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Improved Synthetic Methodology, Substrate Scope and X-ray Crystal Structure for *N*, *N*′-disubstituted Guanidines

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Guanidine is a privileged scaffold in drug discovery. Herein we report our investigations into the acid promoted amination of pyrimidine-bearing cyanamide to produce *N*, *N*′-disubstituted guanidines. Hydrochloric acid was found to be a suitable catalyst, and the substrate scope using conventional heating was investigated with 23 aniline derivatives. The highest yield was obtained with anilines having pKa in the range of 2–4. Further, a microwave synthesis was developed using 3-chloroaniline as a model substrate increasing the yield from 68 to 93%. The microwave method was especially suited for increasing yields with anilines having pKa > 3. The structure of the pyrimidine-bearing guanidines was confirmed by NMR spectroscopy, and one representative compound has been evaluated by X-ray crystallography, showing the trans-isomer as the only tautomer in solid form.

Introduction

Guanidines are a prevalent structural unit in medicinal chemistry owing to their interesting chemical properties and distinctive features.[1,2] They are highly basic compounds (pKa for guanidine = 13.6)[3] giving guanidinium cations upon protonation and can exist in several tautomeric forms.[4] Thus, guanidines are excellent hydrogen bond donors, giving directional interactions with biological targets. Examples of bioactive guanidines include the veterinary antibiotic sulfaguanidine,[2] Iobenguane[2] used as a radiopharmaceutical and anticancer agent, the natural product Cernumidine[5] and experimental drugs with anticancer,[6] antiprotozoal,[7] and antifungal[8] activities. (Figure 1).[2]

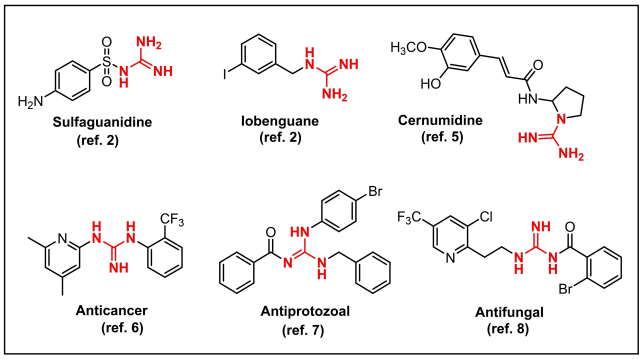

Figure 1. Guanidine containing bioactive compounds.

Guanidines are also a central units in arginine containing peptides and these have been useful for number of therapeutics.[9] Additionally, guanidines are notably used as artificial sweeteners,[10] metal ligands,[11] organocatalysts[12] and serve as essential building blocks for various heterocycles.[4,13] Given their wide applications, several strategies for the synthesis of *N*, *N*′-disubstituted guanidines have been described. Classical methods for the synthesis of guanidines are based on reactions of amines with various guanylating agents (Figure 2).[14]

Though the methods are efficient for the synthesis of *N*, *N*′-disubstituted guanidines, they have some limitations, including the activation of the guanylating agents and that the precursors/reagents pose health and safety issues and reactivity problems. A special class of guanidine contains pyrimidines, which have previously been prepared via amination of the corresponding cyanamides and by condensation of arylbiguanidines with acetylacetone.[15]

In an ongoing project we have identified pyrimidine containing *N*, *N*′-disubstituted guanidines, as candidates for DNA glycosylase inhibitors, and we wanted an easy, efficient, and robust way of preparing a series of compounds. Thus, herein we describe our efforts to improve the acid catalyzed amination of cyanamides by conventional and microwave

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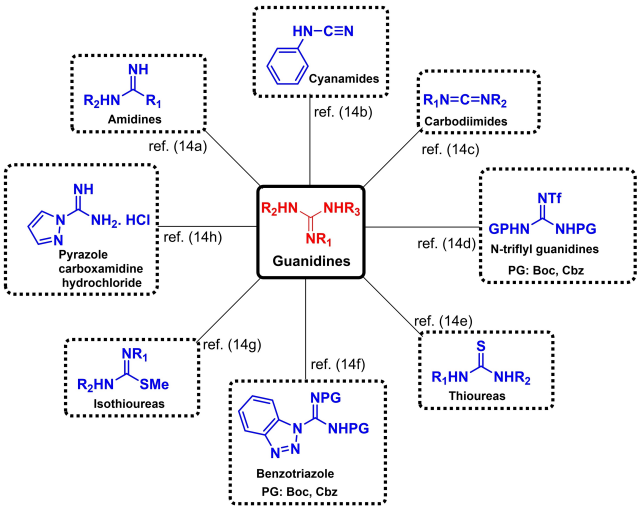


Figure 2. Guanidine synthesis from various precursors (adapted from ref [14a]).

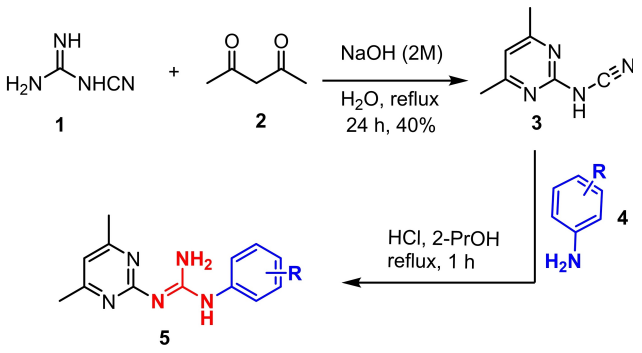
heating and we have examined the substrate scope of these reactions. Finally, the tautomeric form of one representative structure in the solid state was determined by X-ray crystallography.

Results and discussion

Acid-mediated amination of cyanamide using anilines

When going through the available literature, we identified the cyanamide **3** (Scheme 1) as a suitable precursor for preparing the target guanidines **5**.[15] Thus, compound **3** was synthesized via sodium hydroxide-catalyzed condensation of cyanoguanidine and acetylacetone under reflux conditions as previously described and 40% yield was obtained after recrystallization.[16] The reaction was also performed with catalytic amount of potassium carbonate (0.1 equiv.) as a base and attained comparable yield under these conditions. This method permitted scaling to 10 g in 41% yield.

The next step involves amination of equimolar amount of cyanamide with anilines in the presence of acid to afford 1,3-disubstituted guanidines. We first tested a reported amination protocol[15] with the model substrate 3-chloroaniline (**4a**). Gratifyingly, the reaction afforded the desired guanidine **5a** in 68% yield (Table 1, entry 1), indicating that this is a highly useful reaction, and its simplicity was also appealing.



Scheme 1. Base-catalyzed condensation and acid-mediated amination of cyanamide.

To understand the method, we evaluated the reaction in the absence of acid with prolonged time in 2-PrOH and got only traces of product (entry 2), and most of the cyanamide **3** was unreacted. This clearly shows that the amination requires acid to activate the cyanamide. On the other hand, using 3 equiv. of HCl gave a lower 41% yield (entry 3). Adding more acids simply displays the equilibrium position between 3-chloroanilline (**4a**) and its protonated form (**4a-HCl**), giving more of the non-nucleophilic anilinium ion which would reduce the rate of the reaction. Another solvent used for similar reactions is dioxane. Without acid (entry 4) no product was obtained, however combined with H_2SO_4 afforded 60% yield (entry 5).

Although alternative solvents and acid could have been evaluated, the use of 2-PrOH and HCl seemed suitable for amination of **3**.

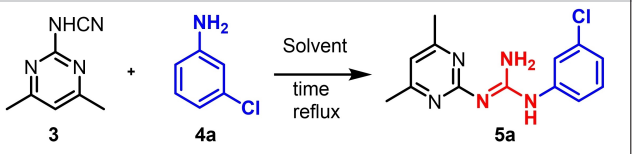
Substrate scope in acid catalyzed amination

We went on to study the substrate scope of the 2-PrOH/HCl process using in total 22 anilines and 2-aminopyrimidines. The results of the reactions are organized in Scheme 2 according to the measured and calculated pKa[17] of the aniline substrates.

Reactions with electron rich anilines, such as the *p*-ethoxy (**4b**), 3,4-methylenedioxy (**4c**), *p*-butyl (**4d**) and *m*-benzyloxy (**4e**) analogues, gave **5b-e** in low isolated yields (17-27%). Mediocre yields were obtained with *N*-methyl-4-fluoroaniline (**4f**), aniline (**4g**) and *p*-fluoroaniline (**4h**). When the pKa of the anilines were in the range of 2–4, the highest yield was obtained (60–74%). These includes the *m*-ethynyl (**4i**), *m*-chloro (**4a**), *p*-chloro (**4j**), the bulky *o*-iodo (**4q**),

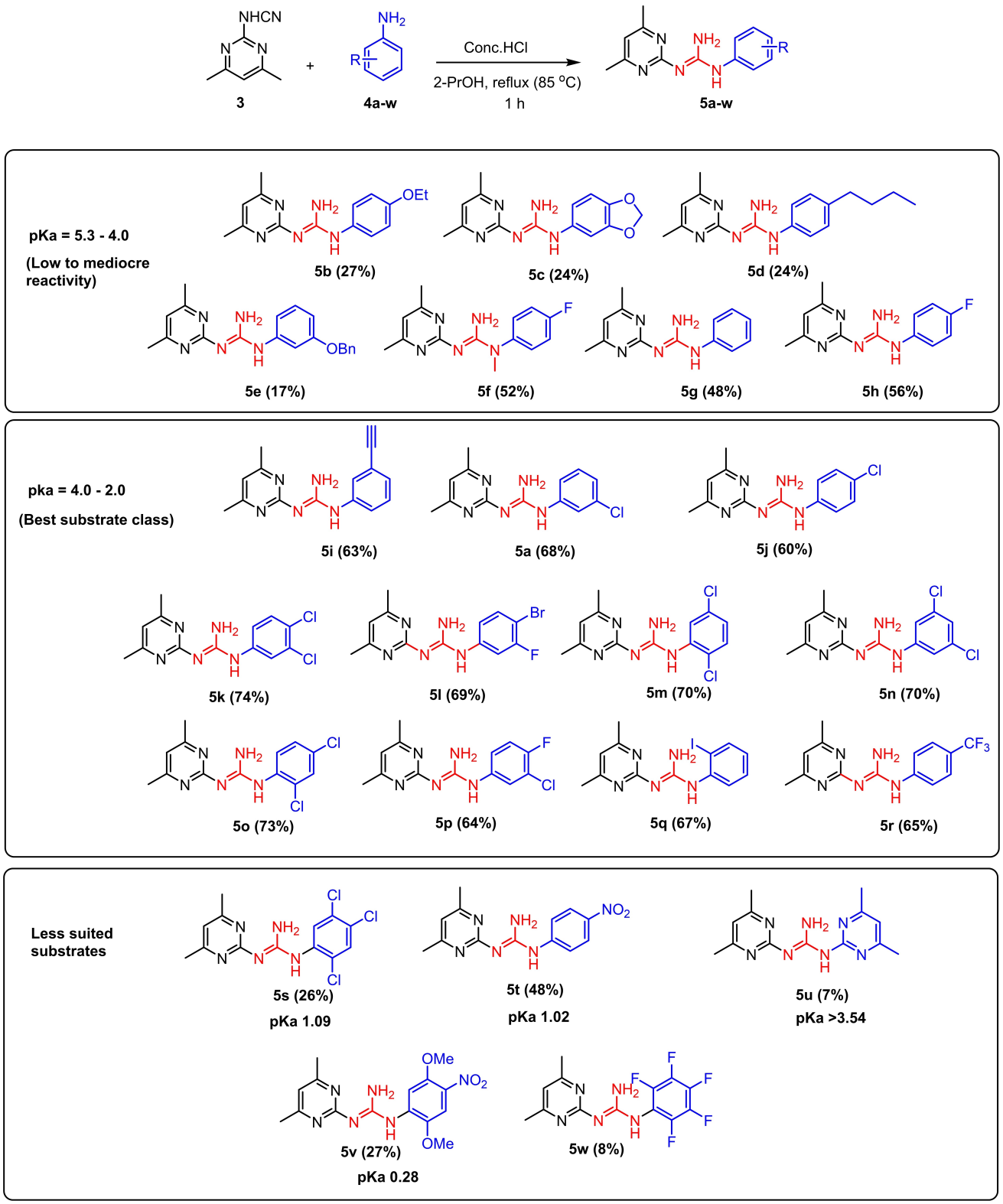
p-trifluoromethyl (**4r**), and the dihalogenated derivatives (**4k–4p**). Finally, reaction with anilines with pKa below 2, the *p*-nitro (**4t**) and the 2,4-5-trichloro (**4s**) analogues,

Table 1. Amination of **3** with **4a** under thermal heating.



Entry	Solvent	Time (h)	Acid/equiv.	Yield 5a (%)[a]
1	2-PrOH	1	HCl /1.2	68
2	2-PrOH	24	None	Traces
3	2-PrOH	1	HCl /3	41
4	Dioxane	24	None	Traces
5	Dioxane	1	H_2SO_4	60

[a] Isolated yields.



Scheme 2. Amination of cyanamide **3** with different anilines and 2-aminopyrimidine.

led to 48% and 26% yield, respectively. Additionally, the bulky 2,5-dimethoxy-4-nitroaniline (**4v**) and electron-deficient pentafluoro aniline (**4w**) afforded a low 27 and 8% yield, respectively. Another poor nucleophile in this reaction was 2-aminopyrimidine (**4u**). The low yield of the latter compound could be due to a delocalization of the electron density over all the nitrogen atoms, as the pKa should be above 3.54.[18]

In conclusion, the efficiency of this amination is strongly dependent on the pKa of the aniline. The products **5a**–**w**, as formed, are more basic than the other components, and therefore consumes one mole equiv. of acid. This means that there will be a relative stable equilibrium of components in the mixture during the reaction. The most basic anilines, although in principle most nucleophilic, compete with the cyanamide **3** as base, and thereby a larger fraction of these anilines is on protonated form, leading to lower rate. The least basic anilines such as **4u** and **4w**, will be much less on the protonated form, but has an intrinsic low nucleophilicity leading to a low rate. Anilines with a pKa between 2–4 seems to be a perfect compromise in terms of basicity and nucleophilicity using 1.2 equiv. of HCl. Possibly, each reaction could be further optimized with respect to the amount of acid in the reaction.

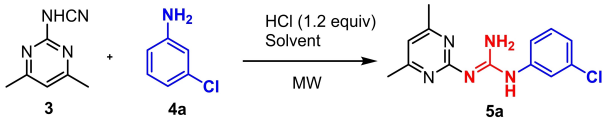
Tuning of amination under microwave (MW) conditions

The use of microwave heating can in many cases increase the yield or shorten the reaction time of processes and is therefore a useful method in the laboratory setting. Thus, we aimed to improve the amination using microwaves, and the results of our experiments are shown in Table 2. Again, we used *m*-chloroaniline (**4a**) as a model substrate, and HCl (1.2 equiv.) as reaction promotor. First, the effect of different solvents was tested, including 2-PrOH as in the thermal process, dioxane, MeOH and water (Table 2, entries 1–5). Mimicking the thermal process using 2-PrOH (entry 1) at 85 °C for 1 h, gave an increase in yield of **5a** from 68% (thermal) to 80% (MW). The use of the other solvent systems (Table 2, entries 2–5) was less efficient. Therefore, additional experimentation was performed with 2-PrOH as solvent. Attempts with shorter the reaction time (entries 6 and 7), at 85 °C and 120 °C for 0.5 h diminished the reaction yield, while prolonging the reaction time up to 2 h gave a comparable yield of **5a** (entry 8).

As the amount of **4a** detected at the end of the reaction was very low, we wondered if **4a** was unstable. Thus, the reaction was run under inert atmosphere and using the HCl salt of **4a** (entries 9 and 10). However, this did not affect the yield, but demonstrated that the reaction with amine salts is a viable alternative. Next, we increased the amount of **4a** to 1.5 equiv. and to our delight the isolated yield was 93% (entry 11). A control experiment using conventional heating (entry 12) led to 78% of **5a**, showing that higher amount of aniline is also beneficial in conventional flask chemistry. A rational explanation for the increase in yield is that the equilibrium position between 3-chloroaniline (**4a**) and its protonated form becomes more favorable. Finally, running the same amination with 1.5 equiv. of the cyanamide **3**, gave 78% of **5a** (entry 13), thus confirming that anilines are the limiting factor.

Obviously, the use of 1.5 equiv. of aniline must be justified in terms of total costs and waste handling for every case. There might also be practical issues, like ease of purification, which

Table 2. Tuning of the MW assisted amination of **3** using *m*-chloroaniline (**4a**). Unless otherwise stated the conditions were: **3** (0.578 g, 3.89 mmol), **4a** (3.89 mmol) in 2-PrOH (15 mL) and HCl (1.2 equiv.).

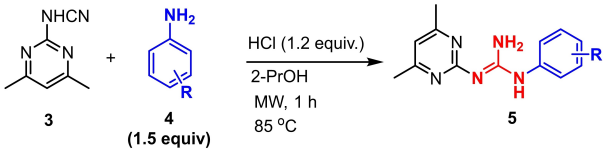


3 4a 5a

Entry	Solvent	3 (equiv.)	4a (equiv.)	Heating	Temp. (°C)	Time (h)	Yield (%) 5a[a]
1	2-PrOH	1	1	MW	85	1	80
2	Dioxane	1	1	MW	105	1	75
3	MeOH	1	1	MW	100	0.5	60[b]
4	MeOH	1	1	MW	100	1	70[b]
5	Water	1	1	MW	150	1	64
6	2-PrOH	1	1	MW	85	0.5	64
7	2-PrOH	1	1	MW	120	0.5	75
8	2-PrOH	1	1	MW	85	2	81
9[c]	2-PrOH	1	1	MW	85	1	79
10[d]	2-PrOH	1	1	MW	85	1	80
11	2-PrOH	1	1.5	MW	85	1	93[e]
12	2-PrOH	1	1.5	Oil bath	85	1	78
13	2-PrOH	1.5	1	MW	85	1	78[f]

[a] Isolated yield.
[b] Approx. 15% of **3** precipitated along with the product.
[c] Reaction under N_2 gas.
[d] Reaction performed with the HCl-salt of **4a**.
[e] Isolated yield based on **3**.
[f] Isolated yield based on **4a**.

Table 3. Effect of MW heating and use on 1.5 equiv. of **4** in amination.



3 **4** (1.5 equiv) **5**

Entry	Aniline	pKa	Yield conv. heating (%)[d]	Yield MW. heating (%)[e]	Rel. change (%)	Product
1	*p*-EtO (**4b**)	5.19[e]	27	64	137	**5b**
2	Aniline (**4g**)	4.58[b]	48	79	64	**5g**
3	*p*-Cl (**4j**)	3.98[b]	60	89	48	**5j**
4	*m*-Cl(**4a**)	3.34[b]	68	93	37	**5a**
5	3,4-di-Cl (**4k**)	2.97[c]	74	90	22	**5k**
6	p-NO_2 (**4t**)	1.02[c]	48	51	6	**5t**

[a] Estimated using substituent constant using the method of Gross et al.[17] Experimental pKa of *p*-methoxyaniline 5.29.
[b] Experimental value taken from reported data.[17a]
[c] Experimental value taken from reported data.[17b]
[d] 1:1 mol ratio of **3** and **4** was used.
[e] 1:1.5 mol ratio of **3** and **4** was used.

could prohibit this approach. We tested this method variant using five additional anilines with different traits and compared the yield with that obtained using conventional heating and relative change was calculated accordingly, see Table 3.

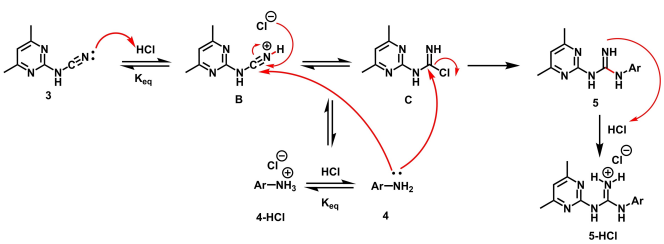
The reaction yield was increased for all the tested amination reaction (Table 3). However, the benefit of using 1.5 equiv. of aniline was most pronounced for the most basic anilines (entries 1 and 2) and gradually dropped as the pKa was lowered (entries 3–6). Thus, in case of the *p*-nitro derivative **5t**, this process change has no or limited value and high amounts of **3** was still present at the end of the reaction, indicating mediocre conversion. The obvious rational for these observations is that adding more of the basic anilines, leads to a higher fraction of anilines on non-protonated nucleophilic form, while for less basic anilines this positive effect is reduced in line with the dropping pKa. Recovery of excess anilines in large scale procedure can be considered using reported methods.[19] Finally, it should be mentioned that the microwave method is also applicable for the isolation of guanidine hydrochloride salt. In case of compound **4k**, we performed a reaction without basic workup and the product was precipitated as guanidine hydrochloride **5k-HCl** in 84% yield. This could be indeed a valuable alternative strategy for the isolation of disubstituted guanidines.

To conclude, amination of **3** under MW heating in 2-PrOH increased the yield as compared to conventional heating. Moreover, the isolated yield of the product can be further increased using more aniline, which is the limiting reactant. The effect of adding more aniline is more pronounced for the most basic anilines, which is easily explained by acid-base equilibrium.

Plausible Mechanism

A tentative mechanism for the amination of cyanamide **3** is shown in Scheme 3. Cyanamides, depending on the conditions, can act as a nucleophile or electrophile on the sp-hybridized nitrogen and carbon, respectively. Under acidic conditions, it is assumed that the cyanamide nitrogen is protonated and thus forming the nitrilium ion **B**. However, IR-studies have also indicated that **B** can tautomerize to chloroformamidine **C**.[20] Intermediate **C** is a likely electrophile, but the fact that both H_2SO_4 and HCl promote this reaction (scheme 3) could indicate that **B** is also involved.

The aniline **4** is also part of the same acid-base equilibrium system giving a mixture of the nucleophilic aniline **4** and the anilinium ion (**4**-HCl). The amination rate will therefore be dependent on the pH and the pKa of the aniline and in this reaction a highly basic guanidine is formed. As it is the most basic compound in the mixture it will abstract one mole equivalent of acid. This ensures that the relative concentration of acid and reactants are maintained. The most basic anilines, while in principle being most nucleophilic under acidic conditions, suffer from an unfavorable equilibrium between the aniline and the anilinium ion. On the other hand, the least basic



Scheme 3. Mechanistic suggestion for the amination of cyanamide **3** under acidic conditions.

anilines will likely be mostly on the neutral form but are less nucleophilic. Anilines with pKa between 2–4 seem to offer a good compromise under the used conditions. By running the reaction with more aniline, the equilibrium concentrations of the aniline and the anilinium ion is altered. The experiment shows that this is beneficial for the basic anilines, while for anilines with a lower pKa this is less favorable.

Spectroscopy, X-ray crystal structure and solubility

The molecular structures of the compounds were confirmed by high-resolution mass spectroscopy and NMR spectroscopic studies. Preferably, NMR spectroscopy of these compounds should be run in deuterated DMSO, to detect the NH protons. However, most of the compounds have limited solubility in this solvent at 22 °C. Therefore, deuterated acetic acid was used instead. The obvious drawback being that all NH protons are not detected due to exchange.

Diagnostic ^{13}C-NMR shifts of **5 a** include the central guanidine at 155.8 ppm and the C-1 pyrimidinyl carbon at 158.6 ppm. When performing ^{1}H-^{15}N HMBC NMR spectroscopy using compound **5 a** (figure 3), we observed two nitrogen signals. One at 268.8 ppm with correlation to the methyl protons, which is from the pyrimidine nitrogens, one at 123.9 ppm originating from the aniline part showing correlation with the two *ortho*-hydrogens.

Both in material science and medicinal chemistry knowledge of the tautomerism of these compounds could be important. In solution, guanidines exhibits imino-amino tautomerism,[21] and in principle the three tautomeric forms shown in Figure 4 can exist. The ratio between the tautomers depends on the detailed structure, temperature, solvent, and pH. We would expect that the double bond is preferably oriented towards the most electronegative group. However, we have only found one example of X-ray crystal structure of diaryl-substituted guanidine (compound **6**, Figure 4).[14b] To confirm the solid-state structure of this compound class, the 3-chloro derivative **5 a** was crystallized from 2-PrOH. The formed crystals had rod-like structure with a $P2_1/c$ space group. Compound **5 a** was found to be on the trans-form of the amino tautomer, structure **5 a-I** shown in Figure 4. The structure 5a-I was deposited into Cambridge Structural Database under number CCDC 2299222 with sample name VE-1-73. The details can be found in the supporting information file.

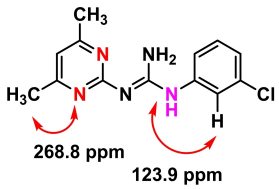


Figure 3. ^{15}N-NMR chemical shift values of pyrimidinyl guanidine **5 a** based on ^{1}H-^{15}N HMBC NMR spectroscopy (calibrated with external reference, nitromethane at 0 ppm)

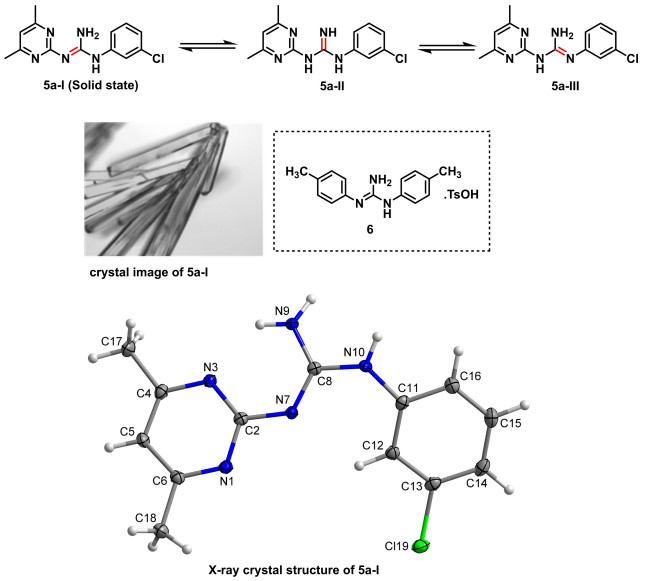


Figure 4. Examples of possible tautomers of **5 a**, and the structure found by X-ray (**5 a–I**). A microscopy image of the rod-like structure of **5 a** is shown, alongside the previously crystallized compound **6**.

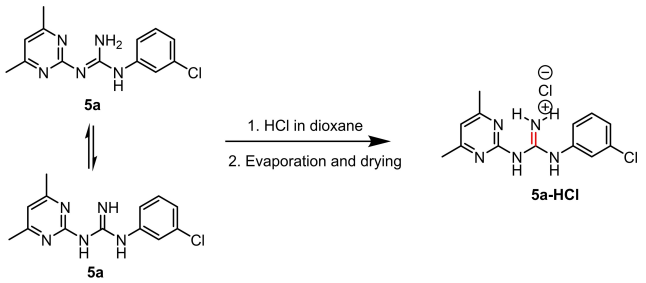


Figure 5. Synthesis of guanidinium salt **5 a-HCl**

Poor water solubility is a major challenge in medicinal chemistry, a problem which is evident also for this class of pyrimidine-based guanidines. A solution to this challenge is to protonate the formed guanidine (Figure 5). We found that the guanidinium cations, provided much higher water and DMSO solubility, which will ease the biological testing.

Conclusions

Amination of cyanamide **3** to form guanidines has been studied using anilines. The process requires acid to occur, and hydrochloric acid has been found to be a suitable choice. Using 2-PrOH as solvent under conventional heating the substrate scope of the amination was investigated using 23 aniline derivatives. The highest yield was obtained with anilines having a pKa in the range of 2–4, while outside this range the amination was less efficient. Anyhow, 20 of the 23 compounds were easily isolated, showing the method to be excellently suited for making compound libraries. Some steric bulk is allowed for in the nucleophile as both *N*-methylated and *ortho*-iodo derivatives were formed in good yields. Using 3-chloroani-

line as a model compound, we have shown that microwave heating is a way to improve the yield. Moreover, by using 1.5 equiv. of the anilines, the yield could be further increased. This effect is most pronounced for reactions with electron rich anilines. Most of the findings can be rationalized by a delicate balance involving acid-base equilibriums of the reacting partners and the nucleophilicity of the aniline. Finally, the solid-state structure of **5a** was confirmed by X-ray crystallography to have a trans-amino structure with the double bond directed towards the pyrimidine.

General Procedure for the synthesis of pyrimidinyl guanidines (5a-w, reflux method)

To the mixture of pyrimidinyl cyanamide **3** (0.578 g, 1 equiv.) and aniline derivatives **4a-w** (1 equiv.) in 2-propanol (20 mL), conc. HCl (37%, 1.2 equiv.) was added, and the reaction mixture was refluxed for 1 hour at 85 °C. After the reaction time, cooled to ambient temperature and treated with a basic solution (0.5 g NaOH in 50 ml distilled water) to attain the target compound as a precipitate (pH: 11–12 basic). The precipitate was filtered off and washed with water until neutral washings and dried under vacuum to obtain the target molecules (**5a**–**w**). For compound **5d**, the solid was recrystallized from 2-PrOH and for the compounds **5e**&**5s**, the solids were washed with ethyl acetate to further purify the products. For some derivatives **5v**–**w**, the attained solid was recrystallized using mixture of solvents (2-PrOH/MeOH/EtOH, 2:1:1) to further purify the products.

General Procedure for the synthesis of pyrimidinyl guanidines (microwave method)

In a 20 mL-microwave vial, pyrimidinyl cyanamide **3** (0.578 g, 1 equiv.), aniline derivatives **4a**, **4b**, **4g**, **4j**, **4k**, & **4t)** (1.5 equiv.), 2-PrOH (15 mL) and conc. HCl (37%, 1.2 equiv.) were added. The vial was sealed, and the reaction mixture was heated under microwave irradiation at 85 °C for 1 hour. After the reaction time, cooled to ambient temperature and followed by transferred the reaction mixture into basic solution containing 0.5 g NaOH in 50 mL distilled water to obtain the precipitate (pH: 11–12 basic). The precipitate was filtered off and washed with water, dried under vacuum to obtain the target molecules (**5a**, **5b**, **5g**, **5j**, **5k**, & **5t)**. For derivative **5t**, the attained solid was recrystallized using mixture of solvents (2-PrOH/MeOH/EtOH, 2:1:1).

Synthesis of (E)-1-(3-chlorophenyl)-2-(4,6-dimethylpyrimidin-2-yl) guanidine [5a]

Following the general procedure (i), pyrimidinyl cyanamide **3** (0.578 g, 3.89 mmol), 3-chloroaniline **4a** (0.41 mL, 0.496 g, 3.89 mmol) and conc. HCl (0.40 mL, 4.67 mmol, 1.2 equiv) were added. The product **5a** was isolated as a pale-white solid (0.727 g, 68%). The desired product **5a** was crystallized from 2-propanol (50 mL, at 110 °C) to obtain pale-white crystals for X-ray crystallographic analysis. mp: 201–202 °C; ^{1}H NMR (400 MHz, AcOH-d_4) δ 7.50–7.46 (m, 2H), 7.42–7.38 (m, 2H), 7.01 (s, 1H), 2.48 (s, 6H); ^{13}C NMR (101 MHz, AcOH-d_4) δ 170.8 (2 C), 158.6, 155.8, 136.9, 136.8, 133.0, 129.9, 127.8, 126.1, 118.2, 24.3 (2 C); HR-MS (TOF, ES$^+$) Calcd $(M+H)^+$ for $C_{13}H_{15}ClN_5^+$ 276.1010; Found 276.1016; IR (neat, cm^{-1}) ν: 3233, 2978, 1576, 1504, 1428, 1398, 1372, 1335, 1247, 807, 645, 628, 561.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Guanidines · cyanamide · anilines · amination · microwave chemistry

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