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Study of *N*-benzoyl-activation in the $HgCl_2$-promoted guanylation reaction of thioureas. Synthesis and structural analysis of *N*-benzoyl-guanidines

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Abstract—In this work, it is demonstrated that the benzoyl group is an activating group for thioureas in the $HgCl_2$-guanylation reaction. Thus *N*-benzoyl-thioureas containing electronically neutral and even electron-withdrawing or electron-releasing substituents are converted into guanidines with reasonable yields. In addition, NMR and X-ray structural analyses were performed to understand the intra- and intermolecular features of the synthesized guanidines.

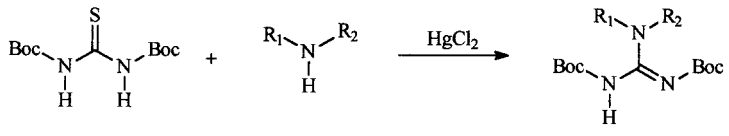
1. Introduction

Recently, we initiated a research program aimed at the synthesis of anticonvulsant agents. In this context, we became interested in the preparation of guanidine derivatives since these substances proved to be potential anticonvulsant compounds.[1] The guanidinium group is also present in many natural and synthetic biologically active compounds.[2–4] Due to its large spectrum of activity such as antibacterial, antidiabetic, antihistaminic, anti-inflammatory and cardiovascular activity,[4] the guanidine unit has been intensively studied as a synthetic goal and a diversity of new methods has been developed. Advances have been described both in solid[5–9] and solution[10–18] phase synthesis of guanidine and, in the latter case, thioureas are the most versatile starting material because they can be obtained in high yield from easily available precursors. However, to efficiently convert thiourea into guanidine by the $HgCl_2$ protocol the thiourea should be activated by a strong electron-withdrawing group, and the most general approach to achieve this is by the use of *N*,*N*′-bis-Boc-protected thioureas (Scheme 1).[12,13,16,17]

Herein, we described our study of the *N*-benzoyl-group as an alternative activation group for thiourea in the guanylation reaction promoted by $HgCl_2$. To the best of our knowledge, only one example of *N*-benzoyl-thiourea conversion into guanidine has been described in the literature but that case was limited to electronically and sterically neutral substituents.[13]

2. Results and discussion

While *N*,*N*′-bis-Boc-thioureas and *N*-Boc-thiourea are easily converted into guanidines by the $HgCl_2$ method,[12,13,16,17] the use of this starting material can be a drawback if guanidines containing different *N*-substituents need to be synthesized, because deprotection/protection steps are necessary. With *N*-benzoyl activation this limitation can be overcome, in principle, by reacting benzoyl isothiocyanate with an appropriate amine followed by the reaction of the resulting *N*-benzoyl-thiourea with another different amine. Thus, the required thioureas **3a**–**e** were prepared in 70–99% yield by the reaction of primary aromatic and aliphatic amines



Scheme 1.

Keywords: guanidines; thioureas; guanylation reaction; X-ray analysis.

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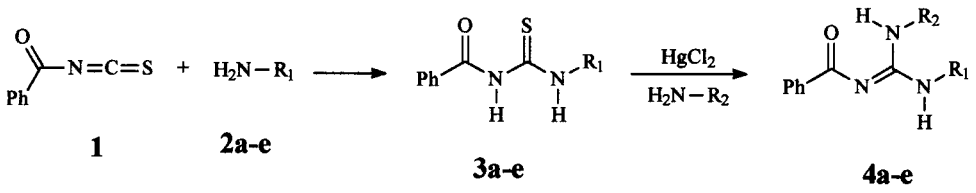
Table 1. Isolated guanidine yields from *N*-benzoyl-thioureas



1 2a-e 3a-e 4a-e

Guanidine	R1	R2	Yield (%)
4a			62
4b	MeO		60
4c			64
4d	MeO	MeO	53
4e			81

with benzoyl isothiocyanate following the literature procedure,[19,20] and were submitted to guanylation. Results are summarized in Table 1. The structure of the guanidine **4a** was unambiguously confirmed by X-ray analysis, as shown in Fig. 1.

The electronic nature of the *N*-substituent in the *N*-benzoyl-thioureas **3** could vary from electronically neutral, as in **3a**, to electron releasing or electron withdrawing, as in **3b** and **3c**, respectively. Thus, it is apparent that the electronic nature of R_1 in the thiourea does not affect the pathway nor the yield of the guanylation reaction and, potentially, a broad spectrum of guanidines can be obtained. Additionally, to study the effect of the amine in the guanylation reaction we reacted thiourea **3a** with the less nucleophile amine **2c**. In this case, guanidine **4c** was obtained in almost the same yield as when the electronically neutral amine **2a** was reacted with thiourea **3c** (**2c**+**3a**→**4c**, 60%; **2a**+**3c**→**4c**, 64%). These results suggest that substituent introduction sequence is not a limiting factor in the guanylation reaction promoted by $HgCl_2$ when *N*-benzoyl-activated thioureas are used.

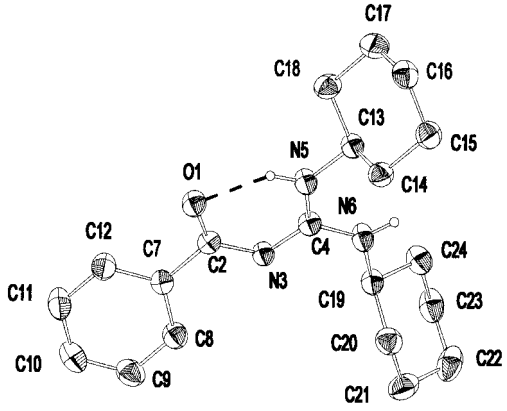
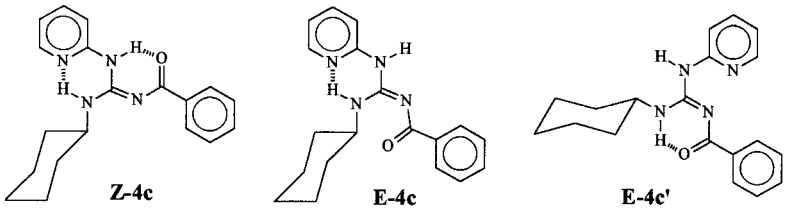


Figure 1. X-ray crystallographic structure of molecule 1 of compound **4a**. Displacement ellipsoids are shown at the 30% probability level.

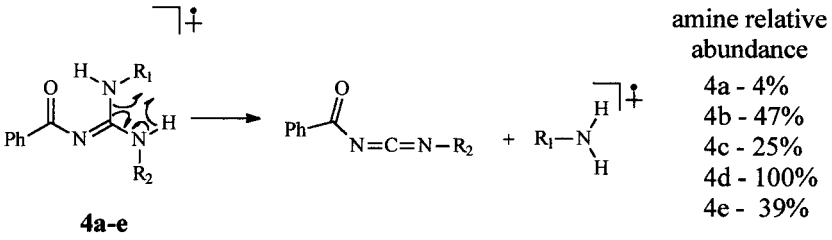
In the ^{1}H NMR spectra of *N*-benzoyl-guanidines **4a**, **4b** and **4d** a broad signal around 10–12 ppm was detectable related to one N–H proton, suggesting the participation of one intramolecular hydrogen bond. However, in the spectra of *N*-benzoyl-guanidine **4c** and **4e**, two sharp low field chemical shift signals were present (~13 and ~10.5 ppm, D_2O exchangeable) characteristic of strong internal hydrogen bonds. To accommodate this observation the typical[21] C=N *cis–trans* configurational interconversion should be frozen by these internal hydrogen bonds, making the *Z*-**4c** configuration favored over the *E*-**4c** (or *E*-**4c**′) configuration (Scheme 2).

A common fragmentation pattern emerged from the mass spectra of **4a**–**e**. In addition to the expected phenyl and benzoyl ion formation, we observed a peak corresponding amine ion formation by the loss of neutral carbodiimide from the guanidines (Scheme 3). In this fragmentation pathway, aromatic amine ion formation was preferable to an aliphatic one (only in **4a**, with two cyclohexyl groups in the molecule, was the aliphatic amine ion detectable, albeit in low relative abundance).

To unambiguously assign the structure of the obtained guanidines and to gain insight into intra- and intermolecular



Scheme 2.



Scheme 3.

interactions, the crystal structure of **4a** was determined. The asymmetric unit has two independent molecules (**4a** and **4a**′), and Fig. 1 shows the unprimed molecule with labeled atoms. However, the molecules show significant differences only in the torsion angles C2–N3–C4–N5 of −20.8(4) and −0.2(4), C2–N3–C4–N6 of 162.7(2) and −179.9(2)° for the unprimed and primed molecules, respectively. The cyclohexane rings have chair conformation, with some distortions as can be seen from the Cremer and Pople[22] parameters. C13→C14→…C18 [Q=0.554(3) Å, θ=2.6(3)°, ϕ=175(9)°; Q=0.558(3) Å, θ=3.7(3)°, ϕ=14(6)°] and C19→C20→…C24 [Q=0.563(3) Å, θ=2.2(3)°, ϕ=110(11)°; Q=0.561(3) Å, θ=2.6(3)°, ϕ=246(8)°] for the unprimed and primed molecules, respectively.

As noted in Fig. 1 of **4a**, strong hydrogen bonding occurs between the carbonyl oxygen and the NH group (intramolecular hydrogen bonds: N5–HN5…O1 [2.627(3) Å] and N5′–HN5′…O1′ [2.595(3) Å]) providing a pseudo six-membered ring. Also, intermolecular hydrogen bonds are observed between N6–HN6…O1′ [x, 1.5−y, 0.5+z, 2.932(3) Å] and N6′–HN6′…O1 [1−x, 2−y, −z, 3.092(3) Å]. The O1 atom is 0.350(4) Å from the least-square plane through the atoms C2 N3 C4 N5 and the O1′ atom is 0.042(4) Å from the corresponding primed plane. Therefore, the intramolecular hydrogen bonds involving O1 and O1′ contribute to the planarity of the conjugated moiety of **4a** and **4a**′.

In summary, we have demonstrated that *N*-benzoyl-thioureas are easily converted to guanidines by the $HgCl_2$ method, being a versatile starting material to densely substituted guanidines containing electronically neutral as well as electron withdrawing and electron releasing groups. In addition, NMR and X-ray studies have indicated that the guanidines synthesized here are able to form inter- and intramolecular hydrogen bonds, and that these features are found in electronically analogous compounds with anticonvulsant activity.[25,26] The pharmacological evaluation of guanidines **4a**–**e** are under investigation and will be described elsewhere.

3. Experimental

Melting points were determined on a Karl Kolb apparatus and are uncorrected. Infrared spectra were recorded as KBr discs on an FT-IR BOMEM MB100 instrument. NMR spectra were obtained for ^{1}H at 300 or 400 MHz and for ^{1}C at 75 or 100 MHz using a Varian Gemini 300, a Bruker AC300P and a Bruker ARX400 spectrometers at Instituto de Química/UNICAMP and at Instituto de Química/UFSCar. Chemical shifts are reported in ppm units downfield from reference (internal TMS). MS spectra were measured on a SHIMATSU CG-MS QP-5050 spectrometer at 70 eV. Elemental analyses were performed on a 2400 CHN Perkin–Elmer instrument at Instituto de Química/UNICAMP. The single crystal X-ray data collection was carried out on a Nonius CAD-4 diffractometer at Departamento de Química/UFSC.

3.1. General synthetic procedure

To a solution of 1 mmol of thiourea in 5 mL of DMF was added 1 mmol of amine and 2 mmol of Et_3N and then 1 mmol of $HgCl_2$ was added to the solution with vigorous magnetic stirring and ice-bath cooling. The suspension became black after a few minutes and was left to react for 20 h at room temperature. After this time, 10 mL of ethyl acetate was added and the suspension was filtered through a pad of Celite and the pad washed with 10 mL of CH_2Cl_2. The filtrate was concentrated and the residue (~5 mL) was dissolved in 15 mL of CH_2Cl_2, extracted with water (3×15 mL) and dried over anhydrous $MgSO_4$. After filtration the solvent was evaporated and the crude residue was treated as indicated in each case.

3.1.1. *N*1-di(cyclohexylamino)methylenebenzamide (4a). Recrystallization from ethyl ether/petroleum ether, mp 151–153°C. ν_{max} 3289, 1605, 1572 cm^{-1}. δ ^{1}H ($CDCl_3$) 1.19–1.48 (8H, m); 1.52–1.70 (4H, m); 1.78–1.80 (4H, m); 1.95–2.15 (4H, m); 3.50 (1H, sl); 4.20 (1H, m);

7.37–7.48 (3H, m); 8.21 (2H, d, J=7.2 Hz); 10.35 (1H, sl). δ ^{13}C ($CDCl_3$) 24.6 (CH_2); 25.5 (CH_2); 33.1 (CH_2); 49.9 (CH_2), 127.7 (CH); 128.9 (CH); 130.7 (CH); 139.2 (C_0); 158.3 (C_0); 176.9 (C_0). MS m/z (%): 328 (12) [M^++1], 327 (47) [M^+], 245 (26), 164 (46), 105 (100), 77 (57). Anal. Calcd for $C_{20}H_{29}N_3O$: C, 73.39%; H, 8.87%; N, 12.84%. Found: C, 73.57%; H, 9.01%; N, 13.11%.

3.1.2. 1-cyclohexylamino(phenylcarbonylimino)methylamino-4-methoxybenzene (4b). Recrystallization from ethyl ether/petroleum ether, mp 129–131°C. ν_{max} 3356, 1594, 1570 cm^{-1}. δ ^{1}H ($CDCl_3$) 1.10–1.26 (3H, m); 1.30–1.51 (2H, m); 1.61–1.73 (3H, m); 2.02–2.05 (2H, m); 3.84 (3H, s); 4.14 (1H, l); 4.64 (1H, sl); 6.95 (2H, d, J=4.8 Hz); 7.19 (2H, d, J=9.0 Hz); 7.40–7.57 (3H, m); 8.26 (2H, d, J=6.6 Hz); 11.86 (1H, sl). δ ^{13}C ($CDCl_3$) 24.6 (CH_2); 25.4 (CH_2); 33.0 (CH_2); 50,0 (CH); 55.4 (CH_2); 115.2 (CH); 127.5 (CH); 127.9 (CH); 128.6 (C_0); 129.1 (2×CH); 131.1 (CH); 138.9 (C_0); 158.6 (C_0); 177.6 (C_0). MS m/z (%): 353 (5) [M^++2], 352 (29) [M^+ +1], 351 (64) [M^+], 269 (41), 123 (47), 105 (100), 77 (35). Anal. Calcd for $C_{21}H_{25}N_3O_2$: C, 71.79%; H, 7.12%; N, 11.97%. Found: C, 71.68%; H, 7.28%; N, 12.12%.

3.1.3. 2-cyclohexylamino(phenylcarbonylimino)methylaminopyridine (4c). Recrystallization from benzene/petroleum ether, mp 107–109°C. ν_{max} 1622, 1592, 1564 cm^{-1}. δ ^{1}H ($CDCl_3$) 1.33–1.56 (4H, m); 1.65 (2H, m); 1.76–1.82 (2H, m); 2.11 (2H, m); 4.31 (1H, m); 6.90 (1H, d, J=8.2 Hz); 6.97 (1H, dd, J=7.3, 5.2 Hz); 7.37–7.50 (3H, m); 7.66 (1H, dt, J=7.5, 1.8 Hz); 8.26 (3H, m); 10.42 (1H, s); 13.35 (1H, s). δ ^{13}C ($CDCl_3$) 24.5 (CH_2); 25.7 (CH_2); 32.8 (CH_2); 49.8 (CH); 113.7 (CH); 117.8 (CH); 127.8 (CH); 129.0 (CH); 131.1 (CH); 138.5 (CH); 138.6 (C_0); 146.0 (CH); 153.2 (C_0); 156.4 (C_0); 176.9 (C_0). MS m/z (%): 324 (23) [M^++2], 323 (100) [M^++1], 322 (96) [M^+], 239 (42), 212 (28), 120 (40), 105 (96), 77 (57). Anal. Calcd for $C_{19}H_{22}N_4O$: C, 70.81%; H, 6.83%; N, 17.39%. Found: C, 70.89%; H, 6.73%; N, 17.63%.

3.1.4. 4-methoxy-1-[4-methoxyanilino(phenylcarbonylimino)methylamino]benzene (4d). Purified by silica gel column chromatography (hexane/ethyl acetate 50%) followed by recrystallization from CH_2Cl_2/petroleum ether, mp 126–128°C. ν_{max} 3373, 1606, 1568, 1506 cm^{-1}. δ ^{1}H ($CDCl_3$) 3.82 (6H, s); 6.94 (4H, d, J=8.8 Hz); 7.33 (4H, d, J=8.8 Hz); 7.53–7.46 (3H, m); 8.18 (2H, d, J=7.0 Hz). δ ^{13}C ($CDCl_3$) 55.7 (CH_3); 115.1 (CH); 126.8 (C_0 and CH); 128.4 (CH); 129.8 (CH); 131.8 (CH); 139.0 (C_0); 158.3 (C_0); 158.4 (C_0); 178.8 (C_0). MS m/z (%): 376 (13) [M^++1], 375 (50) [M^+], 123 (100), 105 (75), 77 (38). Anal. Calcd for $C_{22}H_{21}N_3O_3$: C, 70.40%; H, 5.60%; N, 11.20%. Found: C, 70.49%; H, 5.58%; N, 11.21%.

3.1.5. 2-[*tert*-butylamino(phenylcarbonylimino)methylamino]pyridine (4e). Recrystallization from ethyl acetate/petroleum ether, mp 89–91°C. ν_{max} 3373, 1606, 1568, 1506 cm^{-1}. δ ^{1}H (CD_3OD) 1.63 (9H, s); 6.95 (1H, d, J=8.4 Hz); 7.07 (1H, ddd, J=8.4, 7.4, 1.9 Hz); 7.41–7.46 (2H, m); 7.48–7.52 (1H, m); 7.78 (1H, ddd, J=7.4, 5.0, 1.0 Hz); 8.21 (2H, m); 8.27 (1H, ddd, J=5.0, 1.9, 1.0 Hz); 10.74 (1H, s); 13.09 (1H, s). δ ^{13}C (CD_3OD) 29.7 (CH_3); 53.4 (C_0); 114.7 (CH); 119.6 (CH); 129.0 (CH); 130.0 (CH); 132.5 (CH); 139.7 (C_0); 140.3 (CH); 147.2 (CH); 154.1 (C_0); 158.0 (C_0); 177.9 (C_0). MS m/z (%): 297 (13) [M^++1], 296 (64) [M^+], 239 (62), 212 (27), 120 (31), 105 (100), 77 (66). Anal. Calcd for $C_{17}H_{20}N_4O$: C, 68.92%; H, 6.76%; N, 18.92%. Found: C, 68.17%; H, 6.96%; N, 18.60%.

3.1.6. Crystal structure of 4a. $C_{20}H_{29}N_3O$, M_w=327.46, monoclinic, space group $P2_1/c$, Z=8, a=12.120(2), b=15.812(3), c=19.692(4) Å, β=92.12(3)°, V=3771.2(12) Å^3, d_c=1.154 mg m^{-3}, λ (Mo Kα)=0.71073 Å, μ=0.072 mm^{-1}, 7603 measured reflections, 7379 unique (R_{int}=0.046) of which 3906 were considered as observed with $I \geq 2\sigma(I)$. The single crystals were obtained by diffusion of petroleum ether into a solution of synthesized guanidine **4a** in CH_2Cl_2 at room temperature. The structure was solved with direct methods using SHELXS97[23] and it was refined anisotropically with full-matrix least-squares on F^2 using SHELXL97.[24] The hydrogen atoms were placed at the calculated positions except those involved in H bonds, found on difference maps and refined. Final indices: $R_1(F_0)$=0.048, wR_2 (F^2)=0.139 for 446 refined parameters.

The crystallographic data were deposited at the Cambridge Crystallographic Data Center under the number 150974. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033 or e-mail: deposit@ccdc.camac.uk).

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References

1. Reddy, N. L.; Fan, W.; Magar, S. S.; Perlman, M. E.; Yost, E.; Zhang, L.; Berlove, D.; Fischer, J. B.; Burke-Howie, K.; Wolcott, T.; Durant, G. J. *J. Med. Chem.* **1998**, *41*, 3298–3302.
2. Berlinck, R. G. S. *Nat. Prod. Rep.* **1996**, 337–407.
3. Berlinck, R. G. S. *Fortschr. Chem. Org. Naturst.* **1995**, *66*, 119–295.
4. Greenhill, J. V.; Lee, L. In *Progress in Medicinal Chemistry*, Ellis, G. P., Luscombe, D. K., Eds.; Elsevier: New York, 1993; Vol. 30, Chapter 5.
5. Ostresh, J. M.; Schoner, C. C.; Hamashin, V. T.; Nefzi, A.; Meyer, J-P.; Houghten, R. A. *J. Org. Chem.* **1998**, *63*, 8622–8623.
6. Kearney, P. C.; Fernandez, M.; Flygare, J. A. *Tetrahedron Lett.* **1998**, *39*, 2663–2666.
7. Dodd, D. S.; Wallace, O. B. *Tetrahedron Lett.* **1998**, *39*, 5701–5704.
8. Josey, J. A.; Tareton, C. A.; Payne, C. E. *Tetrahedron Lett.* **1998**, *39*, 5899–5902.

9. Schneider, S. E.; Bishop, P. A.; Salazar, M. A.; Bishop, O. A.; Anslyn, E. V. *Tetrahedron* **1998**, *54*, 15063–15086.
10. Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 8432–8439.
11. Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804–3805.
12. Miel, H.; Rault, S. *Tetrahedron Lett.* **1998**, *39*, 1565–1568.
13. Levallet, C.; Lerpiniere, J.; Ko, S. Y. *Tetrahedron* **1997**, *53*, 5291–5304.
14. Barvian, M. R.; Showalter, H. D. H.; Doherty, A. M. *Tetrahedron Lett.* **1997**, *38*, 6799–6802.
15. Yong, Y. F.; Kowalski, J. A.; Lipton, M. A. *J. Org. Chem.* **1997**, *62*, 1540–1542.
16. Jeong, J-H.; Murray, B. W.; Takayama, S.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 4227–4234.
17. Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677–7680.
18. Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497–2502.
19. Kascheres, A.; Ueno, M. *J. Heterocyclic Chem.* **1991**, *28*, 2057–2058.
20. Sarkis, G. Y.; Faisal, E. D. *J. Heterocyclic Chem.* **1985**, *22*, 137–140.
21. Eliel, E. L.; Wilen, S. H. In *Stereochemistry of Organic Compounds*, Wiley: New York, 1994; p 550.
22. Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354–1358.
23. Sheldrick, G. M. *SHELXS97*: Program for the Solution of Crystal Structures; University of Göttingen, Germany, 1990.
24. Sheldrick, G. M. *SHELXL97*: Program for the Refinement of Crystal Structures; University of Göttingen, Germany, 1997.
25. Edafiogho, I. O.; Moore, J. A.; Alexander, M. S.; Scott, K. R. *J. Pharm. Sci.* **1994**, *83*, 1155–1170.
26. Foster, J. E.; Nicholson, J. M.; Butcher, R.; Stables, J. P.; Edafiogho, I. O.; Goodwin, A. M.; Henson, M. C.; Smith, C. A.; Scott, K. R. *Bioorg. Med. Chem.* **1999**, *7*, 2415–2425.