Efficient Synthesis of Photoreactive 2-Propoxyaniline Derivatives as Artificial Sweeteners

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Experimental Section

4-Bromo-2-nitro-1-propoxybenzene (4)

To a solution of 1-bromo-4-propoxybenzene 3 (329 mg, 1.53 mmol) in acetic anhydride (500 μL) was added dropwise 80% fuming HNO₃ (380 μL) at 0 °C. After stirring for 1 h, the reaction mixture was poured into ice water (100 mL). The organic compound was extracted with ether (2 x 100 mL). The combined organic layer was washed with brine, dried over MgSO₄, and then evaporated. The residue was purified by silica column chromatography (AcOEt/n-hexane 1:5) to yield 4 (227 mg, 57 %) as yellow oil.

1H NMR (270MHz, CDCl₃): δ = 8.74 (d, J = 2.6 Hz, 1H), 8.43 (dd, J = 2.6, 9.2 Hz, 1H), 7.22 (d, J = 9.2 Hz, 1H), 4.22 (t, J = 6.3 Hz, 2H), 2.01 - 1.86 (m, 2H), 1.10 (t, J = 7.4 Hz, 3H). 13C NMR (126MHz, CDCl₃) δ = 156.9, 139.8, 138.9, 129.0, 121.8, 114.2, 72.3, 22.1, 10.3. HRMS (ESI) m/z [M + H]⁺ calcd for C₉H₁₁BrNO₃ 259.9922, found 259.9920.

5-Bromo-2-propoxyaniline (5)

To a solution of 4 (199 mg, 0.77 mmol) in THF (3 mL) and ethanol (2.8 mL) was added sodium dithionite (670 mg, 3.85 mmol) in H₂O (4 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred until the starting material disappeared. The organic compound was extracted with AcOEt, and washed by brine, dried over MgSO₄, and evaporated. The crude product was purified by silica column chromatography (AcOEt/n-hexane 1:3) to yield 5 (137 mg, 78%) as a yellow solid.

1H NMR (270MHz, CDCl₃): δ = 6.82 (d, J = 2.3 Hz, 1H), 6.78 (dd, J = 2.3, 8.6 Hz, 1H), 6.61 (d, J = 8.6 Hz, 1H), 3.92 (t, J = 6.6 Hz, 2H), 3.85 (brs, 2H), 1.90 - 1.74 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H). 13C NMR (126MHz, CDCl₃): δ = 165.0, 145.3, 140.0, 120.8, 117.0, 111.3, 72.1, 22.6, 10.4. HRMS (ESI) m/z [M + H]⁺ calcd for C₉H₁₃BrNO 230.0181, found 230.0181.

N-(2-Propoxyphenyl)acetamide (8)

N-(2-Hydroxyphenyl)acetamide 7 (1.32 g, 8.7 mmol) was suspended in acetonitrile (50 mL). Potassium carbonate (1.57 g, 11 mmol) and 1-bromopropane (1.18 g, 9.6 mmol) in acetonitrile (40 mL) were added to the suspension. The reaction mixture was stirred for 16 h under reflux and filtrated and evaporated. The organic compound was dissolved in AcOEt, washed with brine, dried over MgSO₄, and then evaporated. The crude product was purified by silica column chromatography (AcOEt/n-hexane 1:4) to yield 8 (1.61 g, 95%) as colorless oil.

1H NMR (270MHz, CDCl₃): δ = 8.36 (d, J = 7.7 Hz, 1H), 7.77 (brs, 1H), 7.09 - 6.82 (m, 3H), 4.00 (t, J = 6.6 Hz, 2H), 2.20 (s, 3H), 1.86 (m, J = 7.1 Hz, 2H), 1.06 (t, J = 7.4 Hz, 3H). 13C NMR (68MHz, CDCl₃): δ = 168.2, 147.1, 127.9, 123.6, 120.9, 119.7, 110.9, 70.0, 24.7, 22.3, 10.3. HRMS (ESI) m/z [M + H]⁺ calcd for C₁₁H₁₆NO₂ 194.1181, found 194.1181.

N-(5-Benzoyl-2-propoxyphenyl)acetamide (9)

Aluminium chloride (231 mg, 1.7 mmol) was suspended in 1,2-dichloroethane (1.5 mL) and cooled to 0 °C. Benzoyl chloride (146 mg, 1.0 mmol) was added to the suspension and the reaction mixture was stirred for 10 min at the same temperature. N-(2-Propoxyphenyl)acetamide 8 (137 mg, 0.71 mmol) in 1,2-dichloroethane (1 mL) was added to the mixture and the reaction mixture was warmed to room temperature. After stirring for 3 h, the reaction mixture was quenched with AcOEt/ice water (10 mL/10 mL). The organic layer was washed with saturated NaHCO₃, brine and dried over MgSO₄, and then evaporated.
The residue was purified by silica column chromatography (AcOEt/n-hexane 1:4) to yield 9 (198 mg, 94%) as colorless oil.

$^1$H NMR (270MHz, CDCl$_3$): δ = 8.81 (s, 1H), 7.96 - 7.38 (m, 7H), 6.96 (d, $J = 8.6$ Hz, 1H), 4.10 (t, $J = 6.6$ Hz, 2H), 2.20 (s, 3H), 1.91 (sxt, $J = 7.1$ Hz, 2H), 1.09 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (68MHz, CDCl$_3$): δ = 195.6, 168.3, 150.8, 137.9, 132.0, 130.0, 129.8, 128.1, 127.1, 126.6, 122.4, 110.3, 70.3, 24.4, 22.0, 10.1. HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{18}$H$_{20}$NO$_3$ 298.1443, found 298.1446.

2,2,2-Trifluoro-1-(4-hydroxyphenyl)ethan-1-one (12)

A mixture of 2,2,2-trifluoro-1-(4-methoxyphenyl)ethan-1-one 11 (954 mg, 4.67 mmol) and LiCl (970 mg, 23 mmol) in DMF (30 mL) was refluxed for 4 h under N$_2$. The reaction mixture was poured into water (200 mL), and acidified with 1M HCl. The product was extracted with AcOEt (2 x 150 mL). The combined organic layer was washed with brine and dried over MgSO$_4$, and then evaporated. The residue was purified by silica column chromatography (AcOEt/n-hexane 1:3) to yield 12 (732 mg, 83%) as a white solid.

$^1$H NMR (500MHz, CDCl$_3$): δ = 8.03 (d, $J = 8.8$ Hz, 2H), 6.98 (d, $J = 8.8$ Hz, 2H), 6.34 (brs, 1H). $^{13}$C NMR (126MHz, CDCl$_3$): δ = 179.3 (q, $^2J_{CF} = 35.7$ Hz), 162.3, 133.2, 122.8, 116.9 (q, $^1J_{CF} = 291.7$ Hz), 116.1. HRMS (ESI) m/z [M + H]$^+$ calcd for C$_8$H$_6$F$_3$O$_2$ 191.0320, found 191.0320.

2,2,2-Trifluoro-1-(4-propoxyphenyl)ethan-1-ol (14)

To a solution of 4-propoxybenzaldehyde 13 (2.1g, 12.7 mmol) in THF (30 mL) was added TMS-CF$_3$ (2.77 mL, 19 mmol) and CsF (3 mg) at 0 °C and the reaction mixture was warmed to room temperature. After stirring for 4 h, the reaction mixture was poured into 1 M HCl (5 mL) and stirred for 6 h. The organic compound was extracted with AcOEt (3 x 30 mL). The combined organic layer was washed with brine, dried over MgSO$_4$, and evaporated. The residue was purified by silica column chromatography (AcOEt/n-hexane 1:2) to yield 14 (2.4 g, 81%) as a white solid.

$^1$H NMR (270MHz, CDCl$_3$): δ = 7.19 (d, $J = 8.6$ Hz, 2H), 6.76 (d, $J = 8.6$ Hz, 2H), 4.70 (q, $J = 6.7$ Hz, 1H), 3.77 (t, $J = 6.4$ Hz, 2H), 3.63 (brs, 1H), 1.75 - 1.59 (m, 2H), 0.90 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (68MHz, CDCl$_3$): δ = 160.0, 128.8, 126.2, 124.5 (q, $^1J_{CF} = 282.1$ Hz), 114.6, 72.2 (q, $^2J_{CF} = 31.9$ Hz), 69.6, 22.2, 10.1. HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{11}$H$_{14}$F$_3$O$_2$ 235.0946, found 235.949.

2,2,2-Trifluoro-1-(4-propoxyphenyl)ethan-1-one (15)

To a solution of 12 (418 mg, 2.2 mmol) in DMF (30 mL) was added K$_2$CO$_3$ (607 mg, 4.4 mmol) and 1-bromo propane (600 μL, 6.59 mmol) at 0 °C. The reaction mixture was warmed to 60 °C and stirred for 2 h. The organic solution was removed and the crude product was purified by silica column chromatography (AcOEt/n-hexane 1:5) to yield 15 (449 mg, 88%) as a white solid.

$^1$H NMR (500MHz, CDCl$_3$): δ = 8.03 (d, $J = 8.8$ Hz, 2H), 6.98 (d, $J = 8.8$ Hz, 2H), 4.02 (t, $J = 6.5$ Hz, 2H), 1.90 - 1.80 (m, 2H), 1.06 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (126MHz, CDCl$_3$): δ = 178.8 (q, $^2J_{CF} = 34.1$ Hz), 165.1, 132.7, 122.5, 114.8, 116.9 (q, $^1J_{CF} = 291.9$ Hz), 70.0, 22.3, 10.3. HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{12}$H$_{12}$F$_3$O$_2$ 233.0789, found 233.0790.

Another route from 14

Compound 14 (862 mg, 3.68 mmol) and Dess-Martin periodinane (2 g, 4.72 mmol) were dissolved in absolute CH$_2$Cl$_2$ (40 mL) under N$_2$. To the reaction mixture was added TFA (710 μL) at 0 °C and the reaction
mixture was stirred for 12 h at room temperature. The organic solution was evaporated and the residue was purified by silica column chromatography (AcOEt/n-hexane 1:5) to yield 15 (811 mg, 94 %) as a white solid.

2,2,2-Trifluoro-1-(3-nitro-4-propoxyphenyl)ethan-1-one (16)

To a solution of 15 (136 mg, 0.59 mmol) in acetic anhydride (200 μL) was added dropwise 80% fuming HNO3 (144 μL) at 0 °C. After stirring for 40 minutes, the reaction mixture was poured into ice water (50 mL). The organic compound was extracted with ether (2 x 30 mL). The combined organic layer was washed with brine and dried over MgSO4, and then evaporated. The residue was purified by silica column chromatography (AcOEt/n-hexane 1:3) to yield 16 (136 mg, 84 %) as a yellow solid.

$\text{H NMR (500MHz, CDCl}_3\text{)}: \delta = 8.52 (s, 1H), 8.24 (d, J = 8.8 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 4.24 (t, J = 6.3 Hz, 2H), 1.96 - 1.89 (m, 2H), 1.10 (t, J = 7.3 Hz, 3H). \text{13C NMR (126MHz, CDCl}_3\text{)}: \delta = 177.7 (q, J_{\text{CF}} = 36.0 Hz), 157.5, 139.8, 135.6, 127.7, 121.7, 116.4 (q, J_{\text{CF}} = 290.6 Hz), 114.6, 72.0, 22.1, 10.2. HRMS (ESI) m/z [M + H]$ calcd for C11H11F3NO4 278.0640, found 278.0635.

2,2,2-Trifluoro-1-(3-nitro-4-propoxyphenyl)ethan-1-one oxime (17)

4-Trifluoroacetyl compound 16 (140 mg, 0.49 mmol) and hydroxylammonium chloride (101 mg, 1.47 mmol) were dissolved in pyridine (3 mL). The mixture was warmed to 80 °C and stirred for 3 h and excess pyridine was removed by vacuo. The residue was dissolved in ether (30 mL) and washed by 0.1 M HCl, brine and dried over MgSO4, and then evaporated. The residue was purified by silica column chromatography (CH2Cl2, then AcOEt/n-hexane 1:3) to yield 17 (130 mg, 91%, mixture of syn- and anti- isomers) as a white solid.

$\text{H NMR (500MHz, CDCl}_3\text{)}: \delta = 9.62 (s, 1H), 8.17 (s, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 4.16 (t, J = 6.3 Hz, 2H), 1.93 - 1.84 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H). \text{13C NMR (126MHz, CDCl}_3\text{)}: \delta = 154.0, 144.7 (q, J_{\text{CF}} = 32.7 Hz), 139.3, 134.7, 126.7, 120.4 (q, J_{\text{CF}} = 274.9 Hz), 117.3, 114.4, 71.4, 22.2, 10.2. HRMS (ESI) m/z [M + H]$ calcd for C11H12F3N2O4 293.0749, found 293.0745.

2,2,2-Trifluoro-1-(3-nitro-4-propoxyphenyl)ethan-1-one O-tosyl oxime (18)

4-Oxime compound 17 (225 mg, 0.91 mmol) was dissolved in acetone (7.5 mL) and cooled to 0 °C. Triethylamine (377 μL) and p-toluenesulfonyl chloride (196 mg, 1.0 mmol) were added to the reaction successively. The reaction mixture was stirred for 1 h at the same temperature, followed by concentrated. The crude product was purified by silica column chromatography (AcOEt/n-hexane 1:6) to yield 18 (378 mg, 93%, mixture of syn- and anti- isomers) as a white solid.

$\text{H NMR (500MHz, CDCl}_3\text{)}: \delta = 7.92 - 7.86 (m, 3H), 7.68 - 7.63 (m, 1H), 7.41 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.8 Hz, 0.5H), 7.14 (d, J = 8.8 Hz, 0.5H), 4.18 - 4.11 (m, 2H), 2.49 & 2.47 (s, 3H), 1.93 - 1.84 (m, 2H), 1.07 (m, 3H). \text{13C NMR (shown as complex data due to syn- and anti- isomers). HRMS (ESI) m/z [M + H]$ calcd for C18H18F3N2O6S 447.0838, found 447.0838.

3-(3-Nitro-4-propoxyphenyl)-3-(trifluoromethyl)diaziridine (19)

Tosyl oxime 18 (378 mg, 0.85 mmol) was dissolved in ether (6 mL). In shield tube, liquid ammonia (excess) was added at -78 °C and the ether solution was added. The reaction mixture was warmed to room temperature then stirred for 6 h at the same temperature. After excess ammonium gas was removed in draft chamber, the residual solution was concentrated. The crude residue was purified by silica column chromatography (AcOEt/n-hexane 1:2) to yield 19 (206 mg, 83%) as a white solid.
1H NMR (500MHz, CDCl3): δ = 8.09 (s, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 4.11 (t, J = 6.3 Hz, 2H), 2.87 (d, J = 8.8 Hz, 1H), 2.26 (d, J = 8.8 Hz, 1H), 1.92 - 1.83 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H). 13C NMR (126MHz, CDCl3): δ = 153.6, 133.5, 125.5, 124.3, 123.6, 123.2 (q, J_{CF} = 277.7 Hz), 114.7, 71.4, 56.9 (q, J_{CF} = 36.8 Hz), 22.2, 10.3. HRMS (ESI) m/z [M + H]^+ calcd for C_{11}H_{13}F_{3}N_{3}O_{3} 292.0909, found 292.0906.

3-(3-Nitro-4-propoxyphenyl)-3-(trifluoromethyl)-3H-diazirine (20)
Diaziridine 19 (23.1 mg, 79 μmol) was dissolved in chloroform (1 mL). Activated MnO2 (excess) was added to the reaction solution and the suspension was stirred for 30 minutes at room temperature, and then filtrated insoluble material. The filtrate was concentrated to yield 20 (22.3 mg, 97%) as yellow oil.
1H NMR (270MHz, CDCl3): δ = 7.67 (d, J = 2.3 Hz, 1H), 7.40 (d, J = 8.7 Hz, 1H), 7.10 (d, J = 8.7 Hz, 1H), 4.09 (t, J = 6.4 Hz, 2H), 1.94 - 1.79 (m, 2H), 1.06 (d, J = 7.4 Hz, 3H). 13C NMR (68MHz, CDCl3) δ = 153.7, 140.1, 132.4, 124.5, 122.0 (q, J_{CF} = 274.9 Hz), 121.1, 115.2, 71.6, 27.8 (q, J_{CF} = 41.3 Hz), 22.3, 10.4. HRMS (ESI) m/z [M + H]^+ calcd for C_{11}H_{11}F_{3}N_{3}O_{3} 290.0753, found 290.0755.

2-Propoxy-5-(3-(trifluoromethyl)diaziridin-3-yl)aniline (21)
To a solution of 19 (54.5 mg, 0.19 mmol) in THF (855 μL) and ethanol (723 μL) was added sodium dithionite (651 mg, 3.74 mmol) in H2O (2 mL) at 0 °C. The reaction was stirred at room temperature until the starting material disappeared. The organic compound was extracted with AcOEt, washed by brine and dried over MgSO4, and then evaporated. The crude product was purified by silica column chromatography (CH2Cl2) to yield 10 (34.4 mg, 70%) as a yellow solid.
1H NMR (500MHz, CDCl3): δ = 6.94 (d, J = 8.1 Hz, 1H), 6.93 (s, 1H), 6.76 (d, J = 8.1 Hz, 1H), 3.96 (t, J = 6.5 Hz, 2H), 3.90 (brs, 2H), 2.70 (d, J = 8.8 Hz, 1H), 2.17 (d, J = 8.8 Hz, 1H), 1.88 - 1.79 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H). 13C NMR (126MHz, CDCl3): δ = 147.8, 136.5, 123.9, 123.7 (q, J_{CF} = 279 Hz), 118.1, 114.0, 110.9, 69.8, 57.8 (q, J_{CF} = 35.9 Hz), 22.5, 10.5. HRMS (ESI) m/z [M + H]^+ calcd for C_{11}H_{15}F_{3}N_{3}O 262.1167, found 262.1166.
$^1$H-NMR

$^{13}$C-NMR
$^{1} \text{H-NMR}$

$^{13} \text{C-NMR}$
\[1^H\text{-NMR}\]

\[13^C\text{-NMR}\]
$^{1}H$-NMR

$^{13}C$-NMR
$^{1}H$-NMR

$^{13}C$-NMR
$^1$H-NMR

$^{13}$C-NMR
$^{1}H$-NMR

$^{13}C$-NMR
$^{1}H$-NMR

$^{13}C$-NMR
$\text{H-NMR}$

$\text{C-NMR}$
$^1$H-NMR

$^{13}$C-NMR
The results of activities of photoreactive compound (6), (10), (22) for hT1R2-hT1R3 by a cell-based assay.

Photoreactive 2-propoxyaniline (6) and (22) exhibited a similar activity as sucrose had at the same dose (15 mM). On the other hand, although increasing the concentration of photoreactive 2-propoxyaniline (10), it scarcely exhibited the sweetness activity.