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# A Facile One-Pot Synthesis of 1,2,3-Tri- and 1,1,2,3-Tetrasubstituted Bis(guanidines) from Bis(thioureas)

Valentin Vass, Maximilian Dehmel, Florian Lehni, and Robert Kretschmer*[a]

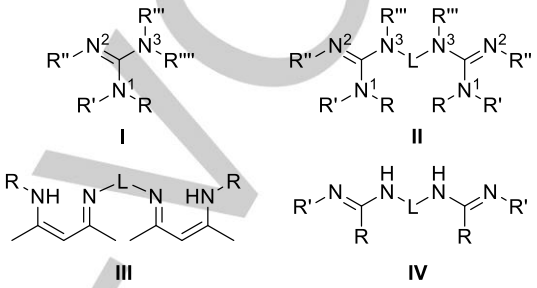
*This work is dedicated to Prof. Dr. Rainer Beckert on the occasion of his 65th birthday.*


## Abstract

A facile and efficient one-pot strategy for the preparation of 1,2,3-tri- and 1,1,2,3-tetrasubstituted bis(guanidines) originating from readily available bis(thioureas) has been successfully developed. The reaction scope covers a range of terminal and bridging groups, and after a simple work-up, the products are obtained analytically pure and in good to excellent yields.

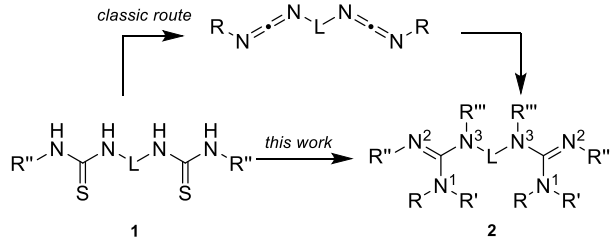

## Introduction

Compounds containing several nitrogen atoms play a central role in biological systems and in a wide range of industrial processes. Over the last few decades, intensive research has been devoted to improve currently employed synthetic methods for the production of this important class of substances.[1] Among the versatile class of multi-nitrogen compounds, guanidines[2] **I** (Scheme 1) attracted significant attention since their first synthesis by Strecker in 1861[3] and are widely used as artificial sweeteners,[4] explosives,[5] and pharmaceuticals.[6] In addition, guanidines, which have been categorized as superbases,[7] found manifold applications either as organocatalysts[8] or as supports for transition metals[9] and main group elements[10] giving rise to guanidinate complexes. As a consequence of the broad interest, synthetic routes towards guanidines have been developed to quite some extent.[7,11] Bis(guanidines) **II**, i.e., compounds composed of two guanidine moieties that are connected by a linker (L), have recently received considerable interest.[12,13] Compared to their mono(guanidine) counterparts, these species show enhanced properties, e.g., in catalysis,[14] as ion sensors,[15] superbases,[16] and ligands in bioinorganic and coordination chemistry.[17] However, protocols aiming for the synthesis of bis(guanidines) strongly depend on the substitution pattern.[18] Persubstituted bis(guanidines) are accessible either from the reaction of *N,N,N',N'*-tetrasubstituted guanidines with a dihalogen compound[19] or by reacting diamines with tetrasubstituted chloroformamidinium chlorides.[12,20] In contrast, less substituted derivatives often require multi-step procedures.[18]




Scheme 1. Structures of guanidines (**I**), bis(guanidines) (**II**), bis(β-diketimines (**III**), and bis(amidines) (**IV**); L = linker group.

1,1,2,3-tetrasubstituted bis(guanidines) are of particular interes as they serve as interesting alternatives to bis(β-diketimines) **III**,[2] bis(amidines) **IV**,[22] (Scheme 1), and the bridged-version of th amidoamine ligand.[23] In addition, 1,2,3-trisubstitute bis(guanidines) offer the possibility to provide two dianioni binding sites within one ligand. Thus, both 1,2,3-tri- and 1,1,2,3 tetrasubstituted bis(guanidines) are promising frameworks for d and polynuclear complexes.[24] Unfortunately, syntheti approaches towards these species usually involve severa reaction steps and are therefore associated with rather lo yields.[25,26] In addition, bis(carbodiimides), which are relativel unstable and must be handled with care, often serve a intermediates. Thus we envisaged a synthetic protocol, whic originates from easily available bis(thioureas) **1** and allows for th synthesis of bis(guanidines) **2** *via* an one pot reaction avoiding th isolation of bis(carbodiimides), Scheme 2.




Scheme 2. Synthesis of 1,2,3-tri- (R & R''' = H) and 1,1,2,3-tetrasubstituted (R''' = H) bis(guanidines) **2** from readily available bis(thioureas) **1**. Noteworthy, different tautomeric forms of **2** are possible depending on the nature of the terminal group (R) and the linker (L), respectively; for the sake of clarity only one form is shown.

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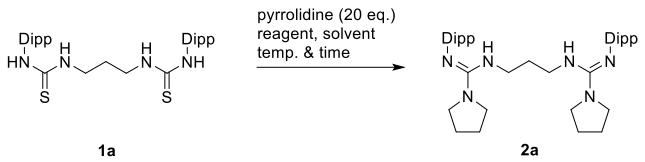
## Results and Discussion

Table 1. Screening of desulfurization agents for the transformation of **1a** to **2a** in the presence of pyrrolidine (Dipp = 2,6-Diisopropylphenyl).

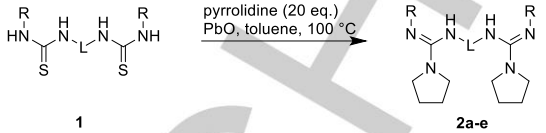



**1a** **2a**

| # | Reagent | Solvent | Temp. & Time | Yield |
|---|---|---|---|---|
| 1 | CuCl | acetonitrile/toluene | 80 °C / 64 h | 45% |
| 2 | $KICl_2$ | acetonitrile/water | r.t. / 64 h | n.r. |
| 3 | HgO | toluene | 100 °C / 16 h | 98% |
| 4 | PbO | toluene | 100 °C / 16 h | 98% |
| 5 | $PbO_2$ | toluene | 100 °C / 16 h | 98% |
| 6 | ZnO | ethanol | 60 °C / 96 h | 10% |

For guanidines, the use of thioureas as starting materials has become a facile strategy[27] and the desulfurization can be achieved by a variety of reagents such as copper(I) salts,[28] mercury(II) oxide,[29] $KICl_2$,[30] lead oxides,[31] or ZnO.[32] As we assumed that these protocols may also be applicable for the synthesis of multi-substituted bis(guanidines), we investigated the applicability of the aforementioned procedures for transforming the bis(thiourea) **1a** and pyrrolidine into the related bis(guanidine) **2a** as summarized in Table 1. The protocol established by Wang *et al*.[28] employing CuCl in a mixture of acetonitrile and toluene, yielded the bis(guanidine) **2a** in only 45% yield after 64 hours, and using potassium dichloroiodate ($KICl_2$), as mentioned by the group of Costa,[30] did not affect any conversion of the bis(thiourea) **1a**. However, using mercury(II), lead(II) and lead(IV) oxide, respectively, affords **2a** in nearly quantitative yield, while two equivalents of zinc oxide give rise to only 10% of the desired product despite the long reaction time of four days. Thus, HgO, PbO, and $PbO_2$ turned out to perform best, not only with respect to yields but also regarding a facile work-up. Here, the products can be easily isolated by filtering-off the insoluble metal sulphides and evaporating the solvent and residual pyrrolidine. Due to the poor solubility of bis(thioureas) in toluene, potentially remaining starting materials may also be separated as part of the remaining residue. Although all three compounds are not plain sailing in terms of eco(toxicity), lead(II) oxide is associated with the least risks.[33] In addition, the formed lead(II) sulphide is easily converted to lead(II) oxide in a roasting process, which allows for its recycling. We thus employed PbO for further experiments. To obtain some insight into the substrate scope of this reaction, we investigated the effect of electron-donating and electron-withdrawing terminal groups (R) as well as the impact of the linking group (L), Table 2. Hence, reactions of bis(thioureas) bearing aryl and alkyl substituents in terminal position were performed under standard reaction conditions, i.e., using 2.1 and 20 equivalents of PbO and pyrrolidine, respectively, with toluene as solvent. For all of these substrates, it was found that the related bis(guanidines) had been formed in good to excellent yields.

Table 2. Substrate scope with respect to the terminal groups R (entries 1-3) and the linker L (entries 3-6), respectively. Different tautomers of **2** are observed depending on the nature of L and R, respectively; for the sake of clarity only one form is shown (Dipp = 2,6-Diisopropylphenyl, $Ph^F$ = Pentafluorophenyl).

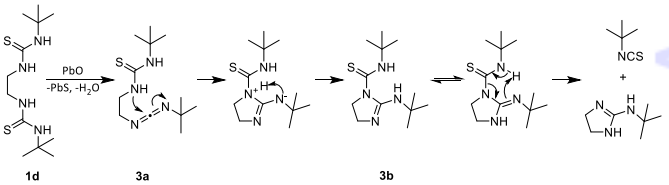



**1** **2a-e**

| # | R | L | Temp. & Time | Yield | Product |
|---|---|---|---|---|---|
| 1 | Dipp | propylene | 100 °C / 16 h | 98% | **2a** |
| 2 | $Ph^F$ | propylene | 100 °C / 16 h | 99% | **2b** |
| 3 | $^t$Bu | propylene | 50 °C / 48 h | 89% | **2c** |
| 4 | $^t$Bu | ethylene | 50 °C / 16 h | 0%[a] | |
| 5 | $^t$Bu | *m*-phenylene | 100 °C / 88 h | 73% | **2d** |
| 6 | Dipp | *m*-xylylene | 100 °C / 16 h | 99% | **2e** |

a) *N*-(*tert*-butyl)-4,5-dihydro-1H-imidazol-2-amine was formed instead of the desired bis(guanidine)

However, the reaction conditions are of crucial importance. Th transformation of bis(thioureas) bearing moderately and stron electron-withdrawing substituents (entries 1 and 2) require temperatures of about 100 °C, while the *tert*-butyl substitute derivative (entry 3) yielded complex reaction mixtures whe heated above 50 °C. However, when extending the reaction tim to 48 hours, a reaction temperature of 50 °C turned out to b suitable to obtain the desired product **2c** in 89% yield. Thus, it ca be concluded that the protocol is applicable to both electron-ric and electron-deficient bis(thioureas), when choosing the prope reaction conditions. Next, we became interested if the linker grou L limits the reaction scope. Indeed, we found that the ethylene bridged bis(thiourea) **1d** (entry 4) does not yield the desire bis(guanidine), but gives rise to *N*-(*tert*-butyl)-4,5-dihydro-1*H*- imidazol-2-amine as the main product. Most likely, this is due t an intermediary formation of the mixed carbodiimide thioure species **3a**, which undergoes a subsequent intramolecula cyclization yielding the imidazolidinecarbo-thioamide **3b** (Schem 3). Next, elimination of *tert*-butyl isothiocyanate gives rise to *N* (*tert*-butyl)-4,5-dihydro-1*H*-imidazol-2-amine. Note that *N*-ary substituted imidazolidine-carbothioamides have already bee isolated and structurally characterized, while no derivative bearin strong electron donating substituents has been reported so far.[3 In case of a longer alkyl chain, i.e., propylene, the desire bis(guanidine) **2c** is formed in 89% yield, as mentioned above Similar results are obtained for the 1,3-phenylene- and 1,3 xylylene-bridged bis(thioureas) (entries 5 and 6), which allow fo the isolation of the related bis(guanidines) **2d** and **2e**, respectively




**1d** **3a** **3b**

Scheme 3. Proposed mechanism for the formation of *N*-(tert-butyl)-4,5-dihydro-1H-imidazol-2-amine **3** from 1,1'-(1,2-ethylene)bis(3-tert-butylthiourea) **1d**.

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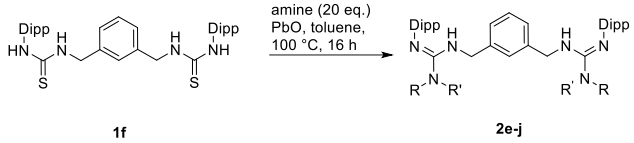
Table 3. Substrate scope with respect to secondary (entries 1-7) and primary (entries 8-9) amines (Dipp = 2,6-Diisopropylphenyl, 2,6-Dmpip = *cis*-2,6-dimethylpiperidine).



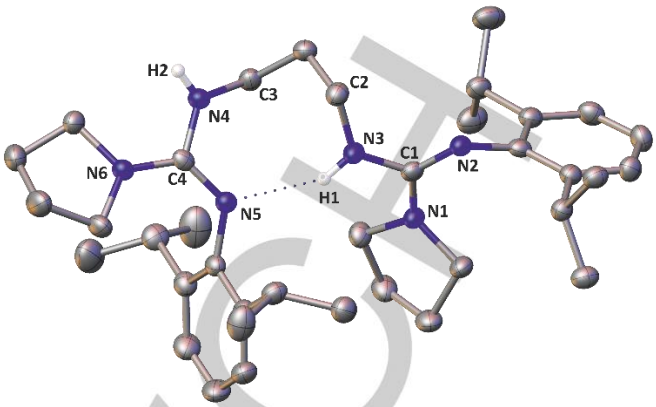

**1f** **2e-j**

| # | Amine | R | R' | Yield | Product |
|---|---|---|---|---|---|
| 1 | pyrrolidine | Pyr | | 99% | **2e** |
| 2 | morpholine | Morph | | 77% | **2f** |
| 3 | *cis*-2,6-dimethylpiperidine | 2,6-Dmpip | | n.r. | |
| 4 | diethylamine | Et | Et | 99% | **2g** |
| 5 | dipropylamine | $^{n}$Pr | $^{n}$Pr | 99% | **2h** |
| 6 | diisopropylamine | $^{i}$Pr | $^{i}$Pr | n.r. | |
| 7 | dicyclohexylamine | Cy | Cy | n.r. | |
| 8 | cyclohexylamine | Cy | H | 96% | **2i** |
| 9 | aniline | Ph | H | 95% | **2j** |

Noteworthy, the formation of **2d** requires longer reaction times and is associated with the lowest yield in the whole series, most likely due to steric reasons.

Having evaluated the impact of the terminal groups R and the linker L, we then studied the utility of the protocol through the use of a variety of amines, Table 3. Applying less-substituted cyclic and acyclic secondary alkyl amines, the corresponding 1,1,2,3-tetrasubstituted bis(guanidines) **2e-h** are readily obtained (entries 1, 2, 4, 5) in good to excellent yields. Higher substituted secondary amines, i.e., *cis*-1,6-dimethylpiperidine, diisopropylamine as well as dicyclohexylamine remained unreactive under the given conditions (entries 3, 6, 7), presumably due to their steric bulk. While limiting the scope of the reaction, this offers an advantage in the reaction selectivity that can be obtained. Noteworthy, the reaction with diisopropylamine was also conducted in the presence of catalytic amounts of a Lewis acid ($AlCl_3$) and/or molecular sieves, which, however, does not facilitate the formation of the desired bis(guanidine). Although less nucleophilic than secondary amines, applying a primary aliphatic and an aromatic amine (entries 8-9) afforded the corresponding 1,2,3-trisubstituted bis(guanidines) **2i** and **2j**, respectively, in excellent yields. Noteworthy, 1,2,3-trisubstituted bis(guanidines) having the same substituents at the terminal position are also accessible from carbodiimides and diamines,[35] but examples for *N,N',N''*-trisubstituted bis(guanidines) carrying three different substituents remain rare and involve rather demanding reaction sequences.[26,36]

The obtained bis(guanidines) are either solids (**2a**, **2b**, **2d-f**, **2i-j**) or highly viscous liquids (**2c**, **2g**, **2h**) at room temperature. To gain insight into the solid-state structure of the bis(guanidines), **2a** was crystallized from a saturated acetonitrile solution. A single crystal X-ray diffraction study revealed the molecular structure of **2a**, Figure 1. **2a** crystallizes in the monoclinic space group $P2_1/c$ with four independent molecules in the unit cell. As expected, the hydrogen atoms reside on the more basic bridging nitrogen atoms (N3 and N4, respectively). In consequence, the terminal C1–N2




(1.3041(19) Å) and C4–N5 (1.2973(19) Å) bond lengths are clos to typical values for C–N double bonds.

Figure 1. Molecular structure of **2a** (hydrogen atoms besides H1 and H2 and th disorder in one $^{i}$Pr substituent are omitted for the sake of clarity). Therma ellipsoids display 50% probability of presence for each atom. Selected bon lengths [Å] and angles [°]: C1-N1 1.3729(19), C1-N2 1.3041(19), C1-N 1.3622(19), C2-N3 1.4491(20), C3-N4 1.4577(19), C4-N4 1.3708(19), C4-N 1.2973(19), C4-N6 1.3637(19), N5-H1 2.0993(198); N1-C1-N2 125.11(13), N2 C1-N3 120.54(13), C1-N3-C2 125.81(13),C1-N3-H1 119.53 (1.18), N3-H1-N 154.4 (16).

The values of the other two sets of carbon nitrogen bonds, e.g C1–N1 (1.3729(19) Å) and C1–N3 (1.3622(19) Å), ar intermediate between those of typical single (1.46 Å) and doubl C–N bonds (1.27 Å),[37] indicating a certain amount c delocalization. However, all bond distances are comparable t values observed in other guanidine compounds (C–N1 1.355 Å C-N2 1.307 Å, C1–N3 1.333 Å), and electronic push-pull effect have been identified to have a crucial impact on the geometry c guanidine compounds.[39]

In addition, **2a** features an intramolecular hydrogen bond in th solid state, i.e., N5–H1, of medium strength as suggested by both the N5–H1 distance (2.099(20) Å) and the N3–H1–N5 bond angl of 154.4(16)°.[38] The N3–H1···N5 hydrogen bond also effects th geometry of the two guanidine groups in such a way, that the C4 N5 (1.2973(19) Å) and C4–N6 (1.3637(19) Å) bonds are to som extent shorter compared to their C1 counterparts (C1–N (1.3041(19) Å), C1–N1 (1.3729(19) Å)) and the increased bon length of C4–N4 (1.3708(19) Å) versus C1–N3 (1.3622(19) Å). I solution, however, only one set of signals is observed for the 2,6 diisopropylphenyl groups, i.e., one methine septet and two methy doublets, in the $^{1}$H NMR spectra of 2a in $CDCl_3$. This is indicativ for only one type of species, where the two guanidine sites ar symmetrically related on the NMR time scale. While $^{1}$H and $^{13}C\{^{1}H$ NMR data indicate that mirror symmetry is also maintained in solution for the bisguanidines 2b and 2d-2j, the $^{1}$H and $^{13}C\{^{1}H\}$ NMR spectra of the more basic bis(guanidine) 2c, however, consist of two separated signal sets for the *tert*-butyl groups, evidencing an asymmetric steric environment as expected if the hydrogen bond remains intact in solution.

## Conclusions

In summary, 1,2,3-tri- and 1,1,2,3-tetrasubstituted bis(guanidines) could be obtained *via* a facile one-pot procedure using readily available bis(thioureas). The protocol is applicable to terminal alkyl (*t*-butyl) and aryl (perfluorophenyl, 2,6-diisopropylphenyl) groups. Various alkyl and aryl linker groups are tolerated, while the ethylene-bridge remains a notable exception. In addition, less sterically demanding cyclic and acyclic secondary alkyl amines are applicable and primary aliphatic and aromatic amines give rise to *N,N',N''*-trisubstituted bis(guanidines).

## Experimental Section

**General Considerations.** The solvents and starting materials were purchased from ABCR, Sigma Aldrich or VWR and used as delivered. *tert*-Butylisothiocyanate[40] and pentafluorophenylisothiocyanate[41] were prepared as described elsewhere.

**Characterization.** The NMR spectra were recorded on Bruker Avance 300 and 400 spectrometers (T = 300 K) with δ (given in ppm) referenced to external trimethylsilane ($^1$H and $^{13}$C) and trichlorofluoromethane ($^{19}$F). $^1$H and $^{13}$C NMR spectra were calibrated using the solvent residual peak ($\delta$ $^1$H ($CHCl_3$) = 7.26 and $\delta$ $^1$H ($CD_3SOCD_2H$) = 2.50) and the solvent peak ($\delta$ $^{13}$C{$^1$H} ($CDCl_3$) = 77.16 and $\delta$ $^{13}$C{$^1$H} ($(CD_3)_2SO$) = 39.52), respectively. The coupling constants *J* are given in Hertz [Hz]. IR spectra were recorded with a Thermo Fisher Scientific FT-IR spectrometer Nicolet iS5 equipped with an iD7 diamond ATR unit. High-resolution mass spectra were measured by using a Waters LCT Micromass spectrometer.

#### Synthesis of 2,6-diisopropylphenylisothiocyanate

68.50 g (900 mmol) of carbon disulphide were added dropwise to a stirred solution of 139.50 g (708 mmol) of 2,6-diisopropylaniline (90% wt.) and 193.40 g (1.4 mol) $K_2CO_3$ in 500 ml of $H_2O$. After the addition was complete (3 hours), the reaction mixture was stirred for 16 hours at room temperature before it was cooled to 0 °C and treated dropwise with a solution of 64.50 g (350 mmol) of 2,4,6-trichloro-1,3,5-triazine in 350 ml of dichloromethane over the course of 3 hours. The resulting brown suspension was then stirred for 4 hours at room temperature before it was basified to pH > 11 by adding 700 mL of a sodium hydroxide solution (7 mol/L). After the addition of 200 ml of dichloromethane and 500 ml of $H_2O$, two layers appeared. The organic layer was separated, washed twice with water (200 ml each) and dried using $MgSO_4$. The volatiles were removed *en vacuo* giving 2,6-diisopropylphenylisothiocyanate as brown oil (105.45 g, 481 mmol, 68%). The NMR spectra were in accordance with those reported in the literature.[43]

#### Synthesis of the bis(thioureas) 1a–f

**1,1'-(1,3-propylene)bis[3-(2,6-diisopropylphenyl)thiourea] (1a):** 5.56 g (75.0 mmol) 1,3-diaminopropane were added to a stirred solution of 32.90 g (150.0 mmol) 2,6-diisopropylphenylisothiocyanate in 200 ml of toluene. A suspension was formed within a few hours and stirring was continued for 48 h. Then, the precipitates were filtered off, washed with *n*-hexane and dried *en vacuo* to yield **1a** in analytically pure form. White solid, 36.18 g, 70.6 mmol, 94%.$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.14 (d, $^3J_{HH}$ = 6.8 Hz, 12H, $CHCH_3$), 1.20 (d, $^3J_{HH}$ = 6.8 Hz, 12H, $CHMe_2$), 1.59 (br, 2H, $CH_2CH_2CH_2$), 3.05 (sept, $^3J_{HH}$ = 6.8 Hz, 4H, $CHCH_3$), 3.53 (dt, $^3J_{HH}$ = 5.5 Hz, $^3J_{HH}$ = 6.1 Hz, 4H, $CH_2CH_2CH_2$), 6.22 (t, $^3J_{HH}$ = 6.4 Hz, 2H, $NHCH_2CH_2CH_2NH$), 7.21 (d, 4H, $^3J_{HH}$ = 7.7 Hz, *m*-$CH_{arom}$), 7.35 (t, $^3J_{HH}$ = 7.6 Hz, 2H, *p*-$CH_{arom}$), 7.40 (s, 2H, $NHCSNH$). $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$): $\delta$ = 23.1 ($CHCH_3$), 24.7 ($CHCH_3$), 28.6 ($CHCH_3$), 30.2 ($CH_2CH_2CH_2$), 40.7 ($CH_2CH_2CH_2$), 124.7 (*m*-$CH_{arom}$), 129.9 (*o*-$CH_{arom}$), 130.1 (*p*-$CH_{arom}$), 147.8 (*i*-$CH_{arom}$), 181.7 ($NHCSNH$). IR [cm$^{-1}$]: *v*(NH) = 3265 and 3169, *v*(CH) = 2960 and 2864, *v*(CN) = 1532, *v*($CC_{arom}$)= 1502, *v*(CS) = 1210. HR-ESI-MS: calcd. for $C_{29}H_{44}N_4S_2$ $[M+H]^+$ 513.3086; found 513.3062.

**1,1'-(1,3-propylene)bis[3-(perfluorphenyl)thiourea] (1b):** 350 mg (4.7 mmol) 1,3-diaminopropane were added to a stirred solution of 2.10 g (9.3 mmol) pentafluorophenylisothiocyanate in 30 ml of diethyl ether. The solution was stirred for 72 hours. The volatiles were removed *en vacuo* an the residue was purified by column chromatography ($SiO_2$, *n*-pentane/ethy acetate: 3/2) yielding **1b** in analytically pure form. Off-white solid, 930 mg 1.8 mmol, 38%. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 1.82 (br, 2H $CH_2CH_2CH_2$), 3.51 (br, 4H, $CH_2CH_2CH_2$), 8.24 (br, 2H, $NHCH_2CH_2CH_2NH$ 9.29 (br, 2H, $NHCSNH$). $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$): 28. ($CH_2CH_2CH_2$), 42.3 ($CH_2CH_2CH_2$), 136.0 (*m*-$CH_{arom}$), 138.5 (*p*-$CH_{arom}$ 142.8 (*o*-$CH_{arom}$), 145.2 (*i*-$CH_{arom}$), 182.3 ($NHCSNH$). $^{19}$F-NMR (282 MHz DMSO-$d_6$): -163.53 (quint, 22.0 Hz, 4F, *m*-$CF_{arom}$), -157.10 (t, 22.3 Hz, 2F *p*-$CF_{arom}$), -144.67 (d, 22.0 Hz, 4F, *o*-$CF_{arom}$). IR [cm$^{-1}$]: *v*(NH) = 3217 an 3043, *v*(CH) = 2928, *v*($CC_{arom}$) = 1704, 1615, 1480 and 984 *v*(CN) = 150 *v*(CS) = 1266. HR-ESI-MS: calcd. for $C_{17}H_{10}F_{10}N_4S_2$ $[M+H]^+$ 525.026 found 525.0208.

**1,1'-(1,3-propylene)bis(3-*tert*-butylthiourea) (1c):** 6.93 g (93.5 mmo 1,3-diaminopropane were added to a stirred solution of 21.55 g (187. mmol) *tert*-butylisothiocyanate in 350 ml of diethyl ether. A suspension wa formed after a few minutes and stirring was continued for 16 h. Then, th precipitates were filtered off, washed with diethyl ether and dried *en vacu* to yield **1c** in analytically pure form. White solid, 19.60 g, 64.4 mmol, 69% $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 18H, $C(CH_3)_3$), 1.82 (br, 2H $CH_2CH_2CH_2$), 3.74 (dt, $^3J_{HH}$ = 5.5 Hz, $^3J_{HH}$ = 6.2 Hz, 4H, $CH_2CH_2CH_2$), 6.1 (br, 2H, $NHC(CH_3)_3$), 6.55 (t, $^3J_{HH}$ = 6.1 Hz, 2H, $NHCH_2$). $^{13}$C{$^1$H} NMR (10 MHz, $CDCl_3$): δ = 29.5 ($C(CH_3)_3$), 30.6 ($CH_2CH_2CH_2$), 41.9 ($CH_2CH_2CH_2$ 52.9 ($C(CH_3)_3$), 180.7 ($NHCSNH$). IR [cm$^{-1}$]: *v*(NH) = 3247 and 3050, *v*(CH = 2961, *v*(CN) = 1536 *v*(CS) = 1189. HR-ESI-MS: calcd. for $C_{13}H_{28}N_4S$ $[M+H]^+$ 305.1833; found 305.1841.

**1,1'-(1,2-ethylene)bis(3-*tert*-butylthiourea) (1d):** 3.00 g (50.0 mmol) 1,2 ethylenediamine were added to a stirred solution of 11.50 g (100.0 mmo *tert*-butylisothiocyanate in 25 ml of methanol. The solution was stirred ove night at room temperature before the volatiles have been removed *e vacuo*. The residue was suspended in water and treated with five drops *conc.* hydrochloric acid. The white precipitate was filtered off and dried *e vacuo* to yield **1d** in analytically pure form. White solid, 9.54 g, 32.8 mmo 66%. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ = 1.39 (s, 18H, $C(CH_3)_3$), 3.43 (s 4H, $(CH_2)_2$), 7.11 (br, 2H, $NHCH_2$), 7.29 (br, 2H, $NHC(CH_3)_3$), $^{13}$C{$^1$H} NM (75 MHz, DMSO-$d_6$): $\delta$ = 28.9 ($C(CH_3)_3$), 42.3 ($(CH_2)_2$), 52.2 ($C(CH_3)_3$ 181.4 ($NHCSNH$). IR [cm$^{-1}$]: *v*(NH) = 3250 and 3056, *v*(CH) = 2973 an 2929, *v*(CN) = 1532 *v*(CS) = 1196. HR-ESI-MS: calcd. for $C_{12}H_{26}N_4S$ $[M+H]^+$ 291.1677; found 291.1710.

**1,1'-(1,3-phenylene)bis(3-*tert*-butylthiourea) (1e):** A mixture of 3.50 (32.4 mmol) 1,3-diaminobenzene and 8.50 g (73.8 mmol) *tert*-butylisothiocyanate in 10 ml of ethanol was stirred at 70 °C for 72 hours. After cooling to room temperature, petrol ether was added (about 50 mL) and the resulting precipitates were filtered off, washed with diethyl ether and dried *en vacuo* to yield **1g** in analytically pure form. White solid, 6.95 g, 20.5 mmol, 63%. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 1.49 (s, 18H, $C(CH_3)_3$), 7.13 (m, 2H, 4,6-$CH_{arom}$), 7.21 (m, 1H, 5-$CH_{arom}$), 7.34 (s, 2H, $CSNHC(CH_3)_3$), 7.75 (t, $^4J_{HH}$ = 3.5 Hz, 1H, 2-$CH_{arom}$), 9.34 (s, 2H, $CSNHC_{arom}$). $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$): $\delta$ = 28.6 ($C(CH_3)_3$), 52.8

($C(CH_3)_3$), 117.1 (2-$CH_{arom}$), 118.0 (4,6-$CH_{arom}$), 128.4 (5-$CH_{arom}$), 139.5 (1,3-$C_{arom}$), 179.1 (NH*C*SNH). IR [$cm^{-1}$]: $\nu$(NH) = 3259 and 3058, $\nu$($CH_{arom}$) = 2980, $\nu$(CH) = 2916, $\nu$($CC_{arom}$)= 1569 and 1479, $\nu$(CN) = 1537, $\nu$(CS) = 1198. HR-ESI-MS: calcd. for $C_{16}H_{26}N_4S_2$ $[M+H]^+$ 339.1677; found 339.1621.

**1,1'-(1,3-xylylene)bis[3-(2,6-diisopropylphenyl)thiourea] (1f):** 10.22 g (75.0 mmol) 1,3-bis(aminomethyl)benzene were added to a stirred solution of 32.90 g (150.0 mmol) 2,6-diisopropylphenylisothiocyanate in 200 ml of toluene. A suspension was formed within a few hours and stirring was continued for 18 h. Then, the precipitates were filtered off, washed with n-hexane and dried *en vacuo* to yield **1f** in analytically pure form. White solid, 34.22 g, 59.5 mmol, 79%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.07 (d, $^3J_{HH}$ = 7.2 Hz, 12H, CH(C$H_3$)$_2$), 1.16 (d, $^3J_{HH}$ = 7.2 Hz, 12H, CH(C$H_3$)$_2$), 3.08 (sept, $^3J_{HH}$ = 7.2 Hz, 12H, C$H$($CH_3$)$_2$), 4.77 (d, $^3J_{HH}$ = 5.8 Hz, 4H, C$H_2$NH), 5.54(br, 2H, $CH_2$N$H$), 7.05 - 7.22 (m, 8H, C$H_{arom}$), 7.55 (br, 2H, *p*-C$H_{arom}$), 8.07 (br, 2H, N$H$C$_{arom}$). $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$): 23.2 (CH(C$H_3$)$_2$), 24.7 (CH(C$H_3$)$_2$), 28.6 (C$H$($CH_3$)$_2$), 48.8 (C$H_2$), 124.6 (*m*-C$H_{arom}$), 127.0 (4,6-C$H_{arom}$), 129.1 (2-C$H_{arom}$), 129.7 (*i*-C$_{arom}$), 130.1 (*p*-C$H_{arom}$), 138.1 (1,3-C$_{arom}$), 147.8 (*o*-C$H_{arom}$), 181.6 (NH*C*SNH). IR [$cm^{-1}$]: $\nu$(NH) = 3381 and 3123, $\nu$($CH_{arom}$) = 2961, $\nu$(CH) = 2924, $\nu$(CN) = 1534, $\nu$($CC_{arom}$)= 1499 and 1289, $\nu$(CS) = 1210. HR-ESI-MS: calcd. for $C_{29}H_{44}N_4S_2$ $[M+H]^+$ 513.3086; found 513.3051.

**Synthesis of the bis(guanidines) 2a-j**

**1,1'-(1,3-propylene)bis[*N*-(2,6-diisopropylphenyl)pyrrolidine-1-carboximidamide] (2a):** A mixture of 0.51 g (1.0 mmol) **1a**, 1.42 g (20.0 mmol) pyrrolidine, and 0.45 g (2.1 mmol) PbO in 20 ml of toluene was stirred at 100 °C for 16 hours. After cooling to room temperature, the solids were filtered off, washed with toluene and the combined filtrates were concentrated *en vacuo* yielding **2a** in analytically pure form. White solid, 0.58 g, 1.0 mmol, 98%. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.12 (d, $^3J_{HH}$ = 6.9 Hz, 12H, CH(C$H_3$)$_2$), 1.14 (d, $^3J_{HH}$ = 6.9 Hz, 12H, CH(*CH*$_3$) $_2$), 1.52 (quint, $^3J_{HH}$ = 7.0 Hz, 2H, $CH_2$C$H_2$$CH_2$), 1.78 (dt, $^3J_{HH}$ = 5.6 Hz, 6.5 Hz, 8H, N($CH_2$)$_2$(C$H_2$)$_2$), 3.03 (sept, $^3J_{HH}$ = 6.9 Hz, 4H, C$H$($CH_3$)$_2$), 3.00 (br, 4H, C$H_2$$CH_2$C$H_2$), 3.19 (t, $^3J_{HH}$ = 6.5 Hz, 8H, N(C$H_2$)$_2$($CH_2$)$_2$), 3.54 (br, CN$H$C), 6.92 (t, $^3J_{HH}$ = 7.4Hz, 2H, *p*-C$H_{arom}$), 7.03 (d, $^3J_{HH}$ = 7.4 Hz, 4H, *m*-C$H_{arom}$). $^{13}$C{$^1$H} NMR(101 MHz, $CDCl_3$): δ = 23.2 (CH(*C*$H_3$)$_2$), 23.7 (CH(*C*$H_3$)$_2$), 25.5 (N($CH_2$)$_2$(*C*$H_2$)$_2$), 28.0 (*C*H($CH_3$)$_2$), 31.5 ($CH_2$*C*$H_2$$CH_2$), 41.3 (*C*$H_2$$CH_2$*C*$H_2$), 48.2 (N(*C*$H_2$)$_2$($CH_2$)$_2$), 121.6 (*m*-*C*H$_{arom}$), 122.7 (*p*-*C*H$_{arom}$), 140.2 (*o*-*C*H$_{arom}$), 145.4 (*i*-*C*H$_{arom}$), 151.0 (NH*C*(N)N). IR [$cm^{-1}$]: $\nu$(NH) = 3236 , $\nu$(CH) = 2955 and 2922, $\nu$($CC_{arom}$)= 1550, 1429 and 1327, $\nu$(CN) = 1515. HR-ESI-MS: calcd. for $C_{37}H_{60}N_6$ $[M+H]^+$ 588.4880; found 588.4842.

**1,1'-(1,3-propylene)bis[*N*-(perfluorphenyl)pyrrolidine-1-carboximidamide] (2b):** A mixture of 0.26 g (0.5 mmol) **1b**, 0.71 g (10.0 mmol) pyrrolidine, and 0.22 g (1.0 mmol) PbO in 10 ml of toluene was stirred at 100 °C for 16 hours. After cooling to room temperature, the solids were filtered off, washed with toluene and the combined filtrates were concentrated *en vacuo* yielding **2b** in analytically pure form. Off-white waxy solid,0.30 g, 0.5 mmol, 99%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.68 (quint, $^3J_{HH}$ = 5.8 Hz, 2H, $CH_2$C$H_2$$CH_2$), 1.80 (dt, $^3J_{HH}$ = 6.0 Hz, 6.5 Hz, 8H, N($CH_2$)$_2$(C$H_2$)$_2$), 3.07 (t, $^3J_{HH}$ = 6.5 Hz, 8H, N(C$H_2$)$_2$($CH_2$)$_2$), 3.41 (q, 4H, $^3J_{HH}$ = 5.8 Hz, C$H_2$$CH_2$C$H_2$), 5.02 (br, 2H, CN$H$C). $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$): δ = 25.5 (N($CH_2$)$_2$(*C*$H_2$)$_2$), 30.6 ($CH_2$*C*$H_2$$CH_2$), 39.0 (*C*$H_2$$CH_2$*C*$H_2$), 47.8 (N(*C*$H_2$)$_2$($CH_2$)$_2$), 127.6 (*m*-*C*H$_{arom}$), 136.7 (*p*-*C*H$_{arom}$), 139.4 (*o*-*C*H$_{arom}$), 141.8 (*i*-*C*H$_{arom}$), 155.1 (NH*C*(N)N). $^{19}$F NMR(282 MHz, $CDCl_3$): δ -171.83 (br, 2F, *p*-C*F*$_{arom}$), -166.60 (t, $^3J_{FF}$ = 21.0 Hz, 4F, *m*-C*F*$_{arom}$), -155.71 (d, $^3J_{FF}$ = 21.0 Hz, 4F, *o*-C*F*$_{arom}$). IR [$cm^{-1}$]: $\nu$(NH) = 3272, $\nu$(CH) = 2958 and 2867, $\nu$($CC_{arom}$)= 1597, 1529 and 986, $\nu$(CN) = 1498. HR-ESI-MS: calcd. for $C_{25}H_{24}F_{10}N_6$ $[M+H]^+$ 599.1981; found 599.1984.

**1,1'-(1,3-propylene)bis(*N-tert*-butylpyrrolidine-1-carboximidamide) (2c):** A mixture of 0.31 g (1.0 mmol) **1c**, 1.48 g (20.0 mmol) pyrrolidine, and 0.11 g (5.0 mmol) PbO in 20 ml of toluene was stirred at 50 °C for 48 hours. After cooling to room temperature, the solids were filtered off, washed with toluene and the combined filtrates were concentrated *en vacuo* yielding **2c** in analytically pure form. Orange viscous oil, 0.36 g, 0.9 mmol, 89%. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.17 (s, 9H, C(C$H_3$)$_3$), 1.23 (s, 9H, C(C$H_3$)$_3$), 1.69-1.77 (m, 8H, N($CH_2$)$_2$(C$H_2$)$_2$), 1.77-1.80 (m, 2H, $CH_2$C$H_2$$CH_2$), 3.13-3.23 (m, 8H, N(C$H_2$)$_2$($CH_2$)$_2$), 3.24-3.33 (m, 4H, C$H_2$$CH_2$C$H_2$). $^{13}$C{$^1$H} NMR(101 MHz, $CDCl_3$): δ = 21.9 (*C*$H_2$*C*H$_2$*C*$H_2$), 25.0 (C(*C*$H_3$)$_3$), 25.4 (N($CH_2$)$_2$(*C*$H_2$)$_2$), 26.0 (N($CH_2$)$_2$(*C*$H_2$)$_2$), 29.5 (C(*C*$H_3$)$_3$), 32.0 (C(*C*$H_3$)$_3$), 43.4 (N(*C*$H_2$)$_2$($CH_2$)$_2$), 46.2 (N(*C*$H_2$)$_2$($CH_2$)$_2$), 50.2 (C(*C*$H_3$)$_3$), 53.3 (C(*C*$H_3$)$_3$), 56.4 (*C*$H_2$$CH_2$*C*$H_2$), 144.8 (NH*C*(N)N), 145.4 (NH*C*(N)N). IR [$cm^{-1}$]: $\nu$(NH) = 3420, $\nu$(CH) = 2952 and 2854, $\nu$(CN) = 1611. HR-ESI-MS calcd. for $C_{21}H_{42}N_6$ $[M+H]^+$ 379.3549; found 379.3566.

**1,1'-(1,3-phenylene)bis(*N-tert*-butylpyrrolidine-1-carboximidamide) (2d):** A mixture of 3.39 g (1.0 mmol) **1e**, 1.42 g (20.0 mmol) pyrrolidine, an 0.45 g (6.0 mmol) PbO in 10 ml of toluene was stirred at 100 °C for 8 hours. After cooling to room temperature, the solids were filtered of washed with toluene and the combined filtrates were concentrated *e vacuo* yielding **2d** in analytically pure form. Brown solid, 0.30 g, 0.7 mmo 73%.$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 18H, C(C$H_3$)$_3$), 1.72 (dt, $^3J_H$ = 6.2 Hz, 6.5 Hz, 8H, N($CH_2$)$_2$(C$H_2$)$_2$), 3.13 (t, $^3J_{HH}$ = 6.5 Hz, 8H N(C$H_2$)$_2$($CH_2$)$_2$), 3.53 (s, 4H, CN*H*C), 6.13 (t, $^3J_{HH}$ = 1.9 Hz, 1H, 5-C$H_{arom}$ 6.24 (dd, $^3J_{HH}$ = 1.9 Hz, $^4J_{HH}$ = 7.8 Hz, 2H, 4,6-C$H_{arom}$), 6.97 (t, $^4J_{HH}$ = 7. Hz, 1H, 2-C$H_{arom}$). $^{13}$C{$^1$H} NMR(101 MHz, $CDCl_3$): δ = 25. (N($CH_2$)$_2$(*C*$H_2$)$_2$), 30.2 (C(*C*$H_3$)$_3$), 48.6 (N(*C*$H_2$)$_2$($CH_2$)$_2$), 51.9 (*C*(CH$_3$)$_3$ 113.7 (4,6-*C*H$_{arom}$), 115.4 (2-*C*H$_{arom}$), 128.6 (1,3-*C*H$_{arom}$), 129.2 (5-*C*H$_{arom}$ 151.7 (NH*C*(N)N). IR [$cm^{-1}$]: $\nu$(NH) = 3362, $\nu$(CH) = 2960 and 286 $\nu$($CC_{arom}$)= 1607, 1505 and 1341 $\nu$(CN) = 1559. HR-ESI-MS: calcd. fo $C_{24}H_{40}N_6$ $[M+H]^+$ 413.3393; found 413.3387.

**1,1'-(1,3-xylylene)bis[*N*-(2,6-diisopropylphenyl)pyrrolidine-1-carboximidamide] (2e):** A mixture of 0.85 g (1.0 mmol) **1f**, 1.42 g (20. mmol) pyrrolidine, and 0.45 g (2.0 mmol) PbO in 20 ml of toluene wa stirred at 100 °C for 16 hours. After cooling to room temperature, the solid were filtered off, washed with toluene and the combined filtrates wer concentrated *en vacuo* yielding **2e** in analytically pure form. White solic 0.66 g, 1.0 mmol, 99%. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, $^3J_{HH}$ = 7. Hz, 12H, CH(C$H_3$)$_2$), 1.18 (d, $^3J_{HH}$ = 7.0 Hz, 12H, CH(*CH*$_3$) $_2$), 1.84 (dt, $^3J_H$ = 5.2 Hz, 6.8 Hz, 8H, N($CH_2$)$_2$(C$H_2$)$_2$), 3.09 (sept, $^3J_{HH}$ = 7.0 Hz, 4H C*H*($CH_3$)$_2$), 3.29 (t, $^3J_{HH}$ = 6.8 Hz, 8H, N(C$H_2$)$_2$($CH_2$)$_2$), 3.81 (br, 2H, CN*H*C 4.26 (s, 4H, C$H_2$$C_6H_4$C$H_2$), 6.93 (t, $^3J_{HH}$ = 7.8Hz, 2H, *p*-C$H_{arom}$), 7.04 (d $^3J_{HH}$ = 7.8 Hz, 4H, *m*-C$H_{arom}$), 7.12 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 4,6-C$H_{arom}$), 7.1 (m, 1H, 2-C$H_{arom}$), 7.21 (t, $^3J_{HH}$ = 8.3 Hz, 1H, 5-C$H_{arom}$). $^{13}$C{$^1$H} NMR(10 MHz, $CDCl_3$): δ = 23.2 (CH(*C*$H_3$)$_2$), 23.7 (CH(*C*$H_3$)$_2$), 25.5 (N($CH_2$)$_2$(*C*$H_2$)$_2$ 28.1 (*C*H(CH$_3$)$_2$), 47.7 ($CH_2$$C_4H_6$*C*$H_2$), 48.4 (N(*C*$H_2$)$_2$($CH_2$)$_2$), 121.8 (*m C*H$_{arom}$), 122.8 (*p*-*C*H$_{arom}$), 125.8 (4,6-*C*H$_{arom}$), 128.8 (2-*C*H$_{arom}$), 140.1 (o *C*H$_{arom}$), 140.3 (*i*-*C*H$_{arom}$), 145.1 (1,3-*C*H$_{arom}$), 151.0 (NH*C*(N)N). IR [$cm^{-1}$ $\nu$(NH) = 3449 and 3399, $\nu$(CH) = 2954 and 2865, $\nu$($CC_{arom}$)= 1611, 150 and 1342, $\nu$(CN) = 1580. HR-ESI-MS: calcd. for $C_{42}H_{60}N_6$ $[M+H]^+$ 649.495 found 649.4975.

**1,1'-(1,3- xylylene)bis[*N*-(2,6-diisopropylphenyl)morpholine-1-carboximidamide] (2f):** A mixture of 0.27 g (0.5 mmol) **1f**, 0.11 g (9.3 mmol) morpholine, and 0.23 g (1.0 mmol) PbO in 10 ml of toluene was stirred at 100 °C for 16 hours. After cooling to room temperature, the solids were filtered off, washed with toluene and the combined filtrates were concentrated *en vacuo* yielding **2f** in analytically pure form. White solid, 0.25 g, 0.4 mmol, 77%. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.13 (d, $^3J_{HH}$ = 6.9 Hz, 12H, CH(C$H_3$)$_2$), 1.16 (d, $^3J_{HH}$ = 6.9 Hz, 12H, CH(*CH*$_3$) $_2$), 2.96 (sept, $^3J_{HH}$ = 6.9 Hz, 4H, C*H*($CH_3$)$_2$), 3.25 (t, $^3J_{HH}$ = 4.0 Hz, 8H, N(C$H_2$)$_2$($CH_2$)$_2$O), 3.69 (br, 2H, CN*H*C), 3.76 (br, 8H, N($CH_2$)$_2$(C$H_2$)$_2$O),

4.17(s, 4H, C$H_2$C$_6$H$_4$C$H_2$), 6.86-7.27 (m, 10H, C$H_{arom}$). $^{13}$C{$^1$H} NMR(101 MHz, CDCl$_3$): **δ**= 23.4 (CH(C$H_3$)$_2$), 28.1 (C$H$(CH$_3$)$_2$), 49.0 (C$H_2$C$_4$H$_6$C$H_2$), 57.8 (N(C$H_2$)$_2$(C$H_2$)$_2$O), 66.7 (N(C$H_2$)$_2$(C$H_2$)$_2$O), 123.0 (*m*-C$H_{arom}$), 123.2 (*p*-C$H_{arom}$), 125.1 (4,6-C$H_{arom}$), 125.7 (2-C$H_{arom}$), 129.2 (2-C$H_{arom}$), 139.4 (*o*-C$H_{arom}$), 139.8 (*i*-C$H_{arom}$), 143.6 (1,3-C$H_{arom}$), 154.5 (NHC(N)N). IR [cm$^{-1}$]: *v* (NH) = 3385, *v*(CH) = 2956 and 2864, *v*(CC$_{arom}$)= 1629, 1446 and 1324 and 1113, *v*(CN) = 1586. HR-ESI-MS: calcd. for $C_{42}H_{60}N_6O_2$ [M+H]$^+$ 681.4856; found 681.4863.

**1,1'-(1,3-xylylene)bis[3,3-diethyl-2-(2,6-diisopropylphenyl)guanidine] (2g):** A mixture of 0.29 g (0.5 mmol) **1f**, 0.73 g (10.0 mmol) diethylamine, and 0.25 g (1.1 mmol) PbO in 10 ml of toluene was stirred at 100 °C for 16 hours. After cooling to room temperature, the solids were filtered off, washed with toluene and the combined filtrates were concentrated *en vacuo* yielding **2g** in analytically pure form. Orange viscous oil, 0.29 g, 0.5 mmol, 99%. $^1$H NMR (400 MHz, CDCl$_3$): **δ** = 1.13 (d, $^3J_{HH}$ = 7.0 Hz, 12H, CH(C$H_3$)$_2$), 1.17 (d, $^3J_{HH}$ = 7.0 Hz, 12H, CH(C$H_3$)$_2$), 1.10-1.19 (m, 12H, N(CH$_2$)$_2$(C$H_3$)$_2$, 3.02 (sept, $^3J_{HH}$ = 7.0 Hz, 4H, C$H$(CH$_3$)$_2$), 3.26 (q, $^3J_{HH}$ = 7.1 Hz, 8H, N(C$H_2$)$_2$(CH$_2$)$_2$), 3.63 (br, 2H, CN$H$C), 4.12 (s, 4H, C$H_2$C$_6$H$_4$C$H_2$), 6.90-7.20 (m, 10H, C$H_{arom}$). $^{13}$C{$^1$H} NMR(101 MHz, CDCl$_3$): **δ** = 12.9 (N(CH$_2$)$_2$(CH$_3$)$_2$), 23.6 (CH(C$H_3$)$_2$), 28.1 (C$H$(CH$_3$)$_2$), 42.6 ,0(N(CH$_2$)$_2$(CH$_3$)$_2$), 48.5 (CH$_2$C$_4$H$_6$C$H_2$), 122.5 (*m*-C$H_{arom}$), 123.1 (*p*-C$H_{arom}$), 125.1 (4,6-C$H_{arom}$), 125.5 (5-C$H_{arom}$), 129.0 (2-C$H_{arom}$), 139.8 (*o*-C$H_{arom}$), 140.1 (*i*-C$H_{arom}$), 144.6 (1,3-C$H_{arom}$), 154.4 (NH*C*(N)N). IR [cm$^{-1}$]: *v*(NH) = 3383, *v*(CH) = 2958 and 2866, *v*(CC$_{arom}$)= 1622, 1437, 1379 and 1082, *v*(CN) = 1585. HR-ESI-MS: calcd. for $C_{42}H_{64}N_6$ [M+H]$^+$ 653.5270; found 653.5258.

**1,1'-(1,3-xylylene)bis[3,3-di-*n*-propyl-2-(2,6-diisopropylphenyl)guanidine] (2h):** A mixture of 0.45 g (0.8 mmol) **1f**, 1.62 g (16.0 mmol) dipropylamine, and 0.35 g (1.6 mmol) PbO in 20 ml of toluene was stirred at 100 °C for 16 hours. After cooling to room temperature, the solids were filtered off, washed with toluene and the combined filtrates were concentrated *en vacuo* yielding **2h** in analytically pure form. Orange viscous oil, 0.57 g, 0.8 mmol, 99%. $^1$H NMR (300 MHz, CDCl$_3$): **δ** = 0.89 (t, $^3J_{HH}$ = 6.8 Hz, 12H, N(CH$_2$)$_4$(C$H_3$)$_2$, 1.13 (d, $^3J_{HH}$ = 6.5 Hz, 12H, CH(C$H_3$)$_2$), 1.16 (d, $^3J_{HH}$ = 6.5 Hz, 12H, CH(C$H_3$)$_2$), 1.50-1.71 (m, 8H, N(CH$_2$)(C$H_2$)$_2$(CH$_3$)$_2$), 3.96 - 3.04 (m, 4H, C$H$(CH$_3$)$_2$), 3.18 (t, $^3J_{HH}$ = 6.8 Hz, 8H, N(C$H_2$)$_2$(CH$_2$)$_2$(CH$_3$)$_2$), 3.63 (br, 2H, CN$H$CH$_2$), 4.10 (d, $^3J_{HH}$ = 6.7 Hz, 4H, C$H_2$C$_6$H$_4$C$H_2$), 6.85 (br, 1H, 2-C$H_{arom}$) 6.94 (t, $^3J_{HH}$ = 7.4 Hz, 2H, *p*-C$H_{arom}$), 7.00 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 4,6-C$H_{arom}$), 7.06 (d, $^3J_{HH}$ = 7.3 Hz, 4H, *m*-C$H_{arom}$), 7.19 (br, 1H, 5-C$H_{arom}$). $^{13}$C{$^1$H} NMR (101 MHz, CDCl$_3$): 11.5 (N(CH$_2$)$_4$(CH$_3$)$_2$), 20.8 (N(CH$_2$)$_2$(CH$_2$)$_2$(CH$_3$)$_2$), 23.5 (CH(CH$_3$)$_2$), 28.0 (CH(CH$_3$)$_2$), 48.4 (CNHCH$_2$), 50.1 (N(CH$_2$)$_2$(CH$_2$)$_2$(CH$_3$)$_2$), 122.4 (*m*-C$H_{arom}$), 123.0 (*p*-C$H_{arom}$), 125.1 (4,6-C$H_{arom}$), 125.5 (2-C$H_{arom}$), 129.1 (2-C$H_{arom}$), 139.6 (*o*-C$H_{arom}$), 140.1 (*i*-C$H_{arom}$,) 154.8 (NH*C*(N)N). IR [cm$^{-1}$]: *v*(NH) = 3379, *v*(CH) = 2959 and 2870, *v*(CC$_{arom}$)= 1625, 1459 and 1079, *v*(CN) = 1586. HR-ESI-MS: calcd. for $C_{46}H_{72}N_6$ [M+H]$^+$ 709.5897; found 709.5905.

**1,1'-(1,3-xylylene)bis[3-cyclohexyl-2-(2,6-diisopropylphenyl)guanidine] (2i):** A mixture of 0.27 g (0.47 mmol) **1f**, 0.92 g (9.3 mmol) cyclohexylamine, and 0.23 g (1.0 mmol) PbO in 8 ml of toluene was stirred at 100 °C for 16 hours. After cooling to room temperature, the solids were filtered off, washed with toluene and the combined filtrates were concentrated *en vacuo* yielding **2i** in analytically pure form. Off-white solid, 0.32 g, 0.5 mmol, 96%. $^1$H NMR (300 MHz, CDCl$_3$): **δ** = 0.83 - 1.97 (m, 46H, CH(C$H_3$)$_2$ + NC$H$(C$H_2$)$_2$(C$H_2$)$_2$(C$H_2$), 3.10 (br, 4H, C$H$(CH$_3$)$_2$), 3.44 (br, 2H, CN$H$C), 3.70-4.8 (m, 4H, C$H_2$C$_6$H$_4$C$H_2$), 4.65 (br, 2H, CN$H$C), 6.99 (t, $^3J_{HH}$ = 7.0Hz, 2H, *p*-C$H_{arom}$), 7.09 (d, $^3J_{HH}$ = 7.0 Hz, 4H, *m*-C$H_{arom}$), 7.35(br, 4H, CH$_{arom}$). $^{13}$C{$^1$H} NMR(101 MHz, CDCl$_3$): **δ**= 23.7 (CH(C$H_3$)$_2$), 24.9 (NCH(CH$_2$)$_2$(CH$_2$)$_2$(C$H_2$) ), 25.1 (NCH(CH$_2$)$_2$(CH$_2$)$_2$(CH$_2$) ), 27.9 (CH(CH$_3$)$_2$), 34.3 (NCH(C$H_2$)$_2$(CH$_2$)$_2$(CH$_2$), 45.7 (C$H_2$C$_4$H$_6$CH$_2$), 50.8 (NCH(CH$_2$)$_2$(CH$_2$)$_2$(CH$_2$), 122.4 (*m*-C$H_{arom}$), 123.1 (*p*-C$H_{arom}$), 126.2 (4,6-C$H_{arom}$), 126.2 (5-C$H_{arom}$), 128.9 (2-C$H_{arom}$), 141.4 (*o*-C$H_{arom}$), 141.5 (*i*-C$H_{arom}$), 144.0 (1,3-C$H_{arom}$), 148.1 (NHC(N)N). IR [cm$^{-1}$]: *v*(NH) = 3402, *v*(CH) = 2925 and 2853, *v*(CC$_{arom}$)= 1630, 1441 and 1326, *v*(CN) = 1584. HR-ESI-MS: calcd. for $C_{46}H_{68}N_6$ [M+H]$^+$ 705.5583; found 705.5592.

**1,1'-(1,3-xylylene)bis[3-phenyl-2-(2,6-diisopropylphenyl)guanidine] (2j):** A mixture of 0.27 g (0.5 mmol) **1f**, 0.87 g (9.3 mmol) aniline, and 0.23 g (1.0 mmol) PbO in 8 ml of toluene was stirred at 100 °C for 16 hours. After cooling to room temperature, the solids were filtered off, washed with toluene and the combined filtrates were concentrated *en vacuo* yielding **2j** in analytically pure form. Off-white solid, 0.31 g, 0.5 mmol, 95%. $^1$H NMR (400 MHz, CDCl$_3$): **δ** = 1.18 (br, 24H, CH(C$H_3$)$_2$), 3.20 (br, 4H, C$H$(CH$_3$)$_2$ 4.07-4.84 (m, 4H, C$H_2$C$_6$H$_4$C$H_2$), 5.41 (br, 2H, CN$H$C), 6.84-7.82 (m, 22H C$H_{arom}$ + CN$H$C). $^{13}$C{$^1$H} NMR(101 MHz, CDCl$_3$): **δ**= 23.8 (CH(C$H_3$)$_2$), 28. (CH(CH$_3$)$_2$), 45.5 (C$H_2$C$_4$H$_6$CH$_2$), 122.1 (C$H_{arom}$), 122.8 (C$H_{arom}$), 123. (C$H_{arom}$), 124.9 (C$H_{arom}$), 126.3 (C$H_{arom}$), 127.0 (C$H_{arom}$), 128.7 (C$H_{arom}$ 129.5 (C$H_{arom}$), 138.3 (C$H_{arom}$), 140.1 (C$H_{arom}$), 141.2 (C$H_{arom}$), 143.9 (1,3 C$H_{arom}$), 149.4 (NH*C*(N)N). IR [cm$^{-1}$]: *v*(NH) = 3403, *v*(CH) = 2958, 292 and 2865, *v*(CC$_{arom}$)= 1634, 1497, 1437 and 1256, *v*(CN) = 1584. HR-ES MS: calcd. for $C_{46}H_{56}N_6$ [M+H]$^+$ 693.4645; found 693.4638.

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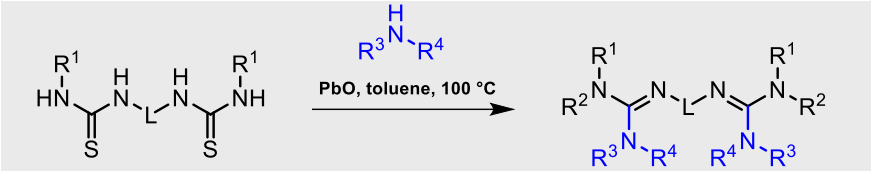


Using an efficient one-pot protocol, 1,2,3-tri- and 1,1,2,3-tetrasubstituted bis(guanidines) are obtained from readily available bis(thioureas) in analytically pure form and good to excellent yields. The facile strategy covers a range of terminal and bridging groups. Less sterically demanding cyclic and acyclic secondary alkyl amines are applicable as well as primary amines and anilines.

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**A Facile One-Pot Synthesis of 1,2,3-Tri- and 1,1,2,3-Tetrasubstituted Bis(guanidines) from Bis(thioureas)**