

SYNTHESIS OF OPTICALLY ACTIVE 2-CHLOROMETHYL-2-OXAZOLINES BY THE ORTHO-ESTER CONDENSATION METHOD USING TRIETHYL ORTHOCHLOROACETATE

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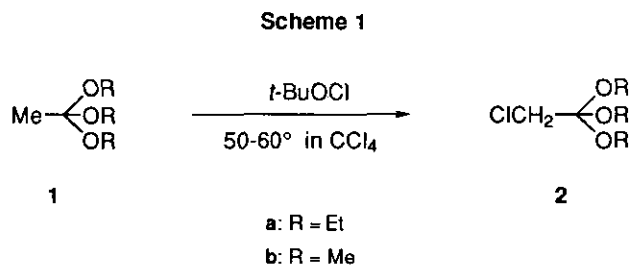
Abstract - A set of optically active 2-chloromethyl-2-oxazolines was synthesized by condensation of optically active 2-amino alcohols with triethyl orthochloroacetate which was prepared conveniently from triethyl orthoacetate by chlorination using *tert*-butyl hypochlorite.

In continuation of our research related to the rearrangement of 2-arylmethoxymethyl-2-oxazolines,¹ we required a series of chiral 2-chloromethyl-2-oxazolines which are a class of compounds that possess a variety of synthetic potential.^{1,2} A few optically active 2-chloromethyl-2-oxazolines have been synthesized exclusively by condensation of non-racemic 2-amino alcohols with ethyl chloroacetimidate hydrochloride.^{2a,b} Since an attempted reaction of the imidate hydrochloride with an achiral 2-amino alcohol failed to furnish the corresponding 2-oxazoline in acceptable yield, we initially planned to prepare some of the required optically active 2-chloromethyl-2-oxazolines (**5**) by chlorination³ of the corresponding 2-methyl-2-oxazolines. However, in one case, a 2-chloromethyl-2-oxazoline could not be isolated pure. It was therefore anticipated that the problem may be circumvented by taking advantage of the ortho-ester condensation method for the synthesis of various 2-oxazolines, which we recently reported.⁴ We describe here a one-pot procedure for the preparation of trialkyl orthochloroacetate (**2a,b**) and its use in the efficient synthesis of optically active **5**.

Preparation of Trialkyl Orthochloroacetates

Although triethyl orthochloroacetate (**2a**) is commercially available, it is rather expensive to use frequently for the preparation of various starting materials. The reagent (**2a**) has been prepared by the alcoholysis of chloroacetimidate hydrochloride,⁵ and more recently by the α -chlorination of triethyl orthoacetate (**1a**) with *N*-chlorosuccinimide.^{6,7} Taking account of the nature of the reaction involved in the latter procedure, it was envisaged that *tert*-butyl hypochlorite may work as well in the chlorination of orthoacetates. As expected,

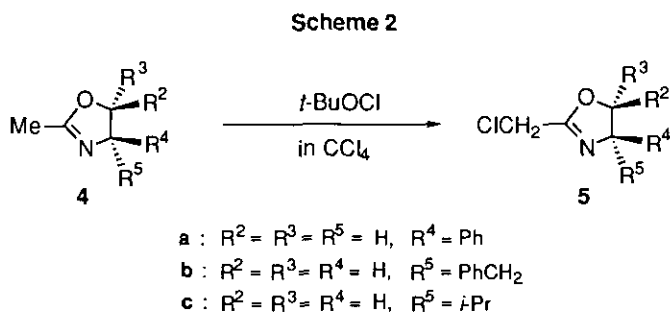
tert-butyl hypochlorite reacted with **1a** in carbon tetrachloride to afford the desired **2a** in 67% yield (Scheme 1). Trimethyl orthochloroacetate (**2b**) was prepared likewise in 57% yield.



Our procedure is characterized by its operational simplicity, the work-up being the removal of volatiles by rotatory evaporation followed by distillation to purify the products.

Synthesis of Optically Active 2-Chloromethyl-2-oxazolines

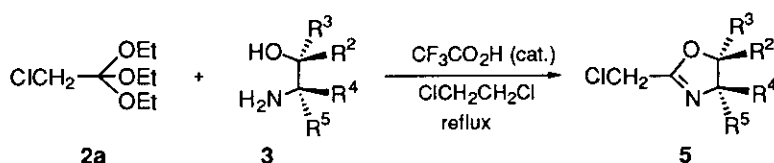
With a quantity of trialkyl orthochloroacetates in hand, we turned our efforts to the synthesis of **5**. We first prepared **5** according to the literature procedure³ that utilizes *tert*-butyl hypochlorite for the chlorination of *achiral* 2-methyl-2-oxazolines. Interestingly, this method has not been applied to the synthesis of *chiral* 2-chloromethyl-2-oxazolines. The reaction of **4a,b,c**⁸ with *tert*-butyl hypochlorite gave the expected compounds (**5**) in reasonable yields [Scheme 2 (method A), **5a**, 69%; **5b**, 63%; **5c**, 74%]. However, **5a** which bears a phenyl group at the 4 position of the oxazoline ring could not be isolated analytically pure, which resulted in a contamination of an inseparable by-product in the following reaction.



Accordingly we expected that a procedure⁴ for the preparation of 2-alkyl-2-oxazolines by condensation of ortho esters with 2-amino alcohols may furnish **5** free of contamination. The reaction of orthochloroacetates with 2-amino alcohols to afford 2-chloromethyl-2-oxazolines is unprecedented. An attempted reaction of **2a** with an amino alcohol (**3a**) without an acid catalyst failed, as anticipated, to furnish the desired product. Thus the condensation reaction of **2a,b** with chiral 2-amino alcohols (**3**) in the presence of an acid catalyst was examined. As was the case with 2-phenyl- and 2-*H*-2-oxazolines,⁴ it was found that trifluoroacetic acid was the choice of catalyst among the acids scrutinized, both acids with higher pK_a's and those with lower pK_a's than trifluoroacetic acid being less effective as catalysts. These acids include acetic

acid, monochloroacetic acid, *p*-toluenesulfonic acid and sulfuric acid. A Lewis acid such as TiCl_4 was found to be ineffective. It was also observed that **2a** gave distinctly better results while **2b** reacted reluctantly with **3** under the similar reaction conditions to give lower yields of the products. This tendency of the reactivity was the same as that observed previously with the corresponding orthoformates and orthobenzoates.⁴ The desired compounds (**5a,b,d-f**) were obtained in good to reasonable yields by the reaction of orthochloroacetate (**2a**) with amino alcohols (**3a,b,d-f**) in refluxing 1,2-dichloroethane in the presence of 17 mol% of trifluoroacetic acid as a catalyst [Scheme 3 (method B)] and the result is summarized in Table 1. If the solvent was replaced by lower boiling dichloromethane, the reaction was quite sluggish. This method is a significant improvement over that described above in that pure 2-chloromethyl-2-oxazolines can be synthesized in one step from 2-amino alcohols.

Scheme 3



- a** : $\text{R}^2 = \text{R}^3 = \text{R}^5 = \text{H}, \text{R}^4 = \text{Ph}$
b : $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}, \text{R}^5 = \text{PhCH}_2$
d : $\text{R}^2 = \text{R}^4 = \text{H}, \text{R}^3 = \text{Ph}, \text{R}^5 = \text{Me}$
e : $\text{R}^2 = \text{Ph}, \text{R}^3 = \text{R}^4 = \text{H}, \text{R}^5 = \text{MeOCH}_2$
f : $\text{R}^2, \text{R}^4 = -\text{CH}_2\text{C}_6\text{H}_4-, \text{R}^3 = \text{R}^5 = \text{H}$

In summary, trialkyl orthochloroacetates (**2a,b**) were prepared by the chlorination of the corresponding orthoacetates using readily available *tert*-butyl hypochlorite in good to acceptable yields, and **2a** was

Table 1. Preparation of 2-chloromethyl-2-oxazolines (5) by the reaction of triethyl orthochloroacetate with amino alcohols (3)^a

entry	amino alcohol	reaction time, h	product		
			compd	yield, %	config.
1	3a	2	5a	65	4 <i>R</i>
2	3b	2.5	5b	65	4 <i>S</i>
3	3d	3.5	5d	49	4 <i>S</i> ,5 <i>R</i>
4	3e	3.5	5e	73	4 <i>S</i> ,5 <i>S</i>
5	3f	3.5	5f	83	4 <i>R</i> ,5 <i>S</i>

^a In refluxing 1,2-dichloroethane in the presence of TFA as a catalyst.

successfully applied to the one-step synthesis of optically active 2-chloromethyl-2-oxazolines from 2-amino alcohols.

EXPERIMENTAL

General. Boiling points and melting points are uncorrected. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were measured on a JEOL EX-400 spectrometer in CDCl_3 with TMS as an internal standard. Wherever necessary, NMR assignments were made with the aid of COSY and DEPT experiments. 1,2-Dichloroethane was stored over 4 Å molecular sieves prior to use. All other reagents and solvents obtained from commercial sources were used without further purification. All reactions were carried out under a dry atmosphere of argon except for otherwise stated. Glassware were generally oven-dried.

General Procedure for the Preparation of Trialkyl Orthochloroacetates (2). To a solution of trialkyl orthoacetate (**1**) (0.12 mol) in 150 mL of dry CCl_4 was added *tert*-butyl hypochlorite (13.0 g, 0.12 mol), and the resulting yellow solution was gently heated with a heat gun at 50–60°C for 15 min. After cooling, volatiles were removed by rotatory evaporation, and the residual liquid was distilled under reduced pressure to give **2**. The isolated products were $\geq 95\%$ pure accompanied by approximately 3% of dichloro-analogue as assessed by ^1H NMR (400 MHz), and repeated distillation gave a fraction with $\geq 98\%$ purity.

Triethyl Orthochloroacetate (2-chloro-1,1,1-triethoxyethane, 2a): colorless liquid (67%), bp 64–66°C/6 Torr [lit.,⁵ bp 68–70°C/10 Torr; lit.,⁶ bp 70–80°C/11–19 Torr; lit.,⁷ bp 91°C/25 Torr]; ^1H NMR δ : 1.23 (t, $J = 6.8$ Hz, 9H), 3.58 (q, $J = 6.8$ Hz, 6H), 3.62 (s, 2H); ^{13}C NMR δ : 15.2, 42.1, 58.1, 112.8.

Trimethyl Orthochloroacetate (2-chloro-1,1,1-trimethoxyethane, 2b): colorless liquid (57%), bp 76–77°C/40 Torr [lit.,⁶ bp 61–64°C/19 Torr]; ^1H NMR δ : 3.33 (s, 9H), 3.63 (s, 2H); ^{13}C NMR δ : 40.6, 49.9, 113.1.

General Procedure for the Preparation of 2-Chloromethyl-2-oxazolines (5).

Method A: By Chlorination of 2-Methyl-2-oxazolines (4) Using *tert*-Butyl Hypochlorite.

To a magnetically stirred solution of **4** (27.0 mmol) in 25 mL of CCl_4 , cooled in an ice-bath, was added dropwise a solution of 2.93 g (27.0 mmol) of *tert*-butyl hypochlorite in 10 mL of CCl_4 in a period of 30 min. After 1 h, the ice-bath was removed, and the resulting yellow solution was allowed to stir at ambient temperature overnight. Any volatiles were removed by rotatory evaporation under reduced pressure to leave an oil which was distilled *in vacuo* to furnish **5a-c**.

(4R)-2-Chloromethyl-4-phenyl-2-oxazoline (5a): colorless oil (69%), bp 67–68°C/0.04 Torr.

(4S)-4-Benzyl-2-chloromethyl-2-oxazoline (5b): colorless oil (63%), bp 85–87°C/0.1 Torr.

(4S)-2-Chloromethyl-4-isopropyl-2-oxazoline (5c): colorless oil (74%), bp 71–72°C/5 Torr; $[\alpha]_D^{25} -97.9^\circ$ ($c = 2.69$, CHCl_3); IR (neat) 1666 cm^{-1} ; ^1H NMR δ : 0.90 (d, $J = 6.8$ Hz, 3H), 0.98 (d, $J =$

6.8 Hz, 3H), 1.78 (m, 1H), 3.97 (m, 1H), 4.07 (dd, $J = 8.3, 8.3$ Hz, 1H), 4.11 (dd, $J = 1.0, 12.7$ Hz, 1H), 4.12 (dd, $J = 1.0, 12.7$ Hz, 1H), 4.35 (dd, $J = 8.3, 9.7$ Hz, 1H); ^{13}C NMR δ : 18.1, 18.6, 32.4, 36.4, 71.2, 72.4, 162.4. Anal. Calcd for $\text{C}_7\text{H}_{12}\text{NOCl}$: C, 52.02; H, 7.48; N, 8.67; Cl, 21.93. Found: C, 51.97; H, 7.45; N, 8.66; Cl, 22.03.

Method B: By Condensation of Triethyl Orthochloroacetate (1a) and Optically Active 2-Amino Alcohols (3) in the Presence of Trifluoroacetic Acid as a Catalyst. To a solution of an amino alcohol (3) (20.0 mmol) and 1a (4.13 g, 21.0 mmol) in 50 mL of 1,2-dichloroethane was added $\text{CF}_3\text{CO}_2\text{H}$ (0.39 g, 17 mol%) and the resulting solution was heated at reflux for the time indicated in the Table. The cooled reaction mixture was poured into 50 mL of ice-cold 10% KHCO_3 , with vigorous stirring, and the organic layer was separated. The aqueous layer was extracted with two 10 mL portions of CH_2Cl_2 , and the combined organic layer and the extracts were dried over anhydrous K_2CO_3 . Filtration and removal of the solvents by rotary evaporation left a residue which was taken up in 300 mL of hexane and dried over anhydrous K_2CO_3 . Filtration of the drying agent followed by evaporation of the solvent under reduced pressure furnished a crude material which on either Kugelrohr distillation *in vacuo* or recrystallization from proper solvents gave pure 5a,b,d-f.

(4R)-2-Chloromethyl-4-phenyl-2-oxazoline (5a): colorless oil (65%), bp 70-73°C/0.05 Torr; $[\alpha]_{\text{D}}^{23} +125^\circ$ ($c = 9.46, \text{CHCl}_3$); IR (neat) 1664 cm^{-1} ; ^1H NMR δ : 4.22 (dd, $J = 1.0, 13.2$ Hz, 1H), 4.23 (dd, $J = 1.0, 13.2$ Hz, 1H), 4.24 (t, $J = 8.3$ Hz, 1H), 4.74 (dd, $J = 8.3, 10.3$ Hz, 1H), 5.27 (m, 1H), 7.23-7.39 (m, 5H); ^{13}C NMR δ : 36.4, 69.8, 75.6, 126.5, 127.8, 128.8, 141.3, 163.8. Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{NOCl}$: C, 61.39; H, 5.15; N, 7.16; Cl, 18.12. Found: C, 61.30; H, 5.28; N, 7.12; Cl, 18.01.

(4S)-2-Chloromethyl-4-benzyl-2-oxazoline (5b): colorless oil (65%), bp 83-85°C/0.04 Torr; $[\alpha]_{\text{D}}^{22} -55.9^\circ$ ($c = 2.72, \text{CHCl}_3$); IR (neat) 1664 cm^{-1} ; ^1H NMR δ : 2.70 (dd, $J = 8.3, 13.7$ Hz, 1H), 3.11 (dd, $J = 5.3, 13.7$ Hz, 1H), 4.08 (br t, $J = 8.3$ Hz, 1H), 4.10 (s, 2H), 4.31 (dd, $J = 8.3, 9.2$ Hz, 1H), 4.47 (m, 1H), 7.19-7.33 (m, 5H); ^{13}C NMR δ : 36.4, 41.3, 67.6, 72.8, 126.7, 128.6, 129.2, 137.4, 162.9. Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{NOCl}$: C, 63.01; H, 5.77; N, 6.68; Cl, 16.91. Found: C, 63.07; H, 5.77; N, 6.78; Cl, 17.03.

(4S,5R)-2-Chloromethyl-4-methyl-5-phenyl-2-oxazoline (5d): colorless oil (49%), bp 75-79°C/0.04 Torr; $[\alpha]_{\text{D}}^{22} -269^\circ$ ($c = 3.68, \text{CHCl}_3$); IR (neat) 1668 cm^{-1} ; ^1H NMR δ : 0.81 (d, $J = 7.3$ Hz, 3H), 4.21 (dd, $J = 1.0, 12.7$ Hz, 1H), 4.23 (dd, $J = 1.0, 12.7$ Hz, 1H), 4.52 (m, 1H), 5.70 (d, $J = 10.3$ Hz, 1H), 7.20-7.39 (m, 5H); ^{13}C NMR δ : 17.4, 36.6, 65.4, 85.0, 126.0, 128.1, 128.4, 136.3, 162.0. Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{NOCl}$: C, 63.01; H, 5.77; N, 6.68; Cl, 16.91. Found: C, 62.87; H, 5.86; N, 6.69; Cl, 16.85.

(4S,5S)-2-Chloromethyl-4-methoxymethyl-5-phenyl-2-oxazoline (5e): colorless oil (73%), bp 87-90°C/0.04 Torr; $[\alpha]_{\text{D}}^{23} -84.6^\circ$ ($c = 3.37, \text{CHCl}_3$) [lit.,^{2a} $[\alpha]_{\text{D}} -84.1^\circ$ ($c = 11, \text{CHCl}_3$)]; IR (neat)

1666 cm^{-1} ; ^1H NMR δ : 3.42 (s, 3H), 3.56 (dd, $J = 5.8, 9.7$ Hz, 1H), 3.63 (dd, $J = 4.4, 9.7$ Hz, 1H), 4.19 (m, 1H), 4.20 (d, $J = 13.2$ Hz, 1H), 4.23 (dd, $J = 1.0, 13.2$ Hz, 1H), 5.43 (d, $J = 7.3$ Hz, 1H), 7.30-7.41 (m, 5H); ^{13}C NMR δ : 36.5, 59.4, 73.7, 74.7, 84.5, 125.5, 128.4, 128.9, 140.1, 163.2. Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{NO}_2\text{Cl}$: C, 60.13; H, 5.89; N, 5.84; Cl, 14.79. Found: C, 60.01; H, 5.89; N, 5.88; Cl, 14.71.

(3a*R*,8a*S*)-2-Chloromethyl-3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole (5f): colorless needles (83%), mp 110-110.5°C (diisopropyl ether); $[\alpha]_D^{23} +295^\circ$ ($c = 0.50$, CHCl_3); IR (nujol) 1666 cm^{-1} ; ^1H NMR δ : 3.30 (dd, $J = 1.4, 18.1$ Hz, 1H), 3.46 (dd, $J = 7.3, 18.1$ Hz, 1H), 4.05 (d, $J = 13.7$ Hz, 1H), 4.09 (d, $J = 13.7$ Hz, 1H), 5.44 (m, 1H), 5.61 (d, $J = 7.8$ Hz, 1H), 7.24-7.31 (m, 3H), 7.45-7.50 (m, 1H); ^{13}C NMR δ : 36.5, 39.6, 76.8, 84.4, 125.4, 125.5, 127.6, 128.7, 139.5, 141.1, 162.9. Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{NOCl}$: C, 63.62; H, 4.85; N, 6.75; Cl, 17.07. Found: C, 63.52; H, 5.01; N, 6.79; Cl, 17.00.

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