Notes

A Convenient Synthesis of Guanidines from Thioureas[1,2]

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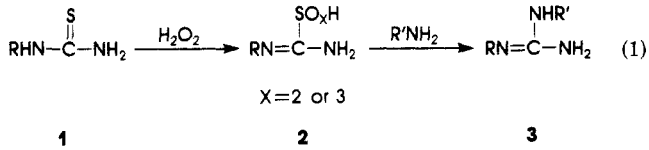
In this note we describe a convenient, cost-effective synthesis of guanidines[3] from thioureas and amines. The key transformation involves activation of the sulfur in the thiourea through S-oxidation, followed by displacement of the activated sulfur group by amine nucleophiles, as depicted in eq 1.



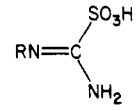
(1)

a. R = phenyl; **b.** R = propyl

The most widely employed commercial method for preparing guanidines is the reaction of ammonia or amines with *S*-alkylisothiouronium salts.[4a,5] Further, most commercial processes utilize *S*-methylisothiouronium salts. The byproduct of this reaction is the noxious gas, methyl mercaptan; this foul smelling gas has a threshold of detection by humans of about 1 ppb. For safety reasons, plant processes utilizing this method must include a step to transform the mercaptan into an environmentally acceptable byproduct. The synthesis described herein eliminates this problem.

Other commercial alternatives for the production of guanidines are the reaction of ammonia or ammonia derivatives with cyanamides,[6] carbodiimides,[7] chloroformamidines,[8] or dichloroisocyanides.[4a] Generally, these starting materials are corrosive, toxic, and/or moisture-sensitive.

Table I. Sulfonic Acids



product	R	yield, %	mp, °C	IR (KBr), cm^{-1}	^{17}O NMR,[a] ppm
2a	Ph	85	157–158[b]	1266, 1232, 1066[c]	164.9
2b	*n*-Pr	56	179–182[d]	1272, 1238, 1060[c]	
2c	2-MePh	83	160–165	1276, 1231, 1050	182.5
2d	4-FPh	76	150–151	1266, 1209, 1063	177.3[e]

[a] Samples run at 48.8 MHz in Me_2SO/CH_3CN relative to water. [b] Lit.[13] mp 171–172 °C. [c] CHNS analyses satisfactory. [d] Lit.[13] mp 186–188 °C. [e] In Me_2SO.

At the initiation of our work, literature precedent included the reaction of the amino acid glycine under basic conditions with formamidinesulfinic acid to yield 36% of *N*-(aminoiminomethyl)glycine.[9] The same paper[9] reported that the reaction of glycine with cyanamide under basic conditions yielded the same product. Also, Danish authors reported that the reaction of *N*-benzyl-*N'*-methylformamidinesulfonic acid with ammonia and primary amines yielded guanidines.[10] Walter had reported extensively on the oxidation of thioamides and thioureas.[11] Oxidation of cyclic thioureas such as mercaptopteridines to the corresponding sulfonic acid using potassium permanganate has been reported.[12]

The guanidine *N*-phenyl-4-morpholinecarboximidamide, (**3a**, R' = morpholine), was our initial target. We expected that oxidation of *N*-phenylthiourea to *N*-phenylaminoiminomethanesulfonic acid (**2a**, X = 3), followed by a displacement reaction with morpholine would furnish the desired guanidine (eq 1). Attempts to repeat the published oxidation procedures using freshly prepared peracetic acid in methanol[13] or hydrogen peroxide[10,14] failed to give the sulfonic acid.[15] Based on the identification of byproducts,[15] we presumed that the oxidation to the sulfonic acid derivative was slow in comparison to the decomposition of intermediates. Therefore, we concentrated our efforts on increasing the rate of the oxidation reaction relative to decomposition.

Metal peroxo d^0 complexes are well-known as catalysts for hydrogen peroxide oxidations.[17] Molybdenum cata-

(1) This work was presented at the 190th American Chemical Society Meeting in Chicago, IL 1985, ORGN 112.

(2) Independent work on the reactions of aminoiminomethanesulfinic and sulfonic acids was developed by A. Miller and J. J. Bischoff and was reported at the 190th American Chemical Society Meeting, ORGN 203.

(3) Our interest in the synthesis of guanidines derivs from the discovery of linogliride,[4] an orally effective hypoglycemic guanidine being developed at McNeil Pharmaceutical.

(4) (a) Rasmussen, C. R. U.S. Patent 4 211 867, 1980. (b) Rasmussen, C. R.; Maryanoff, B. E.; Tutwiler, G. F. *Annu. Rep. Med. Chem.* **1981**, *16*, 173.

(5) (a) Braun, C. E. *J. Am. Chem. Soc.* **1933**, *55*, 1280. (b) King, H.; Tonkin, S. M. *J. Chem. Soc.* **1946**, 1063. (c) McKay, A. F.; Hatton, W. G.; Braun, R. O. *J. Am. Chem. Soc.* **1956**, *78*, 6144. (d) Brand, E.; Brand, F. C. "Organic Syntheses"; Wiley: New York, 1955, Collect. Vol. III, p 440. (e) Jen, T.; Van Hoeven, H.; Groves, W.; McLean, R. A.; Loev, B. *J. Med. Chem.* **1975**, *18*, 90. (f) "The Organic Chemistry of Drug Synthesis"; Lednicer, D., Mitscher, L. A., Eds.; John Wiley and Sons, Inc.: New York, Vol. I (1977) and Vol. II (1980).

(6) (a) Davis, T. L. *Org. Synth.* **1927**, *7*, 46. (b) Kampf, A. *Chem. Ber.* **1904**, *37*, 1681. (c) Arndt, F.; Rosenau, B. *Chem. Ber.* **1917**, *50*, 1260.

(7) (a) Rasmussen, C. R. U.S. Patent 4 414 211, 1980, and references therein. (b) See references contained in the following review: Mikolajczyk, M. M.; Kielbasinski, P. *Tetrahedron* **1981**, *37*, 233.

(8) (a) Bredereck, H.; Bredereck, K. *Chem. Ber.* **1961**, *94*, 2278. (b) Eilingsfeld, H.; Neubauer, G.; Seefelder, M.; Weidinger, H. *ibid.* **1964**, *97*, 1232.

(9) Walter, W. *Angew. Chem.* **1955**, *67*, 275.

(10) Alhede, B.; Gelting, N. C. British Patent 1 587 258, 1977.

(11) A decade of work from W. Walter's laboratory resulted in over thirty publications in this area. Paper XXXI in the series: Walter, W.; Rohloff, C. *Liebigs Ann. Chem.* **1975**, 295.

(12) See the following for leading references on the oxidation of cyclic thioureas: Pfleiderer, W.; Baur, R.; Bartke, M.; Lutz, H. In "Chemistry and Biology of Pteridines"; Blair, J. A., Ed.; DeGruyter: Berlin **1983**; p93.

(13) Walter, W.; Randau, G. *Liebigs Ann. Chem.* **1969**, *722*, 98.

(14) Walter, W.; Randau, G. *Liebigs Ann. Chem.* **1969**, *722*, 80.

(15) Major byproducts of the attempted oxidation included sulfur, *N*-phenylurea, *N*,*N'*-diphenylguanidine, *N*-[imino(phenylamino)-methyl]-*N*-phenylthiourea, and Hector's base[16] (4,5-dihydro-5-imino-*N*,4-diphenyl-1,2,4-thiadiazol-3-amine).

(16) Hector, D. S. *Chem. Ber.* **1889**, *22*, 1176; **1890**, *23*, 357.

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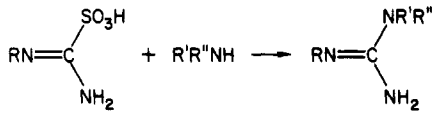
Table II. Guanidine Products from the Reaction of Sulfonic Acids with Amines



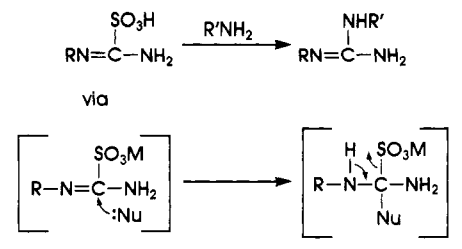
no.	R	R′	time, h	temp,[a] °C	yield,[b] %	mp, °C
		a. Reactions with Primary Amines (R″ = H)				
4	Ph	t-C_4H_9	72	rt	99[c]	90–93[d,e]
5	Ph	i-C_4H_9	0.25	50[f]	56[g,c]	88.5–89.5[h,e]
6	Ph	sec-C_4H_9	0.25	30[f]	50[g,i]	117–118[j,e]
7	Ph	Ph	0.25	35[f]	99[i]	146–147[k,e]
8	Ph	4-OMePh	0.50	32[f]	77[g]	116–120[e]
9	n-Pr	sec-C_4H_9	0.50	Δ	62	72–77[l]
10	Ph	c-C_6H_{11}	24	(42),[f] rt	72	132–134[e]
11	Ph	4-ClPh	0.75	Δ	50[g]	129–134[m,n]
12	Ph	2-Me,4-OMePh	1.0	(27),[f] rt	51[g]	187–189[e]
13	Ph	4-NO_2Ph	6.0	Δ	84	144–147[e]
14	n-Pr	i-C_4H_9	120	rt	23	118.5–120.0[l]
15	n-Pr	n-C_4H_9	0.50	(35),[f] Δ	60[i]	70–75[l]
		b. Reactions with Cyclic Secondary Amines (R′ = R″)				
16	Ph	$-(CH_2)_4-$	0.25	45[f]	73[g]	93.0–95.5[o]
17	Ph	$-(CH_2)_2O(CH_2)_2-$	0.25	(50),[f] Δ	79[g]	128–133[e]

[a] Conditions are not optimized, rt = room temperature, Δ = reflux. [b] Crude isolated yield. [c] Displacement reaction used 5.6 equiv of amine. [d] Lit.[19] mp 93–94 °C. [e] Recrystallized from hexane. [f] Exotherm to reported temperature was observed. [g] Yield corrected for purity. [h] Lit.[20] mp 89.5–90.0 °C. [i] Displacement run in the absence of solvent. [j] Lit.[20] mp 116–117 °C. [k] Lit.[21] mp 148–150 °C. [l] Oxalate salt recrystallized from IPA. [m] Lit.[20] mp 149–150 °C (EtOH). [n] Recrystallized from petroleum ether/EtOH. [o] Recrystallized from ether.

lysts have often been employed in the oxidation of sulfur-containing groups[17a] and we found that use of sodium molybdate catalyzed the oxidation of *N*-phenylthiourea. A high yield of pure sulfonic acid was obtained in a short reaction time when the reaction was run as a slurry in water. The rate of reaction was dependent on the concentration of catalyst employed. Use of 2 equiv of hydrogen peroxide led to the sulfinic acid derivative (**2**, X = 2), while use of 3 equiv led to the sulfonic acid derivative (**2**, X = 3). In general, the sulfonic acid derivatives are thermally stable at room temperature and are the preferred intermediate. The oxidation products were isolated by filtration and air-dried for use in the displacement reaction. The oxidation state of sulfur was unambiguously determined by ^{17}O NMR chemical shifts at 48.8 MHz: the *N*-phenylaminoiminomethanesulfonic acid resonates at 164.9 ppm and the *N*-phenylaminoiminomethanesulfinic acid resonates at 439.0 ppm (in acetonitrile/dimethyl sulfoxide with chemical shifts relative to water), in good agreement with literature values for similar functional groups.[18] Table I lists typical isolated yields for oxidation of several monosubstituted thioureas by 30% hydrogen peroxide in water using sodium molybdate as a catalyst.

The second step of the sequence, displacement of the oxidized sulfur with amine nucleophiles, was carried out under mild conditions. The sulfonic acid derivative was added to an acetonitrile solution of the amine and the reaction was stirred at ambient temperature until complete (typical reaction time was less than 1 h). The reaction mixture was basified and extracted with an organic solvent. Concentration of the organic phase led to isolated of the guanidines as free bases. Yields of displacement reactions are reported in Table II. In general, the isolation yields were good to excellent. A limitation of the reaction was realized by the reaction of *tert*-butylamine with *N*-*n*-propyl-aminoiminomethanesulfonic acid. The only isolated product was the symmetrical triazine N^2,N^4,N^6-tripropylmelamine (which was identified by MS, ^{13}C and ^1H NMR, C, H, N analyses, and molecular weight by osmometry in chloroform). A straightforward trimerization of the sulfonic acid derivative catalyzed by the hindered amine is proposed as a likely mechanism of formation.

During the course of the reaction of morpholine with *N*-phenylaminoiminomethanesulfonic acid at room temperature, a transient intermediate was detected by TLC, but it was not characterizable by proton or carbon NMR. Two likely intermediates are a carbodiimide (resulting from elimination of the oxidized sulfur) which can undergo addition of morpholine or isomerize to a cyanamide (as suggested by W. Walter[9]) or a tetracoordinate adduct (resulting from addition of morpholine, as depicted in eq 2) which can undergo elimination of the oxidized sulfur function. When the reaction was studied by IR spectroscopy, monitoring the region between 1900 and 2300 cm^{-1}, no carbodiimide or cyanamide absorption was observed. Therefore, we favor an addition/elimination mechanism involving addition of the amine nucleophile to an aminoiminomethanesulfonic acid to form a tetrahedral intermediate that collapses to product (see eq 2).



(2)

The relative reactivity of *N*-phenylaminoiminomethanesulfonic acid and the corresponding *S*-methyl-

(17) See, for example: (a) Difuria, F.; Modena, G. *Rev. Chem. In.* **1985**, *6*, 51. (b) Sheldon, R. A.; Kochi, J. K. "Metal Catalyzed Oxidations of Organic Compounds"; Academic Press: New York, 1981. (c) Mimoun, H. "The Chemistry of Functional Groups, Peroxides"; Patai, S., Ed.; John Wiley and Sons: New York, 1982; p 463. (d) Yarovenko, E. Y.; Lastovskii, R. P. *J. Org. Chem. USSR (Engl. Transl.)* **1970**, *6*, 952. (e) De Filippo, D.; Ponticelli, G.; Trogu, E. F. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1500.

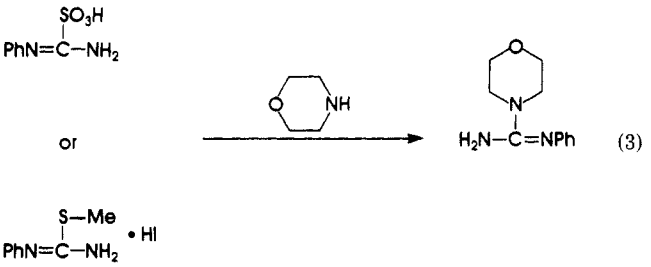
(18) According to R. K. Harris and B. E. Mann, in "NMR and the Periodic Table"; Academic Press: New York, 1978, a typical chemical shift value (relative to water) for the *S*-dioxide group is 513 ppm and for the *S*-trioxide group is 188 ppm.

(19) Kiselev, L. A.; Shvetsova-Shilovskaya, K. D.; Khanina, L. N.; Mel'nikov, N. N. *J. Org. Chem. USSR (Engl. Transl.)* **1967**, *4*, 459.

(20) Kiselev, L. A.; Ruchkin, V. E.; Osipova, N. M.; Mel'nikov, N. N.; Shvetsova-Shilovskaya, K. D. *Ibid.* **1966**, *2*, 2144.

(21) Weast, R. C. Ed. "Handbook of Chemistry and Physics", 51st ed.; CRC Publishing Co.: Cleveland, 1971; C-317.

isothiouronium iodide toward morpholine at 35 °C was studied (see eq 3). It was determined that the *S*-trioxide group was replaced about 15 times faster than the *S*-methyl group by morpholine.



This synthetic route is particularly useful for the direct conversion of N-monosubstituted thioureas to di- and trisubstituted guanidines in good overall yield. The key transformation is sulfur activation through oxidation followed by displacement of the oxidized sulfur group by an amine nucleophile (oxidation/displacement). The experimental procedure is facile, no noxious odors are generated, and the isolated intermediate is stable at ambient temperature. The overall reaction time is short and the yields are good.

Currently, we are determining the scope of the reactions of other nucleophiles with oxidized thioureas.

Experimental Section

Melting points are corrected. Reactions were typically monitored by TLC (silica gel, 90:10 $CHCl_3$/MeOH, oxidation; 95:5:5 MeOH/AcOH/$CHCl_3$, displacement). All reagents and solvents were used without additional purification. Elemental analyses were obtained from Schwarzkopf or Atlantic Laboratories. ^1H NMR spectra were obtained on a Varian EM 390 (90 MHz) or a Bruker AM 360 (360.13 MHz) spectrometer with chemical shifts relative to Me_4Si. All ^{17}O NMR work was done on the Bruker AM 360 (48.8 MHz) with chemical shifts relative to water. Infrared spectra were obtained on a Perkin-Elmer 283 infrared spectrophotometer. All guanidines gave the correct molecular ion peak by chemical ionization mass spectrometry. Mass spectra were obtained on a Finnigan 3300 or a VG 7035 mass spectrometer.

Synthesis of Sulfonic Acid Derivatives from Thioureas. General Procedure. A reaction vessel is charged with thiourea (0.013 mol), water (6 mL), sodium chloride (0.005 mol), and sodium molybdate dihydrate (0.0002 mol) and cooled to 0 °C with efficient stirring. Hydrogen peroxide (30%, 0.041 mol) is added dropwise to the cooled suspension at a rate to minimize decomposition (follow the reaction by TLC). In most cases, a temperature of less than 20 °C was maintained during the addition of the first 2 equiv, while the third equivalent was added to maintain the reaction temperature <40 °C. Once the addition is complete (total addition time about 1 h) and the temperature begins falling, the oxidation reaction is over. The product is isolated by cooling the reaction to 10 °C and collecting the solid sulfonic acid by filtration. The sulfonic acid is then washed with a small portion of cold brine.

Synthesis of Guanidines from Sulfonic Acids. General Procedure. The sulfonic acid (0.01 mol) prepared above is added to the amine (0.013 mol) in 5 mL of acetonitrile at room temperature. In some cases an exotherm is observed. The reaction is monitored by TLC for disappearance of starting material. In some cases it may be necessary to warm the reaction mixture to reflux to ensure complete reaction. The reaction is worked up by adjusting the pH to the range of 12–14 with 3 N NaOH. In some cases, the desired guanidine may form as a solid precipitate and may then be isolated by filtration. Otherwise, the reaction mixture is extracted rapidly with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The desired guanidine is obtained in a purity ranging from 80–95%. The guanidine may be further purified by recrystallization from hexane by or formation of an appropriate salt.

Acknowledgment. We gratefully thank J. L. Spink and R. D. Shah for technical assistance, Drs. V. Paragamian, B. E. Maryanoff, and R. A. Olofson (The Pennsylvania State University) for helpful discussions, Dr. R. R. Inners and M. S. Mutter for ^{17}O NMR spectra, and J. Childers and B. J. Duffy for modifications during scale up.

Registry No. **1a**, 103-85-5; **1b**, 927-67-3; **1c**, 614-78-8; **1d**, 459-05-2; **2a**, 25343-52-6; **2b**, 25348-90-7; **2c**, 101030-88-0; **2d**, 101010-32-6; **4**, 17813-43-3; **5**, 13636-29-8; **6**, 13636-30-1; **7**, 102-06-7; **8**, 101010-23-5; **9**, 101010-24-6; **10**, 101010-25-7; **11**, 13636-36-7; **12**, 101010-26-8; **13**, 101010-27-9; **14**, 101010-29-1; **15**, 101010-31-5; **16**, 65071-09-2; **17**, 75358-18-8; $NH_2C_4H_9$-*t*, 75-64-9; $NH_2C_4H_9$-*i*, 78-81-9; $NH_2C_4H_9$-*sec*, 13952-84-6; NH_2Ph, 62-53-3; 4-$NH_2C_6H_4OMe$, 104-94-9; $NH_2C_6H_{11}$, 108-91-8; 4-$NH_2C_6H_4Cl$, 106-47-8; 2-Me, 4-$MeOC_6H_3NH_2$, 102-50-1; 4-$NH_2C_6H_4NO_2$, 100-01-6; $NH_2C_4H_9$, 109-73-9; pyrrolidine, 123-75-1; morpholine, 110-91-8.

Supplementary Material Available: Spectral data and C, H, N analyses (where appropriate) for the guanidines in Table II (3 pages). Ordering information is given on any current masthead page.

Structure and Torsional Potential Function of Allylsilane: Results from MM2 and ab Initio Calculations (3-21G(*))

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Allylsilanes are species with substantial synthetic utility,[1] and attempts to model the transition-state stereochemical preferences for allylsilane condensation reactions have appeared.[2] Molecular mechanics methods can greatly aid modeling processes when appropriate parameters are available. Frierson and Allinger[3] have recently reported a silane force field for MM2-82; however, there was no explicit parameter development for dealing with the allylsilane group. We report a set of parameters for MM2-77[4] derived from experimental and ab initio data which permits satisfactory modeling of the structure and conformational energies of allylsilane.

Several experimental investigations examining the structure and conformational preferences of allylsilane have been reported.[5-7] These studies were aimed at deriving a better structural model for allylsilane that would explain observed physical properties, particularly UV and IR spectra.[7] Additionally, there has been a general interest in evaluating the conformational preferences of both XCC=Y and C=CXC systems (X = C, N, O, S, Si; Y = C, O).[7-9] Our interest in allylsilane was derived from MM2 force-field investigations of hyperconjugative effects in fixed rings such as silanorbornenes.[10] Numerous articles have examined the "$\sigma-\pi$" conjugation and hyperconjugative effects in silanes, and these have been synopsized in a recent review.[11]

Both electron diffraction (ED)[5] and microwave (MW)[6] studies present results which are consistent with our MM2 and 3-21G(*)[12,13] calculated values for the dihedral angle of the single energy minimum at 103 ± 1°. We also find that the cis conformation (ω = 0°) is now a maximum and should not be populated (barrier height of ~2 kcal/mol above the 103° form). The theoretical and experimental results generally have agreed well (Table I).

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