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Iron Trichloride and Air Mediated Guanylation of Acylthioureas. An Ecological Route to Acylguanidines: Scope and Mechanistic Insights

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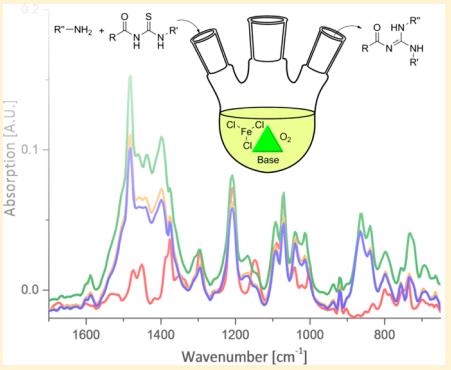
Supporting Information

ABSTRACT: Recently we introduced iron trichloride as an environmentally benign and cost-efficient reagent for the synthesis of *N*-benzoylguanidines. This highly attractive synthetic approach grants access to a broad spectrum of *N*-benzoylguanidines under mild conditions in short reaction times. In this work we present an extended scope of our methodology along with the results obtained from mechanistic studies via in situ IR spectroscopy in combination with LC (liquid chromatography)-MS analyses. On the basis of these new mechanistic insights we were able to optimize the synthetic protocol and to develop an alternative mechanistic proposal. In this context the symbiotic roles of iron trichloride and oxygen in the guanylation process are highlighted.



INTRODUCTION

Owing to their high versatility, via their structural modifiability, guanidines represent an important substance class in many different fields of chemistry, biology, and pharmacology. As an integral part of the amino acid arginine and the nucleobase guanine, the guanidine moiety is present in many proteins and in the base pairs of DNA.[1] Thus, many natural products and biologically active molecules are based on guanidines as structural motifs.[2,3] The high biological and/or pharmaceutical activity of the guanidine moiety is based on its ability to form hydrogen bonds and strong noncovalent interactions with anions such as carboxylates, phosphates, sulfates, and nitrates.[2] Additionally, guanidine entities, located in a protein side chain, are able to build up cation−π interactions with adjacent aromatic systems, influencing protein structures.[4]

For a long time, in organic synthesis, guanidine derivatives were mostly appreciated for their exceptionally high basicity resulting from the resonance stabilization of their conjugate acids.[5,6] It was not until the early 1980s that the synthetic value of guanidine organic superbases was recognized by Barton et al. They described the synthesis of a number of sterically hindered pentaalkylguanidines and their application in organic transformations.[7]

Guanidines have been increasingly applied in the growing field of organocatalysis. Due to the high structural diversity of the guanindine moiety, it can act as a nucleophile or a Brønsted base and it can devolve chiral information to the substrate via hydrogen bonding or ionic noncovalent interactions. The application of guanidine derivatives in organic synthesis has been highlighted in a number of excellent reviews.[8]

Beyond the areas described above, there are several more applications of guanidines. They can be used as ligands,[9] ionic liquids,[10] fluorescent probes,[11] surfactants,[12] peptide mimetics,[13] and membrane materials.[14]

In some cases the high basicity can be disadvantageous: for example, when the respective guanidine is used as a ligand for metal ions in an aqueous medium. Due to the high basicity, the protonated guanidine will be formed almost exclusively, significantly decreasing the Lewis basicity and the ability to coordinate electron acceptors. Hence, acylguanidines represent an important group of guanidines with significantly altered properties. Introducing electron-withdrawing acyl substituents to a guanidine moiety significantly reduces its basicity to pK_a values of about 7−8.[2] *N*-Acyl-substituted guanidines can act as ligands for different metal cations. The resulting complexes exhibit interesting properties, making them useful tools in pharmacology[15] or in organic synthesis as catalysts for hydroformylations.[16] In drug design, acyl substituents are introduced to guanidine moieties to lower the basicity and, thus, enhance their oral bioavailability and CNS penetration.[17]

Figure 1 shows the commercially available acylguanidine-based drugs amiloride (**1**), a diuretic used for the treatment of hypertension, and guanfacine (Intuniv; **2**), which is applied for

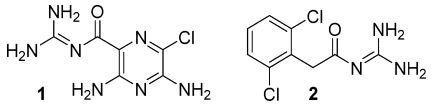


Figure 1. Acylguanidine-based drugs amilorid (**1**) and guanfacine (Intuniv; **2**).

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therapy of attention deficit hyperactivity disorder (ADHD). *N*-Acylguanidines are present in many different drug classes such as β-secretase inhibitors for treatment of Alzheimer's disease,[18] anti-inflammatories,[17] antiarrhythmics,[19] analgetics,[20] and antithrombotics.[21]

We recently published our results on the synthesis of aroylguanidines using iron(III) chloride as a green, highly reactive, and cost-efficient reagent for the conversion of thioureas.[22]

Among a broad variety of synthetic approaches[1,23] toward the synthesis of acylguanidines, conversions starting from thioureas are frequently used. Thioureas are easily accessible and convenient to handle due to their high stability. One possible way to convert the thiourea into a reactive intermediate is desulfurization using condensing agents such as 1-methyl-2-chloropyridiniumiodide ("Mukaiyama's reagent")[24] or ethyl-3-aminopropylcarbodiimide hydrochloride (EDCI).[25] Other approaches to remove sulfur are based on the use of toxic metal salts such as mercury(II) chloride.[26,27] The toxicity precludes the use of those metal salts for pharmaceutical or food applications. Nontoxic alternatives such as bismuth(III) nitrate[28] have also been described. However, we were able to show that our approach using nontoxic and low-priced $FeCl_3$ grants access to *N*-benzoylguanidines in comparable or superior yields under mild reaction conditions using easily accessible and stable starting materials.[22]

The aim of this publication is to highlight the role of iron(III) chloride in the desulfurization of thioureas using in situ IR spectroscopy and other analytical methods. The scope of the reaction and optimization of the synthetic protocol are discussed.

RESULTS AND DISCUSSION

Our studies toward the conversion of *N*-aroylthioureas **3a**–**u** to the corresponding guanidines revealed that iron(III) chloride is a highly efficient reagent for this purpose.

As indicated by the results compiled in Table 1, a broad variety of differently substituted *N*-benzoylthioureas **3a**–**u** can be converted to the corresponding *N*-benzoylguanidines **5a**–**u** by adding the amine **4** in the presence of iron(III) chloride. In most cases, the products were obtained in moderate to good yields. Contemplation of *N*-benzoyl-N′-arylthioureas reveals that electron-withdrawing groups such as 4-nitro and 4-methyl esters (entries 2 and 8) exert a decreasing effect on the yield. In addition, less nucleophilic anilines with an electron-withdrawing substituent such as 4-COOMe can be applied, giving a reasonable yield within 5 h. However, the yield is significantly lower in comparison to the conversion utilizing an electron-rich aniline (entries 8 and 9).

The somewhat higher yield in the case of the 3,5-dimethyl-substituted thiourea **5p** in comparison to the 2,6-dimethyl analogue **5o** indicates that also steric effects might have an impact (Table 1, entries 16 and 17). In addition to the *N*-benzoyl-*N*′,*N*″-diarylguanidines, *N*-benzoyl-*N*′-alkyl-*N*″-arylguanidines were also synthesized. The alkyl moiety can be introduced via the thiourea or by utilizing an aliphatic amine **4**. In both cases the corresponding guanidines **5r**,**t**,**u** were obtained in good yields (entries 19, 21, and 22). By use of hexamethyldisilazane as an ammonia surrogate, the disubstituted *N*-benzoyl-*N*′-arylguanidine **5s** could also be generated (entry 20). An interesting observation was made on comparing thioureas **3i**,**j**, which have 4-CN and 2-CN aryl substituents, respectively. The thiourea bearing a 4-CN moiety was successfully converted, giving the guanidine **5i** in 60% yield. In contrast to that, the target compound **5j** could not be isolated upon conversion of the 2-CN analogue with *p*-anisidine **6**. Instead, the amide **7** was isolated in 44% yield. Interestingly, comparable reaction products were synthesized by Bolm et al. via $FeCl_3$-catalyzed *N*-arylation of amides using aryl iodides.[29] However, it appears implausible to reason that the occurrence of amide **7** is by the reaction path of iron-catalyzed *N*-arylation. Rather, it is likely that the formation of **7** is closely connected with the Lewis acidity of iron(III) chloride. A plausible mechanism for the formation of **7** is depicted in Scheme 1.

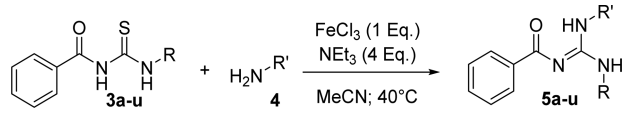
Thus, the ability of the nitrile group to act as a Lewis base makes it an additional coordination site for the iron species. Apparently this changes the reactivity at the carbon atom of the thiocarbonyl moiety to the disadvantage of the guanylation.

In addition, in the case of 2-pyridyl thiourea the desired product **5l** could not be isolated, although the TLC indicated consumption of the starting material. If, on the other hand, the 3-pyridyl thiourea was deployed, the guanidine **5k** could be isolated in 50% yield.

According to this, we assume that the formation of stable iron complexes **8** and **9** is a reasonable explanation in this particular case. Both the thiourea and the guanidine, bearing a 2-pyridyl moiety, are able to form stable six-membered rings upon complexation of an iron species, as is shown in Figure 2.

Similar observations were made by Fürstner et al. during their studies concerning titanium-catalyzed indole syntheses.[30] Due to the complexation of titanium by the carbonyl functionalities, treatment of the crude product with EDTA was necessary to allow further purification and isolation of the product. However, this approach did not contribute to the solution of the problem in the case of the 2-pyridyl derivatives. These two examples

Table 1. Conversion of *N*-Benzoylthioureas with Aryl- and Alkylamines using Iron(III) Chloride



entry	thiourea	R	R′	product	yield
1	**3a**	4-MeO-Ph	4-MeO-Ph	**5a**	76
2	**3b**	4-NO2-Ph	4-MeO-Ph	**5b**	41
3	**3c**	4-F-Ph	4-MeO-Ph	**5c**	64
4	**3d**	4-Cl-Ph	4-MeO-Ph	**5d**	59
5	**3e**	2-Cl-Ph	4-MeO-Ph	**5e**	76
6	**3f**	4-Br-Ph	4-MeO-Ph	**5f**	71
7	**3g**	4-I-Ph	4-MeO-Ph	**5g**	68
8	**3h**	4-MeOOC-Ph	4-MeO-Ph	**5h**	60
9	**3a**	4-MeO-Ph	4-MeOOC-Ph	**5h**	44
10	**3i**	4-CN-Ph	4-MeO-Ph	**5i**	60
11	**3j**	2-CN-Ph	4-MeO-Ph	**5j**	-
12	**3k**	3-Pyridyl	4-MeO-Ph	**5k**	50
13	**3l**	2-Pyridyl	4-MeO-Ph	**5l**	-
14	**3m**	4-Me-Ph	4-MeO-Ph	**5m**	50
15	**3n**	2-Me-Ph	4-MeO-Ph	**5n**	45
16	**3o**	2,6-Me-Ph	4-MeO-Ph	**5o**	50
17	**3p**	3,5-Me-Ph	4-MeO-Ph	**5p**	56
18	**3q**	Ph	4-MeO-Ph	**5q**	66
19	**3r**	*tert*-butyl	4-MeO-Ph	**5r**	71
20	**3s**	4-MeO-Ph	H	**5s**	41[a]
21	**3t**	4-MeO-Ph	*n*-butyl	**5t**	67
22	**3u**	4-MeO-Ph	cyclohexyl	**5u**	67

[a] $(TMS)_2NH$ used as NH_3 surrogate.

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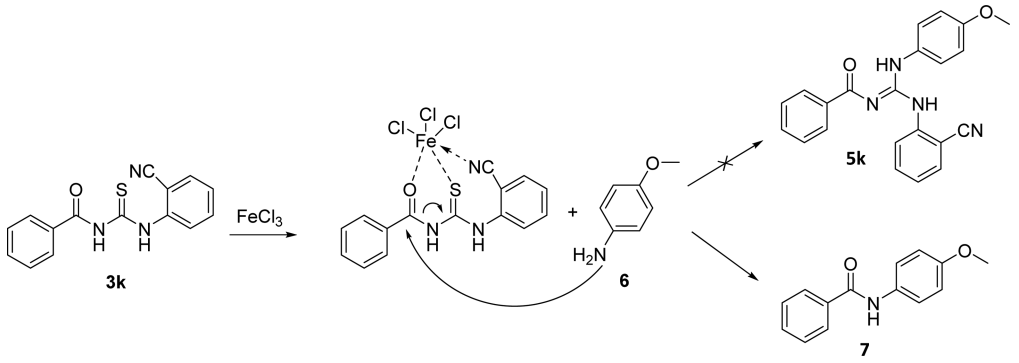
Scheme 1. Rationale for the Formation of *N*-Arylamide 7 as a Competing Reaction with Guanylation



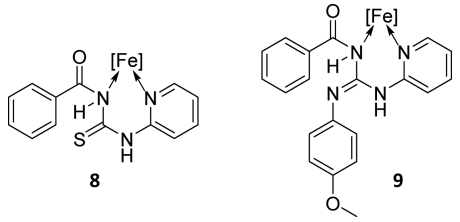


Figure 2. Formation of stable iron complexes **8** and **9** by the 2-pyridyl derivatives.

illustrate that the limitations of the method being presented are most likely caused by the characteristics of iron(III) chloride in general and its Lewis acidity in particular.

In addition to the evaluation of different aryl and alkyl moieties, also the influence of the acyl group on the formation of guanidines was examined. Thioureas bearing an acyl (**10**) and an *N*-ethoxycarbonyl moiety (**11**) were converted with *p*-anisidine (**6**) (Scheme 2).

As depicted in Table 1, *N*-benzoylthiourea **3a** gave the corresponding guanidine **5a** in 76% yield. However, when the benzoyl moiety was exchanged by an *N*-acyl group, the target molecule **12** could only be isolated in a disappointing yield of 6%. Instead, as the main product, deacetylated guanidine **14** was obtained in 46% yield (Figure 3).

Hence, the *N*-acetyl group was cleaved under the given reaction conditions, which disqualifies it for utilization in guanylation reactions using iron trichloride. In contrast to that, *N*-ethoxycarbonylthiourea **11** was converted to the corresponding guanidine **13** in a satisfying 67% yield. Even though the yield was somewhat lower in comparison to that of the *N*-benzoyl substituent, this result illustrates the general suitability of *N*-ethoxycarbonyl groups for the synthesis of guanidines according to our protocol. In general, the preceding results have demonstrated the broad applicability of our synthetic methodology using iron(III) chloride as a guanylating agent.

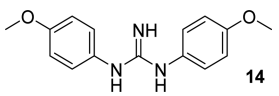


Figure 3. Deacetylated guanidine **14**.

Despite this fact, some limitations have been identified and discussed in this context. In addition, the formation of side products was observed during our initial studies on iron(III) chloride mediated guanylation.

These facts clarify the necessity to gain a sound understanding of the reaction mechanisms, as this is the basic prerequisite for optimized reaction conditions and reaction sequences. To obtain detailed insight into the reaction course and optimize the reaction conditions, we utilized in situ IR spectroscopy in combination with LC-MS analysis. The IR studies were focused on the identification of reaction intermediates, whereas LC-MS analysis was used to investigate the product spectrum dependence on the reaction sequence. In the literature it is commonly accepted that the reaction follows a pathway via carbodiimide intermediate **15** (Scheme 3).

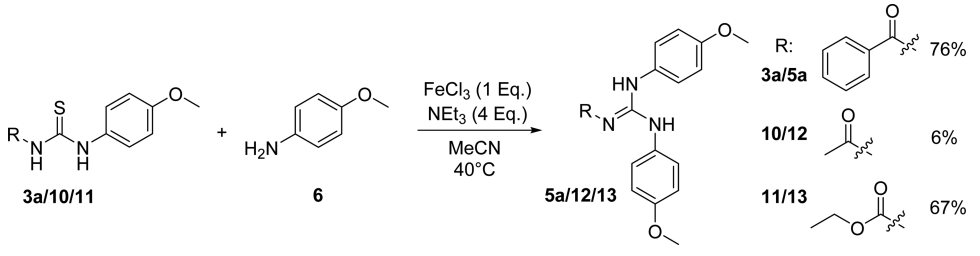
As implied in Scheme 3, an important feature of this mechanistic proposal is the formation of metal sulfides according to the desulfurization of the thiourea by the metal salt being used.

To further investigate the occurrence of intermediate species such as carbodiimides, a test reaction was deployed and the reaction course was monitored by IR spectroscopy.

Hence, 4-bromo thiourea **3f** was converted with *p*-anisidine **6** with variations in the conditions and sequence (Scheme 4 and Table 2).

In addition to the reference spectrum of the pure carbodiimide of thiourea,[31] an additional reference spectrum after the addition of $FeCl_3$ was recorded also. This was done to evaluate if significant bands will be shifted in the presence of iron(III) chloride. The comparison of the reference spectra reveals that the distinctive, asymmetric −N═C═N− bond stretching is attenuated and also slightly shifted from 2158 to 2164 cm^{-1}

Scheme 2. Influence of Different Acyl Moieties on the Guanylation



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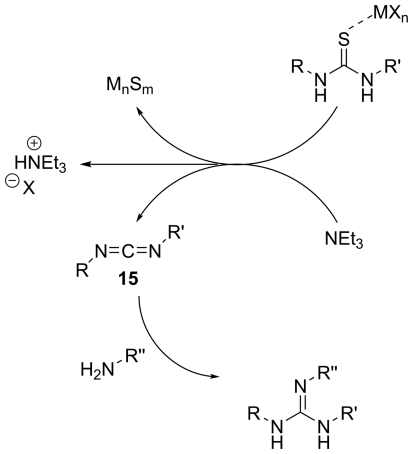
Scheme 3. Proposed Reaction Mechanism via Carbodiimide Intermediate



after addition of $FeCl_3$ (see Scheme SI in the Supporting Information). However, this band remains suitable for the identification of carbodiimide intermediates since it is still sufficiently visible even in the presence of iron(III) chloride.

Also, disturbances by the absorption of other species are not to be expected in this spectral region. In case of test reaction 1 in Table 2, the formation of a carbodiimide would be expected after the addition of iron(III) chloride (Table 2, entry 1). In Scheme SII in the Supporting Information, the IR spectrum directly before addition of iron(III) chloride is compared respectively with the IR spectra 1, 5, and 10 min after the addition.

According to this, no carbodiimide was formed after $FeCl_3$ was added. The reaction conditions as well as the sequence of test reaction 1 (Table 2) are equivalent to those applied for the synthesis of the guanidines enlisted in Table 1. In the test reactions 2−4 the formation of a carbodiimide intermediate was investigated depending on the reaction sequence. Eventually no such intermediate could be identified during any of these test reactions using iron(III) chloride. For comparison another test reaction was conducted with mercury(II) chloride using DMF as solvent (test reaction 5). Immediately after addition of the base, a significant absorption band at 2162 cm^{-1} was formed (see Scheme SIII in the Supporting Information).

A direct comparison with the associated reference band at 2158 cm^{-1} confirmed the origin in the intermediate liberation of a carbodiimide. This important finding confirmed the postulated mechanistic pathway via a carbodiimide intermediate for the synthesis of guanidines using $HgCl_2$. However, the absorption band was only observable directly after addition of the base followed by a rapid regression.

Since there was no amine **6** present at this point of the reaction, the regression cannot be assigned to a reaction of the carbodiimide and amine **6**. Instead, the decrease in intensity might be due to insufficient solubility of the intermediate. To exclude the possibility that the occurrence of the carbodiimide was due to the use of DMF as solvent, an additional test reaction with iron(III) chloride in DMF was carried out (Table 2, test reaction 6). Even under these conditions no carbodiimide intermediate was observed in the case of iron(III) chloride. These results clearly illustrate that the mechanistic pathway of the reaction strongly depends on the choice of metal salt.

Table 2. Reaction Sequences and Conditions of the Test Reactions with Thiourea 3f

test reaction	sequence	carbodiimide
1	MeCN, THS **3f**, TEA (4 equiv), 0 °C, $FeCl_3$, 40 °C, **6**	no
2	MeCN, THS **3f**, TEA (4 equiv), **6**, 40 °C, $FeCl_3$	no
3	MeCN, $FeCl_3$, THS **3f**, 40 °C, TEA (4 equiv), **6**	no
4	MeCN, THS **3f**, **6**, TEA (4 equiv), 0 °C, $FeCl_3$, 40 °C	no
5	DMF, 0 °C, $HgCl_2$, THS **3f**, TEA (2 equiv), **6**	yes
6	DMF, $FeCl_3$, THS **3f**, 40 °C, TEA (4 equiv), **6**	no

The formation of a carbodiimide could not be confirmed in any of the cases when iron(III) chloride was used as guanylating agent. In contrast to that, an intermediate carbodiimide was formed when mercury(II) chloride was used in the same manner.

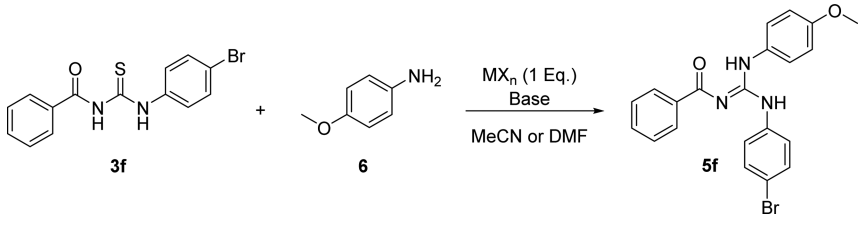
According to the in situ IR experiments discussed so far, the mechanistic pathway of the guanylation is mainly influenced by two major aspects: metal salt and reaction sequence.

In addition to the identification of reaction intermediates, in situ IR spectroscopy also enabled us to visualize the different outcomes of reactions depending on the reaction sequence. As stated before, the reaction sequence influences the mechanistic path of the reaction. Therefore, it is likely that this can also be expressed by the IR spectra of the finished reactions. Accordingly, an IR reference spectrum of guanidine **5f** was compared with the IR spectra of the finished test reactions 1 and 2 (Table 2) (see Scheme SIV in the Supporting Information), showing the IR spectrum at the end of test reaction 1 together with the reference spectrum of guanidine **5f**.

In Scheme SIV in the Supporting Information a comparison of the IR spectrum at the end of test reaction 2 with the reference spectrum is presented. Distinctive absorption bands of guanidine **5f** are found at 1514, 1356, 1073, 1032, 1013, 836, 747, and 715 cm^{-1}. It is obvious how the different reaction sequences affect the outcome of the reactions.

Whereas the reaction spectrum of test reaction 1 (Table 2) exhibits a high degree of discrepancy in comparison to the reference, the reaction spectrum of test reaction 2 matches the reference very well. According to this finding, the sequence

Scheme 4. Test Reaction for the Identification of Reaction Intermediates[a]



[a]The synthesis of the carbodiimide of thiourea **3f** is given as reference.

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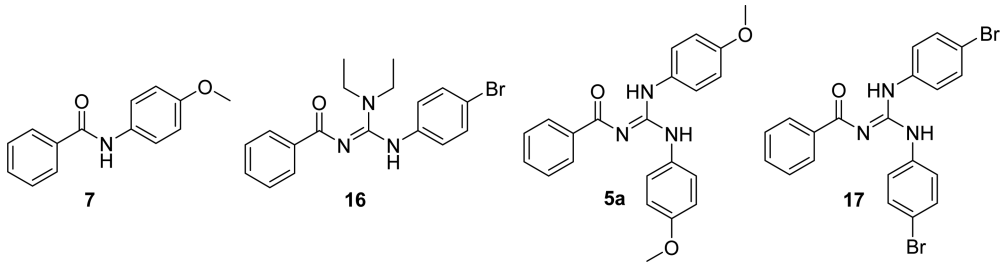
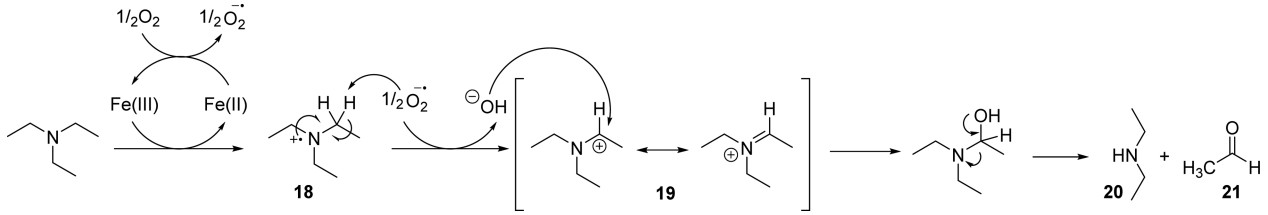
Scheme 5. Side Products Formed in $FeCl_3$-Mediated Guanylation



Scheme 6. Mechanistic Rationale for the Oxidative Degradation of Triethylamine with Involvement of $FeCl_3$ and Oxygen



applied in test reaction 2 is in comparison the more appropriate and purposeful approach for the formation of guanidine **5f**.

Reaction monitoring by in situ IR measurements can provide valuable information about the progress of the reaction: e.g., by plotting the consumption of starting materials and/or formation of product(s). In Scheme SV in the Supporting Information the formation of guanidine **5f** is depicted along with the consumption of *p*-anisidine **6**. The formation of the product **5f** reached a maximum after 3 h of reaction time, whereas the amount of starting material *p*-ansidine **6** was below the detection limit after approximately 1 h 15 min.

As we were able to show that the reaction sequence has a major impact on the course and outcome of the guanylation, the next step toward optimized reaction conditions was taken by LC-MS analysis of the crude products from IR test reactions. Therefore, the crude products of the test reactions 1−4 from Table 2 were characterized regarding their composition. The chromatograms of LC-MS measurements are shown in Scheme SVII in the Supporting Information. These results are in good agreement with findings described before. Hence, the extent of side product formation strongly depends on the reaction sequence.

We were able to identify most of the side products formed in the course of the reaction (Scheme 5).

One of them is the *N*-arylamide **7**, which was described before and whose appearance is probably due to an S_N reaction with direct involvement of iron(III) chloride. The formation of side product **16** has to be assigned to the oxidative degradation of triethylamine, resulting in the formation of diethylamine via the formation of the corresponding amine radical cation.[32]

Scheme 6 illustrates a mechanistic rationale for the oxidative degradation of triethylamine in the presence of the single-electron oxidant $FeCl_3$ and oxygen. After formation of radical cation **18**, abstraction of a proton by oxygen leads to formation of iminium ion **19**. Nucleophilic attack of the hydroxide anion and subsequent tautomerization yields acetaldehyde **21** and diethylamine **20**, which can participate in a side reaction to form guanidine **16**.

In addition to the target compound **5f**, also the side products **5a** and **17** with exchanged phenyl rings were found. A comparison between test reactions 1 and 2 (Table 2) concerning the extent of side product formation clearly illustrates the beneficial effect of the changed reaction sequence. According to this, $FeCl_3$ should be added last after all the starting materials have been added.

Furthermore, it seems conducive to conduct the addition at 40 °C instead of 0 °C. These slight changes had a major effect on the selectivity in favor of the desired product **5f**. In test reaction 2 (Table 2) fewer exchange products were found. In addition, the amount of degradation product **16** was significantly lowered. The formation of *N*-arylamide **7** was prevented completely in test reaction 2.

In test reaction 3 (Table 2) only 2 equiv of triethylamine was used. Apart from that, the reaction sequence was identical with test reaction 1. Consequently, the amount of elimination product **18** was considerably reduced. The influence of the base is discussed later in this paper.

In Scheme SVII in the Supporting Information, chromatogram 4 shows the composition of the crude product from test reaction 4 (Table 2). This example represents the most disadvantageous reaction sequence out of the chosen examples. The extent of the side reactions was by far the highest when iron(III) chloride was furnished first with subsequent addition of the other starting materials. Summarizing the results of the LC-MS studies, it can be stated that test reaction 2 represents the ideal reaction sequence out of those being compared. So far we could carve out that the mechanistic pathway in general and the occurrence of a carbodiimide intermediate in particular are mainly influenced by the metal salt being used. In addition, the reaction sequence plays an important role. When iron(III) chloride is used to convert *N*-benzoyl-*N*′-arylthiourea **3f**, the reaction does not proceed via a carbodiimide intermediate. For the development of an alternative mechanistic proposal the results from IR and LC-MS studies have to be taken into consideration. One of the key questions is how the formation of the exchange products **5a** and **19** is to be explained.

From these results the existing mechanistic proposal, illustrated in Scheme 3, has to be questioned. The hypothesized mechanistic pathway via an intermediate carbodiimide could already be delimited by the results of our in situ IR studies. The desulfurization of thioureas using mercury and copper salts is based on the formation of the corresponding sulfides. In this regard Cunha et al. also described the formation of bismuth(III)

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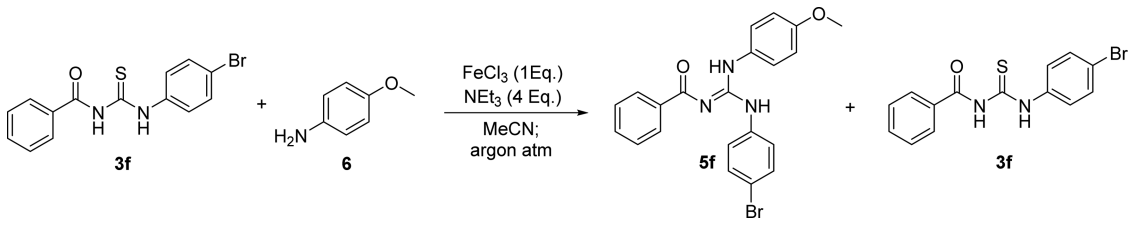
Scheme 7. Test Reaction for the Involvement of Oxygen in the Guanylation



sulfide Bi_2S_3 as a byproduct when bismuth(III) nitrate was utilized as a guanylating agent.[33] We have found that the utilization of other thiophiles such as indium(III) chloride also results in the formation of sulfides. This was proven by filtration of the reaction mixture and subsequent treatment of the solid residue with dilute hydrochloric acid, resulting in the liberation of hydrogen sulfide.

In case of iron(III) chloride, sulfide formation can be ruled out, since no hydrogen sulfide was detected when the same procedure was followed. This finding is in good agreement with results described by Busch and Schier, who found that hydrogen sulfide flowing through a solution of iron(III) chloride in acetonitrile led to the precipitation of sulfur instead of iron sulfides.[34] It is rather likely that desulfurization using iron(III) chloride is based on a redox process instead of sulfide formation. Thus, the oxidation of hydrogen sulfide by iron(III) can be described by the following redox pair:

$$Fe^{3+} + e^- \rightleftharpoons Fe^{2+} \quad (1)$$

$$H_2S \rightleftharpoons 1/8S_8 + 2e^- + 2H^+ \quad (2)$$

Applied to guanylation, this would imply that the oxidation of the thiourea to zerovalent sulfur (eq 2) is accompanied by reduction of iron(III) to iron(II) (eq 1). At this point it becomes apparent that a one-electron reduction is involved in a two-electron oxidation. This leads to the conclusion that another participant has to be involved in the redox process. Consequently, a control experiment was conducted to evaluate if oxygen plays a key role. Thus, thiourea **3f** and **6** were treated with iron(III) chloride with exclusion of oxygen under an argon atmosphere (Scheme 7).

After an observable progress in the first 30 min of the reaction, the TLC sample after 3.5 h revealed stagnation of the conversion. The reaction was aborted after 4 h, which would be sufficient time for conversion under atmospheric conditions. Purification of the crude product gave the product **5f** in 51% yield, and the thiourea **3f** was retrieved in 47% yield.

However, if 2 equiv of iron(III) chloride is applied under an argon atmosphere, reaction control by TLC revealed complete conversion of the thiourea. Despite this fact, guanidine **5f** could only be isolated in only 40% yield due to promoted side reactions under these conditions. In addition, 2 equiv of aniline **6** had to be applied for complete conversion of **3f** due to the increased amount of $FeCl_3$.

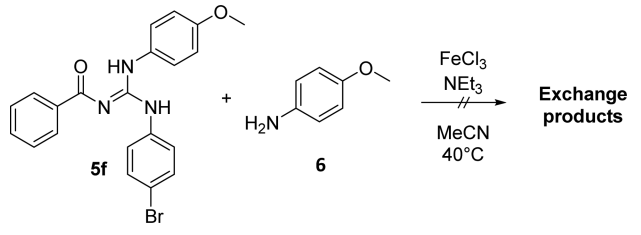
On the one hand, these striking results confirm the hypothesis that the guanylation using iron(III) chloride is based on a redox process. On the other hand, they prove the assumption that oxygen is an essential participant in this redox process, for there is no complete conversion in its absence.

Once iron(III) is reduced completely to iron(II), the oxidation of the thiourea cannot proceed any longer. In this regard oxygen is required to reoxidize iron(II) to iron(III), making it an essential reaction partner. This finding was supported by the fact that we were unable to identify iron(II) species following the literature procedures.[35] Thus, it has to be stated that the presented protocol represents an unprecedented $FeCl_3$/air mediated guanylation reaction sequence. In contrast to our previous assumptions,[22] iron(III) chloride and air are equal reagents in the synthetic method at hand.

It is notable that the conversion of bromo-substituted thiourea **3f** in the presence of 0.5 equiv of iron(III) chloride led to the desired product **5f** in 68% yield, which is only an insignificant decrease of 3% yield in comparison that for to 1 equiv $FeCl_3$. These highly interesting findings show that reoxidation of iron(II) species is obviously influenced by the chemical environment. The formation of complexes between iron species and the corresponding thiourea and the product certainly have a significant influence. In addition, the formation of iron(III) oxo species should be taken into consideration. This finding might pave the road to potential catalytic protocols. Nevertheless, the utilization of substoichiometric amounts of iron(III) chloride in the presence of air remains challenging and the synthetic success seems to depend on the electronic nature of the applied thiourea. Thus, in the case of guanidine **5a** the yield was decreased by 26% (50% vs 76% yield) when 0.7 equiv of iron(III) chloride was used.[22]

Taking one step back to the results of LC-MS analysis, we still needed to find an explanation for the formation of side products. In this regard it would be useful to determine at which point of the guanylation the exchange of aromatic rings occurs. Thus, a control experiment, using guanidine **5f** and aniline **6**, was carried out. The aim of this test was to find out if the formation of exchange products can take place when the targeted guanidine is already formed. Accordingly, both starting compounds were furnished in acetonitrile and then treated with iron(III) chloride and triethylamine (Scheme 8).

Scheme 8. Exchange Experiment with Guanidine 5f and Aniline 6



Since no conversion and hence no formation of exchange products could be observed, we reasoned that the formation of these side products must happen at an earlier stage of the reaction. The formation of the guanidine itself seems to be irreversible, however. From all of the results obtained so far we are now able to postulate an alternative reaction mechanism. For this we need to consider the following key aspects:

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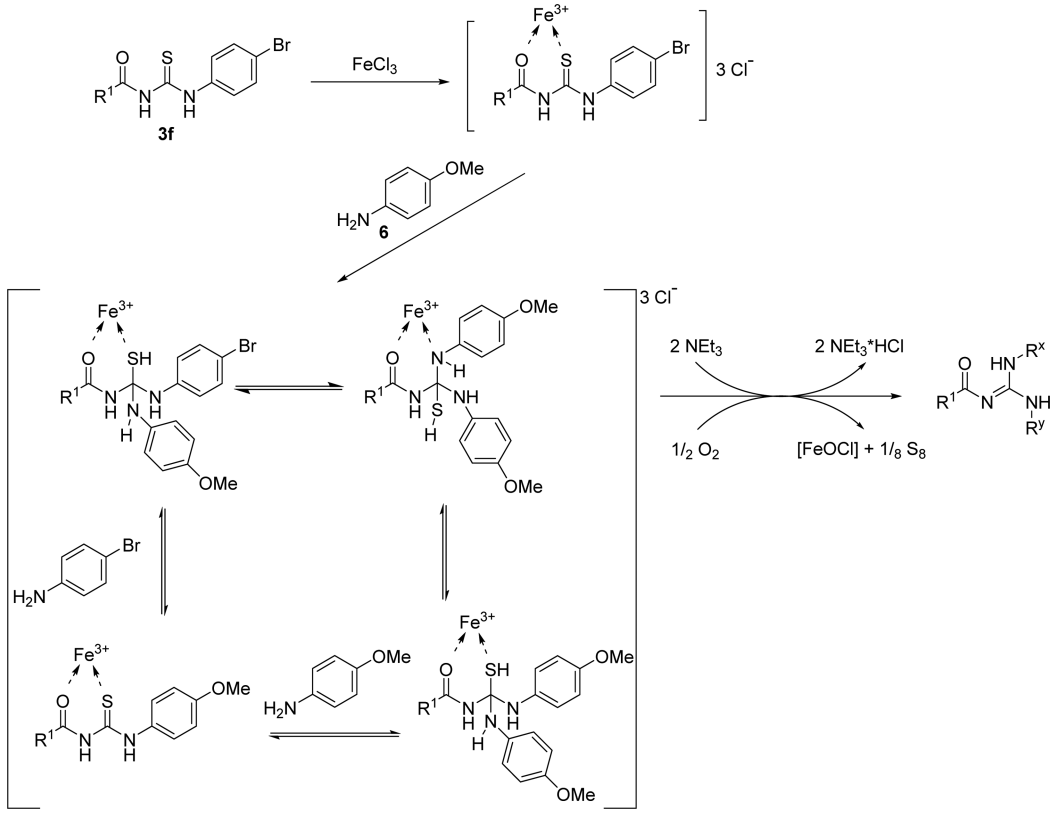
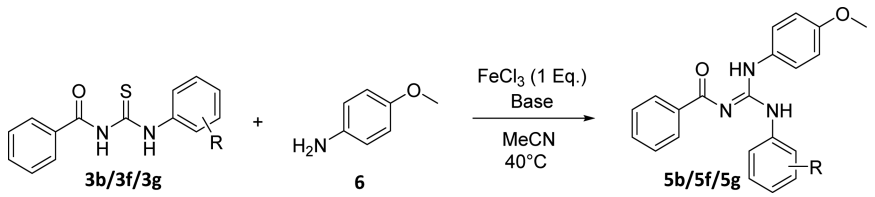
Scheme 9. Mechanistic Proposal for the Formation of *N*-Benzoyl-*N*′,*N*″-arylguanidines



Scheme 10. Test Reaction for the Evaluation of Different Bases



For in situ IR studies, when $FeCl_3$ is used, the appearance of intermediate carbodiimides depends on the thiourea to be converted.

There is no formation of iron sulfides upon use of $FeCl_3$.

As confirmed by earlier results, there is no sulfide formation when H_2S is passed through a solution of $FeCl_3$; formation of sulfur

Iron(III) acts as an oxidant.

Oxygen is an essential reaction partner, reoxidizing Fe(II) to Fe(III)

Formation of exchange products cannot be explained by a mechanism via a carbodiimide intermediate.

Guanylation is irreversible.

Exchange of phenyl rings occurs at an early reaction stage.

According to these major conclusions, we are able to develop a mechanistic proposal for the formation of guanidines using iron(III) chloride. The results of our calorimetric studies[22] as well as the investigations based on in situ IR techniques do suggest that *N*-benzoylthioureas form complexes upon treatment with iron(III) chloride. Scheme SVI in the Supporting Information shows the IR spectrum of thiourea **3f** in comparison to its IR spectrum after addition of iron(III) chloride. The most significant change associated with iron(III) is the splitting of the carbonyl band at 1681 cm^{-1}. The exact structure of these iron thiourea complexes could not be determined in detail so far. However, an octahedral structure seems to be most likely due to the involvement of iron(III). Scheme 9 illustrates a possible reaction mechanism based on the conversion of *N*-benzoyl-*N*′-arylthiourea **3f** with *p*-anisidine **6**. After the addition of the amine, here *p*-anisidine **6**, a tetragonal intermediate is formed. The postulation of this intermediate state is based on the finding that for the utilization of *N*-benzoyl-*N*′-arylthiourea **3f** no carbodiimide was observed in the course of the reaction. In addition, this provides an adequate explanation for the formation of the exchange products **5a** and **17**. It is not known in detail how this exchange reaction proceeds: e.g., if it is a simultaneous or a stepwise process. A possible simplified mechanistic path is included in Scheme 9. Herein, iron(III) is coordinated as a Lewis acid by the S- and O-donor atoms, facilitating a nucleophilic attack by an amine at the thiocarbonyl carbon atom.

Recent findings by Ray et al., who have described the formation of iron(III) chelates bound to 3-methyl-3-phenyl-1-benzoylthioureas,[38] support this mechanistic proposal.

The oxidative cleavage of the C−S bond with subsequent liberation of sulfur has to be considered as the key step of the

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guanylation with iron trichloride. The electrons released are abstracted by iron(III), which is reduced to iron(II). To allow the complete oxidation of the thiourea, the presence of oxygen is required for the reoxidation of iron(II). In this regard oxygen functions as an essential co-oxidant. The iron(III) species resulting from the reoxidation step is formally depicted as [FeOCl] in Scheme 9.

As was shown by LC-MS analysis of the crude products from the test reactions, another side product that was formed in significant amounts is the degradation product **16** of the base triethylamine. Although the exact path for the formation of this side product is not understood in detail, studies concerning the influence of the base were conducted. Thus, different bases were tested for the conversion of different *N*-benzoyl-*N*′-arylthioureas with *p*-anisidine **6** (Scheme 10).

The results of the test reactions using different amine bases are summarized in Table 3

Table 3. Results of Test Reactions with Different Bases

entry	R	base (amt (equiv))	yield (%)
1	4-Br	TEA (4)	71
2	4-Br	TEA (2)	76
3	4-Br	DBU (4)	–
4	4-Br	HB (4)	41
5	4-Br	TMEDA (2)	39
6	4-Br	HB + TMEDA (2 + 1)	38
7	4-Br	PS (2)	82
8	4	KO^{t}Bu (2)	38
9	4-I	TEA (4)	68
10	4-I	PS (2)	77
11	4-I	TMEDA (2)	62
12	4-NO_2	TEA (4)	41
13	4-NO_2	PS (2)	77

1,8-Diazabicyclo[5.4.0]undec-7-en (DBU) was tested as an alternative, non-nucleophilic base for the conversion of thiourea **3f** with a 4-bromo substituent. Despite the non-nucleophilic character of DBU, the formation of side products could not be reduced effectively in this case (Table 3, entry 3).

In contrast, reaction control by TLC already revealed a number of side products, which is why the product was not isolated. Subsequently, *N*,*N*-diisopropylethylamine (HB; Hünig's base) was tested (Table 3, entry 4). Due to steric hindrance by its bulky alkyl substituents, HB is another non-nucleophilic base convenient for our purposes, though. It exhibits a significantly lower basicity in comparison to DBU. Since in the literature[28] the use of 4 equiv of triethylamine is also described and in terms of better comparability, DBU and HB were also applied in this ratio.

In the case of HB, the number of side products was not noticeably diminished. Furthermore, the yield of guanidine **5f** was decreased by 30% in comparison to the use of TEA (Table 3, entry 1). When the thiourea **5g** with a 4-iodo substituent was converted using *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA), the occurrence of unwanted side products was reduced significantly. Even though chromatographic purification was simplified due to this fact, the overall yield was still 6% lower than that of reactions using triethylamine (entries 9 and 11). The decrease in yield was even more drastic for the conversion of the thiourea **3f** (entry 5). A combination of HB and TMEDA also did not improve the performance (entry 6). The best results by far were obtained upon the use of *N*,*N*,*N*′,*N*′-tetramethylnaphthalene-1,8-diamine (PS; "Proton Sponge") **22**. Conversions conducted with PS yielded the desired products with particular high selectivity and minimized side reactions. The obtained yields were consistently higher in comparison to every other base tested. Guanidine **5f**, bearing a 4-bromo substituent, was obtained in 11% higher yield in comparison to triethylamine (entries 1 and 7). In the case of guanidine **5g** with a 4-iodo substituent the yield was increased by 9% (entries 9 and 10). The most remarkable improvement with PS was achieved for the conversion of thiourea **3b**, bearing a 4-nitro group. In case of triethylamine, the corresponding guanidine **5b** was obtained in a rather disappointing yield of 41% (entry 12). In contrast, the yield was improved to 77% by utilization of PS (Scheme 11).

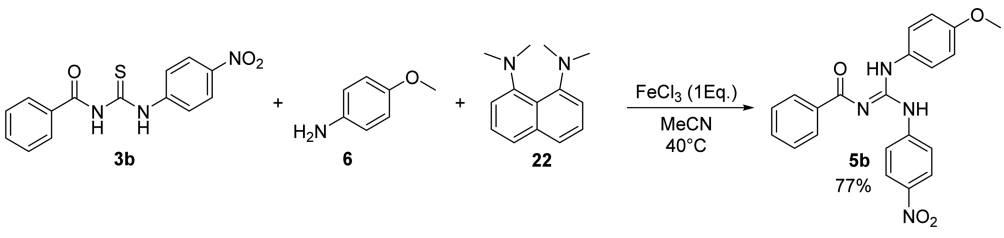
For successful conversion of the tested thioureas 2 equiv of Proton Sponge **22** was sufficient. Even though the molecule contains two amino groups, it will abstract only one proton. This characteristic is explained by the exceptionally high stability of the monoprotonated cation resulting from intramolecular hydrogen bonding. Thus, the use of 2 equiv of Proton Sponge **22** equals 2 instead of 4 base equiv. Accordingly, an additional test was done for the conversion of thiourea **3f** using only 2 equiv of triethylamine (Table 3, entry 2). The corresponding guanidine **5f** was obtained in a very good yield of 76%.

This result shows that 2 equiv of base is adequate for the guanylation of thioureas. Since we could show that triethylamine is involved in side reactions, this finding is especially welcome. This is also valid with regard to ecological and economical aspects. In addition to the different amine bases tested, also the oxygen base KO^{t}Bu was tested. In this case the guanidine **5f** was isolated in an unsatisfactory yield of 38%.

In summary, the obtained results have clearly illustrated that the choice of the base has a major impact on the outcome of the reaction. The utilization of Proton Sponge **22** led to remarkable improvements, since the occurrence of side and exchange products was reduced to a minimum.

Thereby, purification and isolation procedures were highly facilitated, yielding the desired guanidines in superior yields. Despite the superior selectivity and the target-oriented reaction course that were realized with Proton Sponge **22**, the higher costs and the poor atom economy justify our continuing search for even more efficient alternatives.

Scheme 11. Optimized Synthetic Protocol for the Conversion of 4-Nitrothiourea 3b using $FeCl_3$ and PS



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CONCLUSION AND OUTLOOK

The present work summarized the results of our studies toward the guanylation of thioureas using iron(III) chloride. The scope and the limitations of the synthetic protocol were evaluated and discussed. $FeCl_3$ proved to be a powerful tool for the synthesis of various *N*-acylguanidines. Based on an efficient and environmentally benign process, it grants access to an important substance class of interest in different fields such as chemistry, pharmacology, and biology. In addition to an evaluation of the synthetic spectrum, this work focused on gaining a fundamental understanding of the reaction mechanism. In this context we embarked on in situ IR spectroscopy combined with LC-MS analysis. The results enabled us to illustrate that the reaction course mainly depends on the metal salt being applied and the reaction sequence as well. For the conversion of *N*-benzoyl-*N*′-arylthiourea **3f** we could clarify that upon the utilization of $FeCl_3$ the reaction does not proceed via a carbodiimide intermediate. However, the opposite case occurred when $HgCl_2$ was used, which is in good agreement with the literature. Within our ongoing studies on this topic we will further examine the influence that the thiourea exhibits on the reaction course.

The insights gained by LC-MS analyses allowed us to find an optimized reaction sequence with regard to a minimized formation of side products. Since conventionally applied nitrogen bases such as triethylamine and *N*,*N*-diisopropylethylamine **22** are involved in side reactions, the results obtained upon the use of Proton Sponge **22** can be considered as a remarkable improvement. Continuing studies on the effect of different bases are currently being carried out in our group.

With all the results in hand, we were able to develop an alternative mechanistic proposal. The formation of exchange products was taken into account, resulting in the postulation of a tetragonal intermediate which replaced the formerly postulated carbodiimide. Most strikingly, we were able to prove that iron(III) chloride is involved in a redox process, in which oxygen participates as an essential co-oxidant. Therefore, $FeCl_3$ plays a distinctive role among all other metal salts described as guanylating agents so far. In view of this freshly gained knowledge and given the comments of reviewers of our recent publication, we are now pursuing the aim of realizing a guanylating process with catalytic amounts of iron(III) chloride. Among other findings, the results of our efforts in this direction will be reported in due course.

EXPERIMENTAL SECTION

General Methods. All reagents and solvents, obtained from commercial sources, were used without further purification. Reaction products were purified by flash chromatography on silica gel (25 μm) using cyclohexane and ethyl acetate as eluents. TLC was performed on silica gel plates 60 F254. LC-MS analyses were carried out on a HPLC system coupled with a TOF mass spectrometer. HPLC was done using a column with C18-silica gel (2.6 μm) with a water/MeCN gradient.

NMR spectra were measured on a 500 or 400 MHz spectrometer using deuterated solvents with trimethylsilane as internal standard. Chemical shifts δ are given in ppm and coupling constants J in Hz. Multiplicities of NMR signals are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (heptet), tt (triplet of triplets), dtd (doublet of doublets of triplets). IR spectra were recorded with a FT-IR spectrometer using a germanium ATR (attenuated total reflection) unit and are reported in wavenumbers (cm^{-1}). Mass spectra were obtained with GC TOF (EI) and ESI-Q-TOFmicro instruments. Melting points were determined in open glass capillaries. The in situ IR measurements were carried out in 100 mL Mettler-Toledo EasyMax reactors under atmospheric conditions. Recording of IR spectra was done with a ReactIR 15 unit by Mettler-Toledo using a silicon AT probe ((DST-6.3-305-1.5-16300) 6.3 mm AgX SiComp).

General Procedure 1 for Synthesis of *N*-Acylguanidines 5a–u. The reactions were carried out in a 100 mL EasyMax reactor, equipped with a reflux cooler, magnetic stirrer bar, and temperature sensor. To a solution of thiourea (5 mmol) in 30 mL of acetonitrile were added triethylamine (20 mmol, 2.02 g, 2.77 mL, 4 equiv) and the particular amine (5 mmol, 1 equiv) with stirring at 300 rpm. The reaction mixture was cooled to 0 °C (reactor temperature (T_R)) over 10 min. Then iron(III) chloride (5 mmol, 811 mg, 1 equiv) was added. After another 10 min, the temperature was raised to 40 °C (T_R) over 30 min. The progress of the reaction was monitored by TLC (CHx-EtOAc). After complete conversion, the reaction mixture was transferred into a 250 mL round-bottom flask. Activated carbon was added, and the mixture was stirred in a water bath at 70 °C for 5 min. The suspension was filtered through a pad of Celite and washed with dichloromethane. The filtrate was then concentrated in vacuo and the brownish solution was treated with diethyl ether, precipitating triethylamine hydrochloride. The suspension was filtered through a G4-frit and the residue washed subsequently with diethyl ether and tetrahydrofuran. The filtrate was dried in vacuo. Further purification was done by flash chromatography on silica gel with a cyclohexane/ethyl acetate gradient.

Optimized Procedure 2 for Synthesis of *N*-Acylguanidines 5a–u. The reactions were carried out in a 100 mL EasyMax reactor, equipped with a reflux cooler, magnetic stirrer bar, and temperature sensor. To a solution of thiourea (5 mmol) in 30 mL of acetonitrile were added *N*,*N*,*N*′,*N*′-tetramethylnaphthalene-1,8-diamine (10 mmol, 2.143 g, 2 equiv) and the particular amine (5 mmol, 1 equiv) with stirring at 300 rpm. T_R was raised to 40 °C within 10 min followed by the addition of iron(III) chloride (5 mmol, 811 mg, 1 equiv). The progress of the reaction was monitored by TLC (CHx-EtOAc). After complete conversion, the reaction mixture was transferred into a 250 mL round-bottom flask. Activated carbon was added, and the mixture was stirred in a water bath at 70 °C for 5 min. The suspension was filtered through a pad of Celite and the residue washed with dichloromethane. Further purification was done by flash chromatography on silica gel with a cyclohexane/ethyl acetate gradient.

Test Reaction under an Argon Atmosphere. The starting materials were placed in a 100 mL round-bottom flask in acetonitrile, followed by extensive purging with argon. After addition of iron(III) chloride at 40 °C, argon was continuously passed through the reaction mixture. The progress of the reaction was monitored by TLC. In advance every TLC sample was filtered quickly through a small pad of silica to remove iron components that might falsify the results.

*(E)-N-(N,N′-Bis(4-methoxyphenyl)carbamimidoyl)benzamide (**5a**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 4/1) to give the product **5a** (1.423 g, 3.79 mmol, 76%) as a beige solid: R_f (cyclohexane/ethyl acetate 1/1) = 0.41; mp 127.4–128.2 °C (lit. mp 128 °C);[36] ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 3.83 (s, 6H), 6.91–6.97 (m, 4H), 7.31–7.36 (m, 4H), 7.37–7.42 (m, 2H), 7.45 (tt, J = 6.6 and 1.4 Hz, 1H), 8.13–8.24 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm) 178.2, 157.8, 138.5, 131.4, 129.4, 128.0, 126.4, 114.7, 55.7; IR (cm^{-1}) 3376, 3342, 3074, 2963, 2808, 1599, 1565, 1508, 1460, 1374, 1351, 1300, 1240, 1204, 1181, 1106, 1034, 1010, 906, 888, 830, 819, 752, 716, 684; HRMS (EI) calculated for $C_{22}H_{21}N_3O_3$ $[M]^+$ 375.1583, found 375.1571.

*(E)-N-(N′-(4-Methoxyphenyl)-N-(4-nitrophenyl)carbamimidoyl)-benzamide (**5b**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 7/3 > 6/4 > 1/1) to give the product **5b** (0.81 g, 2.07 mmol, 41%) as yellow needles: R_f (cyclohexane/ethyl acetate 1/1) = 0.71; mp 168.6–168.9 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.85 (s, 3H), 6.94–7.04 (m, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.46 (t, J = 7.4 Hz, 2H), 7.51–7.73 (m, 3H), 8.06–8.28 (m, 4H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 143.5, 132.3, 129.4, 129.1, 128.5, 127.2, 125.2, 125.0, 123.1, 121.6, 119.2, 115.6, 55.7; IR (cm^{-1}) 3456, 3369, 3016, 2970, 1738, 1625, 1607, 1592, 1561, 1538 1508, 1490,1420, 1365, 1350, 1336, 1298, 1246, 1217, 1199, 1112, 1028, 975, 856, 846,

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748, 710, 685; HRMS (EI) calculated for $C_{21}H_{18}N_4O_4$ $[M]^+$ 390.1328, found 390.1324.

*(E)-N-(N-(4-Fluorophenyl)-N′-(4-methoxyphenyl)carbamimidoyl)-benzamide (**5c**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 100/0 > 9/1 > 7/3) to give the product **5c** (1.17 g, 3.22 mmol, 64%) as a white solid: R_f (cyclohexane/ethyl acetate 1/1) = 0.55; mp 137.7−137.9 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.83 (s, 3H), 6.96 (d, J = 8.5 Hz, 2H), 7.08 (t, J = 8.4 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.36−7.57 (m, 5H), 8.17 (d, J = 7.4 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 178.3, 160.4 (d, J = 245.4 Hz), 158.6, 157.5, 138.3, 132.9, 131.5, 129.3, 128.4, 128.0, 127.2, 125.8, 115.8 (d, J = 22.8 Hz), 115.1, 55.6; IR (cm^{-1}) 3368, 3072, 2970, 2839, 1737, 1611, 1581, 1566, 1537, 1505, 1445, 1416, 1352, 1292, 1246, 1211, 1198, 1171, 1105, 1030, 979, 908, 886, 829, 797, 74, 713, 685; HRMS (ESI) calculated for $C_{21}H_{19}FN_3O_2$ $[M + H]^+$ 364.1456, found 364.1463.

*(E)-N-(N-(4-Chlorophenyl)-N′-(4-methoxyphenyl)-carbamimidoyl)benzamide (**5d**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 100/0 > 9/1 > 7/3 > 3/2) to give the product **5d** (1.11 g, 2.92 mmol, 59%) as a beige solid: R_f (cyclohexane/ethyl acetate 2/1) = 0.35; mp 128.0−128.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.84 (s, 3H), 6.97 (d, J = 8.6 Hz, 2H), 7.27−7.38 (m, 4H), 7.38−7.59 (m, 5H), 8.18 (d, J = 7.5 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 178.4, 158.8, 157.2, 138.2, 135.8, 131.6, 129.4, 129.1, 128.1, 127.4, 124.6, 115.3, 55.7; IR (cm^{-1}) 3347, 2970, 1737, 1606, 1581, 1560, 1536, 1508, 1492, 1444, 1430, 1407, 1385, 1352, 1287, 1242, 1208, 1191, 1170, 1091, 1032, 912, 879, 830, 809, 752, 713; HRMS (ESI) calculated for $C_{21}H_{19}ClN_3O_2$ $[M + H]^+$ 380.1160, found 380.1160.

*(E)-N-(N-(2-Chlorophenyl)-N′-(4-methoxyphenyl)-carbamimidoyl)benzamide (**5e**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 100/0 > 9/1 > 7/2) to give the product **5e** (1.44 g, 3.78 mmol, 76%) as an off-white solid: R_f (cyclohexane/ethyl acetate 1/1) = 0.54; mp 124.3−124.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.85 (s, 3H), 7.00(d, J = 8.3 Hz), 7.08 (t, J = 7.8 Hz, 1H), 7.31−7.61 (m, 7H), 8.23 (s, 2H), 8.44 (s, 1H); ^{13}C NMR-DEPT135 ($CDCl_3$, 100 MHz) δ (ppm) 131.5, 129.3, 129.1, 128.1, 127.8, 127.3, 125.0, 124.8, 115.3, 55.6; IR (cm^{-1}) 3367, 3002, 2970, 1738, 1619, 1598, 1578, 1561, 1535, 1508, 1443, 1378, 1355, 1298, 1243, 1201, 1169, 1106, 1057, 1029, 982, 910, 879, 838, 731, 742, 706; HRMS (ESI) calculated for $C_{21}H_{19}ClN_3O_2$ $[M + H]^+$ 380.1160, found 380.1159.

*(E)-N-(N-(4-Bromophenyl)-N′-(4-methoxyphenyl)-carbamimidoyl)benzamide (**5f**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 100/0 > 9/1 > 7/3 > 3/2) to give the product **5f** (1.51 g, 3.56 mmol, 71%) as a beige solid: R_f (cyclohexane/ethyl acetate 1/1) = 0.79; mp 136.1−136.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.83 (s, 3H), 6.96 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 7.34−7.58 (m, 7H), 8.18 (d, J = 7.6 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 178.4, 158.8, 157.1, 138.2, 136.3, 132.1, 131.6, 129.3, 128.1, 127.4, 124.9, 118.1, 115.3, 55.6; IR (cm^{-1}) 3455, 3347, 3016, 2970, 1738,1603, 1578, 1558, 1536, 1509, 1489, 1430, 1406, 1352, 1285, 1239, 1216, 1207, 1075, 1032, 1009, 911, 878, 828, 755, 713, 686; HRMS (ESI) calculated for $C_{21}H_{19}BrN_3O_2$ $[M + H]^+$ 424.0655, found 424.0657.

*(E)-N-(N-(4-Iodophenyl)-N′-(4-methoxyphenyl)carbamimidoyl)-benzamide (**5g**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 100/0 > 9/1 > 7/3) to give the product **5g** (1.6 g, 3.39 mmol, 68%) as a white solid: R_f (cyclohexane/ethyl acetate 2/1) = 0.37; mp 143.8−144 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.84 (s, 3H), 6.97 (d, J = 8.7 Hz, 2H), 7.20−7.36 (m, 4H), 7.42 (t, J = 7.4 Hz, 2H), 7.46−7.53 (m, 1H), 7.67 (d, J = 8.6 Hz, 2H), 8.19 (d, J = 7.3 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 178.4, 158.8, 157.1, 138.2, 138.0, 137.1, 131.6, 129.4, 128.1, 127.5, 125.0, 115.3, 88.7, 55.7; IR (cm^{-1}) 3345, 2970, 1737, 1603, 1576, 1557, 1533, 1508, 1486, 1445, 1429, 1403, 1383, 1351, 1282, 1264, 1242, 1207, 1192, 1170, 1117, 1066, 1032, 1006, 912, 877, 836, 827, 810, 756, 713, 685; HRMS (ESI): calculated for $C_{21}H_{19}IN_3O_2$ $[M + H]^+$ 472.0516, found 472.0522.

*(E)-Methyl 4-(3-Benzoyl-2-(4-methoxyphenyl)guanidino)-benzoate (**5h**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 100/0 > 9/1 > 1/1) to give the product **5h** (1.21 g, 2.99 mmol, 60%) as a white solid: R_f (cyclohexane/ethyl acetate 1/1) = 0.79; mp 135.7−136.0 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) δ 3.61−3.95 (m, 6H), 6.82−7.06 (m, 2H), 7.30−7.60 (m, 5H), 7.61−8.14 (m, 6H); ^{13}C NMR-DEPT135 (DMSO-d_6, 100 MHz) δ (ppm) 131.2, 129.5, 128.5, 127.9, 125.7, 122.0, 114.3, 55.0, 51.7; IR (cm^{-1}) 3381, 3365, 3015, 2970, 2948, 1723, 1677, 1611, 1582, 1564, 1531, 1508, 1437, 1415, 1349, 1279, 1241, 1201, 1181, 1107, 1032, 977, 909, 883, 842, 824, 763, 743, 712, 701, 687; HRMS (ESI) calculated for $C_{23}H_{22}N_3O_4$ $[M + H]^+$ 404.1605, found 404.1623.

*(E)-N-(N-(4-Cyanophenyl)-N′-(4-methoxyphenyl)carbamimidoyl)-benzamide (**5i**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 100/0 > 9/1 > 8/2) to give the product **5i** (1.16 g, 3.01 mmol, 60%) as an off-white solid: R_f (cyclohexane/ethyl acetate 1/1) = 0.47; mp 184.2−184.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.85 (s, 3H), 6.99 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.42−7.48 (m, 2H), 7.49−7.68 (m, 5H), 8.12 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 166.7, 159.0, 156.4, 138.9, 133.2, 132.1, 129.1, 128.4, 127.6, 122.2, 119.0, 115.5, 55.7; IR (cm^{-1}) 3349, 2970, 2220, 1737, 1612, 1595, 1580, 1561, 1527, 1508, 1433, 1412, 1378, 1351, 1301, 1277, 1239, 1211, 1176, 1113, 1071, 1028, 982, 912, 879, 837, 807, 754, 744, 712, 687; HRMS (ESI) calculated for $C_{22}H_{19}N_4O_2$ $[M + H]^+$ 371.1503, found 371.1513.

*(E)-N-(N′-(4-Methoxyphenyl)-N-(pyridin-3-yl)carbamimidoyl)-benzamide (**5k**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 4/1 > 2/3 > 1/4) to give the product **5k** (0.87 g, 2.5 mmol, 50%) as a white solid: R_f (cyclohexane/ethyl acetate 1/3) = 0.26; mp 153.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.84 (s, 3H), 6.98 (d, J = 8.4 Hz, 2H), 7.22−7.37 (m, 3H), 7.37−7.57 (m, 3H), 8.01 (d, J = 8.8 Hz, 1H), 8.10−8.24 (m, 2H), 8.39 (d, J = 4.3 Hz, 2H), 8.61 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 178.6, 159.2, 157.4, 145.9, 144.2, 138.0, 134.3, 131.8, 130.5, 129.3, 128.2, 127.8, 123.5, 115.5, 55.7; IR (cm^{-1}) 2970, 1738, 1618, 1600, 1561, 1538, 1513, 1475, 1441, 1397, 1346, 1265, 1243, 1216, 1186, 1031, 981, 914, 839, 807, 750, 716, 688; HRMS (ESI): calculated for $C_{20}H_{19}N_4O_2$ $[M + H]^+$ 347.1503, found 347.1501.

*(E)-N-(N′-(4-Methoxyphenyl)-N-(p-tolyl)carbamimidoyl)-benzamide (**5m**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 100/0 > 8/2 > 75/15 > 1/1) to give the product **5m** (0.87 g, 2.49 mmol, 50%) as a white solid: R_f (cyclohexane/ethyl acetate 1/1) = 0.53; mp 131.7−131.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.37 (s, 3H), 3.84 (s, 3H), 6.95 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 7.30−7.37 (m, 4H), 7.40 (t, J = 7.4 Hz, 2H), 7.44−7.50 (m, 1H), 8.21 (d, J = 7.4 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 178.3, 158.2, 157.5, 138.5, 134.0, 131.4, 130.0, 129.4, 129.1, 128.0, 126.6, 124.2, 114.8, 55.6, 21.1; IR (cm^{-1}) 3347, 2971, 1738, 1600, 1578, 1565, 1532, 1509, 1445, 1410, 1350, 1287, 1242, 1201, 1178, 1135, 1107, 1067, 1034, 979, 908, 884, 826, 811, 764, 743, 718, 704, 686; HRMS (ESI) calculated for $C_{22}H_{22}N_3O_2$ $[M + H]^+$ 360.1707, found 360.1725.

*(E)-N-(N′-(4-Methoxyphenyl)-N-(o-tolyl)carbamimidoyl)-benzamide (**5n**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 100/0 > 8/2 > 75/15 > 1/1) to give the product **5n** (0.81 g, 2.25 mmol, 45%) as an off-white solid: R_f (cyclohexane/ethyl acetate 1/1) = 0.53; mp 135.0−135.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.29 (s, 3H), 3.82 (s, 3H), 6.93 (d, J = 8.5 Hz, 2H), 7.18−7.24 (m, 1H), 7.24−7.33 (m, 2H), 7.32−7.41 (m, 4H), 7.40−7.49 (m, 1H), 7.55 (s, 1H), 8.17 (d, J = 7.5 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 178.3, 157.7, 138.4, 134.9, 131.4, 129.4, 128.0, 127.2, 126.4, 126.2, 114.5, 55.6, 18.1; IR (cm^{-1}) 3380,

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1608, 1595, 1561, 1524, 1508, 1457, 1371, 1350, 1294, 1250, 1203, 1179, 1138, 1106, 1029, 973, 906, 884, 862, 842, 818, 774, 746, 718, 684; HRMS (ESI) calculated for $C_{22}H_{22}N_3O_2$ $[M + H]^+$ 360.1707, found 360.1699.

*(E)-N-(N-(2,6-Dimethylphenyl)-N′-(4-methoxyphenyl)-carbamimidoyl)benzamide (**50**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 100/0 > 9/1 > 8/2) to give the product **5o** (0.93 g, 2.49 mmol, 50%) as a white solid: R_f (cyclohexane/ethyl acetate 2/1) = 0.42; mp 181.5−181.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.38 (s, 6H), 3.83 (s, 3H), 6.00 (s, 1H, NH), 6.90 (d, J = 8.5 Hz, 2H), 7.10−7.23 (m, 3H), 7.29- 7.50 (m, 5H), 8.17−8.24 (m, 2H), 11.98 (s, 1H, NH); ^{13}C NMR-APT ($CDCl_3$, 100 MHz) δ (ppm) 178.4, 158.0, 157.1, 138.5, 136.7, 132.9, 131.4, 130.3, 129.4, 129.2, 128.6, 128.0, 125.2, 113.9, 55.7, 18.5; IR (cm^{-1}) 3370, 3185, 3076, 3023, 2970, 1738, 1599, 1567, 1523, 1507, 1439, 1380, 1373, 1347, 1296, 1247, 1214, 1177, 1139, 1104, 1026, 906, 885, 776, 750, 720 683; HRMS (ESI) calculated for $C_{23}H_{24}N_3O_2$ $[M + H]^+$ 374.1863, found 374.1883.

*(E)-N-(N-(3,5-Dimethylphenyl)-N′-(4-methoxyphenyl)-carbamimidoyl)benzamide (**5p**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 100/0 > 8/2 > 75/15 > 1/1) to give the product **5p** (1.05 g, 2.82 mmol, 56%) as an off-white solid: R_f (cyclohexane/ethyl acetate 1/1) = 0.58; mp 105.4−105.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.35 (s, 6H), 3.84 (s, 3H), 6.87 (s, 1H), 6.96 (d, J = 8.7 Hz, 2H), 7.10 (s, 2H), 7.34 (d, J = 8.6 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.47 (t, J = 7.2 Hz, 1H), 8.23 (d, J = 7.3 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) δ 21.4, 55.6, 114.8, 121.7, 126.7, 127.6, 128.0, 129.1, 129.4, 131.4, 136.6, 138.5, 139.2, 157.3, 158.1, 178.2; IR (cm^{-1}) 3355, 2971, 1738, 1590, 1567, 1537, 1510, 1446, 1353, 1316, 1302, 1277, 1249, 1207, 1178, 1134, 1105, 1034, 1018, 904, 851, 844, 822, 748, 719, 704, 685; HRMS (ESI) calculated for $C_{23}H_{24}N_3O_2$ $[M + H]^+$ 374.1863, found 374.1865.

*(E)-N-(N-(4-Methoxyphenyl)-N′-phenylcarbamimidoyl)-benzamide (**5q**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 100/0 > 9/1 > 8/2) to give the product **5q** (1.15 g, 3.32 mmol, 66%) as a light brown solid: R_f (cyclohexane/ethyl acetate 1/1) = 0.55; mp 111.9−112.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.85 (s, 3H), 6.97 (d, J = 8.1 Hz, 2H), 7.18−7.26 (m, 1H), 7.33 (d, J = 8.3 Hz, 2H), 7.37−7.44 (m, 4H), 7.44−7.51 (m, 3H), 8.21 (d, J = 7.5 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 178.4, 157.4, 138.4, 137.0, 131.5, 129.4, 129.2, 128.1, 127.1, 125.7, 123.9, 115.0, 55.7; IR (cm^{-1}) 3349, 2970, 1738, 1600, 1577, 1564, 1532, 1511, 1499, 1445, 1351, 1290, 1248, 1202, 1178, 1135, 1107, 1067, 1033, 975, 910, 880, 833, 818, 748, 718, 703, 686; HRMS (ESI) calculated for $C_{21}H_{20}N_3O_2$ $[M + H]^+$ 346.1550, found 346.1542.

*(E)-N-(N-(tert-Butyl)-N′-(4-methoxyphenyl)carbamimidoyl)-benzamide (**5r**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 100/0 > 9/1 > 7/3) to give the product **5r** (1.16 g, 3.56 mmol, 71%) as a white solid: R_f (cyclohexane/ethyl acetate 2/1) = 0.42; mp 119.1−119.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.49 (s, 9H), 3.82 (s, 3H), 4.68 (s, NH), 6.89−6.98 (m, 2H), 7.12−7.21 (m, 2H,), 7.37−7.51 (m, 3H), 8.22−8.30 (m, 2H), 11.95 (s, NH); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 177.1, 158.9, 158.5, 139.1, 131.0, 129.1, 128.9, 127.9, 127.5, 115.3, 55.6, 52.4, 29.8; IR (cm^{-1}) 3412, 289, 2970, 1738, 1595, 1570, 1511, 1448, 1358, 1294, 1247, 1227, 1216, 1107, 1026, 916, 894, 853, 821, 758, 749, 710, 692; HRMS (EI) calculated for $C_{19}H_{23}N_3O_2$ $[M]^+$ 325.1790, found 325.1797.

*N-(N-(4-Methoxyphenyl)carbamimidoyl)benzamide (**5s**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 8/2 > 1/1) to give the product **5s** (0.55 g, 2.03 mmol, 41%) as a white solid: R_f (cyclohexane/ethyl acetate 1/1) = 0.18; mp 136.3−136.9 °C (lit. mp 136−137 °C);[37] ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm) δ 3.76 (s, 3H), 6.90−7.01 (m, 2H), 7.35−7.44 (m, 4H), 7.44−7.49 (m, 1H), 8.05−8.12 (m, 2H), 9.29 (s, 2NH); ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ (ppm) 176.0, 159.8, 156.2, 138.8, 130.8, 130.6, 128.6, 127.8, 124.5, 114.2, 55.3; IR (cm^{-1}) 3465, 3070, 3000, 2970, 1738, 1639, 1596, 1558, 1512, 1442, 1354, 1298, 1250, 1205, 1181, 1106, 1087, 1028, 910, 862, 826, 815, 756, 716, 685; HRMS (ESI) calculated for $C_{15}H_{16}N_3O_2$ $[M + H]^+$: 270.1237, found 270.1234.

*(E)-N-(n-Butyl-N′-(4-methoxyphenyl)carbamimidoyl)benzamide (**5t**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 100/0 > 8/2 > 7/3) to give the product **5t** (1.08 g, 3.33 mmol, 67%) as a white solid: R_f (cyclohexane/ethyl acetate 1/3) = 0.69; mp 107.9−108.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.94 (t, J = 7.3 Hz, 3H), 1.36 (h, J = 7.3 Hz, 2H), 1.56 (p, J = 7.2 Hz, 2H), 3.52 (q, J = 6.6 Hz, 2H), 3.81 (s, 3H), 4.76 (s, NH), 6.89−6.98 (m, 2H), 7.18 (d, J = 8.3, 2H), 7.36−7.50 (m, 3H), 8.27 (d, J = 7.0 Hz, 2H), 11.83 (s, NH); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 177.5, 159.5, 158.6, 138.9, 131.1, 129.2, 128.5, 127.9, 127.7, 115.3, 55.6, 41.2, 32.0, 20.1, 13.9; IR (cm^{-1}) 3373, 3175, 2958, 1737, 1601, 1568, 1446, 1355, 1300, 1245, 1204, 1178, 1145, 1027, 893, 856, 816, 751, 712, 686; HRMS (ESI) calculated for $C_{19}H_{24}N_3O_2$ $[M + H]^+$ 326.1863, found 326.1861.

*(E)-N-(N′-Cyclohexyl-N-(4-methoxyphenyl)carbamimidoyl)-benzamide (**5u**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 100/0 > 4/1 > 2/3) to give the product **5u** (1.19 g, 3.37 mmol, 67%) as yellowish crystals: R_f (cyclohexane/ethyl acetate 1/3) = 0.75; mp 131.5−131.9 °C (lit. mp 129−131 °C);[27] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.07−1.25 (m, 3H), 1.44 (dtd, J = 16.7, 11.8, and 5.9 Hz, 2H), 1.56−1.76 (m, 3H), 1.98−2.09 (m, 2H), 3.81 (m, 3H), 4.13 (s, NH), 4.65 (s, NH), 6.89−6.98 (m, 2H), 7.18 (d, J = 8.3 Hz, 2H), 7.34−7.51 (m, 3H), 8.22−8.29 (m, 2H), 11.86 (s, NH); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 177.5, 158.6, 158.5, 138.9, 131.0, 129.1, 128.6, 127.9, 127.5, 115.2, 55.6, 50.1, 33.3, 25.6, 24.9; IR (cm^{-1}) 3367, 2933, 2845, 1738, 1597, 1567, 1512, 1444, 1405, 1358, 1346, 1246, 1204, 1180, 1136, 1066, 1028, 909, 892, 860, 824, 748, 713, 687; HRMS (ESI) calculated for $C_{21}H_{26}N_3O_2$ $[M + H]^+$ 352.2020, found 352.2023.

*N-(Bis((4-methoxyphenyl)amino)methylene)acetamide (**12**) and 1,3-Bis(4-methoxyphenyl)guanidine (**14**).* These compounds were prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 4/1 > 3/1 > 2/1) to give **12** (0.09 g, 0.29 mmol, 6%) as anorange solid: R_f (cyclohexane/ethyl acetate 1/3) = 0.33; HRMS (ESI) calculated for $C_{17}H_{20}N_3O_3$ $[M + H]^+$ 314.1505, found 314.1488. Subsequent purging of the column with ethyl acetate and methanol yielded the deacetylated guanidine **14** (0.62 g, 2.27 mmol, 46%) as a beige solid: R_f (cyclohexane/ethyl acetate 1/3) = 0.75; mp >190 °C dec; ^{1}H NMR (methanol-d_4, 400 MHz) δ (ppm) 3.82 (s, 6H), 6.99−7.04 (m, 4H), 7.23−7.29 (m, 4H); IR (cm^{-1}) 3015, 2970, 1738, 1651, 1586, 1509, 1412, 1366, 1296, 1231, 1165, 1104, 1031, 829, 804, 753, 714; HRMS (ESI) calculated for $C_{15}H_{18}N_3O_2$ $[M + H]^+$ 272.1399, found 272.1388.

*(E)-N-(N,N′-Bis(4-methoxyphenyl)carbamimidoyl)ethyl-carbamate (**13**).* This compound was prepared according to the general procedure 1. Purification was done by flash chromatography on silica gel (cyclohexane/ethyl acetate 100/0 > 9/1 > 7/2) to give the product **13** (1.16 g, 3.37 mmol, 67%) as a brownish oil: R_f (cyclohexane/ethyl acetate 1/1) = 0.35; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.31 (t, J = 7.1 Hz, 3H), 3.80 (s, 6H), 4.15 (q, J = 7.1 Hz, 2H), 6.89 (d, J = 8.7 Hz, 4H), 7.21−7.26 (m, 4H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) 14.8, 55.7, 61.2, 114.8, 126.6, 129.2, 158.0, 164.9; IR (cm^{-1}) 2970, 1738, 1542, 1597, 1509, 1464, 1441, 1371, 1297, 1229, 1180, 1094, 1033, 904, 829, 799, 729; HRMS (ESI) calculated for $C_{18}H_{22}N_3O_4$ $[M + H]^+$ 344.1610, found 344.1595.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00600.

In situ IR spectra, LC-MS chromatograms, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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