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An efficient protocol for solid phase aminothiazole synthesis

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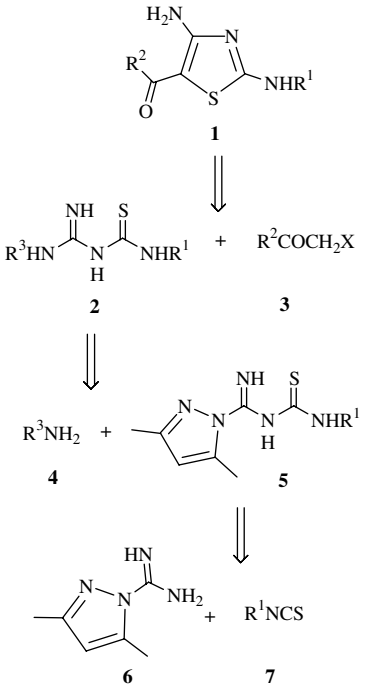
Abstract—An efficient synthesis of 2,4-diamino-5-ketothiazoles under solid phase conditions has been achieved by the reaction of polymer supported amidinothioureas with α-haloketones. This novel synthetic approach involving traceless cleavage from the support is suited for automation, and allows solid phase combinatorial synthesis of 2,4-diamino-5-ketothiazoles in good yields and purities.

The utility of solid phase reactions in combinatorial library synthesis depends largely upon the efficiency of the synthetic route selected and the availability of reagents. Since attractive targets for combinatorial synthesis are often small organic molecules[1] with useful bioactivity profiles, rapid synthesis through simple routes has great appeal. Aminothiazoles, with a wide spectrum of well established bioactivity,[2] are being continually investigated for newer therapeutic applications. We have reported[3] on the solution phase synthesis of 2,4-diamino-5-ketothiazoles **1** and their cytotoxic properties.[4] Moreover, thiazole derivatives of type **1** are reported to be potential inhibitors of cyclin-dependent kinases (CDKs)[5] and glycogen synthase kinase-3 (GSK-3).[6]

The increasing appearance of aminothiazole motifs in potential drug candidates has resulted in the design of solid phase routes[7] to these molecules. A literature survey revealed only two reports[8] on the solid phase synthesis of 2,4-diamino-5-ketothiazoles. As part of our efforts to develop versatile solid phase routes to these scaffolds, we earlier reported the design and synthesis of a novel thiocarbamoylamidine transfer reagent.[9] We now report an efficient, two-step procedure for the solid phase synthesis of 2,4-diamino-5-ketothiazoles starting from aminomethylpolystyrene and employing the above reagent in a solid phase thiocarbamoylamidine transfer protocol.

The design of the solid phase route was based on a retrosynthesis, which is outlined in Scheme 1. We proposed to access the target **1** through a [4+1] ring construction approach in which the C–N–C–S unit for the thiazole



Scheme 1. Retrosynthesis of 2,4-diamino-5-ketothiazoles **1**.

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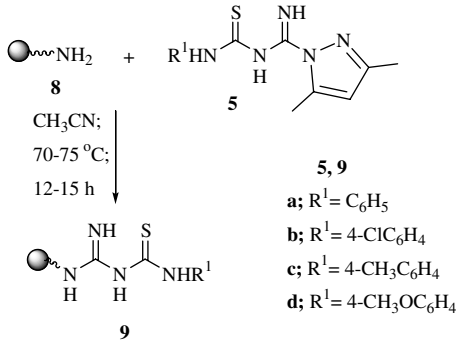
ring would be derived from an amidinothiourea **2** and the remaining C atom from an α-haloketone **3**. It was decided to anchor the amidinothiourea unit onto a solid support using the thiocarbamoylamidine transfer protocol. The transfer reagents **5** required for this step could be synthesized easily from commercially available 1-amidino-3,5-dimethylpyrazole **6** and isothiocyanates **7**, as reported earlier, as a prelude to the present work.[9]

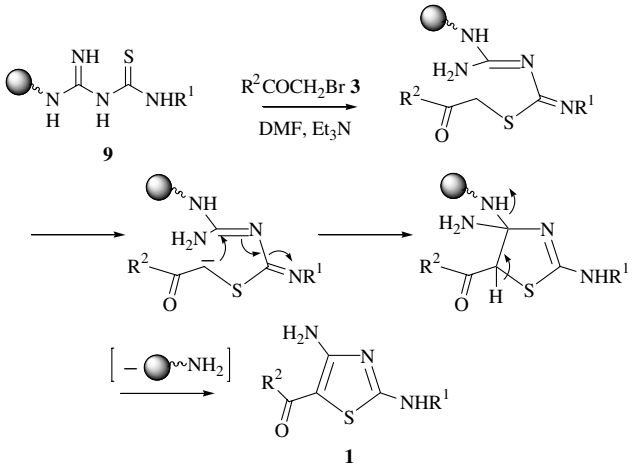
The first step in the synthesis involved the development of polymer anchored amidinothioureas **9** (Scheme 2). This required the selection of amino polymer **8**,[10,11] which could be reacted with **5** to access polymer anchored amidinothioureas **9** which are analogous to **2**. Prior to this step, the reaction conditions for the thiocarbamoylamidine transfer were optimized using pilot reactions in solution phase conditions. For the optimization step, various primary amines **4** and differently substituted thiocarbamoylamidine transfer reagents **5** were employed.[12] The conditions for the reaction between polymer **8** and transfer reagents **5** were also investigated in a number of trials, and the optimized conditions were identified by evaluating the extent of thiocarbamoylamidine transfer reaction[13] by varying the reagent concentrations and the reaction time or temperature. Thus, two equivalents of transfer reagent **5a–d** was added to aminomethylpolystyrene beads swelled in acetonitrile in four separate reaction vessels based on the amino group capacity of the resin. The reaction flasks were kept at 70–75 °C in a constant temperature bath and the reactions proceeded in a parallel fashion. The resin, after work up,[14] was subjected to sulfur analysis (Table 1) and was assigned structure **9** based on IR



Scheme 2. Synthesis of polymer bound amidinothioureas **9** using thiocarbamoylamidine transfer reagents **5**.

Table 1. Sulfur analysis data of polymer bound amidinothioureas **9a–d**

Amidinothiourea **9**	R^1	S capacity (%)
a	C_6H_5	0.80
b	4-ClC_6H_4	1.50
c	4-$CH_3C_6H_4$	0.70
d	4-$CH_3OC_6H_4$	1.40



Scheme 3. Solid phase synthesis of 2,4-diamino-5-ketothiazoles **1**.

studies as well as on the results from solution phase model reactions.

The next step was the reaction of polymer anchored amidinothioureas **9** with various α-haloketones **3**. It was decided to employ α-bromoketones as the active methylene compounds in view of the greater reactivity of these compounds in nucleophilic substitution reactions as well as their commercial availability. The reaction of resins **9** with **3** in DMF[15] proceeded through an acyclic *S*-alkylisothiourea intermediate, which cyclized to a thiazoline. This underwent eliminative aromatization to afford tracelessly, 2,4-diamino-5-ketothiazoles **1** (Scheme 3), after work-up,[16] in good yields and purities. The generality of the synthetic route was evaluated by employing both aryl and heteroaryl substituted haloketones **3**, and the representative compounds thus synthesized are summarized in Table 2. The crude yields of **1** were in the range of 88–92% and the purities of the crude samples[17] were in the range 85–90%. After purification by column chromatography on silica, the pure thiazoles were obtained in 60–73% yields.

Table 2. 2,4-Diamino-5-ketothiazoles **1a–h**

Thiazole **1**	R^1	R^2	Yield (%)	Mp (°C)	Lit. mp (°C)
a	C_6H_5	C_6H_5	65	186–87	186[19]
b	4-ClC_6H_4	C_6H_5	73	200–01	200–01[9]
c	4-$CH_3C_6H_4$	C_6H_5	68	155–56	155–56[19]
d	4-$CH_3OC_6H_4$	C_6H_5	67	205–06	205–06[19]
e	C_6H_5	4-ClC_6H_4	72	196–98	196[9]
f[20]	C_6H_5	2-$C_{10}H_7$	70	221–23	—
g[21]	4-ClC_6H_4	Indol-3-yl	67	258–59	—
h[22]	4-ClC_6H_4	Coumarin-3-yl	60	>320	—

In conclusion, a simple, efficient, two-step synthesis of 2,4-diamino-5-ketothiazoles suited to solid phase combinatorial synthesis has been achieved. This synthetic route allows easy amplification of molecular diversity in the target core structure by varying the isothiocyanates and α-haloketones, many of which are commercially available. The reaction conditions are mild, work-up is simple, and the steps are automation-friendly. The reuse of the spent resin was also investigated.[18] Further studies on the mechanistic aspects as well as the construction of combinatorial libraries are in progress and will be reported in due course.

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10. Aminomethylpolystyrene **8** was prepared from Merrifield resin (Sigma, 1% DVB cross-linked, 200–400 mesh, 0.9–1.1 mmole Cl/g) using the literature method[11] and its amino capacity was estimated to be 0.90 mmole NH_2/g by titrimetry.
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12. Solution phase pilot reactions on individual *n*-alkylamines with thiocarbamoyl transfer reagent **5a** in acetonitrile at 50–55 °C afforded the corresponding 1-(*N*-alkylamidino)-3-phenylthioureas as major products in good yields.
13. The sulfur capacities of the resins were measured after each reaction to evaluate the extent of thiocarbamoylamidine transfer. When transfer reagent **5** (R^1 = alkyl) was used, the extent of thiocarbamoylamidine transfer was found to be low.
14. Each vessel was charged with 1.5 g of resin **8** swelled in acetonitrile (10 mL) followed by the thiocarbamoylamidine transfer reagent **5** (2 M equiv based on the amino group capacity of the resin) and kept at 70–75 °C for 12–15 h with occasional mixing. The suspension was then filtered while hot. The resin beads were washed in succession with the following warm solvents: acetonitrile (5 mL × 3); petroleum ether (2 mL × 3); acetonitrile (5 mL × 2); ethanol (95%, 5 mL × 3) and finally methanol (5 mL × 2). The resin was then dried under vacuum.
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16. To resin **9a** (2.5 g, S capacity 0.8%), pre-swelled in DMF (10 mL), α-bromoketone **3a** (1 M equiv) was added and the suspension was heated at 60 °C with occasional shaking for 30 min. After adding triethylamine (1.1 equiv) which acts as a catalyst as well as a quench for the generated HBr, the suspension was kept at 60 °C for another 30 min and then left at room temperature overnight. The resulting orange-yellow mixture was filtered and the resin beads were washed with DMF (2 mL × 2). The filtrate and washings were combined and slowly added to ice-water (75 mL) with rapid stirring. This afforded a yellow solid (86%). To obtain a pure sample for analysis, the crude product was purified on a silica gel (60–120 mesh) column using ethyl acetate–petroleum ether (3:1) mixture as eluent to obtain **1a** (65%).
17. The crude product was analyzed by HPLC using a Shimadzu ODS column (25 cm × 4.6 mm) using a 1% TFA water–acetonitrile gradient.
18. The reuse of spent resin was explored by thoroughly washing it with a variety of solvents, drying and then taking it through the synthetic cycle as described above. As a typical example, thiazole **1b** was obtained in 68% crude and 47% purified yield. Further repetition of the cycle deleteriously affected the yield and purity of the product.
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20. *Compound* **1f**: IR (KBr) ν_{max}: 3467, 3267, 1622, 1528, 1445, 824, 741 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6): δ 7.20 (t, *J* 7.8 Hz, 1H, ArH), 7.48 (t, *J* 8.1 Hz, 2H, ArH), 7.71–7.77 (m, 4H, ArH), 7.89 (dd, *J* 8.53, 1.73 Hz, 1H, ArH), 8.08–8.18 (m, 3H, ArH), 8.39 (br, 2H, ArH and NH), 10.92 (s, 1H, NH); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ 92.65, 119.05, 123.42, 124.33, 126.86, 127.47, 127.71, 128.15, 132.17, 133.72, 139.31, 139.62, 167.27, 182.61. Anal. Calcd for $C_{20}H_{15}N_3OS$: C, 69.54; H, 4.38; N, 12.17. Found: C, 69.29; H, 4.62; N, 12.05.
21. *Compound* **1g**: IR (KBr) ν_{max}: 3392, 3298, 2993, 1635, 1584, 1490, 1452, 1315, 1242, 1177, 1012, 823, 757, 676 cm^{-1}; ^1H NMR: (200 MHz, DMSO-d_6 + $CDCl_3$): δ 7.15–7.22 (m, 2H, ArH), 7.27 (d, *J* 5.9 Hz, 2H, ArH), 7.34 (br, 2H, NH_2), 7.42 (d, *J* 5.1 Hz, 1H, ArH), 7.59 (d, *J* 5.9 Hz, 2H, ArH), 7.79 (d, *J* 1.9 Hz, 1H, ArH), 8.31 (d, *J* 5.1 Hz, 1H, ArH), 10.28 (s, 1H, NH), 11.06 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6 + $CDCl_3$): δ 92.67, 111.2, 117.41, 119.85, 120.57, 121.53, 122.23, 126.11, 127.09,

127.83, 128.40, 135.92, 138.18, 163.32, 165.59, 179.71; EIMS: *m*/*z* (%): 370 (M+2, 6), 368 (M^+, 12), 367 (7), 353 (7), 351 (15), 153 (4), 145 (10), 144 (100), 116 (26), 111 (3), 89 (24). Anal. Calcd for $C_{18}H_{13}ClN_4OS$: C, 58.61; H, 3.55; N, 15.19. Found: C, 58.56; H, 3.70; N, 15.28.

22. *Compound* **1h**: IR (KBr) ν_{max}: 3400, 3300, 1720, 1600, 1520, 1465, 1160, 1040, 820, 750 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6): δ 7.20–7.89 (m, 8H, ArH), 8.16 (br, 2H, NH), 8.27 (s, 1H, ArH), 10.93 (br, 1H, NH); EIMS: *m*/*z* (%): 399 (M+2, 20), 398 (M+1, 39), 397 (M^+, 65), 396 (100), 395 (68), 394 (47), 360 (15), 218 (8), 188 (13), 173 (52), 147 (72), 145 (18), 127 (70). Anal. Calcd for $C_{19}H_{12}ClN_3O_3S$: C, 57.36; H, 3.04; N, 10.56. Found: C, 57.20; H, 2.92; N, 10.62.