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A FACILE SYNTHESIS OF CYANOGUANIDINES FROM THIOUREAS

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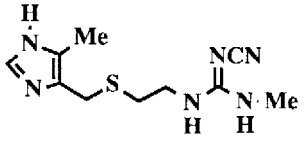
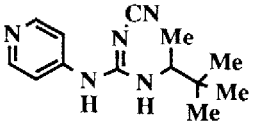
SUMMARY: *A facile synthesis of cyanoguanidines from corresponding thioureas is reported using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (water soluble carbodiimide).*

The cyanoguanidine group is an integral part of important molecules such as the antiulcer drug cimetidine (**1**) and the antihypertensive agent pinacidil (**2**). Cyanoguanidines are usually derived from the corresponding thiourea/urea by a variety of methods, most of which involve isolation of the intermediate carbodiimide or S-alkylisothiouronium salt.[1,2] We attempted

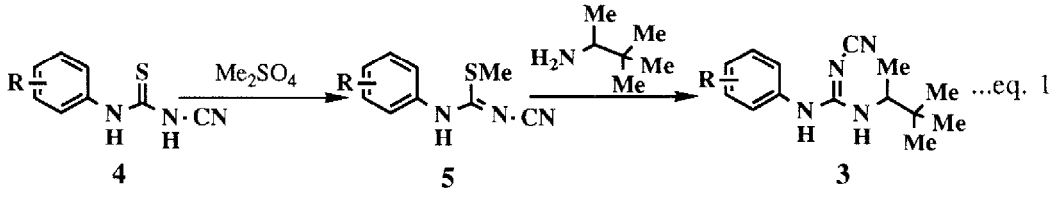


1 Cimetidine



2 Pinacidil

synthesis of arylcyanoguanidines **3** from amines and thioureas **4** via the S-methylisothiouronium salt **5** (eq. 1). The reaction not only proceeded in a poor yield but was accompanied by evolution of noxious methyl mercaptan gas. The reaction conditions (heating upto 150°C) were incompatible with sensitive groups (e.g., when R = CN).

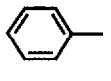
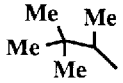
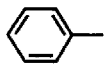
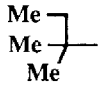
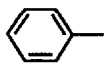
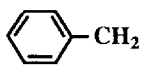
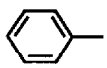
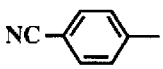
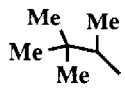
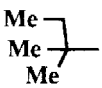
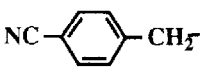
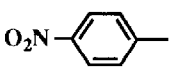
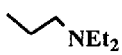


4 **5** **3** ...eq. 1

Based on a recent report[3] on the use of dicyclohexylcarbodiimide (DCC) for the direct conversion of a thiourea into cyanoguanidine (reaction time several days), we treated

...eq. 2

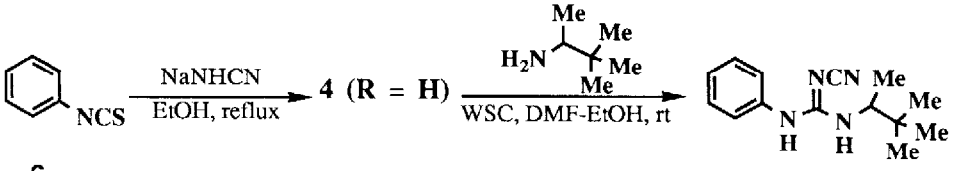
Table: Preparation of cyanoguanidines from thioureas (eq. 2)

Entry	R^1	R^2	R^3	% Yield[a]	mp°C[b]
1			H	78	128-130 (A)[c]
2			H	65	167-168 (B)
3			Me	83	144-145 (B)
4		-$CH_2CH_2CH_2CH_2$-		85	169-170 (B)
5			H	74	191-193 (C)
6			H	82	127-128 (B)
7			H	60	154-156 (D)

[a]yield of the crystallized product, [b]solvent for crystallization (A, acetonitrile/isopropyl ether; B, dichloromethane/isopropyl ether; C, 2-propanol; D, ethyl acetate), [c]reference 1b.

thioureas **4** with DCC and amine and obtained ~20% yield of the products **3** after 24 h.. Faced with the difficulty of separating the product **3** from the contaminating dicyclohexylthiourea, we replaced DCC with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (water soluble carbodiimide: WSC). To our surprise, cyanoguanidine **3** (R = H) was formed from thiourea **4** in 78% yield after 30 min. at room temperature.

To explore the generality of this one step transformation of thioureas into cyanoguanidines, we prepared several additional compounds (eq. 2) and the results are summarized in Table. The use of highly hindered (entry 2) and secondary amines (entries 3 and 4) is allowed in this reaction, as is the presence of a substituent on the aromatic ring (entry 5). The reaction is not restricted to the use of arylthioureas (entry 6). The presence of a basic nitrogen does not affect the outcome of this reaction (entry 7). The isolation of thiourea **4** is not always necessary: isothiocyanate **6** was reacted with sodium cyanamide to give intermediate thiourea which was reacted with WSC and amine in the same pot to give product **3** in 75% overall yield (eq. 3). While dimethylformamide was employed throughout our studies, the reaction could be carried out in various polar solvents.

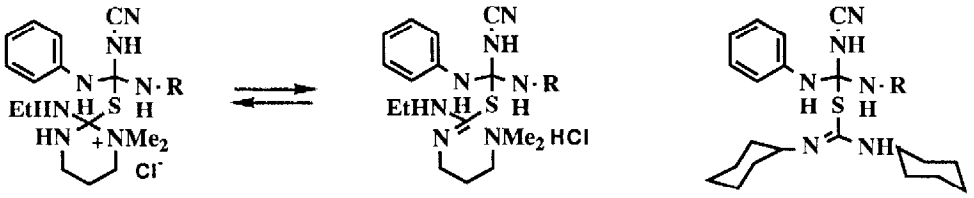


....eq. 3

6 **3**

To gain some insight into the mechanism of this reaction, we performed several additional experiments. We found the reaction requires the presence of participating amine and WSC simultaneously as pretreatment of thiourea **4** (R = H) with WSC followed by addition of amine gave only 17% yield of the product after 24 h.. The reaction proceeds in a normal fashion when the amine is pretreated with WSC followed by addition of thiourea. We found addition of pyridinium tosylate to the reaction (**4 -> 3**) with DCC improves the yield significantly (75% after 24 h), though the reaction with WSC still goes faster.

Based on these observations, we propose the reaction involves simultaneous participation of amine and WSC to give a tetrahedral intermediate A1/A2 (or an equilibrium mixture thereof).[4] The cleavage of carbon-sulfur bond in A1/A2 is facilitated due to the positively charged nitrogen or due to internal protonation by hydrogen chloride. The corresponding intermediate B from the reaction with DCC lacks such a driving force and leads to a slow reaction in the absence of an acid. The possibility that amine hydrochloride in WSC accelerates the formation of the tetrahedral intermediate A1/A2, could not be ruled out.



A1 A2 B

In conclusion, we have shown WSC cleanly converts thioureas into cyanoguanidines in one step. The reaction with WSC is cleaner and faster than that with DCC. Though we do not know the precise mechanistic details of this rate enhancement, our results indicate the presence of an acid plays a role in this reaction.

A representitive procedure is illustrated for N''-cyano-N-phenyl-N'-(1,2,2-trimethylpropyl)guanidine (entry 1): A solution containing N-cyano-N'-phenylthiourea (354 mg, 2.0 mmol) and 2-amino-2,2-dimethylbutane (0.32 mL, 2.4 mmol) in dimethylformamide (2.0 mL) was treated at rt with WSC (480 mg, 2.4 mmol) and the reaction was allowed to stir for 30 min.. It was diluted with ethylacetate, washed with 1N HCl, water and dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue was crystallized from CH_3CN-isopropyl ether to yield N''-cyano-N-phenyl-N'-(1,2,2-trimethylpropyl)guanidine (381 mg), which was identical to the previously reported material[1b].

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References And Notes

1. (a) Mestres, R. and Palomo, C. Synthesis, **1980**, 755 (b) Petersen, H. J.; Neilson, C. K. and Arrigoni-Martelli, E. J. Med. Chem. **1978**, 21, 773.

2. Curd, F. H. S. J. Chem. Soc. **1948**, 1620.

3. Hansen, E. T. and Petersen, H. J. Synth. Comm. **1984**, 14, 1275.

4. A similar mechanism for the formation of guanidines from thioureas has been proposed.[5]

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