Synthesis of Cyclic and Acyclic Tri- and Tetrasubstituted Hydroxyguanidines

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Acyclic trisubstituted and previously unknown tetrasubstituted hydroxyguanidines **6** have been prepared from *C*-chloroformamidinium chlorides **3** (available from ureas or thioureas) via reaction with *O*-(tetrahydro-2-pyranyl)-hydroxylamine (**4**), followed by removal of the protecting group by acid hydrolysis. Cyclic tri- and tetrasubstituted hydroxyguanidines **11** have been prepared by the reaction of phosgene-*O*-(tetrahydro-2-pyranyl)oxime (**7**) or phosgene-*O*-(*N*-methylcarbamoyl)oxime (**8**) with a diamine, followed by removal of the protecting group by acid or base hydrolysis.

Hydroxyguanidines and their derivatives may be active pharmaceutical agents and agrichemicals.[2] Synthetic routes to acyclic 1,1,3-trisubstituted hydroxyguanidines[3] are limited and the 1,1,3,3-tetrasubstituted analogues are unknown. Known cyclic hydroxyguanidines are limited to the acid salts of 1,3-ethylene- and 1,3-trimethylene-2-hydroxyguanidine; the neutral compounds are unstable.[4] This paper describes two useful methods for preparing these compounds.

While selected acyclic 1,1,3-trisubstituted hydroxyguanidines have been made by nucleophilic displacement of either a chlorine or *S*-methyl group of **1** with hydroxylamine[3] (eq 1), yields of **2** are low and the urea is a major by-product.

$$R^1N{=}C(X)NR^2R^3 + NH_2OH \xrightarrow{CH_3OH} R^1N(H)-C(=NOH)-NR^2R^3 + R^1NHC(=O)NR^2R^3 \quad (1)$$

1a, X = Cl; **b**, X = SCH_3

2

These problems can be avoided and the scope of synthesis expanded to tetrasubstituted and cyclic compounds as follows. *C*-Chloroformamidinium chloride salts **3** are prepared in the standard way from reaction of the appropriate urea (or thiourea) with phosgene.[5] Reaction of **3** with *O*-(tetrahydro-2-pyranyl)hydroxylamine (**4**)[6] (a masked hydroxylamine soluble in most aprotic solvents) and a tertiary amine base gives *O*-(tetrahydro-2-pyranyl)hydroxyguanidines **5**. The yield is high for acyclic compounds, and low for cyclics.[7] The protecting group can then be cleaved by acid to generate the desired product **6** (eq 2, 3, 4). Acyclic examples are given in Table I.

$$R^1R^2NCONR^3R^4 \text{ or } R^1R^2NCSNR^3R^4 + COCl_2 \xrightarrow{C_6H_5CH_3} [R^1R^2N-C(Cl)=NR^3R^4]^+Cl^- \quad (2)$$

3

$$3 + NH_2-O-(\text{tetrahydropyranyl}) + 2NEt_3 \xrightarrow[\text{or } CHCl_3]{CH_3CN} R^1R^2N-C(=N-O-(\text{tetrahydropyranyl}))-NR^3R^4 \quad (3)$$

4 **5**

$$5 \xrightarrow{H_3O^+} R^1R^2NC(=NOH)NR^3R^4 \quad (4)$$

6

A better route to the cyclic hydroxyguanidines has been developed. Reaction of either phosgene *O*-(tetrahydro-2-pyranyl)oxime (**7**) or phosgene *O*-(methylcarbamoyl)oxime (**8**)[8] (carbonyl oxime synthons) with the appropriate diamine and tertiary amine base, followed by acid or base hydrolysis, gives **11** (eq 5 and 6). Cyclic examples are given in Table II.

$$Cl_2C{=}NOX + R^1NH(CH_2)_nNHR^2 + 2NEt_3 \xrightarrow[\text{reflux}]{CHCl_3} R^1N(C(=NOX)NR^2)(CH_2)_n \quad (5)$$

n = 2,3

7, X = (tetrahydropyranyl); **8**, X = $CONHCH_3$

9, X = (tetrahydropyranyl); n = 2,3; **10**, X = $CONHCH_3$; n = 2,3

$$\mathbf{9} \xrightarrow{3\ N\ HCl} \mathbf{11} \qquad \mathbf{10} \xrightarrow[\text{or } KOH/CH_3OH]{CH_3ONa/CH_3OH} \mathbf{11} \quad (6)$$

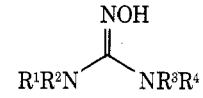
11, R^1 = alkyl, aryl; R^2 = alkyl, H; n = 2, 3

Experimental Section

General. Melting points were taken on a Mel-Temp melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian A-60 in deuteriochloroform unless otherwise stated. All shifts are reported in δ with tetramethylsilane as an internal standard. Mass spectra were determined with a Du Pont CEC 110 B. Analyses were performed by the Central Research and Development Department Analytical Section.

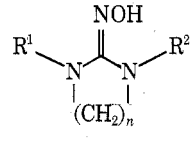
All experiments were carried out under a dry nitrogen atmosphere unless otherwise noted. Solvents were dried with 4A molecular sieve. All equipment was dried with a heat gun while under vacuum. All new compounds were purified by chromatography on SilicAR CC-7, and shown to be single compounds by two different thin layer solvent systems. Oils were converted into their hydrochloride salt with dry hydrogen chloride in ether.

Table I. Acyclic Tri- and Tetrasubstituted Hydroxyguanidines



R^1	R^2	R^3	R^4	Yield, %	Mp, °C (registry no.)	NMR	Mass spectrum, *m/e*
C_6H_5	CH_3	CH_3	CH_3	31	112–114 (59812-83-8)	2.67 (s, 6 H), 3.17 (s, 3 H), 6.65–7.40 (m, 6 H) (phenyl and NOH)	Calcd for $C_{10}H_{15}N_3O$: 193.1214 Found: 193.1220
$C_6H_5CH_2$	CH_3	C_2H_5	C_2H_5	50	HCl salt 149 dec (59812-84-9)	1.12 (t, J = 7 Hz, 6 H), 2.70 (s, 3 H), 2.93–3.45 (m, 4 H), 4.35 (s, 2 H), 7.23 (s, 5 H)	Calcd for $C_{13}H_{21}N_3O$: 235.1683 Found: 235.1689
$C_6H_5CH_2$	CH_3	CH_3	H	42	HCl salt 132–137 (59812-85-0)	1.62 (bs, 2 H), 2.52 (s, 3 H), 2.83 (s, 3 H), 4.15 (s, 2 H), 7.34 (s, 5 H)	Calcd for $C_{10}H_{15}N_3O$: 193.1214 Found: 193.1202
C_6H_5	CH_3	CH_3	H	48	HCl salt 164–168 (59812-86-1)	2.47 (s, 3 H), 3.15 (s, 3 H), 6.43–7.40 (m, 6 H)	Calcd for $C_9H_{13}N_3O$: 179.1058 Found: 179.1041
C_6H_5	CH_3	C_2H_5	H	65	86–88 (59226-52-7)	0.98 (t, J = 7 Hz, 3 H), 2.86 (q, J = 7 Hz, 2 H), 3.16 (s, 3 H)	Calcd for $C_{10}H_{15}N_3O$: 193.1214 Found: 193.1224

Table II. Cyclic Tri- and Tetrasubstituted Hydroxyguanidines



R^1	R^2	n	NMR	Mp, °C (registry no.)	Mass spectrum, *m/e*
$C_6H_5CH_2$	CH_3	3	1.40–2.20 (m, 2 H) 2.86 (s, 3 H) 2.87–3.30 (m, 4 H) 4.45 (s, 2 H) 7.28 (s, 5 H)	108–110 (59812-87-2)	Calcd for $C_{12}H_{17}N_3O$: 219.1371 Found: 219.1369
$C_6H_5CH_2$	CH_3	2	2.84 (s, 3 H) 3.08 (ns, 4 H) 4.58 (s, 2 H) 7.33 (s, 5 H)	94–96 (59812-88-3)	Calcd for $C_{11}H_{15}N_3O$: 205.1214 Found: 205.1202
$C_6H_5CH_2$	H	2	3.12–3.28 (A^2B^2, 4 H)	118–120 (59812-89-4)	Calcd for $C_{10}H_{13}N_3O$: 190.1058 Found: 190.1045

All new compounds have been characterized by spectral techniques and their structures are consistent with spectral data.

General Procedure for Preparation of Acyclic Tri- and Tetrasubstituted Hydroxyguanidines via 2-Chloroformamidinium Chlorides. Preparation of 1-Phenyl-1,3,3-trimethyl-2-hydroxyguanidine. Starting materials are either the corresponding urea or thiourea prepared by standard procedures using either isocyanates or isothiocyanates and amines, or carbamoyl chlorides and amines.

N-Phenyl-*N*,*N*′,*N*′-trimethylurea (8.9 g, 0.05 mol) was dissolved in 50 ml of toluene and cooled to −22 °C. To it was added 4.9 g (0.05 mol) of liquid phosgene. The reaction was run overnight and the 2-chloroformamidinium chloride (3) formed as a white solid. The moisture-sensitive white solid could be either isolated by filtration in a drybox or, after decanting the liquid, redissolved in dry acetonitrile and carried on to the next step.

In some instances the salt did not crystallize but formed an oil and was carried on to the next step.

After removal of toluene, followed by solution in 50 ml of acetonitrile, the salt solution was added dropwise to a cool (−22 °C) solution of 5.85 g (0.05 mol) of *O*-tetrahydropyranylhydroxylamine (4)[6] and 10.1 g (0.1 mol) of triethylamine. The reaction mixture was warmed to 25 °C, stirred for 2 h, then poured into 100 ml of methylene chloride. The methylene chloride layer was extracted six times with 100 ml of water and dried, and the solvent was removed. The resultant liquid was dissolved in 55 ml of 1 N HCl and 100 ml of water and heated on a steam bath for 1 h. The aqueous phase was extracted twice with 100 ml of methylene chloride, then made basic with 60 ml of 1 N NaOH and extracted twice with 100 ml of methylene chloride. The organic layer was dried over $MgSO_4$ and evaporated to give a white solid: 3.0 g (31%); mp 112–114 °C; NMR ($CDCl_3$) δ 2.67 (s, 6 H), 3.17 (s, 3 H), 6.65–7.40 (m, 5 H); mass spectrum 193.1220 (calcd for $C_{10}H_{15}N_3O$, 193.1214).

Preparation of Phosgene *O*-(Tetrahydro-2-pyranyl)oxime (7). Dihydropyran (2.52 g, 0.03 mol) and phosgene oxime[9] (3.6 g, 0.03 mol) were dissolved in 100 ml of dry tetrahydrofuran. Two drops of phosphorus oxychloride was added, and the mixture was heated at reflux for 4–12 h. The reaction was followed by TLC. The solvent was then evaporated and the residue distilled. A colorless liquid (3.4 g, 58% yield) was collected: bp 62–63 °C (0.7 mm); NMR ($CDCl_3$) δ 1.32–2.10 (m, 6 H), 3.40–4.20 (m, 2 H), 5.35 (bs, 1 H); mass spectrum M^+ *m/e* 197 (too small to measure), 139, 113, 96, 85, measured for $C_3H_3NOCl_2$ 138.9590, calcd 138.9591, for $(CH_2{=}CHON{=}CCl_2)^+$.

General Procedure for Preparation of Tri- and Tetrasubstituted Cyclic Hydroxyguanidines. I. Preparation of 1-Benzylimidazolidin-2-one Oxime from a Diamine and 8. To a refluxing solution of *N*-benzylethylenediamine (1.40 g, 0.01 mol) and triethylamine (2.02 g, 0.02 mol) in 100 ml of chloroform was added dropwise (0.5 h) 1.70 g (0.01 mol) of 8[8] in 50 ml of chloroform. The solution was allowed to reflux for 12 h and cooled, and the organic layer was worked up with 2 × 100 ml of water. After drying ($MgSO_4$), 2.33 g (94% yield) of brown oil was recovered. The oil was dissolved in 100 ml of methanol and 1.08 g (0.02 mol) of potassium hydroxide was added. The

solution was heated to reflux for 24 h, poured into 500 ml of water, acidified to pH 1, and extracted with 2 × 100 ml of methylene chloride. The aqueous layer was then made basic (pH 9) and extracted with 2 × 100 ml of methylene chloride; the extracts were dried ($MgSO_4$) and evaporated, then chromatographed to give an off-white crystalline substance (0.6 g, 31% yield).

II. 1-Benzylimidazolidin-2-one Oxime from a Diamine and 7. To a refluxing solution of *N*-benzylethylenediamine (0.75 g, 0.005 mol) and triethylamine (1.01 g, 0.01 mol) in 100 ml of chloroform was added dropwise over 5 h 1.0 g (0.0051 mol) of **7** in 10 ml of chloroform. After the solution was heated at reflux for 4 h, the solvent was evaporated and the residue hydrolyzed with 20 ml of 1 N HCl on a steam bath for 1 h. The workup is the same as part I (from acidification step). The yield was 0.55 g (58%).

Registry No.—**7**, 59812-90-7; **8**, 24248-83-7; **10** (n = 2), 59812-91-8; dihydropyran, 110-87-2; phosgene oxime, 1794-86-1; *N*-benzylethylenediamine, 4152-09-4.

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Fully Automated Solid Phase Synthesis of Protected Peptide Hydrazides on Recycling Hydroxymethyl Resin

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A fully automated solid phase synthesis of Boc-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-$HNNH_2$ (I) on hydroxymethyl resin (II) is described. All of the operations, including esterification of the first amino acid residue to the resin, deprotection of α-amino protecting group followed by coupling reaction with the next amino acid residue, as well as hydrazinolytic cleavage of I from the solid support, have been automated. The regenerated resin II was reused several times for the synthesis of the same compound to give automatically several batches of I. Results of this process are compared with results of other solid phase and classical syntheses of the Gly-Phe-Phe-Tyr-Thr sequence.

In solid phase peptide synthesis,[1] the process of assembling the peptide chain anchored to a polymer support has been quite effectively automated.[2] However, the attachment of the first amino acid residue to the resin and the cleavage of the anchoring linkage in order to release the products from the solid support have to be carried out individually in separate vessels.[3-5] In the following, a completely automatic recycled synthesis of the protected pentapeptide hydrazide Boc-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-$HNNH_2$[6] (I) on the hydroxymethyl resin[7,8] (II) is described. The results of five consecutive syntheses of I on the same batch of resin II are presented and compared with results of several experiments in which the same pentapeptide sequence Gly-Phe-Phe-Tyr-Thr was prepared by different procedures.

For the fully automated synthesis of I, a Beckman Model 990 peptide synthesizer[9] was programmed to perform all operations described below within the same reaction vessel. Boc-Thr(Bzl)-OH was esterified to resin II by the 4-dimethylaminopyridine catalyzed dicyclohexylcarbodiimide (DCC) procedure.[8] After benzoylation to block remaining unreacted alcoholic functions on the resin, Boc-Tyr(Bzl)-OH, Boc-Phe-OH, Boc-Phe-OH, and Boc-Gly-OH were sequentially coupled to the growing peptide chain on the resin according to general principles of the solid phase method.[1-5] In each coupling cycle, the *tert*-butyloxycarbonyl group was removed by a 20-min treatment with 33% trifluoroacetic acid in CH_2Cl_2 and the coupling reaction was effected with 2.5-fold excess each of Boc-amino acid and DCC for 2 h. Upon completion of the chain assembly the pentapeptide resin was stirred with 10% H_2NNH_2 in DMF for 16 h. Product I released from the polymer support was obtained in crystalline form after evaporation of the reaction and wash fluids collected from the vessel outlet. The hydrazinolysis reaction served also to regenerate resin II which remained in the reaction vessel. It was recycled four times through the entire synthetic protocol to give a total of five batches of I, which was purified by recrystallization. Overall yields from each run were approximately 60% with no sign of decreasing (see Table I). The resin particles survived all operations as evident from inspection of the beads before and after these experiments under a microscope. There was no indication of any disintegration of resin particles. The completeness of the hydrazinolytic cleavage was checked after each run by ir spectrophotometry.[8] The rate of hydrazinolysis was found to be surprisingly rapid with a half-life of about 45 min.

Thus, with the possible exception of aspartic or glutamic acid containing peptides, the process described above appears to be rather versatile and generally applicable to rapid synthesis of protected oligopeptide hydrazides. These are useful intermediates for polypeptide synthesis by the azide method[10] allowing effective combination of solid phase techniques and classical procedures[11,12] with retention of the best features of each.[4]

In Table II, the results of recycled automated synthesis of I are compared with those of other processes for the synthesis of the same sequence.[13] A dramatic increase in speed, efficiency, and simplicity can be noted.

The manual solid phase synthesis of I on hydroxymethyl