New synthesis of Mephenoxalone

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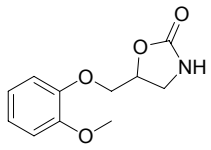
Abstract
Mephenoxalone (**1**) was synthesized through a silanizated intermediate prepared from the addition of trimethylsilyl cyanide (TMSCN) to (*o*-methoxy)phenoxyacetaldehyde (**10**). Three different methods were established to synthesize this aldehyde. Alkylation of guaiacol with bromoacetaldehyde diethyl acetal, followed by acid hydrolysis of acetal group gave the highest overall yield (49%) for the aldehyde **10.** Different reagents as ZnI_2, Montmorillonite K10, (+)-$Eu(tfc)_3$ and (+)-$Yb(tfc)_3$ were used in the addition of TMSCN to the aldehyde giving very good yields with all catalysts.

Keywords: Mephenoxalone, oxazolidinone, BTC

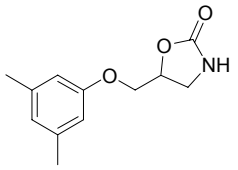
Introduction

Oxazolidinone compounds are important because their broad spectra of pharmacological properties. Especially, 5-aryloxymethyl-2-oxazolidines are a group of compounds which shown activity as interneuron blocking agents or depressants of central synaptic transmission. They are generally antagonists of strychnine convulsions and have been used as skeletal muscle relaxants, anticonvulsants, and tranquilizers. Mephenoxalone (Tripedone®) (**1**) is a skeletal muscle relaxant as well as anxiolytic, and Metaxalone (**2**) is a skeletal muscle relaxant, it acts in the central nervous system to produce the muscle relaxant effects and it is currently commercially available in the U. S. under the trend name of Skelatin®.[1] These products are indicated as an adjunct to rest, physical therapy, and other measures for relief of discomforts associated with acute, painful musculoskeletal conditions.[2-6] In the other hand, another group of oxazolidinones typified by Eperozolid (**3**) and Lynezolid (**4**) (marketed as Zyvox™), represent a new class of synthetic antibacterial agents with potent activity against clinically important susceptible and resistant Gram-positive pathogens. This class of compounds has a novel mechanism of action that shows selective and unique binding to 50S ribosomal subunit, inhibiting bacterial translation

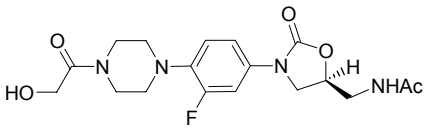
at initiation phase of protein synthesis.[7] It is suggested that oxazolidinones act by disrupting the processing of *N*-formylmethionyl t-RNA by the ribosome.[8]



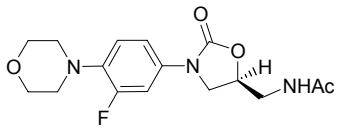
Mephenoxalone-**1**



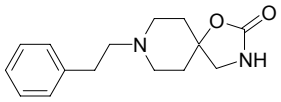
Metaxalone-**2**



Eperozolid-**3**



Linezolid-**4**



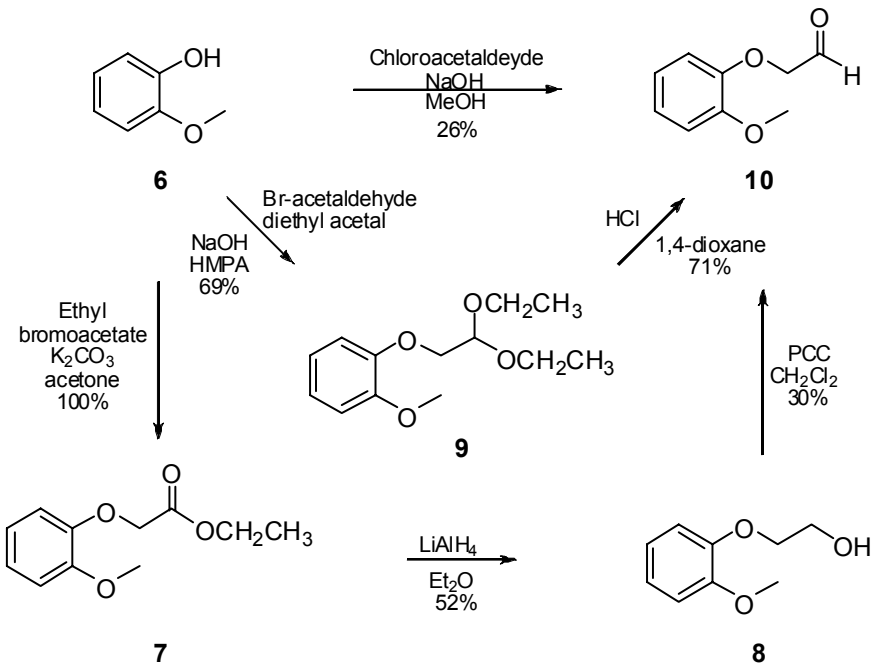
Fenspiride-**5**

The synthesis of Mephenoxalone was reported by Lunsford in 1960.[9] This method consisted in the fusion of one equivalent of urea with one equivalent of 3-*o*-methoxyphenoxy-1,2-propanediol at 180-200^{o}C to produce the crude oxazolidinone which was further purified by fractional distillation and crystallization to gave a 67% isolated product yield. There are only a few reports in literature about the synthesis of Mephenoxalone.[10-13] Previously, we reported the synthesis of a bronchodilator blocker Fenspiride (**5**)[14] and continuing our interest in cyclization reactions using bistrichloromethyl carbonate (BTC or triphosgene) and the addition of trimethylsilyl cyanide to aldehydes,[15] we proposed a new methodology for the synthesis of Mephenoxalone through silanized intermediate.

Results and Discussion

Our goals in this work were to synthesize Mephenoxalone by the addition of trimethylsilyl cyanide to (*o*-methoxy)phenoxyacetaldehyde (**10**) and compare the efficiency of different catalysts in the addition step. The aldehyde used as starting material is not commercially available and was necessary to be prepared. Three different methods were proposed for the synthesis of aldehyde **10** (Scheme 1). 1) Direct alkylation of guaiacol with chloroacetaldehyde under basic conditions with 26% yield. 2) Alkylation of guaiacol with ethyl bromoacetate using K_2CO_3 in acetone followed by reduction of the corresponding ethyl (*o*-methoxy)phenoxyacetate (**7**) to obtain (*o*-methoxy)phenoxyethanol (**8**). This alcohol was oxidized with PCC leading to the

aldehyde **10**. The overall yield with this method was 16%. 3) Alkylation of guaiacol with bromoacetaldehyde diethyl acetal, 25% NaOH aqueous solution and HMPA as solvent gave the (*o*-methoxy)phenoxyacetaldehyde diethyl acetal (**9**) which was hydrolyzed with HCl in 1,4-dioxane to gave the aldehyde **10**.[16] The overall yield with this method was 49%. Comparing these results, we concluded that the best synthetic route was method 3 because required only two reaction steps and gave the highest overall yield.



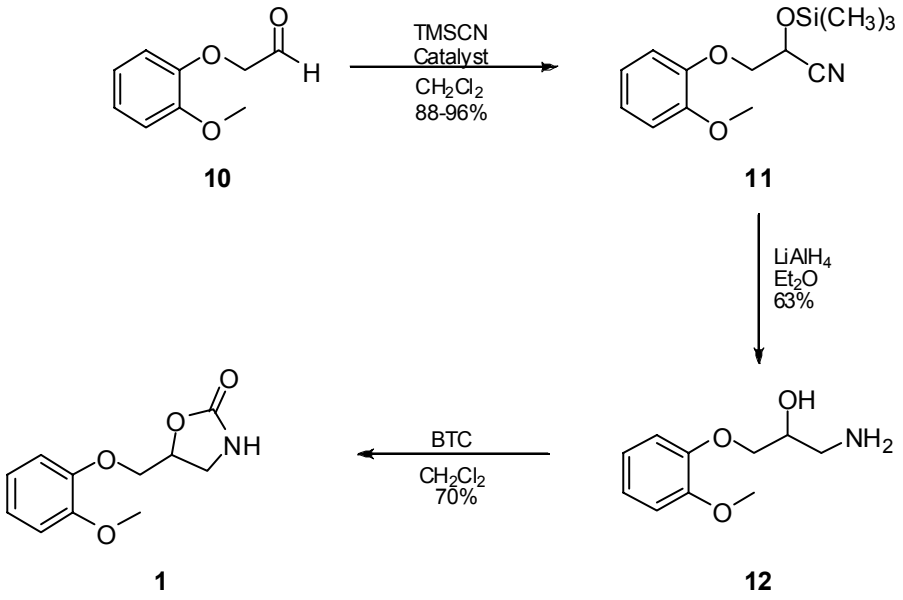
Scheme 1. Synthesis of (*o*-methoxy)phenoxyacetaldehyde (**10**).

The addition of TMSCN to the aldehyde **10** was carried out with ZnI_2, Montmorillonite K10, (+)-Eu(tfc)$_3$ and (+)-Yb(tfc)$_3$ in order to obtain the silanized intermediate **11** with good yield in each case (88-96%) (Scheme 2 and Table 1). Lanthanide reagents are frequently used in organic synthesis as catalysts in different reactions,[17-22] but lanthanide camphorates are typically used as chiral shift reagents for direct determination enantiomeric compositions by nuclear magnetic resonance.[23-25] Here, europium and ytterbium camphorates were used to establish their catalytic capacity and asymmetric induction in the addition of TMSCN to the carbonyl group. They generated excellent activation in both cases, 96% and 88% yield respectively, but asymmetric induction was not observed.

Table 1. Addition of TMSCN to aldehyde **10**

Entry	Catalyst	molar %	Yield (%)[a]
1			8.0
2	ZnI_2	2.5	93.0
3	(+)-Yb(tfc)$_3$	1.0	88.0
4	(+)-Eu(tfc)$_3$	1.0	96.0
5	Mont-K10[b]		95.4

[a]In dichloromethane at room temperature for 8 h. [b]50 mg of catalyst/1.0 g of aldehyde.



Scheme 2. Synthesis of Mephenoxalone **1**.

The silyl ether **11** was reduced using $LiAlH_4$ giving the β-aminoalcohol **12** with 63 % yield.[26] The final step consisted in the cyclization of **12** with BTC to give the oxazolidinone **1** in 70% yield (Scheme 2). The overall yield from aldehyde **10** to Mephenoxalone (**1**) was 42%. ^{1}H and ^{13}C NMR of this product were obtained and signals are in accordance with the date reported in literature.[27]

Conclusions

In summary, the process of addition of trimethylsilyl cyanide to aldehyde **10** allowed us to develop a new methodology to synthesize Mephenoxalone. This reaction occurs with very good yields using different catalysts and subsequent reduction and cyclization with BTC led to form

the oxazolidinone ring. This methodology could be further used for the synthesis of analogous compounds with biological activity.

Experimental Section

General Procedures. Melting points were obtained on an Electrothermal 88629 apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin Elmer FT-IR 1600 spectrophotometer. Nuclear magnetic resonance ^{1}H and ^{13}C spectra at 50.289 Hz were recorded on a Varian Mercury 200 MHz Spectrometer in $CDCl_3$ and DMSO-d_6 with TMS as internal standard. Mass spectra were obtained on a Hewlett-Packard 5989 by EI at 70 eV by direct insertion. Elemental analysis for carbon and hydrogen were performed by Galbraith Laboratories, Incorporated (Knoxville, TN).

General methods for the synthesis of (o-Methoxy)phenoxyacetaldehyde (10)

Method 1

(o-Methoxy)phenoxyacetaldehyde (10). Guaiacol (1.00 g, 8.05 mmol) was dissolved in 40 mL of acetone, K_2CO_3 (1.11 g, 8.05 mmol) was added and the mixture was stirred at room temperature for 15 minutes. A solution of chloroacetaldehyde (1.26 g, 8.05 mmol) in water (5 mL) was added drop wise at 0^{o}C and the mixture was refluxed for 8 hours. The crude mixture was filtered and dried over Na_2SO_4, filtered and the solvent was evaporated to give a yellow solid (0.35 g, 2.11 mmol, 26% yield). M. p. 73-75^{o}C**.** FTIR(KBr): 3061, 2939, 2833, 1737, 1592, 1250 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.89 (t, *J*=1.3 Hz, 1H), 6.90 (m, 4H), 4.60 (d, *J*=1.3 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 200.1, 123, 122.3, 122, 121, 115.2, 114.7, 112.4, 77.9, 77.3, 55.9. EIMS *m/z* (rel. int): 166(100), 137(30), 122(98), 77(95).

Method 2

Ethyl (o-methoxy)phenoxyacetate (7). Guaiacol (1.00 g, 8.05 mmol) was dissolved in 40 mL of acetone, K_2CO_3 (1.11 g, 8.05 mmol) was added and the mixture was stirred for 15 minutes, ethyl bromoacetate (1.34 g, 8.05mmol) was added drop wise at 0^{o}C and then the mixture was refluxed for 8 hours. The mixture was filtered and concentrated; the product was poured into 5% NaOH aqueous solution (50 mL) and extracted with ethyl ether (3 x 25 mL). The organic phase was dried over Na_2SO_4, filtered and solvent was evaporated to give an amber liquid (1.7 g, 8.09 mmol, 100% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.91 (m, 4H), 4.67 (s, 2H), 4.25 (c, *J*=7.2 Hz, 2H), 3.87 (s, 3H), 1.28 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.0, 149.7, 147.3, 122.6, 120.8, 114.6, 112.4, 66.7, 61.4, 56.0, 14.4. EIMS *m/z* (rel. int): 210(100), 137(50), 122(65), 77(55).

(o-Methoxy)phenoxyethanol (8). Ethyl (*o*-methoxy)phenoxyacetate (1.00 g, 4.76 mmol) was dissolved in 40 mL of anhydrous ethyl ether, $LiAlH_4$ was added (0.20 g, 4.76 mmol) at 0^{o}C under argon atmosphere and the mixture was stirred for 12 hours at room temperature. The excess of hydride was neutralized adding a 5% NaOH aqueous solution drop wise. The mixture was

filtered and the organic phase was dried over Na_2SO_4, filtered again and the solvent was evaporated to give an amber liquid (0.42 g, 2.45 mmol, 52% yield). FTIR(KBr): 3481, 3064, 2936, 1592, 1504, 1455, 1254, 1226, 1180, 1124, 1027 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.90 (m, 4H), 4.09 (d, *J*=6.0 Hz, 1H), 4.07 (d, *J*=5.5 Hz, 1H), 3.93 (d, *J*=5.5 Hz, 1H), 3.91 (d, *J*=6.0 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.3, 147.9, 121.5, 120.9, 114.1, 111.6, 70.9, 60.9, 55.7. EIMS *m/z* (rel. int.): 168(55), 124(100), 109(95), 81(30).

***(*o-Methoxy)phenoxyacetaldehyde (10).** (*o*-Methoxy)phenoxyethanol (1.00 g, 5.95 mmol) was dissolved in 40 mL of dichloromethane, pyridinium chlorochromate (7.70 g, 35.7 mmol) was added and the mixture was stirred for 24 hours at room temperature. The mixture was dissolved in ethyl ether and filtered over a silica gel pad and the solvent was evaporated to give a yellow solid (0.30 g, 1.79 mmol, 30% yield).

Method 3

(o-Methoxy)phenoxyacetaldehyde diethyl acetal (**9**). Guaiacol (2.00 g, 16.1 mmol) was dissolved in 60 mL of HMPA, a NaOH aqueous solution (1.28 g, 32.2 mmol, 10 mL) was added drop wise and stirred at 0°C for 15 minutes, bromoacetaldehyde diethyl acetal (3.00 g, 16.1 mmol) was added drop wise at 0°C and the mixture was refluxed for 6 hours. The mixture was poured into 60 mL of a 5% HCl aqueous solution and and extracted with CH_2Cl_2 (3 x 30 mL). The organic phase was separated and washed with water (2x 50 mL), dried over Na_2SO_4 and filtered. The solvent was evaporated to give an amber liquid (2.66 g, 11.08 mmol, 69.0% yield). FTIR(KBr): 2976, 2932, 1509, 1458, 1374, 1233, 1134 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.90 (m, 4H), 4.90 (t, J=5.3 Hz, 1H), 4.06 (d, J=5.3 Hz, 2H), 3.85 (s, 3H), 3.59-3.81(m, 4H), 1.24 (t, J=7.0 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 121.8, 121.1, 114.7, 112.4, 100.9, 70.3, 62.9, 56.2, 15.6. EIMS m/z (rel. int.): 240(10), 149(15), 103(100), 75(65).

(o-Methoxy)phenoxyacetaldehyde (**10**). (*o*-Methoxy)phenoxyacetaldehyde diethyl acetal (2.66 g, 11.08 mmol) was dissolved in 100 mL of 1,4-dioxane and 74 mL of water, 27 mL of concentrate HCl were added at 0°C and the mixture was stirred at room temperature for 10 hours. The mixture was neutralized adding a saturated $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (3 x 50 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated to give a yellow solid (1.30 g, 7.82 mmol, 71 % yield).

General method for the synthesis of Mephenoxalone (1)

1-(o-Methoxy)phenoxy-2-cyano-2-trimethylsilyloxy-ethane (11). (*o*-Methoxy) phenoxy-acetaldehyde (1.00 g, 6.02 mmol) was dissolved in 20 mL of anhydrous chloromethane with 50 mg of catalyst at 0°C. Trimethylsilyl cyanide (1.20 mL, 9.03 mmol) was added drop wise under argon atmosphere and stirred for 8 hours. The mixture was filtered over a celite pad and the solvent was evaporated to give an amber liquid. FTIR(KBr): 3066, 2947, 1589, 1501, 1453, 1252, 1121 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.94 (m, 4H), 4.82 (m, 1H), 4.22 (m, 2H), 3.87 (s, 3H), 0.25 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 123.1, 121.0, 116.2, 112.7, 77.2, 76.6, 71.6, 61.3, 56.0. EIMS *m/z* (rel. int.): 265(30), 166(22), 137(100), 122(55).

1-(o-Methoxy)phenoxy-2-aminomethyl-ethanol (12). 1-(*o*-Methoxy)phenoxy-2-cyano-2-trimethylsilyloxy-ethane (0.94 g, 3.53 mmol) was dissolved in 20 mL of anhydrous ethyl ether at 0°C. An excess of $LiAlH_4$ was added under argon atmosphere. The mixture was stirred at room temperature for 8 hours; the excess of $LiAlH_4$ was neutralized adding a 20% NaOH aqueous solution drop wise and then was filtered. The organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated to give a yellow solid (0.44 g, 2.23 mmol, 63% yield). M. p. 95-96°C. FTIR(KBr): 3374, 3053, 2932, 1593, 1505, 1455, 1254cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.90 (m, 4H), 4.00-3.64 (m, 3H), 3.75 (s, 3H), 2.70 (dd, *J*=12.8, 4.8 Hz, 1H), 2.56 (dd, *J*=12.8, 6.2 Hz, 1H) ^{13}C NMR (50 MHz, DMSO-d_6): δ 149.0, 148.3, 120.9, 120.7, 113.4, 112.2, 71.0, 70.5, 55.5, 45.1. EIMS *m/z* (rel. int.): 197(4), 124(100), 109(20).

5-[(o-Methoxy)phenoxymethyl]-2-oxazolidinone (1). 1-(*o*-Methoxy)phenoxy-2-amino methyl-ethanol (1.00 g, 5.07 mmol) was dissolved in 25 mL of dichloromethane, triethylamine (1 mL) was added and a BTC solution (0.15 g, 5.07 mmol) in dichloromethane (20 mL) was added drop wise at 0°C and stirred at room temperature for 8 hours. The final product was poured into a 3% HCl aqueous solution (50 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated to give a white solid (0.79 g, 3.5 mmol, 70% yield). M. p. 142-144 °C. FTIR(KBr): 3418, 2932, 1742, 1505, 1253 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.95 (m, 4H), 5.63 (s, 1H), 4.91-5.06 (m, 1H), 4.10-4.27 (m, 2H), 3.84 (s, 3H), 3.63-3.80 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 123.1, 127.2, 116.1, 112.8, 74.6, 77.2, 56.2, 43.0. EIMS *m/z* (rel. int.): 223(65), 124(100), 109(50). Analysis calculated for $C_{11}H_{13}NO_4$; C, 59.19; H, 5.87. Found: C, 59.37; H, 5.86.

Acknowledgements

We gratefully acknowledge support for this project by Consejo Nacional de Ciencia y Tecnología (CONACyT, GRANT No SEP-2004-CO1-47835). Adrian Ochoa-Terán thanks CONACyT for a fellowship (Repatriation No. 050318). The authors are indebted to Dr. Daniel Chavez Velazco for encouragement.

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