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o-Iodoxybenzoic acid mediated oxidative condensation: synthesis of guanidines using 1,-3-disubstituted thiourea precursors

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ABSTRACT

An efficient and mild oxidative condensation procedure using *o*-iodoxybenzoic acid and triethylamine or ammonia as base has been developed for the synthesis of guanidines starting from easily synthesizable 1,3-disubstituted thioureas and amines or ammonia.

Chemistry and biology of guanidine derivatives, reviewed periodically, is an attractive area of research and development.[1] Guanidine derivatives are widely used as ancillary ligands[2] for stabilization of a variety of metal complexes. They also find applications as an important pharmacophore with improved pharmacokinetic properties in medicinal chemistry.[3] Guanidine moiety is present in many biologically active natural products such as saxitoxin, a toxic marine natural product that targets multitude of receptors[4] showing CNS[5] and anti-*Helicobacter pylori*[6] activity; in polyamine based analogues useful as biochemical probes and potential therapeutics,[7] in alkaloids like bromopyrroles,[8] in drugs such as anigrilide used for the treatment of essential thrombocytosis and chronic myeloid leukaemia.[9] Guanidine moiety is also found in amino acids such as arginine and in peptides as an important building block. Many methods are reported in the literature for the synthesis of guanidines starting from thioureas, isothioureas, carbodiimides, cyanamides, pyrrazole-1-carboximidamides and triflylguanidines.[10] Combination of thioureas and amines has been used for the synthesis of guanidines via desulfurization using reagents such as Mukaiyama's reagent,[11] diiodomethane,[12] hydrogen peroxide,[13] metal salts like copper chloride or mercuric chloride[14] and copper sulfate.[15] Drawbacks of these methods are use of toxic metals, lower yields and longer reaction times. Newer methods for guanidine synthesis are reported recently using guanylating agents such as *N*,–*N*″,–*N*‴-tri-Boc-guanidine,[16] bis-(benzotriazole-1-yl)methylene amines and benzotriazole-1-carboxamidines.[17] Hypervalent iodine reagents and in particular organo-iodine (V) reagents, are finding wide applications in organic transformations and synthesis of natural products. This growing interest, as indicated by many recent review articles, is due to their nontoxic, mild and highly chemoselective oxidizing property coupled with, easy work–up procedures and eco-friendly features.[18]

Our research group is actively engaged in exploring the utility of hypervalent iodine reagents especially, *o*-iodoxybenzoic acid (IBX) and Dess-Martin periodinane (DMP).[19] Recently we have reported a mild and efficient oxidative desulfurization of 1,-3-disubstituted thioureas to carbodiimides[20a] and synthesis of azoles[20b] by using IBX in the presence of base such as triethylamine (TEA). As an extension to this, it was hypothesized that, a one pot synthesis of guanidine can be realized, if carbodiimides are generated in the presence of amines or ammonia and trap them to form guanidines. This hypothesis was tested by adding a solution of IBX/NH_3 drop wise to a solution of 1,-3-diphenylthiourea in acetonitrile at room temperature, and expected *N*,–*N*″-diphenylguanidine was formed in 90% yield with precipitation of sulfur (Scheme 1).

On the same line when a solution of IBX/TEA in acetonitrile was added to a solution of 1,-3-diphenylthiourea and aniline in acetonitrile, *N*,–*N*″,–*N*‴-triphenylguanidine was obtained in 78% yield (Scheme 2).

IBX is not compatible with amines[21] however the present success is attributed to the rapid desulfurization of thiourea to form carbodiimide. To establish generality of the protocol,[22] a variety

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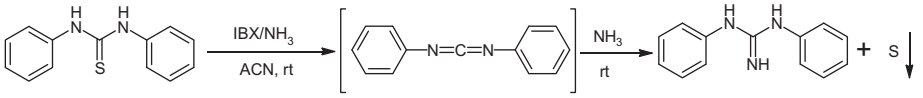
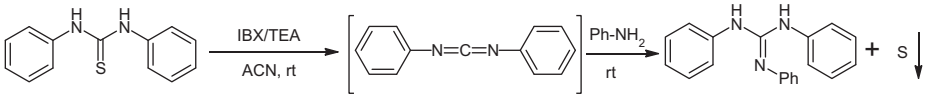


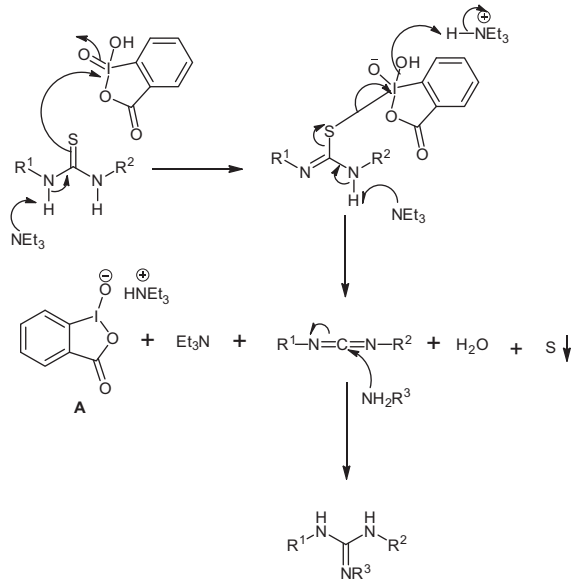
Scheme 1. Oxidative desulfurization and formation of *N*,–*N*″-diphenylguanidine from 1,3-diphenylthiourea with IBX/NH_3 system.



Scheme 2. Oxidative condensation of 1,3-diphenylthiourea and aniline with IBX/TEA to form *N*,–*N*″,–*N*‴-triphenylguanidine.

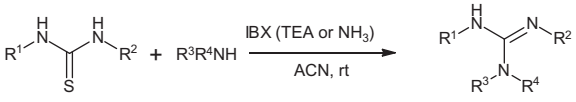
of 1,-3-disubstituted thioureas were studied and the results are summarized in Table 1. In general reactions were very fast and yields were comparable irrespective of the nature of substituents on the aromatic rings. For example substrates carrying methyl, methoxy and chloro substituents at *ortho*-, *meta*- and *para*-positions reacted equally efficient (Table 1, entries 2–8). Reaction proceeded smoothly with cyclohexyl and benzyl substituted thioureas (Table 1, entries 9–10). Reaction was equally efficient in formation of the tri-substituted (Table 1, entries 11–15) as well as the tetra-substituted guanidines (Table 1, entry 16). However reaction was not smooth and gave a complex mixture with monosubstituted and 1,-3-dicyclohexyl thioureas. As far as amine component is concerned reaction occurred efficiently with all, including ammonia, aliphatic amines, anilines and cyclohexyl amine.

A plausible mechanism for the formation of guanidines from 1,-3-disubstituted thioureas is presented in Scheme 3. Precipitation of sulfur during the reaction and observation of spot corresponding to carbodiimide on TLC, taken immediately after addition of IBX, support the postulated mechanism. Recovery of the generated trivalent iodine A for recycling after re-oxidation to IBX by Oxone was also possible.



Scheme 3. Plausible mechanism for the formation of guanidines via carbodiimides, from 1,-3-disubstituted thiourea.

Table 1
Preparation of guanidines from 1,-3-disubstituted thioureas



Entry	R^1	R^2	R^3	R^4	Method[a]	Yield[b]
1	C_6H_5	C_6H_5	H	H	A	90
2	*m*-ClC_6H_4	*m*-ClC_6H_4	H	H	A	88
3	*p*-ClC_6H_4	*p*-ClC_6H_4	H	H	A	90
4	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	H	H	A	86
5	C_6H_5	*o*-ClC_6H_4	H	H	A	88
6	C_6H_5	*p*-ClC_6H_4	H	H	A	86
7	C_6H_5	*o*-$CH_3C_6H_4$	H	H	A	88
8	C_6H_5	*p*-$CH_3OC_6H_4$	H	H	A	90
9	C_6H_5	C_6H_{11}	H	H	A	85
10	C_6H_5	Bn	H	H	A	88
11	C_6H_5	C_6H_5	C_6H_5	H	B	78
12	C_6H_5	Bn	C_6H_5	H	B	82
13	C_6H_{11}	C_6H_5	C_6H_{11}	H	B	78
14	C_6H_5	C_6H_5	CH_3	H	B	85
15	C_6H_5	C_6H_5	C_4H_9	H	B	80
16	C_6H_5	C_6H_5	$(CH_3)_2CH$	$(CH_3)_2CH$	B	85
17	C_6H_5	H	C_6H_5	H	B	—[c]
18	C_6H_{11}	C_6H_{11}	C_6H_5	H	B	—[c]

[a] For general procedures see Ref. 22.
[b] Isolated yields.
[c] Complex mixture.

In summary, an efficient one pot method based on oxidative condensation of 1,-3-disubstituted thioureas and ammonia/amines using IBX as oxidant has been developed for one pot synthesis of guanidines with mild reaction conditions, ease of isolation and suitability for a wide range of substrates. IBX oxidations are selective and tolerate a wide range of functional groups therefore; this method has the potential to be extended to complex substrates.

Spectral data of selected guanidines

1,3-bis(3-Chlorophenyl)guanidine (Table 1, entry 2): Mp 140 °C (lit.[23] Mp 139 °C). IR (KBr): 3434, 1586, 1524 and 1472 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ = 7.18 (m, 2H), 7.33–7.66 (m, 6H), 7.66 (s, 2H), 10.03 (s, 1H).

N,*N*′-di-*p*-Chlorophenylguanidine (Table 1, entry 3): Mp 140 °C (lit.[23] Mp 139 °C). IR (KBr): 3434, 1586, 1524 and 1472 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.30 (m, 4H), 7.34–7.57 (m, 4H), 8.25 (s, br, 2H), 10.03 (s, 1H).

1,3-bis(4-Methoxyphenyl)guanidine (Table 1, entry 4): Mp 156 °C (lit.[24] Mp 157 °C). IR (KBr): 3436, 1628, 1613 and 1402 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ = 3.74 (s, 6H), 6.89 (d, 4H), 7.30 (d, 4H), 9.40 (s, 1H).

1-(2-Chlorophenyl)-3-phenylguanidine (Table 1, entry 5): Mp 127 °C (lit.[25] Mp 129 °C). IR (KBr): 3457, 1635, 1578 and1468 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ = 7.18 (m, 1H), 7.21 (m, 2H), 7.35

(m, 2H), 7.49 (m, 2H), 7.61 (m, 2H), 8.87 (s, br, 1H), 9.35 (s, br, 1H), 10 (s, br, 1H).

1-(4-Chlorophenyl)-3-phenylguanidine (Table 1, entry 6): Mp 148 °C (lit.[26] Mp 150 °C). IR (KBr): 3440, 1656 and 1584 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ = 7.2 (m, 1H), 7.31 (m, 1H), 7.36 (m, 3H), 7.5 (m, 2H), 7.58 (m, 2H), 9.39 (s, 1H), 9.99 (s, 2H).

1-(4-Methoxyphenyl)-3-phenylguanidine (Table 1, entry 8): Mp 137 °C (lit.[25] Mp 140 °C). IR (KBr): 3460, 1638, 1585, 1551 and 1498 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ = 3.80 (s, 3H), 6.86 (m, 2H), 7.17 (m, 1H), 7.25 (m, 4H), 7.43 (m, 2H), 9.60 (s, br, 2H), 10.63 (s, br, 1H).

1-Cyclohexyl-3-phenylguanidine (Table 1, entry 9): Mp 133 °C (lit.[13] Mp 134 °C). IR (KBr): 3402, 1651, 1582 and 1484 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ = 1.25 (m, 4H), 1.51 (m, 2H), 1.7 (m, 2H), 1.89 (m, 2H), 2.44 (m, 1H), 7.14 (m, 1H), 7.33 (m, 2H), 7.43 (m, 2H), 7.61 (m, 1H), 9.33 (s, br, 2H), 10 (s, br, 1H).

1-Benzyl-3-phenylguanidine (Table 1, entry 10): Mp 123 °C (lit.[27] Mp 124 °C). IR (KBr): 3441,1588,1536,1499 and 1659 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ = 4.73 (s, 2H), 7.11 (m, 1H), 7.24–7.34 (m, 7H), 7.43 (m, 2H), 8.14 (s, br, 1H), 8.96 (s, br, 1H), 9.59 (s, br, 1H).

1,2,3-Triphenylguanidine (Table 1, entry 11): Mp 146 °C (lit.[28] Mp 144 °C). IR (KBr): 3060, 3030 and 1659 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ = 6.95 (m, 2H), 7.07 (m, 4H), 7.17 (m, 4H), 7.27 (m, 5H), 7.43 (m, 1H), 7.84 (m, 1H).

1-Benzyl-2,3-diphenylguanidine (Table 1, entry 12): Mp 101 °C (lit.[29] Mp 103 °C). IR (KBr): 3432, 1667, 1494 and 1441 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ = 3.9 (s, 2H), 6.94 (m, 2H), 7.06 (m, 4H), 7.17 (m, 4H), 7.32 (m, 5H), 7.52 (m, 1H), 7.84 (m, 1H).

2-Methyl-1,3-diphenylguanidine (Table 1, entry 14): Mp 108 °C (lit.[29] Mp 109 °C). IR (KBr): 3441, 1588, 1531 and1484 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ = 2.85 (s, 3H), 7.20 (m, 6H), 7.37 (m, 4H).

2-Butyl-1,3-diphenylguanidine (Table 1, entry 15): Mp 127 °C (lit.[30] Mp 129 °C). IR (KBr): 3420, 1530 and 1494 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ = 0.85 (t, 3H), 1.05 (q, 2H), 1.29 (m, 2H), 2.5 (m, 2H), 6.75 (m, 4H), 7.10–7.40 (m, 10H), 7.68 (m, 1H), 8.50 (s, 1H).

1,1-Diisopropyl-2,3-diphenylguanidine (Table 1, entry 16): Mp 48 °C (lit.[29] Mp 50 °C). IR (KBr): 3448, 2950, 1650, 1588 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ = 1.91 (m, 2H), 1.34 (m, 8H), 1.47 (m, 2H), 2.97 (m, 2H), 6.30 (s, 1H), 6.53 (s, 1H), 6.72 (m, 1H), 6.99 (m, 5H), 7.20 (m, 1H), 7.44 (m, 1H), 8.22 (s, br, 1H), 8.77 (s, br, 1H).

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References and notes

1. (a) Berlinck, R. G. S.; Burtoloso, A. C. B.; Kos-suga, M. H. *Nat. Prod. Rep.* **2008**, *25*, 919; (b) Berlinck, R. G. S.; Burtoloso, A. C. B.; Kossuga, M. H. *Nat. Prod. Rep.* **2005**, *22*, 516.
2. Zhu, X.; Xu, F.; Shen, Q. *Chin. J. Chem.* **2009**, *27*, 19.
3. Durant, G. J. *Chem. Soc. Rev.* **1985**, *14*, 375.
4. Llewellyn, L. E. *Nat. Prod. Rep.* **2006**, *23*, 200.
5. Clement, J. A.; Yoder, B. J.; Kingston, D. G. I. *Mini-Rev. Org. Chem.* **2004**, *1*, 183.
6. Muri, E. M. F.; Williamson, J. S. *Mini-Rev. Med. Chem.* **2004**, *4*, 201.
7. Boncher, T.; Varghese, S.; Casero, R. A.; Woster, P. W. *Biochem. Soc. Trans.* **2007**, *35*, 356.
8. Aiello, A.; Fattorusso, E.; Menna, M.; Taglialatela-Scafati, O. In *Modern Alkaloids*; Fattorusso, E., Taglialatela-Scafati, O., Eds.; Wiley-VCH: Weinheim: Germany, 2008; pp 271–304. Chapter 10.
9. Harrison, C. N.; Campbell, P. J.; Buck, G.; Wheatley, K. *N. Engl. J. Med.* **2005**, *353*, 33.
10. Katritzky, A. R.; Rogovoy, R. F. *ARKIVOC* **2005**, 49.
11. Yong, Y. F.; Kowalski, J. A.; Lipton, M. A. *J. Org. Chem.* **1997**, *62*, 1540.
12. Okajima, N.; Okada, Y. *J. Heterocycl. Chem.* **1991**, *28*, 177.
13. Maryanoff, C. A.; Stanzione, R. C.; Plampin, J. N.; Mills, J. E. *J. Org. Chem.* **1882**, *1986*, 51.
14. Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677.
15. Ramadas, K.; Srinivasan, N. *Tetrahedron Lett.* **1995**, *36*, 2841.
16. Prabhakaran, P.; Sanjayan, G. J. *Tetrahedron Lett.* **2007**, *65*, 349.
17. Katritzky, A. R.; Khashab, N. M.; Bobrov, S. *Helv. Chim. Acta* **2005**, *88*, 1664.
18. (a) Ladziata, U.; Zhdankin, V. V. *ARKIVOC* **2006**, *ix*, 26; (b) Duschek, A.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1524; (c) Miura, T.; Nakashima, K.; Tada, N.; Itoh, A. *Chem. Commun.* **1875**, *2011*, 47.
19. (a) Deshmukh, S. S.; Huddar, S. N.; Bhalerao, D. S.; Akamanchi, K. G. *ARKIVOC* **2010**, *ii*, 118; (b) Patil, P. C.; Bhalerao, D. S.; Dangate, P. S.; Akamanchi, K. G. *Tetrahedron Lett.* **2009**, *50*, 5820; (c) Bellale, E. V.; Bhalerao, D. S.; Akamachi, K. G. *J. Org. Chem.* **2008**, *73*, 7324; (d) Deshmukh, S. S.; Huddar, S. N.; Jadhav, R. R.; Akamanchi, K. G. *Tetrahedron Lett.* **2011**, *42*, 4533.
20. (a) Chaudhari, P. S.; Dangate, P. S.; Akamanchi, K. G. *Synlett* **2010**, *20*, 3065; (b) Chaudhari, P. S.; Pathare, S. P.; Akamanchi, K. G. *J. Org. Chem.* **2012**, *77*, 3716.
21. Drouet, F.; Fontaine, P.; Masson, G.; Zhu, J. *Synthesis* **2008**, *8*, 1370.
22. *Method A: General experimental procedure for guanidines* (entries 1–10): To a stirred solution of 1,3-disubstituted thiourea (5 mmol) in acetonitrile (10 mL) was added drop wise a solution of IBX (5.5 mmol), in aqueous ammonia (10 mL of a 28–30% solution) at rt over a period of 10 min. After completion of reaction as analysed by TLC (reaction time 30 min) the mixture was extracted with (2 × 15 mL) ethyl acetate. The organic layer was washed with 10% aqueous sodium bicarbonate solution (2 × 15 mL), evaporated and chromatographed to afford the pure product.
Method B: General experimental procedure for guanidines (entries 11–18): To a stirred solution of 1,3-disubstituted thiourea (5 mmol) and amine (5 mmol) in acetonitrile (10 mL) was added drop wise a solution of IBX (5.5 mmol), in triethylamine (15 mmol) at rt over a period of 10 min. After completion of reaction as analysed by TLC (reaction time 30 min) the mixture was extracted with (2 × 15 mL) ethyl acetate. The organic layer was washed with 10% aqueous sodium bicarbonate solution (2 × 15 mL), evaporated and chromatographed to afford the pure product.
23. Vasileva, M. *Pharm. Chem. J.* **1978**, *12*, 996.
24. Chang, L. H.; Huang, Yu-Ying; Wong, F. F.; Chen, Chun-Yen; Yeh, Mou-Yung; Huang, Jiann-Jyh; Chen, Kun-Lung *Tetrahedron.* **1892**, *2010*, 66.
25. Joshua, C. P.; Rajasekharan, K. N. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1976**, *14B*, 967.
26. Partridge, M. W.; Turner, H. A. *J. Pharm. Pharmacol.* **1953**, *5*, 103.
27. Barvian, M. R.; Showalter, H. D. Hollis; Doherty, Annette M. *Tetrahedron Lett.* **1997**, *38*, 6799.
28. Martin, D.; Tittelbach, F. *J. Chem. Soc.* **1985**, *1007*.
29. Srinivasan, N.; Krishnamurthy, R. *Tetrahedron Lett.* **2001**, *42*, 343.
30. Krishnamurthy, R.; Srinivasan, N. *Tetrahedron Lett.* **1995**, *36*, 2841.