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A New and Environmentally Benign Synthesis of Aroylguanidines Using Iron Trichloride

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A new synthetic approach for the guanylation of aroylthioureas using iron trichloride is presented. Our synthetic method distinguishes itself by benign reaction conditions, low costs and a broad product spectrum. The scope of the reaction and calorimetric studies are described.

Guanidine derivatives have attracted attention as synthetic targets, useful reagents and organocatalysts in organic synthesis.^[1,2] Due to the broad spectrum of biological properties a comprehensive orchestra of synthetic methods for the preparation of guanidine derivatives was developed during the recent years.^[1,3,4]

Especially, the synthesis of acylguanidines as potential bioactive molecules and useful building blocks for the synthesis of natural and therapeutically useful products has generated a major stimulus in academia and industry as well.^[5]

The main synthetic access to these molecular targets includes the guanylation of N-acylthioureas. Beside the displacement of the sulfur in the presence of ethyl-3-aminopropyl carbodiimide hydrochloride (EDCI)^[6] or Mukaiyama's reagent^[7] the most common desulphurizing agents is HgCl₂.^[8] It has been extensively used in the synthesis of guanidines. However, the stoichiometric utilization of mercury salts largely precludes the extended use for the synthesis of pharmaceutical relevant compounds due to their toxicity.

For bypassing this issue Cunha *et al.*^[9] introduced bismuth nitrate pentahydrate (Bi(NO₃)₃ · 5H₂O) as environmentally benign reagent for the guanylation of N-acylthioureas. Despite the reasonable results reports on the use of this synthetic protocol are scarce.

Stimulated by these results we focused our interest in the

utilization of thiophilic metals for the guanylation as less toxic and less expensive alternatives. Therefore, this study presents our first successful steps towards the identification of new alternative guanylation agents. The initial point of our study was the examination of the impact of different metal salts on the guanylation of N-((4-methoxyphenyl)carbamothioyl)benzamide **1** with 4-methoxyanilin **2** using different metal salts, temperatures and equivalents of triethylamine (Table 1):

Table 1 Screening of different thiophiles^a

Entry	Thiophile (MetX _n)	Equiv 2	Temp. [°C]	Yield [%] ^b
1	Bi(NO ₃) ₃ · 5 H ₂ O	2	80	65 ^c
2	Bi(NO ₃) ₃ · 5 H ₂ O	2	80	31 ^d
3	Zn(NO ₃) ₂ · 6 H ₂ O	2	80	12
4	ZnCl ₂	2	80	35
5	MnCl ₂	2	80	23
6	InCl ₃	2	80	53
7	FeCl ₂	2	80	n.d. ^e
8	FeCl ₃	2	80	80
9	FeCl ₃	2	40	82
10	FeCl₃	1	40	76
11	FeCl ₃	1	40	74 ^f
12	FeSO ₄ · 7 H ₂ O	2	80	n.d. ^e
13	Fe(acac) ₃	2	80	58

^a Reactions done in EasyMax[®] 100 ml reactors: **1** (5mmol), **2** (10 mmol); Entry **10/11**: 5mmol, NEt₃ (20 mmol) in 30 ml acetonitrile cooled to 0°C; addition of MetX_n (5 mmol) then heating to temperatures indicated. Progress of reaction monitored by TLC (Chx-EtOAc 1:1). ^b Isolated yield. ^c Ref. 9; ^d Reaction in acetonitrile. ^e not determined; complex mixture. ^f reaction in standard glassware; see ESI for details

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Considering other metal salts as suitable thiophiles we reasoned Zn-, In-, Mn- and Fe-salts as candidates. As can be seen in table 1 the

best results could be obtained by the utilization of FeCl_3 .^[10] Contrary, to Cunha's protocol^[9] using $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ the synthetic approach using FeCl_3 distinguishes itself by milder reaction conditions and higher isolated yields. Thus, good results were obtained at 40°C in acetonitrile (entry 10). While Cunha's protocol describes reaction times of more than 20 hours at 80°C in *N,N*-dimethylformamide (DMF) as solvent with the utilization of two equivalents of amine for obtaining reasonable reaction rates, the use of FeCl_3 can overcome these drawbacks. Strikingly, the reaction was finalized within 3 to 4 hours by using 1 equivalent of FeCl_3 and anisidine. Hence, an increase of the time-space-yield by a factor of five to six was observable. Especially, the utilization of equimolar quantities of anilines and the benign reaction conditions, including the replacement of DMF by acetonitrile, represent a significant ecological advantage of this method. Furthermore, a superior yield compared to HgCl_2 ^[11] and $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ ^[9] could be obtained by means of FeCl_3 . Another appealing feature of FeCl_3 compared to $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ is its attractive price per mole. Thus, FeCl_3 is by a factor of at least 25 less expensive than $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$. Our new synthetic protocol is also applicable to conventional glassware, yielding **3** in 74% (compare Entries 10 and 11, Table 1).

However, it has to be mentioned that the utilization of sub-stoichiometric quantities of FeCl_3 significantly deteriorates the yield. Hence, only 50% isolated yield of **3** could be obtained by means of 0.7 equivalents of FeCl_3 . The fact that iron(III)chloride cannot be used in sub-stoichiometric amounts is in good agreement with the existing literature. To the best of our knowledge, the only way to obtain (aroyl-)guanidines in a catalytic manner, is starting from carbodiimides.^[3] This makes our protocol, using FeCl_3 as a guanylating agent for easily accessible thioureas, even more attractive, regarding the ecologic and economic advantages described above.

Striving for a more profound understanding of the influence that different thiophiles have on the outcome of the reaction, calorimetric measurements were done. Therefore, the heat flow, released by the addition of each metal salt into a solution containing acetonitrile, thiourea **1** and triethylamine was measured. In order to determine the ratio between solvation heat and heat of reaction between thiourea/triethylamine with different metal species, also the heat of solution of each metal salt in pure acetonitrile was measured. The results are shown in Figure 1.

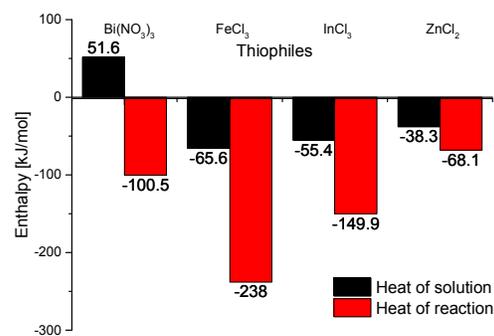


Figure 1 Enthalpies of different thiophiles^a

^a Reactions done in EasyMax[®] 50 ml reactors: **1** (5mmol), NEt_3 (20 mmol) in 30 ml Acetonitrile cooled to 0°C; addition of MetX_n (5 mmol) ^b relating to 5 mmol MetX_n . ^c total values incl. solvation heat. ^e 60 ml Acetonitrile used for FeCl_3 .

Our measurements reveal that, under the given conditions, iron(III)chloride shows the highest reactivity towards the thiourea/triethylamine system, reflected by a exothermic heat of reaction, 88 kJ/mol higher in comparison to indium(III)chloride. The metal chlorides being compared show a similar, moderately exothermic heat of solution. Yet the share of solvation heats in total enthalpy measured differs all the more. For iron(III)chloride, the share is 28 % whereas for zinc(II)chloride it is 56 % in total heat flow (Figure 1). These results show, that the comparatively high exothermic heat of reaction, found with iron(III)chloride, results from a favorable interaction of iron(III) with thiourea **1** in the presence of triethylamine. Bismuth(III)nitrate however represents an exception, exhibiting an endothermic solvation heat. It is the only metal salt of those being compared to remain mostly unsolved in acetonitrile. The poor solubility of bismuth(III)nitrate might be an explanation for the low isolated yield, obtained when using acetonitrile as solvent instead of DMF (Entries 1 and 2 in Table 1).

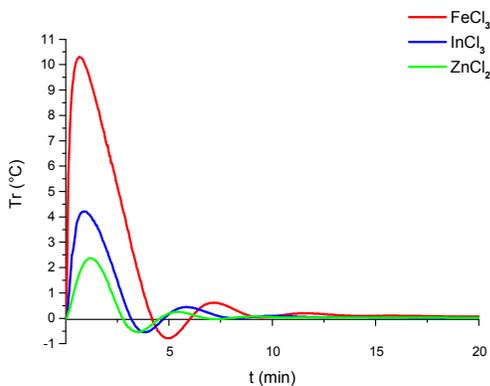


Figure 2 Reaction temperatures of metal chlorides

Underlining the aforementioned results, the recorded temperature profiles of the thiophiles are compared. Figure 2 shows the temperature profiles of the reaction temperatures (T_R) after the addition of the chloride metal salts to a solution of thiourea **1** and triethylamine in 30 ml acetonitrile. The favored interaction of FeCl_3 with thiourea/triethylamine system results in a higher increase of the reaction temperature in comparison to InCl_3 and ZnCl_2 .

The longer reaction times and higher temperatures described for bismuth(III)nitrate^[9] are also reflected by the lower exothermic heat release resulting in a significantly lower reaction temperature in contrast to iron(III)chloride (Figure 3).

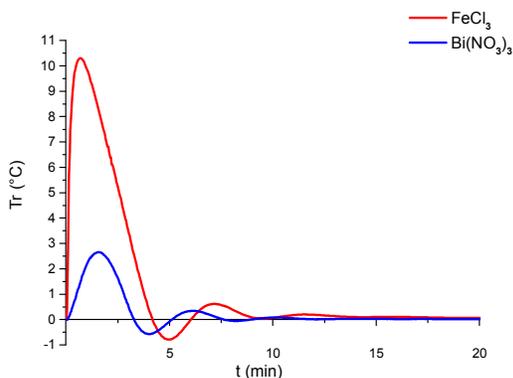


Figure 3 Reaction temperatures of FeCl_3 vs $\text{Bi}(\text{NO}_3)_3$

Since the heat flow of a reaction directly correlates with the reaction conversion and reaction course^[12], the results of the calorimetric measurements done are in agreement with the isolated yields for **3** and the thiophiles that were tested. The high reactivity found for FeCl_3 directly correlates with mild reaction conditions and the good yield found by using it as a guanylation agent. These results indicate a favored formation of Iron-Thiourea-complexes.

To test the scope of this new synthetic method, we examined the reactions of various arylthioureas (Table 2):

Table 2 Conversion of various arylthioureas^a

Entry	R	Product	Yield [%] ^b
1	4-OMe	3	76
2	4-NO ₂	5a	41
3	4-F	5b	64
4	4-Br	5c	71
5	4-Cl	5d	59
6	4-I	5e	68
7	4-COOMe	5f	60
8	2,6-DiMe	5g	50
9	2-Cl	5h	76

^a Reactions done in EasyMax[®] 100 ml reactors: **1** (5mmol), **2** (5 mmol), NEt_3 (20 mmol) in 30 ml acetonitrile cooled to 0°C; addition of FeCl_3 (5 mmol) then heating to 40°C. Progress of reaction monitored by TLC (Chx-EtOAc).
^b Isolated yield.

Almost all the substrates gave the corresponding *N*-aryl-guanidines in moderate to good yields. The best yields were obtained with thioureas bearing halide- or electron-donating-substituents. Besides aromatic systems, heterocyclic derivatives can also be applied in the above-mentioned procedure. Thus, the pyridyl-derivative **6** was easily converted to the corresponding guanidine-derivative **7** in a reasonable yield (Figure 4):

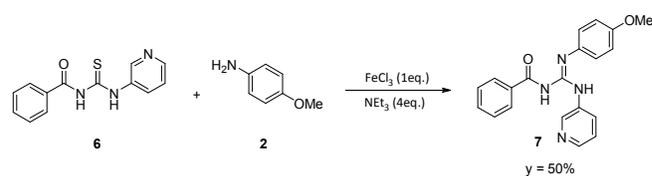


Figure 4 Conversion of Pyridyl-derivatives

Hence, electron-rich and electron-deficient aryl and heterocyclic derivatives participated well in the reaction. With the above results in hand, we investigated the applicability of this protocol to aliphatic systems (Table 3).

Table 3 Conversion of aliphatic arylthiourea and amines^a

Entry	R	R'	Product	Yield [%] ^b
1	t-Bu	4-MeOPh	10a	71
2	4-MeOPh	H	10b	41 ^c
3	4-MeOPh	n-Bu	10c	67
4	4-MeOPh	Cyclohexyl	10d	67

^a Reactions done in EasyMax[®] 100 ml reactors: **1** (5mmol), **2** (5 mmol), NEt₃ (20 mmol) in 30 ml acetonitrile cooled to 0°C; addition of FeCl₃ (5 mmol) then heating to 40°C. Progress of reaction monitored by TLC (Chx-EtOAc)^b Isolated yield. ^c Hexamethyldisilazane used as NH₃-surrogate (Ref. 12)

As depicted in Table 3 both primary and secondary amines could be applied as amines. Thus, the utilization of hexamethyldisilazane as ammonia surrogate was successful for the preparation of disubstituted *N*-aroyl-*N'*-arylguanidine **10b**.¹³

Conclusions

In conclusion, we have presented a new and environmentally benign method for the synthesis of aroylguanidines using FeCl₃. Compared to other reported methods using HgCl₂ or Bi(NO₃)₃ · 5H₂O the new method distinguishes itself by milder reaction conditions and shorter reaction times. The high reactivity of iron(III)chloride under the conditions described above was confirmed by calorimetric measurements. Also the low costs, along with the excellent solubility in many organic solvents such as ethanol, acetonitrile or even diethyl ether, are significant points in favour of FeCl₃. Furthermore, the yields and the spectrum of accessible guanidines are comparable or superior to the above mentioned methods. Further investigations concerning the optimization of the reported reaction conditions, the scope of the reaction, mechanistic studies to enlighten the role of Iron(III)chloride and applications towards target-orientated synthesis are currently underway in our laboratory and will be reported in the due course.

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