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A SIMPLE METHOD FOR THE SYNTHESIS OF UNSYMMETRICAL TRISUBSTITUTED GUANIDINES.+

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ABSTRACT:

A simple method for the synthesis of sweet tasting N, N', N"-trisubstituted guanidines is described. The key intermediate, carbonimidoyl dichloride 6, was prepared using a known method. Reaction of 6 with cyclooctylamine followed by the sodium salt of 5-aminomethyltetrazole or the sodium salt of glycine afforded the desired guanidine. When the carbonimidoyl dichloride was allowed to react with (S)-α-phenethylamine followed by the sodium salt of glycine, the guanidine sweetener 2 was obtained.

INTRODUCTION

Recent discoveries of sweet guanidinoacetic acids by Claude Nofre and Jean-Marie Tinti[1] and the sweet tetrazolylmethyl guanidines by our group[2] have prompted interest in the development of commercially viable synthetic routes for trisubstituted unsymmetrical guanidines. The sweetness potencies of these guanidines range from a few thousand to in excess of 100,000 times that of sucrose[1]. In this report, we describe a general method for the synthesis of unsymmetrical N, N', N"-trisubstituted guanidines which is exploited in the form of a facile synthesis of the sweet tasting guanidines 1-3 (only one tauutomeric form of the guanidines is shown here for simplicity). These simple

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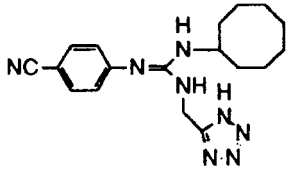
+ This paper is dedicated to Professor Kenneth L. Rinehart in honor of his 63rd birthday.

compounds have been reported earlier to exhibit sweetness potencies of 5,000[2], 27,000[1], 170,000[1] times that of sucrose, respectively. Such levels of sweetness activity until this point have been unknown. The structural simplicity and extraordinary sweetness potencies of guanidine sweeteners make them candidates for commercial development. This report describes the synthesis of N, N', N''-trisubstituted guanidines.



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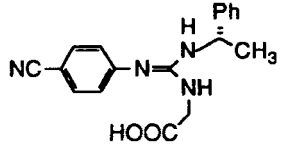
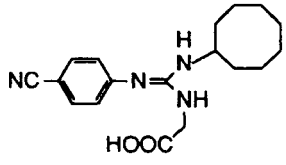


2



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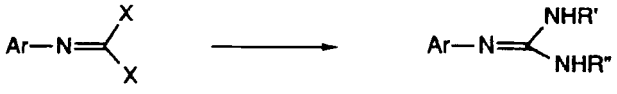
RESULTS AND DISCUSSION

The known methods for the synthesis of guanidines include the reaction of isothioureas with amines[3], reaction of thioureas with amines in the presence of dicyclohexylcarbodiimide[4], reaction of thioureas with iminophosphoranes[5], reaction of ureas or thioureas with phosgene followed by amines[6], addition of amines to carbodiimides[7] and reaction of amines with aminoiminomethane-sulfonic acids[8]. An intermediate of type 4 has also been used for the synthesis of guanidines[9,10] (replacement of both "X" groups by the same amine). However, stepwise replacement of "X" with different amines to give unsymmetrical trisubstituted guanidines has not been reported. Our initial efforts to employ oxygenated functionalities for "X" (phenoxy, and o-phenylenedioxy) were not promising. We then focused on carbonimidoyl dichlorides which has been successfully used for the synthesis of symmetrical guanidines.



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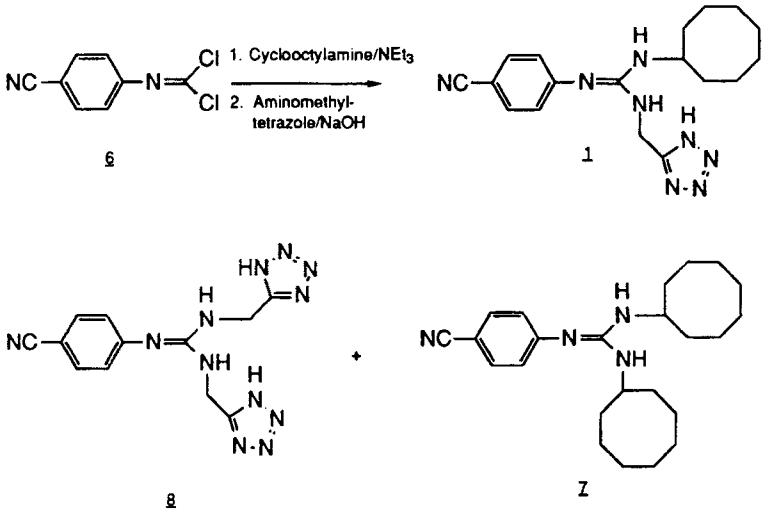
Scheme 1

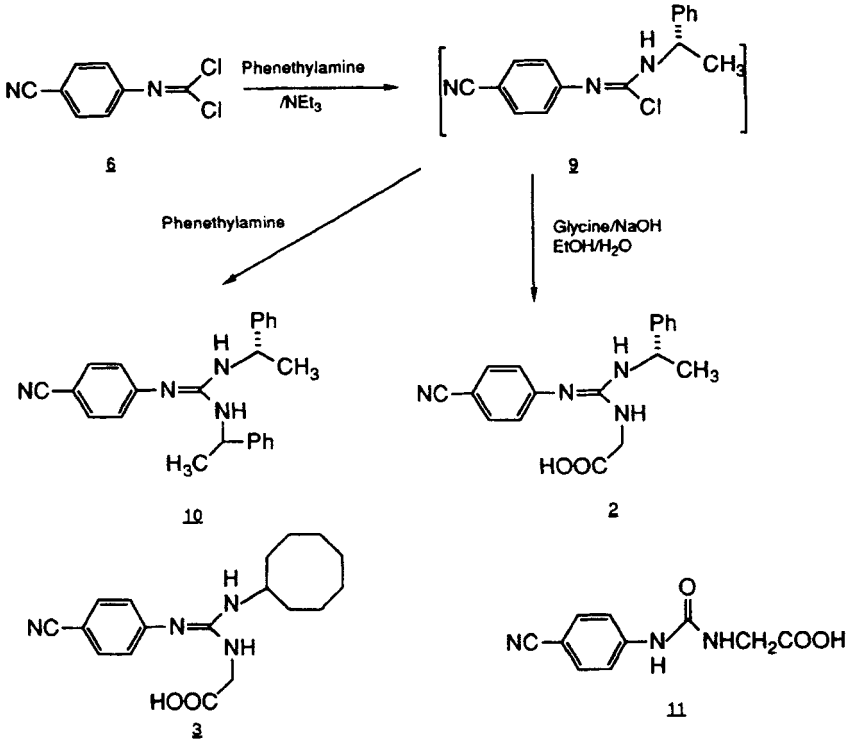


The desired carbonimidoyl dichloride was prepared using a known procedure[10] with modifications. Reaction of p-cyanophenylformamide with one equivalent of sulfuryl chloride (reflux, 24 h) and thionyl chloride (where the latter functions as both reactant and solvent) afforded 6. Large excess of thionyl chloride was necessary due to the poor solubility of the formamide starting material. Excess thionyl chloride was recovered by distillation upon completion of the reaction. Pure 6 was obtained in 79% yield by distillation directly from the concentrated reaction mixture.

The carbonimidoyl dichloride was allowed to react with cyclooctylamine in the presence of triethylamine. This reaction afforded the desired monochloro-amidine intermediate as well as a small amount of dicyclooctylguanidine 7. The reaction mixture was filtered and without further purification, was treated with the sodium salt of aminomethyltetrazole in ethanol. The desired guanidine product 1 was obtained in 61% yield after workup in addition to the two undesired products 7 (22%) and 8 (8%). No chromatographic separation was needed for the isolation of 1. Final purification of 1 was accomplished simply by recrystallization.

The reaction sequence illustrated in Scheme 1 was also extended to the guanidinoacetic acid series. Reaction of the carbonimidoyl dichloride 6 in THF

Scheme 2



with (S)-α-phenethylamine at 0 °C, followed by glycine t-butyl ester in the presence of a base gave the t-butyl ester of the desired guanidine 2. Purification of the guanidine ester proved difficult. Chromatography using silica gel gave only intractable products. It became clear that the t-butyl ester of 2 is unstable to silica gel chromatography. In this work, the glycine t-butyl ester nucleophile was used due to our concern that the aqueous alkaline conditions necessary for the direct use of glycine may result in predominant hydrolysis of the carboniimidoyl dichloride intermediate. Nonetheless, glycine was employed as the second nucleophile in an attempt to circumvent problems associated with the ester intermediate. This modification not only allows the use of a much less expensive reactant but also shortens the process. After reaction of carbonimidoyl dichloride 6 with the phenethylamine, the reaction mixture was filtered and

concentrated. The residue obtained was then dissolved in ethanol and to it an aqueous solution of sodium glycinate was added. Upon work up after 2 h, the desired guanidinoacetic acid 2 was obtained in 22% yield. The crude product from which 2 was isolated was contaminated with 11 (ca. 33%). This method was extended for the synthesis of 3 (42% yield).

In conclusion, we have found that it is indeed possible to achieve stepwise displacement of the halogens in carbonimidoyl dichlorides to prepare unsymmetrically substituted guanidines. The usefulness and the simplicity of the method has been demonstrated by the synthesis of three highly potent guanidine sweeteners. The commercial viability of the process is being examined carefully.

EXPERIMENTAL

General: Melting Points were obtained on a Thomas-Hoover Unimelt capillary apparatus and are not corrected. NMR spectra were obtained on a General Electric QE 300 instrument using tetramethylsilane as an internal standard. Microanalysis was performed by the Midwest Microlabs, 7212 N. Shadeland Avenue, Indianapolis, IN 46250. The known products 1, 2, and 3 were charecterized by comparison with the authentic samples (melting point, HPLC and NMR).

p-Cyanophenylformamide (12). A mixture of 4-aminobenzonitrile (30.0 g, 254.2 mmol) and formic acid (30.0 g) was heated at 150 °C for 3 h. Upon cooling, a solid formed which was filtered, washed with cold dichloromethane and dried to afford 36.0 g (97%) of the desired formamide as a white powder. mp 182-183 °C. ^{1}H NMR (DMSO-d_6) δ 7.76 (s, 4H), 8.37 (s, 1H).

Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.73; H, 4.06; N, 18.99.

p-Cyanophenylcarbonimidoyl dichloride (6). p-Cyanophenylformamide (12, 25.0 g, 171.23 mmol) was slowly added to a stirred mixture of thionyl chloride (500 mL) and sulfuryl chloride (13.75 mL, 171.23 mmol) over a period of 1 h. The mixture was slowly heated at reflux for 24 h. Excess thionyl chloride was removed by distillation and the red residue was distilled in vacuo to afford 27.0 g (79%) of the desired compound as a pale yellow oil which solidified into a crystalline mass. bp. 110° C (1 Torr). ^{1}H NMR ($CDCl_3$) δ 7.04 & 7.70 (AB quartet, 4H, J=9 Hz).

Anal. Calcd for $C_8H_4N_2Cl_2$: C,48.28; H,2.03; N,14.07. Found: C,48.03; H,1.95; N,13.95.

N-(4-Cyanophenyl)-N'-cyclooctyl-N"-(1H-tetrazol-5-ylmethyl)guanidine. (1). A mixture of cyclooctylamine (2.80 g, 22.04 mmol) and triethylamine (2.28 g, 22.57 mmol) in THF (100 mL) was added slowly over 1 h to a solution of the carbonimidoyl dichloride 6 (4.0 g, 20.10 mmol) in THF (300 mL) at 0^o C and the mixture was stirred at rt for 18 h. The precipitate was filtered off and the filtrate was concentrated. A solution of 5-aminomethyltetrazole (2.0 g, 20.20 mmol) and NaOH (0.80 g, 20.0 mmol) in water (16 mL) was added to the residue dissolved in ethanol (150 mL) and the mixture was heated at reflux for 6 h. The reaction mixture was concentrated in vacuo. The residue was dissolved in water (100 mL) and aqueous NaOH (1N, 20 mL) and then extracted with CH_2Cl_2 (200 mL). The organic layer was dried and concentrated to afford 1.7 g (22%) of the bis adduct 7 as an oil. ^{1}H NMR ($CDCl_3$) δ 1.42-1.89 (m, 28H), 3.64 (m, 2H), 6.90 & 7.50 (AB quartet, 4H, J=6 Hz). The aqueous layer was adjusted to pH 5 to afford a white solid and a gum. The solid was filtered and dried to afford 0.5 g, (8%) of 8 as a white powder. ^{1}H NMR (DMSO-d_6) δ 4.69 (s, 4H), 7.53 (AB quartet, 4H, J=6 Hz). The gum, upon addition of acetonitrile followed by cooling, gave a precipitate which was filtered and dried to afford 4.32 g (61%) of 1. A small portion of this was recrystallized from methanol-water to afford pure 1. ^{1}H NMR (DMSO-d_6) δ 1.40-1.78 (m, 14H), 4.53(s, 2H), 7.58 (AB quartet, 4H, J=6 Hz). mp 175-176 °C. Lit[11] 176-178 °C.

Anal. Calcd for $C_{18}H_{24}N_8.H_2O$: C, 58.36; H, 7.07; N, 30.25. Found: C, 58.78; H, 6.99; N, 30.24.

N-(4-Cyanophenyl)-N'-[(S)-α-phenethyl]guanidine acetic acid (2). A mixture of (S)-α-phenethylamine (1.20 g, 9.92 mmol) and triethylamine (1.02 g, 10.09 mmol) in THF (10 mL) was added to a cooled solution of the carbonimidoyl dichloride 6 (2.0 g, 10.05 mmol) in THF (40 mL) and stirred for 16 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved in ethyl alcohol (75 mL) and to this a solution of glycine (0.76 g, 10.13 mmol) and NaOH (0.40 g. 10.0 mmol) in water (13 mL) was added and the reaction mixture was heated at reflux for 4 h, then concentrated. The residue was dissolved in water (50 mL) and NaOH (1N, 5 mL) was added. The basic solution was extracted with dichloromethane (2x100 mL). The organic phase was dried and concentrated to afford 1 g (27%) of the bis adduct 9. ^{1}H NMR ($CDCl_3$) δ 1.36 (d, 6H, J=6 Hz), 4.71 (m, 2H), 7.17 (AB quartet, 4H, J=6 Hz), 6.99-7.03 & 7.21-7.44 (m, 10H). The aqueous layer was neutralized to afford a gum which upon refrigeration gave a solid. NMR of the solid indicated a 2:1 mixture of the desired compound (2) and the

urea 11. Recrystallization from methanol-water afforded 0.9 g (22%) of the desired product (2) as a white powder. mp 175-176 °C, lit[1] 179 °C. ^{1}H NMR (DMSO-d_6) δ 1.43 (d, 3H, J=6 Hz), 3.69 (s, 2H), 4.83 (m, 1H), 7.44 (AB quartet, 4H, J=6 Hz), 7.23-7.30 (m, 5H).

N-(4-Cyanophenyl)-N'-cyclooctylguanidinoacetic acid (3). A mixture of cylcooctylamine (2.55 g, 20.10 mmol) and triethylamine (2.04 g, 20.10 mmol) in THF (10 mL) was added to a cooled solution of the imidoyldichloride (4.0 g, 20.10 mmol) in THF (100 mL) and the mixture was stirred for 16 h, then filtered and the filtrate concentrated. A solution of glycine (2.28 g, 30.40 mmol) and NaOH (1.20 g, 30.0 mmol) in water (40 mL) was added to a solution of the residue in ethanol (175 mL) and the reaction mixture was heated at reflux for 4 h and concentrated. The residue was dissolved in water (100 mL) and NaOH (1N, 10 mL) and extracted with dichloromethane (2X100 mL). The organic layer was dried and concentrated to afford 2 g (26%) of 7 as an oil (for NMR spectra see the exprimental for 2). The aqueous layer was neutralized to afford a gum which upon storage gave 2.50 g (42%) of the intensely sweet 3 as a powder. A small sample was recrystallized from methanol-water to provide the analytical sample. mp 225 °C. lit[11] 223-225 °C. ^{1}H NMR (DMSO-d_6) δ 1.44-1.77 (m, 14H), 3.76 (m, 1H), 4.04 (d, 2H), 7.40 & 7.81 (m, 4H).

Anal. Calcd for $C_{18}H_{24}N_4O_2 \cdot 0.5\ H_2O$: C, 64.07; H, 7.47; N, 16.61. Found: C, 63.98; H, 7.24; N, 16.25.

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11. The authentic samples for 1 and 3 were obtained from Dr. William H. Owens of the NutraSweet Company and Professor Claude Nofre of the University of Claude Bernard, Leons, France, respectively. The authors thank them for providing the samples.

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