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NOVEL SYNTHETIC ROUTE TO FLUOXETINE

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Racemic fluoxetine was synthesized from 3-benzoylpropionic acid in five steps in 54% overall yield.

Keywords: Curtius rearrangement; fluoxetine; isocyanate

The selective serotonin reuptake inhibitor (SSRI), fluoxetine hydrochloride (Prozac), developed by Eli Lilly and Company, was approved by the U.S. Food and Drug Administration in 1987 (Fig. 1).[1] It was a major breakthrough over the tricyclic antidepressants in the management of major depressive disorder. The SSRI class operates in part by blocking the function of the presynaptic transporter for reuptake of the neurotransmitter, serotonin. Patent protection for fluoxetine ended in 2001, and since then the next-generation antidepressants have come to market in the "advanced economies."[2] However, the rise in global population will also cause an increase in mental health problems in the developing world, which will keep fluoxetine and methods of its manufacture relevant for years to come.[3] According to the World Health Organization, by 2020 depression is expected to be a leading cause of disability worldwide, second only to cardiovascular disease.[4] Fluoxetine is marketed as a racemic mixture, so the challenges of a chiral synthesis are avoided. As part of an ongoing study of central nervous system drugs, a new synthesis was developed for laboratory-scale preparation of fluoxetine.[5]

The starting point of our synthesis was 3-benzoylpropionic acid **2** (Scheme 1). For isolation of the hydroxyl acid **3**[6,7] from the sodium borohydride reduction of **2**,[8,9] it was necessary to maintain ice-bath temperature during neutralization (Scheme 1). In this way, the facile lactonization was minimized and **3** could be extracted. All attempts to further purify this compound failed. An attempt of diphenylphosphoryl azide–mediated[10] Curtius reaction on **3** gave a mixture of products, the desired tetrahydro-1,3-oxazin-2-one **7**[11] being a minor component. The lactone **4**[12–15] was a more convenient synthetic intermediate. Reaction of **4** with hydrazine hydrate gave the hydrazide **5**[16–18] in good yield. Reaction of **5** with nitrous acid gave

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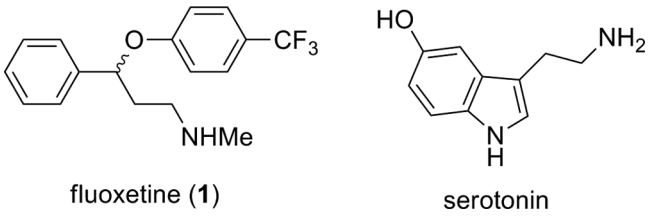
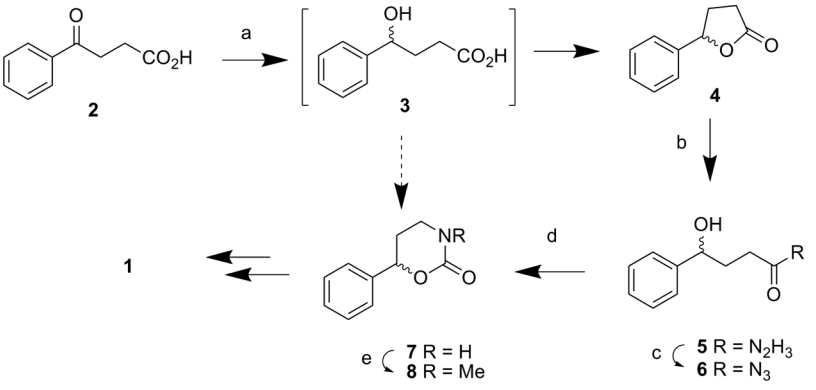


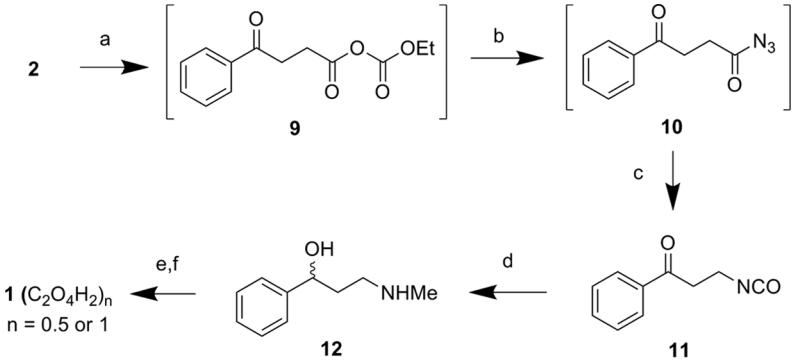
Figure 1. Chemical structures.

the acyl azide **6**, which was refluxed in 1,2-dichloroethane to obtain the intramolecularly cyclized product **7** in 78% yield over the two steps. Potassium *tert*-butoxide was a convenient base for the methylation of **7** with iodomethane to give **8**. Hilborn et al.[19] had previously prepared **8** by the analogous Hoffman reaction. They demonstrated that this intermediate could be hydrolyzed and converted into **1** (vide infra).

Further work was done to try to make the route even simpler (Scheme 2). The acid chloride derived from **2** was difficult to isolate.[20,21] However, **2** was activated by conversion into the corresponding mixed carboxylic carbonic anhydride **9** and then transformed into the acyl azide **10**.[22] Without isolation, **10** was heated to bring about rearrangement to the unreported isocyanate **11** in 69% over the three-step, one-pot process.[23–25] The isocyanate **11** was readily reduced by lithium tetrahydroaluminate to yield the *N*-methylamino alcohol **12**[26–28] in excellent yield.[29] This reaction was performed several times, and in every case, crude **12** was obtained as a solid. Finally, nucleophilic aromatic substitution of 4-chlorobenzotrifluoride by **12** using sodium hydride or potassium *tert*-butoxide in hot dimethylsulfoxide gave fluoxetine (**1**) free base in excellent yield.[27,30,31] The amine was converted into its oxalate salt[32] for storage and handling purposes.



Scheme 1. Curtius route to tetrahydro-1,3-oxazin-2-one **7**. Reagents and conditions: (a) 1. $NaBH_4$, H_2O, KOH; 2. pTsOH · H_2O, PhMe; (b) $N_2H_4 \cdot H_2O$, EtOH, reflux; (c) $NaNO_2$, conc. HCl, DCE; (d) DCE, reflux; and (e) MeI, KO*t*Bu, DMF, THF.



Scheme 2. Synthesis of racemic **1**. Reagents and conditions: (a) $ClCO_2Et$, TEA, DCE, 0 °C; (b) NaN_3, H_2O, DCE, 0 °C; (c) DCE, 80 °C; (d) LAH, THF, reflux; (e) NaH, 4-$ClPhCF_3$, DMSO, 100 °C; and (f) $(HO_2C)_2$, EtOH.

EXPERIMENTAL

The melting point was collected on an electrothermal capillary melting-point apparatus and is not corrected. Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker Avance 300-MHz (^1H, 300 MHz; ^{13}C, 75 MHz) instrument. All samples were referenced to tetramethylsilane as internal standard or to the solvent. The following reagents were purchased from Sigma-Aldrich Chemical Co. (Milwaukee) and used as received: iodomethane (99%), thionyl chloride ($SOCl_2$, 97%), sodium azide (NaN_3, 99%), potassium *tert*-butoxide (KO*t*Bu, 95%), anhydrous dimethylformamide (DMF, 99.8%), sodium borohydride ($NaBH_4$, 99.9%), lithium tetrahydroaluminate (LAH, 95%), hydrazine hydrate (50–60%), 1,2-dichloroethane (DCE, 99%), anhydrous tetrahydrofuran (THF, 99%, inhibited with 250 ppm 2,6-di-*tert*-butyl-4-methylphenol), and oxalic acid dihydrate (99%). All other reagents were obtained commercially and used as received. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

Racemic 5-Phenyltetrahydrofuran-2-one (4)

A 1-L round-bottomed flask equipped with a magnetic stirring bar and protected with an N_2 bubbler was charged with 500 mL H_2O, 5.6 g KOH (1 equiv), and 17.8 g **2** (0.1 mol). The mixture was gently heated to dissolve all the solids, then cooled with ice. $NaBH_4$ (3.8 g, 1.1 equiv) was added over 30 min, and the mixture was stirred for 12 h at rt. The mixture was carefully acidified with conc. HCl (~20 mL) and then extracted three times with 150-mL portions of toluene. The organic phases were collected and washed with 150 mL H_2O and then 150 mL brine. The organic phase was dried over anhydrous $MgSO_4$ and then filtered into a 1-L flask equipped with a magnetic stirring bar and fitted with a reflux condenser and a Dean–Stark trap. A crystal of *p*-toluenesulfonic acid monohydrate was added, and the mixture was refluxed to remove the H_2O from lactonization. The mixture was washed with 100 mL saturated aqueous Na_2CO_3 followed by 100 mL brine. After drying over

anhydrous $MgSO_4$, the solvent was rotary-evaporated to leave 12.18 g of a colorless oil that solidified on drying under vacuum (75%). Mp 31–33 °C (lit.[13] 37–38 °C). δ_H ($CDCl_3$): 7.45–7.03 (m, 5H), 5.47 (dd, $J = 8.4$ and 6.2 Hz, 1H), 2.69–2.54 (m, 3H), 2.15 (m, 1H); δ_C ($CDCl_3$): 176.89, 139.50, 128.75, 128.42, 125.34, 81.22, 30.88, 28.93. Elemental analysis calculated for $C_{10}H_{10}O_2$: C, 74.07; H, 6.17. Found: C, 73.91; H, 6.23.

Racemic 4-Hydroxy-4-phenylbutyric Acid Hydrazide (5)

A 250-mL round-bottomed flask equipped with a magnetic stirring bar was charged with 8.18 g **4** (50 mmol) and 100 mL EtOH. After all the solids had dissolved, 3.3 g hydrazine hydrate (69 mmol, 1.3 equiv) was added in one portion, and the mixture was refluxed for 2 h. After cooling to rt, the product precipitated as a white microcrystalline powder. The mixture was filtered on a medium-porosity glass frit and dried under vacuum (20 torr, 60 °C) to give 7.7 g of the title compound (79%). No further purification was necessary. Mp 120–123 °C (lit.[16] 118–128 °C). δ_H (DMSO): 8.96 (s, NH), 7.4–7.18 (m, 5H), 5.29 (d, $J = 4.3$ Hz, OH), 4.55 (q, $J = 4.9$ Hz, 1H), 4.16 (s, NH_2), 2.14–2.05 (m, 2H), 1.89–1.78 (m, 2H); δ_C (DMSO): 171.73, 145.88, 127.97, 126.67, 125.75, 71.78, 35.07, 29.97. Elemental analysis calculated for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.93; H, 7.23; N, 14.39.

Racemic 6-Phenyltetrahydro-1,3-oxazin-2-one (7)

A round-bottomed flask equipped with a magnetic stirring bar was charged with 30.85 g **5** (159 mmol), 200 mL H_2O, 200 mL DCE, and 17.08 mL conc. HCl (206 mmol, 1.3 equiv). The mixture was stirred in an ice bath, and 14.28 g $NaNO_2$ (206 mmol, 1.3 equiv) in 25 mL H_2O were added dropwise over 30 min. After stirring for 1 h, the mixture was poured into a separatory funnel, and the organic phase was separated. The aqueous layer was extracted with 100 mL DCE. The collected organic layer was washed with 100 mL dilute Na_2CO_3 followed by 100 mL brine. After drying over $MgSO_4$, the solution was heated to reflux for 10 h. Some of the product precipitated during this time. The solvent was rotary-evaporated to leave 22.01 g crude product as colorless flakes (78%). No further purification was necessary. Mp 184–186 °C (lit.[16] 180–181 °C). δ_H ($CDCl_3$): 7.43–7.3 (m, 5H), 6.93 (bs, NH), 5.33 (dd, $J = 9.7$ and 3.0 Hz, 1H), 3.52–3.31 (m, 2H), 2.26–2.14 (m, 1H), 2.13–1.98 (m, 1H); δ_C ($CDCl_3$): 155.06, 139.28, 128.77, 128.48, 125.80, 78.72, 39.00, 28.86. Elemental analysis calculated for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.78; H, 6.25; N, 7.92.

Racemic 3-Methyl-6-phenyltetrahydro-1,3-oxazin-2-one (8)

A 100-mL round-bottomed flask equipped with a magnetic stirring bar was charged with 2.2 g **7** (12.4 mmol) and 25 mL DMF. Some heating was necessary to dissolve the majority of the solids. After cooling to rt, 2.09 g KO*t*Bu (18.6 mmol, 1.5 equiv) was added in one portion. After 20 min, 3.5 g iodomethane (24.8 mmol, 2 equiv) was added, and the mixture was heated to 55 °C for 2 h. The mixture was poured into 100 mL H_2O and extracted with 100 mL EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and rotary-evaporated to an off-white solid. Recrystallization from heptanes gave the title compound as colorless needles

(2.1 g, 90%). Mp 73–75 °C (lit.[11] 83 °C). δ_H ($CDCl_3$): 7.39–7.29 (m, 5H), 5.29 (dd, $J = 9.8$ and 3.1 Hz, 1H), 3.54–3.43 (m, 1H), 3.29–3.21 (m, 1H), 3.04 (s, 3H), 2.31–2.1 (m, 2H); δ_C ($CDCl_3$): 154.31, 139.14, 128.76, 128.47, 125.75, 78.34, 46.46, 36.72, 29.72. Elemental analysis calculated for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.21; H, 7.02; N, 7.29.

3-Isocyanatopropiophenone (11)

A 500-mL round-bottomed flask equipped with a magnetic stirring bar and a 500-mL addition funnel was charged with 50 mL DCE and 9.5 mL ethyl chloroformate (1 equiv), and the mixture was stirred in an ice bath. In a separate flask, 17.82 g **2** (0.1 mol) was suspended in 200 mL DCE, and 10.1 g TEA (1 equiv) was added over 10 min. The resulting hazy solution was charged into the addition funnel and added to the ice-cooled DCE solution of ethylchloroformate over 20 min. Copious white solids precipitated during the addition as TEA · HCl formed. After stirring for another 15 min, the salt (12.6 g, 92%) was filtered off using a medium-porosity glass frit. The filtrate at this stage was a DCE solution of the mixed carboxylic carbonic anhydride **9** [δ_H ($CDCl_3$): 7.99 (dm, $J = 7.8$ Hz, 2H), 7.59 (tm, 7.5 Hz, 1H), 7.48 (tm, $J = 7.2$ Hz, 2H), 4.33 (q, $J = 7.2$ Hz, 2H), 3.37 (t, $J = 6.6$ Hz, 2H), 2.93 (t, $J = 6.6$ Hz, 2H), 1.37 (t, $J = 7.2$ Hz, 3H); δ_C ($CDCl_3$): 197.13, 167.66, 149.01, 136.45, 133.59, 128.86, 128.24, 65.84, 33.04, 28.62, 14.07].

The filtrate was charged into a clean, dry, 500-mL round-bottomed flask equipped with a magnetic stirring bar. The flask was equipped with a clean 50-mL addition funnel, and stirring was initiated with ice cooling. The addition funnel was charged with a solution of 8.1 g NaN_3 (125 mmol, 1.25 equiv) in 50 mL H_2O, which was added dropwise over 15 min. After stirring with ice cooling for 1 h, ^1H NMR showed the reaction was complete and the acyl azide **10** had completely formed [δ_H ($CDCl_3$): 3.33 (t, $J = 6.6$ Hz, 2H), 2.79 (t, $J = 6.4$ Hz, 2H)].

The mixture was poured into a separatory funnel, and the phases were split. The organic phase was washed with a mixture of 100 mL saturated aqueous $NaHCO_3$ and 100 mL brine. The organic phase was dried over anhydrous $MgSO_4$ and filtered into a dry, 500-mL round-bottomed flask equipped with a magnetic stirring bar. The mixture was heated at 75 °C overnight. The solvent was rotary-evaporated to leave 14.64 g of a light orange liquid. The title compound was obtained as a pale yellow oil (12.03 g, 69%) after reduced pressure distillation (0.1 torr) of the crude product. The oil solidified when refrigerated. δ_H ($CDCl_3$): 7.96 (dm, $J = 7.0$ Hz, 2H), 7.59 (tm, $J = 7.3$ Hz, 1H), 7.48 (tm, $J = 7.0$ Hz, 2H), 3.74 (t, $J = 5.9$ Hz, 2H), 3.27 (t, $J = 6.4$ Hz, 2H); δ_C ($CDCl_3$): 197.07, 136.61, 133.78, 128.97, 128.22, 123.51, 39.53, 38.16. Elemental analysis calculated for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.36; H, 5.16; N, 7.86.

Racemic 3-(Methylamino)-1-phenyl-1-propanol (12)

An oven-dried, 1-L, round-bottomed flask equipped with a magnetic stirring bar, a 200-mL addition funnel, and an N_2 bubbler was charged with 3.38 g LAH (0.089 mol, 3 equiv). The addition funnel was charged with 200 mL THF, which was added in a gentle stream to the stirred solid over 20 min. Next, the addition funnel

was charged with a solution of 5.2 g **11** (0.0297 mol) in 20 mL THF. The solution was added dropwise over a period of 2 h. The mixture became warm during the addition. The mixture was heated at a gentle reflux for 10 h. After cooling to rt, the reaction mixture was quenched by adding the following, in sequence, through the addition funnel: 3.38 g H_2O, 3.38 g 15% NaOH, and finally 10.14 g H_2O. After stirring for 2 h, the mixture was filtered through a medium-porosity glass frit. The filter cake was removed, suspended in 50 mL THF, and refiltered; this was repeated. The combined filtrates were rotary-evaporated to remove most of the THF. The residue was dissolved in 200 mL Et_2O, washed with 50 mL brine, and then dried over anhydrous $MgSO_4$. Evaporation of the solvent under vauum left 4.41 g of a crude white solid that was >95% pure by ^{1}H NMR (90%). Recrystallization from 60:40 heptane–toluene gave the title compound as colorless crystals. Mp 46–48 °C (lit.[32] 59–64 °C). δ_H ($CDCl_3$): 7.41–7.29 (m, 4H), 7.27–7.18 (m, 1H), 4.92 (dd, $J = 8.5$ and 3.4 Hz, 1H), 2.93–2.77 (m, 2H), 2.43 (s, 3H), 1.93–1.69 (m, 2H); δ_C ($CDCl_3$): 145.39, 128.38, 127.08, 125.81, 75.74, 50.65, 37.19, 36.26. Elemental analysis calculated for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.47; H, 9.14; N, 8.39.

The hemioxalate of **12** was prepared using 0.5 equiv oxalic acid dihydrate followed by recrystallization from MeCN. Mp 185–187 °C. δ_H (DMSO, 370 K): 7.46–7.11 (m, 5H), 4.68 (t, $J = 5.9$ Hz, 1H), 2.78 (t, $J = 7.0$ Hz, 2H), 2.41 (s, 3H), 1.89–1.79 (m, 2H); δ_C (DMSO, 370 K): 198.21, 145.08, 127.35, 126.07, 125.07, 70.43, 46.92, 36.08, 33.65. Elemental analysis calculated for $C_{10}H_{15}NO \cdot 0.5\ C_2H_2O_4$: C, 62.84; H, 7.67; N, 6.66. Found: C, 63.01; H, 7.74; N, 6.64.

Racemic 3-(*p*-Trifluoromethylphenoxy)-*N*-methyl-3-phenylpropylamine (1)

A 50-mL, round-bottomed flask equipped with a magnetic stirring bar and N_2 bubbler was charged with 364 mg 60% NaH (9 mmol, 1.5 equiv), which was washed twice with dry hexanes. Anhydrous DMSO (10 mL) and 1 g **12** (6 mmol) were added, and the mixture was heated at 60 °C for ~1 h. In one portion, 2.16 g 4-chlorobenzotrifluoride (12 mmol, 2 equiv) was added, and the mixture was heated in an oil bath at 100 °C for 10 h. The dark mixture was cooled to room temperature and poured into a mixture of 50 mL Et_2O and 50 mL H_2O. The organic layer was separated and washed with 50 mL H_2O followed by 50 mL brine. After drying over anhydrous $MgSO_4$, the solvent was rotary-evaporated under vacuum to leave 1.89 g of a slightly brown oil that was >95% pure by ^{1}H NMR. Reduced pressure distillation (0.1 torr) gave 1.61 g of fluoxetine (**1**) as a colorless oil (87%). δ_H ($CDCl_3$): 7.42 (d, $J = 8.7$ Hz, 2H), 7.37–7.21 (m, 5H), 6.90 (d, $J = 8.4$ Hz, 2H), 5.31 (dd, $J = 8.1$ and 4.9 Hz, 1H), 2.76 (t, $J = 7.1$ Hz, 2H), 2.43 (s, 3H), 2.28–2.14 (m, 2H), 2.09–1.96 (m, 1H); δ_C ($CDCl_3$): 160.82 (d, $J_{CF} = 1.1$ Hz), 141.24, 129.00, 128.07, 127.02 (d, $J_{CF} = 3.7$ Hz), 126.92 (d, $J_{CF} = 3.7$ Hz), 126.05, 122.87, 116.05, 78.88, 48.31, 38.63, 36.45.

A 20-mL, round-bottomed flask equipped with a magnetic stirring bar was charged with 290 mg **1** (0.9 mmol) and 5 mL EtOH. A solution of 142 mg oxalic acid dihydrate (1.1 mmol, 1.25 equiv) in 2 mL EtOH was added to the stirrer mixture over 1 min. Copious white solids precipitated and were collected by filtration through a medium glass frit. The solid was dried in a vacuum oven (60 °C, 20 torr) to give 250 mg of oxalate of **1** in analytically pure form (67%). Mp 186–189 °C (dec.;

lit.[33] 179–182 °C). δ_H (DMSO): 7.57 (d, $J = 8.6$ Hz, 2H), 7.45–7.25 (m, 5H), 7.07 (d, $J = 8.6$ Hz, 2H), 5.62 (dd, $J = 8.5$ and 4.5 Hz, 1H), 3.03 (m, 2H), 2.57 (s, 3H), 2.37–2.07 (m, 2H). Elemental analysis calculated for $C_{17}H_{18}ClF_3NO \cdot C_2H_2O_4$: C, 57.17; H, 5.05; N, 3.51. Found: C, 57.21; H, 4.98; N, 3.47.

Similarly, the hemioxalate of **1** was also prepared using 0.5 equiv oxalic acid dihydrate. Recrystallization from MeCN gave a white powder. Mp 158–160 °C. Elemental analysis calculated for $C_{17}H_{18}ClF_3NO \cdot 0.5\ C_2H_2O_4$: C, 61.10; H, 5.40; N, 3.95. Found: C, 61.24; H, 5.49; N, 3.89.

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