The first synthesis of pyridinium *N*-benzoylguanidines by bismuth- and mercury-promoted guanylation of *N*-iminopyridinium ylide with thioureas

Silvio Cunha,[a,*] Manoel T. Rodrigues Jr.,[a] Cleuza C. da Silva,[b] Hamilton B. Napolitano,[c] Ivo Vencato[d] and Carlito Lariucci[d]

[a]*Instituto de Química, Universidade Federal da Bahia, Campus de Ondina, Salvador-BA 40170-290, Brazil*
[b]*Departamento de Química, Universidade Estadual de Maringá, Av. Colombo 5720, Maringá-PR 97020-900, Brazil*
[c]*Ciências Exatas e Tecnológicas, Universidade Estadual de Goiás, BR 153, Km 98, 75001-970, Anápolis-GO, Brazil*
[d]*Instituto de Física, Universidade Federal de Goiás, CP 131, 74001-970, Goiânia-GO, Brazil*

Abstract—This work describes the first successful synthesis of five pyridinium *N*-benzoylguanidines. These new pyridinium ylides were prepared in moderate to good yields through the guanylation reaction of *N*-iminopyridinium ylide with *N*-benzoylthioureas, using both bismuth nitrate and mercury chloride as inorganic thiophiles. X-ray analysis of one pyridinium *N*-benzoylguanidine was investigated and the *E* configuration assigned. Intermolecular interactions of the type C–H···O and C–H···π were observed in the solid state. The results related in this study represent the first description of a ylide as the nucleophilic partner in the guanylation reaction.

1. Introduction

The synthesis of polysubstituted guanidines is a field of intense investigation[1] owing to the presence of guanidinium group in diverse biologically active substances,[2] mainly pharmaceutical compounds with a broad spectrum of activity.[3] To the synthesis of a guanidine-containing compound two general strategies are possible according to

Figure 1. Typical guanylating reagents.

* Corresponding author. Tel.: +55 71 2375784; fax: +55 71 2374117;
  e-mail: silviodc@ufba.br

Batey and co-workers: a guanidinylation reaction or a guanylation reaction.[4] In the first, a pre-formed guanidine is modified/functionalized (for instance, through *N*-alkylation, *N*-acylation or transamination), and in the latter, typically, a nucleophilic amine is reacted with a electrophilic amidine species (or a carbodiimide equiv). Typical electrophilic reagents employed in guanylation reaction are indicated in Figure 1.[5]
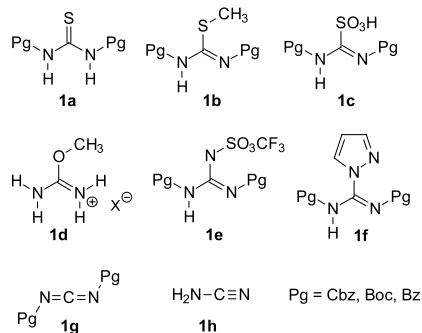
Our research group has continued interest in the area of bismuth- and mercury-promoted guanylation reaction of amines with thioureas in search for new polysubstituted guanidines. Previously, we had described the activation of thioureas by the *N*-benzoyl group in the HgCl₂-promoted guanylation.[6] Later, we extended this guanylation reaction to the bismuth approach, whereby Bi(NO₃)₃ was employed in the same reaction, being the first description of a bismuth-promoted guanylation of thioureas.[7] While a broad spectrum of amine has been investigated in guanylation methodologies, the use of more functionalized nitrogen nucleophiles is scarce.[8]

The preparation of pyridinium *N*-ylides[9] and their use in the synthesis of nitrogen-containing heterocycles[10] such as 2-aminoazines, 2-aminoazoles, imidazopyridines and tetra-hydropyridines has attracted the attention in recent years.[11]

Additionally, pyridinium *N*-ylides are a useful class of compounds in 1,3-dipolar cycloaddition.[12] Thus, these recent developments prompted us to describe here our results in the field of polysubstituted pyridinium *N*-benzoylguanidines synthesis through reaction of thioureas with a pyridinium *N*-ylide. To the best of our knowledge, there is no precedent in the literature of a nitrogen ylide as the nucleophilic component in the guanylation reaction.

2. Results and discussion

To amplify the scope of the nitrogen nucleophile, the *N*-aminopyridinium iodide **2** was submitted to the guanylation reaction conditions, using both $HgCl_2$ and $Bi(NO_3)_3$ as inorganic thiophiles. However, as the active nucleophile from **2** is the in situ formed *N*-iminopyridinium ylide **3**, a small modification of the reaction protocol was necessary, whereby one more equivalent of triethylamine was employed to convert **2** into **3**. Using this modification, **2** was reacted with *N*-benzoylthioureas **4a–e** affording pyridinium *N*-benzoylguanidines **5a–e** in reasonable yields, Scheme 1 and Table 1.
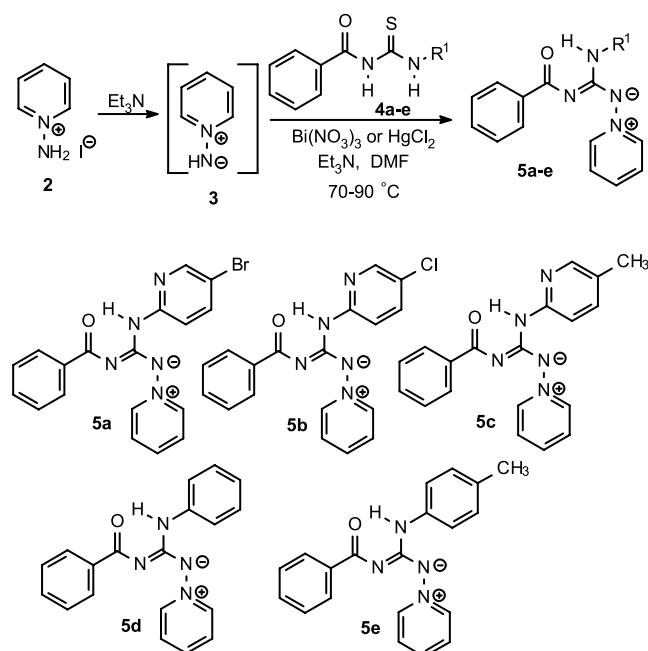
Scheme 1.

Table 1. Isolated pyridinium *N*-benzoylguanidine yields

Compound	Yield, % (time, h)	
	$Bi(NO_3)_3 \cdot 5H_2O$	$HgCl_2$
5a	38 (48)	56 (28)
5b	53 (48)	55 (16)
5c	81 (28)	77 (20)
5d	70 (24)	69 (24)
5e	54 (43)	63 (24)

The electronic nature of the N^2-aryl group in the N^1,N^2-benzoylarylthioureas **4** could vary from electron withdrawing group as in **4a–c** to electron releasing as in **4e**. Hence, potentially, a broad spectrum of pyridinium *N*-benzoylguanidines can be prepared. In addition, both inorganic thiophiles were effective in the guanylation of

ylide **3**, but, in general, $HgCl_2$ afforded better yield and shorter reaction time than $Bi(NO_3)_3$.

Despite two configurational isomers (*E* or *Z*) are in principle possible about the C=N double bond of **5a–e**, only one was detected in the ^1H NMR spectra. So, a low field chemical shift signal was observed for **5a–e** ($\sim$12–13 ppm, D_2O exchangeable) referent to one N–H proton, characteristic of strong internal hydrogen bond. This fact suggests that the *E*-configuration is favored over the *Z*-configuration, because only in the former an intramolecular hydrogen bond is possible, in agreement with the spectral feature. This was further confirmed via an X-ray study (vide infra). Besides, it also suggests that the typical[13] C=N *cis–trans* configurational interconversion should be frozen by this intramolecular hydrogen bond.

From the mechanistic viewpoint, formation of pyridinium *N*-benzoylguanidines **5a–e** can be envisioned as occurring through the reaction of *N*-iminopyridinium ylide **3** with a carbodiimide intermediate, formed from the reaction of thioureas **4a–e** with the inorganic thiophiles, in analogy of previous guanidine synthesis from thioureas.[5] However, an addition–elimination mechanistic pathway involving the
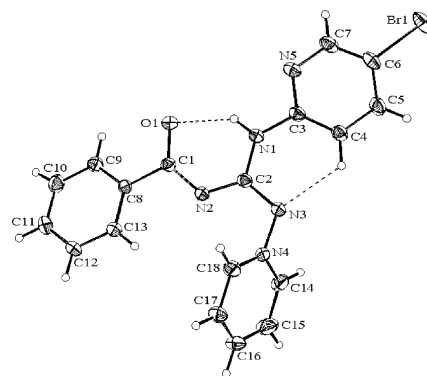

Figure 2. Crystal structure of **5a**. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as spheres of arbitrary radii. The intramolecular H-bonds are shown with dashed lines.

Table 2. Structural parameters for **5a**

Hydrogen bonds				
Atoms	D–H (Å)	H···A (Å)	D···A (Å)	Angle (°)
N1–H1···O1	0.84(4)	1.94(4)	2.630(3)	139(4)
C4–H4···N3	0.99(4)	2.26(4)	2.888(4)	121(3)
C14–H14···O1^i	0.91(4)	2.44(4)	3.328(5)	165(3)
C18–H18···Cg01^{ii}	0.94(4)	2.55(4)	3.414(4)	153(3)
C10–H10···N3^{iii}	0.92(4)	2.65(4)	3.483(4)	150(3)
C15–H15···N5^{iv}	0.86(4)	2.74(4)	3.515(5)	150(3)

Selected dihedral angles (°)	
C(3)–N(1)–C(2)–N(3)	5.9(5)
C(3)–N(1)–C(2)–N(2)	172.2(3)
N(3)–C(2)–N(2)–C(1)	178.4(3)
N(1)–C(2)–N(2)–C(1)	−3.6(4)
C(2)–N(2)–C(1)–O(1)	−3.3(5)
N(2)–C(2)–N(3)–N(4)	−2.8(4)
N(1)–C(2)–N(3)–N(4)	179.1(2)
C(2)–N(1)–C(3)–N(5)	174.4(3)
O(1)–C(1)–C(8)–C(9)	25.6(4)

Symmetry operations: i=2−x, 1−y, −z; ii=2−x, −y, −z; iii=2−x, y, z−1 and iv=1+x, y, z

nucleophilic amine and the activated thiourea can not be ruled out at this moment.[14]

The polysubstituted pyridinium *N*-benzoylguanidine **5a** afforded a monocrystal, which structure could be assigned by X-ray analysis, and several structural features emerged and deserve comment. Thus, the *E* configuration of the **5a** was unambiguously confirmed, as can be seen in Figure 2, which shows an ORTEP[15] view. An intramolecular hydrogen bond between atoms N1–H1···O1 [2.629(3) Å, 140.4°] stabilizes the planarity through the conjugation O1–C1–N2–C2–N1 as shown on Figure 2. While the phenyl ring is rotated in relation to the plane involving atoms C1–N2–C2–N1 (see dihedral angles in Table 2), the ring (N5–C3···C7) at N1 is practically coplanar, what can be attributed to the occurrence of the weak C4–H4···N3 intramolecular hydrogen bond.

The crystal packing of **5a** does not show any strong hydrogen bonds. Nevertheless, the *ortho* hydrogens C14–H14 and C18–H18 of the pyridinium moiety of **5a** are involving in two weak intermolecular interactions of the type C–H···O and C–H···π, linking adjacent molecules in two different centrosymmetric dimeric forms, as noted in Figure 3. Additionally two other intermolecular weak interactions make contributions to the molecular packing stabilization, involving atoms C10–H10···N3[iii], responsible for the formation of the infinity chain along the *b* axis, and
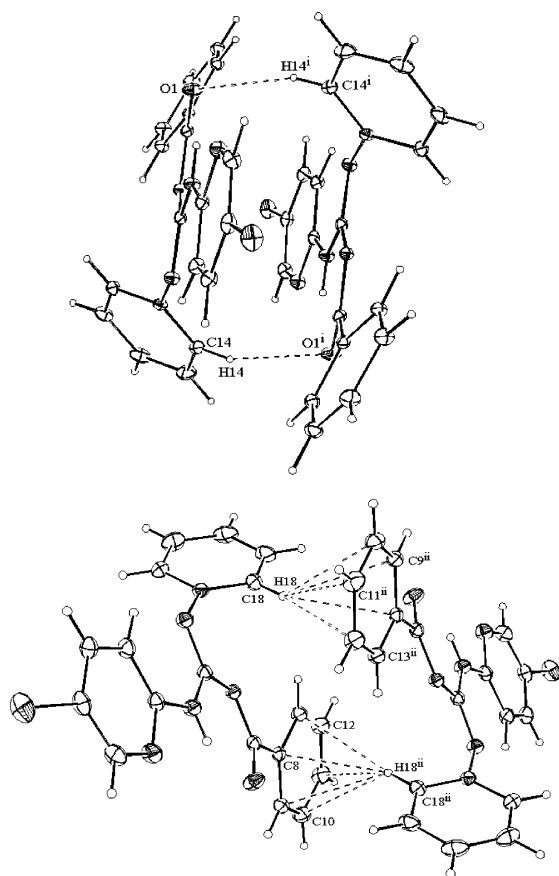
C15–H15···N5[iv], responsible for the formation of the infinity chain along the *c* axis. Table 2 shows these hydrogen-bonding geometries and related symmetry codes.

In conclusion, this work describes the first successful synthesis of pyridinium *N*-benzoylguanidines through the reaction of *N*-iminopyridinium ylide with *N*-benzoylthioureas. The results related in this study represent the first description of a ylide as the nucleophilic partner in the guanylation reaction. The synthetic application of these ylides in the preparation of more complex heterocycles is under investigation in our lab and will be reported opportunely.

3. Experimental

Melting points were determined on a Microquímica MQAPF 301 hot plate apparatus and are uncorrected. Infrared spectra were recorded as KBr discs on a FT-IR BOMEM MB100 instrument. NMR spectra were obtained for ^{1}H at 300 MHz and for ^{13}C at 75 MHz using a Varian Gemini 300 spectrometer. Chemical shifts are reported in ppm units downfield from reference (internal TMS). Coupling constants (*J*) are in Hertz (Hz). Elemental analyses were performed on a 2400 CHN Perkin Elmer. The single crystal X-ray data collection was carried out on a Nonius CAD-4 diffractometer at Instituto de Física-UFG. *N*-benzoylthioureas[16] and *N*-aminopyridinium iodine[17] were prepared according to known procedures.

3.1. General synthetic procedure

To a solution of 0.5 mmol of thiourea **4a–e** in 4 mL of DMF was added 1 mmol of *N*-aminopyridinium iodide **2** and 1.5 mmol of Et_3N and then 0.5 mmol of $Bi(NO_3)_3 \cdot 5H_2O$ (or $HgCl_2$) was added to the solution with vigorous magnetic stirring and ice-bath cooling. The suspension became black after a few minutes and was left stirring at 70–90 °C, while the progress of the reaction was monitored by TLC. When the thiourea was consumed, 20 mL of CH_2Cl_2 was added and the suspension was filtered through a pad of Celite. The filtrate was extracted with water (4×15 mL) and dried over anhydrous $MgSO_4$. After filtration the solvent was evaporated and the crude residue was recrystallized from CH_2Cl_2/petroleum ether.

3.1.1. *N*^{1}-Benzoyl-*N*^{2}-(5′-bromopyrindin-2′-yl)pyridinium guanidine (5a). Mp 234–236 °C. ν_{max} (KBr) 3236, 1600, 1561 cm^{-1}. ^{1}H (DMSO-d_6) δ 7.24 (2H, t, $J=$ 7.2 Hz); 7.33 (1H, d, $J=6.3$ Hz); 7.66 (2H, d, $J=7.2$ Hz); 7.96–8.05 (3H, m); 8.27–8.36 (3H, m); 8.90 (2H, d, $J=$ 6.3 Hz); 12.6 (1H, s). ^{13}C (DMSO-d_6) δ 111.5 (C); 115.9 (CH); 126.8 (CH); 127.5 (CH); 128.3 (CH); 130.3 (CH); 139.3 (C); 140.0 (CH); 140.3 (CH); 144.6 (CH); 148.4 (CH); 151.5 (C); 161.3 (C); 172.8 (C). Anal. Calcd for $C_{18}H_{14}BrN_5O$: C, 54.54%; H, 3.56%; N, 17.67%. Found: C, 54.32%; H, 3.52%; N, 17.58%.

3.1.2. *N*^{1}-Benzoyl-*N*^{2}-(5′-chloropyrindin-2′-yl)pyridinium guanidine (5b). Mp 212–215 °C. ν_{max} (KBr) 3077, 1596, 1577 cm^{-1}. ^{1}H (DMSO-d_6/CDCl$_3$) δ 7.22 (2H, t, $J=6.9$ Hz); 7.33 (1H, m); 7.68 (2H, d, $J=7.5$ Hz);

Figure 3. View of **5a** showing solid state dimerizations due to intermolecular interactions C14–H14···O1[i] (top) and C18–H18···π[ii] (bottom), indicated with dashed lines (symmetry operations: i=2−*x*, 1−*y*, −*z*; ii =2−*x*, −*y*, −*z*).

7.78 (1H, d, $J=8.4$ Hz); 8.01 (2H, t, $J=6.6$ Hz); 8.31 (3H, m); 8.87 (2H, d, $J=6.0$ Hz); 12.60 (1H, s). ^{13}C (DMSO-d_6/CDCl$_3$) δ 115.3 (CH); 123.3 (C); 126.6 (CH); 127.3 (CH); 128.3 (CH); 130.1 (CH); 137.1 (CH); 139.4 (C); 140.0 (CH); 144.6 (CH); 146.0 (CH); 151.2 (C); 161.3 (C); 172.9 (C). Anal. Calcd for C$_{18}$H$_{14}$ClN$_5$O: C, 61.46%; H, 4.01%; N, 10.08%. Found: C, 61.40%; H, 3.98%; N, 10.10%.

3.1.3. N^1-Benzoyl-N^2-(5′-methylpyrindin-2′-yl)pyridinium guanidine (5c).
Mp 155–157 °C. ν_{max} (KBr) 3103, 1615, 1559 cm^{-1}. ^{1}H (DMSO-d_6) δ 2.3 (3H, s); 7.24 (2H, t, $J=7.2$ Hz); 7.33 (1H, d, $J=6.9$ Hz); 7.56 (1H, d, $J=8.1$ Hz); 7.72 (3H, d, $J=7.5$ Hz); 7.97 (2H, t, $J=6.9$ Hz); 8.07 (1H, s); 8.32 (1H, t, $J=7.8$ Hz); 8.78 (2H, d, $J=6.0$ Hz); 12.74 (1H, s). ^{13}C (DMSO-d_6) δ 17.2 (CH$_3$); 113.9 (CH); 126.2 (C); 126.6 (CH); 127.3 (CH); 128.2 (CH); 128.4 (C) 130.1 (CH); 138.2 (CH); 139.9 (CH); 144.7 (CH); 147.6 (CH); 150.1 (C); 161.3 (C); 172.5 (C). Anal. Calcd for C$_{19}$H$_{17}$N$_5$O: C, 68.87%; H, 5.17%; N, 21.13%. Found: C, 68.89%; H, 5.17%; N, 21.32%.

3.1.4. N^1-Benzoyl-N^2-(phenyl)pyridinium guanidine (5d).
Mp 210–213 °C. ν_{max} (KBr) 3242, 1600, 1568 cm^{-1}. ^{1}H (CD$_3$OD) δ 7.06 (1H, t, $J=7.2$ Hz); 7.26 (2H, t, $J=9.0$ Hz); 7.32–7.38 (3H, m); 7.66 (2H, d, $J=7.8$ Hz); 7.75–7.80 (4H, m); 8.11 (1H, t, $J=7.5$ Hz); 8.63 (2H, dd, $J=0.9$, 6.3 Hz). ^{13}C (DMSO-d_6) δ 119.7 (C); 120.0 (CH); 121.6 (CH); 126.5 (CH); 127.3 (CH); 128.1 (CH); 128.5 (CH); 130.0 (CH); 139.6 (CH); 139.7 (C); 144.6 (CH); 162.1 (C); 172.3 (C). Anal. Calcd for C$_{19}$H$_{16}$N$_5$O: C, 69.08%; H, 4.88%; N, 21.20%. Found: C, 68.98%; H, 4.71%; N, 21.32%.

3.1.5. N^1-Benzoyl-N^2-(4′-methylphenyl)pyridinium guanidine (5e).
Mp 227–228 °C. ν_{max} (KBr) 3236, 1601, 1558 cm^{-1}. ^{1}H (DMSO-d_6/CDCl$_3$) δ 7.09 (2H, t, $J=7.8$ Hz); 7.21 (2H, t, $J=6.9$ Hz); 7.30 (1H, d, $J=5.7$ Hz); 7.54 (2H, d, $J=7.5$ Hz); 7.72 (2H, d, $J=7.8$ Hz); 7.92 (2H, t, $J=6.6$ Hz); 8.25 (1H, t, $J=7.5$ Hz); 8.78 (2H, d, $J=5.7$ Hz); 12.06 (1H, s). ^{13}C (DMSO-d_6/CDCl$_3$) δ 20.3 (CH$_3$); 120.1 (CH); 126.5 (CH); 127.4 (CH); 128.1 (CH); 129.0 (CH); 130.0 (CH); 130.5 (C); 137.1 (CH); 138.9 (CH); 144.6 (CH); 162.2 (C); 172.5 (C). Anal. Calcd for C$_{20}$H$_{18}$N$_5$O: C, 69.75%; H, 5.27%; N, 20.34%. Found: C, 69.72%; H, 5.20%; N, 20.21%.

3.2. Crystal structure of 5a

C$_{18}$H$_{14}$BrN$_5$O, $M_w=396.25$, triclinic, space group P-1 [nr 2], $Z=2$, $a=9.274(2)$, $b=9.488(4)$, $c=10.034(2)$ Å, $\alpha=75.44(2)$, $\beta=78.77(2)$, $\gamma=82.07(2)°$, $V=834.5(4)$ Å^3, $D_c=1.577$ Mg m^{-3}, λ(Cu Kα)=1.54180 Å, $\mu=3.498$ mm^{-1}, 3081 measured reflections, 2896 unique ($R_{int}=0.0204$) of which 2700 were considered as observed with $I\geq2\sigma(I)$. The single crystals were obtained by slow evaporation of a solution of **5a** in CH$_3$Cl at room temperature. The structures were solved with direct methods using SHELXS97[18] and it were refined anisotropically with full-matrix least-squares on F^2 using SHELXL97.[19] The hydrogen atoms were placed at calculated position except those involved in H-bonds, found on difference maps and refined. Final indices: $R_1(F_o)=0.0528$, $wR_2(F^2)=0.142$ for 245 refined parameters. All structural details of the intermolecular contacts for **5a** were interpreted as hydrogen bonds on geometrical grounds.[20] The crystallographic data were deposited at the Cambridge Crystallographic Data Center under the number CCDC 261830. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge, CB21EZ, UK (fax +44 1223 336033) or e-mail: deposit@ccdc.camac.uk.

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