An efficient catalytic synthesis of flavanones under green conditions

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An efficient and "green" catalytic conversion of 2′-hydroxychalcones to flavanones in 15 min in the presence of a simple amino acid and a base at room temperature is reported. Liquiritigenin was also efficiently synthesised under these conditions.

Keywords: green chemistry, 2′-hydroxychalcone, flavanone, amino acid, liquiritigenin

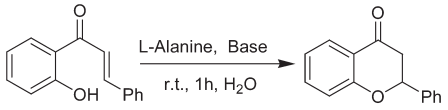
Flavanones are pharmacologically important naturally occurring compounds.[1] showing biological activity as hypertensive, antibacterial, antitumor, antifungal, and anti-inflammatory agents. The synthesis of these compounds has generated significant interest among chemists and biologists.[2,3] The preparation of flavanones has been carried out by intramolecular cyclisation of 2′-hydroxychalcone under various conditions using acids,[4] bases,[5] thermolysis,[6] electrolysis,[7] photolysis[8] and microwave irradiation.[9] However, the yields of these reactions are often moderate, the reaction times are long and the separation of these products requires a lot of organic solvent such as benzene. Tanaka has shown that 2′-hydroxychalcones can be converted into flavanones under mild conditions in an hour. However, the reaction time is still long when compared to microwave irradiation assisted catalysis.[9] We report here that 2′-hydroxychalcones can be converted into flavanones very efficiently under mild green conditions, within a reaction time that is comparable to microwave irradiation assisted catalysis.[9] Furthermore, an efficient catalytic synthesis of Liquiritigenin is also reported under these conditions.

Result and discussion

L-Alanine, the best amino acid additive in the presence of NaOH described previously,[5] was employed as the first additive to test different kinds of bases in the catalytic conversion of 2′-hydroxychalcones to flavanones. Table 1 shows that **1a** can be converted to **2a** efficiently at room temperature within 1h in the presence of NaOH or KOH. Comparison of the alkali hydroxides as bases showed that catalytic activities increase in the order of KOH > NaOH > LiOH. When other bases were introduced, poor to moderate activities are obtained. The conclusion was that a strong base was associated with high cyclisation activity.

Different amino acid additives were examined to further enhance the catalytic activities in the presence of KOH. Table 2 shows that **1a** can be converted to **2a** in just 6% yield in 15 min in the absence of amino acid. However, **1a** can be completely converted to **2a** very easily in the presence of most amino acids in 15 min. This reaction time is comparable to that of microwave irradiation assisted catalysis.[9] The highest activity is obtained in the presence of L-proline. There was no

Table 1 Effect of different bases in the catalytic cyclisation[a]

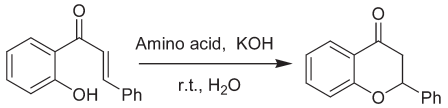


1a **2a**

Entry	Base	Yield/%[b]
1	LiOH	55
2	NaOH	98
3	KOH	>99
4	$Ca(OH)_2$	21
5	Na_2CO_3	1
6	Triethylamine	63

[a] All other conditions are the same with ref. 5.
[b] No optical rotation was observed during optical rotation test.

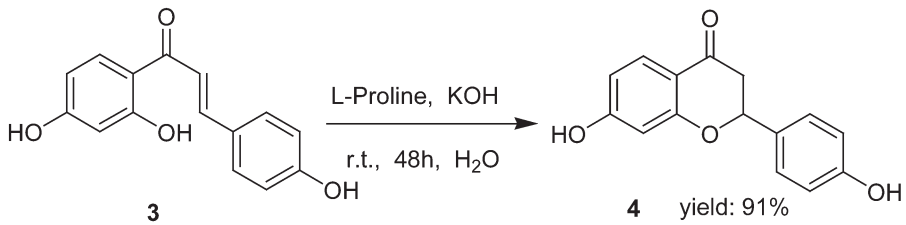
Table 2 Effect of different amino acids in the catalytic cyclisation[a]



1a **2a**

Entry	Amino acid	pKa [b]	Yield/%[c]	
			10 min	15 min
1	None			6
2	L-Alanine	9.69	84	>99
3	L-Proline	9.13	93	>99
4	L-Valine	9.62	54	61
5	L-Phenylalanine	9.13	68	90
6	L-Glutamic acid	9.67	87	99
7	L-Threonine	10.40	92	>99
8	L-Serine	9.15	76	>99
9	L-Histidine	9.17	77	>99
10	L-Glycine	9.60	75	93
11	L-Leucine	9.60	66	85
12	L-Isoleucine	9.68	78	93

[a] All other conditions are the same as Table 1.
[b] pKa of amino group in amino acid.
[c] No optical rotation was observed during optical rotation test.



3 **4** yield: 91%

Scheme 1 Catalytic cyclisation of Isoliquiritigenin. Conditions are the same with Table 1, no optical rotation of product was observed during the optical rotation test.

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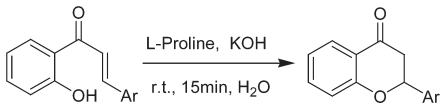
Table 3 Cyclisation of different 2′-hydroxychalcones in the presence of proline and KOH[a]



1 2

Substrate	Ar	Yield (%)[b]
1a	C_6H_4	>99
1b	*o*-ClC_6H_4	89
1c	*m*-ClC_6H_4	94
1d	*p*-ClC_6H_4	95
1e	*o*-$MeOC_6H_4$	75
1f	*m*-$MeOC_6H_4$	95
1g	*p*-$MeOC_6H_4$	50
1h	*p*-$NO_2C_6H_4$	85

[a] All other conditions are the same with Table 1.
[b] No optical rotation was observed during optical rotation test.

clear relationship between the pKa of the amino group in amino acid additives and the cyclisation activity. We speculate that both this property of amino group and steric hinderance of amino acid additives affect the cyclisation activity.

Some representative examples are listed in Table 3 for the cyclisation of different 2′-hydroxychalcones in the presence of L-proline and KOH. The extent of activities appears to be delicately influenced by the structure and the electron properties of substrates. Cyclisation of 2′-hydroxychalcone **1a** gave the best activity. When comparing the chloro-substituents, the steric hinderance clearly influences the catalytic activity, in the order of *p*-Cl > *m*-Cl > *o*-Cl. However, as in the previous report,[5] electronic properties may play the main role in substrates possessing a methoxy substituent.

Liquiritigenin **4** is wildly used as an anti-ulcer agent, in the prevention of atherosclerosis, in the inhibition of monoamine oxidase, in the treatment of mental depression, anti-virus, and as an anti-viral agent. However, liquiritigenin has been prepared in moderate yield at high temperature over a long time.[10,11] Purification of the product in these reports requires a lot of organic solvent. We applied our optimized catalytic conditions to the preparation of liquiritigenin **4** from isoliquiritigenin **3** (Scheme 1). Liquiritigenin was obtained in high yield under mild green conditions with simple work-up procedure.

In conclusion, we have shown that different flavanones can be prepared from 2′-hydroxychalcones very efficiently under mild green condition. Further work on the mechanism and on the asymmetric cyclisation employing amino acids and their derivatives as catalysts is in progress.

Experimental

Melting points were measured using a Mel-Temp melting point apparatus and are uncorrected. IR spectra were recorded with a Thermo Nicolet 370 FTIR Spectrometer using KBr discs. ^{1}H NMR spectra were recorded at 300 MHz, and chemical shifts in ppm were reported relative to internal Me_4Si. Optical rotations of products (MeOH solution) were taken on a Perkin-Elmer Model 341 polarimeter.

Catalytic cyclisation reactions:[5] A suspension of a mixture of powdered 2′-hydroxychalcone **1a** (1.0 g, 4.5 mmol), KOH (8 M, 0.1 mL) and L-alanine (0.01 g) in water (10 mL) was stirred at room temperature for the predetermined time (see Table 2). The crude product was collected by filtration, washed with water and dried in a desiccator to give flavanone **2a**. All prepared products are known compounds and were identified by m.p., IR and ^{1}H NMR. The products did not show any optical rotation.

2a: M.p. 74–75 °C (lit.[5] 75–76 °C); IR(KBr): ν(C=O) 1715cm^{-1}; δ_H(300 MHz, $CDCl_3$) 7.04–7.94 (m, 9H), 5.50 (dd, *J* = 3.0, 13.0 Hz, 1H), 3.12 (dd, *J* = 12.9, 16.2, 1H), 2.88 (dd, *J* = 2.7, 16.2, 1H).

2b: M.p. 96–97 °C (lit.[12] 95–97 °C); IR(KBr): ν(C=O) 1685cm^{-1}; δ_H(300 MHz, $CDCl_3$) 7.09–7.89 (m, 8H), 5.66 (dd, *J* = 2.7, 10.2 Hz, 1H), 2.70–3.15 (m, 2H).

2c: M.p. 97–99 °C (lit.[13] 98–99 °C); IR(KBr): ν(C=O) 1695cm^{-1}; δ_H(300 MHz, $CDCl_3$) 7.10–7.90 (m, 8H), 5. 44–5.47 (m, 1H), 2.83–3. 15 (m, 2H).

2d: M.p. 94–96 °C (lit.[9] 95–96 °C); IR(KBr): ν(C=O) 1690cm^{-1}; δ_H(300 MHz, $CDCl_3$) 7.03–7.65 (m, 8H), 5.43–5.46 (m, 1H), 2.82–3.06 (m, 2H).

2e: M.p. 81–82 °C (lit.[12] 80–82 °C); IR(KBr): ν(C=O) 1685cm^{-1}; δ_H(300 MHz, $CDCl_3$) 6.84–8.60 (m, 8H), 5.75 (dd, *J* = 12.5, 3.0 Hz, 1H), 3.72 (s, 3H), 2.91 (dd, *J* = 17.0, 3.0, 1H), 2.83 (dd, *J* = 17.0, 12.6, 1H).

2f: M.p. 79–80 °C (lit.[14] 78–79 °C); IR(KBr): ν(C=O) 1685cm^{-1}; δ_H(300 MHz, $CDCl_3$) 6.93–8.55 (m, 8H), 5.75 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.70 (s, 3H), 2.82–3.12 (m, 2H).

2g: M.p. 86–88 °C (lit.[9] 87–88 °C); IR(KBr): ν(C=O) 1690cm^{-1}; δ_H(300 MHz, $CDCl_3$) 6.96–7.91 (m, 8H), 5.40 (dd, *J* = 2.7, 13.5 Hz, 1H), 3.80 (s, 3H), 2.86–3.15 (m, 2H).

2h: M.p. 140–142 °C (Authentic product from TCI 141–142 °C); IR(KBr): ν(C=O) 1685cm^{-1}; δ_H(300 MHz, $CDCl_3$) 7.02–7.56 (m, 8H), 5.44–5.47 (m, 1H), 2.82–3.12 (m, 2H).

4: M.p. 196–197 °C (lit.[10] 195–197 °C); IR(KBr): ν(C=O) 1660cm^{-1}; δ_H(300 MHz, acetone-d_6) 9.20 (br, 1H), 8.40 (br, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.51 (dd, *J* = 2.3, 8.8 Hz, 1H), 6.41 (d, *J* = 2.3 Hz, 1H), 5.44 (dd, *J* = 3, 12.9 Hz, 1H), 3.06 (dd, *J* = 12.0, 16.2 Hz, 1H), 2.66 (dd, *J* = 3, 10.8 Hz, 1H).

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