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### SYNTHESIS OF 4-[4-(BROMOMETHYL)-2-OXAZOLYL]-2,6-bis(1,1-DIMETHYLETHYL)PHENOL

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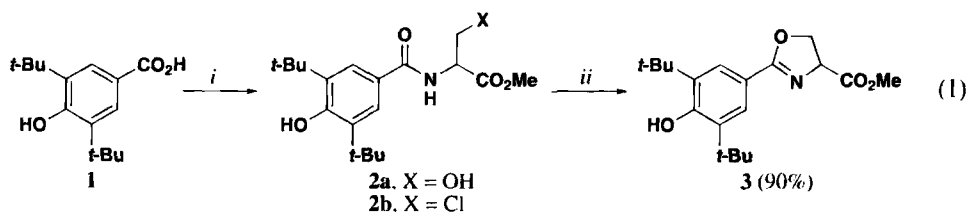
**SYNTHESIS OF 4-[4-(BROMOMETHYL)-2-OXAZOLYL]-  
2,6-bis(1,1-DIMETHYLETHYL)PHENOL**

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An ongoing drug development program required the design of a reliable synthetic route to the oxazole-containing coupling partner **6** which was to be employed in displacement reactions with oxygen nucleophiles. Serine-derived oxazoles containing a C-2 aryl substituent are common pharmacophores present in a number of biologically important agents including the neuroprotective antioxidant compounds currently under investigation in these laboratories.<sup>1</sup> The original approach while strategically sound, employed a number of transformations which were not amenable to large scale production of **6**.<sup>1</sup> We describe herein tactical modifications which not only significantly reduced waste generation and eliminated the need for purification by chromatography but provided generally applicable methodology for the production of related oxazole derivatives.

The free base of *d,l*-serine methyl ester hydrochloride was coupled with 3,5-di-*tert*-butyl-4-hydroxybenzoic acid **1** using 1 equiv of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT)<sup>2</sup> to give the amide **2a** in 75% yield.

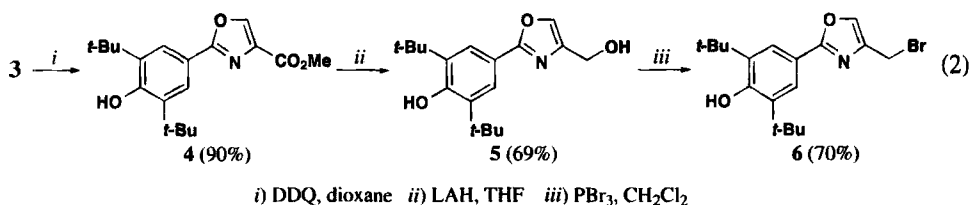
Cyclodehydration of hydroxyamides similar to **2a** with thionyl chloride is well precedented,<sup>3</sup> the cyclization being conducted in neat thionyl chloride or with a large excess in order to drive the reaction to completion. Surprisingly, treatment of **2a** with neat thionyl chloride gave the chloride derivative **2b** instead of the desired oxazoline **3**. The use of 2 equivalents of thionyl chloride afforded a mixture of the desired oxazoline **3** and **2b**. The use of 1.05 equivalent of thionyl chloride yielded the desired oxazoline in 90% yield with less than 5% of **2b** (Eq. 1).



*i*) CDMT, HOCH<sub>2</sub>CH(NH<sub>2</sub>)CO<sub>2</sub>Me    *ii*) SOCl<sub>2</sub> (1.05 equiv.), CH<sub>2</sub>Cl<sub>2</sub>

Examples of the oxidative conversion of oxazolines to oxazoles generally involve the use of

nickel peroxide<sup>4</sup> and manganese dioxide.<sup>5</sup> Manganese dioxide was originally employed in the synthesis of **6**;<sup>1</sup> copious metal waste exacerbated the problem of low and inconsistent yields of the desired oxazole **4**. Attempts to purify **4** by crystallization were unsuccessful. These issues prompted our evaluation of a 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-mediated oxidation. In the single literature report of DDQ-induced oxazoline oxidations, McGravey and co-workers reported that the oxidation of 2-phenyl-5-alkyl-1,3-oxazolines using DDQ in refluxing benzene gave the corresponding oxazoles in high yield.<sup>6</sup> Similar conditions afforded clean and rapid oxidative conversion of **3** to **4** in 94% yield (Eq 2).



Reduction of **4** with lithium aluminum hydride furnished the corresponding alcohol **5**, which was treated with phosphorus tribromide to afford the primary bromide **6**. This protocol facilitated product isolation by yielding a water soluble phosphorus by-product from which **6** was easily separated.

In summary, the useful oxazole-containing intermediate (**6**) was prepared through a six-step synthesis in good overall yield (45%). All intermediates and the final product could be purified without the need for column chromatography. Importantly, a cyclodehydration protocol was developed that avoided the use of large excesses of thionyl chloride which are typically employed in related reactions. Furthermore, a non-metal based oxidation of the resulting oxazoline delivered the corresponding oxazole in good yield.

## EXPERIMENTAL SECTION

Commercially available chemicals of reagent grade were used. All melting points are uncorrected and determined on a MEL TEMP. 3.0. The <sup>1</sup>H NMR spectra were recorded on a Bruker AMX-300 spectrometer in CDCl<sub>3</sub> with TMS as an internal standard.

### N-[3,5-bis(1,1-Dimethylethyl)-4-hydroxybenzoyl]serine Methyl Ester (**2a**)-

**Part A.** In a 12 L flask, 3,5-di-*tert*-butyl-4-hydroxybenzoic acid (250.4g, 1.0 mole) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (179.2g; 98%, 1.0 mole) were dissolved in 5 L of methylene chloride under a nitrogen atmosphere. This solution was cooled to -5 to -10°, and then 4-methylmorpholine (110ml, 101.2g, 1.0 mole) was added over 5 to 10 min. The resulting mixture was stirred at -5 to -15° for 2 h.

**Part B.** In a 5 L flask, *d,l*-serine methyl ester hydrochloride (233.4g, 1.5 mole) was stirred with 2.5 L of methylene chloride under a nitrogen atmosphere. Triethylamine (418ml, 303.6g, 3.0 moles) was added at 20 to 25°, and then stirred 30-90 min. at that temperature. The mixture was cooled to 0 to -5° prior to its use in **Part C**.

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*Part C.* The free base mixture from *Part B* was added in one portion to the 12 L reaction flask (*Part A*) at  $-10^{\circ}$ . The mixture was stirred at ambient temperature overnight (18 h). The reaction mixture was quenched with 1N HCl (4 L), and stirred for 30 min. The layers were separated, and the organic layer was washed with 1N HCl (2x1 L) and with saturated NaCl solution (1 L). The organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated under vacuum to a light yellow semi-solid. Diethyl ether (2 L) was added to the crude solid, and then the solution was concentrated under vacuum to dryness. Another 2 L diethyl ether was added to the crude solid, and the mixture was warmed to  $35^{\circ}$ . This mixture was transferred to a 12 L flask with diethyl ether (1 L), which was then stirred vigorously while heptane (3 L) was added. The resulting slurry was filtered with suction, and the solid was washed with 1:1 diethyl ether:heptane followed by heptane. The resulting white solid was dried *in vacuo* at  $35^{\circ}$  to give **2a** (253.1g, 72%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.65 (2H, s); 7.05 (1H, d); 4.85 (1H, m); 4.05 (2H, d); 3.8 (3H, s); 1.5 (18H, s). MS- FD, 351.

An analytical sample was prepared by crystallization from 2:1 *tert*-butyl methyl ether: diethyl ether, mp. 105-108 $^{\circ}$ .

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{29}\text{NO}_5$ : C, 64.94, H, 8.32, N, 3.99. Found, C, 64.86, H, 8.44, N, 3.97

**2-[3,5-bis(1,1-Dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-4-oxazolecarboxylic Acid Methyl Ester (3).**- Compound **2a** (215g, 0.618 mole) was stirred with 2.15 L methylene chloride under nitrogen atmosphere in a 5 L flask. Thionyl chloride (50 ml, 81.55g, 0.685 mole) was added over 15 min. The temperature rose from 21 to  $29^{\circ}$  over 30 min. before the exotherm subsided. The reaction mixture was stirred at ambient temperature for 5 h and quenched by pouring cautiously into 2 L of saturated sodium bicarbonate. Sufficient saturated sodium bicarbonate solution was added to bring the pH of the mixture to 8. The layers were separated, and the organic layer was washed with saturated sodium chloride and then dried over magnesium sulfate. The drying agent was filtered and the solvent removed under vacuum to give a very light yellow oil. This oil was dissolved in diethyl ether at  $35^{\circ}$ , and the solvent was removed under vacuum to give **3** (189g, 91%) as a white, free-flowing solid.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.8 (2H, s); 5.6 (1H, s); 4.9 (1H, m); 4.6 (2H, m); 3.8 (3H, s); 1.5 (18H, s). MS-FD, 333.

An analytical sample was prepared by crystallization from 1:1 *tert*-butyl methyl ether: hexanes, mp. 116-118 $^{\circ}$ .

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{27}\text{NO}_4$ : C, 68.44, H, 8.16, N, 4.20. Found, C, 68.41, H, 8.19, N, 4.20

**2-[3,5-bis(1,1-Dimethylethyl)-4-hydroxyphenyl]-4-oxazolecarboxylic Acid Methyl Ester (4).**- DDQ (131g) was dissolved in 750 mL dioxane under a nitrogen atmosphere in a 5 L flask that was equipped with a mechanical stirrer and heating mantle. To the resulting solution was added a solution of **3** (170g) in 700 mL dioxane. The mixture was heated to reflux for a total of 1.5 h then allowed to cool to room temperature over 2 h. The mixture was filtered on a 18.5 cm Buchner with 1 inch silica pad. The filter cake was washed with 1 L dioxane followed by 1.5 L *tert*-butyl methyl ether. The filtrate was stirred with 250g Activated carbon (DARCO, 20-40 mesh) for 30 min. The mixture was filtered on a 18.5 cm Buchner over Celite. The filter cake was washed with 2 L *tert*-butyl methyl ether. The filtrate was concentrated by rotary evaporation ( $50^{\circ}$  bath) to give **4** as a light green solid

(169g, 100%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.21 (1H, s); 7.9 (2H, s); 5.6 (1H, s); 3.95 (3H, s); 1.5 (18H, s). MS-FD, 331.

An analytical sample was prepared by crystallization from isopropyl alcohol, mp. 162.5-164°.

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{25}\text{NO}_4$ : C, 68.86, H, 7.60, N, 4.23. Found, C, 68.83, H, 7.70, N, 4.00

**2-[3,5-bis(1,1-Dimethylethyl)-4-hydroxyphenyl]-4-oxazolemethanol (5).**- THF (1L) was stirred in a 2 L Morton flask and cooled under a nitrogen atmosphere to 0°. Then  $\text{LiAlH}_4$  (12.78 g, 0.336mole) was added. A temperature increase of 4° was noted. A solution of **4** (60g, 0.181 mole) in 200 mL THF was added over 40 min at -2 to +2°. Additional portions of THF (50 mL) were used to assist transfer. TLC (*tert*-butyl methyl ether) indicated that the reaction was complete after 40 min. The reaction was quenched by the dropwise addition of water (1 L) (FOAMING). The temperature increased to 20°. The mixture was transferred to a 6 L separatory flask and 1.5 L of water was added. The mixture was stirred 10 min then filtered over glass fiber paper. The filter cake was rinsed with water and 500 mL ethyl acetate. The filtrate was transferred to a separatory funnel. Then 1 L ethyl acetate was added and the mixture was separated. Although the layers separated cleanly, in 15 min, the mixture was dark. The aqueous layer was extracted with ethyl acetate (750 mL x 2). The ethyl acetate extracts were combined and stirred 2 h with  $\text{MgSO}_4$  (150g) and DARCO (20-40 mesh) (150g). The mixture was filtered over glass fiber paper. The filter cake was washed with 1 L ethyl acetate. The filtrate was concentrated by rotary evaporation (50° bath) to give **5** as an off-white solid (38g, 69%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.91 (2H, s); 7.59 (1H, s) 4.65 (2H, s); 3.15 (1H, s); 1.5 (18H, s). MS-FD, 303.

An analytical sample was prepared by slurring compound **5** (38 g) with 200 mL acetonitrile and heating to reflux for 15 min. The mixture was cooled to room temperature over 15 min with stirring followed by stirring in an ice bath for 45 min. The solid was collected, washed with 100 mL acetonitrile and dried at 50° *in vacuo* to give **5** (31 g, 82%) as an olive colored solid, mp. 165-167°.

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{25}\text{NO}_3$ : C, 71.26, H, 8.21, N, 4.62. Found, C, 71.49, H, 8.21, N, 4.75

**4-[4-(Bromomethyl)-2-oxazolyl]-2,6-bis(1,1-dimethylethyl)phenol (6).**- A solution of **5** (30.8g, 0.102 mole) in 800 mL  $\text{CH}_2\text{Cl}_2$  was stirred at room temperature. The mixture was cooled to 18° and  $\text{PBr}_3$  (9.6 mL, 0.102 mole) was added over 5 min. The cooling bath was removed and the mixture was stirred at room temperature overnight (22 h). The reaction was quenched by the addition of a mixture of pH 7 phosphate buffer (750 mL) and saturated NaCl (300 mL). The two layers separated very slowly. The organic layer was stirred with  $\text{MgSO}_4$  (200 g), DARCO (100g), and silica gel (150g) for 30 min. The mixture was filtered over glass fiber paper covered with Celite and the filter cake was washed with dichloromethane (750 mL). The light purple solution was concentrated by rotary evaporation (40° bath) to give a foam to which hexanes (100ml) was added. The solution was evaporated; the process was repeated to give **6** (28.9 g, 78%) as a yellow foam,  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.81 (2H, s); 7.65 (1H, s), 5.55 (1H,s), 4.45 (2H, s); 1.5 (18H, s). MS-FD, 366.

An analytical sample (1.7g) was prepared by dissolving in 17 mL hexanes. The solution was decanted from a gummy residue and held at 5° overnight. The resulting crystals were collected and washed with hexanes to give **6** (1.12g, 66%). mp. 95-96°.

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{24}\text{BrNO}_2$ : C, 59.02, H, 6.60, N, 3.72. Found, C, 59.30, H,6.65, N, 3.72

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