondensation of β-alkoxyvinyl trichloromethyl ketones [$CCl_3C(O)C(R^2)=C(R^1)OR$, where R^1, R^2=H, Me and R=Me, Et] and 2-trichloroacetyl cyclohexanone with hydroxylamine is reported. This work shows that the trichloromethyl group attached to β-alkoxyvinyl trichloromethyl ketones (a heterocyclic CCC building block) is an excellent carboxyl group precursor.

1. Introduction

The isoxazole derivatives possess very interesting pharmacological properties, especially alkoxy carbonyl isoxazoles which show marked action as a diuretic.[1] Also, alkoxy carbonyl isoxazoles are important precursors for the synthesis of other compounds such as agrochemicals and microbicides.[2] The synthesis of isoxazoles from the cyclization of β-diketones, α-acetylenic ketones or aldehydes (CCC block) with hydroxylamine (NO block), and from the condensation of nitrile oxides (CNO block) with triple bond compounds (CC block) has been presented extensively in the literature.[3] However, there are few reports for the synthesis of 5-alkoxycarbonyl isoxazoles. These report the synthesis 5-alkoxycarbonyl isoxazoles using methods where the building block (CCC) or (CC) already has an alkoxycarbonyl group[1,4] or a precursor group.[5] In the case where the building block has a precursor of the alkoxycarbonyl group, the conversion requires a strong oxidant agent such as potassium permanganate, chromium trioxide or nitric acid, and leads to low yields.[5] Although the transformation of the trichloromethyl group in carboxyl derivative groups in a sulfuric acid medium was reported in 1975 for the reactions of chloral,[6] the first work which shows the transformation of the trichloromethyl group attached to an isoxazole ring derivative was reported in 1986 by Spiegler and Götz.[7] These authors reported the conversion

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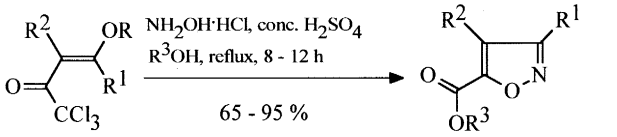
of 5-trichloromethyl-5-hydroxy-4,5-dihydroisoxazoles to 5-carboxyisoxazole, using 96% sulfuric acid at 100–120°C.[7] However, this reaction was an isolated result using only one substrate and did not demonstrate the real scope of the reaction. As a part of our research program, we developed a general one-step procedure for preparing a series of analytically pure β-alkoxyvinyl trihalomethyl ketones, from the acylation of several enol ethers (or acetals), in molar quantities.[8] These compounds have been used as precursors of a variety of substituted five-, six- and seven-membered heterocyclic compounds, e.g., isoxazoles,[8,9] pyrazoles,[10] pyrimidines[11] and diazepines.[12] The aim of this work is to report a one-pot synthesis of 5-carboxyisoxazoles from the cyclocondensation of β-alkoxyvinyl trichloromethyl ketones with hydroxylamine, in a hydrochloric acid or sulfuric acid medium. The trichloromethyl group attached to β-alkoxyvinyl trichloromethyl ketones (the CCC building block) can react with water or alcohol to form the carboxylic acid or ester derivative. In addition, we observed the substituent effect of β-alkoxyvinyl trichloromethyl ketones on the reaction regiochemistry and product yields (Scheme 1).



1a-d **2a-d, 3,4,5c,d**

	R	R^1	R^2		R^3
a	Et	H	H	**2**	H
b	Me	Me	H	**3**	Me
c	Me	H	Me	**4**	Et
d	H	$-(CH_2)_4-$		**5**	*i*-Pr

Scheme 1.

2. Discussion

The β-alkoxyvinyl trichloromethyl ketones **1a**–**c** and trichloroacetyl cyclohexanone **1d** were synthesized from the reaction of the respective enol ether or acetal with trichloroacetyl chloride.[8] Table 1 shows the reaction media tested for the reaction of compounds **1a**–**d** with hydroxylamine hydrochloride. The reactions were carried out with hydrochloric acid (in a molar ratio 3–10:1 of acid:**1**) or 96% sulfuric acid (in a molar ratio 3–5:1 of acid:**1**) in water, methanol, ethanol or isopropanol as solvents. The solvent governs the product of the trichloromethyl group hydrolysis to give carboxylic acid, methyl ester, ethyl ester or isopropyl ester. The reaction of compounds **1a**,**b** with hydroxylamine hydrochloride in 96% sulfuric acid (5:1, acid:**1**) in water, at 100°C, led regiospecifically to 5-carboxylisoxazole derivatives **2a**,**b**. For compounds **1a**,**b** higher temperatures (100–120°C) caused the loss of regiochemistry, and the mixtures of 5- and 3-carboxylisoxazole derivatives were obtained. However, when the reaction was carried out in a sulfuric acid/methanol (or ethanol) mixture (at reflux temperature) or a hydrochloric acid/water mixture (at 40–100°C), 5-trichloromethylisoxazole derivatives were obtained. When methanol (or ethanol) was used as solvent, the presence of 3-trichloromethylisoxazole derivatives (<20%) was detected. An increase of sulfuric acid (>5:1, acid:**1**) resulted in polymerization products (Table 1). Compounds **1c**,**d** reacted with hydroxylamine hydrochloride in 96% sulfuric acid in water (3:1, acid:**1**), at 100°C, leading to regiospecifically 5-carboxylisoxazole derivative **2c**,**d**. For compound **1c**, it was sufficient to use hydrochloric acid in water (3:1, acid:**1**) to give the compound **2c**. The similar reaction

conditions (3–10:1 of hydrochloric acid:**1** in water) for compound **1d** furnished the 5-trichloromethyl isoxazole derivative (Table 1).

Table 1
Yields[a] and reaction conditions[b] used for the synthesis of 5-carboxyisoxazoles **2a–d**, **3**, **4**, **5c**,**d**

NH_2OH · HCl + **1**	Reactional Medium Acid/Solvent	Molar ratio	Temp. (°C)	Product	Yield (%)	NH_2OH · HCl + **1**	Reactional Medium Acid/Solvent	Molar ratio	Temp. (°C)	Product	Yield (%)
1a	H_2SO_4/H_2O	1.2:1:5	40-100	**2a**	85	**1c**	HCl/ MeOH	1.2:1:3	65	**3c**	86
1a	HCl/H_2O	1.2:1:5-10	100	-	(75)[c]	**1c**	H_2SO_4/EtOH	1.2:1:3	78	**4c**	89
1a	H_2SO_4/MeOH	1.2:1:5	65	-	(85)[c]	**1c**	H_2SO_4/*i*-PrOH	1.2:1:3	85	**5c**	65
1b	H_2SO_4/H_2O	1.2:1:5	100	**2b**	95	**1c**	HCl/*i*-PrOH	1.2:1:3	85	**5c**	84
1b	HCl/H_2O	1.2:1:5-10	100	-	(77)[c]	**1d**	H_2SO_4/H_2O	1.2:1:3	100	**2d**	95
1b	H_2SO_4/MeOH	1.2:1:5	65	-	(90)[c]	**1d**	HCl/H_2O	1.2:1:5-10	100	-	(85)[c]
1c	H_2SO_4/H_2O	1.2:1:3[d]	100	**2c**	95	**1d**	H_2SO_4/MeOH	1.2:1:3	65	**3d**	84
1c	HCl/H_2O	1.2:1:3[d]	100	**2c**	92	**1d**	H_2SO_4/EtOH	1.2:1:3	78	**4d**	82
1c	H_2SO_4/ MeOH	1.2:1:3	65	**3c**	84	**1d**	H_2SO_4/*i*-PrOH	1.2:1:3	85	**5d**	70

[a]Yields of isolated products or pure mixture. [b]The reaction time was 12 hours. Molar ratio refers hydroxylamine hydrochloride: **1** : hydrochloric or sulfuric acid. [c]Yield of the corresponding 5-trichloromethylisoxazole derivative. [d]The reaction time was 8 hours.

The reactions of compounds **1c**,**d** with hydroxylamine hydrochloride in 96% sulfuric acid (3:1, acid:**1**) in methanol, ethanol or isopropanol, at the reflux temperature of the solvent, led regiospecifically to 5-carboxylisoxazole alkyl ester derivatives **3**–**5c**,**d**. The ester derivatives **3** and **5c** were also obtained in good yields using hydrochloric acid (3:1, acid:**1**) in the corresponding alcohol as solvent (Table 1).

Our investigation also included the reaction of 1,1,1-trichloro-4-methoxy-4-phenyl-3-buten-2-one (R^1=Ph, R^2=H and R=Me) with hydroxyl amine hydrochloride. The reaction carried out in 96% sulfuric acid (5–10:1, acid:butenone), at 100–120°C, furnished the 5-trichloromethyl isoxazole derivative only.

Finally, all 5-carboxyisoxazoles (**2**–**5a**–**d**) could be obtained from the reaction of 5-trichloromethylisoxazole with water, methanol, ethanol or isopropanol in 96% sulfuric acid (3:1, acid: isoxazole), at reflux of solvent.

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. Yields listed in Table 1 are of isolated compound. Selected physical and spectral data are presented in Ref. 13. Elemental analysis was carried out on a Vario EL elemental analysing system. ^{1}H and ^{13}C NMR: spectra were recorded on a Bruker AC-80 spectrometer (^{1}H at 80 MHz and ^{13}C at 20 MHz), 298 K, digital resolution of ±0.01 ppm, 0.5 M in chloroform-d_1/TMS. The ^{17}O NMR: spectra were recorded on a Bruker DPX 400 at 54.25 MHz, at 313±1 K and the general reproducibility of chemical shift data is estimated to be better than ±1.0 ppm, the half-height widths were in the range 220–600 Hz. All spectra were acquired in a 10 mm tube, at natural abundance, 2.0 M in acetonitrile-d_3 (referenced to external H_2O, in a capillary coaxial tube). For synthesis of 5-trichloromethyl isoxazole derivatives see Refs. 8 and 9.

*2.1. Synthesis of 5-carboxyisoxazoles acid **2a–d**: general procedure*

To a stirred solution of β-alkoxyvinyl trichloromethyl ketones **1** (10 mmol) in water (10 mL), at room temperature, hydroxylamine hydrochloride (0.84 g, 12 mmol) in 96% sulfuric acid (2.94–4.90 g, 30–50 mmol) was added. The mixture was stirred for 2–4 h, then heated at 90–95°C for 8 h. The product **2** was obtained in high purity by filtration from the cold reactional mixture, and washed with water. The product was recrystalized in hexane (Table 1 and Ref. 13).

*2.2. Synthesis of 5-carboxyisoxazoles acid esters **3**–**5c**,**d**: general procedure*

To a stirred solution of β-alkoxyvinyl trichloromethyl ketone **1** (10 mmol) in 10 mL of alcohol (methanol, ethanol or isopropanol, for obtention of **3**, **4**, or **5**, respectively), at room temperature, was added hydroxylamine hydrochloride (0.84 g, 12 mmol) in 96% sulfuric acid (2.94 g, 30 mmol). The mixture was stirred for 2–4 h, then heated to the reflux point of the solvent for 4–8 h. After evaporation of the excess of alcohol in the reaction mixture containing **3** and **4c**, the residue was dissolved in chloroform and washed (3×10 mL) with water and with a 5% solution of potassium carbonate (1×10 mL). After evaporation of the solvent, the product was obtained by distillation; the products **5c**,**d** were purified by column chromatography with silica gel 60, 70–230 mesh using the mixture dichloromethane:hexane (1:1) as eluent; and the products **3** and **4d** were recrystallized from hexane (Table 1 and Ref. 13).

2.3. Synthesis of 5-carboxyisoxazoles acid derivatives from 5-trichloromethylisoxazoles: general procedure

To a stirred solution of 5-trichloromethylisoxazole derivative (5 mmol) a solution (1:1, v/v) of 96% sulfuric acid (1.47 g, 15 mmol) and water, methanol, ethanol or isopropanol, at room temperature was added. The mixture was then heated to reflux for 4–8 h. The products were isolated and purified as described above.

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13. All compounds **2**–**5** were fully characterized by spectroscopic methods. Data for **2a**: $C_4H_3NO_3$, m.p. 142–143°C (lit. 7: 144°C; lit. 13, 144–149°C); ^{1}H NMR: δ 8.8 (H3, 1.9), 7.16 (H4, 1.9); ^{13}C NMR: δ 157.8 (COOH), 109.0 (C4), 151.9 (C3), 160.7 (C5); ^{17}O NMR: δ 352 (O1), 258 (C=O, OH); anal. calcd: C, 42.47; H, 2.68; N, 12.39; found: C, 42.30; H, 2.70; N, 12.50; **2b**: $C_5H_5NO_3$, mp 208–210°C; ^{1}H NMR: δ 2.3 (3H, CH_3), 6.98 (H4); ^{13}C NMR: δ 158.7 (COOH), 110.3 (C4), 161.6 (C3), 161.4 (C5); ^{17}O NMR: δ 347 (O1), 262 (C=O, OH); anal. calcd: C, 42.23; H, 3.97; N, 11.02; found: C, 42.32; H, 4.02; N, 11.00; **2c**: $C_5H_5NO_3$, mp 159–160°C; ^{1}H NMR: δ 8.33 (H3), 2.25 (3H, CH_3); ^{13}C NMR: δ 154.0 (C3), 121.9 (C4), 155.3 (C5), 158.4 (COOH); ^{17}O NMR: δ 347 (O1), 258 (C=O, OH); anal. calcd: C, 42.23; H, 3.97; N, 11.02; found: C, 42.32; H, 4.02; N, 11.09; **2d**: $C_8H_9NO_3$, mp 128–130°C; ^{1}H NMR: δ 2.75–2.82 (8H, -$(CH_2)_4$-); ^{13}C NMR: δ 160.8 (COOH), 123.2 (C4), 152.9 (C3), 162.1 (C5); ^{17}O NMR: δ 347 (O1) 259 (C=O, OH); anal. calcd: C, 57.46; H, 5.43; N, 8.39; found: C, 57.61; H, 5.44; N, 8.51; **3c**: $C_6H_7NO_3$, oil; ^{1}H NMR: δ 8.21 (H3), 2.32 (3H, CH_3); ^{13}C NMR: δ 152.9 (C3), 121.0 (C4), 154.6 (C5), 157.8 (COOR); ^{17}O NMR: δ 354 (O1, C=O)144 (OMe); anal. calcd: C, 51.05; H, 5.00; N, 9.93; found: C, 49.87; H, 4.97; N, 9.84; **3d**: $C_9H_{11}NO_3$, mp 73–75°C; ^{1}H NMR: δ 2.70–2.89 (8H, -$(CH_2)_4$-); ^{13}C NMR: δ 157.5 (C3), 121.4 (C4), 152.9 (C5), 161.4 (COOR); ^{17}O NMR: δ 342 (O1), 354 (C=O), 143 (OMe); anal. calcd: C, 59.64; H, 6.12; N, 7.73; found: C, 59.49; H, 6.04; N, 7.65; **4c**: $C_7H_9NO_3$, bp 69–71°C/20 mBar; ^{1}H NMR: δ (J, Hz) 8.21 (H3, 0.35), 2.32 (CH_3, 0.35); ^{13}C NMR: δ 152.9 (C3), 120.8 (C4), 154.7 (C5), 157.3 (COOR); ^{17}O NMR: δ 354 (O1, C=O), 174 (OEt); anal. calcd C, 54.16; H, 5.85; N, 9.03; found: C, 54.15; H, 5.87; N, 8.95; **4d**: $C_{10}H_{15}NO_3$, mp 66–67°C; ^{1}H NMR: δ 2.71–2.86 (8H, -$(CH_2)_4$-); ^{13}C NMR: δ 157.5 (C3), 121.6 (C4), 153.5 (C5), 161.7 (COOR); Anal. calcd C, 61.51; H, 6.72; N, 7.18; found: C, 61.61; H, 6.67; N, 7.06; **5c**: $C_8H_{11}NO_3$, oil; ^{1}H NMR: δ (J, Hz) 8.3 (H3, 1.1), 2.27 (CH3, 1.1); ^{13}C NMR: δ 153.0 (C3), 120.5 (C4), 155.0 (C5), 157.0 (COOR); anal. calcd: C, 56.78; H, 6.56; N, 8.28; found: C, 56.70; H, 6.60; N, 8.21; **5d**: $C_{11}H_{15}NO_3$, mp 43–45°C; ^{1}H NMR: δ 2.70–2.86 (8H, -$(CH_2)_4$-); ^{13}C NMR: δ 157.0 (C3), 121.2 (C4), 153.6 (C5), 161.6 (COOR); ^{17}O NMR: δ 343 (O1), 352 (C=O, 198 (O–*i*Pr); anal. calcd C, 63.13; H, 7.23; N, 6.70; found: C, 63.10; H, 7.30; N, 6.74.