

Chiral thioureido acid as an effective inductive additive for organocatalyzed enantioselective Michael additions of nitroolefins

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Supplementary Information

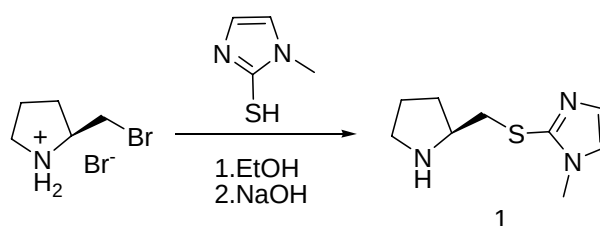
Table of Contents

1. General Methods.....	S2
2. Experimental procedures.....	S2-S3
3. NMR spectra.....	S3-S6

1. General Methods: All reactions were carried out directly under an atmosphere of air. ^1H NMR and ^{13}C NMR spectra were recorded on an AVANCE III 500 MHz spectrometer using deuterated DMSO as the solvent. Chemical shifts of ^1H and ^{13}C signals were given in δ relative to the signal of tetramethylsilane (TMS). GC-MS experiments were performed on a Agilent 6890N gas chromatograph with a 5973N mass selective detector. HPLC experiments were carried out using a JASCO LC-2000 Plus system consisting of MD and CD detectors.

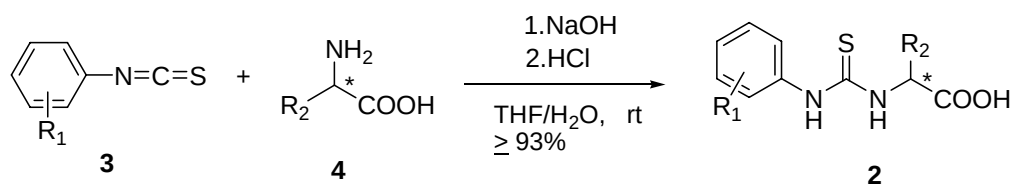
2. Experimental procedures

General procedure for the preparation of pyrrolidiny-thioimidazole 1:



Compound **1** was synthesized by adjusting its hydrobromide salt which was afforded in our previous work¹ in EtOH to pH 11-12 with NaOH.

General procedures for the preparation of thioureido acids 2a-j:

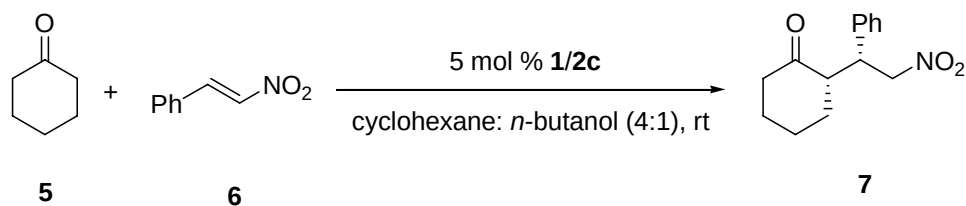


R_1 = 3,5-bis-trifluoromethyl;
 R_2 = H, Ph, PhCH_2

In a 100 mL three-necks flask, the isothiocyanates **3** (20 mmol), amino acids **4** (20 mmol), NaOH (22 mmol), water (20 mL) and THF (40 mL) were added and stirred at room temperature for 24 h. After completion of the reaction, the pH of the mixture was adjusted to pH 2-3 with aqueous 25% HCl, and then solvents were removed under vacuum. The remaining residue was recrystallized from absolute methanol to obtain the desired thioureido acids **2**.

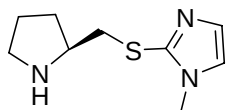
General procedures for the asymmetric Michael addition reactions:

¹ D. Xu, S. Luo, Y. Wang, A. Xia, H. Yue, L. Wang and Z. Xu, *Chem. Comm.*, 2007, 4393.

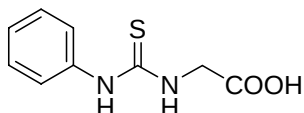


To a solution of the organocatalyst system **1/2c** (0.025 mmol) in cyclohexane (4 mL) and *n*-butanol (1 mL) at room temperature was added cyclohexanone (1 mmol) and nitroolefins (0.5 mmol). The reaction mixture was stirred at room temperature until completion and its progress was monitored by GC. Water (5 mL) was added to the reaction mixture and the organic layer was extracted with ethyl ether (3×5 mL). The combined extracts were concentrated under vacuum and the residue was purified by preparative TLC (hexane/CHCl₃ = 4/1) to give the Michael adducts.

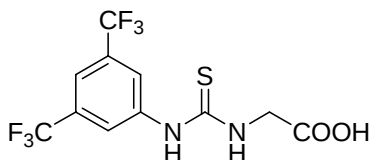
3. NMR Spectra



(S)-1-Methyl-2-(pyrrolidin-2-ylmethylthio)-1H-imidazole (1), 88% yield; ¹H NMR (500 MHz, CDCl₃): δ 1.45-1.50 (m, 1H), 1.73-1.84 (m, 2H), 1.92-1.97 (m, 1H), 2.90-2.94 (m, 1H), 2.98-3.00 (m, 1H), 3.06 (dd, *J* = 13 Hz, 7.5 Hz, 1H), 3.19 (dd, *J* = 13 Hz, 5 Hz, 1H), 3.31 (s, 1H), 3.37-3.41 (m, 1H), 3.62 (s, 3H), 6.92 (d, *J* = 1 Hz, 1H), 7.02 (d, *J* = 1 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃): 25.3, 30.8, 33.2, 39.7, 46.2, 57.9, 122.2, 129.0, 141.7. IR (film, cm⁻¹): 3418, 3107, 2953, 2748, 1631, 1461, 687. MS (ESI): *m/z* 197 [M]. HRMS: (+ESI) *m/z* calcd for C₉H₁₅N₃S 197.0897, found 197.0891.

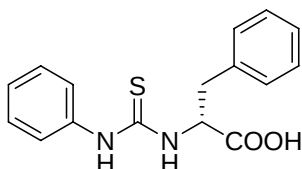


(3-Phenyl-thioureido) acetic acid (2a), 93% yield; m.p. 254.1-254.2 °C; ¹H NMR (500 MHz, DMSO-*d*₆): δ 4.29 (s, 2H), 7.27-7.29 (m, 2H), 7.41-7.44 (m, 1H), 7.47-7.50 (m, 2H), 10.39 (dr, 1H). ¹³C NMR (125 MHz, DMSO-*d*₆): 49.6, 129.0, 129.1, 129.3, 134.0, 172.7, 183.8. IR (film, cm⁻¹): 3153, 3002, 2948, 2914, 1764, 1523, 1403, 1275, 1197, 1153, 696. MS (EI⁺): 192 [M-18]⁺ (77), 191 (22), 163 (18), 135 (49), 77 (66), 51 (30), 32 (100).

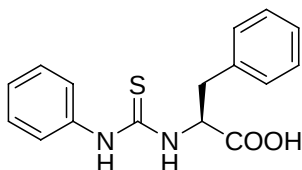


[3-(3,5-Bis-trifluoromethyl)phenyl-thioureido] acetic acid (2b), 94% yield; m.p.

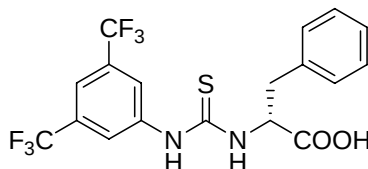
231.6-232.5 ; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 4.32 (s, 2H), 8.16 (s, 2H), 8.24 (s, 1H), 10.69 (dr, 1H). ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$): 49.9, 122.8 (t, $J = 3.8$ Hz), 123.4 (q, $J = 271.3$ Hz), 130.6, 131.0 (q, $J = 33.8$ Hz), 135.88, 172.2, 182.6. IR (film, cm^{-1}): 3186, 3025, 2955, 2848, 1768, 1533, 1288, 1187, 1126, 699. MS (EI^+): 328 $[\text{M}-18]^+$ (22), 271 (20), 231 (9), 72 (12), 69 (33), 32 (100).



(R)-3-Phenyl-2-(3'-phenyl-thioureido) propionic acid (2c), 95% yield; m.p. 184.3-184.6 ; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 3.12 (d, $J = 4.5$ Hz, 2H), 4.77 (dt, $J = 4.5$ Hz, 2.25 Hz, 1H), 6.77-6.79 (m, 2H), 7.20-7.22 (m, 2H), 7.29-7.32 (m, 3H), 7.35-7.39 (m, 3H), 10.62 (dr, 1H). ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$): 37.5, 60.9, 127.8, 128.2, 128.9, 129.1, 129.3, 129.6, 132.5, 134.0, 172.8, 183.7. IR (film, cm^{-1}): 3157, 3061, 2983, 2905, 1750, 1517, 1406, 1266, 1191, 734, 696, 622. MS (EI^+): 282 $[\text{M}-18]^+$ (30), 136 (16), 91 (100), 77 (28), 65 (17), 32 (96).

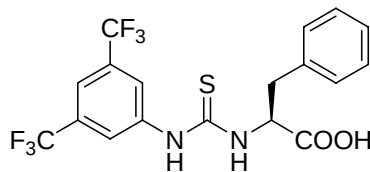


(S)-3-Phenyl-2-(3'-phenyl-thioureido) propionic acid (2d), 94% yield; m.p. 185.8-186.4 ; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 3.12 (d, $J = 4.5$ Hz, 2H), 4.77 (t, $J = 4.5$ Hz, 1H), 6.77-6.79 (m, 2H), 7.20-7.22 (m, 2H), 7.29-7.33 (m, 3H), 7.35-7.40 (m, 3H), 10.62 (dr, 1H). ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$): 37.5, 60.9, 127.8, 128.2, 128.9, 129.2, 129.3, 129.6, 132.5, 134.0, 172.8, 183.7. IR (film, cm^{-1}): 3158, 3061, 2983, 2902, 1752, 1517, 1406, 1271, 1190, 734, 692, 619. MS (EI^+): 282 $[\text{M}-18]^+$ (30), 136 (16), 91 (100), 77 (28), 65 (17), 32 (96).

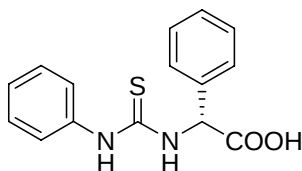


(R)-2-[3'-(3,5-Bis-trifluoromethyl) phenyl-thioureido]-3-phenyl propionic acid (2e), 94% yield; m.p. 170.5-171.1 ; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 3.12-3.20 (m, 2H), 4.82 (t, $J = 4.5$ Hz, 1H), 7.23-7.24 (m, 2H), 7.29-7.33 (m, 3H), 7.53 (s, 2H), 8.20 (s, 1H), 10.91 (dr, 1H). ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$): 36.4, 60.6, 122.6, 122.8 (q, $J = 271.3$ Hz), 127.1, 128.1, 129.2, 129.6, 130.7 (q, $J = 33.8$ Hz), 134.5, 134.9, 172.9, 181.0. IR (film, cm^{-1}): 3202, 3097, 2926, 2856, 1764, 1507, 1407, 1285, 1182, 1135, 694. MS (EI^+): 418 $[\text{M}-18]^+$ (17),

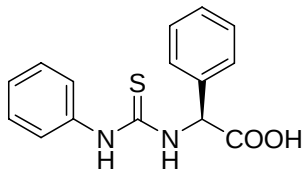
252 (6), 213 (5), 91 (100), 77 (5), 65 (14).



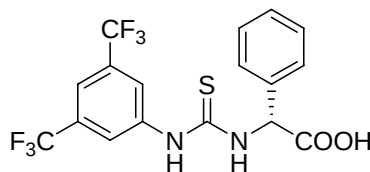
(S)-2-[3'-(3,5-Bis-trifluoromethyl) phenyl-thioureido]-3-phenyl propionic acid (2f), 93% yield; m.p. 168.1-168.7 ; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 3.13-3.21 (m, 2H), 4.82-4.83 (m, 1H), 7.23-7.25 (m, 2H), 7.29-7.34 (m, 3H), 7.54 (s, 2H), 8.20 (s, 1H), 10.91 (dr, 1H). ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$): 36.5, 60.6, 122.6, 122.8 (q, $J = 270.0$ Hz), 127.1, 128.1, 129.6, 129.8, 130.7 (q, $J = 33.8$ Hz), 134.5, 134.9, 172.9, 181.0. IR (film, cm^{-1}): 3203, 3097, 2926, 2856, 1763, 1507, 1407, 1285, 1183, 1135, 694. MS (EI^+): 418 $[\text{M}-18]^+$ (17), 252 (6), 213 (5), 91 (100), 77 (5), 65 (14).



(R)-Phenyl-(3'-phenyl-thioureido) acetic acid (2g), 95 % yield, m.p. 255.4-255.8 ; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 5.62 (d, $J = 1\text{Hz}$, 1H), 7.32-7.34 (m, 2H), 7.40-7.51 (m, 8H), 11.07 (dr, 1H). ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$): 63.2, 127.6, 129.2, 129.3, 129.4, 129.5, 133.8, 134.9, 173.2, 183.2. IR (film, cm^{-1}): 3162, 3063, 2973, 2895, 1763, 1509, 1400, 1250, 1182, 749, 702, 622. MS (EI^+): 268 $[\text{M}-18]^+$ (9), 135 (11), 104 (10), 77 (5), 51 (9), 32 (100).

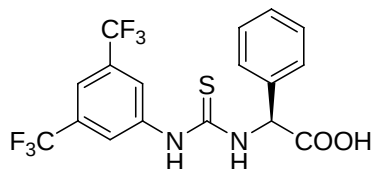


(S)-Phenyl-(3'-phenyl-thioureido) acetic acid (2h), 94% yield; m.p. 256.0-256.1 ; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 5.62 (d, $J = 1$ Hz, 1H), 7.32-7.34 (m, 2H), 7.40-7.51 (m, 8H), 11.07 (dr, 1H). ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$): 63.2, 127.6, 129.2, 129.3, 129.4, 129.5, 133.8, 134.9, 173.2, 183.2. IR (film, cm^{-1}): 3160, 3063, 2973, 2895, 1763, 1511, 1402, 1251, 1183, 749, 703, 696, 622. MS (EI^+): 268 $[\text{M}-18]^+$ (9), 135 (11), 104 (10), 77 (5), 51 (9), 32 (100).



(R)-[3'-(3,5-Bis-trifluoromethyl)phenyl-thioureido]-phenyl acetic acid (2i), 94% yield,

m.p. 210.9-211.2 ; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 5.60 (s, 1H), 7.42-7.53 (m, 5H), 8.26 (s, 1H), 8.29 (s, 2H), 11.27 (dr, 1H). ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$): 63.7, 123.0 (t, $J = 3.2$ Hz), 123.4 (q, $J = 271.0$ Hz), 128.2, 129.3, 129.4, 130.9 (d, $J = 2.8$ Hz), 131.1 (q, $J = 33.3$ Hz), 134.7, 135.8, 172.7, 182.1. IR (film, cm^{-1}): 3231, 3096, 2998, 2908, 1757, 1512, 1412, 1282, 1180, 1131, 699. MS (EI^+): 404 $[\text{M}-18]^+$ (87), 271 (30), 252 (23), 148 (29), 105 (65), 104 (100), 77 (44), 69 (69).



(R)-[3'-(3,5-Bis-trifluoromethyl)phenyl-thioureido]-phenyl acetic acid (2j), 93 % yield; m.p. 210.6-210.7 ; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 5.61 (s, 1H), 7.43-7.53 (m, 5H), 8.25 (s, 1H), 8.29 (s, 2H), 11.28 (dr, 1H). ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$): 63.7, 122.9 (t, $J = 3.4$ Hz), 123.4 (q, $J = 271.3$ Hz), 128.1, 129.2, 129.3, 130.8 (d, $J = 2.8$ Hz), 131.1 (q, $J = 33.8$ Hz), 134.3, 135.8, 172.7, 182.1. IR (film, cm^{-1}): 3169, 2999, 2929, 2860, 1771, 1522, 1410, 1286, 1182, 1131, 694. MS (EI^+): 404 $[\text{M}-18]^+$ (87), 271 (30), 252 (23), 148 (29), 105 (65), 104 (100), 77 (44), 69 (69).