Mapana Journal of Sciences
2019, Vol. 18, No. 2, 21-28
ISSN 0975-3303|https://doi.org/10.12723/mjs.49.3

Solid Supported Peptide Catalyst for the Synthesis of Flavanone and Azaflavanones

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Abstract

A variety of flavanones and azaflavanones have been synthesised from chalcones, catalysed by 30 mol% solid support proline terminal peptide, which is mildly efficient with high conversions yields and could be recycled up to three times without significant loss in its activity.

Keywords: Chalcones, Solid Support Peptide Catalyst, Reusable Catalyst, Cyclisation, Flavanones

1. Introduction

Flavonoids are found abundantly in plants of the family *leguminosae*, *compositae* and *moraceae*. They have been reported to possess a broad spectrum of biological activity [1] such as anti-inflammatory, anti-tumor [2], anti-oxidant and estrogen receptor modulator [3]. In addition, they have been observed to inhibit the activity of cyclooxygenase/lipoxygenase [4]. Their azaflavanone derivatives have been reported to have potential as candidates for NSAIDs [5], while the thioflavanone derivatives have been shown to serve as a precursor for biologically active compounds such as benzothiazepine and thiochroman–4-one [6].

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The synthesis of flavanones often involves an intramolecular conjugate addition of 2-hydroxychalcones, 2-aminochalcones and 2-mercaptochalcones to the corresponding cyclic system through acid or base catalysis. Acid catalysed reactions [7] can be performed using orthophosphoric acid, acetic acid and silica gel [8], while base catalysis has been carried out with strong alkali [9] or L-proline [10]. Other cyclisation methods involve different reaction conditions such as light [11], heat [12], electrolysis [13] and Ni/Zn/K halide catalysis [14]. However, many of these methods suffer from disadvantages such as low yields, long reaction times, use of strong acidic medium leading to environmental pollution, high cost of the catalyst and lack of recovery or reusability of the catalysts. Hence, there is still a need to develop mild, high-yielding protocols for the cyclisation of substituted chalcones to flavanones via environment friendly method.

The main drawback of proline [10] is that when used as catalyst for some cases of preparation of different products, it showed lack of reusability and yielded poor yields. Thus, the authors decided to develop a new method using a solid support base catalyst [15] which is mainly focused on yield improvement and reusability. The authors selected solid support proline terminal peptide which belongs to the class of amide with mild basic nature and has gained importance as a Lewis base catalyst since it is inexpensive, environment friendly and stable at high temperature.

2. Results and Discussions

Cyclisation reactions of chalcones to flavanones were carried out using 30 mol% solid support proline terminal peptide, a mild efficient, reusable catalyst with high conversion yields. This catalyst promotes 2-hydroxychalcone to the corresponding flavanone by intramolecular cyclisation. Following the completion of the reaction, the catalyst was recovered with a simple workup and filtration for further reuse. As shown in Table 1, the recovered catalyst did not show any appreciable loss in its activity since more than 87% yield of the flavanone was obtained even when the catalyst was reused for the third time.

In addition, it was observed that the use of different solvents for the cyclisation reaction of hydroxychalcone indicated that the solid support proline based peptide performs best in N,N-dimethyl formamide. Moreover, high polar solvents may enhance the activity of the catalyst due to hydrogen bonding. Thus, the nature of the solvent plays a key role due to a change in the polarity of the solvent.

All the reactions occurred smoothly as shown in Tables 2 and 3. *o*-Hydroxychalcones reacted faster than 2-aminochalcones to provide the flavanones in excellent yields. This indicated that the presence of the –XH (X= O, NH, group at C2 on the chalcone is required for intramolecular cyclisation to occur. The reaction time for 2-amino chalcones is not significantly longer than 2-hydroxy chalcone.

Amines are more nucleophilic than alcohols due to their basic nature. The amino group on the aromatic ring, however, was found to be involved in resonance. This is why the hydroxy substituted chalcones showed more reactivity over amino chalcones. All the products are known compounds. ^{1}HNMR and other characterisation data were matched with the reported data in the references (Table 2 and 3). All the chalcones were prepared according to the reported procedures [16].

In a typical experiment, a solution of substituted chalcones in DMF was stirred with 30 mol% solid support proline-based peptide under reflux. The reaction was completed in about 8.5 hours. The catalyst was removed by filtration and could be reused up to three times without any appreciable loss in catalytic activity and yield (refer Table 1). The optimal quantity of catalyst was found to be 30 mol%. Excess amount of catalyst did not increase the yields (Table 2 and 3). In all cases, the flavanone (about 93%) was obtained exclusively as confirmed by spectroscopic data.

In summary, 30mol% solid support proline-based peptide is an efficient and reusable catalyst for the cyclisation of various chalcones to the corresponding flavanones. The simple protocol, low cost of the catalyst, reusability and environmental considerations make this procedure useful and attractive.

a) All products were characterised by ^{1}H NMR and mass spectral data.

b) The yield of isolated product.

Table 1: The Cyclisation of 2-hydroxychalcone Catalysed by 30 mol% Solid Support Proline Based Peptide and Catalyst Recycle

	Product	*Condition*	*Yield %*
		Reflux, 30 mol% Solid Support Proline-Based Peptide, 8.5 h	93
		1st Recycle, Reflux, 8.5 h	91
		2nd Recycle, Reflux, 8.5 h	89
		3rd Recycle, Reflux, 8.5 h	87

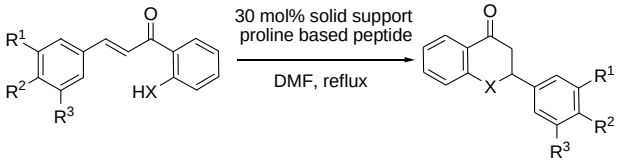
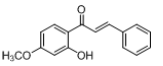


Table 2: Solid Support Proline (30 mol%) Based Peptide Catalysed Cyclisation of Chalcones

Product *(a)*	*X*	*R1*	*R2*	*R3*	*Time* *(h)*	*Yield (%)* *b*	*Mp (Observed)*	*Mp (Reported)*	*Ref*
1	O	H	NO_2	H	8	98	156	161-163	28
2	O	OCH_3	OCH_3	H	9	93	150	154	29
3	O	H	Cl	H	9	96	179	185-187	29
4	O	H	OCH_3	H	9	94	148	155-158	29
5	O	H	OH	H	9	94	185	190-192	30
6	O	H	H	H	8.5	97	91	97	29

7	O	H	CH_3	H	9	80	89	82-83	31
8	NH	H	OCH_3	H	17	55	140	147	31
9	NH	H	H	H	78	52	140	149-150	31

Table 3: Solid Supported Proline (30mol%) Based Peptide Catalysed Cyclisation of Chalcones

Entry	*Substrate*	*Product (a)*	*Time (h)*	*MP (Observed)*	*MP (Reported)*	*Yield (%)b*	*Ref*
1			8.5	140	142	93	10
2			10.5	138	-	85	10

a) All products were characterised by ^1H NMR and mass spectral data.
b) The yield of isolated product.

Table 4: Loading Determined for the Wang Resin-Bound Dipeptides

Dipeptide	Loading (mmol/g)
Pro-Pro	0.65 mmol/g

3. Experimental Study

All reactions were monitored by thin-layer chromatography (TLC), carried out on 0.2 mm silica gel 100-200 and 60F-254 plates (Merck) using UV light (254 and 366 nm) for detection. Chalcones were prepared following the reported procedures [16]. L-proline was purchased from Merck and used to prepare 30 mol% solid support proline-based peptide according to reported procedures [15].

3.1 Solid Phase Peptide Synthesis General Protocol

All peptides were synthesised manually [1] using Wang resin (100-200 mesh, loading = 0.65 mmol/g). Five equivalents of (FMOC)

amino acids were used in each coupling step. The amino acids were activated in DMF by the addition of two coupling solutions. Coupling solution 1 was prepared by dissolving HBTU (5 equiv) and HOBt (5 equiv) in DMF (5 ml). The second solution consisted of DIEA (10 equiv) in DMF (5 ml). After an activation time of 3 min, the activated amino acids were added to the pre-swollen resin in DMF (1 ml) and agitated overnight. The resin was then filtered, washed with DMF (3x10 ml), methanol (3 x 10 ml) and DCM (3 x 10 ml) and dried under high vacuum. The extent of coupling was monitored visually by the use of the ninhydrin test. If the test revealed unreacted NH_2 groups (beads stained blue), the reaction was repeated. After removal of the solution, the beads were washed subsequently with DMF (3 x10 ml), methanol (3 x 10 ml) and DCM (3 x 10 ml). The FMOC protecting group was removed after each cycle by shaking with 20% piperidine in DMF. Typically, the resin was treated with piperidine in DMF (20%, 10 ml), agitated for 30 min and isolated by filtration. This process was repeated twice, agitating for 30 min in the first case and 2 hours in the second. After removal of the solution, the beads were washed with DMF (3 x 10 ml), methanol (3 x 10 ml) and DCM (3 x 10 ml). The acid-labile protecting groups were deprotected after the addition of the last amino acid by treatment of the beads with 10 ml of deprotection mixture (10 ml) containing TEA (6% vol), TMSOTf (34% vol) in DCM for 1 hour [2]. This process was repeated twice. After the removal of the solution, the beads were washed with DMF (3 x 10 ml), methanol (3 x 10 ml) and DCM (3 x 10 ml).

3.2 Estimation of Peptide Loading

The loading of the peptides on the resin was determined by UV spectroscopy of the soluble by-product from the final FMOC deprotection step. FMOC amino acid resin (20 mg, weighed accurately) was placed in a 10 ml volumetric flask and freshly prepared 2% DBU in DMF was added. The resin was agitated for 30 min. Two millilitres of the solution was diluted with ACN to 25 ml in a volumetric flask and then transferred into a UV cell and the absorbance at 304 nm was read. The loading on the resin in mmol/g was obtained from the expression (Abs_{sample} -Abs_{ref}) x 16.4/mg of resin.[3]

3.3. General Method for the Preparation of Flavanones

A mixture of solid support proline-based peptide (30 mol%) chalcone (1 mmol) in DMF(5 cm^3) under N_2 atmosphere was stirred under reflux for the appropriate time (Table 2 and 3). The reaction monitored by TLC, after completion of the reaction of the solvent was removed by reduced pressure and the residue was dissolved in Et_2O (10 cm^3) and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (silica gel 100–200 mesh) using hexane-EtOAc as an eluent to afford pure flavanone. The filtered catalyst was reused after drying.

(Entry 2, Table 2). (2-(3,4-dimethoxyphenyl)chroman-4-one)

Yellow Solid, yield m.p.150 ^oC, IR (ATR): 758, 1023, 1065, 1141, 1259, 1462, 1603, 1689, 2944, 3004 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) : δ 2.87 (dd, J_1= 2.7 Hz J_2= 16.9 Hz, 1H), 3.13 (dd, J_1= 4.6 Hz J_2= 12.6 Hz, 1H), 3.93(s, 3H), δ 3.91 (s, 3H), 5.43 (dd, J_1 = 3.04 Hz, J_2 =13.2 Hz , 1H), 6.91 (d, J = 7.9 Hz, 1H), 7.02-7.07 (m, 1H), 7.48-7.53 (m, 1H), 7.93 (dd, J_1= 1.8 Hz J_2= 7.9 Hz, 1H), ^{13}C NMR (400 MHz, $CDCl_3$):δ 44.6, 56.0, 79.6, 109.4, 111.2, 118.2, 118.9, 121.0, 121.6, 127.1, 136.2, 149.3, 149.5, 161.6, 192.2; HRMS (+ ESI Scan) (M^{+1}, *m/z* (%) 285.1352 , calcd for $C_{17}H_{16}O_4H)^+$ 285.1049.

(Entry 9 Table 2). (2,3-Dihydro-2-phenylquinolin-4(1H)-one)

Yellow Solid, mp 140^oC; IR (ATR): 698, 761, 1153, 1602 , 1331, 1651, 3328, cm^{-1};^1H NMR (400 MHz, $CDCl_3$), δ 2.80 (dd, J_1= 3.9 Hz, J_2= 16.2 Hz 1H), 2.90 (dd, J_1 = 13.7 Hz, J_2 =16.3Hz, 1H), 4.50 (brs, NH), 4.76 (dd, J_1 = 3.9 Hz, J_2 =13.7 Hz, 1H), 6.71(d, J = 8.2 Hz, 1H), 6.80 (t, J = 7.9Hz, 1H) , 7.50- 7.32 (m, 6H), 7.88 (d, J = 7.9 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$):δ 46.5, 58.6, 116.0, 118.5, 119.1, 126.7, 127.7, 128.5, 129.0, 135.5, 141.0, 151.6, 193.4; HR-ESI-MS *m/z* (%) 224.1079, calcd for$(C_{15}H_{13}NOH)^+$ 224.0997.

(Entry 10. Table 2) (2-Phenylthiochroman-4-one)

Yellow Solid;mp 50 ^oC; IR (ATR): 695, 753, 1084, 1284, 1435, 1585, 1673, 2949, 3030, 3059 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 3.20 (ddJ_1 = 3.1 Hz, J_2 =17.9 Hz, 1H), 3.35 (dd, J_1 = 12.9, Hz, J_2 =16.4 Hz, 1H), 4.72 (dd, J_1 = 2.9 Hz, J_2 =12.9 Hz, 1H), 7.16- 7.48 (m, 8H), 8.14 (d, J = 7.8 Hz, 1H);^{13}C NMR (400 MHz, $CDCl_3$):δ 45.5 , 46.7, 125.3, 127.3,

127.5, 128.5, 129.1, 129.3, 133.7, 130.4, 138.5, 142.8, 194.4; HR-ESI-MS *m/z* (%) 241.0687, $(C_{15}H_{12}OSH)^+$ calcd for 241.0609.

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