WITH COMPLINENTS OF THE AUTHORS

SYNTHETIC COMMUNICATIONS, 29(10), 1757-1766 (1999)

A CONVENIENT ROUTE TO CYANOGUANIDINES

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Abstract: A facile and versatile method for the preparation of cyanoguanidines **7** from amines **3** and isothiocyanates **4** *via* a methylation, cyanamide-treatment sequence is described.

The cyanoguanidine moiety is an integral part of numerous biologically active compounds such as *Cimetidine* **1**, the antipeptic ulcer agent[1], and *Pinacidil* **2**, the antihypertensive agent[2]. Therefore, the synthesis of cyanoguanidine derivatives is the subject of various recent researches. Most of these compounds are usually derived from the corresponding urea or thiourea through carbodiimide or *S*-alkylisothiouronium salt intermediates[3,4,5]. These reactions, however,

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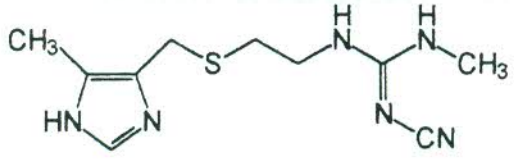
proceeded in poor yields and moreover, the reaction conditions were incompatible with sensitive groups within the molecule.



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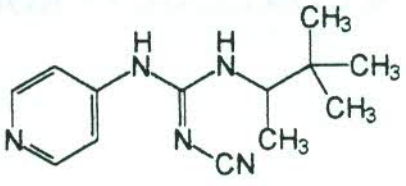

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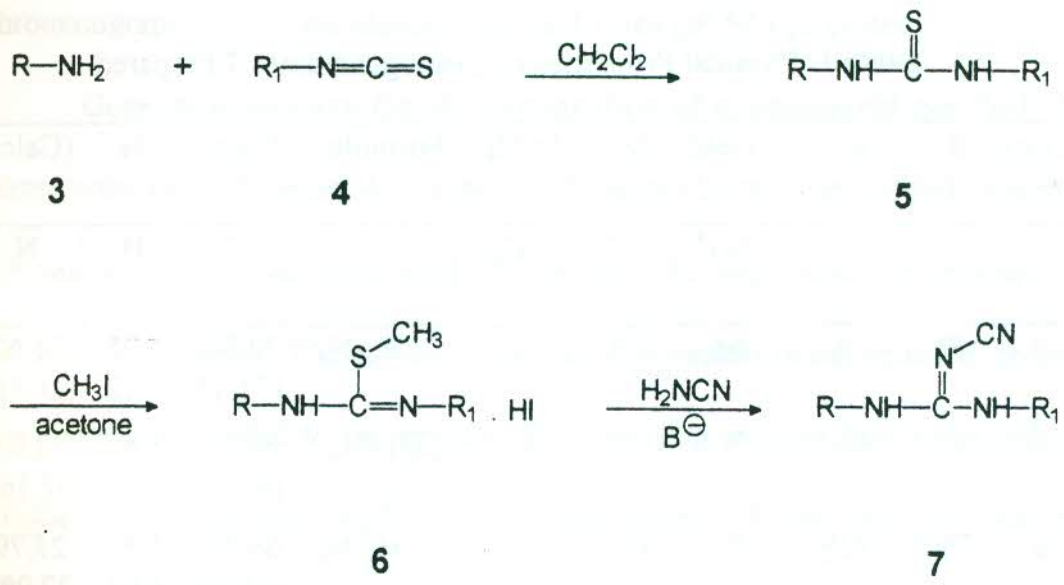
The direct conversion of thiourea into cyanoguanidine by the implication of DCC suffered from the long reaction time (sometimes several days), poor yield (~20%), and difficulty of purification of product[6,7]. Recently *Atwal and co-workers*[8] have improved this reaction by the replacement of DCC with a water-soluble carbodiimide: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. When thiourea derivatives were reacted with cyanamide in ethereal solution, cyanoguanidines were isolated in moderate yields[9]. In the literature, other procedures for the preparation of cyanoguanidines are also described[10].

In our recent investigations, several new cyanoguanidine derivatives were needed. Overcoming the problems of the above synthetic methods, we have elaborated a synthetic procedure for their preparation. In our procedure, amines **3** were reacted with isothiocyanates **4** in CH_2Cl_2 affording thioureas **5** in excellent yield [11]. Methylation of **5** with methyl iodide in acetone furnished thioethers **6** as hydrogen iodide salt almost quantitatively [12] (**Scheme 1**).

Scheme 1



Upon treatment of these salts **6** with cyanamide in boiling butanol in the presence of catalytic amount (15 %) of a strong base (1,4-diazabicyclo-[2.2.2]octane), cyanoguanidines **7** were obtained in high yields. **Table 1** shows the yields and melting points of cyanoguanidines prepared by this route.

NMR measurements of the intermediate **6** showed two series of data, indicating hindered rotation over the N-C-S axis (see experimental).

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on Specord 75 IR spectrometer. If otherwise not mentioned, ^{1}H and ^{13}C NMR were obtained with Bruker DRX-500 spectrometer internal standard TMS. Splitting patterns are designated as "s, d, t, q, m, and br", these symbols indicate "singlet, doublet, triplet, quartet, multiplet, and broad", respectively. All solvents were dried by

Table 1. Physical Properties of Cyanoguanidines **7** Prepared.

Entry	R	R_1	Yield	Mp	lit.Mp	Formula	Found	%	(Calc.)
			(%)♦	(°C)	(°C)		C	H	N
a	Ph	Ph	68	199	202[3]	$C_{14}H_{12}N_4$	70.94 (71.17	5.23 5.12	23.62 23.71)
b	Ph	Me	70	142	142[3]	$C_9H_{10}N_4$	62.21 (62.05	5.61 5.79	32.07 32.16)
c	Ph	Allyl	77	116	-	$C_{11}H_{12}N_4$	66.07 (65.98	5.89 6.04	27.79 27.98)
d	Ph	Cyc*	77	128	-	$C_{14}H_{18}N_4$	69.52 (69.39	7.57 7.49	23.23 23.12)
e	Cyc*	Me	73	150	-	$C_9H_{16}N_4$	59.79 (59.97	8.65 8.59	31.24 31.08)
f	Cyc*	Allyl	76	92	-	$C_{11}H_{18}N_4$	63.91 (64.05	8.75 8.79	26.99 27.16)
g	Cyc*	Cyc*	73	192	177[13]	$C_{14}H_{24}N_4$	67.71 (67.70	9.79 9.74	22.39 22.56)
h	Bz	Ph	67	170	-	$C_{15}H_{14}N_4$	72.09 (71.98	5.76 5.64	22.38 22.29)
i	Bz	Me	73	150	-	$C_{10}H_{12}N_4$	63.72 (63.81	6.29 6.43	29.53 29.76)
j	Bz	Cyc*	69	134	-	$C_{15}H_{20}N_4$	70.21 (70.28	7.98 7.86	21.71 21.86)
k	Bu	Ph	74	118	115[14]	$C_{12}H_{16}N_4$	66.51 (66.64	7.58 7.46	25.78 25.90)
l	Bu	Cyc*	70	124	-	$C_{12}H_{22}N_4$	64.59 (64.83	9.73 9.97	25.04 25.20)

Cyc*= Cyclohexyl; ♦ Yields refer to pure isolated compounds.

means of standard methods. Reactions were followed by thin-layer chromatography (TLC) on Merck precoated silica gel 60 F_{254} plates.

General procedure for the preparation of cyanoguanidines 7a-l: To a stirred solution of thioether **6** (5 mmol) in butanol (20 ml) were added cyanamide (15 mmol) and 1,4-diazabicyclo[2.2.2]octane (80 mg), and the mixture was refluxed for 3 hours. The solvent was then evaporated under reduced pressure, and water was added to the residue. The resulting mixture was extracted with CH_2Cl_2. After drying ($MgSO_4$) and evaporating of the solvent, the pure cyanoguanidines **7** were obtained by recrystallisation.

1-Cyclohexyl-2,3-dimethylisothiourea hydroiodide (**6e**, recryst. hexane): Mp 177-8 °C. IR ν (KBr) cm^{-1}: 3340, 3100 (NH), 1600 (C=N). ^1H NMR (DMSO, δ, ppm): 1.09 (1H, m, H-4'), 1.26 (2H, m, H-3' and H-5'), 1.41 (2H, m, H-2' and H-6'), 1.58 (1H, m, H-4'), 1.72 (2H, m, H-3' and H-5'), 1.82 (2H, m, H-2', and H-6'), 2.65 (3H, br s, S-CH_3), 2.95 (3H, br s, N-CH_3), 3.53 and 3.60 (1H, br m, H-1'), 8.25 (0.4H, br, NH), 8.63 (1.2H, br, NH), 9.02 (0.4H, br, NH). ^{13}C NMR (DMSO, δ, ppm): 14.10 and 14.57 (S-CH_3), 24.67 (C-3' and C-5'), 24.73 (C-4'), 31.26 and 31.36 (N-CH_3), 31.36 and 32.17 (C-2'), 32.17 (C-6'), 53.28 and 55.30 (C-1'), 166.49 and 166.79 (C-S).

1-Allyl-3-cyclohexyl-2-methylisothiourea hydroiodide (**6f**, recryst. hexane): Mp 100 °C. IR ν (KBr) cm^{-1}: 3080 (NH), 1600 (C=N). ^1H NMR ($CDCl_3$, δ, ppm): 1.25 (1H, m, H-4"), 1.63 (2H, m, H-2" and H-4"), 1.78 (2H, m, H-3" and H-5"), 1.89 (4H, m, H-3", H-5" and H-6"), 2.02 (1H, br , H-2"), 2.93 (3H, br s, S-CH_3), 3.68

(0.5H, br s, H-1"), 4.20 (0.8H, br s, H-1'), 4.34 (0.5H, br s, H-1"), 4.59 (1.2H, br s, H-1'), 5.31 (1.5H, br m, H-3'), 5.53 (0.5H, m, H-3'), 5.90 (1H, br s, H-2'), 7.48 (0.4H, br s, NH), 8.43 and 8.92 (1H, br s, NH).

1-Butyl-2-methyl-3-phenylisothiourea hydroiodide (**6k**, recryst. hexane): Mp 105-6 °C. IR ν (KBr) cm^{-1}: 3150 (NH), 1600 (C=N). ^1H NMR (DMSO, δ, ppm): 0.89 (3H, br m, H-4'), 1.34 (2H, br s, H-3'), 1.65 (2H, br s, H-2'), 2.60 and 2.81 (3H, br s, S-CH_3), 3.53 (2H, br s, H-1'), 7.39 (2H, d, *J*= 7.5 Hz, H-2" and H-6"), 7.42 (1H, t, *J*= 7 Hz, H-4"), 7.50 (2H, m, H-3" and H-5"), 9.07 (1H, br s, NH), 10.75 (1H, br s, NH). ^{13}C NMR (DMS-d_6, δ, ppm): 13.70 (C-4'), 15.07 (S-CH_3), 19.40 (C-3'), 29.68 (C-2'), 44.60 (C-1'), 127.39 (C-2" and C-6"), 128.79 (C-4"), 129.64 (C-2" and C-5"), 135.46 (C-1"), 167.89 (C-S).

1-Butyl-3-cyclohexyl-2-methylisothiourea hydroiodide (**6l**, oil): IR ν (KBr) cm^{-1}: 3200 (NH), 1600 (C=N). ^1H NMR ($CDCl_3$, δ, ppm): 0.85 (3H, t, *J*= 7.5 Hz, H-4'), 1.05 (1H, m, H-4"), 1.26 (4H, m, H-3', H-3", and H-5"), 1.42 (1H, br s, H-4"), 1.52 (4H, m, H-2', H-2", and H-6"), 1.68 (2H, br s, H-3", and H-5"), 1.79 (2H, br s, H-2", and H-6"), 2.69 (3H, s, S-CH_3), 3.38 (2H, br s, H-1'), 3.57 and 3.74 (1H, br s, H-1"), 8.22 and 8.52 (1H, br s, NH), 8.60 and 9.02 (1H, br s, NH). ^{13}C NMR ($CDCl_3$, δ, ppm): 13.61 (C-4'), 14.93 and 15.14 (S-CH_3), 19.28 (C-3'), 24.62 (C-3" and C-5"), 29.45 (C-2'), 31.07 and 32.00 (C-6"), 43.63 and 44.42 (C-1'), 53.17 and 55.46 (C-1"), 165.83 (C-S).

N-Allyl-N'-cyano-N''-phenylguanidine (**7c**; recryst. Et_2O: CCl_4: *i*-PrOH= 4:1:4): IR ν (KBr) cm^{-1}: 3220 (NH), 2160 (C≡N), 1580 (C=N). ^1H NMR (80 MHz, $CDCl_3$, δ,

ppm): 4.0 (2H, q, H-1'), 5.1 (1H, m, NH), 5.2 (2H, d, H-3'), 5.7 (1H, m, H-2'), 7.4 (5H, m, aromatics), 7.9 (1H, br s, NH).

N-Cyano-N'-cyclohexyl-N''-phenylguanidine (**7d**; recryst. hexane: acetone= 1:5): IR ν (KBr) cm^{-1}: 3250, 3130 (NH), 2190 (C≡N), 1590, 1610 (C=N). ^1H NMR ($CDCl_3$, δ, ppm): 1.08 (2H, m, H-2' and H-6'), 1.12 (1H, m, H-4'), 1.34 (2H, m, H-3' and H-5'), 1.59 (1H, m, H-4'), 1.65 (2H, m, H-3' and H-5'), 1.93 (2H, m, H-1', and H-6'), 3.72 (1H, m, H-1'), 4.77 (1H, m, NH), 7.22 (2H, d, *J*= 7.5 Hz, H-2" and H-6"), 7.29 (1H, t, *J*= 7.5 Hz, H-4"), 7.42 (2H, t, *J*= 7.5 Hz, H-3" and H-5"), 7.69 (1H, br s, NH). ^{13}C NMR ($CDCl_3$, δ, ppm): 24.61 (C-3' and C-5'), 25.30 (C-4'), 32.86 (C-2' and C-6'), 50.74 (C-1'), 118.13 (N-CN), 125.25 (C-2" and C-6"), 127.22 (C-4"), 130.10 (C-3" and C-5"), 135.59 (C-1"), 157.79 (C-2).

N-Cyano-N'-cyclohexyl-N''-methylguanidine (**7e**; recryst. Et_2O: acetone= 1:5): IR ν (KBr) cm^{-1}: 3330, 3290 (NH), 2140 (C≡N), 1580 (C=N). ^1H NMR (80 MHz, $CDCl_3$, δ, ppm): 1.35-1.95 (10H, m, cyclohexyl), 2.85 (3H, d, N-CH_3), 4.5 (1H, m, H-1'), 5.05 (1H, d, NH), 5.9 (1H, d, NH).

N-Allyl-N'-cyano-N''-cyclohexylguanidine (**7f**; recryst. hexane: acetone= 1:5): IR ν (KBr) cm^{-1}: 3280, 3200 (NH), 2160 (C≡N), 1580 (C=N).

N-Benzyl-N'-cyano-N''-phenylguanidine (**7h**; recryst. hexane: acetone= 1:5): IR ν (KBr) cm^{-1}: 3250, 3200 (NH), 2150 (C≡N), 1590 (C=N). ^1H NMR ($CDCl_3$, δ, ppm): 4.48 (2H, d, *J*= 5 Hz, N-CH_2), 5.19 (1H, br s, NH), 7.21 (2H, d, *J*= 7.8 Hz, H-2" and H-6"), 7.25 (2H, d, *J*= 7.8 Hz, H-2' and H-6'), 7.31 (2H, t, *J*= 7.4 Hz, H-4' and H-4"), 7.34 (2H, t, *J*= 7.6 Hz, H-3', and H-5'), 7.40 (1H, br s, NH), 7.42 (2H, t,

J= 7.7 Hz, H-3" and H-5"). ^{13}C NMR ($CDCl_3$, δ, ppm): 45.72 (N-CH_2), 117.67 (N-CN), 125.74 (C-2" and C-6"), 127.59 (C-2' and C-6"), 127.84 (C-4"), 127.98 (C-4'), 128.91 (C-3' and C-5'), 130.29 (C-3" and C-5"), 134.95 (C-1"), 136.96 (C-1'), 158.79 (C=N).

N-Benzyl-N'-cyano-N''-methylguanidine (**7i**; recryst. Et_2O: *i*-PrOH= 1:1): IR ν (KBr) cm^{-1}: 3400, 3280 (NH), 2160 (C≡N), 1590 (C=N). ^{1}H NMR ($CDCl_3$, δ, ppm): 2.83 (3H, d, *J*= 5Hz, N-CH_3), 4.43 (2H, d, *J*= 5 Hz, N-CH_2), 5.28 (1H, br s, NH), 5.38 (1H, br s, NH), 7.30 (2H, m, H-2' and H-6'), 7.33 (1H, m, H-4'), 7.37 (2H, m, H-3' and H-5'). ^{13}C NMR ($CDCl_3$, δ, ppm): 28.46 (N-CH_3), 45.89 (N-CH_2), 118.27 (N-CN), 127.53 (C-2' and C-6'), 128.25 (C-4'), 129.10 (C-3' and C-5'), 136.48 (C-1'), 160.74 (C=N).

N-Benzyl-N'-cyano-N''-cyclohexylguanidine (**7j**; recryst. *i*-PrOH: acetone= 1:1): IR ν (KBr) cm^{-1}: 3410, 3290 (NH), 2160 (C≡N), 1590 (C=N). ^{1}H NMR ($CDCl_3$, δ, ppm): 1.13 (3H, m, H-2" H-4" and H-6"), 1.30 (2H, m, H-3" and H-5"), 1.56 (1H, m, H-4"), 1.64 (2H, m, H-3" and H-5"), 1.86 (2H, m, H-2", and H-6"), 3.45 (1H, m, H-1"), 4.40 (2H, d, *J*= 5.4 Hz, N-CH_2), 4.84 (1H, br s, NH), 5.82 (1H, br s, NH), 7.30 (2H, d, *J*= 7.8 Hz, H-2' and H-6'), 7.31 (1H, m, H-4'), 7.37 (2H, t, *J*= 7.5 Hz, H-3' and H-5'). ^{13}C NMR ($CDCl_3$, δ, ppm): 24.45 (C-3" and C-5"), 25.22 (C-4"), 32.94 (C-2" and C-6"), 45.82 (N-CH_2), 50.77 (C-1"), 118.49 (N-CN), 127.42 (C-2' and C-6'), 128.15 (C-4'), 129.07 (C-3' and C-5'), 136.70 (C-1'), 159.11 (C=N).

N-Butyl-N'-cyano-N''-cyclohexylguanidine (**7l**; recryst. *i*-PrOH: CCl_4= 5:1): IR ν (KBr) cm^{-1}: 3290, 3250 (NH), 2140 (C≡N), 1580 (C=N). ^{1}H NMR ($CDCl_3$, δ,

ppm): 0.94 (3H, t, *J*= 7.3 Hz, H-4'), 1.20 (3H, m, H-2" H-4" and H-6"), 1.35 (2H, m, H-3" and H-5"), 1.37 (2H, m, H-3'), 1.57 (2H, q, H-2'), 1.64 (1H, m, H-4"), 1.76 (2H, m, H-3" and H-5"), 1.96 (2H, m, H-2", and H-6"), 3.18 (2H, m, H-1'), 3.46 (1H, m, H-1"), 4.76 (1H, br s, NH), 5.03 (1H, br s, NH). ^{13}C NMR ($CDCl_3$, δ, ppm): 13.69 (C-4'), 19.95 (C-2'), 24.70 (C-3" and C-5"), 25.29 (C-4"), 3125 (C-2'), 33.20 (C-2" and C-6"), 41.71 (N-CH_2), 50.89 (C-1"), 118.49 (N-CN), 158.96 (C=N).

ACKNOWLEDGEMENT

We greatly appreciate the consultation of Prof. Gábor Doleschall.

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11. General procedure for the preparation of thiourea **5a-l**: To a stirred solution of the amine **3** (30 mmol) in CH_2Cl_2 (50 ml) was added isothiocyanate **4** (33 mmol) and stirring was continued for 2 hours at room temperature. After evaporation of the solvent under reduced pressure, the residue was crystallised from hexane.

12. General procedure for the preparation of thioether **6a-l**: To a stirred solution of thiourea **5** (25 mmol) in acetone (40 ml) was added CH_3I (75 mmol) and the resulting mixture was stirred further for 1 hour at room temperature. Evaporation of the solvent and crystallisation of the residue afforded thioether **6**.

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(Received in the UK 14 November 1998)