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Report

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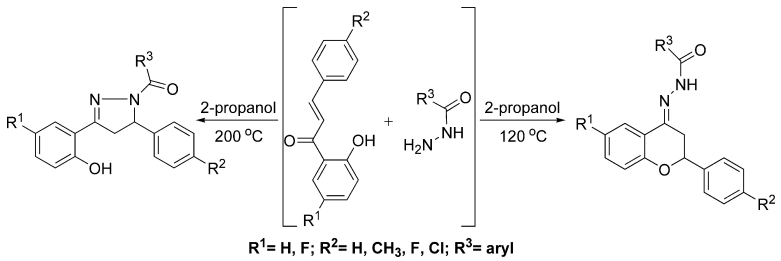

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Microwave-Assisted Reaction of 2′-Hydroxychalcones with Hydrazides to Synthesize Flavanone Hydrazone and 4,5-Dihydropyrazole Derivatives

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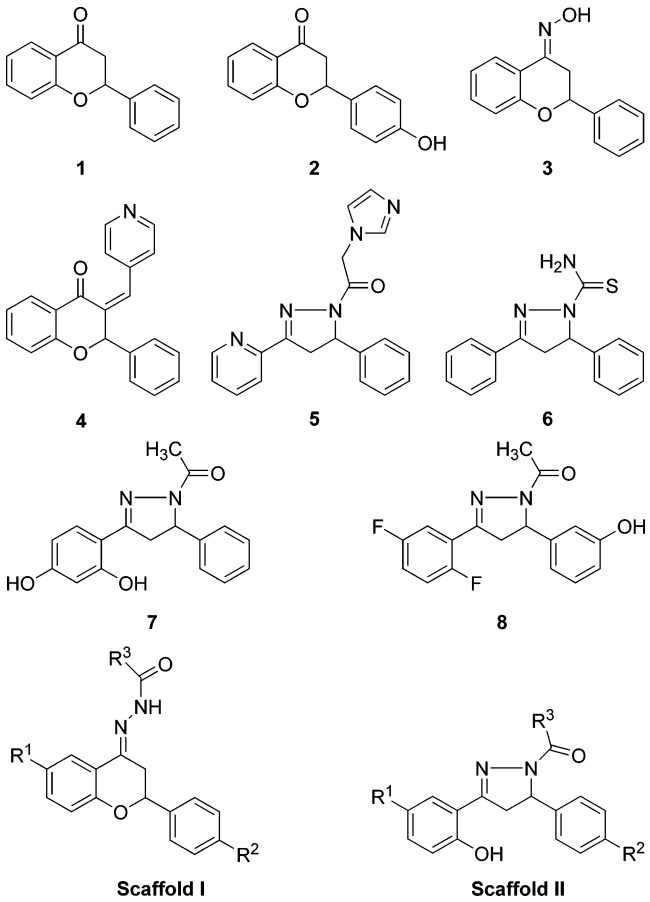
It remains an important challenge to develop concise and effective methodologies for preparing combinatorial libraries of small molecules for drug discovery research. So far, a number of strategies have been developed for meeting such a challenge.[1] In all of these strategies, solid-phase parallel synthesis is commonly employed to prepare molecular diversity libraries, whereas solution-phase parallel synthesis is used to synthesize focused libraries of related compounds sharing certain common structural features. Microwave-assisted organic synthesis (MAOS) has attracted considerable attention in recent years.[2] The rate of a reaction is accelerated in microwave synthesis as compared to conventional heating. The product distributions can be altered, since the reaction temperature can easily be changed, and that high reaction temperature can be rapidly attained under microwave condition when the reaction is performed in a sealed vessel. Here, we report a method combining solution-phase parallel synthesis and MAOS for constructing structurally diversely compound libraries.

Flavanone **1** and its derivatives exhibit versatile bioactivities. Several pharmacological activities, including anti-inflammatory, antitumor, and antioxidant properties, have been reported.[3] 4′-OH or 6-OH-Flavanone **2** and flavanone oximes **3** can induce apoptosis in human leukemia HL-60 cells.[4,5] Pyridinyl-substituted flavanone derivatives **4** have been identified as the aromatase inhibitors.[6] It has been reported that 4,5-dihydropyrazole derivative **5** possesses bactericidal and fungicidal activities.[7] Some 4,5-dihydropyrazole derivatives **6** have been identified as inhibitors of monoamine oxidase and can be used as potential agents in the treatment of Parkinson's disease, Alzheimer's disease, depression, and anxiety.[8] Moreover, recent studies have shown that some 3,5-diaryl-4,5-dihydropyrazoles **7** are potent and selective inhibitors of the mitotic kinesin KSP (kinesin spindle protein)[9] and that some pyrazole derivatives **8** bind to *P*-glycoprotein.[10] These pyrazole derivatives can be optimized to develop candidates of anticancer agents.

Due to their potential therapeutic application in a wide range of human diseases as described above, we are interested in developing a concise methodology for constructing combinatorial libraries of derivatives of flavanone hydrazones derivatives (scaffold I) and 4, 5-dihydropyrazole (scaffold II).



Kállay et al. investigated the reaction of flavanone with hydrazine and substituted hydrazines (H_2N-NHR; R = CH_3, $CONH_2$, C_6H_5, $COCH_3$, etc.).[11,12] Flavanone and monoacetylhydrazine were dissolved in EtOH and refluxed for 12 h. Monoacetylflavanone hydrazone was obtained with a yield of 22.1%. When 2′-hydroxychalkone (or flavanone) in EtOH was mixed with methylhydrazine sulfate and KOH in H_2O and the mixture was refluxed for 3 h, 1-methyl-3-(*o*-hydroxyphenyl)-5-phenylpyrazoline was obtained with a yield of 88.1%. Kállay et al.[13] also reported the thermal rearrangement of 2′-hydroxychalkone hydrazone. Monoacetylflavanone hydrazone was sealed in a capillary tube under N_2 and maintained in an oil bath at 200−210 °C for 1 h; 80.7% of monoacetylflavanone hydrazone was rearranged to *N*-acetyl-3-(*o*-hydroxyphenyl)-5-phenylpyrazoline. Kale et al.[14] prepared *N*-dichlorosalicyloyl flavanone hydrazones by the reaction of 1,3-diarylpropenone with 3,5,2-$Cl_2(HO)C_6H_2$-$CONHNH_2$ in EtOH−HOAc with yields of 50−63%. They also found that when the reaction was performed in DMF, salicycloylpyrazolines (30−68%) were formed.

On the basis of these previous reports, here in our present work, various 2′-hydroxychalcones and hydrazides were used as building blocks (Scheme 1) to construct flavanone hydrazone derivatives (scaffold I) and 4,5-dihydropyrazole derivative libraries (scaffold II). Because of the structural characteristic (2′-OH) of scaffold II, if the reaction was performed in alkaline solution, the purification of products

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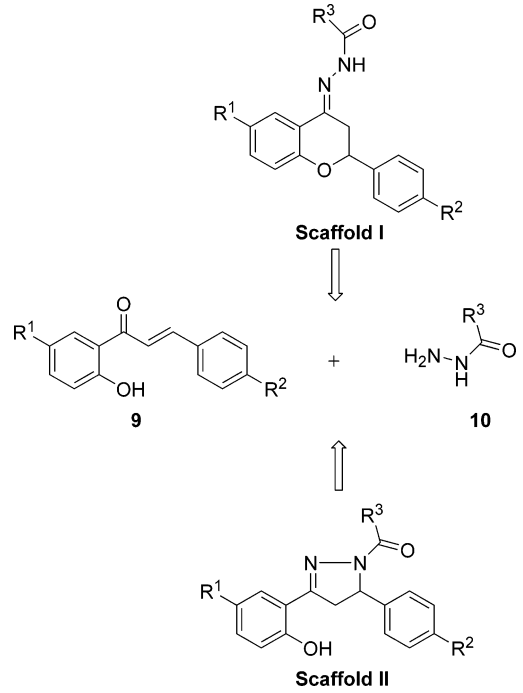
Scheme 1. Proposed Retrosynthesis of 4,5-Dihydropyrazole Derivatives and Flavanone Hydrazone Derivatives[a]

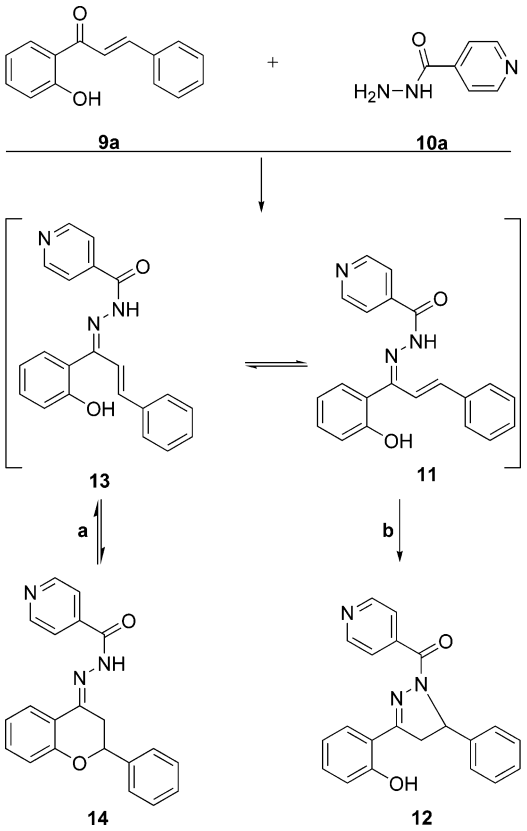


[a] **9**: **9a**, $R^1 = H$, $R^2 = H$; **9b**, $R^1 = H$, $R^2 = CH_3$; **9c**, $R^1 = H$, $R^2 = F$; **9d**, $R^1 = F$, $R^2 = CH_3$; **9e**, $R^1 = F$, $R^2 = F$; **9f**, $R^1 = F$, $R^2 = Cl$. **10**: **10a**, R^3 = 4-pyridinyl; **10b**, R^3 = 4-$CF_3C_6H_4$: **10c**, R^3 = 4-$CH_3C_6H_4$.

would be tedious. Therefore, we attempted the reaction in neutral medium and changed the reaction temperature to alter the distribution of products (scaffold I and scaffold II) under microwave irradiation. By using this method, we expected that two structurally different products would be prepared separately.

The reaction of 1-(2-hydroxyphenyl)-3-phenyl propenone **9a** with isonicotinic acid hydrazide **10a** was chosen as a model reaction (Scheme 2). At first, equimolar reactants were dissolved in 2-propanol, and the reaction was performed under the condition of conventional heating, isonicotinic acid (2-phenylchroman-4-ylidene)-hydrazide of scaffold I was obtained with a yield of 20.4% after reflux for 48 h. No product of scaffold II was found. To reach higher temperature, a microwave synthesizer (Explorer, CEM Company) was used in the experiments. The reaction was carried out in a sealed vessel under microwave irradiation. Considering the need to construct combinatorial compound libraries, an easy method for purification would be desirable. Although some solvents of high boiling point (e.g., DMA, DMF) can reach higher reacting temperatures than 2-propanol and nicotinic acid (2-phenylchroman-4-ylidene)-hydrazide was very hard to dissolve in 2-propanol, we preferred to use 2-propanol as the solvent for the reaction. The product came out as a precipitate from the solvent after the reaction ended. Similarly, all of the products formed precipitate in the later experiments. The products were easily separated from the reaction mixture by filtration. When the temperature was changed from 120 to 200 °C, we found that isonicotinic acid (2-phenylchroman-4-ylidene)-hydrazide **14** was the main product (yield: 48.8%) at 120 °C after 2 h and that [3-(2-hydroxyphenyl)-5-phenyl-4,5-dihydropyrazol-1-yl]-pyridin-4-yl-methanone **12** (of scaffold II) was the main product

Scheme 2. Proposed Mechanism of 1-(2-Hydroxyphenyl)-3-phenylpropenone **9a** Reacted with Isonicotine Acid Hydrazide **10a** at Different Temperatures[a]

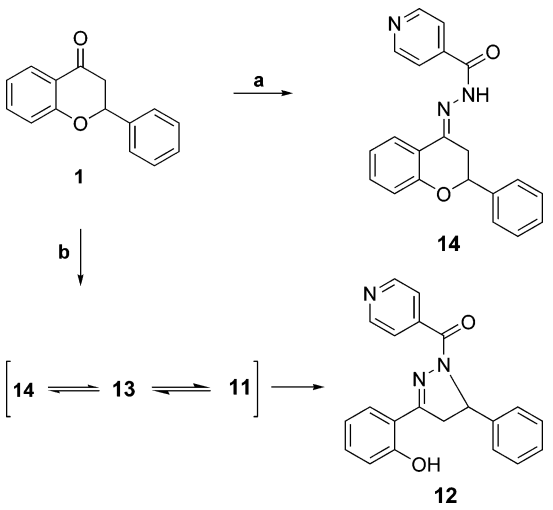


[a] (a) 120 °C, microwave irradiation, 2 h, 2-propanol; (b) 200 °C, microwave irradiation, 2 h, 2-propanol.

(yield: 62.4%) at 200 °C after 2 h. The optimal reaction time was 2 h, although the reactive time of some organic reactions were from 10 to 30 min under microwave irradiation.[2]

After analyzing the two main products formed at different temperatures, we proposed a mechanism of the reaction (Scheme 2). During the course of the reaction, intermediates **11** and **13** were formed. These two intermediates are interconvertible and exist in a dynamic equilibrium. Compound **12** is the thermodynamically controlled product, whereas compound **14** is the kinetically controlled product. When **9a** reacted with **10a** at 200 °C under microwave irradiation, the main product was compound **12**. In contrast, when the temperature was 120 °C or lower, the main product was compound **14**. When the temperature was increased, compound **14** could be changed to compound **12** through intermediates **11** and **13**. To validate this proposed mechanism, we used flavanone **1** to react directly with **10a** at 120 and 200 °C separately under microwave irradiation. If compound **14** could not be rearranged to compound **12** with the increased temperature, compound **14** should be the main product, even if the temperature had been increased. It was found that compound **14** was the main product (59.6%) at 120 °C. After the temperature was increased to 200 °C, the main product of this reaction was compound **12** (77.5%) (Scheme 3). Another observation was that yields of the main products of flavanone reacting with isonicotine acid hydrazide at different temperatures were higher than those of **9a** in the same reaction time (2 h). Therefore, it was very

Scheme 3. Reaction of Flavanone **1** with Isonicotine Acid Hydrazide **10a** at Different Temperatures[a]



[a] (a) **10a**, 120 °C, microwave irradiation, 2 h, 2-propanol; (b) **10a**, 200 °C, microwave irradiation, 2 h, 2-propanol.

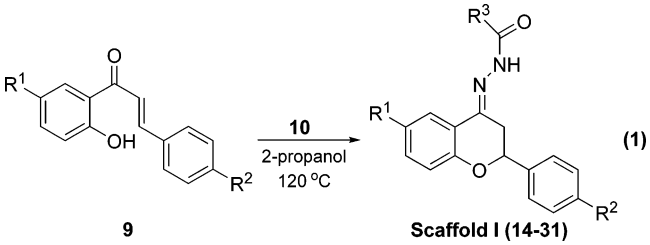
unlikely that flavanone **1** was rearranged initially to compound **9a**, which reacted with **10a**. It was obvious that the higher yields resulted from the reactive activity of carbonyl of flavanone **1**, which was higher than that of **9a**. The results revealed that compound **14** was produced during the progress of the reaction and then rearranged to compound **12** at high temperature through the intermediates **11** and **13** (Scheme 3).

The reaction outlined in Scheme 2 is a typical tandem cascade reaction. Two steps were completed in a sealed vessel. On the other hand, two structurally different compounds were synthesized from the same reactant by changing only the temperature under microwave irradiation. The filtration method for purifying the products is also quite simple. All of these reaction and purification features are desirable for constructing compound libraries using solution-phase parallel synthesis. Using this method, we have performed the reaction of various 2′-hydroxychalcones with hydrazides at 120 and 200 °C under microwave irradiation. The results are shown in Tables 1 and 2.

The structures of all products listed in Tables 1 and 2 were determined by ^{1}H NMR and MS spectra. Moreover, we proved the proposed products using single crystal X-ray experiments (for structural figures and cif files, see Supporting Information).

In this Report, we have demonstrated a method of solution-phase parallel synthesis coupled with MAOS for constructing two distinct combinatorial libraries starting from the same reactants. By using this method, we have synthesized two different series of compounds with high purity from the same reactants by changing only the reaction temperature. These products were separated easily from the reaction mixture by filtration. This is a concise and effective method for constructing molecular libraries of structural diversity that can find application for chemical genomics or drug discovery research. Using this method, we have constructed a focused molecular library of >400 compounds (unpublished results). The biological studies of these compounds are ongoing and will be reported elsewhere.

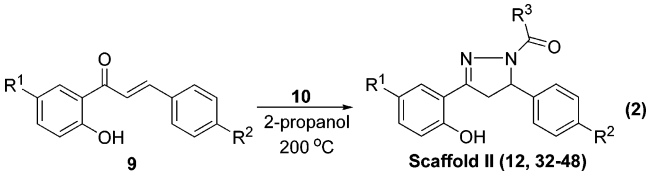
Table 1. 2′-Hydroxychalcones Reacted with Hydrazides to Form Flavanone Hydrazone Derivatives (Scaffold I) at 120 °C under Microwave Irradiation



product	R^1	R^2	R^3	yield (%)[a]
14	H	H	4-pyridinyl	48.8
15	H	H	4-$CF_3C_6H_4$	10.5
16	H	H	4-$CH_3C_6H_4$	16.2
17	H	CH_3	4-pyridinyl	10.6
18	H	CH_3	4-$CF_3C_6H_4$	62.1
19	H	CH_3	4-$CH_3C_6H_4$	12.5
20	H	F	4-pyridinyl	22.2
21	H	F	4-$CF_3C_6H_4$	52.1
22	H	F	4-$CH_3C_6H_4$	9.2
23	F	CH_3	4-pyridinyl	13.9
24	F	CH_3	4-$CF_3C_6H_4$	49.8
25	F	CH_3	4-$CH_3C_6H_4$	21.6
26	F	F	4-pyridinyl	74.2
27	F	F	4-$CF_3C_6H_4$	37.8
28	F	F	4-$CH_3C_6H_4$	11.0
29	F	Cl	4-pyridinyl	21.7
30	F	Cl	4-$CF_3C_6H_4$	31.1
31	F	Cl	4-$CH_3C_6H_4$	20.9

[a] Isolated yields of pure compounds.

Table 2. 1-(2-Hydroxy-5-substituted Phenyl)-3-(4-Substituted Phenyl)-propenones Reacted with Hydrazides to Form 4,5-Dihydropyrazole Derivatives (Scaffold I) at 200 °C under Microwave Irradiation



product	R^1	R^2	R^3	yield (%)[a]
12	H	H	4-pyridinyl	62.4
32	H	H	4-$CF_3C_6H_4$	23.7
33	H	H	4-$CH_3C_6H_4$	35.1
34	H	CH_3	4-pyridinyl	10.6
35	H	CH_3	4-$CF_3C_6H_4$	29.4
36	H	CH_3	4-$CH_3C_6H_4$	32.4
37	H	F	4-pyridinyl	27.7
38	H	F	4-$CF_3C_6H_4$	39.4
39	H	F	4-$CH_3C_6H_4$	29.1
40	F	CH_3	4-pyridinyl	33.7
41	F	CH_3	4-$CF_3C_6H_4$	50.0
42	F	CH_3	4-$CH_3C_6H_4$	36.1
43	F	F	4-pyridinyl	80.5
44	F	F	4-$CF_3C_6H_4$	54.3
45	F	F	4-$CH_3C_6H_4$	40.6
46	F	Cl	4-pyridinyl	14.7
47	F	Cl	4-$CF_3C_6H_4$	56.8
48	F	Cl	4-$CH_3C_6H_4$	33.4

[a] Isolated yields of pure compounds.

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Supporting Information Available. Supporting information is available for experimental procedures and characterization data for **9a**−**9f**, **12**, **14**−**48**; X-ray structural figures and cif files of **20** and **37**; MS spectra of **14**, **24**, **12**, and **41**; and ^{1}H NMR spectra of **12** and **14**−**48**. This material is available free of charge via the Internet at http://pubs.acs.org.

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