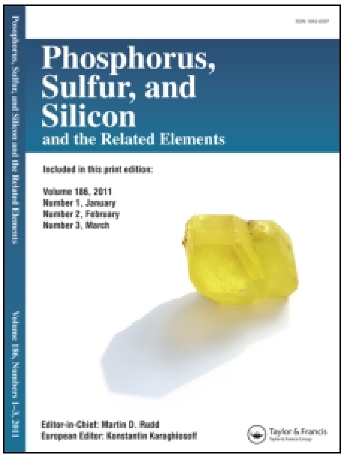

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REACTIONS OF OXIDIZED THIOUREAS WITH AMINE NUCLEOPHILES[1]

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A route for the convenient, cost effective synthesis of di- and tri-substituted guanidines from thioureas has been developed. The key transformation involves activation of the sulfur through S-oxidation followed by displacement of the activated sulfur by an amine nucleophile (oxidation/displacement). This preparation is experimentally facile and results in good isolated yields of desired guanidines. No noxious substances or sensitive intermediates are generated. The reaction time is short and overall yield of desired guanidine from thiourea is good.

In this paper, we describe a convenient, cost effective synthesis of guanidines 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 illustrated in Figure 1.

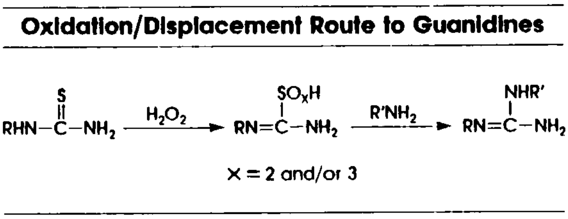
Development of this synthetic method reveals the philosophical approach of the Chemical Development Department at McNeil Pharmaceutical. In order to attain the highest yield of the target molecule at the lowest cost, we seek to study the relevant chemical reaction mechanisms for the route of interest. Then, by using mechanistic rationales, the route is optimized.

Our interest in the synthesis of guanidines stems from the development of linogliride (Figure 2), an orally-effective hypoglycemic guanidine[2] discovered at McNeil. The standard route employed for the synthesis of linogliride at the beginning of our work is outlined in Figure 3.

Numerous methods for preparing guanidines have been disclosed in the literature (see Figure 4). The most widely used commercial method is the reaction of ammonia or amines with S-alkylisothiouronium salts.[2a,3] The by-product of this reaction is the alkyl mercaptan, which is a noxious substance. Alkyl mercaptans are very foul smelling, and the threshold for detection by humans is about one part per billion. Besides, the threshold for employee exposure, because of safety considerations, is in the range of 1-10 parts per million. Thus, plant processes utilizing this method must include a step to transform the noxious material into an inert by-product, to avoid polluting the environment and the workplace.

Other common commercial ways of producing guanidines are the addition of ammonia or ammonia derivatives to dichloroisocyanides,[2a] cyanamides,[4] or carbodiimides.[5,6] Generally, these types of starting materials are corrosive and toxic. Another reported route is addition of amines to chloroformamidines;[7] however, chloroformamidines are moisture sensitive, as well as corrosive and toxic.

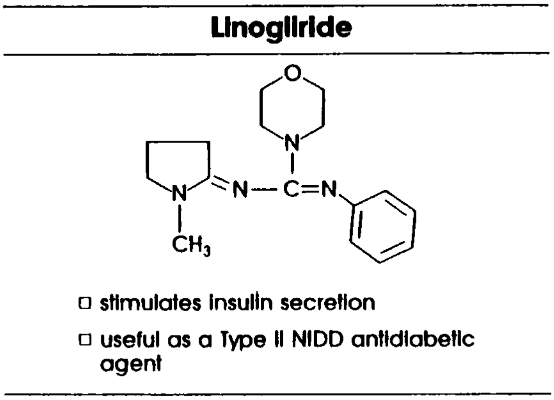
The approach of oxidizing the sulfur of a thiourea to furnish an S-oxidized derivative, followed by an amine displacement reaction appeared to be a simple alternative to the above-mentioned routes and was thus investigated (Figure 1).



$$RHN-\overset{\overset{S}{\|}}{C}-NH_2 \xrightarrow{H_2O_2} RN=\overset{\overset{SO_xH}{|}}{C}-NH_2 \xrightarrow{R'NH_2} RN=\overset{\overset{NHR'}{|}}{C}-NH_2$$

$X = 2$ and/or 3

FIGURE 1



- ☐ stimulates insulin secretion
- ☐ useful as a Type II NIDD antidiabetic agent

FIGURE 2

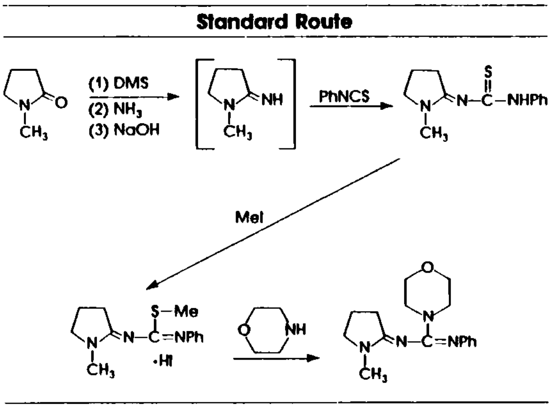
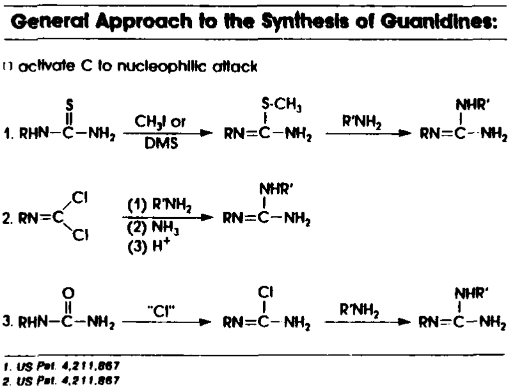


FIGURE 3

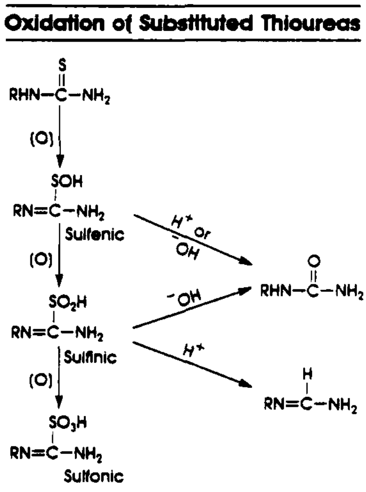


1. US Pat. 4,211,867
2. US Pat. 4,211,867

FIGURE 4

Literature precedent existed at the initiation of our work. A decade of work from W. Walter's laboratory resulted in over 30 publications on the oxidation of thioamides and thioureas.[8a] Furthermore, the amino acid glycine reacted with formamidine sulfinic acid under basic conditions to yield 36% of *N*-(aminoiminomethyl)glycine.[8b] The same paper reported that a control reaction of glycine with cyanamide under basic conditions yielded the same product.

Walter has shown (as depicted in Figure 5) that the thiourea moiety is oxidized to the corresponding S-monoxide (aminoiminomethanesulfenic acid), S-dioxide (aminoiminomethanesulfinic acid), and the S-trioxide (aminoiminomethanesulfonic



W. Walter and G. Randau, Liebigs Ann. Chem. 722, 52-100 (1969).

FIGURE 5

acid).[9,10,12] For our purposes, the S-trioxide derivative is the most desirable intermediate since it is generally the most stable form of an oxidized thiourea.

The S-monoxides, or sulfenic acids, are extremely thermally labile. Walter[9] reported difficulty in the isolation of stable sulfenic acids even at temperatures of −20 °C. In most cases it was only possible to detect this species by chromatographic methods.[9,12] Isolation of sulfenic acids was possible only when bulky *N,N'*-disubstituted thioureas were used.[9] Sulfenic acids heated to above 40 °C decomposed to starting thiourea and the corresponding urea with elimination of sulfur. Sulfenic acids also decomposed to the corresponding urea upon treatment with acid or base; however, depending on the substitution pattern, formamidines were sometimes observed upon acid treatment.[9,10]

The S-dioxides, or sulfinic acids, are more stable thermally than the sulfenic acids. Walter has shown[10] that when R = aryl, the stability of the monosubstituted sulfinic acids was a function of the aryl substituents; but, when R = alkyl, there was no substituent effect on stability. The sulfinic acids were also sensitive to acid or base treatment: base treatment resulted in the formation of the corresponding urea and acid treatment led to elimination of SO_2 to give the corresponding formamidine, as well as the urea.[10] Indeed, synthetic methods for the preparation of formamidines from aminoiminomethanesulfinic acids have been reported.[11]

The S-trioxides, or sulfonic acids, are thermally more stable than the monoxides or dioxides. Walter[12] has found that in general the sulfonic acids were very stable to acid decomposition. Treatment with base resulted in the formation of the corresponding urea under certain conditions.

RESULTS AND DISCUSSION

Our initial target for the synthesis of linogliride was the guanidine *N*-phenyl-4-morpholinecarboximidamide (Figure 1, R = phenyl, R' = morpholine). In principal, oxidation of *N*-phenylthiourea to *N*-phenylaminoiminomethanesulfonic acid, followed by a displacement reaction with morpholine, should furnish the target guanidine. Therefore, our work began with the oxidation of *N*-phenylthiourea. Attempts to repeat the published procedure[12] for the oxidation, using freshly prepared peracetic acid in methanol led to a host of products, only a small amount of which was the S-trioxide. Using the milder conditions described for the oxidation of substituted thioureas by hydrogen peroxide to the S-dioxide,[10] many products were observed by tlc. Examination of the major by-products resulted in identification of sulfur, *N*-phenylurea, *N,N'*-diphenylguanidine, *N*-[imino(phenylamino) methyl]-*N'*-phenylthiourea (commonly referred to as amidinothiourea) and Hector's base.[13] We concluded that, in addition to the acid-catalyzed decomposition of the intermediate S-monoxide or/and S-dioxide (Figure 5, R = phenyl), competing reactions included the condensation of *N*-phenylthiourea with some oxidized form of the thiourea to give an amidinothiourea, and decomposition of the amidinothiourea to *N,N'*-diphenylguanidine (Figure 6, R = phenyl). Furthermore, some of the amidinothiourea was cyclizing to Hector's base (Figure 7, R = phenyl).

The oxidation of *N*-phenylthiourea to Hector's base and the corresponding amidinothiourea has been reported.[14] The amidinothiourea was shown to decompose

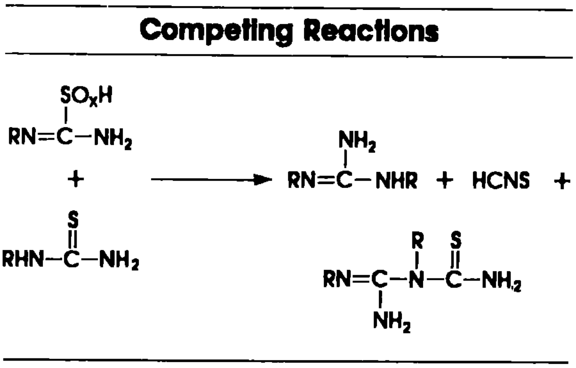


FIGURE 6

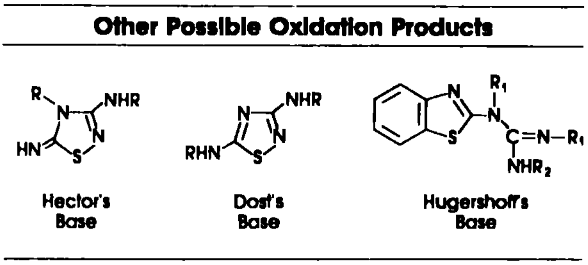


FIGURE 7

to *N*,*N*′-diphenylguanidine upon treatment with base and to oxidize to Hector's base.[13] A proposed mechanism for the formation of Hector's base involves S-oxidation of the amidinothiourea, followed by protonation and subsequent ring closure with loss of water and tautomerization (Figure 8, R = phenyl). Some authors have identified the oxidation product of *N*-phenylthiourea as the thiadiazole, Dost's base (Figure 7, R = phenyl). A single crystal X-ray structure[15] established the structure of Hector's base as that depicted in Figure 7. The structure of Dost's base, an isomerization product of Hector's base, has also been determined.[16]

Two hypotheses were engendered based on identification of the by-products in the oxidation of *N*-phenylthiourea. First, we presumed that oxidation to the S-trioxide was slow in comparison to decomposition of the intermediates, which suggested that increasing the rate of the oxidation process would furnish higher yields. Second, decomposition through a bimolecular mechanism might be lowered if the oxidation was not run in solution.

Catalysis of hydrogen peroxide oxidation by d° metal peroxo complexes is well known [17] and sodium molybdate was utilized to catalyze the oxidation of thioureas to the corresponding S-dioxide products.[18] The desired S-trioxide (Figure 9, R = phenyl, x = 3) was insoluble in water. We found that by carrying out the oxidation of *N*-phenylthiourea by hydrogen peroxide as a slurry in water at low temperature,

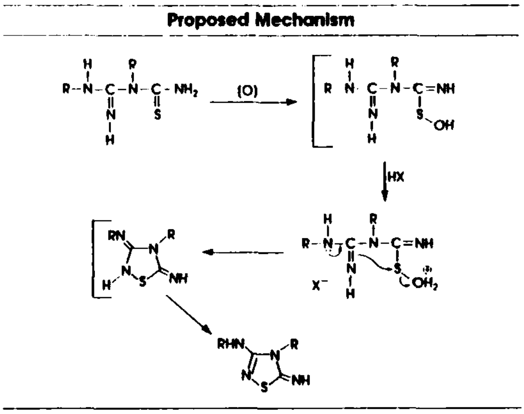
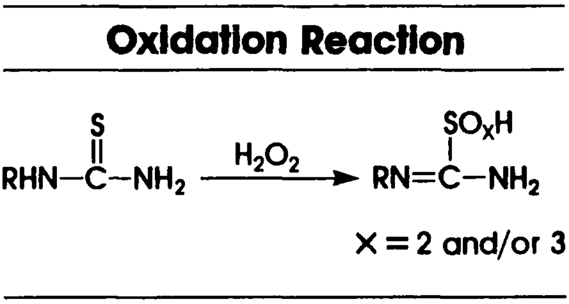


FIGURE 8



$$\mathrm{RHN{-}\overset{\overset{\displaystyle S}{\|}}{C}{-}NH_2} \xrightarrow{H_2O_2} \mathrm{RN{=}\overset{\overset{\displaystyle SO_XH}{|}}{C}{-}NH_2}$$

FIGURE 9

using sodium molybdate as a catalyst, a high yield, rapid oxidation was effected. The rate of reaction was dependent upon the amount of catalyst added; in the absence of catalyst, the starting material deposited sulfur and decomposed. Use of two equivalents of hydrogen peroxide led to the S-dioxide, while use of three equivalents led to the S-trioxide, as expected. Oxidation products were isolated by filtration and air dried for use in the displacement reaction. The products were characterized spectroscopically: the IR spectra and melting points agreed with the literature values (Figure 10).[10,12,18] The oxidation state of the sulfur was unambiguously determined by oxygen − 17 NMR chemical shifts at 48.8 MHz in acetonitrile/dimethyl sulfoxide (relative to the chemical shift of water): the S-trioxide resonated at 164.9 ppm and the S-dioxide resonated at 439.0 ppm, in good agreement with literature values.[19] Figure 11 is a table containing typical isolated yields of S-trioxides.

We next turned our attention to the displacement reaction. We found that displacement of the oxidized sulfur by the amine nucleophile occurred under mild conditions. The sulfonic acid was added to the amine in acetonitrile and the reaction mixture was worked up by concentration followed by basification and extraction with CH_2Cl_2 (taking care not to let the product remain in methylene chloride

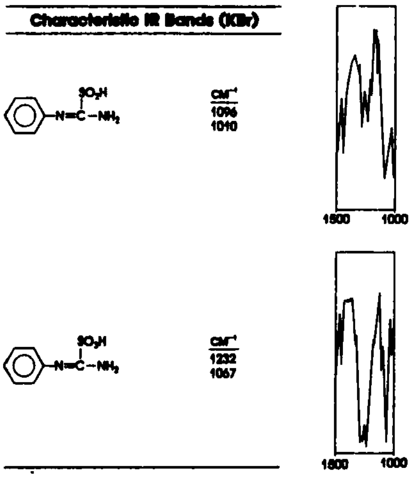
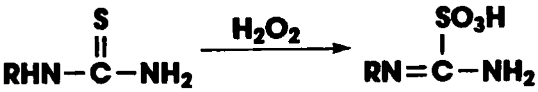


FIGURE 10



$$RHN-\overset{\overset{\displaystyle S}{\|}}{C}-NH_2 \xrightarrow{H_2O_2} RN=\overset{\overset{\displaystyle SO_3H}{|}}{C}-NH_2$$

R	% YIELD[a]
C_6H_5	80
C_3H_7	56
$(4\text{-F})C_6H_4$	47
$(2\text{-Me})C_6H_4$	70

a. not optimized

FIGURE 11

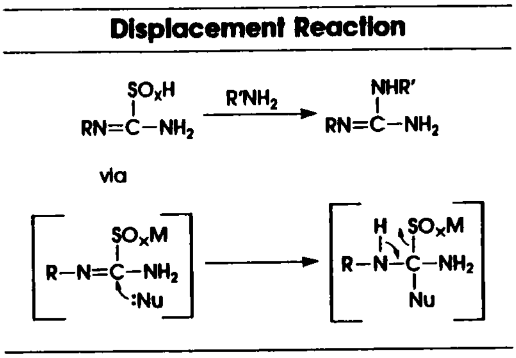
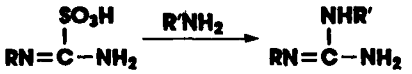


FIGURE 12

overnite[20]). Guanidines were isolated as free bases in good yields from the starting thioureas. During the displacement reaction, an apparent intermediate was observed by tlc; however, when the reaction was followed by IR, monitoring the region between 1900 and 2300 cm^{-1}, no carbodiimide or cyanamide absorption was observed. Therefore, we believe the mechanism involves addition of the nucleophilic amine to form a tetrahedral intermediate that then collapses to product, as illustrated in Figure 12.

Yields of the displacement reaction of morpholine with several S-trioxide derivatives are listed in Figure 13. A higher yield of guanidine resulted from displacement of sulfonic acid than of sulfinic acid for R = phenyl. We are unable to say whether the higher yield obtained implies that the sulfonate has a better reactivity than the sulfinate, or an equivalent reactivity but higher stability (the sulfinate may decompose more rapidly than the sulfonate during the addition/elimination reaction). Figure 14 lists the yields obtained when a series of butylamines were reacted with *N*,*N*′-diphenylthiourea S-dioxide; all isomers gave high isolated yields except *t*-butylamine, which was unreactive.

A comparison of the reactivity of an aryl monosubstituted S-trioxide with an alkyl monosubstituted S-trioxide appears in Figure 15. In general, yields with the



$$RN{=}\overset{SO_3H}{\overset{|}{C}}{-}NH_2 \xrightarrow{R'NH_2} RN{=}\overset{NHR'}{\overset{|}{C}}{-}NH_2$$

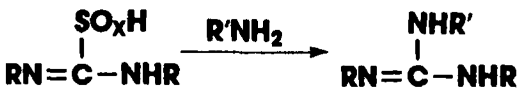
R′	% YIELD^a			
	R = C_6H_5	R = C_3H_7	R = (4-F)C_6H_4	R = (2-Me)C_6H_4
morpholine	65^b 42^c	20	83	62

a. *not optimized*

b. *from phenylthiourea; adjusted for purity*

c. *from phenylthiourea; rxn of sulfinic acid with morpholine acetate; adjusted for purity*

FIGURE 13



$$RN{=}\overset{SO_xH}{\overset{|}{C}}{-}NHR \xrightarrow{R'NH_2} RN{=}\overset{NHR'}{\overset{|}{C}}{-}NHR$$

R′	% YIELD^a R = C_6H_5
n-butyl	98
i-butyl	99
t-butyl	
sec-butyl	87

a. *not optimized*

FIGURE 14

Steric Effects

R'	% YIELD[a]	
	R = C_6H_5	R = C_3H_7
n-butyl	>90	60
i-butyl	66	23
t-butyl	>90	
sec-butyl	50	62

a. not optimized

FIGURE 15

arylsubstituted S-trioxide are higher. The reaction of *t*-butylamine with the alkylsubstituted S-trioxide led to the triazene in Figure 16. A straightforward trimerization of the starting S-trioxide derivative catalyzed by the hindered *t*-butylamine is proposed in Figure 17 as a likely mechanism.

In one case, the relative reactivity of the S-trioxide group and S-methyl group was studied (Figure 18, Ar = phenyl, the amine nucleophile was morpholine). It was found that at 35°C, the sulfonic acid derivative reacted about 15 times faster than the alkylisothiouronium derivative.

We have succeeded in our goal of developing a convenient synthesis of linogliride from *N*-phenylthiourea using experimentally facile conditions. Our successful route to linogliride is depicted in Figure 19. The process has been refined so that impurities are minimized and cost is kept down through the use of inexpensive reagents and reasonable reaction times.

The route developed at McNeil is useful for the preparation of di- and tri-substituted guanidines starting from *N*-alkyl or *N*-aryl thioureas. The key transformation involves activation of the sulfur through S-oxidation followed by displacement

Trimerization

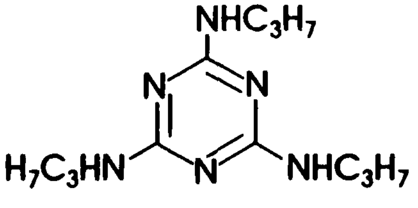


FIGURE 16

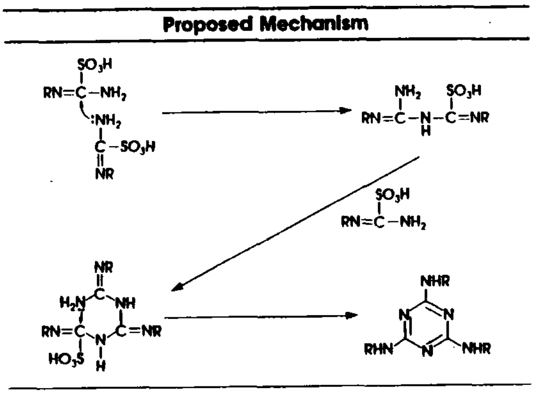


FIGURE 17

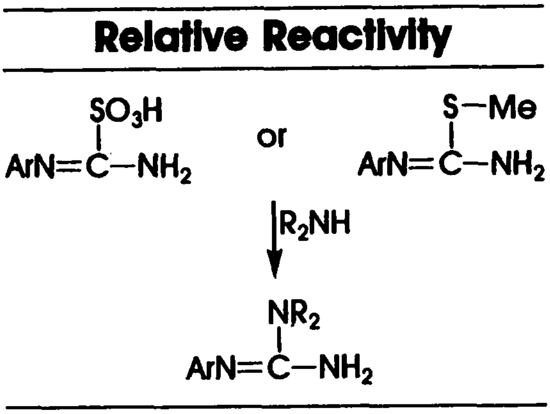


FIGURE 18

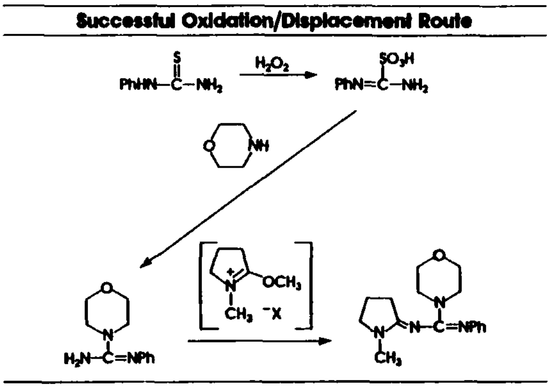
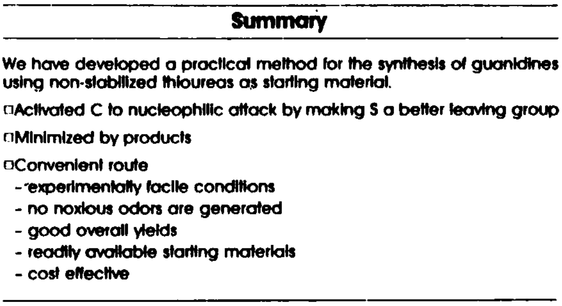


FIGURE 19



Summary

We have developed a practical method for the synthesis of guanidines using non-stabilized thioureas as starting material.

- □Activated C to nucleophilic attack by making S a better leaving group
- □Minimized by products
- □Convenient route
  - - experimentally facile conditions
  - - no noxious odors are generated
  - - good overall yields
  - - readily available starting materials
  - - cost effective

FIGURE 20

of the activated sulfur by amine nucleophiles (oxidation/displacement). This preparation is experimentally facile and results in good isolated yields of desired guanidines. No noxious odors or sensitive intermediates are generated. The reaction time is short and the overall yield of desired guanidine from thiourea is good. Figure 20 is a summary of advantages.

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

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