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TRIMETHYLALUMINUM PROMOTED SYNTHESIS OF CYANOGUANIDINES

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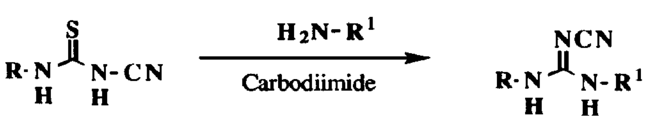
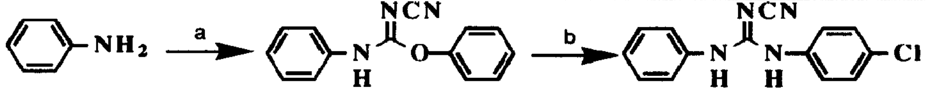
SUMMARY: Synthesis of cyanoguanidines from N-cyano-O-phenylisoureas and relatively nonbasic amines (e.g., aniline) using trimethylaluminum is reported.

The cyanoguanidine moiety is an important surrogate for urea and thiourea functionalities.[1] Its synthesis usually involves treatment of a carbodiimide or S-alkylisothiouronium salt with the requisite amine.[2,3] While the preparation of carbodiimides from ureas/thioureas is often irreproducible, the reaction proceeding via the S-alkylisothiouronium salt is usually accompanied by the generation of a noxious mercaptan byproduct. The use of carbodiimides[4,5] and transition metal salts[6] has alleviated these problems when the reaction involves a relatively basic alkyl amine. Amines of low basicity (e.g. anilines) often fail to participate in the carbodiimide promoted coupling (eq. 1) and the reaction involving the isothiouronium salt. This problem became more obvious during our attempts to prepare [^{14}C]-BMS-180448 (entry 7, Table 1). In this letter, we disclose a simple method for the preparation of cyanoguanidines from N-cyano-O-phenylisoureas (eq. 2).



eq. 1

The intermediate O-phenylisourea **3** for the synthesis of cyanoguanidine **1** could be readily prepared by treatment of aniline with the commercially available diphenylcyanocarbonimidate in acetonitrile.[7] As reported previously[7], the reaction of **3** with aliphatic amines to give cyanoguanidines proceeds smoothly,[8] however, the reaction involving 4-chloroaniline was extremely sluggish. In analogy with the Weinreb amide forming reaction,[9] we employed trimethylaluminum to promote this displacement. Indeed, on heating 4-chloroaniline with O-phenyl ether **3** in the presence of trimethylaluminum at 60-65°C in dichloroethane gave cyanoguanidine **1** in 62% yield.[10]



2 3 1

eq. 2

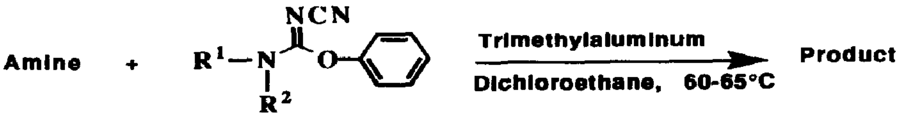
Reaction conditions: a) diphenylcyanocarbonimidate, AcCN, reflux, 2h, 86%; b) 4-chloroaniline, trimethylaluminum, dichloroethane, 65°C, 2 hours, 62%.

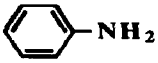
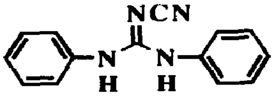
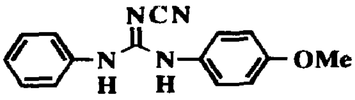
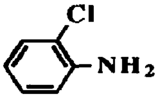
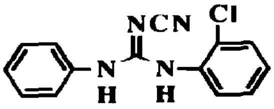
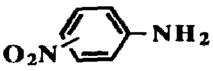
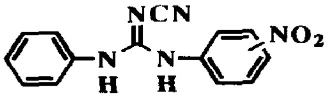
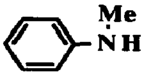
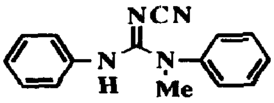
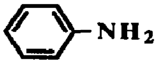
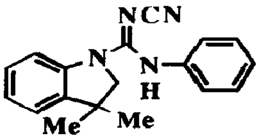
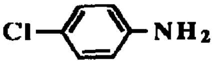
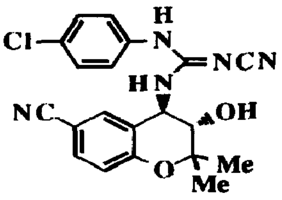
Additional examples, to illustrate the scope of this reaction, are provided in the Table 1. As expected, the best results are obtained with unsubstituted aniline or anilines substituted with electron releasing groups (entries 1, 2). Halo-substituted-anilines satisfactorily participate in the reaction giving good to excellent yields of products (entry 3). The reaction fails with anilines substituted with strong electron withdrawing groups (entry 4). The use of a secondary aniline gave satisfactory results (entry 5). Especially noteworthy is the N,N-disubstituted cyanoguanidine (entry 6) which was inaccessible by a majority of the methods reported in the literature. The flexibility of this method was further demonstrated by the preparation of BMS-180448 (entry 7) in 51% yield. Furthermore, this method could be adopted for the synthesis of [^{14}C]-BMS-180448, wherein the radioactivity was introduced in the form of [^{14}C]-4-chloroaniline.[11]

We have shown that cyanoguanidines can be prepared from readily available O-phenylisourea precursors and poorly basic amines in the presence of trimethylaluminum. The mechanism of this reaction is believed to be similar to the Weinreb amide forming reaction from corresponding esters.[9]

A representative procedure is illustrated for the preparation of **1**: To a solution 4-chloroaniline (0.32 g, 2.5 mmol) in dry dichloroethane (5 mL) at 0°C under argon was added trimethylaluminum (1.26 mL of 2.0M solution, 2.53 mmol). The reaction was stirred at rt for 30 min, treated with N-cyano-N'-phenylcarbamimidic acid phenyl ester (**3**) (0.5 g, 2.11 mmol), and then heated at 60-65°C for 2 hrs. The reaction mixture was cooled to ambient temperature, diluted with dichloromethane and quenched with 10% sodium carbonate solution. The organic layer was separated and the aqueous layer reextracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated, and the residue purified by flash chromatography on silica gel (1:2/EtOAc:Hexanes containing 2% MeOH) to give **1** (356 mg, 62%) as a colorless solid.[10]

TABLE 1



Entry	Amine	Product	%Yield	mp°C
1			67	201-202
2			90	148-150
3			81	150-152
4			0	--
5			85	159-161
6			44	224-225
7		 BMS-180448	51[12]	170-172

REFERENCES AND NOTES

1. Ganellin, R. *J. Med. Chem.* **1981**, *24*, 913.

2. Mestres, R. and Palomo, C. *Synthesis*, **1980**, 755.

3. (a) Curd, F. H. S.; Hendry, J. A.; Kenny, T. S.; Murray, A. G.; Rose, F. L. *J. Chem. Soc.* **1948**, 1630. (b) Ferris, A. F.; Schutz, B. A. *J. Org. Chem.* **1963**, *28*, 71.

4. Atwal, K. S.; Ahmed, S. Z.; O'Reilly, B. C. *Tetrahedron Lett.* **1989**, *30*, 7313.

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

6. Suyama, T.; Iwoka, T.; Ichikawa, E. *Nippon Kagakukai Shi* **1986**, 1246.

7. Garratt, P. J.; Hobbs, C. J.; Wrigglesworth, R. *J. Org. Chem.* **1989**, *54*, 1062.

8. Atwal, K. S.; Moreland, S.; McCullough, J. R.; Ahmed, S. Z.; Normandin, D. E. *Bioor. Med. Chem. Lett.* **1992**, *2*, 87.

9. (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171. (b) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth.* **1979**, *59*, 49 (*Org. Synth. Coll. 8*, 492). (c) Levin, J. I.; Turos, E. Weinreb, S. M. *Synth. Comm.* **1982**, *12*, 989.

10. All new compounds were characterized by spectroscopic and chromatographic methods and gave satisfactory microanalysis.

11. We wish to thank Dr. K. Rinehart and Mr. Michael Lago for carrying out the synthesis of [^{14}C]-BMS-180448.

12. Atwal K. S.; Grover, G. J.; Ahmed, S. Z.; Ferrara, F. N.; Harper, T. W.; Kim, K. S.; Sleph, P. G; Dzwonczyk, S; Russell, A. D.; Moreland, S.; McCullough, J. R.; Normandin, D. E. *J. Med. Chem.* **1993**, *36*, 3971.

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