Efficient Biginelli Synthesis of 2-Aminodihydropyrimidines under Microwave Irradiation

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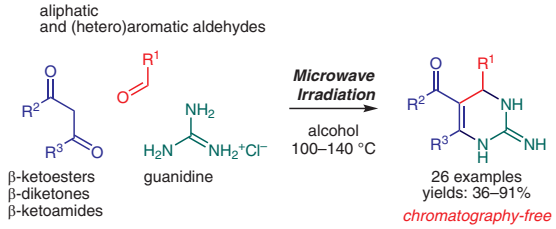

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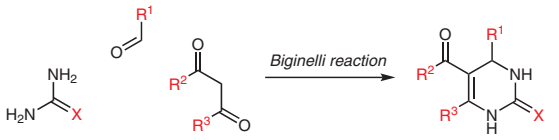
Abstract A practical and general method for the Biginelli cyclocondensation of guanidine with aldehydes and β-dicarbonyl compounds is described and illustrated with the synthesis of a set of 26 functionalized 2-amino-3,4-dihydropyrimidines. The simple protocol involves the microwave-mediated reaction of a twofold excess of guanidine hydrochloride with the required reaction partners in an alcohol at 120 °C. Yields are generally good, with short reaction times and a simple work-up. The scope is considerably wider than that of similar reactions carried out under conventional heating.

Key words Biginelli reaction, microwave heating, guanidine, dicarbonyl compounds, aminodihydropyrimidines, multicomponent reactions

Compounds incorporating the guanidine unit have found numerous applications, due to the peculiar properties of this functional group.[1] They have been used as superbases[2,3] and nucleophilic organocatalysts[4–7] in organic synthesis, as ligands in coordination chemistry,[8,9] as membrane-exchange transporters,[10,11] and as peptide mimics.[12] Moreover, the guanidine group is present in many natural products, especially of marine origin,[13,14] and in bioactive compounds[15,16] that play important roles in medicinal chemistry, including cardiovascular, antihistamine, anti-inflammatory, antidiabetic, antibacterial, antiviral, and antineoplastic drugs. The wide array of biological properties stems from the ability of the guanidine group (and the corresponding guanidinium cation) to establish strong non-covalent interactions with target receptors through multiple hydrogen bonds or, when protonated, ionic interactions.

Incorporation of the guanidine moiety into heterocyclic systems has led to the discovery of novel compounds with appealing pharmacological properties.[17–19] In this respect, the dihydropyrimidine scaffold appears particularly attractive, as 3,4-dihydro-1*H*-pyrimidin-2-imines or their 2-amino tautomers can be, in principle, readily obtained by a modification of the classical Biginelli reaction, a three-component cyclocondensation[20–22] in which urea reacts with an aldehyde and a β-keto ester to give 3,4-dihydro-1*H*-pyrimidin-2-ones (DHPMs) (Scheme 1; X = O).



Scheme 1 General scheme for the Biginelli reaction

Interest in the Biginelli reaction has grown exponentially in recent decades due to the emerging role of DHPMs as valuable compounds in medicinal chemistry,[23] and a wide range of optimized experimental protocols with variations in the three components have been reported.[21] Among these, the replacement of urea with thiourea, giving access to 3,4-dihydro-1*H*-pyrimidin-2-thiones, is well documented (Scheme 1; X = S).[21] Conversely, Biginelli reactions with guanidine, leading to the corresponding 2-iminodihydropyrimidines, (or their 2-amino tautomers), have been much less frequently documented. In an early example,[24] *N,N*-dimethylguanidine and guanidine were reacted with the Knoevenagel adduct of 3-nitrobenzaldehyde and ethyl acetoacetate to give the corresponding cyclocondensation adducts in low yields. In 1997, Milcent et al. described the synthesis of a series of 2-iminodihydropyrimidines in yields of up to 42% by the reaction of guanidine hydrochloride with the Knoevenagel adducts derived from aryl aldehydes

and benzoyl acetate in the presence of $NaHCO_3$.[25] In this case, yields were limited by the concomitant formation of double Biginelli adducts (Figure1).

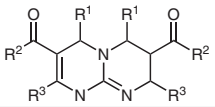
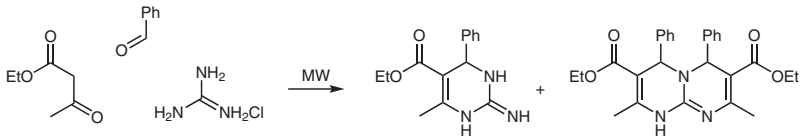


Figure 1 Structure of double adducts formed in the Biginelli reaction with guanidine

In 2001, Kappe and co-workers described the first direct three-component Biginelli reaction with guanidine hydrochloride to give the corresponding 2-aminodihydropyrimidines.[26] However, the method was limited to aromatic aldehydes and ethyl benzoylacetate as the β-dicarbonyl partner. To overcome this limitation and to expand the scope of the reaction, indirect protocols have been developed based on the aminolysis of Biginelli products such as isoureas,[27] isothioureas,[26,28] and 2-pyrazolyl-[29] and 2-cyanoimino-3,4-dihydro-(1*H*)-pyrimidines.[30] However, this approach requires additional steps and is rather inefficient with respect to atom economy. More recently, 2-aminodihydropyrimidines have been obtained by a three-component Biginelli reaction under phase-transfer catalysis,[31] using Ph_3P[32] with ultrasound irradiation.[33] However, applications were limited to aromatic aldehydes. 2-Arylaminodihydropyrimidines bearing no substituents at C-4 have been recently synthesized through a Staudinger/aza-Wittig/cyclization intermediate.[34]

In connection with an investigation into DHMPs as potential protease inhibitors, we required a general, mild and reliable method for the synthesis of 2-aminodihydropyrimidines that is not limited to aromatic aldehydes or specific 1,3-dicarbonyl compounds. It has been extensively shown that Biginelli reactions with urea and thiourea can be conveniently carried out under microwave irradiation,[35,36] thereby avoiding prolonged heating and the use of high-boiling solvents. Surprisingly however, reports on the microwave-promoted Biginelli reaction of guanidine are scarce.[35,37] The unexpected formation of 2-aminopyrimidine-4-ones in the reaction with aromatic aldehydes and benzoylacetates under solvent-free conditions has been reported,[38] and a Biginelli-like reaction of aromatic aldehydes and β-keto esters with 3-amino-5-alkylthio-1,2,3-triazole as the guanidine-like partner has also been described,[37] resulting in mixtures of regioisomeric compounds. We therefore decided to reinvestigate the three-component Biginelli reaction with guanidine under microwave irradiation.

Table 1 Optimized Synthesis of Dihydropyrimidine **1** under Microwave Heating[a]



1 **1a**

Entry	Solvent	Temp (°C)	Time (min)	Guanidine (equiv)	Conversion[b,c] (%)	**1**/**1a**[c]	Yield[d] (%)
1	–	120	10	1	20	ND	10%
2	H_2O	120	10	1	–	–	–
3	DMF	70	10	1	26	ND	18
4	DMF	70	30	1	55	ND	32
5	DMF	100	10	1	24	ND	21
6	THF–H_2O–EtOH	120	10	1	59	80:20	33
7	EtOH	80	10	1	65	80:20	32[b]
8	EtOH	100	10	1	80	80:20	51
9	EtOH	120	7.5	1	80	80:20	48
10	EtOH	120	10	1	85	80:20	58
11	EtOH	130	10	1	90	80:20	41
12	EtOH	120	10	1.5	87	84:16	61
13	EtOH	120	10	2	90	93:7	70

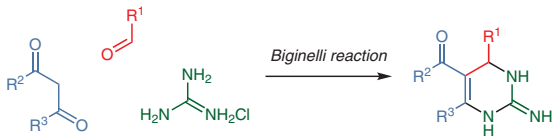
[a] Equimolar amounts of PhCHO and ethyl acetoacetate were reacted in the presence of $NaHCO_3$ (4 equiv) and various amounts of guanidine hydrochloride.
[b] Based on unreacted aldehyde.
[c] From ^{1}H NMR analysis of the crude reaction mixture after evaporation of the solvent.
[d] Isolated yield of **1**.

Our efforts started with the optimization of conditions (solvent, time, and temperature) for the reference reaction of guanidine hydrochloride, benzaldehyde, and ethyl acetoacetate in the presence of $NaHCO_3$ as the base, leading to ethyl 2-amino-6-methyl-4-phenyl-1,4-dihydropyrimidine-5-carboxylate (**1**). The best results were obtained with ethanol as solvent (Table 1, entries 7–13). No reaction was observed in water (entry 2), whereas poor yields were obtained under solvent-free conditions (entry 1) or in other solvent systems (entries 2–5).

Next, the reaction in EtOH was carried out at various temperatures from 80 to 130 °C (entries 7–11), showing that the best conditions are 120 °C for ten minutes (entry 13); the conversion was lower at lower temperatures (entries 7 and 8) or with a shorter reaction time (entry 9), whereas at a higher temperature (entry 11), the yield was compromised by partial decomposition of the product. Finally, increasing the amount of guanidine hydrochloride (entries 12 and 13) improved the conversion to 90% while minimizing the formation of the bis adduct **1a**. Workup by addition of cold water to the reaction mixture and filtration of the solid product allowed complete removal of unreacted materials, and byproduct **1a** was completely eliminated by trituration or recrystallization from an appropriate solvent, giving dihydropyrimidine **1** in 70% yield (entry 13).

To demonstrate the scope of the method, the optimized conditions were applied to various combinations of the three building blocks, affording a set of 26 different 2-aminodihydropyrimidines in yields ranging from 36 to 91% (Table 2). Yields refer to analytically pure compounds (^{1}H NMR, HRMS), isolated after filtration of the solid formed upon addition of water and purified as described in the Supplementary Information. Bis adducts, when formed, were never isolated but were only detected in the ^{1}H NMR (H-4 signal) and ESI-MS spectra of the crude reaction mixtures.

Table 2 Scope of the Microwave-Promoted Biginelli Synthesis of 2-Aminodihydropyrimidines[39]



1–26

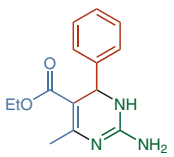
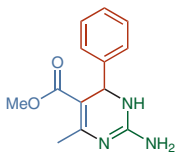
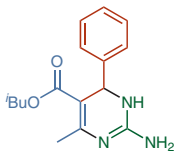
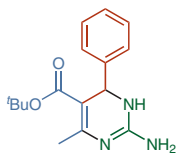
Entry	R^1	R^2	R^3	Solvent	Yield (%)	Product
1	Ph	OEt	Me	EtOH	70	
2	Ph	OMe	Me	MeOH	75	
3	Ph	O-*i*-Bu	Me	*i*-BuOH	71	
4	Ph	O-*t*-Bu	Me	*t*-BuOH	81	

Table 2 (continued)

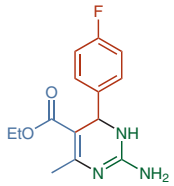
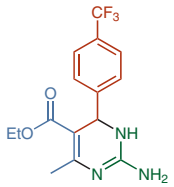
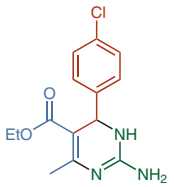
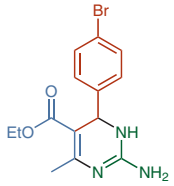
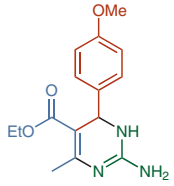
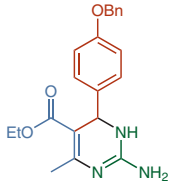
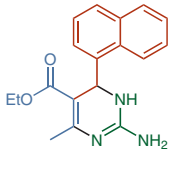
Entry	R^1	R^2	R^3	Solvent	Yield (%)	Product
5	4-FC_6H_4	OEt	Me	EtOH	45	
6	4-$F_3CC_6H_4$	OEt	Me	EtOH	91	
7	4-ClC_6H_4	OEt	Me	EtOH	75	
8	4-BrC_6H_4	OEt	Me	EtOH	72	
9	4-$MeOC_6H_4$	OEt	Me	EtOH	64	
10	4-$BnOC_6H_4$	OEt	Me	EtOH	82	
11	1-naphthyl	OEt	Me	EtOH	80	

Table 2 (continued)

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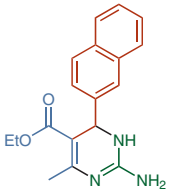
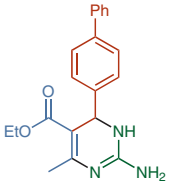
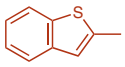
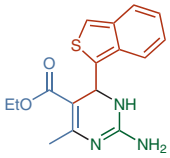
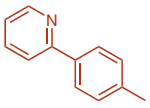
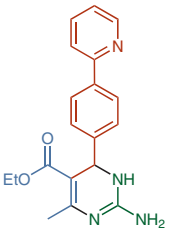
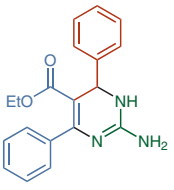
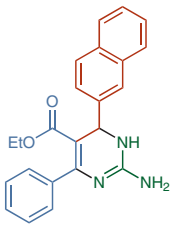
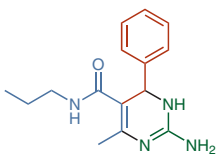
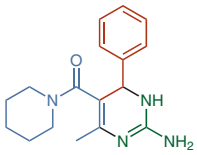
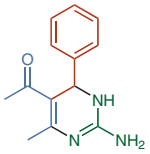
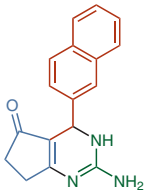
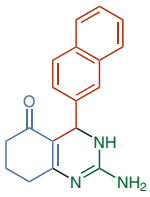
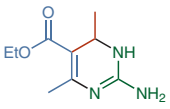
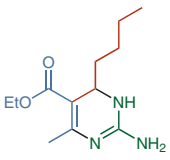
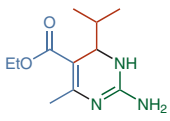
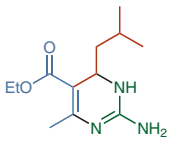
12[40]	2-naphthyl	OEt	Me	EtOH	68	
13	4-PhC_6H_4	OMe	Me	EtOH	51	
14		OEt	Me	EtOH	50	
15		OMe	Me	EtOH	74	
16	Ph	OEt	Ph	EtOH	71	
17	2-naphthyl	OEt	Ph	EtOH	79	
18	Ph		Me	EtOH	73[a]	

Table 2 (continued)

Entry	R^1	R^2	R^3	Solvent	Yield (%)	Product
19	Ph		Me	EtOH	62	
20	Ph	Me	Me	EtOH	85	
21	2-naphthyl	$(CH_2)_2$		EtOH	76[b]	
22[41]	2-naphthyl	$(CH_2)_3$		EtOH	85[c]	
23	Me	EtO	Me	EtOH	36	
24	Bu	EtO	Me	EtOH	48	
25	*i*-Pr	EtO	Me	EtOH	51	
26	*i*-Bu	EtO	Me	EtOH	43	

[a] 100 °C, 8 min.
[b] 140 °C, 40 min.
[c] 140 °C, 20 min.

The results in Table 2 show that the method can be applied not only to aromatic and hetaromatic aldehydes, but also to aliphatic aldehydes, which are prone to self-condensation, giving access to 4-alkyl-2-aminodihydropyrimidines, albeit in lower yields (entries 23–26). In addition to β-keto esters (entries 1–17 and 23–26), the method

is also compatible with 1,3-diketones (entries 20–22) and with secondary or tertiary β-keto amides (entries 18 and 19), but not with acetoacetamide. Reactions with methyl, isobutyl, or *t*-butyl acetoacetate (entries 2–4, 13, 15, and 20) were carried out in the corresponding alcohols to avoid transesterification.

With respect to reactions carried out with conventional heating in DMF,[26] the microwave-promoted aza-Biginelli reaction takes place with comparable or higher yields and is environmentally more benign, avoiding the use of DMF or other aggressive solvents. Furthermore, because reaction times are significantly shorter, this method is compatible with a wide range of starting materials, including reactive and thermally unstable aliphatic aldehydes, making it a general method for the synthesis of 2-aminodihydropyrimidines.

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References and Notes

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(39) **2-Amino-3,4-dihydropyrimidines (Table 2, Entries 1–26); General Method**
The appropriate1,3-dicarbonyl compound (1.1 mmol), guanidine·HCl (2.0 mmol), and $NaHCO_3$ (4 mmol) were added to a 0.5 M solution of the appropriate aldehyde (1 mmol) in EtOH. The mixture was irradiated for 10 min in a microwave oven at 120 °C (unless otherwise stated), then cooled. Cold H_2O was added to dissolve the $NaHCO_3$, and the mixture was left in a refrigerator for 30 min until the product completely precipitated. The solid that formed was collected by filtration, washed with cold water, dried in vacuo, and purified by trituration with *i*-Pr_2O.
(40) **Ethyl 2-Amino-4-methyl-6-(2-naphthyl)-1,6-dihydropyrimidine-5-carboxylate (Table 2, Entry 12)**
Prepared by reacting 2-naphthaldehyde, guanidine·HCl, and ethyl acetoacetate as a pale-brown solid; yield: 210 mg (68%); mp 165–167 °C. IR (Nujol): 3350, 3500–2700 (br), 1703, 1661, 1602 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 1.06 (t, *J* = 7.4 Hz, 3 H, CH_3CH_2O), 2.24 [s, 3 H, C(6)CH_3], 3.92 (q, *J* = 7.4 Hz, 2 H, CH_3CH_2O), 5.38 (s, 1 H, H-4), 6.24 (s, 2 H, NH_2), 7.43–7.51 (m, 4 H, ArH), 7.64 (s, 1 H, ArH), 7.85 (m, 3 H, ArH and NH). ^{13}C NMR (125.68 MHz, DMSO-d_6): δ = 14.77, 23.64, 53.43, 58.68, 97.76,

124.73, 125.62, 126.11, 126.58, 127.88, 128.21, 128.57, 132.72, 133.13, 144.13, 155.35, 160.26, 166.51. HRMS-ESI: *m/z* $[M + H]^+$ calcd for $[C_{18}H_{20}N_3O_2]^+$: 310.1550; found: 310.1558.

(41) **2-Amino-4-(2-naphthyl)-4,6,7,8-tetrahydroquinazolin-5(3*H*)-one (Table 2, Entry 22)**

Prepared by reacting 2-naphthaldehyde, guanidine·HCl, and cyclohexane-1,3-dione at 140 °C for 20 min as a yellow solid; yield: 247 mg (85%); mp >240 °C. IR (Nujol): 3270, 3500–2500, 1684, 1654 (br) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.76, 1.80 (2 m, 1 H each, ring CH_2), 2.12 (m, 2 H, CH_2C=), 2.35 (m, 2 H, CH_2CO), 5.43 (s, 1 H, H-4), 6.49 (br s, 2 H, NH_2), 7.36 (br s, 1 H, NH), 7.41–7.48 (m, 3 H, naphthyl), 7.63 (s, 1 H, naphthyl), 7.81–7.85 (m, 3 H, naphthyl). ^{13}C NMR (DMSO-d_6): δ = 21.11, 29.95, 36.65, 50.57, 108.52, 124.61, 125.26, 125.97, 126.36, 127.62, 128.00, 128.39, 132.48, 132.87, 142.86, 155.30, 163.04, 192.90. HRMS-ESI: *m/z* $[M + H]^+$ calcd for $[C_{18}H_{18}N_3O]^+$: 292.1444; found: 292.1444.