Pergamon

Tetrahedron Letters 43 (2002) 49–52

TETRAHEDRON LETTERS

Bismuth nitrate pentahydrate: a new and environmentally benign reagent for guanidylation of *N*-benzoylthioureas†

Silvio Cunha,* Byanka R. de Lima and Aparecido R. de Souza

Instituto de Química, Universidade Federal de Goiás, CP 131, Goiânia, GO 74001-970, Brazil

Received 31 August 2001; revised 30 October 2001; accepted 31 October 2001

Abstract—The bismuth nitrate-mediated guanidylation of *N*-benzoylthioureas was studied. This salt proved to be an effective guanylating reagent and allowed the obtention of *N*-benzoyl-guanidines in good yields. The methodology described is a promising alternative to the use of toxic $HgCl_2$ in the synthesis of polysubstituted guanidines. © 2001 Elsevier Science Ltd. All rights reserved.

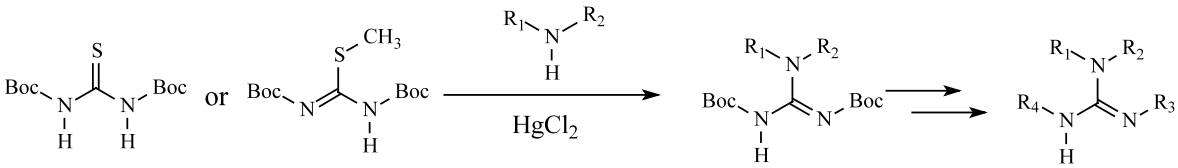
The broad spectrum of biological proprieties,[1] mainly medicinal activity,[2] of natural and synthetic guanidine compounds[3–5] has motivated the development of new methods for guanidine synthesis.[6–12] In solution phase synthesis of this class of compounds, *N*,*N*′-bis-Boc-protected thioureas and *S*-alkyl isothioureas are starting materials extensively used when polysubstituted guanidine is the synthetic goal (Scheme 1).[11,13–20]

In a recent work, one of us described *N*-benzoylthioureas as being conveniently converted into guanidines with reasonable yields using the $HgCl_2$ protocol.[21] In fact, $HgCl_2$ has been extensively employed in guanidine synthesis.[11,13–20] However, the use of stoichiometric amounts of this toxic salt is a serious drawback if medicinal compounds need be synthesized because even backgrounds levels of toxic metals are not desirable.

In a search for safer reagents for guanidylation reaction of thioureas, the chemistry of bismuth caught our attention.[22–24] Many recent papers describing the use of bismuth compounds in organic transformation pointed out its use as being ecologically friendly.[25–35] In addition, bismuth derivatives have been widely used in medicine.[36] Most bismuth salts are commercially available, inexpensive and easy to handle. Among them, bismuth nitrate pentahydrate has the extra advantage of being a crystalline solid insensitive to water and air.[37] Moreover, to the best of our knowledge, this is the unique bismuth salt used to date in transformations involving sulfur-containing compounds as reagents.[38]

This communication presents the first successful synthesis of guanidines using $Bi(NO_3)_3{\cdot}5H_2O$ as a guanylating reagent for *N*-benzoylthioureas. Our strategy to test this salt as a guanylating reagent utilizes the previously reported acylguanidines **3a–e** as model compounds, Scheme 2. In this way, we can compare the efficiency of this method with the $HgCl_2$ methodology.

When a solution of thioureas **1a–e** was treated with equimolar quantities of amines **2a–e** in the presence of $Bi(NO_3)_3{\cdot}5H_2O$ a slow reaction took place and guanidines **3a–e** were observed by TLC and IR, but the starting thioureas were also present even at prolonged



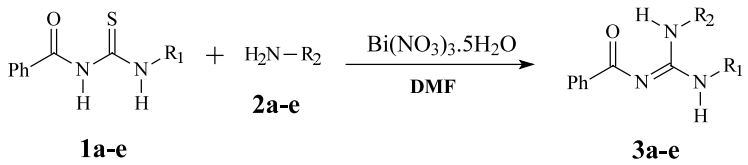
Scheme 1.

Keywords: bismuth; acylguanidines; thioureas.

* Corresponding author. Tel.: +55-62-5211008; e-mail: silvio@quimica.ufg.br

† Dedicated to Professor Dr. Albert James Kascheres, now retired from Instituto de Química, Universidade Estadual de Campinas, for his outstanding contribution to organic chemists' education in Brazil.

PII: S0040-4039(01)02067-6



1a-e 3a-e

Scheme 2.

times. To increase the reaction rate, we used 2 equiv. of amines in relation to thioureas. With this modification, the thioureas were consumed and guanidines **3a–e** were isolated in almost the same yields as when $HgCl_2$ was the guanylating reagent. In addition, the use of triethylamine proved to be crucial to reaction success, as observed in the $HgCl_2$ methodology. In its absence the thioureas were quantitatively recovered. Also, the best yield was obtained with thiourea **1e** containing an electron withdrawing substituent and amine **2e** containing an electron releasing one. The results are summarized in Table 1. The yields were improved and/or reaction times diminished when the reaction was carried out at 70–90°C (see Table 1). We also attempted the reaction with lower amounts of bismuth nitrate. Thus, when *N*-benzoylthiourea **1a** was treated with amine **2a** in the presence of 10 mol% of $Bi(NO_3)_3{\cdot}5H_2O$ guanidine **3a** was not formed, but with 50 mol% it was isolated in 54% yield. In this way, the best yields are obtained with stoichiometric amounts of bismuth nitrate.

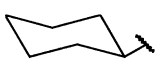
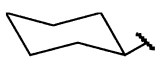
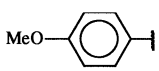
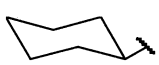
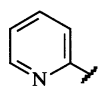
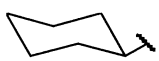
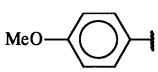
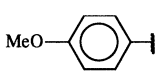
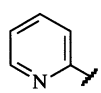
In conclusion, we have demonstrated that $Bi(NO_3)_3{\cdot}5H_2O$ is a novel guanylating reagent of *N*-benzoylthioureas. Additionally, the yields and spectrum of guanidines synthesized are comparable with those of the $HgCl_2$ protocol. Efforts are underway to elucidate the mechanistic details of this reaction and define the scope, limitations and synthetic applications of this new guanylating reagent.

The general experimental procedure is as follows: to a solution of 0.5 mmol of thiourea in 3 mL of DMF was added 1 mmol of amine and 2 mmol of Et_3N and then 0.5 mmol of $Bi(NO_3)_3{\cdot}5H_2O$ 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 the indicated temperature (see Table 1), while the progress of the reaction was monitored by TLC. When thiourea was consumed, 10 mL of CH_2Cl_2 was added and the suspension was filtered through a pad of Celite. The filtrate was concentrated and the residue ($\sim$3 mL) was dissolved in 15 mL of CH_2Cl_2 and extracted with water (4×15 mL) and dried over anhydrous $MgSO_4$. After filtration the solvent was evaporated and the crude residue was treated as indicated in each case.[39]

Acknowledgements

The authors thank the Brazilian Agency CAPES for a studentship to B.R.L.

Table 1. Isolated guanidine yields produced via Scheme 2[a]

Guanidine	R_1	R_2	Yield % (reaction time)		
			$HgCl_2$[b]	$Bi(NO_3)_3.5H_2O$[c]	
3a			62(20h)	63(48h)	91(18h)
3b			60(20h)	64(48h)	69(21h)
3c			64(20h)	62(44h)	73(27h)
3d			53(20h)	40(117h)	64(22h)
3e			81(20h)	92(44h)	56(22h)

[a]All products were identified by comparison of their physical and spectral data with those of authentic samples.[39]

[b]From reference 21.

[c]First column: reaction carried out at room temperature; second column at 70-90°C.

References

1. Hannon, C. L.; Anslyn, E. V. In *Bioorganic Chemistry Frontiers*; Dugas, H., Ed.; Springer-Verlag: Berlin, Heidelberg, 1993; Vol. 3, pp. 193–247.
2. Greenhill, J. V.; Lee, L. In *Progress in Medicinal Chemistry*; Ellis, G. P.; Luscombe, D. K., Eds.; Elsevier: New York, 1993; Vol. 30, pp. 203–326.
3. Berlinck, R. G. S. *Nat. Prod. Rep.* **1996**, *13*, 337–407.
4. Berlinck, R. G. S. *Fortschr. Chem. Org. Naturst.* **1995**, *66*, 119–295.
5. Berlinck, R. G. S. *Nat. Prod. Rep.* **1999**, *16*, 339–365.
6. Dodd, D. S.; Zhao, Y. *Tetrahedron Lett.* **2001**, *42*, 1259–1262.
7. Zapf, C. W.; Creighton, C. J.; Tomioka, M.; Goodman, M. *Org. Lett.* **2001**, *3*, 1133–1136.
8. Ghosh, A. K.; Hol, W. G. J.; Fan, E. *J. Org. Chem.* **2001**, *66*, 2161–2164.
9. Overman, L. E.; Wolfe, J. P. *J. Org. Chem.* **2001**, *66*, 3167–3175.
10. Tamaki, M.; Han, G.; Hruby, V. *J. Org. Chem.* **2001**, *66*, 1038–1042.
11. Linton, B. R.; Carr, A. J.; Orner, B. P.; Hamilton, A. D. *J. Org. Chem.* **2000**, *65*, 1566–1568.
12. Katritzky, A. R.; Rogovoy, B. V.; Chassainy, C.; Vvedensky, V. *J. Org. Chem.* **2000**, *65*, 8080–8082.
13. Srinivasan, N.; Ramadas, K. *Tetrahedron Lett.* **2001**, *42*, 343–346.
14. Isobe, T.; Fukuda, K.; Tokunaga, T.; Seki, H.; Yamaguchi, K.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7774–7778.
15. Isobe, T.; Fukuda, K.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7770–7773.
16. Ramadas, K.; Janarthanan, N.; Pritha, R. *Synlett* **1997**, 1053–1054.
17. Jeong, J.-H.; Murray, B. W.; Takayama, S.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 4227–4234.
18. Levallet, C.; Lerpiniere, J.; Ko, S. Y. *Tetrahedron* **1997**, *53*, 5291–5304.
19. Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677–7680.
20. Poss, M. A.; Ivanowick, E.; Reid, J. A.; Lin, J.; Gu, Z. *Tetrahedron Lett.* **1992**, *33*, 5933–5936.
21. Cunha, S.; Costa, M. B.; Napolitano, H. B.; Lariucci, C.; Vencato, I. *Tetrahedron* **2001**, *57*, 1671–1675.
22. Elliott, G. I.; Konopelski, J. P. *Tetrahedron* **2001**, *57*, 5683–5705.
23. Suzuki, H.; Ikegami, T.; Matano, Y. *Synthesis* **1997**, 249–267.
24. Marshall, J. A. *Chemtracts* **1997**, 1064–1075.
25. Keramane, E.-M.; Boyer, B.; Roque, J.-P. *Tetrahedron* **2001**, *57*, 1909–1916.
26. Keramane, E.-M.; Boyer, B.; Roque, J.-P. *Tetrahedron Lett.* **2001**, *42*, 855–857.
27. Mohammadpoor-Baltork, I.; Aliyan, H.; Khosropour, A. R. *Tetrahedron* **2001**, *57*, 5851–5854.
28. Anderson, A. M.; Blazek, J. M.; Garg, P.; Payne, B. J.; Mohan, R. S. *Tetrahedron Lett.* **2000**, *41*, 1527–1530.
29. Tymonko, S. A.; Nattier, B. A.; Mohan, R. S. *Tetrahedron Lett.* **1999**, *40*, 7657–7659.
30. Eash, K. J.; Pulia, M. S.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2000**, *65*, 8399–8401.
31. Mashraqui, S. H.; Karnik, M. A. *Synthesis* **1998**, 713–714.
32. Laurent-Robert, H.; Garrigues, B.; Dubac, J. *Synlett* **2000**, 1160–1162.
33. Laurent-Robert, H.; Dubac, J. *Synlett* **1998**, 1138–1140.
34. Roux, C. L.; Ciliberti, L.; Laurent-Robert, H.; Dubac, J. *Synlett* **1998**, 1249–1251.
35. Komatsu, N.; Uda, M.; Suzuki, H. *Synlett* **1995**, 984–986.
36. *Comprehensive Coordination Chemistry*; Wilkinson, G.; Gillard, R. D.; McCleverty, J. A., Eds.; Pergamon Press: London, 1987; Vol. 3, pp. 292–313.
37. Krüger, J.; Winkler, P.; Lüderitz, E.; Lück, M.; Wolf, H. V. In *Ullman's Encyclopedia of Industrial Chemistry*; Gerhartz, W., Ed.; VCH: Weinheim, 1985; Vol. A4, pp. 171–189.
38. Komatsu, N.; Taniguchi, A.; Uda, M.; Suzuki, H. *J. Chem. Soc., Chem. Commun.* **1996**, 1847–1848.
39. ***N*1-Di(cyclohexylamino)methylenebenzamide (3a)**: recrystallization from ethyl ether/petroleum ether. ν_{max} (KBr) 3289, 1605, 1572 cm^{-1}. δ ^1H ($CDCl_3$) 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%.

1-Cyclohexylamino(phenylcarbonylimino)methylamino-4-methoxybenzene (3b): recrystallization from ethyl ether/petroleum ether. ν_{max} (KBr) 3356, 1594, 1570 cm^{-1}. δ ^1H ($CDCl_3$) 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%.

2-Cyclohexylamino(phenylcarbonylimino)methylamino-pyridine (3c): recrystallization from ethyl ether/petroleum ether. ν_{max} (KBr) 1622, 1592, 1564 cm^{-1}. δ ^1H ($CDCl_3$) 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, $J=7.3$ Hz, 5.2 Hz); 7.37–7.50 (3H, m); 7.66 (1H, dt, $J=7.5$ Hz, 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%.

4-Methoxy-1-[4-methoxyanilino(phenylcarbonylimino)-methylamino]benzene (3d): recrystallization from CH_2Cl_2/petroleum ether. ν_{max} (KBr) 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%.

2-[*tert*-Butylamino(phenylcarbonylimino)methylamino]-pyridine (3e): recrystallization from ethyl acetate/petroleum ether. ν_{max} (KBr) 1618, 1594, 1568 cm^{-1}. δ ^{1}H (CD_3OD) 1.63 (9H, s); 6.95 (1H, d, $J=8.4$ Hz); 7.07 (1H, ddd, $J=8.4$ Hz, 7.4 Hz, 1.9 Hz); 7.41–7.46 (2H, m); 7.48–7.52 (1H, m); 7.78 (1H, ddd, $J=7.4$ Hz, 5.0 Hz, 1.0 Hz); 8.21 (2H, m); 8.27 (1H, ddd, $J=5.0$ Hz, 1.9 Hz, 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%.