Journal of the American Chemical Society

Supporting information to Accompany:

**The Reaction of Thioacids with Azides:
A New Mechanism and New Synthetic Applications**

Ning Shangguan, Sreenivas Katukojvala, Rachel Greenberg, Lawrence J Williams*

*Contribution from the Department of Chemistry and Chemical Biology, Rutgers, The State University of
New Jersey, Piscataway, New Jersey 08854, USA*

General: Starting materials, reagents and solvents were purchased from commercial suppliers (Aldrich, Bachem, Sigma, Advanced Chem Tech, Fischer) and used without further purification. All reactions were conducted in oven-dried (135 °C) glassware under an inert atmosphere of dry nitrogen. The progress of reactions was monitored by Silica gel thin layer chromatography (tlc) plates (mesh size 60Å with fluorescent indicator, Sigma-Aldrich), visualized under UV and charred using cerium or anisaldehyde stain. Products were purified by flash column chromatography (FCC) on 120-400 mesh silica gel (Fisher). Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared (**FTIR**) spectra were recorded on a ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (**¹H NMR**) were recorded on either a Varian-300 instrument (300 MHz), or a Varian-400 instrument (400 MHz). Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) as the internal standard. Data is reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), and coupling constants (Hz). Carbon nuclear magnetic resonance spectra (**¹³C NMR**) were recorded on either a Varian-300 instrument (75 MHz), or a Varian-400 instrument (100 MHz). Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) as the internal standard. Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer.

General Procedure for Preparation of Amides from azides

To a stirred solution of azide in methanol (or DCM/CHCl₃, water) was added 2,6-lutidine followed by drop wise addition of thioacid under inert atmosphere. The reaction mixture

was stirred and monitored by tlc. After completion of the reaction, the solvent was evaporated and the residue was dried under vacuum. The product was normally purified by a silica gel flash column chromatography (FCC), using ethyl acetate/acetone-hexane as the eluent.

Table 1, Entry **1a**¹:

The reaction was carried out following the general procedure, using 126 mg (0.689 mmol) of azide, 96 mg (0.897 mmol) of 2,6-lutidine and 124 mg (0.899 mmol) of thiobenzoic acid in methanol (conc. of azide 0.7 M) at rt for 15 min. FCC (silica gel, 33% ethyl acetate-hexane) gave 177 mg (98%) of **1a** as a white solid; mp: 148-149 °C (ref: 146-147 °C); IR $\nu_{\max}$ (neat) / cm^{-1} 3282, 3062, 1718; δ_{H} (300 MHz, Acetone- d_6) 11.10-10.90 (1H, bs, NH), 8.13 (2H, d, $J=6.9$ Hz, ArH), 7.93 (2H, d, $J=7.2$ Hz, ArH), 7.75-7.60 (4H, m, ArH), 7.50 (2H, t, $J=8.1$ Hz, ArH); δ_{C} (75 MHz, Acetone- d_6) 165.4, 140.4, 134.3, 133.8, 132.5, 129.5 (2), 129.3 (2), 128.9 (2), 128.8 (2); m/z (ESIMS) 262 ($\text{M}+1$)⁺.

Table 1, Entry **1b**²:

The reaction was carried out following the general procedure, using 124 mg (0.678 mmol) of azide, 94 mg (0.879 mmol) of 2,6-lutidine and 67 mg (0.882 mmol) of thioacetic acid in methanol (conc. of azide 0.7 M) at rt for 15 min. FCC (silica gel, 33% acetone-hexane) gave 130 mg (96%) of **1b** as a white solid; mp: 121-124 °C (ref: 124.5-126 °C); IR $\nu_{\max}$ (neat) / cm^{-1} 3121, 2902, 1688; δ_{H} (400 MHz, CDCl_3) 9.20-8.90 (1H, bs, NH), 8.07 (2H, d, $J=8.0$ Hz, ArH), 7.67 (1H, t, $J=7.2$ Hz, ArH), 7.57 (2H, t, $J=8.0$ Hz, ArH), 2.08 (3H, s, CH_3); δ_{C} (100 MHz, CDCl_3) 168.4, 138.4, 134.1, 129.1 (2), 128.3 (2), 23.5; m/z (ESIMS) 198 ($\text{M}-1$)⁻.

Table 1, Entry **2a**³:

The reaction was carried out following the general procedure, using 100 mg (0.565 mmol) of azide, 78 mg (0.730 mmol) of 2,6-lutidine and 101 mg (0.732 mmol) of thiobenzoic acid in DCM (conc. of azide, 0.94 M) at rt for 15 h. FCC (silica gel, 1:3 ethyl acetate-hexane) gave 142 mg (99%) of **2a** as a white solid. mp: 111-113 °C (ref: 112-114 °C); IR $\nu_{\max}$ (neat) / cm^{-1} 3296, 1763; δ_{H} (400 MHz, CDCl_3) 8.28 (1H, bs, NH), 7.81 (2H, d, $J=7.6$ Hz, ArH), 7.57 (1H, t, $J=7.2$ Hz, ArH), 7.46 (2H, t, $J=7.6$ Hz, ArH), 7.42-7.30

(5H, m, ArH), 5.24 (2H, s, CH₂); δ_c (100 MHz, CDCl₃) 164.9, 150.9, 135.0, 133.0 (2), 132.9, 128.9 (2), 128.71 (2), 128.69 (2), 127.6 (2), 68.0; m/z (ESIMS) 278 (M+Na)⁺.

Table 1, Entry **2b**⁴:

The reaction was carried out following the general procedure, using 51.6 mg (0.292 mmol) of azide, 41 mg (0.383 mmol) of 2,6-lutidine and 29 mg (0.382 mmol) of thioacetic acid in methanol (0.71 M conc. of azide) at room temperature for 15 h. FCC (silica gel, 30% ethyl acetate-hexane) gave 54.2 mg (96%) of **2b** as a white solid. mp: 104-105°C (ref: 104 °C); IR $\nu_{\max}$ (neat) / cm⁻¹ 3209, 3143, 2921, 1747, 1687; δ_H (400 MHz, CDCl₃) 7.70 (1H, bs, NH), 7.41-7.34 (5H, bs, ArH), 5.18 (2H, s, CH₂), 2.43 (3H, s, CH₃); δ_c (100 MHz, CDCl₃) 172.0, 151.8, 134.9, 128.8, 128.7 (2), 128.4 (2), 67.9, 24.0; m/z (ESIMS) 216 (M+23)⁺.

Table 1, Entry **3a**:

The reaction was carried out following the general procedure, using 40 mg (0.220 mmol) of azide, 30 mg (0.283 mmol) of 2,6-lutidine and 40 mg (0.288 mmol) of thiobenzoic acid in methanol (0.44 M conc. of azide) at rt for 15 h. The reaction mixture was concentrated to dryness and the crude product was washed with hexane and dried under vacuum to furnish 54 mg of **3a** (95%) as a yellow solid. mp: 174-177 °C; IR $\nu_{\max}$ (neat) / cm⁻¹ 3312, 1652, 1532; δ_H (300 MHz, Acetone-d₆) 9.96 (1H, bs, NH), 8.78 (1H, dd, J=6.9, 2.7 Hz, ArH), 8.25-8.19 (1H, m, ArH), 8.02-8.06 (2H, m, ArH), 7.47-7.67 (4H, m, ArH); δ_c (75 MHz, Acetone-d₆) 166.5 153.6, 150.1, 137.0, 135.2, 132.8 (2), 129.3 (2), 128.3 (2), 127.8, 119.2, 117.5; m/z (ESIMS) 259 (M-1)⁻.

Table 1, Entry **3b**⁵:

The reaction was carried out following the general procedure, using 33 mg (0.181 mmol) of azide, 25 mg (0.232 mmol) of 2,6-lutidine and 18 mg (0.238 mmol) of thioacetic acid in methanol (0.45 M conc. of azide) at rt for 15 h. The reaction mixture was concentrated to dryness and the crude product was washed with hexane and dried under vacuum to

furnish 34 mg (94%) of **3b** as a yellow solid. mp: 137-139 °C (ref 140-141 °C); IR $\nu_{\max}$ (neat) / cm^{-1} 3355, 1672, 1534; δ_{H} (300 MHz, Acetone- d_6) 9.60 (1H, bs, NH), 8.57 (1H, dd, $J=6.9, 2.7$ Hz, ArH), 7.94-7.88 (1H, m, ArH), 7.43 (1H, dd, $J=11.1, 9.0$ Hz, ArH), 2.13 (3H, s, CH_3); δ_{C} (75 MHz, Acetone- d_6) 168.8, 152.6, 149.2, 136.4, 126.1, 118.6, 115.7, 23.7; m/z (ESIMS) 140 ($\text{M}-1$) $^-$.

Table 1, Entry **4a**:

The reaction was carried out following the general procedure, using 88 mg (0.704 mmol) of azide, 97 mg (0.905 mmol) of 2,6-lutidine and 129 mg (0.933 mmol) of thiobenzoic acid in methanol (0.44 M conc. of azide) at rt for 2 h. The crude product was washed with dichloromethane and acetone to furnish 140 mg (98%) of **4a** as a white solid. mp: 242-244 °C (decompose); IR $\nu_{\max}$ (neat) / cm^{-1} 3287, 1711, 1607; δ_{H} (300 MHz, DMSO- d_6) 10.20 (1H, bs, NH), 6.87 (2H, bs, ArH), 6.56 (1H, bs, ArH), 6.47 (2H, bs, ArH), 4.83 (1H, bs, CH), 4.04 (2H, bs, CH_2); δ_{C} (100 MHz, DMSO- d_6) 173.8, 165.8, 161.0, 133.0, 132.4, 128.8 (2), 128.0 (2), 96.1, 69.3; m/z (ESIMS) 202 ($\text{M}-1$) $^-$.

Table 1, Entry **4b**:

The reaction was carried out following the general procedure, using 96 mg (0.768 mmol) of azide, 107 mg (1 mmol) of 2,6-lutidine and 76 mg (1 mmol) of thioacetic acid in methanol (0.48 M conc. of azide) at rt for 2 h. The crude product was washed with dichloromethane and hexane to furnish 103 mg (95%) of **4b** as a white solid. mp: 198-200 °C; IR $\nu_{\max}$ (neat) / cm^{-1} 3200, 3030, 1715; δ_{H} (400 MHz, Acetone- d_6) 10.20 (1H, bs, NH), 5.63 (1H, s, CH), 5.02 (2H, d, $J=1.2$ Hz, CH_2), 2.14 (3H, s, CH_3); δ_{C} (100 MHz, Acetone- d_6) 174.0, 169.8, 161.0, 95.8, 69.7, 23.6; m/z (ESIMS) 140 ($\text{M}-1$) $^-$.

Table 2, Entry **1a**⁶:

The reaction was carried out following the general procedure, using 100 mg (0.752 mmol) of azide, 104 mg (0.972 mmol, 1.3 eq) of 2,6-lutidine and 207 mg (1.501 mmol, 2.0 eq) of thiobenzoic acid in chloroform (conc. 0.75 M) at reflux for 15 h. FCC (silica gel, 20% acetone-hexane) gave 124 mg (78%) of **1a** as a white solid. mp: 104-105 °C (ref 105-107 °C); Spectral data of **1a** were identical with published data²; IR $\nu_{\max}$ (neat) / cm^{-1} 3321, 3080, 1641; δ_{H} (400 MHz, CDCl_3) 7.78 (2H, d, $J=7.6$ Hz, ArH), 7.51-7.24 (8H, series of m ArH), 6.60-6.52 (1H, bs, NH), 4.63 (2H, d, $J=4.8$ Hz, CH_2); δ_{C} (100 MHz,

CDCl_3) 167.4, 138.2, 134.4, 131.5, 128.8 (2), 128.6 (2), 127.9 (2), 127.6, 127.0 (2), 44.1; m/z (ESIMS) 234 ($\text{M}+\text{Na}$)⁺.

Table 2, Entry **1b**⁷:

The reaction was carried out following the general procedure, using 237 mg (1.78 mmol) of azide, 248 mg (2.32 mmol) of 2,6-lutidine and 177 mg (2.33 mmol) of thioacetic acid in chloroform (1 M conc. of azide) at reflux for 15 h. FCC (silica gel, 1:3 acetone-hexane) gave 230 mg (86%) of **1b** as a white solid. mp: 62-63 °C (ref 60-61 °C); IR ν_{max} (neat) / cm^{-1} 3292, 3087, 1639; δ_{H} (400 MHz, CDCl_3) 7.31-7.21 (5H, series of m, ArH), 6.70-6.62 (1H, bs, NH), 4.32 (2H, d, $J=5.6$ Hz, CH_2), 1.92 (3H, s, CH_3); δ_{C} (100 MHz, CDCl_3) 170.3, 138.4, 128.6 (2), 127.7 (2), 127.3, 43.5, 23.0; m/z (ESIMS) 172 ($\text{M}+\text{Na}$)⁺.

Table 2, Entry **2a**⁸:

The reaction was carried out following the general procedure, using 140 mg (0.848 mmol) of azide, 120 mg (1.12 mmol) of 2,6-lutidine and 152 mg (1.102 mmol) of thiobenzoic acid in chloroform (0.85 M conc. of azide) at reflux for 15 h. FCC (silica gel, 1:8 acetone-hexane) gave 159 mg (85%) of **2a** as a white solid. mp: 65-66 °C (ref 67 °C); IR ν_{max} (neat) / cm^{-1} 3302, 3057, 1642; δ_{H} (400 MHz, CDCl_3) 7.68 (2H, d, $J=7.6$ Hz, ArH), 7.50-7.46 (3H, m ArH), 7.41 (2H, t, $J=7.6$ Hz, ArH), 7.32 (2H, t, $J=7.2$ Hz, ArH), 7.26 (1H, t, $J=7.6$ Hz, ArH), 6.58-6.46 (1H, bs, NH), 4.89 (2H, d, $J=6.4$ Hz, CH_2); δ_{C} (100 MHz, CDCl_3) 167.1, 133.9, 133.7, 131.8, 131.4 (2), 129.3 (2), 127.6 (2), 127.5, 126.9 (2), 44.3; m/z (ESIMS) 266 ($\text{M}+\text{Na}$)⁺.

Table 2, Entry **2b**⁸:

The reaction was carried out following the general procedure, using 157 mg (0.952 mmol) of azide, 133 mg (1.245 mmol) of 2,6-lutidine and 94 mg (1.237 mmol) of thioacetic acid in chloroform (0.95 M conc. of azide) at reflux for 15 h. FCC (silica gel, 1:3 acetone-hexane) gave 146 mg (85%) of **2b** as a white solid. mp: 46-47 °C (ref: 45 °C); IR ν_{max} (neat) / cm^{-1} 3279, 3057, 1657; δ_{H} (400 MHz, CDCl_3) 7.40 (2H, d, $J=7.6$ Hz, ArH), 7.29 (2H, t, $J=6.8$ Hz, ArH), 7.23 (1H, t, $J=7.6$ Hz, ArH), 6.71 (1H, bs, NH), 4.63 (2H, d, $J=6.0$ Hz, CH_2), 1.91 (3H, s, CH_3); δ_{C} (100 MHz, CDCl_3) 170.5, 134.4, 131.0 (2), 129.3 (2), 127.3, 44.0, 23.5; m/z (ESIMS) 204 ($\text{M}+\text{Na}$)⁺.

Table 2, Entry **3a**⁹:

The reaction was carried out following the general procedure, using 50 mg (0.344 mmol) of azide, 55 mg (0.516 mmol) of 2,6-lutidine and 71 mg (0.516 mmol) of thiobenzoic acid in chloroform (conc. 1 M) at reflux for 10 h. FCC (silica gel, 20% ethyl acetate-hexane) gave **3a** as a highly viscous liquid (51 mg, 66%). IR $\nu_{\max}$ (neat) / cm^{-1} 3262, 3297, 3053, 1657, 1636; δ_{H} (400 MHz, Acetone- d_6) 9.80-9.98 (1H, bs, NH), 8.01 (2H, d, $J=7.2$ Hz, ArH), 7.79 (1H, dd, $J^1=14.8$ Hz, $J^2=10.2$ Hz, PhCH=CH), 7.59 (1H, t, $J=7.2$ Hz, ArH), 7.51 (2H, dd, $J^1=8.0$ Hz, $J^2=6.8$ Hz, ArH), 7.40 (2H, d, $J=7.6$ Hz, ArH), 7.31 (2H, dd, $J^1=8.0$ Hz, $J^2=7.2$ Hz, ArH), 7.17 (1H, t, $J=7.2$, ArH), 6.46 (1H, d, $J=14.8$ Hz, PhCH=CH); δ_{C} (75 MHz, Acetone- d_6) 164.7, 137.6, 134.5, 132.4, 129.3 (2), 129.1 (2), 128.1 (2), 126.9 (2), 126.0, 124.6, 113.5; m/z (ESIMS) 222 (M-1)⁺.

Table 2, Entry **3b**¹⁰:

The reaction was carried out following the general procedure, using 50 mg (0.344 mmol) of azide, 85 mg (0.791 mmol) of 2,6-lutidine and 60 mg (0.791 mmol) of thioacetic acid in chloroform (conc. 0.78 M) at reflux for 18 h. FCC (silica gel, 30% ethyl acetate-hexane) gave **3b** as a white solid (44 mg, 79%). IR $\nu_{\max}$ (neat) / cm^{-1} 3262, 3191, 3054, 1660, 1639; δ_{H} (400 MHz, CDCl_3) 7.53 (1H, dd, $J^1=14.8$ Hz, $J^2=10.8$ Hz, PhCH=CH), 7.14-7.40 (6H, series of m, NH, ArH), 6.08 (1H, d, $J=14.4$ Hz, PhCH=CH), 2.11 (3H, s, CH_3); δ_{C} (75 MHz, CDCl_3) 167.1, 135.8, 128.4 (2), 126.4, 125.3 (2), 122.5, 112.2, 23.3. m/z (ESIMS) 160 (M-1)⁺.

Table 2, Entry **4a**:

The reaction was carried out following the general procedure, using 22 mg (0.067 mmol) of azide (70:30 diastereomeric mixture), 9.3 mg (0.087 mmol) of 2,6-lutidine and 12 mg (0.087 mmol) of thiobenzoic acid in chloroform (conc. 0.33 M) at room temperature for 30 h. FCC (silica gel, 15% ethyl acetate-hexane) gave **4a** (70:30 diastereomeric mixture) as a clear viscous liquid (26 mg, 94%). When the reaction was carried with 55:45 diastereomeric mixture of azide, the corresponding amides were obtained in the same 55:45 ratio. Thus, the epimerization of the stereocenter was not observed under the reaction conditions. Spectral data for the major diastereomer: IR $\nu_{\max}$ (neat) / cm^{-1} 3346, 3061, 2954, 1714, 1640; δ_{H} (300 MHz, CDCl_3) 7.79 (2H, d, $J=5.7$ Hz, ArH), 7.51 (1H, t,

$J=5.4$ Hz, ArH), 7.44 (2H, t, $J=5.7$ Hz, ArH), 6.99 (1H, d, $J=6.3$ Hz, NH), 5.47 (1H, t, $J=6.6$ Hz, CHNH), 3.96 (1H, d, $J=7.2$ Hz, CH_2OTBDMS), 3.69 (1H, s, OH), 3.47 (1H, d, $J=7.2$ Hz, CH_2OTBDMS), 1.86-1.72 (2H, m, CH_2^iPr), 1.48-1.40 (1H, m, $\text{CH}(\text{CH}_3)_2$), 1.33 (3H, s, CH_3), 1.07 (3H, d, $J=4.5$ Hz, CH_3), 0.95 (3H, d, $J=4.8$ Hz, CH_3), 0.84 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.04 (3H, s, CH_3), 0.02 (3H, s, CH_3); δ_{C} (75 MHz, CDCl_3) 214.0, 166.4, 134.0, 131.4, 128.3 (2 C), 126.8 (2 C), 80.0, 69.0, 53.2, 41.2, 25.7 (3 C), 25.1, 23.5, 21.9, 21.5, 18.1, -5.52, -5.54; m/z (ESIMS) 379 (M^+).

Table 2, Entry **4b**:

The reaction was carried out following the general procedure, using 13 mg (0.039 mmol) of azide (70:30 diastereomeric mixture), 5.5 mg (0.051 mmol) of 2,6-lutidine and 3.9 mg (0.051 mmol) of thioacetic acid in chloroform (conc. 0.18 M) at reflux for 24 h. FCC (silica gel, 30% ethyl acetate-hexane) gave **4b** (70:30 diastereomeric mixture) as a clear viscous liquid (12 mg, 88%). Spectral data for the major diastereomer: IR ν_{max} (neat) / cm^{-1} 3300, 2956, 1719, 1650; δ_{H} (400 MHz, CDCl_3) 5.95 (1H, d, $J=8.8$ Hz, NH), 5.26 (1H, t, $J=10.0$ Hz, CHNH), 3.91 (1H, d, $J=10.0$ Hz, CH_2OTBDMS), 3.68 (1H, s, OH), 3.45 (1H, d, $J=9.2$ Hz, CH_2OTBDMS), 1.99 (3H, s, CH_3), 1.76-1.66 (3H, m, CH_2^iPr , $\text{CH}(\text{CH}_3)_2$), 1.29 (3H, s, CH_3), 1.01 (3H, d, $J=4.0$ Hz, CH_3), 0.92 (3H, d, $J=4.4$ Hz, CH_3), 0.86 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.05 (3H, s, CH_3), 0.04 (3H, s, CH_3); δ_{C} (75 MHz, CDCl_3) 214.0, 169.1, 79.9, 68.8, 52.5, 40.9, 25.7 (3 C), 25.0, 23.5, 23.2, 21.9, 21.5, 18.2, -5.48, -5.50; m/z (ESIMS) 318 ($\text{M}+1$)⁺.

Table 2, Entry **5a**¹¹:

The reaction was carried out following the general procedure, using 144 mg (0.232 mmol) of azide (all β), 61 mg (0.570 mmol) of 2,6-lutidine and 77 mg (0.558 mmol) of thiobenzoic acid in chloroform (0.26 M conc. of azide) at reflux for 36h. FCC (silica gel, 1:3.5 acetone-hexane) gave 46 mg of starting material azide (all β) and 104 mg (95%, based on recovery of starting material) of **5a** (all β) as a white foam. IR ν_{max} (neat) / cm^{-1} 3350, 3065, 2953, 1727, 1669; δ_{H} (300 MHz, CDCl_3) 8.10-7.20 (26H, series of m, ArH), 6.14 (1H, t, $J=9.6$ Hz, O-CH-N), 5.83 (1H, t, $J=8.7$ Hz, CH-O), 5.81 (1H, t, $J=9.9$ Hz, CH-O), 5.56 (1H, t, $J=9.6$ Hz, CH-O), 4.66 (1H, dd, $J^1=12.3$ Hz, $J^2=2.4$ Hz, O- CH_2), 4.51 (1H, dd, $J^1=12.0$ Hz, $J^2=3.9$ Hz, O- CH_2), 4.40-4.36 (1H, m, CH-O); δ_{C} (75 MHz, CDCl_3) 167.42, 167.40, 166.3, 165.8, 165.3, 134.1, 133.7, 133.5, 133.3, 132.5, 130.2, 130.0, 129.9, 128.9, 128.8, 128.6, 128.5, 127.4, 79.7, 74.3, 73.2, 72.1, 69.5, 63.1.

Table 2, Entry **5b**¹²:

The reaction was carried out following the general procedure, using 116 mg (0.186 mmol) of azide (all β), 52 mg (0.486 mmol) of 2,6-lutidine and 37 mg (0.487 mmol) of thioacetic acid in chloroform (0.31 M conc. of azide) at reflux for 36h. FCC (silica gel, 27% acetone-hexane) gave 115 mg (97%) of **5b** (all β) as a white foam. IR $\nu_{\max}$ (neat) / cm^{-1} 3356, 3065, 2952, 1728; δ_{H} (300 MHz, CDCl_3) 8.04 (2H, d, $J=5.7$ Hz), 7.96 (2H, d, $J=5.7$ Hz), 7.91 (2H, d, $J=5.7$ Hz), 7.85 (2H, d, $J=5.7$ Hz), 7.52-7.26 (10H, series of m), 7.20 (2H, t, $J=5.7$ Hz), 6.97 (1H, d, $J=6.9$ Hz), 6.10 (1H, t, $J=7.5$ Hz, CHOBz), 5.80 (1H, t, $J=7.2$ Hz, CHOBz), 5.73 (1H, t, $J=6.9$ Hz, CHOBz), 5.52 (1H, t, $J=7.2$ Hz, CHOBz), 4.67 (1H, dd, $J^1=9.0$ Hz, $J^2=1.5$ Hz, CH_2OBZ), 4.52 (1H, dd, $J^1=9.3$ Hz, $J^2=3.6$ Hz, CH_2OBZ), 4.37-4.34 (1H, m, CHOBZ), 1.90 (3H, s, CH_3); δ_{C} (75 MHz, CDCl_3) 170.1, 166.5, 165.9, 165.3, 164.9, 133.6, 133.3, 133.1, 132.9, 129.8, 129.6, 129.58, 129.5, 128.3, 128.2, 128.1, 78.6, 73.8, 72.9, 71.5, 69.1, 62.8, 23.3.

Table 3, Entry **1a**¹³:

The reaction was carried out following the general procedure, using 38 mg (0.185 mmol) of azide (all β), 62 mg (0.739 mmol) of sodium bicarbonate and 67 mg (0.486 mmol) of thiobenzoic acid (0.19 M conc. of azide) at 60°C for 36 h. FCC (silica gel, 1:9 methanol-ethyl acetate) gave 43 mg (83%) of **1a** (all β) as a glassy material. IR $\nu_{\max}$ (neat) / cm^{-1} 3330, 3079, 2921, 1650, 1539; δ_{H} (300 MHz, CD_3OD) 7.91 (2H, t, $J=7.5$ Hz, ArH), 7.56 (1H, t, $J=7.2$ Hz, ArH), 7.47 (2H, t, $J=7.8$ Hz, ArH), 5.16 (1H, d, $J=8.1$ Hz), 4.87 (3H, s), 3.87 (1H, d, $J=11.1$ Hz), 3.70 (2H, dd, $J^1=11.7$ Hz, $J^2=4.8$ Hz, CH_2OH), 3.56-3.36 (4H, m), 2.65 (1H, s); δ_{C} (75 MHz, CD_3OD) 169.7, 134.0, 131.9, 128.3 (2 C), 127.5 (2 C), 80.6, 78.6, 77.9, 72.6, 70.3, 61.6.

Table 3, Entry **1b**¹⁴:

The reaction was carried out following the general procedure, using 38 mg (0.185 mmol) of azide (all β), 62 mg (0.739 mmol) sodium bicarbonate and 36 mg (0.474) mmol of thioacetic acid (0.19 M conc. of azide) at 60°C for 36 h. FCC (silica gel, 1:9 methanol-acetone) gave 33 mg (80%) of **1b** (all β) as a glassy material. IR $\nu_{\max}$ (neat) / cm^{-1} 3334, 2925, 1658; δ_{H} (400 MHz, CD_3OD) 4.94 (5H, s, OH, NH), 3.82 (1H, dd, $J^1=12.0$ Hz, $J^2=1.6$ Hz, CHOH), 3.64 (2H, dd, $J^1=12.0$ Hz, $J^2=5.2$ Hz, CH_2OH), 3.40 (1H, t, $J=8.8$

Hz, CHOH), 3.36-3.22 (3H, series of m), 1.99 (3H, s, CH₃); δ_c (75 MHz, CD₃OD) 173.1, 79.8, 78.4, 77.8, 72.8, 70.3, 61.6, 21.8.

Table 3, Entry **2a**:

The reaction was carried out following the general procedure, using 7.7 mg (0.029 mmol) of azide, 0.7 ml of pH 7.40 buffer solution (potassium phosphate monobasic sodium hydroxide buffer, 0.05 M) and 20 mg (0.145 mmol) of thiobenzoic acid (0.04 M conc. of azide) 60 °C for 36 h. FCC (silica gel, ethyl acetate) gave 6.7 mg (68%) of **2a** as a white solid. IR $\nu_{\max}$ (neat) / cm⁻¹ 3488, 3279, 3152, 1714, 1663, 1624; δ_H (300 MHz, CD₃OD) 7.93 (1H, bs, NH), 7.83 (2H, dd, $J^1=7.2$ Hz, $J^2=1.2$ Hz, ArH), 7.55 (1H, t, $J=7.2$ Hz, ArH), 7.46 (2H, t, $J=7.5$ Hz, ArH), 6.30 (1H, t, $J=6.0$ Hz), 4.88 (bs, 3H), 4.73 (1H, q, $J=6.9$ Hz), 4.05-3.99 (1H, m), 3.90 (1H, dd, $J^1=12.0$ Hz, $J^2=2.7$ Hz, CH₂OH), 3.79 (1H, dd, $J^1=12.0$ Hz, $J^2=3.6$ Hz, CH₂OH), 2.44 (2H, t, $J=6.6$ Hz, CH₂), 1.91 (3H, s, CH₃); δ_c (75 MHz, CD₃OD) 166.8, 164.3, 151.0, 136.9, 134.6, 132.0, 128.9 (2 C), 128.0 (2 C), 110.1, 85.7, 84.3, 62.2, 50.4, 37.8, 13.2; m/z (ESIMS) 368 (M+Na)⁺.

Table 3, Entry **2b**¹⁵:

The reaction was carried out following the general procedure, using 8.7 mg (0.033 mmol) of azide, 0.5 ml of pH 7.40 buffer solution (potassium phosphate monobasic sodium hydroxide buffer, 0.05 M) and 7.5 mg (0.099 mmol) of thioacetic acid (0.065M conc. of azide) at 60°C for 36 h. FCC (silica gel, 1:9 methanol-ethyl acetate) gave 7.1 mg (77%) of **2b** as a white solid. IR $\nu_{\max}$ (neat) / cm⁻¹ 3488, 3338, 3266, 2955, 1685; δ_H (400 MHz, Acetone-d₆) 7.88 (1H, bs, NH), 7.72 (1H, d, $J=5.2$ Hz, NHCO), 6.21 (1H, t, $J=6.0$ Hz), 4.50 (1H, p, $J=6.8$ Hz), 3.88-3.84 (1H, m), 3.82 (1H, dd, $J^1=14.8$ Hz, $J^2=2.4$ Hz, CH₂OH), 3.75 (1H, dd, $J^1=12.0$ Hz, $J^2=3.2$ Hz, CH₂OH), 3.00-2.81 (2H, bs), 2.43-2.28 (2H, m), 1.92 (3H, s, CH₃), 1.83 (3H, s, CH₃); δ_c (75 MHz, CD₃OD) 171.3, 164.8, 151.7, 137.3, 111.0, 86.8, 85.0, 62.9, 50.6, 38.6, 23.3, 13.0; m/z (ESIMS) 306 (M+Na)⁺.

Table 3, Entry **3a**:

The reaction was carried out following the general procedure, using 45 mg (0.198 mmol) of azide, 37 mg (0.346 mmol) of 2,6-lutidine and 35 mg (0.254 mmol) of thiobenzoic acid (0.25 M conc. of azide) at rt for 1 h. FCC (silica gel, 38:60:2 ethyl acetate-hexane-acetic acid) gave 56 mg (93%) of **3a** as a white solid. mp: 253-254 °C. IR ν_{max} (neat) / cm^{-1} 3614, 3520, 1688; δ_{H} (400 MHz, Acetone- d_6) 8.26 (4H, s, ArH), 7.94 (2H, d, $J=10.8$ Hz, ArH), 7.64 (1H, t, $J=9.2$ Hz, ArH), 7.51 (2H, t, $J=10.0$ Hz, ArH); δ_{C} (100 MHz, Acetone- d_6) 166.3, 165.9, 144.5, 136.0, 134.2, 132.7, 130.9 (2), 129.6 (2), 129.4 (2), 129.1 (2); m/z (ESIMS) 304 (M-1) $^-$.

Table 3, Entry **3b**:

The reaction was carried out following the general procedure, using 44 mg (0.194 mmol) of azide, 37 mg (0.346 mmol) of 2,6-lutidine and 19 mg (0.250 mmol) of thioacetic acid (0.24 M conc. of azide) at rt for 1 h. Removal of solvent followed by washing the residue with hexane and drying under vacuum gave 46 mg (98%) of **3b** as a white solid. mp: 250 °C. IR ν_{max} (neat) / cm^{-1} 3541, 1692; δ_{H} (400 MHz, Acetone- d_6) 11.40-10.40 (1H, bs, NH), 8.24 (2H, d, $J=8.4$ Hz, ArH), 8.14 (2H, d, $J=8.4$ Hz, ArH), 2.04 (3H, s, CH_3); δ_{C} (75 MHz, Acetone- d_6) 168.7, 166.0, 144.1, 135.6, 130.6 (2), 128.9 (2), 23.5; m/z (ESMS) 242 (M-1) $^-$.

General procedure for the preparation of amides **9a-e**

Entry	8	R	Azide	9	Yield (two steps)
1	a	<i>i</i> Bu	N ₃ -Bs	9a <i>N</i> -Ac-Leu-NH-Bs	91%
2	b	(<i>R</i>)- <i>sec</i> -Bu	N ₃ -Ts	9b <i>N</i> -Ac- <i>alle</i> -NH-Ts	87%
3	c	(<i>S</i>)- <i>sec</i> -Bu	N ₃ -Ts	9c <i>N</i> -Ac- <i>lle</i> -NH-Ts	72%
4	b	(<i>R</i>)- <i>sec</i> -Bu	N ₃ -Dansyl	9d <i>N</i> -Ac- <i>alle</i> -NH-Dansyl	73%
5	a	<i>i</i> Bu	N ₃ -Dansyl	9e <i>N</i> -Ac-Leu-NH-Dansyl	73%

The thioesters **8a-c** were prepared from 2,4,6-trimethoxybenzyl thiol¹⁶ and the corresponding N-protected amino acid.¹⁷ **8a** was prepared from N-acetyl-Leu-OH (Sigma). **8b** and **8c** were prepared from Fmoc-*allo*-Ile-OH (BACHEM) and Fmoc-Ile-OH (Advanced Chem Tech), respectively, in three steps: thioesterification via DCC coupling,¹⁷ Fmoc removal, and acetylation. ¹H and ¹³C NMR indicate commercial Fmoc-*allo*-Ile-OH was diastereomerically pure (>95%), whereas Fmoc-Ile-OH was a diastereomeric mixture of Fmoc-Ile-OH and Fmoc-*allo*-Ile-OH (approximately 75:25). Importantly, conversion of these starting materials to **8b** and **8c** took place without measurable epimerization. [Hence, **8b** was obtained diastereomerically pure (>95%) and **8c** was obtained as a chromatographically inseparable 75:25 mixture of diastereomers, as determined by ¹H and ¹³C NMR.]

Procedure for 9a-e: To a mixture of thioester **8a-c** and triethylsilane at 0°C was added trifluoroacetic acid-DCM (40-80%v/v) drop-wise and stirred under inert atmosphere at rt. After the completion of the reaction (1-3h), solvent was evaporated and the residue was azeotroped using benzene (5 ml). The crude thioacid was dried under vacuum and used as such for the next step.

To a solution of the above thioacid in MeOH (0.16- 0.17 M conc. of thioacid) was added 2,6-lutidine and sulfonyl azide and stirred under inert atmosphere at rt overnight (12h). The solvent and the excess lutidine were evaporated. FCC (silica gel, 25% ethyl acetate-hexanes and 40% acetone-hexanes buffered with 0.1% TFA) gave amide **9a-e** (72-91%, 2 steps). No epimerisation was observed under the reaction conditions.

Table 4, Entry 1: **9a**

The thioester **8a** (60 mg, 0.163 mmol) was deprotected (40%v/v TFA-DCM, 2 ml; Et₃SiH, 0.2 ml for 3h) and the resulting thioacid was converted to amide **9a** (46 mg, 91%, white solid) following the general procedure, using 2,6-lutidine (52 mg, 0.49 mmol) and benzenesulfonyl azide (90 mg, 0.49 mmol) in methanol (0.16 M conc. of thioacid). mp: 201-203 °C; IR ν_{max} (neat) / cm⁻¹ 3333, 3039, 2864, 1708, 1640; δ_{H} (300 MHz, Acetone-d₆) 8.01 (2H, d, J=7.5 Hz, ArH), 7.72 (1H, t, J=7.5 Hz, ArH), 7.62 (2H, t, J=8.1 Hz, ArH), 7.41 (1H, d, J=5.7 Hz, NH), 4.48-4.40 (1H, m, CH), 3.30-2.70 (1H, br, NH), 1.90 (3H, s, CH₃), 1.70-1.40 (3H, m, CH, CH₂), 0.87 (3H, d, J=6.6 Hz, CH₃), 0.83 (3H, d, J=6.3 Hz, CH₃); δ_{C} (100 MHz, Acetone-d₆) 171.8, 171.0, 140.7, 134.4, 129.7 (2), 128.8 (2), 52.9, 40.5, 25.3, 23.2, 22.5, 21.8; m/z (ESIMS) 311 (M-1)⁺.

Table 4, Entry 2: **9b**

The thioester **8b** (30 mg, 0.081 mmol) was deprotected (40%v/v TFA-DCM, 2 ml; Et₃SiH, 0.2 ml for 1h) and the resulting thioacid was converted to amide **9b** (23 mg, 87%, clear viscous liquid) following the general procedure, using 2,6-lutidine (55 mg, 0.516 mmol) and *p*-toluenesulfonyl azide (86 mg, 0.436 mmol) in methanol (0.16 M conc. of thioacid). IR: ν_{max} (neat) / cm⁻¹ 3354, 3065, 2966, 1710, 1651, 1536; δ_{H} (300 MHz, Acetone-d₆) 7.89 (2H, d, J=7.8 Hz, ArH), 7.42 (2H, d, J=7.8 Hz, ArH), 7.23 (1H, d, J=7.8 Hz, NH), 4.55 (1H, dd, J=8.7, 5.1 Hz, CH), 3.68-3.40 (1H, br, NH), 2.43 (3H, s, CH₃), 1.92 (3H, s, CH₃), 1.90-1.75 (1H, m, CH), 1.36-1.25 (1H, m, CH₂), 1.22-1.08 (1H, m, CH₂), 0.84 (3H, t, J=7.5 Hz, CH₃), 0.76 (3H, d, J=6.6 Hz, CH₃); δ_{C} (75 MHz, CDCl₃) 171.8, 170.9, 145.0, 135.8, 129.5 (2), 128.3 (2), 56.8, 37.9, 25.9, 23.0, 21.7, 14.1, 11.4; m/z (ESIMS) 349 (M+Na)⁺.

Table 4, Entry 3: **9c**

The thioester **8c** (25 mg, 0.068 mmol, ~75:25 ratio of diastereomers) was deprotected (80%v/v TFA-DCM, 2 ml; Et₃SiH, 0.2 ml for 1h) and the resulting thioacid was converted to amide **9c** (16 mg, 72%, clear viscous liquid, in a 75:25 ratio of inseparable diastereomers) following the general procedure, using 2,6-lutidine (18.4 mg, 0.172 mmol) and *p*-toluenesulfonyl azide (21.5 mg, 0.109 mmol) in methanol (0.17 M conc. of thioacid). IR: ν_{max} (neat) / cm⁻¹ 3352, 3274, 3066, 2965, 1715, 1654, 1536; δ_{H} (300 MHz, Acetone-d₆) for major isomer: 7.89 (2H, d, J=8.4 Hz, ArH), 7.42 (2H, d, J=7.8 Hz, ArH), 7.29 (1H, d, J=8.1 Hz, NH), 4.33 (1H, t, J=7.8 Hz, CH), 3.00-2.70 (1H, br, NH), 2.43 (3H, s, CH₃), 1.92 (3H, s, CH₃), 1.86-1.70 (1H, m, CH), 1.42-1.20 (1H, m, CH₂), 1.20-1.00 (1H, m, CH₂), 0.82 (3H, d, J=6.6 Hz, CH₃), 0.79 (3H, t, J=6.9 Hz, CH₃); δ_{C} (75 MHz, CDCl₃) 171.2, 170.3, 144.7, 135.6, 129.3 (2), 128.1 (2), 57.2, 37.9, 24.6, 23.0, 21.7, 15.0, 11.0; *m/z* (ESIMS) 325 (M-1)⁻. The minor isomer was identical to **9b** by ¹H and ¹³C.

NOTES ON EPIMERIZATION

The synthesis of **9c** was also carried out under reflux conditions in chloroform solvent (7h, 61% yield). No epimerisation (¹H and ¹³C NMR) was observed under these reaction conditions.

HPLC of **9b** and **9c** failed to fully resolve under a variety of conditions (eg. C-18 RP column, buffer A: 0.05% TFA in H₂O, buffer B: 0.05% TFA in CH₃CN, monitored at 220 nm. Run from 30%B to 70%B over 40 min. Retention time **9b**: 10.83 min; and **9c**: 10.72 min.). NMR, however, proved reliable, providing baseline resolution of diastereomer signals in both ¹H and ¹³C NMR. Key ¹H NMR signals for **9b** and **9c**, which were baseline resolved in *d*₆-acetone and integrated for quantification, are indicated below.

Conversion of 8c to 9c

Conversion of 8b to 9b

Table 4, Entry 4:

9d

The thioester **8d** (30mg, 0.081 mmol) was deprotected (40%v/v TFA-DCM, 2 ml; Et₃SiH, 0.2 ml for 1h) and the resulting thioacid was converted to amide **9d** (24 mg, 73%, yellow gummy liquid) following the general procedure, using 2,6-lutidine (46 mg, 0.43 mmol) and dansyl azide (45 mg, 0.162 mmol) in methanol (0.16 M conc. of thioacid). IR: ν_{max} (neat) / cm⁻¹ 3350, 3072, 2964, 2873, 1709, 1649, 1536; δ_{H} (300 MHz, CDCl₃) 8.59 (1H, d, J=8.4 Hz, ArH), 8.49 (1H, d, J=7.2 Hz, ArH), 8.24 (1H, d, J=8.7 Hz, ArH), 7.58 (1H, t, J=7.8 Hz, ArH), 7.50 (1H, t, J=8.4 Hz, ArH), 7.18 (1H, d, J=7.5 Hz, ArH), 6.16 (1H, d, J=9.0 Hz, NH), 4.71 (1H, dd, J=9.0, 6.6 Hz, CH), 2.87 (6H, s, 2xCH₃), 2.04 (3H, s, CH₃), 1.70-0.80 (3H, series of m, CH and CH₂), 0.66 (3H, t, J=6.9 Hz, CH₃), 0.60 (3H, d, J=6.9 Hz, CH₃); δ_{C} (75 MHz, CDCl₃) 171.3, 170.1, 151.7, 133.1, 131.9, 131.4, 129.4, 129.3, 128.3, 122.9, 118.1, 115.0, 57.0, 45.3 (2C), 37.3, 25.8, 23.0, 14.0, 11.2.; m/z (ESIMS) 404 (M-1)⁻.

Table 4, Entry 5: **9e**

The thioester **8e** (60 mg, 0.163 mmol) was deprotected (40%v/v TFA-DCM, 2 ml; Et₃SiH, 0.2 ml for 1h) and the resulting thioacid was converted to amide **9e** (48 mg, 73%, yellow gummy liquid) following the general procedure, using 2,6-lutidine (92 mg, 0.86 mmol) and dansyl azide (90 mg, 0.326 mmol) in methanol (0.16 M conc. of thioacid). mp: 201-203 °C; IR ν_{max} (neat) / cm⁻¹ 3359, 3076, 2955, 2868, 1719, 1651, 1539; δ_{H} (300 MHz, CDCl₃) 8.57 (1H, d, J=7.2 Hz, ArH), 8.45 (1H, d, J=7.2 Hz, ArH), 8.24 (1H, d, J=8.7 Hz, ArH), 7.55 (1H, t, J=7.5 Hz, ArH), 7.52 (1H, t, J=7.8 Hz, ArH), 7.15 (1H, d, J=7.5 Hz, ArH), 6.11 (1H, d, J=7.5 Hz, NH), 4.62-4.54 (1H, m, CH), 2.87 (6H, s, 2xCH₃), 1.98 (3H, s, CH₃), 1.50-1.20 (3H, series of m, CH and CH₂), 0.72 (3H, d, J=6.0 Hz, CH₃), 0.66 (3H, d, J=6.0 Hz, CH₃); δ_{C} (75 MHz, CDCl₃) 171.6 (2C), 152.0, 131.8, 131.5, 129.7, 129.6, 128.5, 123.2 (2C), 118.5, 115.1, 52.2, 45.4 (2C), 40.1, 24.4, 23.0, 22.5, 22.0; m/z (ESIMS) 428 (M+Na)⁺.

References:

- 1 Sturino, C. F.; Labelle, M. *Tetrahedron Lett.* **1998**, 39, 5891-5894.
- 2 Hermann, C.K.F.; Campbell, J. A.; Greenwood, T. D.; Lewis, J. A.; Wolfe, J. F. *J. Org. Chem.* **1992**, 57, 5328-5334.
- 3 Bailey, P. D.; Bannister, N.; Bernad, M.; Blanchard, S.; Boa, A.N. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 3245-3251.
- 4 Lucente, G.; Pinnen, F.; Zanotti, G. *Tetrahedron Lett.*, **1978**, 3155-3158.
- 5 McFarlane, M. D.; Moody, D. J.; Smith, D. M. *J. Chem. Soc., Perkin Trans. I*, **1988**, 691-696.
- 6 Perreux, L.; Loupy, A.; Volatron, F. *Tetrahedron* **2002**, 58, 2155-2162.
- 7 Agwada, V. C. *J. Chem. Eng. Data* **1982**, 27, 481-483.
- 8 Vankar, Y. D.; Rao, C. T. *Tetrahedron* **1985**, 41, 3405-3410.
- 9 Shen, R.; Porco Jr, J. A. *Org. Lett.*, **2000**, 2, 1333-1336.
- 10 Alonso, D. A.; Alonso, E.; Najera, E.; Ramon, D. J.; Yus, M. *Tetrahedron* **1997**, 53, 4835-4856.
- 11 Avalos, M.; Babiano, R.; Duran, C. J.; Jimenez, J. L.; Palacios, J. C. *J. Chem. Soc. Perkin Trans. 2* **1992**, 2205-2215.
- 12 Sproviero, J. F. *Carbohydrate Research* **1973**, 357-363.
- 13 Sriram, D.; Srinivasan, S.; Priya, K.; Aruna, V.; Loganathan, D. *Acta Cryst. C* **1998**, 54, 1670-1672.

- 14 Sriram, D.; Sreenivasan, D.; Srinivasan, S.; Priya, K.; Thirtha, V.; Loganathan, D. *Acta Cryst. C* **1997**, 53, 1075-1077.
- 15 Hampton, A.; Kappler, F.; Chawla, R. R. *J. Med. Chem.*, **1979**, 22, 621-631.
- 16 Vetter, S. *Synth. Commun.*, **1998**, 28, 3219-3223.
- 17 Neises, B.; Steglich, W. *Angew. Chem. Int. Ed. Engl.*, **1978**, 17, 522-523.