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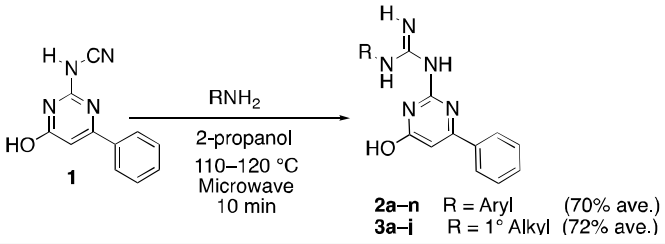

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An Efficient Microwave Assisted Synthesis of *N*'-Aryl/(alkyl)-substituted *N*-(4-hydroxy-6-phenylpyrimidin-2-yl)guanidines: Scope and Limitations

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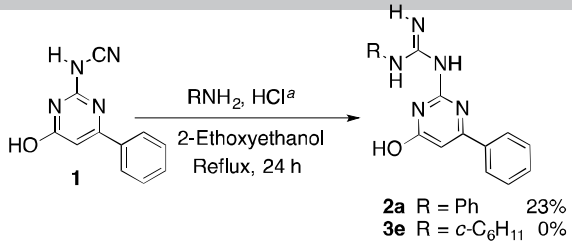
ABSTRACT

Treatment of *N*-[(4-hydroxy-6-phenyl)pyrimidin-2-yl]cyanamide with 1° alkyl or arylamines in isopropyl alcohol for only 10 minutes at 110–120 °C under microwave conditions gave the corresponding *N*'-alkyl(aryl)guanidine derivatives in excellent yields (65–84%). Isolated yields were greatest when > 1.0 equiv. of amines were employed, but excellent results were also obtained when aryl and alkylamines were reacted with a more atom-economical loading (1.0 equiv.; 70% and 72% ave. yields, respectively). Arylamines with either highly electron withdrawing substituents (e.g. CO_2H) or pi-deficient heterocycles (e.g. variously substituted aminopyridines) did not work well under these conditions, and reaction with ureas and/or amino acids did not give detectable products. Work-up was exceedingly simple, and involved simple collection and washing of product on a sintered glass funnel. Products were obtained in analytically pure form and required approximately 1 h to prepare, start to finish.

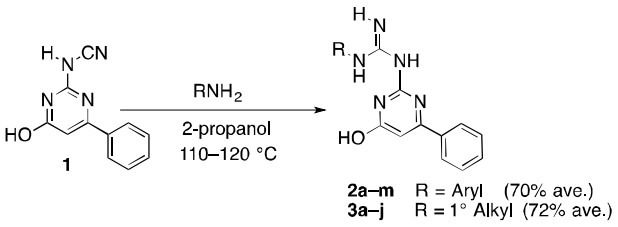
4-hydroxypyrimidines and their 4-(*1H*) or 4-(*3H*) pyrimidinone tautomers[1, 2] are an interesting class of compounds that have been extensively studied. The stimulus for these studies derives from their activities in a wide variety of biological contexts including potential use as antiviral,[3] anticancer,[4] antimicrobial,[5] antimalarial,[6] anti-inflammatory,[7] or anti-ulcer[8] therapeutics. Select derivatives have also exhibited potential for treating diabetes,[9] arthritis,[10] and neurodegenerative disorders,[11] while others have been studied for their activities as enzyme inhibitors,[12] interferon inducing agents,[13] angiotensin receptor blockers,[14] and calcium receptor antagonists.[15] More complex molecular structures which incorporate the 4-hydroxypyrimidine moiety as part of their core also exhibit interesting biological properties, including fungicidal,[16] insecticidal,[17] and anti-obesity[18] activities. Interest in 4-hydroxypyrimidines has also been stimulated by their potential use in a variety of supramolecular systems.[19] The biological properties of the guanidine moiety are also widely recognized, and include such diverse activities as anti-bacterial, anti-microbial, anti-parasitic, and anti-viral, as has been noted in several recent comprehensive reviews.[20]

As part of our research into developing methods for rapid creation of compound libraries that could be screened for novel biological activities, we became interested in modifying the method of Werbel and co-workers[21] for preparing N'-aryl-substituted *N*-(4-hydroxypyrimidin-2-yl)guanidines to give the desired products more efficiently using microwave irradiation. Our interest in the title compounds stemmed from their possession of both the 4-hydroxypyrimidine and guanidine moieties, each of which had previously been shown to impart favorable biological properties (*vide supra*). As has been demonstrated in numerous cases, microwave irradiation frequently leads to shorter reaction times, decreased formation of byproducts, and enhanced isolated yields.[22] As a base-line experiment, we attempted to reproduce the method of Werbel and co-workers for compound **2a** (Scheme 1). In our hands, compound **2a** was obtained in very modest yield (23%, crude), and even lower yields were obtained after recrystallization. Not surprisingly, cyclohexylamine failed to give any detectable product (**3e**) under these conditions, most likely due to the required use of acid catalyst, which would be expected to protonate the alkylamine and greatly reduce or suppress its nucleophilicity.

Here, we report that simple treatment of *N*-[(4-hydroxy-6-phenyl)pyrimidin-2-yl]cyanamide (**1**) with aniline (1.0 equiv.) in isopropyl alcohol at 110–120 °C for only 10 minutes in a microwave reactor (Scheme 2) gave desired product **2a** in excellent yields (67–75%). Product was obtained in pure form after rinsing with minimal volumes of ice-cold isopropyl alcohol (Table 1).[23] Investigation of the impact of varying equivalents of amine revealed that for aniline, yields were not dramatically improved by using > 1.0 equiv. (Table 1, entries 1–3). Indeed, in some cases (e.g. p-octylphenylamine), yields were dramatically



Scheme 1. Reagents and conditions: RNH_2 (1.0 equiv.), HCl (0.5 equiv.), 2-ethoxyethanol:H_2O (3:1; 0.7 M), reflux 24 h.



Scheme 2. Reagents and conditions: RNH_2, 2-propanol, microwave irradiation, 10 min, 110–120°C.

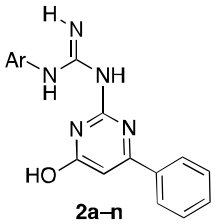

2a–n

Table 1.

Entry	Product	Ar	Yield (%)[e]
1	**2a**	Phenyl	67-75[a]
2	**2a**	" "	81[b]
3	**2a**	" "	81[c]
4	**2b**	*p*-Hexylphenyl	71[a]
5	**2c**	*p*-Octylphenyl	69[a]
6	**2c**	" "	25[d]
7	**2d**	*p*-Phenylphenyl	70[a]
8	**2d**	" "	84[c]
9	**2e**	2-Naphthyl	65[a]
10	**2f**	*p*-Imidazoylphenyl	57[a]
11	**2g**	*p*-Hydroxyphenyl	78[a]
12	**2h**	*p*-Fluorophenyl	58[a]
13	**2h**	" "	84[d]
14	**2i**	*p*-Chlorophenyl	47[a]
15	**2i**	" "	62[d]
16	**2j**	*m*-Chlorophenyl	59[a]
17	**2j**	" "	70[c]
18	**2k**	*p*-Bromophenyl	44[a]
19	**2k**	" "	75[c]
20	**2l**	*m*-Bromophenyl	60[a]
21	**2l**	" "	66[c]
22	**2m**	*p*-Iodophenyl	67[a]
23	**2n**	*m*-Iodophenyl	49[a]
24	**2n**	" "	69[c]

[a]Method A (1.0 equiv. $ArNH_2$); [b]Method B (2.0 equiv. $ArNH_2$) [c]Method C (3.0 equiv. $ArNH_2$); [d]Method D (5.0 equiv. $ArNH_2$) [e]Isolated yields.

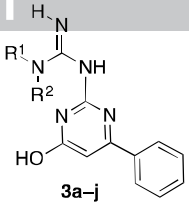

3a–j

Table 2.

Entry	Product	R^1	R^2	Yield (%)[f]
1	**3a**	*n*-Butyl	H	77[a]
2	**3a**	" "	H	80[b]
3	**3b**	*n*-Hexyl	H	71[a]
4	**3c**	Isobutyl	H	69[a]
5	**3d**	Benzyl	H	75[a]
6	**3e**	Cyclohexyl	H	67[a]
7	**3f**	Isopropyl	H	82[e]
8	**3g**	α-Methylbenzyl	H	65[a]
9	**3h**	1-Adamantyl	H	trace[a]
10	**3h**	" "	H	30[b]
11	**3i**	*tert*-Butyl	H	trace[a]
12	**3i**	" "	H	50[d]
13	**3i**	" "	H	0[e]
14	**3j**	*n*-Butyl	*n*-Butyl	26[d]

[a]Method A (1.0 equiv. RNH_2); [b]Method B (2.0 equiv. RNH_2); [c]Method C (3.0 equiv. RNH_2); [d]Method D (5.0 equiv. RNH_2); [e]Methoc E (10.0 equiv. RNH_2); [f]Isolated yields.

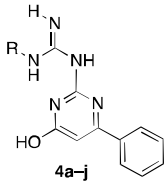
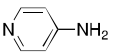
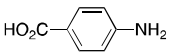
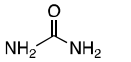
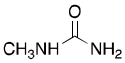
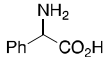
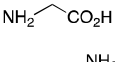
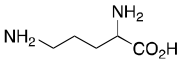

4a–j

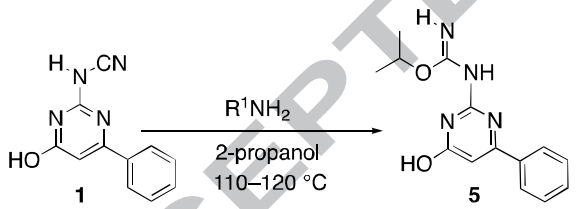
Table 3.

Entry	Product	Amine	Yield (%)[a]
1	**4a**		nd[b,c]
2	**4b**		nd[b], trace[c]
3	**4c**		nd[b], trace[c]
4	**4d**		nd[b,c]
5	**4e**		trace[b,c]
6	**4f**		nd[b,c]
7	**4g**		nd[b,c]
8	**4h**		nd[b,c]
9	**4i**		nd[b,c,d]
10	**4j**		nd[b,c]

[a]nd = Not detected by MS or TLC; [b]Method A (1.0 equiv. amine); [c]Method D (5.0 equiv. amine); [d](5.0 equiv. amine, 1.0 equiv. Hunigs base).

reduced with excess amine. In the case of p-octylphenylamine, the low yield observed when 5.0 equiv. amine was used (Table 1, entry 6) resulted from the insolubility of unreacted amine in the ice-cold isopropyl alcohol used to fully precipitate the product.[24] Since treatment of compound **1** with varying amounts of aniline (2.0 – 3.0 equiv.) did not improve yields significantly (Table 1, entries 2–3), for all subsequent reactions, the more atom-economical loading of arylamine was used (1.0 equiv.), giving most products in excellent yields (70–80%). One exception to this was the yields obtained for the halo-substituted aniline derivatives (**2h**-**n**) where maximal yields were achieved when 3.0 equiv. of arylamine were employed (Table 1, entries 12–24). The microwave conditions also proved useful for preparing derivatives from alkylamines (Table 2). Yields for unhindered 1° alkylamine were generally high (65–82%), but sterically hindered 1° alkylamines (e.g. 1-adamantylamine, *tert*-butylamine) gave products in low yields, which were also contaminated with large amounts of starting material under all conditions examined (Table 2). A majority of the 2° amines we examined failed to give solid product (e.g. diethylamine, diisopropylamine, *N*-methylaniline), and the yield for the only example we examined that gave isolable solid product was quite modest (entry 14).

In order to further test the scope of this reaction, compound **1** was treated with a range of different nucleophiles (Table 3). Desired products were formed in only trace amounts for any of the amines evaluated (as determined by MS and TLC analysis). This was true even when multiple equiv. of the amine were employed (5.0 equiv.). This general lack of reactivity is most likely due to the electron deficient nature of the nucleophiles involved, as one would expect for the pi-deficient heteroarylamines (entries 1–4), *p*-aminobenzoic acid (entry 5), and ureas (entries 6–7). Interestingly, none of the amino acids tested gave detectable products, even when Hünigs base (1.0 equiv.) was added to deprotonate the zwitterion (entry 9). In every instance examined (Table 3), the major product detected was the isopropoxy derivative (**5**) which resulted from competing addition of isopropyl alcohol to the nitrile moiety (Scheme 3).[24, 25]



Scheme 3. Reagents and conditions: R^1NH_2 (R^1NH_2 = electron deficient amine, urea, or amino acid), 2-propanol, microwave irradiation, 10 min, 110–120°C.

The overall method employed for these syntheses was very simple and involved heating a solution of the amine in HPLC-grade isopropyl alcohol for only 10 minutes at 110–120 °C in a microwave reactor.[26] Work-up involved chilling the product on ice to ensure complete precipitation, then collection and washing of solid product with ice-cold isopropyl alcohol (3 X 1.0 mL) on a fine porosity sintered glass funnel. Products were obtained in analytically pure form (after drying *in vacuo*), as determined by ^1H and ^{13}C NMR, and elemental analysis (see Supplementary Material). Total preparation times were approximately 1 h, including work-up/isolation.

In summary, we have developed an efficient one-pot method for converting *N*-[(4-hydroxy-6-phenyl)pyrimidin-2-yl]cyan-amide (**1**) to the corresponding *N*'-alkyl or *N*'-arylguanidine derivatives (**2**–**3**). The method is simple and efficient and avoids the limitations associated with the previously reported method for preparing the title compounds (Scheme 1). The present method involved microwave assisted conversion of compound **1** to compounds **2**–**3** with optimized yields ranging from 57–84% for the arylamines (ave. = 70%; Table 1) and from 65–80% for the unhindered 1° alkylamines examined (ave = 72%, Table 2). The method did possess some limitations given that electron deficient arylamines, ureas, or amino acids did not give detectable products, and highly hindered 1° alkylamines were also ineffective substrates for this reaction. However, the efficiency of the method with an array of electron rich arylamines and unhindered 1°alklamines, demonstrates its potential as a versatile tool for preparing libraries of compounds that may prove useful in a number of biologically and medicinally relevant contexts. There is currently a great deal of interest in such libraries, given the broad range of activities reported for 4-hydroxypyrimidine and/or guanidine derivatives in general, including antibacterial, antimicrobial, antiviral, antimalarial, antifungal, antitumor, anti-inflammatory, anti-diabetic, and antiulcer activities. These activities, in addition to the broad array of biomolecular targets modulated or inhibited by appropriately functionalized 4-hydroxypyrimidine and/or guanidine derivatives, suggest that the method described herein may prove useful for identifying novel analogues with unprecedented activities that could prove useful in these or other applications.

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Supplementary Material

Supplementary data (detailed experimental procedures and NMR data for all new for compounds associated with this article) can be found in the online version at doi:xxxxxxxxx.

[1] It has been well established that 4-hydroxypyrimidine derivatives undergo tautomerism in solution to establish equilibrium mixtures consisting of one (or more) of the three possible tautomers. Whereas a majority of the crystal structures deposited in the Cambridge Structural Database exist as the (*3H*) tautomer,[2] the situation in *solution* can be entirely different. In fact, the dynamic equilibrium between tautomers is generally solvent-dependent, as has been demonstrated in numerous cases.[2,19e] While the NOE experiments we performed suggest that compounds **2** and **3** exist predominantly in the (1*H*) tautomeric form in DMSO-d_6 (see Supplementary Material), we have chosen to depict the 4-OH tautomer in this article to simplify comparison to nomenclature and structural drawings utilized in previous publications (which also specify the 4-OH tautomer; see especially ref. 21). The IR spectrum of a suspension of solid **2a** in a thin film of DMSO shows a broad OH stretch between 3600–3400 cm^{-1}, consistent with the notion that in the solid state a significant population exists as the 4-OH tautomer.

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[23] Details of the preliminary results used in our selection of solvent, reaction time, and reaction temperature are provided in the Supplementary Material. Summarized briefly, the conditions we selected gave the maximum yields while still affording the ease and simplicity of collecting analytically pure compound via simple filtration.

[24] Low yields for compounds **2c** (Method D) and **3i** (Method E) can be rationalized as follows: (**2c**): The excess 4-octylaniline co-precipitated in the ice-cold isopropyl alcohol thus necessitating the use of room temperature solvent to wash it from the product. In addition, larger quantities of the room temperature isopropyl alcohol were required to wash away the precipitated 4-octylaniline than were used for isolating products from other substrates. (**3i**): The major products for this reaction were compound **5** and 2-amino-4-hydroxy-6-phenylpyrimidine. We attribute the failure of Method E with this substrate to the steric hindrance associated with *tert*-butylamine and the increased basicity of the reaction medium (when using 10 equiv. of amine) which would enhance the rate of base-promoted hydrolysis of the cyanamide and as well as favor addition of the isopropyl alcohol rather than give the desired product.

[25] Varying amounts of the product resulting from hydrolysis of compound **1** (i.e., 2-amino-4-hydroxy-6-phenylpyrimidine, *m/z* [M+H] = 188) were observed in all reactions, and compound **5** was also observed as a byproduct in reactions used to prepare compounds **2a**–**n** and **3a**–**j**.

[26] The general experimental procedure for preparing compound **2a** is as follows: To a solution of aniline (11 mg, 0.12 mmol) in HPLC-grade 2-propanol (1.0 mL) was added *N*-(4-hydroxypyrimidin-2-yl)cyanamide (25 mg, 0.12 mmol). The resulting suspension was heated for 10 minutes in a CEM Corp. Discover-S microwave reactor oven using 10 mL Pressure Vials pressure-rated up to 35 Bar (Cat. No. 908035). Temperatures ranged between 110-120 °C during the reaction period. (Maximum temperature setting was 125 °C with 10 minutes ramping time. Cooling times were typically 30 minutes). After chilling on ice, the resulting precipitate was collected on a sintered glass funnel (fine porosity) and washed with ice-cold 2-propanol (3 X 1.0 mL). Product (**2a**) was obtained in 67–75% as a white solid with no further purification necessary. ^{1}H NMR (DMSO-d_6, 500MHz) δ 11.4 (bs, 1H), 9.12 (bs, 1H), 7.90–7.88 (m, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.48–7.47 (m, 3H), 7.28 (t, J = 8.0 Hz, 2H), 7.01 (t, J = 7.5 Hz, 1H), 6.27 (s, 1H); ^{13}C NMR (DMSO-d_6, 125MHz) δ 164.6, 160.9, 159.1, 156.5, 139.5, 137.8, 130.4, 129.15, 129.14, 127.0, 123.0, 120.9, 101.9; HRMS Calcd. for $C_{17}H_{16}N_5O$ [M+H]: 306.1360; Found: 306.1355; Anal. Calc. for $C_{17}H_{15}N_5O$: C, 66.87; H, 4.95; Found: C, 66.47; H, 4.89.

- An efficient method for preparing the title compounds is presented
- The reaction requires only 10 minutes at 110–120 °C under microwave conditions
- Products were obtained in excellent yields (65-84%)
- Products were obtained in analytically pure form
- Total preparation time was approx. 1 h (including isolation)