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Bis(O-nitrophenyl) Carbonate as a New Reagent for the Synthesis of Chiral Oxazolidin-2-ones

Monika Simon [a], Andreea Micle [a], Valentin Badea [a] & Carol Csunderlik [a]

[a] Department of Applied Chemistry and Organic and Natural Compound Engineering, Politehnica University of Timisoara, Industrial Chemistry and Environmental Engineering Faculty, Timisoara, Romania

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Bis(*O*-nitrophenyl) Carbonate as a New Reagent for the Synthesis of Chiral Oxazolidin-2-ones

Monika Simon, Andreea Micle, Valentin Badea, and Carol Csunderlik
Department of Applied Chemistry and Organic and Natural Compound Engineering, Politehnica University of Timisoara, Industrial Chemistry and Environmental Engineering Faculty, Timisoara, Romania

Abstract: *Bis*(o-nitrophenyl) carbonate reacts under mild conditions with chirals 1,2-amino alcohols and, after addition of DMAP, affords the corresponding oxazolidin-2-ones in very good yields.

Keywords: *Bis*(o-nitrophenyl) carbonate, (4R,5S)-4,5-diphenyl-2-oxazolidinone, (4S)-4-isopropyl-2-oxazolidinone, (S)-4-(phenylmethyl)-2-oxazolidinone

INTRODUCTION

Chiral 2-oxazolidinones have been widely utilized as chiral auxiliaries in asymmetric reactions, such as aldol condensation, alkylation, and Diels–Alder reactions, and as intermediates for asymmetric synthesis of biologically active compounds.[1,2] Moreover, many naturally occurring and synthetic molecules with, among others, antibacterial, antiallergenic, or immunosuppressant activities contain 2-oxazolidinone as a core structural unit. (4R,5R)-(−)Cytoxazone[3,4] (**1**) (Scheme 1) is an example of a natural compound isolated from *Streptomyces* spp. It has cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells.

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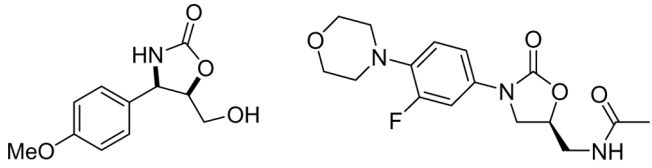
Address correspondence to Monika Simon, Department of Applied Chemistry and Organic and Natural Compound Engineering, Politehnica University of Timisoara, Industrial Chemistry and Environmental Engineering Faculty, P-ta Victoriei 2, 300006 Timisoara, Romania. E-mail: monika.simon@chim.upt.ro or akinomis@yahoo.com



1 2

Scheme 1.

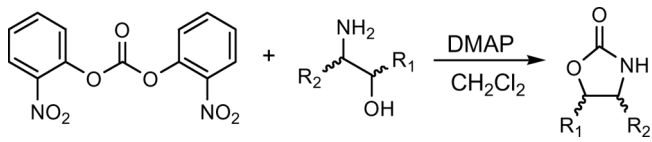
The first commercially available oxazolidinone antibiotic was linezolid[5,6] (**2**) (Scheme 2) (or Zyvox). It is usually reserved for the treatment of serious bacterial infections where older antibiotics have failed as a result of antibiotic resistance. Conditions such as skin infections or nosocomial pneumonia where methicillin or penicillin resistance is found are indicators for linezolid use.[5,6]

Many methods have been developed for the preparation of oxazolidinones using a variety of natural or synthetic precursors, including the reaction of diols with isocyanates, epoxide openings, amino acids, aziridines, oxetanes, 2-oxazolones, hydroxyl acids, and esters, but the reaction of 1,2-amino alcohols with various carbonylation reagents has proved the most direct route.[7,8]

Until now, carbonyl insertion into 1,2-amino alcohol substrates has been achieved by either using toxic and hazardous reagents such as phosgene, diphosgene, or carbon monoxide or by employing nontoxic reagents of low reactivity (diethyl carbonate, ethyl chloroformate, urea, or carbon dioxide), which require severe conditions such as the presence of a strong base or very high temperature and pressure.[7,8]

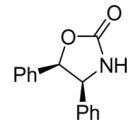
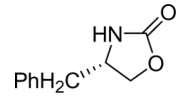
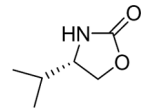
Bis(*o*-nitrophenyl) carbonate[9] is a new alternative to phosgene for obtaining carbonates,[10] carbamates,[11] and ureas.[12] It has the advantages of being less toxic than phosgene, diphosgene, or carbon monoxide but more reactive than diethyl carbonate, bis(p-nitrophenyl) carbonate, or urea while also being very soluble in a wide range of solvents.

We now report a new method for the synthesis of chiral oxazolidin-2-ones by the reaction of chiral 1,2-amino alcohols with *bis*(o-nitrophenyl) carbonate.



Scheme 2.

Table 1. Preparation of oxazolidin-2-one

Entry	Time (h)	Oxazolidin-2-one	η (%)
1	3		95
2	3		90
3	1		96

We recently demonstrated[13] that when *bis*(o-nitrophenyl) carbonate is treated with β-aminoethanol, it reacts readily at room temperature, in the first step giving o-nitrophenyl-N-2-hidroxyethylcarbamate, which cyclizes in the second step in the presence of a base to the corresponding oxazolidin-2-one. The addition of a tertiary amine to the reaction mixture is important because it increases the nucleofilicity of hydroxyl group, favoring cyclization and avoiding the side reaction, which leads to 1,3-*bis* (2-hidroxyethyl)urea formation.

Three chiral oxazolidin-2-ones (Table 1) [(4R,5S)-4,5-diphenyl-2-oxazolidinone,[14] (S)-4-(phenylmethyl)-2-oxazolidinone,[2,14b,e,15] (S)-4-isopropyl-2-oxazolidinone[1,2,15c,d,16] have been obtained by a new method that employs *bis*(o-nitrophenyl) carbonate as the carbonylation reagent for corresponding chiral 1,2-amino alcohols. The reactions were carried out in CH_2Cl_2 in the presence of 4-(dimetilamino)-pyridine (DMAP) at the molar ratio carbonate–amino alcohol–DMAP of 1.1:1:0.1. After 3 h under stirring at room temperature, the reactions were finished. The solvent was removed from reaction mixture, and the desired oxazolidin-2-one was separated from residue by column chromatography with very good yield.

EXPERIMENTAL

Melting points were determined on Boetius apparatus (Carl Zeiss Jena). The infrared (IR) spectra were recorded in KBr pellet for the solid compounds with a Jasco Fourier transform (FT)/IR-430 instrument. Thin-layer chromatography (TLC) analyses were carried out on precoated plates of silica gel 60 F_{254} (Merck). To visualize spots, the

plates were exposed under a ultraviolet (UV) 254 lamp. The ^{1}HNMR and ^{13}C-NMR spectra were recorded on a Bruker DPX at 200 MHz. Optical rotations were measured at 20°C with a Polamat A (Carl Zeiss Jena) polarimeter.

Preparation of Oxazolidin-2-ones

The following procedure for preparation of (4R,5S)-4,5-diphenyl-2-oxazolidinone is representative of the general method used for synthesis of the other two oxazolidin-2-ones.

(4R,5S)-4,5-Diphenyl-2-oxazolidinone

A solution of (1S, 2R)(+) 2-amino-1,2-diphenylethanol (69.4 mg, 0.32 mmol) and DMAP (0.032 mmol, 3.9 mg) in CH_2Cl_2 (5 mL) was added to a solution of *bis*(*o*-nitrophenyl) carbonate (101.9 mg, 0.358 mmol) in CH_2Cl_2 (5 mL). When no acyclic carbamate remained [<3 h TLC analysis, silica; eluent: CH_2Cl_2–EtOAc (1:1)], the solvent was removed by evaporation in vacuo to 1–2 mL volume. The solution was separated by column chromatography on silica gel, first using dichloromethane until the by-product *o*-nitrophenol was separated and then CH_2Cl_2–EtOAc (1:1). The title compound was isolated as a white solid to yield 308 mg (95%). It was recrystallized from toluene. Mp 231–232.5°C; lit.[14a] mp 232.5–233.5°C. $[\alpha]_D + 59.8°$ ($c = 0.86$, MeOH); lit.[14a] $[\alpha]_D{}^{20} + 60.6°$ ($c = 0.86$, MeOH). ν_{max} (KBr)/cm^{-1} = 1748, 1711(C=O); lit.[14a] ν_{max} ($CHCl_3$)/cm^{-1} = 1765. δ_H (200 MHz; $CDCl_3$) 7.1–6.92 (m, 10H, ArH), 5.96 (d, 1H, $J = 8.1$ Hz, OCHPh), 5.78 (s, 1H, NH), 5.2 (d, 1H, $J = 8.1$ Hz, Hz, NCHPh); lit.[14a] 7.6–6.8 (m, 10H), 5.96 (d, 1H, $J = 8.0$ Hz). 5.85 (br, 1H), 5.2 (d, 1H, $J = 8.0$ Hz); δ_C (200 MHz; $CDCl_3$) 159.5 (C=O), 136.0 (Ccuart), 134.3 (Ccuart), 128.1, 127.9, 126.9, 126.1, 82.4(C-O), 61.5 (C-N). M/z (relative intensity): 46.6 (12), 78 (56.5), 79 (24), 80 (45.5), 89.8 (13),104 (74), 105 (42), 107 (100), 239 (4.13, M^+).

(S)-4-(Phenylmethyl)-2-oxazolidinone

It was obtained in 90% yield as a white solid. It was recrystallized from EtOAc/hexane. Mp 86–87°C; lit.[15e] 84.5–86.5°C; $[\alpha]_D + 4.5°$ ($c = 1.10$, EtOH); lit.[15e] $[\alpha]_D + 4.9°$ ($c = 1.10$, EtOH). ν_{max} (KBr)/cm^{-1} = 1753; 1708 (C=O); lit.[15e] ν_{max} (solution in dichloromethane)/cm^{-1} = 1760δ_H; (200 MHz; $CDCl_3$) 7.3–7.1 (m, 5H, ArH), 6.4 (s, 1H, NH), 4.38 (m, 1H), 4.12 (m, 2H, CH_2-O), 2.8 (m, 2H, CH_2-Ar); lit.[15e] 7.5–7.1 (m, 5H,

ArH), 5.6 (s, 1H, NH), 4.0–4.6 (m, 3H, $CHCH_2O$), 2.9 (d, 2H, CH_2-Ar); lit.[15b] 7.2–7.1 (m, 3H), 7.1 (d, 2H), 5.1–5.28 (m, 1H), 4.31 (t, 1H), 3.9–410 (m, 2H), 2.71 (d, 2H); δ_C (200 MHz; $CDCl_3$) 159.7 (C=O), 135.8 (Ccuart), 129,0, 128.8, 127.0, 69.4 (C-O), 53.7 (C-N), 41.2 (CH_2-Ar).

(S)-4-Isopropyl-2-oxazolidinone

It was obtained in 96% yield as a white solid. It was recrystallized from EtOAc/hexane. Mp 69–70°C; lit.[16d] 69–70°C; lit.[16b] 70.5–72.2°C, $[\alpha]_D - 14.5^{\circ}$ ($c = 1.06$, EtOH); lit.[16d] $[\alpha]_D^{18} - 16.6^{\circ}$ ($c = 5.81$, EtOH); lit.[16b] $[\alpha]_D^{18} - 18.5^{\circ}$ ($c = 6$, EtOH), ν_{max} (KBr)/cm^{-1} = 1751; 1725 (C=O); lit.[16b] ν_{max} (film)/cm^{-1} = 1740, δ_H (200 MHz; $CDCl_3$) 7.2 (s, 1H, NH), 4.4 (t, 1H, CH-O), 4.1 (t, 1H, CH-O), 3.6 (c, 1H, CH-N), 1.7 (m, 1H, $J = 7.0$ Hz, Hz, CH-CH_3), 0.94 (d, 3H, $J = 7.0$ Hz, CH_3), 0.91 (d, 3H, $J = 7.0$ Hz, CH_3); lit.[16b] 4.4 (t, 1H, $J = 8.0$ Hz), 4.1 (dd, 1H, $J = 6.0$, 8.0 Hz), 3.6 (m, 1H, CH-N), 1.72 (m, 1H, $J = 7.0$ Hz), 1.0 (d, 3H, $J = 7.0$ Hz), 0.9 (d, 3H, $J = 7.0$ Hz), δ_C (200 MHz; $CDCl_3$) 160.8 (C=O), 68.7 (C-O), 58.5 (C-N), 32.7 (CH-CH_3), 18 (CH_3), 17.7 (CH_3); lit.[16b] 160.63, 68.46, 58.28, 32.52, 17.82, 17.45.

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