Facile Synthesis of Hydroxyformamidines by the N-Oxidation of Their Corresponding Formamidines

Mihaela Cibian, Sophie Langis-Barsetti, Garry S. Hanan*

Department of Chemistry, Université de Montréal, Montréal, QC, H3T 1J4, Canada
Fax +1(514)3432468; E-mail: garry.hanan@umontreal.ca

Received 27 September 2010

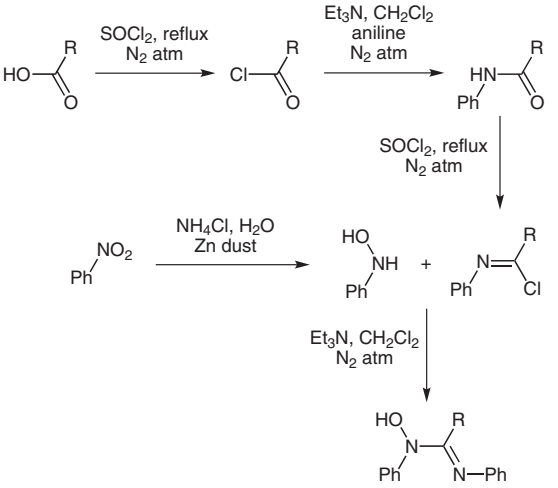
Abstract: The N-oxidation of N,N′-disubstituted amidines with MCPBA (*m*-chloroperoxibenzoic acid) affords a mild, rapid, and efficient route to the corresponding hydroxyamidines This novel synthetic route for the preparation of N,N′-disubstituted hydroxyamidines provides an attractive alternative to the classical one. It was found that the efficiency of the N-oxidation reaction, and the stability of the hydroxyformamidines are influenced by the substitution on the *N*,*N*′-diaryl rings, for example, higher yields (up to 92%) and more stable products are obtained for the compounds bearing substituents in the 2,6-positions of the phenyl rings. ^{1}H NMR and ^{13}C NMR, HRMS and/or elemental analysis were used to characterize the products.

Key words: formamidines, hydroxyformamidines, peroxides, MCPBA, N-oxidation, substituent effects

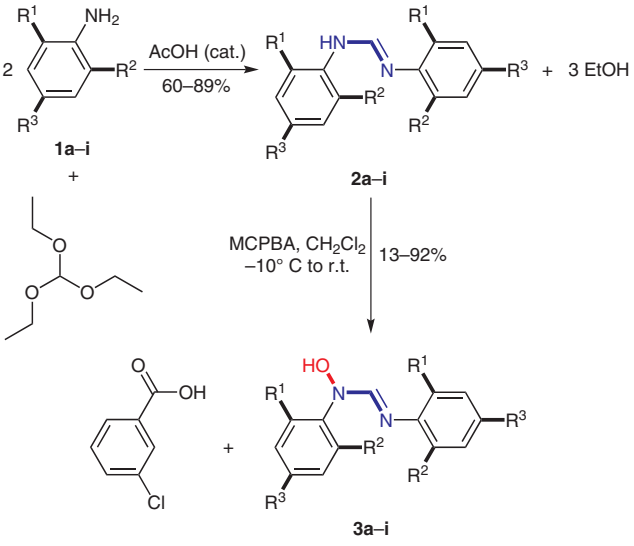
N,N′-Disubstituted hydroxyamidines/amidoximes have been studied for their biological activity (antituberculars, hypotensives), their pharmacological properties (bactericidal, fungicidal, local anaesthetics),[1] and also as precursors in the synthesis of cyclic compounds.[2] Their propensity to form stable five-membered chelate rings with metal ions was exploited for tracing metals in analytical chemistry.[3] They also show good electronic delocalization through the ligand backbone and have interesting design possibilities as far as multiple functionalization is concerned. Due to these properties, the N,N′-disubstituted hydroxyamidines/amidoximes and their mononuclear complexes are interesting candidates for incorporation into supramolecular assemblies based on coordination chemistry and hydrogen bonding. They could also present potential applications in catalysis, as recently many catalysts containing N,O-bidentate ligands have been developed.[4]

Surprisingly, none of these aspects of their chemistry have received much attention in the literature. In this context, our main objective is to synthesize and characterize *N*,*N*′-diaryl-*N*-hydroxyamidine ligands and their different metal complexes, in order to study their properties and their possible applications in the above-mentioned fields. We have developed and optimized a new route for the synthesis of the hydroxyamidines – the N-oxidation of the parent amidines with MCPBA – as a more efficient alternative to the classical one (Scheme 1). We report herein the results obtained using different functionalized formamidines **2a**–**i** as substrates (Scheme 2)

Generally, hydroxyamidines are prepared from the corresponding carboxylic acids, aniline, and hydroxyaniline,



Scheme 1 Synthesis of hydroxyamidines via a classic route[5]



Scheme 2 The two-step synthesis of hydroxyformamidines: step 1: synthesis of the formamidines **2a**–**i** from a mixture of **1a**–**i** and triethylorthoformate (2:1) with AcOH (cat.); step 2: synthesis of **3a**–**i** via the N-oxidation of formamidines **2a**–**i** with MCPBA. Compounds: **a** $R^1 = R^2 = R^3 = H$; **b** $R^1 = R^2 = H$, $R^3 = Br$; **c** $R^1 = R^2 = H$, $R^3 = OMe$; **d** $R^1 = R^2 = H$, $R^3 = Me$; **e** $R^1 = Me$, $R^2 = R^3 = H$; **f** $R^1 = i$-Pr, $R^2 = R^3 = H$; **g** $R^1 = Ph$, $R^2 = R^3 = H$; **h** $R^1 = R^2 = Me$, $R^3 = H$; **i** $R^1 = R^2 = i$-Pr, $R^3 = H$.

SYNLETT 2011, No. 3, pp 0405–0409
Advanced online publication: 19.01.2011
DOI: 10.1055/s-0030-1259329; Art ID: S06510ST

by the multistep procedure shown in Scheme 1.[5] Most of the steps are performed under an inert atmosphere and are relatively time-consuming. Also, the synthesis of hydroxyanilines can be considered as the limiting step due to their instability, leading to low overall yields.

Besides offering an alternative to their difficult classical synthesis, the new two-step preparation method for hydroxyamidines (Scheme 2) presents additional advantages: rapidity, ease of manipulations, and improved overall efficiency. It also avoids the use of chlorination agents ($SOCl_2$ or PCl_5), which are toxic and corrosive. The idea of preparing the amidines first is part of our synthetic strategy, which takes advantage of their facile synthesis, and at the same time, eliminates the use of hydroxyanilines. The proposed procedure can be applied to different amidine substrates (different substitution on the central carbon: formamidines, acetamidines, benzamidines and/or different substitution on the *N*,*N*′-diaryl rings). The specific reaction conditions and yields are reported in Table 1.

The synthesis of the parent formamidines **2a**–**i** (Scheme 2, step 1) was done in one step using commercially available starting materials. The first procedure (method A)[6] employed the classical distillation of ethanol from a mixture of aniline, triethylorthoformate (2:1), and a catalytic amount of glacial acetic acid. The second procedure was a modified microwave reaction (MW, method B)[7] of the same mixture of compounds.[15] Molecular sieves (4 Å) were used in this second case to displace the equilibrium to the products by removing the resulting ethanol. Both procedures give good yields (60–89%, Table 1), but the MW reactions proved to be particularly easy to set up and manipulate, as well as very fast and more efficient. In most cases the reaction times for MW reactions are 10–30 minutes (1 h and 2 h for the more bulky compounds **2h** and **2i**, respectively) vs. a few hours to overnight for distillations. Also, similar or better yields are generally obtained by MW reactions vs. distillation. The only exception is the compound **2i** ($R^1 = R^2 = i$-Pr, $R^3 = H$), the bulkiest in the series, which requires a longer reaction time due to steric hindrance caused by the *ortho* substituents.

The synthesis of the hydroxyformamidines **3a**–**i** by the N-oxidation of the corresponding amidines is a mild, rapid, and fairly efficient procedure. The limit of this approach is the ease with which the amidine is protonated by the *m*-chlorobenzoic acid produced during the reaction. An ion pair is formed and stabilized through H bonding.[16] Several approaches were tried in order to overcome this issue. The most successful ones proved to be: i) the use of the amidine as its own base, ii) the use of other organic bases (e.g., diisopropylethylamine), and iii) the addition of $NaHCO_3$ at the beginning of the reaction. The use of stronger inorganic bases was limited by their poor solubility in CH_2Cl_2. Biphasic reactions were also tried when using inorganic bases, but the overall yield was not improved as the stability of formamidines substrates and hydroxyformamidines products toward nucleophilic attack on the central carbon started to play an important role, which resulted in the formation of the corresponding amide as a side product. The N-oxidation reaction of amidines with MCPBA may undergo a similar mechanism as epoxidation,[17] with the formation of an intermediate of oxaziridine ring type, which could also explain the formation of arylamides as a side product of the reaction.[18]

The efficiency of the N-oxidation reaction is influenced by the substitution on the *N*,*N*′-aryl rings. The substrates with electron-donating bis-*ortho* substituents **3h**–**i** give good yields (88–92%), while moderate yields (41–59%) are obtained for the compounds bearing electron-donating mono-*ortho* substituents **3e**–**g**. The absence of *ortho* substitution (**3a**–**d**) results in poor yields (13–22%), as the compounds also decompose during purification.[19] As the yields were calculated for the isolated products, the effect of *ortho* substitution on the efficiency of the reaction could be explained by the higher stability of the *o*-substituted compounds, as the central carbon is best protected on steric grounds.[20] Electron-donating *ortho* substituents also increase the basicity of the imido-nitrogen, which has the determining role in driving the N-oxidation reaction by electronic considerations. For the very bulky *ortho*-substituted substrates, steric hindrance starts to have an influence on the N-oxidation reaction as well (**3i** vs. **3h**).

The newly synthesized hydroxyformamidines were characterized by ^{1}H NMR and ^{13}C NMR, HRMS, and/or elemental analysis (Supporting Information). A common feature in the ^{1}H NMR of the hydroxyamidines vs. their corresponding amidines is the splitting of the signals due to the asymmetry introduced in the molecule by the presence of the hydroxyl group (Supporting Information – Figure 2).

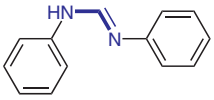
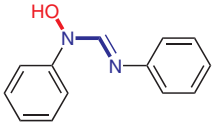
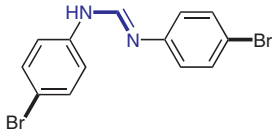
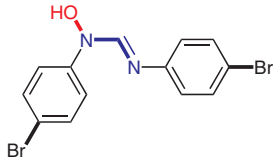
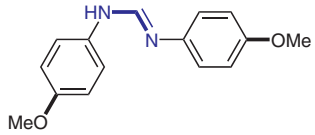
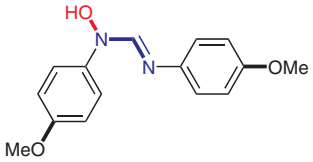
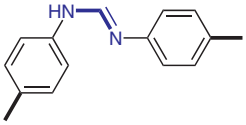
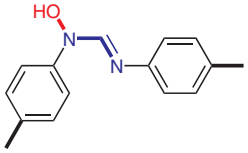
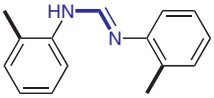
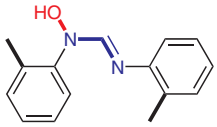
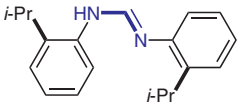
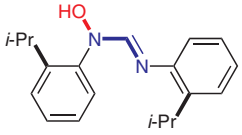
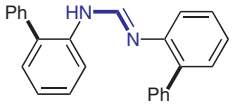
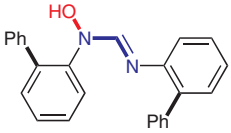
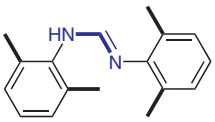
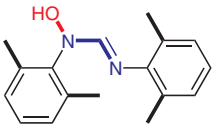
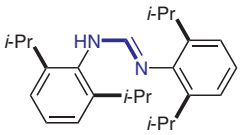
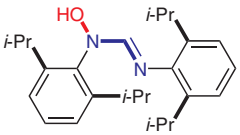
In conclusion the N-oxidation of amidines with MCPBA is a straightforward method for synthesizing their corresponding hydroxyamidines. This method was successfully used with different functionalized formamidines, the *ortho*-substituted ones giving the best results. N-Oxidation with MCPBA of functionalized acetamidines and benzamidines substrates is currently under investigation, as well as the application of the method to aliphatic and unsymmetrical formamidines.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

The authors are grateful to the Natural Sciences and Engineering Research Council (NSERC) of Canada, le Fonds québécois de la recherche sur la nature et les technologies, the Centre for Self Assembled Chemical Structures, and the Université de Montréal for financial support. M.C. thanks NSERC for a Canada Graduate Scholarship and S.L.B. thanks NSERC for an Undergraduate Student Research Award.

Table 1 Specific Conditions and Yields for the Synthesis of the Formamidines **2a–i** and Hydroxyamidines **3a–i**

Compound	Formamidines **2**	Yield (%)[a–c]	Hydroxyformamidines **3**	Yield (%)[i]
a		81 (85)		20
b		82 (–)		13
c		80 (–)		15
d		89 (–)		22
e		85[d] (80)		41[j]
f		78 (66)		58[k]
g		85[e] (81)		59[k]
h		85[f] (60)[g]		92[l]
i		66[h] (75)		88[l]

[a] Isolated yields.
[b] Yield obtained by microwave (MW) irradiation (method B), using the general procedure,[7,8] unless otherwise mentioned.
[c] Yields in brackets obtained using the general procedure (method A),[6] unless otherwise mentioned.
[d] Modified reaction time (30 min).
[e] Modified reaction time and temperature (140–160 °C, 15 min).
[f] Modified reaction time and temperature (140 °C, 1 h).
[g] Modified reaction time (1 h).
[h] Modified reaction time and temperature (140 °C, 2 h).
[i] Yields obtained by the general method,[9] unless otherwise mentioned.
[j] Modified reaction temperature (–10 °C to r.t.) and diisopropylethylamine used instead of $NaHCO_3$.
[k] Modified reaction temperature (–10 °C to r.t.).[10,11]
[l] Modified reaction time (15–30 min) and no $NaHCO_3$ used.[12,13]

References and Notes

(1) (a) Srivastava, R. M.; Brinn, I. M.; Machuca-Herrera, J. O.; Faria, H. B.; Carpenter, G. B.; Andrade, D.; Venkatesh, C. G.; de Morais, L. P. F. *J. Mol. Struct.* **1997**, *406*, 159. (b) Clement, B. *Drug Metab. Rev.* **2002**, *34*, 565.

(2) (a) Durust, N.; Akay, M. A.; Durust, Y.; Kilic, E. *Anal. Sci.* **2000**, *16*, 825. (b) Dueruest, Y.; Akcan, M.; Martiskainen, O.; Siirola, E.; Pihlaja, K. *Polyhedron* **2008**, *27*, 999.

(3) (a) Kharsan, R. S.; Mishra, R. K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1736. (b) Kharsan, R. S.; Patel, K. S.; Mishra, R. K. *Indian J. Chem., Sect. A: Inorg., Bio-inorg., Phys., Theor. Anal. Chem.* **1980**, *19*, 499. (c) Agarwal, C.; Patel, K. S.; Mishra, R. K. *Asian Environ.* **1990**, *12*, 29. (d) Deb, M. K.; Mishra, N.; Patel, K. S.; Mishra, R. K. *Analyst* **1991**, *116*, 323.

(4) (a) Desjardins, S. Y.; Cavell, K. J.; Jin, H.; Skelton, B. W.; White, A. H. *J. Organomet. Chem.* **1996**, *515*, 233. (b) Lee, A. V.; Schafer, L. L. *Eur. J. Inorg. Chem.* **2007**, 2243. (c) Batten, M. P.; Canty, A. J.; Cavell, K. J.; Ruether, T.; Skelton, B. W.; White, A. H. *Inorg. Chim. Acta* **2006**, *359*, 1710. (d) John, A.; Katiyar, V.; Pang, K.; Shaikh, M. M.; Nanavati, H.; Ghosh, P. *Polyhedron* **2007**, *26*, 4033. (e) Ding, F.; Sun, Y.; Monsaert, S.; Drozdzak, R.; Dragutan, I.; Dragutan, V.; Verpoort, F. *Curr. Org. Synth.* **2008**, *5*, 291. (f) Ledoux, N.; Allaert, B.; Schaubroeck, D.; Monsaert, S.; Drozdzak, R.; Van Der Voort, P.; Verpoort, F. *J. Organomet. Chem.* **2006**, *691*, 5482.

(5) (a) Briggs, L. H.; Cambie, R. C.; Dean, I. C.; Rutledge, P. S. *Aust. J. Chem.* **1976**, *29*, 357. (b) Krajete, A.; Steiner, G.; Kopacka, H.; Ongania, K.-H.; Wurst, K.; Kristen, M. O.; Preishuber-Pfluegl, P.; Bildstein, B. *Eur. J. Inorg. Chem.* **2004**, 1740. (c) Tian, L.; Xu, G.-Y.; Ye, Y.; Liu, L.-Z. *Synthesis* **2003**, 1329. (d) Kamm, O.; Marvel, C. S. *Org. Synth.* **1941**, *1*, 445.

(6) **General Procedure[14] – Method A**
The EtOH was distilled from a mixture of aniline, triethylorthoformate (2:1), and a catalytic amount of glacial AcOH at 120–160 °C. The reactions times ranges from 1 h for compound **2h** to overnight. Solids were formed which were further purified as described in ref. 7.

(7) **General Procedure[15] – Method B**
A mixture of aniline, triethylorthoformate (2:1), and a catalytic amount of glacial AcOH (MS 4 Å were also added) was microwave activated at 130 °C for 10 min. At the end of the reactions, oily solids were obtained, which were taken in CH_2Cl_2 (**2a–e** and **2g–i**) or hexane(**2f**). The solvents were evaporated under vacuum to afford solids or oils that were further purified by recrystallization in CH_2Cl_2–hexane (1:1; **2a–e**,**g**), boiling hexane (**2f**,**i**) or by trituration/sonication with hexane(**2h**). Colorless solids were obtained in all cases.[8]

(8) Except for compound **2f**, all of the formamidines are known compounds, and their characterization is similar to reported data.[14]
Compound **2f**: Compound **1f** (7.5 mL, 51 mmol, 2 equiv), triethylorthoformate (4.0 mL, 25 mmol, 1 equiv) and a catalytic amount of glacial AcOH (0.30 mL, 5.1 mmol, 0.2 equiv) were reacted following the general procedure described in ref. 7. After purification by trituration with cold pentane and recrystallization in hot hexane, colorless crystals were obtained; yield 5.56 g, 78%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (s, 1 H, NHC*H*=N), 7.29 (d, *J* = 8 Hz, 2 H, C_6H_4), 7.20–7.08 (m, 4 H, C_6H_4), 7.02 (d, *J* = 8 Hz, 2 H, C_6H_4), 3.29 [sept, *J* = 7 Hz, 2 H, –C*H*$(CH_3)_2$], 1.26 [d, *J* = 7 Hz, 12 H, CH(C*H*$_3)_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): d = 148.6, 139.5, 126.7, 125.9, 124.0, 118.7, 27.73, 23.21 ppm. Anal. Calcd (%) for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.62; H, 9.27; N, 10.17.

(9) **General Procedure – N-Oxidation of Amidines with MCPBA**
A solution of MCPBA (1 equiv) in CH_2Cl_2 was added dropwise by addition funnel to a solution of amidine (1 equiv) and $NaHCO_3$ (1.0–1.5 equiv) in the same solvent, at 0 °C (ice bath) to r.t. The reaction mixture was stirred for other 30–60 min at r.t. and was washed with an aq solution of K_2CO_3 (5%; 2 × 25 mL). The combined organic fractions were dried over anhyd $MgSO_4$ or Na_2SO_4 and filtered. The solvent was removed by evaporation, to afford solids or oils that were further purified by recrystallization or flash chromatography on silica gel.

(10) Compound **3f**: Compound **2f** (2.0 g, 7.1 mmol, 1 equiv) and $NaHCO_3$ (0.61 g, 7.1 mmol, 1 equiv) in CH_2Cl_2 (50 mL) and MCPBA (1.6 g, 7.1 mmol, 1 equiv) in CH_2Cl_2 (50 mL) were reacted following the general procedure described in ref. 9, and modified as specified in Table 1 (footnote k). After purification by flash chromatography on silica gel [gradient of eluants: hexane–EtOAc (2:8), EtOAc–MeOH (9:1), CH_2Cl_2 100%] and recrystallization in hot hexane, a colorless solid was obtained; yield 0.92 g, 58%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (s, 1 H, NHC*H*=N), 7.45–7.39 (m, 2 H, C_6H_4), 7.34–7.31 (m, 2 H, C_6H_4), 7.28–7.08 (m, 3 H, C_6H_4), 6.96 (d, *J* = 8 Hz, 1 H, C_6H_4), 3.67 (br s, OH), 3.40 [sept, J = 7 Hz, 1 H, C*H*$(CH_3)_2$], 3.27 [sept, *J* = 7 Hz, 1 H, C*H*$(CH_3)_2$], 1.33–1.29 [m, 12 H, CH(C*H*$_3)_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.0, 142.1, 137.4, 136.2, 135.4, 130.1, 127.1, 127.0, 126.7, 126.6, 125.5, 124.3, 116.2, 28.12, 27.61, 24.27 (2 C), 23.08 (2 C) ppm. MS (ESI-HRMS, CH_2Cl_2): *m/z* $[M + H]^+$ calcd for $C_{19}H_{25}N_2O$: 297.1961; found: 297.1971. Anal. calcd (%) for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.80; H, 8.23; N, 9.40.

(11) Compound **3g**: Compound **2g** (1.5 g, 4.3 mmol, 1 equiv) and $NaHCO_3$ (0.38 g, 4.3 mmol, 1 equiv) in CH_2Cl_2 (50 mL) and MCPBA (0.96 g, 4.3 mmol, 1 equiv) in CH_2Cl_2 (50 mL) were reacted following the general procedure described in ref. 9, and modified as specified in Table 1 (footnote k). After purification by flash chromatography on silica gel [gradient of eluants: hexane–EtOAc (2:8), EtOAc–MeOH (9:1), CH_2Cl_2 100%] and recrystallization in CH_2Cl_2–hexane (1:1), a colorless solid was obtained; yield 0.93 g, 59%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.78 (m, 1 H, C_6H_4), 7.55–7.32 (m, 14 H, C_6H_5, C_6H_4, NHC*H*=N), 7.21 (dd, *J* = 7, 2 Hz, 1 H, C_6H_4), 7.11 (td, *J* = 8, 2 Hz, 1 H, C_6H_4), 7.05 (td, *J* = 7, 1 Hz, 1 H, C_6H_4), 6.17 (d, *J* = 8 Hz, 1 H, C_6H_4), 3.67 (br s, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.0, 138.2, 137.5, 136.9, 135.7, 135.2, 131.7, 131.40, 130.7, 129.4 (2 C), 129.24 (2 C), 129.19 (2 C), 129.1 (2 C), 128.8, 128.6, 128.5 (2 C), 128.3, 128.1, 126.1, 123.7, 115.4 ppm. MS (ESI-HRMS, CH_2Cl_2): *m/z* $[M + H]^+$ $C_{25}H_{21}N_2O$ calcd for: 365.1648; found: 365.1655. Anal. Calcd (%) for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69. Found: C, 82.33; H, 5.52; N, 7.73.

(12) Compound **3h**: Compound **2h** (1.0 g, 4.0 mmol, 1 equiv) in CH_2Cl_2 (20 mL) and MCPBA (0.89 g, 4.0 mmol, 1 equiv) in CH_2Cl_2 (20 mL) were reacted following the general procedure described in ref. 9, and modified as specified in Table 1 (footnote l). After recrystallization in CH_2Cl_2–hexane (1:1) at –10 °C, a colorless solid was obtained; yield 0.98 g, 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (s, 1 H, NHC*H*=N), 7.20 (t, *J* = 8 Hz, 1 H, C_6H_3), 7.15–7.06 (m, 5 H, C_6H_3), 3.51 (br s, OH), 2.38 (d, *J* = 3 Hz, 12 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.1, 140.4, 135.8, 134.8 (2 C), 133.4, 129.3, 129.0 (2 C), 128.6 (2 C), 126.7, 18.81 (2 C), 17.26 (2 C) ppm. ESI-MS (CH_2Cl_2): *m/z* (%) = 269.2

(100) $[M + H]^+$. Anal. calcd (%) for $(C_{17}H_{20}N_2O)_2CH_2Cl_2$: C, 67.62; H, 6.81; N, 9.01. Found: C, 68.19; H, 6.81; N, 9.00.

(13) Compound **3i**: Compound **2i** (1.5 g, 4.1 mmol, 1 equiv) in CH_2Cl_2 (10 mL) and MCPBA (0.9 g, 4.1 mmol) in CH_2Cl_2 (40 mL) were reacted following the general procedure described in ref. 9, and modified as specified in Table 1 (footnote l). The green-white solid obtained after solvent evaporation was taken in EtOH, as the formamidine **2i** has low solubility in this solvent. After filtration, EtOH evaporation, and drying under vacuum, a pale-yellow solid was obtained; yield 1.4 g, 88%; mp 165–167 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.32 (m, 1 H, C_6H_3), 7.32–7.26 (m, 1 H, C_6H_3), 7.25–7.21 (m, 2 H, C_6H_3 and NHCH=N), 7.20 (d, *J* = 2 Hz, 2 H, C_6H_3), 7.18 (d, *J* = 1 Hz, 1 H, C_6H_3), 3.37 [sept, *J* = 7 Hz, 2 H, C*H*$(CH_3)_2$], 3.25 [sept, *J* = 7 Hz, 2 H, C*H*$(CH_3)_2$], 1.37 [d, *J* = 7 Hz, 6 H, CH(C*H*$_3)_2$], 1.23 [d, *J* = 7 Hz, 12 H, CH(C*H*$_3)_2$], 1.18 [d, *J* = 7 Hz, 6 H, CH(C*H*$_3)_2$]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.6 (2 C), 146.0 (2 C), 141.7, 133.2, 132.5, 130.6, 128.8 (2 C), 124.8 (2 C), 124.7 (2 C), 29.28 (2 C) 29.10 (2 C), 25.98 (2 C), 25.05 (2 C), 24.87 (4 C). ESI-MS (CH_2Cl_2): *m/z* (%) = 381.3 (100) $[M + H]^+$. Anal. Calcd (%) for $C_{25}H_{36}N_2O$: C, 78.90; H, 9.53; N, 7.36. Found: C, 78.79; H, 9.43; N, 7.21.

(14) (a) Hirano, K.; Urban, S.; Wang, C.; Glorius, F. *Org. Lett.* **2009**, *11*, 1019. (b) Krahulic, K. E.; Enright, G. D.; Parvez, M.; Roesler, R. *J. Am. Chem. Soc.* **2005**, *127*, 4142. (c) Roberts, R. M. *J. Org. Chem.* **1949**, *14*, 277. (d) Cole, M. L.; Deacon, G. B.; Forsyth, C. M.; Konstas, K.; Junk, P. C. *Dalton Trans.* **2006**, *27*, 3360. (e) Cole, M. L.; Junk, P. C.; Louis, L. M. *Dalton Trans.* **2002**, *20*, 3906.

(15) Harding, P.; Harding, D. J.; Adams, H.; Youngme, S. *Synth. Commun.* **2007**, *37*, 2655.

(16) Kraft, A.; Peters, L.; Powell, H. R. *Tetrahedron* **2002**, *58*, 3499.

(17) Bartlett, P. D. *Rec. Chem. Prog.* **1950**, *11*, 47.

(18) Srivastava, R.; Pereira, M.; Faustino, W.; Coutinho, K.; dos Anjos, J.; de Melo, S. *Monatsh. Chem./Chem. Monthly* **2009**, *140*, 1319.

(19) For **3a**–**d** pure products are only obtained by recrystallization as decomposition occurs on silica gel chromatography column. Attempts to maximize the yield by repeated evaporation–recrystallization were unsuccessful as the decomposition product (amide) is observed after 1–2 cycles.

(20) Also observed by ^{1}H NMR, as the shielding of formamidine H decreases in the series **3i**, **3h**, **3g**, **3f**, **3e**, **3c**, **3d**, **3b**, **3a** (see Supporting Information – Figure 1).