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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6955–6956

The first bismuth(III)-catalyzed guanylation of thioureas

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Received 10 February 2006; accepted 26 July 2006

Abstract—This work describes the first catalytic bismuth-promoted synthesis of polysubstituted guanidines in good yields through the guanylation reaction of *N*-benzoyl or *N*-phenylthioureas with primary and secondary amines, but now employing equimolar amounts of each organic reagent. Both bismuth iodine and bismuth nitrate were efficient as inorganic thiophiles at only 5 mol % in relation to substrates, being the first example of inorganic thiophiles acting in guanylation at catalytic levels.

Despite of the variety of guanylating reagents to solution synthesis of guanidines, the most used guanylation protocols employ protected thiourea as guanylating reagents and stoichiometric amounts of heavy metal salts as guanylating agent, $HgCl_2$ being the toxic and the most popular.[1]

Bismuth is the least toxic of the heavy metals and their salts have been intensively used in organic transformations.[2,3] We have reported guanylation of *N*-benzoylthioureas using stoichiometric amounts of $Bi(NO_3)_3$ as thiophile, but the use of 2 equiv of the amine was required to achieve an yield comparable to the $HgCl_2$ method.[4] This is a serious drawback when expensive or no commercial amines are necessary. Herein, we describe the first successful catalytic Bi(III)-mediated synthesis of functionalized guanidines. Besides, no excess of nucleophilic amine was needed.

In the previously stoichiometric bismuth-promoted guanylation, we identified Bi_2S_3 as byproduct. Here we hypothesized that stoichiometric amount of $Bi(NO_3)_3$ was necessary because the low solubility of Bi_2S_3 in the reaction medium precluded the continuous thiourea activation, that is, necessary to the guanylation. Thus, we reason that a catalytic cycle could operate if Bi_2S_3 could be in situ transformed into a more soluble Bi(III) derivative, affording guanidines in good yields. To this end, an oxidant agent as co-reagent could be useful because $(SO_x)^{y-}$-derivatives of Bi(III) are more soluble than Bi_2S_3.[1a] To test this hypothesis we reacted thiourea **2a** with amine **3a** in the presence of diverse Bi(III) salts and oxidants. After experimentation, **4a** was obtained in 15% yield after 5 days when BiI_3 5 mol % was used in the presence of $K_2S_2O_8$. The oxidant was thus screened. Changing the oxidant to sodium bismuthate, $NaBiO_3$, guanidine **4a** was isolated in 92% yield and 10 h, Table 1. The use of cheap $NaBiO_3$ is noteworthy because both thiophile and oxidant are now environmental friendly.[2,5] This protocol could be extended to less activated *N*-phenylthioureas, and primary and secondary amines were tolerated as the nucleophilic component using both N-substituted thioureas, affording a representative spectrum of guanidines through this new catalytic guanylation (Table 1). $Bi(NO_3)_3$ 5 mol % was also effective but BiI_3 afforded better yield and shorter reaction time. For instance, guanylation of **2a** with cyclohexylamine and $Bi(NO_3)_3$ 5 mol % afforded **4c** in 69% yield (21 h).

The proposed catalytic cycle for this guanylation is indicated in Figure 1. In analogy to the $HgCl_2$-promoted guanylation,[1] we assumed that a carbodiimide is the key intermediate. In this way, Bi(III) should behave as a thiophilic soft Lewis acid that coordinated to the thiourea followed by reaction with Et_3N and form the carbodiimide by thiourea desulfurization, which is trapped by the amine affording the guanidine, and the insoluble Bi_2S_3 is oxidized to a more soluble Bi(III) derivative.

In conclusion, we have developed the first catalytic Bi(III) guanylation of thioureas, wherein only 5 mol %

Keywords: Thioureas; Guanidines; Bismuth.
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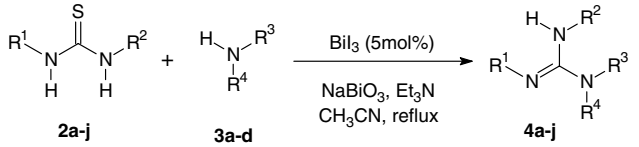
doi:10.1016/j.tetlet.2006.07.138

Table 1. Isolated guanidine yields



2a-j **3a-d** **4a-j**

Guanidine	Thiourea R^1/R^2	Amine R^3/R^4	Yield (%)	Time (h)
4a	Bz/*p*-CH_3OPh	*p*-CH_3OPh/H	92	10
4b	Bz/Ph	*p*-CH_3OPh/H	75	12
4c	Bz/*p*-CH_3OPh	*c*-C_6H_{11}/H	86	3
4d	Bz/*p*-CH_3Ph	*c*-C_6H_{11}/H	65	8
4e	Bz/Ph	*c*-C_6H_{11}/H	77	3
4f	Bz/*c*-C_6H_{11}	*c*-C_6H_{11}/H	69	21
4g	Bz/*o*-ClPh	*c*-C_6H_{11}/*c*-C_6H_{11}	91	11
4h	Bz/*p*-CH_3OPh	$CH_2CH_2OCH_2CH_2$	97	5
4i	Ph/*p*-CH_3OPh	$CH_2CH_2OCH_2CH_2$	95	3
4j	Ph/*c*-C_6H_{11}	*c*-C_6H_{11}/H	95	7

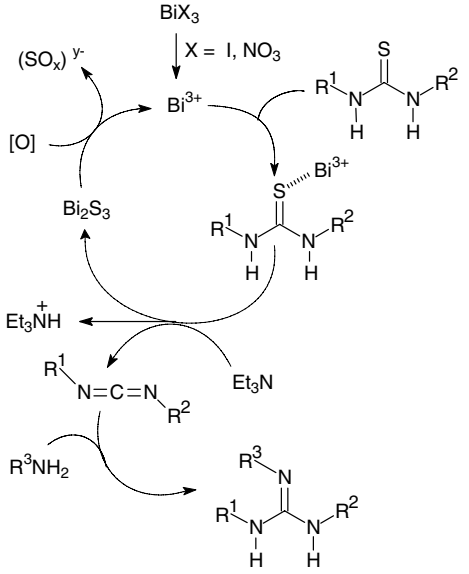


Figure 1. Proposed catalytic cycle for the Bi(III)-promoted guanylation of thioureas.

of inorganic thiophiles and no excess of amine was required, with yields and scope comparable with the stoichiometric $HgCl_2$ protocol.[6] Efforts are underway to elucidate the mechanistic details of this reaction and define the scope, limitations and synthetic applications to natural and unnatural bioactive guanidines.

Acknowledgements

The authors thank CNPq and FAPESB for support and fellowships, and Professor A.C.S. Costa for donation of BiI_3.

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5. The use of $NaBiO_3$ in organic transformations is scarcely reported. For reviews, see Refs. 2a,2b.
6. The general synthetic procedure is as follows: to a solution of 0.5 mmol of thiourea in 7 mL of CH_3CN were added 0.5 mmol of amine and 1 mmol of Et_3N, and then 0.5 mmol of $NaBiO_3$ and 0.025 mmol of BiI_3 were added to the solution with vigorous magnetic stirring. The suspension was left stirring for 10 min at room temperature and became black. After this time, it was heated at reflux at the indicated time in Table 1. The solvent was evaporated and 20 mL of CH_2Cl_2 was added. The suspension was filtered through a pad of Celite and the pad washed with 10 mL of CH_2Cl_2. The filtrate was dried over anhydrous $MgSO_4$, filtrated and the solvent was evaporated. The crude residue was recrystallized from Et_2O/petroleum ether affording a solid or a viscous oleo as indicated in each case.
Compound **4d**: Mp 100–103 °C. IR (KBr): 3287, 1570 cm^{-1}. ^1H NMR ($CDCl_3$): 1.10–2.10 (10H, m); 2.34 (3H, s); 4.15 (1H, m); 4.80 (1H, br); 7.13 (2H, d, $J = 8.0$ Hz); 7.21 (2H, d, $J = 8.0$ Hz); 7.38–7.45 (3H, m); 8.24 (2H, d, $J = 6.3$ Hz); 11.97 (1H, br). ^{13}C NMR ($CDCl_3$): 20.9 (CH_3); 24.7 (CH_2); 25.5 (CH_2); 33.1 (CH_2) 50.0 (CH); 125.3 (CH); 127.7 (CH); 129.0 (CH); 130.9 (CH); 133.4 (C); 136.6 (C); 138.8 (C); 158.0 (C); 177.3 (C).
Compound **4e**: Mp 107–110 °C. IR (KBr): 3250, 1570 cm^{-1}. ^1H NMR ($CDCl_3$): 1.10–2.15 (10H, m); 4.18 (1H, m); 4.84 (1H, br); 7.20–7.30 (3H, m); 7.35–7.50 (5H, m); 8.26 (2H, d, $J = 6.6$ Hz); 12.97 (1H, br). ^{13}C NMR ($CDCl_3$): 24.7 (CH_2); 25.4 (CH_2). 33.0 (CH_2); 50.1 (CH); 125.0 (CH): 126.5 (CH); 127.8 (CH); 128.9 (CH); 129.9 (CH); 131.03 (CH); 136.2 (C); 138.6 (C); 157.7 (C); 177.4 (C).
Compound **4g**: Mp 125–127 °C; IR (KBr): 3065, 1610, 1544, 1366 cm^{-1}. ^1H NMR ($CDCl_3$): 1.00–2.25 (20H, m); 3.25–3.40 (2H, m); 7.00–7.20 (2H, m); 7.30–7.50 (2H, m); 8.26 (1H, d, $J = 6.6$ Hz); 11.07 (1H, br). ^{13}C NMR ($CDCl_3$): 25.5 (CH_2); 26.3 (CH_2); 31.1 (CH_2); 58.6 (CH); 125.2 (CH); 126.0 (CH); 127.2 (CH); 127.2 (CH); 127.8 (CH); 128.7 (C); 129.0 (CH); 130.0 (CH); 130.9 (CH); 138.5 (C); 160.7 (C); 175.4 (C).
Compound **4h**: oil. IR (film): 3013, 1600, 1575 cm^{-1}. ^1H NMR ($CDCl_3$): 3.55 (4H, m); 3.67 (4H, m); 3.78 (3H, s); 6.85 (2H, d, $J = 8.8$ Hz); 7.06 (2H, d, $J = 8.8$ Hz); 7.40–7.55 (3H, m); 8.22 (2H, d, $J = 6.9$ Hz); 11.85 (1H, br). ^{13}C NMR($CDCl_3$): 46.9 (CH_2); 55.4 (CH_3); 66.3 (CH_2); 114.8 (CH); 123.4 (CH); 127.9 (CH); 129.2 (CH); 131.5 (CH); 132.3 (C); 138.2 (C); 156.9 (C); 160.2 (C); 177.1 (C).