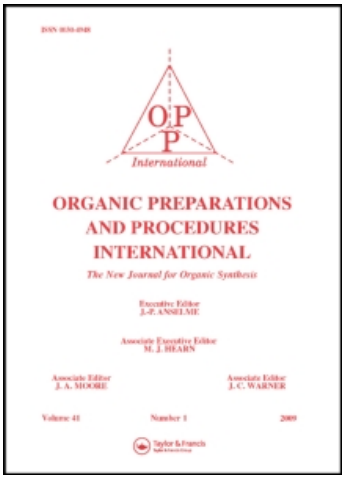

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NEW METHOD FOR THE PREPARATION OF GUANYLTHIOUREAS

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8. The progress of the reaction was followed by capillary GC (Hewlett-Packard): Capillary column 10m X 0.35 mm Carbowax HP-20M; Temp. 1 = 50°, time 1 = 2 min. Rate of heating = 15°/min, Helium flow = 6 ml/min. Temp. 2 = 210°, Time 2 = 3 min.

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NEW METHOD FOR THE PREPARATION OF GUANYLTHIOUREAS

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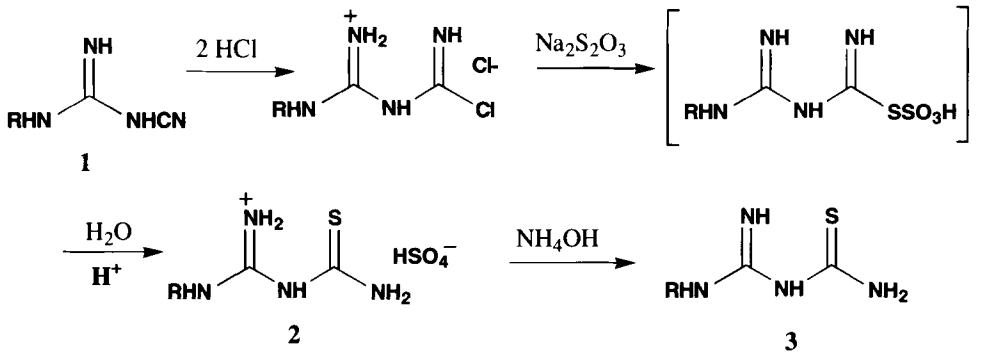
Guanylthiourea (**3a**), often referred to as *gutimine*, is a frequent starting material in preparation of many thiazoles and has been prepared by the reaction of saturated aqueous hydrogen sulfide with N-cyanoguanidine (dicyandiamide, **1a**) at 60-80°.[1] Gutimine also results from the acid hydrolysis of 4,6-diamino-2-thio-1,3,5-thiadiazine[2] and in the dehydrosulfurization of alkyl dithiocarbamic acids as by-product.[3] It was also prepared and used as intermediate for the synthesis of triazines by reacting dicyandiamide with hydrogen sulfide in N-alkylpyrrolidone as solvent, using amines, ammonia, and/or sulfur as catalyst.[4] All of these methods are characterized by *e. g.* elevated temperatures, non aqueous solvents, long reaction times, and reagents which are dangerous and/or bad-smelling such as hydrogen sulfide or carbon disulfide.

We now report that guanylthiourea (**3a**) can be produced by reacting dicyandiamide (**1a**) and sodium thiosulfate in acidic medium followed by neutralization with a base. It is rather surprising that sodium thiosulfate can be used as source of hydrogen sulfide in the production of gutimine, because it is well known that free thiosulfuric acid readily decomposes by adding *sulfur, sulfur dioxide*, and *water*, not *hydrogen sulfide* and *sulfuric acid.*



a) R = H b) R = Me c) R = Et d) R = *n*-Pr e) R = *i*-Pr f) R = *n*-Bu

This reaction involves 3 steps: a) addition of *two* moles hydrogen chloride to dicyandiamide, b) addition of thiosulfuric acid and acidic hydrolysis of the product, and c) release of the free gutimine by treatment with a base. As the base, we prefer ammonium hydroxide instead of sodium hydroxide because of the good solubility of ammonium sulfate in the reaction mixture. In order to broaden the scope of the reaction, we also prepared some N-alkyl derivatives of gutimine from alkyl dicyandiamides, as described in the Experimental Section. The yields were not optimized, except for guanylthiourea. Purification was carried out by recrystallization from water.

EXPERIMENTAL SECTION

Dicyandiamide was commercial material and used without further purification. N-alkyl dicyandiamides were prepared by method described in literature.[5] Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on BRUKER AC-400 spectrometer in DMSO-d_6 or in methanol-d_4 solution using TMS as internal standard, at 400 and 100 MHz, data given in δ.

Guanylthiourea (3a).- A 1-l. round-bottomed flask, fitted with a thermometer, mechanical stirrer, and dropping funnel was immersed in an ice-water bath in order to keep internal temperature between 0-20°. To this was added water (250 mL) and dicyandiamide (42 g, 0.5 mol). Stirring was started and conc. hydrochloric acid (100 mL, d=1.18, 1 mol) was added dropwise over a period of 10 minutes. With continued stirring, a solution of sodium thiosulfate ($Na_2S_2O_3.5H_2O$, 125g, 0.5 mol) in water (125 mL) was added dropwise over 30 minutes, by which time the nearly insoluble gutimine hydrogen sulfate (**2a**) had precipitated out. Then the mixture was treated with conc. ammonium hydroxide (120 mL, 25%) and tested for alkaline pH, pH should be between 8-10. The reaction mixture was cooled to 10°. The precipitate was collected, washed with small amounts of cold water and air dried to give 94.4 g (80%) of colorless crystals. A further amount of 17.7 g (15%) product can be obtained by extraction of the filtrate with *hot ethyl acetate* in a continous extractor, the total yield was 95%. Although the product is fairly pure it can be purified further by recrystallization from water by adding 100 mL of water for 10 g of gutimine and heating the mixture to 60°, followed by treatment with charcoal, hot

filtration and cooling to 0°. The solution was allowed to crystallize overnight in refrigerator, filtered, washed with small amounts of cold water and dried to give 8.10 g (81%) pure product, mp 170-175°.

N-Alkylguanylthiourea (**3**, R = methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl).- The method is essentially the same as we used for gutimine. Ethanol-water was used as solvent instead of water in order to facilitate the solubility of the reactants.

TABLE 1. Yields, mps and Analytical Data of Guanylthioureas

Cmpd	Yield (%)	mp (°C)	^{1}H NMR (δ)	^{13}C NMR (δ)	Elemental Analysis (Found) C	H	N	S
3a	95	172-175	5.93, 6.03 (6H, NH)[a]	161.67 (C-N)[a] 187.98 (C-S)	20.30 (20.16)	5.08 (5.04)	47.45 (47.54)	27.11 (26.80)
3b	74	150-154	2.80 (s, 3H, CH_3)[b] 4.86 (s, 5H, NH) 186.48 (C-S)	27.20 (C-H)[a] 161.07 (C-N)	27.27 (27.32)	6.06 (6.07)	42.42 (42.37)	24.24 (24.11)
3c	72	98-102	1.19 (t, 3H, CH_3)[b] 3.19 (k, 2H, CH_2) 4.87 (b, 5H, NH)	14.65 (C-H_3)[b] 36.76 (C-H_2) 162.11 (C-N) 188.44 (C-S)	32.87 (32.97)	6.84 (6.96)	38.35 (38.23)	21.91 (21.90)
3d	83	141-144	0.97 (t, 3H, CH_3)[b] 1.59 (k, 2H, CH_2) 3.14 (m, 2H, N-CH_2) 4.87 (b, 5H, NH)	11.71 (C-H_3)[b] 23.33 (C-H_2) 43.79 (N-C-H_2) 162.31 (C-N) 188.46 (C-S)	37.50 (37.38)	7.50 (7.75)	35.00 (35.12)	20.00 (19.72)
3e	72	102-107	1.16 (d, 6H, CH_3)[b] 3.85 (b, 1H, CH) 4.86 (s, 5H, NH)	22.93 (C-H_3)[b] 43.48 (C-H) 161.34 (C-N) 188.00 (C-S)	37.50 (37.43)	7.50 (7.37)	35.00 (34.93)	20.00 (20.22)
3f	71	136-139	0.95 (t, 3H, CH_3)[b] 1.3-1.7 (m, 4H, C_2H_4) 3.20 (t, 2H, N-CH_2) 4.87 (b ,5H, NH)	14.02 (C-H_3)[b] 21.06 (C-H_2) 32.00 (C-H_2) 41.87 (N-C-H_2) 161 (C-N) 188 (C-S)	41.37 (41.09)	8.04 (8.00)	32.18 (32.00)	18.39 (18.33)

a) in DMSO-d_6. b) in methanol-d_4

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AN IMPROVED SYNTHESIS OF 3-(2,5-DIMETHOXYBENZYL)PYRROLE

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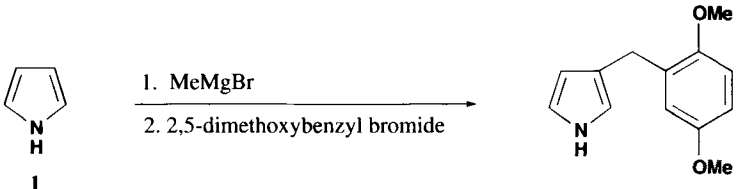
There has been a lot of interest recently in conductive polymers, especially polypyrroles, for their potential in the development of chemical sensor technology.[1,2] Polypyrroles are ideally suited for the design of sensory material because they not only exhibit high conductivity and electroactivity but also their building blocks, *i. e.* pyrrole monomers, can be easily modified by substitution. 3-(2,5-Dimethoxybenzyl)pyrrole[3] (**3**) is an important pyrrole monomer because its polymer can be demethylated to yield a hydroquinone substituted polypyrrole. Despite its simple structure and its importance as a key starting material, no high-yield synthesis of **3** has been described. 3-Alkylpyrroles[4] are



1 **3**

normally prepared by the reaction of the pyrryl Grignard reagent with alkyl halides. Recently Foos *et al.*[3] reported the preparation of 3-(2,5-dimethoxybenzyl)pyrrole (**3**) by reaction of pyrrylmagnesium bromide (**1**) with 2,5-dimethoxybenzyl bromide (**2**) in 3% yield. This yield is not only low but extensive chromatography is required to isolate the desired 3-isomer from 1- and 2-substituted pyrroles. Attempts to improve the yield of 3-isomer by altering the order of addition of benzyl bromide or changing the solvent were unsuccessful.

We required gram quantities of **3** as a starting material for the preparation of the polymer for chemical sensor applications. Although it is well known that the 2-position of the pyrrole ring is the most reactive site for electrophilic substitution, aluminium chloride catalyzed acylation of 1-(benzenesulfonyl)pyrrole[5] (**4**) gives 3-acyl derivatives[6,7] regiospecifically. Thus reaction of 1-(benzenesulfonyl)pyrrole (**4**) with 2,5-dimethoxybenzoyl chloride followed by hydrolysis and reduction was investigated.