Supporting Information for:

TFA-Sensitive Arylsulfonylthiourea Assisted Synthesis of N,N'-Substituted Guanidines

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General

Commercially available reagents and common solvents (reagent grade or HPLC grade) for synthesis and separation were used without further purification as purchased unless otherwise noted. HPLC purification was performed using a variable wavelength detector with a C18 reverse-phase column (25 mm × 150 mm, 5 μm). ¹H-NMR spectra were recorded at 300 MHz, while mass spectra were obtained from an electrospray ion trap mass spectrometer.

Synthesis

(A) N-(4-bromobenzyl)-N'-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)thiourea (2). To a stirred solution of 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonamide (3.6 g, 13.3 mmol) in DMSO (200 ml), was added 13 ml of a 1 M solution of potassium *t*-butoxide in THF. After 15 min, a solution of pentafluorophenyl N-(4-bromobenzyl)thiocarbamate (5.0 g, 12 mmol) in THF was added dropwise into the reaction mixture. After stirring the reaction at room temperature for 20 min, the mixture was heated for 30 ~ 40 min at 50 ~ 60 °C. Then the reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic portion was dried over MgSO₄ and then evaporated. The residue was separated using silica gel chromatography with dichloromethane as eluent to give 4.2 g (70%) of **2** as a white solid. MS: 496.9 and 498.9 (M+H)⁺. ¹H-NMR (CDCl₃) δ 1.53 (6H, s), 2.13 (3H, s), 2.40 (3H, s), 2.54 (3H, s), 2.97 (2H, s), 4.70 (2H, d, *J* = 5.7 Hz), 6.89 (2H, d, *J* = 8.4 Hz), 7.39 (2H, d, *J* = 8.4 Hz), 8.11 (br, 2H).

(B) General procedure for solution synthesis of Pbf protected guanidines (3).

At room temperature, compound **2** and 2-chloro-1-methylpyridinium iodide (2 eq.) were dissolved in a mixture of THF (40 ml) and DMF (5 ml) in a 100 ml round bottom flask. To this stirred solution was added an amine nucleophile (5 eq.). The reaction was allowed to proceed overnight (12 – 18 hours). After removal of solvent under vacuum, the target compounds were purified by silica gel chromatography using a mixture of EtOAc and Hexane (1:4 v/v) as eluent.

N-cyclohexyl-N'-(4-bromobenzyl)-N''-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonyl)guanidine (3a) From 1 mmole of **2** and 5 mmole of cyclohexylamine, **3a** was obtained in 88% yield (0.50 g). MS: 562.1 and 564.1 (M+H)⁺. ¹H-NMR (CDCl₃) δ 1.20 (6H, m), 1.50 (6H, s), 1.85 (4H, m), 2.09(3H, s), 2.49(3H, s), 2.54 (3H, s), 2.95 (2H, s), 3.26 (1H, m), 4.32 (2H, br), 7.06(2H, d, *J* = 8.4 Hz), 7.38(2H, d, *J* = 8.4 Hz).

N-(tert-butyl)-N'-(4-bromobenzyl)-N''-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonyl)guanidine (3b). From 1 mmole of **2** and 5 mmole of *t*-butylamine, **3b** was obtained in 84% yield (0.45 g). MS: 536.1 and 538.1 (M+H)⁺. ¹H-NMR (CDCl₃) δ 1.23 (9H, s), 1.43 (6H, s), 2.08 (3H, s), 2.47 (3H, s), 2.53 (3H, s), 2.92 (2H, s), 4.32 (2H, s), 7.11 (2H, d, *J* = 8.4 Hz), 7.43 (2H, d, *J* = 8.4 Hz).

N,N-diethyl-N'-(4-bromobenzyl)-N''-(2,2,4,6,7-pentamethyl-2,3-dihydro-benzofuran-5-sulfonyl)guanidine (3c). From 1 mmole of **2** and 5 mmole of diethylamine, **3c** was obtained in 85% yield (0.46 g). MS: 536.1 and 538.2 (M+H)⁺. ¹H-NMR(CDCl₃) δ 1.11 (6H, t, *J* = 7.4 Hz), 1.48 (6H, s), 2.11 (3H, s), 2.43 (3H, s), 2.58 (3H, s), 2.95 (2H, s), 3.27 (4H, qt, *J* = 7.4 Hz), 4.27 (2H, d, *J* = 5.7 Hz), 6.95 (1H, br), 7.15 (2H, d, *J* = 8.4 Hz), 7.46 (2H, d, *J* = 8.4 Hz).

N,N-diisopropyl-N'-(4-bromobenzyl)-N''-(2,2,4,6,7-pentamethyl-2,3-dihydro-benzofuran-5-sulfonyl)guanidine (3d). From 0.06 mmole of **2** and 0.18 mmole of diisopropylamine, **3d** was obtained in 88% yield (30 mg). MS: 564.1 and 566.1 (M+H)⁺. ¹H-NMR (CDCl₃) δ 1.11 (12H, d, *J* = 6.6 Hz), 1.37 (6H, s), 2.00 (3H, s), 2.37 (3H, s), 2.48 (3H, s), 2.85 (2H, s), 3.62 (2H, m), 4.29 (2H, d, *J* = 5.7 Hz), 6.34 (1H, br), 7.15 (2H, d, *J* = 8.4 Hz), 7.40 (2H, d, *J* = 8.4 Hz).

(C) General procedures for solid-phase synthesis of N,N'-substituted guanidines (**7** and **9**).

Resin loading: Rink amide MBHA resin (~0.1 g, loading 0.78 mmole/g) was soaked in DMA for 30 minutes and then was deprotected with 20% piperidine in DMA for 30 minutes. After washing the resin thoroughly with DMA, solutions of 3-(N-Fmoc-aminomethyl)benzoic acid **4** (5 eq.) (or 3-(N-Fmoc-amino)benzoic acid **8** for the synthesis of **9**), PyBOP (5 eq.) and N,N-diisopropylethylamine (DIPEA, 10 eq.) in DMA were added to the resin. The reaction mixture was shaken gently overnight to produce resin-supported **5**. After washing, the resin loading was confirmed by the release of 9-methylene-9H-fluorene due to the Fmoc removal by 30 minutes treatment of 20% piperidine in DMA.

Reaction sequence 1: After Fmoc removal and washing, resin-supported **5** (~0.1 g) (or resin prepared from **8**) was suspended in DMA with 10 eq. of DIPEA. To this was added compound **2** (2.5 eq.) and the Mukaiyama reagent (2.5 eq.). The mixture was shaken gently overnight (12 – 18 hours). After washing, the resin was cleaved with a mixture of TFA:H₂O:TIS (94:3:3) for 1 hour. The crude product was extracted with water, filtered and purified by HPLC to give the final product.

N-(4-bromobenzyl)-N'-(3-aminocarbonylbenzyl)guanidine (7a). From 0.078 mmole of resin-supported **5**, **7a** was obtained in 82% yield as the TFA salt (30 mg). MS: 361.0 and 363.0 (M+H)⁺. ¹H NMR (CD₃OD) δ 4.46 (2H, s, CH₂), 4.55 (2H, s, CH₂), 7.31 (2H, d, *J* = 8.4 Hz), 7.62 (4H, m), 7.95 (2H, m).

N-(4-bromobenzyl)-N'-(3-aminocarbonylphenyl)guanidine (9a). From 0.078 mmole of resin prepared from **8**, **9a** was obtained in 78% yield as the TFA salt (28.0 mg). MS: 346.8 and 348.8 (M+H)⁺. ¹H NMR (D₂O) δ 4.31 (2H, s), 7.09 (2H, d, *J* = 7.5 Hz), 7.30 (1H, d, *J* = 7.5 Hz), 7.37-7.43 (3H, m), 7.48 (1H, s), 7.57 (1H, d, *J* = 6.3 Hz).

Reaction sequence 2: After Fmoc removal and washing, resin-supported **5** (~0.1 g) (or resin prepared from **8**) was suspended in 5 ml of methylene chloride. To this was added a

solution of pentafluorophenyl thiochloroformate (5 eq.) and DIPEA (10 eq.) in methylene chloride. The reaction was allowed to proceed for 1 hour at room temperature with gentle shaking. The resin was then thoroughly washed with methylene chloride followed by DMSO. Then a solution of PbfNH_2 (5 eq. to **5**) and potassium *t*-butoxide (1 eq. to PbfNH_2 from 1 M THF solution) in DMSO was added to the resin. The reaction was shaken for 1 hour at room temperature, and then washed thoroughly with DMSO followed by DMF. Subsequently, the resin was treated with a solution of an amine nucleophile (10 eq. to **5**), DIPEA (7 eq.) and EDC (5 eq.) in DMF for overnight at room temperature. After washing, the product was cleaved and purified as in "Reaction sequence 1".

N-(*tert*-butyl)-N'-(3-aminocarbonylbenzyl)guanidine (7b). From 0.081 mmole of resin-supported **5** and *t*-butylamine, **7b** was obtained in 77% yield as the TFA salt (23.2 mg). MS: 249.1 ($\text{M}+\text{H}$)⁺. ¹H NMR (D_2O) δ 1.19 (9H, s), 4.35 (2H, s), 7.36 (2H, m), 7.60 (2H, m).

N,N-diethyl-N'-(3-aminocarbonylbenzyl)guanidine (7c). From 0.094 mmole of resin-supported **5** and diethylamine, **7c** was obtained in 84% yield as the TFA salt (27.0 mg). MS: 249.1 ($\text{M}+\text{H}$)⁺. ¹H NMR (D_2O) δ 1.00 (6H, t, $J = 7.3$ Hz), 3.23 (4H, qt, $J = 7.1$ Hz), 4.36 (2H, s), 7.35 (2H, m), 7.55 (2H, m).

N,N-diisopropyl-N'-(3-aminocarbonylbenzyl)guanidine (7d). From 0.081 mmole of resin-supported **5** and diisopropylamine, **7d** was obtained in 76% yield as the TFA salt (23.0 mg). MS: 277.1 ($\text{M}+\text{H}$)⁺. ¹H NMR (D_2O) δ 1.15 (12H, d, $J = 6.9$ Hz), 3.82 (2H, m), 4.41 (2H, s), 7.36 (2H, m), 7.56 (2H, m).

N-phenyl-N'-(3-aminocarbonylbenzyl)guanidine (7e). From 0.089 mmole of resin-supported **5** and aniline, **7e** was obtained in 95% yield as the TFA salt (32.7 mg). MS: 269.1 ($\text{M}+\text{H}$)⁺. ¹H NMR (D_2O) δ 4.36 (2H, s), 7.42 (7H, m), 7.90 (2H, m).

N-(*tert*-butyl)-N'-(3-aminocarbonylphenyl)guanidine (9b). From 0.105 mmole of resin prepared from **8** and *t*-butylamine, **9b** was obtained in 88% yield as the TFA salt (32.0 mg). MS: 235.0 ($\text{M}+\text{H}$)⁺. ¹H NMR (D_2O) δ 1.22 (9H, s), 7.27 (1H, d, $J = 7.8$ Hz), 7.35 (1H, t, $J = 7.7$ Hz), 7.45 (1H, s), 7.52 (1H, d, $J = 7.8$ Hz).

N-phenyl-N'-(3-aminocarbonylphenyl)guanidine (9c). From 0.105 mmole of resin prepared from **8** and aniline, **9c** was obtained in 70% yield as the TFA salt (27.2 mg). MS: 255.0 ($\text{M}+\text{H}$)⁺. ¹H NMR (D_2O) δ 7.16 (3H, m), 7.27 (2H, m), 7.36 (2H, m), 7.53 (2H, m).

(D) An HPLC purification chromatogram (Figure S1) of crude **9a** obtained from aqueous extraction and filtration. MS analysis of this crude sample indicated absence of contamination due to by-products from TFA cleavage of Pbf.

Figure S1 HPLC chromatogram of crude **9a**.