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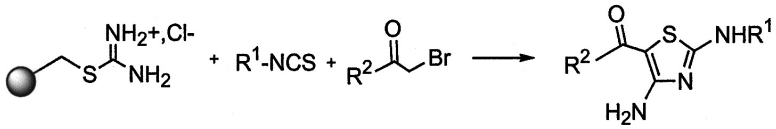

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A Novel Solid-Phase Approach to 2,4-Diaminothiazoles

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A novel solid-phase synthesis of a 2,4-diaminothiazole library starting from a polymer-bound thiouronium salt is described. The synthetic strategy involves formation of polymer-bound thioureido-thiourea intermediates **5** which by treatment with α-bromo-ketones **6** undergoes S-alkylation, followed by a base-catalyzed intramolecular-ring closure/cleavage to give 2,4-diaminothiazoles **8**. This strategy tolerates a wide range of functionality and protecting groups. The novel feature of our method is a polymer-supported auto-scavenging strategy (PSAS), which provides a clean, high-yielding, and traceless synthesis to 2,4-diaminothiazoles.

Introduction

The application of parallel synthesis to generate combinatorial libraries as an efficient means of creating pharmaceutical "drug-like leads" has been a topic of considerable interest in the recent literature.[1−7] In this context, we have developed solid-phase chemistry to furnish various heterocycles to facilitate the automated parallel generation of arrays of compounds. Among them, thiazole derivatives represent attractive targets due to their broad biological activity. In particular, the 2-aminothiazole ring system is a useful structural element in medicinal chemistry and has found a broad application in drug development for the treatment of allergies,[8] hypertension,[9] schizophrenia,[10] and bacterial infections.[11] To our knowledge, there are only few reports on the synthesis and the biological activities of 2,4-diaminothiazoles. The most promising method is a two-step synthesis from amidinothioureas.[12] Motivated by the current interest in this chemical class, we have recently published a new general solution-phase entry to 2,4-diaminothiazole from thiouronium salts.[13]

Herein we report a novel, general, high-yielding solid-phase method for the synthesis of 2,4-diaminothiazoles. In analogy to our solution-phase process,[13] the polymer-bound thiouronium **3** salt and isothiocyanates **4** were combined to form thioureido-thioureas **5**, which when treated with α-bromo ketones **6** subsequently underwent S-alkylation, followed by a base-catalyzed intramolecular-cyclization/cleavage from the solid-support, leading to the corresponding 2,4-diaminothiazole **8** in high yield and purity.

Results and Discussion

This sequence appeared ideally suited for the production of combinatorial heterocycles on solid phase (Scheme 1). Thus, when resin-bound thiouronium salt **3**, prepared by reaction of thiourea **2** with commercially available Merrifield resin **1** (1.8 mmol/g),[14−16] was reacted with isothiocyanates **4** (1.5 equiv) in the presence of *N*-ethyldiisopropylamine (DIPEA; 1.5 equiv) in *N*, *N*-dimethylformamide (DMF) at room temperature for 4 h, the corresponding polymer-bound thioureido-thiourea intermediates of type **5** were obtained. The formation of the resin-bound compounds was followed by ATR/FT-IR (attenuated total reflection method).[17]

As a key step in the sequence, the polymer-bound thioureido-thioureas **5** were treated with 1.3 equiv of α-bromo ketones **6** in DMF at room temperature for several hours, in the presence of diethylaminomethyl polystyrene resin **7** (3.2 mmol/g; 2.1 equiv), leading to the formation of the corresponding 2,4-diaminothiazoles **8** in high yield and purity (Table 1*)*. We assume that this synthetic step involves an initial S-alkylation with α-bromo ketones **6** to give the corresponding S-alkylated intermediates, followed by base-catalyzed ring closure with concomitant release of the final products into the solution (Scheme 1). We anticipate that the reaction sequence probably involves the formation of the HBr salt of the diethylaminomethyl polystyrene resin **9**, as well as the generation of polymer-bound thioether derivatives **10**, as already depicted in the previously published solution-phase approach,[13] providing highly pure 2,4-diaminothiazoles **8**.

In fact, the diethylaminomethyl polystyrene resin **7** is used to both activate the intermediate and sequester the HBr byproduct. After the base-catalyzed intramolecular-cyclization/cleavage process, the resulting resin-bound thiol was used to remove the excess of the α-bromo ketones **6**, affording polymer-bound thioether derivatives **10**.[13] These complementary scavenging processes illustrate perfectly our concept of polymer-supported auto-scavenging strategy (PSAS), affording highly pure 2,4-diaminothiazoles **8** separated from polymer-bound derivatives **9** and **10** after simple filtration and evaporation of the residue, demonstrating an advantage of our method over other strategies for producing 2,4-diaminothiazoles.

We next turned our attention to the elaboration of 2,4-diaminothiazole libraries, using the described reaction sequence. To demonstrate the process could be applied to parallel synthesis, we found that is was possible to use resin-bound thiouronium salt **3**, DIPEA, and diethylaminomethyl polystyrene resin **7** in the same reaction vessel. Interestingly, we found that the simultaneous use of the two resins allows a much cleaner, high-yielding, and traceless isolation of the

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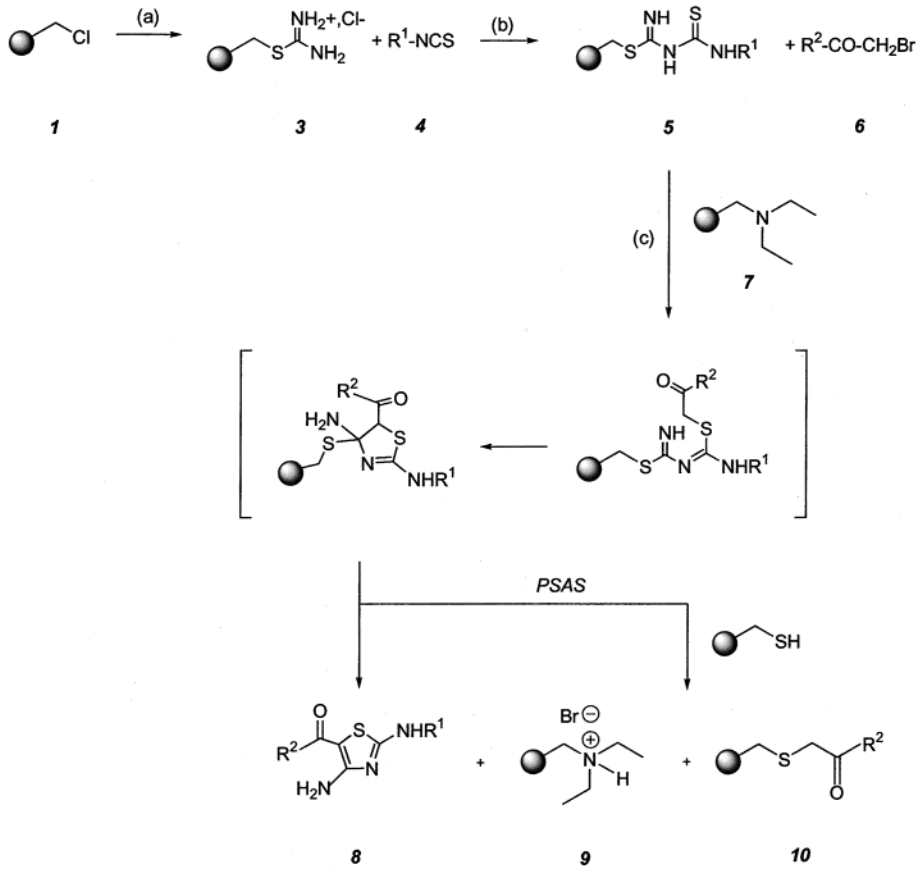
Scheme 1[a]



[a] Reagents and conditions: (a) thiourea **2**, DMA, rt−85 °C; (b) DIPEA, DMF; (c) DMF, rt.

Table 1. 2,4-Diaminothiazole Library (**8**)

R^1-NCS (**4**)	R^2-$COCH_2Br$ (**6**)	yield[a] (product)	purity[b] (%)	observed MS[c]
C_6H_5	C_6H_{11}	85 (**8a**)	92	302 ($[M + H]^+$)
C_6H_5	*p*-MeO-C_6H_4	93 (**8b**)	95	326 ($[M + H]^+$)
C_6H_5	*p*-F-C_6H_4	96 (**8c**)	99	314 ($[M + H]^+$)
C_6H_5	naphthyl	81 (**8d**)	95	346 ($[M + H]^+$)
C_6H_5	*p*-Br-C_6H_4	62 (**8e**)	87	375 ($[M + H]^+$)
m-NC-C_6H_4	*p*-Br-C_6H_4	75 (**8f**)	93	401 ($[M + H]^+$)
m-NC-C_6H_4	cyclopentyl	56 (**8g**)	99	313 ($[M + H]^+$)
m-NC-C_6H_4	*o*-pyridyl	89 (**8h**)	94	322 ($[M + H]^+$)
m-MeO_2C-C_6H_4	C_4H_9	50 (**8i**)	99	334 ($[M + H]^+$)
m-MeO_2C-C_6H_4	*o*-Cl-C_6H_4	56 (**8j**)	95	388 ($[M + H]^+$)
p-MeO_2C-C_6H_4	C_5H_{11}	67 (**8k**)	99	348 ($[M + H]^+$)
m-MeO-C_6H_4	*o*-Cl-C_6H_4	49 (**8l**)	93	360 ($[M + H]^+$)
m-MeO-C_6H_4	*p*-F_2HCO-C_6H_4	53 (**8m**)	95	392 ($[M + H]^+$)
p-F_3C-C_6H_4	*p*-F_2HCO-C_6H_4	87 (**8n**)	93	430 ($[M + H]^+$)
C_6H_5	CH_2-NHBoc	87 (**8o**)	99	349 ($[M + H]^+$)
CH_2CO_2Me	3-thienyl	86 (**8p**)	98	298 ($[M + H]^+$)
Fmoc	*o*-Cl-C_6H_4	52 (**8q**)	97	476 ($[M + H]^+$)
$CH((CH_2)_2SMe)CO_2Me$	*o*-Cl-C_6H_4	63 (**8r**)	98	400 ($[M + H]^+$)

[a] Yields (in %) are based on the weight of crude material and are relative to the initial loading of polymer-bound thiouronium salt **3** (1.6 mmol/g). [b] HPLC purity of the crude material (confirmed by ^1H NMR), measured on YMC-Pack Pro C18 column (75 × 4.6 mm) with a gradient 12% AcCN/H_2O → 95% AcCN within 5.4 min; flow rate, 2.64 mL/min; UV detection at 254 nm. [c] Confirmed by mass spectra (ESI).

2,4-diaminothiazoles. In the course of our work, we notice that the use of a polar solvent such as DMF or DMA is recommended. When less polar solvents (dioxane, methylene chloride) were used, significant amounts of uncharacterized side products were often generated. In all the cases, it is very important to exclude traces of water, which caused a dramatic decrease in yield. Moreover, the use of a large excess of reagents resulted in a decrease in yield. In addition, we found that activation of the resin-bound thiouronium salt with bases such as DBU, BEMP, DABCO, or Phosphazene, led to erratic results. This approach, however, tolerates a wide range of functionality and protecting groups. Finally, using the described method, starting from 40 isothiocyanates **4** and 40 α-bromo ketones **6**, a library of 1530 individual 2,4-diaminothiazoles **8** was synthesized in high purity (68−99%: HPLC purity of the crude material with UV detection and

confirmed by ^{1}H NMR) and good yield (54−87%: based on weight of crude material and relative to the initial loading of polymer-bound thiouronium salt **3** (1.6 mmol/g)).

Summary

In summary, a new and efficient process for the solid-phase synthesis of 2,4-diaminothiazoles has been developed, taking advantage of a novel cyclization/cleavage strategy in combination with a polymer-supported auto-scavenging process (PSAS). Furthermore, we have emphasized the potential of the polymer-bound thiouronium salt, which appeared to us as a highly versatile building block for the generation of polyfunctional heterocycles as well as an efficient traceless linker.[14−16,18,19] This approach is suitable for the parallel synthesis of compound arrays. Further applications of this strategy toward different functionalized thiazoles, as well as extension to other heterocycles, are in progress.

Experimental Section

All chemicals were purchased from Fluka AG and Aldrich. Solvents were purified before use or purchased in absolute quality. The chloromethyl polystyrene (1.8 mmol/g, 1% cross-linking, 200 μm) was from LCC Engineering & Trading GmbH. ATR/FTIR: Nicolet-860 FT-IR spectrometer with an IR microscope NICPLAN; resolution 4 cm^{-1}, 200 or 500 co-added scans, MCT detector, characteristic bands in cm^{-1}. ^{1}H NMR spectra: Bruker-AC-250 apparatus, at 250 MHz; in d_6-DMSO or $CDCl_3$. ^{13}C NMR spectra: Bruker-AC-400 apparatus, at 400 MHz; in d_6-DMSO or $CDCl_3$; TMS as internal standard; chemical shift of signal centers and ranges in ppm (δ), J in Hz. EI-MS: **Finnigan MS9-AEI or Mat90;** *m*/*z* (rel.). ESIMS: PE Sciex API 300; *m*/*z* (rel.).

Polymer-Bound Thiouronium Salt (3). A mixture of Merrifield resin (100 g, 1.80 mmol/g), thiourea (68.5 g, 900 mmol), and DMA (1 L) was shaken at 85 °C for 20 h and then washed with isopropyl alcohol (1 × 5 min), dioxane (2 × 4 min), dioxane−H_2O (1:1, 6 × 4 min), DMA (3 × 4 min), and isopropyl alcohol (5 × 3 min) at room temperature using an automated washing station. Drying under high vacuum for 20 h afforded polymer-bound thiouronium salt (**3**): 92% of conversion based on elemental analysis. IR: 3040s, 2920s, 1640s, 1500m, 1450s, 750m, 700s. Anal. found: N, 4.33; S, 5.21.

General Procedure for the Preparation of 2,4-Diaminothiazole (8). To a suspension of polymer-bound thiouronium salt **3** (1 mmol) and diethylaminomethyl polystyrene **7** (2.1 mmol) in dry dimethylformamide (DMF; 10 mL) under argon at room temperature was added *N*-ethyldiisopropylamine (DIPEA, 1.5 mmol), followed by the isothiocyanate **4** (1.5 mmol). After 3 h at room temperature, the reaction mixture was washed successively with isopropyl alcohol (1 × 5 min), DMF (2 × 4 min), isopropyl alcohol (5 × 4 min), and DMF (3 × 4 min) at room temperature using an automated washing station. To the washed resin was added dry dimethylformamide (DMF; 10 mL) under argon at room temperature, followed by the α-bromoketone **6** (1.3 mmol). The reaction mixture was then stirred at room temperature during 18 h. This eluate and one subsequent wash with DMF (10 mL) were collected and combined, and the solvent was removed to yield **8** in high purity.

2-Phenylamino-4-amino-5-cyclohexylcarbonylthiazole (8a): Yellow solid. ^{1}H NMR (250 MHz, d_6-DMSO): 10.68 (s, NH); 7.95 (br.s, NH_2); 7.62−7.59 (d, J = 7.65, 2 H arom.); 7.39−7.32 (t, J = 7.48, 2 H arom.); 7.10−7.04 (t, J = 7.32, 1 H arom.); 2.29−2.24 (t, J = 10.81, 1 H aliph.); 1.75−1.62 (m, 5 H aliph.); 1.41−1.13 (m, 5 H aliph.). ^{13}C NMR (400 MHz, d_6-DMSO): δ 191.9 (s); 165.66 (s); 164.16 (s); 140.22 (s); 129.56 (2 × d); 123.61 (d); 119.31 (2 × d); 50.71 (s); 29.31 (2 × t); 26.01 (t); 25.80 (2 × t). IR (KBr): 3418w, 2930w, 1611m, 1553s, 1451s, 783m, 700m. ESIMS ([M + H]$^+$): 302 (100%).

2-Phenylamino-4-amino-5-[(4-methoxyphenyl)carbonyl]thiazole (8b): Yellow solid. ^{1}H NMR (250 MHz, d_6-DMSO): 10.76 (s, NH); 8.16 (br.s, NH_2); 7.69−7.65 (d, J = 8.75, 2 H arom.); 7.63−7.60 (d, J = 7.77, 2 H arom.); 7.39−7.33 (t, J = 7.52, 2 H arom.); 7.09−7.04 (t, J = 7.52, 1 H arom.); 7.03−6.99 (d, J = 8.75, 2 H arom.); 3.81 (s, 3 H aliph.). IR (KBr): 3413w, 3201w, 1587s, 1522s, 1251m, 761m, 694m. ESIMS ([M + H]$^+$): 326 (100%).

2-Phenylamino-4-amino-5-[(4-fluorophenyl)carbonyl]-thiazole (8c): Yellow solid. ^{1}H NMR (250 MHz, d_6-DMSO): 10.82 (s, NH); 8.25 (br.s, NH_2); 7.77−7.71 (dd, J = 14.32 and 8.77, 2 H arom.); 7.63−7.60 (d, J = 7.77, 2 H arom.); 7.39−7.27 (m, 4 H arom.); 7.09−7.04 (t, J = 7.52, 1 H arom.). IR (KBr): 3418w, 3197w, 1599s, 1550s, 1431m, 849m, 760m, 694m. ESIMS ([M + H]$^+$): 314 (100%).

2-Phenylamino-4-amino-5-naphthylcarbonylthiazole (8d): Yellow solid. ^{1}H NMR (250 MHz, d_6-DMSO): 10.82 (s, NH); 8.28 (br.s, 1 H arom. and NH_2); 8.07−7.96 (m, 3 H arom.); 7.79−7.77 (dd, J = 8.47 and 1.62, 1 H arom.); 7.65−7.59 (m, 4 H arom.); 7.39−7.33 (t, J = 7.54 2 H arom.); 7.11−7.05 (t, J = 7.54, 1 H arom.). IR (KBr): 3467w, 3267w, 1622m, 1528s, 1445s, 824m, 741m. ESIMS ([M + H]$^+$): 346 (100%).

2-Phenylamino-4-amino-5-[(4-bromophenyl)carbonyl]-thiazole (8e): Yellow solid. ^{1}H NMR (250 MHz, d_6-DMSO): 10.85 (s, NH); 8.27 (br.s, NH_2); 7.70−7.60 (m, 6 H arom.); 7.40−7.33 (t, J = 7.54 2 H arom.); 7.12−7.06 (t, J = 7.54, 1 H arom.). IR (KBr): 3467w, 3267w, 1630m, 1542s, 1409s, 832m, 750m, 690m. ESIMS ([M + H]$^+$): 375 (100%).

2-[(3-Cyanophenyl)amino]-4-amino-5-[(4-bromophenyl)-carbonyl]thiazole (8f): Yellow solid. ^{1}H NMR (250 MHz, d_6-DMSO): 11.14 (s, NH); 8.35 (br.s, NH_2); 8.31 (s, 1 H arom.); 7.79−7.50 (m, 7 H arom.). IR (KBr): 3467w, 3267w, 2225m, 1630m, 1521s, 1404s, 834m, 755m, 679m. ESIMS ([M + H]$^+$): 401 (100%).

***tert*-Butyl [2-(4-amino-2-phenylamino-thiazol-5-yl)-2-oxo-ethyl]-carbamate (8o):** Yellow solid. ^{1}H NMR (250 MHz, d_6-DMSO): 10.85 (s, NH); 7.83 (br.s, NH_2); 7.62−7.60 (m, 2 H arom.); 7.40−7.30 (m, 2 H arom.); 7.10−7.05 (m, 2 H arom. and NH); 3.70−3.60 (d, J = 7.52 2 H aliph); 1.39 (s, 9 H aliph.). IR (KBr): 3435w, 3305m, 2981w, 1685s, 1599m, 1488s, 1418s, 987m, 750m, 686m. ESIMS ([M + H]$^+$): 349 (100%).

9H−Fluoren-9-yl-methyl [4-amino-5-(2-chlorophenyl)-carbonyl]thiazol-2-yl]-carbamate (8q): Yellow solid. ^{1}H

NMR (250 MHz, d_6-DMSO): 12.46 (s, NH); 7.95 (br.s, NH_2); 7.91−7.88 (m, 2 H arom.); 7.75−7.72 (m, 2 H arom.); 7.55−7.53 (m, 1 H arom.); 7.48−7.29 (m, 7 H arom.); 4.47−4.45 (d, J = 4.25 2 H aliph); 4.32−4.26 (t, J = 4.25 1 H aliph); 1.39 (s, 9 H aliph.). IR (KBr): 3455w, 3261w, 2923w, 1723s, 1609m, 1463s, 1231s, 987m, 752m, 738m. ESIMS ($[M + H]^+$): 476 (100%).

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References and Notes

(1) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *9*, 1233.
(2) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *10*, 1386.
(3) Ellman, J. A. *Chemtracts Org. Chem.* **1995**, *8*, 1.
(4) Pirrung, M. C. *Chemtracts* **1995**, *8*, 5.
(5) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527.
(6) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1997**, *53*, 5643.
(7) Obrecht, D.; Villalgordo, J. M. *Solid-supported combinatorial and parallel synthesis of small-molecular-weight compound libraries*; Elsevier Science Ltd.: Oxford, 1998; Vol. 17.
(8) Hargrave, K. D.; Hess, F. K.; Oliver, J. T. *J. Med. Chem.* **1983**, *26*, 1158.
(9) Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor, D. G. J.; Connoly, 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.
(10) Jaen, J. C.; Wise, L. D.; Caprathe, B. W.; Tecle, H.; Bergmeier, S.; Humblet, C. C.; Heffner, T. G.; Meltzner, L. T.; Pusgley, T. A. *J. Med. Chem.* **1990**, *33*, 1453.
(11) Tsuji, K.; Ishikawa, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1601.
(12) Rajasekharan, K. N.; Nair, K. P.; Jenardanan, G. C. *Synthesis* **1986**, 353.
(13) Masquelin, T.; Obrecht, D. *Tetrahedron* **2000**, *55*, 8783.
(14) Chucholowski, A.; Masquelin, T.; Obrecht, D.; Stadlwieser, J.; Villalgordo, J. M. *Chimia* **1996**, *50*, 525.
(15) Masquelin, T.; Sprenger, D.; Baer, R.; Gerber, F.; Mercadal, Y. *Helv. Chim. Acta* **1998**, *81*, 646.
(16) Obrecht, D.; Abrecht, C.; Grieder, F.; Villalgordo, J.-M. *Helv. Chim. Acta* **1997**, *80*, 65.
(17) Griffiths, P. *Chemical Analysis*; John Wiley & Sons: New York, 1974; Vol. 43.
(18) Masquelin, T.; Delgado, Y.; Baumle, V. *Tetrahedron Lett.* **1998**, *39*, 5725.
(19) Masquelin, T.; Meunier, N.; Gerber, F.; Rosse, G. *Heterocycles* **1998**, *48*, 2489.

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