Synthesis of Chiral Polyaminothiazoles

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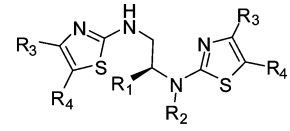
Received December 18, 2009

The thiazole ring system is an important structural element found in numerous biologically active compounds.[1] These have found applications in the development and preparation of drugs for the treatment of allergies,[2] inflammation,[3] schizophrenia,[4] hypertension,[5] and bacterial infections.[6] Compounds containing the aminothiazole moiety are also known to be a ligand of estrogen receptors[7] and adenosine receptor antagonists,[8] while other analogues exhibit antitumor properties.[9] Moreover, thiazole derivatives are reported to be potential inhibitors of cyclin-dependent kinases (CDKs)[10] and glycogen synthase kinase-3 (GSK-3).[11] 2-Aminothiazoles were successfully employed as heterocyclic bioisosteres of the phenol moiety on dopamine agonists and the widely used anti-Parkinsonian agent pramipexole. These resulted in improved pharmacological properties including longer duration of action and improved bioavailability.[12] Conjugated polyaminothiazole films were reported to display electrochemical properties with high thermal stability.[13] Herein, we describe an efficient approach for the parallel synthesis of diversified oligoaminothiazoles. Starting from resin-bound peptides, a range of differing oligothiazoles were synthesized.

Thiourea is known to be a convenient starting material to prepare 2-amino-1,3-thiazoles.[14,15] Our approach using Hantzsc's synthesis for the solid-phase synthesis of a variety of diaminothiazoles is outlined in Scheme 1. The parallel synthesis was performed starting from *p*-methylbenzhydrylamine (MBHA) resin bound acylated amino acid **1**. Following reduction of the amide bonds in the presence of borane-THF,[16] the corresponding resin-bound diamines **2** were treated with Fmoc-isothiocyanate to generate the corresponding dithioureas **3**. Following Fmoc deprotection, the resin-bound dithioureas were treated with a variety of α-halogenoketones to afford following cleavage of the solid-support, the desired diaminothiazoles **5**. The compounds were obtained in good yield (80 to 90%) and high purity (Table 1). The only byproduct observed was the monothiazole due to an incomplete reaction of the amine attached to the solid-support with Fmoc-isothiocyanate. We selected three amino acids, alanine, proline, valine, and phenylalanine, and three different halogenoketones, chloroacetone, 3-chloro-2-butanone, and 2-chlorocyclohexanone. Similar results were obtained with all the amino acids utilized and we did not observe any detrimental effect of the amino acid side chains on the reaction. Some incomplete reaction was observed with the 2-chlorocyclohexanone.



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The same approach was employed for the synthesis of different lengths of chiral polyaminothiazoles from their corresponding resin-bound chiral polyamines.[17] Table 2 shows examples of tetrathiazoles obtained from resin-bound tripeptides. All compounds were analyzed by LC-MS and selected ones by ^{1}H NMR and ^{13}C NMR.

Because of the well-understood chemistry, the availability of a wide diversity of chiral amino acids and the excellent synthetic purity and yields obtained during the solid-phase synthesis of peptides, the work presented offers a unique approach toward the synthesis of chiral polyaminothiazoles using resin-bound amino acids, peptides, and peptidomimetics as starting materials.

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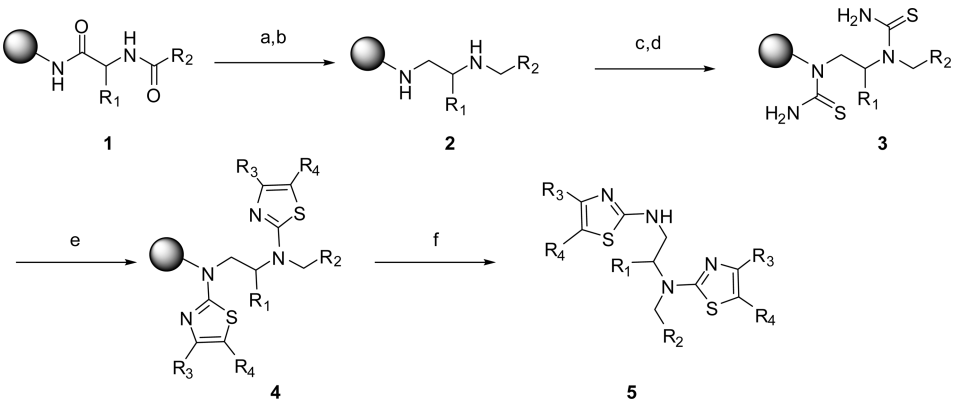
Scheme 1[a]



[a] (a) BH_3-THF, 65°C, 4 days; (b) piperidine, 65°C, overnight; (c) 6 equiv Fmoc-NCS in DMF (0.3 M), RT, overnight; (d) 20% piperidine/DMF; (e) 20 equiv α-halogenoketones in DMF (0.3 M), 70°C, overnight; (f) HF/anisole, 0°C, 90 min.

10.1021/cc9001907
Published on Web 03/10/2010

Table 1. Individual Products of Dithiazolo Derivatives

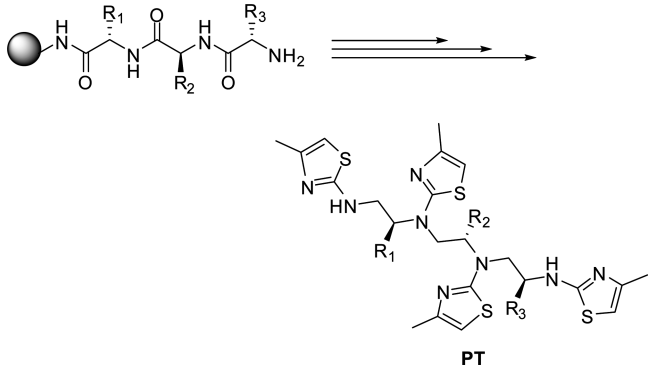
entry	R_1	R_2	R_3	R_4	MW obtained[a]	purity (%)[b]
5a	$-CH_3$	$-H$	$-CH_3$	$-H$	269.08 (MH^+)	88
5b	$-CH_3$	$-H$	$-CH_3$	$-CH_3$	297.11 (MH^+)	84
5c	$-CH_3$	$-H$	$-(CH_2)_4-$		349.19 (MH^+)	85
5d	$-CH_2C_6H_5$	$-H$	$-CH_3$	$-H$	345.13 (MH^+)	91
5e	$-CH_2C_6H_5$	$-H$	$-CH_3$	$-CH_3$	373.15 (MH^+)	86
5f	$-CH_2C_6H_5$	$-H$	$-(CH_2)_4-$		425.24 (MH^+)	82
5g	$-CH(CH_3)_2$	$-H$	$-CH_3$	$-H$	297.10 (MH^+)	90
5h	$-CH(CH_3)_2$	$-H$	$-CH_3$	$-CH_3$	325.14 (MH^+)	88
5i	$-CH(CH_3)_2$	$-H$	$-(CH_2)_4-$		377.25 (MH^+)	85
5j	$-CH_3$	$-CH_2CH_3$	$-CH_3$	$-H$	297.08 (MH^+)	92
5k	$-CH_3$	$-CH_2CH_3$	$-CH_3$	$-CH_3$	325.11 (MH^+)	87
5l	$-CH_3$	$-CH_2CH_2C_6H_5$	$-CH_3$	$-CH_3$	401.17 (MH^+)	89
5m	$-CH_3$	$-CH_2CH_2C_6H_5$	$-(CH_2)_4-$		453.17 (MH^+)	84
5n	$-CH_2C_6H_5$	$-CH_2CH_3$	$-CH_3$	$-H$	373.17 (MH^+)	90
5o	$-CH_2C_6H_5$	$-CH_2CH_3$	$-CH_3$	$-CH_3$	401.13 (MH^+)	92
5p	$-CH_2C_6H_5$	$-CH_2CH_2C_6H_5$	$-CH_3$	$-CH_3$	477.20 (MH^+)	88
5q	$-CH_2C_6H_5$	$-CH_2CH_2C_6H_5$	$-(CH_2)_4$		529.30 (MH^+)	84
5r	$-CH(CH_3)_2$	$-CH_2CH_3$	$-CH_3$	$-H$	325.13 (MH^+)	93
5s	$-CH(CH_3)_2$	$-CH_2CH_3$	$-CH_3$	$-CH_3$	353.15 (MH^+)	85
5t	$-CH(CH_3)_2$	$-CH_2CH_2C_6H_5$	$-CH_3$	$-CH_3$	429.21 (MH^+)	89
5u	$-CH(CH_3)_2$	$-CH_2CH_2C_6H_5$	$-(CH_2)_4-$		481.28 (MH^+)	87
5v	$-(CH_2)_3$[c]$-$		$-CH_3$	$-CH_3$	322.13 (MH^+)	94

[a] Determined by ESI-MS. [b] The products were run on a Vydac column, gradients 5−95% formic acid in ACN in 7 min. The purity was estimated on analytical traces at $\lambda = 214$ and 254 nm. [c] Derived from proline.

Table 2. Individual Products of Tetrathiazole Derivatives

entry	R_1	R_2	R_3	MW obtained[a]	purity (%)[b]
PT-1	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2CH(CH_3)_2$	771 (MH^+)	83
PT-2	$-CH_2C_6H_5$	$-CH_2C_6H_4OH$	$-CH_2CH(CH_3)_2$	787 (MH^+)	85
PT-3	$-CH_2C_6H_5$	$-CH_2CH(CH_3)_2$	$-(CH_2C_6H_5$	771 (MH^+)	88
PT-4	$-CH_2C_6H_5$	$-CH_2CH(CH_3)_2$	$-CH_2CH(CH_3)_2$	737 (MH^+)	85
PT-5	$-CH_2C_6H_4OH$	$-CH_2C_6H_5$	$-CH_2C_6H_5$	821 (MH^+)	88
PT-6	$-CH_2C_6H_4OH$	$-CH_2C_6H_5$	$-CH_2CH(CH_3)_2$	787 (MH^+)	85
PT-7	$-CH_2C_6H_4OH$	$-CH_2CH(CH_3)_2$	$-(CH_2CH(CH_3)_2$	752 (MH^+)	82

[a] Determined by ESI-MS. [b] The products were run on a Vydac column, gradients 5−95% formic acid in ACN in 7 min. The purity was estimated on analytical traces at $\lambda = 214$ and 254 nm.



Acknowledgment. The authors would like to thank the State of Florida Funding, NIH (1R03DA025850-01A1, Nefzi), NIH (5P41GM081261-03, Houghten), and NIH (3P41GM079590-03S1, Houghten) for their financial support.

Supporting Information Available. Structures of all the compounds, LC-MS, ES, and ^1H NMR of some dithiazoles, and LC-MS of all the tetrathiazoles. This information is available free of charge via the Internet at http://pubs.acs.org/.

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(17) General procedure for the synthesis of dithiazolo derivatives: 100 mg of MBHA resin (loading: 1.1 mmol/g) was sealed within a polypropylene mesh packet.[18] Reactions were carried out in polypropylene bottles. A solution of *N*-Boc-amino acid (6 equiv, 0.1 M in DMF), HOBt (6 equiv, 0.1 M in DMF), and DIC (6 equiv, 0.1 M in DMF) was added to the reaction vessel. The reaction mixture was shaken at room temperature for 2 h, followed by washing with DMF (2 times) and DCM (2 times). Upon removal of the Boc group with 55% TFA in DCM for 30 min, the resin was washed and neutralized with 5% DIEA in DCM. The resin-bound amine was reacted with carboxylic acid (10 equiv, 0.3 M in DMF), and DIC (10 equiv, 0.3 M in DMF) overnight, followed by washing with DMF (2 times) and DCM (2 times). Air dried resin-bound acylated peptide was reduced using BH_3-THF. Typical reaction conditions for the solid-phase reduction of polyamides consist of the treatment of resin-bound peptides with BH_3-THF at 65°C for 72 h. The generated resin-bound borane-amine complexes are then disproportionate following overnight treatment with neat piperidine at 65°C. The reduction is free of racemization. The generated amines were treated with Fmoc-isothiocyanate (6 equiv, 0.3 M in DMF) at room temperature overnight. The Fmoc group was removed with 20% piperidine in DMF (2 timesx10 minutes) followed by the addition of α-halogenoketones (20 equiv, 0.3 M in DMF). The reaction with α-halogenoketones was carried out at 70°C overnight. The cleavage of the product was carried out by the treatment with 100% anhydrous HF at 00C for 1.5 h, followed by nitrogen gas flow to remove the HF. The product was extracted by 95% acetic acid. After lyophilization, the products were characterized by electrospray LC-MS under ESI conditions and selected compounds by ^{1}H. **5e**: ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm) 7.17−7.34 (m, 5H), 3.95 (m, 1H), 3.25 (m, 2H), 3.40 (m, 2H) 2.87 (dd, J = 5.6 Hz, J = 13.8 Hz, 1H), 2.78 (dd, J = 7.7 Hz, J = 1.4 Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H); MS (ESI) calcd [MH$^+$] 373.14, found 373.3. **5f**: ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm) 7.16−7.36 (m, 5H), 6.5 (s, 1H), 3.93 (m, 1H), 3.21 (m, 1H), 2.98 (m, 1H), 2.88 (dd, J = 5.6 Hz, J = 14.0 Hz, 1H), 2.78 (dd, J = 7.4 Hz, J = 13.7 Hz, 1H), 2.46 (m, 4H), 2.38 (m, 4H), 1.7 (m, 8H); MS (ESI) calcd [MH$^+$] 425.2, found 425.6. **5p**: ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm) 8.18 (s, 1H), 7.15−7.30 (m, 10 H), 4.18 (m, 1H), 3.62 (m, 2H), 3.31 (m, 2H), 3.10 (m, 1H), 2.90 (dd, J = 6 Hz, J = 13.8 Hz, 1H), 2.75 (m, 1H), 2.63 (m, 1H), 2.49 (s, 3H), 2.07 (s, 3H), 1.97 (s, 3H); MS (ESI) calcd [MH+] 477.2, found 477.7.
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CC9001907