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'One-flask' transformation of isocyanates and isothiocyanates to guanidines hydrochloride by using sodium bis(trimethylsilyl)amide

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ABSTRACT

A 'one-flask' synthesis of guanidines was developed by reacting isocyanates and isothiocyanates with sodium bis(trimethylsilyl)amide followed by addition of primary or secondary amines with a catalytic amount of $AlCl_3$. The desired guanidines were obtained in good yields and the reaction was applicable to aliphatic and aromatic substrates. A plausible mechanism was proposed through the generation of cyanamide anion from isocyanates or isothiocyanates with sodium bis(trimethylsilyl)amide. Addition of amines and catalytic amount of $AlCl_3$ smoothly converted the cyanamides to the desired guanidines.

1. Introduction

Guanidine group is found in many natural occurring substances isolated from algae, sponges, and micro-organisms[1] and is responsible for the biological activity of many pharmaceutically active compounds.[2–4] Guanidine derivatives also exhibit a variety of coordination modes and a range of donor properties. Therefore they can be used as the efficient ligands for the construction of various organometallic catalysts from a wide range of metal ions, especially early transition metals and lanthanides.[5–11]

The conventional method for the preparation of guanidines utilize carbamoyl isothiocyanates (Cbz–N═C═S)[12,13] or *S*-alkylisothiouronium salts[14] as the starting material to react with amines or ammonia. The disadvantage for these methods was the generation of noxious sulfur species and methyl mercaptan by-products.[14] Other commonly alternative for the production of *N*,*N*′-disubstituted and *N*,*N*′-diprotected guanidines are the reaction of amines or ammonia derivatives with an electrophilic guanylating reagent[15] including cyanamides,[16] carboiimides,[17] chloroformamidines, di(imidazole-1-yl)methanimine,[18] or isothiourea,[19] dichloroisocyamides in solution-phase[14] or solid-phase[20] synthesis. The newly established methods are reported recently for the synthesis of guanidines by hydroamination of carbodiimides with metal complex catalysts[21] or coordinate rare earth metal amides.[22] Some of those methods, however, could not provide the satisfactory process since the starting materials are corrosive, toxic, and moisture sensitive. The reactions also have drawbacks such as low yields, long reaction times, harsh reaction conditions, and the difficulties to be work up.

Sodium bis(trimethylsilyl)amide [$NaN(SiMe_3)_2$] is a commercially available strong hindered base widely used in organic synthetic chemistry.[23–28] It is also a good nucleophile at elevated temperature and can be used for functional group transformation, including the selectively mono-*O*-demethylation of arenes,[29] the conversion of aromatic esters[30] or aldehydes[31] to nitriles. In our previous work, we also find that $NaN(SiMe_3)_2$ acts as a deoxygenation and desulfurization agent to convert isocyanates and isothiocyanates to cyanamides.[32,33] In this paper, we expanded the reaction to 'one-flask' synthesis of guanidines hydrochloride. Reaction of $NaN(SiMe_3)_2$ with isocyanates or isothiocyanates followed by addition of primary or secondary amines with catalytic amount of $AlCl_3$ in one flask provided the corresponding guanidines in good yields. This new reaction can be applied in the transformation of

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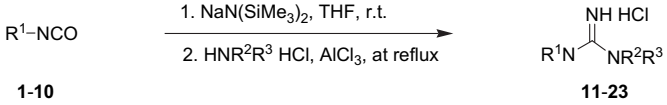
aliphatic, cyclohexyl, and aromatic isocyanates or isothiocyanates and the reaction mechanism involved 1,2-elimination.[34]

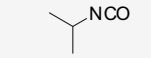
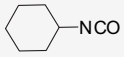
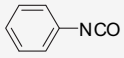
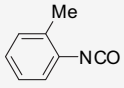
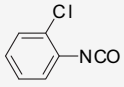
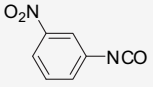
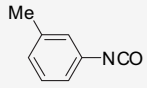
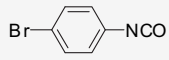
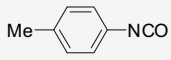
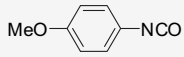
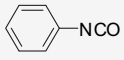
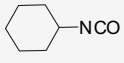
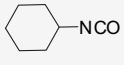
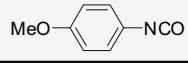
2. Result and discussion

Scheme 1 illustrated the typical reaction condition for the one-flask synthesis of guanidines. The isocyanates **1**–**10**, whose structures were shown in Table 1, reacted with 1.2 equiv of $NaN(SiMe_3)_2$ in THF at room temperature for 30–60 min. The reaction was expected to generate the cyanamide anions (Ar–N^-–C≡N).[32] After the isocyanates were fully consumed, primary or secondary amines hydrochloride were subsequently added to the reaction mixture with a catalytic amount $AlCl_3$ (10 mol %). The reaction was heated at reflux for 6–12 h to give the desired guanidines hydrochloride **11**–**23** in solid form (see Table 1 and Chart 1).



Scheme 1.

Table 1
Transformations of isocyanates to the corresponding guanidines

Entry	Isocyanates R^1NCO		Amine HCl Salts	Guanidines[a]	Yield (%)[b]
1		**1**	$NH_2Ph·HCl$	**11**	77
2		**2**	$NH_2Ph·HCl$	**12**	76
3		**3**	$NH_2Ph·HCl$	**13**	70
4		**4**	$NH_2Ph·HCl$	**14**	71
5		**5**	$NH_2Ph·HCl$	**15**	53
6		**6**	$NH_2Ph·HCl$	**16**	62
7		**7**	$NH_2Ph·HCl$	**17**	83
8		**8**	$NH_2Ph·HCl$	**18**	66
9		**9**	$NH_2Ph·HCl$	**19**	76
10		**10**	$NH_2Ph·HCl$	**20**	66
11		**3**	*p*-Me–$PhNH_2·HCl$	**19**	64
12		**2**	*p*-CF_3–$PhNH_2·HCl$	**21**	86
13		**2**	*p*-$PhOCH_2$–$PhNH_2·HCl$	**22**	84
14		**10**	$NHMe_2·HCl$	**23**	57

[a] Compounds **11**–**16**, **18**–**20**, and **23** were reported previously,[34–39] our spectroscopic data (**11**–**14**,[34–37] **18**,[38] **19**,[37] and **23**[39]) are consistent with those of an authentic sample or published data in the literature.

[b] $AlCl_3$ (10% w/w) was used as the Lewis acid catalyst.

For the use of aliphatic isocyanate **1** and **2** as the substrates, the reaction provided the desired guanidines **11** and **12** (Chart 1) in 77% and 76% yields, respectively, by use of aniline hydrochloride ($PhNH_2·HCl$, entry 1 and 2 in Table 1) as the reaction amine. For aromatic isocyanates **3**–**10** bearing various substituents including CH_3, Br, Cl, NO_2, and OCH_3 at *ortho* or *meta* or *para* position to the isocyanato group, the reaction also gave the corresponding guanidines **13**–**20** in good yields (53–83%, see the entries 3–10 in Table 1). Compounds **11**–**20** were fully characterized by spectroscopic methods and consistent with the literature data.[18,35–39] Served as an example, compound **13** possessed a characteristic peak at 154.12 ppm, which represented the ^{13}C in PhNH–C(=NH)–NHPh·HCl salt. The IR absorptions of **13** showed peaks at 1660 cm^{-1} for the stretching of the –C=NH group and at 3263 cm^{-1} for the stretching of the –NH group. Results in Table 1 demonstrated that various aliphatic and aromatic isocyanates were suitable for the one-flask transformation.

We then investigated the effect of substituents on the phenyl ring of the amines on the reactivity of the reaction. Use of *p*-toluidine hydrochloride, 4-(trifluoromethyl)aniline hydrochloride, and 4-benzyloxyaniline hydrochloride to react with the cyanamide anion generated from isocyanate **3** and **2** provided the corresponding guanidines **19**, **21**, and **22** in good yields (64–86%, see entry 11–13 in Table 1). The yields were similar with that from the use of simple aniline. Applying 4-methoxyphenyl isocyanate **10** under the same condition with the secondary amine dimethylamine hydrochloride (see entry 14 of Table 1) also afforded guanidine **23** in 57% yield.

For the investigation of Lewis acid catalyst, we chose phenyl isocyanate **3** as the model to seek for the best reaction condition and amount of the catalyst for the 'one-flask' transformation. When compound **3** completely consumed in the reaction, the reaction mixture was allowed to react with aniline hydrochloride with various Lewis acid catalysts,[40] including aluminum chloride ($AlCl_3$),[41] boron trifluoride diethyl etherate ($BF_3·OEt_2$), ceric ammonium nitrate (CAN),[42] palladium chloride ($PdCl_2$), palladium acetylacetonate ($Pd(acac)_2$), hexafluoroisopropanol ($(CF_3)_2CHOH$),[43] titanium chloride ($TiCl_4$), and tributylbrorane.[44] Guanidine **13** was isolated and the results were shown in Table 2. We found that the use of 10 mol % of aluminum chloride and ceric ammonium nitrate (CAN) gave compound **13** in better isolated yields (70% and 62%, see the Table 2). However, increasing the amount $AlCl_3$ catalyst added to the reaction from 10 to 40 mol % dramatically reduced the yield of the product to 27% (entry 3). Using more $AlCl_3$ would decrease the yields of **3** (see entries 3–6 in Table 2).

In our previous research, we found isothiocyanates possess the similar reactivity with isocyanates and can also react with $NaN(SiMe_3)_2$ to produce cyanamides.[41] Therefore we applied the reaction to convert isothiocyanate to guanidine (see Scheme 2). First, the reaction was applied to *t*-butyl isothiocyanate **24**, phenyl isothiocyanate **25**, and aromatic isothiocyanates **26**–**28** with methyl group at the *ortho*, *meta*, *para* position (see entry 1–5 in Table 3). They were treated with 1.2 equiv of $NaN(SiMe_3)_2$ followed by aniline hydrochloride ($PhNH_2·HCl$) and catalytic amount $AlCl_3$ (10 mol %). The corresponding guanidine products **13**, **14**, **17**, **19**, and **31** were also obtained in 62–86% yields.

When *p*-toluidine hydrochloride (*p*-Me–$PhNH_2·HCl$) and catalytic amount of $AlCl_3$ reacted with phenyl isothiocyanate **25** and 1-naphthyl isothiocyanate **29** with $NaN(SiMe_3)_2$, the reaction also provided the corresponding guanidine **19** and **32** in 82% and 68% yields, respectively (see the entries 6 and 7 of Table 3). Application of the same procedure by using *n*-propylamine hydrochloride (*n*-$PrNH_2·HCl$) and 1,4-phenylene diamine hydrochloride for phenyl isothiocyanate **25**, 3-methylphenyl isothiocyanate **27**, and 4-methoxyphenyl isothiocyanate **30** also gave the similar results (44–84%, see the entries 8–10 of Table 3). All the desired

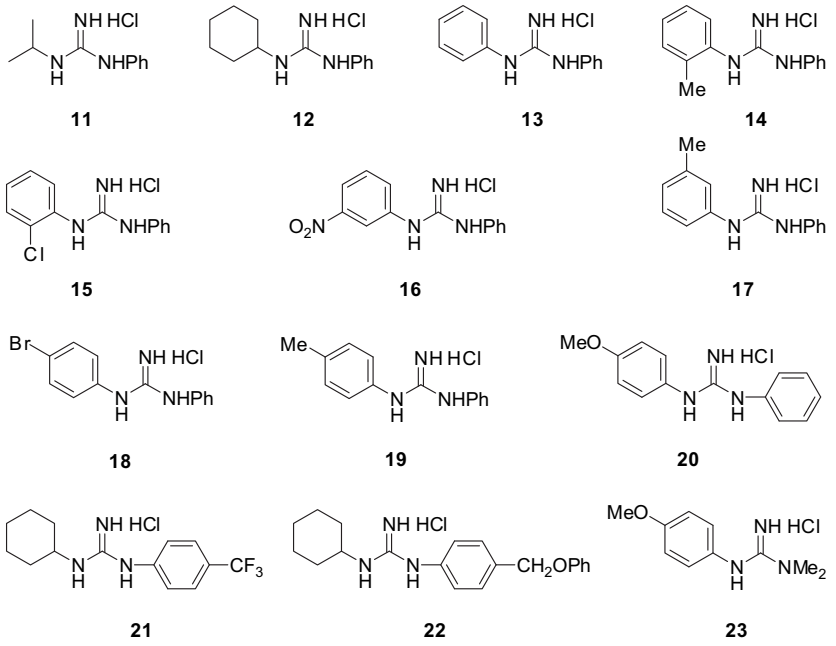
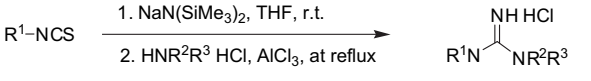


Chart 1.

Table 2
The study of Lewis Acid catalyzed transformations of phenyl isocyanate to *N*,*N*′-diphenyl guanidine

Entry	Lewis Acid		*N*,*N*′-Diphenyl Guanidine **13** Yield (%)
	Catalyst	Amount[a] (w/w %)	
1	Without catalyst	—	16
2	Aluminum Chloride $AlCl_3$	10%	70
3	Aluminum Chloride $AlCl_3$	40%	27
4	Aluminum Chloride $AlCl_3$	80%	21
5	Aluminum Chloride $AlCl_3$	120%	12
6	Aluminum Chloride $AlCl_3$	200%	<5
7	Boron Trifluoride diethyl etherate $BF_3{\cdot}OEt_2$	10%	3
8	Ceric Ammonium Nitrate (CAN)	10%	62
9	Palladium Chloride $PdCl_2$	10%	14
10	Palladium Acetylacetonate $Pd(acac)_2$	10%	—
11	Hexafluoroisopropanol $(CF_3)_2CHOH$	10%	25
12	Titanium Chloride $TiCl_4$	10%	22
13	Tributylborane	10%	23

[a] Based on the weight of phenyl isocyanate.

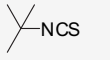
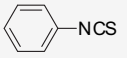
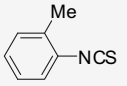
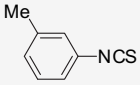
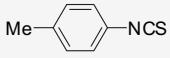
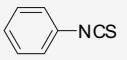
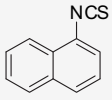
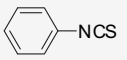
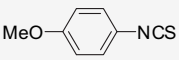
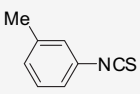
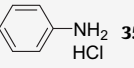


Scheme 2.

N,*N*′-disubstituted guanidines **13**, **14**, **17**, **19**, and **31**–**35** were fully characterized by spectroscopic methods (see Chart 2).

A plausible mechanism for the conversion of isocyanate or isothiocyanate to *N*,*N*′-disubstituted guanidine hydrochloride was depicted in Scheme 3. $NaN(SiMe_3)_2$ underwent nucleophilic addition to **36**, and the deoxygenation and desulfurization via intramolecular 1,2-elimination took place to give cyanamide anion **37** (R^1–N^-–C≡N) and $(Me_3Si)_2O$ or $(Me_3Si)_2S$ as by-products.[31,32,45] When primary or secondary amine hydrochloride with catalytic amount $AlCl_3$ were added, sequential protonation and hydroamination occurred to provide the final *N*,*N*′-disubstituted guanidine hydrochloride **39**. The reactivity difference between isocyanates and isothiocyanates lay on the rate for the formation of cyanamide anion **37** (R^1–N^-–C≡N). Based on our previous studies, the isothiocyanates are more active than isocyanates to react with $NaN(SiMe_3)_2$ to generate cyanamides. In this one-flask transformation, we observed the quicker

Table 3
Transformations of isothiocyanates to the corresponding guanidines

Entry	Isothiocyanates R1NCS		Amine HCl Salts		Guanidines[a]	Yield (%)
1		**24**	$NH_2Ph{\cdot}HCl$		**31**	74
2		**25**	$NH_2Ph{\cdot}HCl$		**13**	85
3		**26**	$NH_2Ph{\cdot}HCl$		**14**	62
4		**27**	$NH_2Ph{\cdot}HCl$		**17**	86
5		**28**	$NH_2Ph{\cdot}HCl$		**19**	77
6		**25**	*p*-Me–$PhNH_2{\cdot}HCl$		**19**	82
7		**29**	*p*-Me–$PhNH_2{\cdot}HCl$		**32**	68
8		**25**	*n*-$PrNH_2{\cdot}HCl$		**33**	84
9		**30**	*n*-$PrNH_2{\cdot}HCl$		**34**	63
10		**27**			**35**	44

[a] Compounds **13**–**14**, **19**, **31**, and **33** were reported previously,[36–39] our spectroscopic data (**13**,[36] **14**,[37] **19**,[37] **23**,[39] **31**,[34] and **33**[34]) are consistent with those of an authentic sample or published data in the literature.

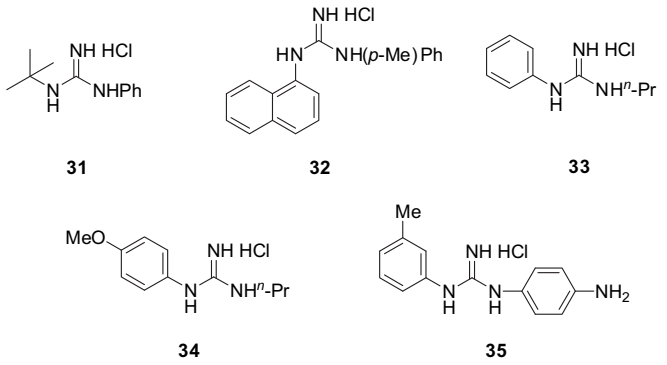
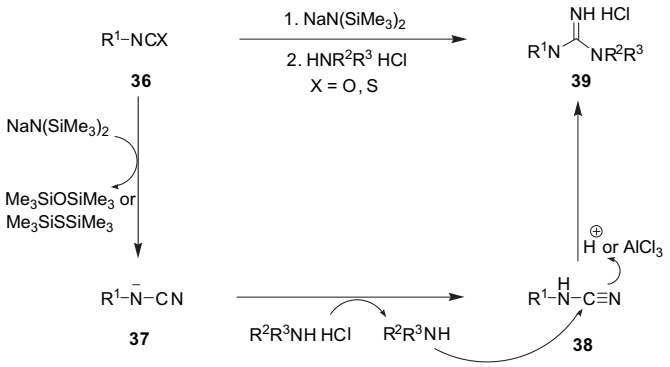


Chart 2.

disappearance of the isothiocyanates than isocyanates before the addition of amines and $AlCl_3$ in the transformation. The reaction proceeded faster by use of isothiocyanates as the reactants, though no significant differences in the yields were observed between the two substrates.



Scheme 3.

3. Conclusion

In conclusion, we have successfully developed a new 'one-flask' method for the synthesis of *N*,*N*′-disubstituted guanidine hydrochloride by reacting isocyanates and isothiocyanates with NaN(SiMe$_3$)$_2$ followed by addition of primary or secondary amines with $AlCl_3$ as the catalyst. This methodology can be applied to aliphatic or aromatic isocyanates and isothiocyanates, and the resultant guanidines could be obtained in good yields. A plausible mechanism was proposed for the transformation through cyanamide as the key intermediate.

4. Experimental section

4.1. General procedure for the 'one-flask' formation of guanidines hydrochloride from isocyanates or isothiocyanates

Isocyanates or isothiocyanates (1.0 mmol, 1.0 equiv) and sodium bis(trimethylsilyl)amide (2.0 M in THF, 1.5 or 1.2 mmol, 1.2 equiv) were added into a two-necked flask at room temperature under nitrogen gas for 1 h. After isocyanates or isothiocyanates were completely consumed and converted to the cyanamide anion intermediates, various aniline hydrochloride (2.2 mmol, 2.2 equiv) with aluminum chloride catalyst ($AlCl_3$, (0.1 mmol, 0.1 equiv, 10% w/w)) was added toward the reaction mixture and heated at reflux for 6–12 h under N_2. After the reaction was completed, the reaction mixture was filtrated, washed with CH_2Cl_2 (20 mL×2), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10% MeOH in CH_2Cl_2 as eluent) to give the corresponding guanidine hydrochloride products in 53–86%.

*4.1.1. N-Isopropyl-N′-phenyl guanidine hydrochloride (**11**)*[35]. White solid; mp 126–127 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13 (d, 6H, J=6.32 Hz, 2×CH_3), 4.08 (m, 1H, CH), 7.06 (d, 2H, J=7.42 Hz, ArH), 7.18–7.20 (m, 1H, ArH), 7.24–7.29 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.37, 44.45, 125.48, 127.54, 129.83, 133.94, 154.09; IR (diffuse reflectance) 3265 (m), 3092 (m), 2971 (m), 1659 (s), 1625 (s), 1588 (s), 1495 (m), 1457 (w), 1387 (w), 1324 (w), 1257 (w), 1167 (m), 1129 (m), 1050 (w), 759 (m), 694 (m) cm^{-1}; MS (ESI) *m*/*z*: 178 (M^++H).

*4.1.2. N-Cyclohexyl-N′-phenyl guanidine hydrochloride (**12**)*[18]. Yellow solid; mp 190–191 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14–1.52 (m, 6H, 3×CH_2), 1.64–1.69 (m, 2H, CH_2), 1.93–1.96 (m, 2H, CH_2), 3.84 (m, 1H, CH), 7.17 (d, 2H, J=7.07 Hz, ArH), 7.24–7.28 (m, 1H, ArH), 7.33–7.38 (m, 2H, ArH), 9.82 (br, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.05, 25.05, 32.59, 50.88, 125.71, 127.73, 130.07, 134.26, 154.27; IR (diffuse reflectance) 3263 (m), 3097 (m), 2930 (m), 2852 (w), 1660 (s), 1632 (s), 1589 (m), 1505 (w), 1494 (w), 1455 (w), 1361 (w), 1259 (w), 1128 (m), 1025 (w), 895 (w), 761 (m), 693 (s) cm^{-1}; MS (ESI) *m*/*z*: 218 (M^++H).

*4.1.3. N,N′-Diphenyl guanidine hydrochloride (**13**)*[36]. White solid; mp 134–135 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.22–7.31 (m, 6H, ArH), 7.39–7.44 (m, 4H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 124.22, 126.51, 130.00, 136.47, 154.12; IR (diffuse reflectance) 3263 (w), 3099 (m), 2931 (m), 1660 (s), 1633 (s), 1494 (m), 1452 (m), 1362 (m), 1257 (m), 1130 (m), 1026 (w), 895 (w), 762 (m), 694 (s) cm^{-1}; MS (ESI) *m*/*z*: 212 (M^++H).

*4.1.4. N-Phenyl-N′-o-tolyl guanidine hydrochloride (**14**)*[37]. Yellow solid; mp 131–132 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.25 (s, 3H, CH_3), 7.11–7.22 (m, 7H, ArH), 7.27–7.32 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.92, 125.68, 127.19, 127.52, 128.25, 129.10, 130.17, 131.75, 131.79, 133.47, 135.76, 155.01; IR (diffuse reflectance) 3154 (m), 1631 (m), 1585 (m), 1492 (m), 1383 (s), 1231 (w), 1192 (w), 1117 (w), 824 (m), 754 (m), 695 (w), 496 (w) cm^{-1}; MS (ESI) *m*/*z*: 226 (M^++H).

*4.1.5. N-Phenyl-N′-(2-chloro-phenyl) guanidine hydrochloride (**15**).* Yellow solid; mp 128–129 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.04–7.09 (m, 6H, ArH), 7.18–7.21 (m, 2H, ArH), 7.25 (d, 1H, J=6.76 Hz, ArH), 7.44 (br s, 3H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 124.38, 126.84, 127.56, 127.77, 128.37, 129.45, 130.19, 130.37, 132.72, 134.50, 153.96; IR (diffuse reflectance) 3147 (m), 1631 (m), 1485 (m), 1444 (m), 1372 (m), 1294 (w), 1233 (w), 1130 (w), 1063 (m), 1033 (w), 755 (m), 734 (m), 696 (m), 499 cm^{-1}; MS (ESI) *m*/*z*: 248 (M^++3), 246 (M^++H); Anal. Calcd for $C_{13}H_{13}Cl_2N_3$: C, 55.34; H, 4.64; N, 14.89. Found: C, 55.38; H, 4.67; N, 14.92.

*4.1.6. N-(3-Nitro-phenyl)-N′-phenyl guanidine hydrochloride (**16**).* Yellow solid; mp 138–139 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.59 (br s, 3H, NH), 6.96–7.04 (m, 3H, ArH), 7.14–7.31 (m, 4H, ArH), 7.67–7.69 (m, 1H, ArH), 7.74 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 117.34, 117.70, 123.05, 124.74, 129.07, 129.40, 129.88, 139.28, 145.39, 148.61, 150.80; IR (diffuse reflectance) 3456 (w), 3311 (w), 3090 (w), 2923 (w), 2852 (w), 1635 (m), 1583 (m), 1515 (s), 1444 (m), 1343 (s), 1301 (m), 1236 (m), 1077 (w), 995 (w), 889 (w), 798 (w), 737 (m), 692 (m) cm^{-1}; MS (ESI) *m*/*z*: 257 (M^++H); Anal. Calcd for $C_{13}H_{13}Cl\ N_4O_2$: C, 53.34; H, 4.48; N, 19.14. Found: C, 53.38; H, 4.51; N, 19.10.

*4.1.7. N-Phenyl-N′-m-tolyl guanidine hydrochloride (**17**).* Yellow solid; mp 182–184 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.24 (s, 3H, CH_3), 6.30 (br s, 3H, NH), 6.93–7.00 (m, 3H, ArH), 7.13–7.20 (m, 4H, ArH), 7.26–7.31 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.11, 121.96,

125.07, 125.68, 127.52, 128.35, 129.60, 129.81, 133.74, 133.99, 140.06, 154.31; IR (diffuse reflectance) 3270 (m), 2916 (m), 1635 (s), 1597 (s), 1577 (s), 1497 (m), 1459 (m), 1379 (s), 1307 (s), 1225 (s), 823 (m), 753 (s), 735 (m), 690 (m) cm^{-1}; MS (ESI) *m*/*z*: 226 (M^++H); HRMS (ESI) calcd for $C_{14}H_{16}N_3$ ($M+H^+$) 226.1344, found 226.1345.

*4.1.8. N-(4-Bromo-phenyl)-N′-phenyl guanidine hydrochloride (**18**)*[38]. White solid; mp 175–176 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.80 (br s, 1H, NH), 7.11 (d, 2H, *J*=6.69 Hz, ArH), 7.22–7.35 (m, 5H, ArH), 7.44 (d, 2H, *J*=6.51. Hz, ArH), 9.84 (br s, 1H, NH), 10.08 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 120.64, 124.80, 126.21, 127.56, 129.78, 132.68, 132.98, 133.54, 154.05; IR (diffuse reflectance) 3439 (m), 3164 (m), 2934 (m), 1631 (m), 1486 (m), 1382 (s), 1231 (m), 1071 (w), 1011 (w), 824 (m), 754 (w), 695 (w), 500 (w) cm^{-1}; MS (ESI) *m*/*z*: 292 (M^++3), 290 (M^++H).

*4.1.9. N-Phenyl-N′-p-tolyl guanidine hydrochloride (**19**)*[37]. Yellow solid; mp 129–130 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.31 (s, 3H, CH_3), 7.18–7.31 (m, 7H, ArH), 7.41–7.46 (m, 2H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20.95, 124.33, 124.65, 126.51, 129.99, 130.45, 133.56, 136.12, 136.43, 154.32; IR (diffuse reflectance) 3273 (m), 3102 (m), 2934 (m), 1634 (s), 1576 (s), 1512 (m), 1498 (m), 1451 (m), 1381 (s), 1313 (m), 1227 (m), 1091 (w), 1041 (w), 824 (m), 748 (m), 693 (m) cm^{-1}; MS (ESI) *m*/*z*: 226 (M^++H).

*4.1.10. N-(4-Methoxy-phenyl)-N′-phenyl guanidine hydrochloride (**20**).* Yellow solid; mp 139–140 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.65 (s, 3H, OCH_3), 6.76 (d, 2H, *J*=8.70 Hz, ArH), 7.03 (d, 2H, *J*=8.70 Hz, ArH), 7.10 (d, 2H, *J*=8.7 Hz, ArH), 7.14–7.17 (m, 1H, ArH), 7.22–7.27 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.50, 115.20, 124.98, 126.02, 127.18, 127.73, 130.02, 133.97, 154.70, 159.19; IR (diffuse reflectance) 3153 (m), 2930 (m), 1631 (m), 1505 (m), 1453 (w), 1379 (w), 1300 (w), 1247 (m), 1179 (w), 1109 (w), 1027 (m), 828 (m), 757 (m), 696 (w), 524 (w) cm^{-1}; MS (ESI) *m*/*z*: 242 (M^++H); Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.65; H, 6.30; N, 17.43.

*4.1.11. N-Cyclohexyl-N′-4-trifluoromethylphenyl guanidine hydrochloride (**21**).* Yellow solid; mp 131–132 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14–1.53 (m, 6H, CH_2), 1.62–1.68 (m, 2H, CH_2), 1.92–1.96 (m, 2H, CH_2), 3.87 (m, 1H, CH), 7.33 (d, 2H, *J*=7.95 Hz, ArH), 7.60 (d, 2H, *J*=7.95 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.18, 24.95, 32.53, 51.18, 124.66, 127.18, 129.06, 138.09, 153.84; IR (diffuse reflectance) 3273 (m), 3108 (m), 2932 (m), 1644 (s), 1633 (s), 1614 (m), 1509 (w), 1452 (w), 1386 (w), 1318 (s), 1263 (w), 1161 (m), 1114 (s), 1067 (m), 1017 (m), 837 (m), 828 (m) cm^{-1}; MS (ESI) *m*/*z*: 286 (M^++H); HRMS (ESI) calcd for $C_{14}H_{19}F_3N_3$ (M^++H) 286.1531, found 286.1532.

*4.1.12. N-Cyclohexyl-N′-4-benzyloxyphenyl guanidine hydrochloride (**22**).* White solid; mp 144–145 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.15–1.53 (m, 6H, CH_2), 1.67–1.69 (m, 2H, CH_2), 1.83–1.86 (m, 2H, CH_2), 3.59–3.63 (m, 1H, CH), 5.11 (s, 2H, OCH_2), 7.06 (d, 2H, *J*=8.46 Hz, ArH), 7.15 (d, 2H, *J*=8.46 Hz, ArH), 7.32–7.46 (m, 5H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 24.40, 25.25, 32.58, 50.05, 69.89, 116.07, 127.38, 128.13, 128.32, 128.49, 128.88, 137.30, 154.88, 157.35; IR (diffuse reflectance) 3272 (m), 3133 (m), 2928 (m), 2856 (m), 1659 (s), 1625 (s), 1588 (m), 1504 (s), 1452 (m), 1384 (w), 1362 (w), 1298 (w), 1244 (s), 1174 (m), 1120 (m), 1026 (m), 829 (m), 740 (m), 693 (s) cm^{-1}; MS (ESI) *m*/*z*: 324 (M^++H); HRMS (ESI) calcd for $C_{20}H_{26}N_3O$ (M^++H) 324.2076, found 324.2074.

*4.1.13. N′-(4-Methoxy-phenyl)-N,N-dimethyl guanidine hydrochloride (**23**)*[39]. Yellow solid; mp 186–187 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.05 (s, 6H, $N(CH_3)_2$), 3.71 (s, 3H, CH_3), 6.76 (d, 2H, *J*=8.76 Hz, ArH), 7.02 (d, 2H, *J*=8.76 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.51, 55.38, 114.81, 126.92, 127.79, 155.82, 158.42; IR (diffuse reflectance) 3416 (m), 3193 (m), 1626 (m), 1513 (m), 1454 (w), 1299 (w), 1246 (m), 1179 (w), 1108 (w), 1022 (w), 833 (w), 814 (w), 768 (w), 589 (w), 522 (w) cm^{-1}; MS (ESI) *m*/*z*: 194 (M^++H).

*4.1.14. N-tert-Butyl-N′-phenyl guanidine hydrochloride (**31**)*[35]. Yellow solid; mp 101–102 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 9H, 3×CH_3), 7.10 (d, 2H, *J*=7.42 Hz, ArH), 7.21–7.24 (m, 1H, ArH), 7.28–7.33 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.86, 52.38, 125.12, 127.42, 129.91, 134.06, 153.62; IR (diffuse reflectance) 3458 (w), 3275 (w), 3183 (m), 2975 (m), 1623 (s), 1590 (s), 1394 (s), 1304 (m), 1203 (m), 1165 (w), 1040 (w), 934 (w), 821 (w), 755 (m), 695 (s) cm^{-1}; MS (ESI) *m*/*z*: 192 (M^++H). HRMS (ESI) calcd for $C_{11}H_{18}N_3$ (M^++H) 192.1501, found 192.1502.

*4.1.15. N-(α-Naphthyl)-N′-p-tolyl guanidine hydrochloride (**32**).* Yellow solid; mp 210–211 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.32 (s, 3H, CH_3), 7.23–7.29 (m, 3H, ArH), 7.57–7.69 (m, 5H, ArH), 7.96–8.05 (m, 3H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20.98, 122.78, 125.21, 125.50, 126.49, 127.02, 127.33, 128.43, 128.82, 129.91, 130.47, 131.87, 133.46, 134.59, 136.30, 155.41; IR (diffuse reflectance) 3130 (m), 2931 (m), 1623 (s), 1595 (s), 1573 (s), 1511 (m), 1394 (m), 1272 (w), 1252 (w), 1234 (w), 1174 (w), 1105 (w), 1018 (w), 803 (m), 785 (s), 774 (s), 749(m) cm^{-1}; MS (ESI) *m*/*z*: 276 (M^++H); HRMS (ESI) calcd for $C_{18}H_{18}N_3$ (M^++H) 276.1501, found 276.1502.

*4.1.16. N-Phenyl-N′-propyl guanidine hydrochloride (**33**)*[35]. Yellow solid; mp 94–95 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, 3H, *J*=7.31 Hz, CH_3), 1.46–1.58 (m, 2H, CH_2), 3.15–3.21(m, 2H, CH_2), 6.82 (br s, 2H, NH), 7.11 (d, 2H, *J*=7.38 Hz, ArH), 7.18–7.23 (m, 1H, ArH), 7.29–7.34 (m, 2H, ArH), 9.42 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.86, 21.72, 43.46, 125.03, 127.41, 129.88, 134.19, 154.88; IR (diffuse reflectance) 3422 (m), 3188 (m), 2968 (m), 2056 (m), 1632 (m), 1384 (m), 1142 (m), 1075 (w), 1042 (w), 825 (m), 757 (m), 698 (w) cm^{-1}; MS (ESI) *m*/*z*: 178 (M^++H). HRMS (ESI) calcd for $C_{10}H_{16}N_3$ (M^++H) 178.1344, found 178.1346.

*4.1.17. N-(4-Methoxy-phenyl)-N′-propyl guanidine hydrochloride (**34**).* Yellow solid; mp 74–75 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3H, *J*=7.32 Hz, CH_3), 1.51–1.60 (m, 2H, CH_2), 3.18–3.24 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 6.85 (d, 2H, *J*=8.45 Hz, ArH), 7.07 (d, 2H, *J*=8.45, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.03, 21.92, 43.56, 55.46, 115.18, 126.46, 127.58, 155.60, 159.09; IR (diffuse reflectance) 3285 (m), 3174 (m), 2966 (m), 2054 (m), 1632 (s), 1511 (m), 1383 (s), 1246 (s), 1180 (m), 1108 (w), 1029 (m), 825 (m), 783 (w), 715 (w), 523 (w) cm^{-1}; MS (ESI) *m*/*z*: 208 (M^++H). HRMS (ESI) calcd for $C_{11}H_{18}N_3O$ (M^++H) 208.1450, found 208.1452.

*4.1.18. N-(4-Amino-phenyl)-N′- m-tolyl guanidine hydrochloride (**35**).* Yellow solid; mp 161–162 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.31 (s, 3H, CH_3), 6.60 (d, 2H, *J*=8.38 Hz, ArH), 6.94 (d, 2H, *J*=8.38 Hz, ArH), 7.03–7.09 (m, 3H, ArH), 7.27–7.30 (m, 1H, ArH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.21, 114.54, 121.56, 122.90, 124.99, 127.07, 129.63, 136.00, 139.26, 146.25, 148.43, 154.75; IR (diffuse reflectance) 3415 (m), 3159 (m), 2920 (m), 1630 (m), 1513 (m), 1372 (w), 1173 (w), 1092 (w), 825 (w), 695 (w), 518 (w) cm^{-1}; MS (ESI) *m*/*z*: 241 (M^++H). HRMS (ESI) calcd for $C_{14}H_{17}N_4$ (M^++H) 241.1453, found 241.1451.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.01.003.

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