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Report

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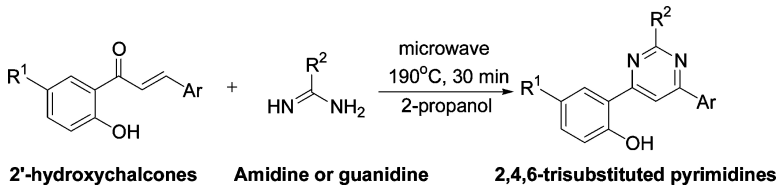

2'-hydroxychalcones **Amidine or guanidine** **2,4,6-trisubstituted pyrimidines**

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Microwave-Assisted Solution-Phase Parallel Synthesis of 2,4,6-Trisubstituted Pyrimidines

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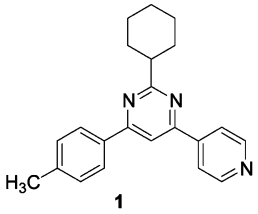
2,4,6-Trisubstituted pyrimidines have been shown to possess diversely biological activities. As examples, compound **1** shows in vitro antimalarial activity against *Plasmodium falciparum*,[1] with an MIC value of 0.25 μg/mL. Compound **2** is a selective adenosine A_1 receptor antagonist[2] with high A_1 affinity (K_i = 4 nM) and selectivity. Compound **3** is a phosphotidylinositol 3 kinase inhibitor and can be used for the treatment of cancer.[3] Compound **4** shows antitubercular activity against *Mycobacterium tuberculosis* at a concentration of 12.5 μg/mL.[4]



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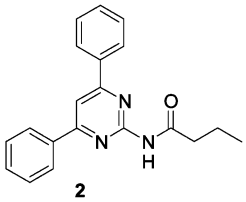

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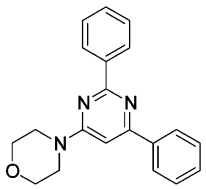

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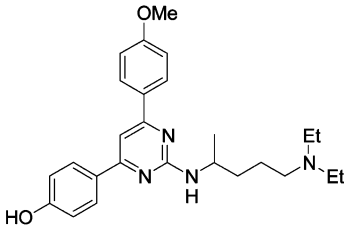
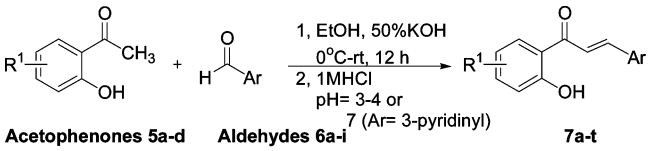


4

We are interested in the development of efficient methods for constructing combinatorial libraries of 2,4,6-trisubstituted pyrimidines, given their value as potential pharmaceuticals. Herein, we report the microwave-assisted reaction of 2′-hydroxychalcones with amidines or guanidines to synthesize 2,4,6-trisubstituted pyrimidines.

Some synthetic methods for 2,4,6-trisubstituted pyrimidines have been developed previously by others. On the basis of the reaction of alkynone with amidines or guanidines, Bagley et al.[5] prepared pyrimidine libraries using microwave-assisted synthesis; however, a limitation of this method is that it is not easy to obtain diverse alkynones from either commercial sources or chemical synthesis. Katritzky et al.[6] reported a synthetic method for 2,4,6-trisubstituted pyrimidines using solid-phase-bound chalcones. Agarwal et al.[7] also published a similar method. Although this solid-phase synthesis method is suitable for the preparation of 2,4,6-trisubstituted pyrimidines, a method for linking chalcones to a solid support must be developed. In fact, not all chalcones can be linked to a solid phase if there is no suitable group in the framework of chalcones or their building blocks. In view of the limitations of existing methods, we attempted to develop a new method of combining solution-phase parallel synthesis and microwave-assisted organic synthesis (MAOS) for constructing structurally diverse libraries of 2,4,6-trisubstituted pyrimidines on the basis of the reaction of chalcones with amidines or guanidines.

Scheme 1. Reaction of Substituted Acetophenones with Aldehydes



Acetophenones 5a-d **Aldehydes 6a-i** **7a-t**

5a R^1=H
5b R^1=F
5c R^1=Cl
5d R^1=Br

6a Ar= C_6H_5
6b Ar= 4-FC_6H_4
6c Ar= 4-ClC_6H_4
6d Ar= 4-$CH_3C_6H_4$
6e Ar= 3-pyridinyl
6f Ar= 2-furanyl
6g Ar= 2-thiophenyl
6h Ar= 5-methyl-2-furanyl
6i Ar= 5-methyl-2-thiophenyl

Table 1. Formation of 2′-Hydroxychalcones **7A**−**t**[a]

acetophenones	aldehydes	chalcones (yield %)[b]
5a	**6a**	**7a** (44.6)
5a	**6b**	**7b** (66.1)
5a	**6c**	**7c** (61.9)
5a	**6d**	**7d** (70.6)
5a	**6e**	**7e** (37.5)
5a	**6f**	**7f** (67.3)
5a	**6g**	**7g** (69.6)
5a	**6h**	**7h** (45.6)
5a	**6i**	**7i** (40.2)
5b	**6b**	**7j** (56.2)
5b	**6c**	**7k** (44.2)
5b	**6d**	**7l** (55.9)
5c	**6b**	**7m** (63.6)
5c	**6c**	**7n** (48.6)
5c	**6d**	**7o** (69.6)
5c	**6f**	**7p** (75.7)
5c	**6 g**	**7q** (71.6)
5d	**6b**	**7r** (62.0)
5d	**6c**	**7s** (56.9)
5d	**6d**	**7t** (52.7)

[a] Reactions were carried out on a 25.0-mmol scale. [b] Isolated yields of pure compounds recrystallized from anhydrous EtOH.

In this present study, chalcones were prepared easily by the reaction of acetophenones with aldehydes according to a reported method[8] (Scheme 1). To a solution of substituted acetophenones **(5a**−**d)** (1.0 equiv) and aldehydes **(6a**−**i)** (1.0 equiv) in EtOH was added 50% KOH (2.5 equiv) at 0 °C. The mixture was stirred overnight at room temperature and then poured into ice water. The pH of this mixture was adjusted to 3−4 or 7 (Ar = 3-pyridinyl) with 2 M HCl aqueous solution. A yellow precipitate was collected by

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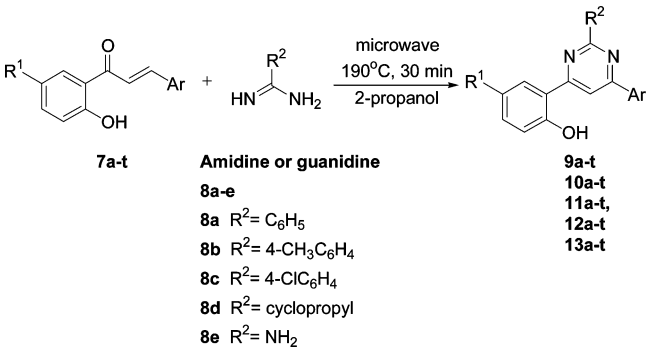
Scheme 2. Reaction of Various 2′-Hydroxychalcones with Amidines or Guanidine under Microwave Irradiation



filtration and purified by recrystallization in anhydrous EtOH. Using this method, 20 2′-hydroxychalcones were synthesized (Table 1).

Dodson and Seyler[9] reported that benzamidine condensed readily with α,β-unsaturated ketones of the type $C_6H_5CH{=}CHCOR$, where R does not possess an α-hydrogen, to give 6-substituted 2,4-diphenylpyrimidines under reflux for 3 h. Zhang et al.[10] also reported a synthesis of triaryl-substituted pyrimidine by using a fluorous tag procedure. A fluorous-substituted α,β-unsaturated ketone reacted with an excess benzamidine in DMA to afford a fluorous-tag-attached, triaryl-substituted pyrimidine. The desired product was obtained by the tag cleavage under microwave irradiation. Kidwai et al.[11] described a microwave-accelerated, one-pot, solid-supported synthesis of 4,6-diaryl-2-(4-morpholinyl/1-piperidinyl/1-pyrrolidinyl)-pyrimidines by the reaction of chalcone with *S*-benzylthiuronium chloride and heterocyclic secondary amines. Varga et al.[12] investigated the reaction of chalcones and guanidine. They found that either 4,6-diarylpyrimidine-2-ylamine or 2-amino-5,5-disubstituted-3,5-dihydroimidazol-4-one was obtained, depending on the order of the addition. We tried to perform this type of reaction through microwave irradiation. The reaction of 2′-hydroxychalcone **7a** with benzamidine **8a** was chosen as the sample reaction (see Scheme 2). A microwave synthesizer, Explorer (CEM), was used for these experiments. Equivalents of 2′-hydroxychalcone **7a** and benzamidine **8a** were dissolved in 2-propanol. The reaction was performed and repeated many times at different temperatures in a sealed vessel under microwave irradiation for 30 min. The product, 4-(2′-hydroxyphenyl)-2,6-diphenylpyrimidine **9a**, was separated from the reaction mixture by filtration. Its yield was increased from 13.9 to 44.7% as the temperature varied from 100 to 190 °C. On the other hand, the yield was raised from 37.8 to 46.4% as the reaction time changed from 10 to 40 min at 190 °C. In comparison, an equivalent of 2′-hydroxychalcone **7a** and benzamidine **8a** was refluxed in 2-propanol for 10 h under conventional heating, and the yield of 4-(2′-hydroxyphenyl)-2,6-diphenylpyrimidine **9a** was 12.0%. Using this method, we performed all the other reactions described in Scheme 2. Because starting materials **8b**, **8d**, **8c**, and **8d** used in these experiments were amidines hydrochloride and guanidine hydrochloride, bases needed to be used to react with hydrochloride to produce the free amidines or guanidine. Products **10a**−**t** and **11a**−**t** were successfully obtained separately in the reactions of **8b** and **8d** with 2′-hydroxychalcone **7a**−**t** when 1.2 equiv of triethylamine was used as the base. From the reactions of **8c** and **8d** with 2′-hydroxychalcone **7a**−**t**, products **12a**−**t** and **13a**−**t** were obtained when 1.2 equiv of *t*-BuOK was used in the experiments. Products **12d**, **12t**, **12o**, **12l**, **12r**, **12s**, **12q**, and **12i** (Table 2) were separated from the reaction mixture by flash chromatography. All the other products (92 compounds) (Table 2) were separated from the reaction mixture by filtration.

Structures of all products were determined by ^{1}H NMR spectra (see Supporting Information). Analysis of purity of

Table 2. Formation of Products by the Reaction of 20 2′-Hydroxychalcones with Amidines or Guanidine at 190 °C under Microwave Irradiation for 30 Min[a]

starting material[b]	product (yield %)	starting material[b]	product (yield %)	starting material[b]	product (yield %)	starting material[b]	product (yield %)[c]	starting material[b]	product (yield %)
8a, **7a**	**9a** (44.7)	**8b**, **7a**	**10a** (35.5)	**8c**, **7a**	**11a** (37.6)	**8d**, **7a**	**12a** (39.9)	**8e**, **7a**	**13a** (27.4)
8a, **7b**	**9b** (54.3)	**8b**, **7b**	**10b** (34.8)	**8c**, **7b**	**11b** (38.2)	**8d**, **7b**	**12b** (34.3)	**8e**, **7b**	**13b** (22.4)
8a, **7c**	**9c** (48.8)	**8b**, **7c**	**10c** (41.0)	**8c**, **7c**	**11c** (37.9)	**8d**, **7c**	**12c** (21.1)	**8e**, **7c**	**13c** (42.6)
8a, **7d**	**9d** (46.8)	**8b**, **7d**	**10d** (35.2)	**8c**, **7d**	**11d** (34.0)	**8d**, **7d**	**12d** (26.8)	**8e**, **7d**	**13d** (29.2)
8a, **7e**	**9e** (46.7)	**8b**, **7e**	**10e** (50.1)	**8c**, **7e**	**11e** (44.7)	**8d**, **7e**	**12e** (22.8)	**8e**, **7e**	**13e** (26.5)
8a, **7f**	**9f** (42.6)	**8b**, **7f**	**10f** (24.4)	**8c**, **7f**	**11f** (18.9)	**8d**, **7f**	**12f** (27.0)	**8e**, **7f**	**13f** (24.5)
8a, **7g**	**9g** (55.4)	**8b**, **7g**	**10g** (35.5)	**8c**, **7g**	**11g** (29.3)	**8d**, **7g**	**12g** (41.8)	**8e**, **7g**	**13g** (28.6)
8a, **7h**	**9h** (44.5)	**8b**, **7h**	**10h** (17.3)	**8c**, **7h**	**11h** (12.3)	**8d**, **7h**	**12h** (26.7)	**8e**, **7h**	**13h** (25.1)
8a, **7i**	**9i** (56.6)	**8b**, **7i**	**10i** (35.2)	**8c**, **7i**	**11i** (23.5)	**8d**, **7i**	**12i** (28.6)	**8e**, **7i**	**13i** (33.9)
8a, **7j**	**9j** (49.1)	**8b**, **7j**	**10j** (41.7)	**8c**, **7j**	**11j** (38.2)	**8d**, **7j**	**12j** (34.6)	**8e**, **7j**	**13j** (34.1)
8a, **7k**	**9k** (50.2)	**8b**, **7k**	**10k** (40.7)	**8c**, **7k**	**11k** (41.8)	**8d**, **7k**	**12k** (33.7)	**8e**, **7k**	**13k** (34.8)
8a, **7l**	**9l** (44.3)	**8b**, **7l**	**10l** (38.6)	**8c**, **7l**	**11l** (38.4)	**8d**, **7l**	**12l** (44.4)	**8e**, **7l**	**13l** (27.1)
8a, **7m**	**9m** (40.1)	**8b**, **7m**	**10m** (39.4)	**8c**, **7m**	**11m** (45.5)	**8d**, **7m**	**12m** (26.4)	**8e**, **7m**	**13m** (31.3)
8a, **7n**	**9n** (48.1)	**8b**, **7n**	**10n** (49.1)	**8c**, **7n**	**11n** (50.0)	**8d**, **7n**	**12n** (29.4)	**8e**, **7n**	**13n** (22.9)
8a, **7o**	**9o** (44.8)	**8b**, **7o**	**10o** (42.6)	**8c**, **7o**	**11o** (41.3)	**8d**, **7o**	**12o** (16.3)	**8e**, **7o**	**13o** (25.0)
8a, **7p**	**9p** (49.0)	**8b**, **7p**	**10p** (38.3)	**8c**, **7p**	**11p** (30.0)	**8d**, **7p**	**12p** (25.2)	**8e**, **7p**	**13p** (21.6)
8a, **7q**	**9q** (48.2)	**8b**, **7q**	**10q** (45.4)	**8c**, **7q**	**11q** (41.3)	**8d**, **7q**	**12q** (16.4)	**8e**, **7q**	**13q** (36.8)
8a, **7r**	**9r** (44.6)	**8b**, **7r**	**10r** (45.5)	**8c**, **7r**	**11r** (53.3)	**8d**, **7r**	**12r** (30.6)	**8e**, **7r**	**13r** (28.3)
8a, **7s**	**9s** (53.0)	**8b**, **7s**	**10s** (47.8)	**8c**, **7s**	**11s** (54.0)	**8d**, **7s**	**12s** (12.7)	**8e**, **7s**	**13s** (32.6)
8a, **7t**	**9t** (34.8)	**8b**, **7t**	**10t** (42.3)	**8c**, **7t**	**11t** (47.3)	**8d**, **7t**	**12t** (31.5)	**8e**, **7t**	**13t** (26.4)

[a] Reactions were carried out on a 0.1 mmol scale with equivalents of starting materials. [b] Starting material: **8a**, benzamidine; **8b**, 4-methylbenzamidine hydrochloride; **8c**, 4-chlorobenzamidine hydrochloride; **8d**, cyclopropylcarbamidine hydrochloride; **8e**, guanidine hydrochloride. [c] **12d**, **12i**, **12l**, **12o**, **12q**, **12r**, **12s**, and **12t** contained staring material **8d**.

selected products was performed by HPLC (for the procedure, see Supporting Information). Except for products **12d**, **12i**, **12l**, **12o**, and **12q**−**t**, the rest of these 92 compounds were pure, as shown by ^{1}H NMR spectra. The results of HPLC showed that the purities of **12d**, **12l**, and **12r** were higher than 80%, whereas the purities of **12i**, **12o**, **12q**, **12s**, and **12t** were lower than 80%. The purities of representatives **9a**, **10a**, **11a**, **12a**, and **13a** of the other 92 products were higher than 98%.

In summary, we have developed a new and efficient method for constructing combinatorial libraries of 2,4,6-trisubstituted pyrimidines. Important features of this microwave-assisted solution parallel synthesis method include the following: (1) Most chalcones are commercially available or can be synthesized easily by the reaction of acetophenones with aldehydes. (2) Most products are separated from the reaction by filtration and are of high purity. (3) This method requires a short reaction time. (4) When R^2 is an aromatic group, an aliphatic group, or $-NH_2$ in the structure of NH_2NHCR^2, products of 2,4,6-trisubstituted pyrimidines can be obtained. (5) Regardless of the substituted groups attached to the benzene ring of chalcones, the reaction can be carried out smoothly to produce 2,4,6-trisubstituted pyrimidines.

This new method as developed here is convenient and efficient for the preparation of combinatorial libraries of 2,4,6-trisubstituted pyrimidines on the basis of the reaction of α,β-unsaturated ketones with amidines or guanidine.

Acknowledgment. This work was supported by grants from NIH and ACS.

Supporting Information Available. Supporting Information is available for experimental procedures and characterization data for **7a**−**t**, **9a**−**t**, **10a**−**t**, **11a**−**t**, **12a**−**t**, **13a**−**t**, and purity analysis of some representative products by HPLC; MS spectra of products **9a**, **9b**, **10c**, **10d**, **11f**, **11g**, **12h**, **12i**, **13j**, and **13k**; and ^{1}H NMR spectra of products **9a**−**t**, **10a**−**t**, **11a**−**t**, **12a**−**t**, and **13a**−**t**. This material is available free of charge via the Internet at http://pubs.acs.org.

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