Oriental Journal of Chemistry Vol. **24**(1), 223-228 (2008)

A fast and new route to synthesis of guanidine derivatives using $HgCl_2$ as a promotor

SUDHIR KUMAR[1]*, LAKSHMAN SINGH[1] and UPMA SINGH[1]

[1]Department of Chemistry, L.R. (P.G.) College, Sahibabad - 201 005 (India)

(Received: March 06, 2008; Accepted: April 24, 2008)

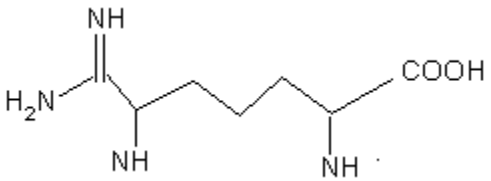
ABSTRACT

A simple and Noval Synthesis of guanidine derivatives is presented in this study. The construction of the Central basic Scaffolds is achieved by the using of $HgCl_2$ as a promoter. The Formation of product of substituted guanidines controlled by amount of reactant. Further a new fast-tract access to N-1(Boc)-N-(2) cyclohexyl-N(3) phenyl-guanidine was developed.

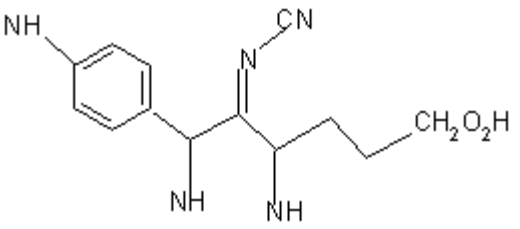
Keywords: N-BOC-N' Substituted thiouria N sulphonyl guanidines. Carbodiamide.

INTRODUCTION

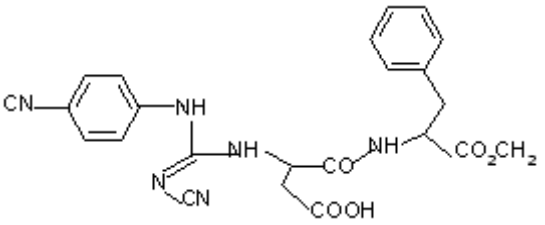
Guanidines possess biological importance. It is a key structural element of many biological active compounds, such as arginine (A small group of about 20 amino acids commonly found in protein)[1]. For the treatment of many disease such as cancer, diabetic[2], metabolic process[3]. Guanidines itself is a strong base (pka of conjugated acid is 12.5) as are substituted guanidines[4]. It was first prepared by strecker in 1861 by oxidizing guanine. The Natural amino acid, L-arginine[1] is often found at active site. In proteins and enzymes; it is critical for the normal function of living organism[5].



Isolation of guanidine compounds as metabolities provides leads for the prevention of metabolic disorders and helps the prognosis of cancer, cardiovascular disease, diabetes[6], antimicrobial activity[7]. thrombin inhibitor[8], transport for the delivery of anticancer agent[9], anti-influenza agents[10]. Guanidines is also a useful basic catalyst[11,12], Gunidiens is found in sucrose unit e.g.



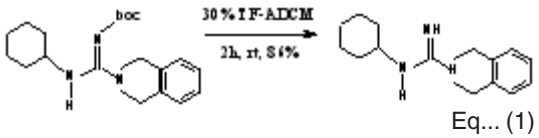
900 × Sucrose



40,000 × Sucrose

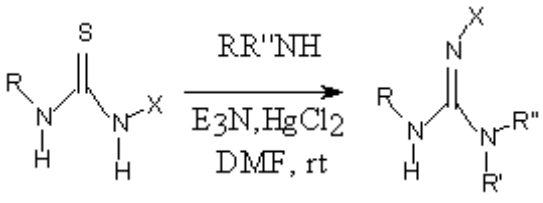
RESULTS AND DISCUSSION

N-Boc-N-substituted thioureas reacted smoothly with an amine in the presence of $HgCl_2$. The substituent on the starting N-Boc-thioureas may be alkyl or aryl; as can the incoming amine. The products, N-Boc-N', N'-disubstituted guanidines, can be easily deprotected, as exemplified in Eq. 2. Thus, this process provides a very efficient route to N, N-disubstituted guanidines. It compares very favorably with the existing methods for the preparation of guanidines, in that the present methods are effective for diaryl-substantiated guanidines as well as alkyl-substantuted ones.



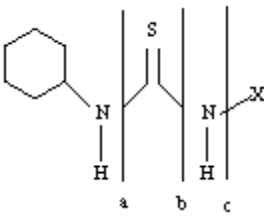
Eq... (1)

N-Carbonyl-, N-cyano; and N-Sulfonyl-Guanidines: The success with N-Boc-N'-substituted guanidines in the $HgCl_2$ promoted process prompted us to try other conjugated substituents such as acyl cyano and suffonyl groups (E.2). These substituents are often found in many drug compounds. In this study, we fixed the substituent R to be cyclohexyl and the incoming amine, R'R¢¢NH, to be tetrahydroisoquinoline as these groups were judged to be electronically and sterically neutral, thus enabling us to study fully the effects of the conjugated substituents, X.



X=COR', CN, SO_2R^1, etc Eq...(2)

The required thiourea starting material was prepared following one of three disconnections (Scheme I). Thus, for N-Boc, N-acetyl-, and N-benzylcarbamoyl-substituted compounds, N-cyclohexylthiourea was treated with $(Boc)_2O$, Ac_2O and BaNCO, respectively (disconnection *a*). N-Tosyl- and N-benzoyl-N'- cyclohexylthioureas were prepared by reacting cyclohexylamine with TsNCS and BzNCS, respectively (disconnection *b*). The difficulty in preparing TsNCS[13,14,15] coupled with easy availability of $TsNH_2$ prompted us to Consider an alternative route for the N-sulfonyl-guanidine. Thus, cyclohexylisothiocyanate was treated with the anion of tosylamide (disconnection). Similarly, treatment with the anion of cyanamide provided the N-cyano-compound. The thioureas prepared *via* disconnection *c* were not isolated, but used *in situ* in their anionic forms for the $HgCl_2$ promoted guanylation steps[16] *(vide infra*).



Disconnection *a*	Disconnection *b*	Disconnection *c*
X-Box(67%)	X=Ts(30%)	X=Ts(in situ)
Ac(84%)	Bz(67%)	CN (in situ)
CONHBn (32%)		

Scheme : Synthesis of N-acyl, N-cyano-, and N-sulfonyl-thioureas

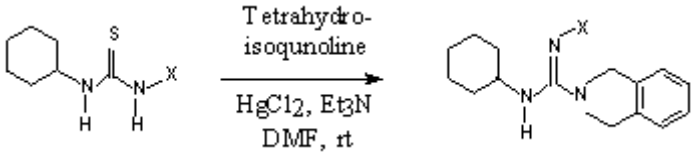
The cyclohexylthioureas substituted with conjugated grous thus prepared were subjected to the $HgCl_2$ procedure in the presence of tetrahydroisoquinoline. The results are summarized in Table 1.

As shown already, N-Boc-N' cyclohexylthic urea reacted smoothly with tetrahydroisoquinoline in the presence of $HgCl_2$ to yield the desired guanidine prduct (entry 1). As anticipated from this result, N-acetyl, N-benzyl-, and N-benylcarbamoyl-substituted thioureas were also converted easily to the corresponding guanidines (entries 2-4), N-Tosyl-N'-cyclohexythiourea, prepared from TsNCS and cyclohexylamine[17].

(disconnection *b*, Scheme 1), was even more reactive than the N-carbonyl-substituted thioureas; the $HgCl_2$- reaction with tetrahydroisoquinoline was complete in 40 min to

yield the N-tosylguanidine product in 83% yield (entry 5).[18] The reaction between cyclohexylisothiocyanate and the anion of tosylamide (disconnection c, Scheme 1) initially produced the anion of N-cyclohexyl-N'-tosylthiourea. The anion was also presumed to be the first intermediate of the reaction of entry 5, Table 2, when Et_3N was added to the thiourea. It was therefore envisaged that the tosylamide anion reaction could be coupled with the $HgCl_2$ steps *in situ* without isolating the tosylthiourea. Thus, tosylamide was deprotonated with Kot-Bu in DMF and treated with cyclohexylisothiocyanate, (1h, rt). When all the isothiocyanate had been consumed (TLC), the reaction mixture was cooled in an ice bath and treated with Et_3N, tetrahydroisoquinoline and $HgCl_2$. The guanylation under these conditions took ca. 4h to complete and the desired N-tosylguanidine product (the same as obtained in entry 5) was obtained in 41% overall yield (entry 6). Thus, the *in situ*, one-pot procedure compares favorably with the two-step process (entry 5) in terms of the overall yields and the convenience. Following the one-pot protocol, cyanamide was similarly incorporated in the N-cyanoguanidine structure in 61% overall yield (entry 7).

Table 1: N-Carbonyl-, N-Cyano-, and N-Sulfonyl-Guanylations



Entry	X	Time	Yield
1	Boc	3.5h	63 %
2	Ac	5 h	75 %
3	Bz	2 h	75%
4	CONHBn	1.5 h	67%
5	Ts	0.6 h	83%
6[A]	Ts	4 h	41 %
7[B]	CN	2 h	61%

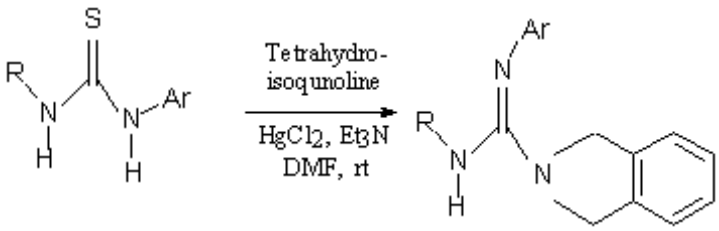
a: in-situ reaction,
b: over-all yield

The $HgCl_2$- promoted guanylation rection
N-Aryl-Guanidines

The above results points to a certain trend in the $HgCl_2$ promoted guanylation process; a conjugated substituent on one of the nitrogens of a thiourea is enough to cause the reaction to work. Therefore we turned our attention to N-aryl substitutions. We had already glimpsed an indication that a certain aryl groups on the nitrogen of thiourea starting material could activate the process considerably. Thus, a series of N-arylthioureas were subjected to the $HgCl_2$ procedure.[19] Once again, the electronically and sterically neutral cyclohexyl group and tetrahydroisoquinoline were chosen in most cases for the R-substituent and for the incoming amine, R'R"NH, respectively. The N-aryl groups studied in this series were all *para*-substituted phenyls, except for one case, in order to weigh the electronic effects of the substituents to the fullest without steric interference. The results are summarized in Table 2.

N-Cyclohexyl-N'-arylthiouras reacted with tetrahydroisoquinoline under the $HgCl_2$-conditions to produce the corresponding guanidines. There seemed to be a clear correlation between the electronic effects of the substitutenet (on the N-aryl)

Table 2: N-Aryl-guanylatons



Entry	R	Ar	Time	Yield
		Ar=p-X-C_6H_4-		
1	cyclohexyl-	X=NO_2	0.5h	89 %
2	-	X = CF_3	24 h	86%
3	-	X = COOMe	7 h	93%
4	=	X = Cl	25.5 h	76%
5	-	X =H	24 h	84%
6	-	X= OMe	48 h	82%
7	-	x = NMe_2	96 h	48%
8	*p*-Cl-C6H_4 -	X= CF_3	0.7 h	96%
9	cyclohexyl-	Ar=C_6F_5-	0.5 h	95 %

and the reaction rate. Thus, electron-withdrawing groups of the N-phynyl substituents faciliated the reaction greatly. The electon-withdrawing effects could be either conjugative (entries 1 and 3) or inductive (entries 2 and 9). The effects also seemed to be additive : N-*p*-chlorophenyul-N''-trifluoromethylphenyl-substituted thiourea underwent the guanylation faster than when either substituent was present alone (entry 8). One the other hand, the guanylation proceeded very sluggishly when the N-phenyl substituents contained electron-donating groups (entries 6 and 7).

In the course of the guanylations with slow-reacting N-arylthioureas (entries 2-7), a 'less-polar intermediate was observed first, which was then slowly converted to the desired guanidine product. The intermediates were presumed to be carbodimides, the isolation and characterization of these compounds were successful.[13] These observations are consistent with the reaction mechanism proposed for the guanylation bis-Boc thiourea. $HgCl_2$ promotes a formal elimination of H_2S from thiourea starting material to produce carbodimide intermediates; amines then add to the carbodimides to yield guanidine products. It appears but $HgCl_2$ causes the first step to proceed efficiently regardless of the nature of the substituents. It is in the second step (addition of amines to carbodimides) that the N-substituents exert their electronic effects on the reaction rates. The observed effects of the substituents- faster reactions with electron withdrawing groups and slower ones with electron donating groups can be explained in terms of stabilization/destabilization of the transition state in the addition step; there is little evidence that $HgCl_2$ participates in this step;

Limitations

The $HgCl_2$ –promoted guanylation is effective only with thiouras containing N-conjugated substituents. Thus, treatment of N,N'-bis-alkyl-substituted thioureas with $HgCL_2/El_3N$ produced the corresponding carbodimides, which failed to react with amine nucleophiles under the standard $HgCl_2$ - conditions employed. While carbodimides are known to react with amines to produce the corresponding guanidines, the reactions generally require excess reagents and/or longer reaction times.[14]

Abating steric hindrance, as in N-monosubstituted (terminal) thioureas, did not help the guanylation to work. In fact, terminal guanidines, even those substituted with activating conjugated groups, failed to produce the guanidine products under the conditions employed[11] (Scheme 2).

In line with the proposed carbodiimide intermediacy in the $HgCl_2$- promoted guanylation process, the successful thiurea substrates require one hydrogen on each of the nitrogens to be present. Also as expected from the postulated reaction mechanism, the 5- and 6-membered cyclic thioureas substituted with N-carbonyl groups failed to react under the standard conditions. Note that the corresponding acyclic thioureas containing the same substituents would undergo guanylation easily under the $HgCl_2$ conditions.

Conclusion

The $HgCl_2$ promoted guanylation process has a wide synthetic applicability. One conjugated substituent on the nitrogen of thiourea starting material is enough to cause the reaction to proceed at room temperature. Such activating groups include N-carbonyl- (acyl, alkoxycarbonyl, carbamolyl, etc.), N-cyano-, N-suflfonyl-, and N-aryl-substitutents.

EXPERIMENTAL

General Procedure for the $HgCl_2$ –promoted Guanyulation

The starting thiourea, the amine (1,1 equiv), and triethylamine (2.2 equiv) were dissolved in dimethyl formamide (5 ml/mmol substrate) at rt. The mixture was cooled in an ice bath. Mercury (II) chloride (1.1. eq. iv) was added and the mixture and stirred for 20 min, before it was warmed to rt. When the reaction was judged complete (TLC), the reaction mixture was diluted with ethyl acetate and filtered through Celite, washing the Celite cake with additional ethyl acetate. The filtrate was washed with warer, then with brine, and the organic phase was dried with $MgSO_4$. The crude product thus obtaine was purified by flas chromatography on a silica column[15].

N-Boc-N'-cylohexyl-thiourea

To a solution of N-cyclohexylthiourea (1.10 g, 7-mmol) in tetrahydrofuran (THF, 40 ml), sodium hydride (60%, 0.28 g, 7 mmol) was added and the mixture was stirred at room temperature for 10 min, under a N_2 atmosphere. The reaction mixture was cooled in an ice bath, and di-*teri-butyl-dicarbonate* (1.78 g, 8 mmol) was added as a solution in THF (15 ml). The mixture was stirred in the ice bath for 30 min, then warned to room temperature. It was stirred at rt overnight. Water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried with magnesium sulfate, and concentrated *in vacuo*. Unreacted starting material was recovered by crystallization (ethyl acetate-hgexane, 0.37 g, 33%). The residue was purified by flash chromatography using ethyl acetate-hexame (1:9) to yield the N-Boc-protected title compound (1,21 g, 67%). ^{1}H NMR ($CDCl_3$) δ9.61 (1H,s,br), 7.74 (1H,s,br), 4.24 (1H,m), 2.11-1.99 (2H,m), 1.81-1.55 (3H, m), .1.47 (9H,s), 1.42-11 (5H,m); IR 3254(m), 2932(m), 1718(s), 1548(s), 1528 (s), 1014(m) cm ; MS m/e 258 (M^+), 121 (100%); mp. 109-111°C.

B-Boc-N'cyclohexyl-3,4-didhyro-H-isoquinoline-2-carboxamiditime

The guanylation was carried out following the general procedure. The title compound was obtained in 63% yield after flash chromatographic purification with ethyl acetate-hexane (1:1). ^{1}H NMR ($CDCl_3$) δ 7.95 (1H,s,br), 7.23-7.07(4H,m), 4.56(2H,s), 3.63(2H,t,J=5.9Hz), 3.29 (1H,m); 2.95(2H,t,j=5.9.Hz), 2.01-1.86 (2H,m), 1.81-15 (3H,m), 1.53(9H,s), 1.45-1.18 (5H,m); IR 3199, 2938(m), 1670(s), 1574(m), 1514 (m) Cm^{-1}; MS *m/e* 358 (MH^+ 100%); mp 136-139 °C; Anal, Found, C, 68.01, H,8.97; N, 11.30. Calcd for C_{21} H_{31} O_2-0.75 H_2O -; C, 67,.98, H, 8.83; N,11.30.

N-Cyclohexyl-3,4-didhydro-1H-isoquinoline-2-carboxamidine

N-Boc-N'-cyclohexyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine (0.209 g, 0.58 mmol) was dissolved in dichloromethane (2.5 ml), and trifluoroacetic acid (1 mL). The reaction mixture was stirred at room temperature for 3h. Evaporation of the solvent afforded a white solid. The product was purified by flash chromatography using dichloromethane-methanol (9:1) to obtain the title compound as the di-trifluoroacetate salt (0.244 g, 86%). ^{1}H NMR (dδ -DMSO)δ 7.65 (H,s) 7.34 (1H, d, *J* = 9Hz), 7.24-7.12 (4H, m), 6.0 (1H, br s), 4.58

(2H,s), 3.63 (2H,t, *J*=6Hz), 3.48 (1H,m), 2.92 (2H, t, *J*=6Hz), 1.95-1.55 (5H,m), 1.45-1.0 (5H,m) IR 3465 (m), 3309 (m), 2948(m), 1653(s), 1616(s)(1213(s), 1180)s), 1142(s) cm^{-1}; MS *m/e* 258 (MH+,. 100%).

N(1)-Boc-N(2)-cyclohexyl-N(3)-phenyl-guanidine

The guanylation was carried out following the general procedure. The title compound was obtained in 70% yield after flash chromatographic purification with ethyl acetate-hexane (1:9) ^1H NMR ($CDCl_3$) δ 7.49-6.96 (5H,m) 6.5 (1H, br, s), 4.73 (1H,br), 3.99 (1H,m), 2./15-0.98 (10H,m), 1.50 ((H,s) IR 3350(w), 2931(m), 16361(m), 1725(m), 1636(m), 1593(s), 1545(m) cm^{-1}, MS *m/e* 318 (NH^+), 262 (100%).

ACKNOWLEDGEMENT

The authors thanks to Prof. S.D. Kaushik (Principal L.R. (P.G) College), Dr. S.K. Aggarwal, Dr. Himanshu Aggarwal and Yougesh Tomar (1.1T Delhi) for their suggestion and help in this work. Specially thanks Delhi University for their spectral help and providing facilities in this work.

REFERENCES

1. R.E. Dickerson, *J. Mol. Biol.,* **57**: 1 (1971).
2. Ojima, 1.; Chakravarty, S., *S. Org. Bioniorg Med. Chem,* **360**: 337-360 (1995).
3. H. Vlassara, R. Bucala and L. Streker, *Lab Invest,* **70**: 138-151 (1994).
4. Kovacevic, B., Maksic, Z.B. *Org. Lett,* **3**: 1523 (2003).
5. Berlinck, R.G.S Progr. *Chem, Org. Nat. Prod,* **66**: 119 (1995).
6. Albert, M; Feierlag P.; Hayn, G., *Soft Biomacromolecules.,* **42**: 9013 (2003)
7. DaeSimone S., *Polone Biochemistry,* **4**: 1811 (2003).
8. Seemasereel., Laeekman, *Eur. J. Med Che,* **38**: 547 (2003).
9. Kralova J. Kral V.J., *Medicinal Che.* **46**: 2049 (2003).
10. Glaser, D.P. *Appl. Chem.* 74, 1153 (2002).
11. Ishikawa, T. Tsoke, *T. Chem. Euro J*, **8**: 553 (2002).
12. McManus, J.C.; Carey J.S.; Taylor, R.J.K *Synthet.,* 365 (2003).
13. Ramada, N. Jnathana, *Synth. Communication.,* **27**(13): 2253-60 (1997).
14. Growthers, A.F., Curd. F.H.S. and Rose F.K., *J. Chem. Soc.* **5**: 86-590 (2003).
15. Randas, K. *Tetrahedron Lett* **37**: 5161 (1996).
16. Lin P. Heng SH.C. Zim, M.KM. *Synthesis.* 255 (2003).
17. Scott, F.L. O. Donovan, D.G; Dety, *J. Ame. Chem Soc.* **75**: 4053 (1995).
18. Cailey P.J. Pacl S. *Cood Chem, Rev.* **214**: 91-141 (2001).