Solid-Phase Synthesis of 2-Aminothiazoles

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The 2-aminothiazole ring system **1** (Figure 1) is a useful structural element in medicinal chemistry. This structure has found application in drug development for the treatment of allergies,[1] hypertension,[2] inflammation,[3] schizophrenia,[4] and bacterial[5] and HIV[6] infections. Given this proven utility, it seems reasonable that the development of libraries of 2-aminothiazoles might provide additional lead molecules for use in drug discovery. Solid-phase synthesis plays a central role in the generation of such small molecule libraries.[7] Herein we report a general, high-yielding solid-phase method for the synthesis of 2-aminothiazoles.[8] Our goal during this work was to provide a clean, high-yielding, and traceless synthesis of 2-aminothiazoles. We also desired that the route would utilize diverse commercially available starting materials and would be simple enough to be used in conjunction with other synthetic methods.

Two characteristics of 2-aminothiazoles suggested their amenability to a solid-phase approach. First, the 2-aminothiazole moiety contains an amino group, which could serve as a convenient, traceless point of attachment to acid-sensitive resins (Figure 1). Second, it is known that 2-aminothiazoles can be synthesized cleanly and in high yields from an α-bromo ketone and a thiourea via the Hantzsch thiazole synthesis (Figure 1).[8,9] This route of synthesis was particularly attractive in light of the large number of commercially available α-bromo ketones, which could be used to introduce diversity at the R_2 and R_3 positions of the thiazole ring.[10] However, our desire to take advantage of both of these characteristics in a single synthetic route highlighted a practical problem of

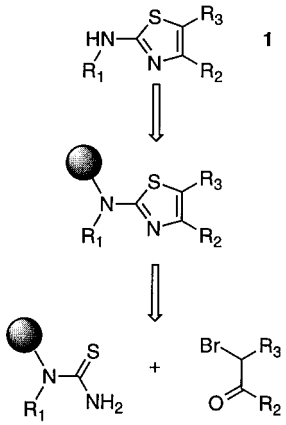
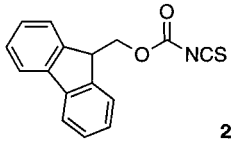


Figure 1.



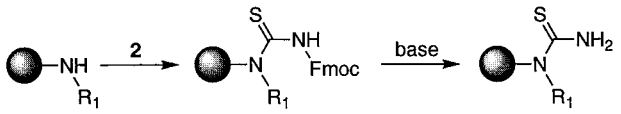


Figure 2.

the solid-phase synthesis of 2-aminothiazoles: one must utilize a resin-bound thiourea.

We decided it was best to produce the thiourea directly from a resin-bound primary or secondary amine. An advantage of this approach was that existing procedures[7,11] for immobilizing various primary amines to resin could be used prior to synthesis of the thiourea, thereby incorporating diversity at the R_1 position of the thiazole. Methods for synthesizing N-substituted thioureas from primary and secondary amines have been reported in the literature.[12] However, these either proceed in low yields or require harsh acidic or basic conditions that are generally incompatible with solid-phase synthesis. Therefore, a new milder reagent was necessary to perform the desired chemical transformation.

Compound **2**, fluorenylmethyloxycarbonyl isothiocyanate (Fmoc-NCS), was designed to overcome this problem. We envisioned that this compound would react directly with resin-bound amines in a low polarity solvent to produce Fmoc-protected thioureas (Figure 2). Subsequent removal of the Fmoc-group under basic conditions

(1) Hargrave, K. D.; Hess, F. K.; Oliver, J. T. *J. Med. Chem.* **1983**, *26*, 1158.

(2) Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor, D. G. Jr.; Connolly, C. J. C.; Doherty, A. M.; Klutchko, S. R.; Sircar, I.; Steinbaugh, B. A.; Batley, B. L.; Painchaud, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olson, S. C. J. *J. Med. Chem.* **1992**, *35*, 2562.

(3) (a) Haviv, F.; Ratajczyk, J. D.; DeNet, R. W.; Kerdesky, F. A.; Walters, R. L.; Schmidt, S. P.; Holms, J. H.; Young, P. R.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 1719. (b) Clemence, F.; Martret, O. L.; Delevallee, F.; Benzoni, J.; Jouanen, A.; Jouquey, S.; Mouren, M.; Deraedt, R. *J. Med. Chem.* **1988**, *31*, 1453.

(4) Jaen, J. C.; Wise, L. D.; Caprathe, B. W.; Tecle, H.; Bergmeier, S.; Humblet, C. C.; Heffner, T. G.; Meltzner, L. T.; Pugsley, T. A. *J. Med. Chem.* **1990**, *33*, 1453.

(5) Tsuji, K.; Ishikawa, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1601.

(6) Bell, F. W.; Cantrell, A. S.; Höberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordon, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M., Jr.; Noréen, R.; Öberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Sahlberg, C.; Ternansky, R. J.; Vasileff, R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X.-X. *J. Med. Chem.* **1995**, *38*, 4929.

(7) (a) Ellman, J. A. *Acc. Chem. Res* **1996**, *29*, 132. (b) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527. (c) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288.

(8) For a report of the solution-phase preparation of libraries of 2-aminothiazoles see: Bailey, N.; Dean, A. W.; Judd, D. B.; Middlemiss, D.; Storer, R.; Watson, S. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1409.

(9) (a) Hantzsch, A. R.; Weber, J. H. *Ber.* **1887**, *20*, 3118. (b) Joshua, C. P.; Nambisan, P. N. K. *Indian J. Chem.* **1973**, *11*, 118.

(10) A search of the Available Chemicals Directory database indicated over 300 commercially available α-bromo ketones.

(11) (a) Ngu, K.; Patel, D. V. *Tetrahedron Lett.* **1997**, *38*, 973. (b) Szardenings, A. K.; Burkoth, T. S.; Look, G. C.; Campbell, D. A. *J. Org. Chem.* **1996**, *61*, 6720. (c) Boojamra, C. G.; Burow, K. M.; Thompson, L. A.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 1240. (d) Gordon, D. W.; Steele, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 47.

(12) (a) Nair, G. V. *Indian J. Chem.* **1966**, *4*, 516. (b) Rasmussen, C. R.; Villani, F. J., Jr.; Weaner, L. E.; Reynolds, B. E.; Hood, A. R.; Hecker, L. R.; Nortey, S. O.; Hanslin, A.; Costanzo, M. J.; Powell, E. T.; Molinari, A. J. *Synthesis* **1988**, 456. (c) Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z. *Tetrahedron Lett.* **1992**, *40*, 5933. (d) Tamura, Y.; Adachi, M.; Kawasaki, T.; Kita, Y. *Tetrahedron Lett.* **1978**, *20*, 1753.

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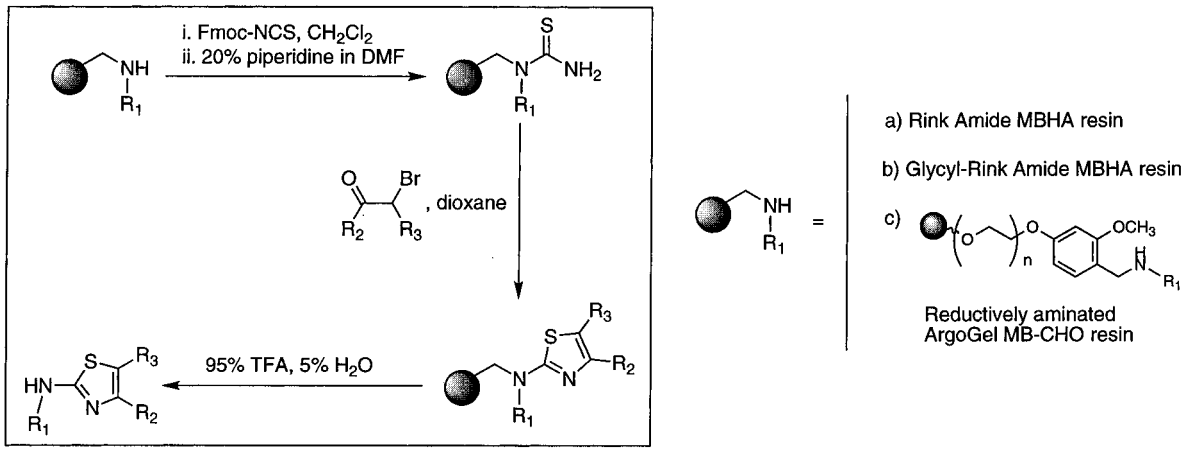
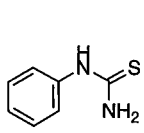
Scheme 1



in a more polar environment would generate the simple thioureas needed for the Hantzsch thiazole synthesis. Given that the reaction of amines with isothiocyanates[13] and the cleavage of the Fmoc protecting group[14] are clean, high-yielding reactions, it seemed plausible that the generation of a thiourea could be achieved with minimal loss of yield.

It was first necessary to synthesize Fmoc-NCS and test its ability to generate thioureas. The molecule was prepared easily through the reaction of Fmoc-chloride with potassium thiocyanate in anhydrous ethyl acetate. Solution phase testing was conducted by reacting Fmoc-NCS with a poor nucleophile (aniline), as well as with a more basic secondary amine (piperidine). The reaction of aniline with 1.2 equiv of **2** in methylene chloride, followed by the addition of a methanolic solution of piperidine, generated phenylthiourea **3**, which was isolated in 88% yield. The addition of piperidine to a solution of Fmoc-NCS (1.1 equiv) in methylene chloride formed exclusively the Fmoc-protected thiourea **4**; the



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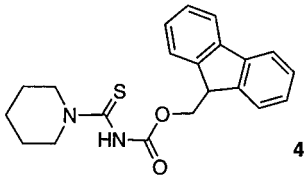


4

dibenzofulvene cleavage product was not observed. Also, there was no evidence of carbamate formation,[13] which might have resulted from a nucleophilic attack on the carbonyl carbon of **2**. Chromatographic workup of this reaction netted compound **4** in 98% yield. These results indicated that Fmoc-NCS could be used to produce thioureas and suggested that favorable transformations of a wide variety of primary and secondary amines could be expected.

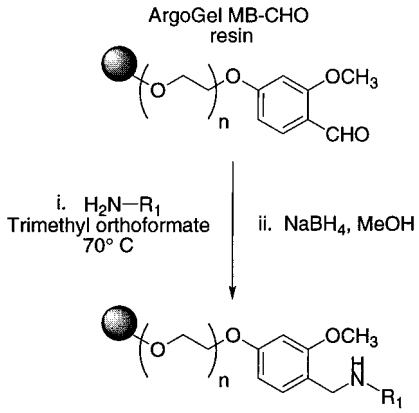
On the solid-phase, the reaction of Fmoc-NCS (5 equiv) in methylene chloride with the free amino group of Rink Amide MBHA resin was rapid, reaching completion within 15 min as indicated by a negative ninhydrin test. After subsequent treatment with 20% piperidine in DMF, the resin maintained a negative response to ninhydrin, suggesting that carbamate formation did not occur. Further evaluation of this reagent was conducted in the context of 2-aminothiazole generation.

Scheme 1 shows our general procedure for synthesizing 2-aminothiazoles. The same procedure was used with the three different resin types shown. Amine-containing, acid-sensitive resins were reacted first with Fmoc-NCS in methylene chloride. A solution of 20% piperidine in DMF was used to remove the Fmoc-group from the resin-bound thioureas, and thiazoles were formed by treatment of the resins with a dioxane solution of an α-bromo ketone at room temperature. Cleavage of the 2-aminothiazoles was effected with 95% TFA, 5% H_2O.

This synthetic procedure was elucidated with the use of Rink amide MBHA resin to produce thiazoles that were unsubstituted at the 2-amino position (R_1 = H, compounds **5**−**9**, Table 1). Purities of the (often crystalline) cleavage materials obtained with this resin were excellent, as determined by HPLC analysis. Purification by passage over basic alumina (to remove residual TFA) and radial centrifugal chromatography (silica gel plates) resulted in the isolation of 2-aminothiazoles as free bases. The isolated yields are high (71−96%), reflective of the high overall efficiency of the reaction scheme.

Thiazoles substituted at the 2-amino position (R_1 = alkyl, compounds **10**−**13**, Table 1) were generated from ArgoGel-MB-CHO resin that had been reductively aminated via the two-step procedure shown in Scheme 2. In

Scheme 2

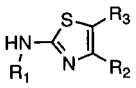


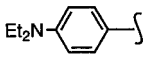
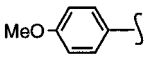
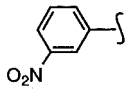
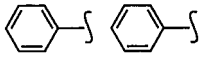
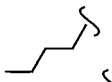
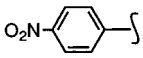
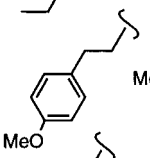
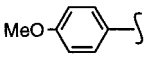
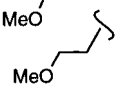
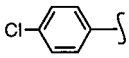
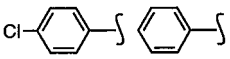
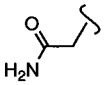
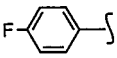
this procedure, the dehydrating agent trimethyl orthoformate was used as the solvent to drive imine forma-

(13) Drobnica, L.; Kristán, P.; Augustín, J. In *The Chemistry of Cyanates and Their Thio Derivatives*; Patai, S., Ed.; J. Wiley & Sons: New York, 1977; Part 2, pp 1109−1115.

(14) Greene, T.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; J. Wiley & Sons: New York, 1991, and references therein.

Table 1



	R_1	R_2	R_3	Purity [a] (%)	Yield [b] (%)
5	H		H	97	71
6	H		H	95	75
7	H		H	95	77
8	H		H	99	96
9	H			99	87
10			H	98	68
11			H	99	65
12			H	97	69
13				94	76
14			H	89	72

a) Purity determined from relative peak areas of HPLC chromatograms with monitoring at 254 nm. b) Isolated product yields determined using the loading level of starting resin.

tion.[11b,15] The arylimines were sufficiently stable, and their reduction could be carried out separately with sodium borohydride. The resulting resin-bound amines were then converted to 2-aminothiazoles with the use of the general procedure described above. Cleavage of the thiazoles from this resin required longer cleavage times (4 h) and modest heating (50 °C). In addition, cleavage efficiency was enhanced when the resins were dried under vacuum before exposure to the TFA cleavage solution. The purities of materials generated in this fashion remained high (94−99%). Compounds **10**−**13** were purified via reverse phase HPLC followed by passage over basic alumina. Yields of these materials were slightly lower than those of **5**−**9**, a result not unexpected given the additional synthetic steps of the reductive amination.

Compound **14** (Table 1) was generated from glycine linked to Rink amide MBHA resin. In this synthesis, the 2-amino group of the thiazole did not serve as the point of attachment to the resin. Despite the additional step of coupling the glycine to the resin, the purity and yield of **14** were comparable to those of compounds **5**−**9**, which were obtained directly from the amino group of Rink amide MBHA resin.

(15) Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937.

Compounds **11**, **13**, and **14** demonstrate an advantage of our method over other strategies for producing 2-aminothiazoles. Because Fmoc-NCS is used to transform primary and secondary amines into thioureas, noncommerically available thiourea structures can be incorporated into our synthesis. As a result, libraries of compounds containing greater diversity at the 2-amino position are accessible.

Some general notes about the synthetic procedure are warranted. In the course of our work we did not observe compound **2** to undergo amine attack at its less electrophilic carbonyl carbon to form the Fmoc-carbamate. As such, it was not necessary to iteratively treat the resin with Fmoc-NCS followed by piperidine deprotection to drive thiourea formation to completion. Solutions of Fmoc-NCS in methylene chloride were stable for several weeks at room temperature. The use of solutions of **2** in DMF is not recommended, as the reagent can decompose over the course of a few hours in this solvent. Solvents other than dioxane could be used for the solid-phase Hantzsch synthesis. However, we found that using dioxane eliminated the need for heating, which is required with the more polar solvent DMF. When the less polar solvent methylene chloride was used, small amounts of uncharacterized side products were often generated. Furthermore, in methylene chloride, the acid produced during the synthesis caused partial cleavage of the 2-aminothiazole products from the Rink amide MBHA resin. Usage of dioxane eliminated both of the problems associated with methylene chloride.

In conclusion, we have demonstrated that 2-aminothiazoles can be produced in good yields and with high degrees of purity from a primary amine and an α-bromo ketone. The key to this method is the conversion of a resin-bound amino group to a thiourea using Fmoc-NCS. The chemistry involved occurs under mild conditions and should easily find use in conjunction with other solid- and solution-phase chemistries. Finally, other chemical manipulations of thioureas are known. We are presently investigating solid-phase adaptations of these reactions and will report in due course.

Experimental Section

General. Except for compound **2**, all reagents used are available from commercial sources. Reagents were used without further purification, except for potassium thiocyanate, which was dried with heating under vacuum at 80 °C before use. Rink amide MBHA resin was purchased from Novabiochem and had a loading capacity of 0.55 mmol/g. ArgoGel-MB-CHO resin was purchased from Argonaut Technologies and had a loading capacity of 0.41 mmol/g. Compounds **5**−**14** were produced using a Rainin Instruments Symphony/Multiplex multiple peptide synthesizer. All NMR spectra (400 MHz) were recorded on a Varian Instruments Gemini-400 spectrometer. Radial centrifugal chromatography was carried out with a Chromatotron Model 8924 apparatus (Harrison Research, Palo Alto, CA) with 1 mm silica gel plates (Analtech). Analytical work employed a Rainin Microsorb-MV C_{18} column (water/acetonitrile 9:1 to 2:8 eluant gradient over 40 min, 1.5 mL/min flow-rate). Preparative HPLC work utilized a Dynamax-60A C_{18} column (water/acetonitrile 9:1 to 2:8 eluant gradient over 40 min, 20 mL/min flow-rate). All HPLC solutions contained 0.1% TFA. Yields of all compounds reported in Table 1 are of purified material and were based upon the loading levels of the starting resins. Purities of all compounds were estimated from integrated peak areas of HPLC chromatographs generated at 254 nm. Mass spectral analysis was performed by M-Scan, Inc., West Chester, PA. Elemental analysis was done at Atlantic Microlab, Inc., Norcross, GA.

Fluorenylmethyloxycarbonyl Isothiocyanate (2). Fluorenylmethyloxycarbonyl chloride (2.60 g, 10 mmol) was dissolved in 10 mL of anhydrous ethyl acetate. This solution was added dropwise to a suspension of *dry* potassium thiocyanate (1.07 g, 11 mmol) in 10 mL of anhydrous ethyl acetate at 0 °C under a nitrogen atmosphere. The solution was allowed to warm to room temperature over several hours, and the reaction was monitored by thin-layer chromatography [silica gel plates; eluant solution, CH_2Cl_2/hexane (1:3)]. After the reaction with the Fmoc-chloride, the reaction mixture was passed through a Celite pad to remove residual salts, and the ethyl acetate was removed by rotary evaporation. The crude product was purified via flash chromatography [silica gel; eluant solution, CH_2Cl_2/hexane (2:3)] to give 2.08 g of the Fmoc-isothiocyanate as an off-white solid (74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.5 Hz, 2H), 7.58 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 4.45 (d, J = 7.4 Hz, 2H), 4.25 (t, J = 7.4 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 150.45, 147.43, 142.89, 141.37, 128.21, 127.39, 125.16, 120.31, 70.75, 46.36. IR (polyethylene film) 2917, 2848, 1965 (N=C=S stretch), 1745, 1450, 1242, 1085, 757, 740 cm^{-1}. FAB-MS *m/z* 281, 179, 165. HR-MS FAB *m/z* for $C_{16}H_{11}NO_2S$ calcd 281.0510 (M^+), obsd 281.0518. Anal. Calcd: C, 68.31; H, 3.94; N, 4.98; S, 11.40. Obsd: C, 68.33; H, 3.93; N, 4.97; S, 11.46.

Phenylthiourea (3). Compound **2** (392 mg, 1.4 mmol) was dissolved in 5 mL of methylene chloride in a 25-mL round-bottom flask. Aniline (109 μL, 1.2 mmol) was added dropwise to this solution. TLC analysis of the reaction mixture after 30 min (silica gel plates, CH_2Cl_2 eluant) indicated complete consumption of the aniline (R_f = 0.4) and the clean formation of a new product (R_f = 0.7) distinct from **2** (R_f = 0.9). A solution of 20% piperidine in methanol (2.5 mL) was added to the flask, and the reaction was allowed to stir overnight. TLC analysis of the reaction (silica gel plates, CH_2Cl_2/acetone 3:2 eluant) indicated the formation of a product that coeluted with a genuine sample of phenylthiourea (R_f = 0.6). Flash chromatography of the reaction (silica gel, CH_2Cl_2/acetone 8:1 eluant) resulted in product isolation of 159 mg, which had clean ^{1}H and ^{13}C NMR spectra identical with those of a genuine sample of phenylthiourea.

3-(Fluorenylmethyloxycarbonyl)-1-piperidinethiocarboxamide (4). In a 50-mL round-bottom flask, Fmoc-NCS (562 mg, 2 mmol) was dissolved in 10 mL of dry methylene chloride. A solution of piperidine (179 μL, 1.81 mmol) in 2 mL of methylene chloride was added dropwise to the stirring solution of Fmoc-NCS over 3 min. TLC (silica gel plates, CH_2Cl_2 eluant) indicated clean transformation of the Fmoc-NCS (R_f = 0.9) into **4** (R_f = 0.2). Chromatographic purification (silica gel, CH_2Cl_2 eluant) netted 649 mg (98% yield) of compound **3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.5 Hz, 2H), 7.56 (d, J = 7.5 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.26 (s, 1H), 4.48 (d, J = 6.6 Hz, 2H), 4.20 (t, J = 6.6 Hz, 1H), 3.98 (bs, 2H), 3.44 (bs, 2H), 1.65 (bs, 6H). HR-MS FAB *m/z* for $C_{21}H_{22}N_2O_2S$ calcd 367.1480 (M + H^+), obsd 367.1486. Anal. Calcd: C, 68.83; H, 6.05; N, 7.64; S, 8.75. Obsd: C, 68.65; H, 6.08; N, 7.62; S, 8.67.

General Synthesis of Unsubstituted 2-Aminothiazoles 5−9. Rink amide MBHA resin (364 mg, 0.55 mmol/g substitution) was placed into a polypropylene reaction vessel. The synthesis was carried out automatically in a Symphony/Multiplex multiple peptide synthesizer. The resin was swollen through the addition of DMF (5 mL, 5 min, 3×). The resin was then treated with a solution of 20% piperidine in DMF (5 mL, 2.5 min, 3×) to remove the Fmoc protecting group from the resin. After washing with DMF (5 mL, 30 s, 3×) and methylene chloride (5 mL, 30 s, 5×), a 0.2 M solution of **2** in methylene chloride was applied to the resin (5 mL, 20 min, 1×). The resin was washed with methylene chloride (5 mL, 30 s, 3×) and DMF (5 mL, 30 s, 3×) and subsequently reacted with 20% piperidine in DMF (5 mL, 2.5 min, 3×) to produce the resin-bound thiourea. The resin was then washed with DMF (5 mL, 30 s, 3×) and dioxane (5 mL, 30 s, 3×). The desired α-bromo ketone (0.2 M in dioxane) was added (5 mL, 1 h), and the resin was washed with dioxane (5 mL, 30 s, 3×). The α-bromo ketone addition and subsequent wash were repeated two more times. The resin was then washed with methylene chloride (5 mL, 30 s, 5×) and dried briefly (10 min) under a stream of nitrogen. The reaction products were cleaved with a solution of aqueous TFA (95%, 5 mL, 2 h); this eluate and two subsequent TFA washes (2.5 mL) were collected and combined, and the solvent was removed with a Speedvac. This crude material was passed over a short column of basic alumina with a methanol eluant to isolate the product as the free base. Purified product was isolated with the use of a Chromatotron centrifugal radial thin-layer chromatograph (1 mm silica gel plates, CH_2Cl_2/acetonitrile gradient).

2-Amino-4-(4-(diethylamino)phenyl)thiazole (5): ^{1}H NMR (400 MHz, CD_3CN) δ 7.61 (d, J = 9 Hz, 2H), 6.68 (d, J = 9 Hz, 2H), 6.54 (s, 1H), 5.49 (bs, 2H), 3.38 (q, J = 7 Hz, 4H), 1.14 (d, J = 7 Hz, 6H). HR-MS FAB *m/z* for $C_{13}H_{17}N_3S$ calcd 247.1143 (M^+), obsd 247.1156. Anal. Calcd: C, 63.12; H, 6.93; N, 16.99; S, 12.96. Obsd: C, 63.06; H, 6.88; N, 17.07; S, 12.89.

2-Amino-4-(4-methoxyphenyl)thiazole (6): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (d, J = 9 Hz, 2H), 6.97 (bs, 2H), 6.90 (d, J = 9 Hz, 2H), 6.81 (s, 1H), 3.75 (s, 3H). HR-MS FAB *m/z* for $C_{10}H_{10}N_2OS$ calcd 207.0592 (M + H^+), obsd 207.0589. Anal. Calcd: C, 58.23; H, 4.89; N, 13.58; S, 15.54. Obsd: C, 58.34; H, 5.01; N, 13.36; S, 15.39.

2-Amino-4-(3-nitrophenyl)thiazole (7): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, J = 2 Hz, 1H), 8.22 (d, J = 8 Hz, 1H), 8.10 (dd, J = 8, 2 Hz, 1H), 7.65 (t, J = 8 Hz, 1H), 7.33 (s, H), 7.21 (bs, 2H). HR-MS FAB *m/z* for $C_9H_7N_3O_2S$ calcd 222.0337 (M + H^+), obsd 222.0336. Anal. Calcd: C, 48.86; H, 3.19; N, 18.99; S, 14.49. Obsd: C, 49.26; H, 3.33; N, 18.81; S, 14.29.

2-Amino-4-adamantylthiazole (8): ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.74 (bs, 2H), 5.98 (s, 1H), 1.97 (bs, 3H), 1.79 (s, 6H), 1.70 (d, J = 12 Hz, 3H), 1.65 (d, J = 12 Hz, 3H). HR-MS FAB *m/z* for $C_{10}H_{10}N_2OS$ calcd 234.1190 (M^+), obsd 234.1174. Anal. Calcd: C, 66.63; H, 7.74; N, 11.95; S, 13.68. Obsd: C, 66.66; H, 7.78; N, 11.86; S, 13.58.

2-Amino-4,5-diphenylthiazole (9). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 (m, 2H), 7.30−7.18 (m, 8H), 7.11 (bs, 2H). HR-MS FAB *m/z* for $C_{15}H_{12}N_2S$ calcd 253.0799 (M + H^+), obsd 253.0800. Anal. Calcd: C, 71.40; H, 4.79; N, 11.10; S, 12.71. Obsd: C, 71.31; H, 4.82; N, 11.10; S, 12.65.

General Procedure for the N-Substituted Thiazoles 10−13. Argogel-MB-CHO resin (366 mg, 0.41 mmol/g substitution) was placed into an Ace pressure tube. Trimethyl orthoformate (TMOF, 5 mL) was added to the flask along with 10 equiv of primary amine. The tube was capped and heated for 2 h at 70 °C in an oil bath. The tube was swirled periodically during heating. After cooling and removal of the TMOF solution with the use of a filtration cannula, the entire process was repeated a second time. The resin was then washed once with TMOF (5 mL) and three times with anhydrous methanol (5 mL.) Anhydrous methanol (5 mL) was then added to the resin, followed by the addition of 133 mg (20 equiv) of sodium borohydride. After vigorous gas evolution had ceased, the tube was capped and agitated for 8 h at room temperature. The resin was then transferred to a polypropylene reaction vessel and washed with methanol (5 mL, 3×), methanol:water (1:1, 5 mL, 3×), DMF:water (1:1, 5 mL, 3×), DMF (5 mL, 3×), and methylene chloride (5 mL, 3×). The reaction vessel was transferred to the Symphony/Multiplex multiple peptide synthesizer, and a modified version of the above-described program for 2-aminothiazole synthesis was executed. In this version, the initial exposure to 20% piperidine was eliminated, and all delivered volumes were reduced to 3.75 mL. After completion of the program, the resin was transferred to a Whatman polypropylene syringe-type reaction vessel (12-mL) and dried under vacuum. A solution of 95:5 TFA:water (5 mL) was added, and the tube was heated at 50 °C for 4 h. The cleavage solution and two subsequent rinses of the resin (one of 5 mL of 95% TFA and one of 5 mL of MeOH) were combined and evaporated to dryness with a Speedvac. The desired compound was purified via preparative HPLC and then passed over a column of basic alumina with acetonitrile as the eluant to afford the free base of the pure compound.

2-(Butylamino)-4-(4-nitrophenyl)thiazole (10): ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.56 (bs, 1H), 8.20 (d, J = 9 Hz, 2H), 7.90 (d, J = 9 Hz, 2H), 6.87 (s, 1H), 5.96 (bs, 1H), 3.29 (m, 2H), 1.65 (m, 2H), 1.41 (m, 2H), 0.94 (t, J = 7 Hz, 3H). HR-MS FAB *m/z* for $C_{13}H_{15}N_3O_2S$ calcd 278.0963 (M + H^+), obsd 278.0969. Anal. Calcd: C, 56.30; H, 5.45; N, 15.15; S, 11.56. Obsd: C, 56.43; H, 5.58; N, 14.89; S, 11.33.

2-((2-(4-Methoxyphenyl)ethyl)amino)-4-(4-methoxyphenyl)thiazole (11): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (bs,

1H), 7.64 (d, $J = 8$ Hz, 2H), 7.14 (d, $J = 8$ Hz, 2H), 6.92 (d, $J = 8$ Hz, 2H), 6.84 (d, $J = 8$ Hz, 2H), 6.42 (s, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.47 (m, 2H), 2.95 (t, $J = 7$ Hz, 2H). HR-MS FAB *m/z* for $C_{19}H_{20}N_2O_2S$ calcd 341.1324 ($M + H^+$), obsd 341.1310. Anal. Calcd: C, 67.03; H, 5.92; N, 8.23; S, 9.42. Obsd: C, 67.03; H, 6.01; N, 8.21; S, 9.51.

2-((2-Methoxyethyl)amino)-4-(4-chlorophenyl)thiazole (12): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, $J = 9$ Hz, 2H), 7.32 (d, $J = 9$ Hz, 2H), 6.66 (s, 1H), 5.38 (bt, 1H), 3.60 (t, $J = 5$ Hz, 2H), 3.51 (m, 2H), 3.38 (s, 3H). HR-MS FAB *m/z* for $C_{12}H_{13}ClN_2OS$ calcd 269.0515 ($M + H^+$), obsd 269.0503. Anal. Calcd: C, 53.56; H, 4.88; N, 10.42; S, 11.93. Obsd: C, 53.74; H, 4.85; N, 10.34; S, 11.83.

2-(Cyclopentylamino)-4-(4-chlorophenyl)-5-phenylthiazole (13): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, $J = 9$ Hz, 2H), 7.26−7.22 (m, 5H), 7.18 (d, $J = 9$ Hz, 2H), 5.18 (bd, $J = 7$ Hz, 1H), 3.81 (m, 1H), 2.06 (m, 2H), 1.80−1.50 (m, 6H). FAB-MS *m/z* for $C_{20}H_{19}ClN_2S$ calcd 355 ($M + H^+$), obsd 355. Anal. Calcd: C, 67.69; H, 5.40; N, 7.89; S, 9.03. Obsd: C, 67.75; H, 5.56; N, 7.68; S, 8.78.

2-(4-(4-Fluorophenyl)-2-thiazoylamino)acetamide (14). Rink amide MBHA resin (364 mg, 0.55 mmol/g substitution) was weighed out into a polyethylene reaction vessel. A Symphony/Multiplex multiple peptide synthesizer was first used to couple Fmoc-glycine-OH to the resin according to the following procedure. The resin was swollen with DMF (5 mL, 5 min, 3×) and subsequently treated with 20% piperidine in DMF (5 mL, 2.5 min, 3×). After washing again with DMF (5 mL, 30 s, 5×), the resin was treated for 2 h with a 0.4 M Fmoc-glycine-OH solution in DMF (2.5 mL) and a 0.4 M solution of diisopropylcarbodiimide in DMF (2.5 mL). The resin was then washed with DMF (5 mL, 30 s, 3×). The coupling reaction and the subsequent wash were repeated two more times. A negative ninhydrin test at this point indicated completion of the coupling reaction. The 2-aminothiazole was then constructed with the use of 4-fluorophenyacyl bromide and the general procedure described above. The desired compound was purified via preparative HPLC ansd passed over a column of basic alumina (MeOH eluant) to afford the free base of the pure compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (dd, $J = 9, 6$ Hz, 2H), 7.80 (bt, $J = 6$ Hz, 1H), 7.41 (bs, 1H), 7.18 (t, $J = 9$ Hz, 2H), 7.06 (bs, 1H), 7.04 (s, 1H), 3.88 (d, $J = 6$ Hz, 2H). HR-MS FAB *m/z* for $C_{11}H_{10}FN_3OS$ calcd 252.0606 ($M + H^+$), obsd 252.0594. Anal. Calcd: C, 52.58; H, 4.01; N, 16.72; S, 12.76. Obsd: C, 52.33; H, 4.02; N, 16.57; S, 12.71.

Supporting Information Available: Copies of ^{1}H NMR, ^{13}C NMR, and IR spectra of compound **2** are provided. Reproductions of ^{1}H NMR spectra of compounds **5**−**14** are also included (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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