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Synthesis of Aminotetrazolyl Esters from Cyanogen Azide with Amino Esters

Young-Hyuk Joo,*[a] Soo Gyeong Cho,[b] Eun Mee Goh,[b] Damon A. Parrish,[c] and Jean'ne M. Shreeve*[d]

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Several α-amino esters (and their hydrochloride salts) were treated with cyanogen azide at ambient temperature in a mixture of water and acetonitrile to form chiral 5-aminotetrazole derivatives in good yields (47–69%). The cyanogen azide was prepared from cyanogen bromide and sodium azide. Other functionalized α-amino esters (cysteine, arginine, histidine, and serine) were formed in only trace amounts and were difficult to purify by column chromatography. All 5-aminotetrazoles (i.e., **1**–**8**) were characterized by IR spectroscopy, ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy, and elemental analysis. The structures of **3**–**7** were obtained by single-crystal X-ray structure analysis.

Introduction

Currently, as the most widely used type of tetrazole or aminotetrazole, substituted aminotetrazoles have been investigated for their use in bioorganic[1] and inorganic materials[2] as well as for their interesting applications to such matters as high energy density materials (HEDMs).[3] In recent years, many research groups have reported on a variety of applications for effective organocatalysts such as the tetrazole or triazole analogue of proline.[4] Many different synthetic methods and applications are known for substituted tetrazoles and are of considerable interest for medicinal and biological uses. Because of the importance of substituted tetrazoles, the development of new synthetic approaches with special reaction conditions continues to be an active area of research.

In 1969, the first investigation into the synthesis of ester-substituted aminotetrazoles led to their generation through alkylation of the triethylammonium salt of tetrazole with either ethyl bromoacetate or methyl chloroacetate.[5] However, the selective alkylation of aminotetrazoles was not possible because of the competitive formation between the 1- and 2-alkylated-5-aminotetrazoles. Separating the isomers was realized by fractional crystallization or fractional distillation, but in low yields. In the past few years, the most convenient route to 1-substituted 5-aminotetrazoles was through the addition of a primary amine to cyanogen azide, which was an efficient reagent under noncatalytic mild conditions.[6]

Herein, we describe the work leading to a series of 5-aminotetrazole derivatives of α-(5-aminotetrazolyl) esters. 5-Aminotetrazole esters may be of interest as a new class of organo materials or biologically active organic materials, which are realized in good yields through straightforward routes.

Results and Discussion

The previously reported synthesis of 5-aminotetrazole compounds through the reaction of cyanogen azide[7] with primary or secondary amines is very useful for the preparation of highly energetic materials.[6,8] We found that a variety of α-amino esters served as versatile intermediates for the synthesis of 1-substituted 5-aminotetrazoles, which could be used for biologically active organic materials. Synthetic reactions to give functionalized aminotetrazoles have now been extended by employing an excellent in situ method that involves reactions between cyanogen azide and primary amines (see Scheme 1).

At ambient temperature, the α-amino ester or its hydrochloride was dissolved in a mixture of water/acetonitrile in the presence of cyanogen azide, which was synthesized at 0 °C from cyanogen bromide and dry sodium azide in dry acetonitrile, and was cleanly converted into the aminotetrazolyl ester (see Scheme 1). In cases where the amino acid was protected by a methyl or ethyl group and was not unusually hindered, the reaction yields were 47–69% (**1**[5a] (47%), **2** (60%), **3** (69%), **4** (65%), **5** (61%), **6** (56%), **7**

[a] Department of Energetic Materials & Pyrotechnics, Hanwha Corporation Defence R&D Center,
Daejeon, 305-156, Korea
Fax: +82-42-8292623
E-mail: joo2011@hanwha.co.kr
Homepage: www.hanwha.com
[b] Defense Advanced R&D Center, Agency for Defense Development,
Daejeon 305-600, Korea
[c] Naval Research Laboratory, Code 6030
Washington, DC 20375-5001, USA
[d] Department of Chemistry, University of Idaho,
Moscow, ID 83844-2343, USA
Fax: +1-208-8859146
E-mail: jshreeve@uidaho.edu
Homepage: www.webpages.uidaho.edu/~jshreeve

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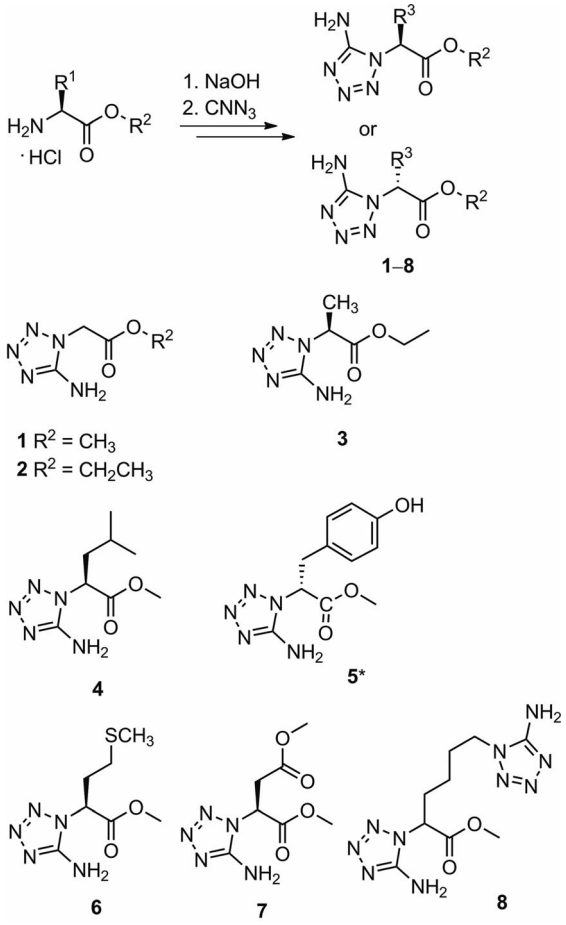

Scheme 1. Synthesis of 5-aminotetrazol-1-yl esters by cyclization. For the synthesis of **5***, neutral L-tyrosine methyl ester was used.

(53%), **8** (68%)]. The attractiveness of this route stems from the ease with which the amino ester precursors can undergo a one-step synthesis to form the aminotetrazole derivatives. Unfortunately, other functionalized amino esters (e.g., cysteine, serine, arginine, and histidine) were formed in only trace amounts and are purified with great difficulty using column chromatography. In contrast to other products, compound **5** formed the *R* enantiomer during the reaction. All of the α-(aminotetrazolyl) esters were characterized by the usual spectroscopic methods, and in the case of **3**–**7**, characterization was done by single-crystal X-ray diffraction analysis (see Figure 1).

Data collection was performed, and the unit cell was initially refined using APEX2 (v 2.1-0).[9a] The data reduction was performed using SAINT (v. 7.34A)[9b] and XPREP (v. 2005/2).[9c] Corrections were applied for Lorentz, polarization, and absorption effects using SADABS (v. 2004/1).[9d] The structure was solved and refined with the aid of the programs from the SHELXTL-plus (v. 6.12) system of programs.[9e] The full-matrix least-squares refinement on F^2 included the atomic coordinates and anisotropic thermal parameters for all of the non-hydrogen atoms. The H atoms were included using a riding model. Selected data and parameters for the X-ray determinations are given in Table 1. The crystallographic data obtained for **3**–**7** were compared to those for 5-amino-1-vinyltetrazole[10] and 1,5-diaminotetrazole (see Table 1 and Figure 1).[11,12] Not surprisingly the bond lengths for N-4–C-5 [1.345(6) Å] and C-5–N-15 [1.346(6) Å] of **6**, for example, are nearly equal, because the approximate planar geometry of the 5-amino group results from the considerable conjugation in the N-4–C-5–N-15 fragment. However, the bond length of N-2–N-3

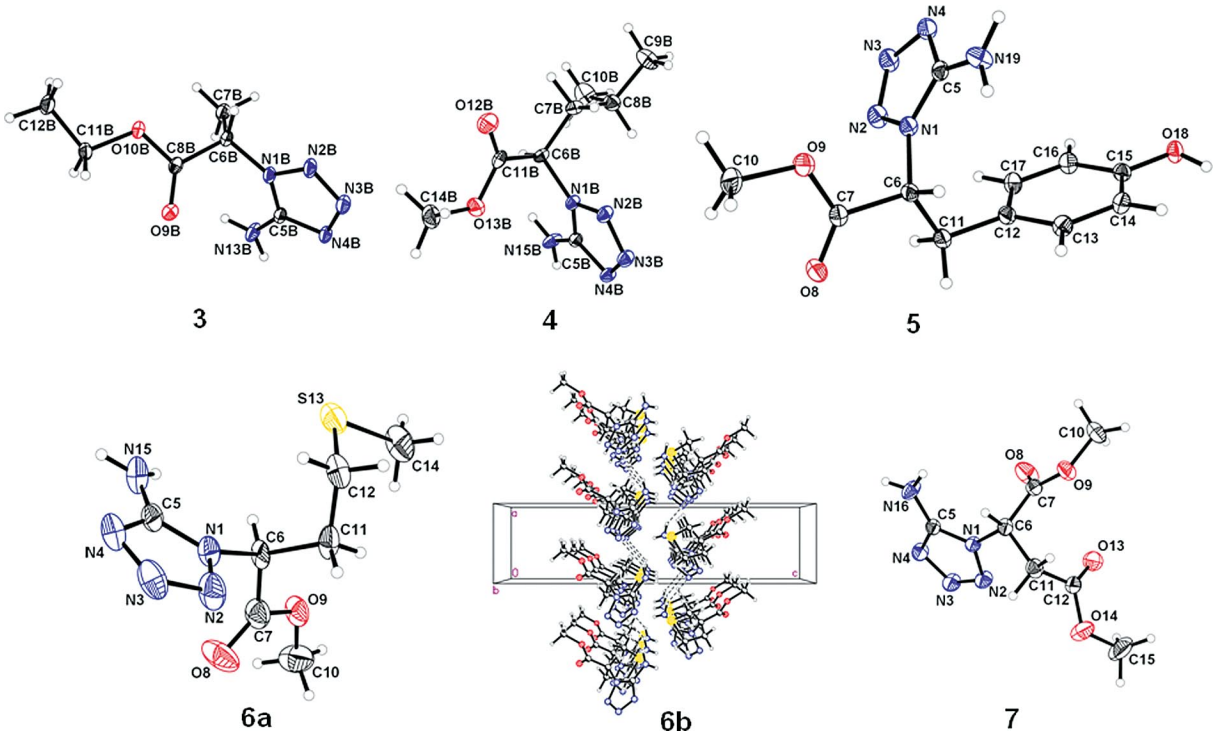

Figure 1. Single-crystal X-ray diffraction analysis of 5-aminotetrazole derivatives **3**–**7**.

Table 1. Crystallographic data for **3**–**7**.

	3	**4**	**5**	**6**	**7**
Empirical formula	$C_6H_{11}N_5O_2$	$C_8H_{15}N_5O_2$	$C_{11}H_{13}N_5O_3$	$C_7H_{13}N_5O_2S$	$C_7H_{11}N_5O_4$
Formula weight	185.20	213.25	263.26	231.28	229.21
Space group	C2	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a [Å]	14.548(3)	5.9590(12)	6.6796(13)	5.515(5)	6.0246(4)
b [Å]	10.364(2)	8.9155(18)	11.582(2)	9.037(5)	7.0045(4)
c [Å]	12.129(3)	42.852(9)	15.963(3)	22.386(8)	24.8977(16)
α [°]	90	90	90	90	90
β [°]	99.691(3)	90	90	90	90
γ [°]	90	90	90	90	90
V [Å^3]	1802.6(7)	2276.6(8)	1234.9(4)	1115.6(12)	1050.67(11)
Z	8	8	4	4	4
λ [Å]	0.71073	0.71073	0.71073	0.71073	0.71073
T [K]	100(2)	100(2)	100(2)	173(2)	293(2)
$D_{calcd.}$ [g cm^{-3}]	1.365	1.224	1.416	1.377	1.449
μ [mm^{-1}]	0.106	0.093	0.107	0.281	0.120
R_1 [$I > 2\sigma(I)$][a]	0.0308	0.0367	0.0286	0.0549	0.0375
wR_2 [$I > 2\sigma(I)$][b]	0.0758	0.0842	0.0725	0.0989	0.0952
CCDC number[c]	892135	892136	892137	892138	892139

[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$. [c] CCDC contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[1.305(5) Å] is slightly shorter than the adjacent single bonds of N-1–N-2 [1.364(5) Å] and N-3–N-4 [1.363(5) Å]. The bond lengths of N-2–N-3 for structures **3**–**7** lie between 1.280(14) and 1.305(5) Å, which are typical values observed for 5-aminotetrazoles. The amino group in **6b** forms an intermolecular interaction because of the weak hydrogen bonding of N-15···N-3_#1 [3.873(6) Å; symmetry transformation used to generate equivalent atoms: #1 = x – 1/2, $-y$ + 5/2, $-z$.].

In Figure 2, the ^{15}N NMR spectra of aminotetrazole derivatives **3**–**5** and **7** were measured in CD_3CN or [D_6]-DMSO solution, and the chemical shifts are given with respect to CH_3NO_2 as the external standard. In each ^{15}N NMR spectrum, there are the five signals for the aminotetrazole. The signals for the amine group (i.e., N-5) bonded to tetrazole appear at the highest field in all of the spectra. In the coupled ^{15}N NMR spectrum for compound **5**, the N-5 resonance is a triplet ($^1J_{N,H}$ = 88 Hz), as expected. The signals for N-2 and N-3 appear at the lowest field because of electronegativity effects. The assignments were made on the basis of the literature values for the chemical shifts of aminotetrazole.[6,8]

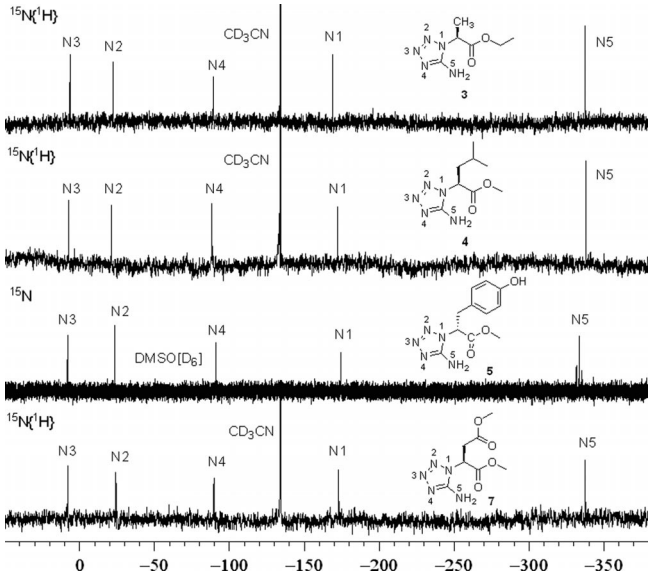

Figure 2. ^{15}N NMR spectra of **3**–**5** and **7**.

The calculations for the heats of formation, which is one of the important characteristics for aminotetrazoles, were performed by using the Gaussian 03 (Revision D.01) program.[13] The geometric optimization of the structures and frequency analyses were carried out by using the B3LYP functional with the 6-31+G** basis set,[14] and single-point energies were calculated at the MP2/6-311++G** level. All of the optimized structures were characterized as true local energy minima on the potential-energy surface without imaginary frequencies. The heats of formation for the compounds were computed by using the method of isodesmic reactions (see Supporting Information). The enthalpy of an isodesmic reaction (ΔH_{r298}°) was obtained by combining the MP2/6-311++G** energy difference for the reaction, the scaled zero-point energies (B3LYP/6-31+G**), and other thermal factors (B3LYP/6-31+G**).

Table 2. Physical properties of aminotetrazolyl esters **1**–**8**.

Compound	Yield [%]	Density[a] [g cm^{-3}]	M.p.[b] [°C]	ΔH_f[c] [kJ mol^{-1}]
1	47	–	188	–59.08
2	60	–	151	–93.21
3	69	1.365	130	–132.27
4	65	1.224	166	–171.61
5	61	1.416	159	–177.80
6	56	1.377	88	13.96
7	53	1.449	134	–452.54
8	68	–	166	192.78

[a] Calculated from X-ray structural data. [b] DSC. [c] Determined by using Gaussian 03.

Tetrazole compounds (**1**–**5** and **7**) exhibited negative heats of formation, whereas **6** and **8** had positive heats of formation (see Table 2). All of the tetrazoles were studied by differential scanning calorimetry (DSC), which showed that **1**–**8** had melting points between 88 and 188 °C (see Table 2). The densities of most of the new aminotetrazoles ranged between 1.224 and 1.449 g cm^{-3}, which were determined by single-crystal X-ray structure analysis.

Conclusions

In summary, under noncatalytic mild conditions, cyanogen azide was an efficient reagent for the synthesis of readily purified 1-substituted 5-aminotetrazoles from primary amino esters. The general procedure described herein is applicable to both amino esters and other primary amines to lead, in each case, to the preparation of 5-aminotetrazole derivatives in good yields.

Experimental Section

Safety Precautions: Pure cyanogen azide is extremely dangerous and toxic. When utilizing the substance as a reactant, it must always be dissolved in a solvent as a dilute solution. During the reaction, trace amounts of moisture resulted in the formation of the sodium 5-azidotetrazolate byproduct, and this highly explosive and shock-sensitive solid was subsequently isolated.[7,15] Manipulations must be carried out in a fume hood. Any excess amount of cyanogen azide in acetonitrile may be destroyed by adding it to triphenylphosphane or norbornene.[16]

General Methods: ^{1}H, ^{13}C, and ^{15}N NMR spectroscopic data were recorded at 300.13, 75.48, and 50.69 MHz, respectively, with 300 MHz (Bruker AVANCE 300) and 500 MHz (Bruker AVANCE 500) spectrometers. CD_3CN or [D$_6$]DMSO was used as the solvent and locking solvent. The melting and decomposition points were obtained with a differential scanning calorimeter (TA Instruments Company, Model Q10) at a scan rate of 10 °C min^{-1}. IR spectra were recorded, using KBr pellets for solids, with a BIORAD model 3000 FTS spectrometer. Elemental analyses were determined using an Exeter CE-440 elemental analyzer.

General Procedure: At 0 °C, cyanogen bromide (10 mmol) was dissolved in dry acetonitrile (50 mL). To this solution was added dry sodium azide (40 mmol). The reaction mixture was stirred at 0 °C for 4 h. The inorganic salt was removed by filtration. (***Caution!*** After filtration, the salt was quickly dissolved in cold water.) The cyanogen azide solution was added to a solution containing the amino ester (for **1**–**4**, **6**, and **7**, 5.0 mmol; for **8**, 2.5 mmol) in water (15 mL) at 0 °C. [For the ammonium chloride, NaOH (4.5 mmol) was required.] After stirring overnight at ambient temperature, the solvent was allowed to evaporate into the air. The product was purified by washing it with water and acetonitrile.

Methyl 2-(5-Amino-1*H*-tetrazol-1-yl)acetate (1): White solid (47%); m.p. 188 °C. IR (KBr): $\tilde{\nu}$ = 3335, 3250, 3153, 2988, 2950, 1737, 1659, 1643, 1589, 1491, 1412, 1377, 1236, 990, 813 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.80 (s, 2 H, NH_2), 5.12 (s, 2 H, CH_2), 3.71 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 167.1, 156.1, 52.5, 45.7 ppm. $C_4H_7N_5O_2$ (157.13): calcd. C 30.58, H 4.49, N 44.57; found C 30.36, H 4.35, N 44.22.

Ethyl 2-(5-Amino-1*H*-tetrazol-1-yl)acetate (2): White solid (60%); m.p. 151 °C. IR (KBr): $\tilde{\nu}$ = 3368, 3266, 3164, 2999, 2961, 2907, 1744, 1651, 1591, 1492, 1376, 1229, 1098, 1024 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.80 (s, 2 H, NH_2), 5.10 (s, 2 H, CH_2), 4.17 (q, ^3J = 7.1 Hz, 2 H, CH_2), 1.21 (t, ^3J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 166.6, 156.1, 61.5, 45.8, 13.9 ppm. $C_5H_9N_5O_2$ (171.16): calcd. C 35.09, H 5.30, N 40.92; found C 34.93, H 5.25, N 41.19.

Ethyl (*S*)-2-(5-Amino-1*H*-tetrazol-1-yl)propanoate (3): White solid (69%); m.p. 130 °C. $[\alpha]_D^{20}$ = –96.7 (c = 1.0, DMSO). IR (KBr): $\tilde{\nu}$ = 3332, 3185, 2985, 1744, 1652, 1589, 1225, 1084, 1023 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.74 (s, 2 H, NH_2), 5.27 (q, ^3J = 7.3 Hz, 1 H, CH), 4.14 (dq, ^2J = 2.4 Hz, ^3J = 7.1 Hz, 2 H, CH_2), 1.71 (d, ^3J = 7.3 Hz 3 H, CH_3), 1.17 (t, ^3J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 168.7, 155.7, 61.6, 52.9, 16.1, 13.9 ppm. ^{15}N NMR (50.7 MHz, [D$_6$]DMSO): δ = 12.8, –19.4, –84.7, –129.1, –168.0, –332.5 ppm. $C_6H_{11}N_5O_2$ (185.18): calcd. C 38.91, H 5.99, N 37.82; found C 38.69, H 6.07, N 37.94. The structure of **3** was supported by single-crystal X-ray structure analysis.

Methyl (*S*)-2-(5-Amino-1*H*-tetrazol-1-yl)-4-methylpentanoate (4): White solid (65%); m.p. 166 °C. $[\alpha]_D^{20}$ = –63.3 (c = 1.0, DMSO). IR (KBr): $\tilde{\nu}$ = 3338, 3161, 2961, 2872, 1757, 1653, 1592 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.83 (s, 2 H, NH_2), 5.25 (dd, ^3J = 4.1 Hz, ^3J = 11.2 Hz, 1 H, CH), 3.69 (s, 3 H, OCH_3), 2.25 (m, 1 H, H_a), 1.95 (m, 1 H, H_b), 1.29 (m, 1 H), 0.86 (s, 3 H, CH_3), 0.84 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 169.2, 156.0, 55.6, 52.8, 38.3, 24.3, 22.5, 20.6 ppm. ^{15}N NMR (50.7 MHz, [D$_6$]DMSO): δ = 12.3, –16.4, –83.5, –129.1, –167.3, –332.9 ppm. $C_8H_{15}N_5O_2$ (213.24): calcd. C 45.06, H 7.09, N 32.84; found C 44.97, H 7.09, N 31.86. The structure of **4** was supported by single-crystal X-ray structure analysis.

Methyl (*R*)-2-(5-Amino-1*H*-tetrazol-1-yl)-3-(4-hydroxyphenyl)propanoate (5): At 0 °C, cyanogen bromide (10 mmol) was dissolved in dry acetonitrile (50 mL). To this solution was added dry sodium azide (40 mmol). The reaction mixture was stirred at 0 °C for 4 h. The inorganic salt was removed by filtration. (Caution! After filtration, the salt was quickly dissolved in cold water.) The cyanogen azide solution was added to a solution containing L-tyrosine methyl ester (5.0 mmol) in acetonitrile (50 mL) at 0 °C. After stirring overnight at ambient temperature, the solvent was allowed to evaporate into the air. The product was purified by washing it with water and acetonitrile to give **5** (61%) as a light yellow solid; m.p. 159 °C. $[\alpha]_D^{20}$ = –1.59 (c = 1.0, DMSO). IR (KBr): $\tilde{\nu}$ = 3465, 3319, 3255, 3198, 3018, 2957, 2897, 2815, 2751, 2693, 2619, 1761, 1641, 1516, 1464, 1283, 1249, 1229, 1175 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 9.24 (br. s, 1 H, OH), 6.89–6.92 (AA′XX′ system, 2 H, Ar), 6.66 (s, 2 H, NH_2), 6.60–6.63 (AA′XX′ system, 2 H, Ar), 5.46 (dd, ^3J = 4.8 Hz, ^3J = 10.8 Hz, 1 H, CH), 3.71 (s, 3 H, CH_3), 3.30–3.48 (m, 2 H, CH_2) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 168.4, 156.2, 156.0, 129.8, 125.9, 115.2, 58.6, 52.9, 34.9 ppm. ^{15}N NMR (50.7 MHz, [D$_6$]DMSO): δ = 8.1 (N-3), –23.6 (N-2), –90.9 (N-4), –174.5 (m, N-1), –333.4 (t, ^1J = 88 Hz, NH_2) ppm. $C_{11}H_{13}N_5O_3$ (263.25): calcd. C 50.19, H 4.98, N 26.60; found C 49.89, H 4.82, N 26.07. The structure of **5** was supported by single-crystal X-ray structure analysis.

(*S*)-Methyl 2-(5-Amino-1*H*-tetrazol-1-yl)-4-(methylthio)butanoate (6): Colorless crystals (56%); m.p. 88 °C. $[\alpha]_D^{20}$ = –10.6 (c = 1.0, DMSO). IR (KBr): $\tilde{\nu}$ = 3329, 3171, 2952, 2923, 1751, 1648, 1579, 1440, 1296, 1275, 1236, 1179, 1123 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.82 (s, 2 H, NH_2), 5.35 (m, 1 H), 3.69 (s, 3 H, OCH_3), 2.31–2.54 (m, 4 H), 2.03 (s, 3 H, SCH_3) ppm. ^{13}C NMR

(75.5 MHz, [D$_6$]DMSO): δ = 168.7, 156.2, 56.0, 52.9, 29.3 (2 C), 14.4 ppm. $C_7H_{13}N_5O_2S$ (231.28): calcd. C 36.35, H 5.67, N 30.28; found C 36.41, H 5.67, N 29.82. The structure of **6** was supported by single-crystal X-ray structure analysis.

(*S*)-Dimethyl 2-(5-Amino-1*H*-tetrazol-1-yl)succinate (7): White solid (53%); m.p. 134 °C. $[a]_D^{20}$ = –67.6 (*c* = 1.0, DMSO). IR (KBr): $\tilde{\nu}$ = 3344, 3173, 2963, 1747, 1661, 1588, 1469, 1439, 1375, 1290, 1236, 1174, 1085, 1015, 988, 858 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.90 (s, 2 H, NH$_2$), 5.55 (dd, ^3J = 7.5 Hz, ^3J = 7.6 Hz, 1 H), 3.69 (s, 3 H, OCH$_3$), 3.60 (s, 3 H, OCH$_3$), 3.30 (d, ^3J = 7.7 Hz, 2 H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 169.6, 167.7, 155.9, 53.6, 53.0, 51.9, 34.6 ppm. ^{15}N NMR (50.7 MHz, [D$_6$]-DMSO): δ = 11.3, –17.6, –84.5, –129.1, –164.2, –332.6 ppm. $C_7H_{11}N_5O_4$ (229.19): calcd. C 36.68, H 4.84, N 30.56; found C 36.13, H 4.69, N 30.16. The structure of **7** was supported by single-crystal X-ray structure analysis.

Methyl 2,6-Bis(5-amino-1*H*-tetrazol-1-yl)hexanoate (8): White solid (68%); m.p. 166 °C. IR (KBr): $\tilde{\nu}$ = 3349, 3175, 2953, 1753, 1656, 1588, 1457, 1270, 1212, 1122, 1080, 1005 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.82 (s, 2 H, NH$_2$), 6.64 (s, 2 H, NH$_2$), 5.24 (dd, ^3J = 7.4 Hz, ^3J = 7.4 Hz, 1 H), 4.04 (t, ^3J = 7.1 Hz, 2 H), 3.67 (s, 3 H, OCH$_3$), 2.17–2.24 (m, 2 H, CH$_2$), 1.71 (m, 2 H), 1.12–1.32 (m, 2 H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 168.7, 156.1, 155.2, 56.9, 52.7, 44.0, 29.4, 27.6, 22.2 ppm. $C_9H_{16}N_{10}O_2$ (296.29): calcd. C 36.48, H 5.44, N 47.27; found C 36.35, H 5.49, N 47.31.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of tetrazoles **1**–**8**, isodesmic reaction scheme, and computational data.

Acknowledgments

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