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A CONVENIENT SYNTHESIS OF CHIRAL OXAZOLIDIN-2-ONES AND THIAZOLIDIN-2-ONES AND AN IMPROVED PREPARATION OF TRIPHOSGENE

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ABSTRACT: Oxazolidin-2-ones and thiazolidin-2-one are conveniently prepared by condensation of L-serine, L-threonine and L-cysteine, respectively with triphosgene. The corresponding methyl esters may be subsequently obtained by quenching the reaction mixture with methanol, without prior need for the isolation of the free acids. An improved procedure for preparation of triphosgene using an internal cooling system is described.

Oxazolidin-2-one and thiazolidin-2-one derivatives of serine, threonine and cysteine can be considered as O,N- and S,N-diprotected amino acids. 2-Oxathiazolin-4-carboxylic acid (OTC) has recently been reported [1] as a non toxic precursor of cysteine capable of penetrating into living cells and serving as a stimulant of the biosynthesis of glutathione [2a]. In HIV-seropositive patients it has been shown to increase the levels of gluthatione, the lack of which could be a factor involved in their immunodeficiency [2b]. Oxazolidin-2-ones **1** and **2** have been prepared in two steps by protecting serine and threonine as the respective N-CBZ- and N-Boc-derivatives followed by reaction with sodium hydroxide [3],

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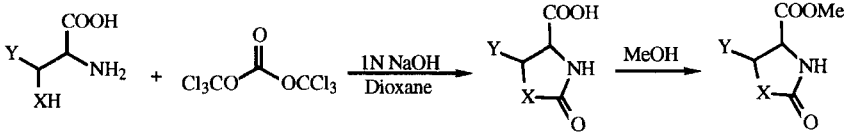
and in low yield from the amino acids and N,N-carbonyldiimidazole [4]. Thiazolidin-2-one **3** has been synthesized by the reaction of cysteine methyl ester with phosgene followed by acid hydrolysis [5].

We report a simple one step synthesis of oxazolidin-2-ones **1** and **2** and thiazolidin-2-one **3** derivatives of L-serine, L-threonine and L-cysteine by their reaction with triphosgene at room temperature. The procedure has the advantage of avoiding phosgene [5,6] as a reagent, and is preferable to that using 1,1'-carbonyldiimidazole [1,4], which in our hands gave satisfactory yields only with cysteine. The products of the reaction with triphosgene depended on the work-up conditions. Evaporation of the solvent gave solid residues from which the free carboxylic acids were obtained by extraction with an organic solvent. However, when methanol was added to the solid residues the respective methyl esters were isolated.

Scheme



Y=H,Me; X=O,S

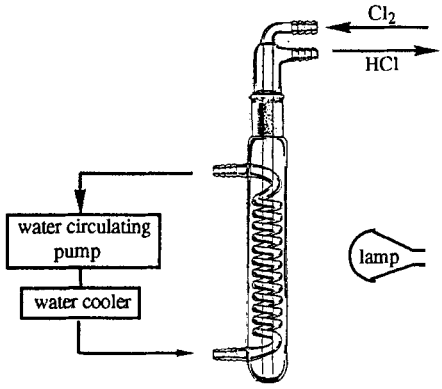
1 Y=H, X=O
2 Y=Me, X=O
3 Y=H, X=S

4 Y=H, X=O
5 Y=Me, X=O
6 Y=H, X=S

The optical rotation of methyl ester **4** ($[\alpha]_D^{20}$ -20.0°) corresponds fairly well to that reported [6a] ($[\alpha]_D^{26}$ -18.89°). The stereochemistry of the threonine derivative **5** is apparently *trans* (δ 4.75, $J_{4,5}$ = 5.5 Hz) and its NMR differs considerably from that of the *cis* isomer (δ 5.00, $J_{4,5}$ = 8.5 Hz) reported [7]. If our compound had undergone partial racemization, some of the *cis* isomer should have been formed. The fact that we did not detect in the NMR of **5** any peaks characteristic of the *cis* isomer, is indicative that the reaction proceeded with no or negligible racemization.

The efficacy of the reaction between dimethyl carbonate and chlorine gas to give triphosgene [8] was improved by the use of the apparatus depicted in the illustration. An

internally cooled system made it possible to control the temperature at 5-10°C, thus increasing the chlorine solubility and decreasing the reaction time by >30%. The cooled reaction mixture was irradiated with a single 300 W bulb in the course of 18 h.



Experimental Section

^{1}H-NMR and ^{13}C-NMR spectra 200-MHz and 300-MHz were obtained on Brucker WH-200 and WH-300 spectrometers. Chemical shifts were expressed in ppm downfield from Me_4Si used as internal standard. Mass spectra were obtained on a Varian Mat 731 spectrometer (EI = electron ionization, CI = chemical ionization).

Triphosgene. The reaction was carried out essentially as described [8] by Eckert and Forster, using the apparatus shown in the Figure. To a solution of dimethyl carbonate (45 g, 0.5 mol) in 250 ml of CCl_4 was added chlorine gas at such a rate that no Cl_2 escaped from the condenser. The reaction was cooled by circulating ice-cold water while irradiating with a 300 W bulb. The course of the reaction was monitored by NMR spectroscopy. After 18 h of Cl_2 addition, no traces of materials possessing protons could be detected. Evaporation of the solvent gave a quantitative yield of triphosgene.^{13}C-NMR ($DCCl_3$) δ 108.2, 140.9.

4-Carboxyoxazolidin-2-ones and 4-carboxythiazolidin-2-one. General procedure I. To a solution of NaOH 1N (15 ml, 15 mmol) was added L-serine,

L-threonine or L-cysteine (5 mmol) respectively, followed by the addition of triphosgene (1.5 g, 5 mmol) in dioxane (10 ml). The reaction mixtures were stirred at room temperature until clear solutions were obtained and were further stirred for 1-2 h. The solvent was evaporated and the solid residues were extracted with hot acetonitrile (10-15 ml). The mixtures were filtered, and the filtrates were evaporated to give amorphous solids which were crystallized from acetone or acetone/ether as cyclohexylamine salts.

4-Carboxyoxazolidin-2-one, 1: From L-serine 67%, ^{1}H-NMR (DMSO-D_6) δ 4.30 (dd, J = 8, 4 Hz, 1H, H-5), 4.35 (dd, J = 8, 4 Hz, 1H, H-5'), 4.48 (dd, J = 8, 8 Hz, 1H, H-4), 8.15 (brs, 1H, NH). ^{13}C-NMR (DMSO-D_6) δ 53.1, 66.2, 158.4, 172.4. MS (CI-isobutane) m/z 132 (MH^+, 100). Cyclohexylamine salt 50%, mp 148-150°C; $[\alpha]_D^{20}$ -25.6° (c = 0.025, H_2O); ^{1}H-NMR (DMSO-D_6) δ 1.0-2.0 and 2.8-3.0 (broad peaks assigned to cyclohexyl), 3.85 (dd, J = 10, 5 Hz, 1H, H-5), 4.18 (dd, J = 8, 5 Hz, 1H, H-5'), 4.36 (dd, J = 10, 8 Hz, 1H, H-4), 7.60 (brs, 1H, NH).

4-Carboxy-5-methyl-oxazolidin-2-one, 2: From L-threonine 72%, ^{1}H-NMR (DMSO-D_6) δ 1.38 (d, J = 6 Hz, 3H, Me), 3.97 (d, J = 6 Hz, 1H, H-4), 4.57 (*a*pentet J = 6 Hz, 1H, H-5), 8.10 (brs, 1H, NH). ^{13}C-NMR (DMSO-D_6) δ 20.7, 59.5, 74.5, 157.6, 171.8; MS (CI-NH_3) m/z 163 (MNH_4^+, 100), 146 (MH^+, 10). Cyclohexylamine salt 65%, mp 163-165°C; $[\alpha]_D^{20}$ +19.5.6° (c = 0.026, H_2O); ^{1}H-NMR (DMSO-D_6) δ 1.0-1.3, 1.6-2.0 and 2.8-3.0 (broad peaks assigned to cyclohexyl), 1.33 (d, J = 6 Hz, 3H, Me), 3.45 (d, J = 6 Hz, 1H, H-5), 4.41 (*a*pentet, J = 6 Hz, 1H, H-4), 7.50 (brs, 1H, NH).

4-Carboxythiazolidin-2-one, 3: From L-cysteine 77%, ^{1}H-NMR (DMSO-D_6) δ 3.45 (dd, J = 11, 5 Hz, 1H, H-5), 3.72 (dd, J = 11, 8 Hz, 1H, H-5'), 4.40 (ddd, J = 8, 5, 1 Hz, 1H, H-4), 8.40 (brs, 1H, NH). ^{13}C-NMR (DMSO-D_6) δ 32.2, 56.8, 172.3, 172.8. MS (CI-CH_4) m/z 148 (MH^+, 100), 120 (MH^+-CO, 25), 102 (MH^+-H_2CO_2, 18). Cyclohexylamine salt 69%, mp >185°C (dec) (lit. [5a] 199°C (dec)), $[\alpha]_D^{20}$ -56.0° (c = 0.025, H_2O); ^{1}H-NMR (DMSO-D_6) δ 1.0-2.0 and 2.8-3.0 (broad peaks assigned to cyclohexyl), 3.28-3.60 (m, 2H, H-5+H-5'), 3.92 (dd, J = 8, 5 Hz, 1H, H-4), 8.00 (brs, 1H, NH).

4-Carbomethoxyoxazolidin-2-ones and 4-carbomethoxythiazolidin-2-one. General procedure II. The crude solid residues obtained after evaporation of the solvent as described in Procedure I were mixed with MeOH (30 ml) and the solutions were stirred overnight. The solvent was decanted and evaporated to give viscous oils which were washed with acetonitrile (10-15 ml) and filtered. The filtrates were evaporated to give the products as clear oils which were distilled.

4-Carbomethoxyoxazolidin-2-one, 4: 47%, bp 126-128°C/0.05 Torr; $[\alpha]_D^{20}$ -20.0° (c = 0.11, CH_2Cl_2) (lit.[6a] $[\alpha]_D^{26}$ -18.89° (CH_2Cl_2)); ^{1}H-NMR and ^{13}C-NMR as in reference [5a]; MS (EI) m/z 146 (MH^+, 100), 100 (MH^+-H_2CO_2, 6), 86 (MH^+-HCO_2Me, 80).

4-Carbomethoxy-5-methyl-oxazolidin-2-one, 5: 56%, bp 150-152°C/0.1 Torr; $[\alpha]_D^{20}$ +30.5° (c = 0.12, CH_2Cl_2) ; ^{1}H-NMR ($CDCl_3$) δ 1.56 (d, J = 6 Hz, 3H, Me), 3.82 (s, OMe), 4.03 (dd, J = 5.5, 1 Hz, 1H, H-5), 4.75 (qd, J = 6, 5.5 Hz, 1H, H-4), 6.6 (brs, 1H, NH); ^{13}C-NMR ($CDCl_3$) 21.0, 53.0, 60.4, 75.7, 158.5, 170.3; MS (EI) m/z 160 (MH^+, 100)

4-Carbomethoxythiazolidin-2-one, 6: 66%, bp 148-150°C/0.3 Torr; $[\alpha]_D^{20}$ -62.5° (c = 0.05, $HCCl_3$); ^{1}H-NMR ($CDCl_3$) δ 3.62 (dd, J = 11, 5 Hz, 1H, H-5), 3.72 (dd, J = 11, 8 Hz, 1H, H-5'), 3.82 (s, Me), 4.47 (ddd, J = 8, 5, 1 Hz, 1H, H-4), 6.7 (brs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ 31.7, 53.1, 55.9, 170.4, 174.6; MS (EI) m/z 161 (MH^+, 100).

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