Electronic Supplementary Material for Organic & Biomolecular Chemistry

Electronic Supplementary Information

Experimental Section

Synthesis

5-*tert*-Butyl-2-hydroxyisophthalic acid,[1] 2-hydroxyisophthalic acid,[2] 2-(benzyloxy)benzoic acid,[3] and 2,4-di-*tert*-butyl-6-aminophenol [4] were prepared by a reported method in the literature. Synthesis and structural analysis of **5–OH** and **5–O$^-$(NEt$_4^+$)** were reported in our paper. [5]

3,5,*N*-Tri-*tert*-butyl-2-hydroxybenzamide (**1–OH**)

3,5-Di-*tert*-butyl-2-hydroxybenzoic acid (1.19 g, 4.8 mmol) and HOBt (644 mg, 4.8 mmol) were dissolved in a mixture of THF (15 mL) and DMF (5 mL). To the solution were added *tert*-butylamine (0.50 mL, 4.8 mmol), triethylamine (0.50 mL, 3.6 mmol), and WSCD (0.90 mL, 4.9 mmol) at 0 °C. The solution was stirred overnight at room temperature and concentrated under reduced pressure. The residue was extracted with ethyl acetate and washed with 2% HCl *aq*. and sat. NaCl *aq*. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed in *vacuo*, and the recrystallization from MeOH/H_2O gave colorless crystals (0.96 g, 66%). mp: 148-150 °C. (Found: C, 74.55; H, 10.29; N, 4.59. Calc. for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23; N, 4.59%); δ_H(270 MHz; CD_3CN; Me_4Si) 13.18 (1H, s, OH), 7.45 (1H, d, *J* 2.2, Ar-H), 7.30 (1H, d, *J* 2.2, Ar-H), 6.80 (1H, s, NH), 1.45 (9H, s, *t*-Bu), 1.39 (9H, s, *t*-Bu), 1.30 (9H, s, *t*-Bu); m/z$^-$ (ESI); 304.3 (Calc. for M–H$^+$; 304.23).

2-Acetoxy-5-*tert*-butylisophthalic acid

5-*tert*-Butyl-2-hydroxyisophthalic acid (4.82 g, 20 mmol) was dissolved in THF (50 mL). To the solution was added acetyl chloride (1.6 mL, 23 mmol) followed by triethylamine (3.0 mL, 22 mmol) cooling in ice-water. The solution was stirred for 6 hours at room temperature. The white precipitate was filtered and the filtrate was concentrated to dryness. The residue was washed with water (5.47 g, 96%). The brown precipitate was collected with filtration and used without further purification. δ_H(400 MHz; DMSO-d_6; Me_4Si) 8.04 (2H, s, Ar-H), 2.19 (3H, s, CH_3), 1.31 (9H, s, *t*-Bu); m/z^- (ESI); 279.1 (Calc. for M–H^+; 279.09).

2,6-Bis(*tert*-butylcarbamoyl)-4-*tert*-butylphenyl acetate

2-Acetoxy-5-*tert*-butylisophthalic acid (5.47 g, 19.5 mmol) and triethylamine (5.5 mL, 40 mmol) were dissolved in THF (150 mL). The solution was cooled to –20 °C. To the solution was added isobutyl chloroformate (IBCF) (5.3 mL, 40 mmol) gradually keeping under –15 °C. After stirring for 5 min., *tert*-butylamine (5.0 mL, 48 mmol) was dropped into the reaction mixture under –15 °C. The reaction mixture was stirred for 1h at –15 °C and overnight at room temperature. The solvent was removed under reduced pressure, and the obtained residue was extracted with ethyl acetate and washed with 2% HCl *aq*., 4% $NaHCO_3$ *aq*., and sat. NaCl *aq*., respectively. The organic layer was dried over anhydrous sodium sulfate. After filtration, the solvent was removed under reduced pressure and the recrystallization from THF/*n*-hexane gave colorless crystals (1.82 g, 22%). δ_H(400 MHz; $CDCl_3$; Me_4Si) 7.65 (2H, s, Ar-H), 5.95 (1H, s, NH), 2.33 (3H, s, CH_3), 1.44 (18H, s, 2 × *t*-Bu), 1.34 (s, 9H); m/z^+ (ESI); 413.2 (Calc. for M+Na^+; 413.24).

5,*N,N'*-Tri-*tert*-butyl-2-hydroxyisophthalamide (**2–OH**)

2,6-Bis(*tert*-butylcarbamoyl)-4-*tert*-butylphenyl acetate (1.20 g, 3.1 mmol) was dissolved in methanol (10 mL). To the solution was added 1M NaOH *aq*. (4 mL). The solution was stirred overnight at room temperature and acidified by 2% HCl *aq*. The white precipitate was collected with filtration. The recrystallization from ethyl acetate/*n*-hexane gave colorless crystals (0.88 g, 80%).

(Found: C, 68.88; H, 9.21; N, 7.92. Calc. for $C_{20}H_{32}N_2O_3$: C, 68.93; H, 9.26; N, 8.04%); δ_H(400 MHz; CD_3CN; Me_4Si) 7.94 (2H, s, Ar-H), 7.81 (2H, s, NH), 1.44 (18H, s, 2 × *t*-Bu), 1.32 (9H, s, *t*-Bu); m/z$^-$ (ESI); 347.4 (Calc. for M–H$^+$; 347.23).

3,5,*N*-Tri-*tert*-butyl-4-hydroxybenzamide (**3–OH**)

3,5-Di-*tert*-butyl-4-hydroxybenzoic acid (1.18 g, 4.71 mmol), HOBt (0.64 g, 4.74 mmol) and *tert*-butylamine (0.5 mL, 4.76 mmol) were dissolved in THF (15 mL). To the mixture was added WSCD (0.9 mL, 4.9 mmol) at 0 °C. The mixture was stirred overnight at room temperature and concentrated. The residue was washed with water. The obtained white powder was reprecipitated from methanol/water and recrystallized from THF/*n*-hexane (0.28 g, 19%).

mp: 217-219 °C. (Found: C, 74.61; H, 10.20; N, 4.60. Calc. for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23; N, 4.59%); δ_H(400 MHz; CD_3CN; Me_4Si) 7.51 (2H, s, Ar-H), 6.41 (1H, s, NH), 5.75 (1H, s, OH), 1.42 (18H, s, 2 × *t*-Bu), 1.40 (9H, s, *t*-Bu); m/z$^-$ (ESI); 304.4 (Calc. for M–H$^+$; 304.23).

N-(3,5-Di-*tert*-butyl-2-hydroxyphenyl)pivalamide (**4–OH**)

2,4-Di-*tert*-butyl-6-aminophenol (207 mg, 0.94 mmol) was dissolved in dichloromethane (10 mL). To the solution was added pivaloyl chloride (0.1 mL, 0.81 mmol) in dichloromethane (0.9 mL)

followed by triethylamine (0.2 mL, 1.44 mmol). The solution was stirred for 4 hours at room temperature. The solution was washed with 2% HCl *aq*. and sat. NaCl *aq*., respectively. After the organic layer was dried over anhydrous magnesium sulfate, the removal of the solvent gave pale yellow powder (197 mg, 69 %).

(Found: C, 74.20; H, 10.23; N, 4.72. Calc. for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23; N, 4.59%); δ_H(270 MHz; CD_3CN; Me_4Si) 8.57 (1H, s, OH), 8.27 (1H, s, NH), 7.22 (1H, d, *J* 2.2, Ar-H), 7.00 (1H, d, *J* 2.2, Ar-H), 1.40 (9H, s, *t*-Bu), 1.31 (9H, s, *t*-Bu), 1.28 (9H, s, *t*-Bu); m/z$^-$ (ESI); 304.3 (Calc. for M–H$^+$; 304.23).

Tetraethylammonium 4,6-di-*tert*-butyl-2-(*tert*-butylamino)carbonylphenolate (**1–O$^-$(NEt$_4^+$)**)

3,5,*N*-Tri-*tert*-butyl-2-hydroxy-benzamide (135 mg, 0.44 mmol) and tetraethylammonium phenolate (91 mg, 0.41 mmol) were dissolved in a mixture of THF (10 mL) and acetonitrile (2.5 mL). After the solution was stirred for 1 hour, the solvent was removed by evaporation. The residue was washed with diethyl ether (3 × 5 mL) and recrystallized from acetonitrile/diethyl ether. Colorless needles were obtained.

δ_H(400 MHz; CD_3CN; Me_4Si) 13.21 (1H, s, NH), 7.63 (1H, d, *J* 3.2, Ar-H), 7.06 (1H, d, *J* 3.2, Ar-H), 3.14 (8H, q, *J* 7.3, 4 × CH_2), 1.370 (9H, s, *t*-Bu), 1.368 (9H, s, *t*-Bu), 1.22 (9H, s, *t*-Bu), 1.19 (12H, t, *J* 3.2, 4 × CH_3).

Tetraethylammonium 4-*tert*-butyl-2,6-bis-[(*tert*-butylamino)carbonyl]phenolate (**2–O$^-$(NEt$_4^+$)**)

5,*N*,*N*′-Tri-*tert*-butyl-2-hydroxyisophthalamide (96.5 mg, 0.25 mmol) was dissolved in a mixture of THF (10 mL) and ethanol (2 mL). To the solution was added 20% tetraethylammonium

hydroxide aqueous solution (0.2 mL). The reaction mixture was stirred overnight at room temperature and concentrated under reduced pressure to dryness. The residue was washed with diethyl ether (3 × 5 mL). The resultant powder was recrystallized from acetonitrile/diethyl ether. The colorless crystals were obtained.

δ_H(400 MHz; CD_3CN; Me_4Si) 11.92 (2H, s, NH), 7.97 (2H, s, Ar-H), 3.14 (8H, q, *J* 7.3, 4 × CH_2), 1.39 (18H, s, 2 × *t*-Bu), 1.24 (9H, s, *t*-Bu), 1.19 (12H, t, *J* 7.3, 4 × CH_3).

Tetraethylammonium 2,6-di-*tert*-butyl-4-(*tert*-butylamino)carbonylphenolate (**3–O$^-$(NEt$_4^+$)**)

3,5,*N*-Tri-*tert*-butyl-4-hydroxybenzamide (111 mg, 0.36 mmol) was dissolved in methanol (5 mL). To the solution was added 20% tetraethylammonium hydroxide aqueous solution (0.2 mL). After stirring for a few minutes, the solvent was removed by evaporation. The residue was washed with diethyl ether (3 × 5 mL) and recrystallized from acetonitrile/diethyl ether. Colorless needles were obtained.

δ_H(400 MHz; CD_3CN; Me_4Si) 7.19 (2H, s, Ar-H), 5.74 (1H, s, NH), 3.15 (8H, q, *J* 7.2, 4 × CH_2), 1.37 (9H, s, *t*-Bu), 1.34 (18H, s, 2 × *t*-Bu), 1.19 (12H, t, *J* 7.2, 4 × CH_3).

Tetraethylammonium 2,4-di-*tert*-butyl-6-pivaloylaminophenolate (**4–O$^-$(NEt$_4^+$)**)

This compound was synthesized similar procedure to **1–O$^-$(NEt$_4^+$)**.

δ_H(400 MHz; CD_3CN; Me_4Si) 10.15 (1H, s, NH), 7.98 (1H, d, *J* 2.8, Ar-H), 6.70 (1H, d, *J* 2.8, Ar-H), 3.14 (8H, q, *J* 7.2, 4 × CH_2), 1.36 (9H, s, *t*-Bu), 1.23 (18H, s, 2 × *t*-Bu), 1.19 (12H, t, *J* 7.2, 4 × CH_3).

N-*tert*-Butyl-2-(benzyloxy)benzamide

2-Benzyloxybenzoic acid (0.5 g, 2.2 mmol) was dissolved in THF (45 mL). To the solution was added triethylamine (0.31 mL, 2.2 mmol). The reaction mixture was cooled to –20 °C. To the mixture was added IBCF (0.30 mL, 2.2 mmol) gradually. After stirring for 10 min., *tert*-butylamine (0.23 mL, 2.2 mmol) in dichloromethane (20 mL) was added slowly. The reaction mixture was stirring for 30 min. at –15 °C and overnight at room temperature. The solvent was then removed. The residue was extracted with ethyl acetate and washed with 2% HCl *aq*., 4% $NaHCO_3$ *aq*., and sat. NaCl *aq*., respectively. The organic layer was dried over anhydrous sodium sulfate. The removal of the solvent gave colorless crystals (0.35 g, 56%). (Found: C, 75.97; H, 7.47; N, 4.90. Calc. for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94%); δ_H(400 MHz; $CDCl_3$; Me_4Si) 8.20 (1H, d, Ar-H), 7.80 (1H, s, NH), 7.3-7.5 (6H, m, Ar-H), 7.06 (2H, m, Ar-H), 5.10 (2H, s, CH_2), 1.20 (9H, s, *t*-Bu).

N-tert-Butyl-2-hydroxybenzamide (**1′–OH**)

N-tert-Butyl-2-(benzyloxy)benzamide (1.3 g, 6.7 mmol) was dissolved in isopropanol (90 mL). To the solution was added 15 % palladium charcoal (2.57 g). The reaction mixture was stirring for 5h under 3 atoms of hydrogen atmosphere. Palladium charcoal was then removed with filtration. The solvent was removed, and the residue was recrystallized from *n*-hexane (0.14 g, 10%).

(Found: C, 68.20; H, 7.82; N, 7.24. Calc. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25%); δ_H(400 MHz; $CDCl_3$; Me_4Si) 12.44 (1H, s, OH), 7.36 (1H, t, Ar-H), 7.24 (1H, d, Ar-H), 6.96 (1H, d, Ar-H), 6.81 (1H, t, Ar-H), 6.07 (1H, s, NH), 1.44 (9H, s, *t*-Bu); m/z^- (ESI); 192.3 (Calc. for M–H^+; 192.10).

Tetraethylammonium 2-(*tert*-butylamino)carbonylphenolate (**1′–O^-(NEt_4^+)**)

N-*tert*-Butyl-2-hydroxybenzamide (0.21 g, 1.1 mmol) was dissolved in ethanol (4 mL). To the solution was added 20 % aqueous solution of tetraethylammonium hydroxide (0.6 mL, 1.0 mmol) in ethanol (3 mL). After stirring for 5 min., the solvent was removed. The resultant white powder was recrystallized from THF/*n*-hexane. The colorless crystals were obtained. δ_H(400 MHz; CD_3CN; Me_4Si) 12.53 (1H, s, NH), 7.64 (1H, d, Ar-H), 6.86 (1H, t, Ar-H), 6.28 (1H, d, Ar-H), 6.01 (1H, t, Ar-H), 3.14 (8H, q, 4 × CH_2), 1.37 (9H, s, *t*-Bu), 1.19 (12H, t, 4 × CH_3).

2-Acetoxy-isophthalic acid

2-Hydroxyisophthalic acid (2.38 g, 2.66 mmol) was dissolved in THF (30 mL). To the solution was added acetic anhydride (10 mL, 106 mmol). The reaction mixture was refluxed for 3h, and additional 30 min. after addition of water (20 mL). The solvent was then removed. The resulting powder was washed with water (0.76 g, 26%). This product is used without further purification. δ_H(400 MHz; DMSO-d_6; Me_4Si) 8.08 (2H, d, Ar-H), 7.46 (1H, t, Ar-H), 2.22 (3H, s, CH_3).

N,N'-Di-*tert*-butyl-2-hydroxyisophthalamide (**2′–OH**)

2-Acetoxy-isophthalic acid (760 mg, 3.39 mmol) was dissolved in a mixture of DMF (50 mL) and THF (50 mL). To the solution was added triethylamine (1.0 mL, 7.2 mmol). The solution was cooled to –24 °C. To the solution was added IBCF (0.9 mL, 6.9 mmol). After stirring for 5 min., to the solution was added *tert*-butylamine (0.8 mL, 7.6 mmol) gradually. The mixture was stirred overnight at room temperature, and the solvent was removed. The precipitate was extracted with ethyl acetate and washed with 2%HCl *aq*., 4% $NaHCO_3$ *aq*., and sat. NaCl *aq*., respectively. After the organic layer was dried over anhydrous sodium sulfate, the removal of the solvent gave white

powder. The white powder was reprecipitated from ethyl acetate/*n*-hexane. The obtained powder (416 mg, 1.66 mmol) was dissolved in a small amount of ethanol. To the solution was added 0.1 M NaOH *aq*. (20 mL). The solution was stirred overnight at room temperature and filtered. The filtrate was concentrated and the solution was acidified by 2% HCl *aq*. The precipitated white powder was collected with filtration. The recrystallization from *n*-hexane gave colorless crystals (0.15 g, 41%). mp: 195-198 °C. (Found: C, 65.57; H, 8.26; N, 9.46. Calc. for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58%); δ_H(400 MHz; $CDCl_3$; Me_4Si) 14.5 (1H, s, OH), 7.86 (2H, d, Ar-H), 7.60 (2H, s, NH), 6.92 (1H, t, Ar-H), 1.48 (18H, s, 2 × *t*-Bu); m/z$^-$ (ESI); 291.4 (Calc. for M–H$^+$; 291.17).

Tetraethylammonium 2,6-bis-[(*tert*-butylamino)carbonyl]phenolate (**2′–O$^-$(NEt$_4^+$)**)

N,N′-Di-*tert*-butyl-2-hydroxyisophthalamide (0.21 g, 0.72 mmol) was dissolved in ethanol (4 mL). To the solution was added 10% methanol solution of tetraethylammonium hydroxide (0.6 mL, 0.7 mmol) in ethanol (3 mL). After stirring for 5 min., the solvent was removed. The precipitated white powder was recrystallized from acetonitrile/diethyl ether. The colorless crystals were obtained. δ_H(400 MHz; CD_3CN; Me_4Si) 11.80 (2H, s, NH), 7.87 (2H, d, Ar-H), 6.18 (1H, t, Ar-H), 3.14 (8H, q, 4 × CH_2), 1.39 (18H, s, 2 × *t*-Bu), 1.19 (12H, t, 4 × CH_3).

Tetramethylammonium 2,6-bis-[(*tert*-butylamino)carbonyl]phenolate (**2′–O$^-$(NMe$_4^+$)**)

This compound was synthesized in similar procedure to **2′–O$^-$(NEt$_4^+$)** using 10% methanol solution of tetramethylammonium hydroxide, and recrystallized from acetonitrile/ diethyl ether.

N-tert-Butyl-2-hydroxy-3-nitrobenzamide

3-Nitrosalicylic acid (5.00 g, 27.3 mmol) and HOBt (4.02 g, 29.8 mmol) were dissolved in THF (100 mL). To the solution was added *tert*-butylamine (3.0 mL, 28.5 mmol). After the solution was cooled to 0 ºC, DCC (5.66g, 27.4 mmol) was added to the solution. After stirring overnight, precipitated white crystals were filtered. The filtrate was concentrated and extracted with ether. The organic layer was washed with 2% HCl *aq*. and reextracted with 4% $NaHCO_3$ *aq*. The aqueous layer was acidified. The yellow crystals were obtained. (3.11 g, 47.8%) δ_H(400 MHz; DMSO-d_6; Me_4Si) 14.13 (1H, s, OH), 8.46 (1H, s, NH), 8.21 (1H, d, Ar-H), 8.05 (1H, d, Ar-H), 7.00 (1H, t, Ar-H), 1.41 (9H, s, *t*-Bu).

N-*tert*-Butyl-3-amino-2-hydroxybenzamide hydrochloride

N-*tert*-Butyl-2-hydroxy-3-nitrobenzamide (700 mg, 2.94 mmol) was dissolved in MeOH (15 mL). To the solution was added Pd-C (200 mg). The reaction mixture was stirred for 8h under hydrogen atmosphere. Pd-C was filtered. The solvent was removed. To the brown precipitate was added HCl saturated ethyl acetate. The crude product was obtained. (605 mg, 84 %) δ_H(400 MHz; DMSO-d_6; Me_4Si) 8.10 (1H, s, NH), 7.55 (1H, s, Ar-H), 7.20 (1H, d, Ar-H), 6.80 (1H, t, Ar-H), 1.40 (9H, s, *t*-Bu).

N-*tert*-Butyl-2-hydroxy-3-pivaloylaminobenzamide (**5′–OH**)

N-*tert*-Butyl-3-amino-2-hydroxybenzamide hydrochloride (711 mg, 2.9 mmol) was suspended in THF (30 mL). To the suspension was added NEt_3 (0.80 mL, 5.8 mmol) followed by pivaloyl chloride (0.31 mL, 2.5 mmol). The suspention was stirred overnight and concentrated. The precipitate was extracted with ethyl acetate and washed with 2% HCl *aq*. After the evaporation of

the solvent, the crude product was redissolved in MeOH. This solution was heated with norit 1. Norit 1 was filtered and the removal of the solvent gave yellow powder. The recrystallization from MeOH/H_2O gave colorless crystals. (214 mg, 25%) mp: 171-173 °C. (Found: C, 65.54; H, 8.30; N, 9.58. Calc. for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58%); δ_H(400 MHz; CD_3CN; Me_4Si) 13.36 (1H, s, OH), 8.32 (1H, dd, Ar-H), 8.18 (1H, s, NH), 7.33 (1H, dd, Ar-H), 6.88 (1H, s, NH), 6.83 (1H, t, Ar-H), 1.45 (9H, s, *t*-Bu), 1.28 (9H, s, *t*-Bu).

Physical Measurements

^{1}H NMR measurements were performed on a JEOL GSX 400 and JNM EX 270 spectrometers. ESI-MS measurements were performed on a Finnigan MAT LCQ ion trap mass spectrometer. Electrochemical measurements were carried out using a BAS 100W instrument in CH_3CN solution containing 0.1 M tetra-*n*-butylammonium perchlorate as a supporting electrolyte.

References

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