Synthesis of *N*-(5-Aminopyrazol-3-yl)amino and *N*-(5-Amino-1,2,4-triazol-3-yl)amino Acids

Masataka Yokoyama,* Katsushi Kumata, Hidehiko Noro, Akemi Kogo

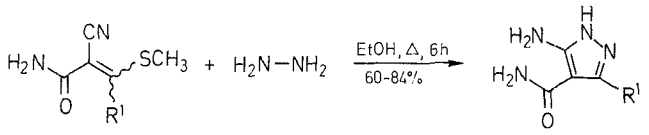
Department of Chemistry, Faculty of Science, Chiba University, Yayoi-cho, Chiba City 260, Japan

Some *N*-(5-aminopyrazol-3-yl) and *N*-(5-amino-1,2,4-triazol-3-yl) derivatives of amino acids or dipeptides are synthesized in good yields from the reaction of α-(aminocarbonyl)-α-cyanoketene dithioacetals with amino acid or dipeptide *tert*-butyl esters and cyclocondensation of the resultant α-(aminocarbonyl)-α-cyanoketene *S,N*-acetals [*N*-(2-aminocarbonyl-2-cyano-1-methylthioethenyl)amino acid derivatives] with hydrazine hydrate.

We recently reported some syntheses of heterocycles using ketene dithioacetals, in which a methylthio group acts as an effective leaving group.[1]

In connection with that study, we now present the synthesis of some pharmaceutically interesting pyrazoles and triazoles.

Reaction of the easily availaible ketene dithioacetal **1a** or the 3-methylthio-3-phenylacrylamide **1b** with hydrazine hydrate in boiling ethanol affords 3-substituted 5-amino-4-aminocarbonyl-pyrazoles **2a, b** in good yields.



1a, b

a $R^1 = SCH_3$
b $R^1 = C_6H_5$

2a, b

Using this method, we could also synthesize some pyrazoles and triazoles having an amino acid moiety which show an antihypertensive effect to be reported later). The amino acid derivatives **3**, which were required for the cyclocondensation with hydrazine, were prepared from 3,3-bis(methylthio)-2-cyanoacrylamide (α-aminocarbonyl-α-cyanoketene dimethyl dithioacetal, **1a** and amino acid *tert*-butyl esters (and a dipeptide ester). Heating of compounds **3** with hydrazine hydrate in boiling ethanol for 6 h gave the *N*-(5-amino-4-aminocarbonylpyrazol-3-yl)amino acid (or -dipeptide) esters **4** in good yields. Treatment of compounds **4** with trifluoroacetic acid at room temperature for 3 h led to ester cleavage to afford the free amino acid trifluoroacetates **5** in nearly quantitative yields.

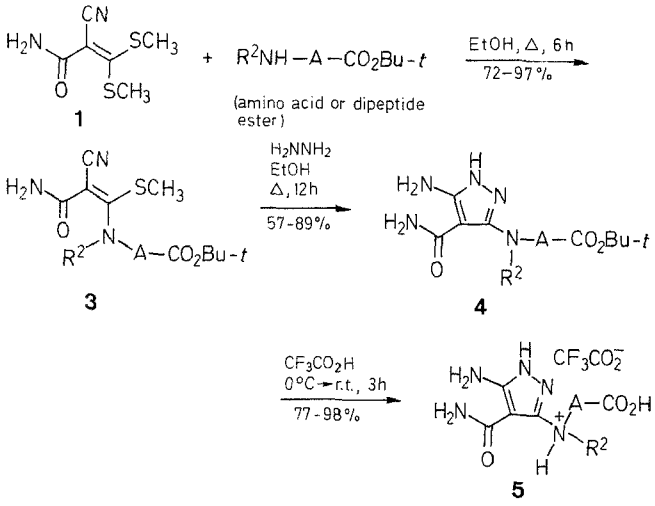
In a similar way, dimethyl *N*-cyanocarbonimidodithioate **(6)** was converted into the *N*-[cyanoimino(methylthio)methyl]-

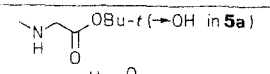
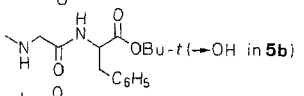
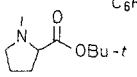
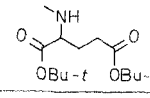
Table. Compounds **1–5**, **7**, **8** Prepared

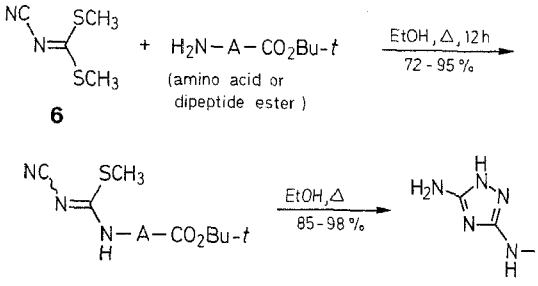
Compound	Yield (%)	mp (°C)	$[\alpha]_D^{25}$ (*c*, Solvent)	Molecular Formula[a]	MS *m/z* (M^+)	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, *J*(Hz)
1b[b]	78	202–204		$C_{11}H_{10}N_2OS$ (218.1)	218	3360, 3140, 2200, 1685	1.62, 1.82 (s, 3H); 5.6–6.2 (br, 2H); 7.1–7.3 (br, 5H)
2a	84	171–172		$C_5H_8N_4OS$ (172.1)	172	3400, 3360, 3300, 3100, 2900, 2840, 1600	2.50 (s, 3H); 3.82 (br, 2H); 6.00 (br, 1H); 6.75 (br, 2H)
2b	60	207–208		$C_{10}H_{10}N_4O$ (202.1)	202	3450, 3380, 3300, 3100, 1660	5.8–6.3 (br, 2H); 7.1–7.6 (m, 8H)
3a	83	126–127		$C_{11}H_{17}N_3O_3S$ (271.2)	271	3350, 3180, 2950, 2200, 1740	1.42 (s, 9H); 2.56 (s, 3H); 4.15 (d, 2H, $J = 4$); 5.90 (br, 2H); 10.9 (br, 1H)
3b	95	136–137	+0.83 (0.96, EtOH)	$C_{20}H_{26}N_4O_4S$ (418.3)	418	3400, 3300, 3170, 2950, 2200, 1720, 1670, 1640	1.40 (s, 9H); 2.48 (s, 3H); 3.05 (d, 2H, $J = 4$); 4.15 (d, 2H, $J = 4$); 4.60–4.80 (m, 1H); 5.82 (br, 2H); 6.60 (d, 1H, $J = 8$); 6.90–7.20 (br, 6H)
3c	72	142–143	+243 (0.38, EtOH)	$C_{14}H_{21}N_3O_3S$ (311.4)	311	3370, 3300, 2900, 2800, 2180, 1710	1.40 (s, 9H); 1.70–2.10 (br, 4H); 2.52 (s, 3H); 3.50–3.70 (br, 2H); 4.60–4.70 (br, 1H); 5.50–5.70 (br, 2H)
3d	97	oil[g]	−9.13 (1.78, EtOH)	$C_{18}H_{29}N_3O_5S$ (399.5)	399	3330, 3190, 2980, 2910, 2190, 1720[c]	1.40 (s, 9H); 1.42 (s, 9H); 1.90–2.30 (br, 4H); 2.58 (s, 3H); 4.50–4.70 (br, 1H); 5.95 (br, 2H); 10.8 (d, 1H, $J = 4$)
4a	89	170–171		$C_{10}H_{17}N_5O_3$ (255.2)	255	3420, 3300, 3150, 2950, 1738, 1720	1.36 (s, 9H); 4.12 (s, 2H); 6.12 (br, 3H); 6.8–7.1 (br, 3H)
4b	71	174–175	+1.59 (1.07, EtOH)	$C_{19}H_{26}N_6O_4$ (402.3)	402	3300, 3050, 2950, 1730, 1640	1.30 (s, 9H); 3.06 (d, 2H, $J = 7$); 3.30 (br, 1H); 4.12 (s, 2H); 4.90 (m, 1H); 5.4–6.2 (br, 3H); 6.85 (br, 2H); 7.04 (s, 5H); 8.30 (br, 1H)[d]
4c	66	165–166	+48.6 (0.29, EtOH)	$C_{13}H_{21}N_5O_3$ (295.3)	295	3420, 3320, 3120, 2960, 1720	1.30 (s, 9H); 1.60–2.10 (br, 4H); 3.20–3.90 (br, 5H); 4.20 (br, 1H); 6.40–6.70 (br, 2H)[d]
4d	57	146–147	+8.60 (0.30, EtOH)	$C_{17}H_{29}N_5O_5$ (383.4)	383	3430, 3340, 2950, 2930, 1720	1.40 (s, 9H); 1.42 (s, 9H); 1.95 (br, 2H); 2.20–2.40 (br, 2H); 3.95–4.20 (dd, 1H, $J = 6$); 5.10–5.40 (br, 1H); 5.80–7.10 (br, 5H)[d]
5a	~98	172–173 (dec)		$C_8H_{10}F_3N_5O_5$ (313.2)		3500–3200, 2950–2800, 1750–1600	4.00 (s, 2H)[e]
5b	77	oil[h]	+14.8 (0.44, H_2O)	$C_{17}H_{19}F_3N_6O_6$ (460.4)		3400–3200, 1760–1620[c]	2.90–3.20 (m, 2H); 3.80 (d, 2H, $J = 5$); 4.50–4.60 (m, 1H); 7.10–7.30 (s, 5H)[e]
7a	90	96–98		$C_9H_{15}N_3O_2S$ (229.1)	229	3220, 2990, 2960, 2200, 1750	1.43 (s, 9H); 2.52 (s, 3H); 3.95 (d, 2H, $J = 4$); 6.4–6.5 (br, 1H)
7b	95	49–51	+0.44 (0.64, EtOH)	$C_{18}H_{24}N_4O_3S$ (376.2)	376	3350, 2960, 2910, 2200, 1730, 1670	1.33 (s, 9H); 2.44 (s, 3H); 2.96 (d, 2H, $J = 6$); 3.85 (d, 2H, $J = 4$); 4.56 (m, 1H); 6.56 (br, 1H); 6.8–7.1 (br, 6H)
7e	72	85–86	+10.4 (0.83, EtOH)	$C_{16}H_{21}N_3O_3S$ (335.2)	335	3540, 2950, 2905, 2200, 1740	1.39 (s, 9H); 2.39 (s, 3H); 3.13 (d, 2H, $J = 6$); 4.64 (m, 1H); 6.2–6.4 (br, 1H); 7.13 (br, 5H)
8a	90	41–42		$C_8H_{15}N_2O_2$ (171.1)	171	3200, 2950, 1730	1.40 (s, 9H); 4.12 (s, 2H); 6.5–7.2 (br, 4H)
8b	98	173–174	+23.0 (0.77, EtOH)	$C_{17}H_{24}N_6O_3$ (360.2)	360	3300, 3050, 2950, 1720	1.28 (s, 9H); 2.85 (d, 2H, $J = 6$); 3.1–4.0 (s, 2H); 4.36 (m, 1H); 5.0–5.7 (br, 4H); 6.99 (s, 5H); 7.60 (br, 1H)[f]
8e	85	126–128	−72.4 (0.46, EtOH)	$C_{15}H_{21}N_5O_2$ (303.2)	303	3410, 3320, 3060, 2960, 1720	1.32 (s, 9H); 3.20 (d, 2H, $J = 6$); 4.72 (m, 1H); 6.4–7.0 (br, 4H); 7.16 (m, 5H)[d]

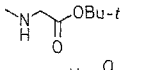
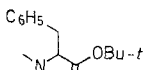
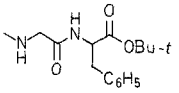
[a] Satisfactory microanalyses obtained: C ± 0.30, H ± 0.25, N ± 0.30.
[b] Obtained as a 1 : 9 mixture of stereoisomers.
[c] Neat, film.
[d] In $CDCl_3$/pyridine-d_5.
[e] In D_2O/TSP-*d*4 (sodium 3-trimethylsilylpropionate-2,2,3,3-*d*4).
[f] In $CDCl_3$/DMSO-d_6.
[g] bp 245–250°C/2 Torr (dec)
[h] bp 166–167°C (dec)

amino acid derivatives **7** which were allowed to react with hydrazine hydrate to give the *N*-(5-amino-1,2,4-triazol-3-yl) amino acid derivatives **8**.



Compound	$-NR^2-A-CO_2Bu-t$ (→ $-NR^2-A-CO_2H$)
3a, 4a, 5a	
3b, 4b, 5b	
3c, 4c	
3d, 4d	



Compound	$-NH-A-CO_2Bu-t$	Compound	$-NH-A-CO_2Bu-t$
7a, 8a		**7e, 8e**	
7b, 8b			

3,3-Bis(methylthio)-2-cyanoacrylamide (α-Aminocarbonyl-α-cyanoketene Dimethyl Dithioacetal, **1a**) was prepared by our method.[2] The amino acid *tert*-butyl esters were prepared from the corresponding amino acids in the usual way.[3] Glycyl-L-phenylalanine *tert*-butyl ester was prepared according to Ref. 4.

2-Cyano-3-methylthio-3-phenylacrylamide (1b):
To a stirred suspension of NaH (50% oil dispersion; 2.8 g, washed with hexane) in THF (10 mL) is added cyanoacetamide (1.68 g, 20 mmol) and the mixture is heated at reflux temperature for 1 h. Then, methyl dithiobenzoate (3.69 , 22 mmol) is added at 0 °C and stirring is continued for 4 h at room tempterature. The mixture is quenched with H_2O (20 mL) at 0 °C, and washed with benzene (~ 20 mL). The H_2O layer is stirred with CH_3I (2 mL) for 4 h, and then extracted with EtOAc (3 × 20 mL). The extract is dried (Na_2SO_4) and evaporated to give a white powder which is recrystallized from hexane/EtOAc; yield of **1b**: 3.4 g (78%); mp 202–204 °C.

5-Amino-4-aminocarbonyl-3-methylthiopyrazole (2a):
A mixture of 3,3-bis(methylthio-2-cyanoacrylamide (**1a**; 206 mg, 1.1 mmol), hydrazine hydrate (0.08 mL, 1.2 mmol), and EtOH (10 mL) is heated to reflux for 6 h.

The solvent is then removed under vacuum. The residue is purified by TLC on silica gel (eluent: EtOAc) to give **2a** as a white powder; yield: 160 mg (84%); mp 171–172 °C.

4-Amino-4-aminocarbonyl-3-phenylpyrazole (2b):
Prepared from 2-cyano-3-methylthio-3-phenylacrylamide (**1b**) by the procedure given for **2a**, and purified by TLC on silica gel (EtOAc/hexane 2:1 as eluent); yield: 60%; mp 207–208 °C.

(*E*)-*N*-(2-Aminocarbonyl-2-cyano-1-methylthioethenyl)-L-amino Acid (or Dipeptide) *tert*-Butyl Esters 3; General Procedure:
A mixture of 3,3-bis(methylthio)-2-cyanoacrylamide (**1a**; 187 mg, 1 mmol), the L-amino acid (or dipeptide) *tert*-butyl ester (1 mmol), and EtOH (10 mL) is heated at reflux temperature for 6 h. The solvent is then removed at reduced pressure. The residue is purified by TLC on silica gel (eluent: hexane/EtOAc) to give 3 (see Table).

***N*-(5-Amino-4-aminocarbonylpyrazol-3-yl)-L-amino Acid (or Dipeptide) *tert*-Butyl Esters 4; General Procedure:**
A mixture of the *N*-substituted L-amino acid (or dipeptide) ester **3** (1 mmol), hydrazine hydrate (0.08 mL, 1.2 mmol), and EtOH (10 mL) is heated at reflux temperature for 12 h. The solvent is then removed at reduced pressure. The resulting precipitate is collected and recrystallized from ethanol to give **4** (see Table).

***N*-(5-Amino-4-aminocarbonylpyrazol-3-yl)glycine Trifluoroacetate (5a); Typical Procedure:**
To the powdered ester **4a** (200 mg, 0.78 mmol), trifluoroacetic acid (2.4 mL) is added dropwise at 0 °C with stirring and the mixture is stirred at room temperature for 3 h. It is then rotary-evaporated to give a pale yellow syrupy material. This is triturated with dry Et_2O to form a white powder which is isolated and washed with dry Et_2O to give product **5a**; yield: 244 mg (98%); mp 172–173 °C (dec).

***N*-(5-Amino-4-aminocarbonylpyrazol-3-yl)glycyl-L-phenylalanine Trifluoroacetate (5b):**
Prepared from **4b** by the same procedure; yield: 77%; oil; bp 166–167 °C (dec).

***N*-[Cyanoimino(methylthio)methylglycine *tert*-Butyl Ester (7a); Typical Procedure:**
A mixture of dimethyl carbimidodithioate (**6**; 731 mg, 5 mmol), glycine *tert*-butyl ester (670 mg, 5 mmol), and EtOH (20 mL) is heated to reflux overnight. The mixture is rotary evaporated to give yellow crystals which are recrystallized from hexane/EtOAc; yield of colorless **7a**: 1.03 g (90%); mp 96–98 °C.

Compounds **7b** and **7e** are prepared in an analogous manner (see Table).

***N*-(5-Amino-1,2,4-triazol-3-yl)-L-amino Acid (or Dipeptide) *tert*-Butyl Esters 8a, 8b, and 8c:**
These compounds are prepared from amino acid (or dipeptide) derivatives **7a**, **7b**, or **7e**, respectively, and hydrazine hydrate using the general procedure given for the synthesis of esters **4**. See Table.

This work was partially supported by The Ministry of Education, Japan, in the form of a Grant-in-Aid for Scientific Research.

Received: 22 June 1987; revised: 15 February 1988

(1) Yokoyama, M., Tsuji, K., Imamoto, T. *Bull. Chem. Soc. Jpn.*, **1984**, *57*, 2954.
Yokoyama, M., Tsuji, K., Kushida, M. *J. Chem. Soc. Perkin Trans. 1* **1986**, 67.
(2) Takeshima, T., Yokoyama, M., Fukada, N., Akano, M. *J. Org. Chem.* **1970**, *35*, 2438.
(3) Anderson, G.W., Callahan, F.M. *J. Am. Chem. Soc.* **1960**, *82*, 3359.
(4) Bodanszky, M., Bodanszky, A. *The Practice of Peptide Synthesis*, Springer-Verlag, Heidelberg, 1984, p. 145.